LEADING ARTICLE

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Do Statins Afford Neuroprotection in Patients with Cerebral Ischaemia and Stroke?

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Abstract

An emerging body of evidence indicates that β-hydroxy-β-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, or 'statins', provide neuroprotection in addition to reducing ischaemic stroke. Statins reduce the incidence of ischaemic stroke by stabilising atherosclerotic plaques in the precerebral vasculature and through antithrombotic actions, and the neuroprotective effects of statins may confer significant clinical benefit. Some of these neuroprotective effects are likely to be cholesterol independent and mediated by the interruption of isoprenoid biosynthesis. Therapy with statins may modulate endothelial function and preserve blood flow to regions exposed to an ischaemic insult. In particular, statin-mediated preservation of endothelial nitric oxide synthase activity in cerebral vasculature, especially in the ischaemic penumbra, may limit neurological deficit. Moreover, putative anti-inflammatory and antioxidant properties of statins may confer additional neuroprotection. Further large clinical trials are necessary to address the role of statin therapy in the primary prevention of stroke, small vessel cerebrovascular disease and vascular dementia.

Recent clinical trials and meta-analyses of β-hydroxy-β-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors ('statins') have demonstrated a significant reduction in ischaemic stroke in patients with a history of coronary artery disease, both with and without elevations of serum cholesterol level.[1-5] The atheroma-retarding properties of statins in both the coronary and carotid arterial beds are well established.[6-8] However, accumulating data suggest that statins have further important adjunctive properties that may confer additional benefit beyond the retardation of atherosclerosis. These data indicate that statins protect neurons from the ischaemia that occurs during stroke. In this article, we review emerging evidence suggesting that statins operate as neuroprotective agents within the cerebral circulation and brain parenchyma during stroke and reperfusion. We also review the anti-inflammatory, antioxidant, and endothelial protective effects of statins and discuss the

putative neuroprotective properties of these compounds in cerebral ischaemic syndromes.

1. Statins: Mechanism of Action

HMG-CoA reductase is the rate-limiting enzyme for cholesterol formation in the liver and other tissues. Expression of the reductase gene is reduced in response to negative feedback regulation by both sterol and nonsterol products of mevalonate metabolism.[9] Through the inhibition of HMG-CoA reductase, statins reduce hepatocyte cholesterol content and increase expression of low density lipoprotein (LDL) receptors which are responsible for LDL-cholesterol uptake via receptor-mediated endocytosis (fig. 1). In addition to lowering intracellular levels of sterols, HMG-CoA reductase inhibitors reduce levels of isoprenoids which are derived from intermediates of the cholesterol biosynthetic pathway. Isoprenoids post-translationally prenylate a variety of cellular proteins that play central roles in both cell growth and signal transduction pathways. Targets include low molecular weight guanine nucleotide binding proteins (G-proteins) which have been shown to modulate signal transduction and mitogenic pathways.[10]

2. Statin Trials and Stroke

Despite the established role of cholesterol in the pathogenesis of coronary artery disease, controversy surrounds the issue of a positive association between elevated cholesterol levels and stroke. Epidemiological evidence does not demonstrate a clear relationship between the risk of stroke and the serum cholesterol level.[11,12] However, clinical studies indicate that cholesterol-lowering therapy with statins significantly reduces ischaemic stroke.

In the Cholesterol and Recurrent Events (CARE) study, pravastatin significantly reduced the specified end-point of stroke by 31%, without increased haemorrhagic stroke.[1] Post-hoc analysis of the Scandinavian Simvastatin Survival Study (4S) showed a similar reduction in stroke.[2] The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) study[3] investigators reported

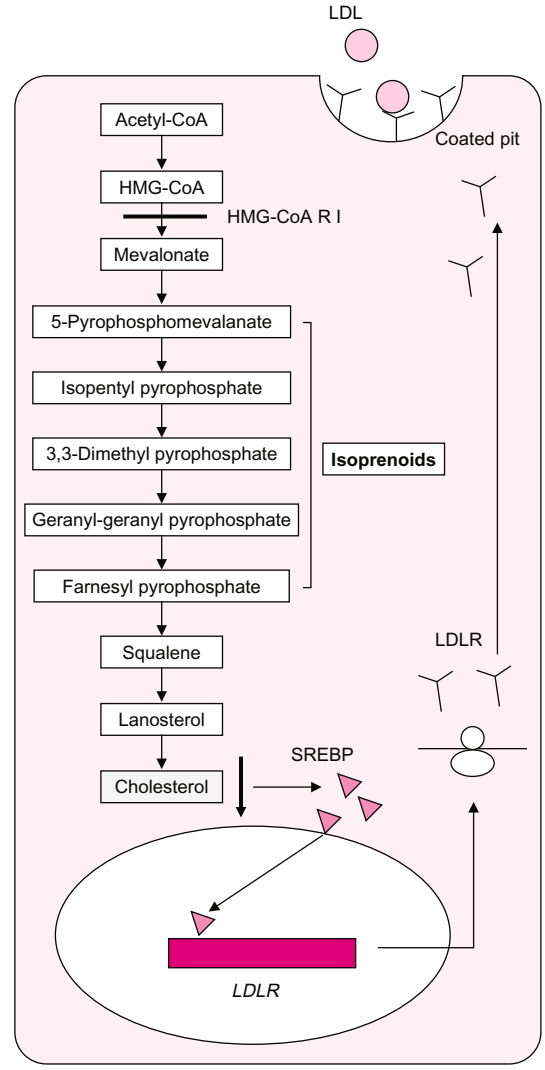

Fig. 1. Regulation of cholesterol synthesis. Inhibition of β-hydroxy-β-methylglutaryl coenzyme A (HMG-CoA) reductase reduces intracellular cholesterol levels, activating a protease which cleaves sterol regulatory element binding proteins (SREBPs) from the endoplasmic reticulum. SREBPs translocate to the nucleus where they upregulate expression of the low density lipoprotein (LDL) receptor (LDLR) gene. Enhanced LDLR expression increases receptor-mediated endocytosis of LDL and thus lowers serum LDL levels. Inhibition of HMG-CoA reductase also reduces intracellular levels of isoprenoids which are intermediates in cholesterol biosynthesis. **Acetyl-CoA** = acetyl coenzyme A; **HMG-CoA R I** = HMG-CoA reductase inhibitor.

the effect of pravastatin therapy on stroke in 9014 patients with previous myocardial infarction or unstable angina. In this study, there were 204 strokes in those receiving placebo and 169 strokes in pravastatin recipients, or a 19% relative risk reduction in stroke with statin therapy.[3] It is noteworthy that these secondary prevention studies were performed predominantly in middle-aged men with ischaemic heart disease. Recently, the Myocardial Ischaemia Reduction with Aggressive Cholesterol Lowering (MIRACL) study reported a 50% reduction in stroke with atorvastatin compared with placebo.[13] There were 24 strokes with placebo and 12 strokes with atorvastatin during the 16-week follow-up in this trial. The clinical benefit seen in secondary prevention trials is corroborated by 2 meta-analyses which demonstrate that statin therapy lowers stroke risk by approximately 30%.[4,5]

Although the absolute stroke rate in these clinical trials was small, the results did suggest that statin therapy decreases ischaemic stroke without increasing haemorrhagic stroke. In addition, statins may reduce the effect of stroke by reducing stroke size and through neuroprotective effects within the cerebral vasculature and brain parenchyma.

3. Carotid and Aortic Plaque Instability

The majority of nonlacunar ischaemic strokes are caused by thromboemboli arising from atheromatous plaques in the carotid artery or the aorta. Hypercholesterolaemia is an important risk factor for the development of atherosclerosis. The Asymptomatic Carotid Artery Progression Study (ACAPS)[7] demonstrated reversal or slowing of the typical progression of intimal-medial thickening in the carotid artery (using B-mode ultrasound) in men and women with moderately elevated cholesterol levels who received lovastatin for 3 years. Similarly, the Pravastatin, Lipids, and Atherosclerosis in the Carotids II (PLACII) study[8] demonstrated a significant 35% reduction in carotid intimal-medial thickness with pravastatin (also using B-mode ultrasound). Several lines of evidence suggest that statins would reduce stroke by stabilising atheromatous plaque in the proximal aorta and carotid artery. This stabilisation occurs through the lowering of lipid levels and cholesterol-independent anti-inflammatory and antithrombotic actions which operate within the plaque and the bloodstream.[14-16] Reduced plaque disruption and thrombosis translates into reduced artery-to-artery thromboembolism.

4. Neuroprotective Properties of Statins

In addition to effects in the precerebral macrovasculature, emerging evidence indicates that statins may ameliorate a number of pathophysiological processes that occur within the cerebral vasculature and brain parenchyma during cerebral ischaemia and reperfusion. There are now experimental data in animal models of stroke showing that statins limit ischaemic damage by improving blood flow to the ischaemic brain and by making the brain parenchyma intrinsically more resistant to the effects of ischaemia. It appears that modulation of the cerebral endothelial nitric oxide (NO) system by statin therapy is of primary importance in providing such neuroprotection.

4.1 Nitric Oxide Synthase Isoforms and Cerebral Ischaemia

The different isoforms of nitric oxide synthase (NOS) play important but opposing roles in cerebral ischaemia. The inducible form of NOS (iNOS) is an important mediator of inflammatory responses during ischaemia and reperfusion.[17] Astrocytes elaborate iNOS in response to a series of proinflammatory cytokines such as interleukin (IL)-1β, tumour necrosis factor-α (TNFα) and IL-6.[18] NO, derived from iNOS in both astrocytes and macrophages, and its oxidative by-product peroxynitrite, are thought to contribute to neuronal death due to oxidation of structural neuronal proteins during ischaemia. Additionally, neuronal NO (produced by neuronal NOS; nNOS) may contribute to neurological damage by promoting glutamate-mediated neurotoxicity. On the other hand, NO produced by endothelial NOS (eNOS) can have a protective physiological role. This form of NO orchestrates the paracrine homeostatic functions of the

endothelium, which include inhibition of leucocyte and platelet adhesion, control of vascular tone, and maintenance of a thromboresistant interface between the bloodstream and the vessel wall. Mice lacking the gene for eNOS experienced larger infarcts after middle cerebral artery occlusion,[19] whereas iNOS null mice had significantly reduced infarct volumes[20] compared with wild-type controls. Together, these observations suggest a relative compartmentalisation of NOS isoform activity in the brain, with contrasting roles for eNOS and iNOS in the setting of ischaemia. Preliminary studies with statins have demonstrated that these compounds may be able to modulate brain NOS isoform activity in a neuroprotective manner.

4.1.1 Statin Therapy Potentiates Endothelial Nitric Oxide Synthase

Statin therapy improves abnormal endothelial control of vasomotor function in both the coronary and forearm circulations in dyslipidaemic individuals.[21,22] Similarly, statin therapy may be beneficial during cerebral ischaemia through the modulation of brain eNOS. Experimental data from a murine model of ischaemic stroke demonstrate that prophylactic statin therapy augments cerebral blood flow, reduces infarct size by approximately 30%, and improves neurological outcomes in normocholesterolaemic animals.[23] In this model, statin therapy directly up-regulated eNOS activity in the brain, without altering expression of nNOS. These effects occurred independent of change in cholesterol level and were reversible with mevalonate or geranyl-geranyl pyrophosphate co-treatment. In a similar study, atorvastatin has been shown to reduce stroke size in normocholesterolaemic mice through cholesterol-independent mechanisms.[24] This effect is mediated by up-regulation of eNOS in the vasculature and platelets and by decreased platelet activation.

The small guanine triphosphate (GTP)–binding protein Rho both downregulates eNOS, and reduces eNOS mRNA stability via effects on the endothelial cell actin cytoskeleton (fig. 2). HMG-CoA reductase inhibitors reduce the isoprenylation (and the activity) of Rho, allowing the up-regulation of eNOS. It has been shown in mice that disruption of endothelial cell actin cytoskeleton with Rho inhibitors such as *Clostridium botulinum* C3 transferase, cytochalasin D and simvastatin increases eNOS activity and expression, increases cerebral blood flow and reduces infarct size.[25] The mechanism by which the actin cytoskeleton modulates eNOS appears primarily to be its action on the post-translational stability of eNOS mRNA. In this regard, other compounds that affect this pathway may also hold promise as neuroprotective agents.

Additional important effects of statins on the bioavailability of NO may be mediated by alterations in the activity of the protein kinase Akt.[26] Akt plays a central role in orchestrating a spectrum of cellular events, including activation of eNOS and promotion of endothelial cell survival.[27] Simvastatin therapy potentiates the activity of Akt, which in turn may stimulate eNOS and lead to an increased production of NO (fig. 2).[26]

The effects of statins on the endothelial cell eNOS-NO pathway may be pivotal in protecting the brain during states of compromised blood flow. Potentiation of NO may improve collateral blood flow to ischaemic areas, enhance cerebral arterial vasodilator responses, prevent apoptosis and possibly promote angiogenesis.

4.2 Antineuroinflammatory Actions of Statins

As well as biochemically remodelling the endothelium, HMG-CoA reductase inhibitors have been shown to inhibit a number of inflammatory processes active during cerebral ischaemia and reperfusion.

4.2.1 Statins and Adhesion Molecule Regulation

Up-regulation of adhesion molecule expression has been documented in animal and human cerebral ischaemia and reperfusion.[28] Enhanced expression of adhesion molecules on both endothelium and glial cells within the infarct and in the surrounding ischaemic penumbra may facilitate postischaemic migration of leucocytes through the brain parenchyma. Statin therapy inhibits leucocyte-

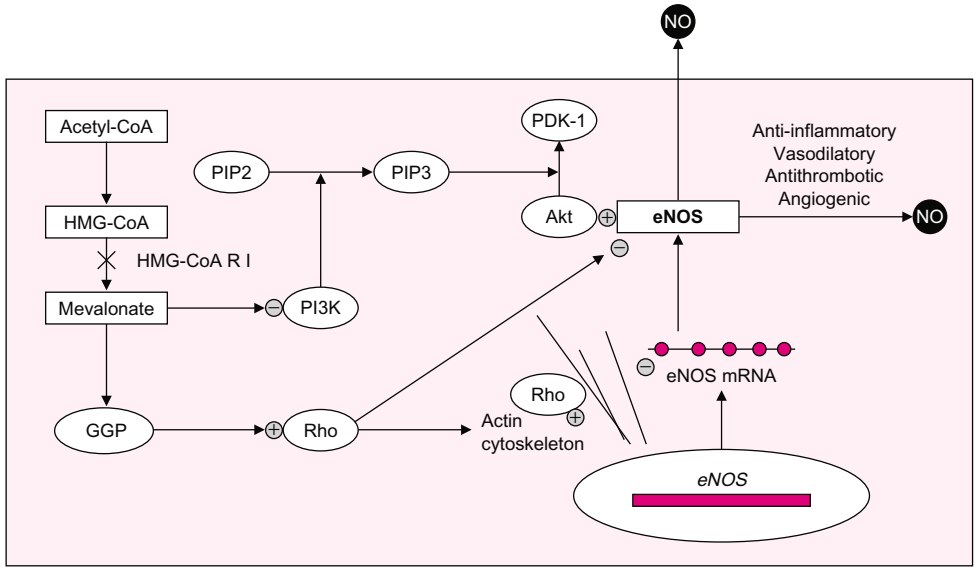

Fig. 2. Molecular actions of statins on the endothelial nitric oxide system. Endothelial nitric oxide synthase (eNOS) mediates the anti-inflammatory and vasodilatory functions of the cerebral endothelium. Mevalonate, the product of β-hydroxy-β-methylglutaryl coenzyme A (HMG-CoA) reductase, inhibits phosphatidylinositol 3-kinase (PI3K). PI3K converts phosphatidylinositol 4,5 biphosphate (PIP2) to phosphatidylinositol 3,4,5 triphosphate (PIP3) which in turn activates protein kinase Akt via phosphoinositide-dependent kinase-1 (PDK-1). **Acetyl-CoA** = acetyl coenzyme A; **GGP** = geranyl-geranyl pyrophosphate; **HMG-CoA R I** = HMG-CoA reductase inhibitor; **mRNA** = messenger RNA; **NO** = nitric oxide; **Rho** = guanine triphosphate–binding protein.

endothelial interactions in hypercholesterolaemic animals[29] and neutrophil adhesion to coronary endothelium.[30] In humans with hypercholesterolaemia, simvastatin and lovastatin both reduce monocyte CD11b expression as well as *ex vivo* CD11b-dependent monocyte adhesion to endothelium.[31] This effect may be mediated through reduced isoprenylation of leucocyte G-proteins,[32] reduced isoprenoid-dependent anchoring or reduced dimerisation of adhesion molecules such as CD11b/CD18 on monocytes.

4.2.2 Statins and Cytokine Activity

Statin therapy may also modulate CNS cytokine production. Cytokines are prominent mediators of inflammatory and immunological responses in the brain and are produced by neurons, glial cells and endothelium. Although the precise role of different cytokines in cerebral ischaemic syndromes remains to be elucidated, cytokines appear to modulate adhesion molecule expression on inflammatory cells and the cerebral endothelium, promote cell migration, enhance thrombogenesis through tissue factor expression, and augment elaboration of platelet-activating factor.[33] IL-1β, a proinflammatory cytokine, is overexpressed in the brains of experimental animals after stroke and appears to contribute to neuronal damage, perhaps through induction of neuronal apoptosis.[34] Other inflammatory cytokines, such as TNFα and IL-6, are also elevated in experimental models of cerebral ischaemia and may contribute to further neuronal loss.[28] TNFα not only up-regulates adhesion molecule expression by glial and endothelial cells, but also alters the blood-brain barrier and mediates a prothrombotic transformation of the cerebral endothelium.[28]

The clinical relevance of such inflammatory mediators is suggested by experimental studies demonstrating a reduction in cerebral infarct size in animals treated with cytokine receptor antagonists.[35] Lovastatin has been shown to inhibit

cytokine-mediated up-regulation of iNOS and production of NO in rat astrocytes and macrophages.[36] Thus, statin therapy may represent a novel means of suppressing cytokine responses occurring during ischaemia and reperfusion, by directly reducing the *in vivo* induction of inflammatory mediators such as iNOS, IL-1β and TNFα in astrocytes and macrophages.[36] When these effects are coupled with the observed effects of statins on eNOS (section 4.1), it appears that they may provide neuroprotection by simultaneously up-regulating eNOS and inhibiting iNOS in the ischaemic brain. Since many of these effects of statins are reversible with coadministration of mevalonate or farnesyl pyrophosphate (section 4.1), statins may reduce inflammation by decreasing the isoprenylation (and hence the activity) of proteins involved in intracellular signalling and inflammation.[36]

Recent data indicate that statins also directly effect immune cell activation. Therapy with statins inhibits interferon-γ–induced expression of class II major histocompatibility complex on antigen-presenting cells and reduces T cell activation.[37] Therefore, some of the antiatherosclerotic and anti-inflammatory actions of statins may be due to modulation of the immune system.

4.3. Antioxidant Effects of Statins

Finally, statins may provide neuroprotection through antioxidant effects. Oxidative injury appears to be a fundamental mechanism of many neurological disorders including cerebrovascular disease.[38,39] Chronic oxidant injury plays a pathophysiological role in precerebral atherogenesis and free radical generation following stroke. Thus, oxidant injury, during both spontaneous and therapeutic reperfusion, may accentuate tissue injury in the ischaemic penumbra. The generation of free radicals causes neuronal and endothelial damage through the induction of lipid peroxidation, protein oxidation and direct damage to nucleic acids. The elaboration of reactive oxygen species has been reported to induce apoptosis of endothelial cells through activation of CPP32-like proteases.[40] Moreover, during ischaemia and reperfusion, the protective endogenous antioxidant systems (such as the enzymes superoxide dismutase and catalase) may be overwhelmed.

Several studies indicate that therapy with statins can reduce lipoprotein oxidation and ameliorate free radical injury. Statins may have broader antioxidant effects than those measured by several *ex vivo* systems, such as increased lag time of copper-induced LDL oxidation[41] and reduced leucocyte-induced LDL oxidation.[42] Hydroxy metabolites of atorvastatin have been shown in an *in vitro* model to inhibit oxidation in a concentration-dependent manner.[43] In a study in patients with hypercholesterolaemia, treatment with simvastatin increased the α-tocopherol : total cholesterol ratio,[44] thereby possibly enhancing membrane-specific antioxidant defences. Most studies have explored the antioxidant properties of statins in relation to LDL, but statins may exert broader antioxidant effects by preserving superoxide dismutase activity.[42]

5. Future Directions

Although it has been demonstrated that statin therapy reduces stroke in secondary prevention trials in patients with coronary artery disease (section 2), a number of important issues are yet to be addressed. Roles for statin therapy in the primary prevention of stroke and in the prevention of small vessel and multi-infarct neurological disease remain unknown. Statin therapy may reduce the incidence of dementia;[45,46] but this has not yet been demonstrated in a prospective clinical trial. However, large prospective clinical trials designed to address some of these issues are underway. For instance, the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) will examine the effect of statin therapy on major combined endpoints (death, myocardial infarction and stroke) and cognitive decline in patients aged 70 to 82 years.[47] Further investigation using a number of modalities, including neuroimaging studies and cognitive studies, are warranted to explore putative neuroprotective properties of statins. If the potential cholesterol-independent neuroprotective effects of statins are proved to be clinically im-

portant in humans, this class of drugs will find wide-ranging utility in the management of a variety of cerebrovascular disease entities in patients with and without hypercholesterolaemia.

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