Invited review

Cholesterol – A putative endogenous contributor towards Parkinson's disease

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ARTICLE INFO

Article history:
Received 9 April 2015
Received in revised form 25 July 2015
Accepted 27 July 2015
Available online 29 July 2015

Keywords:
Hypercholesterolemia
Oxysterol
Oxidative stress
α-synuclein aggregation
Neurodegeneration
Statins

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 α-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.

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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...
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-phenylethylamine 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 the 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 neurons (Rajakumar Prabakar 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 neuro-inflammation by gliosis or by releasing pro-inflammatory mediators in discrete brain regions leading to neuropathological complications (Thirumangalakudi et al., 2008; Ullrich et al., 2010; Pirchil 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; Martin et al., 2014; Marwarha and Chribi, 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; Ghrbi et al., 2006). Cholesterol is metabolized enzymatically or non-enzymatically to produce relatively more polar and active metabolites such 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 (Bjorkhem et al., 1998). Fifty percent of 24S-OHC in circulation is metabolized in liver, while the rest is converted into its conjugates (Bjorkhem 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; Martin 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-Flohe, 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; Pirchil 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; Pirchil 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
modulate the formation and aggregation of toxic α-synuclein in brain (Refolo et al., 2000; Ghribi et al., 2006; Ullrich et al., 2010; Pirch 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, α-synuclein 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 α-synuclein (Prasanthi et al., 2009; Marwarha et al., 2010). While level of 24S-OHC in brain is negatively correlated with α-synuclein levels in brain (Bruleva et al., 2010), 27-OHC-induced endoplasmic reticulum stress inhibits expression of leptin and activates several transcription factors which elevate the transcription of leptin (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, α-synuclein has a high affinity for the lipid rafts (Fantini and Yahi, 2010).

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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 (Martin et al., 2014). The role for cholesterol in the neurodegenerative pathiology 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 kBα 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.
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 Chiribi, 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., 2008), while in cultured dopaminergic neurons, overexpression of α-synuclein significantly upregulates the level of secosterol (Suh et al., 2004). Bieszke 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...
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 (Subh 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
Neuroprotective properties of different statins in experimental models of Parkinson’s disease.

<table>
<thead>
<tr>
<th>Statin</th>
<th>Solubility</th>
<th>PD model system</th>
<th>Effective dose</th>
<th>Neuroprotective properties</th>
<th>Anti-inflammatory properties</th>
<th>Apoptosis</th>
<th>Reference(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simvastatin</td>
<td>Lipophilic</td>
<td>6-OHDA-lesioned PC12</td>
<td>0.6 µg/ml</td>
<td>Restores GSH.</td>
<td>Downregulation of TNF-α, IL-1β, IL-6 and MMP-9.</td>
<td>Prevent neuronal loss.</td>
<td>Yan et al. (2011, 2014a)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6-OHDA-lesioned PC12</td>
<td>1.5 µM</td>
<td>NE</td>
<td>Downregulation of TNF-α, IL-6 and COX-2.</td>
<td>Prevent neuronal loss, inhibit caspase 3.</td>
<td>Xu et al. (2013)</td>
</tr>
<tr>
<td>Rat microglia</td>
<td></td>
<td></td>
<td>5–20 mM</td>
<td>Reduces NO and O₂⁻, prevents TNF-α.</td>
<td></td>
<td>NE</td>
<td>Selley (2005)</td>
</tr>
<tr>
<td>6-OHDA, rat</td>
<td></td>
<td>MPTP, mice</td>
<td>30 mg/kg/day, p.o.; 14 days</td>
<td>Reduces NO– and MDA level, restores GSH. Enhances mitochondrial complex-I and III activity.</td>
<td></td>
<td>Prevent activation of glia. Suppressed expression of p21^{co}, NF-κB, iNOS, IL-1β, and TNF-α in SNpc.</td>
<td>Ghosh et al. (2009)</td>
</tr>
<tr>
<td>PC12</td>
<td></td>
<td></td>
<td>6-OHDA, rat</td>
<td>10 mg/kg/day, 21 days, NE</td>
<td></td>
<td>Prevent dopaminergic neuronal loss.</td>
<td>Yan et al. (2011)</td>
</tr>
<tr>
<td>Lovastatin</td>
<td>Lipophilic</td>
<td>6-OHDA treated mice</td>
<td>100 µg/day, 2 months, orally</td>
<td>Reduces level of oxidized α-synuclein and cholesterol product.</td>
<td></td>
<td>Prevent dopaminergic neuronal loss.</td>
<td>Kumar et al. (2012)</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>Hydrophilic</td>
<td>MPTP, mice</td>
<td>100 µl, 3 after MPTP infusion, orally</td>
<td>Reduces TNF-α expression.</td>
<td></td>
<td>Improves cell viability.</td>
<td>Yan et al. (2014b)</td>
</tr>
</tbody>
</table>

: 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; O₂⁻, 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 neurodegenerative disorders such as AD, acute stroke, epilepsy and multiple sclerosis (Van der Most et al., 2009; Reiss and Wirkowsky, 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 Wirkowsky, 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; Piemartiri 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.

Acknowledgment

RP and AC currently are Senior Research Fellow in the Department of Biotechnology (DBT), Govt. of India funded research project (Sanction Order No. BT/230/NE/TBP/2011, dated April 23, 2012). We acknowledge the funding and support provided by the DBT.

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