OPINION ARTICLE

The Cardiovascular System and Pleiotropic Effects of Statins

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DESCRIPTION

Cardiovascular illnesses continue to be the major cause of death globally. Coronary atherosclerosis is caused by a complicated interaction of metabolic and inflammatory mechanisms. Atherogenesis is caused by apolipoprotein B containing lipoproteins, specifically Low-Density Lipoprotein Cholesterol (LDL-C), according to mechanistic and genetic data. Statins, also known as 3-hydroxy-methylglutaryl coenzyme A reductase inhibitors, reduce cholesterol production while also lowering blood LDL-C and triglyceride levels. The efficacy of statins for both primary and secondary prevention of Coronary Heart Disease (CHD) has been proven in clinical trials. Statins are thought to have both LDL-C-dependent and LDL-C-independent (or pleiotropic) effects. Clinical studies demonstrate statin benefits in conditions not obviously linked to LDL-C, however some of the outcomes may be due to direct cholesterol lowering. Lower gallstone development may be attributed to decreased hepatic cholesterol generation; decreased cholesterol reduces platelet aggregation and may result in less deep vein thrombosis; and decreased cholesterol may improve renal disease progression by decreasing renal artery atherosclerosis. Given the overwhelming benefits of cholesterol lowering in reducing cardiovascular events, the clinical importance of statins' pleiotropic effects in the cardiovascular system remains debatable.

Pharmacokinetic properties of statins

HMG-CoA reductase generates mevalonate and is the rate-limiting enzyme for cholesterol production in the liver; statins inhibit it competitively and reversibly *via* their lactone ring and side chains, which aid in binding to the enzyme's active site. Statins, which were discovered and have been on the market since 1987 are to be a fungal metabolites which vary in lipophilicity, elimination half-lives, and strength.

Lipophilic statins primarily traverse cell membranes by passive diffusion, whereas pravastatin and rosuvastatin need active carrier-mediated transport *via* Organic Anion Transporting Polypeptide (OATP) 1B1 and are more selective for hepatic tissues. Similar transporters, such as OATP 1A4 and OATP 2B1, exist in different tissues, although their efficacy in carrying hydrophilic statins is unknown. The amounts of statins and mevalonate in various cell types remain unknown. It is uncertain if statins' pleiotropic effects are attributable to hepatic or non-hepatic effects of isoprenoid inhibition.

It is uncertain whether statins have effects apart than inhibiting mevalonate production. According to one study, statins can bind to an allosteric location inside the 2 integrin Leukocyte Function associated Antigen-1 (LFA-1). LFA-1 regulates leukocyte trafficking and T cell activation by binding to Intercellular Adhesion Molecule-1 (ICAM-1). ICAM-1 is required for monocyte adherence to the endothelium and is a biomarker for coronary events that is decreased by atorvastatin. However, no statin has been shown to produce consistent mevalonate-independent effects.

CONCLUSION

Given the cell culture and animal studies, as well as the indirect evidence from clinical trials, it is critical to determine whether the non-LDL-C lowering effects of statins can be replicated by other cholesterol-lowering therapies or agents that act downstream of isoprenoid synthesis, such as squalene synthase inhibitors. The concept of statin pleiotropy has opened the door to testing and targeting alternative non-lipid-lowering signalling pathways that may influence cardiovascular disease. Anti-inflammatory agents, such as canakinumab and methotrexate, are currently being evaluated in secondary prevention trials as supplementary therapy to cholesterol lowering. Furthermore, the ROCK inhibitors fasudil and ripasudil, which are currently licenced in Japan for the treatment of cerebral vasospasm following subarachnoid haemorrhage and glaucoma, may be of interest as potential therapeutics for lowering cardiovascular disorders. Finally, PCSK9i may assist give evidence for statin pleiotropy, particularly when low-dose PCSK9i is compared to high-potency statins with equal LDL-C reduction.

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