

The biochemical basis of muscular fatigue

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For centuries, athletes have been frustrated in their pursuit of excellence by the onset of muscular fatigue. However, only within the last 20 years have exercise scientists been able to unravel the actual mechanisms that induce performance-limiting muscular fatigue. Asmussen (1) describes muscular fatigue as, "the transient decrease in performance capacity of muscles when they have been active for a certain time, usually evidenced by a failure to maintain or develop a certain expected force or power." Another leading figure in the field of exercise physiology, R.H.T. Edwards, defines fatigue as, "the inability of a physiological process to continue functioning at a particular level and/or the inability of the total organism to maintain a predetermined exercise intensity" (5).

Although we have been able to define fatigue, research has yet to fully elucidate the biochemical alterations that elicit fatigue. Complicating the matter is the fact that different types of exercise are limited by different types of muscular fatigue. For example, it is known that the fatigue experienced by a marathon runner has a different biochemical basis than the fatigue experienced by a 100-meter

sprinter. This seems logical as research has shown that there are potentially three different sites of muscular fatigue: the central nervous system (CNS), the neuromuscular junction and the muscle fiber (14). The focus of this paper will be the biochemical mechanisms that limit the ability of the muscle fiber to contract. The CNS and neuromuscular sites of fatigue are beyond the scope of this paper.

Blood Circulation and Fatigue

A classic study conducted in 1954 by Merton (12) demonstrated that the flow of blood through the working muscle was necessary to attenuate the effects of muscular fatigue. When subjects were asked to perform maximal voluntary muscle contractions (MVC), force generation quickly decreased to 33 percent of the original level. When blood flow was not artificially impaired, the involved muscle was able to maintain this reduced level of tension for an extended period of time without showing any further decrements in force. However, when the subjects were asked to perform MVCs under conditions in which blood flow was occluded by an

arterial cuff, the muscular force generated quickly decreased to the point where no force could be developed. More recent studies have shown similar results (1, 9, 17, 21).

Blood flow through the exercising muscle can also affect the rate of recovery from fatigue. It has been found that with normal blood circulation, recovery from fatigue is approximately 80 percent of the original MVC within 90 seconds. Conversely, when blood flow is occluded, almost no recovery is evidenced within 90 seconds (21). It was concluded that both during maximal contractions and repeated submaximal contractions, fatigue is induced by the accumulation of fatigue substances within the working muscle (1, 16, 19, 21). Unfortunately, the exact nature of these fatigue substances could not be identified. Recent research, however, has given us a better understanding of what they may be.

Energy Substrates and Fatigue

During intense exercise of short duration, it has been shown that the body's preferred energy substrate is glycogen. Glycogen is the stored form of glucose. Both the liver and

skeletal muscle are known to contain significant amounts of glycogen.

During high intensity exercise there is a reduction in muscle glycogen from 90 mmol·kg⁻¹ in wet weight to 40 mmol·kg⁻¹ in wet weight (7). Since roughly 50 percent of the glycogen stores remain, fatigue cannot be attributed to glycogen depletion. However, a decreased amount of intramuscular glycogen may decrease the rate of glycolysis, and it has been demonstrated that an impaired rate of glycolysis can bring about an earlier onset of fatigue (2). It has also been postulated that during exercise the location of glycogen molecules within the muscle fiber is altered. Consequently, even though intramuscular glycogen may be present in sufficient quantities, it may be positioned in such a way that it cannot be used in glycolysis (20).

It has been shown that in activities such as olympic lifting and powerlifting, the primary energy substrates utilized are intramuscular ATP and phosphocreatine (4). In weight training exercise, it has been suggested that a diminution of intramuscular ATP may be partly responsible for the onset of fatigue (11). However, in running exercise performed to exhaustion it has been demonstrated that ATP levels are not significantly decreased (25).

The Na⁺/K⁺ Pump and Fatigue

In order for a muscle fiber to contract an electrical potential must exist across the membrane of the muscle fiber. The Na⁺/K⁺ pump, located within the muscle fiber's membrane, is responsible for maintaining this electrical potential by pumping Na⁺ out of the muscle fiber while simultaneously pumping K⁺ into the muscle cell. Consequently, the Na⁺/K⁺ pump establishes the excitability of the muscle fiber by ensuring a high extracellular concentration of Na⁺ and a high intracellular concentration of K⁺.

The enzyme that allows the Na⁺/K⁺ pump to function optimally is Na⁺/K⁺ ATPase. The activity of this enzyme is known to be temperature sensitive. During intense exercise a substantial amount of intramuscular heat is produced. This heat, in turn, may alter the activity of Na⁺/K⁺ AT-

Pase resulting in a decrement in the excitability of muscle fibers. Another cause of fatigue then, may be a reduction in the functional capacity of the Na⁺/K⁺ pump.

pH Alterations and Fatigue

By far the greatest amount of research in the area of muscular fatigue has been directed toward exercise-induced acidosis and fatigue. Hermanson (7) has found that intense exercise, with its concomitant production of lactate, can change intramuscular pH from 7.0 to 6.5. It is known that at a pH of 6.5 the glycolytic enzyme phosphofructokinase is almost totally inhibited. Also, a pH of 6.5 has been shown to inhibit the conversion of glycogen phosphorylase b to the more active glycogen phosphorylase a. The inhibition of phosphofructokinase and glycogen phosphorylase leads to an impaired rate of glycolysis.

It has been suggested that acidosis may cause fatigue by inhibiting the ATPase found on the head of the contractile protein myosin (2). This theory is supported by the linear relationship between the decrease in muscular force and the increase in free ADP and H⁺ observed during fatigue.

Possibly the most profound effect that exercise-induced acidosis has upon muscle contraction is its reaction with intracellular Ca⁺⁺. One of the critical components in the series of events that results in muscular contraction is the binding of Ca⁺⁺ to the actin-bound troponin complex. Intramuscular Ca⁺⁺ is sequestered within the sarcoplasmic reticulum and released upon stimulation of the muscle fiber by an action potential. When the Ca⁺⁺ is released it can bind to the troponin complex.

The increased concentration of H⁺ within the contracting muscle fiber is thought to compete with Ca⁺⁺ for binding sites on the troponin complex (2, 5, 23). If, in fact, protons do out-compete Ca⁺⁺ for troponin binding sites, then actin-myosin crossbridges cannot be formed and the contractile process is impaired. Nakamura and Schwartz (14) believe that although

an increase in H⁺ concentration does hinder the ability of Ca⁺⁺ to bind to troponin, it does so through a different mechanism. Their research shows that a lowering of the intramuscular pH to 6.5 causes an increase in the affinity of the membrane of the sarcoplasmic reticulum for Ca⁺⁺. Thus, when the muscle fiber is stimulated by the action potential, calcium remains bound to this membrane and less is available to bind to troponin.

During submaximal muscular work over extended periods of time, a decreased pH may elicit fatigue through still other mechanisms. There is some evidence that the elevation in proton concentration may activate the H⁺/K⁺ exchange within the cell membrane and disrupt the proper Na⁺/K⁺ balance across the cell membrane. Consequently, the excitation process across the cell membrane would be disrupted (18). It has also been indicated that when intramuscular levels of ADP, H⁺ and inorganic phosphate are high, there is a decrease in the energy released from the hydrolysis of ATP (18). That is, in a fatigued muscle we do not see the same energy yield during the splitting of ATP that we do in a nonfatigued muscle.

The accumulation of lactate in the muscle fiber may also indirectly impede circulation during long-term submaximal exercise (18). The buildup of lactate within the cell causes an osmotic gradient that draws water into the cell. In fact, muscle water content can increase by 20 percent during aerobic exercise, resulting in a decreased plasma volume and reduced ability to deliver oxygen to the working muscle (18).

The synthesis of the intracellular second messenger cAMP is also adversely affected by high H⁺ concentrations within the muscle fiber (18). Consequent to this is the inhibition of the conversion of glycogen phosphorylase b to glycogen phosphorylase a as previously described. The diminution of cAMP can also decrease lipolytic activity as evidenced by reduced levels of glycerol and free fatty acids (18). This would be significant during submaximal exercise when fatty acids are used as energy substrates by the

contracting muscle.

As compelling as the evidence is for the role of metabolic acidosis in muscular fatigue, it must still be considered somewhat equivocal. Recent studies on patients with myophosphorylase deficiency, McArdle's Syndrome, showed that these patients are unable to produce lactate yet they still experience muscular fatigue. When these subjects exercised at the same intensity as a group of control subjects, the onset of fatigue was the same for both groups (13). The authors of this report conclude that fatigue is brought about by the efflux of K^+ from the muscle fiber. This extracellular K^+ can stimulate pain receptors, leading to the termination of exercise. Also, the increased levels of extracellular K^+ decrease the excitability of the muscle fiber to neural stimulation and this results in the failure of the muscle to fully contract. Obviously, more research into McArdle's Syndrome is needed in order to further elucidate the mechanisms of fatigue.

Dehydration and Fatigue

The human body is primarily composed of water. Approximately 60 percent of an individual's total body mass is accounted for by body fluids (15). This water serves as the medium in which metabolic processes occur. Thus, to insure optimal physical performance, appropriate levels of body fluids must be maintained.

Data suggest that water deficits of 4 percent can reduce aerobic work capacity by 48 percent (3). Decrements in body water of 8 percent have been demonstrated to significantly reduce maximal muscular force production (19). Similarly, anaerobic work such as bodybuilding workouts may suffer as much as 21 percent when the individual is dehydrated (19).

Dehydration, then, may induce fatigue in virtually any type of athletic endeavor. The biochemical reactions that are necessary to power metabolic processes in sports as diverse as long distance running and powerlifting are hindered under conditions of dehydration.

Muscle Fiber Type and Fatigue

The recent advances in biological technology have made it possible to perform muscle biopsies on human subjects. This technique has allowed us to directly investigate metabolic changes in muscle during exercise and to characterize muscle fibers by their enzymatic and structural characteristics. Type I muscle fibers are believed to be more aerobic in nature due to their high content of oxidative enzymes, rich blood supply, and an isozyme of myosin ATPase that catalyzes a slower rate of ATP turnover during muscle contraction. Conversely, type II muscle fibers are said to have a greater anaerobic capacity because of their high content of glycolytic enzymes, relatively poor blood supply, and an isozyme of ATPase that catalyzes a rapid turnover of ATP during muscular contraction. Typically, type I fibers produce less force, but can resist fatigue more efficiently than type II fibers. Indeed, it has been shown that there is a strong correlation ($r=0.86$) between fatigability and percentage of type II fibers (24). This may at least be partially explained by research indicating that the ATPase found in type II fibers is more sensitive to intramuscular changes in H^+ concentrations than the ATPase found in type I fibers (22). It has also been found that type II fibers produce more lactate than type I fibers when working at the same exercise intensity (10, 22). The impact that intramuscular acidosis has upon the onset of fatigue has already been described. It follows logically then, that type II fibers are more susceptible to fatigue than type I fibers. Research conducted by Donaldson confirms this. Her work shows that when intramuscular pH is changed from 7.0 to 6.5, type II fibers lost 25 percent of their maximum force while type I fibers lost only 12 percent of their maximum force (2).

The body selectively recruits type I or type II fibers depending upon the activity in which it is engaged. For example, following a 30 km run there is no glycogen depletion in type II fibers but there is in type I fibers (20). It is interesting to note that even in these

type I fibers, glycogen depletion does not appear to be significant enough to cause fatigue. However, upon closer examination it was observed that many of the glycogen particles in these fibers were located between the myofilaments (20). Thus, they were inaccessible to the mitochondria and could not be used in glycolysis.

It has been suggested that type I fibers are more sensitive to intracellular Ca^{++} than type II fibers (2). Presumably, it takes less Ca^{++} to elicit actin-myosin cross-bridge formation in type I fibers than in type II fibers. This also would affect the difference in fatigability between type I and type II fibers.

It can be seen that there is preferential recruitment of muscle fiber types during exercise. The rate at which fatigue occurs and the mechanisms that cause fatigue appear to be different with respect to type I and type II fibers as a result of their metabolic characteristics. However, recent evidence indicates that fiber type alone cannot accurately predict the onset and severity of fatigue (8). This is particularly true of non-elite athletes and/or the general population where the ratio of type I to type II fibers is roughly 50:50.

Muscular fatigue is a multi-faceted and complex phenomenon. Several locations for the onset of fatigue have been identified and many mechanisms may interact with each other to lead to the failure of muscular force production. The question of which of these mechanisms is responsible for fatigue depends upon such variables as exercise intensity, exercise duration, muscle fiber type, and the demands of the sport. Further work is needed to reveal the true biochemical nature of muscular fatigue. ●

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