Reduction of Na\(^+\), K\(^+\)-ATPase activity and expression in brain of glutaryl-CoA dehydrogenase deficient mice: a possible mechanism for brain injury in glutaric aciduria type I


1Departamento de Bioquímica, ICBS, UFRGS, Porto Alegre – RS, Brazil; 2Serviço de Genética Médica, HCPA, Porto Alegre – RS, Brazil; 3Laboratório de Biologia Genômica e Molecular, Pontifícia Universidade Católica do Rio Grande do Sul, Porto Alegre, RS, Brazil; 4School Medicine University of Colorado Denver, Aurora, United States; 5Departments of Pediatrics, Molecular and Medical Genetics, Oregon Health & Science University, Portland, OR, USA.

The role of mitochondrial dysfunction in the neuropathology and more specifically the cortical leukodystrophy and the striatum degeneration of glutaric acidemia type I (GA I) is still disputed. Therefore, in the present work we measured the activities of the respiratory chain complexes I-IV, α-ketoglutarate dehydrogenase (α-KGDH), creatine kinase (CK) and Na\(^+\), K\(^+\)-ATPase in brain of 15 and 30-day-old glutaryl-CoA deficient (Gcdh-/-) and wild type (WT) mice submitted or not to a lysine (Lys) overload (single intra-peritoneal injection of Lys (8 µmol/g) for 15-day-old mice and high Lys (4.7%) diet for 30-day-old mice). We verified mild alterations in the activities of some respiratory chain complexes in the brain of 30-day-old Gcdh-/- mice as compared to WT animals. Furthermore, the activities of Na\(^+\), K\(^+\)-ATPase and CK were inhibited in 15-day-old Gcdh-/- mice submitted to Lys overload. We also found a significant reduction of Na\(^+\), K\(^+\)-ATPase activity associated with a reduction of its expression in cerebral cortex of 30-day-old Gcdh-/- mice submitted or not to a Lys overload. In contrast, no significant alterations were verified in the activity of α-KGDH. Since synaptic Na\(^+\), K\(^+\)-ATPase activity is required for cell volume regulation and to maintain the membrane potential necessary for a normal neurotransmission, it is presumed that reduction of this enzyme activity may represent a potential patomechanism involved in the brain swelling and cortical atrophy with leukodystrophy observed in patients affected by GA I.

Keywords: glutaric acidemia type I; Gcdh-/- mice; Na\(^+\), K\(^+\)-ATPase

Supported by: CNPq, PROPESq/UFRGS, FAPERGS, FAPESP, PRONEX, FINEP IBN-Net and INCT-EN