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Role of statins in cerebral vasospasm

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Summary

3-Hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitors, commonly known as statins, are widely used clinically for their lipid lowering properties. Recent evidence shows that statins are also effective in ameliorating cerebral vasospasm, which occurs as sequelae of subarachnoid haemorrhage. This review focuses on the pleiotropic effects of statins, and the putative mechanisms involved in statin mediated attenuation of cerebral vasospasm.

Keywords

Cerebral vasospasm; subarachnoid haemorrhage; statin; pleiotropic effects; Akt; Rho; eNOS

Introduction

Pleiotropic effects of statins

In addition to their cholesterol lowering properties, statins are well known to exhibit many pleiotropic actions. Statins improve the integrity of endothelial cells and preserve the endothelial function [18]. They enhance the stability of atherosclerotic plaques, decrease oxidative stress and inflammation, and inhibit the thrombogenic response. Statins are also believed to have extrahepatic effects on the immune system, CNS, and bone [20]. Furthermore, statins induce apoptosis of vascular smooth muscle [9] and inhibit vascular smooth muscle proliferation [6,11].

Evidence suggests that many of these effects may be mediated by the inhibition of isoprenoids which serve as lipid attachments for intracellular signaling molecules [9,19]. Statins are likely to protect against cerebral vasospasm by improving endothelial function [17], inhibiting Rho-kinase signaling pathway in endothelial cells and vascular smooth muscle, and decreasing oxidative stress and inflammation [40].

Clinical studies

There is limited clinical information on the effects of statins in cerebral vasospasm. Two randomized clinical trials investigating statins as treatment for vasospasm after aneurysmal subarachnoid haemorrhage [21,37] tested the administration of 80 mg simvastatin within 48 h and 40 mg of pravastatin within 72 h of the clinical presentation of SAH, respectively. Each treatment regimen continued for 14 days and showed that acute treatment with statins after SAH is safe and ameliorates vasospasm. A prospective cohort study showed that prior statin users demonstrated lower transcranial doppler highest mean velocity values, and had a significantly lower incidence of delayed cerebral ischemia or stroke from vasospasm [31]. A

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retrospective study with SAH patients who received statin therapy for at least 1 month prior to SAH demonstrated an eleven fold decreased risk of developing symptomatic vasospasm after SAH [23]. On the other hand, however, another study reported that patients on statins before the onset of SAH had a higher risk for subarachnoid haemorrhage-related vasospasm [36]. The abrupt withdrawal of statins after SAH may have been responsible for the higher risk in this particular study.

Experimental studies

Preserving endothelial integrity

Restoration of eNOS activity which releases endothelial-derived nitric oxide— McGirt *et al.* recently showed that simvastatin (20 mg/kg) when administered as pretreatment for 14 days followed by 3 days treatment post SAH, ameliorated cerebral vasospasm with increased eNOS expression [24]. Another group of animals that received only the post treatment regimen also showed decreased vasospasm, however, without any associated increase in eNOS expression. The study, however, did not measure eNOS activity or elaborate upon the cellular mechanisms involved in statin induced eNOS upregulation in cerebral vasculature.

Our present understanding of signaling pathways involved in eNOS upregulation by statins is mostly provided by cardiovascular studies. Laufs *et al*. determined that statins upregulate eNOS expression by prolonging eNOS mRNA half-life but not eNOS gene transcription in human saphenous vein and aortic endothelial cell cultures [19].

Inhibition of Rho activation (geranylgeranylation)—Statins lead to the direct inhibition of geranylgeranyl-transferase or RhoA which leads to increased endothelial Akt phosphorylation [15]. Studies in cardiomyocytes have shown that statin inhibition of RhoA leads to increased eNOS expression through the activation of Akt [4,5,41]. It can be hypothesized that the same pathway may play a significant role in the effect of statins on cerebral vasculature during cerebral vasospasm.

Inhibition of caveolin—Caveolin-1 is a cholesterol binding protein that has been shown to bind to eNOS and inhibit its activity in the caveolae [3]. Pelat *et al*. revealed that rosuvastatin decreased cavelin-1 expression and promoted eNOS function in cardiac and aortic cells [32]. The inhibition of caveolin by statins in the cerebral endothelial cells may be a likely mechanism of prevention of cerebral vasospasm and must be further investigated.

Activation of phosphatidylinositol 3-kinase/protein kinase Akt (PI3K/Akt) pathway—Statins rapidly activate the protein kinase Akt in endothelial cells [15]. Wang *et al*. showed that treatment of human umbilical endothelial cells with pitavastatin induced eNOS phosphorylation at Ser-1177, activated Akt phosphorylation at Ser-473 in a time-and dose-dependent manner, and increased NO production [39]. Simvastatin reduced myocardial injury after acute ischemia and reperfusion in an NO- dependent manner by activating the PI3K/Akt pathway [41]. Thus statins may attenuate vasospasm by activating the PI3K/Akt pathway directly or through the inhibition of RhoA in cerebral endothelial cells. Further studies are required to examine this pathway in cerebral vasculature.

Antioxidant effects—Reactive oxygen species (ROS) contribute to vascular dysfunction in various ways, such as reducing the bio-availability of NO, impairing endothelium-dependent vasodilatation [13,14,27], endothelial cell growth, causing apoptosis or anoikis, stimulating endothelial cell migration, and activating adhesion molecules and inflammatory reaction [43]. Fluvastatin has been shown to have a strong free radical scavenging activity *in vitro*; it recovered endothelium-dependent relaxation responses to acetylcholine *in vivo* [35]. Statins

are known as an inhibitor of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase activity [29,42]. Erdos *et al*. showed that rosuvastatin improved cerebrovascular function in rats by inhibiting NADPH oxidase-dependent superoxide production [7]. The implications of the antioxidant effects of statins need to be studied with respect to cerebral vasospasm.

Inhibition of platelet aggregation—There is increased platelet consumption in patients presenting with cerebral vasospasm [12]. Platelet aggregation also plays an important role in subarachnoid clot formation. The nitric oxide mediated inhibition of platelet aggregation [34] after statin administration needs to be further explored.

Inhibit vascular inflammation—Statins have been suggested to have anti-inflammatory effects [38]. The anti-inflammatory mechanisms may involve the inhibition of adhesion molecules such as intercellular adhesion molecule-1 (ICAM-1) [28].

An *in vivo* report in rabbits has shown that simvastatin (40 mg/kg) administrated after SAH ameliorated basilar artery vasospasm and attenuated perivascular granulocyte (CD18 cell) migration [25].

Inhibit the expression of endothelin-1—Endothelin-1 is a well-known vasoconstrictor [8,22,33]. Simvastatin and atorvastatin inhibited pre-pro endothelin-1 mRNA expression in a concentration- and time-dependent fashion and reduced immunoreactive endothelin-1 levels in bovine aortic endothelial cells [10]. Fluvastatin also reduced the production of endothelin-1 and pre-pro endothelin-1 mRNA expression in human umbilical vein endothelial cells [30]. Endothelin-1 has been suggested as a putative spasmogen in cerebral vasospasm [16] and statins may be effective in decreasing endothelin-1.

Effects on vascular smooth muscle cell

Inhibition of the Rho/Rho kinase pathway—Treatment with simvastatin abolished Rho activation mediated by endothelin-1 in the endothelium-denuded rat aorta preparations [26]. Thus, statins may affect this pathway both in endothelial and vascular smooth muscle cells.

Inhibition of vascular smooth muscle proliferation—Borel *et al*. concluded that cellular proliferation and subsequent vessel wall thickening after SAH may contribute to the syndrome of delayed cerebral vasospasm [2]. Simvastatin inhibited the proliferation of rat aorta myocytes [6]. It also inhibited the migration of cultured porcine smooth muscle cells [11]. Thus, the inhibition of vascular smooth muscle proliferation by statins may be an important pathway in cerebral vasospasm.

Vascular smooth muscle apoptosis—Bochaton-Piallat *et al*. showed that apoptosis is an important mechanism in the regulation of intimal thickening [1]. Atorvastatin was reported to induce apoptosis of rat thoracic aorta smooth muscle cells [9]. The anti-apoptotic effects and mechanisms of statins need to be further investigated in cerebral vasospasm.

Future research direction

There are many studies about statins and their effects in the cardiovascular field. Much of this knowledge may be applicable to the understanding of cerebral vasospasm; however, there are limited studies showing this evidence. More *in vivo* evidence is needed to elucidate the role of statins in cerebral vasospasm and the underlying cellular mechanisms.

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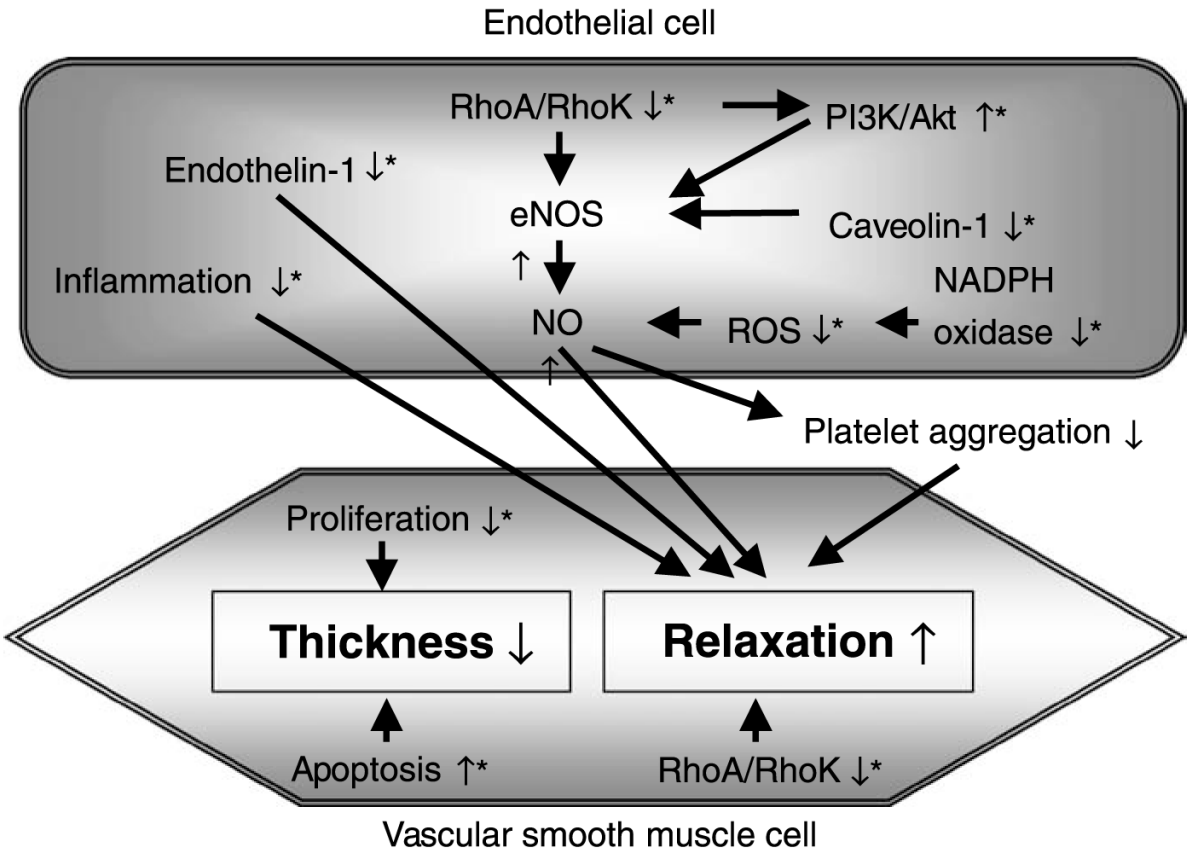

Fig. 1.

Proposed pathways of protection against cerebral vasospasm by statins. *eNOS* Endothelial nitric oxide synthase; *NADPH oxidase* nicotinamide adenine dinucleotide phosphate oxidase; *NO* nitric oxide; *PI3K* phosphatidyl-inositol-3 kinase; *RhoK* Rho kinase; *ROS* reactive oxygen species; ↑ upregulation; ↓ inhibition or down-regulation; *proposed targets of statins