Rho-Kinase
A Potential Link Between Hypercholesterolemia and Abnormal Vascular Smooth Muscle Contraction

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Although elevated serum cholesterol levels and hypertension are independent risk factors for cardiovascular disease, far too often they are manifested in the same individual. Whether this is a coincidental finding between 2 highly prevalent risk factors or perhaps because of some mechanistic link between these 2 processes is unclear. Regardless, the concomitant treatment of hypercholesterolemia and hypertension has yielded additive and possibly synergistic reductions in cardiovascular events.

Previous studies attempting to link hypercholesterolemia with abnormal vascular smooth muscle (SMC) contractions have focused on the endothelium. Hypercholesterolemia and atherosclerosis impair the production and/or availability of endothelium-derived NO, leading to endothelial dysfunction and abnormal vascular reactivity. Indeed, acute lowering of serum cholesterol with low-density lipoprotein-apheresis or with statin therapy improves endothelium-dependent relaxations.

In the present study, Morikage et al extend the effects of cholesterol on vascular reactivity to changes in SMC contractions. They showed that elevated serum cholesterol levels were associated with increased calcium sensitization of SMC through the sphingosylphosphorylcholine (SPC)/Rho-kinase (ROCK)-mediated pathway in humans and rabbits. This enhanced SMC contraction was observed only with ROCK activator SPC and not with phenylephrine or potassium; was accompanied by minimal changes in intracellular calcium concentration; and was unaffected by addition of the eNOS inhibitor, L-arginine, or removal of the endothelium. However, the SMC contraction was abolished by addition of the ROCK inhibitor, Y27632, or by applying a dominant-negative mutant of ROCK (dn-ROK) to the cytosol of permeabilized SMC. Interestingly, Y27632 and dn-ROK had no effect on calcium-dependent SMC contraction, suggesting calcium sensitization of SMC rather than calcium-induced SMC contraction by cholesterol. The authors conclude that cholesterol enhances calcium sensitivity of SMC to SPC via ROCK and suggest that this may be a mechanism by which hypercholesterolemia could precipitate vasospasms or perhaps increase the risk for hypertension.

ROCK plays a central role in diverse cellular functions such as SMC contraction, stress fiber formation, and cell migration and proliferation. Presently, 2 ROCK isoforms have been identified, ROCK1 and ROCK2. ROCK1 and ROCK2 share an overall 65% homology in amino-acid sequence and 92% homology in their kinase domains. Thus, pharmacological inhibitors of ROCK such as Y-27632, fasudil (HA1077), and hydroxyfasudil, which target their ATP-dependent kinase domains, can inhibit both ROCK1 and ROCK2. Furthermore, at higher concentrations, Y-27632 can inhibit protein kinase C–related kinase-2, protein kinase N, and citron kinase, whereas fasudil can inhibit protein kinase A and protein kinase C. Physiologically, ROCKs can be activated by serum lysophospholipids such as lysophosphatidic acid, sphingosine-1 phosphate, and SPC, which stimulate RhoGTPases and lead to the formation of active GTP-bound Rho GTPases. ROCKs are serine-threonine protein kinases and immediate downstream targets of RhoGTPases. They control the assembly of the actin cytoskeleton, increase calcium sensitization, and enhance contractility by phosphorylating a variety of proteins, such as myosin light chain phosphatase, LIM kinases, adducin, and ezrin-radixin-moesin proteins. Indeed, inhibition of ROCK prevents cerebral ischemia, coronary vasospasm, and ath- erosclerosis. Thus, it is likely that SPC-induced calcium sensitization and the subsequent enhanced contractions of SMC, as demonstrated in the present study by Morikage et al, is mediated by ROCK.
process. Thus, cholesterol primes SMC in terms of enhancing ROCK-mediated calcium sensitivity by facilitating ROCK translocation to cholesterol-enriched lipid rafts. Clinically, calcium sensitization of SMC by ROCK is observed in patients with hypertension,22,23 and as shown in the present study, in patients with hypercholesterolemia.10

Although cholesterol may be necessary for ROCK-mediated effects, several questions remain. Because most studies have used ROCK inhibitors, which cannot discriminate between ROCK1 and ROCK2, it is unknown what the relative importance of ROCK isoforms is in calcium sensitization of SMC. Perhaps future studies with isoform-specific ROCK inhibitors or ROCK-deficient mice will shed light on this matter. Furthermore, it is not known whether patients who have lower serum cholesterol levels or who received lipid-lowering therapy have decreased membrane ROCK and lipid rafts, and if so, whether this is associated with decreased blood pressure. Although blood pressure was not monitored as frequently in previous lipid-lowering trials with statins as with hypertensive trials, none of lipid-lowering trials have ever shown a clear reduction in blood pressure with statin therapy. Thus, further studies are required to determine whether the priming effect of cholesterol on ROCK-mediated calcium sensitivity of SMC contributes clinically to higher blood pressure. Unless these questions are addressed, it remains to be determined whether ROCK is an important therapeutic target for hypertension in patients with and without hypercholesterolemia.

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13. Ohara Y, Peterson TE, Harrison DG. Hypercholesterolemia increases endothelial calcium sensitivity by facilitating ROCK translocation to cholesterol-enriched lipid rafts. Clinically, calcium sensitization of SMC by ROCK is observed in patients with hypertension,22,23 and as shown in the present study, in patients with hypercholesterolemia.10

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