INTRODUCTION: Methylmalonic acidemias comprehend a group of inherited neurometabolic diseases clinically characterized by severe neurological dysfunction and biochemically by the predominant accumulation of methylmalonic acid (MMA). Hyperammonemia is also a common finding in children with the disorder but its contribution to the development of the neurological symptoms in the affected patients is poorly known. We investigated the effects of intracerebroventricular (ICV) administration of MMA to 30-day-old rats with hyperammonemia induced by urease treatment on important parameters of redox homeostasis in cerebral cortex and striatum. MATERIAL AND METHODS: We measured reduced glutathione (GSH) concentrations, sulfhydryl content, nitric oxide (NO) production, 2′,7′-dichlorofluorescin (DCFH) oxidation and the activities of the antioxidant enzymes catalase (CAT), glutathione peroxidase (GPx), superoxide dismutase (SOD) and glutathione reductase (GR). RESULTS AND DISCUSSION: We found that MMA decreased GSH concentrations and sulfhydryl content in cerebral cortex and striatum from hyperammonemic rats, whereas high concentrations of MMA under normal levels of ammonia and hyperammonemia alone did not alter these parameters. Furthermore, MMA combined with hyperammonemia decreased GR activity and increased NO production in cerebral cortex. However, isolated or combined high brain MMA and ammonia concentrations did not affect the activities of CAT, SOD and GPx, neither DCFH oxidation. We also found that the antioxidants creatine, ascorbic acid plus α-tocopherol, N-ω-nitro-L-arginine methyl ester (L-NAME) and N-acetylcysteine (NAC) prevented GSH reduction and sulfhydryl oxidation, whereas NAC and L-NAME prevented the increased formation of nitric oxide provoked by the combined actions of MMA and ammonia, suggesting the participation of reactive species in these effects. CONCLUSION: Our data demonstrate a synergistic action of hyperammonemia and high concentrations of MMA disturbing brain antioxidant defenses. It is proposed that high brain levels of ammonia in conjunction with MMA play an important role in the brain dysfunction observed in patients affected by methylmalonic acidemia.

Keywords: Methylmalonic acid; ammonia; methylmalonic acidemia; brain.

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