Cholesterol, Statins and Dementia: How Could Lipid-lowering Strategies Prevent Neurodegeneration?

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The interaction of genetic and multiple environmental factors contributes to the development of Alzheimer disease (AD). Hypertension and hypercholesterolemia have been identified as risk factors for ischemic heart disease (IHD). Recent epidemiological data also have revealed an association between hypercholesterolemia and AD. Experimental models of AD and in vitro studies have shown that cholesterol modulates the amyloidogenic pathway in favour of production and deposition of amyloid in the brain. Dysregulation of the lipid metabolism in the brain due to apolipoprotein E4 or 24-hydroxylase polymorphisms has been observed in patients with AD and related dementias. Furthermore, observational studies have revealed that statin use could have a potential role in the prevention of AD.

Key words: *cholesterol, statins, lipid-lowering, Alzheimer disease, neurodegeneration.*

Introduction

A growing life expectancy is contributing to the increase in cases of dementia. The prevalence and incidence of dementia are very low before the age of 60 (1%), but increase exponentially thereafter to 45% in the age group 95+.[1] Alzheimer disease (AD) is the most common form of dementia in older adults, followed by vascular dementia. Vascular dementia (VaD) is related to vascular risk factors such as hypertension, hyperlipidemia and stroke. Neuropathological studies have revealed that AD and VaD appear concomitantly in many cases. Several vascular risk factors are associated with AD, and are summarized in Table 1. Although previous data on the relationship between cholesterol and AD have been inconclusive, recent publications indicate that hypercholesterolemia during midlife increases the risk of AD later in life.[2-4]

The apolipoprotein E4 (apo E4) allele is a cholesterol transport protein that is a well-established risk factor for elevated cholesterol levels and increased risk for ischemic heart disease (IHD) and ischemic stroke. Apo E4 polymorphism also has been associated with both early- and late-onset AD. The neuropathological features of AD are principally the deposition of β-amyloid (Aβ) in the amyloid plaques and cerebrovascular wall, neurofibrillary tangles and increased hyperphosphorylation of the tau protein. Previous neuropathological studies illustrate the close structural relationship between brain vessels and the plaques in AD brains. The hydrophobic Aβ is a 40-42 amino acid proteolytic cleavage of amyloid precursor protein (APP) by β-secretase and γ-secretase, and is produced by neurons, microglia, astrocytes and platelets. While proteolytic cleavage by β- and γ-secretase leads to Aβ production, α-secretase cleavage leads to production of a completely different molecule—APPsα (Figure 1).[5]

Aβ has been shown to be cytotoxic to neurons, endothelial cells and oligodendrocytes.[6-7] The toxicity of Aβ has been attributed to its ability to induce calcium-permeable channels in cellular membranes, loss of lysosomal membrane impermeablity due to amyloid fibril accumulation and release of free radicals from activated microglia and astrocytes. Subtle changes in Aβ42 levels have been reported to be the likely cause of various forms of hereditary AD due to point mutations in the APP and presenilin genes.[8] Life-long exposure to mild increases in Aβ42 levels may lead to accumulation over time and increased risk of AD.

The Relationship Between Cholesterol and Alzheimer Disease

Cholesterol is the most prevalent steroid in humans. Cholesterol in the brain constitutes 20% of cholesterol in the body, is mainly in the form of unesterified free cholesterol, and is enriched in myelin. Cholesterol metabolism in the brain is regulated by apo E4 and 24-hydroxylase. Observations from epidemiological studies and animal models imply that disturbances in cholesterol metabolism are linked to a susceptibility to AD.

Patients carrying the apo E4 gene polymorphism have elevated cholesterol levels and increased risk for both IHD and AD.[9,10] Conversely, apo E2 allele is protective in AD. The sequestering of Aβ may be influenced by apo E in several ways. Apo E binds with a high avidity to Aβ peptides and enhances the formation of Aβ fibrils.[11] Disturbances in cholesterol regulation and apo E also disrupt calcium signalling.

The rate-limiting enzyme 24-hydroxy-lase is uniquely expressed in the brain,[12] and modulates the removal of cholesterol from the brain through hydroxylation. The gene encoding this enzyme is called CYP 46, and the recently discovered CYP 46 polymorphism was found to be associated with an increased Aβ deposition and tau phosphorylation, as well as with a higher risk of late-onset AD.[13]

Aβ deposits similar to those found in AD brains are often observed in the brains of patients with IHD.[14] *In vitro*, cholesterol depletion has been shown to inhibit the generation of Aβ in hippocampal cells.[15] In transgenic AD animal models, hypercholesterolemia accelerates the development of Alzheimer's amyloid pathology.[16] Cholesterol-fed rabbits also develop changes in their brain that are typical of AD pathology.[17]

The Effect of Statins in Alzheimer Disease

Cholesterol biosynthesis has five major stages (Figure 2). Statins inhibit 3-hydroxy-3-methylglutaryl (HMG) CoA reductase, the rate-limiting enzyme involved in cholesterol synthesis and many non-steroidal isoprenoid compounds, and which converts HMG into mevalonate. The addition of mevalonate *in vitro* has been shown to overcome the action of statins.[18]

Table 1
Major Vascular Risk Factors for Alzheimer Disease*

Aging
Hypercholesterolemia
Hypertension
Stroke
Hypotension
Apo E4 allele
Diabetes mellitus
Ischemic heart disease
Atrial fibrillation
Smoking
High intake of saturated fat
Alcoholism
Lifestyle (i.e., lower education, low level of social activity)
High serum homocysteine
B_{12} and folic acid deficiency

*Many of the risk factors are shared with vascular dementia.

During the past decade, several clinical trials of both secondary and primary prevention have demonstrated the clear benefits of statin treatment for the reduction of IHD events, mortality and ischemic stroke.[19,20] In recent years, data from angiographic regression studies in IHD and from ancillary experimental studies indicate that statins improve various vascular functions. These multiple vascular effects are alluded to as pleiotropic, meaning multiple direction. The pleiotropic effects of statins include the regulation of endothelial function through modulation of endothelial-nitric oxide synthesis (eNOS) and NO production, inflammation, antioxidative properties, activation of signal proteins such as Rho by prenylation, angiogenesis and immunomodulatory actions.[21]

Animal studies and data from carotid endarterectomy patients demonstrate that statins induce not only atherosclerotic plaque regression, but also plaque stabilization by reducing inflammation, oxidized low density lipoprotein and death of smooth muscle cells, as well as by improving endothelial dysfunction.[21,22]

Three recent epidemiological studies have reported that the prevalence of AD is significantly lower in patients treated with statins.[23-25] In these series, the diagnosis of AD was established according to the NINCDS-ADRDA criteria. The frequency of AD was studied in: the whole patient population; patients treated with statins and; patients treated with other cardiovascular drugs, including antihypertensive medication. Jick, *et al.* found a reduction of 70% in the prevalence of dementia in statin-treated patients aged 50 years and older, based on analysis of data from the U.K. General Practice Research Database.[24] Wolozin, *et al.* reported similar observations on the prevalence of AD in patients 60 years and older from three different major hospitals in the U.S.[25] Of all statin drugs examined, lovastatin and pravastatin were the most efficacious. Pravastatin, despite being the most hydrophilic statin drug and with the lowest propensity to penetrate the blood brain barrier, was reported to be one of the two statins to decrease the risk of dementia. The recent MRC/BHF Heart Protection Study, based on 20,536 patients randomized to simvastatin or placebo for five years, demonstrated significant reduction in cardiac events, ischemic stroke and all-cause mortality in patients receiving statin treatment.

Figure 1: The Amyloid Pathway

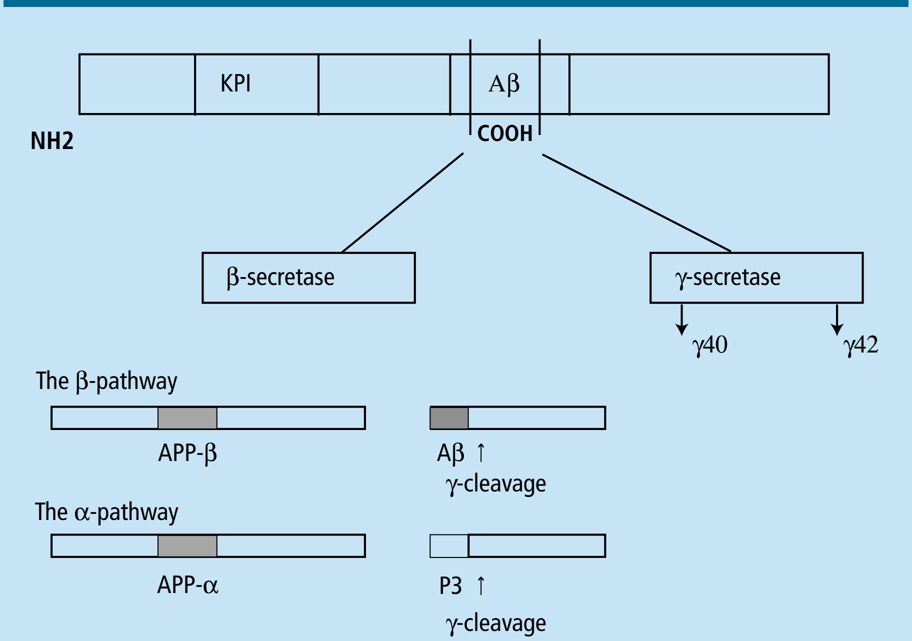
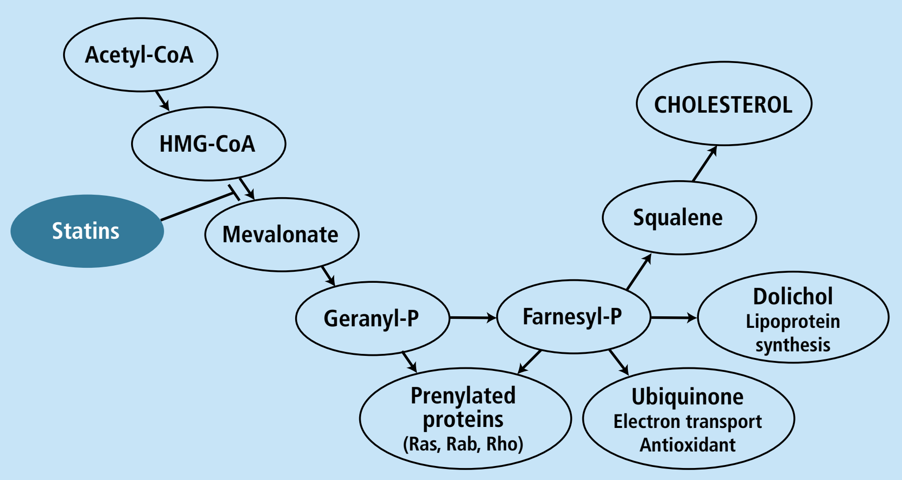


Figure 2: The Mevalonate Pathway



However, no effect of statin therapy was found on cognition.[26] In the PROSPER study, 40mg of pravastatin treatment for three years in patients aged 70 years and older did not show any effect on cognition or stroke rates.[27]

Kojro and colleagues demonstrated that cholesterol-extracting agents such as methyl-β-cyclodextrin and the HMG-CoA reductase inhibitor lovastatin increase the level of α-secretase cleaved soluable APP (APPsα) in various peripheral and neuronal cell lines. The stimulation of α-secretase activity and an increase in the level of APPsα also may be beneficial since the APPsα has trophic effects on cerebral neurons in culture that are mainly through stimulation of neurite outgrowth and synaptogenesis. A simultaneous publication by Fassbender, *et al.* clearly showed that simvastatin reduces levels of Aβ42 and Aβ40 both *in vitro* and *in vivo*. Simvastatin treatment was shown to have direct effect on de novo cholesterol synthesis in neuronal cells, and has also been shown to reduce the level of 24-hydroxycholesterol.[28]

These studies provide valuable information on the probable mechanisms of statins involved in prevention of AD (Table 2). However, the relationship between results from epidemiological studies and *in vitro* and *in vivo* studies require further analysis. The degree of lipophilicity of statins also has been implicated as a property involved in the drugs' differential effects and should be considered further.

Discussion

Several recent observational studies report that statin use decreases the risk of AD. Both the lipid-lowering and non-lipid effects of statins were reviewed, and may influence the pathogenesis of AD, thereby having valuable effects on the prevention of this disease. Treatment of hypercholesterolemia in general and of other vascular risk factors may be beneficial, with great implications in the prevention of AD. However, the direct effects of statins in AD and related dementias need further scrutiny due to the fact that the results of observational studies are subjected to bias.

Early-phase clinical trials using simvastatin and atorvastatin have been initiated in order to evaluate the effect of statins on cognition, progression of AD and other central nervous system outcomes. ◆

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Table 2

Probable Actions of Statins for the Prevention of Alzheimer Disease

Reduction of vascular risk factors, such as stroke.
Stimulation of α-secretase activity.
Modulation of APP metabolism and Aβ production.
Immunomodulation leading to attenuation of inflammatory markers, such as CRP and cytokines.
Reduction of lipoprotein oxidation and free radical injury.
Increase in cerebral endothelial nitric oxide synthase and cerebral circulation.
Activation of signal transcription (Rho-GTPases) through depletion of downstream isoprenoids.

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