Marked Reduction of Na\(^+\), K\(^+\)-ATPase and Creatine Kinase Activities Induced by Lysine Administration in Glutaryl-CoA Dehydrogenase Deficient Mice

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Glutaric acidemia type I (GA I) is a metabolic disorder caused by a deficiency of the mitochondrial glutaryl-CoA dehydrogenase activity leading to accumulation of predominantly glutaric (GA) and 3-hydroxyglutaric (3HGA) acids in brain and other tissues of affected patients. Most patients present progressive cortical leukoencephalopathy, hypotonia and suffer acute encephalopathic episodes with striatum degeneration from 6 to 36 months of age, leading to dystonia and diskinesia. Considering that the pathophysiology of GA I and especially the relevance of bioenergetical impairment in the tissue damage, the major aim of this study was to investigate important parameters of cellular bioenergetics in brain, heart and skeletal muscle from 15-day-old glutaryl-CoA dehydrogenase deficient mice (Gcdh-\(-/\)) as compared to wild type (WT) mice submitted to a single intra-peritoneal injection of saline or lysine (Lys - 8 µmol/g). We evaluated the activities of the respiratory chain complexes II, II-III and IV, \(\alpha\)-ketoglutarate dehydrogenase (\(\alpha\)-KGDH), creatine kinase (CK) and Na\(^+\), K\(^+\)-ATPase. Mild alterations of the respiratory chain complexes II-III and IV activities were observed in heart and of complex II-III in skeletal muscle from Lys-treated Gcdh-\(-/\) mice. The most important effects provoked by Lys were marked decreases of Na\(^+\), K\(^+\)-ATPase in brain and CK in brain and skeletal muscle of Gcdh-\(-/\) mice. In contrast, brain \(\alpha\)-KGDH activity was not altered in WT and Gcdh-\(-/\) injected with saline or Lys. Our results demonstrate that reduction of Na\(^+\), K\(^+\)-ATPase and CK activities may play an important role in the pathogenesis of the neurodegenerative changes in GA I.

Keywords: glutaric acidemia type I, glutaryl-CoA dehydrogenase deficient mice, cellular bioenergetics

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