Performance and endurance in sport: can it all be explained by metabolism and its manipulation?

Asker E. Jeukendrup, PhD, FACSM

Gastorad Sports Science Institute - Barrington, IL - USA and School of Sport and Exercise Sciences - University of Birmingham - Edgbaston - Birmingham - UK

Although sports performance is multifactorial, it is clear that muscle performance plays a major role in most sports. Fatigue is associated with metabolic processes in the muscle and by manipulating these processes, exercise can be maintained for longer or power output and speed can be enhanced. The key metabolic factors in sustaining and modulating performance and endurance in sport are: ATP, phosphocreatine, lactic acid, glycogen, and carbohydrate. So in answer to the question “Can it all be explained by metabolism and its manipulation?” the answer should be that metabolism plays a major role in most performances and can explain a large part of performance in many sports. However, fatigue is a multifactorial process and it is the combined effect of all these factors that ultimately determine performance.

Athletic performance is determined by a multitude of components that may or may not be possible to manipulate or train. Depending on the sport, discipline, or even position within a sport, performance will be determined by many variables that will vary in importance dependent on the specific requirements of the activity. For example, the physiological component is believed to be relatively large in marathon running, whereas in golf the skill component is most important. Performance will be determined not only by physical characteristics, but also by biomechanics, hand-eye coordination, agility, reaction time, decision making, and other cognitive functions. Motivation plays an extremely important role as well, and all of these factors are interrelated and do not operate in isolation. Within this context, it is important to realize that muscle function is only one of many factors that influences performance.

Muscle performance is dependent on the force development and/or the sustained repeated contraction of myofibers. When calcium and adenosine triphosphate (ATP) are present in sufficient quantities, the filaments form actomyosin and shorten by sliding over each other (Figure 1). Sliding begins when the myosin heads form cross-bridges attached to active sites on the actin subunits of the thin filaments. The attachment of the myosin cross-bridges requires the presence of calcium ions as well as the binding of ATP to the myosin head at the ATPase activity site. Hydrolysis of the ATP to adenosine diphosphate (ADP) and inorganic phosphate (Pi) by the ATPase provides the energy required to return the myosin into its activated state, giving it the potential energy needed for the next cross-bridge cycle. ATP is the only source of energy that can be used directly not only for muscle contraction, but also for other energy-requiring processes in the cell. All other processes, such as the breakdown of phosphocreatine (PCr), the breakdown of glycogen or glucose to pyruvate or lactate, the oxidation of carbohydrate and fats, serve to replenish the small, but highly dynamic, ATP pool. On a daily basis, a person can turn over his or her own body weight in ATP or more, depending on the level of physical activity. It is therefore tempting to believe that when the substrates that result in ATP synthesis run out,
performance would be affected. If substrates run out, ATP synthesis would be impaired and therefore muscle contraction would be hampered and the intensity of the exercise would have to be reduced. It is also tempting to speculate that by manipulating these stores, fatigue could be delayed. This review will discuss the evidence that depletion of substrates causes or contributes to fatigue and whether this can be reversed by strategies to manipulate metabolism.

**SUBSTRATE METABOLISM DURING VERY-HIGH-INTENSITY AND INTERMITTENT EXERCISE**

As muscle contracts, ATP is degraded to ADP and Pi to provide the energy. During intense maximal exercise, the ATP stores can only provide energy for about 1 second to 2 seconds. When the whole-muscle ATP concentration falls by about 30%, the muscle fatigues.\(^1\)\(^2\) An important function of PCr in muscle is to provide the high-energy phosphate group for ATP regeneration during the first seconds of high-intensity exercise, thus allowing time for glycogen breakdown and glycolysis (the other main process generating cytosolic ATP during high-intensity exercise) to speed up to the required rate. Transfer of the phosphate group from PCr to ADP is catalyzed by the enzyme creatine kinase, resulting in regeneration of ATP and release of free creatine. PCr is present in resting muscle in a con-

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**Figure 1. Overview of energy sources of muscle contractions and opportunities for manipulation.**

ATP (adenosine triphosphate) is needed for muscle contraction and can be replenished from different sources: (i) phosphocreatine (PCr); (ii) anaerobic glycolysis; (iii) oxidation of carbohydrates; and (iv) oxidation of fat. In red are the potential opportunities for manipulation. The numbers below describe the way these processes can be influenced by nutrition. Running muscle man © Shutterstock Images.

1. PCr concentration can be increased by creatine loading and has been shown to increase performance.
2. At high rates of glycolysis, lactic acid is formed and buffering strategies can be used to minimize the drop in pH that occurs in muscle and blood. Both extracellular buffers (bicarbonate, citrate) and intracellular buffers (carnosine through β-alanine supplementation), have been shown to be effective.
3. Glycogen can be used as a substrate to generate pyruvate, which can generate energy aerobically through the tricarboxylic acid (TCA) cycle. It is clear that when muscle glycogen is depleted, endurance capacity is reduced. By optimizing the muscle glycogen stores, endurance capacity can be extended.
4. Glucose derived from the liver is also used as a substrate for the TCA cycle. When liver glycogen becomes depleted, carbohydrate oxidation cannot be maintained and this can result in reduced endurance capacity. In addition, when hypoglycemia results, this can also affect the brain and reduce performance through that pathway. Optimizing liver glycogen stores by carbohydrate feeding can increase endurance capacity by maintaining blood glucose concentrations and high rates of carbohydrate oxidation.
5. In most conditions, both carbohydrates and fats are used as a fuel. Exercise training can increase the capacity to oxidize fat and this may reduce the reliance on carbohydrate. As a result, muscle glycogen depletion will be delayed and performance will be better.
centration that is 3 to 4 times that of ATP. During the 100-meter sprint, 22 g of ATP is estimated to be broken down per second, or about 50% of the ATP content per kg of active muscle. Because fatigue occurs in human muscle when the whole-muscle ATP concentration falls by about 30%, the need for rephosphorylation of the ADP formed during contraction is obvious. PCr plays an important role in replenishing ATP. The total creatine content in the muscle is between 120 mmol/kg dry weight and 160 mmol/kg dry weight, with 60% to 70% in the form of PCr. With the highest concentrations found in Type II muscle fibers.

Harris et al. were the first to report that ingesting creatine monohydrate could increase total muscle creatine stores (creatinine and PCr). This landmark study showed that ingesting 5 g of creatine 4 times to 6 times a day for several days increased the total creatine concentration by an average of 25 mmol/kg dry weight, and 30% of the increase in total creatine content was in the form of PCr. The authors suggested that these increases could improve exercise performance, but did not test this suggestion in their study. The first performance study was conducted by Greenhaff et al. Subjects ingested 20 g/day of creatine for 5 days, and creatine indeed improved performance by about 6% during repeated bouts of maximal knee extension exercise. After that study, more studies were performed investigating different modes of exercise, and in a review by Hespel and Derave it was concluded that creatine could improve sprint performance. However, in a recent consensus meeting by the IOC, creatine was identified as one of the nutrition supplements that can have a positive effect on performance.

In a study by Casey et al. the changes in performance were related to the changes in total muscle creatine content. A strong correlation was observed in that those individuals who displayed the largest increases in total muscle creatine concentration also exhibited the largest performance benefit. In the literature, these benefits are most obvious in repeated sprints, but also in strength, force production, or torque. In a recent consensus meeting by the IOC, creatine was identified as one of the nutrition supplements that can have a positive effect on performance.

So it appears that creatine metabolism plays an important role in high intensity exercise performance. If creatine stores in the muscle can be increased by creatine supplementation, this may have an impact on exercise performance, in particular in delaying fatigue with repeated sprints. The most obvious explanation for the ergogenic effects with creatine supplementation are an increased PCr availability, particularly in Type II muscle fibers, which may improve contractile function by maintaining ATP turnover as well as increasing the rate of PCr resynthesis.

**GLYCOLYSIS**

During all-out exercise lasting approximately 1 to 7 minutes, the energy for ATP regeneration is derived from glycolysis. The breakdown of glucose (or glycogen) to pyruvate results in ATP being available to the muscle from reactions involving substrate level phosphorylation. However, the pyruvate must be removed for the reactions to proceed. In some situations, the rate of formation of pyruvate is higher than the tricarboxylic acid cycle rate, which would result in pyruvate accumulation. Therefore, pyruvate is rapidly removed by conversion to lactic acid. The lactic acid dissociates into lactate and hydrogen ions, resulting in a reduced muscle pH. The pH in the circulation can drop from the normal 7.4 to as low as 7.1 within a minute of intense exercise. It is this reduction in pH in the muscle that is believed to impair muscle contraction and be responsible for the development of fatigue.

One way to overcome the acidosis, is to start the exercise with a higher than normal blood pH, i.e., induced alkalosis. This can be achieved by pre-exercise ingestion of sodium bicarbonate in a dose of 0.18 to 0.3 g/kg body weight, or another alkalizing agent, such as sodium citrate. Buffering the protons in blood will allow more protons to leave the muscle. This strategy has proven to be successful in enhancing performance in single or repeated high-intensity exercise bouts. More recently it was suggested that by manipulating the carnosine concentration in muscle (intracellular buffer), performance might be improved as well.

β-Alanine ingestion is an effective way to increase the amount of carnosine in skeletal muscle and thereby indirectly increases the buffering capacity of a muscle. β-Alanine is the rate-limiting precursor in the synthesis of carnosine, a dipeptide composed of histidine and β-alanine. Even though the contribution of carnosine to the total buffering capacity of the muscle in particular, and the body in general, is limited (approx 10%), there is a considerable interest in muscle carnosine because its concentration can be nutritionally altered. Harris and coworkers were the first to show that 4 to 10 weeks of oral β-alanine supplementation can markedly increase the muscle carnosine content by 50% to 80%. A more recent study by Baguet et al.
showed that the acidosis during a 6-min high-intensity exercise bout is less pronounced as a result of a 4-week β-alanine supplementation period. This indicates that β-alanine-induced muscle carnosine loading has a significant impact on the pH-buffering capacity during exercise.

Although a number of studies have shown an ergogenic effect on single exercise bouts (summarized in Baguet et al, 201013), there is only a limited availability of studies investigating the effect of β-alanine supplementation on repeated sprint ability. Derave et al14 showed that the fatigue during 5 bouts of 30 maximal knee extension contractions, separated by a 1-min passive recovery period, was attenuated in the 4th and 5th bout following muscle carnosine loading, but this was not confirmed by a study by Sweeney et al15 following 5 weeks of β-alanine supplementation.

In summary, intense contractions during high-intensity exercise results in large production of protons. A significant portion of the contraction-induced protons are rapidly transported out of the active muscles and buffered by the circulating buffers, such as bicarbonate. Therefore, one could term the pH buffers inside the muscle cells (such as carnosine) as the first line of defense and the blood buffers as the second line of defense. From the above, it is evident that nutritional support of both systems can lead to performance-enhancing effects during intense exercise.

**SUBSTRATE METABOLISM DURING PROLONGED EXERCISE**

During more prolonged exercise where aerobic metabolism plays a crucial role, carbohydrate availability might be one of the most important factors for performance. Krogh and Lindhardt16 were probably the first investigators to recognize the importance of carbohydrate as a fuel during exercise. In their study, subjects consumed a high-fat diet for 3 days followed by 3 days on a high-carbohydrate diet (potatoes, flour, bread, cake, marmalade, and sugar). The subjects performed a 2-hour exercise test and reported various symptoms of fatigue when they consumed the high-fat diet. However, when they consumed the high-carbohydrate diet, the exercise was reported as “easy.” The investigators also demonstrated that after several days of a low-carbohydrate, high-fat diet, the average respiratory exchange ratio (RER) during 2 hours of cycling was reduced to 0.80 as compared with 0.85 to 0.90 when a mixed diet was consumed. Conversely, when subjects ate a high-carbohydrate, low-fat diet, RER was increased to 0.95. This clearly shows that diet and this substrate availability can alter substrate use.

Christensen17 showed that with increasing exercise intensity the importance of carbohydrate as a substrate increased. In the late 1960s, this was confirmed by a group of Scandinavian scientists18 who measured the glycogen concentration in skeletal muscle. Muscle glycogen concentration was manipulated by diet and it was shown that a higher muscle glycogen concentration was correlated with increased endurance capacity. These observations have led to the recommendations to carbohydrate-load (ie, eat high-carbohydrate diets) before competition.19

The effect of high-carbohydrate diets and elevated muscle glycogen levels on exercise performance has been summarized in a review by Hawley et al,20 and despite this review being published in 1997, it is still up to date, as evidenced by a recent publication from a consensus meeting by the IOC.21 It was suggested that supercompensated muscle glycogen levels can improve performance (ie, time to complete a predetermined distance) compared with low to normal glycogen (non-supercompensated) by 2% to 3% in events lasting longer than 90 min. There seems to be little or no performance benefit of supercompensated muscle glycogen levels when the exercise duration is <90 min.

Liver glycogen also plays a role, as it appears that liver glycogen depletion can result in hypoglycemia during exercise, and this coincides with reduced endurance capacity. In one elegant early study, subjects exercised to exhaustion at 70%.22 Upon cessation of exercise (after approximately 3 hours), muscle glycogen concentrations were extremely low (47 mmol glucosyl units per kg dry mass). Subjects then rested for 20 min and exercised again. During this second bout of exercise they were given placebo, a carbohydrate drink, or they were infused with glucose. When they received placebo they could only exercise for 10 min. With the glucose ingestion they could exercise longer (26 min), but they could exercise even longer when the glucose was infused directly into the circulation (43 min). Blood glucose concentrations dropped with placebo, were somewhat elevated with glucose ingestion, and were maintained with infusion. This study clearly demonstrated that providing a source of glucose will help to delay fatigue. However, this study also demonstrates that plasma glucose is only part of the explanation of fatigue, as subjects still fatigued even when glucose was infused and euglycemia was maintained. The study also demonstrates that muscle glycogen is not the sole cause of fatigue as muscle glycogen concentrations were very low during the
second bout of exercise, yet with the provision of glucose (ingested or infused), exercise could still be continued. Overall, it appears that when carbohydrate oxidation falls below a certain threshold, it is very difficult or impossible to maintain that exercise intensity. Therefore, it can be concluded that carbohydrate metabolism is important for performance, but the source of the carbohydrate (endogenous or exogenous) is only of secondary importance during moderate intensity exercise.

**STRATEGIES TO REDUCE DEPENDENCE ON CARBOHYDRATE STORES**

In addition to optimizing body glycogen stores, it is possible to reduce the reliance on the relatively small endogenous carbohydrate stores by conditioning the muscle to use fat as a fuel. One of the main effects of exercise training and in particular endurance training is an increased capacity to oxidize fat. This is mainly because of an increased mitochondrial density in combination with increased enzyme concentrations and/or activities. Strategies have recently been investigated that combine exercise training with nutritional strategies to increase adaptations in fat metabolism.

The muscle is an organ that can adapt significantly and rapidly in response to repeated bouts of exercise. These adaptations are determined largely by the mode of exercise and the volume, intensity, and frequency of the training stimulus. However, evidence is accumulating that nutrient availability serves as a potent modulator of many acute responses and chronic adaptations to both endurance and resistance exercise. Changes in macronutrient intake rapidly alter the concentration of blood-borne substrates and hormones, causing marked perturbations in substrate storage and protein synthesis. In turn, muscle energy status exerts profound effects on resting fuel metabolism and patterns of fuel utilization during exercise, as well as acute regulatory processes underlying gene expression and cell signaling. As such, these nutrient-exercise interactions have the potential to activate or inhibit many biochemical pathways with putative roles in training adaptation.

Muscle glycogen stores are related to expression of genes relevant to the adaptation to training. It is generally thought that training adaptations are the result of recurrent changes in gene expression, which occur with every bout of exercise, leading to a change in phenotype such as increases in fatty acid transport and oxidation. For example, a single bout of exercise increases muscle mRNA content of peroxisome proliferator-activated receptor-γ coactivator 1α (PGC-1α), a transcriptional regulator of mitochondrial biogenesis. It has been demonstrated that manipulations of energy/carbohydrate availability as part of an exercise training program can improve adaptations in muscle and enhance fat metabolism. Future studies will have to demonstrate that such improvements also result in improvements in exercise performance.

In summary, low muscle glycogen and low rates of carbohydrate oxidation are associated with reduced exercise capacity. Endurance performance can be improved by manipulating carbohydrate stores in liver and muscle or by ingesting carbohydrate during prolonged exercise. In addition, exercise training (with or without nutritional manipulation) can enhance fat metabolism, reduce the reliance on carbohydrate as a fuel, and enhance exercise performance long term.

**CONCLUSION**

There is a large body of evidence to show that metabolism can explain a large part of performance in many sports. In high-intensity and intermittent sports, the roles of ATP and PCr are crucial and it has been demonstrated that an increase in muscle creatine stores can have a positive effect on performance, especially when high-intensity bouts are repeated, suggesting that the main role of creatine is to allow a faster resynthesis of PCr. During events that last 1 to 7 min, both aerobic and anaerobic metabolism play an important role, but there is little evidence that increasing substrate stores could affect performance. The stores do not run out in this time and other factors have an overriding effect on performance (lactic acid formation from the rapid breakdown of glycogen). During longer exercise bouts, both muscle and liver glycogen may become depleted and strategies to optimize these stores prior to exercise as well as ingesting carbohydrate during exercise have been shown to be highly successful in postponing fatigue and improving performance.

So back to the question: “Can it all be explained by metabolism and its manipulation?” The answer should be that metabolism plays a major role in most performances and can explain a large part of performance. However, fatigue is a multifactorial process and it is the combined effect of all these factors that ultimately determine performance.
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