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Research Article

Simvastatin Inhibits L-Type Ca^{2+}-Channel Activity Through Impairment of Mitochondrial Function

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ABSTRACT

Plasma membrane ion channels and mitochondrial electron transport complexes (mETC) are recognized "off targets" for certain drugs. Simvastatin is one such drug, a lipophilic statin used to treat hypercholesterolemia, but which is also associated with adverse effects like myopathy and increased risk of glucose intolerance. Such myopathy is thought to arise through adverse actions of simvastatin on skeletal muscle mETC and mitochondrial respiration. In this study, we investigated whether the glucose intolerance associated with simvastatin is also mediated via adverse effects on mETC in pancreatic beta-cells because mitochondrial respiration underlies insulin secretion from these cells, an effect in part mediated by promotion of Ca^{2+} influx via opening of voltage-gated Ca^{2+} channels (VGCCs). We used murine pancreatic beta-cells to investigate these ideas. Mitochondrial membrane potential, oxygen consumption, and ATP-sensitive-K^+-channel activity were monitored as markers of mETC activity, respiration, and cellular ATP/ADP ratio respectively; Ca^{2+} channel activity and Ca^{2+} influx were also measured. In intact beta-cells, simvastatin inhibited oxidative respiration (IC_{50} approximately 3 μM) and mETC ($1 < IC_{50} < 10$ μM), effects expected to impair VGCC opening. Consistent with this idea simvastatin > 0.1 μM reversed activation of VGCCs by glucose but had no significant effect in the sugar's absence. The VGCC effects were mimicked by rotenone which also decreased respiration and ATP/ADP. This study demonstrates modulation of beta-cell VGCC activity by mitochondrial respiration and their sensitivity to mETC inhibitors. This reveals a novel outcome for the action of drugs like simvastatin for which mETC is an "off target".

Key words: simvastatin; mitochondria; beta-cell; L-type Ca^{2+} channel.

Mitochondrial electron transport (mETC) complexes (Hargreaves *et al.*, 2016; Nadanaciva *et al.*, 2007; Wallace, 2008) and plasma membrane ion channels are well recognized "off targets" for drugs (Lynch *et al.*, 2017; Real *et al.*, 2018). For some drugs, both moieties may be "off targets;" a situation which confounds the interpretation of adverse drug effects both in the clinic and laboratory. An example of this occurs in insulin secreting beta-cells with the 3-hydroxy-3-methyl glutaryl coenzyme A reductase inhibitor, simvastatin, a lipophilic drug used to treat hypercholesteremia. Such pluripotent effects of simvastatin complicates the mechanistic understanding of how adverse effects arise in the clinic; for example the association between lipophilic statin use and increased risk of glucose intolerance and diabetes (Cederberg *et al.*, 2015; Sattar *et al.*, 2010).

Insulin secretion from the pancreatic beta-cell is promoted by glucose via oxidative metabolism (Affourtit *et al.*, 2018; Maechler *et al.*, 2010). The resultant increase in cytosolic ATP/ADP ratio blocks the activity of ATP-sensitive K^+ channels (K_{ATP}) which leads to depolarization of the plasma-membrane potential (Vm) and activation of voltage-gated Ca^{2+} channels (VGCCs). Ca^{2+} influx through VGCCs promotes insulin secretion (Ashcroft *et al.*, 1994). In pancreatic beta-cells mitochondrial respiration is shown to enhance L-type VGCC activity (Smith *et al.*, 1989).

Several "off targets" for simvastatin are recognized in beta-cells. For example chronic simvastatin impairs mitochondrial respiration and ATP production (Urbano *et al.*, 2017; Zhou *et al.*, 2014). Such chronic effects are mediated by a decrease in activity of the mETC complexes (Urbano *et al.*, 2017) with an