Inborn Errors of Metabolism with Myopathy

Defects of Fatty Acid Oxidation and the Carnitine Shuttle System

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KEYWORDS

• Fatty acid oxidation defects • Carnitine shuttling defects • Cardiomyopathy
• Rhabdomyolysis

KEY POINTS

- Inherited metabolic myopathies should be considered in the differential diagnosis of any individual with muscle pain, fatigue, and recurrent rhabdomyolysis, particularly when triggered by physiologic stress, such as strenuous exercise, intercurrent illnesses, or prolonged fasting.
- Metabolic myopathies, including fatty acid oxidation disorders (FAODs) and carnitine shuttle defects, are heterogeneous disorders that are mostly detected by newborn screening. Because of wide phenotypic variability, diagnostic and treatment challenges remain.
- Referral to a metabolic specialist allows establishing the diagnosis in a timely, cost-effective manner.
- Early recognition of inherited metabolic myopathies allows appropriate choice of therapies conditions and the opportunity to provide genetic counseling to families.

INTRODUCTION

Muscle tissue (heart and skeletal) has a high energy demand to perform essential functions such as ionic homeostasis and contractility. Metabolic fuels for the generation of adenosine triphosphate (ATP) come from different sources, including glucose, free fatty acids, pyruvate, lactate, and ketone body metabolism, and to a lesser extent from amino acids.[1,2] Fatty acids are used as an alternative energy source when glucose is not available. In fetal heart and immediately after birth,

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acetyl-CoA derived from pyruvate metabolism and glycolysis provides reducing equivalents for energy generation. In adult hearts, the main source of ATP is oxidative phosphorylation, with 50% to 70% of the reducing equivalents coming from fatty acid oxidation (FAO).[3] The remaining ATP in the heart is derived from glycolysis and the tricarboxylic acid (TCA) cycle. In skeletal muscle, red muscle fibers rich in mitochondria are used for slow and prolonged contractions, whereas white skeletal muscle fibers depend on anaerobic glycolysis for "fast and short twitch" movements. During rest, glycolysis and oxidative phosphorylation using reducing equivalents from a low basal rate of FAO are the main source of ATP production in skeletal muscle. During fasting or physiologic stress, FAO is upregulated and becomes a major source of energy.[2–4] FAO is regulated by the availability of competing substrates (eg, glucose, lactate, ketones, and amino acids), hormonal influences, contractility, blood supply, and restrictions in oxygen supply. FAO rates are ultimately modulated by transcriptional control of the genes for enzymes involved in fatty acid metabolism and mitochondrial biogenesis.[3,5]

Long-chain fatty acyl-CoAs cross the inner mitochondrial membrane via the carnitine shuttle. Acyl-CoA molecules are first conjugated to carnitine by carnitine-palmitoyl transferase I (CPT1). Acylcarnitines are then transported across the highly impermeable inner mitochondrial membrane by the carnitine-acylcarnitine translocase (CACT). Free acyl-CoAs are then released into the mitochondrial matrix via the action of carnitine-palmitoyl transferase 2 (CPT2) with transport of free carnitine back to the cytoplasm (**Fig. 1**).[3–5] Medium- and short-chain acyl-CoAs enter mitochondria

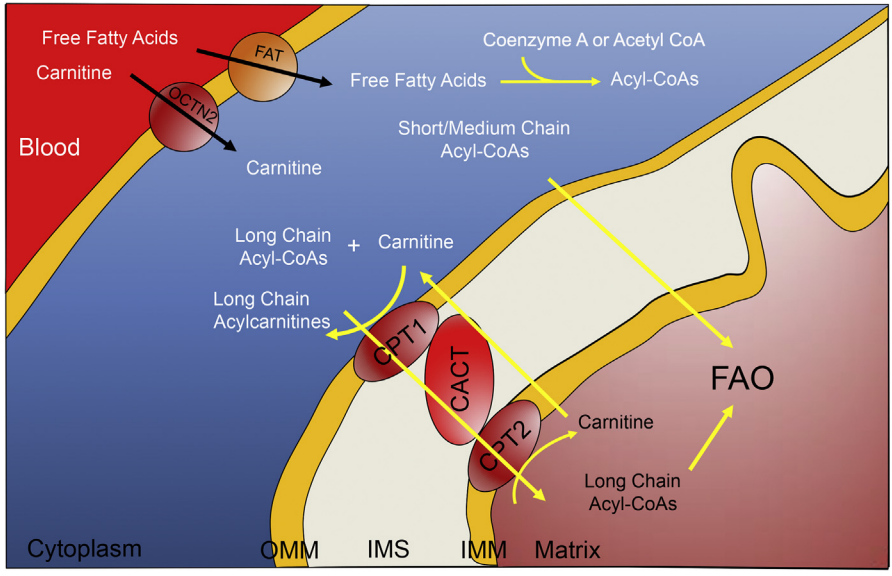

Fig. 1. Fatty acid transport and carnitine shuttle. Carnitine is imported into cells by the carnitine transporter (OCTN2). Free fatty acids enter the cell through dedicated transferases (FAT). Carnitine acyltransferases reversibly transfer an acyl group from an acyl-CoA to carnitine for long-chain substrates. The carnitine shuttle system facilitates the transport of long-chain fatty acids from the cytosol into the mitochondrial matrix, where FAO takes place. This system is made up of CPT1 on the outer mitochondrial membrane (OMM), CACT an inner-mitochondrial membrane space (IMS) protein, and CPT2 on the inner membrane of the mitochondria (IMM).