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Invited review

Cholesterol – A putative endogenous contributor towards Parkinson's disease

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ABSTRACT

Elevated levels of cholesterol and its metabolites (oxysterols) have been reported to be associated not only with several metabolic syndromes, but also become a prognostic risk factor of neurodegenerative diseases particularly Alzheimer's disease. The incidence and the prospect of Alzheimer's disease with respect to elevated levels of cholesterol have been studied extensively and reviewed earlier. Recently, several interesting findings have shown the occurrence of equivalent Parkinsonian pathologies in cellular neuronal models, mediated by oxysterols or excess exposure to cholesterol. In this regard, oxysterols are particular in causing alpha-synuclein aggregation and destruction of dopamine containing neurons in *in vitro* models, which is linked to their direct influence on oxidative stress provoking potency. Inspite of the significant *in vitro* reports, which suggest the relativeness of cholesterol or oxysterol towards Parkinsonism, several prospective clinical reports provided a negative or no correlation. However, few prospective clinical studies showed a positive correlation between plasma cholesterol and incidence of Parkinson's disease (PD). Also, few significant studies have convincingly demonstrated that high fat diet exacerbates parkinsonian pathologies, including loss of dopaminergic neurons and oxidative stress parameters in animal models of PD. The present review brings together all the neuropathological proceedings mediated by excess cholesterol or its metabolites in brain in the light of their contribution towards the onset of PD. Also we have reviewed the possibilities of cholesterol lowering efficacy of statin therapy, in reducing the occurrence of PD.

Contents

1. Introduction

Parkinson's disease (PD), an age related neurodegenerative disorder, arises due to the degeneration of dopamine containing neurons in the midbrain region of substantia nigra pars compacta

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(Hirsch et al., 1988; Jankovic, 2008). The pathological hallmark of PD brain is the presence of the proteinaceous inclusions called Lewy body and Lewy neurite formed mainly by the aggregation of α-synuclein proteins (Kempster et al., 2007; Breydo et al., 2012). Among various factors that have been implicated in PD pathogenesis, several endogenous molecules such as 6-hydroxydopamine and β-Phenethylamine have been reported to aggravate the progression of the disease (Borah and Mohanakumar, 2009, 2010, 2012; Borah et al., 2013; Mazumder et al., 2013). Few significant studies have reported that diet rich in fat or cholesterol can exacerbate parkinsonian neurotoxins-induced loss of dopaminergic neurons (Choi et al., 2005; Bousquet et al., 2012). From a food frequency questionnaire study, Johnson et al. (1999) for first time reported that dietary factors, mainly high fats and cholesterol may also influence the risk for PD. In a retrospective study of 18.8 years, body mass index, a measure of dietary fat intake, was associated with the risk of PD (Hu et al., 2006). Another study documented a positive correlation of plasma cholesterol with the occurrence of PD (Hu et al., 2008). Interestingly, supplementation of the neurons with cholesterol increases α-synuclein aggregation (Bar-On et al., 2008). Also the cholesterol oxidation products-oxysterols act as an inducer of α-synuclein aggregation and resulting apoptosis of dopaminergic cells (Rantham Prabhakara et al., 2008; Marwarha et al., 2011). Considerable evidences have indicated that elevated levels of cholesterol and/or oxysterols in hypercholesterolemic rodents contribute to oxidative stress (Pappolla et al., 2002; Thirumangalakudi et al., 2008; Prasanthi et al., 2010) and neuroinflammation by gliosis or by releasing pro-inflammatory mediators in discrete brain regions leading to neuropathological complications (Thirumangalakudi et al., 2008; Ullrich et al., 2010; Pirchl et al., 2012). The foremost pathological features that synergistically contribute to PD pathogenesis are the generation of reactive oxygen species (ROS) and results in oxidative stress, mitochondrial defects, inflammation and excitotoxicity (Dawson and Dawson, 2003; Blandini, 2010). Some evidences suggest that cholesterol or oxysterols might be involved in PD pathogenesis (Vance, 2012; Martín et al., 2014; Marwarha and Ghribi, 2014). The reports on the effect of cholesterol or oxysterols on brain or in neuronal cells might provide support for its pathogenic contribution in Parkinsonism. In the present review the possible links relating cholesterol or oxysterols to PD pathogenesis are highlighted.

2. Cholesterol in brain

Brain is the most cholesterol rich organ, and has its own cholesterol synthesizing factory (Noguchi et al., 2014). However, few reports have shown that cholesterol rich diet is able to increase the cholesterol content in brain (Refolo et al., 2000; Ghribi et al., 2006). Cholesterol is metabolized enzymatically or non-enzymatically to produce relatively more polar and active metabolites known as oxysterols, predominantly 24S-hydroxycholesterol (24S-OHC) and 27-hydroxycholesterol (27-OHC) (Leoni and Caccia, 2011). The level of oxysterols in cerebrospinal fluid (CSF) has been suggested as a putative marker of cholesterol metabolism and metabolically active neurons in brain (Leoni and Caccia, 2011). High concentration to a level of 30 μM free 24S-OHC is present in brain (Lütjohann et al., 1996), with a net flux of 6–7 mg/day from brain to the periphery in human beings (Björkhem et al., 1998). Fifty percent of 24S-OHC in circulation is metabolized in liver, while the rest is converted into its conjugates (Björkhem et al., 2002). Though 27-OHC is predominantly present in the peripheral circulation, it has free access to brain (Heverin et al., 2005). Brain can also produce 27-OHC, but relatively at very low concentration (Brown et al., 2004). Ozonolysis of cholesterol produces a variety of oxidative metabolites such as secosterol A and B (Wentworth et al., 2003) that has been reported to modify proteins such as beta-amyloid (Aβ), α-synuclein and myelin basic proteins (Zhang et al., 2004; Bieschke et al., 2006; Cygan et al., 2011).

3. Pathogenic contribution of cholesterol in brain

The principal molecular mechanisms that contribute to the pathogenesis of neurodegenerative diseases are oxidative stress, mitochondrial dysfunction, inflammation, and excitotoxicity (Lin and Beal, 2006; Dong et al., 2009). Elevated levels of cholesterol have similarly been attributed not only to cause oxidative stress, mitochondrial dysfunction and inflammation, but also influences the process of α-synuclein aggregation (Bar-On et al., 2008), and therefore may be a risk factor for several neurodegenerative diseases (Vance, 2012; Martín et al., 2014).

Hypercholesterolemia has been reported to cause oxidative stress (Thirumangalakudi et al., 2008; Prasanthi et al., 2010) and associated neuropathological-oxidative changes in the brain (Fig. 1) (Aytan et al., 2008). Elevated levels of cholesterol in animal models of the disease have provided evidence of altered levels of enzymatic as well as non-enzymatic oxidative stress markers in discrete brain regions (Amin et al., 2011; de Oliveira et al., 2011; de Oliveira et al., 2013). Brain has its own antioxidant defense enzymes, including superoxide dismutase (SOD), glutathione peroxidase (GPx) and glutathione reductase (GRd) that can directly detoxify toxic free radicals produced as a result of cellular metabolism (Brigelius-Flohé, 1999). In rodent models of hypercholesterolemia, the activity of SOD, GPx and GRd was reduced significantly in brain (de Oliveira et al., 2011, 2013; Otunola et al., 2014). Significant increase in a specific marker of lipid peroxidation-malondialdehyde in cerebral cortex as well as in whole brain lysate of hypercholesterolemic rodents is indicative of increased oxidative injury (Amin et al., 2011; de Oliveira et al., 2011; Otunola et al., 2014). Hypercholesterolemia triggers oxidative stress by depleting the level of antioxidant molecule-reduced glutathione (GSH) (Prasanthi et al., 2010; Fernández et al., 2009). Inhibition of mitochondrial complex-I activity with a reduction of GSH and its metabolizing enzyme (GRd) in the cortical region of LDL receptor knockout (LDLr−/−) mice demonstrates the involvement of cholesterol in mediating the oxidative stress (de Oliveira et al., 2011, 2013; Carlberg and Mannervik, 1975). Depletion of GSH pool in hypercholesterolemic animals causes endoplasmic reticulum stress response that promotes oxidative damage and neurotoxicity (Prasanthi et al., 2010).

Severe neuroinflammatory processes and associated gliosis (astroglia and microglia) in discrete brain regions, mainly in the cortex and hippocampus of the animals that were maintained chronically on high cholesterol diet is known (Fig. 1) (Xue et al., 2007; Thirumangalakudi et al., 2008; Ullrich et al., 2010; Pirchl et al., 2012). Elevated levels of several inflammatory molecules has been reported in cortex and other brain regions of hypercholesterolemic rodents such as interleukin (IL)-1α, IL-6, IL-10, macrophage inflammatory protein (MIP)-1α, MIP-2, MIP-3α, monocyte chemotactic protein (MCP)-1, tumor necrosis factor (TNF)-α and tissue plasminogen activator (Ullrich et al., 2010; Pirchl et al., 2012; Ehrlich et al., 2012).

4. Cholesterol, oxysterol and beta-amyloid pathology

The hallmark protein in Alzheimer's disease (AD) brain, hydrophobic Aβ (40 or 42 amino acids) that accumulate in extracellular pathogenic senile plaques, produced by secretase mediated cleavage of amyloid precursor protein (APP) (Di Paolo and Kim, 2011). Recent evidences increasingly implicate that cholesterol level can

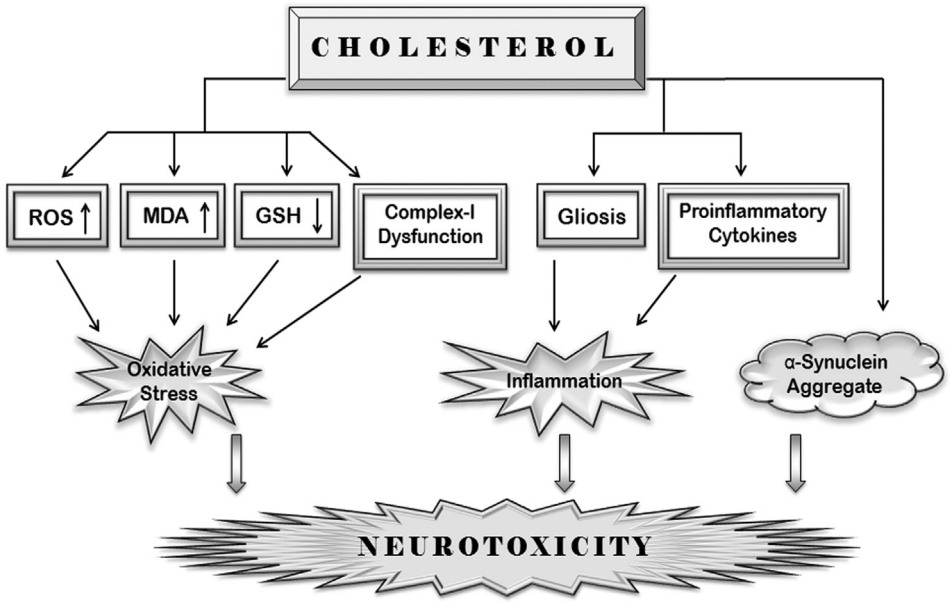

Fig. 1. Pathogenic contributions of cholesterol in brain. Excess cholesterol in brain causes increased generation of reactive oxygen species (ROS) as well as lipid peroxidation marker (MDA, malondialdehyde), mitochondrial complex-I dysfunction, depletes antioxidant molecule (GSH, reduced glutathione) and antioxidant enzymes, particularly superoxide dismutase (SOD), glutathione peroxidase (GPx) and glutathione reductase (GRd); resulting in enhanced oxidative stress. While, cholesterol mediated elevation of proinflammatory factors and over activation of glial cells (reactive gliosis) contributes to neuroinflammation. Cholesterol also binds with α-synuclein making it indolent and aggregate prone. All these pathogenic factors induced by excess cholesterol provide a neurotoxic environment that may lead to degenerative changes.

modulate the formation and aggregation of toxic Aβ in brain (Refolo et al., 2000; Ghribi et al., 2006; Ullrich et al., 2010; Pirchl et al., 2012; Ehrlich et al., 2012). The underlying mechanism of toxic amyloid formation in experimental models of hypercholesterolemia has been suggested to be due to β-secretase and γ-secretase mediated cleavage of APP, which constitutes the amyloidogenic pathway (Frears et al., 1999; Ehehalt et al., 2003). On the other hand, high cholesterol is reported to decrease α-secretase mediated formation of soluble APP that constitute the non-amyloidogenic pathway (Simons et al., 1998; Kojro et al., 2001) due to binding of excess cholesterol in the α-secretase cleaving site of APP (Yao and Papadopoulos, 2002). Another aspect of elevated amyloidogenesis is due to the distribution of APP, β- and γ-secretase in the cholesterol rich area of neuronal membrane-the lipid rafts, which influences the secretase activity under high cholesterol condition (Xiong et al., 2008; Fantini et al., 2013). Also, Aβ has a high affinity for the lipid rafts (Fantini and Yahi, 2010).

Studies with organotypic brain slices and human neuroblastoma SH-SY5Y cells have shown that 27-OHC potentially can increase the production of toxic Aβ (Prasanthi et al., 2009; Marwarha et al., 2010). While level of 24S-OHC in brain is negatively correlated with Aβ levels in brain (Bryleva et al., 2010), 27-OHC-induced endoplasmic reticulum stress inhibits expression of leptin and activates several transcription factors which elevate the transcription of β-secretase (Marwarha et al., 2010, 2013).

5. Cholesterol in Parkinson's disease

Altered brain cholesterol homeostasis have been linked to AD, Huntington's disease, Niemann-Pick type C disease and Smith-Lemli Opitz syndrome, as well as to acute neuronal injuries such as stroke and brain trauma (Martín et al., 2014). The role for cholesterol in the neurodegenerative pathology of PD remains elusive. Few significant prospective studies provided evidences that higher level of plasma cholesterol correlates with the occurrence of PD (Hu et al., 2008; Miyake et al., 2010), whereas some studies offered a contradictory finding (Huang et al., 2011; Gudala et al., 2013; Tan et al., 2015). The hydroxylated metabolites of cholesterol were reported to be significantly high not only in plasma and CSF of PD patients (Lee et al., 2009; Marwarha and Ghribi, 2014) but also in the brain of Lewy body demented patients (Bosco et al., 2006). Significant studies in rodent models of PD demonstrated that high fat diet exacerbated the parkinsonian toxin-induced (used for model PD) depletion of striatal dopamine (Choi et al., 2005; Morris et al., 2010; Bousquet et al., 2012) as well as reducing the tyrosine hydroxylase (TH) immunoreactivity in nigrostriatum (Choi et al., 2005; Bousquet et al., 2012), suggesting a significant contribution of high fat diet in progression of PD. Also, administration of high-fat diet in rodent downregulate the activation of heat shock protein and IκBα protein levels in the substantia nigra region of brain, which is the indication of increased oxidative stress (Morris et al., 2010). The outcome of the most important studies with cholesterol and its oxidized metabolites on PD is summarized in Table 1.

Several studies have demonstrated the potential role of cholesterol in α-synucleinopathy (α-synuclein aggregation) in neuronal cells. Cholesterol or other lipids are associated with neuromelanin pigment and toxic α-synuclein aggregates in brain of PD patients (Halliday et al., 2005). Such association was supported by the fact that the cholesterol binding domain interact with the fusogenic peptide of α-synuclein (Fantini et al., 2011). Cholesterol treatment in excess to cultured neurons promotes α-synuclein aggregation while the cholesterol lowering drug (statins) suppresses its aggregation in neuronal cultures (Bar-On et al., 2008) as well as in animal models of PD (Ghosh et al., 2009; Koob et al., 2010). These studies suggest that reduction of plasma cholesterol in individuals with PD by statins treatment might attenuate the deposition of α-synuclein aggregates in the brain (Roy and Pahan, 2011). Various studies have demonstrated the neuroprotective effect of statins in animal model and cellular model of PD (Fig. 3) (Table 2), which is discussed in a later section of the review.

Table 1
The results of significant studies about cholesterol and oxysterols in Parkinson's disease.

Study paradigm	Significant observations	Reference(s)
HFD in MPTP-induced Parkinsonian mice	HFD significantly exacerbate MPTP-induced i) Reduction in striatal dopamine level and TH expression, ii) Loss of nigral dopaminergic neurons and iii) Nitrosative and neuroinflammatory stress in nigra.	Choi et al. (2005); Bousquet et al. (2012)
HFD in 6-OHDA-induced Parkinsonian rats	6-OHDA treatment in HFD-fed rat exhibit i) Greater striatal as well as nigra DA depletion and ii) Increased oxidative stress in nigra than in chow-fed controls.	Morris et al. (2010)
Cholesterol-rich diet in LDLR-deficient mice; 4 weeks	i) Plasma cholesterol elevated by 3-fold. ii) Cholesterol level negatively correlated with decrease in cortico-cerebral mitochondrial complexes I and II activities. iii) Reduced glutathione depletion and oxidative stress in cerebral cortex.	de Oliveira et al. (2011, 2013)
Cholesterol/fat-rich diet in normal (C57BL/6) mice and LDLR-deficient mice; 4 weeks	i) Plasma cholesterol elevated by ~1.6-fold in normal mice and ~7-fold in LDLR-deficient mice. ii) Reactive gliosis and overexpression of pro-inflammatory mediators in hippocampus. iii) Elevated level of Aβ (42).	Thirumangalakudi et al. (2008); Lu et al. (2010)
Cholesterol-rich diet in Sprague Dawley rats; 12 months	i) Plasma cholesterol elevated by ~2-fold. ii) Microglia activation and overexpression of several cortical inflammation markers. iii) Decreased number of cholinergic neurons and cortical acetylcholine level. iv) Elevated level of cortical Aβ (1–42).	Ullrich et al. (2010); Pirchl et al. (2012); Ehrlich et al. (2012)
Cholesterol-rich diet in rabbits; 28 weeks	i) Cholesterol content elevated in hippocampal neurons. ii) Overproduction of Aβ and Aβ deposits in hippocampus.	Ghribi et al. (2006)
α-synuclein knockout mice	Brain cholesterol, cholesteryl ester, and triacylglycerol elevated by 1.1-fold, 1.6-fold, and 1.4-fold.	Barcelo-Coblijn et al. (2007)
Cholesterol (25 μM, 6 h) treated α-synuclein transfected B103 cells	i) Promotes α-synuclein aggregation and ii) Reduces neurite extension.	Bar-On et al. (2008)
24S-OHC (10–50 μM, 48 h) treated SH-SY5Y human neuroblastoma cells	i) Less than 50% cell viability. ii) Increase in intracellular calcium level.	Kolsch et al. (1999, 2001)
24S-OHC (50 μM, 48 h) treated SH-SY5Y human neuroblastoma cells and Jurkat cells	i) Lipid droplets formed and esterified 24S-OHC accumulates in SH-SY5Y cells. ii) Induces necroptosis in SH-SY5Y cells. iii) Induces apoptosis of Jurkat cells.	Yamanaka et al. (2011, 2014)
24S-OHC and/or 27-OHC (10 μM, 24 h) treated SH-SY5Y human neuroblastoma cells	27-OHC caused i) Reduced immunoreactivity for TH, ii) Elevation of α-synuclein level and iii) Induces apoptosis.	Ranthm Prabhakara et al. (2008); Marwarha et al. (2011)
Secosterols (25 μM) in *in vitro* (Phosphate buffer)	Accelerate α-synuclein aggregation.	Bosco et al. (2006)
Retrospective study of 18.8 years	Body mass index is associated with risk of PD in 272 men and 254 women with PD from study cohorts of 22,367 Finnish men and 23,439 women.	Hu et al. (2006)
Large prospective study of 18.1 years	High dietary intake of cholesterol increases the risk of PD.	Hu et al. (2008)
Case-control study	Higher intake of cholesterol related to an increased risk of PD.	Miyake et al. (2010)
PD patients without severe postural instability	Higher cholesterol associated with slower progression of PD.	Huang et al. (2011)
Large prospective cohort study of Singapore	After an average of 14.6 years, 218 men and 193 women in the cohort of 63,257 men and women developed PD. In men, dietary cholesterol associated with significantly lower risk of PD.	Tan et al. (2015)

Abbreviations: HFD, high fat diet; MPTP, methyl-4-phenyl-1,2,3,6-tetrahydropyridine; 6-OHDA, 6-hydroxydopamine; TH, tyrosine hydroxylase (TH); LDLR, low density lipoprotein receptor; Aβ, beta-amyloid; PD, Parkinson's disease; 24S-OHC, 24-hydroxycholesterol; 27-OHC, 27-hydroxycholesterol.

6. Cholesterol metabolites in Parkinson's disease

Elevated levels of three oxysterols, particularly 24S-OHC, 27-OHC and secosterol have been associated with several neurodegenerative disorders, including PD (Rantham Prabhakara et al., 2008; Marwarha et al., 2011; Leoni and Caccia, 2011). In PD patients, increase in the level of circulating 27-OHC positively correlates with its level in CSF (Heverin et al., 2005; Leoni et al., 2003; Marwarha and Ghribi, 2014) with a concomitant increase in cerebral cortex (Cheng et al., 2011; Umetani et al., 2014). The plasma level of 24S-OHC, derived almost exclusively from brain, is proportional to the metabolically active gray matter, while its level in CSF depends on neurodegenerative process (Leoni et al., 2003). Lee et al. (2009) found a marked decrease by 67% in the level of 24S-OHC in plasma of PD patients and suggested that plasma levels of 24S-OHC can use as a marker for diagnostic tool for PD. While the result of a recent follow up study did not find any significant change in the level of 24S-OHC in plasma of PD patients (Björkhem et al., 2013). Rather, the authors found increased CSF level of 24S-OHC as well as 27-OHC in 10% of PD patients, and that there exists a significant correlation between the value of 24S-OHC but not 27-OHC to the duration of the disease (Björkhem et al., 2013). Like 24S-OHC, elevated level of secosterol was observed in the cortex of Lewy body demented patients (Lee et al., 2009), while in cultured dopaminergic neurons, overexpression of α-synuclein significantly upregulates the level of secosterol (Suh et al., 2004). Bieschke et al. (2006) demonstrated that small molecule oxidation products, especially secosterols derived from cholesterol have the potency to accelerate the aggregation of α-synuclein.

Excess of these oxysterols increase the intracellular level of ROS, induce modification of cellular proteins and alter various signaling pathways, including apoptosis and inflammatory pathways in various neuronal types (Lordan et al., 2009). Studies with cultured neurons have provided evidence of apoptosis-inducing capacity of

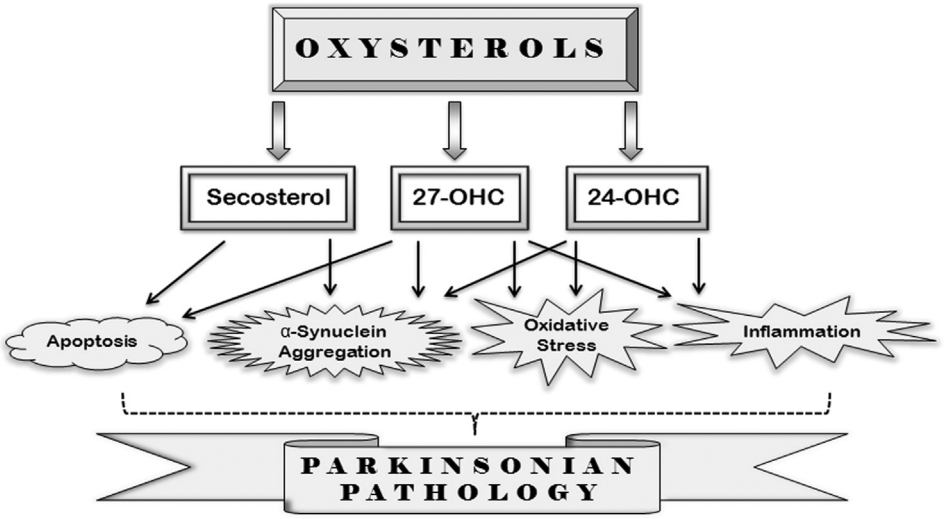

Fig. 2. Schematic representation of possible mechanisms of oxysterols-induced Parkinsonism. Three cholesterol derivatives, particularly 27-hydroxycholesterol (27-OHC), secosterol, and 24-hydroxycholesterol (24S-OHC) which have relevance in Parkinson's disease, are synthesized in brain or liver by either enzymatic (CYP27A1 or CYP46A1) or non-enzymatic (ozonolysis) metabolism. Ninety nine percent of 24S-OHC is synthesized majorly in brain that has access to periphery through blood brain barrier (BBB). On the other hand, 27-OHC is synthesized majorly in liver and has free access to brain. These oxysterols are excreted through liver as either bile acids or oxysterol conjugates. As oxysterols have free access to brain, they form the 'pathogenic pool' of cholesterol in brain. In neurons, both 24S-OHC and 27-OHC mediate oxidative stress, neuroinflammation and α-synuclein aggregation, while the latter exerts a greater effect. Secosterol and 27-OHC upregulate the apoptotic markers and cause neuronal cell loss by apoptotic mode of cell death. Additionally, secosterol promotes α-synuclein aggregation in neurons. Cumulatively, these pathogenic events mediated by oxysterols may contribute to parkinsonian pathology.

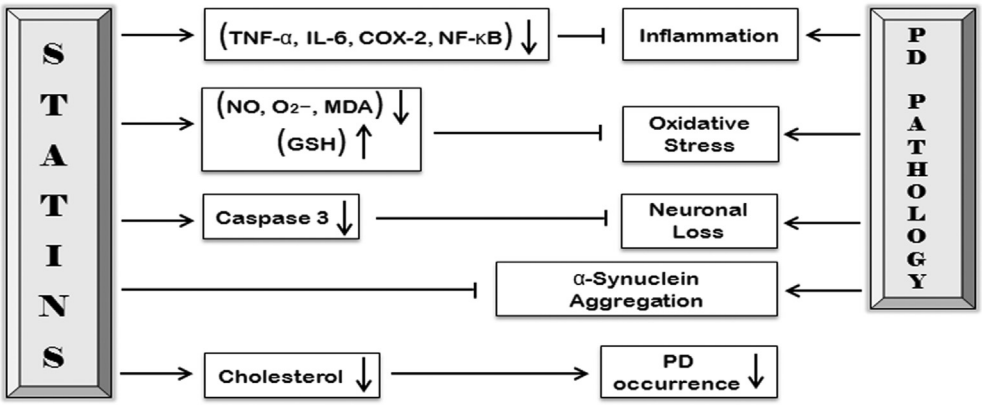

Fig. 3. Statins in Parkinson's disease pathology: schematic illustrations of neuroprotection. Mechanisms that synergistically contribute to Parkinson's disease (PD) pathogenesis are oxidative stress, inflammation and aggregation of α-synuclein. In PD, statins are known to (i) downregulate pro-inflammatory markers (TNF-α, IL-6, COX-2, NF-κB), (ii) ameliorate oxidative stress (increases GSH while decreases NO, O_2^- and MDA), (iii) inhibit caspase dependent cell loss, and (iv) prevent aggregation of toxic hallmark proteins of PD brain, α-synuclein; thus elicit neuroprotection. Most importantly, statin therapy lowers the plasma and brain cholesterol levels and reduces the occurrence of PD. Abbreviations: TNF-α, tumor necrosis factor alpha; IL, interleukin; COX, cyclooxygenase; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; GSH, reduced glutathione; NO, nitric oxide; O_2^-, superoxide; MDA, malondialdehyde.

these three oxysterols (Rantham Prabhakara et al., 2008; Kolsch et al., 1999). At the basal physiological level, 27-OHC reported to mediate apoptosis of human neuroblastoma SH-SY5Y cells, reduces the expression of marker enzyme, TH and increases α-synuclein level (Rantham Prabhakara et al., 2008; Kolsch et al., 1999). However, 24S-OHC did not show any such effect at basal level (Rantham Prabhakara et al., 2008; Kolsch et al., 1999). Nevertheless, co-treatment of these cells with 27-OHC and 24S-OHC synergistically induces apoptosis by several folds, reduces TH expression and increases α-synuclein level (Rantham Prabhakara et al., 2008). The apoptotic mode of cell death by 24S-OHC has been attributed to its ability to elevate the intracellular calcium and ROS that culminate in DNA-fragmentation, caspase-3 activation and with a decrease of the mitochondrial membrane potential (Suh et al., 2004; Kolsch et al., 2001). Marwarha et al. (2011) demonstrated that 27-OHC-induced altered level of TH and α-synuclein is mediated *via* inhibition of estrogen receptors β and activation of Liver X Receptor β respectively. Secosterols are also recognized to accelerate the process of α-synuclein aggregation in *in vitro* system (Bosco et al., 2006). The detailed description about the possibility of these oxysterols in the lime light of PD pathogenesis is shown pictorially in Fig. 2.

7. Statins in the treatment of Parkinson's disease

Statins are the most widely prescribed cholesterol lowering gold standard agents that act by competitively inhibiting the rate limiting enzyme of cholesterol biosynthesis pathway, 3-hydroxy-3-methylglutaryl-coenzyme A reductase (Istvan and Deisenhofer, 2001). Statins are believed to be well-tolerated and safe, having

Table 2
Neuroprotective properties of different statins in experimental models of Parkinson's disease.

Statin	Solubility	PD model system	Effective dose	Neuroprotective properties			Reference(s)
				Anti-oxidant	Anti-inflammation	Apoptosis	
Simvastatin	Lipophilic	6-OHDA-lesioned PC12	0.6 μg/ml	Restores GSH.	Downregulation of TNF-α, IL-1β, IL-6 and MMP-9.	Prevent neuronal loss.	Yan et al. (2011, 2014a)
		6-OHDA-lesioned PC12	1.5 μM	NE	Downregulation of TNF-α, IL-6 and COX-2.	Prevent neuronal loss, inhibit caspase 3.	Xu et al. (2013)
		Rat microglia	5–20 mM	Reduces NO and O_2^-.	Inhibit TNF-α.	NE	Selley (2005)
		6-OHDA, rat	30 mg/kg/day, p.o.; 14 days	Reduces NO– and MDA level, restores GSH. Enhances mitochondrial complex-I and III activity.	Reduces TNF-α and IL-6.	NE	Kumar et al. (2012)
		MPTP, mice	100 μl, 3 h after MPTP infusion, orally	NE	Prevent activation of glia. Suppressed expression of $p21^{ras}$, NF-κB, iNOS, IL-1β, and TNF-α in SNpc.	Prevent dopaminergic neuronal loss.	Ghosh et al. (2009)
		6-OHDA, rat	10 mg/kg/day, 21 days	NE	NE	Prevent dopaminergic neuronal loss.	Yan et al. (2011)
Atorvastatin	Lipophilic	6-OHDA, rat	10 mg/kg/day, p.o; 14 days	Reduces NO– and MDA level, restores GSH. Enhances mitochondrial complex-I and III activity.	Reduces TNF-α and IL-6.	NE	Kumar et al. (2012)
Lovastatin	Lipophilic	α-synucleinopathy mice	100 mg/day, 2 months, orally	Reduces level of oxidized α-synuclein and cholesterol product.	NE	Prevent neuronal loss.	Koob et al. (2010)
		6-OHDA treated PC12	2 μM, 24 h	NE	Reduces TNF-α expression.	Improves cell viability.	Yan et al. (2014b)
Pravastatin	Hydrophilic	MPTP, mice	100 μl, 3 h after MPTP infusion, orally	NE	Prevent activation of glia. Suppressed expression of NF-κB, iNOS, IL-1β, and TNF-α in Substantia nigra.	Prevent dopaminergic neuronal loss.	Koob et al. (2010)

: 6-OHDA, 6-hydroxydopamine; GSH, reduced glutathione; TNF-α, tumor necrosis factor alpha; IL, interleukin; MMP-9, matrix metalloproteinase 9; NE, not estimated; COX, cyclooxygenase; NO, nitric oxide; O_2^-, superoxide; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; iNOS, inducible nitric oxide synthase; MDA, malondialdehyde.

limited side effects (Schachter, 2005). Most of the statins can traverse the blood brain barrier irrespective to its solubility in lipophilic solvents and can inhibit the process of steroidogenesis in brain (Sierra et al., 2011). Along with plasma cholesterol lowering potency, chronic therapies with statins are reported to reduce the cholesterol level of CSF in animal models and human subjects (Sierra et al., 2011; Van der Most et al., 2009). Various reports provided evidence of neuroprotective efficacy of statins in several neuropsychiatric disorders such as AD, acute stroke, epilepsy and multiple sclerosis (Van der Most et al., 2009; Reiss and Wirkowski, 2009). Statins by reducing the expression and release of pro-inflammatory genes and pro-inflammatory cytokines, chemokines, adhesion molecules, as well as matrix metalloproteinases, elicit anti-inflammatory response resulted into neuroprotection (Van der Most et al., 2009). In addition, statins can provide neuroprotection by inhibiting free radical formation, lipid peroxidation and excitotoxicity (Zacco et al., 2003; Reiss and Wirkowski, 2009; Ramirez et al., 2011). Statins can prevent apoptotic mode of neuronal death by inhibiting caspases and by increasing Akt phosphorylation process (Rangel et al., 2005; Piermartiri et al., 2009).

Though considerable epidemiological studies suggested the use of statins therapy with reduced incidence and slower progression of PD (Wolozin et al., 2007; Mutez et al., 2009), but the underlying mechanism of statins mediated neuroprotection in PD is still not fully known. Several statins such as simvastatin, atorvastatin, pravastatin have been shown to ameliorate parkinsonian pathologies induced by parkinsonian neurotoxins in animal models and *in vitro* neuronal cultures (Fig. 3) (Table 2) (Ghosh et al., 2009; Wolozin et al., 2007; Mutez et al., 2009; Selley, 2005; Yan et al., 2011, 2014a, 2014b). The neuroprotective efficiency of statins in PD models attributed largely to their potent anti-inflammatory properties and to some extent to antioxidant and anti-apoptotic properties (Fig. 3) (Ghosh et al., 2009; Koob et al., 2010; Wolozin et al., 2007; Mutez et al., 2009; Selley, 2005; Yan et al., 2011, 2014a, 2014b). Interestingly, statins are found to reduce the aggregation of α-synuclein in cultured neurons (Bar-On et al., 2008) as well as in transgenic mouse models of PD and α-synucleinopathies (Ghosh et al., 2009; Koob et al., 2010). Rodent studies have revealed that chronic treatment with statins also improve the characteristic behavioral abnormalities of PD, including motor deficits (Schuster et al., 2008; Mutez et al., 2009; Yan et al., 2014b; Kumar et al., 2012; Xu et al., 2013; Tison et al., 2013), due to upregulation of dopamine receptors (Wang et al., 2005, 2006). However, the efficacy of statin therapy in PD patients is debatable (Friedman et al., 2013; Huang et al., 2015). Clinical trials on PD patients with simvastatin at higher dose (40 mg/d) manifest no significant effect in lowering the L-DOPA-induced dyskinesia, while in primates, lower dose of simvastatin (3 mg/d) exhibited a positive response (Tison et al., 2013). A large cohort study has provided evidence of lower incidence of PD among statins users (Friedman et al., 2013). Detailed outcome and consequences of statins treatment in *in vivo* and *in vitro* PD models is elaborated in Table 2.

8. Conclusion

The present review brings cholesterol in the domain of endogenous putative neurotoxic molecules that might have the potential to cause the PD pathogenesis. The importance of cholesterol and/or oxysterols as a contributor in PD pathogenesis is debatable but cannot be excluded. Still, the role of cholesterol and/or oxysterols in PD remains elusive. Therefore, studies on the broad molecular

mechanisms of action of these molecules in animal as well as cellular models would probably modify the treatment paradigm of PD as well. Also, therapy with statins that lower the elevated levels of cholesterol in cardiovascular diseases is appraised as a drug to reduce the risk of PD.

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References

Amin, K.A., Kamel, H.H., Abd Eltawab, M.A., 2011. The relation of high fat diet, metabolic disturbances and brain oxidative dysfunction: modulation by hydroxy citric acid. Lipids Health Dis. 10, 74.

Aytan, N., Jung, T., Tamtürk, F., Grune, T., Kartal-Ozer, N., 2008. Oxidative stress related changes in the brain of hypercholesterolemic rabbits. Biofactors 33, 225–236.

Barcelo-Coblijn, G., Golovko, M.Y., Weinhofer, I., Berger, J., Murphy, E.J., 2007. Brain neutral lipids mass is increased in alpha-synuclein gene-ablated mice. J. Neurochem. 101, 132–141.

Bar-On, P., Crews, L., Koob, A.O., Mizuno, H., Adame, A., Spencer, B., Masliah, E., 2008. Statins reduce neuronal alpha-synuclein aggregation in in vitro models of Parkinson's disease. J. Neurochem. 105, 1656–1667.

Bieschke, J., Zhang, Q., Bosco, D.A., Lerner, R.A., Powers, E.T., Wentworth Jr., P., Kelly, J.W., 2006. Small molecule oxidation products trigger disease-associated protein misfolding. Acc. Chem. Res. 39, 611–619.

Björkhem, I., Lövgren-Sandblom, A., Leoni, V., Meaney, S., Brodin, L., Salveson, L., Winge, K., Pålhagen, S., Svenningsson, P., 2013. Oxysterols and Parkinson's disease: evidence that levels of 24S-hydroxycholesterol in cerebrospinal fluid correlates with the duration of the disease. Neurosci. Lett. 555, 102–105.

Björkhem, I., Lütjohann, D., Diczfalusy, U., Ståhle, L., Ahlborg, G., Wahren, J., 1998. Cholesterol homeostasis in human brain: turnover of 24S-hydroxycholesterol and evidence for a cerebral origin of most of this oxysterol in the circulation. J. Lipid Res. 39, 1594–1600.

Björkhem, I., Meaney, S., Diczfalusy, U., 2002. Oxysterols in human circulation: which role do they have? Curr. Opin. Lipidol. 13, 247–253.

Blandini, F., 2010. An update on the potential role of excitotoxicity in the pathogenesis of Parkinson's disease. Funct. Neurol. 25, 65–71.

Borah, A., Mohanakumar, K.P., 2009. Melatonin inhibits 6-hydroxydopamine production in the brain to protect against experimental Parkinsonism in rodents. J. Pineal Res. 47, 293–300.

Borah, A., Mohanakumar, K.P., 2010. L-DOPA-induced 6-hydroxydopamine production in the striata of rodents is sensitive to the degree of denervation. Neurochem. Int. 56, 357–362.

Borah, A., Mohanakumar, K.P., 2012. L-DOPA induced-endogenous 6-hydroxydopamine is the cause of aggravated dopaminergic neurodegeneration in Parkinson's disease patients. Med. Hypotheses 79, 271–273.

Borah, A., Paul, R., Mazumder, M.K., Bhattacharjee, N., 2013. Contribution of β-phenethylamine, a component of chocolate and wine, to dopaminergic neurodegeneration: implications for the pathogenesis of Parkinson's disease. Neurosci. Bull. 29, 655–660.

Bosco, D.A., Fowler, D.M., Zhang, Q., Nieva, J., Powers, E.T., Wentworth Jr., P., Lerner, R.A., Kelly, J.W., 2006. Elevated levels of oxidized cholesterol metabolites in Lewy body disease brains accelerate alpha-synuclein fibrilization. Nat. Chem. Biol. 2, 249–253.

Bousquet, M., St-Amour, I., Vandal, M., Julien, P., Cicchetti, F., Calon, F., 2012. High-fat diet exacerbates MPTP-induced dopaminergic degeneration in mice. Neurobiol. Dis. 45, 529–538.

Breydo, L., Wu, J.W., Uversky, V.N., 2012. α-synuclein misfolding and Parkinson's disease. Biochim. Biophys. Acta 1822, 261–285.

Brigelius-Flohé, R., 1999. Tissue-specific functions of individual glutathione peroxidases. Free Radic. Biol. Med. 27, 951–965.

Brown, J., Theisler, C., Silberman, S., Magnuson, D., Gottardi-Littell, N., Lee, J.M., Yager, D., Crowley, J., Sambamurti, K., Rahman, M.M., Reiss, A.B., Eckman, C.B., Wolozin, B., 2004. Differential expression of cholesterol hydroxylases in Alzheimer's disease. J. Biol. Chem. 279, 34674–34681.

Bryleva, E.Y., Rogers, M.A., Chang, C.C., Buen, F., Harris, B.T., Rousselet, E., Seidah, N.G., Oddo, S., LaFerla, F.M., Spencer, T.A., Hickey, W.F., Chang, T.Y., 2010. ACAT1 gene ablation increases 24(S)-hydroxycholesterol content in the brain and ameliorates amyloid pathology in mice with AD. Proc. Natl. Acad. Sci. U. S. A. 107, 3081–3086.

Carlberg, I., Mannervik, B., 1975. Purification and characterization of the flavoenzyme glutathione reductase from rat liver. J. Biol. Chem. 250, 5475–5480.

Cheng, D., Jenner, A.M., Shui, G., Cheong, W.F., Mitchell, T.W., Nealon, J.R., Kim, W.S., McCann, H., Wenk, M.R., Halliday, G.M., Garner, B., 2011. Lipid pathway alterations in Parkinson's disease primary visual cortex. PLoS One 6, e17299.

Choi, J.Y., Jang, E.H., Park, C.S., Kang, J.H., 2005. Enhanced susceptibility to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine neurotoxicity in high-fat diet-induced obesity. Free Radic. Biol. Med. 38, 806–816.

Cygan, N.K., Scheinost, J.C., Butters, T.D., Wentworth Jr., P., 2011. Adduction of cholesterol 5,6-secosterol aldehyde to membrane-bound myelin basic protein exposes an immunodominant epitope. Biochemistry 50, 2092–2100.

Dawson, T.M., Dawson, V.L., 2003. Molecular pathways of neurodegeneration in Parkinson's disease. Science 302, 819–822.

de Oliveira, J., Hort, M.A., Moreira, E.L., Glaser, V., Ribeiro-do-Valle, R.M., Prediger, R.D., Farina, M., Latini, A., de Bem, A.F., 2011. Positive correlation between elevated plasma cholesterol levels and cognitive impairments in LDL receptor knockout mice: relevance of cortico-cerebral mitochondrial dysfunction and oxidative stress. Neuroscience 197, 99–106.

de Oliveira, J., Moreira, E.L., Mancini, G., Hort, M.A., Latini, A., Ribeiro-do-Valle, R.M., Farina, M., da Rocha, J.B., de Bem, A.F., 2013. Diphenyl diselenide prevents cortico-cerebral mitochondrial dysfunction and oxidative stress induced by hypercholesterolemia in LDL receptor knockout mice. Neurochem. Res. 38, 2028–2036.

Di Paolo, G., Kim, T.W., 2011. Linking lipids to Alzheimer's disease: cholesterol and beyond. Nat. Rev. Neurosci. 12, 284–296.

Dong, X.-X., Wang, Y., Qin, Z.-H., 2009. Molecular mechanisms of excitotoxicity and their relevance to pathogenesis of neurodegenerative diseases. Acta. Pharmacol. Sin. 30, 379–387.

Ehehalt, R., Keller, P., Haass, C., Thiele, C., Simons, K., 2003. Amyloidogenic processing of the Alzheimer beta-amyloid precursor protein depends on lipid rafts. J. Cell Biol. 160, 113–123.

Ehrlich, D., Pirchl, M., Humpel, C., 2012. Effects of long-term moderate ethanol and cholesterol on cognition, cholinergic neurons, inflammation, and vascular impairment in rats. Neuroscience 205, 154–166.

Fantini, J., Carlus, D., Yahi, N., 2011. The fusogenic tilted peptide (67–78) of α-synuclein is a cholesterol binding domain. Biochim. Biophys. Acta 1808, 2343–2351.

Fantini, J., Yahi, N., 2010. Molecular insights into amyloid regulation by membrane cholesterol and sphingolipids: common mechanisms in neurodegenerative diseases. Expert Rev. Mol. Med. 12, e27.

Fantini, J., Yahi, N., Garmy, N., 2013. Cholesterol accelerates the binding of Alzheimer's β-amyloid peptide to ganglioside GM1 through a universal hydrogen-bond-dependent sterol tuning of glycolipid conformation. Front. Physiol. 4, 120.

Fernández, A., Llacuna, L., Fernández-Checa, J.C., Colell, A., 2009. Mitochondrial cholesterol loading exacerbates amyloid beta peptide induced inflammation and neurotoxicity. J. Neurosci. 29, 6394–6405.

Frears, E.R., Stephens, D.J., Walters, C.E., Davies, H., Austen, B.M., 1999. The role of cholesterol in the biosynthesis of beta-amyloid. Neuroreport 10, 1699–1705.

Friedman, B., Lahad, A., Dresner, Y., Vinker, S., 2013. Long-term statin use and the risk of Parkinson's disease. Am. J. Manag. Care 19, 626–632.

Ghosh, A., Roy, A., Matras, J., Brahmachari, S., Gendelman, H.E., Pahan, K., 2009. Simvastatin inhibits the activation of p21ras and prevents the loss of dopaminergic neurons in a mouse model of Parkinson's disease. J. Neurosci. 29, 13543–13556.

Ghribi, O., Larsen, B., Schrag, M., Herman, M.M., 2006. High cholesterol content in neurons increases BACE, beta-amyloid, and phosphorylated tau levels in rabbit hippocampus. Exp. Neurol. 200, 460–467.

Gudala, K., Bansal, D., Muthyala, H., 2013. Role of serum cholesterol in Parkinson's disease: a meta-analysis of evidence. J. Park. Dis. 3, 363–370.

Halliday, G.M., Ophof, A., Broe, M., Jensen, P.H., Kettle, E., Fedorow, H., Cartwright, M.I., Griffiths, F.M., Shepherd, C.E., Double, K.L., 2005. Alpha-synuclein redistributes to neuromelanin lipid in the substantia nigra early in Parkinson's disease. Brain 128, 2654–2664.

Heverin, M., Meaney, S., Lütjohann, D., Diczfalusy, U., Wahren, J., Björkhem, I., 2005. Crossing the barrier: net flux of 27-hydroxycholesterol into the human brain. J. Lipid Res. 46, 1047–1052.

Hirsch, E., Graybiel, A.M., Agid, Y.A., 1988. Melanized dopaminergic neurons are differentially susceptible to degeneration in Parkinson's disease. Nature 334, 345–348.

Hu, G., Antikainen, R., Jousilahti, P., Kivipelto, M., Tuomilehto, J., 2008. Total cholesterol and the risk of Parkinson disease. Neurology 70, 1972–1979.

Hu, G., Jousilahti, P., Nissinen, A., Antikainen, R., Kivipelto, M., Tuomilehto, J., 2006. Body mass index and the risk of Parkinson disease. Neurology 67, 1955–2199.

Huang, X., Alonso, A., Guo, X., Umbach, D.M., Lichtenstein, M.L., Ballantyne, C.M., Mailman, R.B., Mosley, T.H., Chen, H., 2015. Statins, plasma cholesterol, and risk of Parkinson's disease: a prospective study. Mov. Disord. 30, 552–559.

Huang, X., Auinger, P., Eberly, S., Oakes, D., Schwarzschild, M., Ascherio, A., Mailman, R., Chen, H., Parkinson Study Group DATATOP Investigators, 2011. Serum cholesterol and the progression of Parkinson's disease: results from DATATOP. PLoS One 6, e22854.

Istvan, E.S., Deisenhofer, J., 2001. Structural mechanism for statin inhibition of HMG-CoA reductase. Science 92, 1160–1164.

Jankovic, J., 2008. Parkinson's disease: clinical features and diagnosis. J. Neurol. Neurosurg. Psychiatry 79, 368–376.

Johnson, C.C., Gorell, J.M., Rybicki, B.A., Sanders, K., Peterson, E.L., 1999. Adult nutrient intake as a risk factor for Parkinson's disease. Int. J. Epidemiol. 28, 1102–1109.

Kempster, P.A., Hurwitz, B., Lees, A.J., 2007. A new look at James Parkinson's Essay on the Shaking Palsy. Neurology 69, 482–485.

Kojro, E., Gimpl, G., Lammich, S., Marz, W., Fahrenholz, F., 2001. Low cholesterol

stimulates the nonamyloidogenic pathway by its effect on the alpha -secretase ADAM 10. Proc. Natl. Acad. Sci. U. S. A. 98, 5815–5820.
Kolsch, H., Ludwig, M., Lütjohann, D., Rao, M.L., 2001. Neurotoxicity of 24-hydroxycholesterol, an important cholesterol elimination product of the brain, may be prevented by vitamin E and estradiol-17beta. J. Neural. Transm. 108, 475–488.
Kolsch, H., Lütjohann, D., Tulke, A., Björkhem, I., Rao, M.L., 1999. The neurotoxic effect of 24-hydroxycholesterol on SH-SY5Y human neuroblastoma cells. Brain Res. 818, 171–175.
Koob, A.O., Ubhi, K., Paulsson, J.F., Kelly, J., Rockenstein, E., Mante, M., Adame, A., Masliah, E., 2010. Lovastatin ameliorates alpha-synuclein accumulation and oxidation in transgenic mouse models of alpha-synucleinopathies. Exp. Neurol. 221, 267–274.
Kumar, A., Sharma, N., Gupta, A., Kalonia, H., Mishra, J., 2012. Neuroprotective potential of atorvastatin and simvastatin (HMG-CoA reductase inhibitors) against 6-hydroxydopamine (6-OHDA) induced Parkinson-like symptoms. Brain Res. 1471, 13–22.
Lee, C.Y., Seet, R.C., Huang, S.H., Long, L.H., Halliwell, B., 2009. Different patterns of oxidized lipid products in plasma and urine of dengue fever, stroke, and Parkinson's disease patients: cautions in the use of biomarkers of oxidative stress. Antioxid. Redox. Signal 11, 407–420.
Leoni, V., Caccia, C., 2011. Oxysterols as biomarkers in neurodegenerative diseases. Chem. Phys. Lipids 164, 515–524.
Leoni, V., Masterman, T., Patel, P., Meaney, S., Diczfalusy, U., Björkhem, I., 2003. Side chain oxidized oxysterols in cerebrospinal fluid and the integrity of blood-brain and blood-cerebrospinal fluid barriers. J. Lipid Res. 44, 793–799.
Lin, M.T., Beal, M.F., 2006. Mitochondrial dysfunction and oxidative stress in neurodegenerative diseases. Nature 443, 787–795.
Lordan, S., Mackrill, J.J., O'Brien, N.M., 2009. Oxysterols and mechanisms of apoptotic signaling: Implications in the pathology of degenerative diseases. J. Nutr. Biochem. 20, 321–336.
Lu, J., Wu, D.M., Zheng, Y.L., Hu, B., Zhang, Z.F., Shan, Q., Zheng, Z.H., Liu, C.M., Wang, Y.J., 2010. Quercetin activates AMP-activated protein kinase by reducing PP2C expression protecting old mouse brain against high cholesterol-induced neurotoxicity. J. Pathol. 222, 199–212.
Lütjohann, D., Breuer, O., Ahlborg, G., Nennesmo, I., Sidén, A., Diczfalusy, U., Björkhem, I., 1996. Cholesterol homeostasis in human brain: evidence for an age-dependent flux of 24S-hydroxycholesterol from the brain into the circulation. Proc. Natl. Acad. Sci. U. S. A. 93, 9799–9804.
Martín, M.G., Pfrieger, F., Dotti, C.G., 2014. Cholesterol in brain disease: sometimes determinant and frequently implicated. EMBO. Rep. 15, 1036–1052.
Marwarha, G., Dasari, B., Prasanthi, J.R.P., Schommer, J., Ghribi, O., 2010. Leptin is involved in accumulation of amyloid-beta and tau phosphorylation induced by 27-hydroxycholesterol in organotypic slices from adult rabbit hippocampus. J. Alzheimers Dis. 19, 1007–1019.
Marwarha, G., Ghribi, O., 2014. Does the oxysterol 27-hydroxycholesterol underlie Alzheimer's disease-Parkinson's disease overlap? Exp. Gerontol. 68, 13–18.
Marwarha, G., Raza, S., Prasanthi, J.R., Ghribi, O., 2013. Gadd153 and NF-κB crosstalk regulates 27-hydroxycholesterol-induced increase in BACE1 and β-amyloid production in human neuroblastoma SH-SY5Y cells. PLoS One 8, e70773.
Marwarha, G., Rhen, T., Schommer, T., Ghribi, O., 2011. The oxysterol 27-hydroxycholesterol regulates α-synuclein and tyrosine hydroxylase expression levels in human neuroblastoma cells through modulation of liver X receptors and estrogen receptors – relevance to Parkinson's disease. J. Neurochem. 119, 1119–1136.
Mazumder, M.K., Paul, R., Borah, A., 2013. β-phenethylamine-a phenylalanine derivative in brain–contributes to oxidative stress by inhibiting mitochondrial complexes and DT-diaphorase: an in silico study. CNS. Neurosci. Ther. 19, 596–602.
Miyake, Y., Sasaki, S., Tanaka, K., Fukushima, W., Kiyohara, C., Tsuboi, Y., Yamada, T., Oeda, T., Miki, T., Kawamura, N., Sakae, N., Fukuyama, H., Hirota, Y., Nagai, M., Fukuoka Kinki Parkinson's Disease Study Group, 2010. Dietary fat intake and risk of Parkinson's disease: a case-control study in Japan. J. Neurol. Sci. 288, 117–122.
Morris, J.K., Bomhoff, G.L., Stanford, J.A., Geiger, P.C., 2010. Neurodegeneration in an animal model of Parkinson's disease is exacerbated by a high-fat diet. Am. J. Physiol. Regul. Integr. Comp. Physiol. 299, R1082–R1090.
Mutez, E., Duhamel, A., Defebvre, L., Bordet, R., Destée, A., Kreisler, A., 2009. Lipid-lowering drugs are associated with delayed onset and slower course of Parkinson's disease. Pharmacol. Res. 60, 41–45.
Noguchi, N., Saito, Y., Urano, Y., 2014. Diverse functions of 24(S)-hydroxycholesterol in the brain. Biochem. Biophys. Res. Commun. 446, 692–696.
Otunola, G.A., Oloyede, O.B., Oladiji, A.T., Afolayan, A.J., 2014. Selected spices and their combination modulate hypercholesterolemia-induced oxidative stress in experimental rats. Biol. Res. 47, 5.
Pappolla, M.A., Smith, M.A., Bryant-Thomas, T., Bazan, N., Petanceska, S., Perry, G., Thal, L.J., Sano, M., Refolo, L.M., 2002. Cholesterol, oxidative stress, and Alzheimer's disease: expanding the horizons of pathogenesis. Free Radic. Biol. Med. 33, 173–181.
Piermartiri, T.C., Vandresen-Filho, S., de Araújo Herculano, B., Martins, W.C., Dal'agnolo, D., Stroeh, E., Carqueja, C.L., Boeck, C.R., Tasca, C.I., 2009. Atorvastatin prevents hippocampal cell death due to quinolinic acid-induced seizures in mice by increasing Akt phosphorylation and glutamate uptake. Neurotox. Res. 16, 106–115.
Pirchl, M., Ullrich, C., Sperner-Unterweger, B., Humpel, C., 2012. Homocysteine has anti-inflammatory properties in a hypercholesterolemic rat model in vivo. Mol. Cell. Neurosci. 49, 456–463.
Prasanthi, J.R., Dasari, B., Marwarha, G., Larson, T., Chen, X., Geiger, J.D., Ghribi, O., 2010. Caffeine protects against oxidative stress and Alzheimer's disease-like pathology in rabbit hippocampus induced by cholesterol-enriched diet. Free Radic. Biol. Med. 49, 1212–1220.
Prasanthi, J.R.P., Huls, A., Thomasson, S., Thompson, A., Schommer, E., Ghribi, O., 2009. Differential effects of 24-hydroxycholesterol and 27-hydroxycholesterol on beta-amyloid precursor protein levels and processing in human neuroblastoma SH-SY5Y cells. Mol. Neurodegener. 4, 1.
Ramirez, C., Tercero, I., Pineda, A., Burgos, J.S., 2011. Simvastatin is the statin that most efficiently protects against kainate-induced excitotoxicity and memory impairment. J. Alzheimers Dis. 24, 161–174.
Rangel, P., Cysneiros, R.M., Arida, R.M., de Albuquerque, M., Colugnati, D.B., Scorza, C.A., Cavalheiro, E.A., Scorza, F.A., 2005. Lovastatin reduces neuronal cell death in hippocampal CA1 subfield after pilocarpine-induced status epilepticus. Arq. Neuropsiquiatr. 63, 972–976.
Rantham Prabhakara, J.P., Feist, G., Thomasson, S., Thompson, A., Schommer, E., Ghribi, O., 2008. Differential effects of 24-hydroxycholesterol and 27-hydroxycholesterol on tyrosine hydroxylase and alpha-synuclein in human neuroblastoma SH-SY5Y cells. J. Neurochem. 107, 1722–1729.
Refolo, L.M., Malester, B., LaFrancois, J., Bryant-Thomas, T., Wang, R., Tint, G.S., Sambamurti, K., Duff, K., Pappolla, M.A., 2000. Hypercholesterolemia accelerates the Alzheimer's amyloid pathology in a transgenic mouse model. Neurobiol. Dis. 7, 321–331.
Reiss, A.B., Wirkowski, E., 2009. Statins in neurological disorders: mechanisms and therapeutic value. Sci. World J. 9, 1242–1259.
Roy, A., Pahan, K., 2011. Prospects of statins in Parkinson disease. Neuroscientist 17, 244–255.
Schachter, M., 2005. Chemical, pharmacokinetic and pharmacodynamic properties of statins: an update. Fundam. Clin. Pharmacol. 19, 117–125.
Schuster, S., Nadjar, A., Guo, J.T., Li, Q., Ittrich, C., Hengerer, B., Bezard, E., 2008. The 3-hydroxy-3-methylglutaryl-CoA reductase inhibitor lovastatin reduces severity of L-DOPA-induced abnormal involuntary movements in experimental Parkinson's disease. J. Neurosci. 28, 4311–4316.
Selley, M.L., 2005. Simvastatin prevents 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced striatal dopamine depletion and protein tyrosine nitration in mice. Brain Res. 1037, 1–6.
Sierra, S., Ramos, M.C., Molina, P., Esteo, C., Va'zquez, J.A., Burgos, J.S., 2011. Statins as neuroprotectants: a comparative in vitro study of lipophilicity, blood-brain-barrier penetration, lowering of brain cholesterol, and decrease of neuron cell death. J. Alzheimers Dis. 23, 307–318.
Simons, M., Keller, P., De Strooper, B., Beyreuther, K., Dotti, C.G., Simons, K., 1998. Cholesterol depletion inhibits the generation of beta-amyloid in hippocampal neurons. Proc. Natl. Acad. Sci. U. S. A. 95, 6460–6464.
Suh, M.D., Park, C.H., Kim, S.S., Kil, M.O., Lee, G.H., Johnson, G.V., Chun, W., 2004. Tissue transglutaminase is not involved in the aggregate formation of stably expressed alpha-synuclein in SH-SY5Y human neuroblastoma cells. Arch. Pharm. Res. 27, 850–856.
Tan, L.C., Methawasin, K., Tan, E.K., Tan, J.H., Au, W.L., Yuan, J.M., Koh, W.P., 2015. Dietary cholesterol, fats and risk of Parkinson's disease in the Singapore Chinese Health Study. J. Neurol. Neurosurg. Psychiatry, pii: jnnp-2014–310065. http://dx.doi.org/10.1136/jnnp-2014-310065.
Thirumangalakudi, L., Prakasam, A., Zhang, R., Bimonte-Nelson, H., Sambamurti, K., Kindy, M.S., Bhat, N.R., 2008. High cholesterol-induced neuroinflammation and amyloid precursor protein processing correlate with loss of working memory in mice. J. Neurochem. 106, 475–485.
Tison, F., Nègre-Pagès, L., Meissner, W.G., Dupouy, S., Li, Q., Thiolat, M.L., Thiollier, T., Galitzky, M., Ory-Magne, F., Milhet, A., Marquine, L., Spampinato, U., Rascol, O., Bezard, E., 2013. Simvastatin decreases levodopa-induced dyskinesia in monkeys, but not in a randomized, placebo-controlled, multiple cross-over ("n-of-1") exploratory trial of simvastatin against levodopa-induced dyskinesia in Parkinson's disease patients. Park. Relat. Disord. 19, 416–421.
Ullrich, C., Pirchl, M., Humpel, C., 2010. Hypercholesterolemia in rats impairs the cholinergic system and leads to memory deficits. Mol. Cell. Neurosci. 45, 408–417.
Umetani, M., Ghosh, P., Ishikawa, T., Umetani, J., Ahmed, M., Mineo, C., Shaul, P.W., 2014. The cholesterol metabolite 27-hydroxycholesterol promotes atherosclerosis via proinflammatory processes mediated by estrogen receptor alpha. Cell Metab. 20, 172–182.
Van der Most, P., Dolga, A.M., Nijholt, I.M., Luiten, P.G.M., Eisel, U.L.M., 2009. Statins: mechanisms of neuroprotection. Prog. Neurobiol. 88, 64–75.
Vance, J.E., 2012. Dysregulation of cholesterol balance in the brain: contribution to neurodegenerative diseases. Dis. Model. Mech. 5, 746–755.
Wang, Q., Tang, X.N., Wang, L., Yenari, M.A., Ying, W., Goh, B.C., Lee, H.S., Wilder-Smith, E.P., Wong, P.T., 2006. Effects of high dose of simvastatin on levels of dopamine and its reuptake in prefrontal cortex and striatum among SD rats. Neurosci. Lett. 408, 189–193.
Wang, Q., Wang, P.H., McLachlan, C., Wong, P.T., 2005. Simvastatin reverses the downregulation of dopamine D1 and D2 receptor expression in the prefrontal cortex of 6-hydroxydopamine-induced Parkinsonian rats. Brain Res. 1045, 229–233.
Wentworth Jr., P., Nieva, J., Takeuchi, C., Galve, R., Wentworth, A.D., Dilley, R.B.,

DeLaria, G.A., Saven, A., Babior, B.M., Janda, K.D., Eschenmoser, A., Lerner, R.A., 2003. Evidence for ozone formation in human atherosclerotic arteries. Science 302, 1053–1056.
Wolozin, B., Wang, S.W., Li, N.C., Lee, A., Lee, T.A., Kazis, L.E., 2007. Simvastatin is associated with a reduced incidence of dementia and Parkinson's disease. BMC. Med. 5, 20.
Xiong, H., Callaghan, D., Jones, A., Walker, D.G., Lue, L.F., Beach, T.G., Sue, L.I., Woulfe, J., Xu, H., Stanimirovic, D.B., Zhang, W., 2008. Cholesterol retention in Alzheimer's brain is responsible for high beta- and gamma-secretase activities and Abeta production. Neurobiol. Dis. 29, 422–437.
Xu, Y.Q., Long, L., Yan, J.Q., Wei, L., Pan, M.Q., Gao, H.M., Zhou, P., Liu, M., Zhu, C.S., Tang, B.S., Wang, Q., 2013. Simvastatin induces neuroprotection in 6-OHDA-lesioned PC12 via the PI3K/AKT/caspase 3 pathway and anti-inflammatory responses. CNS Neurosci. Ther. 19, 170–177.
Xue, Q.S., Sparks, D.L., Streit, W.J., 2007. Microglial activation in the hippocampus of hypercholesterolemic rabbits occurs independent of increased amyloid production. J. Neuroinflammation 4, 20.
Yamanaka, K., Saito, Y., Yamamori, T., Urano, Y., Noguchi, N., 2011. 24(S)-hydroxycholesterol induces neuronal cell death through necroptosis, a form of programmed necrosis. J. Biol. Chem. 286, 24666–24673.
Yamanaka, K., Urano, Y., Takabe, W., Saito, Y., Noguchi, N., 2014. Induction of apoptosis and necroptosis by 24(S)-hydroxycholesterol is dependent on activity of acyl-CoA:cholesterol acyltransferase 1. Cell Death Dis. 5, e990.
Yan, J., Sun, J., Huang, L., Fu, Q., Du, G., 2014a. Simvastatin prevents neuroinflammation by inhibiting N-methyl-D-aspartic acid receptor 1 in 6-hydroxydopamine-treated PC12 cells. J. Neurosci. Res. 92, 634–640.
Yan, J., Xu, Y., Zhu, C., Zhang, L., Wu, A., Yang, Y., Xiong, Z., Deng, C., Huang, X.F., Yenari, M.A., Yang, Y.G., Ying, W., Wang, Q., 2011. Simvastatin prevents dopaminergic neurodegeneration in experimental parkinsonian models: the association with anti-inflammatory responses. PLoS One 6, e20945.
Yan, J.Q., Ma, Y.J., Sun, J.C., Bai, S.F., Huang, L.N., 2014b. Neuroprotective effect of lovastatin by inhibiting NMDA receptor1 in 6-hydroxydopamine treated PC12 cells. Int. J. Clin. Exp. Med. 7, 3313–3319.
Yao, Z.X., Papadopoulos, V., 2002. Function of beta-amyloid in cholesterol transport: a lead to neurotoxicity. FASEB J. 16, 1677–1679.
Zacco, A., Togo, J., Spence, K., Ellis, A., Lloyd, D., Furlong, S., Piser, T., 2003. 3-Hydroxy-3-methylglutaryl coenzyme A reductase inhibitors protect cortical neurons from excitotoxicity. J. Neurosci. 23, 11104–11111.
Zhang, Q., Powers, E.T., Nieva, J., Huff, M.E., Dendle, M.A., Bieschke, J., Glabe, C.G., Eschenmoser, A., Wentworth Jr., P., Lerner, R.A., Kelly, J.W., 2004. Metabolite-initiated protein misfolding may trigger Alzheimer's disease. Proc. Natl. Acad. Sci. U. S. A. 101, 4752–4757.