Statins: the future of Alzheimer's disease treatment?

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ABSTRACT

Emerging research indicates that the pathological basis of Alzheimer's disease maybe inflammatory in origin, possibly mediated through the pro-inflammatory cytokine, interleukin-1beta. Statins are a class of drugs which reduce circulating lipid levels. There is also evidence that they may have anti-inflammatory properties. This review assesses new evidence that statin therapy may have a role in the treatment of Alzheimer's disease.

Alzheimer's Disease

Alzheimer's disease (AD) is the most common age-related neurological disease. It is responsible for 65-75% of all incidences of dementia (1) and affects 27.7 million people world-wide, costing an estimated $156 Billion annually (2). AD occurs mainly in those over 50 years of age. However in those aged 30-40 a familial form of the disease has been identified, termed *early onset Alzheimer's disease* (EOAD). This inheritable form of the disease is linked to autosomal dominant gene mutations on chromosomes 1, 14 and 21, responsible for coding proteins related to the production of neuritic plaques including, presenilin 2 (PS2), presenilin 1 (PS1) and amyloid precursor protein (APP) respectively (3). However, EOAD accounts for only 2% of all AD cases. The more common sporadic form of the disease, termed *late onset Alzheimer's disease* (LOAD), occurs after the age of 60 years. At 65 years the prevalence of AD is approximately 10%, increasing to 49% by 85 years (4). The aetiological factors involved in AD are complex and multifactorial, encompassing, lifestyle, diet, trauma and genes, including ApoEε4 on chromosome 19
(5).

Pathophysiology of AD

The pathological hallmark of AD is the development of neurofibrillary tangles and senile plaques containing amyloid-β protein (Aβ). These occur throughout much of the neocortex and hippocampus (6). Production of neurofibrillary tangles within neurones is now understood to occur when the microtubule-associated protein, Tau, is converted to a

hyperphosphorylated form. This leads to dissociation and aggregation of Tau within nerve dendrites and axons, resulting in catastrophic loss of microtubular structure (7). There is a growing body of evidence to suggest that this occurs as a result of Aβ protein production. The mechanism by which this may occur is via cyclin-dependant kinases. In post-mitotic cells such as neurones, their importance may be related to their ability to regulate processes in the cell nucleus and in cytoskeletal organisation. Cyclin-dependant kinase 5 (Cdk5) is one such kinase thought to play a role in Tau phosphorylation both constitutively in normal neurons and with increased activity in AD (8). Toxicity of Aβ alters intracellular calcium homeostasis leading to activation of calpains, a family of calcium-dependant proteases. Calpains cleave p35 (Cdk5 activator) to p25, leading to increased activity of Cdk5 which hyperphosphorylates Tau (8). Thus, Aβ is central to the pathophysiological aberration in AD.

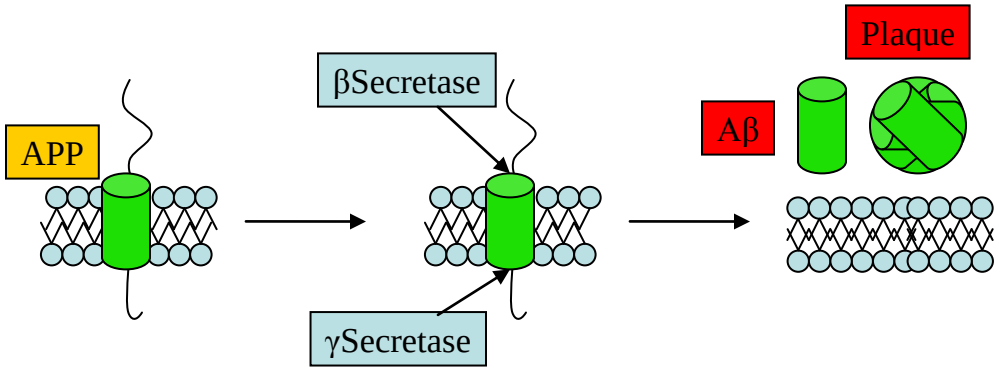

Figure 1. Aβ production results from abnormal clevage of amyloid precursor protein.

Aβ is produced by proteolytic cleavage of the integral membrane glycoprotein amyloid precursor protein (APP) by β- and γ-secretases leading to release of Aβ from the neuronal membrane (Figure 1). Extracellular Aβ aggregates leading to the formation of amyloid plaques. There are a number of mechanisms by which Aβ may exert its neurotoxic effects. One mechanism, which has received much attention in the literature over the last number of years, is inflammation.

Microglia are the major resident immunocompetent cells in the brain. Activated microglia undergo both morphological and secretory changes. Morphological changes include adaptation to an amoeboid appearance and expression of a number of cell surface

proteins including major histocompatability complex type II (9). These proteins confer antigen presenting properties on microglia. Secretory changes include the expression and release of known pro-inflammatory cytokines such as tumour necrosis factor alpha (TNF-α), interleukin-1β (IL-1β) and interferon gamma (IFN-γ) (9).

IL-1β is the most studied pro-inflammatory cytokine in the body. It is produced in a biologically inactive, pro-IL-1β form and activated following cleavage by caspase-1 (10). IL-1β is constitutively expressed in the brain at low levels but following an exogenous or endogenous insult there is an increase in production, release and activity of the molecule. Upon binding to the membrane-bound type I IL-1 receptor (IL-1R1) and association with an accessory protein, a complex permitting intracellular signalling is formed (11). Neurones, glia and invading immune cells all express the IL-1R1 and have been shown to increase activity of the mitogen activated protein kinase (MAPK) signalling cascade on binding with IL-1β (11).

Increased expression of IL-1β has been linked with neurodegenerative disorders such as AD (12). Il-1β has been shown to trigger cell death in primary cultures of human fetal neurons (13). Intracerebroventricular injection of Aβ increases the activation of c-Jun N-terminal Kinase (JNK), a MAP kinase, in rat hippocampus. This results in a decrease in cell survival and long-term potentiation, an electrophysiological model of synaptic plasticity and memory. It has been suggested that this decrease in hippocampal plasticity is dependent upon IL-1β-triggered JNK activation (14).

The increasing realisation that inflammation maybe a significant component in AD, may lead to novel therapeutic strategies in the future. Various forms of immunotherapy, including Aβ vaccination, are currently under investigation (15). One of the most promising emerging treatments is the class of lipid-lowering drugs, statins.

Statins

Statins are a class of drugs which inhibit the enzyme, 3-hydroxy-3methylglutaryl coenzyme A (HMG-CoA) reductase. Lovastatin, the first member of this class, was

introduced in 1987. The licensed indication for statin therapy is in the management of hyperlipidemia. The conversion of HMG-CoA to mevalonate via the enzyme HMG-CoA reductase is the rate limiting step in cholesterol synthesis. Statins act by competitively and reversibly binding the dihydroxy heptanoic/heptenoic acid side chain to HMG-CoA reductase on endoplasmic reticulum and peroxisomes, decreasing mevalonate production and thus cholesterol synthesis (Figure 2) (16). This decrease in intracellular cholesterol levels leads to an increase in production and insertion of low-density lipoprotein receptors into the cellular membrane and a decrease in circulating lipid levels. It has been widely shown that statin therapy reduces the 5-year incidence of major coronary events, coronary re-vascularisation, and stroke (17). However, simultaneous inhibition of isoprenoid production may have an anti-inflammatory effect (18).

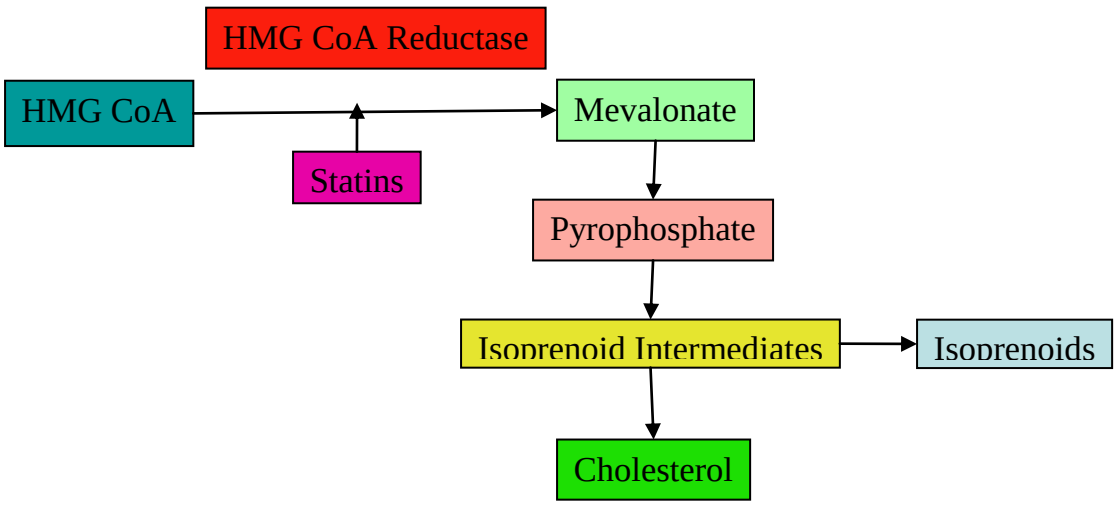

Figure 2: Statins competetively inhibit the enzyme HMG-CoA reductase.

The first indication that stains may have anti-inflammatory properties was a randomised study on cardiac transplant rejection and statin treatment (19). Previous work *in vitro* had shown a decrease in natural killer cell cytotoxicity with statins (20) and the aim of the study was to investigate if this had an application *in vivo*. The results of the study using pravastatin to control post-transplant hypercholesterolemia showed cholesterol-independent effects. These included less frequent cardiac rejection and a decrease in

natural killer cytotoxicity. Coupled with the beneficial effects on cholesterol levels this led to increased survival and lower incidence of coronary vasculopathy (19).

Statin inhibition of mevalonate production also affects the production of isoprenoids. Isoprenoids are critical in the covalent addition of lipid moieties (prenylation) to regulatory proteins (21). Prenylation by the mevalonate products farnesyl diphosphate and geranylgeranyl diphosphate contribute to the regulation of cell signalling and trafficking. The small G-proteins are important substrates of isoprenoid modification, and isoprenylation is critical their role in cytoskeletal rearrangement, cell motility, phagocytosis, intracellular trafficking, transcriptional regulation, cell growth and development (22).

The Rho family of G-proteins regulate the actin-based cytoskeleton with RhoA, Rac and Cdc42 leading to stress fibre, lamellipodia and filopodia formation respectively (23). The Rho family are also important in inflammatory signal transduction cascades with RhoA, Rac and Cdc42 participating in the signalling pathway required for nuclear factor-kappa B (NF-κB) activity leading to cytokine and chemokine release and JNK pathway activation (24). Statin inhibition of isoprenylation is thus one of the many means by which stains are thought to exert an anti-inflammatory effect.

Stains and Alzheimer's Disease

To date, the strongest population-based evidence suggesting a beneficial effect of statins on AD was an observational study published in 2002. A reduction in the incidence of AD by up to 70% was seen in patients receiving statin therapy independent of their lipid-lowering properties (25). Further to this, preliminary results from a pilot proof-of-concept randomised study has shown a cognitive benefit in mild to moderate AD in those receiving 80 milligrams of atorvastatin a day compared to those with AD receiving placebo (26). Several mechanisms have been suggested as to the mechanism of action of statins in AD including, a reduction in brain cholesterol (27), alteration in metabolic enzyme pathways shifting APP cleavage along the β-secretase pathway (28), alteration in the vasculature (5), alteration in the isoprenoid pathway (29) and alteration in

inflammatory pathways (30). Of these theories, isoprenoids and inflammation have received the most attention.

Two papers investigating the role of statin-mediated G-protein inhibition have recently been published. The first attempted to define the mechanism of statin action in AD. In BV-2 mouse microglia cultures and human THP-1 monocyte cell lines it was found that simvastatin inhibited the production of IL-1β following Aβ exposure. To establish if this was cholesterol-dependant, cholesterol levels after statin treatment were measured and shown to be unchanged. Subsequent cholesterol supplementation did not attenuate the simvastatin-mediated reduction of IL-1β (29). It was therefore postulated that blockade of cholesterol biosynthesis does not account for the anti-inflammatory effects of simvastatin. A further hypothesis that lipid intermediates in the cholesterol synthesis pathway may be exerting a pro-inflammatory effect was tested. It was shown that supplementation with these lipid intermediates did not attenuate the anti-inflammatory actions of simvastatin. Using an inhibitor of geranylgeranyl transferase, it was shown that inhibition of isoprenylation attenuates the production of IL-1β following Aβ exposure. This suggests a role for geranylgeranylated proteins such as the Rho family of G-proteins including Rho, Rac and Cdc42. Using a specific clostridial toxin inhibitor of the Rho family of GTPases it was shown that Aβ-induced production of IL-1β was significantly reduced. This is strong evidence for the role of G-proteins in statin-mediated attenuation of AD pathology (29).

The second paper investigated at the mechanisms by which statins may inhibit G-protein function in an effort to delineate altered G-protein regulation and localisation. They report that stain-mediated inhibition of isoprenylation prevented Rho family members from interacting with a negative regulator, the Rho guanine nucleotide dissociation inhibitor (RhoGDI) which lead to an increase in GTP-loaded G-proteins. Lack of isoprenylation also prevented translocation to the plasma membrane thus limiting effector-interaction and decreasing functional signalling, suggesting that the beneficial effects of stains in reducing the risk of AD may arise in part from inhibition of microglia-medicated inflammatory responses (31).

Conclusion

AD is the most common age-related neurological disease. Since it was first described by Alois Alzheimer in 1907 there has been a vast increase in our knowledge of the aetiology and pathophysiology of the disease. With an increasingly elderly population, research has focused on developing treatments that can slow or prevent the progression of AD. One therapeutic strategy that shows particular promise, are statins. These lipid lowering agents are now known to have pleiotropic effects, which may have a role in decreasing the inflammation associated with AD. The beneficial effects of statin treatment on AD appear very promising, although the precise mechanism by which these effects are achieved remain to be elucidated.

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