Evaluation of Mechanisms Involved in Cell Death by Apoptosis in an Animal Model of Maple Syrup Urine Disease

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Introduction: Maple Syrup Disease (MSUD) is an inborn error of metabolism caused by a deficiency of the branched-chain a-keto acid dehydrogenase complex activity. This blockage leads to accumulation of the branched-chain amino acids (BCAA) leucine, isoleucine and valine, as well as their corresponding alpha-keto acids and beta-hydroxy acids. Objectives: We investigated the effects of acute administration of BCAA pool on immunocontent of some markers involved in cell death by apoptosis (Bax, Bcl-2, Bcl-xL, caspase 3 and caspase 8), in order to better understand the pathophysiology of neurologic dysfunction seen in patients with MSUD. Material and Methods: Wistar rats of 10 and 30 days received three subcutaneous administrations of the BCAA pool (15.8 µL/g body weight) with one hour interval between administrations (test group). Control group received three injections of saline with 1 hour interval between injections, or saline alone (control group). One hour after the last administration, the rats were killed by decapitation, the brain was removed and hippocampus and cerebral cortex were isolated. Quantification of Bax, Bcl-2, Bcl-xL, caspase 3 and caspase 8 proteins were measured by Western blotting. Results and Discussion: In 30-days-old rats we observed an increase of pro-apoptotic factor Bax and caspase 3 and 8 immunocontent in the cerebral cortex. On the other hand, we observed decreased caspase 3 and 8 and a concomitant increase in anti-apoptotic factor Bcl-2 and Bcl-xL in hippocampus. Conclusions: These results suggest that the BCAA may induce apoptosis, activated by extrinsic pathway, followed by activation of the intrinsic pathway in cerebral cortex, however. The present results help to explain, at least in part, the neurologic sequelae associated with high plasma concentrations of metabolites accumulated in the disease of maple syrup.

Keywords: Maple Syrup Disease, apoptosis, branched chain amino acids.

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