Disruption of redox and energy homeostasis in fatty acid oxidation disorders: insights from animal and human studies

Moacir Wajner and Alexandre U. Amaral

Department of Biochemistry, Federal University of Rio Grande do Sul, Porto Alegre, RS, Brazil

The mitochondrial fatty acid oxidation (FAO) represents a major source of energy for various tissues, including liver, heart and skeletal muscle and plays a pivotal role for maintaining energy homeostasis especially during catabolic states such as fasting and prolonged exercise. The use of fatty acids as energy substrates requires about 25 enzymes and transport proteins. Inherited defects of FAO have been identified in the majority of these proteins and constitute an important group of inborn errors of metabolism. Affected patients usually present severe hepatopathy and cardiomyopathy, as well as acute and/or progressive encephalopathy whose pathogenesis is poorly known. Since specific fatty acids are accumulated in these patients, especially during situations of catabolic episodes that precipitate the worsening of symptoms, it is conceivable that these compounds may be toxic to the cells. In fact, in recent years growing evidence has emerged indicating that mitochondrial dysfunction is directly or indirectly involved in the pathology of various FAOD. We will briefly summarize the present knowledge obtained from human and animal studies showing that disruption of mitochondrial energy, redox and calcium homeostasis may underlie the pathophysiology of tissue damage in the most frequent disorders of FAO, namely medium-chain acyl-CoA dehydrogenase (MCAD) and long-chain hydroxylacyl-CoA dehydrogenase (LCHAD) deficiencies. We will summarize the deleterious effects of the fatty acids and derivatives that accumulate in these disorders on metabolic pathways that are crucial for ATP formation and transfer, as well as on redox and calcium homeostasis. The elucidation of the mechanisms of toxicity of these acidic compounds may offer new perspectives for potential novel adjuvant therapeutic strategies in selected disorders of this group.