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ATORVASTATIN IN CEREBRAL CAVERNOUS MALFORMATION: ELUCIDATING ROCK INHIBITION AND LIPID-LOWERING MECHANISMS FOR THERAPEUTIC REPURPOSING

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Abstract

Cerebral cavernous malformations (CCMs) are vascular abnormalities in the central nervous system that can lead to seizures, haemorrhagic stroke, and neurological deficits. Emerging evidence implicates the RhoA/ROCK signaling pathway in CCM pathogenesis, where its hyper activation disrupts endothelial junctions and promotes vascular leakage. Atorvastatin, a widely used lipid-lowering agent has demonstrated inhibitory effects on RhoA prenylation and downstream ROCK activity, offering endothelial-stabilizing and anti-inflammatory benefits. Preclinical models and early clinical trials suggest that atorvastatin reduces lesion burden and improves vascular integrity in CCMs. Given its favorable safety profile and dual mechanism of action, atorvastatin presents a promising candidate for therapeutic repurposing in CCM management.

Keywords

Cerebral cavernous malformations, RhoA/ROCK signaling, Atorvastatin, Endothelial dysfunction, Drug repurposing

Cerebral cavernous malformations (CCMs) are vascular anomalies of the central nervous system characterized by abnormally enlarged capillary cavities, which can lead to seizures, haemorrhagic stroke, and neurological deficits (1). Recent research has highlighted the central role of RhoA and its downstream effector Rho-associated coiled-coil containing kinase (ROCK) in the pathogenesis of CCM. Hyperactivation of the RhoA/ROCK signaling pathway contributes to endothelial cytoskeletal rearrangement, cell junction disassembly, and increased vascular leakage, all of which exacerbate CCM lesion development and progression. As such, ROCK inhibitors have emerged as potential therapeutic agents. However, selective ROCK inhibitors are not widely available for long-term clinical use due to limited safety and pharmacokinetic data (2).

Atorvastatin, a widely used HMG-CoA reductase inhibitor for hypercholesterolemia, has demonstrated pleiotropic effects that extend beyond lipid-lowering (3). One of its key non-lipid actions includes the downregulation of RhoA/ROCK signaling. By inhibiting the prenylation of RhoA, atorvastatin prevents its proper membrane localization and activation, thereby indirectly suppressing ROCK activity. This action can stabilize endothelial junctions, reduce oxidative stress, and attenuate inflammatory responses factors crucial in limiting CCM pathogenesis (4) (table 1).

Preclinical studies in mouse models of CCM, particularly those with endothelial-specific knockout of CCM genes, have shown that atorvastatin treatment leads to a significant reduction in lesion burden, improved vascular barrier function, and decreased expression of inflammatory and permeability markers (5). Notably, these effects were

observed at clinically relevant doses, suggesting a strong translational potential. A pilot human clinical trial has explored the safety and feasibility of statin therapy in CCM patients, providing preliminary support for this approach, though larger trials are needed to confirm efficacy (6).

RhoA signaling pathway and its integration with calcium-mediated mechanisms involved in smooth muscle contraction and cytoskeletal dynamics. Upon stimulation by agents such as MCh (methacholine), 5-HT (serotonin), or histamine, the H_2 receptor activates the Gαq protein, which subsequently stimulates phospholipase Cβ (PLCβ). This leads to the generation of inositol triphosphate (IP_3), promoting the release of Ca^{2+} from the sarcoplasmic reticulum. Concurrently, Ca^{2+} influx through voltage-gated calcium channels (e.g., activated by KCl) increases intracellular Ca^{2+} levels. The rise in Ca^{2+} activates calmodulin (CaM), which stimulates myosin light chain kinase (MLCK), leading to phosphorylation of the myosin light chain and facilitating actin-myosin interaction for contraction (Figure 1) (7) (8).

Simultaneously, the RhoA/ROCK pathway operates independently of Ca^{2+} to regulate contraction. RhoA activation stimulates ROCK (Rho-associated coiled-coil kinase), which inhibits myosin light chain phosphatase (MLCP), enhancing MLCK-mediated phosphorylation of myosin. This dual regulation via Ca^{2+}/CaM/MLCK and RhoA/ROCK ensures sustained contractile responses and cytoskeletal rearrangements. In pathological conditions such as cerebral cavernous malformations (CCMs), dysregulated RhoA/ROCK signaling contributes to endothelial barrier dysfunction, making this pathway a key target for therapeutic intervention using agents like atorvastatin that inhibit RhoA prenylation and ROCK activity (9) (10).

In addition to its ROCK-inhibitory properties, atorvastatin's cardiovascular benefits through lipid-lowering may provide secondary advantages by improving overall vascular health and reducing comorbid risks. The established safety profile, affordability, and global availability of atorvastatin make it a compelling candidate for repurposing in CCM, particularly for patients who are poor surgical candidates or have multifocal or inaccessible lesions (11) (12).

In conclusion, the dual action of atorvastatin as a lipid-lowering agent and a ROCK pathway modulator offers a novel therapeutic strategy for managing cerebral cavernous malformations. By targeting both systemic vascular health and the specific molecular mechanisms underpinning CCM pathology, atorvastatin holds promise for non-invasive, long-term disease control. Future large-scale, randomized controlled trials are urgently needed to evaluate its therapeutic potential and establish guidelines for clinical application in CCM patients.

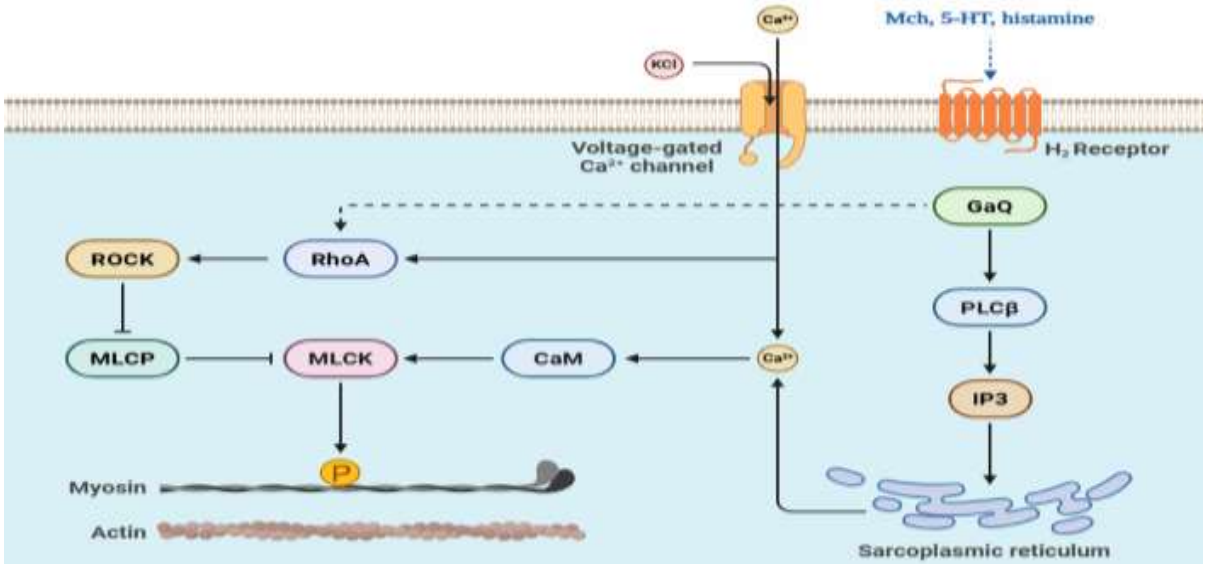

Figure 1 the schematic representation of smooth muscle contraction pathways. Activation of H_2 receptors by agonists (MCh, 5-HT, histamine) triggers the Gαq-PLCβ-IP_3 cascade, increasing intracellular Ca^{2+} via sarcoplasmic reticulum release and voltage-gated Ca^{2+} channels. Ca^{2+}-bound calmodulin activates MLCK, leading to myosin phosphorylation. Independently, the RhoA/ROCK pathway inhibits MLCP, enhancing contractility and cytoskeletal rearrangement.

Mechanism of Action	Molecular Pathway	Effect on Pathophysiology	Therapeutic Outcome in CCMs	References
ROCK Pathway Inhibition	RhoA/ROCK	Inhibits RhoA prenylation reduces ROCK activation	Restores endothelial barrier integrity; limits lesion development	(2), (4), (5)
Myosin Light Chain Modulation	MLCP / MLCK	Prevents ROCK-mediated MLCP inhibition normalizes cytoskeletal tension	Stabilizes endothelial junctions; reduces vascular permeability	(7), (8), (9)
Anti-inflammatory Effects	NF-κB, ICAM-1, VCAM-1	Decreases pro-inflammatory cytokines and adhesion molecules	Attenuates endothelial inflammation and leukocyte adhesion	(4), (5), (10)
Antioxidant Activity	ROS-scavenging, NADPH oxidase	Reduces oxidative stress and endothelial damage	Protects against lesion progression and vascular dysfunction	(4), (5)
Lipid-Lowering Action	HMG-CoA reductase	Reduces LDL-C and improves lipid profile	Improves overall cerebrovascular health; decreases secondary risks	(3), (11), (12)
Vascular Remodeling	eNOS upregulation	Enhances nitric oxide (NO) bioavailability	Improves vasodilation and reduces endothelial stiffness	(5), (10)
Neurovascular Protection	Blood-brain barrier (BBB) integrity	Improves tight junction protein expression	Reduces risk of hemorrhagic stroke and neurological complications	(5), (6), (9)

Table 1 this table summarizes the multifaceted mechanisms by which atorvastatin exerts therapeutic effects in cerebral cavernous malformations (CCMs). It highlights molecular targets, corresponding pathophysiological effects, and clinical outcomes. The dual action on lipid-lowering and ROCK pathway inhibition supports its potential for repurposing in CCM therapy.

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