The role of mitochondria and K_{ATP} channels in the vasodilatation response to simvastatin: Comparison with the effects of simvastatin in pancreatic β-cells.

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Abstract

Clinical trials have established the efficacy and safety of the 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins) in lowering cardiovascular morbidity and mortality in patients with and without coronary artery diseases. Traditionally, the beneficial effects of statins have been ascribed entirely to their ability to lower serum cholesterol. However, evidence indicates that statins may exert cholesterol-independent or pleiotropic effects. As well as reducing plasma cholesterol levels, statins induce acute vasorelaxation which may contribute to the overall benefits of statins in the treatment of cardiovascular disease. The mechanism underlying this relaxation is unknown. Statins have been shown to alter mitochondrial function. Therefore, the aim of this study was to determine the role of the mitochondria in the relaxation to statins. Changes in rhodamine 123 fluorescence showed that simvastatin, but not pravastatin, depolarized the membrane potential of mitochondria in both isolated smooth muscle cells and intact blood vessels. As simvastatin, but not pravastatin, causes relaxation of the porcine coronary artery, this could be due to this effect on mitochondria. Mitochondria are known as the energy generating centre of the cells. However, there is growing consensus that mitochondria actively participate in intracellular signalling, such as production of reactive oxygen species (ROS) and regulation of the intracellular Ca^{2+} concentration. Moreover, ROS could play an important supportive role in a variety of vascular cell signalling processes, including activation of nitric oxide synthase (NOS), modulation of intracellular Ca^{2+}, and AMP kinase activation. Therefore, this study investigated whether the relaxation to the lipophilic statin simvastatin is due to an effect on the mitochondria. Relaxation of porcine coronary artery segments by statins was measured using isolated tissue baths. Simvastatin, but not pravastatin, produced a slow relaxation of the coronary artery, which was independent of K^+ channel activation, nitric oxide, cyclo-oxygenase, or the endothelium. The relaxation was attenuated by the mitochondrial complex I inhibitor rotenone and the complex III inhibitor myxothiazol, or a combination of the two. Simvastatin inhibited

calcium-induced contractile responses, and this inhibition was partially reversed by incubation with the complex I inhibitor rotenone suggesting that mitochondrial function is required for the effect of simvastatin on calcium influx. The effect of mitochondrial complex III inhibitor, antimycin A, was examined as a comparison with simvastatin. Antimycin A induced porcine coronary relaxation and inhibited Ca^{2+} influx in isolated porcine coronary smooth muscle cells.

Evidence from a number of clinical trials highlights a potential association between treatment with lipophilic statins and increased risk of development of diabetes. The close connection between energy metabolism and insulin secretion in pancreatic β-cells suggests that the glycaemic effects of simvastatin may also result from a direct mitochondrial action with reduction in insulin secretion and, hence, result in a reduced control of plasma glucose levels. Although simvastatin depolarized mitochondria in pancreatic *β*-cells, it also directly inhibited K_{ATP} channels. Pravastatin, on the other hand, had no effect on either measurement, suggesting that these phenomena relate to the lipophilicity of the compounds. The inhibition of K_{ATP} channels by simvastatin is likely to underlie the increase in insulin secretion observed within days of simvastatin treatment. On the other hand, the effects on mitochondrial membrane potential may be detrimental, particularly with chronic treatment, although further studies are required in order to determine whether this plays a role in the increased risk of diabetes observed with lipophilic statins.

Overall, our results demonstrated that simvastatin alters mitochondrial membrane potential in vascular smooth muscle cells and pancreatic β-cells. The relaxation to simvastatin in the porcine coronary artery is dependent, in part, upon mitochondrial activity. Alteration of mitochondrial membrane potential by simvastatin may lead to inhibition of calcium influx, hence stimulation of relaxation. On the other hand, the effects on mitochondrial membrane potential in pancreatic β-cell may be detrimental, particularly with chronic treatment due to the increased risk of diabetes observed with lipophilic statins.