IN VITRO EFFECT OF ISOVALERIC ACID ON OXIDATIVE STRESS PARAMETERS IN RAT BRAIN MITOCHONDRIA

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Isovaleric acid (IVA) accumulates in patients affected by isovaleric acidemia (IVAcidemia), an inborn error caused isovaleryl-CoA dehydrogenase deficiency. Patients affected by this disorder suffer from acute episodes of encephalopathy, neurological dysfunction and increased levels of ammonia generally accompanied by IVA accumulation. Considering that the neurotoxic mechanisms in IVAcidemia are virtually unknown, the objective of the present study was to investigate the *in vitro* effect of IVA (0.01-10 mM) on various parameters of oxidative stress in rat brain mitochondria. Thiobarbituric acid-reactive substances (TBA-RS), protein carbonyl formation (PCF), total radical-trapping antioxidant potential (TRAP), total antioxidant reactivity (TAR), and the activity of the antioxidant enzyme glutathione peroxidase (GPx) were assessed. In some experiments the combined effect of IVA plus ammonia (50-200 μM) was tested. Significant increased TBA-RS levels were observed when rat brain mitochondria were exposed to IVA plus ammonia. IVA also provoked a significant PCF increase in the presence or absence of ammonia. TRAP, TAR and GPx activity were not altered by the acid. The data indicate that IVA provokes oxidation of lipids and proteins, mainly in the presence of ammonia. Thus, in case these findings can be extrapolated to the human condition, it may be presumed that oxidative stress is involved in IVAcidemia neurotoxicity.

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