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The Manifold Role of the Mitochondria in Skeletal Muscle Insulin Resistance

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Summary

The pathophysiology of skeletal muscle insulin resistance is likely multifactorial involving many coordinated physiological processes. However, it is apparent that the mitochondria play an essential role in skeletal muscle insulin sensitivity in health, aging and in numerous metabolic diseases. Deciphering the manifold functions of the mitochondria will allow us to understand the complex relationship between mitochondria and skeletal muscle insulin resistance.

Keywords

Mitochondria; muscle; lipid; reactive oxygen species; signaling

Introduction

Approximately 100 million adults, or almost 1/3 of the US population, have either type 2 diabetes or prediabetes; conditions characterized by insulin resistance[1]. Insulin resistance is a condition of decreased responsiveness to insulin (i.e. insulin action) of peripheral tissues including skeletal muscle, liver and adipose tissue. However, due to the large role of skeletal muscle in mediating peripheral glucose uptake in response to insulin (>80%), skeletal muscle thought to be the main contributor to the development of insulin resistance in humans[2].

Identifying the mechanisms for insulin resistance in the development of type 2 diabetes has been vigorously pursued for decades. The role skeletal muscle mitochondria plays in the development of insulin resistance has been particularly an area of intense investigation and debate[3, 4]). Mitochondria are organelles involved in many different cellular functions including energy production, cellular signaling, heme production, Ca^{2+} regulation, apoptosis, and autophagy (reviewed in [5]). The knowledge surrounding the role the mitochondria plays in insulin resistance has significantly advanced over the past 20 years. The purpose of this paper is to review the most recent evidence and current thought regarding the role of the mitochondria in skeletal muscle insulin resistance.

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Conflicts of interest

None declared.

Mitochondrial ‘deficiency’, lipid accumulation and insulin resistance

Over 50 years ago, Randle and colleagues reported that byproducts (acetyl-CoA, NADH, ATP) of fatty acid oxidation can induce skeletal muscle insulin resistance through pyruvate dehydrogenase inhibition, subsequently termed the ‘Randle hypothesis’[6]. Although some tenets of this hypothesis have been challenged[7], numerous studies have since found a strong relationship between fatty acid metabolism and insulin resistance (reviewed in [8]). Several studies using a high-fat diet model in rodents have shown that increasing fatty acid levels lowers mitochondrial biogenesis (e.g. PGC-1 α) and enzyme capacity (reviewed in [3]). Also, obesity, physical inactivity, and the accumulation of lipid in non-adipose tissues has been strongly associated with insulin resistance in humans[9] (also reviewed in [3]). A series of key studies found lower skeletal muscle mitochondrial oxidative enzyme capacity and morphological alterations (i.e. smaller mitochondria) in obese and diabetic participants compared to healthy, lean individuals. In addition, these studies also found accompanying higher skeletal muscle lipid content and lower insulin sensitivity in these obese and diabetic individuals (reviewed in [3, 4]). Other investigators reported impaired mitochondrial and fatty acid oxidative capacity in insulin resistant individuals (reviewed in [10]). Moreover, concurrent improvements in skeletal muscle oxidative capacity, fat oxidation and insulin sensitivity in conjunction with a reduction in skeletal muscle lipid content with exercise training in obese individuals[11] further suggested that increasing mitochondrial oxidative capacity and fat metabolism decreases skeletal muscle lipid content and improves insulin sensitivity. Later evidence found that fatty acid metabolites, specifically fatty acid CoA, diacylglycerol and ceramides, were strongly associated with disrupted insulin signaling in skeletal muscle (reviewed in [7]). Altogether, these findings pointed to mitochondrial deficiency as the cause of impaired fatty acid oxidation capacity and skeletal muscle fat accumulation, ultimately leading to the mitochondrial driven “lipotoxicity” hypothesis of insulin resistance[12].

Although a strong relationship between altered skeletal muscle lipid metabolism and insulin resistance was established, not all studies and thought agreed that mitochondrial deficiency caused lipid-induced insulin resistance. For example, Holloszy[4] highlighted that although mitochondrial capacity is lower in type 2 diabetic muscle, due to the large capacity of skeletal muscle mitochondria to increase oxidative capacity during exercise, reductions in oxidative capacity in insulin resistant muscle should not have any effect on the basal capacity to oxidize fatty acids and thus cannot be the cause of excess skeletal muscle lipid accumulation. Other studies demonstrated that increased fatty acid flux in skeletal muscle during high-fat diets either had either no effect or in contrast increased mitochondrial biogenesis and capacity. Transgenic models upregulating mitochondrial biogenesis targets (i.e. PGC-1 α , PPAR- α) have shown increased mitochondrial oxidative protein content and capacity paradoxically have shown increased susceptibility to diet-induced insulin resistance (all reviewed in [13]). In humans, Fisher-Wellman et al. recently found normal mitochondrial capacity and content in obese, insulin resistant individuals[14]. In a notable and well-publicized study, Goodpaster et al.[15] found that endurance athletes had elevated skeletal muscle lipid content *and* high mitochondrial capacity; a condition termed the ‘athlete’s paradox’. Lastly, a recent study where inducible pluripotent stem cells were generated from genetically insulin resistant humans found that insulin resistance might

induce mitochondrial dysfunction-not the reverse[16]. Taken together, these studies strongly refute the notion that mitochondrial deficiency causes skeletal muscle insulin resistance.

Skeletal muscle mitochondrial bioenergetics

Many of these early studies neglected the role mitochondrial bioenergetics plays in interpretation of the mitochondria-substrate metabolism relationship in skeletal muscle. This idea was highlighted by Neufer and colleagues ([13, 17]) in two eloquent perspective papers. In these papers, the authors suggested that mitochondrial fuel load (carbon flux through β -oxidation), production of reactive oxygen species (ROS), and the resultant inter-relationships with the redox balance more likely causes skeletal muscle insulin sensitivity rather than impaired mitochondrial capacity. In other words, in obesity and during high-fat feeding, fuel supply consistently outpaces energy demands resulting in mitochondrial oxidant production and emission which can result in impaired insulin signaling and insulin resistance[17]. The chemiosmotic theory states that ATP production is contingent on the reduction potential of the electron transport chain accepting electrons from reducing equivalents (e.g. NADH, FADH₂) generated from the Krebs' cycle and the transference (i.e. pumping) of the donated protons into the intermembrane space that ultimately generates the electric, or membrane potential necessary for ATP synthase activation. In the condition of low energy demands (i.e. rest, low ATP resynthesis), that a 'back pressure' of protons on the outer surface of the inner mitochondrial membrane opposes additional pumping of protons from reducing equivalents and slows electron flow and O₂ consumption[17]. Because the inner mitochondrial membrane is inherently 'leaky' to electrons (which generates ROS), electron flow and O₂ consumption continues at a basal or 'idling' rate (state 2 respiration). In the conditions of increase carbon flux (i.e. obesity, high-fat diet) and elevated redox state ($\uparrow$ NADH/NAD⁺, $\uparrow$ FADH₂/FAD⁺, $\uparrow$ NADPH/NADP⁺) and in the absence of high-energy demand (i.e. exercise), there is a constant state of 'back pressure'. This results in incomplete β -oxidation, intermediate production and elevated mitochondrial inner membrane electron leak and ROS generation. This is important because several intermediates and byproducts of β -oxidation, redox and ROS pathways have been shown to be potent primary and secondary signaling mechanisms[5].

Two recent articles have suggested a potential mechanism underlying the relationship between skeletal muscle mitochondrial bioenergetics and insulin resistance. First, Sparks et al.[18•] discovered that gene expression of the mitochondrial inner membrane adenine nucleotide translocator 1 (ANT1), a mitochondrial ATP for cytosolic ADP exchanger, was elevated in exercise-trained subjects compared to untrained subjects and increased ANT1 expression was associated with increased fatty acid-induced uncoupling and insulin sensitivity. Morrow et al.[19••] subsequently found that mitochondrial capacity was decreased and uncoupling and proliferation were increased in ANT1-deficient mice, and that these mice were resistant to high-fat diet-induced lipotoxicity and insulin resistance. Although these findings appear contradictory, both studies used models where energy consumption was increased (e.g. either through exercise or uncoupling). This is an important concept was highlighted by Muoio and Neufer[13] as with increased energy consumption, redox pressure ('back pressure') is relieved, potentially resulting in lower deleterious ROS and β -oxidation intermediate generation.

β-oxidation

β-oxidation is the process of fatty acid catabolism to acetyl-CoA which subsequently enters the Krebs's cycle for the generation of reducing equivalents (e.g. NADH, FADH₂) that enter the electron transport chain. During lipid overload, a constant substrate flux through β-oxidation ensues and in the presence of incomplete β-oxidation, produces short- and long-chain intermediates called acylcarnitines which may play a role in mitochondrial acyl-CoA balance and glucose homeostasis[20]. A recent publication by Aguer et al.[21] in differentiated C2C12, primary mouse, and human myotubes that were treated with acylcarnitines (C4:0, C14:0, C16:0) or with palmitate found a reduction in insulin sensitivity in both conditions and that palmitate-induced insulin resistance was rescued by inhibiting acylcarnitine production. Both conditions of insulin resistance were associated with an increase in oxidative stress levels indicating that excess acylcarnitines might contribute to skeletal muscle insulin resistance through ROS signaling. Another recent mouse study[22] and several recent human studies have confirmed this relationship between acylcarnitines and insulin resistance. In humans, Sun et al. found in a large longitudinal study (n>2,000) that plasma acylcarnitines were strongly predictive of the development of type 2 diabetes[23]. Batchuluun et al. (2018) also found acylcarnitines predicted the development of type 2 diabetes but in this study, following gestational diabetes[24]. Lastly, Consitt et al.[25] found a reduced response in insulin-stimulated acylcarnitine lowering in older individuals that was accompanied by a blunting of acetyl-CoA carboxylase phosphorylation; identifying a potential mechanism for acylcarnitine-mediated metabolic inflexibility and insulin resistance. Together, increased generation of acylcarnitines during times of lipid overload appear to contribute to skeletal muscle insulin resistance.

Reactive oxygen species and redox signaling

Much of the recent data on the relationship between mitochondria and insulin resistance focuses on reactive oxygen species and redox signaling. A large body of evidence suggests that excess mitochondrial ROS production is associated with insulin resistance[26]. An elevated redox state can generate excess ROS which includes the superoxide anion radical (O₂^{•-}), hydrogen peroxide (H₂O₂) and the highly reactive hydroxyl radical (*OH). H₂O₂, has been shown to be the primary signaling ROS generated by the mitochondria[27] and an increased production of H₂O₂ seems to play a significant role in skeletal muscle insulin resistance[28]. A recent study by Konopka et al. in obese humans supported this by demonstrating that exercise training can reduce mitochondrial H₂O₂ emissions, improve mitochondrial efficiency and restore insulin sensitivity[29]. Another recent study suggested that reducing H₂O₂ by increasing antioxidant capacity might improve insulin sensitivity through reducing of intramuscular lipid accumulation rather than a reduction in ROS signaling[30].

H₂O₂ appears to be involved in the regulation of several redox signaling pathways including NADPH/NADP⁺ and the glutathione (GSH/GSSG) and thioredoxin (Trx_{Red}/Trx_{Ox}) redox couples (reviewed in [17, 31]). Evidence suggests that the redox environment regulates protein phosphorylation/dephosphorylation through redox-sensitive sulfur containing Cys residues found in most mammalian phosphatase enzymes[32]. This is potentially important in the mediation of skeletal muscle insulin resistance as the insulin receptor substrate (IRS)

has approximately 70 Ser/Thr residues that are subject to phosphorylation. Also, alterations in Ser/Thr phosphatase tone can also affect the kinetic activity of Ser/Thr kinases; known effectors of skeletal muscle insulin resistance[17, 33]. Recent studies have shown the important role of Ser/Thr protein kinase 25 (STK25) in diet induced skeletal muscle insulin resistance, mitochondrial function and ectopic lipid accumulation[34, 35].

Thioredoxin-interacting protein (TXNIP), an α -arrestin family member of signaling proteins, impairs insulin signaling through inhibition of thioredoxin NADPH-reduction of sulfur residues on phosphatidylinositol 3-phosphatase and blunts glucose uptake[36]. A recent study in obese humans, Johnson et al.[37•] used caloric restriction as a model to improve skeletal muscle insulin sensitivity. In the absence of changes in mitochondrial capacity or oxidant emission or intramuscular lipid (and metabolite) content, this study identified decreased TXNIP as a mediator of improvements in insulin sensitivity in this model. Ahn et al.[38••] subsequently found that TXNIP is regulated by MondoA; transcription factor thought to regulate carbon and energy homeostasis, intramyocellular triglyceride synthesis and de novo lipogenesis. Further, Kaadige et al.[39] found that mammalian target of rapamycin (mTOR), a Ser/Thr kinase, along with ROS, regulates MondoA, providing evidence for a link between redox signaling and lipid-mediated insulin resistance in skeletal muscle.

Mitochondrial derived peptides

Mitochondria contain its own DNA comprised of 37 genes encoding proteins, tRNAs, rRNAs and small RNAs[40]. The mitochondria produce short peptides (also called ‘mitochondrial derived peptides’) that can act as circulating signaling molecules capable of affecting several areas of health and disease[41]. Humanin, the first mitochondrial derived peptide identified, improves insulin sensitivity, β cell survival, and delays the onset to diabetes[42]. Recently, Cobb et al.[43] found an additional six small humanin-like peptides (SHLP 1–6) that improved mitochondrial metabolism, reduced ROS generation, and improved insulin sensitivity. Moreover, a second mitochondria-derived peptide called mitochondrial open reading frame of the 12S rRNA-c (MOTS-c) was recently discovered by Lee et al.[44••]. MOTS-c was shown to positively regulate skeletal muscle insulin sensitivity and prevent obesity during high-fat feeding, likely through AMPK activation. These data indicate that the mitochondria might regulate insulin sensitivity and metabolic homeostasis through secreted peptides encoded by their own genome.

Sirtuins

Sirtuins (SIRT) are NAD⁺-dependent deacetylases that first gained their notoriety in the aging field however; SIRT3 has been shown to play an important role in skeletal muscle insulin sensitivity through alterations in mitochondrial function, oxidative stress, and insulin signaling[45]. Recently, another sirtuin (SIRT6) has also been shown to regulate mitochondrial function and insulin sensitivity [46]. Specifically, Cui et al. found that SIRT6 deletion decreased expression of genes associated with glucose and lipid uptake, fatty acid oxidation, and mitochondrial function and that overexpression of SIRT6 activated AMPK. Taken together, sirtuins appear to play an important role in mitochondrial function and

metabolic homeostasis and alterations in SIRT3/6 could contribute to skeletal muscle insulin resistance.

Concluding Remarks

The role of the mitochondria plays in skeletal muscle insulin resistance has been intensely investigated and debated for over twenty years. Early studies focused on the effects of mitochondrial deficiency (i.e. impaired capacity) on glucose and lipid metabolism but subsequent studies have shown that maximal mitochondrial capacity does not have significant effects on basal mitochondrial metabolism. Other work indicated that specific metabolites/intermediates of ectopic lipid accumulation impedes insulin signaling however not all studies agree on the precise mechanisms of lipid-induced insulin resistance in skeletal muscle. Much of the recent data suggest that mitochondrial signaling, including ROS, redox pathways, acylcarnitines, mitochondrial derived peptides, microRNAs[47] or other novel proteins (e.g. Brca1)[48] play a significant role in mitochondrial function, including the regulation of both lipid and glucose metabolism. In addition, it is apparent that mitochondrial bioenergetic state (i.e. energy flux) can significantly influence the interpretation of the relationship between mitochondrial function and metabolic control. In conclusion, it is clear that the role of the mitochondria in substrate metabolism in skeletal muscle is multi-faceted and dependent on bioenergetic state and advances in scientific technology will ultimately demonstrate in greater detail the manifold role of the mitochondria plays in skeletal muscle insulin resistance.

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Purpose of review

The role of mitochondria in the development of skeletal muscle insulin resistance has been an area of intense investigation and debate for over 20 years. The mitochondria is a multi-faceted organelle that plays an integral part in substrate metabolism and cellular signaling. This article aims to summarize the current findings and thought regarding the relationship between mitochondria and insulin resistance in skeletal muscle.

Recent findings

Skeletal muscle insulin resistance was earlier thought to result from deficiency in mitochondrial oxidative capacity and ectopic lipid accumulation. Recent evidence suggests that skeletal muscle insulin resistance in high-energy intake models (i.e. obesity) results primarily from disrupted mitochondrial bioenergetics and alterations in mitochondrial-associated cell signaling. These signaling pathways include reactive oxygen species and redox balance, fatty acid β -oxidation intermediates, mitochondrial derived peptides, sirtuins, microRNAs and novel nuclear-encoded, mitochondria-acting peptides.

Key Points

- Mitochondrial 'deficiency' (i.e. reduced maximal oxidative capacity) does not appear to mediate ectopic skeletal muscle lipid accumulation and insulin resistance.
- Mitochondrial bioenergetic state (i.e. energy flux) can significantly influence the relationship between mitochondrial function and metabolic control.
- Recent data suggest that mitochondrial signaling, including ROS, redox pathways, acylcarnitines, mitochondrial derived peptides, microRNAs or other novel proteins play a significant role in mitochondrial function, including the regulation of both lipid and glucose metabolism.