CREATINE PREVENTS NA^+,K^+-ATPASE INHIBITION INDUCED BY INTRACEREBROVENTRICULAR ADMINISTRATION OF ISOVALERIC ACID IN CEREBRAL CORTEX OF YOUNG RATS

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Isovaleric acidemia (IVAcidemia) is an inborn error of metabolism caused by deficiency of isovaleryl-CoA dehydrogenase activity, leading predominantly to accumulation of isovaleric acid (IVA). Patients affected by IVAcidemia suffer from acute episodes of encephalopathy, whose underlying mechanisms are poorly unknown. In the present study we investigated whether the effects of intracerebroventricular injection of IVA on important parameters of energy metabolism in cerebral cortex of young rats. IVA administration significantly inhibited $^{14}CO_2$ production from acetate (22%) and the activities of citrate synthase (20%) and Na^+, K^+-ATPase (25%) in cerebral cortex. In contrast, no significant alterations were found on the activities of succinate dehydrogenase, isocitrate dehydrogenase, electron transfer chain complexes and creatine kinase. We also observed that pre-treatment of rats with creatine completely prevented the inhibitory effects of IVA on Na^+, K^+-ATPase. Therefore, it can be presumed that IVA inhibits *in vivo* the citric acid cycle probably at the enzyme citrate synthase, as well as Na^+, K^+-ATPase, a crucial enzyme responsible for maintaining the basal potential membrane necessary for a normal neurotransmission. The present data may be related to the pathophysiology of the neurological damage found in isovaleric acidemic patients. Finally, creatine supplementation may represent a potential novel adjuvant therapeutic strategy in IVAcidemia.

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