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Effect Of Statins On Mitochondrial Membrane Potential And K_{ATP} Activity In Mouse Primary β-Cells

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The role of statins in prevention of cardiovascular diseases is well established. However, evidence from a number of clinical trials highlight a potential association between treatment with lipophilic statins and increased risk of development of diabetes (Bellia et al. 2012, Sattar et al. 2012). The mechanism by which statins increase the risk of development of diabetes is unknown. Previous studies have demonstrated that simvastatin causes mitochondrial depolarization in skeletal muscle (Sirvent. et al. 2005) and hepatocytes (Abdoliet et al. 2013). The close connection between energy metabolism and insulin secretion in β-Cells suggests that the glycaemic affects 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. On the other hand simvastatin has also been shown to increase basal insulin secretion (Kon Koh K et al. 2009, Ishkiwa et al. 2006). ATP-sensitive potassium (K_{ATP}) channels play a critical role in regulation of insulin secretion (Nichols, 2006), therefore the aim of this present work was to identify the effects of statins on both mitochondrial potential ($\Delta\psi_m$) and K_{ATP} channel activity in pancreatic β-cells.

β-cells isolated from NMRI mouse pancreas by collagenase digestion were loaded with 10μg ml^{-1} rhodamine123 at 37 °C for 10 min in Hanks solution (5 *m*M glucose). Changes in fluorescence of Rh123 (excitation 480nm, emission 530nm) during perfusion with 10μM simvastatin was measured at 32 °C. Control cells were perfused with vehicle only (0.1% DMSO). As a further comparison, some cells were perfused with the hydrophilic statin, pravastatin. The signal was calibrated with 1μM FCCP after 10 min superfusion with statin. Single-channel current recordings were carried out in cell-attached and inside-out configurations at a pipette potential of 0 mV or +70 mV respectively. All electrophysiological experiments were performed at room temperature (22°C).

Simvastatin (10μM) caused disruption of $\Delta\psi_m$ as evidenced by a 90.2 ± 9.0% increase in Rh123 fluorescence (n=7, $p<0.001$ unpaired t test). Total K_{ATP} channel activity obtained before and after simvastatin exposure indicated that simvastatin reduced K_{ATP} channel activity in cell attached 71 ± 16% (n=6, $p<0.05$) and inside-out patch 77± 8% (n=8, $p<0.01$). Pravastatin (10μM) has no effect on the parameters tested.

Although simvastatin depolarizes 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 by others (Ishkiwa et al. 2006). 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.

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