The Role of Statins in the Prevention and Management of Alzheimer's Disease: A Focused Review

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Abstract

Alzheimer's disease (AD) is a neurodegenerative disease that is characterized by a progressive decline in cognitive functions that primarily affects older adults. Alzheimer's is pathophysiologically characterized by the accumulation of amyloid-beta (Aß) plaques, neuroinflammation, accumulation of tau proteins in neurofibrillary tangles (NFTs), and tissue loss. Statins, commonly prescribed to lower cholesterol in the blood, and their anti-inflammatory effects have gained attention for their potential impact on influencing AD progression. This literature review explores the relationship between the use of statins and AD, examining the effect of statins on cholesterol metabolism, neuroinflammation, apolipoprotein E (ApoE), and Aß production. Research in both human and rodent models demonstrate statins abilities to reduce inflammatory markers, oxidative stress, and Aß levels while modulating ApoE function. However, the precise mechanism for which statins slow the progression of neurodegeneration in AD is still unclear and warrants further research before clinical application.

Introduction

Alzheimer's disease (AD) has become increasingly prevalent in the United States, with over 6 million Americans living with the disorder, and research suggests this number will continue to rise (1). AD remains the most common type of dementia and is prevalent among 60–70% of dementia cases. AD is characterized by abnormal effects on cognition and behavior, with the underlying pathophysiology involving the manifestation of extracellular amyloid plaques, synaptic deterioration, and neuronal death (2, 3). A retrospective study conducted on 1.8 million individuals found that increased levels of low-density lipoprotein cholesterol (LDL-C) are a possible risk factor for AD (4). Amid these developments, statins, such as atorvastatin, fluvastatin, lovastatin, and others are often prescribed for the management of hypercholesterolemia and the prevention of cardiovascular diseases (5). Statins have also gained recent attention for their potential neuroprotective effects due to their anti-inflammatory properties. The relationship between statin use and AD remains complex, with multiple studies suggesting that statin use may reduce the risk of developing the disease, while others have found no association. This review aims to examine the utility of statins in the management and prevention of AD, focusing on their effects on neuroinflammation, Aß production, and ApoE modulation, while also exploring the mechanisms through which statins may exert neuroprotective effects.

Methods

For this literature review, we used the Google Scholar and PubMed databases to search for articles. Neurodegeneration, statins, pleiotropic, and neuroprotective were keywords used when obtaining applicable articles starting in 1994 to present. Articles focused on the statins and AD relationship and were limited to articles published after 2004. Chemical structures were drawn using KingDraw.

Discussion

Mechanisms of Neurodegeneration and Cognitive Decline in AD

Amyloid-ß Plaques and Neurofibrillary Tangles

Typically occurring together, amyloid-ß plaques (Aß) and neurofibrillary tangles (NFTs) are the hallmarks of neurodegeneration in AD. Plaques result from proteolytic cleavage of the amyloid precursor protein (APP) into 40-43 amino acid-long peptides (6). The Aß peptide forms amyloid fibrils that aggregate, with Aß [1-40] being the most recognized for its role in AD-

affected brains (7). NFTs are aggregates of misfolded and hyperphosphorylated tau proteins (8). These intracellular aggregates disrupt the axoplasmic flow of neuronal communication and directly correlate to the degree of cognitive decline (8, 9). Multiple studies using both human and mouse models (transgenic mouse expressing human APP and tau transgenes (10)) have investigated imaging options to identify Aß and NFTs in the brain (11–13). The main objective of these studies was to identify a relationship between the two and neurodegeneration (10, 14). The transgenic mice expressing human APP and tau trans genes generated Aß and NFTs and subsequently suffered from neurodegeneration (10). During the period of 11 to 13 months, the mice developed significant tissue atrophy and neuronal loss associated with the increases in plaques and NFTs (10). Multitracer positron emission tomography (PET) imaging using Pittsburgh Compound B (PIB) and FDDNP probes allow images of the plaques and tangles to be produced for brain monitoring (11–13). PIB selectively binds to Aß, allowing for PET imaging to measure the binding in AD individuals using a standardized uptake value ratio (SUVR) for gray matter (11). FDDNP probes bind to Aß and NFTs, measuring the binding in AD brains using a SUVR for gray matter as well (11). Multitracer PET imaging using a combination of these probes can be useful in accurately tracking disease progression (11).

Oxidative Stress

The formation of Aß plaques and NFTs can be both initiated and exacerbated by the presence of free radicals (15, 16). Oxidative stress occurs when antioxidants are out of balance with the oxidants in the body, and these oxidants are formed when oxygen molecules have an unpaired electron. The superoxide radical (O2·−) is generated in the brain and removed by conversion to hydrogen peroxide (H2O2) by superoxide dismutases (17). Under normal circumstances, the protective antioxidant mechanisms are in balance with the formation of free radicals, keeping possible tissue damage and buildup under control (18). Brain tissue is composed of oxidation-sensitive lipids and is an organ with high O2 consumption, making it extremely vulnerable to damage and high reactive oxygen species (ROS) (15, 16). The products of peroxidation are co-localized with Aß plaques, with two of the primary metabolites occurring from white and gray matter (16).

There have been investigations looking into whether these lipid peroxidation products could be potential AD biomarkers. Isoprostanes are oxidized from adrenic acid and in the white matter of the brain (Figure 1) (16). Compared to non-AD controls, patients with AD have increased levels of 8-isoprostane in their blood (19, 20). Oxysterols are the oxidized product of normal cholesterols in the brain. In tissue samples from the frontal and occipital cortex, oxysterols are found in excess in AD-affected individuals (21). This links the oxidation of sterols to AD neurodegeneration. However, when observed in cerebrospinal fluid (CSF), isoprostanes were not found to be a viable biomarker (22). In CSF, isoprostanes increased with age independently from established AD CSF markers (Aß and NFTs) (22). Isoprostanes are a promising biomarker for the diagnosis of AD, but further research is needed to substantiate this conclusion and find other suitable biomarkers as well.

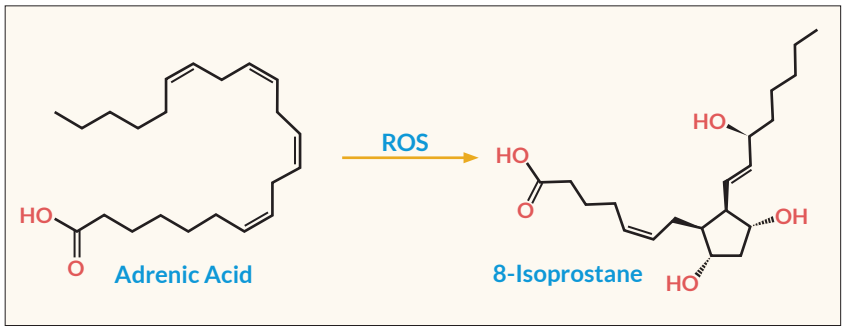

Figure 1. Chemical structures of adrenic acid and 8-isoprostane. Adrenic acid is oxidized in the brain (white matter) into 8-isoprostane due to oxidative stress. This isoprostane is a possible AD biomarker.

Neuroinflammation

Neuroinflammation is a hallmark of many other neurodegenerative diseases, with its main purpose lying in CNS protection. In AD, glial activation and proinflammatory factors influence disease progression (23). The blood-brain barrier (BBB) is a semi-permeable membrane that monitors what can cross the barrier to the brain or what cannot. Surface transporters on the BBB move Aß from the brain to the blood, but Aß can affect the expression

of tight junctions in the barrier (24). A major cause of disruption in the BBB is increased inflammatory cytokines. This disruption can then cause the accumulation of Aß, leading to barrier dysfunction and increased monocyte adhesion (24). Astrocytes and microglia produce cytokines and are the main inflammatory cells in the CNS (23, 24). Microglia use danger-associated molecular pathways (DAMPs) and pathogen-associated molecular pathways (PAMPs) to recognize, activate, and phagocytize Aß fibrils (23, 25). They then send chemokines to the site, and contrary to the normal mechanism, diseased brains show an upregulation of CCL2, -3, and -5 (25). These chemokines exacerbate the inflammatory response. In astrocytes near Aß plaques in diseased brains, CCL4 is upregulated (25).

Multiple rodent trials using transgenic mice have demonstrated a link between neuroinflammation and AD pathology. Both interleukins and inflammasomes, known for their role in inflammatory responses, are produced by the microglial cells in AD mouse models (25). However, the transgenic APP mouse model is not a completely accurate representation of human AD (26). APP knock-in mice showing the appropriate amyloid deposition were used, and it was found that these mice share common neuroinflammatory genes with humans (26). In these mice, the triggering receptors expressed on myeloid cells 2 (TREM2) were upregulated and used as Aß sensors to activate microglia, which in turn activate proinflammatory signals in the brain (26). *In vivo*, magnetic resonance spectroscopy (MRS) is the gold standard for early imaging of neuroinflammation and prevention of further damage (27, 28). MRS has shown that neuroinflammation is an early indication of AD and mainly precedes neurodegeneration (27, 28).

Overall, AD is a multifactorial disease, and there is no single, primary cause. It is a combination of factors like the ones discussed above and in different grades. Treatment mainly involves a regimen of medications like donepezil and memantine. Donepezil is an acetylcholinesterase inhibitor that enhances cholinergic transmission at the synapse (29). It also has an effect in downregulating microglial activation in the brain, reducing inflammation (29). If a patient is unable to take an acetylcholinesterase inhibitor, memantine can be used as a supplement. Memantine blocks the overactivation of the excitatory NMDA receptor, preventing neuronal damage (30).

Statins Lipid-Lowering and Pleiotropic Effects

Low-density lipoproteins are fat molecules that circulate in the blood carrying cholesterol for cellular processes and are deposited on arterial walls (31). Elevated LDL levels can cause a buildup of plaque on the arterial walls. This is the main cause of coronary heart disease (32). LDLs are prone to oxidation, and oxLDL is pro-inflammatory, leading to endothelial dysfunction that exacerbates the deposition of plaques (32). High-density lipoprotein (HDL) is a major component of reverse cholesterol transport. HDL transports cholesterol from peripheral tissues into the liver while also counteracting the oxidation of LDL (32). When LDL outweighs HDL, the counteractive effects of the HDL are not enough to prevent oxidation and deposition of plaques, in turn increasing the risk of heart disease. This also gives LDL the moniker "bad cholesterol." Very low-density lipoprotein triglycerides are produced in the liver and contain a large protein called apoprotein B (33). Through interaction with a lipase and apoprotein E, VLDL converts to LDL unless apoprotein B is targeted for degradation (33).

Statins, like atorvastatin and rosuvastatin, are the main therapeutic drugs used to lower high cholesterol levels in the blood, and they do so by reducing cholesterol biosynthesis in their target organ, the liver (hepatoselective) (34–36). Mechanistically, this occurs through the inhibition of hydroxymethylglutaryl-CoA (HMG-CoA) reductase (35-39). HMG-CoA reductase converts HMG-CoA to mevalonate, a precursor to cholesterol (38). HMG-CoA is a liver enzyme that is regulated by AMPK and activated by a phosphoprotein phosphatase (38). Inhibition of this enzyme results in an increase in LDL clearance from the blood by the liver in patients with high cholesterol, while in patients with hyperlipidemia, the inhibition results in a decrease in both cholesterol and triglycerides by decreasing the production of the transport apoprotein B100 (37). However, with growing evidence of statins exhibiting neuroprotective effects, there may be another mechanism of action.

One such mechanism is an anti-inflammatory downregulation of neuroinflammation. Neuroinflammation, as discussed above, is one of the major mechanisms of neurodegeneration in AD. Statins, except pravastatin which cannot cross the BBB, can bind to leukocyte function antigen-1(LFA-1) and prevent adhesion to intracellular adhesion molecule-1 (ICAM-1) (35, 40). As a result, ICAM-1

signals are reduced, downregulating the inflammatory response (35, 41, 42). In an investigation using Sprague-Dawley rats, fluvastatin reduced both cellular adhesion molecules and oxidative stress, independent of its lipid-lowering effects (42). Another study using atorvastatin and lovastatin in mice and guinea pigs demonstrated reduced substance P and calcitonin gene-related peptide (CGRP) in the dorsal root ganglia (43). These are two main peptides that can induce a proinflammatory response.

AD Responses to Statin Effects

Cholesterol Metabolism in the Brain

In a trial treating individuals with AD with 80 mg of atorvastatin, the statin was shown to reduce cholesterol levels and positively impact the individual's Alzheimer's Disease Assessment Scale-Cognitive (ADAS-Cog) score (44). Compared to the placebo group, atorvastatin use showed a significant increase in the ADAS-Cog score after 6 months, while also showing mild-to-moderate AD cases may incur the largest benefits from statin therapy (44). Cholesterol plays a vital role in neuronal function and maintenance. The highest concentration of cholesterol is within the brain at approximately 20% (45). Of this 20%, cholesterol biosynthesis occurs mainly by glial cells; however, it is also partially synthesized by neurons. Glial cells produce roughly two times more cholesterol than neurons. (45, 46). However, the cholesterol supply is observed at a greater value in astrocytes than in neurons (45). Cholesterol is transferred in the brain with the use of a protein called apolipoprotein E (ApoE), which metabolizes lipoprotein-bound cholesterol (45). ApoE is produced mainly through astrocytes and functions through shuttling cholesterol from glial cells to neurons; this shuttling system plays a large role in the formation of efficient synapses (47).

As mentioned, the average lifespan is expanding; therefore, it is important to understand the impact of cholesterol as we age. The aging process has different effects on different regions of the brain, with the greatest decrease in cholesterol being approximately 40% (46). A study was conducted on 118 brains, ranging from age 20 to 100 years, focused on the lipid composition of the frontal and temporal lobes found that after age 80 is when significant lipid loss occurs (48). The cholesterol and phospholipid concentrations decreased in both the frontal and temporal lobes, with the temporal lobe having about 20% more reduction than the frontal lobe (48). The evidence also showed that phospholipids decreased twice as much as cholesterol as the brain aged, which affects astrocytes due to their cholesterol/phospholipid content (48). The reduced supply of cholesterol through astrocytes was mutually exclusive with the reduced cholesterol within myelin membranes (48). As the brain ages, the density of the synapse declines while the possibility of chronic neuroinflammation becomes more apparent (49). These factors in turn damage the repair processes that astrocytes possess (49).

Statin Therapy and ApoE Genotype

ApoE is the major lipid and cholesterol carrier in the central nervous system (CNS) and one of the most important risk factors for AD (50). The isoform ApoE4 allele is one of the most important genetic risk factors for AD, with individuals who possess the allele performing lower on cognitive tests than those without (44). Statin use has shown the most promising outcomes on individuals with the expression of the ApoE4 allele demonstrating its effectiveness through the modulation of that allele (51). Furthermore, statin use has been seen to be effective in the treatment of AD through the GTPase isoprenylation pathway, resulting in the reduction of Aß formation (51). Although it does have its limitations, it is important to mention the possible differences in outcome in the interaction of an individual's sex and ApoE4 genotype. An analysis of these measures noticed that males with the ApoE4 genotype could benefit more so than their female counterparts. Moreover, these authors also reported that carriers of the ApoE4 genotype have a decreased risk of AD (52).

Statin Therapy Effects on AD Characteristics

The exact mechanism by which statins may slow the development of AD characteristics is unclear, as the evidence is conflicting. This disagreement among studies could pertain to the groups in which statins are categorized: fungal-derived, synthetic-derived, lipophilic, and hydrophilic. Lovastatin and simvastatin are among the most popular when studying statin effects on the brain due to their ability to cross the BBB (53, 54). Simvastatin has been shown to have neuroprotective effects by preventing Aß-induced production of interferon-γ (causing neuronal damage), while lovastatin enhances Wnt signaling that protects against Aß neurotoxicity (55). Statin users also had a lower incidence of neurodegenerative disorders compared to non-users, with pitavastatin showing the

strongest reduction of incidence among the 8 statin types (56).

Statin use has neuroprotective effects and has the possibility to decrease the progression of AD by lowering cholesterol levels and reducing plaque formation (57). An analysis conducted on 40 AD male mice treated with atorvastatin demonstrated a reduction in Aß production and tau hyperphosphorylation, leading to increased learning and memory. The authors found increased levels of phosphorylated AKT and glycogen synthase kinase 3ß (GSK3ß) in the hippocampus (58). The atorvastatin effectively reversed the learning deficit in AD mice when compared to control treated mice (saline) (58). This finding is significant as evidence suggests that these two signaling pathways are impacted by Aß exposure (58, 59). Research has shown the impact that GSK3ß has on the role of AD progression as the hyperfunction GSK3ß is marked by common AD characteristics such as memory impairment and inflammatory responses (59, 60). This information could be used as a basis for future studies examining mechanisms by which we can combat the progression of AD.

Conclusion

AD is a devastating neurodegenerative disease characterized by progressive cognitive decline, primarily driven by the accumulation of Aß plaques, NFTs, synaptic dysfunction, neuroinflammation, and tissue atrophy. As the global population ages, finding effective treatments to slow or halt the progression of this disease is paramount. While statins offer a promising future for mitigating the underlying mechanisms of AD, the evidence of their effectiveness remains partially inconclusive. Limitations in the literature lie in the common reliance on animal studies and the unknown side effects of statin use. Currently, investigations primarily exist in animal model studies which show positive results with reduced inflammation and Aß production but may not replicate the complexity of AD in humans. The mechanism of protection that would benefit humans still requires evidence. The benefits of statin use for AD treatment must be weighed against the risks of side effects and uncertain future implications. As future research occurs, a more nuanced understanding of which AD patients may benefit from statin treatment is required. Future studies should prioritize larger scale, longitudinal studies in order to understand the effects of statins in more diverse populations and the true mechanism of action for more targeted prevention. At this time, statin treatments should be used with caution and as a more individualized approach for AD prevention and management.

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