IMPAIRMENT OF ENERGY METABOLISM IS INVOLVED IN THE MECHANISMS OF NEURODEGENERATION OF GLUTARYL-COA DEHYDROGENASE DEFICIENCY (GDD)

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GDD is an inherited neurometabolic disorder characterized by tissue accumulation of glutaric and 3-hydroxyglutaric (3HGA) acids and by severe neurological symptoms and structural brain abnormalities manifested as cerebral atrophy and striatal degeneration following encephalopatic crises. Considering that the pathophysiology of the brain damage in GDD is still not completed defined, in the present study we investigated the \emph{in vitro} effect of 3HGA (0.01-5.0 mM) on critical enzyme activities of energy metabolism, including the respiratory chain complexes I-V, succinate dehydrogenase (SDH), creatine kinase (CK) isoforms and Na$^+$,K$^+$-ATPase in cerebral cortex and striatum from 30-day-old rats or in rat C6-glioma cells. The effect was further evaluated on the rate of oxygen consumption in mitochondria from rat cerebrum. 3HGA significantly inhibited complex II and SDH in cerebral cortex and C6 cell homogenates, in contrast to the other enzyme activities which were not affected by the acid. Moreover, the inhibition of complex II/SDH activity was only observed when the succinate concentration in the medium was very low (1.0 mM) but not when mitochondrial preparations or striatum homogenates were used. In addition, 3HGA significantly lowered the respiratory control ratio (state III/state IV) in the presence of the respiratory substrates glutamate/malate (non-phosphorilating state IV) and succinate (phosphorilating state III) under stressful conditions or digitonine-permeabilized mitochondria. Since 3HGA stimulated oxygen consumption in state IV and compromised the ATP formation, it could be presumed that this organic acid might act as and endogenous uncoupler of mitochondria respiration. Furthermore, incubation of C6 glioma cells for six hours with 3HGA changed their morphology from a round flat to a spindle differentiated shape, but did not modify cell viability and did not induced apoptosis. Thus, our present data provides evidence that 3HGA impairs the brain energy metabolism which could explain, at least in part, the characteristic brain damage observed in GDD patients.