Impairment of Brain Redox Homeostasis Caused by the Major Metabolites Accumulating in Hyperornithinemia–Hyperammonemia–Homocitrullinuria Syndrome In Vivo

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Hyperornithinemia-hyperammonemia-homocitrullinuria syndrome, a genetic disorder, is biochemically characterized by accumulation mainly of metabolites ornithine, ammonia and homocitrulline. Since the disease is characterized by neurological regression and the pathogenesis is not well understood, this study investigated the in vivo effects of intracerebroventricular administration of ornithine and homocitrulline in the presence or absence of hyperammonemia induced by intraperitoneal treatment of urease on important parameters of oxidative stress in cerebral cortex of young rats. The aim of this study was to better understand the role of these metabolites in brain damage, under high levels of ammonia. Our results demonstrated that ornithine increased thiobarbituric acid reactive substances levels (TBA-RS) and carbonyl formation, but did not alter reduced glutathione (GSH) levels or sulfhydryl content. We also found that combination of hyperammonemia with ornithine lead to a significant decrease in GSH levels and sulfhydryl content, demonstrating a synergistic effect between ornithine and ammonia. In addition, we observed that homocitrulline causes an increase on TBA-RS levels and on carbonyl formation, as well as a decrease on GSH levels, however without changing sulfhydryl content. We also verified that the treatment with urease itself is capable to raise TBA-RS levels. Thus, it can be assumed that the major metabolites accumulating in HHH syndrome cause lipid and protein oxidative damage and even reduction of antioxidant defenses in the brain. It is presumed, therefore, that oxidative stress may represent an important pathogenic mechanism involved in the neurological damage found in patients involved by this disease.

Keywords: Ammonia; cerebral cortex; homocitrulline; ornithine; oxidative stress

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