SUMMARY

1. Contracting skeletal muscle is able to use a number of intra- and extramuscular substrates to generate ATP during exercise. These include creatine phosphate (CP), muscle glycogen, blood-borne glucose, lactate and free fatty acids (FFA), derived from either adipose tissue or intramuscular triglyceride stores.

2. During high-intensity short-duration exercise, CP degradation and the breakdown of muscle glycogen to lactate are the major energy yielding pathways, although oxidative metabolism can make a significant contribution. The ‘anaerobic’ substrates are also important fuels during the transition from rest to steady state exercise.

3. The oxidative metabolism of carbohydrate and lipid supplies most, if not all, of the ATP during prolonged submaximal exercise. Muscle glycogen, blood glucose and FFA are the key fuels. The relative importance of the various substrates for exercise metabolism is primarily determined by exercise intensity and duration, although training status, dietary manipulation and environmental factors can modify the metabolic response to exercise.

Key words: ATP, blood glucose, creatine phosphate, free fatty acids, muscle glycogen.

INTRODUCTION

The immediate energy source for actin–myosin cross-bridge cycling during exercise is ATP. In addition, ATP is required for a number of energy dependent cellular processes that have a key role in excitation–contraction coupling, such as sodium–potassium exchange across the sarcolemma and t-tubule and calcium release and re-uptake by the sarcoplasmic reticulum. Because the intramuscular concentration of ATP is small (5–6 mmol/kg wet weight), other metabolic pathways must be activated in order to maintain the rate of ATP resynthesis necessary for ongoing contractile activity. These include the degradation of creatine phosphate (CP), breakdown of muscle glycogen to lactate in anaerobic glycolysis and the oxidative metabolism of carbohydrates and lipids (Fig. 1).

‘ANAEROBIC’ METABOLISM

During high-intensity exercise of short duration, the ‘high-energy phosphates’ (ATP, CP) and the degradation of muscle glycogen to lactate are the dominant energy yielding pathways. Muscle ATP levels are usually only reduced by 30–50% following maximal exercise, whereas CP levels can be completely depleted following such activity. Muscle glycogen levels are reduced by 50–60%, depending upon exercise intensity and duration, but are not thought to be a limiting factor during this type of exercise. Accompanying the decline in these metabolites are marked increases in the intramuscular concentrations of inorganic phosphate (Pi), lactate and H⁺. Adenosine triphosphate can also be produced in the myokinase reaction 2 ADP → ATP + AMP and the AMP used to produce inosine monophosphate (IMP) and ammonia in a reaction catalysed by AMP deaminase. Although the ‘anaerobic’ substrates provide most of the energy, there can also be a significant contribution from oxidative metabolism during intense exercise of 30–60 s duration.

There is also reliance on ‘anaerobic’ substrates during the transition from rest to steady state exercise and this has been termed the oxygen deficit. The magnitude of the oxygen deficit is directly related to exercise intensity and is reflected in the extent of muscle CP degradation and the accumulation of lactate. Traditionally, the oxygen deficit was thought to be due to a delay in skeletal muscle blood flow and oxygen delivery to contracting skeletal muscle. More recently, this view has been challenged and a lag in mitochondrial metabolism may also contribute. In support of such a contention, administration of dichloroacetate, an activator of the pyruvate dehydrogenase complex, resulted in increased acetyl group availability and attenuation of CP breakdown and lactate accumulation in human skeletal muscle during the early stages of exercise. Thus, substrate supply to the mitochondria appears to be a modulator of mitochondrial respiration and the development of an oxygen deficit at the onset of exercise.

OXIDATIVE METABOLISM

During prolonged submaximal exercise, almost all ATP is produced...
from the oxidative metabolism of carbohydrates and lipids. The major substrates for oxidation are muscle glycogen, blood glucose and free fatty acids (FFA), derived from either adipose tissue or intramuscular triglyceride reserves. In addition, there is evidence that lactate, derived from muscle glycogen or blood glucose, is a substrate for oxidative metabolism in contracting skeletal muscle. The relative importance of these various substrates is primarily determined by the exercise intensity and duration\(^\text{11}\). The oxidation of amino acids, derived from muscle protein, is a relatively minor contributor to overall energy metabolism during exercise, particularly when carbohydrate availability is adequate.\(^\text{13}\)

**Carbohydrate metabolism**

Muscle glycogen is the major carbohydrate substrate during exercise and its rate of degradation is primarily dependent upon exercise intensity.\(^\text{13}\) With increasing duration of exercise at a given intensity, the rate of muscle glycogenolysis declines as a function of reduced glycogen levels and glycogen phosphorylase activity and increased blood-borne substrate (e.g. FFA) availability. The increase in glycogenolysis during exercise occurs due to activation of glycogen phosphorylase, which exists in two forms: (i) a less active \(b\) form; and (ii) the more active \(a\) form. Phosphorylase \(b\) to \(a\) transformation occurs in response to increased sarcoplasmic \([\text{Ca}^{2+}]\) with muscle contractions and hormonal stimulation by adrenaline, mediated via the \(\beta\)-adrenoceptor and the intracellular second messenger cAMP.\(^\text{14,15}\) In addition, allosteric modulators, such as AMP and IMP, as well as the substrates Pi and glycogen itself,\(^\text{16}\) enhance glycogen phosphorylase activity and muscle glycogenolysis. An increase in pyruvate dehydrogenase activity during exercise,\(^\text{17}\) most likely as a result of increased intramuscular \([\text{Ca}^{2+}]\) and [pyruvate], facilitates the increase in carbohydrate oxidation. These regulatory factors ensure that the rate of muscle glycogenolysis and its subsequent oxidation are coupled to ATP demand.

The other source of carbohydrate is blood-borne glucose and muscle glucose uptake during exercise increases in relation to both the intensity and duration of exercise (Fig. 2).\(^\text{11,18,19}\) Glucose and insulin delivery to contracting skeletal muscle are increased during exercise as a consequence of the large increase in muscle blood flow, but can only account for approximately 30% of the exercise-induced increase in muscle glucose uptake.\(^\text{20}\) Thus, local factors within the muscle play the major role. These include increased sarcoplasmic transport of glucose\(^\text{21,22}\) and activation of the glycolytic and oxidative enzymes responsible for glucose metabolism.\(^\text{19}\) Sarcolemmal glucose transport occurs by facilitated diffusion, with the GLUT-4 isoform being responsible for contraction and insulin-stimulated glucose transport. The GLUT-4 transporter is one member of a family of facilitative glucose transporters and is expressed primarily in cardiac and skeletal muscle and adipose tissue.\(^\text{21}\) Translocation of GLUT-4 from an intracellular storage site to the plasma membrane is the major mechanism responsible for the increase in sarcolemmal glucose transport during exercise. This has been demonstrated in both rat\(^\text{24,25}\) and human\(^\text{21,22}\) skeletal muscle. The cellular mechanisms that result in increased sarcolemmal glucose transport during muscle contraction remain to be fully elucidated. However, the increase in sarcoplasmic \([\text{Ca}^{2+}]\) during muscle contraction is likely to play a central role. A more detailed discussion of the regulation of skeletal muscle glucose transport during exercise can be found in a recent review.\(^\text{26}\) The observation that exercise also results in translocation of vesicle-associated membrane protein (VAMP-2) to the sarcolemma\(^\text{22}\) suggests that the molecular mechanisms responsible for exercise-induced translocation of GLUT-4 vesicles may be similar to those responsible for synaptic vesicle and membrane protein trafficking.\(^\text{27}\)

Endurance training results in a decreased reliance on muscle glycogen, liver glycogen and blood glucose during exercise at the same absolute power output\(^\text{28,29}\) with a concomitant increase in lipid oxidation. These effects of exercise training are smaller in magnitude, or less apparent, when exercise is conducted at the same relative intensity. Increasing dietary carbohydrate intake is usually associated with an increased reliance on muscle glycogen, mediated primarily by increased pre-exercise muscle glycogen availability, with little effect on muscle glucose uptake and a reduced lipid oxidation.\(^\text{16}\) Finally, an increase in environmental temperature results in increased muscle glycogenolysis,\(^\text{30}\) a greater increase in liver

**Fig. 1** Energy metabolism in skeletal muscle.

**Fig. 2** The contribution of intra- and extramuscular substrates to energy turnover during exercise of increasing intensity. (□), muscle glycogen; (□), muscle triglycerides; (□), plasma free fatty acids; (□) plasma glucose. VO\(_{2}\) max, maximal oxygen uptake. (Reproduced with permission from Romijn et al.\(^\text{11}\))
glucose output and glycaemia and enhanced carbohydrate oxidation. These effects appear to be mediated by increases in plasma adrenaline and core and muscle temperatures.

Lipid metabolism

The oxidation of FFA during exercise involves a number of steps, the first being the hydrolysis of intramuscular and/or adipose tissue triglycerides (lipolysis) and the transport of FFA in either the plasma or sarcoplasm to the skeletal muscle mitochondria for oxidation. During exercise in the fasted state, the rate of lipolysis exceeds the rate of lipid oxidation, both at rest and during moderate-intensity exercise, suggesting that FFA availability may not limit lipid oxidation under these conditions. In contrast, during intense exercise or following inhibition of lipolysis (e.g. following nicotinic acid administration or carbohydrate ingestion), FFA availability may become rate limiting. In order to be oxidized, FFA must enter the mitochondria where they undergo β-oxidation. The mitochondrial uptake of FFA from the sarcoplasm involves the carrier carnitine, which is combined with fatty acyl-coenzyme A in a reaction catalysed by carnitine acyl-transferase. This is another potential site of limitation of lipid oxidation during exercise. Furthermore, although muscle FFA uptake from plasma has long been thought to occur by simple diffusion, recent studies in both the perfused rat hindlimb and exercising humans have suggested that muscle FFA uptake may be partly carrier mediated and subject to saturation. Attention has focused on various sarcolemmal and cytosolic fatty acid-binding proteins and other potential carriers, such as fatty acid translocase and fatty acid transport protein.

Muscle triglycerides are a potential source of FFA during exercise, although the regulation of intramuscular lipolysis is much less understood. There is even debate as to whether muscle triglycerides are used at all during exercise. Tracer studies and the observation of glycerol release from contracting skeletal muscle suggest significant intramuscular lipolysis, particularly at higher exercise intensities, where FFA mobilization from adipose tissue and plasma FFA levels are reduced. In contrast, direct measurement of muscle triglyceride concentrations before and after exercise has yielded conflicting results. A hormone-sensitive lipase has been found in skeletal muscle and is thought to be under both local control by sarcoplasmic Ca²⁺ levels and hormonal regulation by adrenaline. The increase in lipid oxidation following endurance training could be derived from an enhanced use of muscle triglycerides and/or plasma FFA, although this remains the subject of debate. Much more work is required to fully understand the use of muscle triglycerides and its regulation during exercise.

CONCLUSIONS

Contracting skeletal muscle is able to use a number of intra- and extramuscular substrates to generate ATP during exercise. These include CP, muscle glycogen, blood-borne glucose, lactate and FFA, derived from either adipose tissue or intramuscular triglyceride stores. The relative importance of these various substrates for exercise metabolism is primarily determined by exercise intensity and duration, although training status, dietary manipulation and environmental factors can modify the metabolic response to exercise. Recent research has focused on the intramuscular mechanisms that regulate substrate supply to the mitochondria, in particular the uptake of glucose and FFA from the bloodstream, and the potential signals that match the rate of ATP generation to the metabolic demands of contracting skeletal muscle. The increase in sarcoplasmic Ca²⁺ plays a pivotal role.

REFERENCES


