Statins are Protective Against Beta-amyloid Pathology in Alzheimer's Disease?

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Abstract: An increasing number of studies have supported that high cholesterol is a risk factor for the pathogenesis of Alzheimer's disease (AD), including beta-amyloid peptides (Aβ) pathology. Clinical and biomolecular research studies have accumulated that statins, cholesterol-lowering drugs, could stave off the symptoms of AD and have seemed one of the most promising drugs in the war against AD. The role of cholesterol in the process of Aβ production and deposition has been fully considered on the basis of scientific results during the last 2 decades. It is clear that statins play a neuroprotective role in limiting Aβ pathology via cholesterol-lowering therapies. In addition, statins may favor the a-secretase nonamyloidogenic pathway of APP processing and inhibit the dimerization of β-secretase. According to non-lipid property of statins, statins retard Aβ pathology via its anti-inflammation, anti-atherosclerotic actions, anti-oxidant and anti-apoptosis. However, compelling studies available indicate that statins have no benefit on AD and do not help prevent AD. Regarding statins as preventive medicines, there are a number of individual clinical cases where cognition is clearly and reproducibly adversely affected by statins. Statins have a range of mechanisms that could help or hurt cognition? In spite of limiting Aβ pathology, several evidence reported that statins enhanced the development of Aβ pathology. Statin medications were further harmful to Aβ pathology? It appears that there is still a lot of work to implement statin medications in clinical and preclinical studies of AD.

Keywords: Alzheimer's disease, beta-amyloid peptides, statin

1. Introduction

ALZHEIMER'S disease (AD) is a progressive, degenerative disorder that attacks the brain's nerve cells, or neurons, resulting in loss of memory, thinking and language skills, and behavioral changes[1, 2]. The two pathological hallmarks of AD include beta-amyloid (Aβ) plaques (extracellular Aβ deposition) and neurofibrillary tangles (NFTs, intracellular deposits of hyper-phosphorylated tau protein) [3, 4]. AD pathogenesis is widely believed to be driven by the production and deposition of the Aβ [5, 6]. Accordingly, mounting studies have focused on the research of Aβ generation and deposition to discover the role in the process of AD [7, 8].

The statins, HMG-CoA reductase inhibitors, are a class of drugs that lower blood cholesterol levels [9-11]. It is well known that increased cholesterol levels have been associated with many disorders, including cardiovascular diseases [12-16] and neurodegenerative diseases [17-19]. The value of statins not only has been clearly established in preventing heart disease, but will benefit the inhibition of neurodegenerative pathology as well. A variety of research data has indicated that statins are protective against the development of AD [17, 20, 21], suggesting that statins improve cognitive impairment and restrain beta-amyloid plaques and neurofibrillary tangles via several biomolecular mechanisms (anti-oxidant, anti-inflammation, anti-atherosclerotic progress, anti-apoptosis, and so on ) (Figure 1).

This work reviewed the role of statins in Aβ pathology. The proposed neuroprotective mechanisms of statins were provided in Aβ pathology mainly via increased α-secretase activity and decreased β-secretase and γ-secretase activity and non-lipid effects such as anti-inflammation, anti-atherosclerotic actions, anti-oxidant and anti-apoptosis. Finally, we also looked into the future whether statins are possibly a class of agents as an attractive target for AD prevention and treatment.

2. Statins

Statins (or HMG-CoA reductase inhibitors) are a class of drugs including Lipitor (an atorvastatin), Crestor (a rosuvastatin), Zocor (a simvastatin), Pravachol (a pravastatin), Lescol (a fluvastatin), Vytorin (simvastatin and ezetimibe) and mevatatin. The basic function of statins is to lower cholesterol levels by inhibiting the enzyme HMG-CoA reductase [22]. The main mechanism is that statins lower cholesterol levels by increasing LDL receptors activity and taking cholesterol from the blood, decreasing cholesterol synthesis in liver and free cholesterol concentration [23]. Increasing scientific studies have demonstrated that increased cholesterol levels have been associated with various diseases such as cardiovascular disease (CVD) [24, 25], metabolic syndrome [26, 27], obesity [26], diabetes [26, 28, 29], as well as neurodegenerative diseases [19, 30]. A wide variety of research data has found not only that statins are effective for treating CVD as a secondary prevention strategy [16, 31], metabolic syndrome [32, 33], obesity [24] and diabetes [34, 35], but also statins may be effective neuroprotective agents such as cerebral ischemia and neurodegenerative diseases [21, 22, 30, 36].

3. Dyslipidemia, Statins and Alzheimer's

Increasing data from basic studies and clinical research shows that hypercholesterolemia is a significant risk factor in the...
pathogenesis of AD [19]. The role of cholesterol in the pathogenesis of AD has been especially clarified by the findings of genetic, epidemiological, and biology studies [37]. The findings are supported by several genes involved in cholesterol metabolism or transport as AD susceptibility genes, including apolipoprotein E (ApoE), ApoJ, ATP-binding cassette subfamily member 7 and sortilin-related receptor [37]. Clinical and basic investigation reveals that cholesterol metabolism has a close association with the progression of Alzheimer’s cognitive impairment [38], Aβ pathology [39] and NFTs induced by the hyperphosphorylation of tau [40]. The biochemical literature supports that cholesterol dyshomeostasis play crucial roles in mediating the synaptic loss and cognitive deficits in AD [21], and Aβ pathology [41]. It well recognized that statins, as a class of powerful regulators for cholesterol levels, play a neuroprotective role in neurodegenerative process, such as Huntington’s disease (HD) [19], Parkinson’s disease, cerebral ischemia [42], demyelinating disease, as well as AD [43]. Recent finding further indicates that carriers of the KIF6 719Arg allele (Arg/Arg homozygotes and Arg/Trp heterozygotes) is associated with the effects of statins on cholesterol levels in amnestic mild cognitive impairment and AD patients [44]. Research evidence indicates that atorvastatin, a lipid-lowering agent of statins, prevents cognitive impairments via improving hippocampal synaptic function, and restores BBB integrity to enhance the clearance of Aβ by anti-inflammatory lipid-modulating process [45, 46]. Additional findings have evidenced that it is via limiting the hyperphosphorylation of tau that statins act as the guardian of the brain lesions and neurodegenerative disorders. Overall, cholesterol dyshomeostasis contributes to the pathogenesis of AD and statins plays a neuroprotective role in the progression of AD [38, 39, 47].

4. Statins: effective agents in limiting Aβ pathology?

There is consensus within the AD research community that amyloid plaques and NFTs are the major pathological features in AD. AD pathogenesis is well accepted to be triggered and driven by the production and deposition of Aβ [5, 48]. Aβ is formed after sequential cleavage of the amyloid precursor protein (APP) by successive action of the β- and γ-secretases. In the amyloidogenic pathway, APP is cleaved by β-secretase to produce sAPPβ and subsequent cleavage by γ-secretase releases Aβ. In the non-amyloidogenic pathway, α-secretase cleaves APP to produce secreted sAPPα and membrane-associated carboxy terminal fragment alpha (CTFα), precluding Aβ generation. In most cases, the predominant APP metabolic pathway is non-amyloidogenic and secreted APP derivative is sAPPα.

For the reason that the research evidence points to a link between cholesterol metabolism and AD and numerous studies indicate the role of cholesterol in the process of Aβ production and deposition [49, 50], statins will be of great value via cholesterol-lowering therapies as disease modifying agents [51]. The main mechanisms include increased α-secretase activity and decreased β-secretase and γ-secretase activity and non-lipid effects such as anti-inflammation, anti-atherosclerotic actions, anti-oxidant and anti-apoptosis (Table 1 and Figure 1).

Figure 1 General assumption that statins limit Aβ pathology. Statins could decrease β-secretase and γ-secretase, and inhibit amyloidogenic pathway and limiting the Aβ releasing and the formation of amyloid plaques. Statins could increase α-secretase to limit the Aβ production in the nonamyloidogenic pathway. Statins may also retard Aβ pathology via non-lipid effects such as anti-inflammation, anti-atherosclerotic actions, anti-oxidant and anti-apoptosis, all of which are associated with Aβ pathology.
Several agents of statins may

**Mechanisms for limiting Aβ pathology**

**References**

### 4.1 Statins favor the α-secretase nonamyloidogenic pathway

Research results implicate that statin treatment may favor the α-secretase nonamyloidogenic pathway of APP processing [53, 57, 58]. It is well known that α-secretase non-amyloidogenic pathway produces secreted sAPPα and impedes Aβ generation. Scientific data suggests that statins may reinforce α-secretase activity via modifying the biophysical properties of plasma membranes or modulating the function of unidentified protein kinases [53]. In cultured neuroblastoma cells transfected with human Swedish mutant APP, atorvastatin enhanced the release of α-secretase and soluble APPAlphα (sAPPα), and activated the non-amyloidogenic pathway [53]. Further evidence suggests that statin drugs can boost α-secretase cleavage of APP via the Rho/ROCK1 protein phosphorylation pathway.

### 4.2 Statins limit the amyloidogenic pathway

Several studies demonstrated that statins limit the amyloidogenic pathway via inhibiting the dimerization of β-secretase [60, 61]. At all concentrations of statins, the statin-mediated reduction in Aβ production was determined by an inhibition of β-secretase dimerization into its more active form [60]. Research found that treatment with atorvastatin may be beneficial for brain aging by reducing beta-secretase-1 (BACE1) protein as BACE1 protein levels and activity decreased and correlated with reduced brain cholesterol [62]. Another study further demonstrated that statins indirectly inhibit γ-secretase-mediated cleavage of APP-CTFα and APP-CTFβ in *in vitro* and decrease the yield of APP-CTFy [63]. Considering a critical involvement of lipid raft cholesterol in the modulation of APP processing by β-secretase and γ-secretase [37], statins may regulate lipid raft cholesterol and effect on β-secretase and γ-secretase resulting in altered Aβ production.

### 4.3 Non-lipid effects of statins on Aβ pathology

Non-lipid effects of statins implicate the neuroprotective role which statins attenuate Aβ pathology via its anti-inflammation [64], anti-atherosclerotic actions [65], anti-oxidant [64, 66] and anti-apoptosis [40, 66, 67]. Statins significantly suppressed the Aβ-induced expression of interleukin-1beta (IL-1β) and inducible nitric oxide synthase (iNOS) and nitric oxide (NO) by microglia and monocytes [64]. Statin administration also significantly reduced the rac1-dependent activation of NADPH oxidase and superoxide production [64]. As ApoE has been found necessary for Aβ pathology in *in vivo* and *in vitro*, suppressing ApoE secretion by statins could inhibit the production of Aβ and the formation of amyloid plaques [68]. Additionally statins (atorvastatin) may restore blood-brain barrier (BBB) integrity and enhancing the clearance of Aβ treatment for 2 and 8 weeks, indicated by a substantial reduction of IgG and ApoB, particularly within the hippocampus [45].

### 5. Discussion and perspective

There is a growing body of biological, epidemiological, and clinical evidence that statins lowers serum cholesterol and retard the pathogenesis of AD by a combination of different cellular and systemic mechanisms that are based on the inhibition of the biosynthesis of cholesterol and isoprenoid by-products [17, 69, 70], and inhibiting the production of Aβ by disrupting secretase enzyme function and reducing neuroinflammation [17, 38, 69-71]. However, recent results suggest that statins may provide a slight benefit in the prevention of AD and all-type dementia [72]. Even more studies available indicate that statins have no benefit on AD [73, 74]. A recent large randomized, double-blind, placebo-controlled multicenter trials showed that simvastatin and atorvastatin have not confirmed a clinically demonstrable cognitive benefit for statins in the treatment of AD [75]. Conversely statins induce intracellular accumulation of APP, β-secretase-cleaved fragments, and Aβ via an isoprenoid-dependent mechanism [76]. Thus, the results of research on this topic are inconsistent: some studies evidence beneficial effects, but other studies do not.
Meanwhile, there are a number of individual clinical cases where cognition is clearly and reproducibly adversely affected by statins although statins are considered as preventive medicines for AD [62, 77, 78]. What’s the role of statins that could help or hurt cognition? Furthermore, several evidence reported that statins enhanced the development of Aβ pathology in spite of their limiting Aβ pathology. Statin medications were beneficial or harmful to Aβ pathology? It appears that there is still a lot of work to do to discover the very role of statin medications in clinical and preclinical research of AD. It is actually unclear how much these agents can be helpful or not for AD patients presently.

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References


