Evidence that 3-hydroxy fatty acids accumulating in LCHAD deficiency induce oxidative damage and decrease non-enzymatic antioxidant defenses in brain of young rats

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Long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) deficiency is an inborn error of fatty acid oxidation, considered the most severe and life-threatening disorder of this group of diseases. Affected patients present serum accumulation of 3-hydroxy fatty acids, such as 3-hydroxydodecanoic (3HDA), 3-hydroxytetradecanoic (3HTA) and 3-hydroxypalmitic (3HPA) acids that are potentially toxic intermediates. Clinical presentation usually occurs in the neonatal period or in early childhood frequently after fasting or viral illness. The major neurological manifestations are seizures, lethargy and coma and some children die suddenly. The aim of the present work was to investigate the *in vitro* effects of 3HDA, 3HTA and 3HPA on oxidative stress parameters in cerebral cortex homogenates from 30-day-old rats. It was first verified that all fatty acids significantly increased thiobarbituric acid-reactive species levels (lipoperoxidation), which was prevented by the antioxidants trolox and deferoxamine. In addition, 3HT and 3HPA caused protein damage by enhancing carbonyl formation and inducing oxidation of sulfhydryl groups. Reduced glutathione levels (non-enzymatic defences) were also decreased by 3HTA and 3HPA, being this effect prevented by deferoxamine. We also verified that the strongest effects increased in parallel with the carbonate chain. These results show that the 3-hydroxy compounds tested elicit oxidative stress in rat brain raising the possibility that oxidative damage may be involved in the pathophysiology of the neurologic symptoms manifested by patients affected by LCHAD deficiency.
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