Evidence for functional coupling between the mitochondria and the L-type calcium channel in the heart

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Transient exposure of ventricular myocytes to hydrogen peroxide leads to an increase in L-type calcium channel basal current and increased superoxide production by the mitochondria. Activation of the channel with the dihydropyridine receptor agonist Bay K(-) mimics this response. Enhanced superoxide production occurs with enhanced calcium uptake into the mitochondria. However, superoxide is also produced when the mitochondrial membrane potential is increased. We examined the relationship between activation of the L-type calcium channel and regulation of the mitochondrial membrane potential. Ventricular myocytes were isolated from hearts excised from anesthetised guinea-pigs. Activation of the L-type calcium channel with Bay K(-) or 45 mM KCl caused a modest but statistically significant increase in mitochondrial membrane potential assessed with the fluorescent indicator JC-1. The increase in membrane potential occurred in the absence of extracellular calcium and presence of the Na/H exchanger inhibitor amiloride and Na^+ channel inhibitor tetrodotoxin. In addition Ru360, an inhibitor of the mitochondrial calcium uniporter did not prevent the increase in mitochondrial membrane potential induced by 45 mM KCl. Regulation of channel activation is mediated through the auxiliary β subunit that is also tethered to the cytoskeleton. Depolymerisation of F actin with latrunculin A prevented the increase in mitochondrial membrane potential by 45 mM KCl but did not affect the increase in superoxide production by the mitochondria induced by 1 mM caffeine. We conclude that the L-type calcium channel can regulate mitochondrial function. A functional coupling of the channel with the mitochondria may assist with regulating ATP production on a beat to beat basis.