MARKED DISRUPTION OF MITOCHONDRIAL ENERGY AND CALCIUM HOMEOSTASIS PROVOKED BY LONG-CHAIN HYDROXYLATED MONOCARBOXYLIC FATTY ACIDS IN HEART OF YOUNG RATS

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Introduction: Mitochondrial trifunctional protein (MTP) and long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) deficiencies are disorders biochemically characterized by tissue accumulation and high urinary excretion of long-chain fatty acids, including the monocarboxylic long-chain 3-hydroxy fatty acids (LCHFA) 3-hydroxytetradecanoic (3HTA) and 3-hydroxypalmitic (3HPA) acids. Affected patients commonly present severe cardiac symptoms and mild neurological dysfunction, whose pathogenesis is poorly established, especially for heart alterations. Objectives: In the present work we investigated the effects of 3HTA and 3HPA on important parameters of mitochondrial bioenergetics.

Materials and methods: We measured mitochondrial membrane potential (ΔΨm), matrix NAD(P)H content, swelling, Ca²⁺ retention capacity and ATP synthesis in rat heart Ca²⁺-loaded mitochondrial preparations. Brain mitochondria were also used to compare the effects of these LCHFA. Results: 3HTA and 3HPA decreased ΔΨm, NAD(P)H pool and Ca²⁺ retention capacity in heart and brain, as well as induced mitochondrial swelling, although the effects were more pronounced and achieved with lower concentrations of these compounds in the heart. We also observed that these LCHFA provoked a marked decrease of ATP production in heart that clearly reflect deficient energy production. In contrast, 3HTDA, the dicarboxylic analogue of 3HTA, did not change any of the tested parameters, indicating a selectively for the effects elicited by the monocarboxylic LCHFA. Since 3HTA effects on Ca²⁺-loaded heart mitochondria were completely prevented by cyclosporin A plus ADP and ruthenium red, it is presumed that LCHFA induce mitochondrial permeability transition (mPT). Conclusions: The present data indicate that the major monocarboxylic LCHFA accumulating in MTP and LCHAD deficiencies markedly impair mitochondrial energy and Ca²⁺ homeostasis in the heart by inducing mPT and this may explain at least in part the severe cardiac alterations characteristic of patients affected by these diseases.

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