Muscle metabolism I

Muscle contraction is associated with a high level of ATP consumption (see p. 332). Without constant resynthesis, the amount of ATP available in the resting state would be used up in less than 1 s of contraction.

A. Energy metabolism in the white and red muscle fibers ◑

Muscles contain two types of fibers, the proportions of which vary from one type of muscle to another. **Red fibers** (type I fibers) are suitable for prolonged effort. Their metabolism is mainly aerobic and therefore depends on an adequate supply of O_2. **White fibers** (type II fibers) are better suited for fast, strong contractions. These fibers are able to form sufficient ATP even when there is little O_2 available. With appropriate training, athletes and sports participants are able to change the proportions of the two fiber types in the musculature and thereby prepare themselves for the physiological demands of their disciplines in a targeted fashion. The expression of functional muscle proteins can also change during the course of training.

Red fibers provide for their ATP requirements mainly (but not exclusively) from **fatty acids**, which are broken down via β-oxidation, the tricarboxylic acid cycle, and the respiratory chain (right part of the illustration). The red color in these fibers is due to the monomeric heme protein **myoglobin**, which they use as an O_2 reserve. Myoglobin has a much higher affinity for O_2 than hemoglobin and therefore only releases its O_2 when there is a severe drop in O_2 partial pressure (cf. p. 282).

At a high level of muscular effort—e.g., during weightlifting or in very fast contractions such as those carried out by the eye muscles—the O_2 supply from the blood quickly becomes inadequate to maintain the aerobic metabolism. White fibers (left part of the illustration) therefore mainly obtain ATP from **anaerobic glycolysis**. They have supplies of **glycogen** from which they can quickly release glucose-1-phosphate when needed (see p. 156). By isomerization, this gives rise to glucose-6-phosphate, the substrate for glycolysis. The $NADH+H^+$ formed during glycolysis has to be reoxidized into NAD^+ in order to maintain glucose degradation and thus ATP formation. If there is a lack of O_2, this is achieved by the formation of **lactate**, which is released into the blood and is resynthesized into glucose in the liver (Cori cycle; see p. 338).

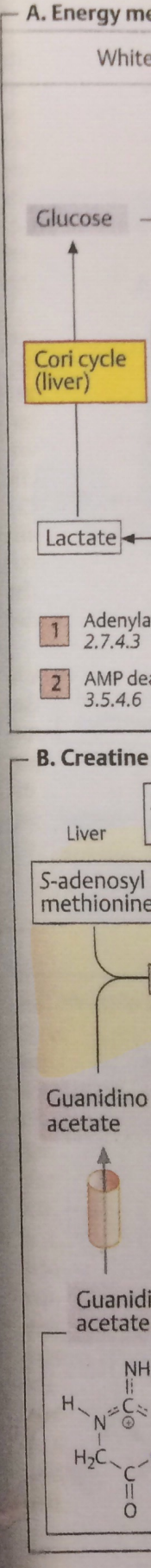
Muscle-specific auxiliary reactions for ATP synthesis exist in order to provide additional ATP in case of emergency. **Creatine phosphate** (see **B**) acts as a buffer for the ATP level. Another ATP-supplying reaction is catalyzed by *adenylate kinase* [1] (see also p. 72). This disproportionates two molecules of ADP into ATP and AMP. The AMP is deaminated into IMP in a subsequent reaction [2] in order to shift the balance of the reversible reaction [1] in the direction of ATP formation.

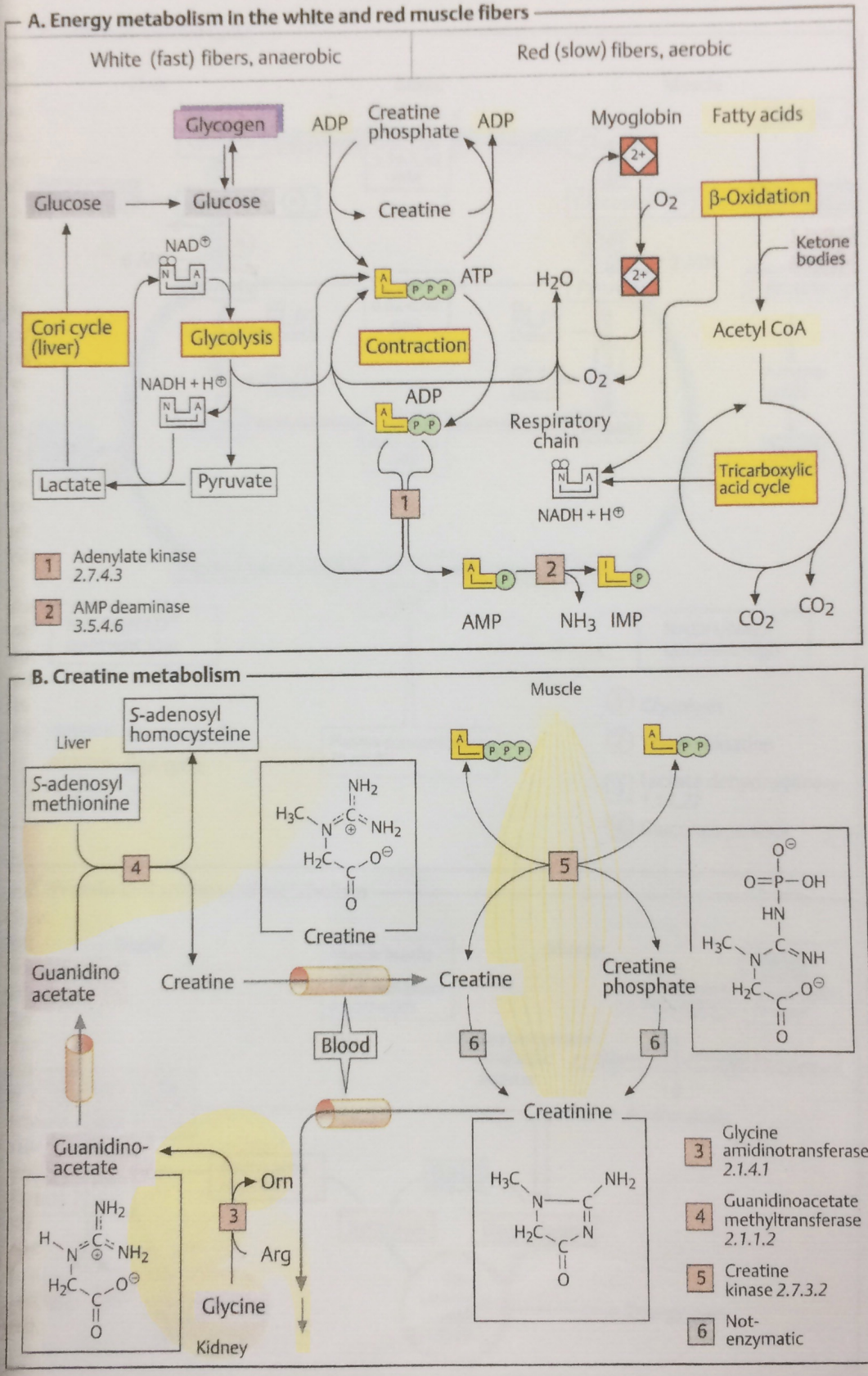
B. Creatine metabolism ◑

Creatine (*N*-methylguanidoacetic acid) and its phosphorylated form **creatine phosphate** (a guanidophosphate) serve as an ATP buffer in muscle metabolism. In creatine phosphate, the phosphate residue is at a similarly high chemical potential as in ATP and is therefore easily transferred to ADP. Conversely, when there is an excess of ATP, creatine phosphate can arise from ATP and creatine. Both processes are catalyzed by *creatine kinase* [5].

In resting muscle, creatine phosphate forms due to the high level of ATP. If there is a risk of a severe drop in the ATP level during contraction, the level can be maintained for a short time by synthesis of ATP from creatine phosphate and ADP. In a nonenzymatic reaction [6], small amounts of creatine and creatine phosphate cyclize constantly to form **creatinine**, which can no longer be phosphorylated and is therefore excreted with the urine (see p. 324).

Creatine does not derive from the muscles themselves, but is synthesized in two steps in the kidneys and liver (left part of the illustration). Initially, the guanidino group of arginine is transferred to glycine in the kidneys, yielding **guanidino acetate** [3]. In the liver, *N*-methylation of guanidino acetate leads to the formation of creatine from this [4]. The coenzyme in this reaction is *S-adenosyl methionine* (SAM; see p. 110).




A. Energy metabolism in the white and red muscle fibers
White (fast) fibers, anaerobic
Red (slow) fibers, aerobic
Glycogen
Glucose
Glucose
NAD⊕
Cori cycle (liver)
Glycolysis
NADH + H⊕
Lactate
Pyruvate
ADP
Creatine phosphate
ADP
Creatine
ATP
Contraction
ADP
Myoglobin
2+
O2
2+
Fatty acids
β-Oxidation
Ketone bodies
Acetyl CoA
H2O
O2
Respiratory chain
NADH + H⊕
Tricarboxylic acid cycle
CO2
CO2
1
2
AMP
NH3
IMP
1 Adenylate kinase 2.7.4.3
2 AMP deaminase 3.5.4.6
B. Creatine metabolism
Muscle
Liver
S-adenosyl homocysteine
S-adenosyl methionine
4
Guanidino acetate
Creatine
Creatine
Blood
Creatine
5
Creatine phosphate
6
6
Creatinine
Guanidino-acetate
Orn
3
Arg
Glycine
Kidney
3 Glycine amidinotransferase 2.1.4.1
4 Guanidinoacetate methyltransferase 2.1.1.2
5 Creatine kinase 2.7.3.2
6 Not-enzymatic

Muscle metabolism II

A. Cori and alanine cycle ◑

White muscle fibers (see p. 336) mainly obtain ATP from **anaerobic glycolysis**—i. e., they convert glucose into lactate. The **lactate** arising in muscle and, in smaller quantities, its precursor **pyruvate** are released into the blood and transported to the liver, where lactate and pyruvate are resynthesized into glucose again via *gluconeogenesis*, with ATP being consumed in the process (see p. 154). The glucose newly formed by the liver returns via the blood to the muscles, where it can be used as an energy source again. This circulation system is called the **Cori cycle**, after the researchers who first discovered it. There is also a very similar cycle for erythrocytes, which do not have mitochondria and therefore produce ATP by anaerobic glycolysis (see p. 284).

The muscles themselves are not capable of gluconeogenesis. Nor would this be useful, as gluconeogenesis requires much more ATP than is supplied by glycolysis. As O_2 deficiencies do not arise in the liver even during intensive muscle work, there is always sufficient energy there available for gluconeogenesis.

There is also a corresponding circulation system for the amino acid alanine. The **alanine cycle** in the liver not only provides alanine as a precursor for gluconeogenesis, but also transports to the liver the amino nitrogen arising in muscles during protein degradation. In the liver, it is incorporated into urea for excretion.

Most of the amino acids that arise in muscle during proteolysis are converted into glutamate and 2-oxo acids by *transamination* (not shown; cf. p. 180). Again by transamination, glutamate and pyruvate give rise to alanine, which after glutamine is the second important form of transport for amino nitrogen in the blood. In the liver, alanine and 2-oxoglutarate are resynthesized into pyruvate and glutamate (see p. 178). Glutamate supplies the urea cycle (see p. 182), while pyruvate is available for gluconeogenesis.

B. Protein and amino acid metabolism ◑

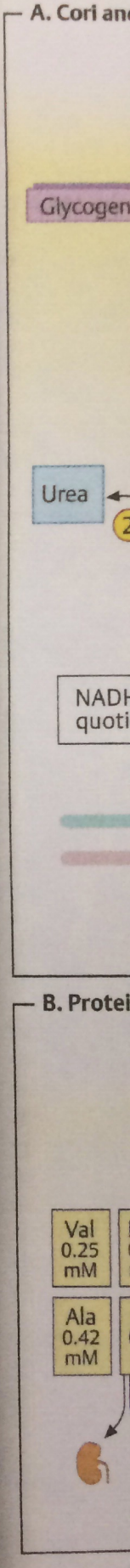
The skeletal muscle is the most important site for degradation of the *branched-chain amino acids* (Val, Leu, Ile; see p. 414), but other amino acids are also broken down in the muscles. **Alanine** and **glutamine** are resynthesized from the components and released into the blood. They transport the nitrogen that arises during amino acid breakdown to the liver (*alanine cycle;* see above) and to the kidneys (see p. 328).

During periods of hunger, **muscle proteins** serve as an energy reserve for the body. They are broken down into amino acids, which are transported to the liver. In the liver, the carbon skeletons of the amino acids are converted into intermediates in the tricarboxylic acid cycle or into acetoacetyl-CoA (see p. 175). These amphibolic metabolites are then available to the energy metabolism and for gluconeogenesis. After prolonged starvation, the brain switches to using ketone bodies in order to save muscle protein (see p. 356).

The synthesis and degradation of muscle proteins are regulated by hormones. **Cortisol** leads to muscle degradation, while **testosterone** stimulates protein formation. Synthetic **anabolics** with a testosterone-like effect have repeatedly been used for doping purposes or for intensive muscle-building.

Further information

Smooth muscle differs from skeletal muscle in various ways. Smooth muscles—which are found, for example, in blood vessel walls and in the walls of the intestines—do not contain any muscle fibers. In smooth-muscle cells, which are usually spindle-shaped, the contractile proteins are arranged in a less regular pattern than in striated muscle. Contraction in this type of muscle is usually not stimulated by nerve impulses, but occurs in a largely spontaneous way. Ca^{2+} (in the form of Ca^{2+}-calmodulin; see p. 386) also activates contraction in smooth muscle; in this case, however, it does not affect troponin, but activates a protein kinase that phosphorylates the light chains in myosin and thereby increases myosin's ATPase activity. Hormones such as epinephrine and angiotensin II (see p. 330) are able to influence vascular tonicity in this way, for example.



A. Cori and alanine cycle