Mitochondrial dysfunction in skeletal muscle of fukutin deficient mice is resistant to exercise- and AICAR-induced rescue

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Abstract

New findings: What is the central question of this study? Does fukutin deficiency in skeletal muscle cause mitochondrial dysfunction, and if so, can AMPK stimulation via AICAR attenuate this through regulation of mitochondrial biogenesis and autophagy? What is the main finding and its importance? Mitochondrial dysfunction is associated with fukutin deficiency and AMPK stimulation may benefit muscle contractility to a greater extent than mitochondrial function.

Abstract: Disruptions in the dystrophin-glycoprotein complex (DGC) are clearly the primary basis underlying various forms of muscular dystrophies and dystroglycanopathies, but the cellular consequences of DGC disruption are still being investigated. Mitochondrial abnormalities are becoming an apparent consequence and contributor to dystrophy disease pathology. Herein, we demonstrate that muscle-specific deletion of the fukutin gene [Myf5/fktn-KO mice (Fktn KO)], a model of secondary dystroglycanopathy, results in ~30% lower muscle strength (P < 0.001) and 16% lower mitochondrial respiratory function (P = 0.002) compared to healthy littermate controls (LM). We also observed ~80% lower PGC-1α gene expression (P = 0.004), a primary transcription factor for mitochondrial biogenesis, in Fktn KO mice that likely contributes to the mitochondrial defects. PGC-1α is post-translationally regulated via phosphorylation by AMPK. Treatment with the AMPK agonist AICAR (5-aminoimidazole-4-carboxamide ribonucleotide) failed to rescue mitochondrial deficits in Fktn KO mice (P = 0.458) but did have beneficial (~30% greater) effects on recovery of muscle contractility following injury in both LM and Fktn KO mice compared to saline treatment (P = 0.006). The beneficial effects of AMPK stimulation via AICAR on muscle contractile function may be partially explained by AMPK’s other role of regulating skeletal muscle autophagy, a cellular process critical for clearance of damaged and/or dysfunctional organelles. Two primary conclusions can be drawn from this data, 1) fukutin deletion produces intrinsic muscular metabolic...
defects that likely contribute to dystroglycanopathy disease pathology, and 2) AICAR treatment accelerates recovery of muscle contractile function following injury suggesting AMPK signaling as a possible target for therapeutic strategies. This article is protected by copyright. All rights reserved.

**Keywords:** dystroglycan; fukutin; mitochondrial oxygen consumption; mitochondrial respiration; muscle regeneration; muscle torque; muscular dystrophy; oxidative plasticity.

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