Disruption of Brain Redox Homeostasis in Glutaryl-CoA Dehydrogenase Deficient Mice Supplemented with Lysine


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INTRODUCTION: Glutaric aciduria type I (GA I), a neurodegenerative autosomal recessive disorder, is neuropathologically characterized by progressive cortical leukoencephalopathy and acute striatum degeneration. The present work aimed to investigate whether oxidative stress occurs in the brain of glutaryl-CoA dehydrogenase deficient knock out (Gcdh -/-) mice.

MATERIAL AND METHODS: We determined oxidative stress parameters in distinct brain regions and in peripheral tissues from 30-day-old Gcdh/- and WT mice. A group of animals was administered intraperitoneally with a single injection of lysine (Lys, 8 µmol) and sacrificed 24 h later. Another group of animals was submitted to a normal (0.9 % Lys), or high Lys diets (2.8 % or 4.7 % Lys) for 60 hours.

RESULTS AND DISCUSSION: Lys acute injection provoked an increase of brain glutaric acid (GA) concentrations, without altering 3-hydroxyglutaric (3OHGA) levels. Furthermore, GA and 3OHGA concentrations were approximately 40% higher in the striatum compared to the cerebral cortex in these mice. Acute and chronic dietary Lys administration provoked lipid and protein oxidative damage and impaired the antioxidant defences in the striatum and cerebral cortex, but no in heart and liver from Gcdh -/-, as compared to WT mice. Furthermore, alterations of oxidative stress parameters in cerebral cortex and striatum were more accentuated in symptomatic, as compared to asymptomatic Gcdh +/- mice exposed to 2.8 % or 4.7 % Lys diet. CONCLUSION: The results indicate that a disruption of redox homeostasis in cerebral cortex and striatum of young Gcdh +/- mice exposed to increased Lys diet may possibly represent an important pathomechanism of brain injury in GA I patients.

Key words: glutaric acidemia type I, glutaric acid, high lysine, oxidative stress, Gcdh +/- mice

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