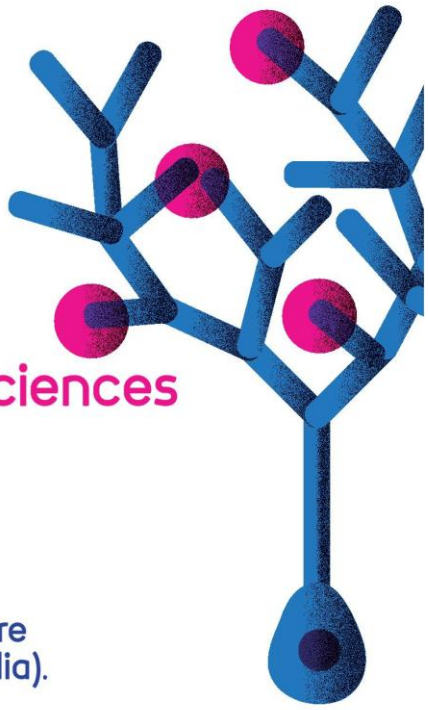
ABSTRACT BOOK

IAN- 2016

October 19-21, 2016

molecules to mind 2016



34th annual meeting of
Indian Academy of Neurosciences

Organized by:
National Brain Research Centre
Manesar, Gurgaon, Haryana (India).

XXXIV Annual Meeting of Indian Academy of Neurosciences (IAN 2016)
"Molecules to Mind"

October 18, 2016 (Tuesday)

Pre-conference Workshops	
09.30 – 16.30 hrs.	***Science Communication and Career Workshop*** **Convener: S Iqbal, DBT Wellcome India-Alliance, New Delhi** **Venue:** Main Auditorium, National Brain Research Centre, Manesar, Gurugram
09.00 – 17.00 hrs.	***Workshop on Neurostereology and Assessment of Pain in Animals and Humans*** **Convenors: TS Roy**, All India Institute of Medical Sciences, New Delhi **S Jain**, All India Institute of Medical Sciences, New Delhi **Venue:** Department of Neurophysiology and Anatomy, All India Institute of Medical Sciences, New Delhi
14.00 – 19.00 hrs.	**Registration for IAN 2016**
17.30 – 18.30 hrs.	**IAN EC Business Meeting** **Venue: National Brain Research Centre, Conference Hall (IB-3 Building)**

Day 1: October 19, 2016 (Wednesday)

08.00 hrs. onwards	**Registration**
09.00 – 10:00 hrs. Hall A Main Auditorium	**Inauguration and Presidential Address**
10:00 – 10:30 hrs Hall A Main Auditorium	**Plenary Talk 1** **Chairperson:** N Jain, National Brain Research Centre, Manesar **G Hassan,** National Center for Biological Sciences, Bengaluru *Neural circuit development and function: the role of Orai mediated Ca2+ entry*
10:30 – 11.30 hrs.	Group Photograph and Tea/Coffee Break - IB-1 Lawns, NBRC
11.30 – 13:00 hrs. **Symposium 1** Hall A Main Auditorium	***Genetic & Environmental Perturbations and Programming Risk for Psychiatric and Developmental Disorders*** **Chairpersons:** V Vaidya, Tata Institute of Fundamental Research, Mumbai M Sharma, Indian Council of Medical Research, New Delhi **J Chelliah**, Jawaharlal Nehru Centre for Advanced Scientific Research, Bengaluru *Role of Syngap1 in cognitive development* **A Bhattacharya**, Institute for Stem Cell Biology and Regenerative Medicine, Bengaluru *Therapeutic potential of p70S6K1 in Fragile X Syndrome* **LT Rao**, National Institute of Mental Health & Neurosciences, Bengaluru *Developmental facets of brain connectivity on fear extinction* **R Mudashetty**, Institute for Stem Cell Biology and Regenerative Medicine, Bengaluru *Stem cell models to understand fragile X syndrome* **V Vaidya**, Tata Institute of Fundamental Research, Mumbai *Serotonin and the development of psychiatric vulnerability*
11.30 – 13:00 hrs. **Symposium 2** Hall B	***Role of Non-nicotinic Acetylcholine Receptors in Nicotine Dependence : Implications for Smoking Cessation Treatment*** **Chairpersons:** S Sharma, All India Institute of Medical Sciences, New Delhi R Jain, All India Institute of Medical Sciences, New Delhi **R Jain**, All India Institute of Medical Science, New Delhi *Current understanding of the neurobiology of the nicotine dependence: the role of NAchRs and dopamine and their treatment implications* **B Chatterjee**, All India Institute of Medical Science, New Delhi *The role of the endogenous opioid system in nicotine dependence and its treatment implications* **P Mandal**, All India Institute of Medical Science, New Delhi *The role of the glutamate and cannabinoid neurotransmitter systems in the nicotine dependence and their treatment implications* **M Patri**, Ravenshaw University, Cuttack *Neuropeptide Y expression confers benzo[a]pyrene induced anxiolytic like behavioral response during early adolescence period of male Wistar rats*
11.30 – 13:00 hrs. **Symposium 3** Hall C	***Adaptive Brain - Measurement to Stimulation Methods in Cognitive Neuroscience*** **Chairpersons:** P Joshi, National Institute of Mental Health & Neurosciences. Bengaluru M Asthana, Indian Institute of Technology, Kanpur **S Subramanian**, National Institute of Mental Health & Neurosciences, Bengaluru *Neuroprotective and cognition enhancing effects of dark chocolate on non-transgenic AD model rats* **P Srivastava**, International Institute of Information Technology, Hyderabad *Evaluation of 360 degree Indirect Visual Local Area Awareness: Through the Lenses* **MK Asthana**, Indian Institute of Technology, Kanpur

	Transcranial direct current stimulation and associative fear learning **BSS Rao**, National Institute of Mental Health & Neurosciences, Bengaluru *Novel therapeutic strategies to treat depression-induced cognitive deficits*
11.30 – 13:00 hrs. Short Talks Session (15+2 min) Hall D	**Chairpersons:** MK Thakur, Banaras Hindu University, Varanasi RD Mehra, Hamdard Institute of Medical Sciences & Res., New Delhi **RK Soni**, KN Government PG College, Bhadoi *Neural mechanism of spatial memory and acquisition of the navigational map in pigeon (Columba livia).* **MH Shahi**, Aligarh Muslim University, Aligarh *Identification of novel transcription factors in the tumorigenesis of most common pediatric brain tumor medulloblastoma* **A Dasgupta**, Pondicherry University, Pondicherry *Divergent network interactions due to human endothelial derived humoral factors affecting self-renewal and differentiation fate of human glial progenitor cells?* **R Mehta**, Jawaharlal Nehru University, New Delhi *Rapid eye movement sleep loss induces epigenetic modifications for the regulation of gene-expression in specific brain regions of rats* **S K Rajesh,** National Institute of Mental Health & Neurosciences, Bengaluru *Geinistein in Diet: Ameliorating Impact on Ischemic Stroke?*
13:00 – 15.00 hrs. IB-1 Building 2nd floor	**Working Lunch + Poster Presentation**
15.00 – 16.30 hrs. Hall A Main Auditorium	***Multilevel Integration of Brain Function*** **Chairpersons:** TS Roy, All India Institute of Medical Sciences, New Delhi N Jain, National Brain Research Centre, Manesar **Invited Talk - 1** **SP Arun**, Indian Institute of Science, Bangalore *What does the visual system know about the world?* **Invited Talk – 2** **S Iyengar**, National Brain Research Centre, Manesar *Effects of Mu-opioid receptor modulation on singing in adult male zebra finches* **Invited Talk – 3** **J Gomes**, Indian Institute of Technology, Delhi *Sequential sub-graph algorithm for analysis of biological boolean networks* **Invited Talk – 4** **K Das**, Indian Institute of Science Education and Research, Kolkata *Neural correlates of cognitive and behavioral performance in humans*
15.00 – 16.30 hrs. Hall B	***Molecular Aspects of Neurodegeneration*** **Chairpersons:** S Wadhwa, New Delhi MM Godbole, Sanjay Gandhi PG Institute of Medical Sciences, Lucknow **Invited Talk – 5** **S Bhattacharyya**, Indian Institute of Science Education and Research, Mohali *Metabotropic glutamate receptor (mGluR) trafficking: Ins & Outs* **Invited Talks – 6** **NR Jana**, National Brain Research Centre, Manesar *Proteostasis impairment in Huntington's disease* **Invited Talk – 7** **A Jagota**, University of Hyderabad, Hyderabad *Understanding biological clock dysfunction in age induced neurodegeneration and parkinson disease* **Invited Talk – 8** **SK Trigun**, Banaras Hindu University, Varanasi *Identification of non-NMDAR targets for excitotoxic brain disorders*

16.30 – 17.00 hrs. IB-1 Lawns, NBRC	**Tea/Coffee Break**
16.30 – 18.30 hrs. **Symposium 4** Hall A Main Auditorium	***Yoga and Neuroscience - Convener – A Anand, Editor, Annals of Neuroscience*** **Chairpersons:** J Arya, Patanjali Yog Peeth, Haridwar BN Ganagadhar, National Institute of Mental Health & Neurosci., Bengaluru **HR Nagendra,** S-VYASA Yoga University, Bengaluru, India *Prana – The Bridge between Body and Mind* **BN Gagngadhar,** National Institute of Mental Health & Neurosciences, Bengaluru *Neurobiology of Yoga and Psychotherapeutic Affects* **SC Manchanda,** Sir Ganga Ram Hospital, New Delhi *Reversal of Atherosclerosis by Yoga Life Style Intervention: Implications for the brain* **S Telles,** Patanjali Research Foundation, Haridwar *Neurophysiology of a High Frequency Yoga Breathing Technique* ***Panel discussion*** *- Avenues for Integration of Traditional Medicine with Modern Medicine* *Guest of Honor* - Vineet Joshi, Chairman, Joshi Foundation, Chandigarh **Chair:** Jaideep Arya, Patanjali Yog Peeth, Haridwar **Convener:** Akshay Anand, Additional Professor, Neuroscience Research Lab, PGIMER, Chandigarh **Member:** N B Nair, Exec Editor, Indian Science Journal, Delhi. P K Seth, CEO Biotech Park, Lucknow, Amarjit Singh, Professor, Community Medicine, PGIMER, Chandigarh, Sangram Patnaik, Senior Advocate, Supreme Court of India, BR Laxmi MDCRC, Coimbatore, Tamil Nadu, Mitali Mukerji, Programme Director, CSIR Ayurgenomics Unit, IGIB, Delhi Bhavana Prasher, Senior Scientist, IGIB, Delhi Sunil Kaul, Chief Senior Research Scientist, AIST, Japan Indrani Gupta, Professor and Head, Health Policy Research Unit, Institute of Economic Growth, Delhi *(IB-3 Conference room) –* ***Please see the insert in registration kit***
17.00 – 18.30 hrs. **Symposium 5** Hall B	***Sleep and Cognition: Brain at Stake!*** **Chairpersons:** D Nag, Lucknow KK Gulia, Sree Chitra Tirunal Institute for Medical Sciences and Technology, Thiruvananthapuram **M Tripathi**, All India Institute of Medical Sciences, New Delhi *Sleep and cognition in children and elderly* **BM Kutty**, National Institute of Mental Health & Neurosciences, Bengaluru *Sleep in schizophrenia* **KK Gulia**, Sree Chitra Tirunal Institute for Medical Sciences and Technology, Thiruvanthapuram *Prenatal sleep disruptions and early cognitive development* **S Jha**, Jawaharlal Nehru University, New Delhi *The central chemosensory machinery: A novel target for sleep regulation* **Arathi R**, Sree Chitra Tirunal Institute for Medical Sciences and Technology, Thiruvananthapuram *Alpha-asarone mediated improvement in sleep and anxiety in rat model of insomnia*

17.00 – 18.30 hrs. **Symposium 6** Hall C	***Chemical Induced Neurotoxicity and Neurodegenerative Diseases - Emerging Concepts and Technologies in understanding the Complexities*** **Chairpersons:** IK Patro, Jiwaji University, Gwalior S Raisuddin, Jamia Hamdard, New Delhi **VK Khanna**, CSIR – Indian Institute of Toxicology Research, Lucknow *Impact of stress on the neurobehavioral toxicity of lambda-cyhalothrin : Effect on brain cholinergic and dopaminergic functions* **AB Pant**, CSIR – Indian Institute of Toxicology Research, Lucknow *Differential responses of Trans-Resveratrol on proliferation of neural progenitor cells and aged rat hippocampal neurogenesis* **S Mehta**, University of Wisconsin, Wisconsin, USA *Oxidative Stress and Post-TBI Secondary Brain Damage* **I Kaur**, LV Prasad Eye Institute, Hyderabad *Neurodegenerative changes in the retina could be predictive for abnormal vascular changes in diabetic retinopathy* **R Sandhir**, Panjab University, Chandigarh *Pathogenesis of Hepatic Encephalopathy following liver failure*
18.30 – 19.30 hrs. Hall A Main Auditorium	**Chairperson:** S Sinha, National Brain Research Centre, Manesar **Special Evening Lecture 1** **TR Raju**, National Institute of Mental Health & Neurosciences, Bengaluru *Amyotrophic Lateral Sclerosis-An interplay between Microglia and Astrocytes* **Special Evening Lecture 2** **PK Roy**, National Brain Research Centre, Manesar *How the brain strives to heal?*
19.30 – 20.30 hrs. Hall A Main Auditorium	**IAN General Body Meeting**
20.30 hrs. onwards **IB-1 Lawns, NBRC**	**Dinner**

Day 2: October 20, 2016 (Thursday)

08.00 – 09.00 hrs.	**Registration**
09.00 – 09.45 hrs. **Main Auditorium**	***ISN Wiley Blackwell JNC International Lectureship Award*** **Chairperson:** G Hassan, National Center for Biological Sciences, Bengaluru **K Swartz**, NINDS, National Institutes of Health, Bethesda, USA *Structure and temperature sensing mechanisms in capsaicin receptor TRPV1 channel*
09.45 – 11.00 hrs. **Main Auditorium**	**Chairpersons:** HB Singh, Department of Science and Technology, New Delhi P Mandal, National Brain Research Centre, Manesar **Plenary Talk 2** **A Murthy**, Indian Institute of Science, Bangalore *Computational mechanisms underlying the control of simple and complex movements* **Plenary Talk 3** **A Jubin**, Vita Salute San Raffaele, Milan, Italy *Multilingualism and Neuroprotection*
11.00 – 11.30 hrs. **Main Auditorium**	**Chairperson:** A Basu, National Brain Research Centre, Manesar **Tech Talk 1** **Ramanjaneya Reddy**, Life Sciences Solution, Bengaluru *iPSC Workflow Solutions from Thermo Fisher Scientific* **Tech Talk 2** **Mukesh Poddar,** BioRad, New Delhi *Changes for better data quality in the western blotting world: Stain Free Technology & Beyond*
11.00 – 11.30 hrs. IB-3 Conference Room	***Expert Group Meeting for Advocacy in Neuroscience*** **Moderator/Chairperson: M Sharma, New Delhi**
11.30 – 12.00 noon	**Tea/Coffee Break - IB-1 Lawns, National Brain Research Centre**
12.00 – 13.00 hrs. **Hall B**	***Innovative Interventions for Insights into Neurodegenerative Disorders*** **Chairperson:** AK Agrawal, Lucknow **Invited Talk - 9** **R Pal**, Manipal University, Manipal *Human pluripotent stem cells in neurological disease modeling and target discovery* **Invited Talk – 10** **A Mishra**, Indian Institute of Technology, Jodhpur *Understanding the pathomechanism of cellular quality control machinery in misfolded proteins aggregation: Implications in neurodegeneration and ageing* **Invited Talk – 11** **I Mariappan**, L V Prasad Eye Institute, Hyderabad *Understanding retinal tissue development and disease using iPSCs*
12.00 – 13.00 hrs. **Main Auditorium**	**NASI Sponsored - Children Interaction with Peers** **Moderator: M Sharma, India** **Short talk by** NR Jana, National Brain Research Centre, Manesar *Plasticity in your Brain.* **Expert Group -** **B Roeder, Hamburg, Germany** **SB Singh, New Delhi, India** **PK Seth, Lucknow, India** **UC Srivastava, Allahabad, India** **K Swartz, Bethesda, USA** **S Sinha, Manesar, India** **C Kaur, Singapore** **R DeSilva, Nugegoda, Sri Lanka**
13.00 – 15.00 hrs. IB-1 Building 2nd floor	**Working Lunch + Poster Session**

15.00 – 16.30 hrs. **Symposium 7** **Hall A**	***Neuroinflammation and Plasticity in Neurodegenerative Disorders*** **Chairpersons:** S Jain, All India Institute of Medical Science, New Delhi PK Seth, Biotech Park, Lucknow **JD Sarma**, Indian Institute of Science Education and Research Kolkata *Neuroimmune crosstalk in virus induced central nervous system demyelination and axonal loss* **P Bhattacharya**, National Institute of Pharmaceutical Education & Res., Ahmedabad *Intra-arterial stem cell therapy to aid ischemic stroke recovery: implication of BDNF signaling* **P Alladi**, National Institute of Mental Health & Neurosciences, Bangalore *Baseline neuroinflammation is an earnest factor in neurodegeneration: A tale of two mice strains* **RK Mishra**, Banaras Hindu University, Varanasi *Impact of Pax6 on immunological surveillance of brain* **S Bose**, All India Institute of Medical Science, New Delhi *Disease modifying effect of magnetic field stimulation in Parkinson's disease: inflammation to motor function*
15.00 – 16.30 hrs. **Symposium 8** **Hall B**	***Neurocognitive Networks in Health, Disease and Recovery*** **Chairpersons:** P Raghunathan, National Brain Research Centre, Manesar A Banerjee, National Brain Research Centre, Manesar **JP John**, National Institute of Mental Health & Neurosciences, Bengaluru *Aberrant cortical networks in dementia and schizophrenia* **D Ray**, National Brain Research Centre, Manesar *Evaluating the dual stream hypotheses of visual information processing: Insights from an fMRI study* **S Diwakar**, Amrita University, Kollam *Computational neuroscience of circuit function and dysfunction: A cerebellum perspective* **D Roy**, Centre of Behavioural and Cognitive Sciences, University of Allahabad, Allahabad *Brain recovery to normalcy following structural insult: A computational Neuroimaging framework* **A Banerjee**, National Brain Research Centre, Manesar *Neurocognitive networks: Concepts & Constraints*
15.00 – 16.30 hrs. **Oral Session -1** **Hall C**	**Chairpersons:** G Kaur, Guru Nanak Dev University, Amritsar R Shukla, Lucknow **S Prasad**, Banaras Hindu University, Varanasi *Bacopa monnieri extract (CDRI-08) plays neuroprotective role in the recovery of learning and memory impairments by modulating scopolamine-induced oxidative stress and altered synaptic plasticity markers in the hippocampus of amnesic mice* **SP Singh**, Banaras Hindu University, Varanasi *Neuroprotection and alleviation of Parkinsonian phenotypes by inhibiting apoptotic pathways in dopaminergic neurons by ayurvedic herbs* **TK Ghosh**, University of Calcutta, Kolkata *Blood brain barrier is impaired in the intracerebroventricular colchicine injected rats* **N Chakraborty**, University of Calcutta, Kolkata *Multiple biomarkers signify multi-targeted therapy for Parkinson's diseases: Preclinical studies*
15.00 – 16.30 hrs. **Symposium 9** **Hall D**	***New Insights in Vertebrate Brain Organization : Role of Specialized Brain Centers and Neural Systems*** **Chairperson:** A Gopesh, University of Allahabad, Allahabad C Kaur, National University of Singapore, Singapore **S Srivastava**, K N Government Post Graduate College, Bhadoi

	Avian brain organization involved in vocal communication- New perspectives of evolution of language and language deficit disorders **M Pal,** Bose Institute, Kolkata *Azadiradione induces HSF1 activity by direct interaction and ameliorates diseases of protein conformation in cell and animal models* **S Shrivastava**, Barkatullaha University, Bhopal *Striking similarities in neuroarchitecture of avian pallium and mammalian neocortex* **C Kaur**, National University of Singapore, Singapore *Hypoxia induced inflammation in the developing cerebellum*
16.30 – 17.00 hrs.	**Tea/Coffee Break - IB-1 Lawns, National Brain Research Centre**
17.00 – 18.00 hrs. **Main Auditorium** **Platform presentation - selected posters (10 min each)**	**Chairpersons:** LT Rao, National Ins. of Mental Health & Neurosciences, Bengaluru N Patro, Jiwaji University, Gwalior **P Saha**, CSIR-Indian Institute of Chemical Biology, Kolkata *Timp-1 protects neurons against A-beta toxicity through Akt/FoxO3a signal transduction pathway* **R Raghav**, All India Institute of Medical Sceinces, New Delhi *Nalbuphine could decrease the rewarding effects induced by morphine in rats* **K Taneja**, Indian Institute of Kanpur, Kanpur *Dendritic spine abnormalities and cognitive decline in mice models of progressive myoclonus epilepsy* **P Chatterjee**, Kolkata *Intermuscular coherence of patients with writer's cramp* **B Mattoo**, All India Institute of Medical Sceinces, New Delhi *Beneficial effect of low frequency repetitive transcranial stimulation on dorsolateral pre-frontal cortex in chronic tension-type headache*
17.00 – 18.00 hrs. **Hall B** **Oral Session - 2**	***Glia in Health and Disease*** **Chairperson:** G Gupta, Department of Biotechnology, New Delhi **I Singh**, Medical University of South Carolina, USA *Role of nitrobiolome in neurodegeneration, neuroprotection & neurorepair is stroke disease* **N Chatterjee**, Sankara Nethralaya, Hyderabad *Biochemically defining differential immune response in retinal glia to clade specific HIV 1 Tat variants* **C Mukhopadhyay**, Jawaharlal Nehru University, New Delhi *Ceruloplasmin protects astroglial cells from norepinephrine mediated toxicity*
17.00 – 18.00 hrs. **Hall C** **Oral Session - 3**	**Chairperson:** R Velayudhan, National Brain Research Centre, Manesar **A Chauhan**, University of Iowa, USA *Novel players in thrombosis and acute ischemic stroke* **J Banerjee**, AIIMS-NBRC, New Delhi *Enhanced GABAergic activity in drug-resistant epilepsy: The dysmaturity hypothesis of focal cortical dysplasia (FCD)* **S. Imam,** US Food And Drug Administration, USA *Repositioning of Leukemia Drugs for Neuroprotection*
18.00 – 18.40 hrs. **Main Auditorium**	**Special Evening Lecture** **Chairperson:** TR Raju, National Institute of Mental Health and Neurosciences, Bengaluru **Gottfried Wilhelm Leibniz Awardee Brigitte Roeder**, University of Hamburg, Germany *Experience dependent development of (multi)sensory functions*
18.45 pm	**Buses will leave for Heritage Resort from NBRC Lawns**

19.15 pm onwards **Heritage Village Resort, Manesar**	**"Opportunities in Germany for Research and Training"** by Alexander von Humboldt Foundation (AvH), German Research Foundation (DFG), Max Planck Society (MPG) and Forschungszentrum Jülich **followed by Banquet Dinner and Cultural Night** **(Entry by Dinner Ticket Only provided in registration kit)**

Day 3: Friday; October 21, 2016 (Friday)

09.00 – 09.45 hrs. **Hall A** **Main Auditorium**	**KT Shetty Memorial Oration** **Chairperson:** SB Singh, Defence Institute of Physiology & Allied Sciences, New Delhi **V Vaidya**, Tata Institute of Fundamental Research, Mumbai *Adult Neurogenesis - Modulation by norepinephrine and thyroid hormone*
09.45 – 11.00 hrs. **Hall A** **Main Auditorium**	**Chairperson:** MK Thakur, Banaras Hindu University, Varanasi **Plenary Speaker – 4** **T Abel**, University of Pennsylvania, Philadelphia, USA *Molecular Mechanisms of Long-Term Memory Storage* **Plenary Speaker – 5** **C Sarkar**, All India Institute of Medical Sciences, New Delhi *Exploiting molecular biology for diagnosis and management of gliomas*
11.00 – 11.30 hrs.	**Tea/Coffee Break - IB-1 Lawns, National Brain Research Centre**
11.30 – 13.30 hrs. **Hall A** **Main Auditorium**	**Young Scientist Colloquium** **Chairpersons**: VK Khanna, CSIR-Indian Institute of Toxicology Research, Lucknow R Giri, National Brain Research Centre, Manesar **Oral Presentations for DM Kar Prize** **R Mittal,** Panjab University, Chandigarh *Rutin in experimental paradigms of STZ-induced diabetic neuropathy* **Kalaiarasi S,** Sathyabama University, Chennai *Cerebrospinal ventricle injection of human beta amyloid peptide and its effect in embryonic zebrafish* **P Kumari,** Defense Institute of Physiology & Allied Sciences, Delhi *Temporal influence of hypobaric hypoxia and derived neurodegeneration on fear conditioning* **P Acharjee**, Banaras Hindu University, Varanasi *Pannexin1 blockage modulates NMDAR-nNOS profile in a rat model of Hepatic Encephalopathy* **UD Kumaresan,** National Institute of Mental Health and Neurosciences, Bengaluru *Altered sleep pattern and its neural correlates as a consequence of prenatal valproic acid insult* **A Dheer,** Defence Institute of Physiology and Applied Sciences, Delhi *Connexin-43 mediated glutamate excitotoxicity in rat hippocampus upon exposure to chronic hypobaric hypoxia* **Oral Presentations for Tulsabai Somani Educational Trust Award** **D Srinivasan,** Sathyabama University, Chennai *Ultra Structure Imaging Studies of Alcohol Treated Zebrafish Brain* **M Kambali,** National Institute of Mental Health and Neurosciences, Bengaluru *Cognitive flexibility and sustained attention in rats experienced early maternal separation and isolation stress* **S J Tripathi ,** National Institute of Mental Health and Neurosciences, Bengaluru *Basolateral Amygdala Mediates Stress-induced Cognitive Deficits by Modulating the Medial Prefrontal Cortical Functions*

	M Gautam, All India Institute of Medical Sciences, New Delhi *Characterization of antinociceptive effect following activation of the spinal cannabinoid type 1 receptor in rats* **S Akter,** South Asian University, New Delhi *Exogenous ATP modulates inflammatory activity in immune cells*
13.30 – 14.15 hrs. **IB-1 Lawns, NBRC**	**Lunch**
14.15 – 16.00 hrs. **Symposium 10** **Hall A** **Main Auditorium**	***Molecular Basis and Epigenetics of Brain Disorders*** **Chairpersons:** S Roy, University of Miami, USA BSS Rao, National Institute of Mental Health & Neurosciences, Bengaluru **S Buch**, University of Nebraska Medical Center, Omaha, USA *Drug abuse mediated potentiation of HAND: Blaming the messenger* **S Roy**, University of Miami, Miami, USA *Opioid Modulation of Gut Immune brain Axis : Implications in HIV neuropathogenesis* **A Dikshit**, All India Institute of Medical Sciences, New Delhi *Understanding the molecular mechanisms underlying epileptogenesis and/or pharmaco-resistance in patients with mesial temporal lobe epilepsy (MTLE)* **S Mishra,** Maulana Azad Medical Centre, New Delhi *Expression of N CAM and MAP2 in developing human auditory cortex*
14.15 – 16.00 hrs. **Symposium 11** **Hall B**	***IAN - FAONS Symposium - Brain Health - Hypes & Hope from Herbs*** **Chairpersons:** S Kaul, National Institute of Advanced Industrial Science and Technology, Tsukuba, Ibaraki, Japan R DeSilva, University of Sri Jayewardenepura, Nugegoda, Sri Lanka **MK Thakur**, Banaras Hindu University, Varanasi *Memory enhancement by Ashwagandha leaf extract* **R Wadhwa**, National Institute of Advanced Industrial Science and Technology, Tsukuba, Ibaraki,Japan *Herbal solution to stress and neurodegeneration - molecular mechanisms* **Y Onishi**, National Institute of Advanced Industrial Science and Technology, Tsukuba, Ibaraki, Japan *Herbs for circadian rhythm* **D Sundar**, Indian Institute of Technology Delhi, Delhi *Computational Insights in to the bioactivities of withanolides* **M Doi**, National Institute of Advanced Industrial Science and Technology, Tsukuba, Ibaraki, Japan *Novel screening system to identify herbs to fight neurodegenerative diseases* **M Kaushik**, Tsukuba University, Japan *Somnogenic component of Ashwagandha: an alternative insomnia therapy* **G Kaur**, Guru Nanak Dev University, Amritsar *Molecular insights in the multifunctional neuroprotective activities from Withania somnifera leaf extract* **R DeSilva**, University of Sri Jayewardenepura, Sri Lanka *The neuroprotective role of Ceylon tea, coffee and green vegetables*
16.00 – 17.00 hrs. **Main Auditorium**	**Valedictory Address & Prize Distribution**

Plenary Talks

Intracellular calcium signaling in neural circuit development and function

Gaiti Hasan

National Centre for Biological Sciences, TIFR, Bangalore 560065, India

Neuron-specific knockdown studies have previously demonstrated a requirement for STIM/Orai mediated Store-operated Ca^{2+} entry (SOCE) in *Drosophila* flight circuit neurons (1). Despite the heterogeneous calcium dynamics associated with excitable cells, the existence of single genes for STIM and Orai in the *Drosophila* genome coupled with ease of genetic manipulation, allowed for the cellular and molecular analyses of SOCE in neurons. These studies have demonstrated a requirement for SOCE both during maturation of the flight circuit (2) and in adult brains (unpublished). Based on genetic RNAi screens designed to identify membrane receptors coupled to SOCE in neurons, signals that stimulate neuronal SOCE appear to be neuromodulatory in character, and include neuropeptides and neurotransmitters (3). We hypothesized that during circuit formation, such neuromodulatory signals might regulate gene expression required for appropriate synaptic maturation. To identify SOCE-regulated genes in maturing circuits, a high throughput comparative transcriptomic analysis was performed. Results from this analysis support a role for SOCE in regulating the expression of specific genes at defined stages of neural circuit development. Moreover, preliminary results by attenuating SOCE in the adult brain suggest significant differences between SOCE-regulated genes of mature and maturing circuits. The significance of these findings in the context of vertebrate circuits and neurodegenerative diseases will be discussed.

1. Venkiteswaran, G and Hasan, G (2009). Intracellular calcium signaling and store operated Ca^{2+} entry are required in Drosophila neurons for flight. *Proc. Natl. Acad. Sci. USA, USA,* 106, 10326-10331.
2. Pathak, T., Agrawal, T., Richhariya, S., Sadaf, S. and Hasan, G. Store-operated calcium entry through Orai is required for transcriptional maturation of the flight circuit in Drosophila (2015). *J. Neurosci*, 35, 13784-13799.
3. Agrawal, T., Sadaf, S. and Hasan, G. (2013). A Genetic RNAi screen for IP_3/Ca^{2+} coupled GPCRs in Drosophila identifies the PdfR as a regulator of insect flight. *Plos Genet* 9: e1003849. Doi:10.1371/journal.pgen.1003849

Computational mechanisms underlying the control of simple and complex movements.

Aditya Murthy

Professor, Centre for Neuroscience, Indian Institute of Science, Bangalore, 560012

A fundamental computation that our brains must perform is the conversion of a stimulus into a motor act. This operation implicitly requires decision-making and motor planning. Using fast eye movements called saccades that rapidly direct our gaze to points of interest in the visual scene we investigate the computational architecture underlying flexible motor planning and control. Using the insights from gained from these experiments we describe how motor plans for sequential saccades are organized. Finally, we will describe results from recent experiments that provide insights into how the brain might coordinate and control simultaneous eye and hand movements.

Multilingualism and Neuroprotection

Jubin Abutalebi

University San Raffaele Milan, Italy

With the population aging and a dramatic increase in the number of senior citizens, public health systems will be increasingly burdened with the need to deal with the care and treatment of individuals with dementia. Enabling people to function independently for longer has immediate social and economic benefits by adding quality of life to the patient and time during which health care resources are not required. Importantly, some environmental factors have been shown to maintain cognitive functioning with aging and postpone the onset of symptoms of dementia. These factors contribute to a concept called 'cognitive reserve', and include education, occupational status, socio-economic class, and involvement in physical, intellectual and social activities.

During my presentation, I provide evidence demonstrating how a particular experience, multilingualism, has been shown to protect cognitive function in older age and delay onset of symptoms of dementia. Indeed, as I will review, lifelong multilingualism may represent a powerful cognitive reserve delaying the onset of dementia by approximately 4 to 5 years. As to the causal mechanism, because speaking more than one language heavily relies upon executive control and attention, brain systems handling these functions are more developed in bilinguals resulting in increases of grey and white matter densities that may help protect from dementia onset. These neuro-cognitive benefits are even more prominent when second language proficiency and exposure are kept high throughout life.

Epigenetics of Memory Storage

Ted Abel

University of Pennsylvania

New experiences are initially encoded as labile short-term memories, which are converted into stable long-term memory by gene transcription-dependent processes. In the hours after learning, the induction of gene expression follows a specific pattern that involves transient waves of transcriptional activity, which are needed for memory consolidation. Recent work has also identified persistent, long-lasting transcriptional changes that are induced by learning, which appear to contribute to storage of long-term memory. It is emerging that this transcription is regulated by epigenomic mechanisms such as histone acetylation and DNA methylation. These epigenetic modifications are critical for the long-lasting regulation of gene expression during development and may be a major mechanism of information storage in the brain. Changes in epigenetic modifications occur in animal models of depression and anxiety disorders, and alterations in DNA methylation have been found in post-mortem brains from patients with post-traumatic stress disorder, schizophrenia, autism and bipolar disorder. Defects in epigenetic modifications may contribute to impairments in synaptic plasticity and cognitive function associated with many psychiatric disorders. Our work suggests that epigenetic modifications are a critical component of both synaptic plasticity and memory formation and storage, and we are working to identify the genes targeted by these epigenetic regulatory processes. We are examining the role of the NR4A "orphan" nuclear receptors, which are critical for long-term memory and long-term potentiation, as well as for the enhancement of memory and plasticity by HDAC inhibition. Co-repressor molecules like SIN3A, which coordinate a transcriptional regulatory complex that includes histone-modifying enzymes HDAC1 and HDAC2, negatively regulates long-term memory and synaptic plasticity. Our work suggest that SIN3A is a memory suppressor gene and genetic ablation of SIN3A leads to enhancements in memory and synaptic plasticity. Our understanding of the master transcriptional regulatory proteins involved in consolidation and storage of long- term memory may ultimately lead to the development of new treatments for the debilitating cognitive deficits associated with psychiatric disorders such as schizophrenia, bipolar disorder, post-traumatic stress disorder and depression.

Exploiting Molecular Biology for Diagnosis and Management of Gliomas

Chitra Sarkar

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Diffuse gliomas are a heterogenous group of tumors and thus far, they have been classified based on their morphologic resemblance to normal glial cells, such as astrocytes, oligodendrocytes, etc., and on pathological grade. However, integration of genomic, transcriptomic, and morphologic data from numerous high throughput studies in recent years has shown that there is substantial diversity in biological behaviour within each of these morphologically defined entities, and identification of behaviourally distinct molecular subgroups has diagnostic, prognostic as well as therapeutic connotations. Most recently, the

Most recently the 2016 updated WHO classification has been published which has set down guidelines for incorporation of molecular biomarkers into the classification of CNS tumors for providing an integrated diagnosis. Narrowing down definitions of diagnostic entities in this manner also aims at reducing inter-observer reproducibility and ensuring uniformity in clinical trials.

The most important molecular markers in the classification of gliomas include p53, EGFR, IDH1, ATRX, 1p/19q and MGMT. Mutation of the tumour suppressor gene TP53 in astrocytomas has been known for decades while mutations in the IDH1/2 and ATRX genes have been identified more recently. These alterations are seen in majority of Grade II and III astrocytic tumors, as well as in secondary GBM, while primary GBM are devoid of them. Primary GBM, on the other hand, demonstrate alterations in the EGFR oncogene, either as amplification or as EGFR VIII mutation. Mutations in TP53, IDH and ATRX genes can be identified by sequencing. In addition, immunohistochemistry with p53, ATRX and mutation specific IDH1 antibodies can be used as a surrogate technique, which is inexpensive and pathologist friendly. Oligodendroglial tumors are characterized by a signature set of genetic alterations viz. 1p/19q co-deletion, IDH1/2 mutation and wild-type ATRX. 1p/19q deletion is the hallmark of these tumors and is of diagnostic, prognostic and predictive value. It can be detected easily by fluorescence in situ hybridization. MGMT promoter methylation is an important epigenetic modification, relevant from a therapeutic point of view. GBMs harbouring MGMT promoter methylation are associated with a better clinical response to alkylating agents as well as better clinical outcome. Recently, mutations

of the TERT gene have been reported in gliomas associated with poor prognosis.

All this molecular data has served to enhance our knowledge of brain tumor development and to challenge our grading systems, underscoring the importance of developing subclassifications with prognostic and potentially therapeutic implications. A classification scheme incorporating clinical, pathologic, and molecular information may facilitate improved prognostication, development of more effective clinical trials, and rational testing of targeted therapeutics.

KT Shetty Memorial Lecture

Norepinephrine and Thyroid Hormone Regulation of Adult Hippocampal Neurogenesis

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The fact that the adult mammalian brain can generate new neurons, at least in discrete regions, throughout the lifespan of the organism has generated immense excitement for both basic neurobiologists and clinicians interested in the promise that this discovery holds. In distinct neurogenic zones in the mammalian nervous system, stem cells/ progenitors divide to give birth to immature neurons that then migrate and integrate functionally into neuronal circuitry. Understanding the regulation of this complex process is likely to yield insights of relevance to both the basic function of adult neurogenesis and in the discovery of therapeutic targets that can control this process. In my talk I will discuss the influence of Norepinephrine and Thyroid Hormone in the regulation of adult hippocampal neurogenesis and the implication of this regulation to Mood disorders and Antidepressant action. Noradrenergic control of hippocampal neurogenesis impinges on proliferation of quiescent stem cells, maturation of neuroblasts and functional integration of differentiated neurons into hippocampal circuitry. Noreprine has vastly differing effects based on the specific noradrenergic receptor at play and this has interesting implications to the onset of action of classical antidepressant drug treatments. Thyroid hormone on the other hand does not appear to influence the stem cell pool, but rather has profound effects on the postmitotic survival of neuroblasts and immature neurons. The drastic consequences of unliganded thyroid hormone receptor alpha1 provide insights into the steep neurogenic decline noted in adult-onset hypothyroidism. Finally, I will discuss how these neurotransmitter and neurohormonal pathways may influence signaling of developmental signaling morphogens such as Sonic Hedgehog.

NBRC Special Lectures

Amyotrophic Lateral Sclerosis-An interplay between Microglia and Astrocytes

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Amyotrophic Lateral Sclerosis (ALS) is a crippling, devastating and debilitating disease with no cure. Studies from our laboratory using in vivo and in vitro models suggest that cerebrospinal fluid (CSF) from sporadic ALS patients induces glial mediated inflammation, which could play a major role in ALS pathogenesis. ALS-CSF induces phenotypic activation and self-propagation of mostly toxic M1 microglial cells, which ultimately leads to enhanced secretion of inflammatory molecules. - Microglial propagation of inflammation appears to be aided by micro vesicles, while phagocytic morphology justifies its role in scavenging. The astrocytes also undergo morphological transformation akin to the microglia to induce neurotoxicity. There was a down regulation of GLT-1 and up-regulation of S-100 Beta and glutamate. These cells lose their capacity to provide trophic support and adopt an inflammatory phenotype. Quest for identification of toxic factor(s) in ALS-CSF by quantitative mass spectrometry revealed more than a 10 fold increase in the level of Chitotriosidase (CHIT). ELISA data showed that CHIT was up-regulated by 19 folds in ALS-CSF. CHIT was expressed exclusively by microglia and not by astrocytes or motor neurons. The expression of CHIT was also seen to be increased upon exposure of microglia to ALS-CSF suggesting its role in neuroinflammation. The initial response to toxic insult is by microglia triggering the inflammatory cascade; while the astrocytes further provide a "forward-push" by producing the inflammatory and toxicity mediators in a sustained manner. The ensuing neuroinflammation by glia accentuates neurodegeneration seen in our sporadic models of ALS.

Microglia, Astrocytes, Neuroinflammation

How the Brain Strives to Heal ?

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Vasospastic-hypoxic brain damage, as by senescence, stroke and traumatic injury has become the second foremost disease burden globally, after cardiac ischaemia. However, as a homeostatic protective process, there is an intrinsic tendency of restorative remodeling in electrically excitable tissue, as brain, heart and muscle. We explore how such restorative/regenerative process can naturally occur as a protective measure inherently in the aforesaid oligaemic or hypoxic brain hazards.

We study the process of brain's plasticity and coping with as ageing progresses in humans, utilizing tensor MRI (myelination marker) of about 400 individuals, 20-90 years age. By devising a novel graph-theoretic analysis of Brain Connectomics, we find that that centralized nodal processing diminishes with ageing, due to increasing ischaemic changes at deep white matter. However. this decrease is compensated by increase of peripheral nodal processing, maximizing in the elderly at 57-62 years age. We corroborate this observation of unexpected old-age neuroplasticity and remodelling, by means of histological findings of the adult human brain which show that oligodenroglial myelination activity peaks in older age.

For probing the neuroprotective process in brain injury as stroke or trauma, we investigate endogenous neuroregeneration, under growth factor release, that may be internally-upregulated or externally-modulated. Here, we analyse and develop a systems biology model of the neurogenesis and gliogenesis from endogenous neural stem cell zone around ependymal region. We then validate the approach using findings from (i) MRI/neurological investigation during human patient recovery, (ii) immunohistochemical study of rodent preparation. This neuro-protective response of brain parenchyma offers an incisive window for enhancement by pharmacological or neurorehabilitative therapies. The lessons that regenerative cardiology has for regenerative neurology is delineated.

Structure and temperature sensing mechanisms in capsaicin receptor TRPV1 channel

Kenton Swartz

NINDS, National Institutes of Health, USA

Protein toxins from venomous organisms have been valuable tools for investigating the structure and gating mechanisms of voltage-activated ion channels. Transient Receptor Potential (TRP) channels are a large family of ion channels that are activated by diverse stimuli and ligands, including second messengers, temperature, voltage and natural products such as capsaicin, menthol and wasabi. We have begun to investigate the structure and gating mechanisms of the heat-activated TRPV1 channel using the double-knot toxin (DkTx) from tarantula venom. I will present the structure of DkTx that we solved using NMR, and show how we have docked DkTx into the electron density maps from the recent single particle EM structure of the toxin bound TRPV1 channel to reveal a range of interesting features of the toxin-channel interaction. In particular, our results reveal that DkTx binds to the perimeter of the external pore of TRPV1 at the interface of the channel with the surrounding lipid membrane. I will also talk about functional experiments suggesting that DkTx and extracellular ions profoundly alter activation of TRPV1 by heat, implicating the external pore in the mechanism of temperature-sensing.

Experience-dependent development of (multi)sensory functions

***Brigitte Röder*[1]**, *Maria Guerreiro*[1], *Suddha Sourav*[1], *Davide Bottari*[1], *Ramesh Kekunnaya*[2]

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Sensitive periods in development are epochs during which the effects of experience on the brain are particularly strong. After the end of the sensitive period neural circuits develop only incomplete resulting in permanent behavioral deficits. We investigate sensitive periods in humans using a prospective developmental approach (studies in infants and children) and a retrospective developmental approach (studies in permanently blind humans and in sight-recovery individuals). Both behavioral and neuroscience techniques are used. Here we show that brain development is characterized by selection, differentiation and grow resulting in functional specialized representations and connectivity. Evidence from retrospective studies demonstrate that these processes are partially experience dependent and linked to sensitive phases. The first arriving input seems to have a privileged role in functional brain development and seems to leave permanent traces in neural circuits.

This work has been approved by one or more of the following ethics boards: German Society for Psychology (Germany), LV Prasad Eye Institute (India), Medical Association Hamburg (Germany)

The work has been funded by the European Research Council (ERC-2009-AdG 249425-CriticalBrainChanges) and the German Research Foundation (DFG)

Invited Talks

What does the visual system know about the world?

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Two-dimensional images of the world pose a fundamental problem for any visual system. Different objects can produce very similar images, and the same object can produce drastically different images across viewing conditions. How does our brain solve this problem? What is the nature of the underlying object representation and what are its rules? We have been investigating this question using a combination of monkey neurophysiology and human behaviour. I will present some recent studies from our lab showing that: (1) Single neurons in monkey inferotemporal cortex (IT) are invariant to objects across 3d rotations; (2) IT neurons encode the relative size of objects in a display, forming a possible neural substrate of size constancy; (3) In human visual search, the dissimilarity between objects is driven by local and global feature differences according to a surprisingly linear rule. Taken together, our results suggest that the brain incorporates systematic knowledge about the world according to simple linear rules.

Ethics statement: All experiments have been performed according to experimental protocols approved either by the IISc Institutional Human Ethics Committee (for human experiments) and by the Institutional Animal Ethics Committee (for animal experiments).

Acknowledgements: Funding sources: Wellcome-DBT India Alliance, DBT-IISc partnership programme

Effects of Mu-opioid Receptor Modulation on Singing in Adult Male Zebra Finches

Soumya Iyengar

NBRC, Manesar, India

Endogenous opioids are known to modulate motivated behaviours. Male songbirds (zebra finches) are motivated to sing a highly stereotyped song in adulthood [directed (FD)] used for courtship or sing in isolation [undirected (UD)], which are learned during a sensitive period early in development. Systemic administration of low doses of the μ-opioid receptor (OR) antagonist naloxone resulted in the production of significantly fewer FD and UD songs by adult male zebra finches. In contrast, high doses of naloxone led to a decrease solely in UD song. Blocking μ-ORs also led to changes in the acoustic features of song such as changes in the pitch, frequency and length of songs. Changes in the number of songs following the above manipulations appear to result from opioid neuromodulation within Area X (a song control nucleus of the avian basal ganglia) and LMAN (a cortical nucleus), which are both upstream of the VTA-SNc (ventral tegmental area – substantia nigra complex). We found that blocking μ-ORs specifically in Area X led to an increase in the number of songs whereas blocking μ-ORs in LMAN had the opposite effects. Our results suggest that changes in opioid neuromodulation in LMAN and Area X lead to changes in dopamine secreted by the VTA-SNc, ultimately leading to changes in the motivation to sing.

Sequential Sub-Graph Algorithm for Analysis of Biological Boolean Networks

James Gomes

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The innumerable interactions between signalling molecules, genes and proteins are graphically represented as Biological Networks. Primarily, information is conveyed through and processed by various entities constituting these networks. One way to analyse outcomes of cellular events, is to use Boolean algebra to describe information processing of biological networks. The on (0) or off (1) state of a vertex, for example, indicates if a gene is active or inactive, and the stables states or singleton attractors of the network denotes cell fate. However, determination of singleton attractors is a NP-hard problem and limits detection of singleton attractors of biological Boolean networks (BBN) to sizes of about 20 vertices. Therefore, the development of fast algorithms is crucial.

We developed an algorithm that examines vertex sub-graphs sequentially and detects singleton attractors of BBNs rapidly. The sequential sub-graph (SSG) algorithm detected singleton attractors in two orders of magnitude lesser time compared to the explicit enumeration method. It was tested on five published BBNs of sizes ranging from 10 to 40, and random networks with in-degrees k_i = 1, 2, 3 and 4. For in-degree equal to 4, SSG took O (1.297^N) time assuming self-degrading vertices and O (1.548^N) assuming non-self-degrading vertices. The SSG algorithm was tested on a 146 vertex 193 edge γ-secretase network to explain some of the reported observations in Alzheimer's disease. Overall, SSG algorithm can rapidly detect singleton attractors of BBNs, and may be applied to understand other diseases.

Neural Correlates of Cognitive and Behavioral Performance in Humans

Koel Das, *Arpita Saha-Chowdhury, Ashutosh Mishra*

Indian Institute of Science Education and Research,Kolkata, India

Perceptual decision making typically involves evaluation of evidence based on sensory information and is influenced by several factors including prior and contextual information. Since visual information is one of the primary source of sensory evidence in humans and primates, visual perception plays an important role in decision making. Technological advances in the last two decades had made it possible to study perceptual decision making in the visual and somatosensory domain and explore neural correlates of perceptual decision. Previous research has demonstrated that prior expectation modulates perceptual decision making. We also know from real world examples that individual decision making is influenced by contextual information. Contextual cues guide and facilitate visual search in both synthetic (Chun & Jiang, 1998) and natural images (Eckstein et al., 2006; Torralba et al., 2006). Although studies have identified the neural correlates of the attentional shifts with synthetic cues (Woodman & Luck, 1999; Johnson et al., 2007; Woodman et al., 2009), little is known about the neural basis of contextual cueing in natural scenes. We used multivariate pattern classifiers to analyze neural activity (electroencephalography, EEG) during search for objects in natural scenes and predict the contextual location of the expected target from a single trial. Our findings suggest that contextual locations in natural scenes can be predicted reliably from neural activity recorded when observers are searching for targets. The identified neural mechanisms predicting context are distinct from those coding the physical presence of the target.

Ethics statement: Handling of human subjects was carried out in strict accordance with the guidelines of Institutional Ethics Committee, Indian Institute of Science Education and Research,Kolkata, India.

Acknowledgements: This work was supported by research Ramalingaswami Fellowship Grant from Department of Biotechnology, India, and Cognitive Science Research Initiative, DST, India.

Metabotropic Glutamate Receptor (mGluR) Trafficking: Ins and Outs

Samarjit Bhattacharyya

IISER Mohali

In the brain, a variety of neurotransmitters and neuromodulators act on target receptors to activate cellular signaling events which transfer information from one cell to the next. Normal signaling depends on accurate localization of such receptors in specific regions of the cell, and the process of receptor trafficking plays a critical role in controlling this localization. In addition, in case of most G-protein-coupled receptors (GPCRs), receptor trafficking also plays crucial role(s) in the regulation of the receptor. Despite the obvious significance of this process, we still know very little about the molecular mechanisms that mediate trafficking of neurotransmitter receptors in the brain. Our labs specific interest lies in studying the cellular and molecular mechanisms that regulate the trafficking of Glutamate receptors in the CNS. These trafficking events are thought to be critical for virtually all forms of experience-dependent plasticity, including learning and memory and are believed to play crucial role in various neuropsychiatric disorders. The talk will be focused on the trafficking of metabotropic Glutamate receptors.

Proteostasis impairment in Huntington's disease

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A common pathological feature of most age-related neurodegenerative disorders including Huntington's diseases (HD) is the accumulation of intracellular protein deposits as inclusion bodies. HD is caused by abnormal extension of CAG repeat in the exon 1 of *IT15* or *HD* gene. In the normal individual, CAG repeat length varies from 6-35, while the disease phenotype is concomitant with more than 36 repeats and there is an inverse connection between CAG repeat length and disease inception. After the discovery of the HD gene in 1993, there have been tremendous progress in understanding the disease biology. Extensive studies using cellular models, transgenic animal models and post-mortem HD brain samples discovered multiple abnormalities of cellular function that are connected to the progression of HD. Appearance of aggregates of the misfolded mutant huntingtin indicate that the cell is unable to efficiently eliminate them, and failure of clearance leads to the severe disturbance of the cellular protein quality control system. The recruitment of molecular chaperones, ubiquitin proteasome system and autophagic components to the mutant huntingtin aggregate could be an adaptive response of the cell to get rid from abnormal protein deposits. Therefore, it is hypothesized that boosting up of cellular protein quality control system could decrease the load of aggregated huntingtin and thereby offers neuroprotection. In my talk, I will focus on dysfunction of quality control system in HD and how its rescue could slow the disease progression in a mouse model of HD.

Understanding biological clock dysfunction in age induced neurodegenration and Parkinson disease

Anita Jagota

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The age-related sleep disturbances have been attributed to circadian disfunction. The suprachiasmatic nucleus (SCN) in hypothalamus contains a light-entrained circadian clock that regulates melatonin synthesis in the pineal gland in mammals. Parkinson's disease (PD) is age related neurodegenerative disorder, associated with degeneration of dopaminergic neurons in the Substantia nigra pars compacta (SNpC). We used Rotenone induced Parkinson's disease (RIPD) rat model. We have studied the neural degenerative changes with aging and in RIPD rat model in the functional integrity of circadian system i.e. daily rhythms in serotonin metabolism, gene expression for various clock genes such as *bmal1, per1, per2, cry1 and cry2,* protein profiles and locomotor activity in suprachiasmatic nucleus (SCN). Daily rhythms in serotonin metabolism were studied in SCN in hypothalamus by RP-HPLC at variable time points in 3 age groups 3 (adult), 12, and 24 months old male Wistar rats and RIPD rat model in light–dark conditions (LD 12:12). The molecular clock components *bmal1, per1, per2, cry1 and cry2* were studied by quantitative PCR. The protein profiles were studied by 2-D electrophoresis. Locomotor activity was studied by preparing activity profiles using Chronobiology kit. Alterations in the levels and chronomics of various serotonin metabolism components such as Tryptophan (TRP), 5-Hydroxytryptophan (5-HTP), 5-hydroxytryptamine (5-HT, Serotonin), N-acetylserotonin (NAS), N-acetyl 5-methoxytryptamine (Melatonin, MEL), 5-hydroxyindoleacetic acid (5-HIAA), 5-methoxyindole acetic acid (5-MIAA), 5-hydroxytryptophol (5-HTOH), 5-methoxytryptophol 5-MTOH) and N-acetyltryptamine (NAT) were observed. The results obtained in present study will help in targeting novel treatments of circadian dysfunction for age induced disorders and PD.

Identification of non-NMDAR targets for excitotoxic brain disorders

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Excitotoxic brain disorders implicate glutamate-NMDAR over activation led neurochemical aberrations. However, NMDAR inhibition is considered unphysiological due to its role in maintaining higher order brain functions. In search of characterizing non-NMDAR targets we have examined functional interaction between NMDAR-PSD95-nNOS-apoptosis axis, Pannexin1 (Pnx1); whose activation associates with NMDAR activity leading to ATP depletion and Sirt-1; as a metabolic sensor for such cell bioenergetic deficits, in the brain of rats with chronic hepatic encephalopathy (HE); a relevant excitotoxic brain disorder model. HE in rats was induced by administration of 50-100 mg/kg b.w of thioacetamide i.p. for 10-14 days. In comparison to the control rats, the HE rats showed over expression and activation of NMDAR-PSD-95-nNOS axis and Panx1 level, which could be reversed due to the treatment with nNOS inhibitors and mehtylcobalamin vis a vis NMDAR blocker. Also, over activation of NMDAR-PSD-95-nNOS axis in the HE rats in cerebellar neurons were reversed due to the treatment with Panx1 inhibitor. These parameters were also normalized due to the *in vivo* treatment with Bacopa monnieri extracts (BE: CDRI-08). Since Panx1 inhibition mimicked the downstream effects of NMDAR blockage, it is argued that Panx1 could serve as a relevant therapeutic target to normalize HE. Additionally, recovery of declined activity of Sirt-1 in the brain of HE rats due to the treatment with resverotrol, a Sirt-1 activator, was consistent with a similar recovery in neurobehavioural scores of those HE rats and thereby suggesting Sirt-1 as another target for managing neurochemical aberration associated with HE.

Human pluripotent stem cells in neurological disease modelling and target discovery

Rajarshi Pal

Manipal University

Experimental modelling of human disorders enables the definition of the cellular and molecular mechanisms underlying diseases and the development of therapies for treating them. The availability of human pluripotent stem cells (PSCs), which are capable of self-renewal and have the potential to differentiate into virtually any cell type, can now help to overcome the limitations of animal models. Several strategies are used to generate such disease models using either embryonic stem cells (ESC) or patient-specific induced PSCs (iPSCs), creating new possibilities for the establishment of models and their use in drug screening. Gestational alcohol exposure is known to have deleterious effect on the developing embryo, predominantly the nervous system owing to neural tube and crest abnormalities. We identified an aberrant molecular signature as a result of alcohol-induced brain damage using human ESCs derived neural progenitors. We detected impairment in the expression of key genes and protein related to forebrain and hindbrain development, hippocampus, neuronal migration, neuromuscular junction development, neural tube closure etc. Abnormal expression of AFF2, SLC24A2, NEUROD2 and their role in learning and memory could possibly relate to the cognitive disabilities exhibited during FASD. Our initial observations were further validated using Zebrafish model. We postulate that alteration observed in these genes might owe to the epigenetic constitution, since the methylation of H3K27 and H3K9 and the acetylation of H3K4 and H3K9 were found to be modulated. Apart from these and other results, in this presentation, I will discuss the current progress and future challenges of neurological disease modelling.

Understanding the pathomechanism of cellular quality control machinery in misfolded proteins aggregation: Implications in neurodegeneration and ageing

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Efficient and regular performance of Ubiquitin Proteasome System and Autophagy continuously eliminate deleterious accumulation of nonnative proteins. In cellular quality control system, E3 ubiquitin ligases are significant employees for defense mechanism against abnormal toxic proteins. Few findings indicate that lack of functions of E3 ubiquitin ligases can be a causative factor of neurodevelopmental disorders, neurodegeneration, cancer and ageing. However, the detailed molecular pathomechanism implying E3 ubiquitin ligases in cellular functions in multifactorial disease conditions are not well understood. Our current findings systematically represent the unique characteristics, molecular nature, and recent developments in the knowledge of neurobiological functions of few crucial E3 ubiquitin ligases. Here, we focused on the roles of cellular quality control E3 ubiquitin ligases in the neuropathobiological mechanisms, with precise focus on the processes of neurodegeneration, and thereby propose new lines of potential targets for therapeutic interventions.

Ethical Statement: All animal experiments were conducted with the approval of the Animal Care Committee of RIKEN Brain Science Institute and Nagoya University and were in accordance with their requirements.

Acknowledgement: This work was supported by the Department of Biotechnology, Government of India. AM was supported by Ramalinganswami Fellowship (BT/RLF/Reentry/11/2010) and Innovative Young Biotechnologist Award (IYBA) scheme (BT/06/IYBA/2012) from the Department of Biotechnology, Government of India.

Retinal Organoids Generated From Human Induced Pluripotent Stem Cells

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To generate patient-specific iPSCs and to differentiate them to retinal cell types.

Dermal fibroblast cultures were established from human skin biopsies and reprogrammed into iPSCs using lentiviral vectors expressing the Yamanaka factors. Stably reprogrammed iPSC colonies were characterized for stemness, genetic identity, genomic stability and pluripotency. Differentiation towards eye field commitment was carried out using an optimized protocol. The iPSC-derived retinal tissues were characterized for lineage differentiation and tissue-specific marker expression.

We have successfully generated three patient-specific iPSC lines from dermal fibroblasts. These cells exhibited the properties of pluripotent stem cells such as, multi-lineage differentiation and teratoma formation in nude mice. Retinal differentiation was normal with control iPSC line and was comparable to hESCs. Pure cultures of mature RPE cell sheets and three dimensional neuro-retinal cups and minicorneal tissues could be generated successfully within a period of 2-3 months and they expressed several of the tissue-specific markers. When transplanted in nude mice models, the iPSC-derived RPE cells survived for up to 8-10 weeks in the subcutaneous space and did not induce any tumor formation. Though the retinal dystrophic patient-specific lines were not efficient in teratoma formation, they retained their retinal differentiation potential albeit showing mild neuro-retinal defects.

Patient specific iPSCs can be efficiently differentiated into retinal cell types to generate complex 3D retinal tissues meant for basic research and regenerative applications.

Ethical statement: The study was reviewed and approved by the Institutional Review Board (IRB), Institutional Committee for Stem Cell Research (IC-SCR) and the human ethics committee of the LV Prasad Eye Institute, Hyderabad, India and the research followed the tenets of the Declaration of Helsinki. All experiments involving animals were conducted in adherence to the ARVO statement for use of animals in

ophthalmic and vision research and with the approval of the animal ethics committee at the National Centre for Laboratory Animal Sciences, National Institute of Nutrition, Hyderabad, India.

Acknowledgements: We thank DBT, HERF and Champalimaud Foundation for the financial support.

Symposium Talks

Role of Syngap1 in cognitive development

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Mutations that cause Intellectual Disability (ID) are increasingly found in genes that encode for synaptic proteins. However, it remains unclear how genetic mutations that disrupt synapse function impact intellectual ability. In the Syngap1 haploinsufficiency mouse model of ID, we found that dendritic spine synapses (DSS) develop prematurely during early postnatal development. Premature DSS maturation severely disrupted the balance of excitation and inhibition in the developing hippocampus, which corresponded with the first evidence of behavioural abnormalities. Inducing Syngap1 haploinsufficiency in mature animals had minimal impact on hippocampal DSS function, while repairing pathogenic *Syngap1* mutations in adults did not improve basic behavioural and cognitive abnormalities. Further, *Syngap1* mutations restricts critical period plasticity during development. These data demonstrate that developing excitatory synapses in vivo are exquisitely sensitive to SYNGAP1 protein levels and Syngap1 mutations present during development lead to enduring intellectual disability. Thus, we concluded that Syngap1 haploinsufficiency syndrome is characterised by a fundamental disruption to the pace of neural development, and this leads to the failure of cognitive and social maturation during childhood.

Acknowledgement: DST-SERB (SERB/LS-779/2013)

Therapeutic potential of p70S6K1 in Fragile X Syndrome.

Aditi Bhattacharya,

reader (e), Center for Brain Development and Repair, InStem-NCBS, Bangalore

Protein synthesis is considered an inescapable requisite to proper brain functioning. Conversely dysregulated protein synthesis and expression is being linked to an increasing number of neurological disease. In the brain,tTranslation of mRNA to yield proteins is controlled by an elaborate control mechanism that is primarily downstream of signaling cascades that involve mTORC1 and ERK1/2. Both converge on p70 ribosomal S6 Kinase 1 (S6K1) which then modulates the activity of downstream molecules that directly influence ribosome processing, initiation and elongation steps of translation. S6K1 has been implicated in pathology of several neurological conditions, however it's potential in being a therapeutic target has been understudied. I will showcase how modulating S6K1, using genetic manipulation in mice and novel small molecule inhibitors, helped ameliorate disease-associated phenotypes in Fragile X Syndrome, a leading cause of inherited autism and intellectual disability. In addition, I will discuss early work in elaborating how naturally occurring variants in S6K1 can alter enzyme function and extend our knowledge of the biology of this kinase.

Developmental facets of brain connectivity during fear extinction.

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Maternal separation stress during early life is known to affect the corticosterone release under basal conditions. However, how differences in corticosterone secretion affect the fear memory and its extinction is not clear. In addition, neural mechanisms underlying such changes are not being studied till now. In the present study, we show that chronic maternal separation and isolation stress during stress hyporesponsive period leads to impair the fear memory and extinction in the offspring. The impaired fear extinction was caused by a reduction in infralimbic region of medial prefrontal cortical (ILC) activity. Together, we suggest that differences in the ILC activity are associated with stress during early life and deficits in the ILC activity may be involved in the impaired fear extinction. These findings will have implications for neurodevelopmental disorders such as Schizophrenia, as well as in increasing risk factors for the genesis of depression during adulthood.

Funding support: This project was funded by ICMR, CSIR, New Delhi and NIMHANS, Bengaluru.

Stem cell models to understand fragile X syndrome

Ravi Muddashetty

inStem, Bangalore

Fragile X syndrome (FXS) is the most common inherited cause of cognitive disability and part of autism spectrum disorders (ASD). Loss of FMRP is the cause of the disease which affects development of nervous system leading to cognitive deficits, anxiety and higher susceptibility to seizures among other defects. While animal models of fragile X syndrome have contributed enormously to investigate the etiology of this disease, they do have limitation in addressing potentially human specific developmental and genetic aspects. Human embryonic stem cell (hESC) and induced pluripotent stem cells (iPSC) from fragile X patients are very powerful tools which could fill this gap. In this talk, I will describe how we are using these stem cell based models to understand the basic biological function of FMRP and its relevance to fragile X syndrome.

Serotonin and the programming of psychiatric vulnerability

Vidita Vaidya

TIFR, Mumbai

Early life stress is associated with enhanced susceptibility to adult psychopathology. Diverse early life animal models ranging from the early stress of maternal separation to pharmacological elevation of serotonin levels in postnatal life, as well as maternal immune activation, impinge on the 5-HT2A receptor, regulating receptor function and expression, in particular within the prefrontal cortex. Further, pharmacological blockade of the 5-HT2 receptor overlapping with the early life perturbations can prevent the emergence of anxiety and depressive behavior in adulthood. In contrast, stimulation of the 5-HT2A receptor during postnatal life is sufficient to evoke changes in mood-related behavior in adulthood. Using DREADD based pharmacogenetic approaches to evoke excitation in CAMKII-positive excitatory neurons in cortical circuits we show that transient DREADD-based stimulation in postnatal life is sufficient to enhance anxiety and depressive behavior well into adulthood. In my talk, I will discuss our working hypothesis indicating potential cellular targets for early life trauma that may mediate persistent effects on early life perturbations on the emergence of mood-related behavior in adulthood.

Current understanding of the neurobiology of the nicotine dependence: the role of NAchRs and dopamine and their treatment implications

Raka Jain

National Drug Dependence Treatment Centre (NDDTC), Department of Psychiatry, All India Institute of Medical Sciences (AIIMS), New Delhi

Tobacco use is a major cause of mortality and morbidity worldwide. Nicotine is one of the main psychoactive ingredients in tobacco that contributes to its harmful effects. Chronic consumption of nicotine has been shown to produce both tolerance and dependence in humans and animals. Nicotine dependence is mediated by complex neural mechanisms that involve multiple brain circuits and neuro-adaptive changes in a variety of neurotransmitter and neuropeptide systems. Recent research advances at the molecular, cellular, neuro-circuitry, and behavioral levels have provided substantial information for our understanding of the neurobiological mechanisms contributing to various aspects of nicotine dependence (such as craving, tolerance, withdrawal, and relapse). The presentations will focus on current knowledge of nicotine dependence, role of the nicotinic cholinergic system and dopaminergic system via the reward pathway in the nicotine dependence and their treatment implications. It will also focus on the limitations in the understanding of the various aspects of the nicotine dependence.

The role of the endogenous opioid system in nicotine dependence and its treatment implications

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About 35% of population of India use tobacco in some form or the other. Among many other chemicals, it contains nicotine which is considered as one the most addictive of all substances. It acts primary through nicotinic Acetylcholine receptors (NAChRs). However, much of its addictive properties also involve other neurotransmitter systems, the main among them is endogenous opioid system. The endogenous opioid system which is largely expressed in the CNS is closely associated with reward and motivation which are essential component of any drug dependence. There is strong evidence that this system is modified in the course of chronic drug abuse. Also, mu-opioid modulators have shown effect on various addictive behaviors related to nicotine use. Some of them are also in clinical use for treatment of dependence, both for opioids and others. The presentation will summarize the role of the endogenous opioid system in nicotine dependence. Also, evidences from the effect of various mu-opioid modulators on various aspects of nicotine dependence and their role in treatment will be presented. The information presented will provide a better understanding of these receptors in development of potential pharmacotherapy for treatment of nicotine dependence.

Ethical statement: The references in the presentation are published work of other authors and are available in public domain. The study by the author was carried out after due clearance from the Institutional Ethics Committee, AIIMS, Delhi.

Acknowledgement: The author does not acknowledge any specific individual/institution for the presentation.

The role of the glutamate and cannabinoid neurotransmitter systems in nicotine dependence and their treatment implications

Piyali Mandal

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Tobacco smoking is a chronic relapsing disorder that results in significant morbidity and mortality worldwide. Nicotine is the major psychoactive component, which is largely responsible for the maintenance of the harmful tobacco smoking habit in humans. The central actions of nicotine are mediated by nicotinic acetylcholine (nACh) receptors that are distributed throughout the brain through various neuro-transmitter systems. There is mounting evidence supporting a significant role of the glutamate neurotransmission and endocannabinoid system in mediating the seeking, reinforcing and other addiction-related effects of nicotine. The presentation will summarize the recent pre-clinical and clinical research findings on the role of the glutamate and cannabinoid neurotransmitter systems signalling in nicotine dependence. This will include the role of glutamate endocannabinoid system in nicotine seeking, withdrawal, reinforcement, conditioned reward, reward enhancement in terms of receptors, transporters, or enzymes that regulate the actions of glutamate and endocannabinods. Overlapping receptor functions, modulatory interactions between these systems will also be discussed. Possible clinical application and future research scopes including novel targets for smoking cessation medications will also be discussed.

Neuropeptide Y expression confers benzo[a]pyrene induced anxiolytic like behavioral response during early adolescence period of male Wistar rats

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Environmental neurotoxicant like benzo[*a*]pyrene (B[*a*]P) is known to induce neurobehavioral changes. Our previous reports address the adverse effect of B[*a*]P on the neurobehavioral responses and neuromorphology of sensitive brain regions in adolescent rats. Present study was conducted on male Wistar rat neonates at postnatal day 5 (PND5) to ascertain B[*a*]P induced anxiolytic like behavioral response could be an outcome of neuropeptide Y (NPY) overexpression in brain. Single intracisternal administration of B[*a*]P was carried out at PND5 to elucidate the role of NPY on neurobehavioral responses at PND30. The behavioral studies showed anxiolytic like effect of B[*a*]P in both light and dark box and elevated plus maze tests. Antioxidant assay involving glutathione peroxidase activity was significantly decreased where as lipid peroxidation was significantly augmented in both hippocampus and hypothalamus of B[*a*]P treated group as compared to naive and control. The neurotransmitter estimation by HPLC-ECD showed significant increase in 5-HT level in both hippocampus and hypothalamus of B[*a*]P treated group. Significant elevation in NPY expression was observed in both hippocampus and hypothalamus of B[*a*]P group. Intracellular Ca^{2+} estimation using Fura-2AM by fluorometry showed that B[*a*]P induced increase in Ca^{2+} influx was associated with augmented NPY expression in brain. As NPY has orexigenic effect, our result revealed that there was a significant increase in body weight at PND30 following B[*a*]P administration to rat neonates at PND5. These findings suggested that NPY overexpression in brain regions might be associated with anxiolytic like behavioral response and orexigenic effect in rats following single intracisternal B[*a*]P administration.

Keywords: Benzo[a]pyrene, Anxiety, Neuropeptide Y, Calcium, Oxidative stress, Serotonin

Acknowledgement: Funding to M. Patri from WOS 'A', DST, Govt. of India and DAE-BRNS, Mumbai, India

Neuroprotective and cognition enhancing effects of dark chocolate on non-transgenic AD model rats

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The vulnerability to oxidative stress and cognitive decline keep increasing during normal as well as pathological aging. Dietary changes and sedentary life style resulting in mid-life obesity and type 2 diabetes, if left uncorrected, further add to the risk of cognitive decline and Alzheimer disease (AD) in the later stages of life. Certain antioxidant agents such as dietary polyphenols, taken in adequate quantities have been suggested to improve the cognitive processes. In this study, we examined the effect of oral administration of dark chocolate (DC) to non-transgenic Alzheimer disease (NTAD) model rats developed and available in the laboratory, on reversal of obesity, diabetes and consequent cognitive impairments. The results demonstrated that DC reduced the hyperglycemia, inhibited the cholinesterase activity in the hippocampal tissue homogenates and improved the cognitive performance in spatial memory related Barnes maze task. Histological studies revealed an increase in cell volume in the DC treated rats in the CA3 region of the hippocampus. These findings demonstrated the benefits of DC in enhancing cognitive function and cholinergic activity in the hippocampus of the NTAD rats while correcting the metabolic disturbances in them.

Through the Lenses: Evaluation of 2D-360° User Interface

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Despite growing research on technological development of 360° vision, very few studies have assessed the cognitive challenges, specifically spatial awareness, while using 360° user interface (UI). The current study focuses on evaluating the effect of 2D-360° on remote local area awareness (LAA) by employing psychophysical and eye-tracking measurements. LAA is assessed by measuring the efficacy and efficiency of direction judgment and cognitive mapping across various 2D-360° visual designs. Since 2D-360° UI entails first person shooter perspective, which is primarily used in gaming, we evaluated the role of gaming experience and its relationship with the speed of processing across various 2D-360° UI. The current preliminary result shows 1). Reduced pointing error with visual boundary compared to seamless 3600 UI, consistent with the previous study (Boonsuk et al., 2012).; 2). Pointing error appears to be a function of the angle of orientation made to judge the target direction.; 3). Unlike Boonsuk et al. (2012), gamers vs. non-gamers showed reduced pointing error, supporting our hypothesis. Further, we plan to conduct the inferential and eye-tracking analysis to evaluate 2D-360° UI while performing spatial tasks with and without time pressure. Current findings will enable us to evaluate the limitations/ strength of 2D-360° UI designs for teleoperation systems.

Ethical Statement Data collection was carried out in accordance with the Americal Psychological Association ethical guidelines for conducting behavioral experiment. In addition, local research board committee at IIIT-Hyd evaluated the risk and benefits involved in the research.

Acknowledgement This work is partially supported by research grant no. SR/CSR/192/2015 from Department of Science and Technology, India.

Transcranial direct current stimulation and associative fear learning

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Social learning helps humans and animals to avoid threat in a dynamically changing environment. Indeed, excessive or fewer social fear learning is the root cause of social anxiety and related disorders. The underlying mechanism of impaired social fear learning is limited; furthermore the role of left DLPFC with regard to anxiety is less explored. Here, we used a novel a novel tDCS paradigm to examine the efficacy of tDCS on fear and safety learning. Fear and safety learning was measured by self-report rating scales, skin conductance response (SCR), and heart rate variability (HRV). We show the direct effect of tDCS on social fear learning. However, the effect was predominantly present in anodal group of neuromodulation compared with the sham group. These results indicate moderating effects of tDCS in social fear learning. These data provide biological correlates of neurostimulation, social fear learning, and potential biomarkers for understanding anxiety and related disorder.

Ethics statement: The study will be in accordance with the declaration of Helsinki in their latest version from 2008, and was be approved by the local ethic board. All participants were asked to give a written informed consent.

Acknowledgements: (This work was supported by postdoctoral research grant i.e. CAPES/PNPD**: 2014-2016** from and Cognitive Neuroscience Laboratory, Mackenzie Presbyterian University, Brazil).

Novel therapeutic strategies to treat depression-induced cognitive deficits

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Major depression is a chronic psychiatric disease and is associated with significant morbidity and severely affects cognitive capabilities and executive functions. Severe depression compromises structural and functional integrity of the brain leading to cognitive deficits. The precise mechanisms underlying cognitive dysfunctions in depression remain largely unknown. We have demonstrated that depression causes impairments in spatial learning, alters the levels of monoamines and their metabolites and suppresses hippocampal long-term potentiation (LTP). These deficits were completely reversed after chronic treatment with high doses of SSRI-escitalopram or SNRI-reboxetine. The first line of treatment in depressive illness is antidepressant drugs are associated with several side effects, poor response and recurrence. Therefore, it has become increasingly necessary to develop more effective strategies to treat and manage depressive disorders. Accordingly, we have attempted to understand depression-induced cognitive deficits, anxiety and the effect of exposure to environmental enrichment (EE), or the combination of short duration EE with sub-effective doses of escitalopram or reboxetine on depression-induced deficits as novel antidepressant therapy. In depressive rats subjected to concomitant escitalopram / reboxetine - EE treatment, resulted in complete behavioral recovery and improved spatial learning along with a complete restoration of dentate gyrus and amygdalar volumes and restored hippocampal LTP. Thus, positive environmental stimuli even relatively for short term exposure can potentiate the effect of sub-effective doses of antidepressants in alleviating depression induced deficits. These strategies will be used to develop effective antidepressant therapies that are free from side effects and reduce recurrence of depressive episodes and associated disorders.

Keywords: Endogenous depression, neurodegeneration, Learning and memory deficits, enriched environment, antidepressants, hippocampal synaptic plasticity, long-term potentiation, anxiety, hippocampal and amygdalar volumes, major depressive disorders

Acknowledgements: Authors acknowledge financial support from UGC, CSIR, DST, DBT and NIMHANS

Ethics Statement: All experiments were approved by the Institutional Animal Ethical Committee of National Institute of Mental Health and Neuro Sciences (NIMHANS), Bengaluru and performed according to the guidelines of the Committee for the Purpose of Control and Supervision of Experiments on Animals, Government of India.

Prana – The Bridge between Body and Mind

HR Nagendra

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The mind-matter relationship has been the most intriguing challenge for centuries. This challenge has become most relevant to the scientists today who have understood enough about the physical world surrounding us and is now heading towards subtler dimensions of the universe. From the matter-based approach, the scientist is proceeding ahead to find something new. In their request of the unknown, seeking a major break-through in this worldly vision, many renowned scientists have started looking at the findings of the East for new insights.

Upanisads, the quintessence of the Vedas, talk about this basic mind-matter problems in depth, unraveled through experimentation called "Tapas". It is found that the entity called Prana is the basic life principle which acts as a bridge between mind and matter. We know that energy is the basic fabric of the whole physical world. In Prashnopanisat, Prana is defined as that basic entity of the whole universe. Matter is its grossest manifestation and its subtle manifestation is mind. Deeper and deeper dimensions of mind (we may call them as higher states of consciousness) are still subtler manifestations of Prana.

In Prashnopanisat we find a detailed description or study of main Prana and its five components called Panca Pranas. It is the Varishtha prana, the first born of Parama Atman or Self of all of us and of the whole creation (pure consciousness) that divides itself into five facets: Prana, Apana, Samana, Vyana and Udana at the Pranamaya Kosha level which govern different functions of the physical body. As per the Yoga Shastra modern NCDs have their origin in Manomaya Kosha as Adhis due to imbalances which percolate to Physical body to become Vyadhis through imbalances in Prana at Pranamaya Kosha.

Working at the level of Pranamaya Kosha can probably help in pre-diagnose of NCDs very early. Also getting mastery over Prana through breathing can correct the imbalances to prevent diseases and to set right the Vyadhis (NCDs) effectively. Extensive research in VYASA over the last 35 years has shown these possibilities distinctly. A brief of the same will be presented especially related to neurological disorders.

Neurobiology of Yoga and Psychotherapeutic Affects

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Stress is ubiquitous and is responsible for psychiatric disorders. Among the commonly popularly observed effects of yoga is the reduction in stress. Logically it leads to its potential therapeutic role in psychiatric disorders. Indeed, yoga has been successfully used as either a sole or adjunct intervention, in the treatment of anxiety, depression and psychotic disorders. Levels of cortisol drop after exposure to yoga and this correlated with antidepressant effect. Yoga enhanced neuroplastic effects as evidenced by increases in the level of Brain-derived-neurotropic-factor (BDNF) in the blood. Antidepressant effects were related to BDNF elevations. Those patients who obtained drop in cortisol following yoga had substantial elevations in BDNF. Yoga also led to elevations in the lelvel of Gama Amino Butyric Acid (GABA) in the brain. This too could be related to the anti anxiety and anti depressant effects of yoga. In a preliminary study on those elderly who had minimal cognitive decline, 6-month yoga practice led to significant elevations in the hippocampal grey matter. Aged related total grey matter reductions as seen in healthy adults is not seen in age-sex matched long term yoga practitioners suggesting neuroprotective effects of yoga.

There are other effects of yoga that are emerging; yoga enhances mirror neuron activity (MNA) in healthy subjects and schizophrenic subjects as well. This may be mediated through elevations in oxytocin. These effects are expected to benefit patients of schizophrenia. Indeed schizophrenia patients exposed to yoga obtained elevations in serum oxytocin levels. The patients also improved in the social cognition.

In summary neurobiological basis of yoga provide a much needed foundation and evidence for the therapeutic role in psychiatry. This has potential for better understanding of the molecular mechanisms/pathways of yoga effect.

Reversal of atherosclerosis by Yoga Life Style Intervention: Implications for the brain

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Atherosclerotic Cardiovascular Diseases (CVD) are the leading cause of death and disability throughout the world and their incidence is increasing in the developing countries especially India. The main reason for increase in CVD is considered to be unhealthy life style consisting of psychosocial stress, high fat diet, smoking and lack of exercise. Psychosocial stress (especially depression, anger, hostility) has emerged as a strong risk factor for causation of CVD, hypertension, insulin resistance and cardiovascular mortality. Psychosocial stress appears to act through hypothalamic pituitary axis, neurohumoral and coagulation changes, alterations of sympathetic/parasympathetic tone, oxidative stress etc. which can lead to endothelial dysfunction, inflammation and atherosclerosis suggesting a strong brain heart connection.

Yoga which is a holistic mind body technique can control psychosocial stress and has the potentiality to control atherosclerosis. Several scientific studies suggest that yoga can control the risk factors for CVD like mental stress, hypertension, diabetes, smoking, obesity, lipids etc. Yoga has also been demonstrated to cause regression of early and advanced atherosclerosis.

We conducted a randomized control study in patients with metabolic syndrome and observed that early atherosclerosis (assessed by carotid intimal medial thickness CIMT) was significantly reduced in the yoga group as compared to controls. Three other randomized studies utilizing coronary angiography in nearly 400 patients of advanced atherosclerotic obstructive disease also showed significant regression and relief of angina. The probable mechanism by which yoga confers its benefit in reversal of atherosclerosis appears to be psychoneuro-endocrine.

Thus it is apparent that there is a strong brain heart connection and yoga by controlling mental stress can benefit the heart in several way and even reverse atherosclerosis.

Neurophysiology of a High Frequency Yoga Breathing Technique

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There are several yoga breathing techniques. Increasing the rate of breathing to 1.0 Hz is described in the traditional texts to influence/enhance the functioning of the brain.

To assess the effects of High Frequency Yoga Breathing (HFYB) called Kapalabhati on (i) electrophysiological measures of attention, (ii) cerebral blood flow based on functional near infrared spectroscopy and (iii) performance in tasks to assess selective attention, visual scanning and repetitive motor activity.

There were separate studies. In each study there were 50 male volunteers with ages between 20 and 45 years. They were each assessed in three types of sessions. These were (i) high frequency yoga breathing (HFYB), (ii) Breath awareness and (iii) Quiet sitting. Sessions were on separate days at the same time of the day. Participants were assessed for the P300 using the auditory oddball paradigm; fNIRs; and tasks for selective attention (e.g., cancellation and substitution tasks).

After HFYB there was a significant decrease in the P300 latency and increase in P300 amplitude which suggests better attentional capabilities. Similarly HFYB also improved performance scores in tasks for selective attention. Despite these changes there was no change in cerebral blood flow recorded over the pre-frontal region.

The findings suggest that HFYB does improve attentional abilities; the fact that there was no global increase in pre-frontal cerebral blood flow suggests the changes may be localized to very specific regions of the brain.

Manjari Tripathi

AIIMS, New Delhi, India

Schizophrenia and Sleep Abnormalities: Implications towards Dysfunctional Thalamo-Cortical Mechanisms

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Patients with schizophrenia show major sleep abnormalities such as prolonged periods of sleeplessness, frequent intermittent awakenings, long sleep onset latency, increased N1 duration, reduced N2 duration and N3 and REM sleep alterations leading to overall poor sleep efficiency.Beyond such descriptions of macro sleep abnormalities, studies do not provide any explicit details of mechanisms associated with sleep initiation and maintenance. A proper understanding of the subtle deficits in NREM-REM alternations would throw more light on dysfunctional thalamo cortical mechanisms associated with schizophrenia pathophysiology. We attempt to describe the sleep cycle and spindle delta dynamics across night sleep in patients with recent onset schizophrenia.

Whole night polysomnography showed macro sleep architecture abnormalities similar to the previous studies as mentioned above. Sleep cycle-wise analysis revealed transient features of sleep instability due to significantly increased intermittent awakenings and the unstable and recurrent stage transitions in both NREM and REM sleep-periods. The spindle deficits were persistent across sleep cycles and were positively correlated with the sleep disruption during the subsequent REM sleep states. The study help us to delineate the subtle deficits in sleep initiation and maintenance suggestive of a possible maladaptive interplay between unstable thalamo-cortical networks resulting in sleep-cycle specific instability patterns associated with schizophrenia pathophysiology.

Symposium title: Sleep and cognition: Brain at stake! Prenatal sleep disruptions and early cognitive development

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Sleep loss during pregnancy is an emerging health concern. Our recent findings showed that developing fetal neural networks are highly vulnerable to maternal sleep loss and are at a high risk predisposition to various anxiety disorders/ learning disabilities in growing children. In strictly controlled experiments in an animal model, effects of deprivation of different components of sleep (rapid eye movement sleep and total sleep) during third term of pregnancy were evaluated in pups at different post natal days. The sleep-wakefulness and ultrasonic vocalizations (using isolation paradigm) were tested during postnatal days 1- 20. After weaning, the anxiety levels of pups were tested in the elevated plus maze during peri-adolescence from postnatal day 26 to 46.

Litters born to rapid eye movement sleep deprived dams had lower body weights during entire development in comparison to controls. These pups made reduced vocalizations and showed higher percentage of active sleep. The still-birth and infant mortality were also observed in this group. However, total sleep deprivation of 5h in dams produced strikingly different effects. The neonates of this group displayed increased vocalizations during early development, and showed hyperactivity and increased risk-taking behaviour during adolescence. The ontogenetic profiles of sleep-wakefulness in these neonates provided further evidences for an altered neural development. The changes in sleep-wakefulness during initial development in these neonates from sleep derived dams provided an early marker for a modified neural development. Sleep during pregnancy plays an important role in emotional and cognitive development of infants.

The research grant was received from Department of Science & Technology, India (SR/CSI/110/2011) & (SR/CSRI/102/2014)

The Central Chemosensory Machinery: A Novel Target for Sleep Regulation.

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With a recent discovery that protons are neurotransmitters [2], they become a novel target to study their role in the regulation of different physiological functions. The acid-sensing chemosensory machinery in the brain plays an important role in the modulation of several physiological functions including breathing, pain, synaptic plasticity, learning, memory, etc. [1,5,6]. Also, some studies suggest that chemosensory and sleep circuitries are closely linked [3,4]. However, the underlying chemosensory circuitries involved in sleep modulation are not known.

We have investigated the effect of "lansoprazole" the proton pump inhibitor in the LC on sleep-wake (S-W) architecture in the rat. Animals were surgically prepared for chronic S-W recording and microinjection of drugs in the LC. After baseline S-W recording, two different doses of lansoprazole [low-dose: 2mM and high-dose: 10 mM] and vehicle were microinjected in the LC. Lansoprazole did not alter Wake and NREM sleep, REM sleep, however, was significantly increased. REM sleep increased by 32 % (compared to vehicle, ($p<0.001$)) and 60 % (compared to low-dose ($p<0.001$)). Through, immune-histochemical techniques, we observed that the proton pump are located on the LC neurons. In addition, using c-fos expression in the LC, we found that the inhibition of proton pumps altered the LC neuronal activity. These results suggest that acid sensing machinery in the LC plays an important role in REM sleep modulation. It further supports our view that REM sleep possibly acts as a sentinel to keep CO_2 level within a physiological limit by increasing breathing rate and thus helps maintain longer sleep duration.

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Acknowledgments: Funding from DBT, DST and UPOE-II is highly acknowledged.

Modeling and Parallelization of Cerebellar Microcircuit for Combinatorial Operations

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Cerebellum granular layer contains about 10^{10} neurons and 10^{13} synaptic connections. In order to effectively model granular layer connections, large scale network need to be reconstructed. We have developed detailed biophysical model and spiking network model to reconstruct neuronal dysfunctions and functions[1]. In this study we have parallelized a large cerebellar neuronal network using pleasantly parallel method. In the distributed mode, we have assigned global identifier(gid) for each cell to avoid connections in same assignment [2]. We have used excitatory and inhibitory synaptic mechanisms and tested both *invitro* and *invivo* like inputs under different plasticity conditions to understand learning in cerebellar circuit. Modeling the coding properties helps in understanding the granule cell activity organized in center-surround structures, implementing combinatorial operations on multiple mossy fiber inputs, controlling spike timing and burst transmission, intensity and duration of long-term synaptic plasticity at the mossy fiber-granule cell relay[3]. These properties are validated using this model. Although it depends on network size and nature of synaptic connections, we could see a significant reduction of computational cost in terms of power and time while simulating parallelized code. As a comparison study, we have simulated our model in both CPU and GPU and results indicated that GPGPUs showed 15X time efficiency than CPU version of the algorithm [4].

Acknowledgment: The work derives ideas and direction from the Chancellor of Amrita University, Sri Mata Amritanandamayi Devi. This work is partially supported by DST grants SR/CSRI/60/2013 and SR/CSRI/61/2014 and by Virtual Labs Phase II of MHRD, Government of India and by Embracing The World.

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Impact of stress on the neurobehavioral toxicity of lambda-cyhalothrin Effect on brain cholinergic functions in rats

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Although there are convincing evidences exhibiting that exposure to lamda-cyhalothrin (LCT), a new generation type II synthetic pyrethroid may cause neurobehavioral toxicity, effect of stressors and their impact on the severity of changes is not known. The present study has been aimed to investigate role of immobilization stress (IMS, psychological stressor) and forced swim stress (FSS, physical stressor) on the neurobehavioral toxicity of LCT and effect on brain cholinergic functions studied in rats. Pre-exposure of rats to IMS (15 min/day) or FSS (3 min/day) for 28 days on LCT (3.0 mg/kg body weight, p.o.) treatment for 3 days resulted to affect spatial learning and memory and muscle strength associated with alterations in cholinergic-muscarinic receptors in frontal cortex and hippocampus. Consistent with this, decrease in acetylcholinesterase activity, protein expression of ChAT and PKC-b1 associated with decreased mRNA expression of CHRM2, AChE and ChAT in frontal cortex and hippocampus was distinct in rats pre-exposed to IMS or FSS on LCT treatment, compared to rats exposed to IMS or FSS or LCT alone. Interestingly, cholinergic alterations in these rats were associated with mitochondrial dysfunctions. There were marginal changes both in behavioral and neurochemical endpoints in rats subjected to IMS or FSS for 28 days or those exposed to LCT for 3 days alone, compared to controls. Although neurobehavioral changes were more intense in rats pre-exposed to IMS as compared to those exposed to FSS on LCT exposure, the results of present study clearly exhibit that stress may significantly contribute to enhance LCT neurotoxicity.

Ethical Statement: The experimental protocol was approved by the Institutional Animal Ethics Committee (IAEC) of CSIR-IITR, Lucknow and all experimental procedures were carried out in accordance with the guidelines laid down by the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), Ministry of Environment and Forests (Government of India), New Delhi, India.

Acknowledgement: The study is part of the INDEPTH programme of Council of Scientific and Industrial Research, New Delhi.

Differential responses of *Trans*-Resveratrol on proliferation of neural progenitor cells and aged rat hippocampal neurogenesis

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The plethora of literature has supported the potential benefits of Resveratrol (RV) as a life-extending as well as an anticancer compound. However, these two functional discrepancies resulted at different concentration ranges. Likewise, the role of Resveratrol on adult neurogenesis still remains controversial and less understood despite its well documented health benefits. To gather insight into the biological effects of RV on neurogenesis, we evaluated the possible effects of the compound on the proliferation and survival of neural progenitor cells (NPCs) in culture, and in the hippocampus of aged rats. Resveratrol exerted biphasic effects on NPCs; low concentrations (10 µM) stimulated cell proliferation mediated by increased phosphorylation of extracellular signal-regulated kinases (ERKs) and p38 kinases, whereas high concentrations (>20 µM) exhibited inhibitory effects. Administration of Resveratrol (20 mg/kg body weight) to adult rats significantly increased the number of newly generated cells in the hippocampus, with upregulation of p-CREB and SIRT1 proteins implicated in neuronal survival and lifespan extension respectively. We have successfully demonstrated that Resveratrol exhibits dose dependent discrepancies and at a lower concentration can have a positive impact on the proliferation, survival of NPCs and aged rat hippocampal neurogenesis implicating its potential as a candidate for restorative therapies against age related disorders.

Oxidative Stress and Post-TBI Secondary Brain Damage*Raghu*

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Traumatic brain injury (TBI) leads to long-term neurological functional deficits. Secondary neuronal death that starts within hours and continues for months is a major proponent of this. Many pathophysiologic mechanisms contribute to the secondary neuronal death including oxidative stress, inflammation and endoplasmic reticulum stress which promote each other. In particular, oxidative stress is mediated by the the enzyme NADPH oxidase NOX2 that forms reactive oxygen species (ROS). Whereas, the transcription factor Nrf2 induces many antioxidant enzymes and mitigate ROS. In an effort to protect post-TBI brain, we treated adult mice subjected to controlled cortical impact injury with apocynin (10 mg/Kg; i.p; NOX2 inhibitor) and TBHQ (25 mg/Kg; i.p; Nrf2 activator) individually and in combination. Drugs were given twice at 5 min/2h and 24h after TBI and mice were subjected to rotarod test and beam walk (for motor function) between days 1 to 7 and to Morris water maze test (for cognition) between days 26 to 30. Both TBHQ and apocynin treated mice showed significantly improved motor function after TBI compared to vehicle control, but there is no additive effect in combo therapy group. However, combo group showed significantly better cognitive outcomes in the Morris water maze test compared to vehicle control. Cortical secondary contusion volume was not different between control and apocynin or TBHQ groups but the combo therapy group showed a significantly smaller cortical contusion compared to vehicle group. Thus, therapies that inhibit formation and promote disposal of ROS are beneficial after TBI. Funded by NIH.

Neurodegenerative Changes in the Retina Could be Predictive for Abnormal Vascular changes in Diabetic Retinopathy

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Diabetic Retinopathy (DR) is the leading cause of irreversible vision loss globally. It affects the entire neurovascular unit of the retina, with gradual neuro-degeneration and neuro-inflammation. Early clinical signs of DR include microaneurysms, hard exudates, and retinal hemorrhages. However, functional visual changes due to neural degeneration have been reported in the retina of patients with the history of diabetes much before the clinically visible retinal vascular changes thereby suggesting that neurodegeneration precedes retinovascular changes. Histopathological studies have also confirmed neural changes in the eyes with diabetes such as neural apoptosis, retinal ganglion cells (RGCs) loss, reactive changes in macroglia, thinning of the inner retina, glial reactivity, neurofilament abnormality, and slowing of optic nerve retrograde transport. Hyperglycemia in diabetic retinopathy eyes alters the calcium level in microglial cells and neurons by activating purine receptors (P2X7 and P2Y) and this elevated intracellular calcium cause damage and apoptosis of the neuronal cells in the retina. The quantitative estimation of glial calcium flux could be helpful in determining the early neuronal damage in conditions such as diabetic retinopathy where it's a prominent feature. To test that, we have established primary cultures of retinal glial (astrocyte, muller and microglia) and neuronal cells from cadaveric donor eye balls and exposed them to stress: hypoxia and hyperglycemia mimicking conditions in diabetes. The response to the stress experienced by these cells and their subsequent interactions were studied by changes in the calcium flux and molecular signaling by real time PCR and immunofluorescence. Our preliminary data indicated a significant increase in the glial activation as indicated by the changes in the calcium flux and molecular signaling notably complement activation, HIF1 alpha and others. These findings independently support the role of glia in neuro-degeneration and abnormal vascularization as experienced in diabetic retinopathy. Further this model system can be effectively used for drug screening and monitoring for effectively controlling the progression of the disease.

Pathogenesis of Hepatic Encephalopathy Following Liver Failure

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Hepatic Encephalopathy (HE) is a serious central nervous system complication of liver failure characterized by various neurological symptoms. A growing body of evidence demonstrates that inflammatory mechanisms act synergistically with ammonia toxicity causing alterations in neurotransmission, leading to neuropsychiatric problems. The present study was designed to study the role of inflammatory factors and neurotransmitters in the development of HE. Male Wistar rats were subjected to bile duct ligation (BDL) surgery. Development of animal model of HE was assessed by routine liver function tests, ammonia levels, collagen content staining along with ^{99m} Tc labeled mebrofenin hepatic biliary clearance test. Cognitive assessment in BDL rats exhibited a progressive decline in learning, memory formation, retrieval, exploration of novel environment along with a decrease in serotonin levels. BDL rats also showed a significant decline in the time spent on the rotating rod, increased foot faults with difficulties to cross the narrow beam walk which was accompanied by a global decrease in the dopamine content in the brain. BDL also resulted in mitochondrial respiratory chain dysfunctions leading to generation of bio-energetic defects along with an increase in lipid peroxidation and protein carbonyls. Moreover, BDL also resulted in an increase in the inflammatory factors such as IL-6, TNF and MCP-1 in different regions of brain along with liver and serum suggesting for a role in development of HE. Histopathological studies using hematoxylin–eosin (H & E), cresyl violet exhibited anatomical changes in terms of marked neuronal degeneration, wherein neurons appeared more pyknotic, condensed and damaged. Overall, attenuation of oxidative stress, inflammation and restoration of neurotransmitter levels can provide new strategies for the prevention of HE.

Neuro-immune crosstalk in virus induced central nervous system demyelination and axonal loss.

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Neurotropic mouse hepatitis virus (MHV) infection in mice provides a useful tool for studying mechanisms of demyelination in a virus-induced experimental model of Multiple Sclerosis (MS). It has been known for long time that in absence of conventional $\alpha\beta$T cells microglia play a major role in neurotropic MHV-induced demyelination but the mechanisms of Central Nervous System (CNS) infection were not very clearly known. Our current microglial tropism studies revealed that RSA59, an isogenic demyelinating strain of MHV, can infect and activate CNS resident microglia, and microglia can help to mediate demyelination by engulfing myelin debris. Affymetrix microarray analysis was performed to compare differential spinal cord mRNA levels between mice infected with demyelinating and non-demyelinating strains of MHV to identify host immune genes expressed in this demyelinating disease model. The study reveals that during the acute stage of infection, both strains induce inflammatory innate immune response genes, whereas upregulation of several immunoglobulin genes during chronic stage infection is unique to infection with the demyelinating strain. Results suggest that the demyelinating strain induced an innate-immune response during acute infection that may promote switching of Ig isotype genes during chronic infection, potentially playing a role in antibody-mediated progressive demyelination even after viral clearance. RSA59-induced neuroinflammatory models are helpful in understanding direct CNS cellular injury and demyelination that does not require an intact adaptive immune system. Understanding the role of direct CNS resident microglial infection and activation will shed some light on the pathogenesis of CNS inflammatory disease and chronic CNS disorders.

Intra-arterial stem cell therapy to aid ischemic stroke recovery: Implications of brain derived growth factor (BDNF) signaling

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Intra-arterial (IA) mesenchymal stem cells (MSCs) delivery reduces the infarct volume if delivered at 1 day but not at 1h after a reversible middle-cerebral artery occlusion (MCAo) in female rats. The observed difference in the efficacy of IA MSC therapy delivered at 1h and 1 day after MCAo emphasis a need to understand:(1) reason (2) mechanism(s) by which IA MSCs protect the brain and (3) optimal time window for IA MSC therapy for stroke. Since homing of MSCs at the site of injury require chemokines such as stromal cell derived factor-1 (SDF-1) and MSCs mediated neuroprotection occurs via brain-derived neurotrophic factor (BDNF), we hypothesized that the SDF-1 availability is low at 1h after stroke and IA MSCs treatment after MCAo increase brain-derived neurotrophic factor (BDNF) release and tyrosine kinase receptor sub-type B (TrkB) signaling in the brain. SDF-1 protein level was gradually increased over the period of 24 h after MCAo, suggesting lower levels of SDF-1 at an hour might not be enough for attraction of MSCs after their IA delivery. IA MSCs injection significantly increases in the protein levels of BDNF and phosphorylated TrKB in the penumbra region, as compared to control. To investigate an optimal time window of protection we treated rats with IA MSCs at 1, 2 or 4 days after MCAo. We observed significant reduction in infarct volume and improved neurological score in rats treated at 1 and 2 days, suggest that IA MSCs is efficacious at 2 day time window.

Ethical Statement: All animal procedures were carried out in accordance with the Guide for the Care and Use of Laboratory Animals published by the U.S. National Institutes of Health and approved by the Animal Care and Use Committee of the University of Miami, USA.

Acknowledgements: This study was supported by Department of Neurology, University of Miami (DRY); James and Esther King Biomedical Research Program, Florida Department of Health Grant # 2KN09 (DRY); University of Miami intramural grant: Interdepartmental Research Development Initiative grant 2009-2010 (DRY); the Anderson Family Gift

(DRY), and by Grant Number 1UL1TR000460, Miami Clinical and Translational Science Institute, from the National Centre for Advancing Translational Sciences and the National Institute on Minority Health and Health Disparities. The contents this study are solely the responsibility of the authors and do not necessarily represent the official views of the NIH.

Baseline neuroinflammation is an earnest factor in neurodegeneration: A tale of two mice strains

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Monoamine oxidase inhibitors targeting the glial monoamine oxidase enzyme B (MAO-B) are the earliest drugs of choice in Parkinson's disease (PD). The glial origin of MAO-B hints at a modulatory role for glia. Further, autopsied tissues of PD patients and animal models suggest uncontrolled neuroinflammation as the trigger for nigral neuronal apoptosis. However the underlying cascades are not very well understood. Another interesting aspect about the prevalence of PD is that it has a racial or ethnic bias. Its prevalence is highest among Hispanics, followed by non-Hispanic Whites, Asian Indians, and African non-Whites. The mechanisms for differences can be best understood by evaluating different mice strains with differential susceptibility to neurotoxin MPTP, which produces PD reminiscent changes in the mice basal ganglia. Here we studied two mice strains with markedly differing vulnerability to the neurotoxin MPTP.

Unbiased stereological estimation of immunoperoxidase stained midbrain sections revealed that the vulnerable strain C57Bl/6 had fewer nigral neurons than the resistant CD-1 mice. Interestingly, C57BL/6 nigra had significantly more microglia and fewer S100β positive astroglial cells than the CD-1. MPTP administration caused significant upregulation of proinflammatory cytokines like TNF-α, IL-1β, IL-6 on days 1, 4 and 7 following MPTP administration in the C57BL/6 while the anti-inflammatory cytokines TGF-β, IL-4, IL10 plummeted. Thus the baseline levels of pro-inflammatory factors and microglia are higher in the susceptible mice, which may result in a 'quasi-inflamed state'. Thus the glial correlates pertaining to neuroinflammation may be decisive factors influencing the prevalence of the disease in different populations too.

Acknowledgement: DBT grant No. BT/PR12518/MED/30/1462/2014 to PAA

Impact of Pax6 on immunological surveillance of brain

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The Pax6 has been critical for neurogenesis and/or neurodegeneration in immunologically privileged brain. Its impaired functions in brain result to variable phenotypes matching age-associated neurological disorders, mental retardation, neuroendocrine tumors, glioblastoma and astrocytomas. However, information on its impact on immunological surveillance in brain is not clear. It is presumed that Pax6 may modulate brain immunity by neurodegeneration and/or inflammation associated activation of microglia. Therefore, status of expression and co-localization, binding abilities to regulatory genetic-sequence elements, transcription networks and interactions in brain were evaluated in immunologically challenged mice. Expression and co-localization of Pax6 at transcript and protein levels were analysed by RT-PCR, western blotting, and immunohistochemical staining, respectively. Chromatin Immunoprecipitation (ChIP) with anti-Pax6 using extracts of brain from control and immunologically challenged experimental mice were done. Pulled DNA from brain was analysed by gene specific polymerase chain reaction (PCR). Amplified PCR products were sequenced. Following serves http://genome.ucsc.edu/cgi-bin/hgBlat,http://www.fruitfly.org/seq_tools/promoter.html, http://blast.ncbi.nlm.nih.gov/Blast.cgi, http://www.uniprot.org/, http://www.genecards.org/ were used for sequence and promoter analysis, in silico. Alterations in levels of expression and binding to genetic sequence elements by Pax6/Pax5 were observed. Sequence analysis of amplified genes predicts promoters and binding sites for proteins involved in neuronal survival (Bdnf, Sparc), specificity of astrocyte (S100β, Gfap), microglia (Tmem119 and Iba1), cell-proliferation (Pcna), inflammation and immune response (Ifn-γ, Tnf-α), management of oxidative stress (Sod, Cat) and hypoxia (Ldh). The Pax6, binds to promoter sequences and interacts to proteins either directly or indirectly which are essential for immunological surveillance and energy metabolism in brain.

Evaluation of recovery from inflammation and motor dysfunction, and providing neuro-protection through magnetic field stimulation in Parkinson's disease: A novel tool.

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Parkinson's disease is the second most common progressive age related neurodegenerative disorder. Our aim was to evaluate the neuroprotective effect of Magnetic field stimulation in 6-OHDA rat model of PD. The rats were exposed to MF (17.96 μT, 50 Hz for two hours daily) after striatal 6-OHDA injection for seven days (acute) or for four weeks starting three weeks after injury (chronic). General locomotor activity, postural balance and gait were recorded along with markers for inflammation, oxidative stress and dopaminergic neuronal viability. A significant improvement in postural balance of the acute exposure group was indicated by increased rotarod run time. There was also an increase in base of support and overlap of steps in paw print test suggesting improved gait. Flow cytometric analysis showed a significant reduction in free radical generation and amelioration of mitochondrial function with acute exposure. Sparing of dopaminergic neurons were also observed in the acute exposure group. However, in chronic group of rats, only a trend for recovery was observed. The present results suggest neuroprotective potential of acute magnetic field exposure in 6-OHDA PD rat model.

Cortical network aberrations in dementia and schizophrenia

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Dementia and schizophrenia, two of the most devastating neuropsychiatric conditions, are currently understood as disorders arising out of brain 'disconnection'. Brain network connectivity aberrations of the resting state and task-associated functional magnetic resonance imaging (fMRI) time series have been consistently demonstrated in both the conditions. Collaborative research involving the Geriatric Clinic & Services and the Multimodal Brain Image Analysis Laboratory (MBIAL) at the National Institute of Mental Health and Neurosciences (NIMHANS) has identified overlapping patterns of cortical network aberrations in mild cognitive impairment and dementia, which we believe have the potential to be utilized as neuroimaging markers of dementia. We have demonstrated not only hypoconnectivity in resting state networks, notably the default mode network (DMN), but also hyperconnectivity in other networks such as the executive and attention networks, in mild cognitive impairment (MCI) and dementia. Hyperconnectivity in dorsal attention network was found to be linked to poor delayed recall in patients with MCI, which in turn predicted impending conversion to dementia. Increased connectivity in functional networks has been suggested as a compensatory mechanism that offsets the effect of cognitive aging and/or brain pathology. Taken together, these findings have the potential to be used as neuroimaging markers of the progressive neurodegeneration underlying mild cognitive impairment and its conversion to dementia. Furthermore, schizophrenia research at MBIAL using functional magnetic resonance imaging in patients experiencing auditory verbal hallucinations provide preliminary insights into the cortical brain disconnection underlying such disordered conscious awareness in schizophrenia.

Ethics Statement: The above research projects in dementia and schizophrenia were carried out at the National Institute of Mental Health and Neurosciences (NIMHANS), Bangalore, India with due approval from the Institute Ethics Committee, thus conforming to the ethical standards laid down in the 1964 Declaration of Helsinki. Written informed consent was obtained from all participants (and their legally qualified representatives in case of patients with dementia schizophrenia) before enrolling them for the study.

Acknowledgements: The above research projects were funded by research grants No. DST-SR/CSI/70/2011 & SR/CSI/73/2011(G) from Department of Science and Technology as well as BT/PR/8363/MED/14/1252 from Department of Biotechnology, Govt of India.

Dual stream hypothesis of visual processing: model comparison and exploration of functional plasticity

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Despite being one of the landmark theoretical approaches in cognitive neuroscience, *dual stream hypothesis* of visual information processing is still hotly debated. In the present functional MRI study, we critically assess different variations of dual stream hypothesis in a single experiment and explore the functional plasticity in ventral and dorsal visual stream areas both at the regional and network levels.

10 right-handed normal subjects (mean age 24years, 4 females) were scanned using 3T MRI scanner (TR=2 s TE= 35ms, flip angle =90□) while each of them was performing three pure visual perception tasks and three visually guided motor tasks. The fMRI scans were repeated after participants practiced similar tasks outside the scanner for half an hour each day for 7 days.

Behavioral data shows significant improvement in reaction time during all three visually guided motor tasks with practice, but no statistically significant change in the error rate in perceptual tasks was observed. The initial ROI-based analysis in SPM shows a shifting of cortical activity from ventral stream areas to dorsal stream areas in visually guided motor tasks with practice. Effective connectivity analysis between neural populations in primary visual cortex and multiple nodes in ventral and dorsal visual streams using Dynamic Causal Modelling is currently undergoing.

Initial ROI-based analysis support Goodale-Milner version of the hypothesis. In addition to the dual stream hypothesis, the findings are interpreted in light of other related theoretical approaches like Integrated model of visual processing and "magnocellular advantages".

Ethics statement: The study was carried out in strict accordance with the guidelines of Institutional Human Ethics Committee of National Brain Research Centre, India.

Acknowledgements: This work was supported by research grant No. SR/CSRI/PDF-13/2014 under Cognitive Science Research Initiative from Department of Science and Technology, India.

Computational Neuroscience of Circuit Function and Dysfunction: a Cerebellum Perspective

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Primary degeneration of the granular layer of the cerebellum is also an autosomal recessive disorder exhibiting clinical features such as delayed motor development, nonprogressive ataxia, delayed language development with dysarthria and mental retardation (Pascual-Castroviejo, 1994). Information transmission at the Mossy Fiber (MF) - Granule cell (GrC) synaptic relay is crucial to understand mechanisms of signal coding in the cerebellum (Albus,1971) (Marr, 1969). Using mathematical models (Diwakar 2009, Medini, 2012) information transmission and signal recoding in the granular layer was reconstructed to test observations like center-surround organization and time-window hypothesis. The models allow to look into how cerebellum input layer operates a robust population code for a wide range of intervals, modulated by the Golgi cell inhibition and regulated by the post-synaptic excitability. Understanding population activities such as local field potentials (LFPs) of underlying neurons reveal emergent behavior as patterns of information flow in neural circuits. Such modeling reconstructions of LFP signals (Diwakar, 2011; Parasuram, 2011) also helped understand the nature of interaction in cerebellar microcircuitry. The reconstruction also modeled changes in synaptic plasticity revealing the role of single neurons in neural ensembles. Changes to single cell properties during LTP and LTD were reflected in the LFP wave suggesting the sparse recoding function of granule neurons as spatial pattern generators. An open source toolkit called LFPsim, for reconstructing LFPs has been developed (Parasuram 2016). This model was also abstracted towards a cerebellum-inspired control strategy for low cost robotic articulators.

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Acknowledgement: This work derives direction and ideas from the Chancellor of Amrita University, Sri Mata Amritanandamayi Devi. The study is supported by Grants SR/CSI/49/2010, SR/CSI/60/2011, SR/CSRI/60/2013, SR/CSRI/61/2014 and Indo-Italy POC 2012-2014 from DST and BT/PR5142/MED/30/764/2012 from DBT, Government of India and partially by Embracing the World.

Brain recovery to normalcy following structural insult: A computational Neuroimaging framework

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CBCS Allahabad,

Computational modelling of the spontaneous dynamics over the whole brain provides a critical window in understanding the spatiotemporal brain dynamics that unfolds on a given anatomical connections. These connections in the healthy brain exhibits gradual deterioration or dysfunction of structure (e.g. in diseased states, aging, across individuals). Recent, experimental evidence further suggests that the adverse effect of such dysfunction is clearly visible on spontaneous dynamics characterized in particular by changes in resting state functional connectivity and its graph theoretical properties (e.g. modularity, hub classification, rich club index). These changes originate from altered neural dynamics in individual brain areas that are otherwise poised towards a homeostatic equilibrium to maintain a stable excitatory and inhibitory activity. Using a mean-field network model that operates close to criticality we show excitation-inhibition (E/I) balance (that is the local Glutamate/Gaba ratio) has the potential to provide substantial recovery and restore the functional connectivity in the higher order neurocognitive networks. Further, recent findings suggest that these cognitive networks e.g. Saliency network (SN), Default Mode Network (DMN) and Dorsal Attention Network (DAN) are hubs of the brain and important for cognitive functions. Their dysfunction also lead to a variety of neurological disorders and pathological spatiotemporal brain dynamics. We show that local homeostatic plasticity provides a functional recovery by re-establishing excitation–inhibition balance in all areas that are affected lesion. We systematically compare the extent of recovery in the primary hub areas and demonstrate that stability, richness similar to normal resting state is achievable.

Neurocognitive networks underlying multisensory perception

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The Cognitive Brain Lab is engaged in developing techniques for visualization and quantitative characterization of neurocognitive networks relevant for cognitive tasks as well as development of experimental paradigms that require information processing via neurocognitive networks. I will present an example from multisensory speech perception where perceptual categorization can be controlled by one psychophysical parameter, the temporal asynchrony between auditory and visual components. We further show the spatial and temporal characteristics of underlying functional brain networks using fMRI and EEG recordings. Finally, I will highlight how computational models can highlight the mechanisms of neural information processing across putative neurocognitive network of speech perception.

Avian brain organization involved in vocal communication- New perspectives of evolution of language and language deficit disorders

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Human language is a completely unique and complicated phenomenon, of mixture of imitation, memory, thought, emotions, judgment, syntax, reasoning and so forth, and requires a massive quantity of brain resources'. These sources are essential to collect information, syntactic constructions of a number of words and their interconnections. The neuronal components of these brain resources are not yet investigated accurately. A number of them we can absolutely find with animal communication. A few vertebrates communicate acoustically, however a few birds' group- songbirds, humming birds and parrots can learn to produce complex vocalization and to comprehend the meanings of sound. This vocal production learning and Imitation (the substrate for human language) is uncommon trait and highest mode of social learning. We studied network organization of brain of Indian Ring neck parrot, exceptional for oratory skill of human language by Golgi impregnation, Nissl staining and Sholl analysis methods and revealed that their brain is organized very differently from that of mammals and other birds as well, but neuronal classes are remarkably similar to upper layers of cortex of human and other vocal learning mammals. Despite distance among birds and mammals and the variations in their brain structures, regions related to high-level cognition such as vocal acquisition, long-term memory and problem solving, are wired up in similar way.

Brain organization with compact nuclei in parrot distinct from laminar cortex in mammals is important to understand the common blueprint of brain wiring of high-level cognition in evolution and related neurodegenerative disorders.

Ethics statement: This work was carried out in strict accordance with the guidelines of Institutional animal Ethics Committee and guidelines of WHO animal ethic regulations.

Acknowledgement: This work was not supported by research grant. We thank Prof. U.C. Srivastava Professor in Neurobiology, Dept of Zoology, and University of Allahabad U.P. India. for allowing us to use laboratory space and to perform photography by using digital photo automat camera (Nikon eclipse- Boi).

Azadiradione induces HSF1 activity by direct interaction and ameliorates diseases of protein conformation in cell and animal models.

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Toxicity associated with protein aggregation in the brain underlies various neurodegenerative diseases (NDs). Upregulation of function of heat shock factor 1 (HSF1) and its downstream target gene encoding protein chaperones has shown promising results in animal models of NDs. We have isolated azadiradione by a HSF1-sensitive reporter based screening of methanolic extracts of seeds of Azadirachta indica. Azadiradione ameliorates toxicity due to protein aggregation and associated disease symptoms in cell, mouse and fly models. All these activities are correlated with activation of HSF1 function and expression of its target protein chaperone genes. Notably, HSF1 activation by AZD is independent of cellular HSP90 or proteasome. And AZD directly interacts with purified HSF1 with high specificity and facilitates binding to its recognition sequence with higher affinity. These unique properties discovered by this study qualify AZD as an ideal lead molecule for consideration for drug development against NDs that affect millions worldwide.

Striking similarities in neuroarchitecture of avian pallium and mammalian neocortex

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The cognitive abilities of birds suggest that the avian brain contains sophisticated information processing circuitry. The avian pallium has a nucleated rather than laminated architecture. The avian pallial domain consists of four divisions called hyperpallium, mesopallium, nidopallium and arcopallium which generate executive functions without displaying any visible lamination. The main function of the pallium is to link sensory inputs and motor outputs and serve as an interface between sensory and perceptual processing and mechanisms that regulate behavior. The nidopallium caudolaterale (NCL) and the dorsolateral Corticoid Area (CDL) in the avian pallium, shows important neural similarities to the mammalian prefrontal cortex and anterior cingulated cortex respectively. Cytoarchitectonic and Morphological characterization of neural features in avian pallium have been executed by Nissl staining and Golgi colonier techniques. A very specialized and unique neuroarchitecture in NCL and CDL have been observed which exhibits striking similarity with mammalian cortical layers. Localization of thick, long bipolar spindle shaped projection neurons comparable to von-Economo neurons of mammals, pyramidal neurons and fork neurons in these pallial domains provides important clues to explain how birds are able to execute higher levels of complex cognition and consciousness. Presences of these cells have been reported in most of the vocal learner mammals. Report of such neural features in avian pallium suggests their role in generating and controlling complex behavior like vocal learning.

Ethical statement: Protocol has been used accordance of the animal ethics.

Hypoxia induced inflammation in the developing cerebellum

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The involvement of cerebellum in motor functions such as co-ordination, posture and equilibrium is well documented. Ataxia or incoordination of movements often occurs as a result of cerebellar injury. In neonates or preterm infants cognitive functions and growth of the cerebellum have been reported to be affected adversely by hypoxia that results in apoptosis of the Purkinje neurons and reduced thickness of the molecular and granular layers. Hypoxia is known to enhance the production of several inflammatory mediators in the developing brain and these may be an underlying cause of hypoxia-induced cell death. We have demonstrated the production of several proinflammatory cytokines including tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1β) and chemokines in the developing cerebellum by microglia in a hypoxic injury. Along with the expression of TNF-α and IL-1β, expression of their respective receptors, namely, TNF-R_1 and IL-1R_1 was also elevated and they were localized on the Purkinje neurons. It was suggested that enhanced expression of TNF-α and IL-1β by microglia may induce apoptosis of some the cells via binding to their receptors TNF-R_1 and IL-1R_1 and this may be a pivotal pathophysiological mechanism that causes damage to the Purkinje neurons in the developing hypoxic cerebellum. Microglial cells also released increased amounts of nitric oxide through the inducible nitric oxide synthase isoform which could have further abetted cell damage. Based on these results it appears that microglial cells may be a prime therapeutic target for amelioration of hypoxia induced cerebellar neuroinflammation in the developing brain.

Drug abuse mediated potentiation of HAND: Blaming the messenger

Shilpa Buch*, *Guoku Hu, Ke Liao, Lu Yang, YeonHee Kook*

Opiate abuse and HIV-1 are two linked global health crises. Despite the advent of anti-retroviral therapy, HIV-associated cognitive disorders are on a rise with opiate abuse being the most popular drug of choice among the infected individuals. Using morphine-dependent rhesus macaques (RMs) infected with CCR5-SIVR71/17E we demonstrated augmentation of neuropathology & neuroinflammation and rapid disease progression compared with SIV-infected RMs without opiate dependence. Mortality in these rapid progressors was associated with robust microglial activation and neuronal injury. MicroRNA (miR)-mediated regulation of disease pathogenesis represents an evolving area of research. Herein we demonstrated that morphine & HIV Tat modulate increased neuropathology via two y mechanisms: **a)** Morphine exposed astrocytes upregulate expression & release of miR-138 in the extracellular vesicles (EVs), which, following uptake by the microglia, results in their activation via TLR7-dependent pathway and, **b)** HIV Tat exposure resulted in increased induction/release of miR-9/-29b in the astrocyte EVs. MiR-9-enriched EVs, were in turn, taken up by the neurons, resulting in neuronal injury. Corroboration of these cell culture findings was further validated *in vivo* wherein morphine administration in wild-type mice resulted in activation of microglia. Furthermore, we also demonstrated that upregulation of miR-9 and -29b in EVs released from HIV Tat or morphine exposed astrocytes could target the tropic factor platelet-derived growth factor (PDGF) in neurons, resulting in neuronal damage. Taken together, our findings implicate that morphine and HIV protein-Tat co-operatively dysregulate EV miRNAs, thereby resulting in neuroinflammation and neuronal degeneration in HIV-infected opiates abusers.

(Grant support: DA035203, DA036157 and MH062261)

Key Words: miRNA; Drug abuse; extracellular vesicles; HIV; Microglia; CNS

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HIV-Opioid Modulation of GUT-Immune-Brain Axis: Targeting the Microbiome as a therapeutic strategy against HAND.

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Gut leakiness, microbial translocation and systemic inflammation are hallmarks of HIV disease progression and contribute to HIV Associated Neurocognitive Deficits. Interestingly, chronic opioid abuse is also well documented to induce gut leakiness and sustained systemic inflammation. HIV patients that use intravenous heroin display accelerated HIV disease progression particularly HAND. Although HIV replication is suppressed in HIV-infected adults on modern ART regimens microbial translocation continues long after peripheral CD4+ T cell restoration. The resulting activation of both the innate and adaptive immune systems in ART treated HIV individuals is reported to be associated with markers of inflammation and is an independent predictor of morbidity and mortality. Increasing number of studies strongly support the concept that the gut microbiota, play a significant role in maintaining gut homeostasis and gut barrier function. Using BLT-NSG humanized mice in the context of drug abuse, we demonstrate these key novel findings: 1. Significant increase in gut bacterial translocation and systemic inflammation in HIV infected and HIV+ Morphine treated animals when compared to their respective control. Using 16s ribosomal gene sequencing we demonstrate a distinct shift in the microbial composition in HIV infected and HIV+Morphine treated animals when compared to their respective control. We show that treatment with Probiotics restores gut homeostasis and delay HIV disease progression in the context of opioid abuse. Our studies show that treatment with probiotics can be used as an adjunct therapy for neurodegenerative diseases that have an inflammatory etiology.

Acknowledgement: NIDA (R01DA034582, K05DA33881, R01 DA 037843-01).

Understanding the molecular mechanisms underlying epileptogenesis and/or pharmaco-resistance in patients with Mesial temporal lobe epilepsy (MTLE)

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Chronic epilepsies like PRE lacks effective therapies due our lack of understanding of the cellular and molecular mechanisms that leads to aberrant neuronal network formations during the course of epileptogenesis. Array-based profiling studies have shown implication of aberrant gene expression patterns in epileptogenesis. We have performed trancriptome analysis of hippocampal tissues resected from patients with MTLE-HS using RNAseq approach. Healthy tissues from tumour margins obtained during tumour surgeries were used as non-epileptic controls. RNA sequencing was performed using standard protocols on Illumina HiSeq 2500 platform. Differential gene expression analysis of the RNAseq data revealed 56 significantly regulated genes in MTLE patients. Gene cluster analysis identified 3 important hubs of genes mostly linked to, neuroinflammation and innate immunity, synaptic transmission and neuronal network modulation which are supportive of intrinsic severity hypothesis of pharmacoresistance. This study identified various genes like *FN1* which is central in our analysis, *NEUROD6*, *RELN*, *TGFβR2*, *NLRP1*, *SCRT1*, *CSNK2B*, *SCN1B*, *CABP1*, *KIF5A* and antisense RNAs like AQP4-AS1 and KIRREL3-AS2. We have shown that altered levels of Glutamine synthetase (GS) might be responsible for the hyperexcitability in the hippocampus as well as the anterior temporal lobe regions (ATL) of the MTLE patients. We also propose that significantly higher levels of NR2A and CDK5 mediated phosphorylation of NR2A in the ATL region as compared to the hippocampus might account for the differences in the two epileptogenic networks. These studies provide novel insights in the understanding of the pathophysiology and the genomic basis of MTLE.

Expression of N CAM and MAP2 in developing human auditory cortex

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Hearing in humans begins around the mid gestational period. Following birth, sensitivity to sound is rapidly acquired, and many simple aspects of hearing achieve maturity during the first year. Though there are a number of studies on the morphological maturation of the central auditory pathway in lower animals, human studies are still limited. The present study was conducted on 10 foetuses, from 14 weeks to 30 weeks, obtained from the labour room of Lok Nayak hospital. Institutional ethical clearance was obtained for the study. The morphological maturation of auditory cortex and expression of markers MAP2, an antibody to a microtubule-associated protein for dendritic development and NCAM, a neural cell adhesion molecule important in sterotyped migration and axon guidance was studied by immunohistochemistry. NCAM expression was visualized in the most superficial layers at 14 weeks; while in the later ages expression was in the deeper layers. Thus N-CAM expression is present throughout as the cortex reaches maturity. The neurons showed initial evidence of MAP2 at 20 weeks of gestation, but no dendritic structures were formed. By the 24th fetal week, auditory neurons were showing an intense immunostain and thin filamentous processes. At 30 weeks the staining of neurons and processes were stronger.

Conclusion: From the above study it is evident that the auditory cortex is continuing to attain morphological maturation at 30 weeks of gestation.

Memory Enhancement by Ashwagandha Leaf Extract

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Ashwagandha is at the zenith of nootropic herbs owing to its tremendous potential to recover memory decline in disorders as well as enhance memory of healthy individuals. However, limited evidences for its underlying mechanisms have outweighed the translational value. Therefore, the present study deciphered the cellular and molecular targets of memory enhancing potential of Ashwagandha leaf extract (i-Extract) in scopolamine-induced amnesic mouse model. As anticipated, i-Extract remarkably restored loss in spatial and object recognition memory of amnesic mouse evident from specific behavioral paradigms. It exhibited both preventive and therapeutic potential in recovery of memory loss and even increased memory of control animals. In-vitro and in-vivo approaches revealed multitude of targets of i-Extract in enhancing memory. These included activation of antioxidant defense system, up-regulation of memory linked neuro-plasticity genes and increasing neuronal arborization. Precisely i-Extract rescued neural cells from scopolamine induced oxidative stress. Molecular studies revealed that i-Extract up-regulated the expression of neurotrophins, immediate early genes, cytoskeletal elements, synaptic proteases and astrocytic proteins. i-Extract also regenerated loss of dendrite growth and increased spine density in amnesic mouse brain. These multidimensional effects intrigued us to search for the master regulator and we observed that i-Extract up-regulated the key transcription factors pCREB and NRF2 in the brain of amnesic mice. Our study identified the mechanism for memory enhancement by Ashwagandha stepping ahead to its clinical application in memory disorders.

Ethics statement: The work has been approved by the Animal Ethical Committee, Institute of Science, Banaras Hindu University, Varanasi, India.

Acknowledgement: This work was supported by research grant No. BT/PR3996/MED/97/57/2012 from the Department of Biotechnology, Government of India

Herbal solution to stress and neurodegeneration - molecular mechanisms

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Stress, an inevitable component of life, is defined as a response of nervous system to unfavorable intrinsic or extrinsic environment conditions. Amongst enormous kinds of stresses, some evoke immediate changes in physiology/behavior or even connect to disease symptoms, the others stay un-noticed and may rather be good for survival physiology. It has been established that (i) stress leads to molecular damage that accumulates with age and (ii) accumulated damage evokes feed-forward responses that accentuate decline in repair and regenerative capacity of living systems. Several herbs are known for their health supporting effects that range from treatment of stress, common cold to cancer. However, their mechanisms remain unclear. We have investigated the molecular mechanisms of anti-stress, anticancer, neurodifferentiation and neuroregenerative activities in leaves of *Withania somnifera* (Ashwagandha), a popular Ayurvedic herb. Using cell-based *in vitro* and *in vivo* assays, we defined the active components to Withanone, and Withaferin A in the alcoholic extract and triethylene glycol in the water extract. Molecular insights to their mechanisms of action by bioinformatics and experimental strategies revealed that they cause activation of tumor suppressor genes and induction of oxidative stress in cancer cells at high doses. The low doses caused (i) protection against stress and increase in *in vitro* lifespan of normal cells and (ii) differentiation of glioblastoma and neuroblastoma. Our data inspire aggressive and comprehensive high-end research, resource and product development of NEW (Natural Economic Efficient and Welfare) herbal drugs for sustaining healthy rapidly increasing aging societies worldwide.

Ethical statement: This study was carried out in strict accordance with the recommendations in the Animal Experiment Committee, Safety and Environment Management Division, National Institute of Advanced Industrial Science & Technology (AIST), Japan

Acknowledgement: This work was supported by grants from the DBT-AIST International Laboratory for Advanced Biomedicine (DAILAB) Special Fund.

Herbs for circadian rhythm

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Circadian rhythms in behavior and physiology have an adaptive significance for living organisms from bacteria to humans and reflect the existence of an underlying intrinsic circadian oscillator or biological clock. To adapt circadian rhythms to various environments, biological rhythms are orchestrated by a cell-autonomous clock system that drives the rhythmic cascade of clock genes. Diseases with circadian rhythm disturbance are closely related to mental activities, eg. Schizophrenia, Senile dementia, Bipolar disorder and so on, indicating that controlling circadian rhythms is very important for human health. Some of herbal plants for traditional forklore have been used for diseases of CNS disorder and Insomnia etc., suggesting that constituents of herbs are a candidate of a circadian modulator. We analysed the circadian transcription of a critical clock gene, Bmal1 and established an assay system based on NIH 3T3 cells combined with the Bmal1 promoter-driven luciferase gene to screen circadian modulators. Using this assay system we have succeeded to find components as a circadian modulator from herbal plants. In this session, I would like to introduce our recent screening results and also touch breifly on its possible mechanism.

Ethical statement: This study was carried out in strict accordance with the recommendations in the Animal Experiment Committee, Safety and Environment Management Division, National Institute of Advanced Industrial Science & Technology (AIST), Japan

Acknowledgement: This work was partly supported by grants from the DBT-AIST International Laboratory for Advanced Biomedicine (DAILAB) Special Fund.

Herbal targets for anticancer activities for brain and body

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Cancer is a disease marked by genetic instability and thus specific inhibition of individual proteins or signalling pathways holds a great potential for subversion of this genetic plasticity of cancers. Many active compounds from traditional medicinal sources could serve as good scaffolds for rational drug design. Combinatorial chemistry approaches based on natural product scaffolds are being used to create screening libraries that closely resemble drug-like compounds. Most of these compounds are part of routinely used traditional medicines and hence their tolerance and safety are relatively better known than any other chemical entities that are new for human use. Thus traditional medicine-based bio-prospecting offers unmatched structural variety as promising new leads. Recent surge towards usage of high-specificity drugs having reduced side effect profile is urging explorations with naturally occurring herbal drug candidates. Computational tools can be used to elucidate the interactions between the drug and its target molecules and to identify the stability of such interactions. The understanding obtained from these studies will help in developing future approaches towards cure of these nefarious cancerous diseases. This seminar will describe the progress in computational approaches for drug discovery and its potential application in biomedicine.

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Novel screening system to identify herbs to fight neurodegenerative diseases

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Visualization of protein dynamics in living system is helpful to understand its *in vivo* functions and roles directly, and to identify effective molecules for disease therapy. In several neurodegenerative diseases such as Alzheimer and Parkinson, protein oligomerization and/or aggregation are the main cause of disease onset. However, several features of these causal proteins have prevented us to directly visualize protein dynamics in living cells and thus limit fundamental understanding of molecular mechanisms in several neurodegenerative diseases. We have developed novel visualization proteins to monitor protein dynamics of Amyloid-β, a primary factor of Alzheimer disease. The Amyloid-β protein gets catalyzed from its precursor protein APP and form large aggregations called senile plaques in the brain. Recent studies suggest that the intracellular small oligomers of Amyloid-β protein in the neuronal cells are more toxic than extracellular large plaques for the onset of Alzheimer disease. By arranging the linker sequences between Amyloid-β and fluorescent proteins, we have developed two fusion proteins that enable us to do live cell and animal imaging, and monitor the aggregation states. Characterization of these proteins revealed that the short linker fusion protein loses its fluorescence dependent on its aggregation. On the other hand, the long linker protein can express fluorescence independent of aggregation. Thus, these proteins can be used to isolate suppressive factors in Amyloid-□ aggregation by directly visualizing its fluorescent level in living system. We will discuss the results of genetic and chemical screenings using herbal extracts to identify effective components against Amyloid-β aggregation and toxicity.

Ethical statement: This study was carried out in strict accordance with the recommendations in the Animal Experiment Committee, Safety and Environment Management Division, National Institute of Advanced Industrial Science & Technology (AIST), Japan

Acknowledgement: This work was partly supported by grants from the DBT-AIST International Laboratory for Advanced Biomedicine (DAILAB) Special Fund.

Somnogenic component of Ashwagandha: an alternative insomnia therapy

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Insomnia is a persistent disorder with difficulty falling asleep and maintaining it. Currently available drugs (benzodiazepines) develop dependency and impart adverse effects. Natural therapies hence become an alternative choice of treatment. The root or whole plant extract of Ashwagandha has sleep-inducing effects. However, the active component for somnogenic activity is not yet known. We investigated the effect of various components of Ashwagandha leaf extract on amount and quality of sleep. With the help of polysomnography on wild-type mice, sleep-wake behavior was studied. Various doses of alcoholic (i-Ex), water extracts (cd-WEX and WEX) and purified water based component (triethylene glycol, TEG) of Ashwagandha leaves were administered in mice. Result showed that alcoholic leaf extract i-Ex (with high ration of Withanone to Withaferin A) was ineffective to induce sleep in mice. However, water extract WEX and purified component (TEG) induced significant amount of NREM sleep and in a dose dependent manner. Our data clearly showed that involvement of withaferin or withanone, those are believed to be major active components of Ashwagandha leaves, in sleep-induction can be ruled out. Further, we strongly put forward TEG as the active component for sleep induction that can be used as an alternative to replace synthetic sleep-inducing drugs.

Ethical statement: The experimental protocols were approved by the University of Tsukuba Animal Ethics Committee, and every effort was made to minimize the number of animals used as well as any pain and discomfort.

Acknowledgement: University of Tsukuba is acknowledged for supporting this project financially.

Molecular insights in the multifunctional neuroprotective activities from Withania somnifera leaf extract

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Search for herbal medicines that may possibly act as therapeutic agents is an active area of research. We report whether water extract from Ashwagandha leaves (ASH-WEX) confers protection against glutamate induced excitotoxicity and neuroinflammation. Primary hippocampaus neuron cultures and microglial BV2 cell line were used as *in vitro* model system. Cell viability and differentiation markers expression was examined in glutamate challenged neurons in the presence and absence of ASH-WEX and were further used to study the expression of plasticity markers neural cell adhesion molecule (NCAM) and their post-translationally modified polysialylated form (PSA-NCAM). The expression of microglial cell activation markers such as Iba-1, GFAP and transcription factors AP-1 and NF-kB were studied in LPS stimulated BV2 cells in the presence and absence of ASH-WEX at both translational and transcriptional levels. Primary neuron cultures, on exposure to glutamate were seen to lose neural network and underwent degeneration. Pre-treatment with ASH-WEX rescued them and upregulated the expression of plasticity markers NCAM and PSA-NCAM thus suggesting its potential neuroprotective role. LPS challenged microglia BV2 cells showed activation and the expression of specific markers such as GFAP, Iba 1, tubulin as well as transcription factors like AP-1 and NF-kappaB. Pre-treatment of BV2 cells with ASH-WEX prior to LPS exposure was seen to suppress these changes. The data suggests that ASH-WEX and its active components may prove to be suitable candidate for adjunct therapy due to its anti-neuroinflammatory and neurodifferentiation inducing activity.

The Neuroprotective Role of Ceylon Tea, Coffee and Green Vegetables.

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The possible protective effect of Sri Lankan diet on healthy brain ageing were studied in; 1).Human ageing brain samples (n= 76) for cytoskeletal pathologies to assess the neuropathological diagnosis using histopathological/ immunohistochemical techniques and atherosclerosis of the circle of Willis , antimortem questionnaire was administrated to obtain the consumption pattern of pure black tea, green-yellow vegetable, and fish, of the deceased via kin, 2).1415 individuals; Stroke: n=772; [Stroke < 45 yrs16% (124/772), and, PD: n=143; [Male 61% (87/143), female 39%(56/143), median age of onset 57 yrs] & age matched controls: n=500 were assessed by a stranded questionnaire for tea and coffee consumption, 3).In vitro hypoxic model using human brain epithelial cells was studied with treatment of Ceylon green tea extract before inducing hypoxia.Our findings revealed a possible protective effects: 1). between diet and ageing cytoskeletal pathologies: a moderate consumption of green-yellow vegetables (1-6times/week) and frequent consumption of pure black tea =4cups/day.2).In case control study: regular consumption of Ceylon tea is associated with a decreased risk of early onset of Stroke & PD, whereas coffee consumption plays a protective role towards early onset of PD. 3).In vitrostudy demonstrated flavonoids extracted from Ceylon green tea act as potential therapeutic ingredients. This comprehensive study provide evidence that natural products are neuroprotectors, lay a stepping stone in developing neuroprotective nutraceuticals based on unique regional natural products.

Ethics statement: This study meets the ethical guidelines of the Ethics Committee, Faculty of Medical Sciences, University of Sri Jayewardenepura, Sri Lanka which is in compliance with the Helsinki Declaration.

Acknowledgements: This study was supported by Sri Lanka Council for Agricultural Research Policy (CARP Project Grant No– 12/684/515), Sri Lanka National Science Foundation (Grant No– RG 2000/M/16), University of Sri Jayewardenepura (Grant No– ASP/06/RE/2010/07), World Health Organization, University of New South Wales and the International Brain Research Organization–Asia Pacific Regional Committee (IBRO–APRC).

Short Talks

&

Oral Sessions

Neural mechanism of spatial memory and acquisition of the navigational map in pigeon (Columba livia)

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Birds capability to travel thousands of miles for migrations is a remarkable feat of navigation. Yet their homing sense is different from the seasonal migrations, homing pigeons are capable to use visual landmarks, magnetic fields, gravity, odors, and listening microseisms continuously generated by interfering oceanic waves, as sources of information on location. It has also been noticed that magnetic field information influences pigeon navigation in ways that are consistent with magnetic map components, but this sense of direction is not sufficient to return them to their home loft. They need a map to relate their position to their destination. Infrasound plays an important role in this very precise homing process but the sensory and neural bases of the navigational map used by pigeons are not yet fully understood. Cytoarchitectonic and Morphological characterization of neural features in pigeon brain have been executed by Nissl staining and Golgi colonier techniques. A very specialized and unique neuroarchitecture in hippocampal complex, nidopallium and a few areas of striatum have been observed. These areas possess thick, long bipolar spindle shaped projection neurons comparable to von-Economo neurons in mammals, pyramidal neurons and fork neurons. This is the first report of these unusual neuronal types, in birds. Presences of these cells have been reported in most of the vocal learner mammals. Report of such neuronal components in pigeon brain may provide some special clues to understand their role in identifying infrasonic sounds for navigation.

Ethical statement: Protocol has been used accordance of the animal ethics.

Identitification of Novel transcription factors in the tumorigenesis of most common pediatric brain tumor medulloblastoma

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Pediatric brain tumors are more complex than other cancers not only due to the blood brain barrier but also due to the incomplete anatomical picture and inadequate drug therapy compared to other malignant tumors. Medulloblastoma is the most common and contributes significantly to the high mortality among children throughout out the world. Sonic hedgehog-Gli1 signalling pathway (Shh) is thought to be the major contributor to brain tumor development, especially medulloblastoma. Therefore, this study illustrates new insights into this pathway role in the medulloblastoma development and to target these steps towards a systematic approach to treat medulloblastoma. Shh signalling begins with the binding of Shh protein to its receptor Patched and the relief of inhibition of another transmembrane receptor Smoothened (SMO). Relieved SMO leads to the activation of Gli transcription factors, which consequently translocate into the nucleus and binds to the promoter of many target genes including Ptch1, and Myc. However, our study indicated that in addition to above mentioned downstream target genes there are two putative downstream homeodomain transcription factors viz Pax6 and Nkx2.2, which are also under the regulation of Shh-Gli1 signalling. Gli1 siRNA-mediated knockdown in medulloblastoma cell line suggested that both transcription factors Pax6 and Nkx2.2 were regulated by Gli1. Moreover high expression of both transcription factors Pax6 and Nkx2.2 in medulloblastoma primary samples further strengthen that these two transcription factors are up regulated by Shh-Gli1 signalling in medulloblastoma. Therefore, our study suggests that these two transcription factors would be potential targets for the medulloblastoma therapy.

Key words: Shh signalling, medulloblastoma, Pax6, Nkx2.2, Gli1

Divergent network interactions due to human endothelial derived humoral factors affecting self-renewal and differentiation fate of human glial progenitor cells?

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Homeostasis in a stem cell niche is established by interplay between interacting signaling pathways of all the resident cell types that constitute the niche. The survival and differentiation lineage of all cells belonging to such a niche are understandable to be the result of a net balance of soluble and substratum derived factors. Humoral factors from the endothelial cells thus might contribute towards the self-renewal of the glial progenitor cells and specification of their differentiation lineage. Previous experimental results indicate towards astroglial specification by such intercellular humoral interactions.

In the present study, these experimental results have been interrogated using networking tools applying nearest neighborhood algorithms. The likelihood of expression of markers of the two key glial lineages being affected by the endothelial derived humoral factors are thus being examined.

The results of these network analyses will be presented. The study will be a demonstration of the possible effects of human endothelial cell derived humoral factors on the expression patterns determining self-renewal and differentiation pattern of human glial progenitor cells.

Keywords: Network Analysis, Neighborhood analysis, human endothelial cells, human glial progenitor cells, glial lineage.

Ethics Statement: The actual study results presented here didnot involve the use of any animal/human subject and is based on network analysis conducted at Pondicherry University.

The background study involved cells derived from aborted human fetus of about 16-18 weeks of age and endothelial cells derived from human umblical cord following appropriate ethical permissions for use of the same by the laboratory under approved protocols with the Centre for Translational Neuromedicine, Department of Neurology, University of Rochester Medical Centre, New York - 14642, USA.

Acknowledgement: Acknowledgements are due to the University of Rochester Medical Centre, New York - 14642, USA for the grant of Postdoctoral Fellowship to the author during March 2008 - December 2009 under its Neurology Fellowship Program for investigative training in Clinical Neuroscience in the area of Cell and Gene Therapy at the Centre of Translational Neuromedicine.

Rapid Eye Movement Sleep Loss induces Epigenetic Modifications for the Regulation of Gene-Expression in Specific Brain Regions of Rats

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Rapid eye movement sleep (REMS), a unique physiological process, is expressed by almost all animals higher in evolution including humans. REMS-loss has been correlated with several patho-physiological states, many of them are chronic in nature. Most of the effects of REMS-loss are mediated by elevated level of noradrenaline in brain. Noradrenaline level is regulated by its synthesis, release, reuptake, degradation and its action are regulated by presence of its receptors. Several of these functions are modulated by multi-step processes involving various molecules, which are transcriptionally regulated by specific genes.

REMS-loss would modulate all or some of the factors mentioned above, which would in turn affect REMS-loss associated patho-physiological changes.

Rats were REMS deprived for 96h using classical flower pot method. Specific brain regions related and unrelated to REMS regulation viz. locus coeruleus, pedunclo-pontine tegmentum, hippocampus and hypothalamus were dissected out. qPCR was done to quantify transcript expressions of dopamine β-hydroxylase, monoamine oxidase-A, tyrosine hydroxylase, glutamic acid decarboxylase, synapsin-I, choline acetyltransferase, caspase-3, neuron specific β-III tubulin. This was followed by chromatin immunoprecipitation assay to elucidate histone modifications (AcH3K14 & AcH4K5) of respective genes.

Although significant differences in transcript expressions as well as histone modifications were observed in samples from locus coeruleus and pedunclo-pontine tegmentum, samples from hypothalamus and hippocampus did not show most of the changes.

REMS-loss associated transcriptional modifications will help explaining associated patho-physiological symptoms particularly under chronic condition.

Acknowledgement: RM received DST-WOSA fellowship. Research funding from DBT (BUILDER), DST (PURSE), UGC-Networking, UGC project and JC Bose fellowship to BNM are acknowledged.
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Genistein in diet: Ameliorating impact on Ischemic Stroke?

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Environmental factors such as diet are important risk factors in stroke incidence and outcome. Diets high in soy are known to render neuroprotection against ischemic stroke, due to the presence of phytoestrogens. It is well documented that the incidence of stroke is less in women than in men, suggesting that estrogen confers neuroprotective. However clinical trials seem unpromising because of the potential detrimental side-effects. Phytoestrogens,particularly Genistein are being increasingly investigated as potential protectors in ischemic stroke In the current study pharmacological dose of Endotehlin–1 was injected into the MCA area to induce stroke in Sprague Dawley male rats (3-4months old). In order to test the role of nutrition, Genistein was administered intraperitonialy- acute (1 hr) as well as chronic (10days), prior to ischemic stroke. Validation of stroke was confirmed through morphological and behavioral studies. Morphological studies by TTC staining confirmed stroke, while neurological deficits were assessed based on reach to grasp, cylinder test, horizontal ladder test as well as gait behavioural analysis.There was significant improvement in skilled reaching and motor coordination in genistein pretreated rats. Golgi staining of pyramidal neurons in the layer V of motor cortex showed significant difference in the branching intersection and length of dendrites between control(contralateral peri infarct cortex) and stroke (ipsilateral peri infarct cortex), suggesting neuronal atropy in stroke rats. However there was significant reduction in neuronal atropy in genistein treated groups indicating that genistein ameliorated structural impairment of motor cortical neurons caused by ET-1 which correlated with our behavioural data. Hence, we show that both acute and chronic administration of Genistein was effective in inducing neuroprotection.

Keywords: Genistein, Endothelin-1, Ischemic stroke, behavior, structural recovery.

Bacopa monnieri extract (CDRI-08) plays neuroprotective role in the recovery of learning and memory impairments bymodulating scopolamine-induced oxidative stress and altered synaptic plasticity markers in the hippocampus of amnesic mice

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Amnesia i.e. loss of memory, is attributed to aging and various age-associated neurological diseases and the Bacopa monnieri extract, a nootropic drug, has been used in the treatment of amnesia in above conditions, however, the underlying mechanisms of its neuroprotective effects are not well established. In the present study, efforts have been made to understand the underlying mechanisms of action of Bacopa monnieri extract in the recovery of scopolamine-induced memory loss in amnesic mice model. Mice were treated with i.p. injection of scopolamine (2 mg/Kg BW) for seven days. Thereafter, they were treated with CDRI-08, a characterized extract of Bacopa monnieri (200 mg/Kg BW for 15 days). Control, scopolamine-treated (amnesic) and CDRI-08 treated amnesic mice were analyzed for the spatial memory using Morris water- and eight arm radial maze test paradigms. Alterations in the dendritic spines and neuronal cell density, cell death, oxidative stress, acetylcholinesterase activity, expression of AMPA receptor GluR2 subunit and its trafficking proteins were analyzed in hippocampus of the control as well as experimental mice. Data revealed that the scopolamine-induced amnesia was correlated with significant decline in the dendritic spine and neuronal cell density and GluR2 subunit expression, and up regulation of the acetylcholinesterase activity and oxidative stress compared to control mice. CDRI-08 treatment was found to have neuroprotective effects leading to reversal of the effects of amnesia towards that in the normal or CDRI-08 treated control mice.

Key words: Amnesia, learning and memory, AMPA receptor, Bacopa monnieri extract, oxidative stress

Conflict of interests: Authors declares that there is no conflict of interests.

Ethical statement: Experiments were carried out following the guidelines of Institutional Ethical Committee of Banaras Hindu University for the use of experimental animals.

Acknowledgements: This work was supported by major funding from CSIR & BRNS Govt. of India and partial funding from UGC-CAS, DBT-ISLS and UGC-UPE Program programs, Institute of Science, BHU to SP. RR acknowledges CSIR-UGC for providing Junior and senior research fellowships.

Neuroprotection and alleviation of Parkinsonian Phenotypes by Inhibiting Apoptotic Pathways in Dopaminergic Neurons by Ayurvedic herbs

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Parkinson's disease ("Kampavata" in Ayurveda) is a neurological disorder that affects about 1% of the population over age of 65 and it is the second most common neurodegenerative disorder after Alzheimer's disease found in the elderly. Levodopa therapy is a major medical treatment for the symptoms of PD. Levodopa treatments include side effects like nausea, vomiting, low blood pressure, involuntary movements, and, at higher doses in the elderly individuals lead to frail and confusion. The two herbs e.g. Ashwagandha (*Withania somnifera*) and Kapikachhu (*Mucuna pruriens*) have been used to treat PD for several hundred years in Ayurveda.

Our laboratory has focused on the herbal treatment of Parkinson's disease especially by the above two common herbs *Withania* somnifera *(Ws)* and *Mucuna pruriens (Mp)*. We have shown the neuroprotective function of the Ws root extract and Mp seed extract against MB–PQ induced dopaminergic neurodegeneration, in PD mouse model. Both the extracts are capable of inhibiting the oxidative stress occurring in nigrostriatal tissues and simultaneously increase the counts of TH positive cells in SN region of the MB–PQ induced PD mouse brain.

We have evaluated the neuroprotective effect of one of the component e.g. Ursolic Acid (UA) of Mp seed extract on their neuroprotective effect against MPTP induced neurotoxicity in mice. The results of this study suggest that the UA has a strong antioxidant property, which helps to reduce the oxidative stress generated in PD mice. The treatment of the MPTP-intoxicated mice with UA improved motor behavior impairment by reduction of oxidative stress in SN and also improved the expression of TH in SN region of the brain and protected the dopaminergic neurons. It is evident from this study that UA has strong antioxidant potential and it is known to have partial MAO-B inhibitor activity. Altogether, this study demonstrates that UA could be used as a potential drug for the prevention/treatment of PD by both reversing the symptoms and correcting the underlying cause.

Ethical Statement: Guidelines of the Banaras Hindu University's Institutional Ethics Committee for use of laboratory animal were followed in this study. And the above worked has been approved by the Institutional Animal Ethics Committee of B.H.U.

Blood brain barrier is impaired in the intracerebroventricular colchicine injected rats.

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The intracerebroventricular injection of colchicine in rats produces neurodegeneration and cognitive impairment which are similar to that of Alzheimer's Disease (AD). Inflammation has been identified as a cause of neurodegeneration in intracerebroventricular colchicine injected rats (ICIR). Some peripheral immune responses are altered in ICIR due to neuroinflammation. There are reports of bidirectional exchanges between brain and blood in AD patients probably due to altered BBB. The blood brain barrier (BBB) may also be affected in colchicine induced neuroinflammation. The role of BBB in neuroinflammation mediated immune responses in ICIR was investigated by altering BBB in a time dependent manner with the i.v. injection of mannitol which caused BBB more leaky. After 30 and 60 minutes of mannitol injection in ICIR, the inflammatory markers in brain and serum along with some immune responses were measured. The serum inflammatory marker and peripheral immune responses showed greater changes after 60 minutes than that of 30 minutes of mannitol injection in ICIR. The changes of peripheral immune responses in ICIR after 30 and 60 minutes of mannitol injection is related to the impairment of BBB in that condition. This study indicates that impairment of BBB in ICIR is related to the changes of peripheral immune responses.

Ethical Clearance: Ethical clearance for the present study has been obtained from the Animal Ethical Committee, University of Calcutta.

Acknowledgement: This research work was supported by the University Grants Commission [Major Research Project {F. No. 42-532/2013 (SR), 22nd March 2013}]. Susmita Sil was UGC senior research fellow and Arijit Ghosh is a DBT Research Associate.

Multiple Biomarkers signify Multi-targeted Therapy for Parkinson's Diseases: Preclinical studies

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Parkinson disease (PD) is a multi-factorial disorder caused by age, genetic and environmental toxins. PD has been characterized as a progressive degeneration of nigro-striatal dopaminergic neurons with manifestation of broad spectrum of motor and non-motor/cognitive symptoms. The available treatment strategy of PD is symptomatic with appearance of motor dysfunction and available drugs have side effects. Although several putative biomarkers of PD have been suggested from different points of view (clinical, biochemical, genetic, proteomics and neuroimaging), there is no specific, sensitive and economical biomarker(s) that unequivocally confirms the diagnosis, prognosis and treatment of PD. Therefore, the evaluation of suitable diagnosis and treatment for PD management are great challenge in the present scenario. The cognitive impairment is particularly prevalent in PD and varies from mild deficits at early stages through to severe dementia at advanced stages of the disease, the exact cause of which is not clear. Our published reports on PD model of mice indicates the differential pattern of dopaminergic neurotoxicity in association with crosstalk of oxidative stress, neuro-inflammation and hormonal milieu in three regions (substantia nigra, hippocampus and frontal cortex) of mice brain, where tocopherol (antioxidant) supplementation attenuates partially the neuroinflammation. Further studies will evaluate the utility of combine therapy of anti-oxidant and anti-inflammatory drugs as the suitable treatment procedure to protect PD. The holistic systems (brain regional, cellular and molecular) approach of preclinical research in future will unveil the exact mechanism of PD, its progression, and potential treatments.

Ethical Statement: The research study had been approved by the IHEC, Department of Physiology, University of Calcutta.

Acknowledgement: I am thankful to the grunting authorities of Govt. of India (DST, DBT, UGC) for their funding support to execute the research work. I am thankful to Dr. Arindam Bhattacharyay, Department of Zoology, University of Calcutta for his support to execute the research work. I acknowledge my research scholars, Soham Mitra, Siddhartha Dutta, Priyobrata Sinha, Parama Bhttacharya and Debanjana Sen for their efforts to perform the research works.

Recovery from Experimental Stroke through the HIF-1 alpha/VEGF Pathway

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In stroke patients, the stimulation of neurorepair mechanisms is necessary to reduce morbidity and disability. Our studies on brain and spinal cord trauma show that an exogenous treatment with the S-nitrosylating agent S-nitrosoglutathione (GSNO) stimulates neurorepair and aids functional recovery. Using a rat model of cerebral ischemia reperfusion (IR), we tested the hypothesis that GSNO invokes the neurorepair process and improves neurobehavioral functions through the angiogenic HIF-1α/VEGF pathway.

Stroke was induced by middle cerebral artery occlusion for 60 min followed by reperfusion in adult male rats. The injured animals were treated with vehicle (IR group, n=7), GSNO (0.25 mg/kg, GSNO group, n=7), and GSNO plus the HIF-1α inhibitor 2-mthoxyestradiol (0.25 mg/kg GSNO+5.0 mg/kg ME, GSNO+ME group, n=7). The groups were studied for 14 days to determine neurorepair mechanisms and functional recovery. Brain capillary endothelial cells were used to show that GSNO promotes angiogenesis and that GSNO-mediated induction of VEGF and the stimulation of angiogenesis are dependent on HIF-1α activity.

GSNO treatment of IR enhanced the expression of HIF-1α, VEGF, and PECAM-1. This GSNO treatment also led to increased expression of neurorepair mediators including BDNF. Increased expression of VEGF/BDNF and the degree of tube formation (angiogenesis) by GSNO were reduced in an endothelial cell culture model after the inhibition of HIF-1α by ME. ME treatment of the GSNO group also blocked not only GSNO's effect of reduced infarct volume ($p<0.05$) and enhanced expression of PECAM-1but also its improvement of motor and neurological functions ($p<0.001$).

GSNO shows therapeutic promise for.

Ethics statement: The experimental protocol was approved by the IACUC committee of Medical University of South Carolina, Charleston, SC. 29425

Acknowledgements: This study was supported by VA Merit and NIH grants to Inderjit Singh and Avtar K. Singh

Biochemically defining differential immune response in retinal glia to clade specific HIV 1 Tat variants

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Differential immune response to viral proteins can dictate disease progression. In the retina, Müller glia is a dominant player of immune response. The HIV-1 transactivator viral protein (Tat) induces production of several neurotoxic cytokines. HIV-1 clades Tat B and C act differentially on Müller glia, which is reflected in activation of cell death pathway components and innate immune response. The greater pathology of Tat B, as opposed to milder effects of Tat C, manifests at several signal transduction pathways, notably, MAPK, STAT, SOCS, the NFκB signalosome, and Tristetraprolin (TTP). Anti-inflammatory effects on activated cells, with the endocannabinoid anandamide (AEA), acting as an immune-modulator, also occurs differentially with the NFκB signalosome as a major fulcrum. Müller glia exposed to Tat shows enhanced PBMC attachment. AEA decreases Tat-induced leukocyte adhesion to Müller cells. In this study detailed biochemical assessment of the potential of variant Tat proteins allow one to determine the relative contribution of factors such as the chemokines, overproduction of pro—inflammatory cytokines, and attachment of PBMCs which could define prognosis of HIV associated neurodegeneration.

Ceruloplasmin protects astroglial cells from norepinephrine mediated toxicity

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Norepinephrine (NE), a biogenic amine, acts as a neurotransmitter. It is released in nerve endings where astroglial cells are present to provide structural and functional support to neurons. NE is known to cause cellular toxicity; however, not much is known for causing cytotoxicity to astroglial cells. Ceruloplasmin (Cp), a copper containing protein, plays a significant role in brain iron homeostasis as aceruloplasminemia patients and Cp knock-out mice exhibit brain iron overload. Cp is also reported to act as an amine oxidase in vitro. We observed that NE could induce toxicity to various astroglial cells that was blocked by addition of soluble Cp. Given the recent observation of NE as a direct modulator of cellular iron homeostasis; we considered that Cp might protect astroglial cells from NE-induced toxicity either by modulating iron homeostasis and/or by metabolizing NE due to its amine oxidase activity. We detected NE could induce heme oxygenase-1 and block iron storage component ferritin. This should increase intracellular iron level and if not released appropriately could cause iron-induced cell death. NE increased expression of iron release component Cp in a concentration and time dependent manner. We dissected the molecular mechanism by which NE increased Cp expression by a transcriptional mechanism. Transfection of Cp siRNA caused toxicity to astroglial cells even in hundred fold less concentration of NE. Our experiments also suggested that Cp had little role in oxidizing NE by virtue of its amine oxidase activity. These observations revealed a crucial role of Cp in protecting astroglial cells from NE-induced toxicity by modulating astroglial iron homeostasis.

Novel players in thrombosis and acute ischemic stroke

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Despite advances in prevention and therapy during the last 20 years, ischemic stroke continues to be the fourth leading cause of death worldwide. Other than mechanical recanalization, the only approved therapy for acute ischemic stroke is tissue plasminogen activator, which triggers fibrinolysis of clot in the occluded vessels, thus promoting reperfusion and salvage of the ischemic brain. Although prompt reperfusion can improve clinical outcomes, evidence from human subjects and animal models suggests that cerebral reperfusion also promotes oxidative stress and inflammation, which can cause neuronal death in the ischemic penumbra. We have found that ADAMTS13 (A Disintegrin And Metalloprotease with Thrombospondin type I repeats-13) prevents spontaneous thrombosis by cleaving ultra large von Willebrand factor (ULVWF) multimers, the most thrombogenic form of VWF, into smaller less active multimers, thereby, reducing potential thrombotic activity. Using in vivo imaging, we show that recombinant ADAMTS13 promote thrombus dissolution in injured arterioles. In ischemia/reperfusion injury model, we show that ADAMTS13-deficient mice exhibited significantly enlarged infarct size, concordant with increased postischemic inflammation. In contrast, VWF-deficient mice exhibited significantly reduced postischemic inflammation. Mice deficient for both ADAMTS13 and VWF exhibited an identical reduction of the same inflammatory parameters, demonstrating that the increased inflammation observed in ADAMTS13-deficient mice is VWF-dependent. Finally, infusion of recombinant human ADAMTS13 into a wild-type mouse immediately before reperfusion significantly reduces both infarct volume and improves functional outcome without producing cerebral hemorrhage. These findings suggest that recombinant ADAMTS13 could be considered as a new therapeutic agent for prevention and/or treatment of ischemic stroke.

Enhanced GABAergic activity in drug-resistant epilepsy: The dysmaturity hypothesis of focal cortical dysplasia (FCD).

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Tonically active $GABA_A$ receptor contributes to the abnormal synaptic transmission associated with patients with focal cortical dysplasia (FCD) owing to immature cerebral cortex. We have compared the spontaneous GABAergic activity in epileptic foci of adult and paediatric patients with FCD. To this end, targeted brain samples were obtained from brain specimens obtained from the maximally abnormal area (MAX) and minimally abnormal area (MIN) of the epileptic foci of patients undergoing epilepsy surgery. Whole cell patch clamp technique was used to record spontaneous inhibitory postsynaptic currents (IPSCs) from pyramidal neurons in the MIN and MAX samples of both adult and paediatric patients. In paediatric cases the frequency of IPSCs in both MIN and MAX area was higher compared to that in case of non-epileptic control specimens and the IPSCs frequencies in MIN and MAX samples were comparable. In adult patients the frequency of IPSCs in samples from the MAX region was higher compared to non-epileptic controls, while in the MIN region the frequency was comparable to non-epileptic controls. These findings demonstrates that in adult patients with FCD immaturity is confined only to the MAX region of epileptic foci, but in paediatric patients it is also present in the regions beyond the MAX area suggesting more diffused epileptiform activity.

Repositioning of Leukemia Drugs for Neuroprotection.

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Abl Kinase (c-Abl) mutations are the cause of Chronic Myeloid Leukemia (CML). Activation of c-Abl has also been implicated in Alzheimer's disease (AD) and, recently, we have shown an extensive role of c-Abl in the pathogenesis of Parkinson's disease (PD). We have shown that under oxidative and dopaminergic stress, both *in vitro* and *in vivo,* and in the striatum of patients with PD, c-Abl is activated and tyrosine phosphorylates parkin, causing loss of it's ubiquitin ligase and cytoprotective activities, as well as the accumulation of parkin substrates, AIMP2 (p38/JTV-1) and FBP-1. STI-571, a selective c-Abl inhibitor prevents tyrosine phosphorylation of parkin and restores its E3 ligase activity and cytoprotective function both *in vitro* and *in vivo*. Additionally, we also showed the efficacy of a potent and clinically relevant second-generation irreversible Abl kinase inhibitor, INNO-406, as a therapeutic agent for PD. Subsequently, various other groups expanded on this discovery and elucidated a much broader role for c-Abl in PD and various related neurological disorders. Several c-Abl Kinase inhibitors are FDA approved and in clinical use for the treatment of various forms of CML and other forms of leukemia. Our studies and those from other PD research groups have shown promising therapeutic effects of these inhibitors in pre-clinical models, thus making them highly suitable candidates for repositioning as neuroprotective agents during the pathogenesis of PD and related neurological disorders. The current discussion will review the data suggesting the potential of c-Abl kinase inhibitors to serve as possible therapeutic agents for the prevention of disease progression during PD and other neurological disorders.

NCTR Protocol E746601

Platform Presentation

Timp-1 protects neurons against Aβ toxicity through Akt/FoxO3a signal transduction pathway

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Tissue inhibitor of matrixmetalloproteinase-1 (Timp-1) is a cytokine that has been found to be elevated in CSF of Alzheimer's disease (AD) patients. Apart from neutralizing deleterious action of MMPs, this astrocyte secreted protein has got anti-apoptotic and neuroprotective potential. Here, we sought to identify Timp-1 mediated neuroprotective properties and the mechanisms behind it in an AD model. Previously we found that Timp-1 secretion is significantly enhanced upon Aβ treatment from cultured astrocytes. In this study, we found that, Timp-1 enriched astrocyte conditioned medium (ACM) and supplementation of recombinant Timp-1 exert a significant protection to neuronally differentiated PC-12 cells and primary cortical neurons against Aβ toxicity. Timp-1 administration in Aβ infused rat, further confirmed the neuroprotection. Next, in order to identify the Tmp-1 mediated survival signal axis in neurons, we found Akt as a mediator which is activated by TIMP-1 and is essential for Timp-1 induced neuron survival as its inhibition by Akt-specific inhibitor blocked TIMP-1 mediated cell survival. Finally we found that, forkhead transcription factor, FoxO3a, a downstream target of Akt is also involved in neuron survival evoked by Timp-1. Foxo3a is known to be activated upon Aβ treatment and enters into nucleus to upregulate target genes those are involved in cell death. Here, we showed that Timp-1 treatment on primed PC-12 cells, even in the presence of Aβ prevents FoxO3a activation and thereafter entering into nucleus. So, taken together, our study shows a prominent neuroprotective role of Timp-1 which is mediated through Akt-FoxO3a signal axis in an AD model.

Nalbuphine could decrease the Rewarding Effects Induced by Morphine in Rats

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Nalbuphine, a κ-opiate agonist and μ-opiate partial antagonist, stimulate**s** κ- receptors and antagonizes the acute reinforcing/rewarding effects of morphine, has been widely used as an analgesic or an adjuvant with morphine. The aim of the present study was to compare the acute and chronic effects of nalbuphine in morphine dependent rats. Male adult Wistar albino rats (170-175gms, N=160) were made physically dependent by administrating increasing dose of morphine. Nalbuphine was co-administered acutely and chronically in variable doses (0.1, 0.3, 1.0, 3.0 mg/kg, i.p.) with morphine and saline in experimental and control groups respectively. The blood was drawn from the heart for Plasma corticosterone levels. Brains were dissected out and were snap-frozen in liquid nitrogen for c-AMP levels and molecular work. The opiate dependent rats showed a significant increase in motor activity, Gellerts-Holtzman rating scale, plasma corticosterone levels and tissue C-amp levels whereas significant decrease was observed in protein and m-RNA expressions of tyrosine hydroxylase (TH) and tryptophan hydroxylase (TPH). Combination of acute dose of nalbuphine and morphine showed no effect at all doses on these parameters in morphine dependent rats. Moreover, chronic co-administration of nalbuphine resulted in significant decrease in naloxone precipitated morphine withdrawal and up-regulation of protein and m-RNA expressions of TH and TPH. These findings suggest that monoaminergic changes play a role in the behavioral expression of opiate withdrawal. The findings further supports that co-administration of nalbuphine with morphine may constitute a preferable superior approach to the treatment of opiate addiction.

Acknowledgement: Supported by research grant No. 58/24/2011-BMS, Indian Council of Medical Research, Govt. of India, New Delhi and Rusan Pharma Limited for gifting Nalbuphine Drug.

Key words: Nalbuphine, Morphine, Reward, Tyrosine Hydroxylase, Tryptophan Hydroxylase, Protein and mRNA.

Institutional Animal Ethics No. 608/IAEC/11

Dendritic spine abnormalities and cognitive decline in mice models of progressive myoclonus epilepsy

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The unique ability of mammalian brain to learn and memorise information is based on alteration in number or structure of synaptic contacts between neuronal circuits that are formed primarily on the dendritic spines. The morphology of spines determines the strength and function of these synapses and thus is crucial for memory and cognitive functions. Dendritic spine abnormalities have been linked to cognitive deficits in many neuronal disorders: Alzheimer's disease, Huntington's disease and Fragile X syndrome, to name a few. We have explored synaptic pathology in Lafora disease (LD), using established mice models. LD is a fatal neurodegenerative disease caused by defects in the EPM2A gene (laforin phosphatase) or in the NHLRC1 gene (malin ubiquitin ligase). LD is characterized by the presence of glycogen-like inclusions in neurons and wide spread neurodegeneration. The mechanism behind cognitive deficits in LD remains unknown; therefore we explored possible change in the spine morphology through developmental stages of LD mice using primary neuronal cultures and Golgi impregnation techniques. The hippocampal LD neurons display alterations in number as well as structure of the dendritic spines. We have also found that the level of the Fragile X mRNA binding protein (FMRP), a known regulator for the neuronal morphology, is altered in LD mice. Both laforin and malin appear to regulate the level, activity and the localisation of FMRP. We propose that the abnormalities in spine morphology could underlie cognitive defects in LD, and that the altered FMRP activity could be the cause for the synaptic dysfunctions.

Intermuscular coherence of patients with writer's cramp

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Kolkata

Intermuscular coherence analysis is a simple and non-invasive electrophysiological test which has potential for clinical investigation. In addition, it might also indicate the origin of neural drive. Hence, we present our pilot study on the IMC pattern comparing writer's cramp patients with healthy volunteers.

Surface EMG was recorded from three forearm and hand muscles while the participants performed a repetitive pinch grip on a force transducer; the target force was set to 10% of maximum voluntary contraction. IMC between first dorsal interosseous and both flexor digitorum superficialis and extensor digitorum communis were calculated from the period of steady contraction.

The average IMC plot for 10 healthy volunteers and 20 WC patients demonstrated a characteristically different pattern. A peak IMC was noted at 4- 7 Hz in WC patients in contrast to healthy volunteers who had negligible IMC in that band (mean 4-7 Hz coherences 0.013 for healthy and 0.067 for WC, significantly different, P= 0.009). A cumulative distribution plot comparing the two groups revealed that 4-7 Hz IMC above 0.03 (the largest IMC seen in healthy volunteers) was noted in 50% of WC patients.

We report, for the first time, a clear IMC at 4- 7 Hz in WC patients. This is strongly indicative of dystonia and dystonic tremor present in patients with WC. The similar coherence pattern in patients with and without writing tremor possibly indicates that they belong to the same spectrum of dystonia with a diverging clinical presentation.

Beneficial effect of low frequency repetitive transcranial stimulation on dorsolateral pre frontal cortex in chronic tension-type headache

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This study evaluated the effect of rTMS on (1) pain perception by visual analogue scale and headache impact test-6 scores(2) modifying anxiety, stress and quality of life of Chronic tension-type headache patients

A randomized control trial was conducted after approval from institute ethics committee and registered in the clinical trials registry of India. Both male and female patients between 18-50 years were recruited from neurology O.P.D. of A.I.I.M.S.

Randomisation was done by random number generation, and patients(n=22) were recruited to either active(n=11) or sham(n=11) rTMS.1Hz 1200 pulses in 8 trains consisting of 150 pulses at 110% of the resting motor threshold were given on the right dorsolateral prefrontal cortex.

Subjective assessment of pain was done both before and after the intervention by Visual Analogue Scale. Patients were also asked to fill out questionnaires- Spielberger State-Trait Anxiety Inventory test (STAI) ,WHO-Quality of Life questionnaire (QOL) and Headache Impact test-6(HIT-6). Significant improvement in Vas $P<0.0001$,HIT-6($P=0.0006$) was seen in the active vs sham rTMS.

rTMS therapy of right dorsolateral prefrontal cortex (DLPFC) may be used as a pain relieving measure in chronic pain conditions such as headaches, low backache and Fibromyalgia (for which it is FDA approved also TMS therapy is non-invasive and safe after careful selection of patients. The analgesic effect lasts longer and overall quality of life is also better. TMS may be considered as a adjuvant therapy or independent therapy for chronic pains.

Poster's Abstracts

Connexin-43 mediated glutamate excitotoxicity in rat hippocampus upon exposure to chronic hypobaric hypoxia

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Ascend to high altitude encounters a decrease in atmospheric pressure resulting in low O_2 availability to the tissues. Such a condition is referred to "Hypobaric Hypoxia". The Brain being most vulnerable to oxygen deprivation is reported to be one of the first organs to be affected. HH has severe effects on the central nervous sytem. Neuronal apoptosis, glutamate excitotoxicity, oxidative stress and cognitive decline have been associated with hypobaric hypoxia. The extent of damage is a direct effect of the degree and duration of hypoxic exposure. Owing to the significance of glial cells in monitoring various vital brain functions the present study was carried out to understand the role of glial cells in HH condition. The study was carried out in-vivo and in-vitro to understand HH induced glutamate excitotoxcity. Our results have suggested that HH induced glutamate excitotoxicity is due to the reduced glial glutamate transporter (GLT-1/EAAT2) expressed abundantly in astrocytes on chronic exposures to HH. We also looked into the mechanism of glutamate increase and study suggests that it could be accounted for by upregulated connexin43 which form hemichannels and gap junction in the cells. These findings reflect that upon chronic exposure to hypoxia the astrocytes instead of protecting the brain add to neurodegeneration thereby leading to cognitive decline. HH mediated neurodegeneration can be associated with glutamate excitotoxicity. The study highlights the role of astrocytes in HH.

Ethics statement: The experiments conducted on animals was done after obtaining necessary permission and in strict accordance to the guidelines issued by CPCSEA and Institutional Animal Ethics Committee (IAEC), DIPAS with reference no. IAEC/DIPAS/2015-13.

Acknowledgements: This work was supported by DIPAS (DRDO), NBRC and ICMR.

1-trichloromethyl-1,2,3,4-tetrahydro-β-carboline (TaClo) mediates apoptosis through G_2/M arrest in neuroblastoma cells

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Trichloroethylene, a common industrial solvent and a metabolic precursor of chloral hydrate, occurs widely in the environment. Chloral hydrate, which is also used as a hypnotic, has been found to condense spontaneously with tryptamine, *in vivo*, to give rise to a highly unpolar 1-trichloromethyl-1,2,3,4-tetrahydro-β-carboline (TaClo) which has structural analogy to the dopaminergic neurotoxin N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), a known complex I inhibitor. TaClo has been shown to cross the blood-brain barrier and induce Parkinson-like symptoms in rats. In this project, we show that TaClo induces apoptosis in the human neuroblastoma cell-line, IMR-32, and rodent Neuro2A cells. TaClo dose-dependently reduces cellular ATP levels and causes cell cycle arrest at G_2/M phase of cell cycle. We are currently identifying upstream targets of TaClo which can be used for rescuing cells from apoptosis.

Microglial Ignition Of Astrocytoma Fatality: A Study On Glioma Samples

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Astrocytic tumor in human happens to be one of the most dreaded type of neoplasm comprising of 27% of all the CNS malignancies and 75% among all the glioma. The uncontrolled proliferative and invasive potential of astrocytoma is hypothesized to be zapped up by microglia or brain macrophage. The post operative histopathologically gradaded human astrocytoma tissue samples were collected from the nodal superspeciality center of this region for brain diseases. Sections of the samples were stained with Iba1 antibody, a noted pan microglial marker reinforced with modified Silver-gold impregmentation staining to specifically mark the array of microglia. Immunohistochemical study for Ki67 positivity was analyzed to determine proliferative index with WHO gradation which showed a prominent increase of index value with grades. The Correlation between microglial association with proliferative property of astrocytoma was also fortified. Furthermore, freshly isolated as well as paraffin embedded tissue derived tumor cells have undergone flow cytometry process using PI/BrdU and differential cell cycle phasic patterns were analyzed. Understanding of epigenetic regulation in terms of methylation has also been initiated by studying DNMT expression. Presently the attempts have been taken to extract the invading and non invading neoplastic cells and assess the differential proliferative potentials of these components from the samples. Intermingling between astrocytic tumors and microglia could commemorate to understand the glioma biology at a greater extent for more effective treatment of the malady.

Key Words: Astrocytoma, Flow cytometry, Glioma, Immunological, Iba1, Ki67, Microglia, Silver-gold.

Ethical Statement: Procurement of post operative human glioma samples and processing has been ethically consoled by "Institutional Ethics Committee", Institute of Post Graduate Medical Education & Research (IPGME&R), Kolkata vide Memo No. Inst/IEC/553 dated 15.01.2014.

Acknowledgement: The authors would like to acknowledge Council of Scientific and Industrial Research (CSIR), Extramural Research Division, MHRD, Govt. of India for funding the project vide sanction No. 37(1587)/13/EMR-II dated 09.04.2013.

Spatial and Functional heterogeneity of Microglia in cortex and hippocampus of adult rodent brain

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Microglia, the innate immune cells in CNS was studied in two region of brain, the cerebral cortex which plays a key role in higher brain functions and in hippocampus which is the site of adult neurogenesis. Microglial cells, visualized with the different histoenzymatic and immunophenotypic techniques, were present in both mature adult and aged rodent brain considered in this study (Day 45 and Day 270) and their distribution through the above mentioned brain areas selected for this comparative study i.e. cerebral cortex and hippocampus. Microglial cells distinguished by specialized silver-gold staining, NDPase staining providing us their distribution pattern in specified regions. NDPase staining of organotypic brain slice shows diverse morphotypes in an age dependent region specific manner. Immunophenotyping of microglia and their distribution was verified for DAPI/Iba1$^+$ and showed differences in spatial pattern and density among the studied regions. Further, we quantified reactive oxygen species (ROS) generation by microglia from both regions separately by DCFH assay followed by flow-cytometric/ fluorimetric analysis as ROS generation plays an important role for maintaining functional integrity of the delicate brain tissue. Finally acridine orange (AO) staining of organotypic sliced tissue of both regions may focus on phagocytic involvement of the cells from both the regions. Present work shows a comparative account of two regions in terms of microglial position and function where one is the centre of higher learning and advanced brain functions and other is the important site of adult neurogenesis with evolutionary conserved functions.

Ethical Statement: The Sprague-Dawley rats were maintained for the experiment as approved by Institutional Animal Ethical Committee (IAEC) [Approval no. IAEC/CU/BIOCHEM/SM (1) dated 14.12.2012] and according to the animal experiment procedures strictly followed the "Principles of Laboratory Animal Care" [NIH Publication No. 85-23, Revised in 1985].

Acknowledgement: This work is financially supported by Indian Council of Medical Research (ICMR) [Project No.-61/8/2011- BMS (IMM)], Govt. of India.

A Comparative study on effect of Retinoic acid (RA) and Withania somnifera leaf extract (WSLE) on Benzo[a]Pyrene induced neurotoxicity in Zebrafish (Danio rerio)

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Polycyclic aromatic hydrocarbon (PAH) are potent to cause oxidative stress in aquatic animals, altering their neurobehavioral and biochemical responses and benzo[a]Pyrene (B[a]P), is one such prototype of PAHs. Zebrafish is presently being used as an experimental model in neurobehavioral studies. Retinoic acid (RA), exhibits neuroprotective property in brain cells. Withania *somnifera* (WS) has been used in ayurved as an anti-stress agent, exhibiting significant neuroprotective effects in various experimental models of neurological disorders. However, the role of RA and WS as a potent anti-oxidant to ameliorate B[a]P induced oxidative stress in zebrafish model need to be studied. Therefore in the present study we aimed to evaluate the neuroprotective potential of RA and Withania somnifera leaf extract (WSLE) following exposure to waterborne B[a]P. Behavioural studies with light/dark box and diving tank and biochemical assay were performed post treatment. Administration of B[a]P resulted in increased lipid peroxidation with concomitant decrease in the level of brain antioxidants. RA and WSLE supplementation separately attenuated all these alterations which indicate their antioxidant effect which was further confirmed by histopathological observation. Overall the above data showed that the antioxidant effect of WSLE is more pronounced as compared to RA when used as an neuroprotective agent against B[a]P induced neurotoxicity.

Keywords: Benzo[a]pyrene (B[a]P); Withania *somnifera* (WS); Retinoic acid (RA); Neurotoxicity

Neonatal exposure to Benzo[a]pyrene induces oxidative stress leading to neurobehavioral changes and altered antioxidant defence system

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Benzo[a]pyrene (B[a]P) is an environmental neurotoxicant belonging to the family of Polycyclic Aromatic Hydrocarbon (PAH), produced by incomplete combustion of carbon. B[a]P is metabolised by cytoplasmic enzymes forming a reactive metabolite which intercalates with DNA. Being lipophilic in nature, B[a]P crosses over the blood brain barrier and gets deposited in the adipose tissue of brain. Early exposure to B[a]P may affect the antioxidant defence system leading to neurobehavioral changes. The present study is aimed to investigate the effects of B[a]P on behaviour, hippocampal antioxidant defence system and histopathological alterations. The male Wistar rats were divided into three experimental groups: naive group with no treatment, control group with DMSO and intracisternally B[a]P administered group exposure to. Behavioural analysis showed significant increase in time spent and transfer latency in open arm of elevated plus maze and light zone of light and dark box whereas there is significant reduction in fall off time in Rota rod test in B[a]P treated group. Reduced ATPase, GR, GPx along with elevated catalase and GST activity significantly in B[a]P treated group as compared to the Naïve and Control groups. Histopathological studies of hippocampus by hematoxylin and eosin (H&E) staining revealed the neurodegenerative potential of B[a]P. The findings of our study suggest that the neurobehavioral and neuromorphological alteration caused by B[a]P may occur through elevation of oxidative stress and inhibition of hippocampal glutathione scavenging system and ATPase activity.

Keywords: Benzo[a]pyrene; Mood behaviour; Oxidative stress, Glutathione antioxidant system; Hippocampus.

Beryllium induced Neurotoxic manifestations and its Amelioration by Naringenin and Iron supplementation in rats

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Beryllium is a light metal that is extensively used in many modern industries due to its outstanding physical and chemical properties. Neurotoxic consequences on beryllium exposure were explored experimentally for the first time along with therapeutic potential of naringenin and iron supplementation. Total 30 female albino rats were divided into five groups. Group 1was control, 2-5 were administered beryllium nitrate (1mg/kg, i.p.) daily for 28 days. Group 2 served experimental control, group 3 received naringenin (20 mg/kg), group 4 received iron (5mg/kg) and group 5 received both naringenin and iron at the same doses for seven days. All the animals were subjected to anxiety model, physical development, motar coordination assessment and several biochemical variables. Therapy groups showed decreased anxiety level, improved motar coordination and gain in body weight in comparison to toxicant group. Combination therapy decreased oxidative stress, elevated serum amino transferases as well as alkaline phosphatase and lipid content in brain tissue and in serum in comparison to toxicant group. Glutathione level and activity of other antioxidant enzymes i.e. catalase and superoxide dismutase as well as enzymes of GSH-cycle got enhanced significantly after combined treatment of naringenin and iron supplementation. Activity of acetyl cholinesterase and histoarchitecture of brain were improved towards control after administration of naringenin and iron supplementation for seven days. It can thus, be concluded that combination of naringenin and iron supplementation may be an excellent choice for suitable antidote against beryllium induced neurotoxicity.

Tetrahydroisoquinoline a Novel Ayurvedic Molecule: Evaluation for Neuroprotection in Parkinsonian Neurotoxicity

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Parkinson's disease (PD) treatment remains vastly symptomatic with disabling side-effects. Thereby search for novel therapeutic molecules in PD continues. Here tetrahydroisoquinoline (TIQ) an identified alkaloid in Ayurveda treatment for parkinsonism was evaluated for neuroprotection in the MPTP PD mouse model and in a cell co-culture system. Adult C57/BL6 mice intraperitoneally injected with MPTP (16 mg/kg 4 times 2 h intervals) showed 53% striatal dopamine loss by HPLC ECD on 7th day. Oral TIQ administered (200 mg/kg body weight, bi-daily) on the 7th day showed a significant 16% increase in MPTP-induced striatal dopamine loss and upregulated the reduced expression of tyrosine hydroxylase enzyme at the striatal terminals. Effect of TIQ was studied in co-cultures of murine neuronal (Neuro2a), microglial (EOC20) and astrocytic (C8D30) cells exposed to the parkinsonian neurotoxin MPP+ for 24 h. TIQ (0.1-10 µM) incubated for 24 h post-MPP+ was evaluated for neuroprotection against MPP+-induced dopaminergic neuronal death. Significant attenuation of total cell viability loss (MTT assay) by TIQ (10 µM) was confirmed by a sensitive flow cytometry procedure (Live Dead Assay). TIQ treatment caused a significant increase (37%) in the number of live (Calcein AM-positive) dbcAMP-induced differentiated dopaminergic neurons compared to MPP+ alone. Interestingly, such TIQ-mediated neuroprotection in vitro was evident at the level of significant reduction (30%) of MPP+-induced mitochondrial superoxide radicals (MitoSOX dye flow cytometry). These findings provoke further investigation of the mode of neuroprotective action of this novel anti-parkinsonian herbal molecule TIQ along pathways associated to mitochondrial superoxide toxicity *in vivo* and *in vitro.*

Ethics: The experimental protocol was approved by the Institutional Animal Ethics Committee (IAEC) that is appointed and authorized by the Committee for the Purpose of Control and Supervision of Experimentation in Animals (CPCSEA) of the Division of Animal Welfare, under the Ministry of Environment and Forests, Govt. of India. Murine cell lines were purchased from ATCC USA.

Acknowledgement: This work was supported by Women Scientist -A Fellowship to Rebecca Banerjee from Department of Science and Technology, India.

Timp-1 protects neurons against Aβ toxicity through Akt/FoxO3a signal transduction pathway

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Tissue inhibitor of matrixmetalloproteinase-1 (Timp-1) is a cytokine that has been found to be elevated in CSF of Alzheimer's disease (AD) patients. Apart from neutralizing deleterious action of MMPs, this astrocyte secreted protein has got anti-apoptotic and neuroprotective potential. Here, we sought to identify Timp-1 mediated neuroprotective properties and the mechanisms behind it in an AD model. Previously we found that Timp-1 secretion is significantly enhanced upon Aβ treatment from cultured astrocytes. In this study, we found that, Timp-1 enriched astrocyte conditioned medium (ACM) and supplementation of recombinant Timp-1 exert a significant protection to neuronally differentiated PC-12 cells and primary cortical neurons against Aβ toxicity. Timp-1 administration in Aβ infused rat, further confirmed the neuroprotection. Next, in order to identify the Tmp-1 mediated survival signal axis in neurons, we found Akt as a mediator which is activated by TIMP-1 and is essential for Timp-1 induced neuron survival as its inhibition by Akt-specific inhibitor blocked TIMP-1 mediated cell survival. Finally we found that, forkhead transcription factor, FoxO3a, a downstream target of Akt is also involved in neuron survival evoked by Timp-1. Foxo3a is known to be activated upon Aβ treatment and enters into nucleus to upregulate target genes those are involved in cell death. Here, we showed that Timp-1 treatment on primed PC-12 cells, even in the presence of Aβ prevents FoxO3a activation and thereafter entering into nucleus. So, taken together, our study shows a prominent neuroprotective role of Timp-1 which is mediated through Akt-FoxO3a signal axis in an AD model.

Exogenous ATP modulates inflammatory activity in Immune cells

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Inflammation is a common occurrence in response to varied insults such as tissue injury, bacterial infection, and metabolic stress. A common mediator of tissue inflammation is prostaglandin E_2 (PGE_2), produced by the action of cyclooxygenase (COX) enzymes, COX-1 and COX-2. Conventionally, acute inflammation was controlled by non-specific inhibition of COX enzymes by non-steroidal anti-inflammatory drugs (NSAIDs) such as aspirin. However, chronic inflammation, such as arthritis or neurodegeneration, requires alternative approaches. This is due to the ubiquitous role of PGE_2 in multiple essential physiological processes. We have proposed a two-hit hypothesis for inflammation wherein we the first-hit is mediated by the injury at the site of tissue and the second-hit comes from adenosine triphosphate (ATP) released by the injured cells. Here, we show that exogenous ATP significantly enhances LPS-mediated PGE_2 release in murine RAW264.7 macrophages. We further show that this is mediated through P2Y6 receptor. P2 receptors, therefore, can serve as a promising therapeutic target in the control of inflammation. It paves the way for P2 receptor-based anti-inflammatory drugs (PBAIDs) which will retain the activities of essential COX enzymes, yet will significantly reduce neuroinflammation by decreasing the enhanced production of PGE_2 by extracellular ATP.

Ethics statement: Handling of human/animal celllines was carried out in strict accordance with the guidelines of Institutional Human Ethics Committee and Stem Cell and Research Committee of South Asian University, India, and the Indian Council of Medical Research (ICMR), India.

Acknowledgements: This work has been supported by SAU intramural research grant.

Upregulation of Neural parameters, molecular mechanisms and antioxidant status mediated by 17β-estradiol in mesenteric lymph nodes of middle-aged ovariectomized female Sprague-Dawley rats

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The transition from regular reproductive cycles to eventual acyclicity and ultimate loss of fertility are the characteristics of reproductive aging in females. With aging, the aberrations of the functions of neuroendocrine-immune network, concomitant decline in gonadal steroid hormones and increase in oxidative stress in females render them vulnerable to age-associated, neurodegenerative and autoimmune diseases.

Purpose: To investigate the mechanisms of estrogen-induced regulation of expression of neural parameters, molecular markers, and antioxidant status in mesenteric lymph nodes (MLN) of ovariectomized (OVX) female rats.

Middle-aged female Sprague-Dawley rats (n=8/group) were ovariectomized and treated with 17β-estradiol (E_2) 30-day release pellets (0.6 µg and 300 µg). At the end of the treatment period, MLN were isolated and examined for the expression of Nerve growth factor (NGF), Tyrosine hydroxylase (p-TH), p-ERK, p-Akt and p-CREB, the activities of antioxidant enzymes (Superoxide dismutase (SOD), Catalase (CAT), Glutathione peroxidase-1 (GPx-1) and Glutathione-S-transferase (GST)) and the extent of lipid peroxidation (LPO).

E_2 supplementation reversed the OVX-induced decline in the expression of NGF and p-TH, levels of cell signaling molecules and activities of the antioxidant enzymes (SOD, CAT and GST). However, E_2 treatment suppressed the activity of GPx-1 and enhanced LPO.

E_2 has a neuroprotective role in MLN by enhancing the expression of neural parameters and antioxidant status indicating its crucial role in the immune functions of secondary lymphoid organ lead by the maintenance and enhancement of neural-immune interactions.

Keywords: 17β-estradiol, MLN, lymphoid organs, NGF, p-TH.

Ethics statement: All animal experiments were conducted in accordance with the principles and procedures outlined and approved by the SRM Medical College Animal Ethics Committee, SRM University, India.

Acknowledgements: This work is supported by the Department of Science and Technology (F. No. SR/SO/HS-46/2007), Government of India, New Delhi.

Estrogen modulates Neural factors, intracellular signaling molecules and antioxidant status in thymus of middle-aged ovariectomized female Sprague-Dawley rats

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Dysregulations in neuroendocrine-immune network with age, contributed by decline in neural-immune interactions in lymphoid organs, endocrine output and immune reactivity, may promote age-related disorders. In females, there are marked fluctuations and eventual decline in ovarian hormone levels, which may alter immune functioning through regulation of growth factors and intracellular signaling molecules in lymphoid organs.

The purpose of the study is to determine the effects of 17β-estradiol on alterations of neural factors, intracellular signaling pathways and antioxidant enzymes in thymus of middle-aged (MA) ovariectomized (OVX) female rats.

17β-estradiol (E_2) pellets (0.6µg and 300µg) were implanted subcutaneously in ovariectomized middle-aged (MA) female Sprague-Dawley rats (n=8/group) for a period of 30-days. At the end of treatment period, thymus was isolated and analyzed for the expression of tyrosine hydroxylase (p-TH), Nerve Growth Factor (NGF), molecular markers such as p-ERK, p-Akt, p-CREB, activities of antioxidant enzymes (superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx-1) and glutathione-S-transferase(GST)) and extent of lipid peroxidation.

An age-related decline was observed in NGF expression and in activities of antioxidant enzymes. Estrogen treatment suppressed p-TH expression significantly, while it increased NGF expression. Both doses of estrogen significantly enhanced the levels of p-ERK, p-CREB and activities of antioxidant enzymes (GPx-1, GST, LPO) while only high dose increased p-Akt levels and catalase activity.

Estrogen upregulates NGF expression and intracellular signaling molecules, while down regulating p-TH expression. This substantiates the differential effects of estrogen in regulating the thymic neural-immune crosstalk.

Keywords: 17β-estradiol, Thymus, p-TH, NGF

Ethics statement: All animal experiments were conducted in accordance with the principles and procedures outlined and approved by the SRM Medical College Animal Ethics Committee, SRM University, India.

Acknowledgements: This work was supported by the Department of Science and Technology, Government of India, New Delhi (F.NO.SR/SO/HS-46/2007).

Exploring the inflammatory mediators, microRNAs and transcription factors regulatory networks in mesial temporal lobe epilepsy (MTLE) and focal cortical dysplasia (FCD)

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There is limited information regarding the regulation of cytokine/chemokine-receptor regulatory network in epilepsy, suggesting contribution of miRNAs and transcription factors (TFs). Therefore, in this study we have used a multiplex immunoassay approach to measure multiple inflammatory mediators (IL1β, IL1Ra, IL6, IL10, MIP-1α (CCL3), MIP-1ß (CCL4) and TNFα), as well as transcriptional changes of miRNA and mRNA expression levels of downstream targets of significantly altered cytokines using quantitative RT-PCR in MTLE and FCD patients.

Bioplex TM Pro-human cytokine 8-plex panel kit was used to evaluate the cytokine levels in tissue samples collected from MTLE (10), FCD (10) and tumor periphery (8) of glioma patients (non-epileptic controls). Expression level of downstream targets (*STAT-3, C-JUN, ICER, and CCR5*) and upstream microRNAs were evaluated by quantitative real time PCR.

Upregulation of IL-1 ß, IL-6, MIP-1α and MIP-1ß were observed in both MTLE and FCD patients as compared to controls ($p<0.05$). TNF-α, VEGF A and IL-1RA did not show any significant change between groups.

STAT-3, C-JUN, ICER, and *CCR5* are also found to be significantly altered in MTLE and FCD as compared to controls ($p<0.05$). Only *CCR5* has been found to be significantly upregulated in FCD as compared to MTLE. Significant upregulation of *CCR5* in FCD is may be due to differences in the inflammatory processes involved. The mechanism and clinical implications of these epilepsy-related immune alterations need to be clarified in a larger cohort of patients with a goal of developing potential anti-epileptic treatment strategies.

Prospective Route of Microglial Repopulation in Adult Rodent Cerebral Cortex: In Search of another Window in Brain Immunity

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Microglia, the key player of CNS immunity, is determined as myelomonocytic lineage cells and found dispersed throughout the CNS in adult. Their resident status in brain is an adult phenomenon and thought to be populated in the tissue in early developmental phase. However, with the perception of existence of some window for monocytic cell entry in maturing brain, particularly in cerebral cortex, a detailed scanning of the brain sections with specific monocyte/microglia sensitive staining methods were applied. Perinatal to matured adult cerebral cortex stained with specialized silver-gold impregnation/toning and specialized enzymatic staining with NDPase in organotypic brain slices hinted towards another prospective route of entry of blood borne monocytic lineage cells. Both the methods identified monocytic cells breaching the capillaries and taking proximate positions with capillary in the tissue throughout maturation continuum in normal rodent cerebral cortex. Immunohistochemistry for DAPI-Iba1+ cells in association with endothelial cell marker CD31 fortified the fact of close association and invading of monocytic cells through capillary lining in both confocal and normal immunofluorescence microscopy. Confocal images also clarified the positional difference of those cells with low and high Iba1 positivity within blood and tissue side of the capillary wall. Invasion of monocytic cells through capillary walls are also evidenced in SEM. These observations opened the possibility of existing of an alternate low intensity route of monocytic cell passage in adult normal brain cortex that may convert into microglia phenotype after entering the tissue.

Ethical Statement: Sprague-Dawley rats were maintained for the experiment as approved by Institutional Animal Ethical Committee (IAEC) [Approval no. IAEC/CU/BIOCHEM/SM (1) dated 14.12.2012] and according to the animal experiment procedures strictly followed the "Principles of Laboratory Animal Care" [NIH Publication No. 85-23, Revised in 1985].

Acknowledgement: This work is financially supported partially by Science & Engineering Research Board (SERB) [SR/FT/LS-81/2011] and Indian Council of Medical Research (ICMR) [Project No.-61/8/2011- BMS (IMM)], Govt. of India. Payel Ghosh is financed through UGC-NET-JRF.

Regulation of Protein Phosphatase 1 (PP1) in NMDA Receptor-Mediated Excitotoxicity

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Excitotoxicity is a cellular phenomenon that leads to death of neurons in many neurodegenerative diseases. Excessive activation of the glutamate receptor, N-methyl-D-aspartate receptor (NMDAR), is one of the major causes for excitotoxicity. Activity of protein phosphatase 1 (PP1) is thought to confer neuroprotection. Previous findings from our lab demonstrate a decrease in GluN2B-Ser-1303 phosphorylation of NMDAR that involves PP1 during glutamate treatment (Unpublished data). We aim to find the mechanism leading to activation of PP1 in excitotoxicity. Glutamate-induced excitotoxic treatment was performed on DIV9 primary cultures of cortical neurons in the presence or absence of various inhibitors. The treated cells were analysed by Western blotting and also by neuronal staining for the marker MAP-2. Western blot analysis has shown that glutamate treatment causes changes in phospho-PP1α and phospho-I2 levels. Immunocytochemical analysis has revealed a decrease in MAP-2 positive dendrites after glutamate treatment which was prevented in the presence of MK-801 and roscovitine, inhibitors of NMDAR and Cdk5 respectively. Changes in the levels of phospho-PP1α and phospho-I2 levels might result in changes in PP1α activity upon glutamate treatment. ICC experiments have revealed the neuroprotective effect of MK-801 and roscovitine on glutamate-treated cortical neurons.

Ethics Statement: Animal research was carried out as per the guidelines of Institutional Animal Ethical Committee (IAEC) of Rajiv Gandhi Centre for Biotechnology, Thiruvananthapuram, Kerala, India.

Acknowledgements: This research work was supported financially by intramural funding from Rajiv Gandhi Centre for Biotechnology. Fellowships were received from Department of Science and Technology and Council of Scientific and Industrial Research, Govt. of India.

Quest for AChE inhibitors from Donepezil analogs and their Neuroprotective properties against Glutamate induced excitotoxicity

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Donepezil is a very potent inhibitor of acetylcholin esterase (AChE) and has been approved for the treatment of Alzheimer's disease (AD). The rationale of using AChE inhibitors is to elevate the acetylcholine levels that can compensate for the cholinergic deficiency associated with AD.

The primary aim of the present work is to identify structural analogs of donepezil with better inhibitory potency against AChE. By utilizing molecular modeling approach, structural analogs of donepezil (similarity criteria ≥ 50%) were selected from the ZINC database, filtered based on their ADME profile and then docked to the crystal structure of AChE. The *in silico* studies revealed that the compounds ZINC11996936 and ZINC11709541 can bind to the active site of AChE with a number of non-covalent interactions. Enzyme inhibition studies have been carried out using these compounds in order to determine their IC_{50} values and also to elucidate their possible mode of inhibition. Although donepezil is not a very potent modulator of NMDA receptor, it is known to be protective against glutamate/NMDA-induced excitotoxicity. The neuroprotective as well as NMDA receptor inhibitory activities of the donepezil analogues are also being investigated using rat primary cortical neuronal cultures and NMDAR transfected HEK-293 cell lines respectively.

Ethics Statement: Animal research was carried out as per the guidelines of Institutional Animal Ethical Committee (IAEC) of Rajiv Gandhi Centre for Biotechnology, Thiruvananthapuram, Kerala, India.

Acknowledgement: The authors gratefully acknowledge the 'Bioinformatics Infrastructure Facility' (supported by Department of Biotechnology, Govt. of India) located at the Department of Biotechnology and Microbiology, Kannur University for providing the computational facility. The authors also acknowledge the financial support in the form of project (No.BIC/12(23)/2012) from Indian Council of Medical Research (ICMR) and intramural funding from RGCB. Fellowships from ICMR, Kerala State Council for Science Technology and Environment, Council of Scientific and Industrial Research, Department of Science and Technology are gratefully acknowledged

Effect of Lithium on migration and invasion in C6 Glioma cultures

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Glioblastoma Multiforme (GBM) is the most frequently occurring, highly invasive, recurrent malignant tumor. The current treatment of GBM involves surgical resection, radiation and chemotherapy, however, the survival rate post resection continues to be extremely low. Lithium has been used in treatment of neuropsychological disorders for over 60 years because of its neuroprotectant activity in low doses. It is also known to act through Wnt and JNK signaling pathways. C6 is a rat derived astrocytic glioma cell line that we have used as a model system to study the effects of lithium on migration and invasion of gliomas and identify the mode of action of Li in intracellular signaling pathways. C6 cells cultured in DMEM supplemented with 10% FBS were used for all the assays. Cultures were treated with 5 and 10 mM concentrations of Li to check its effect on migration and invasion through scratch and spheroid invasion assay. Morphology studies and MTT assay were carried out to check the effect on morphology and change in metabolic activity post Li treatment. 10mM concentration of Li showed inhibitory effects on migration and invasion in C6 cultures. It also showed process formation and altered morphology with an increase in nuclear: cytoplasmic area ratio along with altered metabolic activity. We conclude that lithium has a prominent inhibitory effect on migration and invasion and promote differentiation in C6 cultures. We further suggest that studies could be carried out to check changed expression of genes involved in adhesion molecules as a result of Li action.

Ethics Statement: This project has been approved by the Institutional Ethics Committee.

Acknowledgements: We would like to thank Dr. Neelam Shirsat for providing us with C6 cell line and Shruti Kurve for technical support.

Role of iNOS/NO/ CamKII-α in Cadmium mediated Neuroinflammation: Neuroprotective Potential of Quercetin

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Protective potential of quercetin in cadmium induced brain cholinergic and dopaminergic alterations due to disruption in the mitochondrial integrity and MAPkinase signaling was demonstrated by us recently. In continuation to this, the present study is focused to understand the impact of cadmium on inflammatory targets in brain and assess the protective potential of quercetin, a flavonoid. Exposure of rats to cadmium (5 mg/kg body weight, p.o., 28 days) resulted to increase the expression of GFAP and IBA1 in corpus striatum, frontal cortex and hippocampus as compared to controls. Further, increase in the levels of proinflammatory (TNFα, IL1β, IL6) cytokines associated with decrease in the levels of anti-inflammatory cytokine (IL10) was distinct in these brain regions on cadmium exposure. Cadmium also activated the iNOS/NO system and thus exhibiting enhanced inflammatory response. Interestingly, simultaneous treatment with quercetin (25 mg/kg body weight, p.o., 28 days) resulted to ameliorate cadmium induced changes in these brain regions. The results exhibit potential of quercetin to inhibit the inflammatory response of cadmium by modulating the iNOS/No pathway.

3-Methylcholanthrene induces Aryl hydrocarbon receptor mediated Neurotoxicity in differentiating Neuronal cells derived from Human Umbilical cord Blood Stem cells

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The present study was aimed to investigate the xenobiotic metabolizing capabilities of human umbilical cord blood stem cell derived developing neuronal cells, for its utilization as a pre-screening tool to assess the drug/ chemical-induced developmental neurotoxicity. Developing neurons, derived from the human umbilical cord blood stem cells (hUCBSCs), were investigated for their stage-specific responses against 3-methylcholanthrene (MC), a well-known polycyclic aromatic hydrocarbon-environmental pollutant and a known inducer of cytochrome P4501A1. Three-dimensional molecular docking demonstrates the strong hydrogen bonding and hydrophobic interactions of MC with amino acids of aryl hydrocarbon receptor (AHR) and aryl hydrocarbon receptor nuclear translocator (ARNT) within 4A° and subsequent inhibition of cAMP response element-binding protein (CREB), a-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and N-methyl-D-aspartate (NMDA) receptors. Protein docking also confirms that induced levels of AHR inhibit the neurogenesis-related transcription factor (CREB) with maximum docking scores. In concurrence with *in silico* data, MC exposure significantly up regulates the expression and activity of AHR, CYP1A1 and glutathione S-transferase P1-1 and down regulates the expression of CREB, AMPA and NMDA receptors in hUCBSC-derived neuronal cells at various maturity (0, 2, 4, 8 days of differentiation). MC-mediated significant down regulation in the expression of stage-specific neuronal markers (Nestin, synaptophysin, CREB, AMPA and N-methyl-D-aspartate receptor subunit 2A-NR2A) was also noticed in cells all through the differentiation. Data identify the possible interference of MC in neuronal transmission and neurogenesis. Our data also confirm that the early stage of neuronal development is metabolically more active than mature cells, hence more vulnerable to the polycyclic aromatic hydrocarbons.

Tylophora indica as a potential anti-neuroinflammatory agent against the microglial mediated neuroinflammation.

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Microglial mediated neuroinflammation is a crucial hallmark underlying the pathogenesis of many neurodegenerative disorders and also important target for the development of neuroinflammation targeted therapeutics. Microglial cells play important role in immune surveillance, but their chronic activation exacerbates neuronal damage through excessive release of inflammatory mediators leading to neuroinflammation and subsequent neurodegeneration. Conventionally, anti-inflammatory drugs are prescribed but they are associated with long term potential risks. Nowadays, herbal medicines are attracting attention as future potential therapeutics. Tylophora is well known for its antitumor, immunomodulatory, antioxidant, anti-asthmatic, anti-inflammatory and antirheumatic activities in Ayurveda. The present study was aimed to evaluate the anti-neuroinflammatory potential of *Tylophora indica* leaf hydroalcoholic extract (THyE) and water extract (TWE) using LPS (lipopolysaccharide) stimulated BV-2 microglia as model system. Non cytotoxic doses of the THyE and TWE were selected by MTT assay. α-tubulin, Iba-1 and various inflammatory cascades proteins like NFκB, AP1 immunocytochemistry was done to study the effect of Tylophora on LPS induced microglial morphological changes and activation. Further, its effect on microglial migration was analysed by Wound Scratch Assay. Appropriate dose of THyE and TWE selected were 0.2 µg/ml and 20 µg/ml, respectively. Both THyE and TWE inhibited LPS induced expression of Iba-1, NFκB and AP-1 as revealed by Immunofluorescence staining. Both extracts also attenuated nitrite production and microglial migration towards site of injury. This study suggests that Tylophora inhibited LPS-induced microglial activation and migration suggesting its anti-neuro-inflammatory role and may be further explored as a potential therapeutic candidate for the treatment of neurodegenerative diseases.

Acknowledgement: Muskan Gupta is thankful to Council of Scientific and Industrial Research (CSIR), India for the fellowship. Infrastructure provided by University Grants Commission (UGC), India under UPE and CPEPA schemes and Department of Biotechnology (DBT), India under DISC facility is highly acknowledged.

Resveratrol normalizes Hyperammonemia induced Proinflammatory and Proapoptotic conditions in rat brain

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Hepatic Encephalopathy (HE) is a disorder of mental activity, neuromuscular function and consciousness due to liver dysfunction. Although the exact neurochemical basis of HE remains elusive, hyperammonemia (HA) is considered as an important factor responsible for neuronal dearrangements. It is now evident that the microglia and astroglia cells in brain synthesize TNF-α to regulate higher order brain functions and astrocyte induced synaptic strengthening. Even development of MHE has been described to be dependent more on enhanced inflammatory markers than the severity of CLF or HA in the CLF patients. Resveratrol (RSV) is a natural antioxidant and known to mediate its therapeutic actions by scavenging ROS. It confers neuroprotection under the variety of neurological complications. We have studied profile of neuroinflammatory markers Tnf-α, NF-κB, apoptotic marker Bcl2, Bax and p53 in cerebral cortex and cerebellum of rats with chronic HA (administration of 100 mg/Kg b.w of thioacetamide i.p. for 10 days) and in CLF + resveratrol (10 mg/Kg b.w. for 7 days) treated rats. In comparison to control, a significant increase in transcript of TNF-α in cortex and cerebellum of HE rats was consistent with enhancement in the level of NFκB. A significant decline in Bcl2/Bax ratio further suggested a neurodegenerative condition in both the brain regions of the HE rats. Moreover, resveratrol treatment could normalize the Bcl2/Bax ratio in both the brain regions of the CLF rats. The findings suggest that Resveratrol is able to ameliorate moderate HA induced TNF-α led inflammatory cascade and proapoptotic neurodegenerative condition in rat brain.

Keywords: p53, Bcl2, Bax, Resveratrol, Hepatic encephalopathy

Acknowledgement: This work was financially supported by ICMR grant (54/38/CFPGER/2011/NCD-II) to Prof. S.K.Trigun.

Conflict of interest: The authors declare no conflict of interest.

Ethical clearance: The use of animals for the present study was approved by the institutional animal care and use committee (IACUC); Animal ethical committee of the Banaras Hindu University, Varanasi.

Neuroprotective potential of aqueous extract of *Tinospora cordifolia* against Glutamate and MPTP induced excitotoxicity.

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Neurodegeneration is characterized by progressive loss of structure and function of neurons which ultimately leads to various neurodegenerative disease conditions and cognitive dysfunction. Glutamate is a major excitatory neurotransmitter in CNS but excessive glutamate levels lead to neuronal dysfunction and degeneration. The neurotoxin MPTP is used to induce neurodegeneration in model systems by destroying dopaminergic neurons. We designed this study to elucidate neuroprotective potential of aqueous extract of *Tinospora cordifolia* (Aq. TC Extract) against Glutamate and MPTP induced neurotoxicity using primary astrocytes as model system. We studied the effect of extract and neurotoxic compounds glutamate and MPTP. Selected concentrations for experiments from MTT assay were 2mM of Glutamate, 1µM MPTP, 10µg/ml and 20µg/ml Aq. TC extract. Astrogliosis induction and suppression was studied by immunofluorescent staining for GFAP. Upregulation of expression of GFAP in Glutamate and MPTP as compared to control was observed which was reduced in Aq. TC extract pretreated cells indicating the role of it in suppressing the astrogliosis induction. Further, Astrocytic- Neuronal co-culture system studies also revealed that Aq. TC extract enhances neurite length of primary cerebellar neurons and astrocyte secreted factors were seen to protect the cerebellar neurons from neurite degeneration due to Glutamate and MPTP induced stress. The study suggested that Aq. TC extract possess potential neuroprotective activity against Glutamate and MPTP neurotoxins.

Ethics Statement: Handling of animals used in this work was strictly carried out according to guidelines of Institutional Animal Ethics Committee (IAEC).

Acknowledgements: Anuradha Sharma is thankful to Department of Science and Technology (DST), India for the fellowship. Infrastructure is provided by University Grants Commission (UGC), India under UPE and CPEPA schemes and Department of Biotechnology (DBT), India under DISC facility is highly acknowledged.

IGF-1 hinders LPS induced acute inflammatory response

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Bacterial lipopolysaccharide (LPS) is a potent immunogenic substance causes peripheral and central inflammatory response in animal model on single or repetitive exposure. The central or neuroinflammatory response is coupled with increase in ROS, nitrite and release of pro-inflammatory cytokines. LPS induced rat model of neuroinflammation has been widely used by researchers for several purposes, namely to assess the role of BBB permeability and pro-inflammatory cytokine release. In the present study, we have assessed the effect of intranasal application of IGF-1 on LPS induced acute neuroinflammatory response in rats.

Experimental animals were divided into control group, LPS group and IGF-1 pretreated group. IGF-1 pretreated group received 50 µg of IGF-1 per day for 3 days prior the experiment. The LPS group and IGF-1 pretreated group received LPS 5 mg/kg of body weight whereas the control group received normal saline. The animals were sacrificed following 4 h of LPS / saline injection and the brain was isolated and processed for analyses.

Different brain regions were analysed for ROS and nitrite levels. ROS levels were significantly reduced ($p < 0.05$) in IGF-1 pre-treated animals in frontal cortex, hippocampus, corpus striatum and amygdala in comparison to LPS group. Similar findings were observed in case of nitrite level. Moreover LPS couldn't increase significantly the IL-1β level in the frontal cortex and hippocampus in IGF-1 pretreated animals.

Our data reveals that IGF-1 has some anti-inflammatory properties that hinder LPS induced acute inflammatory response. Further studies needed to explore the effect of IGF-1 administration in chronic neuroinflammation.

Key words: IGF-1, LPS, Neuroinflammation

Ethical clearance: Ethical clearance for the study has been obtained from the animal ethical clearance committee, University of Calcutta.

Acknowledgements: Authors would like to acknowledge the Department of Biotechnology (DBT), Govt. of India for supporting the project financially.

The Polysialic acid mimetic 5-nonyloxtryptamine in repair of Glial and Neuronal cells after acute glutamate excitoxicity

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Glutamate excitotoxicity is considered as a risk factor for various neuropathological ailments. The carbohydrate moiety polysialic acid (PSA) may be one of the potential targets for promoting nervous system repair after glutamate excitotoxicity. We have previously reported the beneficial effects of PSA mimicking compound 5-nonyloxytryptamine oxalate (5-NOT) in promoting repair after spinal cord injury in mice. The current study was aimed to evaluate the ability of 5-NOT to promote repair of glial and neuronal cells after acute glutamate excitoxicity. For this purpose, the effect of 5-NOT treatment on the morphology of astrocytes and cerebellar neurons was evaluated after acute glutamate challenge to these cells. The PSA analogue, colominic acid was used as a positive control. Glutamate challenge in astrocytes resulted in distortion of cell morphology, swelling of cell bodies and filopodia formation. 5-NOT treatment during the acute phase led to reversion of glutamate-induced changes in the cell morphology, reduction in the filopodia formation and reduction in apoptosis and upregulation of PSA-NCAM expression in astrocytes. In contrast to its effect on astrocytes, axonal retraction was observed in cerebellar neurons after glutamate challenge whereas; 5-NOT and colominic acid treatment resulted in pronounced neurite outgrowth from the cerebellar neurons. Further, 5-NOT treatment also rescued cerebellar neurons from astrocyte-mediated glutamate-induced excitotoxicity. Hence, the current study suggests that the PSA mimicking compound 5-NOT may be a promising candidate for promoting repair after acute glutamate excitotoxicity and it may find therapeutic applications in a wide range of neuropathological ailments and traumatic injuries that include glutamate excitotoxicity.

Keywords: Polysialic acid, 5-nonyloxytryptamine oxalate, glutamate excitotoxicity, astrocytes, cerebellar neurons, co-culture

Ethical Statement: Animal care and procedures were followed in accordance with the guidelines of the Animal Ethical Committee, Guru Nanak Dev University, Amritsar, India

Andrographolide attenuates Neuroinflammation and working memory impairment via HMGB1 mediated TLR4/NFκB signaling pathway

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Toll like receptor 4 (TLR4) signalling in the cortical region of brain, induces neuro-inflammation that results in neurodegenerative diseases, like working memory impairment, due to over activation of both microglial cells and astrocytes. In this study we have investigated the role of Andrographolide, major constituent of *Andrographis paniculata* plant, in reduction of neuroinflammation and working memory impairment. Andrographolide inhibited lipopolysaccharide (LPS)-induced High mobility group box 1 (HMGB1) mediated TLR4 downstream signalling cascade proteins and inflammatory mediators at both transcriptional and translational levels in primary mix glial culture, glial cell line and mice brain prefrontal cortex. Flow cytometric analysis showed a significant decrease of LPS induced CD 284 (TLR4) expression after Andrographolide treatment. Andrographolide also suppresses LPS induced expression of P_2X7 receptor and its downstream signalling mediators including-inflammasome NRLP3, caspase1 and IL-1β. Immunocytochemestry studies demonstrated reduced translocation of HMGB1 to the cytosol and reduced activation of microglial and astrocytic cell in LPS induced and Andrographolide treated group. Furthermore, *in vivo* studies suggested that Andrographolide treatment reversed LPS-induced behavioral and working memory disturbances and also attenuated LPS-induced increases in the expression of memory impairment markers, such as Amyloid beta (Aβ), p-tau. Andrographolide also improved synaptic functionality via enhancing the activity of synaptic marker PSD-95. Radial arm maze data demonstrated that Andrographolide reduced LPS induced working memory impairment. Overall, these studies indicated that Andrographolide could be a novel pharmacological countermeasure for the treatment of neuroinflammation derived neurodegenerative disorders related to memory impairment.

Characterization of Neurotropic virus infection in motor neuron cell line

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Viral infections in central nervous system are a major cause for neurodegenerative disorders. Japanese Encephalitis and Chandipura Virus are the two major neurotropic viruses causing clinical encephalitis in a vast region of south-east Asia and Indian subcontinent. Hind limb paralysis and neurocognitive dysfunction are common phenomenon associated with both these + and – strand RNA viruses. Thus, in order to characterize the effect of the viruses on motor neurons, we infected undifferentiated and differentiated NSC34 cells (a hybrid cell of motor neuron and mouse neuroblastoma cells) with both Japanese Encephalitis (JE) and Chandipura (CHPV) virus. We studied the morphological alterations and interferon responses in this cell line upon viral challenge and along with we found an increase in PARP cleavage accompanied with caspase 3 activation at different time points post infection. Inflammation was evident from the elevation of the cytokines like MCP-1, TNF-a and IL-6. Subsequently in a separate *in vivo* study we isolated three major regions (Cervical, Thoracic and Lumbar) of 10 day old BLAB/c mice spinal cord infected with both the viruses, and found the congruity in PARP cleavage, caspase 3 activation along with pro-inflammatory cytokine surge during progressive viral infection. Apoptosis of the motor neurons due to sustained inflammation is proposed to be the principle cause behind deterioration of motor functioning in both these RNA virus infection which was hypothesized from both *in vitro* and *in vivo* observations. Hence, our study can be a pioneer one in discovering the molecular pathway guiding the motor neuron destruction by the aforementioned neurotropic RNA-viruses.

Keywords: Motor neuron, Japanese Encephalitis, Chandipura Virus, Inflammation, Cytokine.

Funding: This project is funded by National Brain Research Core Funding. SM is a recipient of DST-INSPIRE Fellowship (IF140074), Government of India.

Novel molecular pathway of ATP release perturbed in astrocytes contributes to neuronal death in HIV-1 induced neurodegeneration

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Neuronal damage is the pathological substrate of HIV-1 associated neurocognitive disorder (HAND) featuring compromised higher executive functions, cognitive and motor skills. Robust HAART therapy has reduced the severity of HAND due to lowered opportunistic infections and reduced inflammation. But the viral CNS reservoirs are persistent threat to CNS health. Astroglia are indispensable component of the tripartite synapse that regulates neuronal functions, health and survival through neuroglia crosstalk. Astrocytes susceptibility to viral infection and subsequent latency contributes towards insults to neuronal networks and culminates into compromised neuronal survival. The viral protein HIV-1 Transactivator of Transcription (Tat) is neurotoxic and is released in the brain even when the viral load is non-detectable in successful HAART cases. Recently, we have demonstrated that astrocytes mediate indirect neuronal death by releasing excess ATP through activation of purinergic receptors. Using well characterized model system of human primary astrocytes and neurons differentiated from human neural precursor cell, we further probed into the molecular mechanism for enhanced ATP release in astrocytes in response to HIV-1 Tat. It was observed that HIV-1 Tat modulates the miRNA machinery in astrocytes to disrupt expression of VDAC1, a channel present in the outer mitochondrial membrane and plasma membrane which regulates extracellular ATP release. We report a novel molecular cascade of miRNA-mediated ATP release through regulation of VDAC1 and provide evidence that HIV-1 Tat dysregulates miR-320a that in turn perturbs astrocytic ATP release. Down-regulation of VDAC1 either with miR-320a mimic or VDAC1 siRNA in HIV-1 Tat affected astroglia could rescue the neurons from glia-mediated indirect death. Our findings reveal a novel upstream therapeutic target that could be employed to abolish the astroglia-mediated neurotoxicity in HIV neuropathogenesis.

Ethical statement: The protocol used for neural precursor cells isolation from aborted human fetal tissue was approved from National Brain Research Centre (NBRC) human ethics committee and Indian Council of Medical Research (ICMR), India. Fetal tissue was obtained through

elective termination of pregnancy and further used after confirming mother's consent.

Acknowledgment: Financial support for the study from NBRC, India core funds to PS is greatly acknowledged. Senior Research Fellowship to Ms. Mahar Fatima from CSIR, India and Mr. Bharat Prajapati from UGC, India and project assistantship to Ms. Kanza Saleem & Ms. Rina Kumari from National Brain Research Centre (NBRC), India are sincerely acknowledged.

Effects of Opioids on Early Pathogenesis and Microbial Dysbiosis in a Murine HIV Model

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Opioids are known to exacerbate HIV pathogenesis. However, current studies have been limited by models of HIV infection. HIV causes many systemic effects via direct infection of host cells as well as indirect bystander effects. It is important to establish a systemic infection model in a small animal so that genetic tools can be utilized to elucidate the mechanisms of action. In this study, the systemic effects of EcoHIV infection, a modified HIV which can infect mouse cells, are examined in conjunction with morphine. EcoHIV infection with opioid treatment induced bacterial translocation, which is similar to observations in human patients with LPS. Bacterial translocation corresponds with alterations in gut morphology, disruption of epithelial barrier, and a concurrent increase in systemic inflammation in both IL-6 and TNFα. Long term infection also had increased expression of inflammatory cytokines in the CNS when treated with morphine. Overall, this study shows that EcoHIV is an appropriate model to study the effects of opioids on HIV pathogenesis in the gut. It also shows the effect of opioids and HIV on gut defenses, including epithelial barrier, immune function, dysbiosis from the normal microbiome and distinct metabolomics profile.

Ethics statement: All studies using mice were approved by the University of Minnesota Animal Care and Use Committee and were conducted in full compliance with NIH guidelines.

Acknowledgment: This work was supported by NIH grants: RO1 DA012104, RO1 DA037843, RO1 DA031202, K05 DA033881 and R01 DA034582 (to S.R.).

Environmental Exposure and Oxidative stress in Maternal and Foetal tissues of Pregnant Women Living in Jajpur District, Odisha, India

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Pregnant women and their foetus were regularly exposed to multiple polycyclic aromatic hydrocarbons (PAHs) in highly polluted industrial areas like Jajpur, Odisha. Hence, the possibility of related adverse effects on the foetus is uncertain. In the present study, pregnant women in their first or second trimester presenting at hospitals were told about the study & questioners and written consent was taken from each participant. Tissue samples were collected from 35 pregnant women living in Jajpur industrial area and 30 from Cuttack, Odisha, and matched placental weight were recorded at birth. We have also analysed the MDA concentration (lipid peroxidation) in both maternal and foetal tissues to estimate the level of oxidative stress due to industrial exposure. We observed that industrial exposure to pregnant women in Jajpur reduced the birth weight, head circumference of neonates and affected the placental weight in comparison to Cuttack district. Industrial exposure also adversely affected the antioxidant level with increased MDA concentration and protein content in both maternal and foetal tissues in Jajpur showing more vulnerability of pregnancy women and their significant impact on prenatal development in comparison to Cuttack. The preliminary findings of the present study inferred that chronic exposure to industrial pollution during pregnancy leads to augmented oxidative stress in placental tissues with adverse impact on foetus leading to reduction in birth weight and head circumference of neonates. Statistical analysis also indicates significant differences with respect to the number of complicated pregnancies cases in industrial areas as compared to normal control areas ($p<0.05$).

Ethical statement: The study was approved by the Institutional Ethical Committee on Biomedical Research on Human Subjects of SCB medical college, Odisha, India (Ethics committee registration number ECR/84/INST/OR/2013). Written consent letter was obtained from the Sub- Divisional Medical Officer (S.D.M.O.) of Govt. Community Health Centre, Danagadi, Jajpur Road, Odisha to conduct investigation on human beings in accordance with the guidelines of Indian Council of Medical Research (ICMR).

Acknowledgement: We are thankful to the Ravenshaw University for providing basic infrastructure and preliminary basics to conduct our research.

A switch over from autophagy induced by 2-deoxy-D-glucose to apoptosis in combination with cisplatin in glioma cells

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In spite of many advances in the research and treatment modalities, survival of glioma patients is still in dismal. Hypoxia zone present in the core of the tumor is the main cause for chemoresistance and relapse of the disease. Drugs like cisplatin (CP) and 2-deoxy-D-glucose (2-DG) which are used in preclinical and clinical research are not very effective as single agents. So there is a need for rational combination of the drugs which can effectively abrogate the chemoresistance. In this study we investigated the effect of the combination of CP and 2-DG and their mechanism of action on glioma cells under varying oxygen concentrations. Combination of CP and 2-DG showed a synergistic effect on the glioma cell lines under normoxia (20% O_2) and hypoxia (0.2% O_2) with combination index less than 1. Autophagy induced by 2-DG was attenuated when combined with CP, which was evident from reduction in the autophagic markers as well as increase in apoptotic markers and caspase 3/7 activity. Reduction in the ATP levels and endoplasmic reticulum stress were observed in the cells treated with the combination as compared to 2-DG alone. The pAKT levels were also reduced by the combination. We further found that the AKT inhibitor was able to replicate the effect of CP in the combination. Thus, the combination of CP and 2-DG can prove to be effective for reducing chemoresistance under normoxia and hypoxia in glioma cells.

Acknowledgements: The study has been supported by core institutional grant of National Brain Research Centre, India**.**

Beneficial effect of low frequency repetitive transcranial stimulation on dorsolateral pre frontal cortex in chronic tension-type headache

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This study evaluated the effect of rTMS on (1) pain perception by visual analogue scale and headache impact test-6 scores(2) modifying anxiety, stress and quality of life of Chronic tension-type headache patients

A randomized control trial was conducted after approval from institute ethics committee and registered in the clinical trials registry of India. Both male and female patients between 18-50 years were recruited from neurology O.P.D. of A.I.I.M.S.

Randomisation was done by random number generation, and patients(n=22) were recruited to either active(n=11) or sham(n=11) rTMS.1Hz 1200 pulses in 8 trains consisting of 150 pulses at 110% of the resting motor threshold were given on the right dorsolateral prefrontal cortex.

Subjective assessment of pain was done both before and after the intervention by Visual Analogue Scale. Patients were also asked to fill out questionnaires- Spielberger State-Trait Anxiety Inventory test (STAI) ,WHO-Quality of Life questionnaire (QOL) and Headache Impact test-6(HIT-6). Significant improvement in Vas $P<0.0001$,HIT-6($P=0.0006$) was seen in the active vs sham rTMS.

rTMS therapy of right dorsolateral prefrontal cortex (DLPFC) may be used as a pain relieving measure in chronic pain conditions such as headaches, low backache and Fibromyalgia (for which it is FDA approved also TMS therapy is non-invasive and safe after careful selection of patients. The analgesic effect lasts longer and overall quality of life is also better. TMS may be considered as a adjuvant therapy or independent therapy for chronic pains.

Effect of Transcranial Magnetic Stimulation on chronic pain and the related symptoms in fibromyalgia patients

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Fibromyalgia (FM) is characterized by chronic widespread pain, tenderness, fatigue, sleep disturbances, morning stiffness and psychological distress. The pathophysiology of FM is not completely clarified, but a number of neuroendocrine, neurotransmitter-related, and neurosensory disturbances, as well as genetic predisposition, have been implicated in its generation. Aberrations in physiological pain-processing mechanisms, together with psychological and environmental factors, interact in the development and maintenance of widespread pain and tenderness in FM. The symptoms can be controlled, to some degree, with pharmacological and non-pharmacological treatments. Over the last decade, it has been repeatedly shown that repetitive transcranial magnetic stimulation (rTMS) of the primary motor cortex (M1) induces analgesic effects both in experimental pain and in various chronic pain conditions, probably by activating pain modulation systems.

We assessed the effect of repetitive transcranial magnetic stimulation (rTMS) in patients with chronic widespread pain due to fibromyalgia. Subjective and the objective assessment of pain and related symptoms were performed before and after rTMS therapy.

The experimental protocol approval was obtained from the local ethics committee (AIIMS Ethical Committee, New Delhi; Ref No: IESC/T-251/15.06.2013). Fifty two consecutive patients were randomly assigned, in to two groups: one receiving active rTMS (n = 24; Dropouts=2) and the other, sham stimulation (n = 18; Dropouts=8). The stimulation site was the right dorsolateral prefrontal cortex. rTMS therapy was given for one month (total 20 sessions/ 5 consecutive days/week and for 30 min/day). Subjective assessment of pain and associated symptoms was done with help of selected questionnaires (Visual Analogue Scale, McGill Pain Questionnaire and WHOQOL-BREF Questionnaire) and objective assessment of pain was recording nociceptive flexion reflex (NFR) or R-III reflex. Blood samples were collected before and after rTMS therapy for the assessment of selected hormones (TSH and cortisol).

Before rTMS therapy, Sham and rTMS groups have higher VAS rating of pain, greater score for anxiety, depression and poor quality of life. Active rTMS significantly reduced pain intensity and improvement in pain related emotions (depression, anxiety). The quality of life for Fibromyalgia patients is severely affected in all aspects i.e. physical, psychological, social and environmental domains. Our data collected using WHOQOL-BREF scores showed an improvement in these conditions in active rTMS group.

Pain assessment was also done by objective methods by recording R-III reflex. Data of R-III reflex parameters showed that RIII threshold and Latency increased in active rTMS group as compared to sham rTMS group. However no change was observed the in levels of TSH and cortisol pre and post rTMS therapy.

In conclusion, these results suggest that rTMS may be a valuable and safe new therapeutic option in patients with fibromyalgia.

Keywords: Repetitive transcranial magnetic stimulation, fibromyalgia, chronic pain, nociceptive flexion reflex.

Estimation of Total Ventricular Volume and Volume Fraction of Brain in normal CT scans- A Stereological Study

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The study of ventricular volume has recently become a centre of attraction in some neuropsychiatric diseases like schizophrenia, Alzheimer's disease and chronic alcoholism. Volumetric analysis of ventricular system is also helpful in the diagnosis and classification of hydrocephalus and in the assessment, follow-up during its therapy (ventricular shunts). Some of these diseases also present with brain parenchymal atrophy leading to ventricle/brain ratio changes. This baseline study was done to determine the total ventricular volume and ventricle-total brain volume fraction related to different gender and age groups in normal adult population. 50 cranial non-contrast computed tomography (CT) scans of normal adult subjects (29 females and 21 males) were collected from the museum of department of Anatomy, Maulana Azad Medical College, New Delhi. The total ventricular volume and volume fraction of total ventricular volume to total brain volume were estimated using the Cavalieri method and volume fraction-stereological methods. Statistical analysis was done using the independent t-test in SPSS version 23.The difference in mean total brain ventricle volume was statistically significant between the two genders (27.55 cm^3 in males and 22.34 cm^3 females). Mean volume fraction of total ventricular volume to total brain volume was found to be 2.77% in males and 2.25% in females which was also significant. Both mean ventricular volume and volume fraction was found to increase with age.

Thus, we calculated a normal baseline data of total ventricular volume and volume fraction of total ventricle to total brain in adult population by stereological tools from simple CT scans.

Ethics statement: No ethical issue is declared.

Acknowledgements: No acknowledgement is present

Efficiency of Mindful Eating as an Intervention to improve Memory & Attention of Type 2 Diabetes Patients

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Mindfulness is a way of paying attention to present moment experience with open curiosity & a willingness to be with it. Mindful eating decreases dietary intake through awareness of food texture & taste. Mindful eating offers an effective approach to improve blood glucose control in type 2 diabetes patients. Plasma glucose levels have a direct effect on their memory & attention, with chances of developing deficits in memory reducing when blood glucose levels are maintained at a controlled level. Yet little research has been done to check the effect mindful eating has, when used as an intervention to improve plasma glucose levels,on a patient's memory & attention span.This study endeavours to use mindful eating as a potential intervention to halt the progression of memory deficits in patients with type 2 diabetes. Participants included patients aged 40 - 75 years with type 2 diabetes for one year or more.The participants were assigned for a 10 session course of mindful eating intervention.The follow-up took place 2 weeks post-intervention completion. Dietary intake,physical activity,weight & plasma glucose levels were measured prior to the study & cognitive functioning was measured using Stroop test (Attention), Sternberg Effect (Short Term Memory)& Memory Span Tests (Working Memory) from the CogLab2.0® software. Over the course of the intervention,due to the significant awareness in dietary intake,there was an observable change in the cognitive functioning of the participants. This was measured using the same tests as pre.

Ethics Statement: This project has been approved by the Institutional Ethics Committee.

Acknowledgements: We would like to thank Divya Sinha for her guidance & support.

Developmental Dyslexia, a Neurocognitive Disorder, and Smartphone-Based Intervention

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Developmental dyslexia is a highly prevalent neurocognitive difficulty that impairs the individual's ability to read, write, and spell, despite normal intelligence and adequate training. Although the causes underlying dyslexia are not fully understood, the condition is typically characterized by a dysfunction of the normal left hemisphere language network, and also abnormal white matter development. An emerging theory is that certain risk genes disrupt neuronal migration leading to an interchange of gray and white matter in parts of the brain. From a neuropsychological perspective, dyslexia is characterized by deficits in phonological awareness, visual attention, and rapid naming skills. Deficits in visual attention impair the individual's ability to recognize and to concentrate on individual letters in a word or a cluster of words. A smartphone may aid dyslexic readers, as the font size of the text can be altered to display only a few words in each line. In this work, we investigate the possibility of using smartphone-based reading in dyslexic intervention strategies. We compare the reading performance of dyslexic children when they read from printed text, a widely used tablet-based educational software (AmritaRITE), and a smartphone application specifically designed for these children. Our data collection methods include quantitative data from eye tracking experiments, standard tests for reading comprehension and reading speed, and questionnaires.

Acknowledgements: This work derives its inspiration and direction from the Chancellor of Amrita University, Sri Mata Amritanandamayi Devi.

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Therapeutic effect of Non-invasive Vagus Nerve stimulation in Gait disturbances and freezing in Parkinson's disease patients

Banashree Mondal

Freezing of gait (FOG) and other gait disturbances are common yet difficult to manage symptoms in Parkinson's disease(PD). In animal studies, electrical non-invasive vagus nerve stimulation (VNS) has been shown to modify cortical excitability via central cholinergic pathways; whether VNS has similar effects in humans is unknown.

1. Confirm that VNS increases cortical excitability by activating cholinergic pathways;

2. Complete an observationalopen-label pilot study to explore the effects of non-invasive VNSon gait pattern and FOG in PD patients.

Eleven PD patients with gait disturbance were recruited. VNS was applied to each of them for 15 minutes (2 standard doses). Pre- and post-VNS, Gait parameters were recorded using a GAITRite electronic walkway. Differences between gait parameters before and after VNS were $P<0.01$. The parameters of FOG were assessed by video recording of the gait of the patients by independent raters using a rating scale adopted from FOGQ.

In healthy controls VNS significantly increased SAI (paired t-test; $p<0.05$) and the non-specific muscarinic receptor antagonist scopolamine blocked thiseffect.

In patients there were statistically significant improvements in gait parameters including: velocity (52.164; Post 62.136; $p=0.012$); swing time (Pre 0.38; Post 0.055; $p=0.001$); and stride length(Pre 65.408; Post 74.624; $p=0.025$). Video analysis suggested objective improvements in start hesitation and FOG (walking and turning)after VNS.

Non-invasive VNS enhances cholinergic transmission in cortical networks and is a promising potential non-pharmacological therapeutic intervention with minimal side-effects for managing FOG in PD.

Intermuscular coherence of patients with writer's cramp

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Kolkata

Intermuscular coherence analysis is a simple and non-invasive electrophysiological test which has potential for clinical investigation. In addition, it might also indicate the origin of neural drive. Hence, we present our pilot study on the IMC pattern comparing writer's cramp patients with healthy volunteers.

Methods: Surface EMG was recorded from three forearm and hand muscles while the participants performed a repetitive pinch grip on a force transducer; the target force was set to 10% of maximum voluntary contraction. IMC between first dorsal interosseous and both flexor digitorum superficialis and extensor digitorum communis were calculated from the period of steady contraction.

Results: The average IMC plot for 10 healthy volunteers and 20 WC patients demonstrated a characteristically different pattern. A peak IMC was noted at 4- 7 Hz in WC patients in contrast to healthy volunteers who had negligible IMC in that band (mean 4-7 Hz coherences 0.013 for healthy and 0.067 for WC, significantly different, P= 0.009). A cumulative distribution plot comparing the two groups revealed that 4-7 Hz IMC above 0.03 (the largest IMC seen in healthy volunteers) was noted in 50% of WC patients.

Conclusion: We report, for the first time, a clear IMC at 4- 7 Hz in WC patients. This is strongly indicative of dystonia and dystonic tremor present in patients with WC. The similar coherence pattern in patients with and without writing tremor possibly indicates that they belong to the same spectrum of dystonia with a diverging clinical presentation.

Large-scale networks facilitate task-specific information processing of periodic auditory stimulus

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The entire spectrum of human abilities emerges from the communication between distributed neuronal assemblies. These neuronal assemblies operate coherently after getting stimulation by some intrinsic or extrinsic factor. In the real world we are bombarded with a range of acoustic stimuli having a number of frequencies. In the present study, subjects were presented with pure tones at a frequency of 40Hz. We were interested in the evoked cortical electrical activity in response to a periodic auditory stimuli and the presence of large-scale neuronal networks underlying such activity. Additionally, our aim is to see the variation in brain response from binaural stimulus to monaural stimulus. The responses were analyzed by measuring global coherence that provides a measure of the synchronized activity in the whole brain at a particular frequency range. At the lower frequency range (2-3 Hz) monaural tones exhibit higher global coherence comparative to binaural tone. At 10 Hz, all the stimuli, including baseline shows coherence peak at similar levels, indicating a common network that is active at this frequency. But at 40 Hz there were a sharp increase in differences between the coherence during rest and stimulation period. Furthermore, the cumulative global coherence was more in case of binaural tone compared to the monaural tone. These observations indicate that the increase in global coherence during presentation of periodic auditory stimuli compared to baseline reflects a task-specific activation of a large-scale neuronal network. We also observed global coherences in each hemisphere separately. There was relatively higher coherence during monaural left stimulus in left hemisphere compared to right hemisphere. Likewise, during monaural right stimulus coherence is higher in right hemisphere compared to left hemisphere. Thus, our results indicate the dominance of an ipsilateral network underlying processing of repetitive auditory stimuli.

Does the regulation of local excitation-inhibition balance aid in recovery of functional connectivity? A computational account

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Computational modeling of the spontaneous dynamics over the whole brain provides critical insight into the spatiotemporal organization of brain dynamics at multiple resolutions and their alteration to changes in brain structure (e.g. in diseased states, aging, across individuals). Recent experimental evidence further suggests that the adverse effect of lesions is visible on spontaneous dynamics characterized by changes in resting state functional connectivity and its graph theoretical properties (e.g. modularity). These changes originate from altered neural dynamics in individual brain areas that are otherwise poised towards a homeostatic equilibrium to maintain a stable excitatory and inhibitory activity. In this work, we employ a homeostatic inhibitory mechanism, balancing excitation and inhibition in the local brain areas of the entire cortex under neurological impairments like lesions to understand global functional recovery (across brain networks and individuals). Previous computational and empirical studies have demonstrated that the resting state functional connectivity varies primarily due to the location and specific topological characteristics of the lesion. We show that local homeostatic balance provides a functional recovery by re-establishing excitation-inhibition balance in all areas that are affected by lesion. We systematically compare the extent of recovery in the primary hub areas (e.g. default mode network (DMN), medial temporal lobe, medial prefrontal cortex). Our findings suggest that stability and richness similar to the normal brain dynamics at rest are achievable by re-establishment of balance. Currently, we are investigating how structural changes (compared to healthy subjects) observed in temporal and frontal lobe epilepsy patients effect the excitation-inhibition balance across the cortex.

Multi-scale representation of the cross-modal perception during McGurk illusion

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Visual cues from the face of the speaker influence the perception of speech. A prominent example of the influence is demonstrated by the McGurk effect. In this effect, an illusory (cross-modal) speech sound is perceived by the listeners when presented with incongruent audio-visual (AV) speech stimuli. In this combined psychophysical and electroencephalography study, we were interested in the neural representation of subjective perception of the McGurk effect at different scales. Therefore, we examined the markers of illusory perceptual processing in the event-related responses, spectro-temporal evolution of EEG signals and at the large scale network estimated by computing pairwise coherences underlying the cross-modal perception during synchronous and asynchronous AV speech. We show that a reduced ERP component at 120 ms followed by an enhanced peak at 300 ms post stimulus onset as a potential marker for cross-modal perception. At the spectral level, McGurk perception was marked by an overall decrease in power. At the level of large scale network, during synchronous speech stimuli, we demonstrate that an enhanced global coherence at gamma band facilitates McGurk effect. Besides, during asynchronous speech stimuli, an enhanced global broadband coherence marks cross-modal perception. Together, we report a multi-scale representation of task relevant activity in the temporal, spectral and at network level, capturing the complex neuronal mechanisms underlying multisensory speech perception.

Keywords: EEG, AV, multisensory, perception, coherence

Dual stream hypothesis of visual processing: model comparison and exploration of functional plasticity

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Introduction: Despite being one of the landmark theoretical approaches in cognitive neuroscience, *dual stream hypothesis* of visual information processing is still hotly debated. In the present functional MRI study, we critically assess different variations of dual stream hypothesis in a single experiment and explore the functional plasticity in ventral and dorsal visual stream areas both at the regional and network levels.

10 right-handed normal subjects (mean age 24years, 4 females) were scanned using 3T MRI scanner (TR=2 s TE= 35ms, flip angle =90°) while each of them was performing three pure visual perception tasks and three visually guided motor tasks. The fMRI scans were repeated after participants practiced similar tasks outside the scanner for half an hour each day for 7 days.

Behavioral data shows significant improvement in reaction time during all three visually guided motor tasks with practice, but no statistically significant change in the error rate in perceptual tasks was observed. The initial ROI-based analysis in SPM shows a shifting of cortical activity from ventral stream areas to dorsal stream areas in visually guided motor tasks with practice. Effective connectivity analysis between neural populations in primary visual cortex and multiple nodes in ventral and dorsal visual streams using Dynamic Causal Modelling is currently undergoing.

Initial ROI-based analysis support Goodale-Milner version of the hypothesis. In addition to the dual stream hypothesis, the findings are interpreted in light of other related theoretical approaches like Integrated model of visual processing and "magnocellular advantages".

Ethics statement: The study was carried out in strict accordance with the guidelines of Institutional Human Ethics Committee of National Brain Research Centre, India.

Acknowledgements: This work was supported by research grant No. SR/CSRI/PDF-13/2014 under Cognitive Science Research Initiative from Department of Science and Technology, India.

Comparative analysis of cortical sources underlying P300 component across multiple sensory modalities

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The P300 wave is associated with cognitive processes such as attention and memory. It is usually evoked by the oddball paradigm in which, a deviant stimuli is infrequently presented to the subject amidst repetitive stimuli. Its significance ranges from being a marker of neurological disorders to BCI applications. Various source localization techniques have been implemented over the years to localize the underlying neural generators of P300 wave suggesting involvement of frontal, temporal and parietal regions. However, due to usage of different paradigms and sensory modalities (e.g., visual, auditory, somatosensory) and corresponding parameters in respective studies, results have varied from one another.

In this study, electroencephalogram recordings (EEG) of 8 human volunteers of age between 20 and 30, were obtained using multiple combinations of sensory modalities i.e. Auditory, Visual and Audio-Visual. The Visual stimuli consist of two events, each corresponding to different shapes and colors, one of which was deviant and infrequent (14% of total events) and the other recurring. Analogously, Auditory consist of two separate tones of different frequency one of which is deviant and infrequent (14% of total events) and the other recurring. The stimuli were presented via Presentation software (Neurobehavioral Systems Inc.) and 64 channel EEG data was recorded at a sampling frequency of 1000 Hz. Additionally, a 3D coordinate system, Polhemus was used to estimate respective electrode positions in a comparable reference frame.

Preprocessing and analysis of the data was carried out to compare the amplitude and latency of Visual, Audio and Audio-Visual ERPs, especially the P300 component. Moreover, sources of the P300 peak were computed separately for each paradigm, by co-registration of the Polhemus data and the respective T1 MRI image.

We obtained similar latency of Audio and Visual P300 (358 ms), but a lower latency of Audio-Visual P300 (315 ms). The amplitudes of the Visual and Audio-Visual P300 were similar and were slightly lower than the Audio P300. Source localization using eLORETA indicated activity in the temporal, frontal and occipital regions. For Auditory and Visual stimuli, activity was seen in the temporal and occipital regions, respectively, along with the activity in the frontal region was seen to be

overlapping in both kinds of stimuli. This indicates that P300 may arise from a combination of sensory and cognitive components that may not be mutually exclusive. Nonetheless, more subjects are required for more accurate results. Future research includes source localization of other ERPs namely N100, P200 and P400.

Mean Diffusivity reveals microstructural anatomical differencesbetween bilinguals and monolinguals

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Diffusion Tensor Imaging (DTI) permits inferences about white matter microstructure in the brain. Research comparing bilingual and monolingual speakers has mainly focused on differences in mean diffusivity (MD) and fractional anisotropy (FA) withlessresearchcharacterising tract geometry. We compared the mean, radial and axial diffusivity of bilingual and monolingual speakers. Results from Tract Based Spatial Statistics (TBSS) show higher mean, radial and axial diffusivity in right superior longitudinal fasciculus (SLF) and forceps minor and lower fractional anisotropy in the bilingual group compared to monolinguals.We suggest increased isotropic diffusion of water molecules reflects greater rate of diffusion in the perpendicular and parallel directions in the right SLF for bilingual speakers that may reflect neuroplasticity associated to the extra cognitive demands linked to speaking more than one language.

Universal and Cultural Influences in Emotional Music Experience

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The emotional expressiveness of music is universal and arises from a combination of universal and culture-specific cues. While musical features like tonality and rhythmic regularity are music universals common to all tonal systems, cultures vary in the experience and use of emotion labels. Recently it was shown that *ragas* of North Indian Classical Music (NICM) elicit distinct emotional responses in enculturated participants and that musical features differentially modulate emotional response. *Ragas* are now globally popular musical stimuli, yet little is known about the emotional response elicited by *ragas* across cultures and the role of distinct musical features in modulating them.

The primary objectives of this study were to compare across cultures (a) emotional response labels to *ragas* and (b) to determine the roles of tonality and rhythmic regularity in determining the emotions experienced. A total of 255 participants, 143 enculturated and 112 non-enculturated provided responses to 'experienced emotions' to 12 NICM *ragas*. Analysis of behavioural responses showed universality in labels of experienced emotions except for 'longing' and association of rhythmic regularity with high arousal emotions. Distinct roles for tonality and rhythmic regularity were observed in experienced emotions such that non-enculturated participants' utilized tonality cues better in the presence of cue of rhythmic regularity. We also found that intensity of emotion ratings was significantly influenced by musical training, irrespective of culture. Our findings elucidate for the first time, similarities and differences across cultures in determining emotional music experience to *ragas*.

Acknowledgements: Funding for this work was provided by National Brain Research Centre, India.

Computational reconstruction of fMRI BOLD from cerebellar input layer

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Identifying the brain regions attributed to performing different sensory, motor and cognitive tasks has become an important domain in neuroscience research[1] . BOLD fMRI (blood oxygenation level dependent functional magnetic resonance imaging) is increasingly used to detect developmental changes in human brain function to estimate neural activity with respect to a specific task [2]. Increase in blood oxygen metabolism to the activated region of the brain is accompanied by increase in cerebral blood flow (CBF), cerebral blood volume (CBV) which leads to decrease of oxyhemoglobin content in blood vessels and increase in activated area [3] [4]. Brain responses in fMRI are implicitly suggesting some underlying dynamic system that converts neuronal responses into observed hemodynamic responses. In the pioneering work by Buxton 'Balloon model'[5] and Mandeville 'Windkessel model' [6] has proven the detailed biophysical models of the neurovascular coupling have been validated by physiological experiments. In this study, we modeled BOLD signals using different computational models, modified version of the Windkessel model by incorporating compliance and balloon model, to generate cerebellar granular layer and visual cortex blood oxygen-level dependent (BOLD) responses[7] . The correlation between neural activity and blood inflow changes through modified windkessel and balloon mathematical models collectively, highlight the importance of neurovascular coupling to the health of the normal brain and suggest a therapeutic target for improving brain function in pathologies associated with cerebellar dysfunction.

Acknowledgment: The work derives ideas and direction from the Chancellor of Amrita University, Sri Mata Amritanandamayi Devi. This work is partially supported by DST grants SR/CSRI/60/2013 and SR/CSRI/61/2014 and by Virtual Labs Phase II of MHRD, Government of India and by Embracing The World.

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Modeling and Parallelization of Cerebellar Microcircuit for Combinatorial Operations

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Cerebellum granular layer contains about 10^{10} neurons and 10^{13} synaptic connections. In order to effectively model granular layer connections, large scale network need to be reconstructed. We have developed detailed biophysical model and spiking network model to reconstruct neuronal dysfunctions and functions[1]. In this study we have parallelized a large cerebellar neuronal network using pleasantly parallel method. In the distributed mode, we have assigned global identifier (gid) for each cell to avoid connections in same assignment [2]. We have used excitatory and inhibitory synaptic mechanisms and tested both *invitro* and *invivo* like inputs under different plasticity conditions to understand learning in cerebellar circuit. Modeling the coding properties helps in understanding the granule cell activity organized in center-surround structures, implementing combinatorial operations on multiple mossy fiber inputs, controlling spike timing and burst transmission, intensity and duration of long-term synaptic plasticity at the mossy fiber-granule cell relay[3]. These properties are validated using this model. Although it depends on network size and nature of synaptic connections, we could see a significant reduction of computational cost in terms of power and time while simulating parallelized code. As a comparison study, we have simulated our model in both CPU and GPU and results indicated that GPGPUs showed 15X time efficiency than CPU version of the algorithm [4].

Acknowledgment: The work derives ideas and direction from the Chancellor of Amrita University, Sri Mata Amritanandamayi Devi. This work is partially supported by DST grants SR/CSRI/60/2013 and SR/CSRI/61/2014 and by Virtual Labs Phase II of MHRD, Government of India and by Embracing The World.

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Mathematical Modelling of Post Synaptic Evoked Local Field Potential Using Neural Mass Model

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Sensory processing in term of population activity and post synaptic responses in the cerebellum is crucial to understand movement related function. Neural population activity has been reconstructed from single neuron or microcircuit models to study brain activity and function [1], [2]. Population of neurons generate extracellular currents due to electrical activity, an electrode usually reads the activity as a signal which may be EEG or LFP depends on the vicinity (invasive or non-invasive) of that electrode. Previous studies have allowed reconstruction of local field potentials as an ensemble response[3]–[5]. Though they are some drawbacks with simplification of reality these models, however, the good mathematical model gives insight to basic underlying process that generates the brain activity. In order to understand activity from large scale perspective average behaviour from a predictive model to correlate circuit level activity during in-vitro and in-vivo conditions may provide insight for single neuron roles in circuit function[6]–[8].In this study we developed a neural mass models to correlate local field potentials in-vitro generate N2a, N2b waveforms and invivo are seen as Trigeminal and Cortical waveforms for sensory inputs. The model allowed to correlate circuit level activity without fine-grained perspectives of underlying neural circuitry and reconstruction of N2a , N2b and T ,C Waves as seen in experimental data [9], [10].

Acknowledgment: This work derives direction and ideas from the Chancellor of Amrita University, Sri Mata Amritanandamayi Devi. This work is funded by Grants SR/CSRI/60/2013, SR/CSRI/61/2014, Government of India and by Embracing the World

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Phosphorylation status of α-CaMKII and NMDAR subunit GluN2B upon brief and extended calcium stimulation

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Interaction of Ca^{2+}/calmodulin dependent protein kinase type II (CaMKII) and NMDA receptor subunit GluN2B is known to be important for formation of memory. Pharmacological blockade and mutation studies in GluN2B have shown its importance in synaptic plasticity and learning. It is known that short stimulation can lead to reversible binding (S-site binding) and longer stimulation leads to persistent binding (T-site binding) of α-CaMKII to GluN2B. High affinity binding of GluN2B to α-CaMKII at the synapses is thought to lead to persistent autonomous activity in the synaptic compartments. GluN2B binding to the T-site of α-CaMKII significantly modulates α-CaMKII catalysis. This has been reflected in the alterations in kinetic parameters of ATP for substrate phosphorylation and autophosphorylation**.** Using computational methods we have studied the phosphorylation of GluN2B and α-CaMKII during calcium stimulation of various doses and durations. We find that when GluN2B is included in the Ca^{2+}/calmodulin-CaMKII phosphorylation cascade, GluN2B bound states dominate among the phosphorylated states and account for much of the activity. To substantiate the above results, experiments are being conducted by giving brief and extended stimulation using calcium and the ionophore, ionomycin, to HEK cells in which α-CaMKII and GluN2B are transiently expressed followed by analysis of the phosphorylation status of GluN2B and α-CaMKII.

Acknowledgements: This work was supported by funding from Kerala State Council for Science, Technology and Environment and Rajiv Gandhi Centre for Biotechnology. Fellowship was received from Council of Scientific and Industrial Research, Govt. of India.

Endogenous neuro-plasticity mechanisms as therapy for Stoke: A Multi-disciplinary translational approach to drug selection and therapy optimization

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Stroke is a leading cause of worldwide mortality with annually 16 million new cases and 6 million deaths. The only FDA approved therapy, Tissue Plasminogen Activator has extremely limited scope because of the small permissible time window of administration of 3.5-4.5 hrs. Hence the seminal need of designing neuroregenerative therapies.

Systems biology tool GeneGo- MetaDrug was used which allows visualization and identification of interactive canonical pathways, capturing signaling networks and their interactions during pathology and subsequent activation during recovery. This results in histograms of p-value indices showcasing the molecules which could most effectively optimize pathways of recovery icluding endogenous neural stem cell activation from niches in sub-ventricular zone, their proliferation and migration to form synapses in the penumbra to reintegrate into existing synaptic network. These processes can be enhanced by growth factors such as IGF-1 and Statins. These were then modeled using differential equations incorporating the principles of Michaelis-Menten kinetics to optimize cell migration, and neurogenesis and synaptogenesis. Further, we validated the model by establishing the Middle Cerebral Arterial Occlusion model in rats on which Biochemical and MRI & Diffusion imaging were done to visualize the lesion and recovery.

We saw a neurogenesis peak of which 19% went on to form functional synapses under the effect of predicted drug doses within 3-4 weeks.

The study helps furnish and validates (i) drug dosage and interval of administration to optimize therapeutic performance, (ii) mechanism of recovery employing ipsilesional SVZ progenitor cells.

Biophysically realistic Neuronal models for audio-visual speech perception

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In an earlier study, we have observed the presence of large scale neuronal network in the brain underlying multisensory speech perception. Interestingly the communication across the network peaks at certain frequencies as observed by the measure of global coherence spectra. In this work, we capture the mechanism of generation of neuronal coherence using a computational model. First, we have analyzed a fully connected network of population of excitatory and inhibitory Hindmarsh-Rose neurons representing a node or a cortical brain area (eg. auditory cortex). The dynamics of this node can be broadly categorized into three types: stable oscillations with single frequency (unimodal), two frequencies (bimodal) and three frequencies (trimodal). Then, we coupled two such nodes (representing auditory and visual cortex) with a non-zero coupling to capture more complex dynamics. A simple way to extract meaningful information from these complex dynamics is to look at those frequencies in which the system is either in in-phase or anti-phase synchronization. This is achieved by observing the coherence spectra. Lastly, we connected three nodes representing auditory cortex, visual cortex and a multisensory area. This is a more realistic model for audio-visual speech perception in which the nodes representing auditory and visual cortex are connected to multisensory area but not to each other. Later, we plan to introduce time-delays in the systems with multiple nodes and observe the change in dynamics with respect to the change in time-delays.

Ethics Statement: All ethics were followed.

Aknowledgement: The study was supported by IPR and NBRC Core support staff and infrastructure. Ramalingaswami fellowship, DBT (BT/RLF/Re-entry/31/2011) and Innovative Young Bio-technologist Award (IYBA), DBT (BT/07/IYBA/2013) from the Department of Biotechnology (DBT), Ministry of Science and Technology Government of India to Arpan Banerjee(AB). AB also acknowledges the support of Centre of Excellence in Epilepsy and MEG (BT/01/COE/09/08/2011) from DBT.

Benzo[a]pyrene and 6-hydroxydopamine induced similar neurobehavioral responses during early adolescence period is associated with altered striatal monoamine neurotransmitters level in rats

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Exposure to persistent genotoxicants like benzo[a]pyrene (B[a]P) during postnatal days causes neurobehavioral changes in animal models. However, neurotoxic potential of B[a]P and 6-hydroxydopamine (6-OHDA) leading altered striatal monoamine neurotransmitters level need to be explored. The growth of rat brain peaks at first week of birth and continues up to one month with the attainment of adolescence. Hence, the present study was conducted on male Wistar rats at postnatal days 5 (PND5) following single intracisternal administration of B[a]P to compare with neurobehavioral and monoamine neurotransmitters changes induced by 6-OHDA at PND30. Neurobehavioral responses were measured by open field and elevated plus maze tests. Total distance travelled in novel open field arena and elevated plus maze was significantly increased following B[a]P and 6-OHDA administration. Spontaneous motor activity was significantly increased by 6-OHDA showing similar trend following B[a]P administration. Further study on monoamine neurotransmitters profiling showed that there was a significant alteration in striatal neurotransmitters level following B[a]P and 6-OHDA administration. Histopathological studies of striatum by hematoxylin and eosin (H&E) staining revealed the neurodegenerative potential of B[a]P and 6-OHDA. Our results indicating spontaneous motor hyperactivity in rats following 6-OHDA and B[a]P treatment is associated with altered striatal monoamine neurotransmitters level. In conclusion, early postnatal exposure to B[a]P in rats causing neurobehavioral changes may leads to serious neurodegenerative consequences during adolescence which might be associated with altered neurotransmitters level.

Ethical Statement: All protocols followed in the experiments were ratified by the ethics board of the institute (SOA University, Odisha, India) according to the guidelines of "Committee for the Purpose of Control and Supervision of Experiments on Animals" of Govt. of India. Utmost care was taken to decrease suffering of animals throughout the sampling and toxicants administration.

Acknowledgement: The authors acknowledged the financial support provided by Board of Research in Nuclear Sciences (BRNS), Department of Atomic Energy (DAE), Government of India (Sanctioned No: 37(1)/14/27/2015/BRNS). The authors also acknowledged the financial support provided by Science and Engineering Research Board (SERB), Department of Science and technology (DST), Government of India (Sanctioned No: PDF/2015/000573).

Effects of CB1 receptors in the ventral tegmental area on the potentiation of morphine rewarding properties

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The ventral tegmental area (VTA) is a critical part of the brain reward system and has been engaged in mediating rewarding actions. CB1 receptors mediate the effects of cannabinoid and endocannabinoid in the central nervous system. Our aim is to determine the potentiating effects of CB1 receptors within the VTA during the acquisition of morphine-induced conditioned place preference (CPP).

Stereotaxic surgery was performed bilaterally on each rat to administrate WIN55,212-2 (1, 2 and 4 mmol/0.3µl DMSO) as CB1 receptor agonist and AM251 (15, 45 and 90 mmol/0.3µl DMSO) as CB1 receptor antagonist. In all of groups the CPP paradigm was done and CPP score was determined for each rat.

The results showed that two doses of Win55,212-2 (2 and 4 mmol) potentiates the rewarding properties of ineffective dose of morphine (2 mg/kg). We did not see any significant difference between any other doses of Win55,212-2 and vehicle in the group which received the effective dose of morphine (5 mg/kg). Additionally, conditioning scores decreased significantly with the highest administrated dose of AM251 (90 mmol) compared to the vehicle group.

Administration of cannabinoid agonist and ineffective dose of morphine concurrently induced morphine-CPP. It seems that the cannabinoid and opioid systems are in interaction with each other and also the pre-synaptic CB1 receptors existing in GABAergic neurons affect dopaminergic and/or non-dopaminergic neurons in the VTA. Additionally, blockade of CB1 receptors may increase GABA release and result in a decrease of acquisition of morphine-CPP in the rats.

Effects of prenatal exposure to third generation antiepileptic drug, eslicarbazepine on neurochemical and neurobehavioral alterations in rat offspring

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Numerous antiepileptic drugs (AEDs) are available for the treatment of epilepsy. However, some classical AEDs are proficient with critical safety profiles, whereas atypical AEDs are also associated to different forms of side effects. Recently, pharmaceutical companies have developed 3rd generation AEDs with improved safety profiles than Ist and 2nd generation. The developmental neuronal safety and neurobehavioral disturbances in offspring of 3rd generation AEDs are unknown. Therefore, present study is an attempt to elucidate the effect of maternal exposure of eslicarbazepine acetate (ESL) on neurochemical as well as neurobehavioral changes in rat offspring.

As per experimental protocol, nulliparous sperm positive Charles-Foster rats were exposed to ESL orally through canula from gestation day 6-20. Records of daily food consumption and body weight gain were maintained throughout the experiments. About 50% of pregnant experimental rats were sacrificed on GD21 through intracardial perfusion; their brains were dissected out and homogenized for estimation of AChE. Remaining subjects were allowed to deliver naturally and their pups were weighed from PND 1 to 56. After PND56, young offspring were tested by a battery of behavioural tests based on paradigms of anxiety, cognition and depression. Our results revealed the substantial decreased pattern of AChE level in fetal brains of exposed groups; and their long-lasting impact of the drug on increased state of anxiety, cognitive impairment and depressive signs in young offspring. It concludes that prenatal use of ESL may induce neurochemical and neurobehavioral alterations in rat offspring, hence neural safety of this drug may be in question.

Ethics Statement: The animals were maintained with the permission of Institutional Animal Ethics Committee (IAEC); and used in accordance with the Animal Welfare Act and protocol for use of experimental rats.

Acknowledgements: Authors are thankful to Head, Department of Zoology, University of Allahabad, for providing laboratory facilities and University Grant Commission, New Delhi, India for financial assistance.

Gestational exposure to pregabalin: Effects on neurostructural, and neurochemical alterations in fetal brain, and its impact on cognitive impairment in rat offspring

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Epilepsy, in human population, is treated with antiepileptic drugs (AEDs). The neuroteratogenic safety of 1st and 2nd generation AEDs have been well documented, but neuroanatomical, neurochemical and neurobehavioural study of 3rd generation AEDs have not been explored so far extensively, if these drugs are administered during pregnancy. Therefore, present study has been undertaken to reveal whether in utero exposure to pregabalin (PGB) may induce developmental neurotoxicity in fetal brain and psychopathological changes in offspring.

Keeping these views in consideration, present study has been designed to evaluate the alterations in level of neurochemicals (AChE, Protein and RNA) due to prenatal exposure to pregabalin (PGB) in fetal brain and its effect on memory of offspring.

The pregnant Charles-Foster rats were exposed to equivalent therapeutic doses of PGB from gestation days 6-20. On day 21, about half of the dams were sacrificed by intracardial perfusion and fetus were collected; their brains were dissect out, and further processed for quantification of total AChE, Protein and RNA; and remaining dams were allowed to deliver naturally for cognitive assessment at postnatal day 56 using Morris water maze, and passive avoidance tests.

In utero PGB exposed rat offspring displayed significant alterations in fetal hippocampus, decreased level of total AChE, Protein and RNA; and its lasting impact on cognitive impairment in young rat offspring.

This study concluded that in utero exposure to pregabalin may induce neuropathological, neurochemical and neurobehavioural changes in fetal brain and young subjects, respectively, hence neural safety of novel AEDs be evaluated.

Ethics Statement: The animals were maintained with the permission of Institutional Animal Ethics Committee (IAEC); and used in accordance with the Animal Welfare Act and protocol for use of experimental rats.

Acknowledgements: Authors are thankful to Head, Department of Zoology, University of Allahabad, for providing laboratory facilities and University Grant Commission, New Delhi, India for financial assistance.

L-DOPA treatment potentiates psycho-motor behavioral abnormities in mice model of hepatic encephalopathy

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Hepatic Encephalopathy is a neuro-psychiatric condition arises due to acute or chronic liver failure. Motor behavioral abnormalities are also associated with HE. As 3,4-dihydroxyphenylalanine (L-DOPA) is one of the most prescribed drug to treat the motor complications of neurological disorders such as Parkinson's disease, we tested the effect of this drug in animal model of Hepatic Encephalopathy. Necrotic lesions and deficits in liver functional status were evident in thioacetamide administered mice, with neuropsychiatric complications. L-DOPA treatment in these animals potentiates the neuropsychiatric behavioral abnormalities without altering the liver functions. The results clearly demonstrate depressive like behavior in these animals after L-DOPA treatment. Moreover, an increase in inflammatory and oxidative stress markers were observed in brain of thioacetamide administered mice treated with L-DOPA. The present study suggests potential side-effects of L-DOPA treatment in patients with Hepatic Encephalopathy.

Ethics statement: Handlings of animals were carried out in strict accordance with the guidelines of Institutional Animal Ethics Committee of Assam University, Silchar, India.

Acknowledgements: We sincerely acknowledge the funding and support provided by Department of Biotechnology (DBT), Govt. of India (Sanction Order No. BT/230/NE/TBP/2011, dated April 23, 2012 and BT/PR6806/GBD/27/480/2012, dated August 5, 2013) and Department of Science and Technology (DST), Govt. of India (SERB/F/6636/2014-15 dated 29.12.2014).

Arsenic exposure induces apoptosis in hippocampal neurons and cognitive impairment in rats via BMP signaling pathway

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Arsenic induces apoptosis in the brain cells and impairs cognitive function. Nonetheless, whether arsenic affects neuronal apoptosis in the brain hippocampal region, that is mainly responsible for spatial memory, is less studied. In terms of mechanism, bone morphogenetic proteins (BMP) are expressed in the hippocampus. However, involvement of BMP signaling in the apoptosis of hippocampal neurons and subsequent cognitive impairments remain unexplored. We treated rats with an environmentally relevant dose of arsenic, and detected decreased Y-maze scores, indicating a loss in cognitive performances. Further, increased Terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL)-reactivity in the NeuN cells of hippocampus proved As-induced neuronal apoptosis. Enhanced cleaved Poly ADP-ribose polymerase (c-PARP) and c-caspase-3 levels, detected through Western blotting (WB) and Immunoflourescence(IF), corroborated the increased neuronal apoptosis. Exploring the mechanism revealed that arsenic augmented the BMP2 and BMP receptor 2 (BMPR2) and its downstream, p-Smad1/5, in the hippocampal neurons. Interestingly, these BMP signaling molecules co-expressed with the TUNEL-positive neurons, suggesting a link between BMP pathway and arsenic-induced neuronal apoptosis. To understand whether BMP signaling truly participated in the apoptosis, we co-treated arsenic-exposed rats with BMP antagonist, noggin. We detected that noggin not only decreased the arsenic-induced TUNEL-positive neurons, but also restored cognitive Y-maze score. Overall, our results for the first time identified the involvement of BMP signaling in arsenic-induced hippocampal neuronal loss, culminating in memory impairment. On the whole, our study appears important in enlightening a neurodegenerative role of BMP pathway that may be targeted for treating cognitive dysfunction.

Ethics statement: Experimental animals were handled and maintained according to the strict guidelines of the Institutional Animal Ethics Committee of Indian Institute of Toxicology Research(CSIR-IITR), India.

Acknowledgements: This work was supported by University Grant Commission(GAP-155) and Science and Engineering Research Board-Department of Science and Technology(GAP-278) India.

Role of astrocytic MeCP2 in the regulation of central nervous system myelination

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Astrocytes are one of the most abundant and essential glial cells in central nervous system in terms of regulating neuronal homeostasis, differentiation and myelination. Recently studies emphasizing on the role of astrocytes in regulating myelination by secreting pro-myelinating factors like growth factors, neurotrophins and ECM proteins has been investigated by many researchers. Methyl-CpG-Binding Protein 2 (MeCP2), an epigenetic protein, binds to CpG islands in the genome and induces multiple gene regulatory functions by conforming changes in the chromatin structure. MeCP2 deficient astrocytes have been linked with abnormal neuronal functions like decreased dendritic arborisation and decreased dendritic outgrowth. However its influence on myelination is still unclear. The present study thus mainly focuses on the ability of astrocytic MeCP2 to support myelination. Transcript expression studies of myelin genes was studied over time in co-cultures of dorsal root ganglion neurons and oligodendrocytes, wherein these dissociated cells were plated on a monolayer of normal and MeCP2 siRNA transfected astrocytes. Influence of MeCP2 on astrocyte secreted neurotrophins (BDNF and NGF), known pro-myelinating factors, was studied using ELISA. We also studied the effect of astrocytic MeCP2 on survival of the oligodendrocytes by MTT assay. Our preliminary results indicate involvement of astrocytic MeCP2 in the regulation of myelination by altering the transcript levels of myelin proteins [MBP and MAG] along with regulating the levels of pro-myelinating neurotrophins and by influencing survival of oligodendrocytes.

Ethics Statement: All the protocols were duly approved by the institutional ethical committee, Animal House facility, Department of Biochemistry, The Maharaja Sayajirao University of Baroda, Reference No. ZD/13/2014.

Acknowledgements: This work was supported by research grant No. BT/PR4974/MED/30/773/2012 from Department of Biotechnology, India and Instrument facility: Confocal microscopy and Real time PCR from DBT-MSUB ILSPARE, The M.S.University of Baroda.

Stereological investigation of morphometric parameters of developing Cochlear Nucleus by Nissl and Neu-N staining

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This study aims to provide quantitative data of morphometric parameters of the developing human cochlear nucleus and to compare the results of conventional Nissl staining with NeuN immunostaining (marker for developing neuron). After obtaining ethical clearance and due consent, five fetal brains (18-25 weeks) were collected from the department of Obstetrics and Gynecology at All India Institute of Medical Sciences, New Delhi. Their brainstem was dissected, fixed in 4% buffered paraformaldehyde (0.1M phosphate buffer, pH 7.4), cryopreserved in 30% sucrose and serially sectioned (40µm). Using systematic random sampling and different starting section number, every 5th section was stained with CV and NeuN (ab177487, 1:1000) separately, using standard protocol. These sections were used independently to estimate the total volume of CN (Cavalieri), total number of neurons (Optical Fractionator), and neuronal volume (Nucleator), with StereoInvestigator software (Microbrightfield Inc. VT, US). The total mean volume of CN estimated was 7.1±1.57 x 108 µm3. The estimated total number of neurons stained by CV were18,741; 26,200; 30,487; 30,902; 34,103 in 18, 20, 22, 23, 25 weeks, respectively. The count by NeuN immunostaining were 30,694; 31,823; 37,546; 44,345; 42,495 in the same ages, respectively. The mean volume of neurons and its nucleus was 181.63 um3± 603.94 and 190.97 um3± 73.61, respectively. Estimates of neuronal count with NeuN are higher because it is an early marker of neuronal differentiation, hence can identify a neuron even before they can be identified morphologically.

Acknowledgements: Indian council of Medical Research (BMS/FW/CMP/2014-23710/Oct-14/DL/govt All India Institute of Medical Science, New Delhi.

Stereological Estimate of number of Neurons expressing GABA and NMDA-2B Receptor in Human Spiral Ganglion

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Excessive noise may act on the neurons of the spiral ganglion (SG) of cochlea through neurotransmitters that sometimes become neurotoxic. The loss of SG neurons is the commonest cause of neural presbycusis, which is the progressive deterioration of hearing associated with aging. The commonest inhibitory and excitatory neurotransmitters in the SG, involved in the transmission of sound, are GABA and Glutamate. The present study aims to provide estimates of the number of GABA and NMDAR-2B (receptor of glutamate) positive neurons in the SG in the age groups 21-30 (G1), 31-40 (G2) and 61-70 (G3) years. Human temporal bones of these groups were obtained from the mortuary at All India Institute of Medical Sciences, New Delhi, with approval from Institute's Human Ethics Committee. The temporal bones containing the SG were dissected, fixed, decalcified, cryoprotected and serially sectioned. The sections were immunostained with GABA (1:2000) and NMDAR-2B (1:2000). Every seventh section was used for unbiased estimation of the total number of neurons with StereoInvestigator software. The estimated total number of inhibitory SGNs in G1, G2 and G3 was 25643, 27153 and 11202 respectively. The NMDAR-2B positive SGNs in G1, G2 and G3 was 24940, 26217 and 12040 respectively. The number of GABAergic and NMDAR 2B neurons was significantly lower in G3 ($p < 0.05$) respectively. We conclude that the number of GABAergic and NMDAR 2B positive neurons falls significantly with age, thus producing an imbalance of neurotransmission with aging. This may lead to neuronal loss that manifests as neural presbycusis.

Acknowledgement: This work was supported by the Indian Council of Medical Research (Senior Research Fellowship to Charanjeet Kaur, 45/19/2012-Ana/BMS) and All India Institute of Medical Sciences, New Delhi (Institutional Research grant no. - 218/A-218/2013/RS)

Role of NR2C/2D Receptor Interaction within Mediodorsal Thalamus in Memory Acquisition

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Mediodorsal (MD) thalamus has been implicated in the pathophysiology of cognitive symptoms of Schizophrenia (SZ). Significant NR2C transcript reductions have been found in dorsomedial and anterior thalamic nuclei (ATN) in SZ. Earlier, we have established the antipsychotic-like profile of CIQ (NR2C/2D potentiator). Present study investigates the interaction of GluN2C/2D subunit within MD thalamus with beneficial effects of CIQ on cognitive symptoms using adult male Swiss albino mice (25-30g). We have studied MK-801 (non-competitive NMDA antagonist; 0.025, 0.05, 0.075, 0.15 mg/kg, i.p.) induced alterations of cognitive symptoms in Y-maze task. Separately, CIQ (5 µg, 10 µg and 20 µg/side, iMD) was injected 15 min after MK-801 (0.15 mg/kg, i.p.) and memory acquisition in NOR, Y-maze and passive avoidance (PA) tests was observed. We found that CIQ attenuated the MK-801 induced deficits. To confirm the role of NR2C/2D receptors, DQP-1105 (non-competitive NMDA antagonist; 5, 10µg/side, iMD) was administered 15min before CIQ (iMD) and memory acquisition was observed in all the above tests. Yet again, CIQ reversed these effects significantly except for working memory, since DQP itself didn't show any effect. Recognition memory was assessed by NOR, working memory by Y-maze and learning memory by PA test. Thus, we found that CIQ (iMD) significantly reversed the alterations induced by MK-801 and deficits induced by DQP-1105 in all three tasks for memory acquisition. The present study revealed that CIQ has the potential to decrease the deficits in memory acquisition in cognitive disorders and this effect probably involves the GluN2C/2D receptors interactions within MD.

Ethics statement: Handling of mice was approved by Institutional Animal Ethics Committee and carried out under strict compliance with Committee for the Purpose of Control and Supervision of Experiments on Animals, Ministry of Environment and Forests, Government of India, New Delhi, India.

Acknowledgements: We would like to thank Dr. Shashank Dravid, Creighton University, Omaha, NE 68178 for the gift sample of CIQ.

Expression of selective neurotransmitters and neuropeptides in the spinal cord of morphine tolerant rats

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Opioids like morphine are used for the treatment of moderate to severe pain. However, chronic use of morphine produces tolerance which limits its use. As yet, the mechanism of tolerance is unknown. It was hypothesized that many of the neurotransmitters and neuropeptides, involved in the transmission or modulation of pain, could also be responsible for the development of tolerance to morphine. Some of these are neuropeptide Y (NPY), Gamma-Aminobutyric acid (GABA), nitric oxide (NO) and endocannabinoids (CB). The aim was to evaluate the expression of these in the spinal cord of morphine tolerant rats.

Sprague Dawley rats (N=24), each implanted with an intrathecal catheter, were equally divided into control and morphine-treated groups. Morphine (10µg twice daily) was administered intrathecally by the catheter for 9 days. The control group received saline. Antinociception was tested by the hot-plate apparatus, once a day. Behavioural testing for tolerance was followed by immunohistochemical localization of these neurotransmitters/neuropeptides at the end of the week.

Repeated intrathecal administration of morphine produced tolerance compared to the control group. The antinociceptive effect was found to decrease from day 4 onwards. Immunohistochemical localization showed decreased expression of NPY, GABA and CB receptors in the morphine tolerant group whereas there was an increase in the expression of inducible NOS in Rexed's laminae I-II of the dorsal horn.

The results reveal that the selected neurotransmitters/neuropeptides could play a role in the development of tolerance. Further studies are ongoing with escalating dose of morphine for elucidate the mechanism of tolerance.

Neurochemical profiles and neuronal morphology across ages in female animal model of childhood depression

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There exists a gender bias in the establishment of animal models for neurological disorders with very few studies in adolescents. Females are highly vulnerable to develop stress-related affective disorders. Rapid structural, molecular and neurochemical changes, particularly those involving various monoaminergic pathways underlie brain development during adolescence. Understanding these pathways in female animal models is necessary to identify the development trajectory and time window for better clinical interventions. The Wistar-Kyoto (WKY) rat has been established as an animal model for childhood depression. The current study was aimed at detecting changes in neuronal morphology and neurochemical profiles in female WKY and age-matched Wistars. A forced swim test to measure behavioural helplessness was carried out on postnatal days (P) 30, 40, 60 and 90, rats were then sacrificed and candidate brain areas microdissected to assay monoamines using HPLC. Formalin-perfused brains were processed for neuro-morphological measures with modified Golgi method followed by Sholl analysis. Reduced levels of norepinephrine, dopamine and serotonin were observed in striatum of WKY rats during P30. Hippocampus exhibited decreased levels of dopamine, whereas medial prefrontal cortex showed increased concentration of metabolite homovanillic acid. Similar differences were not observed in other age groups. Morphological variations in neurons were also observed in implicated brain areas in WKY across ages. The results establish the key role played by dopamine in regulating formation of appropriate synaptic connections in plastic brain areas and underline that the high vulnerability to pathological insults induced either genetically or environmentally that exists during adolescence is propelled by neurochemical changes.

Ethics Statement: This study was performed in strict accordance with the recommendations for the use of animals in experiments as laid down by the CPCSEA, Govt. of India and approved by the Institutional Animal Ethics Committee.

Acknowledgements: University Grants Commission, New Delhi, Grant No. 41-545/2012 (SR)

Calcium influx in cultured cerebellar granule neurons induces expression of α-CaMKII

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Ca2+/calmodulin dependent protein kinase type II (CaMKII) mediates glutamate signaling underlying learning and memory. CaMKII is composed of different subunits such as □, □, □ and □□□□Specific brain regions have enzyme isoforms with different ratios of subunits. It is known that cerebellar granule neurons (CGN) which form a major type of neurons in cerebellum contain □-CaMKII and lack □-CaMKII. Previous work done in our laboratory has shown that, CGNs express □-CaMKII that is induced by KCl in the medium (Unpublished observation). It is known that KCl induced depolarization and consequent activation of voltage-gated calcium channels (VGCC) are important for CGN survival. The present work involves investigation of the role of VGCC activation in the expression of □-CaMKII in cultured CGNs. We used inhibitors and activators of VGCC to investigate the role of VGCC in the expression of □-CaMKII. Our results suggest that KCl induced expression of □-CaMKII is mediated through VGCC.

Ethics statement: Animal research was carried out as per the guidelines of Institutional Animal Ethical Committee(IAEC), of Rajiv Gandhi Centre for Biotechnology, Thiruvananthapuram, Kerala, India.

Acknowledgements: This work was supported by intramural funding from Rajiv Gandhi Centre for Biotechnology, Thiruvananthapuram, Kerala. Fellowships were received from Council of Scientific and Industrial Research, Govt. of India.

Nalbuphine could decrease the Rewarding Effects Induced by Morphine in Rats

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Nalbuphine, a κ-opiate agonist and μ-opiate partial antagonist, stimulates κ- receptors and antagonizes the acute reinforcing/rewarding effects of morphine, has been widely used as an analgesic or an adjuvant with morphine. The aim of the present study was to compare the acute and chronic effects of nalbuphine in morphine dependent rats. Male adult Wistar albino rats (170-175gms, N=160) were made physically dependent by administrating increasing dose of morphine. Nalbuphine was co-administered acutely and chronically in variable doses (0.1, 0.3, 1.0, 3.0 mg/kg, i.p.) with morphine and saline in experimental and control groups respectively. The blood was drawn from the heart for Plasma corticosterone levels. Brains were dissected out and were snap-frozen in liquid nitrogen for c-AMP levels and molecular work. The opiate dependent rats showed a significant increase in motor activity, Gellerts-Holtzman rating scale, plasma corticosterone levels and tissue C-amp levels whereas significant decrease was observed in protein and m-RNA expressions of tyrosine hydroxylase (TH) and tryptophan hydroxylase (TPH). Combination of acute dose of nalbuphine and morphine showed no effect at all doses on these parameters in morphine dependent rats. Moreover, chronic co-administration of nalbuphine resulted in significant decrease in naloxone precipitated morphine withdrawal and up-regulation of protein and m-RNA expressions of TH and TPH. These findings suggest that monoaminergic changes play a role in the behavioral expression of opiate withdrawal. The findings further supports that co-administration of nalbuphine with morphine may constitute a preferable superior approach to the treatment of opiate addiction.

Ethics Statement: Institutional Animal Ethics No. 608/IAEC/11

Acknowledgement: Supported by research grant No. 58/24/2011-BMS, Indian Council of Medical Research, Govt. of India, New Delhi and Rusan Pharma Limited for gifting Nalbuphine Drug.

Identifying mechanisms involved in guiding retinal ganglion cell axons to brain visual centers during retinal development

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Glaucoma is one of the leading causes of blindness affecting 60 million people worldwide, with a projected increase of 80 million by 2020. It is a chronic neuro-degenerative disorder characterized by the progressive, permanent visual loss resulting from the degeneration of retinal ganglion cells (RGCs). RGC's, are the sole output neurons which carry visual information from the retina to the brain visual centers. We have shown that embryonic stem cell derived neural progenitors (ES-NP's) can be transplanted into the retina to replace the degenerated RGCs. Our results have shown integration of the transplanted cells into the host retina but there was no evidence which demonstrated that the transplanted cells can extend their axons into the brain visual centers. This is as expected in the adult retina since the adult retinal environment lacks any axonal guidance factors/molecules to guide the nascent axon originating from the transplanted cells. Therefore, to overcome this issue we need to understand the process of axonal guidance during early development. Here, using microarray and other techniques we have identified a group of genes involved in intra-retinal axonal guidance. The identified genes were grouped into different classes consisting of Robo-slits, ephrins and semaphorins. Our results show that these genes are differentially regulated during different stages of early retinal development. Further characterization and regulation of the molecules involved in axonal guidance could possibly help in guiding the transplanted RGCs axons to brain visual centers.

Ethics Statement: All animal experiments were approved by the Institutional Animal Ethics Committee (IAEC) of Rajiv Gandhi Center for Biotechnology and carried out as per CPCSEA guidelines.

Acknowledgement: This work was supported by intramural funding from RGCB and INSPIRE fellowship from DST, Govt. of India.

Involvement of alpha-melanocyte stimulating hormone (α-MSH) containing brain nuclei in reward and reinforcement in rats

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Although earlier studies have showed the involvement of α-melanocyte stimulating hormone (α-MSH) in rewarding behavior, but the underlying mechanism is not understood. Herein, we test the modulation of α-MSH in different rewarding brain nuclei like nucleus accumbens (Acb), arcuate nucleus (ARC) and ventral tegmental area (VTA) by intracranial self stimulation (ICSS) paradigm. The cannula implantation with stimulating electrode was targeted at medial forebrain bundle (MFB), Acb and VTA in rats. After the recovery period rats were trained for ICSS conditioning in an operant chamber. Number of lever pressings was assessed for this behavior. Brains of naïve and trained rats were isolated and processed for the immunohistochemical analysis. We found that there is significant increase in the α-MSH immunoreactivity in AcbSh after intra-pVTA stimulation whereas, no significant difference was observed in ARC compared to control rats. Another cohort of animals in which electrode placed in the AcbSh, showed significant increase in α-MSH immunoreactive cells in ARC, as well as fibers in the AcbSh. In the third set of animals, wherein electrode placed in the LH-MFB, noticed significant increase in α-MSH immunoreactive fibers in AcbSh, while no changes were found in ARC after intra-MFB stimulation as compared to control rats. Whereas consistent with the previous findings, no change was observed in the α-MSH immunoreactive fibers after MFB, VTA and Acb stimulation. It appears promising for development of new treatment strategies that target the MC4R or the α-MSH system for the treatment of addiction.

Differential mode of Hes-1 activation is required for maintenance of neural stem cells and its transition into radial glial cells in developing neocortex

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In neural progenitors, Hes-1 expression is primarily activated by Notch signaling pathway transduced through cell-cell interaction. Despite the canonical activation of Notch-dependent Hes-1 (NDHes-1) in developing neocortex, recent advances have laid considerable emphasis on Notch-independent Hes-1 (NIHes-1) expression with poor understanding of its existence and functional significance. Using in utero electroporation with reporter systems we have clearly demonstrated that in developing neo-cortex, NIHes-1 expression is restricted to neural stem cells and NDHes-1 expression is found in neural progenitors/radial glial cells. Though Hes-1 expression is maintained in neural progenitors, a transition from Notch-independent to dependent state makes it pleotropic as the former maintains the neural stem cells in a non-dividing/slow dividing state, whereas the latter is very much required for maintenance and proliferation of radial glial cells. It is interesting to note that in both NIHes-1 and NDHes-1 expressing states the Hes-1 protein is the same. It is only the mode of Hes-1 activation that differs in the neural stem cells and neural progenitors/radial glial cells. Therefore, to understand the reason behind this differential activation of Hes-1, it is important to look into the changes in the niche/micro-environment of NIHes-1 expressing neural stem cells and NDHes-1 expressing neural progenitors in the developing neo-cortex. The possible reason for the observed transition from NIHes-1 to NDHes-1 expression state could be due to differential expression of Notch ligand Dll1 and Notch receptors on NIHes-1 and NDHes-1 expressing neural progenitors during early neocortical development.

Ethics Statement: All animal experiments were approved by the Institutional Animal Ethics Committee (IAEC) of Rajiv Gandhi Center for Biotechnology and carried out as per CPCSEA guidelines.

Acknowledgement: This work was supported by intramural funding from RGCB and extramural grants from DBT, Govt. of India and research fellowships from CSIR, Govt. of India.

Carvedilol and Labetalol Exhibits Significant Anticonvulsant Properties in Ptz and Mes Induced Seizure Model Tests in Experimental Laboratory Animals

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Epilepsy is a central nervous system disorder with predisposition for development of repetitive seizures. The incidence of epilepsy varies from 0.3 -0.5% among different population around worldwide. There are numerous classes of drugs with different mechanism of action are available for the management of this condition. The available current drugs can completely control the seizures in only 50% of epileptic individuals and in another 25% with significant improvement. It has been postulated that, oxidative stress and neuroinflammation being the other important pathological mechanisms for predisposition of seizures in epileptic patients. Being some of the beta blockers possessing antioxidant and anti-inflammatory properties, hence it has been hypothesized that beta blockers possess significant anticonvulsant properties in animal models. This warrants the further more research and understanding about the pathogenesis of this disorder for better pharmacotherapy in future.

To evaluate the anticonvulsant activity of carvedilol and labetalol in PTZ and MES induced seizure model tests in Wistar albino rats

This study was conducted on adult healthy Wistar albino rats of either sex, weighing between 180 -250 g. The study protocol was approved by the Institutional Research Committee [IRC] and Institutional Animal Ethics Committee [IAEC]. All the standard guidelines as per the Committee for the Purpose of Control and Supervision of Experiments on Animals [CPCSEA] were strictly adhered while conducting this study.

This study included total 8 groups, with 6 animals in each group [n=48]. Group-I: Control for PTZ, Group-II: Standard for PTZ [Sodium valproate 150 mg/Kg BW i.p], Group-III: Carvedilol for PTZ [5 mg/kg BW i.p], Group-IV: Labetalol for PTZ [220 mg/kg BW i.p], Group-V: Control for MES, Group-VI: Standard for MES [Diphenylhydantoin 25 mg/Kg BW i.p], Group-VII: Carvedilol for MES [5 mg/kg BW i.p] and Group-VIII: Labetalol for MES [220 mg/kg BW i.p]. The data was analysed by using one way ANOVA with Bonferroni Post hoc test. P value of less than 0.05 was considered as statistically significant.

The sodium valproate [Standard drug] in Group II and experimental test drugs [carvedilol and labetalol] in Group III and IV respectively, produced

statistical significant decline in onset [2001±51.41, 1827.2±57.24], duration [18.17±2.73, 42.50±3.32] and number of seizures when compared to the control group [Group-I] in PTZ model. The diphenylhydantoin [Standard drug] in Group VI and experimental test drugs [[carvedilol and labetalol] in Group VII and VIII respectively, also produced statistical significant decline in THLE and scores of seizures when compared to the control group [Group-V] in MES model.

Carvedilol and labetalol has significant anticonvulsant activity in PTZ and MES induced seizure model tests in Wistar albino rats

Key Words: Carvedilol, Labetalol, MES, Pentylenetetrazole, PTZ, Epilepsy, Convulsions

Evaluation of Antiepileptic Activity of Fluoxetine & Citalopram in Pentylenetetrazole and Maximal Electroshock Seizure Models in Wistar Albino Rats

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The term epilepsy "describes a condition in which a person has recurrent seizures due to a chronic, underlying process" and the incidence is around 0.3-0.5% and prevalence is 5-10 persons per 1000 among world population. The present antiepileptic drugs have certain limitations due to their toxicity profile, drug-drug interactions and resistance in some patients. Many studies have proved that, there is direct link between the oxidative stress levels in the brain and occurrence of seizures in epileptic disorder. The commonly used antidepressant drugs like Selective Serotonin Reuptake Inhibitors [SSRIs] had been shown to exhibit their antioxidant properties in preclinical as well as clinical settings. Hence it has been planned to evaluate the antiepileptic properties of fluoxetine and citalopram in various experimental animal models for further better pharmacotherapy of epilepsy in near future.

To evaluate the antiepileptic activity of fluoxetine and citalopram in pentylenetetrazole and maximal electroshock seizure models in Wistar albino rats

Wistar albino rats [n=48] were randomly assigned to 8 groups with 6 animals in each group. All the experimental laboratory animals were procured, 1 week before from the Institutional Central animal house and were housed in the departmental preclinical research laboratory for acclimatization. The animals were kept overnight fast before the experiment except water ad libitum. All the experiments were carried in day time, with adhering to CPCSEA guidelines. The study approval was obtained from the Institutional Review Board [IRB].

The groups of study were Group-I: Control for PTZ, Group-II: Standard for PTZ [Sodium valproate 150 mg/Kg BW i.p], Group-III: Fluoxetine for PTZ [5.5 mg/kg BW i.p], Group-IV: Citalopram for PTZ [5.5 mg/kg BW i.p], Group-V: Control for MES, Group-VI: Standard for MES [Diphenylhydantoin 25 mg/Kg BW i.p], Group-VII: Fluoxetine for MES [5.5 mg/kg BW i.p] and Group-VIII: Citalopram for MES [5.5 mg/kg BW i.p]. GraphPad Instat 3.0 version was used to analyze the study data.

Both the test drugs fluoxetine and citalopram significantly reduced the onset, duration and number of seizures when compared to the control group in Pentylenetetrazole [PTZ] model. It was also observed that, the

findings were comparable to the standard drug in Group II. Similarly in Maximal Electroshock Seizure [MES] model, there was statistically significant decrease in scores of seizures and Tonic Hind Limb Extension [THLE] in both the experimental test drug groups [Group VII and VIII] when compared to the control group for MES model. The Findings of fluoxetine and citalopram in MES model test were also comparable to their parent standard group.

Fluoxetine and citalopram exhibits significant antiepileptic activity in pentylenetetrazole and maximal electroshock seizure models in Wistar albino rats

Key Words: Fluoxetine, Citalopram, MES, Maximal Electroshock Seizure, Pentylenetetrazole, PTZ, Epilepsy, Convulsions

Regulation of neuronal microtubule cytoskeleton

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Microtubules are dynamic polymers that are critical for physical transformations that cells undergo in order to divide, develop and generate motility. Neuronal microtubules are unusual in that they are generated and stabilized without the influence of centrosome, during development and regeneration. Stabilization of microtubules is limiting in neuronal polarization. Loss of kinesin-13 family microtubule destabilizing factor klp-7 (kinesin-like protein) leads to excess stabilization of microtubules leading to a multipolar neuronal phenotype in C. elegans mechanosensory and other neurons. This neuronal phenotype in klp-7(0) can be reversed when they are reared in plates containing a microtubule-destabilizing drug Colchicine. We hypothesized that a genetic screen for the suppressors for klp-7(0) mutant will help us identify regulators of microtubule cystoskeletonWe conducted a genetic screen covering 70% of the mutagenized genome and isolated 7 suppressors. By combining meiotic recombination and whole genome sequencing, we have identified candidates such as tubulin genes, post-translation modification factors and other novel factors.

We have characterized the effects of these mutants in neuronal development and maintenance. We are testing the roles of the novel players by imaging the plus and minus ends of microtubules in neuron. We will present a genetic pathway regulating microtubule dynamics in neuron. Understanding the fine regulation of microtubule dynamics will help design therapeutic strategy in neurodegenerative disorders and axon regeneration.

Effect of noradrenaline on dynamic properties of neurons in primary culture

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Rapid eye movement sleep (REMS) is a unique psycho-cognitive-physiological state so far identified in species higher in evolution including humans. Among many functions REMS has been shown to affect memory and brain excitability, while its loss induces neuronal cytomorphometric changes, apoptosis and neurodegeneration. It has been proposed from this lab that "REMS maintains house-keeping function of the brain" and the effects are mediated by elevated level of noradrenaline (NA) in the brain. Neuronal connections and synaptogenesis are among the major contributors for hard wiring of the brain and thus, contribute significantly in memory formation. Therefore, we were interested in evaluating the effects of NA on neuronal plasticity in primary culture of neurons. Objective: How NA affects neuronal plastic properties particularly during early development.

We first developed/established a method forin vitro long-term (months) primary culture of neurons extracted from the developing brain of 7-9D chick embryo hatched in the lab under control conditions. Parameters of dynamic stability/instability like numbers, growth, pause and retraction of the neurite (axons) were estimated using time-lapse camera connected to a live-cell culture imaging microscopic incubator-fitted set-up. A large number (>10 under every condition from 3-sets of replicates) of dynamic events were randomlycollected under control (with serum and serum free medium) and NA treated conditions were stored in a computer, meticulously traced manually and analyzed statistically using dedicated Axiovision software. Pre- and post-synaptic structures, growth cones and neurotransmitter vesicles were characterized immunocytochemically as well as by transfection to evaluate the dynamic properties.

Statistical analysis: Statistical difference between the values of controls and test groups were evaluated using ANOVA followed by Holm-Sidak test using Sigma Stat software (Jandel Scientific, USA); at least $p < 0.05$ was considered significant.

Lower dose (0.1, 1 and 10 µM) of NA increased neurite growth,pause events of neurites but decreased m-calpain expression; while at higher dose (50 and 100 µM) it showed opposite effects. As calpain is involved in cleavage of variouscytoskeletal proteins, it might play an important role in NA induced neural growth.

Our findings suggest that NA modulates the dynamic properties of

neurons and its optimum level is critical for circuit formation (synaptogenesis).

Acknowledgement: Fellowship to A.K. from CSIR and DBT-BUILDER program is acknowledged. Research funds were made available from DBT-BUILDER; UGC-Networking; DST-PURSE; UGC project and J.C.Bose Fellowship to BNM.

Presence of Pseudobranchial neurosecretory system in a hill-stream fish

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Pseudobranchial neurosecretory system is the third system of neurosecretion found to be present uniformly in all catfishes, and a few groups of teleosts. It falls under the category of paraneuronal "Diffused NE systems" which recently has become a pioneering field in vertebrate physiology. This system has been thoroughly studied in about 25 sp. of teleosts belonging to both fresh as well as marine waters of India. However, no report is available for hill-stream fishes, so far. This system is found in close association of carotid labyrinth, in catfishes.

Recent investigation undertaken on Schizothorax richardsoni revealed the presence of a full-fledged pseudobranchial neurosecretory system in a hill-stream carp, in close association of Pseudobranch- a structure from which the carotid labyrinth is thought to be derived. This is the first report of occurrence of this system in a carp which is discussed.

Scanning electron microscopic investigation has also been undertaken to elucidate the ultrastructure of this system in which it appeared as a mass of cells supplied with nerves and blood capillaries. The cell mass is made up of numerous pear shaped neurosecretory cells, which is confirmed by neurosecretion specific stains i.e. Acid violet and Iron alum.

The functional significance of this system in biology of these fishes awaits further investigation but the experimental investigations undertaken in the system has revealed it's involvement in condition of hypoxia and surfacing behaviour of fishes.

Ethics statement: Handling of fishes were carried out in strict accordance with the guidelines of Human Ethics Committee.

Acknowledgement: This work was supported by Department of Zoology and National Centre of Experimental Mineralogy and Petrology, University of Allahabad,Allahabad,U.P.,India.

Fluorophore assisted light inactivation (FALI) – Tool to study synaptic ribbons

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Ribbon synapses are features of non-spiking sensory neurons of the retina and inner ear. These synapses are named for their electron dense synaptic ribbons, which tether an abundance of synaptic vesicles near release sites. Generation of free radicals by illuminating fluorescein-tagged ribbon-binding peptide inflicts damage to the synaptic ribbons of the rod bipolar cells. While monitoring neurotransmitter release from a post-synaptic AII amacrine cell the functions of the synaptic ribbons can be evaluated. By using this technique of fluorophore assisted light inactivation (FALI), we identified important functions of the ribbons in neurotransmitter release and in coordinating multivesicular release.

Ethics statement: All procedures were approved by the Yale University Animal Care and Use Committee, Yale University, USA

Acknowledgements: (This work was funded by the National Institutes of Health Grant No. EY014990).

MicroRNAs as crucial players during the induction of pluripotency in somatic cells

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Generation of induced pluripotent stem cells (iPSCs) from somatic cells of neurological disease patients and their subsequent differentiation into the desired neurons has allowed development of in vitro models that may provide patient specific information. Almost a decade ago, transcription factors were used for reprogramming the genome of somatic cells and to induce pluripotency. However, the problems of low efficiency and genome insertional mutagenesis paved new ways to induce pluripotency. Recently, microRNAs - the small non-coding RNAs, gathered attention of researchers due to their small size, tissue specific expression and regulation of large number of genes. Besides their established roles in several physiological processes including metabolism, apoptosis and differentiation, their functions in cell fate transitions and pluripotency have just beginning to soar. We generated iPSCs from cord blood and then derived neurons from these iPSCs via neural stem cells (NSCs). To explore the biological significance of miRNAs in reprogramming, we performed an in silico analysis using the predicted targets of all reprogramming inducing miRNAs. Metabolic processes, biological regulation, cellular processes and developmental processes were the highest rated biological processes. Molecular pathways including FGF signaling pathways, hypoxia response, Insulin/IGF pathway, PI3 kinase pathway and p53 pathway were among the most significant pathways. Collectively, our in silico analysis offers new mechanistic insight into the nature and complexity of molecular events during miRNA induced cellular reprogramming. Further investigations of these biological functions and signaling pathways may help in the development of miRNAs as reprogramming tool for regenerative medicine.

Acknowledgement: This work is supported by DST INSPIRE grant (Code-IFA 13-LSBM-90) by DST and INSA and also by core funding of NBRC.

Bacteria and the Brain

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Bacterial Infections are the most common cause of the human infectious diseases. Many bacteria like *Escherichia coli*, *Mycoplasma pneumoniae* and *Campylobacter jejuni* are pathogenic to human. They carry virulent agents that cause pathogenic inflammatory responses in the host. The common severe inflammatory response to an infection that afflicts people is called sepsis. Patients with sepsis have a high risk of morbid complications and death. Neuroinflammation triggers autoimmune reactions affecting both glial and neuronal population of the nervous system, causing different neurodegerative and demyelinating diseases. In this review, we explore the cause and mechanism of various bacterial induced neuroinflammatory disorders in the brain. This could help us in better disease diagnosis and effective medical prognosis.

Keywords: Bacteria, Infection, Neuroinflamation, Neurodegeneration and Demyelinating disease.

Ethical statement: This review does not involve any animals/humans studies on its own.

Acknowledgements: Department of Biotechnology, Government of India.

Effect of low intensity electromagnetic field exposure on severely contused spinal cord rats: an electrophysiological study

Supti Bhattacharyya

Rutin in experimental paradigms of STZ-induced diabetic neuropathy

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Diabetes mellitus is a serious global health problem and its prevalence is estimated to be 366 million worldwide by the year of 2025. Diabetic neuropathyaffects more than 50% of diabetic patients and is a major cause of disability. Rutin has been demonstrated in number of pharmacological activities including anti-diabetic, anti-oxidant and anti-inflammatory activities.

Streptozotocin (STZ, 55 mg/kg) dissolved in 0.1 M citrate buffer (pH 4.5) was administered intraperitoneally (i.p.) to overnight fasted rats. Animals with blood glucose level more than 250g/dl are considered diabetic and are used for further studies.Naive and diabetic rats were randomly selected and divided into eight groups of six animals in each group. Rutin (100 and 200 mg/kg,i.p.) (Sigma-Aldrich, USA) and Ramipril (0.2 and 2.3 mg/kg, p.o.) (IPCA, Mumbai) was suspended in 0.25% sodium carboxy methyl cellulose. All the behavioural parameters (Measurement of body weight, Mechanical allodynia, Cold allodynia, Mechanical hyperalgesia, Thermal hyperalgesia) were performed on day 0 , 2nd , 4th, 6thand 8thweek. On last day (of 8th week), blood was collected retro-orbitally and mean nerve conduction velocity was assessed. The animals were then sacrificed sciatic nerves were isolated for further biochemical estimations (Lipid peroxidation, Nitrite estimation, Superoxide dismutase activity, reduced glutathione (GSH) estimation, and Catalase estimation).

Rutin(100 and 200 mg/kg) for 8 weeks significantly protected all the behavioral alterations (loss in body weight, mechanical allodynia, cold allodynia, mechanical hyperalgesia, thermal hyperalgesia), oxidative damage (lipid peroxidation, nitrite estimation, superoxide dismutase activity, reduced glutathione (GSH) estimation, and Catalase estimation) and change in mean nerve conduction velocity induced by STZ. Further, combination of Rutin (100 and 200 mg/kg) with ramipril (0.2 mg/kg) significantly reversed all the behavioural, biochemical and changes in nerve conduction velocity as compared to their effect per se in STZ-induced diabetic neuropathy.

The present study suggests the protective effect of *Rutin* against STZ-induces diabetic neuropathy. Study further provides a an evidence that rutin produces better effect in combination with rampril against STZ-induces diabetic neuropathy.

Age, Sex and Estrous Cycle Influence Nocturnal Behavior of Mice under Light

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Light at night alters behavior and cognitive performances in rodents, the variations of which in age, gender and stages of reproductive cycle in females are elusive. Young and aged mice habituated in light:dark (12:12 hours) cycle were given a single exposure of light (100 lux) at early night for 1 hour duration followed by experimentations in circular open field (OF), elevated plus maze (EPM) and square habituated field for memory recognition. The effects of light at night on mice behavior were compared with the nocturnal behavior of mice without exposure to light. The parity and disparity in alterations of locomotor activity and anxiety found in three experimental fields were considered to explain the results including memory performances. Light maximally affected proestrous females with both ages where locomotor activity decreased and anxiety increased. Light differentially altered locomotor activity and anxiety in males and diestrous females of both ages. Exceptionally, light increased locomotor activity and decreased anxiety in aged males and diestrous females during (OF) and EPM tests, the explanation of which is undefined in the present study. Aged animals did not perform memory tasks. Young proestrous females failed to perform memory recognition in association with increase in anxiety. Young males and diestrous females performed memory recognition without alteration of anxiety. Therefore, the impacts of light on nocturnal behavior of mice depend on physiological aspects like age, sex and estrous cycle. Furthermore, the present study indicates an association of memory performance with locomotor activity and anxiety in mice.

Ethics statement: All experimental protocols were preapproved by the Institutional Animal Ethics Committee (IAEC-III/proposal/Ph.D/NC-01/2012, dated 17/02/2012) at the Department of Physiology, University of Calcutta, India.

Acknowledgements: The present study was funded by the grants [BI 92(7)] provided by the University of Calcutta. We are thankful to Dr. Richard Mills (Vice President, Stoelting Co, USA), Dr. Anita Talawar (Managing Director, Gentech Marketing & Distribution (P) Ltd, India), and Mr. Sandip Majumder (Regional Sales Manager, Gentech Marketing & Distribution (P) Ltd, India) for their kind support to providing us the automated animal tracking software, ANY-Maze™ for collecting the experimental data.

Prenatal infection alters hippocampal neuronal morphology in adult Wistar rats: rescued by adolescent physical exercise and environmental enrichment.

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Adverse in utero events, especially prenatal infection, affects the vital processes of brain development that predispose to emergence of neuropsychiatric illness in adulthood. The present study aimed to elucidate the role of physical exercise and environmental enrichment during adolescence in rescuing the altered dendritic morphology of adult hippocampal CA3 neurons due to prenatal infection.

Pregnant Wistar dams were injected intraperitoneally either saline (0.5ml; control group) or lipopolysaccharide (LPS group) (0.5mg/kg), Gram-negative bacterial endotoxin, on alternate days from embryonic day 14 [E14] till delivery. After delivery, pups were divided into following groups [n=6 per group]:

(1) Control, (2) LPS-Non-exercise, (3) LPS-exercise, (4) LPS-environmental enrichment and (5) LPS-exercise-environmental enrichment.

Animals of group 3, 4 and 5 were subjected either to running exercise or environmental enrichment or both respectively, on postnatal day (PND) 15 to 60. Animals were euthanized on PND 67, brain sections were stained by Golgi-cox and hippocampal CA3 neuronal morphology was traced by camera lucida and analysed by Sholl's method.

Young adult rats of LPS-Non-exercise group exposed to prenatal infection showed significant reduction in dendritic arborization of hippocampal CA3 neurons. Whereas, LPS-exercise-environmental-enrichment group that were exposed to prenatal inflammation and later subjected to running exercise with environmental enrichment, showed significant increase in dendritic branching points and dendritic intersections of CA3 hippocampal neurons.

Physical exercise combined with environmental enrichment during juvenile/adolescent age effectively rescues the prenatal infection induced changes in dendritic arborization of neurons of CA3 sub-region of young adult hippocampus.

Ethical Statement: The experimental protocol was reviewed and approved by Institutional Animal Ethics Committee of Manipal

University. Maintenance of animals were followed according to the prescribed guidelines of the Committee for the Purpose of Control and Supervision of Experimental Animals (CPCSEA), Govt. of India.

Acknowledgements: We are extremely thankful to Manipal University for providing infrastructure to carry out this study and financial support to attend this conference.

Cellular Consciousness: A Theoretical Survey

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The universe is made up of matter, microbes, plants, animals and humans. It is consciousness that makes us aware of the universe. The baffling question in science is how physical working of the brain gives rise to conscious awareness. Scientists proposed various theories that consciousness can be present in atom, molecule, cell, neuron (glia), synapse, neurotransmitter, reticular formation. Descartes said that consciousness resides in the pineal gland. Ancient Indian Philosophy states that in the higher state of consciousness, the subject and object becomes one through Dhyana (meditation), Jnana (understanding), Karma (work) and Bhakti (devotion).

This paper presents various Physical theories of consciousness in general such as quantum mechanical theory, space-time theory, electromagnetic field theory and Cellular theories in particular such as cell membrane theory, microtubule theory and single neuron theory. The cell membrane theory states that the exchange of metabolites and information between the cytoplasm and the environment is mediated by the cell membrane whose activities are controlled by the Integral Membrane Proteins. IMPs are functionally classified into signal receiving receptors and action producing effectors, linked by processor proteins. A Receptor-Effector complex represents a fundamental unit of perception. Protein perception units form the base of cellular consciousness. The microtubule theory states that computation within tubulin proteins produce consciousness. The single neuron theory states that phonons produce piezoelectric effects in the cell membrane producing consciousness.

None of the above mentioned theories are conclusive. However, they provide clues to solve the mystery of consciousness.

Keywords: Consciousness, Physical theories, Cell Membrane theory, Microtubule theory, Single Neuron theory.

Efficacy of fenugreek seed extract and choline with docosahexaenoic acid in attenuating menopause-induced neurocognitive deficits

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During menopause women experience a variety of symptoms, including anxiety, depression, learning and memory, due to cessation of ovarian estrogen production. The Global Consensus Statement on Menopausal Hormone Therapy (2012) highly recommends hormone replacement therapy to treat menopausal symptoms, but with complex pattern of risks and benefits that limits its clinical use. Alternately, supplementation of fenugreek seed extract (FSE) that contains phytoestrogens or in combination with Choline and DHA (docosahexaenoic acid) may be an alternative strategy to treat menopause induced neurocognitive deficits.

To evaluate the efficacy of FSE and Choline with DHA in attenuating menopause-induced memory impairment and hippocampal damage in ovariectomized rats.

Female Wistar 9-10 months aged rats were divided into groups (n=6/group): (1) Normal Control, (2) ovariectomy (OVX), (3) Sham OVX, (4) OVX + Fenugreek (FG-hydro-alcoholic extract), (5) OVX + Choline-DHA, (6) OVX + FG + Choline-DHA and (7) OVX + Estradiol.

Groups 2, 4, 5, 6 and 7 were subjected for surgical ovariectomy. After 30 days of supplementation, learning and memory performance was assessed by passive avoidance and Radial Arm Maze test. Alterations in CA1 and CA3 neuronal morphology was analyzed by Nissl stain of hippocampal sections.

Ovariectomized rats showed impaired spatial abilities correlated with degeneration of CA1 and CA3 hippocampal neurons. Ovariectomized rats supplemented with FSE and Choline with DHA showed significantly improved learning and memory abilities as well as decreased neuronal degeneration in the specific hippocampal regions.

Supplementation of FSE in combination with Choline-DHA can significantly reverse menopause-induced neurocognitive deficits.

Ethical Statement: The experimental protocol was reviewed and approved by Institutional Animal Ethics Committee of Manipal University. Maintenance and handling of animals were carried according

to the prescribed guidelines of the Committee for the Purpose of Control and Supervision of Experimental Animals (CPCSEA), Govt. of India.

Acknowledgements: We are extremely thankful to Manipal University for providing infrastructure to carry out this study and financial support to attend this conference.

Amygdalo-hippocampal connectivity during REM sleep after differential fear conditioning

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Fear memories are formed much rapidly than other memories. What, when and how fear memory is formed not clearly known. In the present study, we show in rats how hippocampus and amygdala gets connected during the rapid eye movement sleep after retrieval of differential fear conditioning.

Local field potentials (LFPs) were recorded simultaneously from CA1 hippocampus and Lateral nucleus of amygdala (LA) during sleep in rats. The recordings were carried out within30 minutes after differential fear conditioning (DFC). The procedure consisted of habituation to the context, differential fear conditioning and retrieval test. Sleep recordings were compared between habituation and retrieval test.

The freezing behavior was used as an index of fear. Results showed DFC increased freezing more specifically to CS+ and less fear to CS-. Further increased freezing behavior during retrieval session was associated with increased REM sleep when compared to that following habituation. The study further showed that the network activity is very different in hippocampus and amygdala during REM sleep.Strong correlation was observed between fear memory and network activity in the amygdala-hippocampal circuit during REM sleep making a strong evidence for the memory consolidation takes place during REM sleep.

Fear conditioning has enhanced REM sleep, with increase in theta power in Lateral Amygdala (LA) and reduced theta power in CA1 hippocampus. But, increased theta power observed in LA during the first 2 hours of sleep was reduced gradually during the later stage of the sleep. In the case of CA1 hippocampus, reduction in theta power was consistent throughout the recording session during REM sleep. This indicates that there is a gradual reduction in fear conditioning-induced theta modulation over the period of sleep. The time scale of this gradual change in LA theta power may vary for the reasons of memory consolidation process.

Keywords: Differential Fear Conditional, Lateral Amygdala, Hippocampus, REM sleep, Amygdala-hippocampal circuit, Theta power.

Acute and long term neurological consequences of mild malaria.

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Neurological complications are well studied in context of cerebral malaria. However neurological sequelae due to uncomplicated mild malaria have received relatively less attention. Given that almost ninety five percent of the population including a majority of children under the age of five is affected with mild malaria, the hidden burden of neurological impairments seems substantial. Hence using a rodent model, we investigated the cellular, molecular and behavioural consequences of a single episode of self-resolving mild malaria. Our data indicates that an acute self -resolving mild malaria challenge leads to transient neurogenic decline, microglial activation and alteration in social and anxiety-like behaviours at the peak of infection in adult male mice. We also investigated if a single episode of mild malaria has long term neurological consequences. We found that history of the infection affected juveniles and adults differentially. Mice with history of single episode of malaria in their juvenile life period show increased vulnerability to neuropsychological dysfunction like anxiety on exposure to chronic mild stressors. By contrast, suffering from the infection in adulthood did not have significant long=term consequences. Thus, malaria infection during a crucial period of development can affect stress vulnerability in individuals and even a single episode of self-resolving malarial infection has both immediate and relatively long term neurological implications.

Ethical statement: All experiments were approved by the TIFR animal ethics committee, and were in accordance with the guidelines of CPCSEA (Committee for the Purpose of Control and Supervision of Experiments on Animals; registration No. 56/1999/CPCSEA).

Acknowledgements: We thank Dr. S. Suryavanshi and Dr. Sachin for their help with the animal studies. This study was funded by intramural funds from the Tata Institute of Fundamental Research, Mumbai, India.

Beneficial role of Curcumin on cognitive functioning of mice subjected to arsenic trioxide exposure.

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Arsenic trioxide (As_2O_3) has been in use for inducing complete remission with no myelosuppression in patients of acute promyelocytic leukemia (APL). However, neurodegenerative changes and cognitive dysfunction has been reported even with low doses of As_2O_3. Basal forebrain (BF) is a collection of heterogeneous nuclei in the forebrain associated with cognitive functioning. It is one of the various brain areas that show increased susceptibility towards environmental insults. The present study was designed to determine the beneficial effects of Curcumin (an antioxidant) supplementation on cognitive functioning in mice subjected to As_2O_3 exposure. Healthy Swiss albino mice (adult male) were divided into control (I) and experimental groups receiving As_2O_3 alone(II), Curcumin alone(III) and both As_2O_3 and Curcumin(IV) respectively. Groups II and IV were further subdivided according to the dosage of As_2O_3 (2mg; 4mg/kg bw). The test substances were administered orally over 45 days. During the experimental period, exploratory ability, anxiety level & memory and learning ability were determined using Open field, Elevated plus maze and Morris water maze tests respectively. The animals were perfusion fixed on day 46 and the brain tissue obtained from these was processed for immunohistochemical localization of specific proteins. A decrease in exploratory ability and increase in anxiety level, escape latency, distance travelled and swimming duration suggested As_2O_3 induced cognitive deficits in As_2O_3 alone treated groups. Histochemistry revealed altered expression of various proteins in BF of mice following As_2O_3 exposure. Curcumin supplementation improves cognitive functioning and upregulates expression of various proteins, thereby suggestive of beneficial role of Curcumin.

Ethics statement: The ethical clearance was obtained from Institutional Animal Ethics Committee (/Ref, No. 844IAEC/15), All India Institute of Medical Sciences (AIIMS), New Delhi, India and Handling of animals was carried out in strict accordance of with desired guidelines.

Acknowledgements: This work was supported by Department of Anatomy, AIIMS, New Delhi, India.

Temporal influence of hypobaric hypoxia and derived neurodegeneration on fear conditioning

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Learning about fear is an essential for survival but its generalization leads to disorders. Evidence suggest that Fear memory gets modulated under stressful conditions. Hypobaric hypoxia (HH) causes impairment in cognitive processes, however, the effect of HH on emotional memory is still an enigma. This study is first to investigate the temporal influences of HH on fear conditioning behavior.

Animals were divided into ten groups: Normobaric Normoxia (NN) and HH [1, 3, 7 and 14, 21 days] each. SD Rats were trained for fear conditioning paradigm and exposed to HH under a simulated condition in an animal decompression chamber. Animals were tested for changes on cued and contextual fear conditioning. Medial Prefrontal cortex, (mPFC) hippocampus and amygdala were studied for pyknosis by Cresyl violet staining and caspase 3 for neurodegeneration.

A significant decrease was found in freezing time at 3 days HH as compared to the NN group. No significant difference was found in freezing scores with HH on days 1, 7, 14 and 21. However, 7 days HH showed a significant increase in total freezing time in comparison to 3 days HH. Further, a significant pyknosis was found in limbic brain regions at 3 and 7 day HH as compared to NN.

These findings clearly indicated dysregulation of fear conditioning behavior under HH and moreover, neurodegeneration in limbic brain regions was associated with fear memory dysregulation under HH.

Ethics statement: Experiments to be conducted were approved by the Institutional Animal Ethical Committee. The guidelines documented in the National Institutes of Health's Guide for the Care and Use of Laboratory Animals were followed and all effort were made to minimize animal suffering.

Acknowledgements: This study is supported by Defence Research and Developmental Organization (DRDO), Ministry of Defence, Govt. Of India and Council of Scientific and Industrial Research (CSIR) Govt. of India.

Cognitive flexibility and sustained attention in rats experienced early maternal separation and isolation stress

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Early life adversity has a profound impact upon brain development and executive functions later in life which are of developmental origin. Even trivial changes in the neural connectivity due to early life stress may result in disproportionate deficits in cognitive functions.

In the present study, the executive functions were studied in animals subjected to maternal separation and isolation stress (MS) during stress hyporesponsive period (SHRP). MS was done for 6 hours daily from postnatal day (PND) 4-14. On PND 22, these rats were reared in groups of 3-4 per cage and higher cognitive test was carried out in young adult age during P60-P90 using 5-choice serial reaction time task (5-CSRTT). This task examines the attention process involved in the executive functions.

In order to evaluate the attentional performance, response accuracy and premature responses were calculated. When challenged with random variable inter-trial intervals (vITI), MS rats showed significantly reduced the premature responses, with no difference in omissions and percent accuracy when compared with NMS males. In addition, during vITI session, MS rats showed significant increase in repetitive nose poke entries in stimulus hole after performing the correct response indicating increased preservative responses. The increase in perseverative response is known as impaired cognitive flexibility.

In summary, the results indicate that MS in early postnatal period particularly during SHRP period enhances attentional capacity with better control on behavioural inhibition but reduces cognitive flexibility in terms of increased perseverative responses.

Keywords: Maternal separation stress, cognition, attention, 5-choice serial reaction time task (5-CSRTT), premature responses, response latency, perseverative responses, compulsive behaviour, cognitive flexibility,

Ethics Statement: All the procedures performed in the above abstract are approved by Institute Animal Ethics committee (IAEC), NIMHANS,

Bengaluru. Also the project was approved by the Institute Animal Ethics committee (IAEC), NIMHANS.

Acknowledgments: NIMHANS for the financial support and student fellowship.

Effect of Guanfacine on hypobaric hypoxia induced EEG slowing in prefrontal cortex

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Guanfacine, an alpha 2A adrenoceptor agonist facilitates structural and functional plasticity in medial prefrontal cortex under hypobaric hypoxia (HH). The electrophysiological correlates of prefrontal neuronal plasticity with guanfacine treatment under HH are not known. We therefore designed the present study considering this lacuna in literature. Male Sprague Dawley rats (n=6 in each group) were used as an experimental model. They were exposed to HH in an animal decompression chamber at an altitude of 25, 000 ft for 7 consecutive days. Guanfacine was administered at a dose of 1 mg/ Kg via IM route daily for 7 days during normoxia and hypoxia. EEG and EMG were recorded from frontal and occipital cortex in freely moving rats. HH showed a pronounced and significant increase in EEG spectral power over 1-30 Hz as compared to normoxia group. The EEG spectra evoked by HH demonstrated the synchronization of EEG in all power bands. Guanfacine treatment during normoxia and hypoxia decreased EEG spectral power over almost all the frequency range, with a marked effect seen over 9-30 Hz. A decrease in power induced by guanfacine was considered as desynchronization of EEG. On spectral analysis, there was a significant increase in slow waves (delta and theta) while a significant decrease in fast frequency waves (alpha and beta) of EEG activity in HH exposed group as compared to normoxia group. However, Guanfacine treatment during normoxia and hypoxia conditions showed a significant decrease in slow waves and increase in fast waves. These results demonstrate a beneficial role of guanfacine on HH induced EEG synchronization and it's slowing.

Post-weaning social isolation induces behavioural, neurochemical and neuromorphological effects during early and late adolescence in Wistar-Kyoto rats

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Adolescence is a critical period of brain development with social and environmental influences playing a very vital role, leading to irreversible changes in the amygdala-hippocampus-striatum-prefrontal circuitry. The Wistar-Kyoto (WKY) rat strain was inbred from Wistar and has been proposed as an endogenous animal model of depression as it exhibits sensitivity to stress. Here, we investigated whether WKY rats demonstrate depressive-like profile also in adolescents, as exposure to stressors during adolescence can lead to adult depression. The stressor used here was subtle, post-weaning social isolation for six hrs per day. Effects on inherent/induced anxiety-like behaviours were tested on a battery of tests during two critical time periods: early- and mid-adolescence. Isolation induced immediate effects on behavioural measures such as novelty-induced hyperactivity, elevated plus maze-induced anxiety-like behaviours, behavioural despair in the forced swim test and anhedonia via the sucrose preference test. Behavioural measures were compared with neurochemical and neuromorphological profiles. Frequency of 50-kHz ultrasonic vocalizations emitted by adolescent WKYs were not affected. Further, we observed that socially-isolated rats, despite subsequent social/group-housing, demonstrated long-lasting effects on social interaction and anhedonia when tested during late adolescence/early adult hood. This establishes that the depressive-like profile observed during early- and mid-adolescence persists into late adolescence/early adulthood in WKY. To assess the model further, behavioural profiles were compared to age-matched Wistar rats. Overall, the results indicate differential expression of anxiety-related and despair behaviours in pre-pubertal rats belonging to the 'depressed' strain, suggesting that this strain constitutes a suitable model for the study of adolescent depression.

Ethical Statement: The study was carried out in accordance with the ethical regulations for animal experimentation laid by CPCSEA and cleared by the Institutional Animal Ethics Committee.

Acknowledgement: This work was supported by a research grant from the DBT (BT/PR4676/MED/30/735/2012).

Ultra Structure Imaging Studies of Alcohol Treated Zebrafish Brain

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Zebrafish is a tiny freshwater fish, also known as *Danio rerio* in scientific community, and it is an effective vertebrate model organism. In this work, effort has been made to study the brain structure of alcohol treated zebrafish using field emission scanning electron microscopy. Adult zebrafishes of 3 months old were exposed to ethanol for a period of 20 days with series of concentrations. The acute exposure of 5min each day with the ethanol concentration of 15% showed unique behavioral changes. These fishes were sacrificed and the brain was sectioned for ultra structure imaging. Mostly alcohol consumption alters the levels of neurotransmitters and glial cell thus impair memory and walking ability. The hypothalamic region of the brain has been shrunken which is the major remarkable outcome of this experiment. Most of the glial cells were not present in rhombencephelon. The ultra imaging reveals that, the whole brain structure itself has been altered compared to control on binge ethanol exposure. To sum up, the study concerns the relation between alcohol exposure and brain structure changes, memory and impairment of neurosignaling in zebrafish model and therefore this study can be reminiscent with human.

Keywords: zebrafish, brain, SEM, ultra structure, imaging, alcohol, glial cells

Activation of peripheral immune system results in age related decline of neurobehavioral and cognitive abilities

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Exposure to early life infections has been widely associated with increased vulnerability to behavioral, cognitive and neuropsychiatric disorders of developmental origin.

Bacterial endotoxin induced glial changes were studied with reference to behavioral and cognitive impairments in young, adult and aged rats.

In a model for neonatal bacterial infection using LPS, we have evaluated how inflammation during development would influence later life brain function. Pups were treated with LPS (0.3 mg/kg b.w., i.p.) on PND3 followed by booster dose at PND5. Cryocut sections through hippocampus from various age time points were used for immunnohistochemistry. Glial activation was assessed with Iba 1, OX-6, OX-42, and GFAP. Cellular death and degeneration was analyzed by Caspase-3 and NF-200 markers. Prior to sacrifice all animals were tested on array of behavioral and cognitive test, e.g., Rotarod, Open field test, Elevated Plus Maze and Morris Water Maze.

Neonatal LPS exposure caused persistent neuroinflammation resulting in expression of inflammatory molecules. An increased level of cellular death was evident with elevated expression of caspase-3 and NF200 accumulation in the hippocampus and cortex. Such neuroinflammatory impacts leads to hyperactivity and anxiety like behaviour at adulthood and senility as evident from open field test and EPM. A deficit in spatial reference memory was also noticed with Morris Water Maze in the adult and senile animals exposed to bacterial infection during early life.

Our findings suggest that early life infection can induce age-associated decline in behavioral and cognitive disabilities.

Some social isolation infunces courtship behaviours and dendritic remodeling in male zebra finches

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Zebra finches (*Taeniopygia guttata*) are highly monogamous birds that maintain lifelong pair bonds. Females make the mate choice based on the quality of males who initiate pair-bond formation by courting the female. A mate separation-reunion paradigm can help to evaluate the adaptive value of social affiliation of male finches and their affinity to new females in absence of mated females which can manifest at a neuronal level by dendritic measures. The aim of this study was to examine behavioural and neuronal changes as a result of social isolation following pair-bonding in male Zebra finches. Towards this, male Zebra finches from a pair-bonded group were isolated for a period of ten days and then exposed to either the mate or a new female. Four main courtship behaviours: clumping, allo-preening, nest-box occupancy and directed singing were recorded and analyzed. Brains were processed by a modified Golgi technique to detect changes in dendritic arborizations using the Sholl analysis. Baseline behavioural results showed an increase in clumping and nestbox activity by day ten. Post isolation, males re-introduced with the mate showed increased nestbox activity. Alternatively, males introduced to new females post isolation demonstrated increased directed singing when compared to paired males, but lower than when exposed to same female. Neuro-morphological changes assessed through quantification of dendritic intersections and branch points were observed in the hippocampus and pallial brain areas known to implicate in the development of social/sexual preferences with the paired-bonded group demonstrating more branching and longer dendrites when compared to the socially-isolated group.

Ethical Statement: This study was performed in strict accordance with guidelines approved by Institutional Animal Ethics Committee and CPCSEA, Govt. of India.

Acknowledgment: SERB Grant Support (SR/SO/AS-38/2011) and DBT Grant Support (No. BT/PR4984/MED/30/752/2012).

Competing interests: The authors declare no conflict of interest.

Chronic N-Acetyl Cysteine Treatment Restores Depression-Induced *Spatial Learning Deficits and* Structural Changes in the Hippocampus and Amygdala

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Major depression is a severe psychiatric disorder associated with impairment in cognitive functions. Our previous studies have demonstrated depression-induced dendritic retraction and hippocampal atrophy, reduction in the levels of biogenic amines and its metabolites and abnormal hippocampal synaptic plasticity. The depression-induced regressive plasticity and associated cognitive deficits were restored by chronic treatment with escitalopram or reboxetine. However, most of the antidepressants that target monoaminergic system are partially effective or ineffective even following long-term treatment and is typically associated with lack of remission or recurrence. Current research has engendered a great deal of interest in glutamatergic targets for the treatment of depression. We hypothesized that restoring normal glutamatergic transmission might restore depression-induced cognitive deficits. Accordingly, we investigated the effect of N-acetyl cysteine (NAC), a glutamatergic modulator on depression-induced cognitive dysfunction and also evaluated if morphological changes in sub-regions of hippocampus and amygdala underlie the behavioural effects. The depression was induced by neonatal clomipramine administration and in the adulthood these animals exhibited depressive-like symptoms with enhanced anxiety and impaired spatial learning. The behavioural deficits were associated with decreased volumes of the CA1, hilus and dentate gyrus regions of the hippocampus and contrastingly, hypertrophy of the basolateral amygdala. Interestingly, chronic treatment with NAC restored the depression-induced cognitive deficits and associated structural changes in the hippocampus and amygdala. These results indicate that modulation of glutamatergic system might be beneficial in restoring depressive symptoms and associated cognitive deficits.

Keywords: Endogenous depression, cognitive deficits, anhedonia, N-acetyl cysteine, spatial learning deficits, hippocampal atrophy, enhanced anxiety, amygdala hypertrophy, Structural plasticity

Acknowledgements: We acknowledge financial support from CSIR, DST, DBT and NIMHANS

Ethical Statement: All experiments were approved by the Institutional Animal Ethical Committee of National Institute of Mental Health and Neuro Sciences (NIMHANS), Bengaluru and performed according to the guidelines of the Committee for the Purpose of Control and Supervision of Experiments on Animals, Government of India.

Basolateral Amygdala Mediates Stress-induced Cognitive Deficits by Modulating the Medial Prefrontal Cortical Functions

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Chronic stress is associated with cognitive decline and precipitates psychiatric illnesses including depression and anxiety. We previously demonstrated that stress-induced morphological, neurochemical and electrophysiological alterations in the hippocampus, prefrontal cortex (PFC) and amygdala results in cognitive deficits. The changes in basolateral amygdala (BLA), in particular, are thought to be central to the deleterious effects of chronic stress because it exerts a positive regulation on the HPA axis and undergoes hypertrophy following stress. However, it is unknown if the BLA hyperactivity is responsible for the stress-induced prefrontal cortical dysfunction and cognitive deficits. Accordingly, we examined the effects of temporary inactivation of BLA during stress on cognitive functions and associated structural and molecular changes in the prelimbic and anterior cingulate cortex. Male Wistar rats were subjected to temporary inactivation of BLA using lidocaine, prior to each stress session followed by behavioural, morphological and biochemical assessment. Stressed rats showed a decrease in the novelty seeking behaviour, impaired reference memory and enhanced anxiety-like behaviour. Interestingly, inactivation of the BLA prevented impaired learning and decreased anxiety-like behavior. The stress-induced astroglial loss, microgliosis and decrease in the volumes of the prelimbic and anterior cingulate cortex were precluded by BLA inactivation. Further, the stress-induced increase in corticosterone levels and expression of glucocorticoid receptors in the prelimbic and anterior cingulate cortex were also prevented. These findings reveal an important regulatory role by BLA in stress-induced deleterious effects on functioning of the PFC and have implications for developing novel strategies to treat stress-related disorders including PTSD and depression.

Keywords: Inactivation of basolateral amygdala, Chronic stress, Prefrontal cortex, Corticosterone, glucocorticoid receptors, microgliosis.

Acknowledgements: We acknowledge financial support from CSIR, DST, DBT and NIMHANS.

Ethical Statement: All experiments were approved by the Institutional Animal Ethical Committee of National Institute of Mental Health and Neuro Sciences (NIMHANS), Bengaluru and performed according to the guidelines of the Committee for the Purpose of Control and Supervision of Experiments on Animals, Government of India.

Toxic effects of artificial sweetener: Sucralose on Glucose homeostasis of *Daphnia pulex*

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Sucralose is a non-nutritive artificial sweetenerr. It is a chlorinated sucrose sugar which is 600 times sweeter than normal sugar. Previous studies have shown that sucralose does not get metabolized easily in the body and only 70% of it gets excreted and less has been known about its toxic effects. In our study we have used *Daphnia* as a model system to study the effect of Sucralose on glucose homeostasis. *Daphnia pulex* is reared using COMBO media and reared for several generations to obtain a synchronized culture. Adult *Daphnia* were subjected to 2mg/l, 5mg/l, 10mg/l concentrations of Sucralose, and glucose levels were checked in treated organisms (hyper/hypoglycemic), changes in heart rate, light & temperature effects, feeding behavior, reproduction and transgenerational effects were also studied.

Ethics statement: This project has been approved by the Institutional Ethics committee.

Acknowledgements: Daphnia cultures were brought from local aquariums in Mumbai

Hyperglycemia alters behavior in *Caenorhabditis elegans*

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Hyperglycemia causes various intracellular changes resulting in oxidative stress. It also has an effect on the lipid deposition in cells, leading to loss of integrity and cell death. While cellular effects of hyperglycemia have been reported extensively there no clarity on whether the cellular changes translate into alterations in behavior. This aspect of effect of hyperglycemia deserves attention as it might be the first indicator of neurodegenerative changes. *Caenorhabditis elegans* is an excellent model to address these questions since it has a simple nervous system and the ability to respond to various cues. We have investigated alteration in behavior which involves various sensory and motor function of the *C. elegans* nervous system under hyperglycemia. Exposure of *C. elegans* to 400 mM glucose for 2h did not kill the worm but gave rise to decreased number of progeny. This dosage was considered to cause hyperglycemic stress and used further in the studies. Various assays that quantified behavior, such as feeding (pharyngeal pumping/min), locomotion (distance travelled by the worms/min), olfactory response towards Butanol (response index), gustatory response NaCl (response index) and reproduction (number of eggs laid by the worms), were conducted under both normal and hyperglycemic conditions. Our results indicate that hyperglycemia robustly altered several behavioral patterns of the worm.

Ethics Statement: This project has been approved by the Institutional Ethics Committee.

Acknowledgements: We would like to acknowledge Dr. Momna Hejmadi, University of Bath, UK for gifting us wild-type N2 *C. elegans*.

Altered sleep pattern and its neural correlates as a consequence of prenatal Valproic acid insult

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Prenatal exposure to teratogens such as Thalidomide, Valproic acid are known to cause various neurodevelopmental disorders such as Autism spectrum disorder, Attention Deficit Hyperactivity Disorder (ADHD), etc. Epidemiological findings indicate that the prevalence of neurodevelopmental disorders has been increasing over the last two decades, cause for which is not clearly known. The prevalence of Autism Spectrum Disorder (ASD) which is increasing from 0.02% to 1.2% current globally. 40% to 80% of children with ASD have sleep disturbances, but the neurobiology of sleep disturbances in ASD and its neural network is poorly understood. The aim of the present study was to unravel the neurobiology behind the sleep abnormality in ASD. Sprague Dawley rats were exposed to sodium valproate on embryonic day 12.5. To validate the model, social interaction, repetitive behaviour, sensory motor integrity and anxiety levels in these rats were evaluated using 3-chamber social interaction test, marble burying test, startle response test and light-dark test during early adolescent age of the animal. Polysomnography recordings were carried out 24 hours after the behavioural validation. Results show that rats exposed to VPA prenatally showed repetitive behaviour, increased amplitude of startle response and decreased prepulse inhibition (especially at 85db/30ms interval), decreased anxiety and increased exploratory behaviour when compared to controls. Our preliminary findings of sleep data showed abnormality in sleep architecture, specifically with REM sleep. Further details on neural correlates of sleep will be discussed during presentation.

Ethics: Handling of animals was carried out in strict accordance with the guidelines of Institute Animal Ethics Committee (IAEC).

A Three-Dimensional Digital Atlas of The Indian House Crow (Corvus splendens) Brain

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The cognitive abilities of the birds of the Corvidae family are comparable to those of higher mammals. These birds exhibit higher brain functions such as tool-use, long-term facial memory and the use of working memory which are almost at par with those of apes and chimpanzees. Amongst corvids, crows are especially proficient at these tasks and fast emerging as a potential model to study these complex cognitive behaviors. Currently, there is an increasing interest in understanding the neural basis of higher cognitive functions across different species using non-invasive neuroimaging modalities such as functional Magnetic Resonance Imaging (fMRI) and Positron Emission Tomography (PET). MRI-based anatomical brain atlases are used as the standard reference space in neuroimaging studies. To decrease the variability between various brain structures or functions and to compare across animals of the same species, individual MR images are normalized to the brain atlas space. A 3D MRI brain atlas of the Indian house crow (Corvus splendens) is constructed for the first time using high resolution iso-voxel structural MR images of their brain. The atlas encompasses an MRI brain template and a parcellation map delineating major avian brain areas like the striatum, areas of the pallium and brainstem. Our brain atlas provides a standard reference space for neuroimaging-based studies and would be useful for marking stereotaxic locations of brain regions at any given head-angle, aid in various surgical procedures such as injecting neuroanatomical tracers or pharmacological agents into the brain, electrophysiological recordings as well as brain tissue sectioning.

Topographic Representations in the Mouse Motor Cortex is not well defined.

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Mouse model is becoming increasingly important in neuroscience research because of the availability of a wide variety of genetically modified strains, which enables us to understand the role of individual cell types and molecules in information processing in the brain. While the rat motor cortex has been extensively studied, little is known about organization of the mouse motor cortex. We determined topographic organization of the mouse motor cortex by electrically stimulating neurons using intracortical microstimulation (ICMS). The movements evoked at threshold currents, i.e. the minimum current required to evoke a visible movement showed that mouse motor cortex was organized broadly similar to that of rats, with whisker representation present rostro-medial to the lateral forelimb representation. The trunk and hindlimb regions were present caudally. However, unlike rats, stimulation of neurons at most of the locations using currents even few microamperes (μA) above the threshold current, evoked movements of additional adjacent or distant body parts. The results suggested that in mouse motor cortex regions representing movements of different body parts are less well circumscribed as compared to rats. Projection pattern of motor cortical neurons via the corticospinal tract does not entirely explain these differences.

Ethics Statement: All animal procedures were approved by the National Brain Research Centre Animal Ethics Committee.

Acknowledgements: This work was funded by NBRC core funds.

Sensory and Motor Changes in Ageing Rats

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Advancing age is accompanied with a decline in sensory function and motor control. Motor abilities will also be affected by decreased tactile sensitivity. We used two standard sensorimotor tasks to determine how ageing affects behavioural performance of rats from 16 to 100 weeks of age. In the first test, the tactile stimulation test, stickers of a standard size were attached to the plantar surface of the forepaws, and the time taken to remove the stickers within a 90 second window was determined using video recordings. In the second test, the grid-walk test, the rats were placed on a wire mesh and allowed to freely explore the arena. Frequency of errors in placement of the paws on wires of the grid during normal locomotion was determined. Data show that there was no increase in the time taken to remove the stickers until 70 weeks of age. The time taken to remove the stickers increased gradually between 70 and 100 weeks of age. The number of trials in which the stickers were not removed remained same until 80 weeks and then rapidly increased. Performance in the grid-walk test also showed a decline between 70 and 100 weeks in the hindlimb placing. There were no deficits in the forelimb placement until 100 weeks of age, the oldest age tested. The results show that sensorimotor deficits appear in rats at around 70 weeks, which gradually increase with advancing age.

REMS loss induced elevated noradrenaline damages hippocampal CA3 neurons in rats

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Rapid eye movement sleep (REMS) is essential to maintain cognitive functions and REMS-loss affects cognition, behaviors, memory, and motor coordination; however, the mechanism is unknown. We have shown in rats that REMS deprivation (REMSD) affects neuronal cytomorphology, increases apoptosis, and the effects were mediated by elevated noradrenaline (NA) in the brain. Therefore, we proposed that REMSD is likely to affect hippocampal CA3 neuronal cytomorphology, dendritic length, branching, spine density, which in turn might be responsible for the associated effects. Male Wistar rats (220-270gms) were REMS deprived for 6 days by the flowerpot method. Each set consisted one rat each of REMSD, free moving control, large platform control, recovery, and prazosin-treated and five such sets were carried out. At the end, the rat brains were perfused and processed for modified Golgi-Cox staining. Using a vibratome, the brains were sectioned at 200µM and Golgi-stained CA3 neurons traced using Neurolucida and the soma size, dendritic length, branching, and spine density estimated and statistically compared. Soma size, dendritic length, dendritic branching, and spine density were significantly reduced upon REMSD as compared to controls. The changes were prevented by prazosin suggesting that the effects were mediated by NA acting through α_1-adrenoceptor. The findings support our contention.

Acknowledgement: *DST-PURSE, UGC-Networking and JC Bose fellowship to BNM*

Molecular Insights of Mental Retardation and Effects of Special Training

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The Mental retardation (MR) is a condition with gross impairment of neuro-physiological state and characterized by impaired cognitive, linguistic, and social abilities. We evaluated the changes in cellular oxidative stress biomarkers, serum neurotransmitters, structural alterations of brain, cellular morphology and associated proteins of RBC responsible for the health status and behavioral aspects of MR children. Special training was given to children for psycho-behavioral improvement increasing their acceptability in the society. MR children were classified as mild, moderate and severe according to their intelligence test scores. Lipid peroxidation, glutathione level and SOD activity were determined from PBMC and RBC. Morphological studies of RBC, platelet, isolated mitochondria from PBMC and immunofluorescence study from RBC were done using microscopy. β-actin and GLUT-1 from RBC membrane and serum inflammatory cytokine expressions were analyzed by immunoblots. Magnetic resonance Imaging (MRI) was employed to evaluate the structural changes of brain. Our findings suggest that oxidative stress parameters remained a crucial factor with increasing severity of retardation. Levels of serum neurotransmitters changed in between the tested groups of MR children. Morphological alterations of RBC and platelet were evident in severely retarded group. RBC membrane GLUT-1 and β-actin expressions declined whereas serum inflammatory cytokines elevated with severity of MR. Significant structural alterations were found in specific regions of brain associated with retardation. The special training improved the psychological status of the children. Perhaps it is the first comprehensive report associating

essential parameters with the severity of MR and the stipulation of special training for the differently-abled children.

Ethics statement: We obtained ethical approval for the human subjects from the Institutional Human Ethics Committee (IHEC), Department of Physiology of University of Calcutta (Ref. No. IHEC/SD/P29/13 dated 22.03.2013). An information sheet describing the rationale of the study and individuals' rights was handed to the parents and caregivers to read. Written informed consent was obtained from parents or caregivers of each individual.

Acknowledgements: The authors acknowledge all subjects and concerned persons participated in this study for their generous understanding and unconditional support. This work was supported by the University Grants Commission (UGC), New Delhi, India under the scheme of "Center with Potential for Excellence in Particular Area (CPEPA)", project sanction no. [F No. 8-2/2008 (NS/PE), dated: 14.12.2011]. Professor Sanjit Dey would also like to acknowledge the research support from LSRB, DRDO [DLS/81/48222/LSRB-244/SH&DD/2012] and CSIR, Government of India [23(0024)/12/EMR-II]. The authors would like to acknowledge the Directors, Secretaries, Office bears, Governing body members and care givers of both Bodhipeet and Nivedita Centre for Challenged Children, Institute of Child Health, Kolkata.

Transcription factor FoxO3a regulates Fas Ligand via microRNA 21 in a cellular model of Parkinson's disease

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Parkinson's disease (PD) results from the selective loss of dopaminergic neurons in SNpc region of midbrain. Neuron death involves transcriptional activation of pro-apoptotic genes in various neurodegenerative diseases. In the present study we used 6-OHDA treated neuronal PC12 cells as cellular model of PD. Recently we reported that the transcription factors FoxO (Forkhead box class 'O') are activated and mediate neuron death by upregulating pro-apoptotic Bim in Alzheimer's disease models. Consistent with this finding we found that FoxO3a is activated in PD model as well. FoxO3a being a transcription factor can control the expression of a number of genes including Bim and Fas ligand (FasL). In PD model, we found a significant upregulation of pro-apoptotic FasL both at transcript and protein levels. We could successfully show that siRNA mediated down regulation of FoxO3a blocks upregulation of FasL. Simultaneously with the activation of FoxO3a and up regulation of FasL we found a significant down regulation of microRNA21 (miR21) in 6-OHDA-tretaed cells. Previous work from our lab has shown that FoxO3a can negatively regulate miR21 and it has been reported that FasL is regulated by miR21 in cardiac myocytes following hypoxia. Our result showed that down regulating FoxO successfully blocks 6-OHDA mediated upregulation of FasL. Also, upregulating mir21 using microRNA mimics could effectively block the 6-OHDA mediated upregulation of FasL. Thus, our results indicate that FoxO3a regulates pro-apoptotic FasL at least by parts via miR21 in cellular model of PD. Our findings reveal a new signaling pathway associated with neuro-degeneration in PD.

Acknowledgement: The work was supported by CSIR-Network project miND (BSC0115) from Council of Scientific & Industrial research, Govt. of India.

Developmental exposure to zinc/paraquat enhances the susceptibility to dopaminergic neurodegeneration on adulthood re-exposure

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Exposure to heavy metals and pesticides individually or concurrently is implicated in dopaminergic neurodegeneration leading to Parkinson's disease (PD) in humans and experimental animals. The present study aimed to investigate the effect of post-natal exposure of zinc (Zn) or paraquat (PQ) on nigrostriatal dopaminergic neurodegeneration following adulthood re-exposure. Male Wistar rats were treated with zinc/paraquat during post natal (5-19) days followed by re-exposure during adulthood for 12 weeks. Neurobehavioral parameters, striatal dopamine content along with oxidative stress indexes viz., lipid peroxidation (LPO), superoxide dismutase (SOD) activity and glutathione (GSH) content were assessed in control and treated groups. Additionally, protein expression of dopamine synthesizing enzyme- Tyrosine hydroxylase (TH) was also analyzed in exposed and unexposed groups. A significant reduction was obtained in neurobehavioral parameters, dopamine levels, GSH content and TH protein expression in exposed adult animals however greater modulations were observed in developmentally exposed and adulthood re-exposed groups. Animals exposed only during post-natal days showed no change in aforementioned indices. Similarly, LPO levels and SOD activity was markedly augmented in animals exposed in adulthood alone with more pronounced increase exhibited in animals exposed during post-natal days and adulthood both. Post-natal exposure alone did not alter oxidative stress indexes in exposed groups. The results of the study demonstrate that developmental exposure enhances the susceptibility of adult animals for Zn/PQ-induced neurodegenerative changes leading to increased neurotoxicity in pre-exposed animals.

Ethical Statement: The animals were used in the experiment meets the Institutional Ethical Committee compliance and the Ethical Letter Number IITR/IAEC/57/13/56.2016.

Acknowledgements: We thank CSIR-Indian Institute of Toxicology Research for providing the working facilitates and DST-INSPIRE New Delhi for funding my work at the above institution.

Iron accumulation is critical in maneb- and paraquat- induced Parkinsonism

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Parkinson's disease (PD) is a central nervous system disorder and is characterized by the selective degeneration of the nigrostriatal dopaminergic neurons. While iron accumulation in the substantia nigra has been found to be associated with PD, its implication in maneb- and paraquat-induced Parkinsonism has not yet been known. The study was aimed to investigate whether iron accumulation is critical in maneb- and paraquat-induced Parkinsonism or not. Animals were treated with maneb and paraquat (30 mg/kg and 10 mg/kg, respectively, twice a week for 9 weeks) along with respective controls. Nigral tyrosine hydroxylase (TH)-positive neurons and iron content were measured employing standard methods. Level of divalent metal transporter (DMT)-1, ferroportin and caspase 3 proteins was also measured along with cytochrome c release B-cell lymphoma associated protein X (Bax) translocation. Maneb and paraquat reduced the number of TH-positive neurons and increased iron content as compared with respective control. While maneb and paraquat increased DMT-1 and caspase 3 levels, Bax translocation and cytochrome c release and ferroportin level was significantly attenuated. The results thus indicate that iron accumulation plays a key role in maneb- and paraquat-induced Parkinsonism.

Modeling of Biochemical Pathways in Parkinson's disease

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Parkinson's disease (PD) is a neurodegenerative disorder mainly affects motor system and symptoms include resting tremor, muscle rigidity and slowness of movement [1]. These symptoms are caused by loss of dopaminergic neurons in substantia nigra pars compacta (SNc) leading to dopamine deficiency [2]. Substantial evidence suggests that alpha-synuclein (SNCA) have an important role in PD and aggregation of α-synuclein plays a critical role in aetiology of the disease [3]. The main objective of this work is to understand how α-synuclein is involved in PD. Failure in homeostasis of this protein can result in its accumulation thus leading to their aggregation and deposition in cells and in tissues [4]. Eliminating these aggregates has been proposed as a therapeutic approach for PD and other synucleinopathies. Though the role of SNCA aggregates has not completely understood, computational models can help to predict the disease condition that follows. The model can be used to analyze dynamic behavior over the course of the disease as well as identify which processes would be the most effective targets for treatment. The system was modelled using biochemical systems theory (BST) [5] and visualized using Celldesigner and Cytoscape. From information obtained through literature survey, we have modeled a pathway for α-synuclein and other genes and proteins that are involved in this pathway. Finding these proteins and genes could help us to propose therapeutic approaches for PD and other synucleinopathies, by eliminating the aggregates through different intracellular protein degradation pathways.

Keywords: Parkinson's Disease, α-synuclein, Lewibody, BST.

Acknowledgment: The work derives ideas and direction from the Chancellor of Amrita University, Sri Mata Amritanandamayi Devi. This work is partially supported by DST grants SR/CSRI/60/2013 and SR/CSRI/61/2014 and by Virtual Labs Phase II of MHRD, Government of India and by Embracing The World.

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Elevated cholesterol levels in Parkinson's disease potentiate dopaminergic neurodegeneration by diminishing mitochondrial functions

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Elevated blood cholesterol level (hypercholesterolemia) is regarded as a potential risk factor for cardiovascular and metabolic diseases. We recently reviewed (*Paul et al., 2015, Neurochemistry International, 90, 125-33*) the pathological implications of hypercholesterolemia on brain functions and suggested its possible impact towards the occurrence of Parkinson's disease (PD). Despite several epidemiological reports that link hypercholesterolemia with the occurrence PD symptoms, experimental finding from animal/human brain is missing from the available literatures. The present study tested the potential effect of hypercholesterolemia on dopaminergic system in PD. Mice with chronic high-cholesterol diet exhibited motor abnormalities similar to that in PD with dopamine-neuronal loss in substantia nigra (SN). The hypercholesterolemic mice when administration the PD-neurotoxin potentiated not only the neurotoxin-induced motor behavioral abnormalities but also the dopamine-neuronal loss in SN. Diminished mitochondrial complexes (I, II, III) activity in dopaminergic regions of hypercholesterolemic as well as hypercholesterolemic-PD mice is suggested as a mechanism of dopamine-neuronal loss by elevated cholesterol. Mitochondrial dysfunction and resultant oxidative stress (as evident from increased hydroxyl radical, nitric oxide synthase activity, GFAP and anti-oxidant enzymes in dopaminergic regions) is suggested as the underlying events of dopaminergic neurodegeneration that contributes towards the occurrence of PD.

Ethics statement: Handlings of animals were carried out in strict accordance with the guidelines of Institutional Animal Ethics Committee of Assam University, Silchar, India.

Acknowledgements: We sincerely acknowledge the funding and support provided by Department of Biotechnology (DBT), Govt. of India (Sanction Order No. BT/230/NE/TBP/2011, dated April 23, 2012 and BT/PR6806/GBD/27/480/2012, dated August 5, 2013) and Department of Science and Technology (DST), Govt. of India (SERB/F/6636/2014-15 dated 29.12.2014).

Molecular Mechanisms Underlying Proteasomal Modulation and its Significance in Therapeutics

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Proteins are building blocks of cells that are regularly synthesized for proper functioning and maintenance of living cell. However, proteins are always at risk of misfolding and aggregation leading to toxicity and disease. Thus for survival, healthy cells employ a tightly regulated mechanism for elimination of misfolded or damaged proteins. Ubiquitin proteasome system is one such mechanism that degrades such damaged or misfolded proteins with help of proteasome. Proteasome is a complex that is made up of 20S core particle and 19S regulatory particle. The 20S core contains protein degradation sites whereas the 19S regulates the degradation of polyubiquitylated proteins. Inhibition of proteasome was initially done to understand the catalytic activity of proteasome. As proteasomes are involved in degradation of proteins, blocking its activity leads to accumulation of those proteins, resulting in anti-proliferative and apoptotic effects. Systemic administration of these inhibitors is thus being targeted for cancer treatment. Interestingly, proteasome inhibition has also been shown to be potential therapeutic strategy for treatment of some form of neurodegenerative diseases. Diclofenac is one of the commonly used drugs with analgesic and anti-inflammatory effect. Here, we have explored the mitochondrial apoptotic effects of diclofenac, which can be due to disturbance in proteasomal function. This study may be a potential therapeutic avenue for cancer and neurodegenerative disease treatment.

Acknowledgement: This work was supported by the Department of Biotechnology, Government of India. AM was supported by Ramalinganswami Fellowship (BT/RLF/Reentry/11/2010) and Innovative Young Biotechnologist Award (IYBA) scheme (BT/06/IYBA/2012) from the Department of Biotechnology, Government of India.

Understanding the cross talk between autophagy and apoptosis in a model of Alzheimer's disease

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Reports suggest a vicious crosstalk between apoptosis and autophagy during neurodegeneration in Alzheimer's disease (AD). Various transcription factors and BH3-only proteins of Bcl-2 family may play common roles in the regulation of both the processes. Here, we studied the role of a BH3-only protein PUMA and the transcription factors FoxO (Forkhead box class 'O') in the regulation of the crosstalk, in a model of AD. We found that downregulation of PUMA and FoxO by respective shRNAs in differentiated PC12 cells, inhibits autophagy in respone to amyloid-β (Aβ) treatment as checked by the autophagy markers LC3 and p62. We have recently reported that downregulation of PUMA and FoxO by respective shRNAs blocks neuronal apoptosis. We further looked into the time kinetics of upregulation of p62 and LC3, and TUNEL and pH2AX (apoptotic markers), by western blot, in Aβ-treated neuronal cells to monitor the time of occurrence of the two processes. We found that there occurs a simultaneous induction of both autophagy and apoptosis after Aβ treatment. We further checked the survival of the cells by interfering with autophagy. We found that on inhibition of autophagy by 3-Methyladenine (3MA) protected neuronal cells from death induced by Aβ. In contrast, induction of autophagy by Rapamycin did not provide protection to neuronal cells against Aβ treatment. Further, inhibiting both autophagy and apoptosis by pan-Caspase inhibitor and 3MA simultaneously, resulted in higher viability even after Aβ treatment. Taken together our results indicate a probable crosstalk between autophagy and apoptosis during neurodegeneration in AD.

Role and regulation of the cell cycle molecule Cdc25A in Parkinson's disease related Neurodegeneration

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Parkinson's disease (PD) results primarily due to death of dopaminergic neurons in substantianigra pars compacta (SNpc). Current PD medications treat symptoms; none halt or retard dopaminergic neuron degeneration. A growing body of evidence suggests that components of cell-cycle machinery also get activated in neurons when subjected to apoptotic stimuli and play required roles in their death. However, the exact linking mechanism of cell-cycle related molecules with neuron death is still under veils. One such molecule that is observed to play a paradoxical role in neurodegeneration is cell division cycle 25A (Cdc25A) phosphatase. Cdc25A is a dual specificity phosphatase that activates cyclin dependent kinases by dephosphorylation to promote cell-cycle progression. In this study, we investigated the role of Cdc25A in the neurodegeneration in PD. We used a well accepted cellular model of PD that is neuronally differentiated PC12 cells treated with 6-OHDA. Checking out both transcript and protein levels of Cdc25A, we observed that there was no significant change in the transcript levels of Cdc25A upon 6-OHDA treatment. But the protein level of Cdc25A was increased upon the treatment of 6-OHDA for 8 h and 16 h with respect to that of control. Thus we are testing if the increment in the level of Cdc25A be post-translationally regulated in PD that leads to its stability. Most importantly, RNAi mediated knockdown and inhibition of Cdc25A resulted in prevention against PD relevant toxins. Our study suggests that Cdc25A might get stabilized and activates apoptotic cell-cycle pathway that contributes to neuron death in PD.

Cross-talk between Insulin Receptor and Neurotrophins in neural stem cells differentiation

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The self-renewal and multipotency of the neural stem cells in brain are modulated by both cell-intrinsic and cell-extrinsic factors. Ability of insulin to induce neurogenesis suggests potential role of insulin receptor signaling in plasticity of neural stem cells. Moreover, neurotrophic factors- Nerve growth factor (NGF) and Brain derived neurotrophic factor (BDNF) have been shown to play very crucial roles in the enhancement of neural stem cells differentiation. The present study was carried out to understand the cross-talk between Insulin receptor and neurotrophin signaling in the neural stem cell differentiation. Neural stem cells were transfected with Insulin receptor (IR) siRNA followed by studying its subsequent effects on neurotrophins (NGF & BDNF) and their receptor levels. Our results indicate down-regulation of transcript levels of neurotrophins (NGF and BDNF) and their receptors (TrkA and TrkB) in IR knock-down neural stem cells. Also, levels of brain cell markers- Glial fibrillary acidic protein (GFAP) and Neurofilament (NF) were significantly down-regulated in IR transfected neural stem cells indicating cross-talk between IR and neurotrophin mediated signaling pathways.

Ethics statement: All the protocols were duly approved by the institutional ethical committee, Animal House facility, Department of Biochemistry, The Maharaja Sayajirao University of Baroda, Reference No. ZD/13/2015.

Acknowledgements: This work was supported by research grant No. BT/PR5033/MED/30/797/2012 from Department of Biotechnology India. Instrument facility: Confocal microscopy and Real time PCR from DBT-MSUB ILSPARE, The M.S.University of Baroda.

Amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD)

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Amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD) are related neurodegenerative disorders which are characterized by a rapid decline in cognitive and motor functions, and short survival. Both syndromes may be present within the same family or even in the same person. The genetic findings for both diseases also support the existence of a continuum, with mutations in the same genes being found in patients with ALS, FTD or FTD/ALS. Little is known about the molecular mechanisms underlying the differences in mutations of the same protein causing either ALS or FTD. Here, we shed light on 348 ALS and FTD missense mutations in 14 genes focusing on genic intolerance and protein stability based on available 3D structures. Using ENCoM (Elastic Network Contact Model) that predicts stability based on vibrational entropy, we predicted that most of the missense mutations with destabilizing energies are in the structural regions that control the protein-protein interaction, and only a few mutations affect protein folding. We found a trend that energy changes are higher for ALS compared to FTD mutations. The stability of the ALS mutants correlated well with the duration of disease progression as compared to FTD-ALS mutants.

Drosophila as a model of neurodegenerative diseases: Relevance and applications

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The incidence of neurodegenerative diseases increases with age and, considering the aging process of the population worldwide, the prevalence of neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease is expected to rise in the next years. Accurately understanding the etiopathogenic mechanisms of these diseases is a crucial step for developing disease-modifying drugs able to preclude their emergence or at least slow their progression. Animal models contribute to increase the knowledge on the pathophysiology of neurodegenerative diseases. *Drosophila melanogaster*, the common fruit fly, is one of the oldest and most powerful genetic models and has been used for studying human disease for more than two decades. Its complex nervous system, conserved neurological function, and human disease-related loci allow *Drosophila* to be an ideal model organism for the study of neurodegenerative disease such as Alzeimer's and Parkinson's. Because of the genomic similarity between *Drosophila* and humans, *Drosophila* neurodegenerative disease models exhibit a variety of human-disease-like phenotypes, facilitating fast and cost-effective *in vivo* genetic modifier screening and drug evaluation.

Ethics statement: Ethical clearance is not required for insects (fruit fly, *Drosophila melanogaster*)

Acknowledgements: VB is grateful to DST, New Delhi for the Financial assistance (SB/EMEQ-78/2014).

Alteration in kynurenic acid synthesis in resected hippocampus tissues obtained from patients with mesial temporal lobe epilepsy-hippocampal sclerosis (MTLE-HS)

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Mesial temporal lobe epilepsy-hippocampal sclerosis (MTLE-HS) is most common form of drug-resistant epilepsy where hippocampus is responsible for unprovoked seizures. The hallmark of MTLE is enhanced glutamatergic excitatory neurotransmission. Kynurenic acid (KYNA), a tryptophan metabolite, is a specific inhibitor for NMDA type glutamate receptor. It is synthesised and released from cortical astrocytes. The present study was designed to test the hypothesis that in MTLE, endogenous kynurenic acid synthesis is altered in hippocampus.

Hippocampus from MTLE patients and tissues resected from the tumour margin during brain tumour surgery of seizure-free patients as non-epileptic control were used for the study. To determine total KYNA concentration, tissues were kept in perchloric acid at -80°C. Tissues were homogenised, centrifuged and supernatants were collected, stored at -80°C. To determine endogenous KYNA synthesis, 350µm thick slices were prepared from the tissues and incubated with 100µM kynurenine (precursor for KYNA) containing artificial cerebrospinal fluid for 2 hours at 30°C; incubating solutions were stored at -80°C. KYNA was estimated using UHPLC-MS/MS.

We observed that Total KYNA concentration was significantly less in MTLE hippocampus (0.00144 ± 0.001 µg/mg of protein) compared to non-epileptic Controls (0.00889 ± 0.003 µg/mg of protein). Endogenous kynurenic acid production was also significantly reduced in MTLE hippocampus (2.894 ± 0.35 ng/mg of wet tissue) compared to non-epileptic Controls (0.883 ± 0.21 ng/mg of wet tissue).

Our findings suggest that decreased endogenous KYNA synthesis could be a reason for hyperactive glutamatergic neurotransmission and targeting this pathway could act as a potential therapeutic target for MTLE.

Acknowledgment: This work was supported by the Centre of Excellence for Epilepsy, a collaborative project between All India Institute of Medical Sciences, New Delhi and National Brain Research Centre, Manesar; and

funded by Department of Biotechnology, Ministry of Science & Technology, Govt. of India [Grant: BT/01/COE/09/08].

Ethical Statement: The experiments mentioned in this study have been performed as per the guidelines of institutional ethics committee (IEC), All India Institute of Medical Sciences, New Delhi, India (Ref. No. IECPG/-38/27/11/2015, RT-4/30.12.2.15).

Effect of Trichostatin A-an HDAC inhibitor, on Juvenile and adult Zebrafish fin regeneration

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In higher vertebrates, including humans, barring a few tissues such as skin and liver, very little regeneration occurs to replace dead or damaged tissues. However, the zebrafish offers an opportunity to study mechanisms underlying regeneration since several organs, including heart, spinal cord and fin regenerate, allowing for complete gain of function.Recent studies have highlighted the vital role of epigenetic modificationsin several physiological functions.Our earlier observations have demonstrated that TSA, an inhibitor of histone deacetylases inhibits the regeneration of the amputated finfold of a 2 days post fertilization (dpf) zebrafish larvae. Thisstudyaims to extend the observation on juvenile and adult zebrafish. Zebrafish aged 15 dpf and 30 dpf were anesthetized and their caudal fins were amputated.The amputated fishes/larvae were treated with varying concentrations of TSA.The regeneration was monitored daily by individually imaging each fish. The regenerative index was calculated as the ratio of the regenerated region to the original fin area of the fish. As compared to our earlier observation which showed complete inhibition of fin regeneration in 2 dpf larvae, TSA did not have a similar inhibitory effect on older fish. However an alteration was observed in the kinetics of regeneration. This study will be extended to understand the underlying molecular mechanisms.

Ethics Statement: This project has been approved by the Institutional Ethics Committee.

Acknowledgements: We would like to thank TIFR, DBS for providing us with wild type strain of Zebra fish.

*The presenting author would like to apply for Prof. S.S. Parmar Research Foundation Award for paper presented in poster session and also for Ravindra and Lalita Nath Travel Fellowship

Differntial Immune response to MPTP neurotoxin, Evidences from two mice models of Parkinson's disease

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Parkinson's disease (PD) is an-age related slow and progressive neurodegenerative disorder, characterized by loss of dopaminergic neurons (DA) in substantia nigra pars compacta (SNpc). Studies on postmortem samples of PD patients and animal models suggest uncontrolled neuroinflammation as the putative cause for the death of nigral neurons. Although the underlying causes are unknown, the interesting aspect about the prevalence of PD is that it has a racial or ethnic bias; highest among Hispanics, followed by non-Hispanic Whites, Asian Indians, and African non-Whites. Similarly different mice strains also show differential susceptibility to MPTP neurotoxin. Among the mice strains, the C57BL/6 mice are most susceptible whereas CD-1 white mice are resistant to MPTP. In the present study, unbiased stereological estimation of immunoperoxidase stained midbrain sections revealed significantly higher number of microglial cells in SNpc of C57BL/6 (susceptible) than the CD-1 white mice(resistant) whereas number of S100β positive astroglial cells was less. Upon MPTP administration; C57BL/6 mice showed significantly higher level of proinflammatory cytokines such as TNF-α, IL-1β, IL-6 on post MPTP day1, day4 and day7, whereas the compensatory response by anti-inflammatory cytokines (TGF-β, IL-4, IL10) was low compared to CD-1 white mice. Thus our study suggests that glial responses are critical in determining the differential susceptibility to MPTP.

Acknowledgements: AP is a UGC SRF. Dr. Gayathri. N, Department of Neuropathology, NIMHANS. The study is funded by DBT (No. BT/PR12518/MED/30/1462/2014)

Investigating early amyloid deposits in brain and imaginal discs in the GMR-Aβ42 strain, an Alzheimer's disease model of *Drosophila*

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Alzheimer's disease (AD) is the most common neurodegenerative disorder with progressive impairment of cognitive ability leading to dementia and death in elderly population. However, approximately 10% of people with disease have early onset Alzheimer's which often appears at young age of 40-50. Aggregation of β-amyloid peptides and hyperphosphorylated tau protein (in the form of amyloid plaques and neurofibrillary tangles) trigger an array of events ultimately leading to neurotoxicity, is central to AD progression. We have in our laboratory transgenic *Drosophila* strain for Alzheimer's disease (GMR-$A\beta_{42}$) in which the defective protein is expressed in the eye displaying a 'rough-eye' phenotype in the adult fly. Recent reports discuss the expression of GMR in tissues other than the eye in *Drosophila.* We had earlier reported behavioral differences in the adult flies. However, no distinct external phenotypic or behavioral characteristic is reported in the larvae of this mutant. We present here results of our study of different parameters such as amyloid protein staining and apoptosis at different stages to assess the early presentation of the disease. In addition, biochemical estimations (Catalase and Lipid peroxidation assays) are also performed to evaluate the oxidative stress.

Ethics Statement: This project has been approved by the Institutional Ethics Committee.

Acknowledgements: We would like to thank Dr. Mousumi Mutsuddi and Dr. Subhash C. Lakhotia of BHU for providing us with GMR-$A\beta_{42}$ and TIFR, Mumbai for CsBz flies.

*The presenting author would like to apply for Prof. S.S. Parmar Research Foundation Award for paper presented in poster session and also for Ravindra and Lalita Nath Travel Fellowship

Staging and Apoptosis in larvae of *park13* mutants, a Parkinson's Disease model of *Drosophila*

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Parkinson's Disease (PD) is the second-most common neurodegenerative disease in the world, after Alzheimer's. It has affected nearly 10 million people globally with approximately 60,000 new cases per year and is characterized by tremors, bradykinesia, muscle rigidity, impaired posture and balance and loss of autonomous movement. We have obtained a PD loss-of-function mutant strain of the fruit fly *Drosophila melanogaster*, generated by a deletion in the Parkin gene. These *park13* flies show distinct defects in locomotor ability. However, we have also observed a variation in the morphology and duration of their stages. Whether this occurs as a consequence of heightened apoptosis is investigated here.

Using CsBz as a control, we compare the duration of stages and distribution of apoptosis, particularly in the larval stages. We report a difference in the life cycle duration between CsBz and *park13*along with a morphological difference between their respective 3rd instar larvae, while through Acridine Orange staining, we demonstrate the extent of apoptosis in the brain and imaginal discs. This paves the way for understanding molecular players in the neurodegenerative disease.

Ethics Statement: This project has been approved by the Institutional Ethics Committee.

Acknowledgements: We would like to thank Dr. Mousumi Mutsuddi and Dr. Subhash C. Lakhotia of BHU for providing us with *park13* and TIFR, Mumbai for CsBz flies.

*The presenting author would like to apply for Prof. S.S. Parmar Research Foundation Award for paper presented in poster session and also for Ravindra and Lalita Nath Travel Fellowship.

Exploring the role of Transforming Growth Factor Beta (TGFβ) signalling in Mesial Temporal Lobe Epilepsy (MTLE) patients

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TGFβs are pleiotropic cytokines which are found to be upregulated in various brain disorders. Experimental evidence shows that TGFβ is upregulated in neurons and astrocytes in animal models of epilepsy. Recent studies in rats show that following blood brain barrier (BBB) damage, albumin binding leads to TGFβ signalling activation and contribution to network excitability in epileptogenesis. However no translational studies on the role of TGFβ signalling in epileptogenesis are reported in MTLE patients. In the present study we aim to investigate the expression level change of TGFβ1 and its downstream signalling molecule pSMAD3 in MTLE versus non epileptic control patients.

Protein was isolated from the resected hippocampal samples from MTLE patients (n=14) and control patients (n=7). Western blot was done with goat anti-human TGFβ1 and pSMAD3 and appropriate secondary antibody. Protein expression was normalised to expression of GAPDH.

TGFβ1 is upregulated in MTLE (106.3±67.4) in comparison to tumor periphery tissue (62.44±7.8). pSMAD3 is significantly upregulated (p=0.003) in MTLE (pSMAD3: 128.10±40.3) in comparison to autopsy tissue(pSMAD3:66.79±45.26) and also significantly upregulated (p=0.004) in MTLE (pSMAD3: 114.44±40.7) in comparison to tumour periphery tissue(pSMAD3: 57.86±22.1).

Our study demonstrates that TGFβ signalling is activated in MTLE patients, through the phosphorylation of SMAD3. TGFβ pathway activation is an important aspect of brain inflammation and may be associated with BBB damage. Alterations in BBB may affect excitability of brain and lower the threshold for seizures, enhancing epileptogenesis. Further studies on more number of patients are required to elucidate how this pathway is contributing to epileptogenesis

Corelation of DNA Methylation & RNA Sequencing manifest alteration in Gene Expression in Focal Cortical Dysplasia: An Epigenetic Study

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In an attempt to decipher the molecular basis of the pathologic modifications in neuronal circuits in Epilepsy, studies have revealed a remarkably diverse pattern of gene expression resulting from epigenetic changes. DNA methylation is a pertinent type of epigenetic modification which influences brain development, function, and aging. Here Microarray profiling of methylated DNA and RNA sequencing have been used to investigate gene expression in the human tissue samples of Focal Cortical Dysplasia (FCD), with the aim of identifying functional pathways which are significantly activated or repressed during epileptogenesis.

Methylated DNA was immunoprecipitated using anti-5-methyl cytidine antibody from surgically resected tissues of FCD patients and controls from Autopsy. Whole Genome Amplification and Microarray Hybridization was then carried out using Agilent ChIP on ChIP kit G4495A. RNA sequencing was performed using standard protocols on Illumina HiSeq 2500 platform. Differential gene expression analysis was done using Cuffdiff. Gene Spring Software was used for quantification of methylation and its co-relation with RNA Sequencing data.

A total of 918 genes were identified to be differentially expressed, whose gene expression directly correlated with methylation status. Out of these, 604 genes were hypermethylated and their gene expression depressed and 314 overexpressed genes and hypomethylated. Gene Ontology and pathways analysis revealed important pathways like Glutamatergic, Gabaergic, Cholinergic, Adrenergic, Calcium, PI3-AKT, RAS, Synaptic Vesicle Cycle, CAM, BDNF, MAP Kinase, WNT among others involving aberrantly expressed genes. These genes will be further validated as may prove to be potential prognostic and diagnostic biomarkers in FCD.

Acknowledgment: This work was supported by theCentre of Excellence for Epilepsy, a collaborative project betweenAll India Institute ofMedical Sciences, New Delhi and National Brain Research Centre, Manesar; andfunded by Department of Biotechnology, Ministry of Science & Technology, Govt. of India [Grant:BT/01/COE/09/08].

Ethical Statement: The experiments mentioned in this study have been performed as per the guidelines of institutional ethics committee (IEC), All India Institute of Medical Sciences, New Delhi, India (Ref. No. IEC/NP-178/08.05.2015).

Characterization of antinociceptive effect following activation of the spinal cannabinoid type 1 receptor in rats

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Treatment of pain with opioids like morphine is accompanied by unpleasant and at times, life-threatening side effects. Cannabis produces antinociception as well as psychotropic effects like euphoria. It was hypothesized that selective activation of spinal cannabinoid receptors can lead to credible antinociception without side effects.

Sprague Dawley rats (weighing ~310 g; n=108) were used for this study. Initially, these were subjected to hind paw incision and the expression of cannabinoid type 1 receptor (CB1r) in the spinal cord was studied by Immunohistochemistry and Western blot. Rats were then implanted with intrathecal catheters and arachidonylcyclopropylamide (ACPA), a CB1r agonist (1, 3 or 10 mcg), was administered. The antinociceptive effect was evaluated by guarding, allodynia and thermal hyperalgesia of the incised paw. This was compared to morphine. Reversal of this effect was tested by CB1r antagonist. Antinociception was also evaluated using the formalin test. Finally, motor function was tested using rotarod apparatus.

Expression of CB1r was observed over the superficial laminae of the dorsal horn. Post-incision, expression increased at 2 h but subsequently decreased. Intrathecal ACPA attenuated behavioral parameters of nociception after paw incision but not formalin injection. AM 251 reversed CB1r-mediated antinociception. Comparison with morphine showed higher antinociceptive effect after ACPA treatment. Motor function was not affected.

Selective activation of the spinal CB1r produces significant antinociception without any motor deficit after surgical incision. These findings could have clinical relevance.

Ethics statement: Handling of rats was carried out in strict accordance with the guidelines of Institutional Animal Ethics Committee of AIIMS, New Delhi, India (F. No. 903/IAEC/15).

Acknowledgements: (This work was supported by research grant No. BT/PR14279/Med/30/452/2010 from Department of Biotechnology, India and Indian Council of Medical Research SRF to Mayank Gautam, No.3/1/2/52/Neuro/2013-NCD-I).

Smokeless tobacco induced neurodegeneration: an *in vitro* approach

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The use of smokeless tobacco (SLT) assorted with areca nut, betel leaves, lime and catechu commonly known as "*gutkha*" or "chewing tobacco" is global threat to human health including possible harmful effects on nervous system. In this study we investigated whether SLT is a causative factor of neurodegeneration and to explore the probable mechanism of action of SLT *in vitro*. We studied the effects of graded doses of water soluble lyophilised SLT (0.5-10 mg/ml) using PC12 (rat pheochromocytoma) and SH-SY5Y (human neuroblastoma) cell line after differentiation. We investigated critical effects of SLT *in vitro* using cell viability by MTT assay, ROS generation by DCFDA method, mitochondrial ROS generation by mitosox assay, mitochondrial trans-membrane potential (MMP) by TMRM staining, mitochondrial health by mitotracker red staining and status of some pro- and anti-apoptotic proteins by immunoblot. We found increased neuronal cell death with increasing doses of SLT. We selected three effective doses of SLT for ROS production studies. We found increased ROS and altered MMP and mitochondrial morphology with three doses. We selected five time points of specific SLT dose with 50% cell death for expression of apoptotic markers. We found increased expression of pro-apoptotic proteins and decreased level of anti-apoptotic protein upon SLT treatment. Our results suggest that SLT may induce neuronal death via the production of ROS, alteration of MMP, mitochondrial morphology and activation of apoptotic proteins. This is perhaps the first report on the role of SLT on neurodegenerative mechanism.

Acknowledgements: This work was supported by Grant No.: UGC/486/Fellow (Univ.), University Grants Commission (UGC), India. Professor Sanjit Dey would also like to acknowledge the research support from CPEPA [F No. 8-2/2008 (NS/PE)], LSRB, DRDO [DLS/81/48222/LSRB-244/SH&DD/2012] and CSIR, Government of India [23(0024)/12/EMR-II].

The connection between oxidative stress and intracellular abnormal amyloid-β production

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Alzheimer's disease (AD) is the most common form of neurodegenerative disease. Aging has been the greatest risk factor for this disease and it has been postulated that increase in oxidative stress with age might trigger abnormal amyloid-β (Aβ) production inside cell. In this study we mimicked an aging cell *in vitro* by treating differentiated neuronal SH-SY5Y and PC12 cells with a range of sub-lethal doses of Camptothecin (Cpt). Cpt is a known DNA damaging agent which actually inhibits DNA Topoisomerase I and induces oxidative stress. The window of dose which was selected started from 10 nM to 10 μM. It has been observed that doses upto 100 nM, there were no significant cell death. But there was sign of significant oxidative stress below the dose of 100 nM Cpt. The mitochondrial health was also compromised with the low dose of Cpt. The mitochondrial membrane potential and morphology were studied by staining differentiated SH-SY5Y cells with TMRM and mitotracker red stain respectively under fluorescence microscope. Both the morphology and membrane potential was compromised. There was reduction in the expression of total PARP-1 with increasing doses of Cpt but the appearance of cleaved PARP-1 appeared from the dose of 100 nM Cpt. Most importantly, there was an increase in appearance of immunogenic multimeric bands of Aβ with increase in doses of Cpt. Taken together this data provides a platform to study the aging condition *in vitro* and links oxidative stress to the abnormal production of Aβ inside the cell.

Acknowledgements: The work is supported by CSIR-12FYP Network Project (BEND BSC-0206).

Insilico targeting of miRNAs: The Next Generation therapeutic targets in Neurodegenerative disorders

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microRNAs (miRNAs), the small noncoding RNAs (ncRNAs) are key regulators of gene expression. They act on wide range of targets by binding to mRNA via imperfect complementarity at 3' UTR. Complex miRNA network topology suggests that miRNAs regulate many biological processes including neuronal development, differentiation, and disease. Altered expression of several miRNAs has been reported in many neurodegenerative disorders (NDDs). miRNA 15, miRNA 21, and miRNA 146a are identified as important miRNA which play critical role in NDDs. As these miRNAs regulate many genes, miRNA targeted approaches would allow concurrently targeting of multiple effectors of pathways that regulate disease progression. In present work, we have found the complex network of miRNAs regulating expression of many genes, which provide a powerful clue in next generation therapeutic targeting of generalized neurodegeneration phenomenon in several NDDs.

Heat Stress Induced Physiological perturbations and Molecular changes in the Rat Brain and an Insight into key molecules unravelling some of the therapeutic targets

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Exposure to high ambient temperature is a natural hazard with large number of mortality across the globe. Heat Stress (HS) has remarkable impact on brain structure and functions which are further exacerbated in Heat Stroke. Published literature provides limited insight into HS induced damage in brain; therefore, present study is designed to explore molecular mechanism behind HS. *Sprague dawley* rats were exposed to Heat Simulation Chamber (Ambient Temperature, T_a=45±0.5°C and Relative Humidity, RH=30±10%). Continuous monitoring of Core Temperature (T_c), Skin Temperature (T_s) and NIBP were done. On completion of exposure, rats were decapitated and hypothalamus, hippocampus, cortex and prefrontal cortex were excised out for histological, biochemical and molecular analysis. T_c, T_s, MAP and HR were found to be higher in HS groups. Nissl Staining revealed greater number of pyknotic neurons in brain of heat exposed rats. We observed elevated CRH & ACTH whereas decreased Corticosterone levels in HS rats. Marked increase in expression of Hsp70, NF-κB, Caspase3 and n-NOS was detected in rat cortex and prefrontal cortex post exposure. Upsurge in pro-inflammatory cytokines like IL-1, IL-6 and TNF-α gave clear picture of exaggerated neuroinflammation in rat brain after exposure to HS. Based on the observations, we postulate that HS induced neuroinflammation in hypothalamus, hippocampus, cortex and prefrontal cortex of rats, which may act as causative factors for neurodegeneration. Further, microarray of hypothalamus provided insight into some of the genes and the pathways that might unravel some of the therapeutic targets which would help in conferring thermotolerance to living organisms.

Ethical Statement: This study was performed in strict accordance with the recommendations for the care and use of laboratory animals. All the experimental protocol and animal care were approved by the Institutional Animal Ethical Committee (IAEC) of Defence Institute of Physiology and Allied Sciences (DIPAS), Delhi, India.

Acknowledgements: We would like to thank DRDO for financial support and our sincere thanks to DIPAS for help and support.

Pax6 as a potential biomarker for brain tumour diagnosis

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The paired box 6 (PAX6) encodes a homeodomain transcription factor that is involved in the development of the brain. Pax6 expression is regulated by Sonic hedgehog (Shh) signalling pathway which play vital role in neural tube development and patterning. The role of Shh signalling in brain tumour development is well known. However the role of Pax6 in brain tumour development is not very well study. In this study we attempted to explore the role of Pax6 in brain tumour development.

This study focuses on homeodomain transcription factor Pax6 and its potential role in brain tumorigenesis.

Human primary brain tumour samples were collected from the Department of Neurosurgery, Jawaharlal Nehru Medical College (JNMC) AMU, Aligarh. Thereafter, processed primary brain tumour samples for histochemistry, immunohistochemistry and PCR to check the expression of Pax6.

A higher expression of Pax6 transcription factor was observed in human brain tumour samples.

Observed high expression pattern of Pax6 confirms that Pax6 could be considered as one of the novel biomarkers for early detection of brain tumours in the suspected patients.

Nkx2.2 transcription factor a potential target for brain tumor treatment.

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Sonic hedgehog signalling pathway is a developmental key regulator of nervous system. Binding of sonic hedgehog active ligand (Shh-N) to 12 transmembrane patched1 (PTCH1) triggers the cascade of this signalling pathway. Signalling cascade begins with the retrieval of Smoothened (SMO) a 7 transmembrane protein which is repressed by PTCH1 in the absence of activated Shh signalling ligand. Now, activated Gli1, an immediate downstream activator of Shh pathway enters nucleus and binds to the promoter region of target genes and regulate their expression. Nkx2.2 is a putative downstream target gene of Shh signalling pathway, which is positively regulated by Gli1 and has great role in neuron development and regeneration. Therefore this study is aimed to determine the role of homeobox transcription factor *II* Nkx2.2 in human brain tumour development.

Surgically removed human brain tumour samples were collected from Jawaharlal Nehru Medical College AMU, Aligarh, and performed histochemistry, immuno histochemistry and PCR.

Higher expression of Nkx2.2 found in surgically removed brain tumor samples compared to normal human brain samples.

Elevated Nkx2.2 expression in human brain tumor samples supports the hypothesis that, Nkx2.2 transcription factor could be used as one of the potential targets for early detection and treatment of brain tumor.

Diminished brain Acetylcholinesterase activity leads to cognitive impairment in chronic kidney disease: A study in mice model.

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Chronic kidney disease (CKD) is an independent somatic risk factor for the development of cognitive dysfunction, which is found to be prevalent in 30-40% of patients on dialysis. However, the mechanism underlying the cognitive dysfunction in CKD patients has not been elucidated yet. In the present study, a female mouse model of CKD was developed by administration of adenine at the dose of 0.3% w/w mixed with feed for 4 weeks. The model was validated by elevated serum urea level and histopathological changes with uroliths in the renal tissue. Novel Object Recognition test (ORT) was performed to verify prevalence of cognitive dysfunction in the model. Since the enzyme Acetylcholinesterase (AChE) is implicated in cognitive impairment, the activity of the enzyme in different brain regions was estimated using histoenzymological and spectrophotometric methods. The results of ORT revealed the prevalence of cognitive dysfunction CKD mice. Thus, the activity of brain AChE was estimated, and was found to be diminished in the prefrontal cortex, cerebral cortex, hippocampus and striatum of mice with CKD. The percentage decrease in AChE activity was found to be 37.76%, 43.97%, 27.07% and 42.95% in the prefrontal cortex, cerebral cortex, striatum and hippocampus respectively, compared to control mice. Thus, the present study is the first of its kind in understanding the mechanism underlying the neurological complications (cognitive dysfunction) of CKD and is of immense significance.

Ethical statement: Handlings of animals were carried out in strict accordance with the guidelines of Institutional Animal Ethics Committee of Assam University, Silchar, India.

Acknowledgements: The funding and support provided by Department of Biotechnology (DBT), Govt. of India (Sanction Order No. BT/230/NE/TBP/2011, dated April 23, 2012 and BT/PR6806/GBD/27/480/2012, dated August 5, 2013) is greatly acknowledged.

Memory impairment under Hypobaric Hypoxia (HH): Role of histone acetylation

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Hypobaric hypoxia (HH) is a high altitude hypoxia associated with oxidative stress and brain dysfunction. Epigenetic modification play significant role in response to oxygen depletion. Epigenetic modification involve in regulation of neuronal functions and gene expression. Histone acetylation is one of the principles epigenetic modifications, associated with transcription activation of the targeted gene and involve in cellular response against hypoxia. Acetylation homeostasis of cell which is govern by two antagonistic enzyme HAT (Histone acetyltransferase) and HDAC (Histone deacetyltransferase). HDAC associated with oxidative stress, neuroinflamation, neurodegeneration and memory impairment though the repression of transcription. In the present study we used *Sprague dawley* (SD) male rats and exposed to hypobaric hypoxia (HH). We explore the histone modification in hippocampus and cortex under different time exposure of HH. We also evaluate the role of histone modification in neurodegeneration and memory impairment under same condition. HH disturb the homeostasis of HAT and HDAC and lead to neurodegeneration and memory impairment. Neurodegeneration explore by Cresyl violet/ Fluoro Jade staining and memory impairment assessed by the Morris water maze (MWM). Our finding show direct correlation between increased HDAC activity and neurodegeneration and further with memory impairment. Further increased expression of caspase 3 may accounts for involvement of apoptotic pathway in HH induced cognitive decline.

Ethical statement: This abstract is in compliance to IAEC regulations. This study was performed in strict accordance with the recommendations for the care and use of laboratory animals. All the protocols were duly approved by the institutional ethical committee.

Acknowledgement: This work was supported by DIPAS, DRDO and sincere thanks to UGC for the financial support.

Epigenetic mechanism play an important role in regulation of gene expression and functions of the neurons. Histone acetylation is a principle epigenetic modification involve in the cellular response against hypoxia. Acetylation homeostasis of cells which is govern by Histone acetyltransferase (HAT) and histone deacetyltransferase (HDAC)is closely associated with learning and memory and other physiology of neuronal cells. Studies has reported that high altitude exposure induced hypobaric hypoxia is associated with oxidative stress, neurodegeneration and memory.

Unilateral administration of Hcy into the median forebrain bundle of rats causes striatal dopamine depletion and displays behavioral abnormalities similar to Parkinsonism

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Homocysteine, a non-essential amino acid has been considered as a major risk factor for cardiovascular diseases, and patients with hyperhomocysteinemia exhibit neurological and psychological abnormalities. Elevated level of this molecule in the blood as well as cerebrospinal fluid of Parkinson's Disease patients receiving L-DOPA therapy prompted us to investigate the effect of homocysteine towards the dopaminergic system in Sprague-Dawley rats. Unilateral Intra-Median Forebrain Bundle infusion of different doses of Hcy (2, 4 and 8 μmole in 2μl) in these animals exhibited significant and dose-dependent decrease in dopamine levels in the ipsilateral striatum on 19th day of post-infusion. On the other hand 3,4-dihydroxyphenylacetic acid level in the striatum showed a dose-dependent decrease, while the diminished level of homovanillic acid was observed only in the highest dose. Moreover Amphetamine administration in these animals on the 14th day caused stereotypic turning behavior, ipsilateral to the side of infusion whereas Apomorphine challenge on the 16th day elicited stereotypic contralateral circling behaviour. All these results indicate nigrostriatal lesions similar to that observed following intranigral infusion of the dopaminergic neurotoxin, 6-hydroxydopamine, providing evidence for the neurotoxic nature of homocysteine to dopaminergic neurons. Furthermore, these findings also suggest that elevated level of this molecule in parkinsonian patients may be conducive to accelerate the progression of the disease.

Ethics statement: Handlings of animals were carried out in strict accordance with the guidelines of Institutional Animal Ethics Committee of Assam University, Silchar, India.

Acknowledgements: We sincerely acknowledge the funding and support provided by Department of Biotechnology (DBT), Govt. of India (Sanction Order No. BT/230/NE/TBP/2011, dated April 23, 2012 and BT/PR6806/GBD/27/480/2012, dated August 5, 2013) and Department of Science and Technology (DST), Govt. of India (SERB/F/6636/2014-15 dated 29.12.2014).

Cerebrospinal ventricle injection of human beta amyloid peptide and its effect in embryonic zebrafish

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Beta amyloid is the major protein converted as plaques during Alzheimer's disease. Rise in the release of beta amyloid leads to aggregation and thus replace dopaminergic cells in the brain. The main aim of the study is to understand the role of beta amyloid peptide during embryonic development stages. Although, the deposition of this protein has severe effects at elderly stage, studying the *in-vivo* effects on injected beta amyloid on embryos will draw a way to understand the neurogenesis of zebrafish. The phenotypical analysis of treated embryos showed delayed growth and small heads compared to control. The cartilage to bone transformation rate has been reduced significantly. Dopamine levels on 15dpf embryos have been decreased to 2.8ng protein/mg of brain protein. Histological sectioning and behavioral assays also supported the same. Cerebral spinal fluid was quantified in order to determine the normal functioning of brain signaling. Thus the study aids to understand the role of beta amyloid as well the regeneration of embryonic brain during the developmental stages.

Keywords: beta amyloid, amyloid peptide, zebrafish, cerebrospinal, dopamine, neurogenesis

Identification and cloning of miRNAs associated with Calcium signaling in schizophrenia

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Schizophrenia is a severely challenging and chronic mental disorder, the etiology of which remains a mystery. Studies show that aberrations in post-transcriptional gene expression, mediated by non-coding microRNA (miRNA), are associated with schizophrenia. Objective of our study is to address the molecular mechanisms of certain miRNAs that target Grin2A and Grin2B genes, coding for GluN2A and GluN2B subunits respectively of NMDAR receptor whose dysregulation has a major role in schizophrenia.The basic approach is to first identify the miRNAs that bind to the 3'UTRs of Grin2A and Grin2B using bioinformatics and validation of their target interaction by luciferase reporter based assay. Further, the expression of miRNAs will be modulated in neuronal cells in culture for checking the expression of the target genes and for their effect on cell biological parameters. A few miRNAs targeting Grin2A and Grin2B were identified by screening using the prediction programs such as TargetScan, RNA hybrid and microrna.org. The pre-miRNA's were amplified from rat genomic DNA and were cloned into the PGEMT-Easy vector. Further, they were cloned into an expression vector, pRipM that contains dsRed as marker and the clones were confirmed by sequencing. Similarly, 3'UTRs of Grin3A and Grin3B were amplified and were cloned into PGEMT-Easy vector. Subsequently they were cloned into a dual luciferase vector pSicheck and were confirmed by sequencing. The interaction between miRNA and its 3'UTR is being performed using Dual Luciferase assay. This study could reveal the role of certain miRNAs in the regulation of NMDAR and their effect on schizophrenia.

Acknowledgements: This research work was supported financially by intramural funding from Rajiv Gandhi Centre for Biotechnology. Fellowship was received from Department of Science and Technology, Govt. of India.

Association of brain-derived neurotrophic factor (BDNF) gene SNPs G196A and C270T with Parkinson's Disease: A Meta-Analysis.

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The objective of this study was to search for brain-derived neurotrophic factor (*BDNF*) gene polymorphisms 196 G/A and 270 C/T association with susceptibility to Parkinson's disease (PD). The association between PD and the G196A and C270T polymorphism in the BDNF gene has already been investigated in several case-control studies, producing contradictory results. In order to explore these contradictory findings, the authors conducted a meta-analysis of the associations between the *BDNF* 196 G/A and 270 C/T polymorphisms and PD in all the available case-control studies on the topic published from 2002 to 2015. In present study 17 case-control studies of the *BDNF* 196 G/A polymorphism and 4 case-control studies of the *BDNF* 270 C/T polymorphism associated with PD is analysed. The results showed no association between BDNF 196 G/A allele in overall studies except for AA Vs GG+AG genotype. However, ethnicity specific meta-analysis identified an association between AA Vs GG+AG genotype and PD but no association identified between *BDNF* 196 G/A polymorphism and PD in european studies. On the other hand, association between BDNF 270 C/T allele in overall studies was observed for T Vs C allele and TC+TT Vs CC genotype. There were no sources of publication bias in all the selected studies, as calculated by Egger's Regression Analysis. In conclusion, evidence for associations between *BDNF* polymorphisms (G196A and C270T) and PD risk for few allele and genotype combinations are present.

Acknowledgements: (This work was supported by UGC Central University Fellowship from Central University of Jharkhand, Brambe, Ranchi, India).

Comparative effects of lithium salt and lithium counter ions associated with ironoxide nanoparticles on C6 cells

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Neuroprotection in various neurodegenerative conditions is the area of interest in biology. Lithium chloride, a drug in use for a long time for treating bipolar disorder, has been demonstrated to be having neuroprotective qualities. However, the dose of lithium administered has to be monitored carefully as it has a narrow range of therapeutic value and can be nephrotoxic at a higher dose or prolonged usage. It has been of interest to investigate whether an alternative form of lithium as counter ions associated with functionalised iron oxide nano particles can be used for this purpose. We have conducted a comparative study of effect of the said two forms of lithium on cell viability and morphology. C6 cells were maintained according to standard cell culture protocol and at 24h were treated with lithium as salt (10 mM) and as counter ions (10ul / 100 ul) independently for four hours. The uptake of nanoparticles was confirmed with Pearl's blue reaction. Cell viability and metabolic activity checked with MTT assay. Viability of cells was less when treated with lithium counter-ions as compared to cells treated with lithium salt.

Ethics Statement: This project has been approved by the Institutional Ethics Committee.

Acknowledgements: We would like to thank Dr. Ghosh, BARC for gifting us with counter-ions and Shruti Kurve for technical support.

*The presenting author would like to apply for Prof. S.S. Parmar Research Foundation Award for paper presented in poster session and also for Ravindra and Lalita Nath Travel Fellowship.

Neuroprotective effects of plant extracts in paraquat-induced neurotoxicity in *Drosophila melanogaster*.

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In has been envisaged that in this century, disorders of the central nervous system will have a significant bearing on the healthcare concerns of the human population worldwide. As brain is highly sensitive to oxidative damage as it consumes a large amount of oxygen and is relatively deficient in antioxidant defenses. Neuronal degeneration in the brain is linked with increased oxidative stress which is implicated in neurodegenerative diseases such as Parkinson's and Alzheimer's diseases. Accumulation of oxidative damage in the nervous system is implicated in the decreased cognitive function. The study of antioxidants has gained great attraction recently due to their health implications. Antioxidants neutralize free radicals and are effective in suppressing or preventing neurological disorders. In the present study, we demonstrated the antioxidant and neuroprotective effects Indian medicinal plants against paraquat-induced oxidative stress in *Drosophila melanogaster* as evidenced by glutathione depletion, lipid peroxidation and enhanced activities of antioxidant enzymes such as catalase, superoxide dismutase as well as elevated levels of acetylcholine esterase. Pretreatment of flies by feeding with plant extract boosted the activities of antioxidant enzymes and prevented the paraquat-induced oxidative stress. Dietary feeding of plant extracts prior to paraquat exposure in *Drosophila melanogaster* showed a lower incidence of mortality and enhanced motor activity of flies in a negative geotaxis assay; both suggesting the neuroprotective potential of plant extracts.

Ethics statement: Ethical clearance is not required for insects (fruit fly, *Drosophila melanogaster*).

Acknowledgements: VB is grateful to DST, New Delhi for the financial assistance (SB/EMEQ-78/2014).

Effect of PUFA on Diabetic Retinopathy

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Mammalian brain depends upon glucose as its main source of energy. It plays a critical role during physiological brain function; therefore disruption of this glucose metabolism can bring about pathophysiological changes. Glucose uptake which is insulin dependent, fluctuations can induce metabolic stress. This can also bring about changes in retinal epithelial layer leading to Diabetic Retinopathy. Superoxide dismutase is an antioxidant enzyme known for prevention of cell damage. Developing chick embryo serves as a model organism in which organogenesis can be observed as it can be cultured *in ovo*. Embryos are semi transparent making view of internal tissues possible under the microscope and are of sufficient size to make several types of micromanipulations practical at these early stages. Chick embryos were exposed to 50µl of 100 mM D-Glucose is given to a developing chick embryo (*Gallus Gallus Domesticus*) in vitro at multiple time points. On embryonic day 8, retinal epithelial layers were separated and Superoxide Dismutase activity was estimated (Weydert and Cullen, 2009). Additionally the effect of 10% PUFA as a neuroprotective agent was also undertaken along with glucose exposure. Specific activity of SOD was altered in multiple dosage treated embryos in comparison to the control embryos. Omega- 3 treatment led to a significant change in SOD activity. The role of PUFA (polyunsaturated fatty acid), as a neuroprotector favoring neuronal survival was investigated.

Ethics Statement: This project has been approved by the Institutional Ethics Committee.

Acknowledgements: I would like to acknowledge my senior Silvia Fernandes for technical help.

*The presenting author would like to apply for Prof. S.S. Parmar Research Foundation Award for paper presented in poster session and also for Ravindra and Lalita Nath Travel Fellowship.

Functional significance of Tlx3 expression in developing cerebellum and its link to Autistic Spectrum Disorders

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Tlx3 belongs to the *Tlx* family of Homeobox domain transcription factors that has been identified as a major selector gene determining the glutamatergic neuronal fate over its GABAergic fate in embryonic spinal cord. We have found that Tlx3 is expressed in proliferating granule neurons of External Granular Layer (EGL) of posterior cerebellum during the window of cerebellum development (E16-PN20). Using Pax6 sey KOs we have shown that Pax6 mediated expression of Tlx3 specifically in the posterior lobes of cerebellum during development has a role in regulating expression of Chrnα3, an important candidate gene involved in autistic spectrum disorders (ASD). Our results further confirmed that the expression of Chrnα3 is tightly correlated/linked with the expression of Tlx3. We found that the expression of Chrnα3 is down regulated upon down regulation of Tlx3 in the cerebellar granule neuron (CGN) cultures using Tlx3 siRNA. We further looked at the link between Tlx3 and ASD since expression of Chrnα3 was found to be down regulated in patients with ASD. To confirm this we down regulated expression of Tlx3 in cerebellar granule neuron cultures using Tlx3 SiRNA and carried out expression analysis for candidate genes involved in ASD. These genes include Astrotactin1, Astrotactin2, Neurexin1, and Neuroligin3 that participates in the neuronal migration events and formation of synaptic connections. Out of these Astrotactin2 and Neurexin1 showed a significant reduction in expression. These results suggest that Tlx3 has a role in regulating genes involved in ASD and could be regulating these genes directly or indirectly.

Ethics Statement: All animal experiments were approved by the Institutional Animal Ethics Committee (IAEC) of Rajiv Gandhi Center for Biotechnology and carried out as per CPCSEA guidelines.

Acknowledgement: This work was supported by intramural funding from RGCB and extramural grants from KSCSTE, Govt. of Kerala and research fellowships from CSIR, Govt. of India, INSPIRE, DST, Govt. of India.

Hydrogen sulfide attenuates homocysteine-induced cognitive deficits and neurochemical alterations by improving endogenous hydrogen sulfide levels

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Homocysteine (HCY) is associated with mild cognitive impairment and dementia. Hydrogen sulfide (H_2S), a metabolite of HCY, plays an important role in brain as endogenous modulator and neuroprotectant. However, the effect and mechanisms involved in beneficial effect of H_2S has not been investegated in HCY induced cognitive deficits. The present study has been designed to explore the effect of exogenous H_2S on behavioral deficits and neurochemical alterations in hyperhomocysteinemic (HHcy) animals. HHcy was induced in rats by subcutaneous administration of HCY, twice a day at 8 h interval for 30 days. Mild Hhcy was observed in the animals in terms of plasma and brain HCY levels. HHcy animals had a progressive decline in memory functions as assessed by Morris water maze. The HCY treated animals showed increased anxiolytic behavior as assessed by elevated plus maze. There was decrease in endogenous levels of H_2S which were accompanied by decrease activity of cystathionase (CSE) and cystathionine β-synthase (CBS). Additionally, the levels of biogenic amines were reduced and the activity of monoamine oxidase (MAO) was increased in the brain regions. Haematoxylin and eosin (H&E) staining revealed higher number of pyknotic cells in cortex and hippocampus of HHcy animals. Administration with H_2S at daily dose of 30 µmol/kg (i.p) for 30 days significantly suppressed the elevated HCY levels. The activities of CBS and CSE were increased and H_2S levels were restored in HHcy animals. H_2S treatment also ameliorated behavioral deficits observed in HHcy animals and these were accompanied by significant increase in the levels of biogenic amines. Histological sections revealed normal morphology following H_2S supplementation. These results clearly demonstrate the protective effect of H_2S on HCY-induced cognitive deficits, mediated through restoration of H_2S metabolism, suggesting beneficial role of H_2S in preventing HHcy-induced neurodegenerative conditions.

Key words: Behaviour; Catecholamines; Homocysteine; Hydrogen sulfide; Hyperhomocysteinemia; Neurotransmitters.

Acknowledgments: The financial assistance provided by Department of Bio-Technology (DBT), Govt. of India, New Delhi [grant number BT/361/NE/TBP/2012] is acknowledged. The fellowship to MK from the University Grants Commission (UGC), New Delhi [F.17-7(J)/2004(SA-1)] is also acknowledged.

Study on Role of RAGE in Alzheimer's disease pathology

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Receptor for advanced glycation end products (RAGE) is immunoglobulins like cell surface receptor which act as cellular cofactor for Amyloid β peptide (Aβ) interact in neurons, microglia and vascular cells. This interaction shown to amplify deleterious effects by enhancing the production of pro inflammatory cytokines via the activation of NF-κB pathway in Alzheimer's disease (AD). The soluble RAGE (sRAGE) is other facet of RAGE acts as a decoy receptor for Aβ. The sRAGE/ Aβ interaction inhibit the binding of Aβ to fRAGE and also mediate Aβ clearance. The objective of the present work is to quantify total and sRAGE in blood sample of AD patients (n=10) compare to non demented normal control subjects (n=10) by quantitative real time PCR using GAPDH as endogenous reference gene. Based on the Ct values it is observed that in AD patients sRAGE was found to be down regulated compare to total RAGE. In relation to control subjects the total RAGE is down regulated by 1- 6 fold in all AD patients whereas sRAGE is down regulated by 10 fold in 60% AD patients and 1-3 folds in remaining AD patients. Decreased expression of sRAGE could lead to defective clearance of Aβ thereby enhancing the interaction with fRAGE resulting in activation of inflammatory pathway, augmenting the AD pathology.

Ethical statement: The study was approved by institutional ethical committee PSG IMSR, Coimbatore and informed consent was obtained from subjects.

Acknowledgements: (This work is supported by research grant no: SR/WOS-A/LS-1312/2014 from Department of Science and Technology, India

Trans-resveratrol protects ischemic stem cell derived neuronal cells by inhibiting the hypoxia associated transcription factors and boosting the anti-oxidant defense mechanisms

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We investigate the anti-ischemic potential of *trans* resveratrol (RV) in a human cord blood stem cell (hCBSCs) derived *in vitro* model of ischemic cerebral stroke [oxygen-glucose deprivation (OGD) for 6 h followed by 24h reoxygenation (R)]. OGD-R model increases Ca^{2+} influx by upregulating native L-type Ca^{2+} channels and subsequently induces the ROS mediated apoptotic damages in the cells. The ROS generation and increased levels of intracellular Ca^{2+} trigger the expression of hypoxic homeostasis transcription factors like- hypoxia induced factor-1alpha (HIF-1α), Cav-beta 3 (Cav □□□, signal transducer and activator of transcription 3 (STAT3), heat shock protein-27 (hsp-27), and cationic channel transient receptor potential melastatin 7 (TRPM7). The hCBSC derived neuronal cells receiving OGD-R insult were exposed to biologically safe doses (5, 10 and 25 μM) of RV in three different exposure groups i.e., 24h prior to OGD; 24h post OGD and from 24h before OGD to end of reoxygenation period (whole exposure). Anti-ischemic potential of the RV was assessed by estimating the restored levels of lipid peroxidation, ROS generation, glutathione content, and apoptotic markers such as Bax, Bcl2 and Caspase-3. Hypoxia inducible factors were also assessed to correlate the changes with ischemic injuries. Our findings demonstrated that RV has significant potential for increases the viability of OGD-R insulted hCBSCNCs assessed by MTT, NRU and LDH release assays. Our data also indicate that the whole exposure group of RV is most efficient to decrease the levels of ROS, intracellular Ca^{2+}, hypoxia associated transcription factors and increase the level of antioxidant defense enzymes.

Ethics statement: The study protocols were duly approved from the Institutional Human Ethics Committee. In the experiments, the cord blood was collected after the birth of a healthy child through open surgery, by registered medical practitioner at KG Medical University, Lucknow.

Acknowledgements: The authors are grateful to the Director, IITR, Lucknow, India, for his keen interest in the study. Financial support from Department of Science and Technology, Ministry of Science & Technology, Government of India, New Delhi, India [Grant No. SR/SO/Z 36/2007/91/10].

Oxygen glucose deprivation-reoxygenation model of ischemic cerebral stroke in neuronal cells derived from human cord blood stem cells

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The deprivation of blood supply to the brain induces ischemic stroke, the third largest cause of mortality and cause of long-lasting disability in humans. No suitable human specific tool to screen the anti-ischemic potential of drugs is available so far. We explore the applicability of human cord blood stem derived neural stem cells (hCBSCNCs) as rapid and reliable tool for the purpose. The optimum time points for oxygen-glucose deprivation (OGD) and re-oxygenation have been identified to suggest the suitability of hCBSCNCs as rapid and sensitive *in vitro* tool to screen anti-ischemic potential of new drug entities. The neuronal cells receive an OGD insult of 1-8 h followed by re-oxygenation for 6 to 96 h in medium having glucose concentration between 0-10 mg/ml. The cell viability loss was assessed using trypan blue dye exclusion and MTT assays. A significant loss ≈ 20% (p<0.05) in viability count got started from 2 h OGD insult and continued further gradually and peaked by 8h i.e., ≈95%. The cells grown in glucose-free medium have shown a gradual (p<0.001) decrease in cell viability throughout the re-oxygenation. Re-oxygenation of 24 h was found to be first statistically significant time point for all the glucose concentrations. Glucose concentration during re-oxygenation was found to be one of the key factors involved in the growth and proliferation in hCBSCNCs. The OGD of 6 h followed by a re-oxygenation period of 24 h with 4-6 mg/ml glucose concentration could be recorded as optimum conditions under our experimental conditions.

Ethics statement: The study protocols were duly approved from the Institutional Human Ethics Committee. In the experiments, the cord blood was collected after the birth of a healthy child through open surgery, by registered medical practitioner at KG Medical University, Lucknow.

Acknowledgements: The authors are grateful to the Director, IITR, Lucknow, India, for his keen interest in the study. Financial support from Department of Science and Technology, Ministry of Science & Technology, Government of India, New Delhi, India [Grant No. SR/SO/Z 36/2007/91/10].

Metabolic pathway Construction and expression analysis of highly conservedneuroprotective genes of oxidative stress and their validation through comparative system biology approach

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Neurodegenerative diseases are irredeemable and incapacitating conditions that result in progressive degeneration. Associations of these problems are correlated with different pathological features including a major inclination towards the oxidative stress. Impaired mechanism in correlation with reduced expression of antioxidant proteins are very common feature among most of the age related disorders. Role of Nrf2 gene is well established as a neuroprotective gene especially in concern to neurodegenerative disorders against oxidative stress. Nrf2 is (bZIP) transcription factor forms heterodimers with JUN and FOS proteins that regulates transcription by binding to ARE which coordinates the transcription of genes involved in phase II detoxification and antioxidant defense. Protein expressed by these genes is used to protect the cell from oxidative stress. The current *Insilco* based genomic study filtrations of twenty one genes were done on the availability of their existence in public domain databases as well as on the basis of literature from the NCBI database for detailed analysis to establish the correlation and designing the network among the related genes. Gene expression profiling of filtered genes along with their network pathway analysis is an integral part of this study. In the study we performed a network analysis of human protein-protein interaction database mined from four different sites including STRING, Gene MANIA, Reactome-Fls &APID (Agile Protein interaction Dataanalyzer) on the basis of their experiment, co-expression, prediction &functional enrichmentwas also carried out to validate our findings. The overall comparative network analysis reveals that NFE2L2, JUN, JUND, FOS genes are closely associated with neuroprotection against oxidative stress induced neurodegeneration in human.

Keywords: Neurodegenerative diseases, STRING Database, GeneMANIA, Reactome Fls, APID.

Acknowledgement: Traineeship provided by Biotech Park, Lucknow and the guidance provided by Prof P.K Seth, Senior Advisor, Biotech Park is gratefully acknowledged.

Dendritic spine abnormalities and cognitive decline in mice models of progressive myoclonus epilepsy

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The unique ability of mammalian brain to learn and memorise information is based on alteration in number or structure of synaptic contacts between neuronal circuits that are formed primarily on the dendritic spines. The morphology of spines determines the strength and function of these synapses and thus is crucial for memory and cognitive functions. Dendritic spine abnormalities have been linked to cognitive deficits in many neuronal disorders: Alzheimer's disease, Huntington's disease and Fragile X syndrome, to name a few. We have explored synaptic pathology in Lafora disease (LD), using established mice models. LD is a fatal neurodegenerative disease caused by defects in the EPM2A gene (laforin phosphatase) or in the NHLRC1 gene (malin ubiquitin ligase). LD is characterized by the presence of glycogen-like inclusions in neurons and wide spread neurodegeneration. The mechanism behind cognitive deficits in LD remains unknown; therefore we explored possible change in the spine morphology through developmental stages of LD mice using primary neuronal cultures and Golgi impregnation techniques. The hippocampal LD neurons display alterations in number as well as structure of the dendritic spines. We have also found that the level of the Fragile X mRNA binding protein (FMRP), a known regulator for the neuronal morphology, is altered in LD mice. Both laforin and malin appear to regulate the level, activity and the localisation of FMRP. We propose that the abnormalities in spine morphology could underlie cognitive defects in LD, and that the altered FMRP activity could be the cause for the synaptic dysfunctions.

Role of Curcumin against arsenic trioxide induced adverse effects on CA-1 of mice hippocampus.

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Arsenic trioxide (As_2O_3) is one of the most effective drugs used against APL (Acute Promyelocytic leukaemia), however As_2O_3 induced adverse effects on various organ systems (CNS, CVS, GIT) always pose a challenge. Aim of the present study was to determine if exogenous antioxidant supplementation such as - Curcumin could have any ameliorative role on As_2O_3 induced alterations on behavioural, biochemical and morphological parameters. Thirty adult male mice of Swiss albino strain were divided into control (Ia and Ib) and experimental groups (II-IV) with six animals per group/subgroup. The experimental groups received As_2O_3 (2mg/kg bw) and Curcumin (100 mg/kg bw) by oral route for 45 days. During the experimental period, the behavioral study (OFT, EPM and MWM) was carried out from Day 33-45 (12 days). On day 46, the animals were sacrificed by cervical dislocation and the brain samples were subjected either to immersion fixation (for morphological and morphometric observations) or used afresh for biochemical estimation. The behavioural testing showed significant alterations in anxiety levels and cognitive functions (learning and memory) in As_2O_3 alone exposed animals. The hippocampal antioxidant (GSH) levels in As_2O_3 exposed mice were significantly decreased. Morphometric observations of CA-1 region of hippocampus showed significant decrease in pyramidal cell density along with reduced layer thickness and area of pyramidal neurons in As_2O_3 alone exposed animals. However, these parameters were substantially reversed in groups receiving Curcumin along with As_2O_3. These findings do suggest the neuroprotective effects of Curcumin against arsenic trioxide induced adverse effects on CA-1 of mice hippocampus.

Ethics Statement: This study was undertaken after obtaining ethical clearance from Institutional Animal Ethics Committee (IAEC, AIIMS) (Ref. no.852/IAEC/15).

Cell-based screening of phytochemical library in search of compounds to treat stress and old age related pathologies

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Stress, a highly complex factor, affects body functions in multitude of ways. It is recognized by nervous system as an undesirable change in the internal or external environment. Capacity of body to cope up with such changes declines with age, and connects to age-related pathologies including neurodegeneration and cancer (highly stressed physiological states). Oxidative stress has been established to be a significant contributor to these phenomena and hence anti-stress compounds possess preventive and therapeutic potential. Our group has earlier identified anticancer activity in the leaves of Ashwagandha and has defined mechanisms involved in selective killing of cancer cells. The active phytochemicals (Withanolides) caused oxidative stress to cancer cells. At the same time, they were shown to protect normal cells against a variety of stresses. We currently screened a small library of natural compounds, using cell-based stress survival assays, to identify new NEW (Natural Efficient Economic and Welfare) drugs for preventive and therapeutic treatment of stress, cancer and neurodegenerative diseases. Oxidatively stressed human normal (TIG-3, fibroblasts) and cancer (U2OS, osteosarcoma) cells were subjected to recovery with or without the drugs. In these assays, we identified CCB-11 (Curcubitacin B) as an anticancer and anti-stress compound and demonstrate the molecular mechanism of its effect either alone or in combination with Withanone. CCB-11 sensitizes cancer cells to stress, implicating its value as adjuvant in cancer treatment. Interestingly, its low doses caused differentiation of IMR32 and C6 cells, and protected them from oxidative stress suggesting its value for stress and age related pathologies.

Dementia mutants does not alter the Tau Glycation in Alzheimer's Disease

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Alzheimer's Disease (AD) is a neurodegenerative disease characterized by progressive cognitive decline. It accounts for 60%- 70% of total dementia cases. The extracellular plaques of amyloid beta and the intracellular neurofibrillary tangles of Tau protein are the hallmarks of AD. Tau is a microtubule-associated protein, which stabilizes the microtubules and maintains neuronal structure as well as trafficking. It is amenable to various post-translational modifications (PTMs), which influences its microtubule binding affinity. The most exclusively studied PTM is hyperphosphorylation, which affects the microtubule binding and leads to Tau aggregation. Other PTMs include glycation, acetylation, methylation, nitration *etc.* Glycation is an irreversible non-enzymatic addition of sugar to the lysines of protein leading to formation of advanced glycation end-products (AGEs). Glycation modifies protein and alters its structural and functional properties. Pseudophosphorylation of Tau at specific serine and threonine residues impart differential aggregation properties depending on the motifs as well as combination of pseudophosphorylated residues**.** Apart from the abnormal PTMs, Tau can aggregate due to several mutations in the Tau gene, which are linked to fronto-temporal dementia, and Parkinsonism associated with chromosome 17 (FTDP-17). These FTDP-17 mutations affect the microtubule binding ability of Tau and also alter the Tau 4R: 3R isoform ratio. Hence, the overall objective of the study is to elucidate the effect of glycation on the Tau dementia mutants, pseudophosphorylation mutants and Tau isoforms in the pathology of AD. Since, glycation is an irreversible modification we are also screening the natural herbs for Tau glycation inhibitors.

Acknowledgement: Funding was received from DBT-JRF(SKS), CSIR (SBC) and NCL (SBC), DST- SERB (SBC);GAP307326

Targeting amyloid aggregation using a novel peptide

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Alzheimer's disease (AD) is the most common form of dementia. The discovery of extracellular amyloid β deposits known commonly as Amyloid β plaques, and intracellular neurofibrilllary tangles of hyperphosphorylated Tau, are the two hallmarks of AD pathology. Genetic studies have shown that mutations in the amyloid precursor protein (APP), Presenelin 1 and Presenelin 2 lead to AD. The findings so far zero in on to amyloid β accumulation as the primary culprit in AD. Amyloid β is derived from the proteolytic processing of APP. The innate tendency of amyloid β to undergo aggregation leads to formation of several forms including the oligomeric form. It is now clear that the soluble oligomeric forms of amyloid β cause neuronal loss, neuro-inflammation and deficits in memory. Fibrillation of amyloid β is thought to sequester this toxic peptide. So, strategies to inhibit oligomerization or break existing aggregates or promote fibrillation of amyloid β may be of great value in AD.

We tested the ability of a novel peptide to inhibit amyloid β oligomerization *in-vitro* in cell free system using Tricine-SDS PAGE. We found that the peptide inhibited amyloid β oligomerization. We also used Thioflavin-T (ThT) assay to examine the effect of the peptide on amyloid β fibril formation. We found an increase in ThT fluorescence when amyloid β was incubated under fibril forming conditions in the presence of the peptide. This could be due to augmentation of fibrillation. Thus, the results suggest that the peptide inhibits oligomerization of amyloid β, but promotes fibrils formation.

Acknowledgements: The work is supported by National Brain Research Centre core funds.

Association of DUF1220 copy number change with dyslexia risk in multigenerational family

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Dyslexia, a neurodevelopmental disorder, is characterized by reading impairment despite normal intelligence. In this study, we aimed to identify susceptible copy number variations (CNVs) in a multigenerational dyslexic family, employing exome CNV-seq. We used CNV detection tool, CoNTRA for the identification of CNVs from Whole Exome Sequencing (WES) data by using an approach of base level log ratio. Whole exome data generated from 14 individuals were used for analysis, of which seven were diagnosed to be dyslexic through psychometric testing. Exome CNV-seq analysis revealed potential pathogenic CNVs. After filtering and prioritization, seven CNVs were identified. These CNVs covered brain expressive coding genes viz. NBPF1, NBPF10, NBPF20, NBPF14, PDE4DIP, MUC4 and MUC12. Interestingly, five of these identified genes belong to Neuroblastoma Break Point Family (NBPF) and are reported to contain tandem repeats of DUF1220 domain. We validated all the CNVs through Taqman® copy number assay. Validation showed gain in copy number in the DUF1220 domain of NBPF family in ~80% of dyslexic cases. Furthermore, identified CNVs were validated in the MUC4 and MUC12 genes in ~60% of cases. Copy number variations present in DUF1220 domain have been previously associated with neuro-cognitive disorders such as Autism, Schizophrenia, Microcephaly and Macrocephaly. Further, we also studied the underlying molecular mechanism driven by these genes and their interacting molecular partners to elucidate the molecular basis of dyslexia using fetal brain derived neural precursor cells. Results indicate role of these genes in initial neurogenesis and pleuripotency through network correlation analysis and PCA.

Whole exome sequencing and genome-wide genotyping in a multiplex family identified novel genetic loci on chromosome 5 for dyslexia

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Dyslexia is a complex, heritable, neurodevelopmental disorder characterized with reading, writing and spelling difficulties. Incidence of dyslexia has arisen to 10-15% but the genetic basis of dyslexia is not yet fully understood. Identification of specific gene/genes may provide a comprehensive explanationof the biology of this disorder.We have investigated the genetic basis of dyslexia using whole exome sequencing and genome wide SNP array in a three generation multiplex family with dyslexia belonging to an endogamous population from India. Among seven unaffected and thirteen affected people in the family, whole exome sequencing was performed for four unaffected and nine affected individuals. The affection status for this family was ascertained with the test battery of 'Dyslexia Assessment in Languages of India' which complements with self-reports, pre-diagnosed history and records of intervention therapy. Following dominant inheritance model we identified multiple variations in chromosome 1, 3, 5, 17 and 21 which were segregated with the disorder. The associated genes mapping to chromosome 3p26 and 5q31 were identified in both exome sequencing and genome wide genotyping array.Strikingly, the dominantly inherited variations present across 1.9 Mb region of chromosome 5q31 were segregated as a single haplotype block within affected members of this family. The associated genes are predominantly expressed in developing central nervous system and neither of them has previously been reported with dyslexia. They also are co-expressed within synaptic junction and actively involved in establishing neuronal connections. Since the associated genes are involved in neuronal connectivity they could play important role in development of dyslexia.

Ethical statement: This study was carried out in strict accordance with the guidelines of Institutional Human Ethics Committee of the National Brain Research Centre, India.

Acknowledgements: Authors wish to sincerely acknowledge all the members of KA family and all the participants. This work was supported by National Brain Research Center core grant. Senior Research Fellowship was provided by Indian Council of Medical Research (ICMR), New Delhi, India to Teesta Naskar.

Chronic exposure to global hypoxic stress accelerates Neuronal aging: A comprehensive marker based study

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Though chronological brain ageing and its correlation with age related cognitive decline in healthy individuals has been studied extensively, the understanding on neuronal responses towards environmental stressors and its effect on biological brain ageing is still preliminary. The present study was aimed at investigating the effect of a single episode of chronic global hypoxic stress on biological brain ageing. Histological, ultrastructural and molecular markers of chronological ageing were investigated in young male Sprague Dawley rats exposed to global hypoxia simulating an altitude of 25,000 ft. Our results show deposition of lipofuscin along with ultrastructural changes in mitochondria of hippocampal neurons in hypoxic rats which is similar to normal chronological ageing. Hypoxic rats also exhibited altered expression of SNAP25 and Tau which are associated with vesicular trafficking, docking and fusion as well as APOE that plays a crucial role in lipid homeostasis and has been previously reported to be associated with chronological brain ageing. Chronic exposure to hypoxia resulted in decreased expression of Sod2 which normally plays a crucial role in preventing oxidative stress. A novel finding of the study was the upregulation of the pro-inflammatory protein S100A9 in hippocampus of hypoxic rats as well as normally aged rats. The information obtained from investigations on molecular markers of chronological ageing were further corroborated by behavioral studies that showed decline in memory acquisition as well as retrieval in normally aged and young hypoxic rats. The present study therefore provides evidence for chronic hypoxic stress induced accelerated neuronal ageing in the hippocampus.

Ethical Statement: All animal procedures were approved by the animal ethics committee of the Defence Institute of High Altitude Research in compliance to the guidelines of 'Committee for the Purpose of Control and Supervision of Experiment on Animals' of Government of India (F. No.DIHAR/IAEC/16/2014), and care was taken to minimize the sufferings of the animals during the experiment.

Acknowledgement: The present study was funded by Defence Research & Development Organization, Ministry of Defence, Govt of India.

Understanding the role of Sarmi in age-associated Neurodegeneration

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Aging is one of the most fundamental but poorly understood biological processes. Aging poses a risk factor for the development and progression of neurodegenerative diseases like Alzheimer's (AD) and Parkinson's disease (PD) which share common morphological features of mitochondrial dysfunction and axonal degeneration as an early pathological mechanism. Although recent evidence suggests that normal aging and the degeneration of specific neuron populations in AD or PD may be linked by the same cellular mechanisms, this remains a topic of intense debate. Environmental toxins that induces oxidative stress is a major risk factor for age-associated neurodegeneration but relatively few studies have examined the influence of toxic chemical exposures on the neurodegenerative process. Age related decrements in mitochondrial function, metabolic impairments and increased vulnerability to oxidative stress might provide a favorable environment for synaptic damage and developing pathological conditions like Alzheimer's and Parkinson's disease. This study seeks to identify the mechanisms of age-related neurodegeneration in relation to oxidative stress using aging Drosophila model. Here we show that exposure to Rotenone, a broad spectrum insecticide, leads to locomotor deficits and decreased survival in Drosophila in an age-dependent manner and the neurodegenerative molecule SARM1 plays an important in this process.

Genistein in diet: Ameliorating impact on Ischemic Stroke?

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Environmental factors such as diet are important risk factors in stroke incidence and outcome. Diets high in soy are known to render neuroprotection against ischemic stroke, due to the presence of phytoestrogens. It is well documented that the incidence of stroke is less in women than in men, suggesting that estrogen confers neuroprotective. However clinical trials seem unpromising because of the potential detrimental side-effects. Phytoestrogens,particularly Genistein are being increasingly investigated as potential protectors in ischemic stroke In the current study pharmacological dose of Endotehlin–1 was injected into the MCA area to induce stroke in Sprague Dawley male rats (3-4months old). In order to test the role of nutrition, Genistein was administered intraperitonialy- acute (1 hr) as well as chronic (10days), prior to ischemic stroke. Validation of stroke was confirmed through morphological and behavioral studies. Morphological studies by TTC staining confirmed stroke, while neurological deficits were assessed based on reach to grasp, cylinder test, horizontal ladder test as well as gait behavioural analysis.There was significant improvement in skilled reaching and motor coordination in genistein pretreated rats. Golgi staining of pyramidal neurons in the layer V of motor cortex showed significant difference in the branching intersection and length of dendrites between control(contralateral peri infarct cortex) and stroke (ipsilateral peri infarct cortex), suggesting neuronal atropy in stroke rats. However there was significant reduction in neuronal atropy in genistein treated groups indicating that genistein ameliorated structural impairment of motor cortical neurons caused by ET-1 which correlated with our behavioural data. Hence, we show that both acute and chronic administration of Genistein was effective in inducing neuroprotection.

Keywords: Genistein, Endothelin-1, Ischemic stroke, behavior, structural recovery.

Genome-wide microRNA expression profile in Ganglioglioma

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Ganglioglioma (GG)-a rare type of tumor that develops in the central nervous system, mainly originates from glial and nerve cells and is usually associated with intractable epilepsy. Recently microRNAs (miR) are considered to be one of the crucial post-transcriptional regulators in tumor, yet molecular mechanisms underlying the GG development remains unexplored. This study aims to extensively profile and study the role of microRNAs in GG.

Genome-wide microRNA expression profiling was performed for 9 GGs against normal brain controls using affymetrix genechip 4.0 microarray platform. All validation experiments were performed on validation cohort (n=20) by RT-PCR method using SYBR green chemistry. Functional enrichment analysis was performed using EnrichR and miRSystem softwares.

Expression data showed 32 miRNAs upregulated while 34 miRNAs down-regulated with a fold change value of (FC) >2/<-2 and p-value <0.05. miR-187-3p, miR-23a-5p, miR-217, miR-216a-3p were the top dysregulated miRNAs which were further validated using q-RT PCR. Besides this, *In-silico* target analysis revealed HTRC2, FGF9 and IL6 among the top gene targets. EnrichR ranked MAPK signaling and mTOR as significant pathways affected by our set of dysregulated miRNAs providing evidence for the role of these pathways in GG related epilepsy. Upon ROC curve analysis of all validated miRNAs we found miR-187-3p as the highest diagnostic marker with a significance value, AUC >0.85 and p-value <0.033.

This study is the first to report a global miRNA profile of GG. miR – 187-3p and miR-217 found to be significantly downregulated which have a known connections with inflammatory molecule i.e. IL6. Our findings further reveal miRNAs mediated MAP kinase pathway and mTOR pathway activation which may have a contributory role in tumor development and seizure onset. In addition to this, miR-187-3p has been evaluated as a potential diagnostic biomarker for GG.