

Statins and the prevention of dementia

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Dementia is thought to affect an estimated 10% of the population over the age of 65 years.¹ In a multicentre, cross-sectional analysis that examined the relation between treatment with statins and Alzheimer's disease, it was reported that patients who received lovastatin or pravastatin, but not simvastatin, had a prevalence of the disease that was 70% lower than that found in a control group.² In another case-control study, individuals aged 50 years and older who were prescribed statins had a substantially lowered risk of developing dementia.¹ Thus, statins may decrease the risk of dementia and, in particular, Alzheimer's disease. This apparent beneficial action of statins has been attributed to their ability to increase endothelial nitric oxide (NO) synthase and reduce endothelin-1, thereby increasing cerebral blood flow,¹ but there could be several other paths by which statins might do this.

Statins are potent competitive inhibitors of HMG-CoA

(3-hydroxy-3-methylglutaryl-coenzyme A) reductase, which catalyzes the synthesis of mevalonate and is the rate-limiting enzyme of the mevalonate pathway. Mevalonate is the precursor of cholesterol and isoprenoid-containing compounds. Isoprenoid precursors are necessary for posttranslational lipid modification (prenylation) and, hence, the function of Ras and other small guanosine triphosphatases (GTPases), which are a group of intracellular molecular switches that transduce signals from extracellular stimuli to cytoplasm and the nucleus. They inhibit the expression of bone morphogenetic proteins (BMPs), especially BMP-2. BMPs are a family of growth factors that are present in the central nervous system during development and throughout life. They play an important role in the development, survival and phenotypic maturation of neurons in the central nervous system. BMP-2, BMP-4, BMP-6, BMP-7, BMP-9 and BMP-12 induce and maintain the neuronal cholinergic phenotype in the central

nervous system.³ Inhibition of the mevalonate pathway by statins prevents the function of small GTPases and, thus, enhances the expression of BMP-2 and, possibly, other BMPs.⁴ Acetylcholine, which is secreted by cholinergic neurons, is known to participate in memory consolidation. Furthermore, acetylcholine is a potent stimulator of NO synthesis.⁵ Thus, the reported beneficial effect of statins in the prevention of dementia and Alzheimer's disease may be related to their capacity to increase NO synthesis and enhance the concentration of various BMPs in the brain (Fig. 1).

Inflammation plays a significant role in the pathobiology of Alzheimer's disease and cardiovascular diseases. Ridker and colleagues^{6,7} showed that in healthy men and postmenopausal women the median concentrations of interleukin-6 (IL-6) and C-reactive protein respectively were higher among those who subsequently had cardiovascular events. Healthy, nondisabled elderly people with higher circulating levels of IL-6 and C-reactive protein were 2.6 times more likely to die of cardiovascular and noncardiovascular causes during a mean follow-up period of 4.6 years than those with low levels of both measurements. It is interesting that a high plasma concentration of tumour necrosis factor- α (TNF- α) is associated

with dementia in centenarians.⁸ This suggests that higher circulating levels of proinflammatory molecules such as C-reactive protein, IL-6 and TNF- α may serve as markers of underlying cardiovascular diseases and noncardiovascular diseases such as Alzheimer's disease. If so, methods designed to suppress the production of these proinflammatory molecules may prevent dementia and decrease mortality.

Statins inhibit the production of the proinflammatory cytokines TNF- α and IL-6⁹ and, thus, may have anti-inflammatory properties. It is known that heightened expression of TNF- α can decrease the capacity of insulin-like growth factor-1 to promote the survival of neurons.¹⁰ By suppressing the production of TNF- α , statins may promote the survival of neurons and, thus, may be of benefit in Alzheimer's disease and other dementias. The reported beneficial actions of statins in the prevention of osteoporosis, stroke, coronary heart disease and regulation of immune response can also be attributed to their actions on NO, TNF- α , IL-6 and BMPs, because these molecules play an important role even in these diseases (Fig. 1).

In view of this suggested interaction between statins and NO, BMPs and cytokines, further study is needed to determine whether the incidence of dementia and cardiovascular and noncardiovascular diseases is lower in individuals who are taking statins. It will be necessary to correlate these disease events with the plasma concentrations of C-reactive protein, IL-6 and TNF- α in current and future cohort studies.

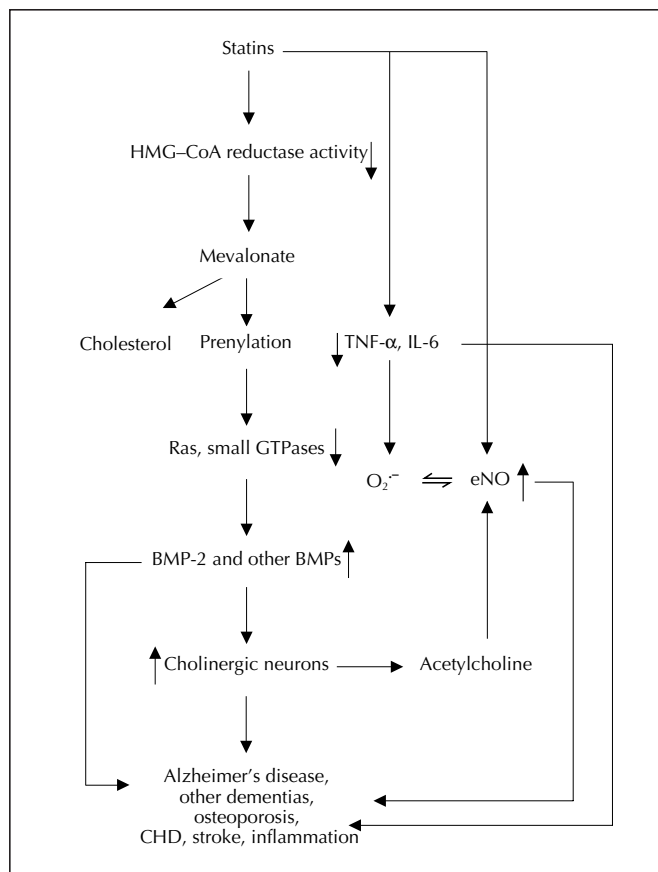


Fig. 1: The possible relation between statins and endothelial nitric oxide (eNO), bone morphogenetic proteins (BMPs), proinflammatory cytokines, Alzheimer's disease and other diseases. TNF- α = tumour necrosis factor- α , IL-6 = interleukin-6, GTPase = guanosine triphosphatase, CHD = coronary heart disease.

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