Disturbance of Mitochondrial Energy Homeostasis Caused by 3-Hydroxytetradecanoic Acid Accumulating in LCHAD Deficiency in Rat Heart

Tonin A.M.¹, Busanello E.N.B.¹, Lobato V.G.A.¹, Ribeiro C.A.¹, Leipnitz G.¹, Wajner M.¹,²

¹Dep. de Bioquímica, ICBS, UFRGS, Porto Alegre, Brazil
²Serviço de Genética Médica, HCPA, Porto Alegre, Brazil.

Long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) deficiency is recognized as one of the most severe fatty acid oxidation disorders, since affected patients present serious symptoms including cardiomyopathy and hepatopathy usually with a fatal outcome. Biochemically, individuals present tissue accumulation of the long-chain 3-hydroxy fatty acids such as 3-hydroxytetradecanoic acid (3HTA). In the present work, we investigated the in vitro effects, 3HTA on respiratory parameters in mitochondrial preparations from heart of young rats. First, we evaluate effect of 3HTA on the respiratory parameters state 4, state 3, as well as the mitochondrial membrane potential, peroxide production and the matrix NAD(P)H levels. We found that 3HTA markedly increased state 4 of respiration and diminished the respiratory control ratio (RCR) indicating that this compound may be dissipating the proton gradient. Then we investigate 3HTA effect in the mitochondrial membrane potential and we observed that 3HTA diminished the membrane potential as well as the peroxide production indicating an uncoupler action. Moreover, the matrix NAD(P)H levels were also diminished by 3HTA. However, 3HTA did not alter state 3 of respiration. It is presumed that the impairment of heart energy homeostasis caused by this endogenous accumulating compound may contribute at least in part to the heart dysfunction found in LCHAD deficient patients.

Keywords: bioenergetics, long-chain 3-hydroxy-acyl-CoA dehydrogenase deficiency, rat heart

Financial support: Research grant from CNPq, PRONEX, FINEP, Instituto Brasileiro de Neurociências (IBN-NET) #01.06..0842-00 and Instituto Nacional de Ciência e Tecnologia- Excitotoxicidade e Neuroproteção (INCT-EN).