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Review Article

Significance of calcium: its correlation with red and white muscle contraction, fatigue and potential

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ABSTRACT

According to the predominant types of muscle fibers in an individual, they will have the ability to perform different types of exercises (both aerobic and anaerobic). To comprehend the mechanism of muscle fibers, which can act in diverse ways, enhancing either resistance or power, it is essential to examine the significance of calcium. Calcium plays a crucial role in both red and white muscle fibers. The release of calcium in white (fast-twitch) muscle fibers is significantly greater and faster, resulting in increased energy consumption, facilitating explosive physical activities. Conversely, in red (slow-twitch) muscle fibers, the release of calcium occurs in smaller amounts and over a prolonged period, leading to sustained energy consumption. The characteristics of contraction in red fibers enable endurance activities. A reduction in the amount of calcium results in diminished muscle contractile capacity, known as fatigue. The primary contributing factor, as previously mentioned, is the decline in calcium, but factors such as lactic acid and the dephosphorylation of the myosin head also contribute to its onset.

Keywords: Contraction, Muscle, Neuromuscular junction, Calcium, Fatigue, Correlation between muscle types

INTRODUCTION

Aerobic exercise is based on the development of activities of lower intensity than those performed in anaerobic exercise but over longer periods, with the aim of achieving greater endurance rather than strength. Aerobic exercises involve large muscle masses (legs, gluteus maximus, and muscles of the lumbar region). Unlike anaerobic exercise, aerobic exercise does not significantly increase muscle mass. For aerobic exercise to take place, there must be a continuous demand for oxygen in the body, allowing the muscles to primarily utilize fat reserves as fuel. A common example of aerobic exercise is running a marathon, where marathon runners are characterized by having oxygen-dependent (aerobic) red muscle fibers, resulting in muscles that are not hypertrophied, as seen in athletes engaging in oxygen-independent (anaerobic) exercise. Anaerobic exercise comprises brief physical activities based on strength rather than endurance, such as sprints or weightlifting.

However, it is important to remember that the initial phase of every exercise is anaerobic. Anaerobic exercise is a brief and high-intensity activity where metabolism occurs exclusively in the muscles and their energy reserves, without utilizing oxygen from respiration. There are two

types of anaerobic energy systems: the ATP-PC system, which uses creatine phosphate during the first 10 seconds of exercise, and the lactic acid system, which utilizes glucose in the absence of oxygen.[1]

Muscle contraction, broadly speaking, can be described by a chain of events that begins with an action potential and ends with the folding of actin and myosin fibers. When these fibers fold, the distance between them decreases, leading to muscle contraction.[2]

In humans, muscles have a variable percentage of fast-twitch (type II) and slow-twitch (type I) fibers. Depending on the type of muscle, the predominant fiber type will vary. For example, the gastrocnemius muscle has a significant number of fast-twitch fibers, as it is necessary for powerful and short-duration activities. On the other hand, the soleus muscle predominantly contains slow-twitch fibers, making it useful for prolonged activities. An athlete's athletic capabilities are based on the predominant fiber type they possess, highlighting the significant role of genetic inheritance in their development. Training has not proven to be capable of altering the proportions of fast or slow fibers, even if an athlete desires to develop a specific athletic capacity over another. Considering the aforementioned, an individual having a considerably higher number of fast or slow fibers will determine, to some extent, their athletic capacity.[2]

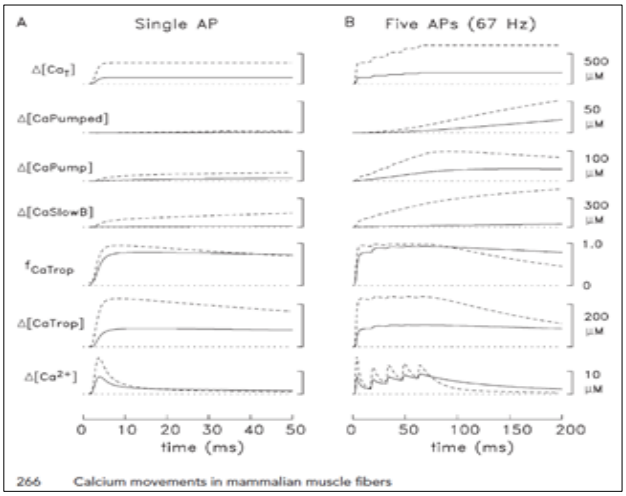

Figure 1: Calcium movement between slow fibers (solid line) and fast fibers (dashed line).[5]

For a muscle to function, it requires energy, and the energy needed to perform an effort must be obtained from the body's reserves. The primary resource available to active muscle fibers is a small local reserve of high-energy phosphate compounds (ATP and creatine phosphate). During physical activity, ATP is degraded to ADP or AMP, while creatine phosphate is converted to creatine. Each released phosphate molecule produces an amount of energy around 46 kJ/mol, which can be applied to the actin-myosin interaction for muscle contraction.

Adaptive changes in metabolic enzymes and capillaries are among the better-described consequences of endurance training and likely rank among the most important for muscular capacity. The ability of skeletal muscle cells to adapt to metabolic changes has been shown to be quite remarkable, and it is well-known that endurance training induces significant adaptive changes in various structural components and metabolic variables of the involved skeletal muscles.[3]

THEORETICAL FRAMEWORK

Contraction

Myocytes are known to be the cellular unit of muscle structure and contain high concentrations of proteins that generate mechanical force in the form of cellular contraction.[4] Muscle contraction begins with an action potential traveling through a motor neuron. This stimulus propagates as an ion gradient moving along the neuronal axon. Upon reaching the terminal button, this voltage gradient activates voltage-sensitive calcium channels. Calcium ions bind to vesicles containing the neurotransmitter acetylcholine. As calcium attaches to the vesicles, it promotes their movement to the plasma membrane, where the content is released into the synaptic cleft. This process is called exocytosis or hemecytosis. Acetylcholine is captured by receptors on the muscle's plasma membrane, triggering the opening of sodium channels. As these channels open, they generate an action potential that travels similarly to the action potential in the neuron. This depolarization of the plasma membrane opens voltage-sensitive calcium channels in the muscle. However, unlike the action potential that acts in the neuron, in the muscle, the electrical impulse spreads across the entire membrane of the muscle cell and penetrates the T-tubule system. Within the T-tubules are specialized molecules stimulated by voltage, activating calcium-releasing channels from the sarcoplasmic reticulum (SR). Due to a difference in calcium ion osmolarity, calcium from the SR enters the myoplasm. This calcium diffusion extends across the sarcomere and binds to different myoplasmic constituents. The most relevant of these components is troponin C.[5] When calcium binds to troponin, it induces a conformational change, exposing the active sites of actin that have a high affinity for myosin heads. However, for the myosin heads to bend and generate muscle contraction, the release of energy is required by breaking an ATP energy bond. Similarly, for a reconfiguration to the original conformation of the myosin and actin fibers, the cleavage of an ATP bond is required.[2]

Calcium-dependent regulation

The regulation of muscle contraction largely depends on Ca^{2+}. When a stimulus signal reaches the neuromuscular junction, the action potential spreads to invaginations of the muscle cell plasma membrane, called the transverse (T)-tubules. The membrane depolarization triggers an influx of Ca^{2+} into the muscle cell through voltage-gated

Ca^{2+} channels called dihydropyridine receptors in skeletal muscle.[6]

The increase in local Ca^{2+} concentration caused by $Ca_v1.2$ or the direct interaction with DHPR activates another type of Ca^{2+} channel, called ryanodine receptors (RyRs). RyRs are located in the membrane of the sarcoplasmic reticulum (SR) and release Ca^{2+} from the SR into the cytoplasm. Ca^{2+} ions then bind to troponin on the thin filament, resulting in a shift of tropomyosin. This allows myosin to bind to the thin filament and ultimately leads to muscle contraction. Ca^{2+} is then actively pumped back into the SR by the sarco/endoplasmic reticulum Ca^{2+}-ATPase (SERCA). In the absence of Ca^{2+}, troponin changes the position of tropomyosin so that myosin can no longer bind to the thin filament, causing the muscle to relax.[6]

Muscle contraction in muscle types

Muscle fibers can be categorized into two types: white fibers, and red fibers. This distinction originates from the appearance of the fibers in living tissue; however, the differences between the fibers are not limited to their macroscopic coloration. At the cellular level, red fibers have a higher concentration of myoglobin (which gives them their reddish color) and an increased number of mitochondria compared to white fibers. There is also a considerable difference in the size of the sarcoplasmic reticulum, which is up to four times larger in white fibers than in red fibers.[7]

These cellular differences lead to physiological differences. White muscle fibers are considered fast-twitch muscle fibers, or type 2, as their contraction is stronger, faster, and more intense than that of red muscle fibers.[8] With a larger sarcoplasmic reticulum, the amount of stored calcium in the cell is greater. Likewise, the amount of calcium that can be released to initiate muscle contraction is higher, reducing the time required for troponin-calcium binding, as illustrated in Figure 1 by the dashed lines. However, due to less available myoglobin and mitochondria, these fibers cannot sustain activity for prolonged periods due to a lack of ATP and oxygen. In contrast, red or slow muscle can maintain prolonged activity levels due to the availability of ATP produced by its mitochondria and oxygen transport facilitated by myoglobin.

Another difference between these two fibers occurs at the structural level of the plasma membrane and ion channels. Fast-twitch muscle fibers are more prone to excitability regulation through a massive increase in membrane conductance compared to slow muscle fibers, involving alterations in the function of potassium and chloride channels.

Because fast fibers are of high intensity, it is consistent that ion channels are more likely to be restricted in their permeability than those of slow fibers, which require more prolonged contractions of lower intensity.[7]

Fatigue

Muscular fatigue is defined as the decrease in the muscle's ability to contract. Prolonged and intense muscle contraction leads to fatigue. Various factors influence this muscular phenomenon, including a decrease in calcium levels, accumulation of metabolites such as lactic acid, reduced availability of oxygen, and dephosphorylation of the myosin light chain, as the latter is believed to influence troponin sensitivity to calcium. According to Hortemo et al, there is evidence suggesting that acidification due to high levels of lactic acid reduces the speed of calcium reuse and recycling, influencing muscle relaxation. An integral component in muscle contraction is the interaction between myosin and actin fibers. Myosin consists of both a light and a heavy chain. Although both are crucial for overall muscle contraction, the focus in this case is on the light chain, as it contains the myosin heads undergoing phosphorylation and subsequent dephosphorylation. Muscle contraction, as mentioned earlier, requires high levels of ATP. By donating a phosphate to the myosin light chain, ATP provides the necessary energy, resulting in the release of a molecule of ADP and inorganic phosphate.[9]

Some studies have demonstrated that muscular fatigue increases in an almost direct proportion to the speed of glycogen depletion in the muscle. Therefore, fatigue is mainly due to the inability of the contractile and metabolic processes of muscle fibers to continue generating the same amount of work. It has also been shown that the transmission of nerve signals, such as action potential through the neuromuscular junction, may decrease after prolonged and intense muscular activity, further reducing muscle contraction. Additionally, the interruption of blood flow through a contracting muscle result in almost complete muscular fatigue within 1 to 2 minutes due to the loss of nutrient supply, especially oxygen.[2]

A study by Hortemo and colleagues investigates fatigue mechanisms during red muscle contraction. In this research, muscles were repetitively stimulated at 30 Hz for 15 minutes. Subsequent fatigue was examined at three different time intervals: 20 s, 100 s, and 15 minutes during the exercise. According to the results of this research, muscular fatigue developed in three distinct phases.[9]

During the first phase (first 20 seconds), the regulatory protein of the myosin light chain rapidly underwent dephosphorylation; therefore, a reduced rate in force development and contraction was observed as a consequence of ATP consumption. It is postulated that muscles fatigue more quickly during shortening contractions compared to isometric contractions in which no sliding of myofibrils occurs.

According to Hortemo et al this concept is explained by a higher ATP consumption rate during shortening contractions. The high ATP consumption results in a higher concentration of inorganic phosphate, which is a primary cause of muscular fatigue. As mentioned earlier,

this accumulation of inorganic phosphate decreases the sensitivity of myofibrils to calcium, inhibiting the association of actin and myosin, and consequently, contraction also decreases.[9]

n the second phase, there was a degradation of high-energy phosphates and an accumulation of lactate as a metabolite. These changes are associated with a decrease in muscle relaxation that culminated at 100 seconds of exercise due to an increase in the leakage of calcium ions from the endoplasmic reticulum. As shown in Figure 2, the leakage of calcium ions favors the decrease in contraction since there is less calcium available to facilitate the binding of actin and myosin filaments necessary for contraction.[9]

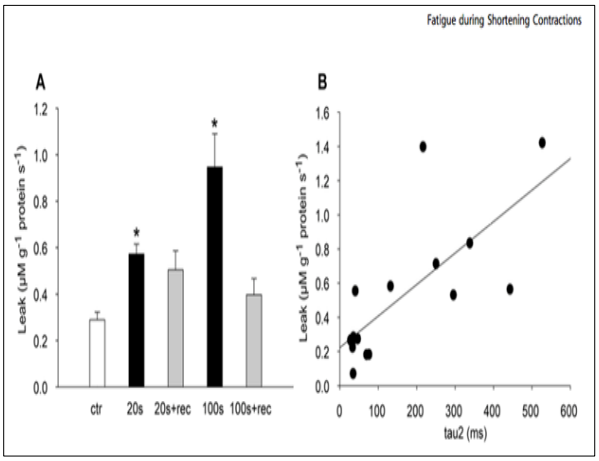

Figure 2 (a and b): Calcium efflux, correlation between calcium efflux and exercise time (with and without recovery).

During the final phase of the exercise, there was a restoration of high-energy phosphates as well as the elimination of lactate. It is observed that the decrease in relaxation disappears, while dephosphorylation of the myosin light chain and the reduction of muscle contraction prevail. The decrease in muscle relaxation is a key point indicating fatigue and can limit movement during dynamic exercise, resulting in perceived muscular stiffness. Additionally, the decrease in isometric relaxation is closely associated with an accumulation of lactic acid, which increases calcium leakage from the sarcoplasmic reticulum.[9]

FATIGUE AND MUSCLE TYPES

As mentioned earlier, the distinction between red and white muscle usage depends directly on the type of exercise practiced, either aerobic or anaerobic, respectively. Each type of exercise induces fatigue as the muscle works and secretes metabolites. According to Dr. Michael W. King, "In addition to phosphoryl group transfers, ATP in muscle is also generated via glycolysis and oxidative phosphorylation. Muscles relying on oxidative phosphorylation as their ATP source need high levels of oxygen. To ensure oxygen availability, these muscles store oxygen as oxymyoglobin. Oxidative muscles with myoglobin appear red due to their high myoglobin content. In red muscle, the pathway between substrate (e.g., glucose) and ATP involves more steps in the reaction (e.g., glycolysis plus the tricarboxylic acid cycle, in addition to electron transport) and constitutes a longer process than that in white muscle. Slow-twitch muscles, responsible for maintaining tone, are generally red and oxidative".[10] Therefore, muscular fatigue in red muscle correlates primarily with a depletion of oxygen stores.

On the other hand, glycolytic muscles, which are not as rich in myoglobin, appear white. These muscles typically store large amounts of glycogen and generate most of their ATP through glycolytic reactions. White fibers produce ATP through a shorter pathway between substrates (e.g., glucose) and ATP appearance. Skeletal muscles composed predominantly of glycolytic white fibers are fast-twitch.[10] Consequently, muscular fatigue in white muscle is primarily associated with a decrease or depletion of glycogen stores in the muscle.

In summary, red and white muscles exhibit fatigue for distinct reasons and factors. Despite both fiber types utilizing ATP as the phosphate donor to the myosin light chain for muscle contraction, the ATP acquisition mechanism differs between red and white muscles. Red muscles primarily obtain ATP from oxygen, while white muscles primarily generate ATP from glycogen.

POWER

In bioenergetics, power serves as a quantitative measure to describe muscular activity. To articulate and quantify power, two fundamental concepts must be considered: force and work.[11]

The contraction force of a muscle is primarily determined by its size, with each square centimeter of the muscle's cross-sectional area having an approximate maximum contractile force of 3 to 4 kg/cm^2. Force measures the capacity to accelerate 1 kg of muscle mass by 1 m/s^2. This relationship can be explained by Newton's second law of mechanics, where 'm' represents mass in kilograms and 'a' denotes acceleration in meters per second squared.

$$F = m \times a$$

Conversely, work (W) is defined as the application of force over a distance, expressed by the formula given, where 'F' is force in Newtons and 'd' is distance in meters.

$$W = F \times d$$

Power is reliant on the energy transfer per unit of time, considering the fore-mentioned principles, power is defined as given below. This power is pivotal for undertaking the most physically demanding activities.[11]

$$P = \frac{W}{t} = F \times d \times t^3$$

DISCUSSION

In order for there to be a proper understanding of muscle contraction we must understand that the mechanical mechanism by which this occurs. Calcium plays a pivotal role in both white and red muscle fibers, as investigated in this study, wherein we examined the release of this chemical element, along with the associated time dynamics and energy consumption. It is established that white muscle fibers exhibit a substantial and rapid calcium release, resulting in higher energy consumption. Conversely, red muscle fibers release a smaller quantity of calcium ions over an extended duration, leading to prolonged energy consumption. Not to mention, that inside these muscle fibers we can find smaller fibers which are known as myofibrils, which are composed of parallel thick and thin filaments.[12]

The exercises explored in this research encompassed aerobic and anaerobic activities, exemplified by sports such as tennis, swimming, skating, brisk walking. In aerobic exercises such as these, participation of red muscle fibers can be notably emphasized due to their heightened oxygen demand.[13] Anaerobic exercises like weightlifting, abdominal exercises, and high-intensity sprints primarily rely on muscle metabolism and energy reserves without imposing a significant oxygen demand.[14]

A crucial association between contraction and fatigue emerges, as prolonged contraction leads to muscular fatigue.[15] Factors contributing to this muscular phenomenon include decreased calcium levels, insufficient oxygen, accumulation of metabolites like lactic acid, and the dephosphorylation of the light chain of myosin, with the latter believed to influence troponin sensitivity to calcium.[16]

It is of significant relevance to sports medicine the concept of power, serving as a quantifiable descriptor of muscular activity. Power is determined by the force of contraction and the resultant work, providing valuable insights into muscular performance in clinical sports settings.[17]

The relationship between aging muscle and cellular senescence. It notes that cellular senescence, characterized by cell growth arrest, is triggered by various stimuli including oncogene activation, oxidative stress, and DNA damage. Markers of cellular senescence such as p16, p21, and p53 are discussed, as well as the phenotypic changes associated with senescent cells such as reactive oxygen species production and mitochondrial metabolism alteration. It is mentioned that while markers of senescence have been observed in aged skeletal muscle, their correlation with age-associated issues like decreased muscle mass and inflammation is still not fully understood. The effects of senolytic therapy on muscle strength and skeletal muscle regeneration in young and old mice are discussed, as well as the persistence of senescent cells after acute and chronic muscle injuries. It is suggested that senescent cells negatively affect muscle regeneration through their pro-inflammatory and profibrotic paracrine function, reducing the proliferation of muscle stem cells. Additionally, it is noted that increased intracellular calcium concentration is associated with cellular senescence, and the calcium channels involved in this process, particularly ITPR1-3, are identified.[18,19]

The article emphasizes the importance of understanding the relationship between intramuscular connective tissue, fasciae, and muscle function, supporting the concept of the myofascial unit. It suggests that efficient muscle contraction relies on the harmonic activation of motor units, good muscle vascularization, and proprioception, all interconnected by intramuscular connective tissue and fascia. These elements act as a bridge, connecting various components involved in movement. Any disruption to one element can affect others, potentially exacerbating problems. Understanding this interconnection is crucial for understanding myofascial pain and proposing effective treatments. The article suggests that myofascial pain can result from alterations in the myofascial unit, requiring a different approach to patient management. It underscores the role of fascia in transmitting tensions and affecting pain perception, muscle contraction, vascularization, and proprioception. This perspective highlights the need for a physically focused treatment approach to address myofascial pain effectively and prevent its worsening or progression.[20]

CONCLUSION

This investigation delved into the nuanced functions of the human musculature in specialized contexts such as physical activity, including the physiological alterations inherent to both aerobic and anaerobic exercises, each determined by the specific muscle type of the individual. A critical understanding of the distinction between aerobic and anaerobic exercises is paramount for discerning the varied muscular substrates engaged. Moreover, it facilitates a comprehensive grasp of the intricate mechanisms governing contraction, fatigue, and power as expounded upon in this study. An adept comprehension of these mechanisms affords insights into why aerobic and anaerobic exercises selectively recruit disparate muscle fiber types. Additionally, it sheds light on the morphological distinctions in athletes, influenced by the nature of the practiced exercise. Athletes exhibiting a prevalence of white muscle fibers and engaging in exercise conducive to their development (anaerobic) manifest a greater hypertrophic response compared to counterparts dominated by red fibers, as elucidated by the physiological mechanisms delineated throughout this research.

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