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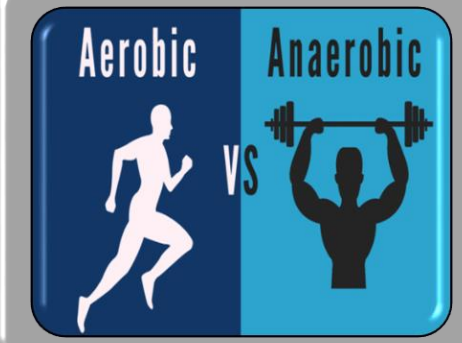
Metabolism Regulation 6

Coping with some extreme situations

Ref: Keith N. Frayn. Metabolic Regulation: A Human Perspective. 3rd Edition. Wiley Blackwell, 2010. Chapter 9.

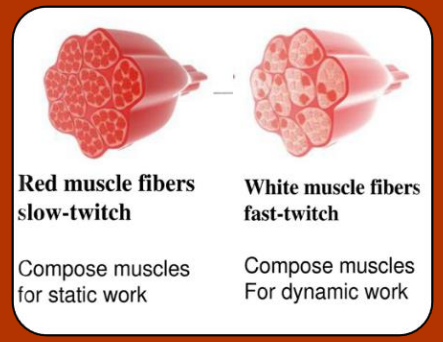
Types of Exercise

- It is convenient to think of two extreme types of exercise, sometimes called anaerobic and aerobic.
- **Anaerobic exercise** is typified by *sprinting* or *weightlifting*; it is of short duration, but may involve great strength. It is dominated by the activity of the fast-twitch (Type II) muscle fibers. The key feature of anaerobic exercise is rapid generation of energy over a short period. Energy is generated too rapidly for the diffusion into the muscle of substrates, including O_2, from the blood and this is achieved by utilization of the muscle's own energy stores, phosphocreatine and glycogen.
- **Aerobic exercise**, on the other hand, involves prolonged exercise but at a lower intensity than can be achieved anaerobically. It is typified by *long-distance running*, *cycling*, *swimming*, or *cross-country skiing*. Here, the duration is such that it could not be maintained solely from the fuels stored within muscle; the fuel stores in the rest of the body (fat in adipose tissue, glycogen in the liver) must be used. Hence, these substrates must be brought to the muscle in the blood, and there are necessary adjustments to the circulatory system. The muscle fibers involved are predominantly the oxidative, Type I fibers. It is called aerobic because, to maximize efficiency, substrates (fatty acids and glucose) are completely oxidized.



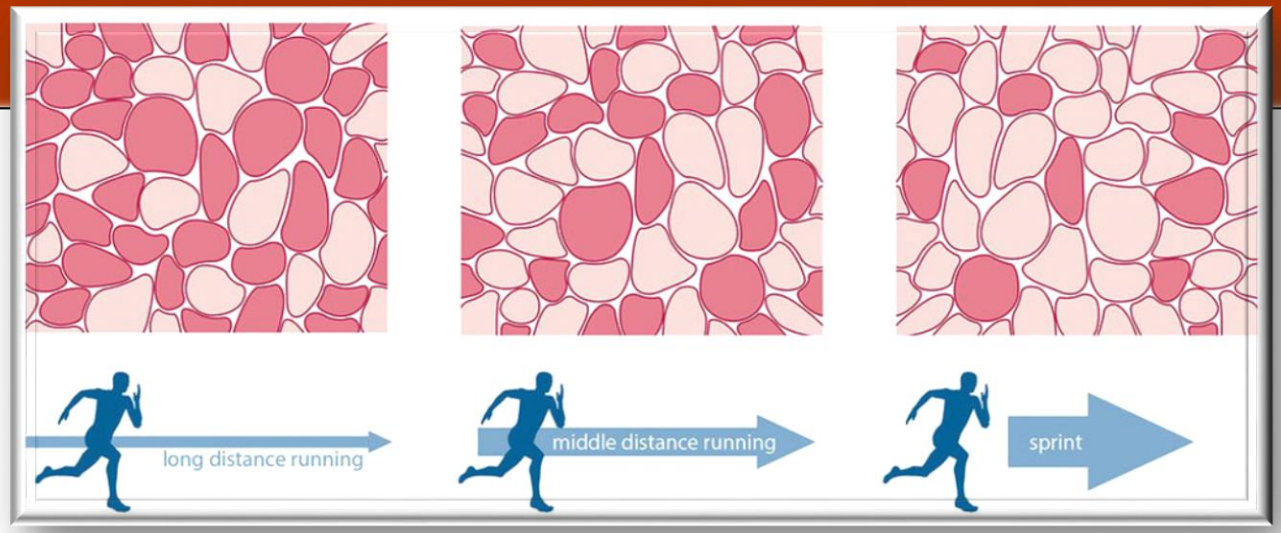
Types of Exercise

- Aerobic (Long duration, Moderate intensity, Presence of oxygen)
- Anaerobic (Short duration, High intensity, Absence of oxygen,)



Muscle fibers

- Red muscle fibers (I) (High mitochondrial content)
- White muscle fibers (II) (Low mitochondrial content)



Metabolic Regulation During Anaerobic Exercise

- Exercise begins in the brain.
- ATP is hydrolyzed as the muscle contracts. It must be replaced rapidly or the muscle would run out of energy; *the amount of ATP present in skeletal muscle is sufficient for about one second of maximal effort.*
- In fact, measurements of the *ATP concentration in contracting skeletal muscle show it to be remarkably constant* (Figure 9.7).
- Mechanisms for resynthesizing ATP must be turned on extremely rapidly. Initially the utilization of ATP is "buffered" by the phosphocreatine system.

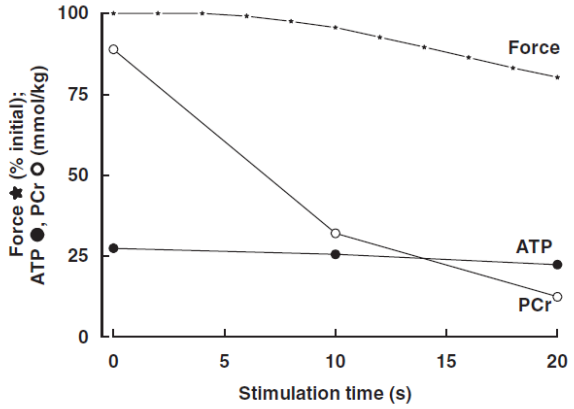


Figure 9.7 Concentrations of ATP and of phosphocreatine (PCr) in Type II fibers in human muscle during contractions brought about by electrical stimulation. After six contractions (each 1.6 s long; i.e., at ~10 s) and after 12 contractions (~20 s) a muscle biopsy was taken and rapidly frozen, and later the Type I and Type II fibers were separated for analysis. With repeated contractions, the force generated decreases slightly, the PCr concentration falls sharply, but the concentration of ATP remains almost constant. The implication is that ATP is being rapidly resynthesized at the expense of PCr. Data from Söderlund et al. (1992), replotted following Maughan et al. (1997) from Biochemistry of Exercise and Training (eds Maughan R., Gleeson M., and Greenhaff P.L.), with permission from Oxford University Press. www.oup.com.

Nervous impulse arrives at end-plate

↓

Acetylcholine is liberated into the synaptic cleft, and binds to receptors in the sole-plate

↓

A wave of depolarisation spreads over the muscle cell membrane (sarcolemma) and down the T-tubules

↓

Ca^{2+} ions are released from stores in the sarcoplasmic reticulum into the cell cytoplasm (sarcoplasm)

↓

Ca^{2+} ions bind to troponin C in the thin filaments, causing a conformational change and exposing myosin binding sites on the actin

↓

Myosin 'heads' in the thick filaments bind to actin; the filaments 'slide' relative to one another and thus the muscle contracts. During this process ATP is hydrolysed to ADP + P_i

- But the amount of phosphocreatine is relatively small – it would sustain intense sprinting for about *four seconds*. The phosphagen store (phosphocreatine + ATP) must then be replenished and this occurs initially by *glycogen breakdown* and *glycolysis*.
- There is a rapid increase in the flux through the glycolytic pathway in muscle at the start of strenuous exercise. It may increase by something like 1000-fold. However, it is clear that the flux cannot increase unless there is substrate to sustain it and in rapid, intense exercise. This substrate is glucose 6-phosphate produced by glycogen breakdown, rather than glucose taken up from the plasma. Therefore, there must be mechanisms for coordinated stimulation of glycogenolysis and muscle contraction.
- There are several aspects to this coordinated control. They depend in part on the special regulatory characteristics of the muscle isoform of glycogen phosphorylase, which are different from those of the liver isoform. Firstly, elevation of sarcoplasmic Ca^{2+} concentration brought about by motor nerve firing also activates glycogen phosphorylase (Figure 9.8). Muscle glycogen phosphorylase (b form) is also strongly activated by AMP, which will be produced during exercise by utilization of ATP. In addition, glycogen phosphorylase cannot act unless the concentration of its co-substrate, inorganic phosphate (Pi), increases. This happens through the splitting of ATP in muscle contraction (Figure 9.8). Since the ATP concentration is kept "topped up" by phosphocreatine, this Pi really comes from phosphocreatine. Thus, glycogen breakdown and muscle contraction are intimately connected within the muscle; there is no need for rapid stimulation by hormones.

During intense exercise, energy is thus derived very rapidly from anaerobic glycolysis. There is no need for increased delivery of other substrates or oxygen in the plasma. Anaerobic glycolysis produces lactic acid which, at physiological pH, will be in the form of lactate ions and hydrogen ions. There is, therefore, an increase in the local hydrogen ion concentration in the muscle. This may be one cause of fatigue. A local fall in pH may have a number of effects that tend to cause lessening of the force of muscle contractions. These include effects on the interaction between myosin and actin, on the binding of Ca^{2+} to troponin, and on the enzyme phosphofructokinase, an important regulatory enzyme in glycolysis that is inhibited at low pH. The ability to perform this type of exercise depends largely upon the bulk of the glycolytic, Type II fibers, and this bulk can be increased through training. Certain interventions may aid performance. Recently, there has been considerable interest in dietary supplementation with creatine in amounts of 5 g/day. This has been shown to improve anaerobic performance, by increasing the amount of phosphocreatine in the muscles. Another intervention that has shown some success in experimental situations is to ingest large amounts of sodium bicarbonate ($NaHCO_3$), which acts as a buffer to minimize hydrogen ion accumulation and thus postpone fatigue.

Metabolic Regulation During Anaerobic Exercise

During contraction, ATP is hydrolyzed to ADP + Pi. It is partially replenished by phosphocreatine. The following associated reactions occur:

Reaction	Effect
$ATP \rightarrow ADP + P_i$ (associated with contraction)	ATP ↓, P_i ↑
$2ADP \rightarrow ATP + AMP$ (adenylate kinase)	AMP ↑
$PCr + ADP \rightarrow Cr + ATP$ (creatine kinase)	PCr ↓↓
$AMP + H_2O \rightarrow IMP + NH_3$ (AMP deaminase)	NH_3 ↑

PCr, phosphocreatine; Cr, creatine; IMP, inosine monophosphate (a degradation product of AMP).

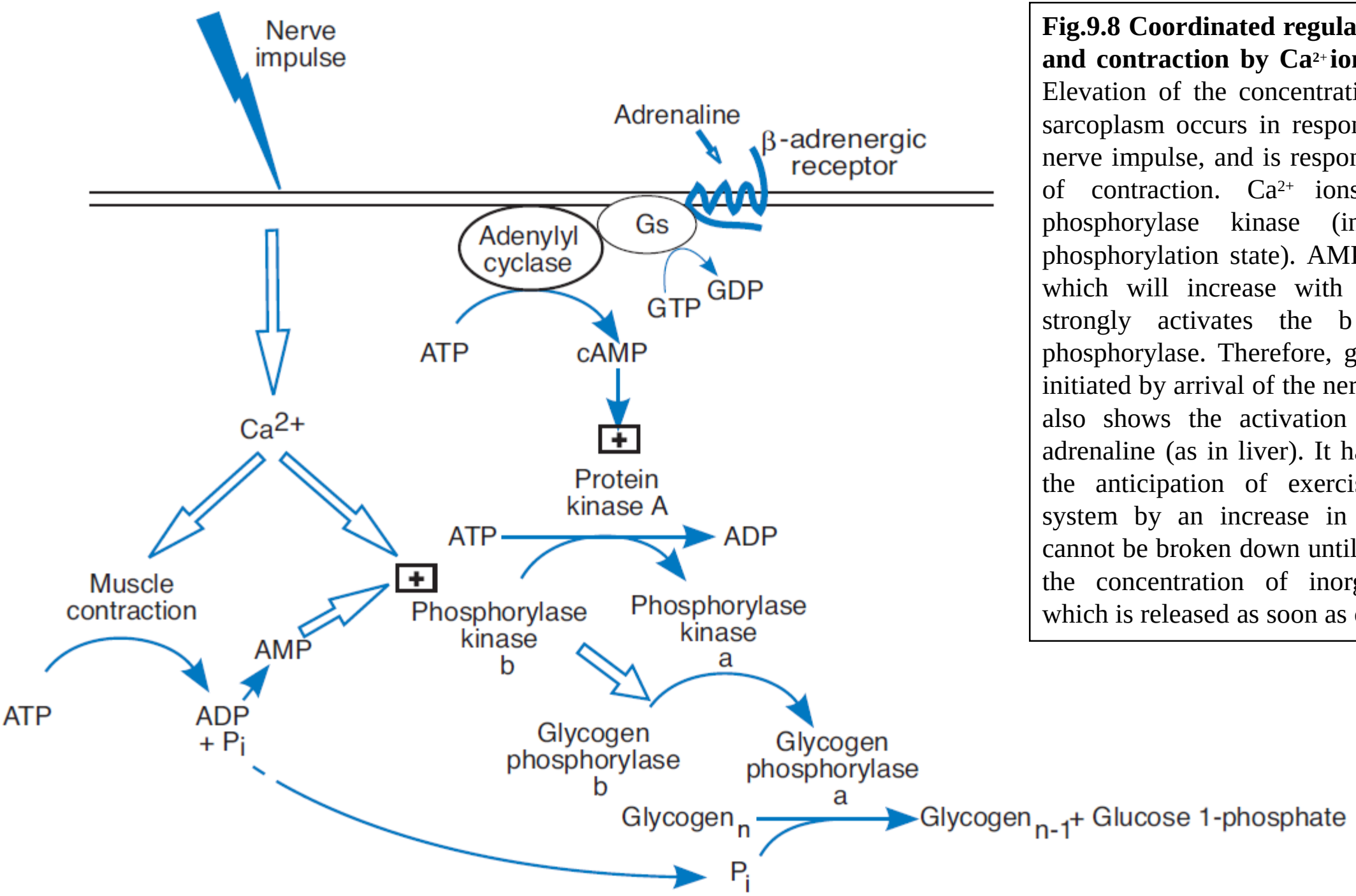
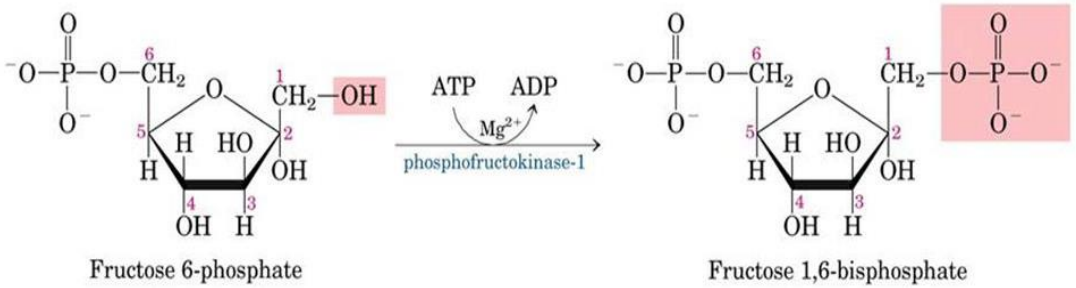
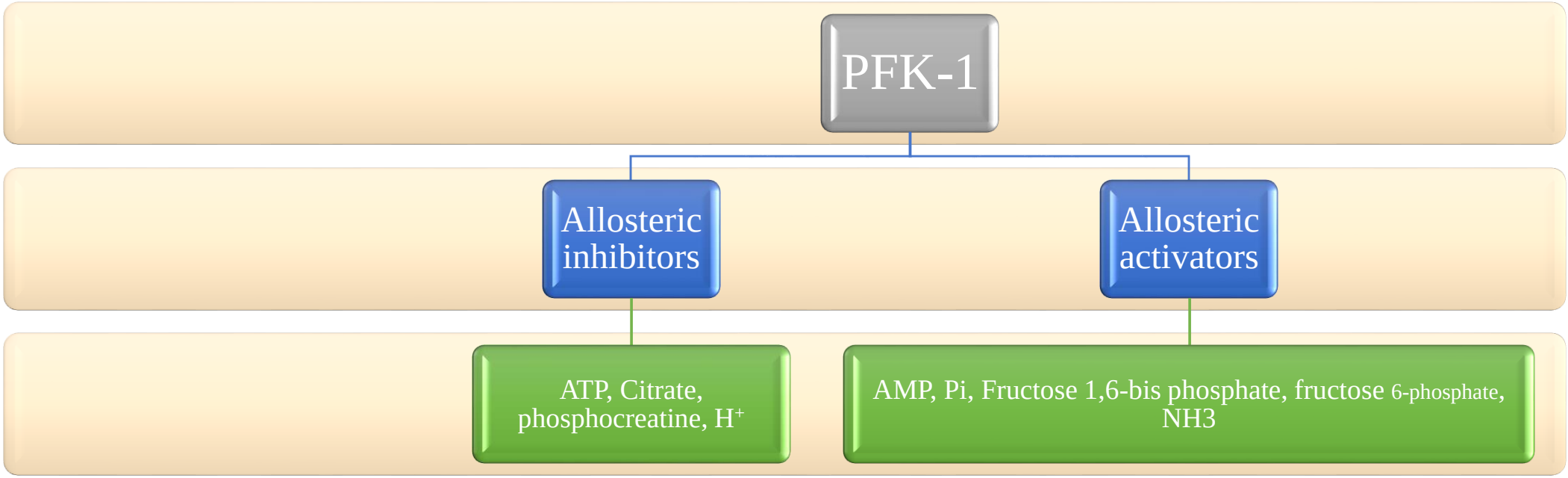


Fig.9.8 Coordinated regulation of glycogenolysis and contraction by Ca^{2+} ions in skeletal muscle. Elevation of the concentration of Ca^{2+} ions in the sarcoplasm occurs in response to the arrival of a nerve impulse, and is responsible for the initiation of contraction. Ca^{2+} ions can also activate phosphorylase kinase (independently of its phosphorylation state). AMP, the concentration of which will increase with ATP utilization, also strongly activates the b form of glycogen phosphorylase. Therefore, glycogen breakdown is initiated by arrival of the nerve impulse. The figure also shows the activation of phosphorylase by adrenaline (as in liver). It has been suggested that the anticipation of exercise may "prime" the system by an increase in adrenaline. Glycogen cannot be broken down until there is an increase in the concentration of inorganic phosphate (P_i), which is released as soon as contraction begins.



Fructose 6-phosphate

Fructose 1,6-bisphosphate



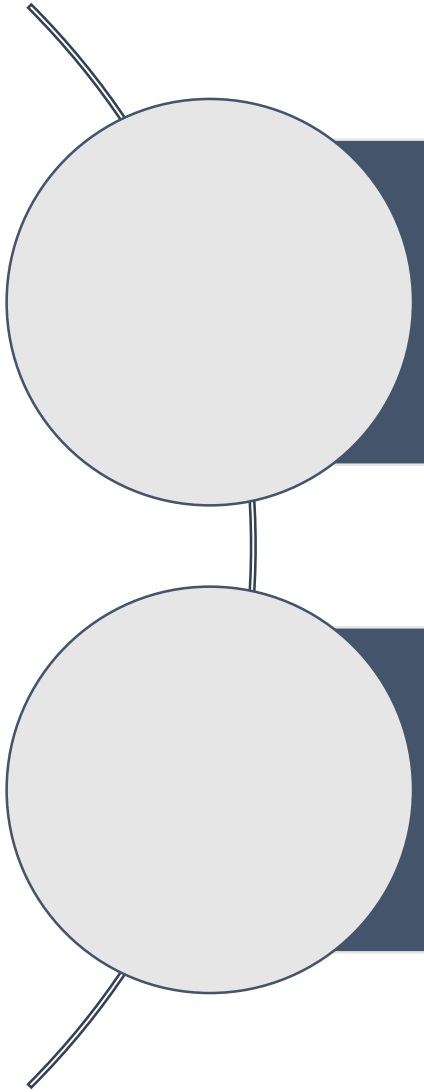
- The ability to perform this type of exercise depends largely upon the bulk of the glycolytic, Type II fibers, and this bulk can be increased through training. Certain interventions may aid performance. Recently, there has been considerable interest in dietary supplementation with creatine in amounts of 5 g/day. This has been shown to improve anaerobic performance, by increasing the amount of phosphocreatine in the muscles. Another intervention that has shown some success in experimental situations is to ingest large amounts of sodium bicarbonate ($NaHCO_3$), which acts as a buffer to minimize hydrogen ion accumulation and thus postpone fatigue.

Metabolic Regulation During Aerobic Exercise

- Anaerobic and aerobic exercise were described as the two extreme forms of exercise.
- Many forms of exercise consist of a *combination of the two*. Games such as tennis and soccer require moments of intense power output (serving, kicking), accompanied by endurance performance (running about the court or pitch for 90 minutes or more).
- In running events, *the 100 meter sprint is virtually completely anaerobic*: it is said that the elite sprinter has no need to draw breath during it. (Most of us would doubtless need several breaths!) *The 400 meter run is a combination of both anaerobic and aerobic exercise* and, with increasing distance, the aerobic component becomes more dominant. The *marathon run (42.2 km, 26.2 miles) is often taken as an example of almost pure aerobic exercise*.

- The characteristic of aerobic exercise is that it can be sustained for long periods. Of necessity, this means that stored fuels other than those in the muscles must be used and must be completely oxidized, so that partial breakdown products such as lactic acid do not build up. Complete oxidation of substrates also gives a much higher energy yield than partial breakdown; for instance, complete oxidation of one molecule of glucose gives rise to 30 molecules of ATP, whereas anaerobic glycolysis to two molecules of lactate generates three molecules of ATP. Not surprisingly, then, the muscle fibers most involved in aerobic exercise are the more oxidative, slow-twitch Type I fibers. In order for these muscles to produce external work at a high rate over a long period, they must be supplied with substrates (including O_2), and the products of metabolism such as CO_2 must be removed, at a sufficiently high rate. This necessitates coordinated changes in the circulatory system.

Metabolic Regulation During Aerobic Exercise



Fuel and ATP

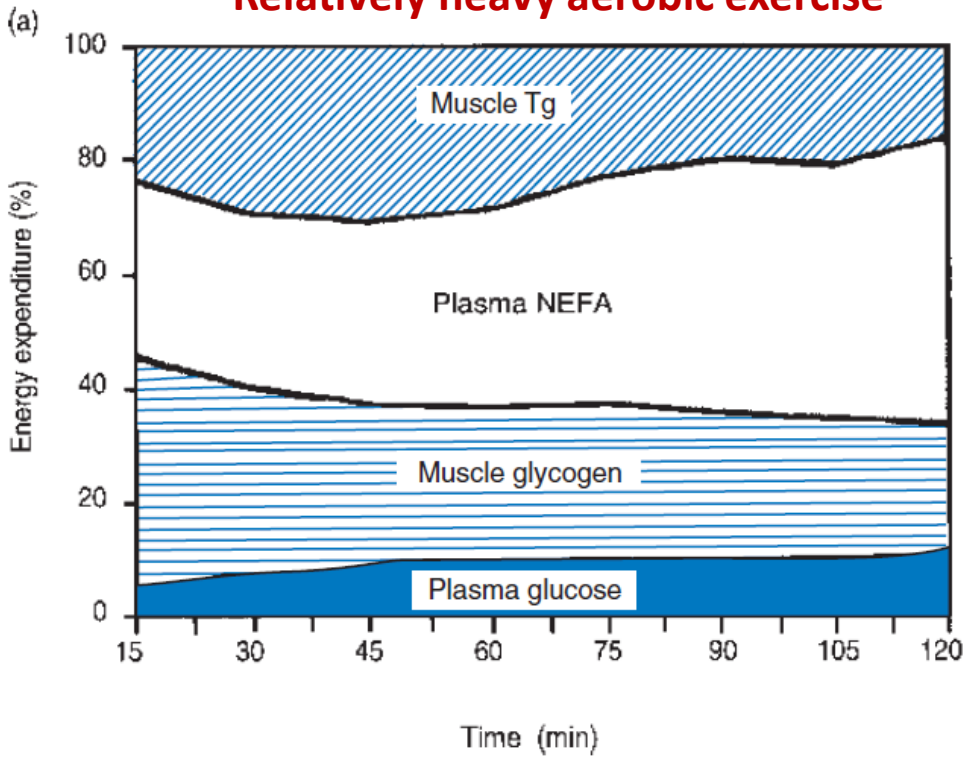
- **Fat or Carbohydrate??**
- **The major fuels used in aerobic exercise vary with the intensity of the exercise and with the duration.**
- **In relatively light exercise most of the energy required comes from non-esterified fatty acids delivered from adipose tissue. At higher intensities, carbohydrate tends to predominate early on, fat becoming more important later as glycogen stores are depleted.**

O_2 and CO_2

- **In more prolonged, "aerobic" exercise, fuels are supplied to the muscle via the blood.**
- **Aerobic exercise also requires coordinated changes in blood delivery to the muscles, and in breathing, to achieve the necessary O_2 intake and CO_2 excretion.**

- *The major fuels used in aerobic exercise vary with the intensity of the exercise and with the duration*. In relatively light exercise most of the energy required comes from non-esterified fatty acids delivered from adipose tissue. At higher intensities, carbohydrate tends to predominate early on, fat becoming more important later as glycogen stores are depleted. As we have seen several times, the amount of glucose present in the circulation and the extracellular fluid is small, and cannot be depleted without harmful effects. Therefore, the carbohydrate used during endurance exercise comes from glycogen stores, both in exercising skeletal muscle and in the liver. In principle, it might also come from gluconeogenesis: exercising muscles always produce some lactic acid, even in aerobic exercise, and this should be a good substrate for hepatic gluconeogenesis. In fact, gluconeogenesis seems to be restricted during exercise, perhaps because blood flow to the liver is restricted as blood is diverted to other organs and tissues (mainly, as discussed below, skeletal muscle). The use of different fuels at different intensities of exercise is illustrated in Figure 9.9.

Relatively heavy aerobic exercise



Relatively light aerobic exercise

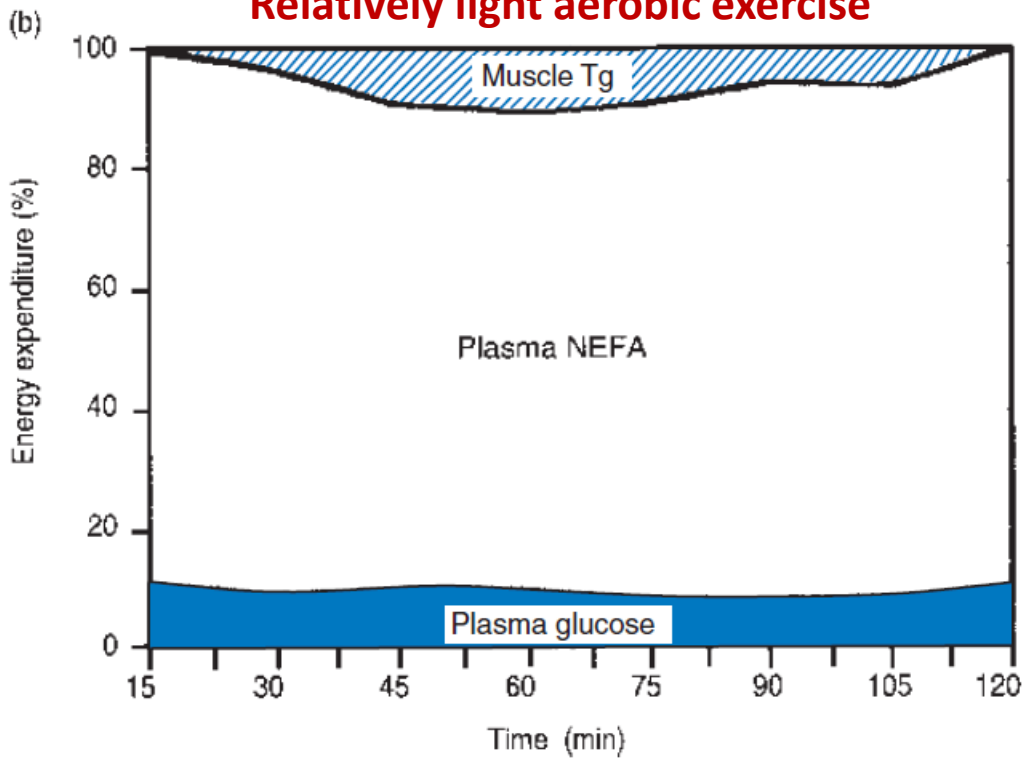
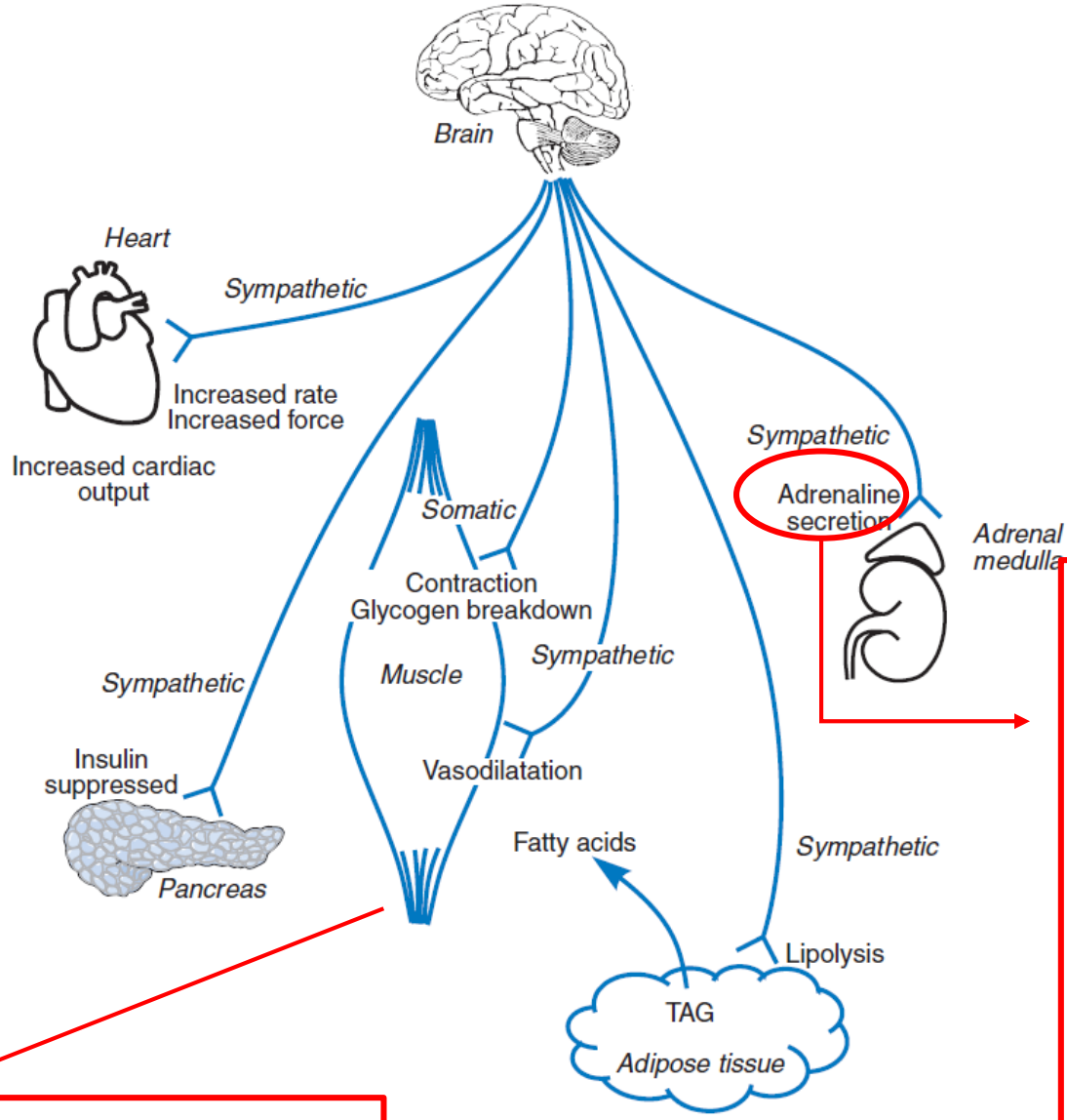


Figure 9.9 Utilization of different fuels during exercise at two intensities. The intensities of exercise are judged by oxygen consumption, in relation to the maximal rate of oxygen consumption for the individual ($\dot{V}O_2max$). Panel (a) shows exercise at 65% $\dot{V}O_2$max; 2 h at 65% $\dot{V}O_2$max is relatively heavy exercise. (An elite marathon runner would maintain about 85% of $\dot{V}O_2$max for 2 h 10 min.) Panel (b) shows exercise at 25% $\dot{V}O_2$max; 2 h at 25% $\dot{V}O_2$max is relatively light. The figure shows the relative contribution to energy expenditure (total energy expenditure is taken in each case to be 100%, although it is 65/25 or 2.6 times greater in the top panel). The data were obtained by a combination of indirect calorimetry and use of isotopic tracers to measure the whole-body turnover of glucose, glycerol and fatty acids. From Romijn *et al.* (1993), *American Journal of Physiology*. Copyright American Physiological Society. Reproduced with permission of American Physiological Society.

Nervous System and Cardiovascular Responses During Aerobic Exercise

- The sympathetic nervous system, accompanied by adrenaline secretion from the adrenal medulla, brings about the necessary changes in the cardiovascular system and the mobilization of stored fuels, glycogen, and triacylglycerol.
- An important part of the physiological response during endurance exercise is an increase in *cardiac output* (both the rate and force of heart contraction increase), and *an increased delivery of blood to skeletal muscle*. Blood flow through exercising skeletal muscle can be 100 times that observed at rest. The increase in cardiac output is mediated mainly by the sympathetic nervous system, acting on β-adrenergic receptors in the heart. An increase in cardiac output in itself might cause an increase in muscle blood flow, but there is an additional specific dilatation of the blood vessels in the muscle. Blood flow to the active muscle increases almost instantaneously at the onset of exercise.
- Increased delivery of O_2 to the muscles and removal of CO_2 from the body also requires increased depth and rate of breathing. This is brought about mainly by the fall in blood pH (increase in H^+ ion concentration), which occurs as lactic acid and CO_2 are produced. The change in pH is sensed by receptors in the brainstem, which trigger changes in respiration.



- Acting on β-adrenergic receptors in the heart
- An increase in cardiac output in itself might cause an increase in muscle blood flow
- Inhibition of insulin secretion from the pancreas → HSL acitivation
- Promote glycogen breakdown in muscles

$\uparrow O_2 \rightarrow \uparrow CO_2 \rightarrow \uparrow [H^+]$ Blood → pH is sensed by receptors in the brainstem, which trigger changes in respiration

- The fatty acids oxidized during endurance exercise come from two main sources: *triacylglycerol stored in adipose tissue* and *triacylglycerol stored in the muscles themselves*. The latter is difficult to study and the factors controlling muscle triacylglycerol utilization are not clear. Nevertheless, the muscle triacylglycerol concentration falls during intense, long-lasting exercise. The regulation of fat mobilization from adipose tissue is better understood. The main stimulus for this to increase during exercise is adrenergic. Blockade of β-adrenergic receptors in adipose tissue with the drug propranolol largely prevents the increase in lipolysis during exercise. The main stimulus may be circulating adrenaline or activation of the sympathetic nerves. Studies of exercise in people who have had spinal cord injuries, so that some of their adipose tissue is innervated while some is not, suggest that circulating adrenaline is more important than the sympathetic innervation. The adrenergic stimulation of lipolysis may be reinforced by the slight fall in insulin concentration (thus relieving the normal suppression of lipolysis by insulin). In addition, the component of exercise induced lipolysis that cannot be blocked by propranolol reflects in part the action of Atrial Natriuretic Peptide (ANP) on lipolysis. In sustained exercise (longer than, say, 30–60 min) then the increases in plasma growth hormone and cortisol concentrations may potentiate the adrenergic stimulation of lipolysis, perhaps by an increase in the amount of enzyme (adipose triglyceride lipase and hormone-sensitive lipase) present.
- The fatty acids liberated in adipose tissue must be *transported through the plasma bound to albumin to the muscles* for uptake and oxidation. It may be a step in this pathway which limits the rate at which fatty acids can be oxidized, leading to the restriction of the contribution of fatty acid oxidation to about 60% of the maximal sustainable rate of energy expenditure. The evidence, from experiments in which the availability of fatty acids in the plasma is increased by the means described earlier, suggests the following. In moderate-intensity exercise, up to about 65% of the maximal aerobic power, increased availability of fatty acids increases the rate of fat oxidation, implying that the normal limitation on their oxidation is at the level of release from adipose tissue. However, in higher intensity exercise (an elite marathon runner maintains 80–85% of maximal aerobic power) then increased availability of fatty acids leads to very little increase in fat oxidation; it appears that the rate of fatty acid utilization by muscle is limited.

- There is some information as to why these steps may be limiting. *The release of non-esterified fatty acids into the plasma depends upon the availability of albumin.* If the blood flow through adipose tissue is restricted, there may be insufficient albumin available to carry away all the fatty acids formed in lipolysis. Non-esterified fatty acids may then accumulate in the tissue, as described in the case of physical trauma. To some extent this may cause an increase in their reesterification to form triacylglycerol, but it also appears that they accumulate as such. When exercise stops, there is often a sudden release of fatty acids into the general circulation not accompanied by the expected one mole of glycerol for each three moles of fatty acids. It is not, perhaps, surprising that blood flow through adipose tissue should be restricted. We have already seen that a high sympathetic activity or circulating adrenaline concentration can restrict blood flow through many tissues by α-adrenergic effects on the blood vessels, and during exercise this occurs as part of the redistribution of blood to the working muscles. Adipose tissue is affected in just this way.
- *At higher intensities of exercise, the muscles appear unable to oxidize more fatty acids even if they are available in the plasma.* The reason may be this. Glucose metabolism in muscle proceeds at a high rate during intense aerobic exercise. Acetyl-CoA is produced, via the action of pyruvate dehydrogenase, but will primarily be oxidized in the tricarboxylic acid cycle. However, the high concentration may cause some increase in flux through the first part of the pathway of de novo lipogenesis, thus increasing the concentration of the next intermediate in that pathway, malonyl-CoA. (Fatty acid synthase is not expressed in muscle.) Malonyl-CoA inhibits the entry of fatty acids into the mitochondrion for oxidation. Thus, glucose oxidation proceeding at a high rate may limit the muscles' ability to oxidize fat.

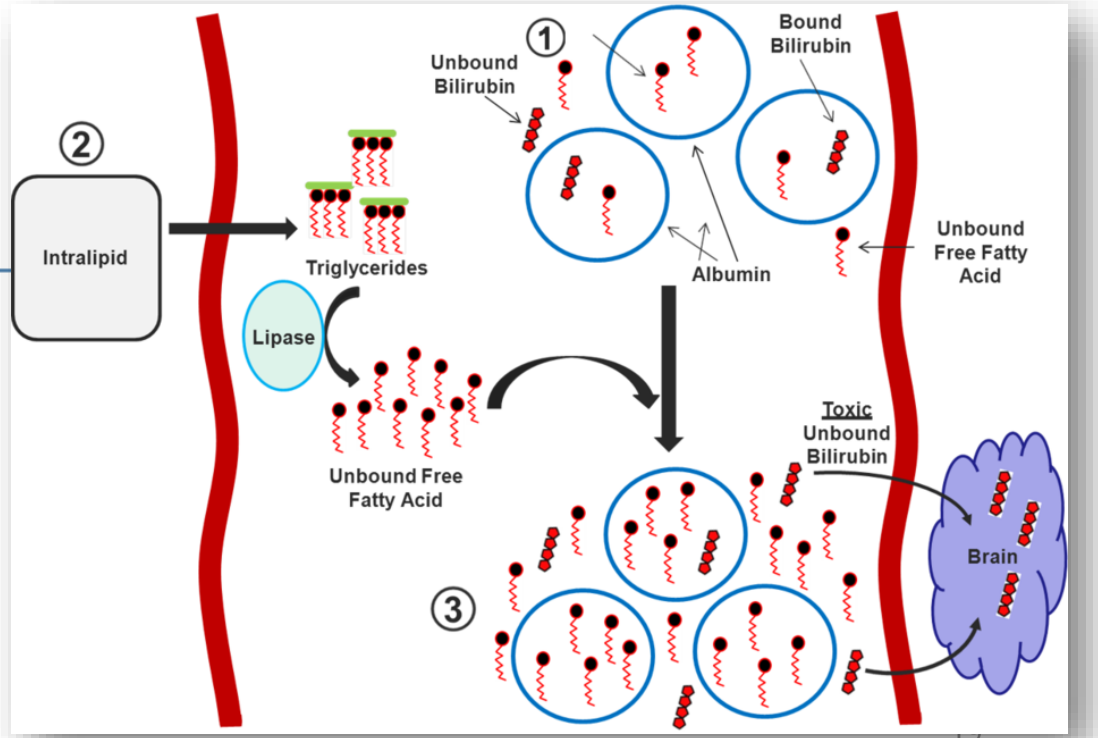
Light aerobic exercise

- Used Fuel (Muscle): Free Fatty Acids

???

At higher intensities of aerobic exercise

- Used Fuel (Muscle): Glucose

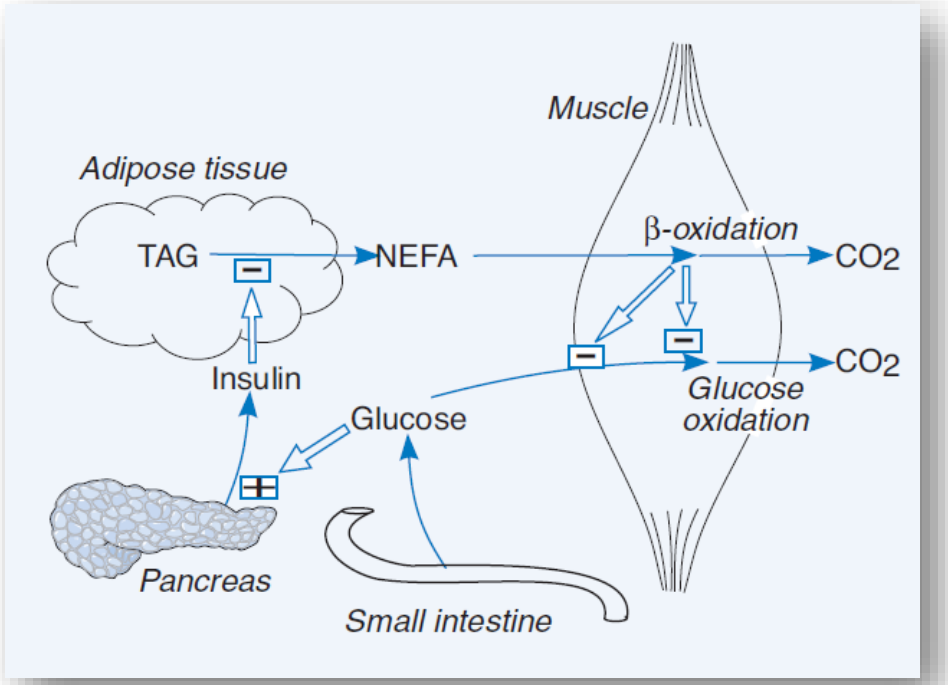


- Cause of fatigue during anaerobic exercise: ↑[H^+] and glycolysis inhibition
- Cause of fatigue during anaerobic exercise: Depletion of glycogen
- The amount of glycogen stored within the muscles therefore limits the duration of high-intensity exercise.

- The activity of muscle hexokinase is sufficient, in principle, for all the energy for sustained aerobic exercise to be derived from uptake of plasma glucose. In fact, as we have seen, this would reduce the length of time during which the exercise can be sustained at the highest rate. Simultaneous oxidation of glucose and fatty acids therefore produces the longest possible period of sustained high intensity exercise. *The availability of fatty acids to the muscles also reduces the rate of glucose oxidation, by operation of the glucose – fatty acid cycle.*

- **The Glucose–Fatty Acid Cycle**

The glucose–fatty acid cycle integrates the utilization of fatty acids and glucose. These interactions between glucose and fatty acid metabolism were first described in 1963 by Philip Randle and colleagues. *Central to this is a mechanism whereby the oxidation of fatty acids in muscle reduces the uptake and oxidation of glucose*. Randle and colleagues described a metabolic mechanism for this effect, in which a high rate of fatty acid oxidation generates acetyl-CoA; this would lead to a high rate of citrate formation (via citrate synthase). In addition, the NADH/NAD^+ and ATP/ADP ratios will be increased. The high acetyl-CoA/CoA and NADH/NAD^+ ratios inhibit pyruvate dehydrogenase (via phosphorylation, by pyruvate dehydrogenase kinase). Thus, the oxidation of pyruvate (derived from glycolysis) is suppressed. This is linked with coordinated inhibition of glucose uptake and glycolysis. Randle et al. proposed that citrate (in the cytosol) would inhibit the regulatory glycolytic enzyme phosphofructokinase.



- Thus, fat metabolism during high-intensity endurance exercise does not follow the rules we might expect on the basis of everything we know about human metabolism. The contribution of fatty acids is limited and the availability of glycogen limits the time for which high-intensity exercise can be maintained. Nevertheless, homo sapiens does seem to have evolved with remarkable distance-running capabilities compared with other mammals, particularly with regard to heat loss (and avoidance of overheating). Maybe two hours was long enough for our ancestors to catch the game they needed.