Bioenergetic Disfunction Induced by 1,3,4-Thiadiazolium Mesoionic Derivatives is Related to Their Interaction with Mitochondrial Membranes

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The mesoionic derivatives of 1,3,4-thiadiazolium-2-phenylamine chloride are compounds of biological interest due to their potential use as antitumoral agents, particularly against melanoma. These derivatives differ only at the cinnamoyl ring substituents (MI-D, X=NO, MI-J, X=OH; MI-4F, X=F; MI-2,4diF, X=Y=F). We previously showed that they reduce the oxidative phosphorylation efficiency at different intensities, according to the ring substituent. We now report the effects of MI-J, MI-2,4diF and MI-4F on osmotic volume changes (swelling) of rat liver mitochondria and on the fluidity of artificial dimyristoylphosphatidylcholine (DMPC) membranes, which was evaluated by the fluorescence of the probe 1,6-diphenyl-1,3,5-hexatriene (DPH). MI-J, MI-4F and MI-2,4diF (65 nmol.mg^{-1}protein) decreased the amplitude of swelling induced by valinomycin plus potassium, by ~18%, ~32% and ~43%, respectively. At the highest concentration (130 nmol.mg^{-1}protein), MI-4F was the most effective, decreasing the swelling amplitude by ~67% in relation to MI-2,4diF (~50%?) and MI-J (~50%?). Swelling of energized mitochondria in the presence of sodium acetate was completely inhibited by all compounds at 65 and 130 nmol.mg^{-1}protein. Fluorescence polarization of DPH, probing the core regions of synthetic membranes, showed that MI-J (5 and 15 µmol.L^{-1}) increased the polarization values in gel and fluid phases, while MI-4F at the same concentrations increased the probe polarization only in the fluid phase. In contrast, MI-2,4diF did not affect the polarization values in these concentrations. These results suggest that the effects of 1,3,4-thiadiazolium mesoionic derivatives on mitochondrial bioenergetics are related to their interaction with mitochondrial membrane and also depend of the cinnamoyl ring substituent. Supported by CAPES and CNPq.