Review

Skeletal muscle: Energy metabolism, fiber types, fatigue and adaptability

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ABSTRACT

Skeletal muscles cope with a large range of activities, from being able to support the body weight during long periods of upright standing to perform explosive movements in response to an unexpected threat. This requires systems for energy metabolism that can provide energy during long periods of moderately increased energy consumption as well as being able to rapidly increasing the rate of energy production more than 100-fold in response to explosive contractions. In this short review we discuss how muscles can deal with these divergent demands. We first outline the major energy metabolism pathways in skeletal muscle. Next we describe metabolic differences between different muscle fiber types. Contractile performance declines during intense activation, i.e. fatigue develops, and we discuss likely underlying mechanisms. Finally, we discuss the ability of muscle fibers to adapt to altered demands, and mechanisms behind these adaptations. The accumulated experimental evidence forces us to conclude that most aspects of energy metabolism involve multiple and overlapping signaling pathways, which indicates that the control of energy metabolism is too important to depend on one single molecule or mechanism.

Keywords:
Skeletal muscle
Energy metabolism
Muscle fatigue
Endurance training
Calcium
Reactive oxygen species

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Abbreviations: AMPK, AMP-dependent protein kinase; [Ca2+]i, cytosolic free Ca2+ concentration; Cr, creatine; MAPK, mitogen-activated protein kinase; MHC, myosin heavy chain; PCR, phosphocreatine; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator 1α; Pi, inorganic phosphate ions; ROS, reactive oxygen species; SERCA, sarcoplasmic reticulum Ca2+ pump; SR, sarcoplasmic reticulum

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doi:10.1016/j.yexcr.2010.05.019
Skeletal muscle is unique in its ability to rapidly increase its rate of energy consumption in situations where explosive contractions are required. The increase in energy turnover can amount to 300-fold from the resting to the fully activated state, and this can occur within a few milliseconds [1]. On the other hand, skeletal muscle also has to be able to maintain a moderate increase in energy consumptions during prolonged periods of low-intensity contractions. In this short review we will first outline the metabolic systems that make it possible to rapidly increase energy turnover as well as maintain a moderately increased turnover for long periods. We will then discuss the fact that one important reason behind the ability of skeletal muscles to cope with their diverse tasks is that they contain cells with different metabolic and contractile properties, i.e. different fiber types. Next we will discuss muscle fatigue, which is a decline in contractile function that, in principle, occurs as a consequence of an inability of the energy systems to maintain energy homeostasis during periods of high energy consumption. Finally, we will describe mechanisms by which muscle cells can adapt to better sustain problems in energy metabolism. In this short review we cannot deal with all aspects of the covered topics and the content will inevitably reflect our own research interests and opinions. Moreover, the number of references in this review is limited and we frequently refer readers to comprehensive reviews of the respective topics rather than quoting the appropriate original work.

Energy metabolism

During contraction energy is mostly consumed by the molecular motors, the myosin heads or cross-bridges, and by ion pumps, mainly the sarcoplasmic reticulum (SR) Ca$^{2+}$ pumps [2]. The relative proportion of energy required by the cross-bridges and by the SR Ca$^{2+}$ pumps depends on the type of contraction (e.g. continuous vs. short repeated contractions, and maximal vs. submaximal) and it is currently debated whether the cross-bridges or the SR Ca$^{2+}$ pumps are the major energy consumers under physiological conditions [3,4].

The immediate energy source during muscle contraction is ATP. The intracellular store of ATP is small (5–6 mM) and if the muscle was fully activated, the store would be depleted within 2 s [1]. Hence other metabolic pathways must be activated to avoid ATP depletion. These can be divided into anaerobic and aerobic pathways, of which the former are faster and therefore dominate during high-intensity physical activity of short duration whereas the latter predominate during prolonged submaximal exercise [1].

Anaerobic metabolism

The dominating anaerobic pathways to regenerate ATP are degradation of phosphocreatine (PCr) and breakdown of muscle glycogen to lactate and hydrogen ions, although a minor contribution can also come from myokinase, which is considered to be a near-equilibrium reaction in vivo (2 ADP $\rightarrow$ ATP + AMP). When AMP increases sufficiently it will be deaminated to IMP + NH$_4^+$.

The degradation of PCr occurs via creatine kinase (CK), which catalyzes a near-equilibrium reaction (PCr + ADP $\rightarrow$ Cr + ATP).

The reaction is driven to the right during periods of high ATP consumption and the initial net effects are a reduction in [PCr] and increases in the concentrations of creatine ([Cr]) and inorganic phosphate ions ([P$_i$]), whereas [ATP] remains almost constant. In contrast, during the recovery after periods of high ATP consumption, the synthesis of PCr is favored (i.e. the reaction is driven to the left). When [PCr] reaches low levels, [ATP] starts to fall and [ADP] and [AMP] show transitory increases, which are reflected in a gradual accumulation of IMP [5]. Studies on whole muscles or muscle homogenates indicate that the intracellular [ATP] does not decrease below ~60% of the resting value during intense exercise. However, studies on individual muscle fibers suggest that markedly larger changes can occur. For instance, after maximal cycling exercise ATP was reduced to ~20% of the resting value and IMP increased from undetectable levels to ~5 mM in the fastest muscle fibers (type IIx) [6].

Glycogen breakdown is regulated by glycogen phosphorylase, which exists in two forms: phosphorylated (generally considered to be the more active form in vivo) and non-phosphorylated (generally considered to be the less active form in vivo). Phosphorylation of glycogen phosphorylase is catalyzed by phosphorylase kinase at one specific serine residue (Ser$^{14}$) and dephosphorylation is catalyzed by protein phosphatase 1 [7]. Glycogen synthesis is catalyzed by glycogen synthase and this enzyme is also controlled by phosphorylation. The situation here is more complex than for glycogen phosphorylase, because glycogen synthase is a substrate for many kinases (including protein kinase A, glycogen synthase kinase-3, and phosphorylase kinase) and several phosphatases. It is phosphorylated on about ten sites and dephosphorylation of three specific sites is associated with increased activity of the enzyme [8].

The exact mechanisms by which glycogen breakdown is regulated in muscle cells during periods of high energy turnover remain unclear [9]. Phosphorylase releases glucose residues from glycogen, which enter glycolysis and are ultimately converted to pyruvate. During intense exercise, lactate dehydrogenase converts NADH + H$^+$ + pyruvate to lactate + NAD$^+$. The purpose of this reaction is to regenerate NAD$^+$ (which is consumed in an upstream glycolytic reaction) in order to maintain glycolysis [10]. In principle, the rate at which lactate formation occurs depends on the availability of oxygen relative to the energy demand. Thus, lactate accumulation occurs mainly during heavy exercise when the rate of ATP consumption is high. Hydrogen ions accumulate in parallel with lactate ions and during high-intensity exercise there is a decrease in muscle pH from ~7.0 to ~6.5 [11]. A major disadvantage with a high dependency on lactate formation is that this yields much less ATP per glucosyl unit as compared to aerobic breakdown (theoretically 3 vs. 38 ATP/glucosyl unit). It is well documented that depletion of intramuscular glycogen stores can limit muscle performance during prolonged exercise, such as marathon running [12].

Aerobic metabolism

Oxidative metabolism of carbohydrates and lipids are the dominating ATP-producing systems during prolonged submaximal exercise [13]. The major carbohydrate substrate for aerobic metabolism during short-term and prolonged exercise is muscle glycogen but the contribution of extracellular glucose to oxidative ATP production increases with exercise duration [14]. Intriguingly, the highest rates of glucose uptake (~50-fold higher than basal) actually occur during short-term maximal dynamic exercise,
although the contribution of extracellular glucose to the ATP production is negligible under these conditions [15].

The regulation of glucose uptake by muscle during exercise is not fully understood, but it is clear that this occurs via an insulin-independent pathway [16]. In recent years numerous studies have implicated the activation of AMP-dependent protein kinase (AMPK) in this process [17]. It is believed that a major mechanism for activating AMPK is the increase in AMP during exercise; but the increase in AMP is generally small and transient [5] and additional mechanisms are probably involved [17]. For instance, it was recently shown that reactive oxygen species (ROS) play an important role in contraction-mediated glucose uptake via signaling that involves AMPK [18]. The rate of ROS production is increased throughout periods of submaximal exercise [19], where uptake of extracellular glucose is known to make a significantly contribution to aerobic ATP production [14].

The substrate for lipid metabolism is free fatty acids derived from triglyceride stored in muscle or adipose tissue. The relative contribution from triglyceride stored in muscle or adipose tissue. The relative contribution of fatty acids to aerobic ATP production is essentially maximal at an exercise intensity corresponding to ∼60% of maximal oxygen uptake and at higher exercise intensities fatty acid oxidation actually decreases [1] (Fig. 1).

An additional substrate for aerobic metabolism is amino acids derived from muscle protein degradation but this contributes very little to the overall energy metabolism during prolonged exercise, especially with adequate carbohydrate metabolism (∼5%) and even in the almost complete absence of carbohydrate availability (∼10%) [20].

**Muscle fiber types**

Skeletal muscles have to cope with a large range of activities, from supporting the body weight during long periods of upright standing, to performing explosive movements in response to an unexpected threat. To deal with these divergent activities, our muscles are composed of muscle cells with large differences in metabolic profile, contractile speed, and cellular Ca²⁺ handling [21,22]. The presently dominating classification system for mammalian skeletal muscle is based on myosin heavy chain (MHC) isoforms. The major fiber types are type I, IIA, IIX and IIb. In addition, a minority of fibers expresses more than one MHC. Rodent muscles express all four types of MHC, whereas IIb MHC is not expressed in human muscle. The rate of cross-bridge cycling is determined by the MHC isoform and type I is the slowest, type IIa intermediate and IIX/b the fastest. In addition to MHC, the expression pattern of isoforms of numerous other proteins differs between muscle fibers. A pattern of gene co-expression exists for some protein isoforms, that is, the slow MHC type I is co-expressed with "slow" isoforms of other proteins. However, this is not always the case and gene expression of different protein isoforms is controlled by multiple interacting mechanisms [22]. This complex scenario can be exemplified by the fact that there are also differences in the shape of action potential-induced transients in free cytosolic [Ca²⁺] ([Ca²⁺]ₖ) between muscle fibers and there is only partial overlap between the shape of [Ca²⁺]ₖ transients and MHC isoforms [23].

From an energy metabolic perspective, a classification system based on MHC isoforms is relevant because the cross-bridges of a fast MHC isoform consume ATP more rapidly than a slow isoform. However, there are also other important differences between fibers related to energy metabolism. For instance, the other major ATP consuming protein in skeletal muscles, the SR Ca²⁺ pumps, also exists in two isoforms, SERCA1 in fast type II fibers and SERCA2 in slow type I fibers, and the density of pumps is much higher in fast than in slow fibers [21,24]. Moreover, fast type II fibers generally have a lower oxidative capacity than slow type I fibers, although this is not always the case; for example, a higher oxidative capacity in type IIa than in type I fibers has been observed in rat muscle [25].

To sum up, skeletal muscles are composed of muscle fibers with marked differences in their metabolic profile, ranging from slow, energy conserving and highly oxidative fibers that are optimized for prolonged low-intensity activities to fast, highly energy-consuming fibers that depend mainly on anaerobic metabolism and are suited for short explosive movements.

**Fatigue**

Intense activation of skeletal muscles generally results in decreased contractile function that is reversed after a period of rest. This activity-induced decline in performance is called fatigue and is in most instances highly dependent on the capacity of the aerobic metabolic system. Accordingly, slow oxidative muscle fibers are markedly more fatigue resistant than fast glycolytic fibers under normal conditions (Fig. 2A and C). When mitochondrial respiration is inhibited with cyanide, even slow-twitch fibers fatigue rapidly (Fig. 2B).

The contraction of skeletal muscle is controlled by a series of events and fatigue can be due to impaired function in any of these events. The series starts in the central nervous system where eventually the α-motorneurones are activated. Each α-motorneuron activates a number of muscle fibers and together they represent the smallest unit in the motor system, the motor

![Fig. 1 – Schematic representation of the relationship between different energy substrates and pathways as a function of exercise intensity. The rate of ATP turnover was estimated in human leg muscles during upright cycling. Note that phosphocreatine (PCr) and lactate become significant contributors to ATP production only at high exercise intensities. The contribution of protein metabolism is considered to equal zero. The figure is derived from [50].](image-url)
unit. All muscle fibers in a motor unit are of the same type and hence metabolically matched to fit the discharge properties of their α-motorneuron. Fatigue may occur as a consequence of impaired α-motorneuron activation and this is called central fatigue [26]. There is a complex interplay between the nervous system and skeletal muscles during most types of strenuous exercise, which makes it difficult to design experiments to unequivocally assess the extent of central fatigue. Thus, the question whether central fatigue is important or not for the decline in performance during various types of physical activity is rather controversial [27]. Nevertheless, the general picture is that central fatigue is of greater importance during prolonged low-intensity activities, where metabolic changes within muscle cells are likely to be limited, whereas intramuscular factors appear to dominate during activities of higher intensity [28].

Peripheral fatigue relates to factors within the muscle that cause impaired contractile function during strenuous exercise. The activation of skeletal muscle cells starts with the generation of action potentials at the neuromuscular junction [29,30]. The action potentials propagate along the surface membrane of the muscle cell and also into the t-tubular system. Action potentials activate voltage sensors in the t-tubular wall, the dihydropyridine receptors, which open Ca$^{2+}$ channels in the sarcoplasmic reticulum (SR), the ryanodine receptors. Ca$^{2+}$ is then released from the SR into the cytosol where it binds to and changes the configuration of myofibrillar regulatory proteins, the troponin–tropomyosin protein complex. The cross-bridges can now bind to the actin filament and contraction starts. Ca$^{2+}$ is constantly pumped back into the SR and when action potentials cease, the cytosolic free Ca$^{2+}$ concentration ([Ca$^{2+}]_i$) rapidly declines and the muscle fiber relaxes. All of these steps can be adversely affected by metabolic changes during intense muscle activity, especially when a large component of anaerobic metabolism is required [12]. Fatigue can then be manifest as decreased isometric force production, reduced shortening speed, altered force–velocity relationship, and slowed relaxation [31,32]. The combination of decreased force production and slowed shortening results in a decreased power output and hence impaired performance in all types of locomotion that depend on muscle shortening. Slowed relaxation will decrease the frequency at which alternating movements can be performed.

Experiments on isolated intact muscle fibers have shown that the decrease in isometric force during fatiguing stimulation involves reduced ability of cross-bridges to generate force and decreased myofibrillar Ca$^{2+}$ sensitivity, both of which develop early during fatiguing stimulation. As fatiguing stimulation progresses, SR Ca$^{2+}$ release is decreased and when [Ca$^{2+}]_i$ is on the steep part of the force-[Ca$^{2+}]_i$ relationship, this results in a rapid decrease in force production [12,31]. This decrease in SR Ca$^{2+}$ release can be seen as a safety mechanism because it occurs at a stage where the muscle fiber is metabolically exhausted. If SR Ca$^{2+}$ release remained high at this stage, [ATP] might fall to critically low levels where cross-bridges enter rigor states and SR Ca$^{2+}$ uptake fails, both of which result in non-functional muscle cells. However, when [Ca$^{2+}]_i$ declines, the recruitment of energy-consuming cross-bridges is decreased and the energy required to pump Ca$^{2+}$ back into the SR is reduced. Consequently, the rate of energy consumption declines and devastating effects on muscle cell integrity are avoided.

Acidosis occurs as a consequence of anaerobic breakdown of glucosyl units to lactate and hydrogen ions. Classically, acidosis was
considered as the most important factor behind the impaired contractile function in fatigued muscles. However, more recent results indicate that acidosis is not a key cause of fatigue in mammalian muscle because when studied at physiological temperature, acidosis of the magnitude observed in severely fatigued muscle fibers (~0.5 pH-units) has little impact on force production, contractile speed, and rate of fatigue development [12,33]. Despite the fact that acidosis is not a major cause of fatigue, blood lactate is easy to measure and can serve as a good indicator of the extent of anaerobic metabolism used by muscles during exercise.

An aerobic metabolism in skeletal muscle cells includes the breakdown of phosphocreatine, which results in a rise of $[\Pi]$. Increased $[\Pi]$ has multiple negative effects on the contractile function of skeletal muscle. It decreases force production and myocardial Ca$^{2+}$ sensitivity by reducing the number of force generating cross-bridges [12,34], although this effect becomes smaller at physiological temperatures where it can only account for ~10% of the decrease in maximum force production [35]. In addition, $[\Pi]$ might enter the SR during fatigue, which can result in the Ca$^{2+}$–$[\Pi]$ solubility product being exceeded, precipitation of Ca$\Pi$, and decreased free Ca$^{2+}$ available for release [36]. Genetically modified muscle fibers lacking CK cannot break down PCr. These fibers display impaired contractile function at the onset of high-intensity stimulation, where PCr breakdown functions as an important energy buffering system, whereas they show neither decreased cross-bridge force production, reduced myocardial Ca$^{2+}$ sensitivity nor decreased SR Ca$^{2+}$ release during more prolonged stimulation. Intriguingly, all these features partially returned towards the wild-type phenotype after CK injection in CK deficient cells, which allowed PCr breakdown to occur [37]. Thus, these experiments on CK deficient muscle clearly illustrate an important role of $[\Pi]$ in fatigue.

Another consequence of the increased energy consumption during fatiguing stimulation is accelerated ROS production [19]. High concentrations of ROS can have multiple adverse effects on muscle function, whereas low concentrations can have important roles in normal cellular signaling. Accordingly, the effects of ROS on fatigue development are rather variable and anything from muscle activity has the opposite effect. One adaptation that is frequently discussed is the transition between MHC isoforms. Developing and regenerating muscle cells have a greater ability to switch between different fiber types than adult muscle fibers [40]. Major fiber type switches in adult muscles actually require rather severe changes in, for instance, hormonal status (especially of the thyroid hormones) or activation/contraction pattern, e.g. external electrical stimulation, paralysis due to spinal cord injury, denervation, cross-reinnervation (fast muscle reinnervated by a slow nerve and vice versa), and mechanical unloading [40–42]. On the other hand, physical training studies show little or no transformations between MHC isoforms, especially not between type I and type II isoforms [42]. Instead, physical exercise induces marked changes of many other functionally important cellular properties. In principle, exercise can be characterized as resistance (strength) training, which involves relatively few high-force contractions, and endurance training, which consists of repeated low-force contractions. Resistance training results in an increase in muscle fiber cross-sectional area and hence larger force production due to an increased number of parallel myofibrils [43].

Endurance training has beneficial effects on most aspects of skeletal muscle energy metabolism. For instance, it stimulates mitochondrial biogenesis, resulting in increased oxidative capacity and increased fatigue resistance. It also enhances glucose uptake and insulin sensitivity, which counteracts insulin resistance and type 2-diabetes. It increases fatty acid metabolism, which leads to better preserved glycogen stores during prolonged exercise (e.g. marathon running). Finally, it stimulates angiogenesis and capillary formation resulting in improved oxygen delivery to mitochondria [39,44]. The effects of endurance training can be induced by metabolic, mechanical, neuronal and hormonal stimuli (Fig. 3). In the muscle cells these stimuli can, for instance, result in (i) hypoxia, (ii) increased [Ca$^{2+}$], (iii) increased ROS, and (iv) changes in the concentration of high energy phosphates (e.g. AMP and ATP) [39,44,45]. These intracellular changes can in turn be detected by e.g. (i) hypoxia-inducible factor 1α (HIF-1α), (ii) calcineurin and Ca$^{2+}$/calmodulin-dependent protein kinase II (CaMKII), (iii) mitogen-activated protein kinases (MAPK), and (iv) AMPK. These signaling factors then alter the activity of a number of transcription factors with the final result being a switch in protein distribution towards a more oxidative phenotype [39,44,45]. It is important to note that there is considerable overlap between these signaling events. For instance, in addition to affecting MAPK, increased ROS can affect the function of calcineurin and AMPK [18,45]. And an important role for ROS is supported by recent studies showing that antioxidant treatment hampers the beneficial effects of endurance training [46,47]. Nevertheless, many of the signaling events appear to be integrated by the peroxisome proliferator-activated receptor gamma coactivator 1α (PGC-1α), which can detect changes in signaling factors and interact with transcription factors [44]. Thus, changes in PGC-1α gene expression and post-translational modifications of the PGC-1α protein potentially play a central role in the response to endurance exercise. However, it must be recognized that the response to endurance training also involves PGC-1α-independent signaling because training-induced changes are also observed in PGC-1α deficient mice [48].

**Adaptation**

One important property of skeletal muscles is their immense potential to adapt in response to altered functional demands [39]. In other words, with training it is possible to induce changes in muscle cells that improve contractile performance, whereas lack of muscle activity has the opposite effect. One adaptation that is frequently discussed is the transition between MHC isoforms. Developing and regenerating muscle cells have a greater ability to switch between different fiber types than adult muscle fibers [40]. Major fiber type switches in adult muscles actually require rather severe changes in, for instance, hormonal status (especially of the thyroid hormones) or activation/contraction pattern, e.g. external electrical stimulation, paralysis due to spinal cord injury, denervation, cross-reinnervation (fast muscle reinnervated by a slow nerve and vice versa), and mechanical unloading [40–42]. On the other hand, physical training studies show little or no transformations between MHC isoforms, especially not between type I and type II isoforms [42]. Instead, physical exercise induces marked changes of many other functionally important cellular properties. In principle, exercise can be characterized as resistance (strength) training, which involves relatively few high-force contractions, and endurance training, which consists of repeated low-force contractions. Resistance training results in an increase in muscle fiber cross-sectional area and hence larger force production due to an increased number of parallel myofibrils [43].

**Perspective**

In this review we have outlined the complex systems that make it possible for skeletal muscle to cope with their divergent demands related energy metabolism. The importance and complexity of energy metabolism in muscle make it unlikely that a certain property depends on a single molecule [49]. In other words, it is unlikely that there is one critical sensor of the energy status, one unique cause of fatigue or one key regulator of adaptation. Instead experimental data show that most aspects of energy metabolism in muscle involve multiple and overlapping signaling pathways.
This complexity has to be considered when interpreting results from experiments where one single molecule is manipulated (e.g. in knockout or transgenic animals), because this inevitably results in adaptations and altered function in overlapping signaling pathways. Additional caution is required when interpreting results obtained in experiments performed on immature muscle cells or muscle-like cell lines. In this review we have downplayed the importance of data obtained from these cell types. This is because they show major differences to adult skeletal muscle cells regarding central properties, such as, contractile function (some cultured muscle cells cannot even contract), metabolic responses, and cellular Ca\(^{2+}\)-handling. Thus, while these cell types are convenient to use in initial basic experiments (e.g. to establish protein interactions in a signaling pathway), their direct usefulness in more complex conditions (e.g. revealing mechanisms underlying adaptations to endurance exercise) is more doubtful and can lead to the establishment of oversimplified or even erroneous models.

**Fig. 3** – Schematic diagram illustrating the complex interplay between different factors in the signaling by which endurance training can induce an oxidative phenotype in skeletal muscle via PGC-1α. The diagram is not meant to cover all aspects of the signaling; for instance, PGC-1α-independent signaling also occurs and the transcription factors that PGC-1α interacts with are not included.

**Acknowledgments**

We thank the Swedish Research Council and the Swedish National Center for Sports Research for research funding.

**REFERENCES**


