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MEETING ABSTRACT Open Access

# The effects of mitochondrial $Ca^{2+}$ transport on intracellular $Ca^{2+}$ waves in cardiomyocytes

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## Background

Recent studies have implicated that mitochondria play important roles in intracellular $Ca^{2+}$ homeostasis of cardiac myocytes. The major pathways for mitochondrial $Ca^{2+}$ transport include mitochondrial $Ca^{2+}$ uniporter and $Na^+/Ca^{2+}$ exchanger, as well as mitochondrial permeability transition pore (mPTP) under certain pathophysiological conditions. However, it is still unclear if mitochondrial $Ca^{2+}$ flux can affect the generation of $Ca^{2+}$ waves and triggered activities in cardiomyocytes.

## Methods and results

Cytosolic $Ca^{2+}$ ($Ca_i^{2+}$) was imaged in fluo-4-AM loaded ventricular myocytes isolated from mice. Spontaneous SR $Ca^{2+}$ release and $Ca^{2+}$ waves (CaWs) were induced in the presence of high external $Ca^{2+}$ ($Ca_o^{2+}$, 4 mM). The protonophore carbonyl cyanide *p* - (trifluoromethoxy) phenylhydrazone (FCCP) reversibly raised basal $Ca_i^{2+}$ levels in the presence, as well as absence of $Ca_o^{2+}$, suggesting $Ca^{2+}$ release from intracellular stores. Mitochondrial membrane potential ($\Delta\Psi m$) was monitored by TMRM fluorescence. FCCP at 0.01- 0.1 μM, which partially depolarized $\Delta\Psi m$, increased the frequency and amplitude of CaWs in a dose-dependent manner. Simultaneous recording of cell membrane potentials showed the augmentation of delayed after depolarization amplitudes and frequencies, and induction of triggered action potentials. On the contrary, FCCP at higher concentrations (>0.5 μM), which completely dissipated $\Delta\Psi m$, eliminated CaWs while the basal $Ca_i^{2+}$ remained high. The cease of CaWs was most likely due to the reduction of SR $Ca^{2+}$ content as evaluated by rapid exposure to10 mM caffeine. Blocking sarcolemmal $Na^+$-$Ca^{2+}$ exchanger by substituting $Na^+$ with $Li^+$ in the perfusant further elevated basal $Ca_i^{2+}$ and restored CaWs. The effect of FCCP on CaWs was mimicked by antimycin A (an electron transport chain inhibitor disrupting $\Delta\Psi m$) or Ru360 (a mitochondrial $Ca^{2+}$ uniporter inhibitor), but not by oligomycin (an ATP synthase inhibitor) or iodoacetic acid (a glycolytic inhibitor), excluding the contribution of intracellular ATP levels. The effects of FCCP on CaWs were counteracted by the mitochondrial permeability transition pore blocker cyclosporine A, or the mitochondrial $Ca^{2+}$ uniporter activator kaempferol.

## Conclusions

Mitochondrial $Ca^{2+}$ release and uptake control plasma $Ca^{2+}$ levels and plays an important role in regulation of intracellular CaWs and arrhythmogenesis.

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