Cholesterol-independent Effects of Statins and New Therapeutic Targets: Ischemic Stroke and Dementia

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The 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, or “statins”, are used as cholesterol-lowering agents worldwide. Statins inhibit cholesterol biosynthesis, leading to enhanced uptake of low-density lipoprotein (LDL) from the circulation via LDL receptors. This strong cholesterol-lowering action contributes to the beneficial effects of statins. For example, large clinical trials have demonstrated that statins significantly reduce cardiovascular risk. Recent research has shown that statins have other multiple actions involved in endothelial function, cell proliferation, inflammatory response, immunological reactions, platelet function, and lipid oxidation. These “pleiotropic actions” of statins probably provide a significant contribution to the reduction of cardiovascular events. This review summarizes the pleiotropic actions of statins in both basic and clinical studies. It also considers the potential for statin therapy in the treatment of stroke and dementia. J Atheroscler Thromb, 2004; 11: 253–264.

Key words: Isoprenoid, Pleiotropic effect, Stroke, Dementia

Introduction
Numerous epidemiological studies have clearly shown that hypercholesterolemia is the most important risk factor for coronary heart disease (CHD) in industrialized countries (1–5). In Japan, pravastatin, one of the 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins), came onto the market in 1989. Statins reduce the low-density lipoprotein-cholesterol (LDL-C) concentration more than any other cholesterol-lowering drug, such as resin (6), probucol (7), niacin (8), or fibrates (9). Many randomized controlled trials have demonstrated that statins decrease CHD risk in patients with or without CHD, independent of their baseline cholesterol levels (10–15). Such benefits have been reported in elderly people in Japan (16) and Europe (17). Recent data provided further evidence that statins improve the prognosis of patients with acute coronary syndrome (18) and those undergoing percutaneous transluminal coronary intervention (19). According to our local survey, nearly all general practitioners and hospital doctors use statins as a first-choice drug for the treatment of hypercholesterolemia (20).

The benefits of statins are considered to depend initially upon LDL-C reduction, followed by the subsequent regression of atherosclerotic lesions. In prospective studies, approximately 20 to 30% fewer cardiovascular events occurred in patients receiving statins than in controls receiving a placebo (10–15). The time-to-event curves usually being to diverge within one year. However, the subgroup analyses of these studies suggest that statins have direct effects on vascular walls (21, 22). This concept is consistent with the angiographic data that the...
actual regression of coronary atherosclerosis in statin-treated patients is too small to explain the large reduction in cardiovascular events (23). Recently, a wide spectrum of studies have indicated that statins have multiple actions (“pleiotropic effects”) beyond cholesterol lowering (21, 22). These actions may play an important role in protecting statin-treated patients from the development of atherosclerosis or plaque rupture. In this review, we focus on the pleiotropic effects of statins in vitro and in vivo. We also discuss the future clinical application of statins for the treatment of stroke and dementia.

Cholesterol Biosynthesis Pathway and Inhibition of HMG-CoA Reductase by Statins

Cholesterol is an essential component of cell membranes, and its metabolites, such as bile acids and steroid hormones, also play important roles in vivo. Mammalian cells acquire cholesterol through exogenous and endogenous pathways. In the exogenous pathway, cells incorporate cholesterol as apolipoprotein B-containing lipoproteins, mainly low-density lipoprotein (LDL), via receptor-mediated endocytosis (24). After lipoproteins are degraded in lysosomes, lipoprotein-derived cholesterol is recycled for further processing. In the endogenous pathway, cells synthesize cholesterol (25, 26). Since excess free cholesterol is cytotoxic, intracellular cholesterol homeostasis is strictly maintained by the mechanism described below.

In humans, cholesterol is synthesized from acetyl CoA in approximately 30 enzymatic reactions. Figure 1 shows that these reactions are grouped into five steps: 1) the synthesis of mevalonate from acetyl CoA, 2) the formation of isoprenoid units from mevalonate, 3) squalene condensation from six isoprenoid units, 4) the cyclization of squalene and lanosterol formation, and 5) cholesterol synthesis from lanosterol. Isoprenoids such as geranylgeranylpyrophosphate (GG-PP) and farnesyl pyrophosphate (F-PP) are generated as intermediates in the second step of the cholesterol biosynthetic pathway. As discussed below, these intermediates are very important for the cholesterol-independent actions of statins, designated as pleiotropic effects.

Recent work has provided convincing evidence that transcriptional factors, called sterol regulatory element binding proteins (SREBPs), play crucial roles in regulating intracellular cholesterol homeostasis. SREBPs are inserted into endoplasmic reticulum (ER) membranes and interact with SREBP-cleavage-activating protein (SCAP), which has a sterol-sensing domain. When the intracellular cholesterol content falls, this complex moves from the ER to the Golgi apparatus. Then, the active N-terminus of SREBP is released into the cytosol via a two-step proteolysis and is transferred to the nucleus (27, 28). The genes of many enzymes involved in cholesterol biosynthesis (i.e., HMG-CoA synthase, HMG-CoA reductase, F-PP synthase, squalene synthase, and squalene epoxidase) have an eight-nucleotide base sequence called sterol regulatory element-1 (SRE-1) in their promoter regions (29–34). The LDL receptor gene also has SRE-1 in its promoter region (35). After SREBPs attach to SRE-1, the expression of these genes increases significantly, accelerating both cholesterol synthesis de novo and receptor-mediated uptake of LDL. When the cellular cholesterol contents is sufficient, SREBP processing is suppressed, leading to reductions in cholesterol synthesis and LDL uptake.

HMG-CoA reductase is the rate-limiting enzyme for cholesterol formation in the liver and other tissues (36). This enzyme catalyzes the initial step of cholesterol biosynthesis by reducing HMG-CoA, generating mevalonate. Since HMG-CoA reductase synthesis is regulated transcriptionally by SREBP, the cellular cholesterol content changes the HMG-CoA reductase activity. HMG-CoA reductase is a 97-kDa membrane-bound protein composed of 887 amino acid residues (37). The N terminus includes seven hydrophobic regions, allowing this enzyme to penetrate the endoplasmic membrane seven times. The catalytic site is located in a hydrophilic carboxyl region. HMG-CoA reductase is also regulated at the post-translational level by a cholesterol sensor domain located in a membrane-bound domain (38). If the cellular cholesterol content increases, the degradation of HMG-CoA reductase is accelerated (39).

Statins competitively inhibit the binding of HMG-CoA at the catalytic site of HMG-CoA reductase and reduce mevalonate synthesis. However, the cholesterol-lowering effects of statins result mainly from the enhanced receptor-mediated uptake of LDL and not from reduced cholesterol synthesis. Since mevalonate is a precursor of isoprenoids as well as cholesterol, statins also suppress isoprenoid production (40). The decreased isoprenoids likely induce various cholesterol-independent actions (“pleiotropic effects”) related to the downstream molecules.

Clinical Trials Suggest the Presence of Pleiotropic Effects of Statins

Various clinical trials have demonstrated that statins reduce the CHD risk, more than was expected, by LDL-C lowering. In the subgroup analysis of the West of Scotland Coronary Prevention Study (WOSCOPS), a primary prevention trial with pravastatin, the investigators compared the event rates between placebo and pravastatin groups with the same LDL-C levels. In the overlap patients whose plasma LDL-C levels were 140–180 mg/dl (3.6–4.7 mmol/l), the CHD risk was 36% lower in the pravastatin group than in the placebo group (p = 0.014). In the same study, the authors also calculated the CHD
risk using the Framingham risk equation in the placebo and pravastatin groups, and compared them with the individual actual event rates. In the placebo group, there was a high correlation between the actual event rate and the estimated risk. Conversely, in the pravastatin group, the actual event rate was about 10% lower than the estimated risk (41).

A secondary prevention trial also suggested that statins produce beneficial effects beyond cholesterol lowering. In the Cholesterol and Recurrent Events (CARE) study, pravastatin significantly decreased both the mean and median C-reactive protein (CRP) concentrations. However, a change in the LDL-C concentration was not a significant predictor of change in CRP. Moreover, pravastatin reduced CHD risk more in the inflammation (+) group than in the inflammation (–) group (–54% vs –25%), although their baseline lipid levels were identical (42, 43).

Statin therapy decreases ischemic events much earlier in patients exhibiting acute coronary syndromes than in stable CAD patients. In the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) study, patients with unstable angina or non–Q-wave acute myocardial infarction were assigned to the atorvastatin (80 mg/day) or placebo group 24 to 96 hours after admission to a hospital. The efficacy of atorvastatin treatment was evaluated after a 16-week treatment period. Atorvastatin significantly reduced LDL-C by 52%. The incidence of a primary combined endpoint (death, nonfatal acute myocardial infarction, cardiac arrest with resuscitation, or recurrent symptomatic myocardial ischemia with objective evidence requiring emergency rehospitalization) was 16% lower in the atorvastatin group than in the placebo group (p = 0.048). Previous prospective trials aimed at the primary or secondary prevention of CHD have usually required one- or two-year treatment regimens to produce a significant difference between the statin and placebo groups. A 16-week treatment regimen is probably too brief to observe the regression of coronary atherosclerotic lesions (44).

Angiographic trials have provided further evidence supporting the cholesterol-independent benefits of statin therapy. In the Familial Atherosclerosis Treatment Study (FATS) trial, for example, statin therapy in combination with bile acid resin decreased the incidence of coronary events by 70%, although treatment produced only a 0.7% change in lesion regression (45, 46). These results strongly suggest that statins have some direct (cholesterol-independent) effects on vascular walls ("pleiotropic effects") at clinical doses.

**Isoprenoids and Pleiotropic Effects of Statins**

As described in second section, isoprenoids such as F-PP and GG-PP are intermediates in the cholesterol biosynthesis pathway (Fig. 1). They serve as important lipid attachment molecules for the post-translational modification (isoprenylation) of many bioactive proteins, including the γ-subunit of heterotrimeric G-proteins, Hem A, nuclear lamins, and small GTP-binding proteins (small G-proteins), such as Ras and Rho (47). Ras and Rho are major substrates for isoprenylation with F-PP and GG-PP, respectively. GDP-bound Ras and Rho are localized in the cytoplasm as inactive forms. When F-PP or GG-PP is bound to the inactive Ras or Rho, they are translocated to cell membranes and converted to GTP-bound active forms (Fig. 2). Then, activated Ras and Rho modulate the functions of the next proteins downstream. For instance, GTP-bound Rho activates Rho kinase and focal adhesion kinase (FAK), while GTP-bound Ras activates MAP-kinase. These proteins further modulate many downstream effector proteins and cause various specific actions in the target cells (Table 1). At present, however, additional effectors are still unidentified in the downstream regions of the Rho and Ras pathways (48).

In addition to a strong cholesterol-lowering effect, statins have favorable cholesterol-independent effects on endothelial function, inflammatory activity, oxidative stress, blood coagulation, platelet function, cellular proliferation and differentiation, plaque stability, vascular formation, and the immune system. Most of the pleiotropic effects of statins are explained by the reduced level of isoprenoids and the subsequent accumulation of inactive small G-proteins.

**Statin-mediated effects on NO synthesis**

Endothelial function is commonly impaired in patients with hypercholesterolemia or atherosclerosis (49, 50). This endothelial dysfunction is related to the decreased synthesis or activity of endothelium-derived nitric oxide (NO) (51, 52). NO, a physiological vasodilator, is synthesized by endothelial NO synthase (eNOS) in vascular walls. NO has many biological functions, including the 1) inhibition of platelet aggregation and leukocyte adhesion, 2) inhibition of thrombogenesis, 3) inhibition of proliferation of smooth muscle cells, and 4) suppression of oxidative stress.

Statins improve endothelial dysfunction by increasing NO production. In hypercholesterolemic patients, statin treatment attenuates the vasoconstriction mediated by acetylcholine (an endothelium-dependent vasodilator), and increases coronary blood flow (49). These favorable effects have been observed within 24 hours of treatment and in the absence of significant cholesterol reduction (53). A similar effect was observed in the flow-mediated dilation of brachial arteries (54, 55).

Statins can increase NO production independent of cholesterol lowering. Several mechanisms have been proposed from the experimental data (58). For example, statins inactivate the Rho/Rho kinase pathway and increase eNOS expression. This effect can be reversed by...
Fig. 1. Cholesterol biosynthesis pathway. Cholesterol is synthesized from acetyl CoA by many enzymes that are regulated by the sterol regulatory element binding proteins (SREBPs). Isoprenoids (farnesyl pyrophosphate and geranylgeranyl pyrophosphate) modify the proteins (Rho, Rac, Ras, etc) that are important for many cellular responses.

Fig. 2. Activation of small GTP-binding proteins by isoprenoids, and subsequent signal transduction. When small GTP-binding proteins are attached to isoprenoids, they are translocated to the cell membrane and turn into GTP-bound active forms. The subsequent activation of effector proteins finally causes diverse cellular responses via signal transduction. GG-PP: geranylgeranyl pyrophosphate, F-PP: farnesyl pyrophosphate, FAK: focal adhesion kinase, SMC: smooth muscle cell, EPC: endothelial progenitor cell.
Vascular Effects of Statins

the addition of GG-PP, but not F-PP, supporting this hypothesis. The increased eNOS expression is caused by the stabilization of eNOS mRNA (57, 58). Furthermore, mevalonate (the product of HMG CoA reductase) inhibits phosphatidylinositol 3-kinase (PI3-K), an enzyme that promotes activation of Akt via phosphoinositide kinase-1 (Fig. 1). Statins decrease mevalonate, resulting in the activation of protein kinase Akt, which phosphorylates eNOS and increases NO production. Other mechanisms have been summarized in a recent review (56).

**Statin-mediated effects on smooth muscle cells**

In atherosclerotic lesions, the migration and proliferation of smooth muscle cells (SMCs) contribute to the formation and development of atherosclerosis. Small G-proteins, including Ras and Rho, promote SMC migration and proliferation. Therefore, statins inhibit SMC migration and proliferation via inactivation of the Ras and/or Rho pathways and activation of the PI 3-kinase/Akt pathway (Fig. 1, Table 1). Statins also inhibit the migration and proliferation of endothelial progenitor cells (EPCs) via activation of the PI 3-kinase/Akt pathway (59–61). Ras can promote cell-cycle progression via activation of the MAP kinase pathway. Rho/Rho kinase can promote cellular proliferation via destabilization of p27^kip1 [Cdk (cyclin-dependent kinase) inhibitor] and DNA synthesis of SMCs, and, finally, mediates PDGF-induced SMC proliferation (62). Therefore, inactivation of the Ras/MAP kinase and Rho/Rho kinase pathway by statins results in the reduced proliferation of SMCs (63, 64).

In addition to the effects on SMC proliferation, statins affect both angiogenesis and vasculogenesis. Simvastatin enhances the phosphorylation of eNOS, inhibits apoptosis, and accelerates vascular structure formation in vitro via activation of the PI3-K/Akt pathway (65). Low doses of statins induce a pro-angiogenic effect via Akt activation and increased NO production, whereas high doses of statins decrease protein prenylation and inhibit cell growth and proliferation (66, 67). Furthermore, atorvastatin induces NO production by decreasing caveolin-1 expression in endothelial cells, independent of extracellular LDL-C levels (68). These effects contribute to the stabilization of atherosclerotic plaques.

**Statin-mediated effects on inflammation**

Chronic inflammation of vascular walls is also associated with atherosclerosis. Inflammatory responses contribute to the development of atherosclerosis from the
initial stage (leukocyte-endothelial interaction) to the end stage (plaque rupture). Statins decrease pro-inflammatory cytokines, and reduce the expression of adhesion molecules on vascular walls (69). In monocyte U937 cells, statins inhibit adhesion to a cytokine-activated human umbilical vein endothelial cell (HUVEC) monolayer. Probably, statins inhibit the monocyte-endothelial interaction via RhoA inactivation (70). Furthermore, statins decrease the number of macrophages and T cells and reduce matrix metalloproteinase (MMP) expression in atherosclerotic lesions. Clinically, statins significantly decrease the concentrations of acute phase proteins, such as C-reactive protein and serum amyloid A (SAA). These effects were observed both in hypercholesterolemic humans and in animals with a low serum cholesterol concentration. Therefore, these anti-inflammatory effects of statins are probably independent of the cholesterol-lowering effects.

Other statin-mediated effects

Recent studies have suggested that the mevalonate pathway plays an important role in skeletal metabolism. Osteoporosis is one of the most common bone diseases in elderly people. Both in vitro and animal studies demonstrate that statins stimulate the production of BMP-2, a potent regulator of osteoblast differentiation and activity (71). These findings suggest that statins have an anabolic effect on bone. Therefore, statins may be used as therapeutic agents to treat osteoporosis.

In vitro studies have shown that statins can induce the apoptosis of acute myelogenous leukemia cells in a sensitive and specific manner (72). Statin-mediated apoptosis is partially caused by the disruption of the downstream product GG-PP, but not of F-PP or other products of the mevalonate pathway, including cholesterol (73). Further clinical trials are necessary to investigate the possible use of statins as anti-cancer agents.

Future Perspectives

Ischemic stroke and Alzheimer’s disease (AD) are promising new targets for statin therapy. Both conditions are associated with hypercholesterolemia epidemiologically (74–76). Moreover, recent data have suggested that statins reduce the risk of stroke and AD.

Preventive effect of statins on stroke

Stroke is the third leading cause of death in Japan. Even if patients are not killed by the initial events, a disabling stroke severely reduces the patient’s quality of life. There are three major types of stroke: hemorrhagic stroke, ischemic stroke, and subarachnoid hemorrhage. A meta-analysis of 11 cohort studies in China and Japan revealed trends toward an increased risk of non-hemorrhagic stroke with increasing cholesterol concentration (74), although this association was not as strong as that between the incidence of ischemic heart disease and cholesterol level.

Despite such a weak association, many clinical trials have consistently indicated that statins reduce stroke by 10–30% (Table 2). In the heart protection study (HPS),

<table>
<thead>
<tr>
<th>Study Name</th>
<th>CHD/CVD at entry (%)</th>
<th>Drug (Daily Dose)</th>
<th>Follow-up (Years)</th>
<th>Risk Reduction in Stroke (P value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overseas Trials</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>WOS-COPS (6,595)</td>
<td>5 / 0%</td>
<td>Prava (40 mg) vs Placebo</td>
<td>4.9</td>
<td>~ 11% (NS)</td>
</tr>
<tr>
<td>CARE (4,159)</td>
<td>100 / 0%</td>
<td>Prava (40 mg) vs Placebo</td>
<td>5</td>
<td>~ 31% (p = 0.03)</td>
</tr>
<tr>
<td>LIPID (9,014)</td>
<td>100 / 4%</td>
<td>Prava (40 mg) vs Placebo</td>
<td>6.1</td>
<td>~ 19% (p = 0.048)</td>
</tr>
<tr>
<td>4S (4,444)</td>
<td>100 / 0%</td>
<td>Simva (20-40 mg) vs Placebo</td>
<td>5.4</td>
<td>~ 30% (p = 0.024)</td>
</tr>
<tr>
<td>HPS (20,536)</td>
<td>65 / 16%</td>
<td>Simva (40 mg) vs Placebo</td>
<td>5</td>
<td>~ 25% (p &lt; 0.0001)</td>
</tr>
<tr>
<td>ASCOT-LLA (10,305)</td>
<td>0 / 10%</td>
<td>Atrova (10 mg) vs Placebo</td>
<td>3.3 (median)</td>
<td>~ 27% (p = 0.0236)</td>
</tr>
<tr>
<td>Domestic Trials</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>KLIS (5,640)</td>
<td>7 / 0%</td>
<td>Prava (10-20 mg) vs Usual care</td>
<td>5</td>
<td>~ 22% (CI) (NS)</td>
</tr>
<tr>
<td>PATE (665)</td>
<td>13 / 13%</td>
<td>Prava (5 mg) vs Prava (10-20 mg)</td>
<td>3.9</td>
<td>~ 26% (CI) (NS)</td>
</tr>
<tr>
<td>J-LIT (52,421)</td>
<td>10 / 3%</td>
<td>Simva (5-20 mg) group</td>
<td>6</td>
<td>Not reported</td>
</tr>
</tbody>
</table>

Prava: pravastatin, Simva: simvastatin, Atora: atorvastatin, CI: cerebral infarction, CVD: cerebrovascular disease, NS: not significant

1 Patients with stable angina who had not been hospitalized within the previous 12 months.

1 The relative risk of death due to CVD and other vascular disease was the highest in those with a mean total cholesterol > 280 mg/dl (> 7.3 mmol/l) during the follow-up period.
is bound to cell membranes. Three types of proteolytic product of a larger amyloid of platelet aggregation, and anti-inflammatory actions. Of endothelial dysfunction, plaque stabilization, inhibition of platelet aggregation, and anti-inflammatory actions.

Preventive effect of statins on dementia
As people continue to live longer in our country, the prevalence of dementia has increased. In European and American Caucasians, AD dominates over vascular dementia (78). In rural Japan, vascular dementia dominates over AD (79). In urban Japan, however, AD has been increasing in recent years, with a reduction in vascular dementia (80). Interestingly, the distribution of dementia subtypes in Japanese-Americans in Seattle is similar to that in Caucasians (81). These epidemiological data strongly suggest that environmental factors, such as a high-cholesterol diet, increase the risk for AD.

Many in vitro experiments support the link between cholesterol metabolism in the central nervous system (CNS) and AD. Pathologically, the brain of an AD patient is characterized by two types of insoluble protein aggregates: amyloid plaques and neurofibrillary tangles. Since amyloid plaque deposits precede neurofibrillary tangles, amyloid plaque formation is considered an upstream phenomenon in the pathological cascade of AD (amyloid hypothesis) (82). Amyloid plaques are mainly composed of aggregated β-amyloid (Aβ), which is a proteolytic product of a larger amyloid β protein precursor (APP) that is bound to cell membranes. Three types of proteolytic enzymes cleave APP. In the major (non-amyloidogenic) pathway, α-secretase cleaves APP within the Aβ domain (83). In this case, the large ectodomain of APP (sAPPα) is released into the cerebrospinal fluid (CSF). ADAM10 is one of the candidate enzymes for α-secretase (83). It has been reported that sAPPα is neuroprotective, neurotrophic and regulates cell excitability and synaptic plasticity (84). In the minor (amyloidogenic) pathway, in contrast, β-secretase and γ-secretase cleave APP at both ends of the Aβ domain, and release Aβ into the CSF (83). If the Aβ concentration in the CSF is high, soluble Aβ turns into a neurotoxic aggregate. The non-amyloidogenic proteolysis takes place predominantly in cholesterol-poor microdomains, while amyloidogenic proteolysis occurs in cholesterol-rich microdomains, called lipid rafts (83).

Hypercholesterolemia may shift the proteolysis of APP to the amyloidogenic pathway, promote Aβ aggregation, and eventually increase the risk of AD. Based on this hypothesis, several classes of drugs are expected to inhibit this cascade (85). Statins are one of the most promising types of agents for treating AD among clinically available drugs. In primary cultures of hippocampal neurons and mixed cortical neurons, simvastatin and lovastatin reduce intracellular and extracellular Aβ40 and Aβ42 (86). Since Aβ production is regulated by the Rho/Rho kinase pathway (87), statins are likely to reduce Aβ42 levels by decreasing GG-PP. In rabbit experiments, Aβ accumulated in the brains of the cholesterol-fed group, but not in the brains of the control group (88). Furthermore, cross-sectional human studies have indicated that those treated with statins had a lower rate of dementia or probable AD than those without hyperlipidemia or those treated with non-statin lipid-lowering agents (89, 90). The same results were obtained in a secondary analysis of the Canadian Study of Health and Aging (91).

In vitro and in vivo studies suggest that statin therapy affects cholesterol metabolism in the CNS. In the CNS, essentially all cholesterol is synthesized locally and is removed from the CNS by diffusion, predominantly as 24S-hydroxycholesterol (a soluble neurotoxic oxysterol), through the blood-brain barrier. Since almost all plasma 24S-hydroxycholesterol is derived from CNS cholesterol, the plasma 24S-hydroxycholesterol level reflects cholesterol metabolism in the CNS. In both plasma and CSF, 24S-hydroxycholesterol levels are higher in AD patients than in healthy controls (82). Simvastatin treatment (80 mg/day) significantly decreased the plasma 24S-hydroxycholesterol concentrations in hypercholesterolemic patients (93) and AD patients (94). These results suggest that high doses of simvastatin suppress de novo cholesterol biosynthesis in the CNS. In a more recent American study, three statins (simvastatin, lovastatin, and pravastatin) at the standard dose (40mg/day) also reduced serum 24S-hydroxycholesterol levels (95).
It is very important to confirm whether statins reduce the risk of AD or slow the progression of AD in prospective studies. Presently, only a few small-scale prospective clinical trials have been completed. In 19 patients with mild to moderate AD, 12-week simvastatin treatment (20 mg/day) decreased both $\alpha$- and $\beta$-secretase-cleaved APP in CSF by 12%, although the A$_{1-42}$ concentration in CSF did not change significantly (96). Two large-scale prospective studies are under way. In the trial designated SPARKS, 120 AD patients have been randomly assigned to the atorvastatin (80 mg/day) or placebo groups, and are being treated for 12 months (97). The effects will be evaluated by the improvement of the Alzheimer’s Disease Assessment Scale-Cognition (ADAS-cog) and Clinical Global Impression of Change (CGIIC) scores. This study will be completed in 2004. The Cholesterol-Lowering Agent to Slow Progression (CLASP) of Alzheimer’s Disease Study is currently recruiting patients with mild to moderate AD (98). This randomized, double-blind, placebo-controlled trial will investigate the safety and effectiveness of simvastatin at slowing the progression of AD. In the statin group, patients will receive 20 mg of simvastatin for the first six weeks, and the dose will be increased to 40 mg for the following 18 months. The expected number of enrolled patients is 400. These trials should answer whether we can use statins to treat AD in the clinic.

Conclusion
At clinical doses, statins appear to have certain pleiotropic effects beyond cholesterol lowering. As discussed here, these cholesterol-independent actions are mostly mediated by the inhibition of isoprenoid synthesis. Recent studies have suggested that statins are also effective in preventing ischemic stroke, and possibly Alzheimer’s dementia. Future studies will determine how pleiotropic effects contribute to the clinical outcome in patients treated with statins.

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Vascular Effects of Statins

263


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