Thioridazine Induces Cell Death in K562 Leukemic Cells by Intracellular Ca^{2+} Overload

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During cellular Ca^{2+} overload, mitochondria are able to uptake cytosolic Ca^{2+}, which in turn induces the opening of permeability transition pore and disrupts the mitochondrial transmembrane potential (??), this event can induce cell death. In this work we investigated the effect of the antipsychotic drug thioridazine (TR) on Ca^{2+} homeostasis, investigating the possible mechanisms of induction of cell death in human leukemic K562 cells. Our results demonstrated that TR induced the loss of viability of K562 cells while the pre-incubation with BAPTA-AM or EGTA inhibited this effect, suggesting the involvement of the Ca^{2+} in the control of cell death induced by TR. Confocal images of K562 cells loaded with the vital fluorogenic dye acridine orange showed that TR treatment induced lysosomal membrane permeabilization with nuclear fragmentation, formation of membrane blebbing and cytoplasmic vesicle. Images of cells double-loaded with the fluorescent probes fluo-3 and rhod-2 showed that TR induced a sudden increase in the cytosolic Ca^{2+} concentration ($[Ca^{2+}]c$) followed by Ca^{2+} uptake by mitochondria ($[Ca^{2+}]m$) with disruption of ??. These results indicate that the TR is able to induce cell death in human leukemic K562 cells by a sudden cytosolic Ca^{2+} overload. (Supported by FAPESP CNPq and FAEP)