EVIDENCE THAT BRANCHED-CHAIN PHYTANIC ACID ACCUMULATING IN PEROXISOMAL DISORDERS DISRUPTS BIOENERGETICS IN CEREBELLUM OF YOUNG RATS

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Refsum disease is a peroxisomal disorder characterized by raised phytanic acid (Phyt) tissue concentrations and is characterized mainly by cerebellar ataxia, polyneuropathy, and progressive retinitis pigmentosa. Although Phyt exerts strong cytotoxic effects on brain cells, little is known about its action in cerebellum and the pathophysiology of this disorder is practically unknown. Phyt effects on important parameters of bioenergetics and mitochondrial homeostasis were investigated in rat cerebellum in order to clarify the pathogenesis of cerebellar ataxia, which is the main target in affected patients. Homogenates and mitochondrial preparations were obtained from cerebellum of 30-day-old rats. Various parameters of energy metabolism were then determined in the presence of 20-200 µM Phyt. Phyt markedly reduced the activity of complexes I-III, II and II-III of the respiratory chain, without affecting complex IV activity. Phyt markedly increased state 4 respiration and diminished the RCR using both glutamate plus malate or succinate as substrates. In addition, Prist decreased state 3 respiring mitochondria, the mitochondrial membrane potential and NAD(P)H levels. Prist did not induced mitochondrial swelling, but markedly impaired the Na⁺-K⁺-ATPase activity. These results provide evidence that Phyt provokes impairment of cerebellum energy metabolism, acts as an uncoupler of oxidative phosphorylation and as a metabolic inhibitor, besides affecting neurotransmission. It is therefore postulated that bioenergetic deficits may possibly contribute to the pathophysiology of the cerebellar ataxia present in Refsum disease.

Keywords: Refsum disease, phytanic acid, energy metabolism, rat cerebellum

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