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The role of mitochondria in health and disease

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Abstract

Mitochondria play a key role in energy metabolism in many tissues, including skeletal muscle and liver. Inherent disorders of mitochondria such as DNA deletions cause major disruption of metabolism and can result in severe impairment or death. However, the occurrence of such disorders is extremely rare and cannot account for the majority of metabolic disease. Recently, mitochondrial dysfunction of a more subtle nature in skeletal muscle has been implicated in the pathology of chronic metabolic disease characterized by insulin resistance such as obesity, type 2 diabetes mellitus, and aging. This hypothesis has been substantiated by work from Shulman and colleagues, showing that reduced mitochondrial oxidative capacity underlies the accumulation of intramuscular fat causing insulin resistance with aging. However, recent work by Nair and coworkers has demonstrated that mitochondrial activity may actually be higher in persons exposed to high-calorie diet leading to obesity, suggesting that the accumulation of intramuscular fat and associated fatty acid metabolites may be directly responsible for the development of insulin resistance, independent of mitochondrial function. These inconsistent findings have promoted ongoing investigation into mitochondrial function to determine whether impaired function is a cause or consequence of metabolic disorders.

Introduction

Mitochondria are the power-generating units of the cell and are abundant where energy-requiring processes take place, such as skeletal and cardiac muscle. The primary role of mitochondria is to convert the products of carbohydrate, protein, and fat metabolism to CO₂ and water, using key enzymes of the electron transport chain; NADH dehydrogenase (Complex I), succinate dehydrogenase (Complex II), cytochrome bc₁ (Complex III), and cytochrome *c* oxidase (Complex IV). During these reactions, protons (H₊) are pumped from the matrix to the intercrisat space, establishing a proton gradient. Protons diffusing back along this gradient drive the synthesis of ATP by the enzyme ATP synthase (Complex V). The coupling of substrate oxidation with ATP formation in the mitochondria is called oxidative phosphorylation and is central to the health of a variety of tissues and organs. Dysfunction of these mitochondrial complexes may also play an important role in the pathogenesis of some chronic diseases, as the occurrence of metabolic disorders is often accompanied by a disruption in mitochondrial function. However, what is not clear is whether the mitochondria are perpetrators or victims of the metabolic disarray. In this chapter, we will present and review some of the data for and against the hypothesis that the presence of an inherent mitochondrial dysfunction underlies some of the observed metabolic abnormalities.

Overview of mitochondrial oxidative phosphorylation

The mitochondria generate most of the energy used by cells. Electrons from $\text{NADH} + \text{H}^+$ and FADH_2 (generated from the oxidation of acetyl-Co A in the TCA cycle) are transferred to complexes I and II of the electron transport chain (ETC). These electrons are subsequently passed along the ETC and are eventually donated to oxygen ($1/2 \text{O}_2$) to create H_2O . Energy is released as the electrons flow along the ETC and this energy is used to pump protons out across the mitochondrial inner membrane through complexes I, III, and IV. This creates a proton electrochemical gradient or proton motive force (ΔP), and the potential energy stored in ΔP can be used to import proteins and Ca^{2+} into the mitochondrion, to generate heat, and to synthesize ATP within the mitochondrial matrix. Specifically, the synthesis of ATP occurs when protons flow from the intermembrane space to the matrix through the ATP synthase. Matrix ATP is then exchanged for cytosolic ADP through the inner membrane adenine nucleotide translocators (ANTs).

The efficiency by which reducing equivalents (from oxidation of acetyl-CoA) are converted to ATP by oxidative phosphorylation is called the coupling efficiency. Mitochondria are imperfectly coupled, such that during normal oxidative phosphorylation, some of the redox energy in substrates is lost as heat. Incomplete coupling is due mostly to a natural leak of protons across the mitochondrial inner membrane. The uncoupling of proton transport across the membrane from ATP production may be responsible for up to 20–25% of whole-body basal metabolic rate (BMR) [1]. A naturally occurring uncoupler of mitochondria is the uncoupling protein 1 (found only in brown fat), and perhaps the uncoupling proteins 2, and 3 (found primarily in skeletal muscle). These proteins cause the inner membrane to ‘leak’ by allowing protons to cross into the matrix without creating ATP, dissipating the energy as heat.

Mitochondrial efficiency and body weight

The alteration of mitochondrial coupling efficiency caused by variation among mitochondrial proteins has been proposed to determine the proportion of calories that are used to generate ATP versus those that are used to create heat [2,3]. A greater amount of skeletal muscle UCP may cause the mitochondria to be less efficient, shifting a greater proportion of potential ATP energy to be lost as heat. In turn, this inefficiency causes the mitochondria to oxidize additional acetyl-CoA in order to generate the ATP required by the cell. The additional acetyl-CoA must either come from the diet (in the form of increased food intake) or from primarily adipose stores, and the latter would eventually cause a significant decrease in body weight. Thus, in individuals with high coupling efficiency, most of the energy from substrate oxidation is used to create ATP, with relatively little lost as heat, and excess energy is stored as fat. In individuals with low efficiency, a greater percent of energy from substrate oxidation is dissipated as heat causing additional substrate to be oxidized in order to meet cellular energy demand. This variation in coupling could partly explain why individuals have very different responses in body weight to conditions of equal calorie restriction or calorie excess [4,5].

Mitochondrial efficiency and oxidative stress

In addition to energy, oxidative phosphorylation OXPHOS also generates reactive oxygen species (ROS). The pumping of protons across the inner membrane with the accumulation of electrons causes the mitochondria to be the major source of cellular ROS production (Figure 1). When the ETC becomes highly reduced (saturated with electrons), excess electrons from complexes I and III can be passed directly to O_2 to generate superoxide anion which can eventually be further reduced to form $\text{OH}^\bullet$, a very potent oxidizing agent. Between 0.2 and 2% of oxygen taken up by cells is converted into ROS [6].

Defects in the transfer of electrons across the mitochondrial membrane can cause electrons to accumulate on the ETC complexes and enhance ROS production. The accumulation increases the potential for electrons to bind with free oxygen species and may contribute to a wide variety of pathologic conditions including degenerative diseases, cancer and aging [7]. Under conditions of excess energy intake (relative to metabolic energy requirements) and tight mitochondrial coupling, the ETC complexes become saturated with electrons, and the proton motive force is driven to a maximum. The ETC slows and electrons are released directly to oxygen to form O_2^- . With time, this excess ROS production may exceed the antioxidant capacity of the mitochondria eventually causing cell damage or death. Accordingly, Brand [8] has hypothesized that greater mitochondrial uncoupling, which helps to dissipate the electron gradient, reduces ROS production thereby protecting the mitochondria and other cellular proteins and lipids from superoxide radical damage. Supporting his theory, he and Speakman [9•] showed that increased mitochondrial uncoupling was related to longer lifespan in rodents. Therefore, conditions that decrease the proton gradient (uncoupling, calorie restriction) are thought to be protective against conditions or diseases linked with oxidative stress (aging, diabetes mellitus, some forms of cancers).

Mitochondrial function and insulin resistance

Insulin resistance may be caused by mild mitochondrial dysfunction (or, 'impaired mitochondrial fitness') or may be a result of increased lipid supply due to a high-energy diet or increased lipolysis [10]. Insulin resistance could also occur because of increased storage of lipid inside cells of tissues that normally hold negligible amounts (muscle and liver), otherwise referred to as ectopic lipid. All conditions of increased lipid availability are thought to cause insulin resistance by the production of intracellular lipid metabolites (long-chain fatty acyl-CoA, diacylglycerol, and ceramides), which are known to stimulate inflammatory pathways that interfere with insulin signaling [11]. Reduced mitochondrial function (thus, reduced lipid oxidation) may lead to ectopic lipid accumulation and insulin resistance [12]. Indeed, previous studies have shown that abnormalities in mitochondrial number and/or size, structure and function are present in insulin-resistant states [13•]; however, there is still no conclusive evidence whether the alterations are primary or secondary, that is, the cause or consequence of the condition.

To summarize, mitochondrial functions such as respiratory coupling, reactive oxygen species production, enzymatic activity (fatty acid oxidation), and mitochondrial content and size have been associated with conditions of aging, insulin resistance and type 2 diabetes. However, the cross-sectional nature of most associations limits the determination of cause and effect relationships. Below is a review of conditions associated with true mitochondrial dysfunction as well as a more subtle dysfunction (impaired mitochondrial fitness). Despite considerable advances in technology to measure human mitochondria, we are still unable to determine whether impaired function or 'fitness' is because of alterations in individual mitochondria, a reduction in mitochondrial density (number and/or size of normally functioning mitochondria), differences in O_2 delivery to the mitochondria, or decreased cellular energy demand [10].

Mitochondrial dysfunction of rare diseases

The first recognition that mitochondria may play a role in disease pathogenesis came from a report by Luft and colleagues almost 50 years ago of a patient with severe hypermetabolism and weight loss. The skeletal muscle of this patient contained large numbers of abnormal mitochondria, a condition now known as mitochondrial myopathy [14•]. Symptoms included severe hypermetabolism (BMR between 50 and 100% above normal), excessive thirst, and extreme thinness (BMI 14.4 kg/m²) despite consuming between 3000 and 3500

kcal/day. Studies of isolated mitochondria revealed a nearly absent ability of the mitochondria to adjust the respiratory rate according to access to phosphate acceptor. This lack of adjustment resulted in nearly maximal rates of oxidative phosphorylation activity unaffected by substrate availability or presence of uncoupling agents. Thus, the muscle mitochondria could produce only a fraction of the ATP required by the cell (especially during physical activity), and the unconverted fuel was diverted into heat production.

Most 'true' mitochondrial diseases, such as above, are the result of mitochondrial DNA (mtDNA) deletions, which cause the formation of mutant mtDNA. Examples of these diseases include Kearns–Sayre syndrome and Pearson syndrome, which result in severe impairment and even death, usually in infancy or early childhood. These conditions are rare, however, and the question often posed is, could mutations in mtDNA contribute to more common conditions such as insulin resistance, type 2 diabetes and muscle atrophy in aging? Or is it more likely that environmental factors including high-fat diet and physical inactivity are to blame (Figure 2)?

Mitochondrial mutations are known to be present in approximately 2% of patients with type 2 diabetes mellitus (T2DM) and are also found in elderly individuals. In addition, a polymorphism of the mitochondrial coding region of the *ND1* gene (a subunit of reduced NADH dehydrogenase) has been found to be associated with resting metabolic rate (RMR) in a large ($n = 245$) group of nondiabetic Pima Indians, a population highly susceptible to developing T2DM [15]. Specifically, a single-nucleotide polymorphism resulting in a change from isoleucine to valine at amino acid 81 (site 3457) is associated with a lower RMR. However, further investigation into the functional mitochondrial consequences in a small subsample ($n = 14$) revealed no detrimental effect of the polymorphism on the coupling or the maximal capacity of isolated mitochondria [15]. Therefore, while it is clear that mitochondrial deletions and myopathies result in major metabolic disruption, it is unknown whether less significant mitochondrial mutations can cause mitochondrial dysfunction. Nonetheless, common manifestations of aging such as muscle weakness, diabetes, vision and hearing losses and dementia, are also symptoms of overt mitochondrial disease.

Mitochondrial dysfunction of common metabolic disorders

Aging

Petersen *et al.* [16•] found that *in vivo* rates of mitochondrial oxidative and phosphorylation activity were both reduced by approximately 40% in elderly (aged 61–84 years) compared to young (aged 18–39 years) subjects. Intramyocellular lipid content (IMCL) was also higher in the elderly volunteers, and insulin sensitivity was lower. Conclusions from this paper suggested that insulin resistance in the elderly is related to increase IMCL, which may be a result of an age-associated decrease in mitochondrial activity. Decreased mitochondrial number and/or function (versus a defect in coupling) were implicated as the cause for reduced activity. However, it is important to keep in mind that the relationship between mitochondrial phosphorylation activity and IMCL was significant only after rank transformation of the data ($r_s = -0.54$, $P = 0.03$), and was reported only for the group combined (not separately by age group). Additionally, these cross-sectional data do not enable us to determine which factor was causative (i.e. mitochondrial dysfunction causing IMCL accumulation, or vice versa).

Other studies [17] have shown that maximal ATP production rate (MAPR) declines approximately 8% per decade (5% after adjusting for mitochondrial protein content). This group also reported a significant inverse relationship between mitochondrial content and age [17]. Because MAPR was reduced with age when either expressed per unit of total muscle

or per mitochondrial protein, the results indicate that the decline is because of a combination of reduced mitochondrial content and a functional alteration in the existing mitochondria. Overall, the majority of studies with aging show that mitochondrial oxidative and phosphorylation capacity and/or mitochondrial content are decreased with age [16•,17–24]. However, whether or not this is related to IMCL accumulation and in turn reduced insulin sensitivity is still unclear, with some studies showing a relationship [16•] and others showing no association [25].

Type 2 diabetes

Mitochondrial dysfunction has also been implicated in the pathogenesis of insulin resistance related to type 2 diabetes. Much of this research has been done in isolated mitochondria from muscle biopsy tissue of insulin-resistant individuals, and has demonstrated reduced levels of mRNA for mitochondrial genes [26•,27,28,29•], decreased mtDNA [30,31], lower protein expression of respiratory chain subunits [27], reduced oxidative enzyme activities and decreased mitochondrial size and density [13•,27,29•,30]. Impaired basal and insulin-stimulated mitochondrial metabolism *in vivo* was also demonstrated in patients with T2DM [32,33] and first-degree relatives of T2DM patients [34–36]. Therefore it is generally well accepted that muscle mitochondrial capacity to produce ATP is reduced in T2DM patients and insulin-resistant offspring. What remains to be determined is whether this is a result of primary mitochondrial dysfunction or is secondary to the diabetic or insulin-resistant state. From the aforementioned papers, over the past five years the theory evolved that either inherent (genetic) or acquired (high-fat diet and/or low physical activity) defects of the skeletal muscle mitochondria causes the accumulation of IMCL, which subsequently interferes with appropriate insulin signaling and GLUT 4 translocation to the cell membrane, leading to insulin resistance and eventually T2DM.

Recently, Koves *et al.* [37•] challenged this theory by proposing a ‘metabolic overload’ of muscle mitochondria as the key player in insulin resistance. In a sophisticated set of experiments, this group showed that obesity, diabetes, and high-fat feeding are accompanied by increased rather than decreased rates of β -oxidation in skeletal muscle, and that suppression of mitochondrial fatty acid translocation protects against lipid-induced insulin resistance. The detrimental effects of high rates of fatty acid catabolism in insulin-resistant muscle were attributed to ‘incomplete’ fat oxidation, in which a large proportion of fatty acids entering the mitochondria were only partially oxidized. In the absence of work (namely, in the form of physical activity), the Krebs cycle not only remains inactivated at a transcriptional level but also is constrained by redox pressure and depletion of intermediates. This imbalance exacerbated incomplete oxidation and promoted the accumulation of acyl-CoAs, acyl-carnitines, and perhaps other as yet unidentified metabolites, which may contribute to mitochondrial dysfunction.

Other recent work implicates mitochondrial oxidative stress as a major cause of insulin resistance [38]. In Anderson's studies, a high-fat diet increased the H_2O_2^- emitting potential of human and rodent skeletal muscle mitochondria, shifted the cellular redox environment to a more oxidized state, and decreased the redox-buffering capacity in the absence of any change in mitochondrial respiratory function. When rodents were treated with a mitochondrial-targeted antioxidant or were genetically engineered to overexpress mitochondrial catalase, H_2O_2 emission was attenuated, and insulin sensitivity was preserved, even in the face of a high-fat diet [38].

Contradicting results on the interplay between mitochondrial function, IMCL, and insulin sensitivity are abundant. Phielix *et al.* [39] reported that a reduced basal ADP-stimulated and maximal mitochondrial respiratory capacity underlies reduced *in vivo* mitochondrial function in T2DM patients, independent of mitochondrial content, and implied that a

reduced intrinsic ADP-stimulated mitochondrial respiration was an important factor in the pathogenesis of type 2 diabetes. However, although insulin sensitivity was reduced in the diabetic subjects, sensitivity was not related to mitochondrial dysfunction or IMCL content, and the latter was not different among diabetic, first-degree relatives, or normoglycemic healthy volunteers. Another recent paper from the same group [40] reported that insulin sensitivity was improved after rosiglitazone (insulin-sensitizer) treatment; however, this improvement was not mediated through either an improvement in mitochondrial function or reduced cellular lipid accumulation.

Nair *et al.* [41] recently highlighted the importance of considering race/ethnicity when investigating the role of mitochondria in insulin resistance. This group studied diabetic and nondiabetic Indians and Northern European-Americans who were matched for age, BMI, and sex, and compared insulin sensitivity by a hyperinsuliemic–euglycemic clamp, IMCL and mitochondrial function by biopsy. Insulin sensitivity was markedly lower in the diabetic Indians as well as in the nondiabetic Indians, compared with the Northern European-Americans, and this was related to higher IMCL content, particularly in the diabetic group. However, mitochondrial function (as measured by mtDNA copy number, oxidative phosphorylation gene transcripts, citrate synthase activity and maximal mitochondrial ATP production rate) was similar among diabetic and nondiabetic Indians. Regardless of diabetic status, Indians had higher mitochondrial content and capacity than Northern European-Americans [41]. These findings indicate dissociation between mitochondrial dysfunction, IMCL content and insulin resistance, and imply that diabetes per se does not cause mitochondrial dysfunction, and that mitochondrial dysfunction cannot account for insulin resistance, at least among certain ethnic groups.

Conclusion

From this brief review we can conclude that true mitochondrial dysfunction is not responsible for the majority of metabolic disorders. Although decreases in mitochondrial content and/or activity have been demonstrated in aged individuals, diabetic patients and in first-degree relatives, the cross-sectional nature of these studies does not allow us to determine the causative factor; that is whether diabetic status causes mitochondrial dysfunction or vice versa. Indeed, conditions associated with insulin resistance (aging, obesity, T2DM) may also be influenced by an environment of sedentary lifestyle and high-fat intake. Sedentary behavior has been shown to have deleterious consequences on muscle mitochondrial oxidative capacity [25,42], and, at least in the aging model, the participation in regular endurance exercise partly normalizes mitochondrial function and prevents age-associated insulin resistance [43]. Thus, in conclusion, the underlying mechanisms responsible for impaired mitochondrial function in metabolic disorders such as insulin resistance and type 2 diabetes are far from being elucidated. Prospective clinical trials investigating mitochondrial function in various ethnic populations (at rest and during exercise) and the impact on muscular lipid accumulation and development of insulin resistance and type 2 diabetes need to be conducted to delineate the complex interplay between these variables.

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Figure 1.

Electron transport chain (ETC) of mitochondria. Energy obtained through the transfer of electrons (white arrows) down the ETC is used to pump protons (blue arrows) from the matrix into the intermembrane space, creating an electrochemical proton gradient across the mitochondrial inner membrane. This gradient allows ATP synthase to use the flow of H⁺ through the enzyme back into the matrix to generate ATP from ADP and inorganic phosphate. Complex I (NADH coenzyme Q reductase) accepts electrons from the electron carrier nicotinamide adenine dinucleotide (NADH), and passes them to coenzyme Q (ubiquinone), which also receives electrons from complex II (succinate dehydrogenase). Ubiquinol passes electrons to complex III (cytochrome bc₁), which passes them to cytochrome *c* (cyt *c*). Cyt *c* passes electrons to Complex IV (cytochrome *c* oxidase), which uses the electrons and hydrogen ions to reduce molecular oxygen to water. Sites of superoxide radical production occur primarily at Complexes I and III, particularly under conditions such as high proton gradient. Source: Obesity Online Slide Library, www.obesityonline.org.

Figure 2.

Rare mitochondrial diseases owing to DNA deletions and mutations usually results in severe functional impairment leading to myopathy, severe weakness and often death. The role of mitochondrial function/dysfunction in more common conditions such as aging, obesity, insulin resistance, and type 2 diabetes is speculative and controversial, and may be mediated through environmental factors such as poor diet and inactivity, and/or through common DNA mutations or decreased cellular energy requirement.