Mechanisms of Statin Treatment in Cerebral Vasospasm

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Abstract 3-Hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitors, commonly known as statins, are widely used clinically for their lipid lowering properties. Recent experimental evidence shows that statins are also effective in ameliorating cerebral vasospasm, which occurs as sequelae of subarachnoid hemorrhage. This literature review focuses on the literature-based putative mechanisms involved in statin mediated attenuation of cerebral vasospasm, such as eNOS, vascular inflammation, apoptosis, especially the phosphatidylinositol 3-kinase/Akt (PI3K/Akt) pathway from our experimental study.

Keywords Statin · Cerebral vasospasm · Mechanism · PI3K · Akt · eNOS

Introduction

In addition to their cholesterol lowering effect, statins are well known to exhibit many pleiotropic actions. Statins improve the integrity of endothelial cells and preserve the endothelial function [8]. Statins are likely to protect against cerebral vasospasm by improving endothelial function [7], inhibiting Rho kinase [1], Endothelin-1 [6], Inflammation [12], NADPH oxidase [4], and Caveolin-1 [11] signaling pathway in endothelial cells and vascular smooth muscle. These statins' effects on each pathway have been shown mainly in the cardiovascular fields. To date, only five animal studies evaluated the effect of statins on cerebral vasospasm have been published (Table 1).

This statins' effect on cerebral vasospasm was shown by McGirt et al. in 2002 [9] for the first time. They showed that simvastatin pretreatment increased middle cerebral artery diameter and reduced neurological deficits with increasing eNOS protein simultaneously; however, simvastatin post-treatment caused a modest increase in middle cerebral artery diameter and reduced neurological deficits without increasing eNOS protein. They concluded that the mechanism may be attributable in part to eNOS upregulation. McGirt et al. also showed inflammation as the possible mechanism in 2006 [10]. They reported that basilar artery diameter was greater in simvastatin treated rabbits versus vehicle and simvastatin attenuated the increase in perivascular CD18-positive cells after SAH simultaneously. They concluded that subcutaneous administration of simvastatin after the onset of SAH attenuates perivascular granulocyte migration and ameliorates basilar artery vasospasm after experimental SAH in rabbits, and simvastatin may potentially serve as agents in the prevention of cerebral vasospasm after SAH.

Bulsara et al. evaluated amelioration of cerebral vasospasm during simultaneous upregulation of NO with simvastatin and immunosuppression with cyclosporin A in 2006 [2]. They showed that vasodilation greater than baseline is seen at day 10 in the simvastatin group, but the combination of simvastatin and cyclosporine does not ameliorate cerebral vasospasm in a canine model to a greater extent than simvastatin alone. They concluded that the results lead us to suggest that combined therapy with cyclosporine and simvastatin is not as efficacious in ameliorating vasospasm as simvastatin alone; interestingly, cyclosporin may limit the beneficial effect of simvastatin.

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Gao Cheng et al. explored apoptosis inhibiting effects of atorvastatin and its potential apoptotic signal pathway in 2009 [3]. They reported that ameliorating cerebral vasospasm was obtained after prophylactic use of atorvastatin with marked reducing TUNEL positive cells both in basilar artery and in brain cortex by atorvastatin; apoptosis-related proteins P53, apoptosis-inducing factor and cytochrome c (in hippocampus and basal cortex) were up-regulated after SAH while they were not affected by atorvastatin, and up-regulation of caspase-3 and caspase-8 (in hippocampus and basal cortex) after SAH was decreased by atorvastatin treatment both in mRNA and in protein levels. They concluded that the neuroprotective effects of atorvastatin after SAH may be related to its inhibition of caspase dependent proapoptotic pathway based on their results.

We investigated the role of the PI3K/Akt pathway and endothelial nitric oxide synthase (eNOS) in the cerebral vasculature in statin-mediated attenuation of cerebral vasospasm using wortmannin, a pharmacologic irreversible PI3K inhibitor, and a rat endovascular perforation model of SAH.

Materials and Methods

Simvastatin was administered intraperitoneally in two dosages (1 mg/kg and 20 mg/kg) at 0.5, 24, and 48 h after SAH. Morphology, such as diameter, perimeter, and wall thickness, with histology of the ipsilateral intracranial carotid artery (ICA); proteins, such as Akt, eNOS, phosphorylated Akt (pAkt), and phosphorylated eNOS (peNOS), with western blot and fluorescence immunohistochemical staining; and neurological deficits with a modification of the scoring system reported by Garcia et al. [5], were assessed at 24 and 72 h after SAH.

Results

SAH significantly decreased ICA diameter and perimeter while increasing wall thickness at both 24 and 72 h. High dosages of simvastatin prevented the reduction of ICA diameter and perimeter following SAH, and both high and low dosages significantly reduced wall thickness at 24 and 72 h. The effects of simvastatin were reversed by wortmannin. High-dosage simvastatin increased pAkt and peNOS (phosphorylated forms) levels without increasing Akt and eNOS expression when compared with the SAH group. This treatment also improved neurological deficits at 24 and 72 h. Simvastatin did not induce changes in protein levels in the absence of SAH, as both vehicle and simvastatin treated shams at equal levels. This study elucidates the critical role of the PI3K activation leading to phosphorylation of Akt and

Table 1 Published animal studies evaluating the effect of statins on cerebral vasospasm

Authors and year	Statin used	Model	Sample size	Vasospasm criteria	Statin therapy	Statin effect	Mechanism
McGirt et al. (2002)	Simvastatin	Mice, endovascular perforation	34 statin, 36 nonstatin	MCA diameter at necropsy at 72 h	20 mg/kg s.c. (daily for 14 days pre-SAH)	Increased MCA diameter	eNOS upregulation
McGirt et al. (2006)	Simvastatin	Rabbit, injection	5 statin, 5 nonstatin	Cross-section of BA at 72 h after SAH	40 mg/kg s.c. (30 min, 24 h, 48 h postSAH)	Increased BA diameter	Attenuates perivascular granulocyte migration
Bulsara et al. (2006)	Simvastatin	Dog, double injection	4 statin, 5 nonstatin	BA diameter on angiography at 3, 7, 10 days after SAH	20 mg/kg orally (daily for 10 days postSAH)	Increased BA diameter	–
Sugawara et al. (2008)	Simvastatin	Rat, endovascular perforation	35 statin, 45 nonstatin	Cross-section of IC at 24 h and 72 h after SAH	1 mg/kg, 20 mg/kg i.p. (30 min, 24 h, 48 h postSAH)	Ameliorated cerebral vasospasm	Upregulated PI3K/Akt/eNOS pathway
Gao Cheng et al. (2009)	Atorvastatin	Rat, endovascular perforation	16 statin, 16 nonstatin	Cross-section of BA at 24 h after SAH	20 mg/kg orally (daily for 15 days preSAH)	Ameliorated cerebral vasospasm	Reduced the expression of cleaved caspase-3 and caspase-8

eNOS in simvastatin-mediated attenuation of cerebral vaso-spasm after SAH.

Conclusion

This study showed that PI3K activation, leading to phos-phorylation of Akt and eNOS by statin, may be one of the important roles in simvastatin-mediated attenuation of cere-bral vasospasm after SAH. Further investigation of proposed pathway is needed to clear the mechanisms of cerebral vasospasm after SAH.

Conflict of interest statement We declare that we have no con-flict of interest.

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