P-125 - HEART MITOCHONDRIAL DYFUNCTION PROVOKED BY METABOLITES ACCUMULATING IN PROPIONIC ACIDEIMIA

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INTRODUCTION: Propionic acidemia (PAcidemia) is an inherited disorder of organic acid metabolism caused by absence of propionyl-CoA carboxylase activity. It is biochemically characterized by predominant tissue accumulation of propionic acid (PA) in biological fluids and clinically by severe encephalopathy and cardiomyopathy. Maleic acid (MA) derived from PA is also highly excreted in urine of the affected patients. OBJECTIVES: Considering that the underlying mechanisms of cardiac disease in PAcidemia are practically unknown, we investigated the effects of PA and MA (0.1 - 5 mM) on important mitochondrial functions in the heart. MATERIALS AND METHODS: Mitochondrial membrane potential (ΔΨm), NAD(P)H content, Ca²⁺ retention capacity and hydrogen peroxide (H₂O₂) production were evaluated using mitochondrial preparations from heart of developing rats supported by pyruvate/malate (PM) or α-ketoglutarate (α-KG) in the absence or presence of exogenous Ca²⁺ (30 micromolar). Data were analyzed by one-way analysis of variance followed by the post-hoc Duncan multiple range test. This study was performed with the approval of Ethics Committee for Animal Research of the Universidade Federal do Rio Grande do Sul. RESULTS: AND DISCUSSION: MA markedly decreased ΔΨm, NAD(P)H content and Ca²⁺ retention capacity in Ca²⁺-loaded mitochondria respiring with PM that were significantly reduced by cyclosporin A (CsA, inhibitor of mitochondrial permeability transition, mPT), indicating the involvement of mPT pore opening. These effects induced by MA were even higher using α-KG-supported mitochondria, but not prevented by CsA. Furthermore, PA provoked a moderate reduction of ΔΨm and NAD(P)H content in Ca²⁺-loaded mitochondria supported by α-KG, as compared to MA, and did not alter mitochondrial Ca²⁺ retention capacity. Finally, we verified that MA and PA did not induce H₂O₂ production regardless the respiratory substrate, ruling out the involvement of oxidative stress in the observed effects. CONCLUSIONS: The data indicate that MA and PA to a lesser extent, disturb mitochondrial energy and calcium homeostasis in the heart. It is therefore proposed that mitochondrial dysfunction provoked by the accumulating metabolites may be involved in the cardiomyopathy occurring in patients affected by PAcidemia. Financial support: PROPESQ/UFRGS, CAPES, FAPERGS and CNPq.