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Mini-Review

Mitochondria-SR interaction and mitochondrial fusion/fission in the regulation of skeletal muscle metabolism

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ABSTRACT

Mitochondria-endoplasmic/sarcoplasmic reticulum (ER/SR) interaction and mitochondrial fusion/fission are critical processes that influence substrate oxidation. This narrative review summarizes the evidence on the effects of substrate availability on mitochondrial-SR interaction and mitochondria fusion/fission dynamics to modulate substrate oxidation in human skeletal muscle. Evidence shows that an increase in mitochondria-SR interaction and mitochondrial fusion are associated with elevated fatty acid oxidation. In contrast, a decrease in mitochondria-SR interaction and an increase in mitochondrial fission are associated with an elevated glycolytic activity. Based on the evidence reviewed, we postulate two hypotheses for the link between mitochondrial dynamics and insulin resistance in human skeletal muscle. First, glucose and fatty acid availability modifies mitochondria-SR interaction and mitochondrial fusion/fission to help the cell to adapt substrate oxidation appropriately. Individuals with an impaired response to these substrate challenges will accumulate lipid species and develop insulin resistance in skeletal muscle. Second, a chronically elevated substrate availability (e.g. overfeeding) increases mitochondrial production of reactive oxygen species and induced mitochondrial fission. This decreases fatty acid oxidation, thus leading to the accumulation of lipid species and insulin resistance in skeletal muscle. Altogether, we propose mitochondrial dynamics as a potential target for disturbances associated with low fatty acid oxidation.

1. Introduction

Low fatty oxidation in contexts of high fatty acid availability (e.g., high-fat diets or fasting) may contribute to the development of obesity and insulin resistance [1–4]. Regulating substrate oxidation may thus help in obesity prevention and treatment. Nevertheless, the mechanisms that regulate the adaptation of substrate oxidation to the changes in substrate availability are not fully clear. Evidence suggests that the mitochondrial fusion/fission dynamics and the mitochondrial-sarcoplasmic/endoplasmic reticulum (SR/ER) interaction play a role, either as separate or coupled processes [5–10]. Indeed, data in humans, animals, and cell lines show that fasting-to-feed and feed-to-fasting transitions – which influence fatty acid and glucose availability – modify mitochondria fusion/fission dynamics and mitochondria-SR interaction [6–10]. These modifications ultimately help adapt substrate oxidation appropriately [9,11].

In this mini-review, we summarized the evidence on the effects of substrate availability on mitochondrial-SR interaction and mitochondria fusion/fission dynamics to modulate substrate oxidation. We focused on human skeletal muscle due to its relevant role in whole-body metabolic control. Based on the current evidence, we also postulated some hypotheses about the link between mitochondrial dynamics and insulin resistance in skeletal muscle.

1.1. Association between fatty acid oxidation and insulin resistance in human skeletal muscle

In humans with normal weight, skeletal muscle represents ~40 % of the body mass and is responsible for ~80 % of insulin-stimulated glucose uptake [12]. This makes skeletal muscle highly relevant for metabolic control. Obesity and physical inactivity are associated with skeletal muscle insulin resistance, which increases the risk for type 2 diabetes [13]. Yet the underlying causes of skeletal muscle insulin resistance have not been fully elucidated. An excessive accumulation of lipid species resulting from a low capacity to oxidize fatty acids has been proposed [1–4]. These lipid species would disturb insulin signaling through several mechanisms, thus reducing glucose uptake [13]. For example, the accumulation of diacylglycerol increases the activity

Abbreviations: SR, sarcoplasmic reticulum; PKC, protein kinase C; IR, insulin receptor; PKB, protein kinase B; GLUT4, glucose transporter protein type 4; RQ, respiratory quotient; Mfn, mitofusin; Opa1, Optic Atrophy 1; DRP1, Dynamin-related Protein 1; MFF, Mitochondrial Fission Factor; MID, Mitochondrial Dynamics Protein; FIS1, Mitochondrial Fission 1; XeB, xestosponginB; MetF, metabolic flexibility; ROS, reactive oxygen species; MtPTP, mitochondrial permeability transition pore; IP3-R, inositol (1,4,5)-trisphosphate receptor

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