2-Methylacetoacetate Induces Oxidative Stress in Rat Brain

Leipnitz, G.[1], Amaral, A.U.[1], Seminotti, B.[1], Fernandes, C.G.[2], Wajner, M.[1,2]

[1]Departamento de Bioquímica, ICBS, UFRGS–Porto Alegre, Brazil; [2]Serviço de Genética Médica, HCPA, Porto Alegre, Brazil.

Mitochondrial ß-ketothiolase (KTD) and 2-methyl-3-hydroxybutyryl-CoA dehydrogenase (MHBD) deficiencies are inherited neurometabolic disorders affecting isoleucine catabolism. Biochemically, KTD is characterized by intermittent ketoacidosis and urinary excretion of 2-methylacetoacetate (MAA), 2-methyl-3-hydroxybutyrate (MHB) and tiglylglycine, whereas in MHBD only MHB and tiglylglycine accumulate. In the present study, we studied the in vitro effects of MAA and MHB on important parameters of oxidative stress in cerebral cortex from 30-day-old rats. Our results demonstrate that MAA significantly increased chemiluminescence and thiobarbituric acid-reactive substances (TBA-RS) levels, indicating that this compound induces lipid peroxidation, whereas MHB did not alter these parameters. We also observed that the addition of free radical scavengers fully prevented MAA-induced increase of TBA-RS, suggesting that free radicals were involved in MMA effect. Furthermore, MAA, but not MHB, significantly decreased the reduced glutathione (major naturally ocurring non-enzymatic antioxidant defense) and increased sulfhydryl group oxidation, indicating that MAA induces protein oxidative damage. Finally, we verified that both metabolites did not induce nitric oxide production in cerebral cortex. Our data indicate that oxidative stress elicited in vitro by MAA may contribute at least in part to the pathophysiology of the brain injury in KTD.

Keywords: 2-methylacetoacetate, oxidative stress, cerebral cortex

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