DISRUPTED ENERGY METABOLISM AND OXIDATIVE STRESS INDUCED BY QUINOLINIC ACID IN GLUTARYL-COA DEHYDROGENASE KNOCKOUT MICE

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Introduction: Patients with glutaric acidemia type I (GA I) present progressive cortical leukoencephalopathy and acute striatum degeneration that are usually triggered by acute encephalopathic crises during inflammatory processes. The kynurenine pathway is stimulated by inflammatory cytokines, resulting in the production of quinolinic acid (QUIN). Objectives: Our purpose was to investigate the effect of an enriched lysine (Lys) diet associated with QUIN injection on cellular redox and bioenergetic homeostasis in striatum of knockout mouse for GCDH (model of GA I, Gcdh⁻/⁻) since the pathogenesis of the brain damage in GA I is still poorly established. Material and Methods: We evaluated lactate release, respiratory chain complexes and creatine kinase (CK) activities, thiobarbituric acid reactive substances (TBA-RS) levels, reduced glutathione concentrations, the activities of antioxidant enzymes and the immunocontent of Nrf2, Keap1, NFκB, IkBα, HO-1 and Akt, in striatum of 30-day-old Gcdh⁻/⁻ and wild type mice (Gcdh⁺/⁺) fed a high Lys (4.7 %) chow for 48 hours and injected with QUIN. Results: A moderate increase of lactate production, and reduction of complex IV and CK activities were observed in striatum from Gcdh⁻/⁻ mice under a high Lys chow 24 h after QUIN injection. We also observed an increased TBA-RS levels and glutathione peroxidase, superoxide dismutase 2 and glutathione-S-transferase activities. Furthermore, QUIN striatal administration increased Nrf2, NFκB and Akt expression and diminished Keap1 and IkBα 30 minutes after QUIN injection. Conclusions: Our data demonstrates that QUIN impairs bioenergetics and disrupts redox homeostasis in striatum from Gcdh⁻/⁻ mice fed a high Lys chow.

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