Evidence That 3-methylcrotonylglycine and 3-methylcrotonic Acid Provoke Lipid and Protein Oxidative Damage in Cerebral Cortex of Young Rats

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Isolated 3-methylcrotonyl-CoA carboxylase deficiency (3MCCD) is an autosomal recessive disorder of leucine metabolism biochemically characterized by accumulation of 3-methylcrotonylglycine (3MCG), 3-hydroxyisovaleric acid and 3-methylcrotonic acid (3MCA). Affected individuals present neurological symptoms and abnormalities whose pathogenesis is poorly known. In the present study, we investigated the in vitro effects of 3MCG and 3MCA on important parameters of oxidative stress in cerebral cortex of young rats. Our results show that 3MCG and 3MCA increased thiobarbituric acid-reactive species (TBA-RS) and carbonyl formation, indicating that these compounds provoke lipid and protein oxidation, respectively. Furthermore, 3MCG-induced elevation of TBA-RS was prevented by melatonin and trolox, indicating that these effects were due to reactive oxygen species that are scavenged by these antioxidants. Considering that the nitric oxide inhibitor L-NAME did not alter lipid oxidation and that nitric oxide production was not affected by 3MCG and 3MCA, it is presumed that reactive nitrogen species were not involved in these effects. In contrast, GSH levels and sulfhydryl oxidation were not changed by these metabolites. Similarly, the activity of the antioxidants enzymes glutathione peroxidase, catalase, superoxide dismutase and glutathione reductase were not altered by 3MCG. It is presumed that oxidative damage to lipids and proteins provoked by 3MCG and 3MCA may contribute to the pathogenesis of the neurological dysfunction characteristic of the patients affected by 3MCCD.

Key words: 3-methylcrotonylglycine; 3-methylcrotonic acid; oxidative stress

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