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Mechanisms of muscle fatigue in intense exercise

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The manifestations of fatigue, as observed by reductions in the ability to produce a given force or power, are readily apparent soon after the initiation of intense activity. Moreover, following the activity, a sustained weakness may persist for days or even weeks. The mechanisms responsible for the impairment in performance are various, given the severe strain imposed on the multiple organ systems, tissues and cells by the activity.

At the level of the muscle cell, ATP utilization is dramatically accelerated in an attempt to satisfy the energy requirements of the major processes involved in excitation and contraction, namely sarcolemmal Na^+/K^+ exchange, sarcoplasmic reticulum Ca^{2+} sequestration and actomyosin cycling. In an attempt to maintain ATP levels, high-energy phosphate transfer, glycolysis and oxidative phosphorylation are recruited. With intense activity, ATP production rates are unable to match ATP utilization rates, and reductions in ATP occur accompanied by accumulation of a range of metabolic by-products such as hydrogen ions, inorganic phosphate, AMP, ADP and IMP. Selective by-products are believed to disturb Na^+/K^+ balance, Ca^{2+} cycling and actomyosin interaction, resulting in fatigue. Cessation of the activity and normalization of cellular energy potential results in a rapid recovery of force. This type of fatigue is often referred to as metabolic.

Repeated bouts of high-intensity activity can also result in depletion of the intracellular substrate, glycogen. Since glycogen is the fundamental fuel used to sustain both glycolysis and oxidative phosphorylation, fatigue is readily apparent as cellular resources are exhausted.

Intense activity can also result in non-metabolic fatigue and weakness as a consequence of disruption in internal structures, mediated by the high force levels. This type of impairment is most conspicuous following eccentric muscle activity; it is characterized by myofibrillar disorientation and damage to the cytoskeletal framework in the absence of any metabolic disturbance. The specific mechanisms by which the high force levels promote muscle damage and the degree to which the damage can be exacerbated by the metabolic effects of the exercise remain uncertain.

Given the intense nature of the activity and the need for extensive, high-frequency recruitment of muscle fibres and motor units in a range of synergistic muscles, there is limited opportunity for compensatory strategies to enable performance to be sustained. Increased fatigue resistance would appear to depend on carefully planned programmes designed to adapt the excitation and contraction processes, the cytoskeleton and the metabolic systems, not only to tolerate but also to minimize the changes in the intracellular environment that are caused by the intense activity.

Keywords: Calcium, cytoskeleton, eccentric activity, fibre types, muscle damage, potassium.

Introduction

Chest heaving and recoiling in uncontrolled pitch. Lungs locked in a desperate struggle for oxygen. Heart pounding in incessant rhythm. Skin flushed and blanketed by sweat; legs unresponsive to higher authority; mind tormented by pain; the joy of effort denied.

To the participant who has engaged in intense and sustained exercise, the symptoms described represent a humiliating and distasteful experience, vividly etched into the deepest recesses of the mind. To the physiologist, however, this behaviour is intriguing and challenging. It is intriguing because of the severe insult imposed by this form of exercise on a wide range of physiological systems. It is challenging because of the difficulty in isolating the mechanisms for the inability to sustain performance among a complexity of changes in the multiple systems, organs, tissues and cells of the body.

In this review, a primary objective is to provide insights into the possible causes of the rapid and profound fatigue which results from participation in

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intense activity, particularly where large muscle groups are involved. Given the multiple manifestations of contractile behaviour that are possible, ranging over a broad spectrum of velocities and muscle lengths (Sargeant, 1994), identification of a single definitive mechanism appears unrealistic. Rather, the informed reader is invited to use the information presented and apply it to the peculiarities of a particular activity. Several recent and excellent reviews are available addressing various aspects of neuromuscular fatigue and the mechanisms involved (Green, 1990, 1995b; Enoka and Stuart, 1992; Fitts, 1994; Allen *et al.*, 1995; Korge, 1995; Lindinger *et al.*, 1995; McKenna, 1995; Williams and Klug, 1995).

Intense contraction and physiological strain

Intense contraction, particularly with large muscle groups, imposes a major strain on a wide variety of physiological systems. To generate the high force levels accompanying intense activity, maximal or near maximal activation of all of the synergistic muscles is a fundamental requirement. In the case of cycling, for example, seven different synergistic muscles are recruited, their activation pattern being highly ordered and dependent on the limb and pedal position (Green and Patla, 1992). At the level of the individual muscle, maximal tetanic force for maximal work depends on full recruitment of all motor units at high firing frequencies (Deluca, 1985).

From the perspective of the motor control system, purposeful and successful performance of the activity demands a precise temporal and spatial recruitment and rate-coding behaviour, not only at the level of the individual motor units within a muscle but between groups of agonist and antagonist muscles as well (Deluca, 1985). A failure to coordinate the motor drive would be reflected in a lack of both skill and efficiency.

In terms of the individual muscle cell, a successful response to the high firing frequencies is critically dependent on the sarcolemma and T-tubule system being able to regenerate action potentials at high frequency to the interior of the cell. Depending on the type of activity, action potential frequency may exceed 100 per second (100 Hz) (Enoka and Stuart, 1992). The ability to sustain an action potential at high frequency is primarily dependent on the ability to re-sequester the potassium ions (K^+) back into the cell from the interstitial space and to expel the excess sodium ions (Na^+), which enter during the action potential, back to the interstitial space. Re-establishment of the electrochemical gradients is primarily under the control of an electrogenic pump which expends energy in the form of ATP to pump both Na^+ and K^+ against their concentration gradients. The enzyme involved, for hydrolysing the ATP and producing the necessary energy for this process, is embedded in the membrane and is called the Na^+/K^+-ATPase (Clausen and Nielsen, 1994). It is apparent that if the sarcolemma and the T-tubule membranes are to conduct action potentials at a high rate, necessary for the maximal activation of the fibre, the pump must possess a high ATPase activity, and a high capacity for rapid ATP hydrolysis and rapid production of free energy.

Once the excitation is inside the cell, it must also be rapidly conducted from the T-tubule membrane to the sarcoplasmic reticulum and specifically the region of the calcium release channel, located primarily in the terminal cisternae and in apposition to the T-tubules (Melzer *et al.*, 1995). The specific mechanisms involved in the transmission of the excitation signal from the T-tubule to the terminal cisternae are not yet fully understood. Recent developments suggest that receptors located in the T-tubule membrane, labelled dihydropyridine receptors, are capable of conducting a charge and initiating movement of specific molecules. The movement of these molecules is believed to unblock the calcium release channel in the sarcoplasmic reticulum, allowing calcium (Ca^{2+}) to escape to the surrounding cytoplasm and resulting in an increase in the levels of free Ca (Ca_f^{2+}). As with sarcolemma and T-tubules, excitation-contraction coupling must remain responsive to elevate Ca_f^{2+} for maximal activation of the myofibrillar apparatus. In most skeletal muscles, approximately a 100-fold increase is necessary (Melzer *et al.*, 1995).

The generation of high force levels depends on the Ca^{2+} signal begin translated via the regulatory proteins, troponin and tropomyosin, leading to a transformation of actomyosin from a weak binding to a dominant strong binding, force-generating state (Moss *et al.*, 1995). Weak to strong binding is mediated via activation of an ATPase, located in the myosin heavy chains (myosin ATPase), which allows for generation of free energy via ATP hydrolysis and the release of the metabolic by-products ADP and inorganic phosphate. High levels of myosin ATPase (actomyosin) are essential for work performed at high velocities (Moss *et al.*, 1995).

The generation of high force levels by muscle fibres also depends on the ability to control Ca^{2+} removal from the cytoplasm rapidly. This property primarily resides in the sarcoplasmic reticulum and predominantly in the longitudinal reticulum of the sarcoplasmic reticulum where an enzyme, the Ca^{2+} ATPase, is located. This enzyme, as with the other major enzymes involved in excitation and contraction, is capable of hydrolysing ATP for the production of the energy necessary to pump the cytosolic Ca^{2+} against a concentra-

tion gradient, into the lumen of the sarcoplasmic reticulum, where it is stored or used for release through the Ca^{2+} channel of the sarcoplasmic reticulum.

It is apparent that for dynamic activity in particular, all excitation and contraction processes must be coordinated and able to translate high frequencies of impulse activity at each step, and ultimately produce a mechanical response consistent with the intentions of the neural command. As might be expected, muscle cells differ fundamentally in the structural, compositional and molecular features that they possess and which make them exquisitely adapted for specific types of mechanical responses. The fast-twitch or Type II fibres, in contrast to the slow-twitch or Type I fibres, possess the properties most suited to dynamic or high-velocity activities (Moss *et al.*, 1995). Isometric performance, in which no movement is involved and in which peak tetanic force is the major objective, can be accomplished with approximately equal success by both fibre types when adjustment is made on the basis of cross-sectional area (Green, 1995b).

Since in humans, most muscles contain a mixture of slow- and fast-twitch motor units and muscle fibres and since recruitment appears to follow an orderly sequence (Deluca, 1985), all fibre types and subtypes are recruited during intense activity. The mechanical response elicited by the muscle and/or groups of synergists must be viewed as a composite response, dependent on the contribution of both fibre type populations.

The high force levels generated by the large population of actin and myosin in the strong binding conformation also have implications for the internal organization of both the force and non-force generating structures within the cell. In the muscle cell, a large number of cytoskeletal proteins function to position the internal structures within the cell in a fixed array. The cytoskeletal proteins form both an exosarcomeric lattice and an endosarcomeric lattice (Thornell and Price, 1991). The exosarcomeric lattice, which consists of proteins such as desmin and vitamin and which are external to the myofibrils, serves to anchor the myofibrils to the sarcolemma, nucleus and other structures. The endosarcomeric lattice connects structures within the myofibrils, including the myosin to the Z disc and the myosin to each other. Titin and nebulin are prominent endosarcomeric proteins. High levels of force generation within a fibre impose considerable strain on the cytoskeleton. Maintaining the integrity of the cytoskeleton during periods of maximal activation is essential for the efficient production and translation of forces to the tendon.

The transition from rest to maximal or near maximal exercise intensities can result in a several hundred-fold increase in the rates of ATP hydrolysis, necessary to supply the energy for restoring Na^+/K^+ gradients across the sarcolemma and T-tubules, re-sequestering Ca^{2+} into the sarcoplasmic reticulum and for the actomyosin power stroke. The energy supplying systems, oxidative phosphorylation, glycolysis and high-energy phosphate transfer, must be precisely geared to regenerate ATP at a rate necessary to prevent any substantial depletion of ATP, which exists only in low concentration in the muscle. These metabolic pathways differ widely in the rate at which ATP can be synthesized and consequently are specialized to subserve the energy requirements of specific mechanical tasks. During single repetitions of intense contractile activity, for example, the hydrolysis of phosphocreatine serves as a primary source of regeneration of ATP from ADP. The rate at which this system can regenerate ATP is far in excess of that which can be hydrolysed by the major ATPase enzymes involved in supplying energy for specific excitation and contraction functions (Connett *et al.*, 1990; Hochachka, 1994). Moreover, given the equilibrium nature of the creatine phosphokinase reaction, the flux is intimately sensitive and protective of reductions in ATP concentration (Connett *et al.*, 1990). Depending on the temporal characteristics of the intense contractile cycle, glycolysis may also contribute extensively to the stabilization of ATP levels. This system, although possessing a lower capability for peak ATP production than the high-energy phosphate transfer system, is also capable of being rapidly activated and generating ATP (Hochachka, 1994). According to current thinking, ATP production is compartmentalized with the synthesis located near the ATP hydrolysing enzymes (Korge, 1995). According to this concept, both phosphocreatine and glycolysis serve to regenerate ATP via enzymes which are bound to structures in close proximity to the site of ATP utilization. In this model, oxidative phosphorylation is viewed as a means of synthesizing phosphocreatine via ATP production, which then diffuses to the site of utilization (Korge, 1995). Indeed, the mitochondria themselves also appear to be strategically positioned in different regions to the cell (Howald, 1982).

Muscle fibre types differ dramatically in the expression of the metabolic pathways used for ATP production (Hochachka, 1994). Fast-twitch fibres, for example, given their high capability for ATP utilization, also possess a high potential for high-energy phosphate transfer and glycolysis. In contrast, slow-twitch fibres possess metabolic pathway specialization geared to aerobic ATP production. These fibres are invariably characterized by a low potential for high-energy phosphate transfer and glycolysis and a high potential for oxidation phosphorylation. A population of the fast-twitch fibres may also possess a high mitochondrial content and, consequently, a high potential for the

aerobic synthesis of ATP (Green, 1995b). Although preferential recruitment of fast-twitch fibres may be desirable during intense exercise, given the specialized capability for high rates of ATP synthesis, this does not appear to be the case. The recruitment of slow-twitch fibres within a muscle appears to be invariable regardless of the force generated (Deluca, 1985).

Repetitive activity and neuromuscular fatigue

If the intense activity is performed on a repetitive basis, and particulary if large muscle groups are involved, the strain on the neural, muscular and metabolic systems is greatly exaggerated. Under such conditions, the exercise intensity cannot be sustained beyond a relatively brief period and fatigue is readily apparent (Sargeant, 1994). The inability to sustain high force outputs may be due to failure at one or more sites in the neuromuscular system. At the peripheral level, an inability to generate action potentials repeatedly at the high frequency required for maximal or near maximal force generation by the fibre may result in excitation failure or a failure to translate fully the neural signal to the interior of the fibre. This form of fatigue, often referred to as high-frequency fatigue (Fitts, 1994; Allen *et al.*, 1995; Green, 1995b), appears to occur because of an inability to restore Na^+ and K^+ gradients across the sarcolemma before the next neural impulse (Clausen and Nielsen, 1994). As a consequence, substantial amounts of K^+ are lost from the cell, resulting in a lower resting membrane potential and a loss of excitability. Under these conditions, a substantial shift of water also occurs from the interstitium into the cell (Lindinger *et al.*, 1995). The problem appears to reside in an inappropriately low activity of the Na^+-K^+ enzyme, and consequently insufficient free energy to quickly re-establish Na^+ and K^+ gradients across the cell membrane (Clausen and Nielsen, 1994). Problems with membrane excitability during intense activity have also been suggested from measurements of electromyographic (EMG) activity. A reduction in the integrated EMG, particularly when obtained in conjunction with a normal mass action potential (M-wave), has frequently been found where repetitive intense contractions occur (Bigland-Ritchie and Woods, 1984; Enoka and Stuart, 1992).

Various studies have also provided evidence of a failure at the level of the sarcoplasmic reticulum (Byrd *et al.*, 1989; Gollnick *et al.*, 1991; Allen *et al.*, 1995). For the sarcoplasmic reticulum to be implicated in fatigue, the coupling signal from the T-tubule, designed to elicit elevations in Ca_f^{2+} consistent with maximal activation under non-fatigued conditions, must result in an inappropriate response from the sarcoplasmic reticulum. The inappropriate response could result from reductions in Ca^{2+} release or from reductions in Ca^{2+} sequestration. Direct measurement of cytosolic Ca^{2+} levels with repetitive activity is not possible *in situ*, but these measurements can be made in single intact fibre preparations with the use of fluorescent dyes (Allen *et al.*, 1995). These studies have found depressions in cytosolic Ca_f^{2+} in conjunction with depressed force levels, the reduction in Ca_f^{2+} being primarily attributed to a reduction in Ca^{2+} release from the sarcoplasmic reticulum (Allen *et al.*, 1995). At high force levels and high excitation levels, the reduction in Ca^{2+} release has been attributed not so much to a problem at the level of the Ca^{2+} release channel itself, but to a failure in excitation (Allen *et al.*, 1995). Although there is minimal experimental evidence, excitation–contraction coupling is not considered limiting (Fitts, 1994). Single fibre studies are more conclusive in attributing a failure at the level of the sarcoplasmic reticulum to less intense schedules of contractile activity (Allen *et al.*, 1995). However, the limitation in single fibre experiments with an imposed and stereotyped activation pattern cannot provide for possible accommodation strategies. Evidence has been provided (Bigland-Ritchie and Woods, 1984), although still somewhat controversial (Enoka and Stuart, 1992), using needle electrodes inserted into the muscle, of a reduction in firing frequency coinciding with a prolongation of relaxation time. The lower firing frequency minimizes excitation failure while still retaining the minimal frequency necessary to activate fully the partially fatigued muscle. Under these circumstances, the loss of force that occurs could well reside in the sarcoplasmic reticulum or some process more distal to the sarcoplasmic reticulum, such as the myofibrillar complex.

Other evidence of sarcoplasmic reticulum dysfunction, albeit indirect, comes from *in vitro* studies. In these studies, samples of the muscle tissue are harvested after the exercise and sarcoplasmic reticulum function is studied in homogenates or fractions highly enriched with sarcoplasmic reticulum membrane. Under such conditions, high-intensity exercise has been shown to depress Ca^{2+} uptake and Ca^{2+} ATPase activity in both horses (Byrd *et al.*, 1989) and humans (Gollnick *et al.*, 1991). The depression in Ca^{2+} sequestering abilities, measured under supposedly optimal conditions, suggests a persistent change in the Ca^{2+} ATPase enzyme, possibly at the adenine nucleotide binding site (Green, 1995a), which renders part of the Ca^{2+} ATPase population dysfunctional and incapable of accumulating Ca^{2+} into the lumen of the sarcoplasmic reticulum. There is a possibility also that the Ca^{2+} release channel may be adversely affected in intense exercise. Prolonged running in rats has been shown to

depress Ca^{2+} release when measured *in vitro* (Favero *et al.*, 1995). It should be cautioned, however, that although these studies implicate abnormalities in sarcoplasmic reticulum function with intense exercise, they still must be clearly related to the decrement in mechanical performance. Moreover, analytical issues remain a problem and depressions in sarcoplasmic reticulum Ca^{2+} uptake and Ca^{2+} ATPase activity do not always occur when intense activity is performed and the measurements are made on *in vitro* homogenates (Dossett-Mercer *et al.*, 1994). The situation is also compounded by potential differences in species and muscle fibre types.

During high-intensity repetitive activity, fatigue may also occur because of a failure of the myofibrillar apparatus to respond appropriately to a given cytosolic Ca_f^{2+} signal (Allen *et al.*, 1995; Fitts, 1995). This problem may arise from a change in the sensitivity of the regulatory protein, troponin C, for Ca^{2+}, from the ensuing conformational changes within the thin filament that ultimately sterically unblocks the site on actin that forms strong binding with myosin, or from a direct effect on actomyosin itself, which constitutes the molecular motors involved in force generation. Moreover, since the number of cross-bridges in the strong binding, force-generating configuration also depends on cooperative feedback from strong binding cross-bridges to the thin filament (Fuchs, 1995), failure to turn on the thin filament optimally may also contribute to fatigue. Rapid transition between weak and strong binding actomyosin at dissociated states is a fundamental requirement where dynamic activity and muscle shortening is an objective (Moss *et al.*, 1995). Moreover, there is a persistent requirement for each actomyosin complex to develop as much force as possible during the limited time of the cross-bridge cycle, since force decreases as the velocity of movement increases (Moss *et al.*, 1995). The rate at which the actomyosin cycles between states is critically dependent on the activity of myosin ATPase, and the rate at which free energy can be made available from the hydrolysis of ATPase (Moss *et al.*, 1995). Depressions in myosin ATPase activity, as have been shown *in vitro* following intense activity (Fitts, 1994) and in skinned single fibre preparations with a microenvironment created to simulate heavy exercise (Cooke and Pate, 1990), have profound effects on the force and velocity characteristics of the fibre (Cooke and Pate, 1990).

Although the greatest manifestation of fatigue appears to reside in the muscle, a failure in cental processes, culminating in a suboptimal neural drive, also appears to have a role in intense activity. It has been found that under conditions of intense, voluntary activity, which produces a rapid and pronounced decrease in force, some recovery in force can occur at different times during the activity by superimposing a brief, electrical stimulus to the motor nerve or muscle directly (Bigland-Ritchie and Woods, 1984; Enoka and Stuart, 1992; Gandevia, 1992). The fact that the muscle can demonstrate some positive response under these circumstances has been used as evidence for a failure in central command. More recent work, using direct transmagnetic stimulation to the motor areas of the brain, has also identified a central component contributing to the fatigue observed during intense, small muscle group activity (Gandevia *et al.*, 1996).

The peripheral mechanisms underlying the fatigue observed during repetitive, high force-generating activity appear to have both non-metabolic and metabolic components (Davies and White, 1981; Moussavi *et al.*, 1989). The non-metabolic component of fatigue appears to exist independently of a disturbance in the energetic potential of the muscle fibre. This type of fatigue appears to be mediated as a result of the high repetition forces that are generated and which results in muscle damage (Newham *et al.*, 1983; Byrnes *et al.*, 1985; Fridén and Leiber, 1992). Although concentric activity can produce some degree of damage to the muscle cell (Fridén and Ekblom, 1988), eccentric exercise, most probably because of the much higher force levels that can be generated, have the most lethal effect. At various times, the damage has been characterized by sarcoplasmic sarcolemma disruption, Z-band streaming, myofibrillar disorganization, leukocyte and phagocyte infiltration, central nuclei, loss of cytoskeletal proteins such as desmin and fibre necrosis (Armstrong *et al.*, 1991; Fridén and Leiber, 1992; Leiber *et al.*, 1996). Such exercise-induced muscle damage is also commonly associated with soreness and swelling of the tissue.

The post-exercise degenerative changes are believed to be exacerbated by one or more of several potential mechanisms, including activation of proteolytic enzymes such as calpain, generation of oxygen free radicals and an autophagic response resulting from the invasion of phagocytes and increases in lysosomal acid hydrolysis in the injured muscle cell (Armstrong *et al.*, 1991; Fridén and Leiber, 1992).

Regardless of the mechanism, the damage appears to result in a pronounced weakness, the recovery of which, at least in unconditioned individuals, may take several days or even weeks (Newham *et al.*, 1983; Clarkson and Tremblay, 1988). During high-intensity activity, this non-metabolic component would be expected to be progressive with the duration of the activity and, in fact, may represent a major aspect of the fatigue observed. High-intensity exercise performance is impaired if attempted before recovery from this form of weakness is complete (Sargeant and Dolan, 1987). Since the activity is at near maximal levels, there

remains only a limited ability to increase firing frequency or recruit other motor units and synergistic muscles.

Metabolic fatigue or fatigue associated with the energetic changes in the muscle would appear to be intimately involved in the ability to sustain high-intensity exercise. The actual manifestation and progression of fatigue depend to a large extent on the ratio of the time of contraction to the time of relaxation or recovery. This ratio, defined as the duty cycle, is most conspicuous during dynamic activity, where a period of muscle shortening is characteristically followed by a period of muscle relaxation when the muscle is returned to its original position by antagonistic muscles, before the beginning of the next repetition. In cycling, the muscles of the opposite leg perform this function, such that the muscles of the thrust leg are only on duty for a maximum period of 50% of the time. In actual fact, the duty cycle for each of the muscles appears to be much less than 50% (Green and Patla, 1992). The duty cycle is a major factor in the relative importance of metabolic pathways used for ATP supply.

As previously emphasized, a single movement, even at maximal force levels, can be performed without serious threat to ATP levels by using phosphocreatine to regenerate ATP. However, as the number of repetitions increases and depending on the duty cycle, activation of both glycolysis and oxidative phosphorylation is essential in maintaining adequate levels of ATP. During the recovery phase, replenishment of phosphocreatine stores depends on the ATP regenerated from aerobic processes, a process that even at peak levels of oxidative phosphorylation ($\dot{V}O_2$ max) takes minutes to complete (Harris *et al.*, 1976). As a consequence, glycolysis generally assumes increasing importance as the number of repetitions is increased. During this period, the mitochondria are also increasingly activated and the ATP supplied by oxidative phosphorylation becomes progressively more important both during the contractile and recovery phases.

Following a period of repetitive, high-intensity activity, the muscles and muscle fibres are characterized by extreme metabolic perturbations. These muscles display reductions in ATP which may approach 40% (McCartney *et al.*, 1986; Hultman *et al.*, 1991; Gaitanos *et al.*, 1993) and near complete reductions in phosphocreatine. The metabolic by-products generated from the high-energy phosphate reactions result in large increases in inorganic phosphate, creatine, free ADP and free AMP. Activation of AMP deaminase also occurs, leading to increases in inosine monophosphate and ammonia (NH_4^+). These changes are accompanied by large increases in lactic acid generated by the increase in glycolytic flux. The increase in lactic acid in combination with the hydrogen ions generated by ATP hydrolysis, produces a profound muscle acidosis which may decrease pH to below 6.4 (Green, 1995b).

According to current thinking, it is not the reduction in ATP that is the primary cause of force failure in itself, since the concentration of ATP remains well in excess of that needed to saturate the ATPase enzymes (Korge, 1995). Rather, it is the accumulation of selected metabolic by-products that precipitates the fatigue process. Accumulation of ADP, inorganic phosphate and H^{2+}, for example, serves not only to reduce the free energy liberated by ATPase hydrolysis, but also to cause a profound down-regulation in ATPase activity (Korge, 1995). This down-regulation has been demonstrated not only for the sarcoplasmic reticulum Ca^{2+} ATPase, but for Ca^{2+} release channel function, using an artificial microenvironment with specific manipulation of selected metabolites either alone or in combination (Zhu and Nosek, 1991). Skinned fibre preparations have also been used to demonstrate the effect of changes in specific metabolites on myosin ATPase activity and actomyosin function (Cooke and Pate, 1990). Interestingly, the effect of changes in specific metabolites is, to some degree, specific to the velocity of contraction. Skinned fibre studies have also been complemented by *in vitro* studies in which the behaviour of either the sarcoplasmic reticulum Ca^{2+} ATPase (Williams and Klug, 1995) or the myofibrillar ATPase (Parkhouse, 1992) is examined at different background concentrations of metabolites, typical of those found in heavy exercise. The results are generally consistent and show a dominant effect of selected metabolites such as inorganic phosphate, ADP and H^+ on the regulation of ATPase activity and the liberation of energy.

The down-regulation of ATPase is viewed as protective, allowing relatively tight regulation of ATP levels (Korge, 1995). By reducing ATP utilization, a better balance can be achieved with the ATP synthesizing pathways. The penalty, however, for the down-regulation is fatigue, promoted by a loss in the ability to use ATP at high rates. At present, it is not possible to implicate a specific excitation or contraction process as the definitive weak link, since all processes appear to be disturbed by the adverse microenvironment created by intense exercise. It is possible that metabolite levels may be different in the different compartments separating the major ATPase enzymes. Since ATP synthesis is believed to be locally regulated (Korge, 1995), an imbalance between ATP utilization and ATP synthetic rates may be more pronounced in one compartment than another.

The high glycolytic rate induced by intense activity also results in the predominant utilization of carbohydrate and, in particular, the glycogen reserves in the working muscle. Even short periods of repetitive activ-

ity result in large depletions of glycogen, especially from the fast-twitch glycolytic muscle fibres possessing a low mitochondrial potential (Vollestad and Blom, 1985). Glycogen depletion has repeatedly been shown to be associated with fatigue during prolonged, submaximal exercise by processes yet unknown, since ATP levels appear to be well preserved (Green, 1991). Loss of muscle glycogen may well be a factor in fatigue in some work schedules demanding repeated, intense efforts, especially where large muscle groups are involved.

Intense effort, conducted intermittently over an extended time and involving large muscle groups, may also provoke other factors which modify the fatigue process. This type of activity induces maximal or near maximal activation of ventilation and cardiac output. The repeated activation of the diaphragm and cardiac tissue may also result in fatigue in these organs (Hales, 1995), promoting a reduction in pulmonary diffusion (Johnson *et al.*, 1993; Powers *et al.*, 1993) and cardiac output (Hales, 1995) respectively, with both disturbances contributing to a reduction in arterial oxygen delivery to the working muscle. At least with the diaphragm, there is some evidence that fatigue may be monitored centrally and result in a reduction in motor command to the locomotor muscles (Boutellier *et al.*, 1992; McKenzie *et al.*, 1992). The large amounts of heat generated from the metabolic processes, primarily in the working muscle, must also be dissipated (Ekblom *et al.*, 1971), a process which depends essentially on increasing blood flow to the cutaneous areas and on evaporation. Excessive diversion of blood to the cutaneous vasculature could promote cardiovascular instability and further increase the strain on the heart (Green, 1995a). Significant increases of 2–3¡C in body temperature, which can occur during heavy exercise, appear to be strongly correlated with fatigue and exhaustion (Nielsen *et al.*, 1993). Heavy exercise can only be performed with the assistance of a wide range of hormones involved in fluid and electrolyte balance and metabolism and substrate utilization. The catecholamines, for example, increase profoundly and appear to have a central role in sustaining the function of a wide range of tissues. An inability to elicit an appropriate hormonal response may have drastic consequences on the ability to sustain high-intensity effort (Galbo, 1992).

Meaningful and attainable adaptations

The resistance to fatigue observed during the performance of intense exercise can be greatly extended with purposeful and focused interventions. Preparing the muscle and the muscle cells for the trauma and damage invoked by repeated, high force generation would appear to be one area where dramatic improvement is possible. Following a schedule of acute concentric or eccentric contractions, the repair and remodelling of the damage may take several days and, depending on the severity, up to 2 weeks (Newham *et al.*, 1983; Fridén and Leiber, 1992). After the repair period, the muscle appears to be able to tolerate the same exercise task not only with less damage but also with a faster recovery and consequently less weakness and soreness (Byrnes *et al.*, 1985; Clarkson and Tremblay, 1988). Moreover, it appears that the protective effect may extend for at least a period of a week (Clarkson and Tremblay, 1988). Consequently, a planned preparatory programme should include periodic and systematic exposure to activities demanding the generation of large forces to stimulate adaptations in the cytoskeletal framework. For this type of adaptation to be significantly transferable to a specific task, care must be taken to incorporate high force activities that fully exploit the muscles and motor units, the range of motion and the contraction velocity typical of the task. An inviting but unproved possibility is that eccentric activity, given the small insult needed to induce damage and adaptation (Fridén and Leiber, 1992), may have a valuable role to play. If this is the case, it may not be necessary to concentrate exclusively on intense and sustained training activities, with the accompanying and diverse physiological strain that results, to promote increased resistance to muscle damage.

Adaptations in energy metabolic potential are undoubtedly crucial to improving fatigue resistance. Since high-intensity activity results in an imbalance between ATP regeneration and ATP utilization, resulting in a reduction in ATP of as much as 40% (McCartney *et al.*, 1986; Gaitanos *et al.*, 1993), major benefits would result from increasing ATP synthetic rates. Moreover, since the greatest imbalance occurs during the rest to work transitions, improvements in the ability to increase flux rates of the ATP supplying pathways rapidly, particularly where repetitive, dynamic activity is involved, would be particularly significant. Although high-energy phosphate transfer potential appears relatively insensitive to further adaptation, the metabolic pathways and segments involved in glycogenolysis, glycolysis and oxidative phosphorylation can change markedly if appropriately stimulated (Holloszy and Coyle, 1984; Cadefau *et al.*, 1990). High-intensity activity appears to represent a potent stimulus for eliciting increases in the maximal activities of a wide range of enzymes involved in these pathways and segments (Dudley *et al.*, 1982; Cadefau *et al.*, 1990). In the case of glycolysis, greater flux would be expected at a given effector concentration or, alternatively, a given flux could be sustained at a lower effector

concentration (Connett *et al.*, 1990; Spriet, 1995). Increases in buffer capacity should also promote an improved work performance given the need to minimize the drastic changes in H^+ concentration which occurs with repeated stimulation of glycolysis (Sharp *et al.*, 1986). Improvements in oxidative phosphorylation could effectively lower the dependency on high-energy phosphate transfer and glycolysis at a given ATP requirement and, consequently, reduce metabolic by-product accumulation and glycogen dependency (Connett *et al.*, 1990).

Increases in maximal aerobic power ($\dot{V}O_2$ max) could prove extremely valuable, allowing increases in $\dot{V}O_2$ during the non-steady-state (Hagberg *et al.*, 1980; Phillips *et al.*, 1995) as well as providing for a faster rate of phosphocreatine synthesis during the rest and recovery intervals. Since phosphocreatine re-synthesis is an aerobic-dependent process (Harris *et al.*, 1976), ensuring that tissue oxygen tension remains high during the recovery period could promote a faster normalization of the by-products of high-energy phosphate reactions and quicker restoration of energy potential. In the long term, improvements in O_2 availability would appear to depend on increases in capillary density (Hudlicka *et al.*, 1992). Oxygen kinetics may also be improved independent of changes in $\dot{V}O_2$ max of mitochondrial potential. Recent evidence indicates that alterations in blood flow may provide an early adaptation to short-term training, leading to an increase in ATP supplied by mitochondrial respiration and a lowering of by-product accumulation (Green, 1996).

Important adaptations are not only limited to the ATP synthesizing machinery. The ATPase enzymes involved in ATP hydrolysis may also be altered. The sarcolemma Na^+-K^+ ATPase, for example, has been shown to be quickly up-regulated with sprint activity (McKenna *et al.*, 1993) and there is evidence that these adaptations result in an improvement in Na^+ and K^+ homeostasis (McKenna, 1995). If an improved ability to re-establish Na^+ and K^+ gradients occurs, the sarcolemma should allow for a more rapid re-establishment of the resting membrane potential and an improved ability to conduct action potentials at a high frequency (Clausen and Nielsen, 1994).

Whether adaptations elicited by high-intensity activity include increased activity of the other major ATPases, the sarcoplasmic reticulum ATPase and the actomyosin ATPase remain unclear. It is well known that extensive modifications can be elicited by extreme non-physiological patterns of contractile activity (Pette and Düsterhöft, 1992), but whether an up-regulation in the maximal activity of these pumps can be induced by voluntary training to meet the requirements of intense, dynamic activity remains to be determined. At least for the myosin ATPase (actomyosin), pronounced changes would not be expected, given the ability of sprint training to induce only minor changes in fibre types (Simoneau *et al.*, 1985).

Particularly noteworthy are the increases that result to the areas of all fibre types and subtypes with dynamic training in general and high-resistance training in particular (Howald, 1982). The increase in cross-sectional area should have the effect of delaying fatigue by allowing a smaller number of motor units to be initially recruited at a given force level, or by allowing a submaximal activation of the fibres where recruitment of the motor neuron pool remains fixed. It would appear, however, that for increases in fibre size to be a meaningful adaptation in sustained, high-intensity effort, capillary density should also be increased. Moreover, training routines should also address the velocity requirements of the task, so that neural recruitment patterns and muscular contractile properties are developed in a manner consistent with what is desired.

Overview

In summary, pronounced improvements in exercise performance are attainable with regular and systemic training routines. Extensive adaptations are possible at a variety of levels of organization. The real challenge is to devise appropriate strategies so that adaptations can result in desired outcomes. For the participant, experiencing the joy of effort, at least in part, remains a possibility.

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