Intrastriatal Administration Of 3-Hydroxy-3-Methylglutaric Aciduria Metabolites Induces Oxidative Damage And Alters The Enzymatic Antioxidant Defenses In Rat Brain

da Rosa, M.S.¹, Seminotti, B.¹, Fernandes C.G.¹, Borges, C.G.¹, Leipnitz, G.¹, Wajner, M.¹,²

¹Departamento de Bioquímica, ICBS, UFRGS - Porto Alegre, RS, Brazil
²Hospital de Clínicas de Porto Alegre - Porto Alegre, RS, Brazil

3-Hydroxy-3-methylglutaric aciduria (HMGA) is a disorder biochemically characterized by tissue accumulation of 3-hydroxy-3-methylglutarate (HMG), 3-methylglutarate (MGA), 3-methylglutaconate (MGT) and 3-hydroxyisovalerate (OHIVA). Although neurological abnormalities are relatively pronounced in HMGA and hepatic dysfunction is found during metabolic crises, the mechanisms of tissue damage in this disorder are poorly known. We investigated the in vivo effects of intrastriatal administration of HMG and MGA on parameters of oxidative stress namely thiobarbituric acid-reactive substances (TBA-RS, lipid peroxidation), sulfhydryl content, reduced glutathione (GSH) concentrations and the activities of the antioxidant enzymes catalase (CAT), glutathione peroxidase (GPx), glutathione reductase (GR), superoxide dismutase (SOD) and gluco-6-phosphate dehydrogenase (G6PD) in striatum from 30-day-old rats. Our results demonstrate that all metabolites induced similar degree of lipid peroxidation (TBA-RS increase) and GSH oxidation in striatum. Furthermore, HMG and MGA injections significantly increased GPx activity, and inhibited the SOD and GR activities. HMG also increased CAT and decreased G6PD activities. In contrast, the sulfhydryl content was not altered by these metabolites. Our present data showed that the striatum present vulnerability to oxidative stress elicited by the metabolites accumulating in HMGA.

Financial support: Research grants from CNPq, PROPESq/UFRGS, FAPERGS, PRONEX, FINEP Rede Instituto Brasileiro de Neurociência (IBN-Net) # 01.06.0842-00 and INCT-EN.

Keywords: 3-hydroxy-3-methylglutaric aciduria, oxidative stress, striatum, liver.