IN VIVO ADMINISTRATION OF 3-HYDROXY-3-METHYLGLUTARIC AND 3-METHYLGLUTARIC ACIDS INHIBITS CREATINE KINASE ACTIVITY AND ELICITS OXIDATIVE STRESS IN VIVO IN RAT HEART

Da Rosa, M. S.1; Seminotti, B.1; Ribeiro, C. A. J.1; Wajner, M.1,2; Leipnitz, G1.

1Departamento de Bioquímica, Instituto de Ciências Básicas da Saúde, Universidade Federal do Rio Grande do sul, Porto Alegre, RS, Brazil.
2Serviço de genética Médica do Hospital de Clínicas de Porto Alegre, Porto Alegre, RS, Brazil.

Introduction and objectives: 3-Hydroxy-3-methylglutaric aciduria (HMGA) is a neurometabolic disorder biochemically characterized by tissue accumulation of 3-hydroxy-3-methylglutaric (HMG) and 3-methylglutaric (MGA) acids. Affected patients present cardiomiopathy, especially during metabolic crises, whose pathophysiology remains to be established. In the present work we evaluated the effects of intraperitoneal injection of HMG and MGA on creatine kinase (CK) activity and oxidative stress parameters in heart of young rats. Material and methods: Thirty-day-old Wistar rats were intraperitoneally administered with three injections of HMG, MGA or NaCl (the first injection of 10 μmol/g followed by two injections of 5 μmol/g body weight), with an interval of 90 min, and euthanized 1 h after the last injection. Supernatants of heart were prepared and then used to assess CK activity, carbonyl formation, 2',7'-dichlorofluorescein (DCFH) oxidation, reduced glutathione (GSH) concentrations, thiobarbituric acid-reactive substances (TBA-RS) and the activities of the antioxidant enzymes glutathione peroxidase (GPx), glutathione reductase (GR), superoxide dismutase (SOD), catalase (CAT), glucose-6-phosphate dehydrogenase (G6PDH) and glutathione-S-transferase (GST). Results and Conclusions: We verified that the intraperitoneal administration of HMG and MGA significantly decreased the activities of CK and G6PDH, whereas only MGA reduced SOD and CAT activities. Furthermore, both organic acids diminished GSH concentrations and increased carbonyl formation and DCFH oxidation, as well as the activities of GPx and GR. In contrast, HMG e MGA did not significantly alter TBA-RS levels and GST activity in heart. Our findings suggest that an impairment of energy transfer and oxidative stress induced by HMG and MGA in vivo may contribute to the pathophysiology of cardiac dysfunction found in HMGA. Acknowledgements: Research grant from CNPq, PRONEX, FINEP, IBN-Net #01.06.0842-00 and INCT-EN.

Keywords: 3-hydroxy-3-methylglutaric aciduria; oxidative stress; hearth.