MITOCHONDRIAL DISFUNCTION INDUCED BY 1,3,4-THIADIAZOLIUM MESOIONIC DERIVATIVES

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Mesoionic compounds are a group of chemical agents whose pharmaceutical potential and other applications have been recognized. An antimelanoma effect has been described for a series of 4-phenyl-5-(2'-Y,4'-X or 4'-X-cinnamoyl)-1,3,4-thiadiazolium-2-phenylamine chlorides, that differed from each other in the cinnamoyl ring substituent (MI-J, X=OH; MI-F, X=F; MI-2,4diF X=Y=F; MI-D X=NO_2). We previously showed that MI-4F and MI-4diF depress significantly the efficiency of mitochondrial electron transport and oxidative phosphorylation with NADH-linked substrates. We now report that in isolated rat liver mitochondria, supplied with succinate, MI-J, MI-4F and MI-2,4diF (130 nmol.mg^{-1}protein) inhibited state 3 by ~33%, ~72% and ~73%, respectively. State 4 was strongly stimulated by all derivatives. For this reason, CCR value and ADP/O ratio were determined only for the lowest concentration (6.5 nmol.mg^{-1} protein), which showed decreases. The inhibition sites in the respiratory chain were determined as being complexes I and IV. In the melanoma model, MI-D was the most effective, although, our present results show that the effect of MI-4F and MI-2,4F on the mitochondrial function was more pronounced when compared to MI-J and MI-D. We therefore suggest that other mechanisms not involving mitochondria may contribute for the reported antimelanoma activity.

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