DNA Damage in an Animal Model of Maple Syrup Urine Disease

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Introduction: Maple Syrup Urine Disease (MSUD) is caused by a hereditary enzyme deficiency, with consequent accumulation of branched-chain amino acids (BCAA) leucine, isoleucine and valine. Objectives: Considering the mechanisms underlying the neuropathology of brain damage in this disorder are poorly known, we investigated if the administration of a BCAA pool (leucine, isoleucine and valine) causes transient DNA damage in brain of rats, and if antioxidant treatment prevented the alterations. Methods: For acute administration, Wistar rats (10 days) received three injections (1h interval) a pool of BCAA or saline (control group), subcutaneously. For chronic administration, Wistar rats (7 days) received a pool of BCAA or saline twice a day for 21 days; the animals were also supplemented with N-acetylcysteine (NAC) (20mg/kg) twice a day and deferoxamine (DFX) (20mg/kg) every two days. One hour (acute) or twelve hours (chronic) after the last injection, the animals were killed by decapitation and the brain was removed; DNA damage was determined by the alkaline comet assay. Results: Our results showed that acute administration of BCAA increased DNA damage frequency and index in hippocampus. However, that chronic administration of BCAA increased DNA damage frequency and index in hippocampus and striatum, and antioxidant treatment is able to prevent on DNA damage in hippocampus and striatum. Conclusion: The present study demonstrated that metabolites accumulating in MSUD induce DNA damage in hippocampus and striatum, and may be implicated in the neuropathology observed in the affected patients, and that the antioxidant treatment is able to partially reverse these alterations.

Keywords: Maple syrup urine disease; DNA damage; comet assay; antioxidants.

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