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METABOLIC FACTORS IN FATIGUE

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KEY POINTS

- Sustained production of muscular force during exercise depends on the generation of chemical energy (ATP) by nonoxidative (anaerobic) and oxidative (aerobic) metabolism.
- Fatigue develops when the compounds needed to produce ATP are depleted or when by-products of metabolism accumulate in muscle.
- These metabolic changes can cause fatigue by acting on nerve processes that activate muscles. Both central and peripheral nervous systems may be impaired.
- Reductions in muscle levels of ATP, phosphocreatine, and glycogen, and low blood glucose availability can impair skeletal muscle performance. Low blood glucose can also adversely affect central nervous system function.
- Increases in intramuscular levels of magnesium, ADP, inorganic phosphate, hydrogen ion, and reactive oxygen species can impair muscle function. Increased ammonia and hyperthermia can also contribute to fatigue, probably via effects on the central nervous system.
- Appropriate training programs and nutritional interventions enhance fatigue resistance and exercise performance by improving the ability of the muscles to sustain ATP production.

INTRODUCTION

Adenosine triphosphate (ATP) is the immediate source of chemical energy for muscle contraction. Because the intramuscular stores of ATP are small, the continual regeneration of ATP is critical for the maintenance of muscle force output during sustained exercise performance. At high power outputs (such as those observed during high-intensity sprint exercise), this is achieved through non-oxidative (anaerobic) ATP production following the breakdown of phosphocreatine (PCr) or the degradation of muscle glycogen to lactate. At the lower power outputs required for prolonged endurance performance, the oxidative or aerobic metabolism of carbohydrates (muscle glycogen and blood-borne glucose) and lipid (fatty acids derived from triglyceride stores either in the muscles or in adipose tissue) provides virtually all of the ATP required for energy-dependent cellular processes within skeletal muscle. These metabolic processes and their importance during exercise have been well described (Coyle, 2000; Sahlin et al., 1998).

Considerable attention has focused on potential fatigue mechanisms responsible for the decline in force and/or power output by skeletal muscle during exercise and the role of metabolic factors in those changes. These metabolic factors can be broadly categorized as depletion of energy substrates (ATP and other biochemical compounds used in the production of ATP) and accumulation of metabolic by-products (Table 1).

TABLE 1. ***Metabolic factors in fatigue***

Substrate depletion
ATP
Phosphocreatine
Muscle glycogen
Blood-borne glucose
Metabolic by-products
Magnesium ions (Mg^{2+})
Adenosine diphosphate (ADP)
Inorganic phosphate (P_i)
Lactate ions
Hydrogen ions (H^+)
Ammonia
Reactive oxygen species
Heat

Potential sites of fatigue

Fatigue is a multifactorial process that reduces exercise and sport performance. It can be broadly defined as a failure to maintain the required or expected force and power output, or as a reduction in the capacity to generate force and power. Although fatigue may involve many organ systems, most attention has focused on skeletal muscle and its ability to generate force. Thus, in searching for potential sites of fatigue, one needs to consider the steps involved in the activation of skeletal muscle. These are summarized in Figure 1 and represent potential sites of fatigue or processes that can be affected by substrate depletion and/or metabolic by-product accumulation.

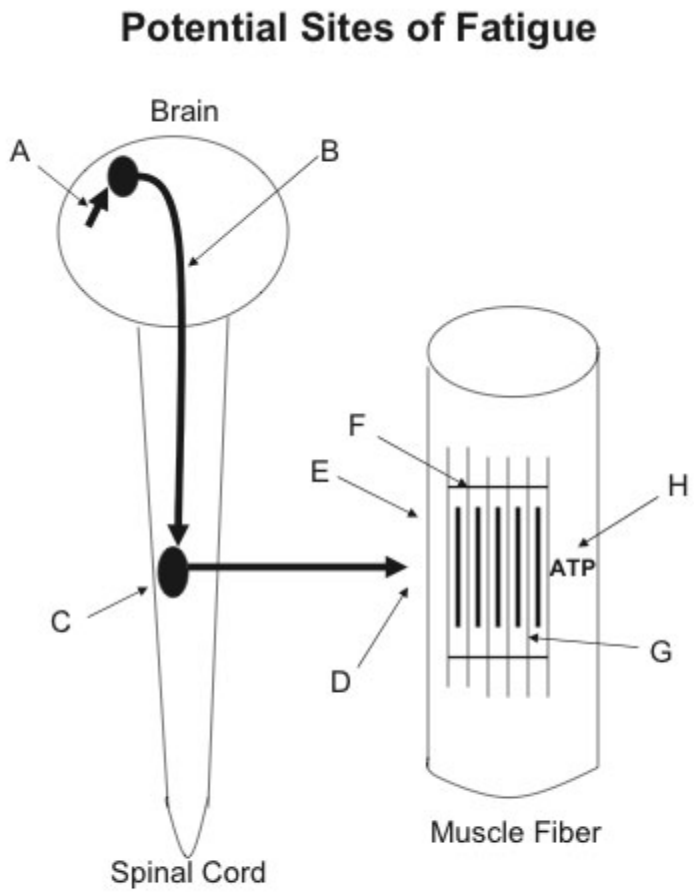

FIGURE 1. *Potential sites of muscle fatigue.* A: excitatory input to motor cortex; B: excitatory drive to lower motoneuron; C: excitability of lower motoneuron; D: neuromuscular transmission; E: excitability of sarcolemma; F: excitation-contraction coupling; G: contractile mechanism; H: supply of metabolic energy. (Modified from Bigland-Ritchie, 1981)

It has been common for exercise scientists to consider both central and peripheral mechanisms in the etiology of fatigue and, indeed, both levels contribute to reduced skeletal muscle performance during exercise. More detailed information on aspects of central and peripheral fatigue can be found in two comprehensive reviews (Fitts, 1994; Gandevia, 2001).

Substrate Depletion

Reduced availability of key biochemicals involved in energy production can limit ATP supply during exercise and compromise skeletal muscle and central nervous system function. These substrates include PCr, muscle glycogen, and blood glucose.

ATP. Numerous studies have demonstrated that ATP concentration in samples of mixed muscle fi bers is reasonably well protected during intense exercise, falling by ~30-40%. However, in analyses of single muscle fi bers, ATP levels can fall to a greater extent in type II "e;fast"e; fi bers following intense exercise and limit the ability of these fi bers to contribute to power development (Casey et al., 1996). Furthermore, there may be small temporal and spatial reductions in ATP availability within the local microenvironment of certain key ATP-dependent enzymes (myosin ATPase, Na+/K+ ATPase, sarcoplasmic reticulum Ca2+ ATPase) and within the Ca2+ release channels of the sarcoplasmic reticulum. That decreases in ATP can contribute to fatigue was shown in rats by Dutka and Lamb (2004). In their experiment, a lowering of ATP concentration impaired excitation-contraction coupling and force production in skinned skeletal muscle fi bers. In humans, during brief high-intensity exercise and the latter stages of prolonged strenuous exercise, large increases in breakdown products of ATP imply that rates of ATP utilization can exceed rates of ATP resynthesis (Sahlin et al., 1998).

PCr. Another high-energy phosphate, PCr, has a key role in helping to resupply ATP during muscle activity (PCr + ADP <=> Cr + ATP). Muscle PCr

levels can be almost totally depleted after maximal exercise (Bogdanis et al., 1995; Casey et al., 1996), and this depletion of PCr contributes to the rapid decline in power output observed during such exercise (Sahlin et al., 1998). The recovery of power-generating ability following maximal exercise is closely linked to the resynthesis of PCr (Bogdanis et al., 1995). Increased muscle PCr availability is one potential explanation for the enhanced performance during high-intensity exercise that is sometimes observed following dietary creatine supplementation (Casey & Greenhaff, 2000). PCr levels may also be reduced in a large number of muscle fi bers at the point of fatigue during prolonged, submaximal exercise, coinciding with muscle glycogen depletion, perhaps refl ecting an inability to maintain a suffi cient rate of ATP resynthesis (Sahlin et al., 1998). However, other studies have not observed such changes in high-energy phosphates with prolonged exercise (Baldwin et al., 2003).

Muscle glycogen. The association between fatigue and reductions in stores of muscle glycogen during prolonged, strenuous exercise has been observed consistently for nearly 40 years (Hermansen et al., 1967). Early studies from Scandinavia informed the practice of "e;glycogen loading,"e; which can improve endurance exercise performance in events lasting longer than ~90 min (Hawley et al., 1997). Muscle glycogen availability may also be important for the maintenance of high-intensity, intermittent exercise (Balsom et al., 1999). The link between muscle glycogen depletion and muscle fatigue has been proposed to be an inability to maintain a suffi cient rate of ATP resynthesis, secondary to reduced availability of pyruvate and key metabolic intermediates (Sahlin et al. 1990). In contrast, another study observed little disruption to the muscle levels of ATP, PCr, or metabolic intermediates following exercise to fatigue with differing pre-exercise muscle glycogen availability (Baldwin et al., 2003). The possibility that there is depletion of glycogen at key sites within muscle, unable to be determined in a muscle biopsy sample, cannot be excluded. Alternatively, it is possible that glycogen depletion causes fatigue by mechanisms other than impaired muscle energy metabolism. For example, it has been observed that muscle glycogen depletion can impair excitation contraction coupling (Chin & Allen, 1997; Stephenson et al., 1999). Regardless of the underlying mechanism(s), there is a strong association between muscle glycogen depletion and fatigue during prolonged, strenuous exercise.

Blood glucose. In the absence of glucose supplementation (e.g., by carbohydrate ingestion), blood glucose levels decline progressively during prolonged exercise, as liver glycogen levels become depleted. Lowered blood glucose availability is associated with reduced rates of carbohydrate oxidation and fatigue, and increasing glucose levels by carbohydrate ingestion increases carbohydrate oxidation and enhances endurance performance (Coyle et al., 1983, 1986). This may be partly due to enhanced uptake of glucose into muscle (McConell et al., 1994) and improved muscle energy balance (Spencer et al., 1991), but apparently not to attenuation of muscle glycogen utilization (Coyle et al., 1986). Because glucose is the key substrate for the brain, low blood glucose (hypoglycemia) may also reduce uptake of glucose into the brain and thereby contribute to central fatigue (Nybo & Secher, 2004). Thus, the ergogenic benefi t of carbohydrate ingestion during prolonged strenuous exercise may be caused by improved cerebral energy balance and the maintenance of central neural drive (Nybo & Secher, 2004). Recent studies have also observed improved physical and mental function with carbohydrate ingestion during intermittent exercise of the type used in team sports (Welsh et al., 2002; Winnick et al., 2005).

Accumulation of Metabolic By-Products

Activation of the metabolic pathways that produce ATP also results in increased muscle and plasma levels of numerous metabolic by-products that potentially contribute to fatigue during exercise. These include magnesium (Mg^{2+}), ADP, inorganic phosphate (Pi), lactate and hydrogen ion (H^+), ammonia (NH_3), reactive oxygen species, and heat.

Mg^{2+}, ADP, Pi. During rapid breakdown of ATP and PCr, there are increased levels of these Mg^{2+}, ADP, and Pi within skeletal muscle. Increased Mg^{2+} can inhibit Ca^{2+} release from the sarcoplasmic reticulum and impair force production, especially in combination with lowered levels of ATP in muscle (Dutka & Lamb, 2004). Elevated concentrations of ADP in muscle can reduce force and slow relaxation in muscle by adversely affecting the contractile myofi laments and Ca^{2+} uptake into the sarcoplasmic reticulum (MacDonald & Stephenson, 2004). An increase in Pi also reduces contractile force and Ca^{2+} release from the sarcoplasmic reticulum. The latter effect appears to be due to precipitation of calcium phosphate within the sarcoplasmic reticulum (Allen & Westerblad, 2001). Increases in both ADP and Pi also reduce the energy release during ATP breakdown (Sahlin et al., 1998).

Lactate, H^+. Rapid breakdown of glycogen and glucose in muscle during intense exercise causes a large increase in lactic acid production. Generally, the lactate ion does not appear to have any major negative effects on the ability of skeletal muscle to generate force, although confl icting data exist in the literature. Of greater consequence is an increase in the intramuscular concentration of H^+ (decreased pH and acidosis) that is associated with a high rate of ATP breakdown, non-oxidative ATP production, and the movement of strong ions (e.g., K^+) across the muscle cell membrane. It has been widely believed that increased H^+ can interfere with excitation-contraction coupling and force production in the myofi laments. However, in many of the preparations of isolated muscle studied under physiological temperatures, acidosis does not appear to exert major negative effects. Consistent with these fi ndings are observations that maximal isometric force (Sahlin & Ren, 1989) and dynamic power (Bogdanis et al., 1995) recover relatively quickly following intense exercise, despite a persistently low muscle pH. In contrast, the ability to maintain isometric force and power output in humans is compromised by acidosis, with one potential explanation being reduced ATP turnover (Sahlin & Ren, 1989). Of note, in human skeletal muscle, acidosis can inhibit glycogen breakdown (Spriet et al., 1989) and oxidative ATP production (Jubrias et al., 2003). Moreover, ingestion of sodium bicarbonate, an alkalinizing agent, enhances time to fatigue during high-intensity exercise following repeated sprints (Costill et al., 1984), although it is diffi cult to separate the various mechanisms contributing to fatigue under these conditions. Of note, a major adaptation to sprint training (Sharp et al., 1986) and high-intensity, interval training (Weston et al., 1997) is an increase in skeletal muscle buffer capacity.

Ammonia (NH_3). Ammonia can be produced by skeletal muscle as a byproduct of the breakdown of either ATP or amino acids. During exercise, there is increased release of NH_3 from contracting skeletal muscle into the blood and a corresponding rise in plasma NH_3 levels. Because NH_3 can cross the bloodbrain barrier, a rise in plasma NH_3 increases cerebral NH_3 uptake, and this has the potential to infl uence brain neurotransmitters and cause central fatigue (Nybo & Secher, 2004). More work is required to fully examine the role of NH_3 in the etiology of fatigue. However, carbohydrate ingestion attenuates plasma NH_3 accumulation (Snow et al., 2000) and cerebral NH_3 uptake (Nybo & Secher, 2004) during prolonged exercise, and

this is a potential mechanism underlying the ergogenic effect of carbohydrate ingestion.

Another aspect of central fatigue during prolonged exercise involves the potential interactions among the metabolism of branched-chain amino acids (BCAA; leucine, isoleucine and valine), cerebral tryptophan uptake, and brain serotonin levels. Tryptophan is a serotonin precursor, and cerebral tryptophan uptake is related to both the plasma concentration of free tryptophan and the ratio of the plasma concentration of free tryptophan to that of BCAA. During exercise, a fall in plasma BCAA levels and an increase in plasma tryptophan may thus lead to increased serotonin levels in the brain and to central fatigue (Nybo & Secher, 2004). Ingestion of BCAA has been proposed as a strategy to maintain plasma BCAA levels and reduce brain tryptophan uptake, but this does not appear to be effective (Van Hall et al., 1995). A better strategy is to ingest carbohydrate, which blunts the exercise-induced rise in plasma free fatty acids. (Because free fatty acids and tryptophan compete for binding sites on albumin in the plasma, the lower free fatty acid level during exercise with carbohydrate ingestion attenuates the rise in the free tryptophan-BCAA ratio (Davis et al., 1992).)

Reactive oxygen species. During exercise, reactive oxygen species such as hydrogen peroxide and superoxide anions can be produced from oxidative metabolism and other cellular reactions (Reid, 2001). At low levels, these metabolites may play an important role in the regulation of skeletal muscle function, but their accumulation at higher levels is associated with fatigue (Barclay & Hansel, 1991; Moopanar & Allen, 2005). There are several enzymatic antioxidants (superoxide dismutase, catalase, glutathione peroxidase) within skeletal muscle that degrade reactive oxygen species, and there are nonenzymatic antioxidants such as reduced glutathione, ß-carotene and vitamins E and C that can counteract reactive oxygen species (Reid, 2001). Administration of the compound N-acetylcysteine can increase nonenzymatic antioxidants in skeletal muscle. This effect is associated with reduced fatigue during muscle stimulation (Reid et al., 1994) and with enhanced endurance cycling performance in trained subjects (Medved et al., 2004). Studies with vitamin E and C supplementation are equivocal, but endogenous enzymatic antioxidant levels are increased by training.

Heat. Only ~20% of the oxygen consumption during exercise is converted to mechanical work, whereas ~80% ends up as heat, the major metabolic byproduct of strenuous exercise. While much of this heat is dissipated, at high intensities of exercise and when the environmental temperature and/or humidity are elevated, there can be a signifi cant increase in body core temperature (hyperthermia) that can cause fatigue and, in extreme cases, death. Hyperthermia can affect both central and peripheral processes involved in the production of muscle force and power (Nybo & Secher, 2004; Todd et al., 2005) and impair the performance of both sprint (Drust et al., 2005) and endurance (Gonzalez-Alonso et al., 1999) exercise. Strategies to minimize the negative impact of elevated core and muscle temperature on exercise performance include heat acclimatization, pre-cooling (Gonzalez-Alonso et al., 1999) and fl uid ingestion (Hamilton et al., 1991).

SUMMARY

Increased non-oxidative and oxidative ATP production via metabolic pathways in skeletal muscle is essential for the maintenance of force and power production during exercise. However, substrate depletion and accumulation of metabolic byproducts are potential causes of fatigue. Reduced PCr availability can limit power production during sprint exercise, whereas carbohydrate depletion is a major limitation to endurance performance. During sprint exercise increased Pi and H+ may contribute to fatigue, and during prolonged strenuous exercise, the accumulation of NH3, reactive oxygen species, and heat can limit performance. Appropriate training programs and nutritional interventions are potential strategies to enhance fatigue resistance and exercise performance.

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SUPPLEMENT
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MANAGING FATIGUE IN SPORTS

Fatigue is a multifactorial process. Depletion of energy sources, including adenosine triphosphate (ATP), phosphocreatine (PCr), plus carbohydrates (CHO) like muscle glycogen and blood glucose can contribute to fatigue. Fatigue can also be caused by accumulation of metabolic byproducts, including inorganic phosphate (Pi), hydrogen ions (H+), especially from lactic acid, ammonia (NH3), hydrogen peroxide and other reactive oxygen species (ROS), and heat. Table S1 summarizes potential metabolic factors in fatigue during selected sporting events.

EVENT	DEPLETION OF ENERGY SOURCES			ACCUMULATION OF METABOLIC BYPRODUCTS				
	ATP	PCr	CHO	P_i	H^+	NH_3	ROS	HEAT
100-m run	**	**	*	**	**	*	*	*
400-m run	**	***	*	***	***	**	*	*
1500-m run	*	**	*	**	***	**	*	**
1500-m swim	*	**	*	**	**	*	*	**
Marathon, Tour de France stage races	*	*	***	*	*	**	***	***
"Stop & Go" sports (soccer, tennis, basketball)	*	**	***	*	**	**	**	***

* Unlikely ** Possibly *** Very Likely

Strategies to Enhance Fatigue Resistance

Training. Perhaps the best strategy to enhance fatigue resistance is to undertake sport-specifi c training that causes adaptations that improve performance. These adaptations to various types of training include, but are not limited to, increased muscle mass, enhanced muscle buffer capacity, greater stores of energy sources in the muscles, increased synthesis of proteins that transport energy compounds across cell membranes, enhanced capacity of mitochondria in muscles to produce energy oxidatively, greater capacity to utilize carbohydrate at high intensities of exercise, and greater capacity for fat oxidation with a concomitant reduction in carbohydrate utilization at the same power output. Nutrition. Nutritional strategies are also effective in enhancing exercise performance. Consuming high-carbohydrate meals to load the muscles with glycogen improves performance in endurance events lasting longer than ~90 min. Ingestion of carbohydrate during exercise also enhances performance by acting both in the brain and in the muscles to maintain physical and mental function. Other nutritional practices that can potentially modify metabolic factors associated with fatigue include dietary creatine supplementation, bicarbonate ingestion, and antioxidant supplementation. However, the research literature is less defi nitive on these interventions, at least relative to carbohydrate supplementation.

Strategies to minimize the development of hyperthermia during strenuous exercise in the heat, thereby potentially enhancing performance, include acclimatization, pre-exercise cooling, and adequate fl uid ingestion during exercise.

SUGGESTED ADDITIONAL RESOURCES

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