SYNERGISM BETWEEN CA^{2+} AND REACTIVE OXYGEN SPECIES (ROS) ON MITOCHONDRIAL PERMEABILITY TRANSITION: A SYSTEMATIC STUDY USING SUCCINATE-ENERGIZED MITOCHONDRIA

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Mitochondrial Permeability Transition (MPT), elicited by Ca^{2+} in different conditions and characterized by cyclosporine A (CsA)-sensitive mitochondrial swelling, has been often associated with exhaustion of antioxidant defense mechanisms of membrane protein thiols. We performed a systematic study of this process using succinate-energized mitochondria exposed to Ca^{2+} and/or *t*-butylhydroperoxide (*t*-BOOH). MPT started to be shown at around 25 µM Ca^{2+} or at 25 µM *t*-BOOH in the presence of at least 10 µM Ca^{2+}; it reached a maximum at around 250 µM. Ca^{2+} predominantly changed energy-linked parameters like respiration, membrane potential and ATP levels, while *t*-BOOH changed mostly oxidative stress-linked processes like GSH and NAD(P)H oxidation. The extent of swelling did not run in parallel with the extent of membrane protein thiol oxidation. Our hypothesis for the synergism between Ca^{2+} and ROS on MPT is as follows: Ca^{2+} reveals critical protein thiols on the mitochondrial membrane. At high Ca^{2+} levels relatively high amounts of these groups are available to oxidation that occurs even in presence of the very low levels of ROS generated by normally respiring mitochondria. In contrast, at low Ca^{2+} levels only relatively small amounts of those groups are available, and high levels of accumulated ROS are required to their oxidation and MPT induction.

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