Disruption of mitochondrial homeostasis and Na⁺,K⁺-ATPase by phytanic acid in cerebellum of young rats: possible underlying mechanisms of cerebellar ataxia in Refsum disease

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Introduction: Refsum disease is a peroxisomal disorder biochemically characterized by elevated phytanic acid (Phyt) concentrations in tissues from affected patients with predominantly neurological symptoms including cerebellar ataxia. Material and methods: Considering that the pathophysiology of cerebellum abnormalities of Refsum disease is not yet established, the present work investigated the in vitro effects of Phyt on various parameters of energy metabolism and on synaptic Na⁺,K⁺-ATPase activity in cerebellum of young rats. Results: Phyt significantly diminished the activities of the respiratory chain complexes I, I-III, II and II-III and state 3 respiration, indicating that oxidative phosphorylation is probably compromised by this fatty acid. Moreover, Phyt markedly increased state 4 respiration and reduced the respiratory control ratio, as well as the mitochondrial membrane potential and the matrix NAD(P)H levels, strongly indicating an uncoupling effect caused by this fatty acid on respiratory chain. In addition, synaptic Na⁺,K⁺-ATPase activity was drastically reduced by Phyt, probably by disturbing the lipid-protein interactions since Phyt was shown to increase fluidity of the synaptic membrane where the enzyme is embedded. Conclusions: Taken together, our results suggest that Phyt compromise energy metabolism, acting as an uncoupler and as metabolic inhibitor of oxidative phosphorylation, as well as by impairing neurotransmission which depends on Na⁺,K⁺-ATPase activity. It is feasible that these mechanisms may be involved in the cerebellum damage observed in patients affected by Refsum disease in which Phyt acid accumulates.

Keywords: Refsum disease; rat cerebellum; energy homeostasis

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