Neurochemical evidence that the major metabolites accumulating in 3-hydroxy-3-methylglutaric aciduria induces oxidative stress in vivo in striatum of young rats

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3-Hydroxy-3-methylglutaric aciduria (HMGA) is a neurometabolic disorder biochemically characterized by the predominant accumulation of 3-hydroxy-3-methylglutaric (HMG) and 3-methylglutaric (MGA) acids in tissues and biological fluids of affected individuals. Patients usually suffer from lethargy and coma accompanied by severe alterations of the basal ganglia. Considering that the pathomechanisms involved in the neurological symptoms observed in HMGA are partially understood, in the present study we investigated the in vivo effects of intrastriatal administration of HMG and MGA to rats on important parameters of oxidative stress. Our results demonstrate that HMG and MGA induced lipid and protein oxidative damage in rat striatum and decreased GSH concentrations, the most important brain antioxidant. Furthermore, HMG increased nitric oxide production, reflecting a role for reactive nitrogen species in HMG toxic effects. Regarding to the enzymatic antioxidant defenses, both organic acids altered these antioxidant enzyme activities. We finally observed that some antioxidants attenuated or fully prevented HMG-induced alterations of oxidative stress parameters, indicating the participation of reactive species in these effects. Interestingly, the NMDA receptor antagonist MK-801 also prevented some of these effects, suggesting the involvement of NMDA overstimulation by these organic acids. Therefore, it is presumed that oxidative stress is induced in vivo by HMG and MGA in rat striatum and may possibly represent, at least in part, a pathomechanism of brain damage in HMGA.

Keywords: 3-hydroxy-3-methylglutaric aciduria, oxidative stress, striatum
Supported by: CNPq, PROPESq/UFRGS, FAPERGS, PRONEX, FINEP IBN-Net and INCT-EN