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Educational Paper

Clinical Nutrition University: Muscle physiology and bioenergetics

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SUMMARY

Skeletal muscle relies on a constant, adequate ATP supply to sustain contractile activity and preserve tissue mass and protein content. Skeletal muscle mitochondrial oxidative phosphorylation provides adequate amounts of ATP under physiological conditions, contributing to preserve muscle protein mass and playing a major role in glucose and lipid substrate utilization. Inflammation, oxidative stress and insulin resistance are emerging contributors to skeletal muscle mitochondrial dysfunction occurring under several disease conditions including insulin resistant states and obesity. Skeletal muscle mitochondrial dysfunction may lead to loss of muscle mass and strength as well as to altered glucose and fatty acid utilization, and these effects are associated with poor clinical outcome. Exercise training enhances skeletal muscle mitochondrial biogenesis and whole-body oxygen consumption (aerobic capacity), and these effects are likely to represent relevant mediators of the positive clinical impact of controlled exercise programs.

1. Muscle substrate metabolism and mitochondria

Skeletal muscle is an obvious, essential component of the locomotive apparatus, and its locomotive function requires maintenance and renewal of tissue contractile proteins as well as an adequate energy supply in the form of adenosine tri-phosphate (ATP). ATP cannot be stored in tissues, implying the need for continuous ATP production in the contracting muscle. ATP is provided by anaerobic glycolysis in relatively small amounts under resting conditions, and by oxidative phosphorylation in tissue mitochondria (as described below).

The concept that mitochondrial function and ability to produce ATP is crucial for muscle contraction is supported by the observation that physiological differences in mitochondrial density in different muscle groups are closely related to their ability to sustain contractile work and are inversely related to muscle fatigability. High mitochondrial density characterizes type I or "slow" fibers and is associated with prolonged aerobic contractile activity and resistance to fatigue[1] Skeletal muscles with low mitochondrial density and a majority of type II fibers in turn rely strongly on anaerobic glycolysis for energy supply and are adapted to short sets of contraction due to early fatigue. Most human muscle groups are considered to have a mixed fiber content, but prevalence of either type may have an important impact on muscle characteristics in terms of function and substrate utilization, with potential clinical implications.

From a metabolic standpoint, skeletal muscle represents a major protein reservoir. Muscle protein balance is regulated by nutritional, endocrine and cytokine-mediated signalling pathways to maintain body protein homeostasis and inter-organ amino acid exchange, in turn regulating protein metabolism in different organs and tissues.[2–5] Under fasting conditions, net amino acid release from skeletal muscle due to net excess of protein breakdown over synthesis represents a major source of precursors for hepatic gluconeogenesis. On the other hand, dietary protein and energy intake reverse net muscle protein catabolism through anabolic signalling involving insulin and amino acid elevation, leading to net muscle amino acid uptake and protein deposition.[2–5] Adequate ATP availability is necessary for muscle contraction during exercise. ATP is however also required to sustain muscle protein turnover (i.e. the continuing processes of protein renewal through breakdown and synthesis) which also represents a relevant component of tissue energy requirements. Glucose and lipid substrates are the major sources utilized for by skeletal muscle for ATP production both at rest and during exercise. Utilization at the skeletal muscle level is conversely an important component of both glucose and lipid whole-body metabolism and disposal.

1.1. Mitochondrial glucose and fatty acid oxidation and oxidative phosphorylation

Mitochondria are the key site of tissue oxygen consumption for energy production[6] A detailed description and review of glucose

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and fatty acid metabolism and of mitochondrial biochemical reactions is beyond the scope of this work. Catabolism of exogenous substrates, mostly fatty acids and glucose, leads to the formation of acetyl-coenzyme A (CoA) which enters the mitochondrial tricarboxylic acid cycle. Glucose is initially catabolised through the major metabolic pathway of glycolysis, that converts glucose into pyruvate under anaerobic conditions with concomitant production of relatively limited amounts of ATP. Glucose-derived pyruvate can be then converted to acetylCoA before transport into the mitochondria, through decarboxylation and combination with coenzyme A by pyruvate dehydrogenase (PDH) that links anaerobic and aerobic glucose metabolism (Fig. 1). Long-chain free fatty acids are entirely catabolised in the mitochondria, where they are transported through the rate-limiting enzyme carnitine palmitoyl transferase – I (CPT-I) 7. Acetyl-CoA also represents the product of mitochondrial fatty acid beta-oxidation, and therefore a major common step of substrate oxidative utilization.

Regulation of glucose and fatty acid utilization for skeletal muscle energy production is a key metabolic process involving both substrate availability (through exogenous dietary intake or endogenous supply) and hormonal regulation. In particular, it has been reported that enhanced glucose availability and PDH activation result in higher glucose utilization with relative suppression of fat oxidation[8] Insulin is a major regulator of this process by stimulating PDH via activation of PDK[8] resulting in net stimulation of muscle oxidative glucose disposal under hyperinsulinemic conditions as observed in the post-prandial state. Lower glucose availability or excess fatty acid supply (such as observed following a fatty meal) may in turn result in PDH suppression[7] Fatty acid elevation has been in turn reported to induce resistance to insulin's effect on PDK activation[8] with potential net shift towards fat oxidation.

Acetyl-CoA is combined with oxaloacetate to produce citrate, the first substrate of the tricarboxylic acid (TCA) cycle in the mitochondrial matrix. TCA cycle reactions provide reduced FAD (flavin adenine dinucleotide) and NAD (nicotinamide adenine dinucleotide) in the form of $FADH_2$ and $NADH_2$, which support electron flux through the respiratory chain. Respiratory chain enzymes (from NADH reductase to cytochrome c oxidase: complexes I to IV) are located in the inner mitochondrial membrane where they transport electrons to oxygen as final acceptor, while creating an electrochemical transmembrane proton gradient. The gradient is utilized by ATP synthase (complex V of the respiratory chain) to synthesize ATP from ADP and phosphate, thereby providing chemical energy in the from of high-energy bonds. Modulation of mitochondrial biogenesis and mitochondrial gene expression and oxidative capacity are key processes for maintenance of skeletal muscle homeostasis. It is important to point out that mitochondria contain DNA molecules encoding for a small but essential fraction of mitochondrial proteins. The above characteristic implies that mitochondrial biogenesis and modulation of mitochondrial gene expression requires the coordinated expression of both nuclear and mitochondrial genomes.

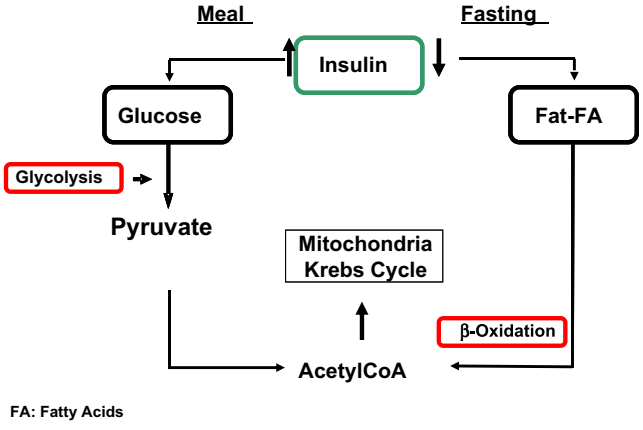

Fig. 1. Scheme of substrate interaction for utilization for mitochondrial-energy production; insulin may favor glucose utilization under post-prandial conditions by enhancing pyruvate conversion to acetylCoA.

2. Altered muscle mitochondrial function in disease states

Mitochondrial respiration is regulated by tissue and cell energy needs (Fig. 2). Cell energy status is typically sensed as the absolute and relative abundance of adenosine phosphates (ATP, ADP, AMP with AMP excess as a major signal of low energy availability and need for ATP production: this aspect will be described in detail as a mediator of exercise-stimulated mitochondrial changes). Changes in muscle mitochondrial biogenesis (i.e. the process by which mitochondria are formed in the cell) and oxidative capacity are further modulated by complex nutritional and endocrine factors as well as cytokine networks. Several important and common disease-associated alterations have been described to negatively affect both muscle protein balance and mass and muscle energy metabolism, with particular regard to impaired mitochondrial gene expression, mitochondrial protein synthesis, enzyme activities and ATP production. The following section will focus on inflammation, oxidative stress and insulin resistance (Fig. 3), although it should be kept in mind that additional factors may also contribute to muscle mitochondrial changes, including changes in muscle blood supply and neuromuscular signalling alterations.

2.1. Inflammation

Both local and systemic inflammation result from imbalanced production of proinflammatory and anti-inflammatory cytokines. While acute inflammation at both local and systemic levels may represent an adaptive mechanism contributing to limit and reverse a specific infectious or traumatic insult, a sustained activation of systemic inflammatory responses is associated with a major negative metabolic and nutritional impact.[9–12] Several chronic disease conditions lead to sustained low-grade activation of chronic systemic inflammation,[9–12] and regardless of the underlying mechanism, the onset and maintenance of a chronic elevation of the pro- to anti-inflammatory cytokine balance represents a common pathogenetic mechanism underlying wasting and cachexia.[9–12] Skeletal muscle protein catabolism by stimulation of protein degradation and inhibition of synthesis is specifically enhanced by proinflammatory TNF-alpha whose effect involves nuclear translocation of transcriptional factor NF-kB,[13–15] in turn

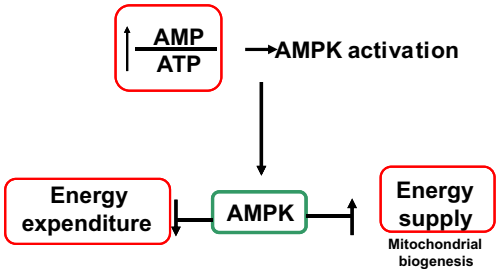

Fig. 2. AMP-activated protein kinase is a key sensor of cellular energy status favoring mitochondrial biogenesis after activation in the presence of lower energy availability.