Mitochondrial energetic defects in muscle and brain of a Hmbs-/- mouse model of acute intermittent porphyria

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Résumé en anglais	Acute intermittent porphyria (AIP), an autosomal dominant metabolic disease (MIM #176000), is due to a deficiency of hydroxymethylbilane synthase (HMBS), which catalyzes the third step of the heme biosynthetic pathway. The clinical expression of the disease is mainly neurological, involving the autonomous, central and peripheral nervous systems. We explored mitochondrial oxidative phosphorylation (OXPHOS) in the brain and skeletal muscle of the Hmbs(-/-) mouse model first in the basal state (BS), and then after induction of the disease with phenobarbital and treatment with heme arginate (HA). The modification of the respiratory parameters, determined in mice in the BS, reflected a spontaneous metabolic energetic adaptation to HMBS deficiency. Phenobarbital induced a sharp alteration of the oxidative metabolism with a significant decrease of ATP production in skeletal muscle that was restored by treatment with HA. This OXPHOS defect was due to deficiencies in complexes I and II in the skeletal muscle whereas all four respiratory chain complexes were affected in the brain. To date, the pathogenesis of AIP has been mainly attributed to the neurotoxicity of aminolevulinic acid and heme deficiency. Our results show that mitochondrial energetic failure also plays an important role in the expression of the disease.

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