PHENOTHIAZINES INDUCE MITOCHONDRIAL PERMEABILIZATION AND CYT *C* RELEASE IN ISOLATED MITOCHONDRIA

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Mitochondrial permeability transition (MPT) is a process Ca^{2+}-dependent and CsA-sensitive characterized by the opening of the PTP and consequently mitochondrial swelling, uncoupling, loss of Ca^{2+} homeostasis and release of proapoptotic proteins such as cytochrome *c*, resulting in cell death. At low concentrations (10 µM), phenothiazines (PTZ) exhibited antioxidant properties and they were able to inhibit the MPT/cytochrome *c* release in isolated mitochondria. However, it was demonstrated the PTZ-induced cell death in tumor cell lines. We studied PTZ-induced MPT in isolated mitochondria at a higher concentration range. PTZ (100 µM) induced a mitochondrial permeabilization characterized by swelling, ∆? dissipation and uncoupling. It was partially inhibited by CsA and associated with decrease of protein thiol groups in the mitochondrial membrane and cytochrome *c* release. PTZ did not induce LPO or GSH oxidation, and even at this concentration PTZ inhibited the Fe^{2+}-induced LPO. Fluorescence studies with membrane models showed that PTZ present higher affinity with cardiolipin-containing vesicles. By using labeled phospholipids, we showed that PTZ induced changes in the PCPECL liposomes fluidity, probably disordering the acyl chains close to the polar head groups. Since literature shows that alterations in the physical state of mitochondrial membrane may induce PTP opening, these results suggests that the interaction of PTZ with the mitochondrial membrane changes its fluidity resulting in mitochondrial permeabilization and cytochrome *c* release. Keywords: phenothiazines, mitochondrial permeabilization, cytochrome *c* release, membrane interaction. Supported by FAPESP, CNPq and FAEP-UMC.