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*Review Article*

# Neuroprotective mechanisms of statins in neurodegenerative diseases

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**Abstract:** Statins can induce neuroprotective effects by various mechanisms, such as by lowering cholesterol levels; decreasing β-amyloid production, serum apolipoprotein E (APOE) levels, and anti-inflammatory responses; modifying cognition-related receptors, and augmenting endothelial nitric oxide synthase. The use of statins has been related to many neurodegenerative conditions, such as Alzheimer's disease and Parkinson's disease. In our previous review, we discussed the neuroprotective effects of statins by enhancing the levels of endothelial nitric oxide synthase, impairing β-amyloid production, reducing reactive oxygen species, and modulating cognition-related receptors. The present review discusses the recent finding that statins slow down the progression of these neurodegenerative diseases.

**Keywords:** Statins, vascular dementia, Alzheimer's disease, Parkinson's disease

## Introduction

Statins, which are inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, are commonly used as cholesterol-lowering drugs. However, more effects of statins have been increasingly found, including neuroprotection, immunomodulation, and anti-inflammation. Statins can induce neuroprotective effects by various mechanisms, such as by lowering cholesterol; inhibiting intracellular adhesion molecule-1 (ICAM-1); decreasing β-amyloid production, serum apolipoprotein E (APOE) levels, antithrombotic effects, and anti-inflammatory responses; modifying cognition-related receptors; and augmenting endothelial nitric oxide synthase [1-7]. The present review provides further understanding of the multiple mechanisms by which statins work in the treatment of neurodegenerative diseases.

## Statins and vascular dementia

Statins can have neuroprotective effects in patients with vascular dementia (VaD) [8-10]; these effects have been well documented, the mechanisms of which may be associated with modulation of nitric oxide (NO). Nitric oxide can prevent the progression of VaD by modulating the cerebral blood flow. Lower NO levels can lead to cognitive decline in serum of VaD patients [11, 12], whereas statins can increase NO production [13]. Different mechanisms have been proposed to explain the protective role of statins in eNOS [14-18]. Statins can decrease the risk of VaD through their favorable effects on eNOS and by modulation of the cerebral microvasculature [19, 20]. The modulatory role of statins in eNOS may have an important effect on the functional regulation of the cardiovascular system [21]. The Rho/ROCK pathway can negatively regulate endothelial function by regulating the expression and activity of eNOS, whereas statins can upregulate eNOS by inhibiting the Rho/ROCK pathway [22]. In an Sprague Dawley (SD) rat model of transient middle cerebral artery occlusion (tMCAO), rosuvastatin inhibited the upregulation of glycoprotein 91 (phox) and p22phox, the phosphorylation of nuclear factor-kappa B, and the induction of cyclooxygenase 2 and inducible nitric oxide synthase [23].

Atherosclerosis can increase the risk of VaD and plays a key role in the development of this illness [24-26]. Hypercholesterolemia and atherosclerosis can induce eNOS dysfunction and decrease the expression of eNOS and NO [27], whereas statins can prevent cognitive impairment by their anti-atherosclerotic effects [28-30]. Statins can also prevent the progression of vascular-related cognitive impairment by an antiplatelet mechanism [31]. Treatment with statins can decrease the incidence of VaD [32].

The association between blood pressure and dementia seems to be complex. The impairment of cognitive function has been associated with both high and low blood pressure levels in older subjects [33, 34]. Age-related changes in both blood pressure level and cognitive function, as well as vascular brain damage and systemic arterial aging, may have a confounding role. Hypertension is an independent risk factor for mild cognitive impairment [35]. A previous systematic review showed that antihypertensive medication could decrease the risk of vascular dementia, by a mechanism that may be associated with reducing the risk of stroke through improved blood pressure control [36]. One study found that higher ambulatory pulse pressure is associated with poor cognitive outcomes [37]. Pulse pressure has been related to neurodegenerative change before the onset of dementia; higher pulse pressure has also been associated with cerebral amyloidosis in neurodegeneration and more rapid progression to dementia [38].

However, excessive lowering of systolic blood pressure may be harmful in older patients with cognitive impairment [33, 39]. The possible reason for this is associated with hypoperfusion, which subsequently enhances the risk of ischemic injury. Thus, the mechanism of blood pressure modulation in cognitive dysfunction may be a double-edged sword.

### Statins and Alzheimer's disease

In 2013, as many as 5 million Americans were living with Alzheimer's disease [40]. By 2050, this number is projected to reach to 14 million, a nearly three-fold increase [40]. Elevated levels of β-amyloid and apolipoprotein E have been found to be associated with AD [41-48]. In addition, atherosclerosis and increased levels of plasma total cholesterol or triglyceride and low-density lipoprotein cholesterol (LDL-C) aggravate the symptoms of AD.

During middle age, high serum cholesterol levels are associated with an increased risk of AD, and even moderately elevated cholesterol levels increase the risk of dementia [49]. In β-amyloid peptide (Aβ) 25-35-injected mice, the Aβ25-35-induced apoptosis of hippocampal CA1 pyramidal cells and the Aβ25-35-impaired high-frequency stimulation (HFS)-dependent long-term potentiation (LTP) induction were rescued by simvastatin treatment in hippocampal Schaffer collaterale-CA1synapse. The anti-amnesia effect was attenuated by simvastatin-induced neuroprotection or simvastatin-rescued LTP induction [50].

Pravastatin has been found to significantly improve cognitive function by ameliorating the β-amyloid burden of the hippocampus in a mouse model of Alzheimer's disease [51]. Statins can significantly reduce the risk of incident AD by lowering cholesterol levels [52]. In a rat model injected with Aβ1-42, atorvastatin attenuated the Aβ-stimulated injury to learning and memory and partly inhibited the inflammatory responses in the hippocampus of the rat brain [53]; these findings suggested that atorvastatin could have a non-cholesterol-lowering effect and that statin treatment may be an independent factor in the incidence and progression of AD. Statins also influence the development of AD through interacting with apolipoprotein E (ApoE), besides mediating the metabolism of β-amyloid peptides and lowering the serum cholesterol level [54-58]. Apolipoprotein E (ApoE) is a 299 amino acid protein encoded by the APOE gene. The APOE gene has three common polymorphisms: varepsilon2, varepsilon3, and varepsilon4, which result in the likelihood of developing Alzheimer's disease and cerebral amyloid angiopathy. In particular, APOE varepsilon4 is associated with an increased risk of Alzheimer's disease [59]. A study of 566 pathologically confirmed AD cases showed that AD pathology may manifest itself differently based on the ApoE genotype and suggested that ApoE carriers and non-carriers may have different patterns of AD neuropathology location and density [60]. In a population-based cohort study, statins were found to ameliorate the impaired cognition in older participants who had increased atherogenic lipoproteins [10].

### Statins and Parkinson's disease

Many studies have shown that statins can decrease the incidence of PD, although cholesterol level may be associated with a higher incidence of this illness. Some clinical studies have reported that statin use is irrelevant to the progression of PD and dementia [61-63]. In a meta-analysis of observational studies, statin use significantly reduced the risk of PD by 23% [62]. Lipophilic statin therapy can decrease the incidence of PD in statin users, especially in subgroups of women and elderly [64]. One study showed the statins can reduce the elevation of the levodopa equivalent daily dose over 2 years in PD patients, which suggested that statin use may be involved in the onset and development of PD [65]. A study of 1035 incident cases of PD showed that statin use was associated with a significant decrease in the incidence of PD (odds ratio, 0.73; 95% confidence interval, 0.60-0.88; P=.001). No relation was found between baseline LDL-C levels and PD risk [66]. A 12-year follow-up of 644 incident PD cases found that regular use of statins was associated with a modest reduction in PD risk [67]. Interestingly, a prospective study showed that statin use may be related to a higher risk of PD, whereas higher total cholesterol level may be associated with lower risk [61]. These findings are inconsistent with the results of many other studies, which indicate that statins protect against PD. Further research needs to be done to substantiate the effects of statins on PD.

Different mechanisms are involved in the pathogenesis of PD; however, increasing evidence indicates that inflammatory responses are responsible for the progression of PD. Because statins have shown anti-inflammatory and cholesterol-lowering effects, both of which are beneficial against neurodegenerative disorders, studies related to how statins influence the progression of PD are increasingly done.

Animal studies in PD explore the different mechanisms of statin-mediated neuroprotection, among which the anti-inflammatory response has attracted interest. Our previous study showed that simvastatin had a neuroprotective role in experimental Parkinsonian cell models by reducing the expression of the pro-inflammatory cytokines TNF-alpha, IL-1beta, and IL-6 [68, 69]. In MPTP-induced PD rats, simvastatin reduced nigral activation of p21 (ras), attenuated nigral activation of NF-kappaB, inhibited nigral expression of pro-inflammatory molecules, and suppressed nigral activation of glial cells [70]. The results indicated that statins obviously attenuated the accumulation of alpha-synuclein and upregulated neurite outgrowth, implying a novel approach to PD therapy [71]. Further, Koob found that lovastatin could reduce alpha-synuclein aggregation, the neuropathologic hallmark of PD, in a transgenic model [72].

In addition to their anti-inflammatory effects, the mechanisms of statin-mediated neuroprotection are associated with the modulation of receptors. Our recent works involved exploring the mechanisms of how statins ameliorate cognitive dysfunctions by mediating the alteration of NMDA receptors in PD rat brain. One of our studies showed that, in a 6-OHDA-lesioned PD rat model, simvastatin treatment obviously attenuated the cognitive deficits correlated with alterations of different receptors in various brain regions [73]. This result is consistent with the study of Wang, which reported that simvastatin induced a hyperlocomotive activity and reduced anxiety-like behavior; this could be correlated with the simvastatin-mediated modulation of NMDA receptors in several brain regions [74]. Following this study, we also observed that simvastatin-mediated NMDAR1 modulation decreased the TNF-alpha, IL-1beta, IL-6 mRNA, and protein expression levels in 6-OHDA-stimulated PC12 cells by inhibiting NMDAR1 [68]. Further, our research results indicated that Hcy and CRP played very important roles in the pathogenesis of PD. The combination of Hcy and CRP may be used to assess the progression of PD and VP. Based on our series of studies, we propose that statins may improve cognitive decline by modulating various receptors in the brain, which may be one of the mechanisms by which statins affect the progression of PD. However, more research needs to be done to explore this mechanism with the use of different statins.

## Conclusion

Taken together, statins may show pronounced neuroprotective effects in neurodegenerative diseases. Our future works should focus on the immune system and cerebral receptor function.

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## Disclosure of conflict of interest

None.

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