Oxidative Stress is Induced in Glutaryl-CoA Dehydrogenase Deficient Knock Out Mice by Lysine Administration

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Glutaric aciduria type I (GA I), a neurodegenerative autosomal recessive disorder, is characterized by a progressive cortical leukoencephalopathy and acute striatum degeneration. The present work aimed to investigate whether oxidative stress is involved in the brain damage of glutaryl-CoA dehydrogenase deficient knock out mice (Gcdh -/-). We determined oxidative stress parameters in distinct brain regions and peripheral tissues from 30-day-old Gcdh-/- and WT mice. The measured parameters were normal in all tissues obtained from WT and Gcdh-/- mice. A group of animals were administered intraperitoneally with a single injection of lysine (Lys, 8 µmol) and sacrificed 24 h after injection. Lys injection provoked a moderate increase of brain glutaric acid (GA) concentrations, without altering 3-hydroxyglutaric (3OHGA) levels. Furthermore, GA and 3OHGA concentrations were approximately 40% higher in striatum compared to cerebral cortex in mice submitted to Lys administration. Lys provoked marked increases of lipid peroxidation, DCFH oxidation, superoxide dismutase (SOD) and glutathione reductase activities, as well as significant reductions of GSH levels and glutathione peroxidase activity in the striatum. Increased lipid peroxidation and SOD activity and a decrease of GSH levels were observed in the cerebral cortex 24 hours after Lys administration, whereas in the hippocampus only a slight increase of SOD activity and DCFH oxidation were found. In contrast, all parameters were normal in liver and heart of Gcdh-/- mice. Furthermore, these parameters were not altered in WT tissues after Lys injection. The data indicate that cerebral tissue, particularly the striatum, from Gcdh-/- mice is more vulnerable to Lys administration.

Key words: glutaric aciduria, lysine, oxidative stress.

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