INVITED REVIEW

Neuroprotective effects of statins against amyloid β-induced neurotoxicity

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Abstract
A growing body of evidence suggests that disruption of the homeostasis of lipid metabolism affects the pathogenesis of Alzheimer's disease (AD). In particular, dysregulation of cholesterol homeostasis in the brain has been reported to considerably increase the risk of developing AD. Thus, dysregulation of lipid homeostasis may increase the amyloid β (Aβ) levels by affecting amyloid precursor protein (APP) cleavage, which is the most important risk factor involved in the pathogenesis of AD. Previous research demonstrated that Aβ can trigger neuronal insulin resistance, which plays an important role in response to Aβ-induced neurotoxicity in AD. Epidemiological studies also suggested that statin use is associated with a decreased incidence of AD. Therefore, statins are believed to be a good candidate for conferring neuroprotective effects against AD. Statins may play a beneficial role in reducing Aβ-induced neurotoxicity. Their effect involves a putative mechanism beyond its cholesterol-lowering effects in preventing Aβ-induced neurotoxicity. However, the underlying molecular mechanisms of the protective effect of statins have not been clearly determined in Aβ-induced neurotoxicity. Given that statins may provide benefits beyond the inhibition of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, these drugs may also improve the brain. Thus, statins may have beneficial effects on impaired insulin signaling by activating AMP-activated protein kinase (AMPK) in neuronal cells. They play a potential therapeutic role in targeting Aβ-mediated neurotoxicity.

Key Words: *statins; neuroprotective effects; amyloid β-induced neurotoxicity; insulin signaling; AMP-activated protein kinase*

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Introduction
Alzheimer's disease (AD) is a neurodegeneration disorder that is pathologically characterized by cerebral atrophy (particularly within the hippocampus and temporal and parietal lobes), senile plaques, neurofibrillary tangles, and neuronal cell death (Zhang et al., 1989). The clinical features are loss of short-term memory and cognitive function. The pathogenesis of AD is associated with amyloid β (Aβ) peptide and tau hyperphosphorylation, which are a crucial hallmark (Ghiso and Frangione, 2002; Bloom, 2014). Statins have a pathophysiological relationship with AD and brain metabolism abnormalities (Zissimopoulos et al., 2017). Moreover, Aβ accumulation is associated with a number of metabolic brain abnormalities (Sato and Morishita, 2015). Abnormal neuronal metabolism is considered a risk factor for developing AD (Vance, 2012; Sato and Morishita, 2015). As a result, an imbalance in the metabolic status of the brain is believed to be one of the underlying pathophysiologic mechanisms contributing to AD (Kang and Rivest, 2012). In particular, dysregulation of cholesterol homeostasis in the brain considerably increases the risk of developing AD (Vance, 2012). The levels of cholesterol are elevated, which are a central risk factor in the development of AD (Vance, 2012). However, lowering cholesterol levels may benefit the brain of a patient with AD (Vance, 2012). Therefore, cholesterol-lowering medications such as statins are considered to prevent the development of AD. Epidemiological studies indicated that the global use of statins to treat hypercholesterolemia can reduce the risk of AD (Zissimopoulos et al., 2017). The present review highlights the results of brain metabolic abnormalities accelerating the pathogenesis of AD and explains the potential mechanism of statin's protection against Aβ-induced neurotoxicity.

Cholesterol Homeostasis Abnormalities Accelerate the Pathogenesis of AD
AD can be classified broadly into two groups: early onset AD and late-onset AD. Early onset AD occurs among individuals < 65 years, whereas late-onset AD affects individuals > 65 years. Although early onset AD only accounts for a small percentage of AD cases, early onset AD is the most severe form, with the majority of cases caused by mutations in one of three genes, namely, the amyloid precursor protein (APP), presenilin 1 (PS1), and presenilin 2 (PS2). By contrast, late-onset AD accounts for the vast majority of AD cases (about 95%). Age is the major risk factor for late-onset AD, and possession of an apolipoprotein ε4 allele (ApoE ε4) is also a risk factor. ApoE ε4 allele-carrying individuals also have an increased risk of developing diabetes, dyslipidemia, hypertension, and hypercholesterolemia. Thus, in the

1990s, high levels of plasma cholesterol and the presence of coronary artery disease were positively correlated with the incidence of AD (Martins et al., 2009).

Imbalanced metabolic status of the brain is believed to be one of the underlying pathophysiologic mechanisms contributing to AD (Kang and Rivest, 2012). To maintain optimal neuronal functions, cholesterol levels are precisely controlled by the brain; altered cholesterol metabolism may contribute to the pathogenesis of neurodegeneration (Nicholson and Ferreira, 2010; Cartocci et al., 2017). Clinical evidence has suggested that dysregulated lipid metabolism may participate in the progression of AD (Vance, 2012; Sato and Morishita, 2015), especially, hypercholesterolemia increases susceptibility to AD (Kang and Rivest, 2012; Vance, 2012; Sato and Morishita, 2015). Increasing evidence suggests that cholesterol plays a role in the pathophysiology of AD. For instance, an elevated serum cholesterol level has been shown to be a risk factor for AD (Wolozin et al., 2000). The presence of ApoE ε4, which is associated with high circulating levels of cholesterol, is a well-established risk factor for developing AD in humans (Jarvik et al., 1994; Gomez-Isla et al., 1996), and cholesterolemia is a frequent finding among patients with AD (Ledesma and Dotti, 2012). As we known the ApoE gene encodes a ~34 kDa protein that serves as a crucial regulator of cholesterol homeostasis throughout the body. Particularly, evidence identifies ApoE is the primary cholesterol carrier in the central nervous system. In humans, ApoE exists as three major alleles including ApoE2, ApoE3, and ApoE4, and inheritance of the ApoE4 allele increases the risk of developing AD. Previously studies have identified that the cholesterol transporter ATP-binding cassette transporter A1 (ABCA1) is a crucial regulator of ApoE levels and lipidation in the brain. Deficiency of ABCA1 leads to a loss of approximately 80% of ApoE in the brain, and the residual 20% that remains is poorly lipidated (Hirsch-Reinshagen et al., 2009). Several independent studies have also shown this poorly lipidated ApoE increases amyloid burden in mouse models of AD, demonstrating that ApoE lipidation by ABCA1 affects key steps in amyloid deposition or clearance. Conversely, robust overexpression of ABCA1 in the brain promotes ApoE lipidation and nearly eliminates the formation of mature amyloid plaques (Hirsch-Reinshagen et al., 2009; Di Paolo and Kim, 2011). These suggest that the lipid binding capacity of ApoE is a major mechanism of its function in the pathogenesis of AD, and imply that increasing ApoE lipidation may display therapeutic importance for this devastating disease (**Figure 1**). It is known the high cholesterol levels are related to the development of AD neuropathology (Nicholson and Ferreira, 2010). In particular, imbalanced metabolic status of the brain is believed to be one of the most underlying pathophysiologic mechanisms contributing to AD (Kang and Rivest, 2012).

One of the most widely accepted theories of Alzheimer's pathology is the aggregation of Aβ into extracellular cortical and hippocampal plaques. Aβ denotes peptides of 36–43 amino acids that are crucially involved in AD as the main component of amyloid plaques found in the brains of AD's patients (Hamley, 2012). The Aβ peptides derive from the APP, which is cleaved by β-secretase and γ-secretase to yield Aβ. Aβ molecules can aggregate to form flexible soluble oligomers which may exist in several forms such as monomeric, oligomers and fibrillary forms. Although the normal functional of Aβ is not well understood (Hiltunen et al., 2009), several potential studies have been indicated that Aβ-caused neurotoxicity, including oxidative stress (Li et al., 2016), regulation of cholesterol transport (Igbavboa et al., 2009) and anti-microbial activity, which potentially associated with Aβ-induced inflammatory activity. Therefore, transgenic AD mice studies found that mitochondrial cholesterol overloading exacerbates Aβ-induced inflammation and neurotoxicity in AD (Fernández et al., 2009). A recent study indicated that the involvement of cholesterol in APP metabolism is suggested by the fact that cholesterol is a membrane lipid and Aβ is produced by intra-membrane cleavage of APP. Therefore, cholesterol may increase the activity of β-secretase or γ-secretase enzymes that generate Aβ from APP, decrease the flux of APP through the non-amyloidogenic α-secretase pathway, and affect various non-amyloid factors such as local inflammation or tau metabolism (Cole et al., 2005; Shinohara et al., 2014). As a result, the potential mechanisms for cholesterol's apparent adverse effect on the development of AD act on APP primarily at the cell surface. However, the accumulation of Aβ protein in the brain is a slow process that takes several years before manifesting its neurotoxicity (Spires-Jones and Hyman, 2014). The presence of amyloid plaques in elderly subjects without cognitive impairment suggests that the accumulation of the peptide by itself is not the only causative condition of neuronal damage; for unknown reasons, Aβ becomes progressively toxic in the brain of patients with AD (Geula et al., 1998; Fjell and Walhovd, 2012). The brain is the organ with the highest cholesterol content, the majority of which stems from *de novo* synthesis (Pfrieger and Ungerer, 2011). Notably, high cholesterol levels have recently been found to be significantly elevated in patients with either vascular dementia or AD, and a positive correlation has been reported (Nina et al., 2011). Some study reported that isolated mitochondria from brain or cortical neurons of transgenic mice overexpressing sterol regulatory element binding protein 2 (SREBP-2) or Niemann-Pick type C1 (NPC1) knock-out mice, which contribute to polygenic hypercholesterolaemia, exhibited mitochondrial cholesterol accumulation, mitochondrial glutathione (mGSH) depletion and increased susceptibility to Abeta1–42-induced oxidative stress and release of apoptogenic proteins. Similar findings were observed in pharmacologically GSH-restricted rat brain mitochondria, while selective mGSH depletion sensitized human neuronal and glial cell lines to Aβ1–42-mediated cell death (Fernández et al., 2009). *In vitro* studies have demonstrated that secretion of cholesterol leads to neuronal damage (Zhang and Liu, 2015), but the potential molecular mechanisms for cholesterol's apparent adverse effect on Aβ-induced neurotoxicity are unclear.

Statin Prevents Cholesterol-Accelerated AD Pathogenesis

Several lines of evidence suggest that dysregulated lipid metabolism may participate in the progression of AD (Sato and Morishita, 2015). In particular, imbalances in the cholesterol homeostasis of the brain considerably increase the risk of developing AD (Vance, 2012). Brain cholesterol levels increase the susceptibility of neurons to Aβ toxicity, thereby revealing a possible role in triggering AD (Nicholson and Ferreira, 2010). Therefore, elevated cholesterol levels are a major risk factor for AD. And, lowered brain cholesterol levels may benefit patients with AD. Given these concepts, cholesterol-lowering medications, such as statins, are considered to help prevent or lower the risk of AD. Epidemiological studies highly suggest that statins can globally reduce the risk of AD (Jick et al., 2000; Wolozin et al., 2000; Zissimopoulos et al., 2017). The global use of statins to treat hypercholesterolemia has led to the hope that statins may prove useful in treating or preventing AD.Statins, also known as 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, are a class of lipid-lowering medications (Stancu and Sima, 2001). Statins are principally used in the treatment of hypercholesterolemia (Catapano et al., 2016). They include medications such as atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, mevastatin, rosuvastatin, cerivastatin, and simvastatin. The synthetic statins atorvastatin, rosuvastatin, cerivastatin, and fluvastatin appear to be as efficacious as the natural ones, such as mevastatin lovastatin, pravastatin, and simvastatin (Chong et al., 2001). Statins have been categorized into two types: lipophilic and hydrophilic (Fong, 2014). Lipophilic statins, which include simvastatin, lovastatin, atorvastatin, and cerivastatin, can easily cross the blood brain barrier. By contrast, hydrophilic statins, which include fluvastatin, mevastatin, and pravastatin, are a group of compounds that block cholesterol biosynthesis *via* competitive inhibition of HMG-CoA reductase. HMG-CoA reductase is the rate-limiting enzyme that catalyzes the conversion of HMG-CoA to mevalonate in cholesterol biosynthesis (Chong et al., 2001; Fong, 2014). Excess free cholesterol in the cell is converted into cholesteryl esters by the enzyme sterol O-acyltransferase 1 (ACAT1; also known as acyl CoA:cholesterol acyltransferase 1), followed by accumulation in intracellular lipid droplets or efflux through the plasma membrane into the extra-cellular environment (Chang et al., 2006). Increasing levels of cholesteryl esters enhances Aβ release in cultured cells, whereas pharmacological inhibition of ACAT1 leads to the reduction of both Aβ and cholesteryl ester. Genetic ablation of ACAT1 reduces both Aβ pathology and cognitive impairments in a mouse model of AD (Bryleva et al., 2010). Together, these suggested that the balance between free cholesterol and cholesterol esters is a key parameter controlling amyloidogenesis (**Figure 1**). The bioavailability of statins varies from less than 5% with simvastatin to approximately 60% with cerivastatin. They inhibit the enzyme HMG-CoA reductase, which plays a central role in the production of cholesterol and other sterols (Chong et al., 2001). This mechanism of action and its effect on lipids (low-density lipoprotein (LDL) cholesterol reduction, triglyceride reduction, and high-density lipoprotein cholesterol elevation) are well established (Vaughan et al., 2000; Stancu and Sima, 2001). Statins lower cholesterol production and promote hepatic removal of serum LDL cholesterol. In addition to their conventional use in lowering cholesterol in humans, statins have been widely used for the treatment of a variety of conditions.

Several lines of evidence have indicated that statins can reduce AD pathology in both clinical studies and animal studies (Sano et al., 2011; Geifman et al., 2017; Zissimopoulos et al., 2017). Clinical studies found that cholesterol may be implicated in the pathogenesis of AD, and statins administered in midlife might prevent AD in late life (Geifman et al., 2017; Zissimopoulos et al., 2017). However, Sano et al. (2011) reported that statins do not benefit the progression of symptoms in individuals with mild to moderate AD despite a significant reduction in cholesterol. A recent re-analysis of AD patient-level data from failed clinical trials suggested that the use of statins may benefit all patients with AD with potentially greater therapeutic efficacy than those homozygous for ApoE4 (Geifman et al., 2017). However, increasing evidence suggests that the reduction in AD risk varied across statin molecules, sex, and race/ethnicity (Zissimopoulos et al., 2017), and there is a lower prevalence of diagnosed probable AD in patients taking 2 different statin such as lovastatin and pravastatin (Wolozin et al., 2000) (**Table 1**). In summary, statins may prevent the pathology of AD. Significant emerging evidence has linked cholesterol, Aβ, and AD, and several studies have shown a reduced risk for AD and dementia in populations treated with statins. In experimental settings in animal models, statins were found to reduce the Aβ level and tau hyperphosphorylation in the brain (Ostrowski et al., 2007; Kurinami et al., 2008; Shinohara et al., 2010; Kurata et al., 2011; Papadopoulos et al., 2014). Aβ reduction is associated with a reduction in the APP-carboxyl terminal fragment (APP-CTF) by statin treatment (Shinohara et al., 2010). Statins reduce brain Aβ levels by increasing APP-CTF trafficking through isoprenylation inhibition (Shinohara et al., 2010). Moreover, statin enhances Aβ clearance by upregulating LDL receptor-related protein 1 expression in brain microvessels (Shinohara et al., 2010). Hence, prevention of Aβ-induced memory impairment by fluvastatin has been associated with reduced brain Aβ accumulation and oxidative stress in an AD mouse model (Kurinami et al., 2008). Some studies indicated that atorvastatin and pitavastatin can improve cognitive function and reduce senile plaque and phosphorylated tau in aged APP mice (Kurata et al., 2011). Handattu et al. (2009) also showed that pravastatin significantly ameliorates Aβ burden in the hippocampus and improves cognitive function in an AD mouse model. As a result, statin can significantly attenuate cholesterol-accelerated AD pathogenesis in animal and AD patient studies (**Table 1**). Mechanistically, whether the regimen of statins

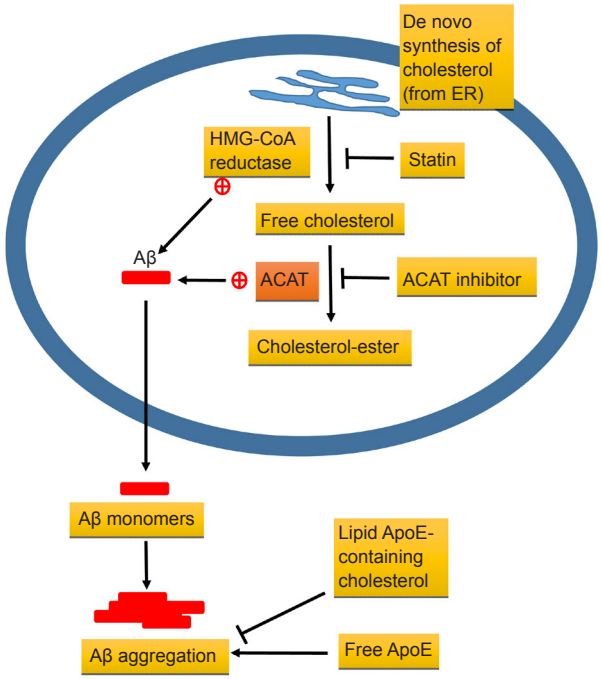

Figure 1 Contribution of cholesterol to biogenesis and degradation of amyloid β (Aβ).
Cholesterol in the brain is mainly derived from *de novo* synthesis from the endoplasmic reticulum (ER). HMG-CoA reductase mediates the rate-limiting step in *de novo* cholesterol biosynthesis. Excess free cholesterol is converted into cholesterol ester by ACAT. Inhibition of HMG-CoA reductase by statins leads to decreased levels of Aβ and ACAT inhibition has been also shown to reduce Aβ levels. ApoE-containing HDL-like particles inhibit the aggregation of Aβ, whereas free ApoE has been shown to promote Aβ aggregation. HMG-CoA: 3-Hydroxy-3-methyl-glutaryl coenzyme A; ACAT: sterol O-acyltransferase 2, also known as acyl-coenzyme A:cholesterol acyltransferase 1; HDL: high-density lipoprotein.

used in this trial influences pathogenic mechanisms of AD in the brain or affected biomarkers of amyloid, tau, or other neuropathologies remains unclear.

Statin Prevents Cholesterol-Promoted Aβ Deposit Formation and Neurotoxicity

Clinical studies demonstrated that elevated levels of serum or cerebrospinal fluid cholesterol are linked to the production of Aβ peptides and the development of AD (Papassotiropoulos et al., 2003; Guasti et al., 2008). Aβ is a 38 to 43 amino acid peptide that is derived from the APP through sequential cleavages by β- and γ-secretase enzyme activities. The cleavage site for another APP processing enzyme, α-secretase lies within the Aβ sequence and thus precludes Aβ formation. Excess Aβ is believed to be a main contributor to the dysfunction and degeneration of neurons that occurs in AD (Thinakaran and Koo, 2008). A previous study reported that statin may reduce the cellular cholesterol level of living hippocampal neurons by 70%, and the formation of Aβ is completely inhibited while the generation of a nonamyloidogenic secreted form is unperturbed. This indicates that depletion of cholesterol in the brain inhibits the generation of Aβ in hippocampal neurons (Simons et al., 1998). Moreover, some study indicated that treatment with lovastatin results in a higher expression of the α-secretase ADAM 10, and inhibit the generation of Aβ in neural cell lines (Kojro et al., 2001). Zandl-Lang et al. (2018) also demonstrated the use of simvastatin displays intriguing effects among cellular cholesterol metabolism, Aβ production metabolism, and clearance at the blood–brain interface. Statins also promote the degradation of extracellular Aβ peptide by microglia *via* stimulating exosome-associated insulin-degrading enzyme secretion (Tamboli et al., 2010) (**Table 2**). Thus, statins indeed attenuate cholesterol-accelerated Aβ production (**Figure 1**).

Several lines of evidence suggest that dysregulated lipid metabolism may also participate in the pathogenesis of AD. Epidemiologic studies reveal that elevated mid-life plasma cholesterol levels may be associated with an increased risk of AD, and the statin use may significantly reduce the prevalence of AD. Cellular studies have shown that intracellular cholesterol markedly affects the processing of APP into Aβ peptides. A large body of data suggest that statins prevent Aβ-induced cell death by decreasing cholesterol levels (Longenberger and Shah, 2011; Geifman et al., 2017; Kornelius et al., 2017). In fact, Aβ can induce the production of pro-inflammatory cytokines interleukin-1β (IL-1β), tumor necrosis factor-α (TNF-α), and interleukin-6 (IL-6) from activated microglia (Chong et al., 2001) leading to the overload of inflammatory cytokines in the hippocampus (Geifman et al., 2017). For example, the administration of atorvastatin ameliorates cognitive deficits, depresses inflammatory responses, improves long-term potentiation impairment, and prevents Aβ-induced neurotoxicity in cultured hippocampal neurons. These protective functions of atorvastatin involve the pathway of reducing farnesyl pyrophosphate (Zhao et al., 2016). Atorvastatin also attenuates the production of IL-1β, IL-6, and TNF-α in the hippocampus of an Aβ1-42-induced rat model of AD (Corrao et al., 2013). Moreover, simvastatin has been demonstrated to cause a shift in cytokine production from proinflammatory to anti-inflammatory response (Barbosa et al., 2017). Simvastatin also protects Aβ-induced neuron cell death in hippocampal dentate gyrus, which may improve spatial cognitive function in animal studies and clinical studies (Longenberger and Shah, 2011) (**Table 3**). Thus, HMG-CoA reductase inhibitors (statins) have various pleiotropic effects such as reducing Aβ-induced neuroinflammation, and Aβ-induced neuronal cell death. Although the Aβ-induced neurotoxicity remain controversial, dysregulation of calcium homeostasis and oxidative stress are likely to be a major mechanism that mediates Aβ toxicity. In mixed cultures containing hippocampal neurons and astrocytes, neurotoxic Aβ cause sporadic cytosolic calcium signals in astrocytes but not in neurons, initiating a cascade that ends in neuronal death (Catapano et al., 2016). Considering that mevastatin is a common group of drugs clinically prescribed to treat high cholesterol, we proposed that it may also exert neuroprotective effects by decreasing intracellular cholesterol levels (Kornelius et al., 2017). Actually, high exogenous cho-

Table 1 Statins reduce AD pathology in clinical studies and animal studies

Type	Study	Effect	Reference
AD patient	Re-analysis clinical studies	Statins may benefit all AD patients with potentially greater therapeutic efficacy in those homozygous for ApoE4.	Geifman et al., 2017; Zissimopoulos et al., 2017
	Re-analysis clinical studies	Statin had no benefit on the progression of symptoms in individuals with mild to moderate AD despite significant lowering of cholesterol.	Sano et al., 2011
	Clinical trials	The reduction in AD risk varied across statin molecules, sex, and race/ethnicity.	Zissimopoulos et al., 2017
	A cross-sectional analysis	There is a lower prevalence of diagnosed probable AD in patients taking 2 different 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors—lovastatin and pravastatin.	Wolozin et al., 2000
Animal study	Mouse model	Prevention of Aβ-induced memory impairment by fluvastatin, associated with the decrease in Aβ a accumulation and oxidative stress in Aβ injection mouse model.	Kurinami et al., 2008
	AD mouse model	Pravastatin significantly ameliorates Aβ burden in the hippocampus and improves cognitive function in an AD mouse model.	Handattu et al., 2009
	APP-CTF	Statins reduce the brain Aβ levels by increasing APP-CTF trafficking. Statin enhanced Aβ clearance through up-regulating LDL receptor-related protein 1 (LRP1) expression in brain microvessels.	Shinohara et al., 2010
	Aged APP mice	Atorvastatin and pitavastatin improve cognitive function and reduce senile plaque and phosphorylated tau in aged APP mice.	Kurata et al., 2011

AD: Alzheimer's disease; ApoE4: apolipoprotein 4; Aβ: amyloid β; APP: amyloid precursor protein; CTF: carboxyl terminal fragment; LDL: low-density lipoprotein.

Table 2 Statins attenuate cholesterol-accelerated amyloid β (Aβ) production.

Type	Study	Effect	Reference
Aβ production	Hippocampal neurons	Cholesterol depletion inhibits the generation of Aβ in hippocampal neurons.	Simons et al., 1998
	Neural cell lines	Low cholesterol stimulates the nonamyloidogenic pathway by its effect on the α-secretase ADAM 10.	Kojro et al., 2001
	Effects of simvastatin in endothelial cells	Simvastatin in brain capillary endothelial cells (BCEC) indicating a interplay of cellular cholesterol metabolism, and Aβ production metabolism and clearance at the blood-brain interface.	Zandl-Lang et al., 2018
	Effects of atorvastatin in microglial activation	Statins also promote the degradation of extracellular Aβ peptide by microglia *via* stimulation of exosome-associated insulin-degrading enzyme (IDE) secretion.	Tamboli et al., 2010

Table 3 Statins attenuate cholesterol-promoted Aβ-induced neurotoxicity

Type	Study	Effect	Reference
Aβ cytotoxicity	Atorvastatin	The administration of atorvastatin ameliorates cognitive deficits, depresses inflammatory responses, improves long-term potentiation impairment, and prevents Aβ-induced neurotoxicity in cultured hippocampal neurons.	Zhao et al., 2016
	Simvastatin	Simvastatin has been demonstrated to cause a shift in cytokine production from proinflammatory to anti-inflammatory response.	Barbosa et al., 2017
	Atorvastatin	Atorvastatin attenuates the production of IL-1β, IL-6, and TNF-α in the hippocampus of an Aβ1–42-induced rat model of AD.	Corrao et al., 2013
	Simvastatin	Simvastatin protects Aβ-induced neuron cell death in hippocampal dentate gyrus, which may improve spatial cognitive function in animal studies and clinical studies.	Longenberger and Shah, 2011
	Atorvastatin	Atorvastatin against neuronal toxicity induced by Aβ1–40 demonstrating that a pretreatment with atorvastatin prevents the spatial learning and memory deficits induced by a single intracerebroventricular injection of aggregated Aβ1–40 in mice and promotes changes antioxidant systems mainly in prefrontal cortex.	Martins et al., 2015
	Mevastatin	Mevastatin prevents Aβ-induced cell death by decreasing cholesterol levels.	Kornelius et al., 2017

Aβ: Amyloid β; IL-1β: interleukin-1β; IL-6: interleukin-6; TNF-α: interleukin-6; AD: Alzheimer's disease.

lesterol levels may render neurons vulnerable to Aβ-induced neuronal cell death (Mendoza-Oliva et al., 2013). Several studies have indicated that statins can attenuate Aβ-induced neuronal cell apoptosis *in vivo* and *in vitro* (Papassotiropoulos et al., 2003; Guasti et al., 2008; Fernández et al., 2009; Handattu et al., 2009). The extracellular accumulation of Aβ is one of the characteristic neuropathological hallmarks of AD in neuritic plaques. Experimental data indicate that different molecular forms of Aβ affect a wide array of neuronal and glial functions, and thereby lead to neuronal death in the nervous system. Martins et. al. demonstrated that atorvastatin prevents the spatial learning and memory deficits by upregulating antioxidant systems mainly in an AD mice model (Martins et al., 2015). Similarly, our recent study reported that mevastatin prevents Aβ-induced cell death by decreasing cholesterol levels (Kornelius et al., 2017) (**Table 3**). This indicates statin may play a beneficial role in Aβ-induced neurotoxicity through reducing cholesterol levels.

Statins Attenutates Aβ-Induced Neuronal Apoptosis Through Activation of Akt and/or AMP-Activated Protein Kinase (AMPK) Signaling

The dysregulation of lipid metabolism may be initiated or accelerated in the progression of AD pathology (Sato and Morishita, 2015). In particular, dysregulation of cholesterol homeostasis in the brain substantially increases the risk of developing AD (Vance, 2012). This finding indicates that dysregulated lipid homeostasis in the brain can be induced by an increase in Aβ levels or production of longer species of Aβ, such as Aβ42 and Aβ43 peptides (Vance, 2012; Sato and Morishita, 2015). The raised Aβ levels increase neurotoxicity including oxidative stress, mitochondria dysfunction and neuronal cell apoptosis. Previously research demonstrated that Aβ-induced cell death can be enhanced by inhibition of neuronal insulin signaling (Li et al., 2016). In fact, there is widening recognition that AD is closely linked to a state of relative insulin resistance in the brain, so-called "type III diabetes" (de la Monte et al., 2006). It is known that AD is a neurodegenerative disorder defined at the molecular level by the presence of neurofibrillary tangles (NFTs) and insoluble Aβ plaques. NFTs are composed of hyper-phosphorylated forms of the microtubule-associated protein tau, whereas Aβ is derived from the proteolytic cleavage of APP (Hardy, 2006). Tau proteins are essential in assembly as well as maintenance of the structural integrity of microtubules (Hooper et al., 2008). However, Tau is abnormally hyper-phosphorylated and aggregated in AD. Aβ can stimulate hyper-phosphorylation of the Tau protein, which is the main event responsible for NFT formation in AD brains (Hooper et al., 2008). Therefore, neuronal insulin signaling are often dysregulated in AD brain (Messier and Teutenberg, 2005). In normal brain, insulin promotes glucose utilization, energy metabolism, and neuronal survival through PI3K/Akt signaling. Akt is an important regulator of cell survival and apoptosis (Freude et al., 2009). Thus, Akt is activated by PI3K and then phosphorylates glycogen synthase kinase-3β (GSK-3β) activation. Downregulation of PI3K/Akt signaling causes GSK-3β activity increase and leads to Tau hyper-phosphorylation, the main component of NFT (Hooper et al., 2008; Freude et al., 2009). It has been shown that Akt activation may play a therapeutic role in neurodegenerative diseases such as AD (Kitagishi et al., 2014). Therefore, dysregulated lipid homeostasis can be induced Aβ production, which may accelerate Aβ toxicity and leaded to neuronal apoptosis.

Epidemiological studies suggested that statin use is associated with a decreased incidence of AD. Particularly, some studies have reported that statin protects against Aβ-induced neurotoxicity and apoptosis through Akt activation. For example, atorvastatin and pitavastatin reduced the level of oxidative stress, as revealed by the presence of 4-hydroxy-2-nonenal (4-HNE) and advanced glycation end products (AGEs) in AD mouse brains by improving insulin/Akt signaling in AD mouse brains (Kurata et al., 2013). Simvastatin also prevents Aβ-impaired neurogenesis in hippocampal dentate gyrus through cascading PI3K-Akt and increasing BDNF *via* reduction in farnesyl pyrophosphate (Wang et al., 2015). Moreover, lovastatin exhibits neuroprotective benefits in preventing neurodegeneration by activating the Akt pathway and inhibits downstream GSK-3β activity (Lin et al., 2016). Our results also indicated that mevastatin attenuates Aβ-induced cell death by upregulating insulin signaling, which can be mediated through the repression of GSK-3β and tau phosphorylation (Kornelius et al., 2017). These findings suggested that GSK3β may trigger phosphorylated tau aggregation and lead to cell apoptosis, whereas statin effectively represses Aβ-induced tau pathology and apoptosis by retuning impaired neuronal insulin signaling (**Figure 2**).

Discussion

Previously studies demonstrated that statins activate AMPK signaling (Sun et al., 2006). AMPK signaling plays an important role in the coordination of cellular energy and metabolic status in various organs (Lin et al., 2017). AMPK is a trimeric enzyme comprising a catalytic α-subunit and regulatory β, γ-subunits (Stapleton et al., 1997). It was first identified as an upstream kinase that phosphorylates and hence inactivates HMG-CoA reductase and acetyl-CoA carboxylase (ACC), the key enzymes controlling cholesterol/isoprenoid and fatty acid biosynthesis, respectively. AMPK can function as a fuel gauge to regulate the homeostasis of energy in the form of glucose and fatty acids in skeletal muscles, liver, and adipocytes (Kahn et al., 2005). Recent findings suggest that the fuel-sensing mechanism of AMPK is also present in the hypothalamus in regulation of food intake and energy expenditure (Minokoshi et al., 2004). The involvement of AMPK in diabetes mellitus is demonstrated by insulin resistance, with associated high levels of plasma glucose and low levels of insulin in mice with ablated AMPK (Viollet et al., 2003). Previous study reported that statins activate endothelial nitric oxide (NO) synthase (eNOS) with

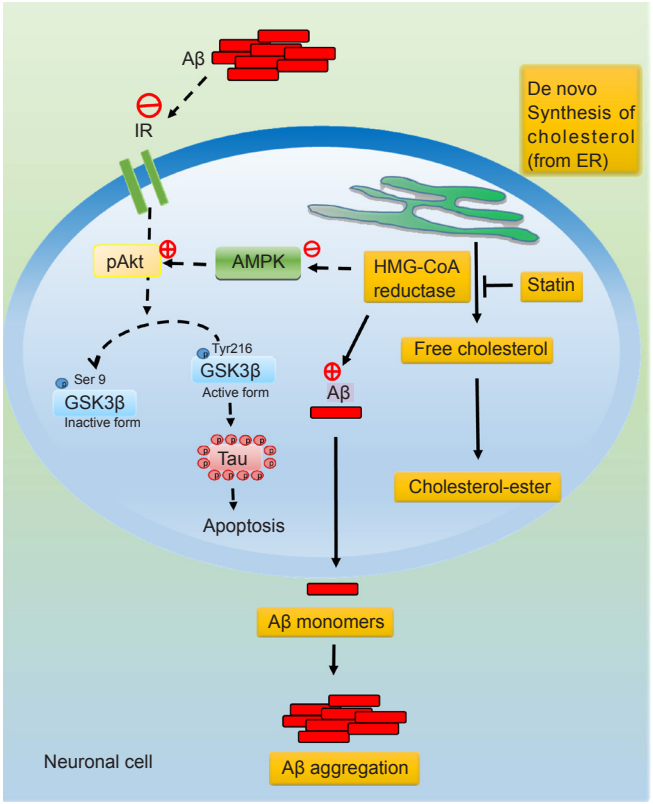

Figure 2 Statins attenuates amyloid β (Aβ)-induced neuronal apoptosis through activation of Akt and/or AMP-activated protein kinase (AMPK) signaling.
De novo synthesis of cholesterol in the brain is mainly derived from the endoplasmic reticulum (ER). 3-Hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase mediates the rate-limiting step in cholesterol biosynthesis. Inhibition of HMG-CoA reductase by statins leads to decreased levels of Aβ and the Aβ aggregation.
Aβ induces the hyper-phosphorylation of the Tau protein and neuronal death. Aβ can trigger neuronal insulin resistance, then blocked down-stream of Akt, and activation of glycogen synthase kinase-3β (GSK-3β), which leaded to neuronal cell apoptosis. The statin can reduce Aβ-induced neuronal apoptosis through upregulation of Akt and thereby inhibit GSK-3β-stimulated Tau hyperphosphorylation. This depends on AMPK-alleviated neuronal insulin resistance, and thereby repression of GSK3β-stimulated tau hyperphosphorylation.

increased NO production, which has been suggested to be mediated through the phosphoinositide 3-kinase (PI3K)/Akt pathway (Sun et al., 2006). Some studies indicated that a sustained decrease in AMPK activity accompanies insulin resistance, whereas AMPK activation increases insulin sensitivity (Steinberg and Kemp, 2009; Salminen et al., 2011). In addition, AMPK activity can reduce Aβ-induced neurotoxicity and restore neuronal insulin signaling (Kornelius et al., 2015). The activated AMPK is one of the possible mechanisms underlying the proposed neuroprotection of statins against Aβ-induced neurotoxicity, rather than directly to their cholesterol-lowering effects. Given that statins can effectively increase activation of AMPK, they may also improve brain insulin action and exert protective effects against AD-impaired insulin signaling (Kornelius et al., 2017). Considering the important roles of Aβ-induced cell death and insulin resistance in AD pathogenesis, these observations unveil a potential neuroprotective mechanism by statin through restoration of AMPK and insulin signaling (**Figure 2**).

Conclusion

AD is the most common form of neurodegenerative dementia. The overproduction or reduced clearance of Aβ peptides in the brain are thought to be central in the pathogenesis of AD. Understanding the variations in the body's metabolism that can influence brain Aβ levels is important for the development of therapies to reduce the incidence of AD. Although some licensed drugs are used to improve certain symptoms, no drug treatment can provide a cure for AD. AD may be a brain-specific form of metabolism abnormality disease, but the underlying mechanism remains largely unknown. However, dysregulation of cholesterol homeostasis in the brain notably increases the risk of developing AD. In particular, epidemiological studies indicated that the global use of statins to treat hypercholesterolemia can reduce the risk of AD. The above findings indicate that dysregulation of brain cholesterol metabolism by impaired brain insulin action may provide a novel mechanism of altered brain and neuronal function, which represents a potential mechanistic association between insulin resistance and cholesterol lowering treatment by statins. However, the precise mechanism of action for statin-mediated neuroprotection remains to be fully elucidated. Taken together, this review provides important insights of statins and lipid homeostasis on Aβ-induced neurotoxicity. Accordingly, attenuation neurodegeneration by targeting statin-mediated neuronal insulin signaling may lead to novel diagnostic or therapeutic strategies against AD in future.

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Reviewer 1: *Jérôme Braudeau, AgenT, France.*
Comments to authors: *The author pertinently summarize the potential interest of the statins use in order to counteract or slow down AD. Despite the fact that this interest is not new, the potential beneficial effect of statins is yet controversy. The review smartly highlighted the potential for statin use resulting from both in vivo and in vitro studies.*
Reviewer 2: *Sandra I. Mota, University of Coimbra, Portugal.*
Comments to authors: *The proposed review aims to summarize the potential role of statins, normally used as anti-cholesterol treatment, in AD and their impact on amyloid-beta neurotoxicity. The theme is interesting since there is no recent review about it. However, the article as is, should be improved in a consequent way.*

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