MITOCHONDRIAL PERMEABILITY TRANSITION INDUCED BY PHENOTHIAZINES

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Phenothiazines (PTZ) are compounds widely used in the treatment of schizophrenia and other psychotic diseases. Mitochondrial permeability transition (MPT) is classically described as a process Ca^{2+}-dependent and CsA-sensitive characterized by the opening of a permeability transition pore (PTP) and consequently, mitochondrial swelling. Literature data have demonstrated that, at 10μM concentration, PTZ present potent antioxidant effects and are able to inhibit MPT. On the other hand, several studies have showed that PTZ induce cell death in tumor cell lines. In this work, we studied the effects of higher concentrations of PTZ on MPT in isolated mitochondria. At high concentration (100μM), PTZ induced a mitochondrial swelling that was Ca^{2+}-dependent, partially prevented by CsA and $MgCl_2$, not prevented by DTT and not accompanied by LPO and GSH depletion. Surprisingly, high concentrations of PTZ maintained the ability to inhibit the LPO. Considering that PTZ are amphiphilic drugs, they could induce PTP opening by changing the membrane fluidity with consequent protein misfolding. In this regard, preliminary studies of PTZ binding by using fluorescent probe Laurdan showed that these drugs exhibited higher affinity to a mitochondrial membrane model than to a plasmatic membrane model. Keywords: phenothiazines, MPT, membrane fluidity. Supported by FAPESP, CNPq, FAEP-UMC.