PHENOTHIAZINES-INDUCED CELL DEATH IN LEUKEMIC K562 CELLS

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Phenothiazines (PTZ) are widely used in Medicine in the treatment of schizophrenia. The presence of hydrophobic and proton trapping basic amino groups in the structure of PTZ suggests that these molecules has lysosomotropic properties. We have investigated the involvement of lysosomal membrane permeabilization (LMP) in PTZ-induced apoptosis in myeloid leukemia K562 and peripheral mononuclear blood (MBC) cells. Our results demonstrated that PTZ induced the loss of viability of K562 cells while the viability of MBC was poorly affected. The pre-incubation of K562 cells with E-64, a specific irreversible inhibitor of cysteine cathepsin, decreased the pro-apoptotic effect of PTZ, suggesting the involvement of the lysosomal cathepsins in the control of cell death induced by PTZ. Confocal images of K562 cells loaded with the vital fluorogenic dye acridine orange showed that PTZ treatment induced classical apoptosis hallmarks with concomitant relocation of the acridine orange probe from lysosomes to cytosol indicating that PTZ was able to induce lysosomal membrane permeabilization. It was not observed activation of caspase-3 by PTZ, suggesting that caspase-3 activation was not involved in PTZ-induced apoptosis. These results indicate that the PTZ are able to induce a selective apoptotic cell death K562 cells with involvement of LMP. Supported by FAPESP, CNPq, FAEP.