45 Physiology of Skeletal Muscle

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45.2 Organization of Skeletal Muscle

This and the following section present a brief overview of muscle structure and function; more details will be given in Sects. 45.4–45.7 and in Chap. 46.

45.2.1 Motor Units

Skeletal muscle is hierarchically organized, as shown in Fig. 45.1. Macroscopic muscle is composed of many long muscle fibers, which in turn consist of myofibrils that contain filaments.

As discussed in Chap. 15, muscle fibers are innervated by skeletomotoneurons whose cell bodies are located in the anterior horn of the gray matter of the spinal cord or in corresponding nuclei of the brain stem. Each motoneuron innervates a subset of muscle fibers; this complex of motoneuron and muscle fibers is referred to as the “motor unit” because it represents the functional unit of muscle contraction (see Chaps. 46, 49). Motor units may contain anything from a few muscle fibers (e.g., in extraocular muscles) up to more than a thousand (in large skeletal muscles). As detailed in Chaps. 46 and 49, motor units vary in contractile, biochemical, and fatigue properties [16]. Since most mammalian skeletal muscles are composed of many motor units, a high proportion of slowly contracting motor units – as in the soleus muscle – will make the whole muscle slow, and an abundance of fast motor units – as in the gastrocnemius muscle – makes the entire muscle fast. Table 45.1 shows a schematic classification of muscle types and properties.

45.2.2 Anatomy

Muscle Cells. Muscles are built up of cellular elements. Smooth muscles are usually mononucleated and are small, e.g., a few micrometers wide and 10–100 μm long. By contrast, the units of skeletal muscle are larger: multicellular syncytia (see Fig. 45.1), resulting during development from the fusion of originally mononuclear myoblasts yielding myotubes, or from the fusion of myoblasts with previously formed myotubes [1,64]. The resulting muscle fibers are typically 10–100 μm thick and several centimeters long; they may have a thousand or more nuclei, usually of normal diploid constitution. In between these muscle fibers,
there are so-called satellite cells, which, while in contact with differentiated muscle fibers, remain as quiescent myoblasts even in the adult animal. If the muscle fibers are damaged, however, the satellite cells begin to differentiate and merge, and thus they are responsible for muscle regeneration [1]. A muscle taken out, chopped finely, and returned to its original site can, in contact with a muscle nerve, give rise to a whole new muscle. Cardiac muscle consists of branching muscle fibers, compartmentalized by intercalated disks, or of fiber-like arrangements of cardiocytes; the intercalated discs, 20–100 μm in size, are of much lower electrical and diffusional resistance than ordinary cell borders (see Chaps. 90, 91). Cardiocytes are mono- or binuclear. For example, in the adult human heart, 80% are binuclear. By contrast, in the pig there may be five to eight nuclei per cell, and at embryonic ages mononuclear cardiocytes are the rule.

**Sarcomeres.** Muscle fibers are cross-striated, as are their constituent fibrils, resulting from an alignment of sarcomeres (see Figs. 45.1 and 45.2). A sarcomere is a single unit, measured from one fibrillar Z disk or Z line (in longitudinal sections) to the next. It is the smallest element containing the whole property of contractility. As discovered by Leeuwenhoek in 1682 (see Chap. 1), a periodicity, usually of 2.0–2.5 μm, is seen microscopically on account of differences in optical density; its visibility can be accentuated by staining or immunostaining or by the use of polarization optics. The so-called A band, the central part of each of the sarcomeres, is of greater density and shows anisotropy in polarized light. By contrast, the I band appears isotropic and is bisected by the Z line. The periodicity can also be visualized and measured by light diffraction from a laser beam, since the regular sarcomere spacing constitutes an optical diffraction lattice. Sarcomeres contain two types of longitudinally oriented myofilaments: actin and myosin (see Figs. 45.2, 45.5). Actin filaments are fixed in their middle at the Z disk and extend into the two adjacent sarcomeres (see Fig. 45.2). Where they are present alone (close to the Z disk), the sarcomeres are optically isotropic (I band). Where myosin filaments overlap with actin filaments (in the middle part of the sarcomeres), they form the A bands. Myosin filaments are held together by structures appearing as the M line. At normal rest length (2.0–2.5 μm), the sarcomere contains only myosin filaments in its middle portion, giving rise to the H zone (Figs. 45.1, 45.2, 45.15).

Actin consists of a double-stranded linear assembly of globular molecules, G actin, forming filamentous F actin (see Fig. 45.5). This chain is twisted, with 13–15 actin pairs per full turn of about 750 nm. There is polymerized tropomyosin, with troponin molecules attached, in both

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**Table 45.1. Classification of muscle types**

<table>
<thead>
<tr>
<th>Smooth or plain muscles</th>
<th>Sarcomeric muscles</th>
<th>Cardiac muscle: β-Atrophicventricular</th>
</tr>
</thead>
<tbody>
<tr>
<td>Great variety among vertebrate and invertebrate animals</td>
<td>Skeletal muscles: Fast (F-)type Slow (S-)type Isogene selection mainly decided by the nervous system Direct motor innervation as the only mode of activity in these muscles FF: white; glycolytic and fatigueable FR: red; mixed metabolism; little fatigue S: red; not fatigueable; oxidation much like in cardiac muscle</td>
<td>Isogene selection regulated by the thyroid hormone, among others Regulating dependence vis-a-vis sympathetic–parasympathetic muscles Oxidative, red; no fatigue over a lifetime</td>
</tr>
</tbody>
</table>

Innervation: great variety

No fatigue, as a rule

General rule: the larger the animal, the slower the muscles with respect to contraction velocity, myosin-ATPase, cardiac frequency etc. FF, fast, fatiguable; FR, fast, fatigue resistant; S, slow

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mental afferent inputs, the action potential generated at its initial segment travels down the myelinated axon into its branches and, at the neuromuscular junctions to its muscle fibers, causes the release of acetylcholine (ACh) from the presynaptic terminals (see Chap. 15). At the postsynaptic muscle fiber membrane, ACh docks to ligand-gated ion channels, which thereby open to small cations (in particular Na⁺ and K⁺), depolarizing the muscle membrane to threshold for an action potential. This then runs bidirectionally along the length of the fiber, entering membrane invaginations, so-called T tubules on the way, to conduct depolarization into the fiber’s interior. Here, the complex process of conversion of an electrical signal into a mechanical event, referred to as excitation–contraction (EC coupling (see below), occurs. As is evident from everyday experience, it is closely coupled to the turnover of energy, part of which is dissipated as heat. Muscle activation the refer can be measured in terms of three variables: electrical, mechanical, and thermal.

### 45.3.1 Excitation

**Electromyography.** The muscle fiber is a conductive element in much the same way as an unmyelinated nerve fiber. Its electrical excitation can be monitored by various methods of electromyography, yielding electromyograms (EMG) of diverse sorts [59].

**Motor Unit Action Potentials and Interference Pattern.** With very selective electrodes inserted into the muscle, it is possible to extracellularly record the action potentials of single muscle fibers (see Fig. 45.4C, part b). More often, however, intramuscular electrodes are used in research and clinical applications to record the compound action potentials generated by many or all of the muscle fibers belonging to one motor unit (motor unit action potential MUAP; see Fig. 45.4A, second trace from left). These potentials are the weighted sum of the muscle fibers’ individual action potentials conducted by volume conduction to the site of recording (usually the electrode tip). Since motoneuron action potentials are normally translated one-to-one into MUAP, this technique yields an insight into the normal patterns of motoneuron activity. However, it is also used as a tool for differentiating neurological disorders (for two examples, see Fig. 45.4B, C). At somewhat elevated levels of muscle activation when many motor units are active, the individual MUAP cannot be discerned anymore, but intermix to yield an interference pattern (see Fig. 45.4A, right-hand trace; Fig. 45.3B, part a). Another, more integrative technique is to monitor the compound activity of usually many motor units by percutaneous recording with surface electrodes (surface EMG). Surface EMG recordings are used for a variety of purposes:

- To determine the normal patterns of muscle activation during various motor acts so as to be able to identify pathological patterns occurring in various neurological diseases (see below)

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**45.3 Activation**

**Neuromuscular Junctions and T Tubules.** The function of muscle is to generate force by contraction, initiated by action potentials on motor nerve fibers. This overall electrical-to-mechanical conversion involves a number of intermediate processes. Once a motoneuron in the brain stem or spinal cord is activated by descending and/or seg-

grooves of the actin double-strand. Each myosin molecule (see Fig. 45.6) consists of a tail, a neck, and two movable heads that under conditions of rest stick out about 90° from the longitudinal axis. The tails of many myosin filaments are aggregated in the middle sarcomere region, while the heads stick out between the actin filaments to potentially bind to them at specific binding sites (see below). The heads contain ATPase, which is activated during contraction and can split adenosine triphosphate (ATP), which during rest is bound to the head.

**Sarcoplasmic Reticulum.** Skeletal muscle fibers are composed of long myofibrils (see Fig. 45.1). These are typically 1–2 μm in diameter, although in some types they are grouped secondarily into what, on a cross-section, appears as broader, massed “fields”: field structure, as compared with fibrillar structure. The myofibrils are surrounded by sarcoplasm containing the sarcoplasmic reticulum (SR), which comprises the terminal cisternae and longitudinal elements; the transverse (T) tubules, which are in contact with the terminal cisternae in triads; glycolgen granules (see Fig. 45.3); mitochondria; and occasionally some fat droplets. The sarcoplasmic reticulum stores Ca²⁺ ions.
45.3.2 Excitation–Contraction Coupling

The chain of events continues with the conversion of electrical muscle activation into contraction. This process is described in detail in Chap. 46 and is only briefly summarized here (see Fig. 45.5).

Voltage Sensors. In skeletal and cardiac muscle, contraction is initiated by electrical excitation of the sarcolemma, which causes a cascade of processes leading to contraction. This entire sequence is called EC coupling. In normal EC coupling the “all-or-nothing” surface excitation (muscle fiber action potential, step 1 in Fig. 45.5) is conducted inward through the branching array of T tubules (step 2) and thus reaches the entire cross-section of the muscle fiber at each sarcomeric level. The T system is closely associated with the longitudinal sarcoplasmic reticulum, which serves as a large reservoir of Ca\(^{2+}\) ions. Once the T system is depolarized, voltage sensors in its membrane undergo a complex conformational change, which is conveyed to the Ca\(^{2+}\) channels of the adjacent sarcoplasmic reticulum (step 3). This opens the Ca\(^{2+}\) channels and effects a release of Ca\(^{2+}\) (step 4) into the sarcoplasm, where at rest the Ca\(^{2+}\) concentration is very low, e.g., \(10^{-8}\) mol/l or less.

Troponin. The liberated Ca\(^{2+}\) reaches the myofibrillar parts of the sarcomere and here initiates the contraction process proper by acting on troponin (step 6). The role of troponin is best understood as follows. It consists of three parts, referred to as T, I, and C. The T part connects it to tropomyosin, a long molecule twisted around the actin double-strand (Fig. 45.5). At rest, i.e., at low Ca\(^{2+}\) concentration, troponin I inhibits the interaction between myosin heads, actin, ATP, and Mg\(^{2+}\). Troponin C binds Ca\(^{2+}\). When Ca\(^{2+}\) is released and binds firmly to troponin C, the allosteric interactions between troponins I, C, and T and tropomyosin change, freeing the binding sites for the myosin heads on actin (step 7). This binding makes actin activate the ATPase, whereby ATP is split and released.

- To relate EMG measures to muscle force, which is very difficult to measure without invasive techniques (for this purpose, the surface EMG interference pattern is mostly fullwave rectified and lowpass filtered)
- To look for indicators of physiological variations of muscle function, such as in muscle fatigue (see Sect. 45.7).
Fig. 45.3A–C. Electromyographic (EMG) recordings in health
and disease. A Recruitment of increasing numbers of motor units
during increasing strength of voluntary contraction in a normal
subject, recorded with an intramuscular needle electrode. The
leftmost trace shows the baseline without motor unit activity
during rest. The second trace from left during weak contraction shows
a single motor unit’s action potentials (MUAP), characterized by
constant size and shape and representing the compound
potentials picked up by the electrode from the muscle fibers
belonging to the unit. Upon recruitment, motor units typically start
firing regularly at low rates of five to ten spikes/s [35]. The middle
trace at somewhat stronger contraction shows that the previously
recruited motor unit (large spikes) has increased its discharge rate
and another motor unit (smaller spikes) has resumed firing. The
second trace from right at intermediate contraction strength shows
the activity of even more motor units; some single spikes are still
identifiable; the baseline becomes wavy. The rightmost trace ex-
hibits a typical full interference pattern, in which the spikes of a
single motor unit are no longer clearly distinguishable because of
overlap. (Modified from [59], Appendix Fig. 4.30). B EMG pattern
in myopathy. Due to muscle fiber loss, i.e., disorganization of
the motor unit, the MUAP may be reduced in size, polyphasic, and
split up (a), but an interference pattern (b) may still look fairly
normal because motor units may be activated normally. C EMG
pattern in muscle denervation due to motoneuron disease. Motor
units can no longer be neurally activated. Small, sharp fibrillation
potentials appear spontaneously; they are action potentials of sin-
gle muscle fibers whose associated contractions cannot be seen at
the muscle surface, however. They indicate a hypersensitivity of
the denervated muscle fibers. (Modified from [67], Fig. 30c,d)

from the myosin heads. These then reduce their angle from
90° to 45°, thus pulling in the actin filaments. Detachment
of the myosin heads from actin requires rebinding of ATP
to the myosin heads. With Ca²⁺ still being high, a new cycle
can then begin. Many such cycles occur during a single
muscle activation (“twitch”). Shortly after its release, Ca²⁺
begins to be resequestered by the sarcoplasmic reticulum
(step 5) using an ATP-dependent pump, thus reestablishing
the condition of rest.

45.3.3 Energy Turnover

It is apparent from the preceding description that the me-
chanical activity of muscle and metabolism are directly
coupled. Most immediately, this involves the breakdown of
ATP. However, ATP is in rapid phosphate-transfer equilib-
rium with phosphoryl-creatine (or creatine phosphate,
CrP), which thus constitutes an immediate ATP reserve.
Metabolism aerobically reconstitutes the ATP used by me-
tabolizing, in particular, carbohydrate and fat. It may do so
more or less immediately, enabling the muscle to maintain
a steady state of activity over a long time. Alternatively, it
may do so with a delay, but in the end an aerobic recovery
or restitution period is required (in behavior terms, taking
a rest). On these grounds, different muscles have become
specialized for endurance on the one hand and brief,
strong force generation on the other (see Table 45.1). Thus,
muscles can be classified in terms of a spectrum with the
glycolytic fatigue type at one end (“twitch now, pay later”)
and the aerobic steady state at the other (“pay as you go”).
The latter muscles are characterized by a high number of
mitochondria present. A prominent example of this type is
the heart, which never rests. Most of the energy consumed
during muscle contraction is dissipated as heat, whose
elimination poses a problem to thermoregulation (see
Chap. 110).
45.4 Actomyosin and the Discovery of the Sliding Filament Model

The following gives a brief historical account of the development of the sliding filament model. The present state of knowledge is discussed in detail in Chap. 46.

**Myosin.** The so-called A rods turned out to be mostly myosin, and I filaments to be actin, associated with troponins and tropomyosin. A protein originally termed “myosin” was discovered by Kühne [60] in a study of proteins obtainable from muscle and other assorted cells, mainly characterized in terms of coagulation properties. However, Kühne’s “myosin” later turned out to be composed of actin together with what is now known as myosin [84]; the aggregate “actomyosin” (see below) is dissociable into its constituents by the action of ATP [86]. More than a century ago, T.H. Huxley [54] stated that the birefringence of muscle fibers disappeared upon extraction with salt solutions known to extract “myosin”, an observation which was confirmed by Schipoloff and Danilevsky [79], who also found that such extracts, when allowed to dry down, deposited birefringent precipitates. Von Muralt and Edsall [88] reported that “myosin” solutions became birefringent in a flow field, showing the presence of dissolved units long enough to become oriented in a hydrodynamic flow gradient. In 1934, Noll and Weber [70] showed that the birefringence of the A bands could be explained by that of the “myosin” threads. The first demonstration of a link between “myosin” structure and function was made by Engelhardt and Ljubimova [28], who found that “myosin” is an enzyme that causes the splitting of ATP. The finding that a structural component of the sarcomere catalyzes the putative driving reaction was one of the high points in molecular physiology, which was emerging at that time.

As to the molecular structure of myosin (see Fig. 45.6), it is a long molecule, about 160 nm in total length, consisting of two peptide chains of 200–220 kDa. The C-terminal halves of these chains are almost completely helical and coiled along each other to form the “tail,” except for in two proline-containing hinge areas; the N-terminal “head,” carries the active sites for both ATPase and association with actin (see below). This dimeric molecule (myosin heavy chain-2, MHC,) is, furthermore, intimately associated with four MLC (light chain) molecules with molecular masses of around 20 kDa (MLC₉,MHC₇). One pair of these is detached relatively easily with dithionitrobenzene. (DTNB). The other, A-ŁC (or alkaline detachable), is held more tenaciously, but can still be removed without inactivation. The whole molecule (about 480 kDa) is expected to have two ATP sites. In principle these are equal, but it appears possible that binding one ATP may allosterically
The myosin molecule has a remarkable internal complexity. In part, it is unraveled by proteolytic digestion with chymotrypsin or papain, dividing the molecule as shown. Light meromyosin (LMM) and a part of heavy meromyosin (HMM) together form a double helix, supercoiled except for the looser structure of the presumed "hinges," which are areas rich in proline. HMM is further separated into HMM-S, and S2, the N-terminal S1, being the "head" of the molecule proper. S1 has a single chain of 95 kDa in three domains of 25, 50, and 20 kDa. The former contains the ATPase site, and the latter two bind to actin. Amino acid positions 633–642 are a lysine-rich sequence, undoubtedly of significance in the electrostatic interaction with actin. The double parallel lines are the double-helical tail. Vertical arrows point to the location of the proposed "hinges." The amino-terminal is on the left; the carboxyl-terminal is on the right.

Alter the other so as to change its affinity. Nonetheless, it is thought that both heads are fully functional in vivo, quite within keeping with the allosterism concept.

Contractility. Even when it became known that myosin splits ATP, no contraction phenomenon had been demonstrated. This took place in 1941–1942 in the laboratory of Albert Szent-Györgyi in Szeged, Hungary, when several properties of myosin-ATPase were being studied. The standard preparation procedure consists in extracting freshly minced rabbit muscle with 0.6 mmol KCl/l for 20 min at a cold temperature. The extract is centrifuged clear, and myosin, soluble at high ionic strength, is precipitated by dilution with ten to 20 volumes of water. The precipitated myosin is redissolved in 0.6 mmol KCl/l and precipitated once more. This simple procedure yields a protein which, even by present-day rigorous testing, is remarkably pure, albeit of multiple subunit composition. Its ATPase activity depends enzymologically in a complex way upon the electrolyte composition of the medium; the most significant feature is its extremely strong inhibition by Mg2+ at physiological concentrations coupled with its activation by Mg2+ in the presence of actin.

An observation in Szent-Györgyi's laboratory provided the clue to myosin's contractile activity. When myosin extraction was allowed to continue overnight instead of for only 20 min, the resulting myosin was far more viscous than the previously known form, as a result of some kind of aggregation process. Its solution viscosity was drastically reduced by ATP, and this was the first hint toward a transduction property. The new form differed from the old one on two crucial points.

The first is that its ATPase was not inhibited by Mg2+ unless studied in a dissociative medium. The second requires separate description. Myosin precipitated at low ionic strength, and Weber had shown how this could be done by extrusion from a narrow pipette into the precipitating solution, so that fragile threads are obtained. Such a thread showed no relevant activities when made from 20-min myosin. However, a thread from overnight myosin contracted markedly when immersed in a fresh aqueous muscle extract [86] (see Fig. 45.7). The active ingredient was identified as ATP, in combination with Mg2+ and K+ at about physiological concentrations; in addition, there were also traces of Ca2+, but that was only found later.

An even simpler demonstration was available than that involving the extruded actomyosin thread, called "superprecipitation." This consisted of the contraction of precipitating actomyosin flocculi, visible from the changes in forward light scattering by the suspension. However, the extruded thread was a more explicit demonstration.

The question arises, then, as to the difference between the two myosin preparations. During the prolonged extraction, the myosin already in solution recombined with a constituent left behind after the ATP and CrP in the extract had been decomposed. This constituent was a new protein discovered in 1942 by F.B. Straub in the same laboratory by using water to extract an acetone-dried muscle powder [84]. This solution showed no remarkable properties except for one additional salt, which caused rapid polymerization of the protein; even at a concentration of 1 g/l, it formed a firm gel, called polymerized, fibrous, or F actin, which combines with myosin:

\[ \text{myosin + F-actin} \rightarrow \text{actomyosin} \]

\[ \text{ATP} \]

Actin. In its monomeric form, actin is a globular protein of about 43 kDa whose primary structure is completely

Fig. 45.7. A historic experiment performed in 1942, showing the contraction of a myosin thread upon the addition of adenosine triphosphate (ATP). Left, acto-myosin thread. Right, myosin. There is no response in the latter [86]
known. It has been rigorously purified (although contamination with tropomyosin is still possible) by a new principle: extraction using aqueous ATP, polymerization using salt, and isolation of the actin polymer by preparative ultracentrifugation. The presence of ATP protects the protein against denaturation. In the course of polymerization, about 1 mol ATP becomes dephosphorylated per monomer entering, and the resulting adenosine diphosphate (ADP) remains very firmly bound to or within the polymer. At first it was thought that this ATP splitting is a fundamental part of the reaction, but the two processes can be separated. Muscle contains a bound form of ADP, which is considered a part of the normal in vivo actin structure. In myofibrils, actin is polymerized; as shown by Hanson and Lowy [40] for actin polymerized in vitro, it consists of a double-stranded linear assembly of G actin or, in other words, a linear array of actin doublets. This chain is twisted, with 13–15 actin pairs per full turn of about 750 nm. There is polymerized tropomyosin, with troponin molecules attached, in both grooves of the actin doublet strand.

**Actomyosin.** Contracting threads are formed by actomyosin (see Fig. 45.7). They differ from muscles in that they become both shorter and thinner and are too fragile to lift any load; their structure is of low coherence. A more perfect model was introduced by Szent-Györgyi by preparing thin strips of muscle, bundles of just a few muscle fibers, that were tied to small rods and kept below 0°C in 50% aqueous glycerol, which made them permeable and leached out most cell constituents: the prototype of the “skinned” muscle fiber. When immersed in ATP with accompanying electrolytes, they contracted lengthwise and became thicker, developing a force similar to that of living muscle. They were also used to measure force development or shortening with simple kymograph equipment. Their molecular arrangement was not significantly altered in the preparation. In fact, electron microscopical studies were largely done on these glycerol fibers because most nonfibrillar proteins were removed in the process, resulting in clearer pictures.

**Sliding Filaments.** According to H.E. Huxley and Hanson [53] and A.F. Huxley and Niedergerke [51], contraction consists of an inward sliding of the F filaments toward more complete overlapping interdigitation with the A rods, e.g., until they touch in the middle of the H zone or even beyond, sliding oppositely past one another. Conversely, stretching a muscle involves a sliding of F filaments away from the center of the A band; when they stop overlapping with the A rods altogether, no more tension is developed. (Note that in muscle physiology “tension” is mostly used synonymously with “force,” although in the physical sense this is not strictly correct.) This is the sliding filament model, which has been the prevailing model in the field since the mid-1950s, with details added along the way (see Chap. 46). This first phase of the model did not explain the nature of the forces effecting the described motions; more crucial facts were needed. One such point was described in an outstanding paper by H.E. Huxley [52] on isolated structures consisting of Z bands with F filaments on both sides (“IZI brushes”). Myosin molecules (or rather H meromyosin, i.e., myosin with much of the helical tail enzymatically cut off, which has better solubility characteristics for the present purpose) were allowed to combine with them on the electron-microscope grid and were then visualized. The myosin heads were attached in a pinelace, branch or chevron pattern, showing that in the absence of other influences (including ATP) this was their preferred angle of attachment. Second, X-ray diffraction showed that in rigor mortis the myosin cross-bridges are indeed placed at such an angle, while in resting muscle they show wide orientation scatter, but on average are about perpendicular (see Fig. 45.8). Third, the structure of the A rods was examined: they were found to be liquid-crystalline structures of great dimensional regularity in which the myosin tails (insoluble at physiological ionic strength) were more or less parallel and made up the body of the A rods, whereas the heads and parts of the tail as far as the hinge point stuck out into interdigital space, where they could interact with the actin rods when circumstances allowed. Thus, the second phase of the sliding filament model ascribed the sliding motion to interactions between the myosin heads, i.e., the cross-bridges, and the actin filaments. At rest, the bridges stick out sideways. When interaction is set off, the bridges attach to sites on the actin filament; they seek to attain the preferred angle, reach that position, and then detach in the course of a cycle in which an ATP is broken down (see Chap. 46).

### 45.5 Mechanics of Muscle Contraction

In parallel to the studies aimed at revealing the microscopic events underlying muscle contraction, research has been conducted into its macroscopic behavior ever since 1780, when Galvani [36] discovered that electricity made frog muscles twitch.

**Concentric and Eccentric Contractions.** The contraction studies described below can be performed on whole muscles, groups of muscle fibers (e.g., motor units), or isolated single muscle fibers. Both whole muscles and their constituent muscle fibers can be stimulated directly or indirectly. Indirect activation is achieved by stimulation of the muscle nerve or a single motoneuronal axon defining a motor unit. Upon the event of excitation, the coupling of excitation and mechanical activity causes the muscle to develop force with or without a change in length, where the length change may be shortening or lengthening, thus giving rise to shortening (concentric) and lengthening (eccentric) contractions, respectively.

**Isometric and Isotonic Conditions.** The form and time course of muscle contraction depend not only on the type of muscle fiber, but also on the mechanical conditions met
Fig. 45.8. A didactic model of the myosin cross-bridges in the state of rigor mortis, presumed to represent the permanent fixation of the terminal swing of the cross-bridge cycle. The acute angle of attachment corresponds to that shown electron microscopically (EM) by H.E. Huxley [52]. B Cross-bridges in resting muscle. They have been drawn in the perpendicular position, but could be in an other position or randomly arranged. Z, Z band; M, M band. (Adapted from [77], Fig. 6)

and the stimulation patterns used. Thus, as to the conditions, we can distinguish two extreme cases: isometric and isotonic contractions, most contractions not reaching either extreme and therefore being mixed. Isometric contractions are ideally performed by keeping the muscle or muscle fiber length constant and measuring the force generated, whereas under isotonic conditions it is the force that is constant with length allowed to change. Under natural conditions, muscles contract almost isometrically when a posture, e.g., upright stance, is being maintained. Isotonic contractions occur more seldomly because in many cases in which length changes, so does force. Shortening contractions of increasing force are also referred to as auxotonic contractions. Forced lengthening of a contracting muscle is not an experimental artifact, but a functionally important activity mode. It occurs mainly when someone goes down a slope or a staircase or slowly lifts a heavy load. It also occurs in the later part of the swing of a limb when the muscles initiating the opposite movement are activated; they are first stretched by the persisting contraction of their antagonists and by the inertia of the limb.

With artificial stimulation, contraction can be elicited by a single stimulus in the form of a brief electrical shock or by a defined time series of stimuli. The first protocol yields a twitch response, the second a summed response whose time course depends on the precise temporal pattern of stimuli.

### 45.5.1 Twitch Response

**Contraction and Relaxation Time.** Examples of isometric twitch responses for a fast and a slow mammalian muscle are illustrated in Fig. 45.9a and Fig. 45.9b, respectively. A twitch consists of an upstroke of force that follows excitation (at zero time) after a latency of a few milliseconds and a subsequent relaxation phase that usually lasts roughly twice as long as the rising phase. The contraction time (usually determined from base foot to the peak of force development) and the subsequent relaxation time depend on the contractile property. This is a compound property determined by the way the muscle is composed of motor units (see above and Chaps. 46 and 49). In several mammalian species, all limb muscles are slow at birth, and only during postnatal development do part of them develop...
and only occasionally from brief tetani. Rate adjustment occurs even during the adverse condition of muscle fatigue, when the contractile speed of motor units, particularly of the rapidly fatiguing ones, slows down; these then reduce their discharge and contraction rates (see Chap. 50). The twitch force may equal the tension reached in a tetanus, but is usually less and sometimes much less (twitch to tetanus ratio < 1 less than 1; see Fig. 45.10). As in

![Graph showing summation of twitch tension over time](image1)

into fast muscles. While the contraction and half-relaxation times of both slow (soleus) and fast (extensor digitorum longus) muscles decrease postnatally, this change is much more pronounced in the fast muscle [22].

### 45.5.2 Force Summation upon Repetitive Activation

**From Single Twitches to Fused Contraction.** Repetition of stimulation leads to a sequence of twitches, which at closer spacing of the stimuli may merge and summate (see Figs. 45.10, 45.11a, 45.12). A sustained smooth contraction, called a smooth tetanus, results when the stimulus frequency reaches or exceeds the fusion frequency, at which the contraction cannot even partially relax before the next activation. When a smooth tetanus is attained, the muscle exerts the full contractile force of which it is capable under the circumstances. Any continuous activation below fusion frequency, but with summation of successive twitches, entails an unfused tetanus characterized by tension fluctuations which may contribute to muscle tremor [82,95]. The dependence of average tension on stimulus rate is that of an S-shaped (sigmoidal) function. This curve naturally extends over a range of low rates for slow-contracting motor units and over higher rates for fast-contracting motor units (see Chap. 49), because a short twitch contraction time goes hand in hand with a high tetanic fusion frequency and vice versa. The steepest portion of this S-shaped curve spans the region in which rate modulation of muscle force output is most powerful. For the central nervous system to have efficient rate control of force output, it thus needs to optimally adjust the firing rates of its motor units to their contractile properties. This may be the reason why, in ordinary motor functions, most contractions result from unfused contractions of motor units

![Graph showing ratio of tension-time area](image2)
nerve, the excitatory event in skeletal muscle is followed by a refractory period. The possibility of a tetanic contraction occurring therefore depends on the contractile response outlasting that refractory period. The heart is a prominent example of a muscle that has a long refractory period and which cannot be tetanized, though this may become possible in unphysiological ionic media (see Chap. 91).

Potentiation. A muscle or motor unit's force production depends not only on the instantaneous neural input, but also on its preceding activation history. This feature can take various forms. For example, a second twitch following a preceding one often does not superimpose linearly upon the force generated during the first twitch. The initial part (force rise) of the second twitch may be depressed [83], while the force output during the relaxation phase is usually more or less increased and prolonged (facilitation or potentiation) depending on the muscle [72]. Potentiation is illustrated in Fig. 45.11a for a single, slow-contracting (type-S) motor unit of the cat medial gastrocnemius muscle. As compared to a single twitch (lower trace in upper left panel), a second stimulus following the first at 10 ms adds a disproportionately large amount of tension (second trace), while third and fourth stimuli do not generate as much additional force. With an interstimulus interval of 50 ms, all successive twitches are potentiated, and this potentiation nearly disappears again at an interval of 100 ms (see right graphs plotting the added tension–time areas contributed by the second, third, and fourth twitch as a function of interstimulus interval). As seen in Fig. 45.11, individual twitches may also be potentiated after short tetanic stimulation (post-tetanic potentiation). These phenomena are found in both slow and fast motor units, albeit possibly to different extent [18,69].

Catch-like Property of Muscle. Another nonlinear property may have a similar function. Occurring in invertebrate [94] and mammalian muscles [17], the so-called catch-like property implies that the precise temporal patterning of stimuli influences force output over long time spans. As illustrated in Fig. 45.12 for a slow motor unit in the cat [17], force rise during repetitive activation is much faster when the stimulus sequence starts with a much briefer than average interval (here 10 ms; compare trace c with traces a and b). When a brief interval (here 26 ms) is inserted later in c, force suddenly rises in a step wise fashion. Conversely, a longer than average interval in b entails a step wise decrease in force. This phenomenon is particularly pronounced in slow motor units, but is also found in fast units [17]. The precise mechanism underlying the catch-like property is not yet known. Short intervals between successive spikes ("doublets"), which might elicit the catch-like force enhancement, have been observed under various circumstances in humans and animals (e.g., [3,7]) and their potential significance for boosting force output has been discussed controversially. In fact, it appears that they may be particularly effective during muscle fatigue [11,13] (see Sect. 45.7), and doublets seem to occur more often in this condition.

Hysteresis. Post-tetanic potentiation and the catch-like property may also form the basis of the hysteretic relationship between force and activation rate when a muscle or motor unit is stimulated with a sequence of stimuli whose rate is rhythmically (e.g., sinusoidally) modulated [12,73,74,94]. These nonlinear features may be of physiological significance in mitigating the effects of muscle fatigue. In fact, when a motor unit is activated over a long period of time, the force loss during developing fatigue may be temporarily counteracted by a parallel force potentiation [96] (see Chap. 50).

Nonlinear Interactions Between Motor Units. Other forms of nonlinearity may arise from the mechanical interactions of muscles or motor units during their simultaneous activity. The forces contributed by active motor units of a muscle to its overall force do not necessarily summate linearly, but may add up to less or more than the theoretical algebraical sum [21,24,69,76]. Such nonlinear interactions may have aftereffects on the force production of a single motor unit when muscle length is changed or another motor unit is derecruited.

All these phenomena attest to skeletal muscle's profound nonlinearity, which is typical of nonlinearities, is dependent on the particular input, appears in multiform forms, and cannot be described by a single mathematical framework (see Chap. 1). Since many of these nonlinearities also depend on peripheral parameters (see below), their effects are difficult to predict for the central nervous system, (CNS), whose way of coping with them is hardly understood (see Chap. 48).
The same differences are found between the tension–length relations of the cat medial gastrocnemius (pinnated) and soleus (fairly parallel-fibered) muscles. The length-dependency of the active increment curve can in part be explained in terms of the sliding filament model, as illustrated in Fig. 45.15. The upper part (a) shows the dependence of isometric tetanic tension of a single frog muscle fiber on sarcomere length [38]. It exhibits a plateau between 2.0 and 2.25 μm, where maximal tension is achieved. On both sides of the plateau, tension declines with shortening (<2.0 μm) or lengthening (>2.25 μm). The shape of this curve resembles that of active increment (Figs. 45.13, 45.14) and is produced as shown in the lower part of Fig. 45.15b [38]. At long sarcomere length (3.65 μm), actin (solid horizontal bars) and myosin (blue horizontal bars) filaments do not overlap (row 1, this

### 45.5.3 Length–Tension Relation

Not only is the force produced during muscle or motor unit contraction dependent on the pattern of neural input, but it is also a function of the length at which the muscle is held. The twitch forces and tetanic tensions of whole muscles and motor units are all influenced by length in a way described by the length–tension relation.

**Isometric Length–Tension Relation.** Even a passive muscle exerts some force when stretched beyond a certain length, as schematically illustrated by the curve labeled “passive tension”; in Fig. 45.13. This passive resistance to stretch results from minor stretch of the sarcolemmal sheaths and of intermingled connective and tendinous tissues, i.e., from parallel- and series-elastic elements (see Fig. 45.19). When the isometric muscle is tetanically activated at different lengths, the curve labeled “total active force” is obtained. It is also referred to as the “curve of isometric maxima.” Such a curve often displays a local peak at some optimal length $L_o$, which is usually close to the resting length in the body. Subtracting the passive tension from the total active force yields the portion of force contributed by active contraction alone (curve labeled “active increment”). The shape of these various curves depends on muscle architecture, as demonstrated for the rat medial gastrocnemius and semimembranosus muscles in Fig. 45.14a–c [97], where active increment curves are given for both single twitches (stars) and tetani (squares) in parts a and b. The medial gastrocnemius muscle is a pinnated muscle, whereas the semimembranosus muscle consists of fibers running fairly in parallel with the muscle’s long axis. Figure 45.14c compares total active force curves for twitch and tetanic contractions of semimembranosus (1 and 2) and medial gastrocnemius (3 and 4) muscles. The
number referring to that in part a), and hence no force is produced. Shortening the sarcomere from 3.65\(\mu\)m to 2.20\(\mu\)m results in an increasing overlap of the actin and myosin filaments such that the number of cross-bridges and, hence, force production capacity increase proportionally [38,39], until a maximum is reached between 2.20 and 2.25\(\mu\)m (row 2). Further shortening to 2.05\(\mu\)m (row 3) makes actin filaments touch in the middle or even slide past each other (rows 4 and 5), augmenting the resistance to shortening. This effect may be enhanced when myosin filaments touch the Z lines (vertical solid bars, row 5) or even kink (row 6). Application of this model to in vivo muscles is not straightforward, however. There are differences between theoretical tension–length relations derived from this model and experimentally measured relations, e.g., in the human rectus femoris muscle [41]. These differences might be explained by the fact that, while the above

**Isotonic Length–Tension Relation.** Instead of isometric recording, the experiment can be arranged so that the muscle lifts a constant load isotonically from a point on the passive length–tension curve. For instance, in Fig. 45.16 the point PT, on the passive curve PT is the starting point from which a maximal contraction moves an additional load of about 0.1 N to an end point IT, on the curve of

---

**Fig. 45.15a, b.** Dependence of force on sarcomere length (a) and its explanation in terms of the sliding filament model (b). a shows a summary of data obtained on isolated frog muscle fibers made to contract tetanically at different isometric lengths. b shows the configurations of the actin (black horizontal bars) and myosin (blue) filaments at different sarcomere lengths, as indicated by the numbers above each configuration. The numbers to the left refer to the vertical dashed lines in a labeled the same way. (Adapted from [38], Figs. 12a and 14b)
product of load multiplied by the distance moved and is maximal in some intermediate range of load and muscle length, falling off toward the extremes.

### 45.5.4 Force–Velocity Relation

**After-Loaded Contraction.** When a muscle is tetanically stimulated at isometric length and then, by removing a stop, allowed to shorten against a set load (after-loaded contraction), the muscle initially shortens at a velocity maximal for that load (see Fig. 45.17b). However, as the muscle shortens it slows down, because the force it can produce decreases with shortening according to the length–tension curve. Ultimately, a steady state length is reached corresponding to that point on the length–tension curve which yields the force that corresponds to the load. Another important point is made in Fig. 45.17a: the greater the load, the longer the latency from the start of stimulation to the start of shortening and the smaller the initial shortening velocity. The velocity $V$ can be expressed in mm/s or as muscle lengths or sarcomere lengths per. The force $P$ can be expressed as g or kg or N or these units per

---

**Isometric Maxima.** The entire curve IT is obtained by other loads with different starting points on PT. By contrast, a maximal isometric contraction would augment the force from PT to point IM on the curve of isometric maxima, IM. As seen in Fig. 45.16, IM lies above IT.

**Mixed Contraction.** Many contractions are of a mixed nature. For instance, when an additional load is to be lifted from a point PT, on the passive length–tension curve (Fig. 45.16), the contracting muscle(s) must first produce, under fairly isometric conditions, the force corresponding to the additional load before this can be elevated. The first part of the contraction then corresponds to an isometric contraction. The force increase ends on the curve of isometric maxima if the load exceeds the available maximal force at this muscle length. If it does not, the isometric contraction is followed by an isometric contraction with muscle shortening. This ends in $X_1$ on a curve connecting IT and IM, as indicated in Fig. 45.16 (see legend). On the other hand, the reverse order of partial contractions is seen when a load is first moved isotonically and then hits a mechanical stop. This sequence of events ends in $X_1$ on another intermediate curve, as shown in Fig. 45.16. Hence, the length–tension diagram is specific to the type of contraction. With mixed contractions, the work performed corresponds to the

---

**Fig. 45.16.** Length–tension relations for isometric, isotonic, and mixed contractions of an isolated frog muscle. The passive curve (rightmost) is labeled PT. Starting at a point PT, on PT, a maximal isometric contraction ends in IT, and a maximal isometric contraction in IM. Starting from various points on PT, such contractions lead to points on the curves of isometric maxima (IT, blue curve) and isometric maxima (IM), respectively. When lifting, from a point PT, on PT, an additional load to the one corresponding to PT, the muscle must first contract isometrically (upward dashed line) to match the additional load before it shortens isotonically, a movement which ends in $X_1$ on a curve connecting IT and IM. Conversely, when the muscle initially passively carries the load corresponding to point PT, upon maximal activation it shortens and, when meeting a stop, isometrically increases force towards a point X, on another line connecting IT and IM. Thus, mixed contractions of various sorts end on curves between those of isotonic and isometric maxima. (Modified from [14], Fig. 239)

**Fig. 45.17a,b.** “After-loaded” isotonic tetanic contractions. The muscle is stimulated indirectly via its nerve. A high-rate (above fusion rate) stimulus sequence is indicated by the black bar. In response to this stimulus, muscle force rises (second trace from bottom), first isometrically, until it matches the fixed load and starts moving it isotonically (blue trace). The initial velocity of this movement is given by the slope of the movement trace, as emphasized by the dashed blue line. A When loads are varied from low to high, the start of the movement phase is successively delayed and the slope declines. (Redesigned from [58], Fig. 9.7)
Another important point emerging from the data in Fig. 45.18 is that the force–velocity relation depends on the degree of muscle activation, here in terms of the rate of activation. In addition, for fast muscles, the force–velocity relation is the same as that for slow muscles at birth, but is scaled up postnatally by a factor of $2.5-3$ (increase in speed of shortening/sarcomere for a given fraction of maximal load), whereas slow muscles (soleus) retain their initial relation [22]. Under certain conditions, there are more significant deviations of the measured points from the Hill relationship, even for muscle shortening [26].

Shortening velocities throughout the animal kingdom can vary by a hundredfold or even several thousandfold if smooth muscles are taken into consideration. In contrast, contractile forces do not vary very much, not even when standardized with respect to myosin amounts. This implies that such variations in myosin properties as are encountered, mainly in its ATPase, are correlated with variations in contraction velocity, but may not be similarly correlated with differences in force. When animals of different sizes belonging to taxonomically or behaviorally similar body types are compared, it is found that the contraction speeds (in muscle lengths or sarcomere lengths per s) decrease markedly with increasing body sizes: the elephant trots more slowly than the mouse scurries. Moreover, the same organism may contain muscles or fibers of different speeds. Mammalian limb muscles usually contain “fast”-twitch (F) and/or “slow”-twitch (S) muscle fiber types, the speeds of which often differ by a factor greater than 3 within the same body or muscles (see Table 45.1, Fig. 45.9; Chap. 49). The heart also follows a reciprocal size rule and differs about threefold between athyroid and hyperthyroid forms. The size dependence may have different values for different muscles.

A Muscle Model. In the experiment shown in Fig. 45.17 the initial isometric force development is accompanied by a shortening of the contractile apparatus and the compensatory lengthening of a passive elastic component in series with the contractile elements, thus storing potential energy that may later be released upon a load (see Fig. 45.19). The serial elasticity can reside in deformable components in the experimental setup, which would be artificial and must be eliminated by good experimental design. Another series-elastic part is found in the extensibility of the tendons and aponeuroses; this part is functional, but not at the molecular level. At this level, there may be serial compliances within the force-generating mechanisms themselves, due either to the extensibility of the exposed parts of the I filaments, to the liquid-crystalline deformability of the A rods, or to the distortion of the cross-bridges. In certain forms of natural movements, for instance running or hopping, the series elasticity may be of immense importance [2]. Kangarooos are particularly good at utilizing the potential energy stored in their Achilles tendons during landing when taking off for the next leap. There are also elastic structures parallel to the contractile apparatus (see Fig. 45.19). These can be the sarcolema or passive, longitudinally distributed filament structures. A major compo-

\[
(P + a) \times (V + b) = (P_v + a)b = (V_{max} + b)a = \text{constant}
\]  

(45.1)

where $a$ and $b$ are constants, $P_v$ is the isometric tension at zero velocity, and $V_{max}$ is the maximal velocity attained with no external load. Equation 45.1 represents a rectangular hyperbola [56].

Also illustrated in Fig. 45.18 are extensions of the relations into the region of eccentric contraction ("lengthening," left of the ordinate). As can be seen, when active muscles are forcefully made to lengthen instead of allowed to shorten, the relation between velocity and force becomes more complicated than expected from a simple extrapolation of Hill’s relation (Eq. 45.1).
Fig. 45.19. Mechanical muscle model. The model depicts how a displacement of the load leads to passive deformations. The parallel-elastic element consists of sarcolemma and more or less connective tissue, as well as possible internal components, such as extension by sliding of myosin molecules within the A rods. The series-elastic element would, for example, contain the extensibility of the I filaments. The terms “parallel” and “series” are used to distinguish these elements from the contractile element, which is a composite of variable molecular components in the sarcomere. \( P \), force; \( V \), velocity; \( a \) and \( b \) are constants.

Of this filament system is titin, which connects myosin to the Z disk (see Chap. 46, Fig. 46.4) and accounts for over 10% of the total muscle protein. Nebulin, another intermediate filament system in skeletal muscle, is located only in conjunction with the thin contractile filaments (actin) and probably does not contribute to passive elasticity (see Chap. 46). The mechanical muscle model shown in Fig. 45.19 is one among several proposed to represent mechanical muscle properties. Others take into account the fact that muscle also exhibits viscous and thixotropic properties. Thixotropy implies a motion-dependent viscosity, such as is seen in paint, which becomes less viscous upon stirring. These dynamic properties are not represented in the mechanical muscle model of Fig. 45.19, but the contractile element is assumed to account for the hyperbolic force-velocity relationship.

### 45.6 Energetics of Muscle Contraction

This field, the foundations of which were laid by Helmholtz [87], Fick [33], and Hill (from 1912 onwards) and which was correlated with biochemical work initiated by Meyerhof [65] and others (from 1920; see [68]), is of great importance in physiology, since it is concerned with the fundamental problem of how cells utilize chemically generated energy in performing their functions. Muscles are useful for such research because of the magnitude of their activity and on account of the ease with which they can be switched on and controlled. Between rest and full activity, the energy flux can vary 100- to 1000-fold or more. The primary purpose of skeletal muscle is to convert chemical energy into work. However, inevitably this is accompanied by the dissipation of energy in terms of heat production. We will address these issues in turn.

#### 45.6.1 Work and Power

**Mechanical Energy.** When a muscle contracts while moving the point of action of a force, it performs work (mechanical energy), which is physically defined as the product of force and distance moved (unit N × m). In real body functions, this can consist in lifting objects to a higher level (or the reverse i.e., negative work), including the locomotory work of lifting our own bodies, accelerating the body and keeping it moving against frictional forces, or accelerating a mass, as in throwing a ball or javelin. Work divided per unit time defines power, which consequently can also be defined as force multiplied by the velocity of movement.

**Isometric and Unloaded Isotonic Contractions.** Consequently, no work is done during isometric contractions because there is no movement; the same applies during unloaded isotonic movements, because force equals zero. In addition, power is zero at these limits [56]. If the force exerted remained constant during the movement, determining the work performed would be straightforward. However, as is evident from the length-tension and force-velocity curves, force usually changes during movement; otherwise, when force is kept constant, length would not change linearly with time. For instance, the length-tension relation (see Figs. 45.13-45.15) indicates that, within the physiological range, muscle force declines with decreasing length. Hence, the work performed during (slow) shortening must be evaluated in terms of the integral below the length-tension curve within the limits of long (initial) and short (final) lengths. Between the limits specified above, e.g., isometric and unloaded isotonic contractions, the work performed by muscle during the contraction phase of isotonic twitches varies greatly with load according to a function that looks like an inverted parabola peaking at a load about halfway between no load and isometric load [56]. Power as the product of force and (initial) shortening velocity peaks at about 0.3 times the isometric force when shortening velocity also is about 0.3 times the maximal unloaded velocity [58].

#### 45.6.2 Heat and Work

It is readily apparent from everyday experience that muscular exercise is accompanied by heat production. This results from the fact that the chemical energy available to the muscle can only partially be converted into mechanical
energy (work), while the rest is lost in heat. According to
the law of the conservation of energy, the chemical energy
liberated, \( E \), is the sum of work, \( W \), plus heat, \( H \):

\[
E = H + W \tag{45.2}
\]

**Components of Heat.** How \( E \) is divided into \( H \) and \( W \) is a
matter of mechanical conditions and contraction forms.
This has been detailed for work in the preceding section,
but it also applies to the heat term per se, which can be
droken down into various components. Early results were
obtained from experiments done on frog muscles (e.g.,
[30,31,46]). During the first tens of milliseconds of an
isometric tetanus, heat is released at a high rate. This fairly
constant activation heat has been related to the ATP splitting
necessary for the \( \text{Ca}^{2+} \) release and uptake by the
sarcoplasmic reticulum [49,81]. This component rapidly
falls off to a lower maintained heat, referred to as main-
tenance heat. If the muscle is allowed to shorten, an addi-
tional shortening heat appears that is approximately
proportional to the distance moved. This may be supple-
mented by a component during relaxation (relaxation
heat), particularly when the load does work on the muscle.
Finally, after contraction and relaxation, there is a pro-
longed recovery heat, reflecting oxidative processes in the
mitochondria by which the ATP and/or CrP used are being
slowly resynthesized (see below). This process is especially
pronounced in glycolytic muscle fibers that rely on anaerobic
energy supply. Apparently, then, some heat components
depend on mechanical conditions, which will now be
discussed in more detail.

**Isometric Contractions.** Under isometric conditions,
muscle activation leads to no movement and, hence, no
work. During a tetanus, the energy released in form of heat
\( (H) \) can be empirically described as follows [47]:

\[
H(t) = (20-40 \text{ mJ/g}) \left[ 1 - \exp(-1t) \right] + (14 \text{ mW/g}) t \tag{45.3}
\]

Note that \( H(t) \) grows with time \( t \). For comparison, the
energy \( E \) liberated by high-energy phosphate breakdown
has turned out to be as follows:

\[
E(t) = (15 \text{ mJ/g}) \left[ 1 - \exp(-1t) \right] + (14 \text{ mW/g}) t \tag{45.4}
\]

The difference in the first right-hand terms of Eqs. 45.3 and
45.4 indicates that during isometric contraction another
energy-producing process must occur, which has been
hypothesized to involve \( \text{Ca}^{2+} \) binding to troponin and
parvalbumin [47].

**Isotonic Contractions.** Fenn [30,31] found that during
isotonic twitches the total energy liberated, \( E \), could be
described as follows:

\[
E = I + kW \tag{45.5}
\]

where \( I \) is the heat developed under isometric conditions
and \( W \) the external work done, with \( k \) being a constant
close to unity (see [48]).

By contrast, Hill [42] found that in isotonic tetanic con-
tractions an additional heat term appeared in excess to the
work done. The energy \( E \) released up to a time \( t \) into the
contraction was as follows:

\[
E = M + \alpha x + W \tag{45.6}
\]

where \( M \) is the maintenance heat, \( x \) the distance moved, \( \alpha \)
a coefficient; \( \alpha x \) thus represents the shortening heat. As
compared to Eq. 45.5, therefore, the shortening heat here
appears in addition to the work performed, something
which has been corroborated by others [4,48]. It is
approximately proportional to the distance moved, except
- due to its load dependence - at high shortening velocities
[42,45,47]. According to a more recent detailed analysis,
for the shortening phase of isotonic twitches, energy
liberation can be split into four terms [50]:

\[
E = A + f(P,t) + \alpha x + W \tag{45.7}
\]

\( W \) is again the work performed, and \( A \) is the activation heat
(see above). The function \( f(P,t) \) describes the fact that
there is an energy turnover that depends on the force \( P \)
exerted and the time \( t \) of its maintenance. The sum of \( A + f(P,t) \)
in a tetanus thus denotes the isometric heat produc-
tion of a muscle developing a peak force of \( P \). Its rate
depends notably on the repeat or fusion frequency. This
rate is higher the faster the muscle is, because the fusion
frequency increases; it also increases with temperature.
Thus, slow muscles, particularly smooth muscle, are more
economic with regard to force maintenance. The term \( \alpha x \)
is again the shortening heat, but \( x \) is indexed with \( F \) be-
cause the heat has been determined as the “difference be-
tween the heat produced when shortening occurs and that
produced in an isometric contraction which develops the
same peak force and performs the same amount of internal
work” ([50], p. 678). It brings to mind the constant \( a \) in the
force-velocity relations (Eq. 45.1) and is of similar magni-
tude; however, the two coefficients are not identical. The
last three right-hand terms in Eq. 45.5 describe the variable
energy associated with the interactions between myosin
and actin filaments and resulting from the breakdown of
ATP and/or CrP.

The four right-hand terms in Eq. 45.7 can be separated
experimentally. When the muscle is stretched to a
sarcomere length at which the actin and myosin filaments
do not interact, then there is no active force, no shortening,
and hence no work. Only \( A \) remains and has thus been
determined both thermally and chemically [50]. Under iso-
metric conditions, there is \( A \) and \( f(P,t) \), but no shortening
and hence no work. At zero load, there is \( A \) plus a maximal
manifestation of \( \alpha x \).

**Dependence on Muscle Length and Shortening Velocity.**
Energy liberation varies with muscle length and velocity of
shortening. When caution is exercised in determining heat
production during dynamic muscle length changes (see
[47]), the rate of total energy liberation \( E = H + W \) can be
Fig. 45.20. The instantaneous rate of muscle energy liberation by frog skeletal muscle, contracting at 0°C, as a function of relative shortening velocity and muscle length. Energy liberation is expressed relative to the maximal force ($P_o$) at a sarcomere length of 2.2 μm and relative to maximal velocity of shortening ($V_{max}$). (Modified from [47], Fig. 1)

calculated to depend on muscle length and shortening velocity, as shown in Fig. 45.20.
For instance, when a muscle shortens at $V_{max}$ by 15% of its initial length, the heat produced is three times as much as during isometric contraction over the same time span; when shortening by the same amount at 0.1 $V_{max}$, the muscle produces 30% more heat [47].

45.6.3 Efficiency

With regard to energy conversion, a question of interest is the efficiency of muscle as a bioenergetic engine or transducer. The term “efficiency” was first used in connection with the theory of heat engines working in a Carnot cycle, as treated in thermodynamics. The issue involved an attempt to understand the conversion of heat into work and thus to improve the performance of the steam engines that were coming into use. For this particular case, efficiency was given as follows:

$$E = \frac{W}{Q} = \frac{(T_1 - T_2)}{T_2}$$

in which $W$ is the work performed, $T_1$ and $T_2$ the temperature of the hot and cold reservoirs, and $Q$ the heat transferred to the cold reservoir.

This reference to combustion machines is interesting because the situation in muscle is completely different. It works under nearly isothermal conditions, implying that no heat can be transformed into mechanical work [92]. Efficiency is thus simply defined as that part of the total energy released that is converted into work or, since the total energy is composed of work and heat, as follows:

efficiency = work/(work + heat)

Estimates for the time during contraction lead to a maximal efficiency of the order of 0.4 in frog and 0.8 in tortoise muscle, which is very high. For a heat engine to be equally efficient, it would, with $T_1$ being 37°C = 310 K, involve a value for $T_2$ on the order of 240°C; such temperatures are nowhere observed and would be incompatible with higher life. Therefore, muscle is quite efficient indeed, allowing physiological action at a low cost in nutrients. However, efficiency is not only related to the initial process, but also to the oxidative recovery as well, which sooner or later has to take place. This would give a “metabolic-energetic” efficiency on the order of 0.2 and 0.35 for the above two muscles, respectively. This is the maximum efficiency achievable with shortening at a speed of approximately 0.2 times maximal velocity [58].

Efficiency depends upon the velocity of movement, as is evident from everyday experience. Let us examine the work involved in bailing out water. This can be done using a spoon, which is moved quickly and therefore inefficiently. At the other extreme, it can be done using a bucket of huge dimensions, which can only move very slowly; however, the maintenance heat is high in this case. In practice, we choose an intermediate value of the bucket and its load (this is the point of many tools). Each actual work process involving muscle has a velocity–efficiency relation. During tetanic isotonic contraction, this lies at about 0.2 times the maximal shortening velocity $V_{max}$ [44].

45.6.4 Energy Source

Having discussed the output side of the energy balance equation (Eq. 45.2) at some length, we now turn our attention to the energy source. Ultimately, all chemical energy is
derived from food and its breakdown. Chemical energy reaches the muscle in the form of glucose and fatty acids and may be stored as glycogen. These substances are metabolized to the primary energy supplier that drives many cell processes, ATP. The supply of ATP in skeletal muscle is secured in three ways operating on different time scales:

- Phosphorylation by CrP, which is a short-term store of high-energy phosphate
- Anaerobic glycolysis (medium-term supply)
- Aerobic respiration (oxidative phosphorylation) of glucose and fatty acids to CO₂ and water (long-term supply).

**Creatine-Phosphate.** In muscle, a second high-energy phosphate carrier, CrP, represents an intermediate energy store or buffer that is used to replenish ATP when this is being dissipated during muscle contraction. CrP is immediately available, but quickly exhaustible. Whereas 5 μmol ATP/g muscle provide for approximately ten contractions, 25 μmol CrP/g muscle enables another 50 contractions to occur before it is exhausted. The CrP reserve thus enables short-term, maximum efforts to take place over some 10–20 s (e.g., 100 m sprint) or, together with ATP, a minute of brisk walking, amounting to about 16kJ [58]. The ATP concentration does not significantly decrease during these bouts of muscle exercise, while CrP does (see below).

Via the Lohmann reaction, CrP and ATP are in equilibrium:

\[
\text{ADP + CrP} \leftrightarrow \text{ATP + Cr}
\]

**creatinine phosphotransferase**

The actual demonstration of a use of ATP or CrP was provided when several types of fast-freezing methods were developed, by which a muscle could be frozen rapidly at arbitrary moments in the contraction cycle. The muscles were frozen by plunging them into liquid propane or by compression between copper blocks at liquid N₂ or helium temperature, fixing their chemical composition with a time resolution of milliseconds. Davies and colleagues [19] used 1-fluoro-2,4-dinitrobenzene (FDNP) to block the Lohmann enzyme, creatine phosphotransferase, so that ADP could not be rephosphorylated after the breakdown of ATP. In an isotonic twitch, the frog muscle lost an average of 0.22 μmol ATP/g muscle. With a heat production of 34 kJ per mol ATP during hydrolysis, this loss amounted to 7.5 × 10⁻³J, whereas the work done by the muscle amounted to 1.7 × 10⁻³J. ATP breakdown could thus well account for the work done, excess energy being dissipated as heat.

The breakdown of CrP during contractions has also been demonstrated by comparing its concentration in stimulated and unstimulated muscles and preventing its resynthesis by inhibiting glycogen breakdown by iodoacetate [58]. The stimulated muscle then contains less CrP than the unstimulated muscle. While CrP is thus undoubtedly implicated in energy supply for contraction, a certain amount of “unexplained energy” remains [47]. By comparing energy output (work plus heat) and CrP breakdown under various conditions, Wilkie [93] found that the two measures are linearly related with a proportionality constant of 46.4 kJ per mol CrP. However, CrP hydrolysis should yield only 32kJ. Part of this unexplained energy may be accounted for by Ca²⁺-binding processes associated with contraction [47].

**Anaerobic Glycolysis.** Since CrP is readily exhaustible, further processes to replenish the ATP supply are needed. With some delay, anaerobic glycolysis is the first to set in. Reaching its maximum about 30s after the start of muscle exercise, it works under anaerobic conditions. Glycogen in muscle and liver provides a variable, medium-term energy store on the order of 4000 kJ, allowing several hours of moderate exercise [58]. Glycogen is metabolized via glucose-6-phosphate to lactic acid, yielding only two ATP molecules per unit of glucose [25]. A much more productive pathway is the aerobic pathway via the citric acid cycle (Krebs cycle, [11]), yielding 38 ATP molecules [25], which in fact sets in after about 1 min and replaces anaerobic ATP production during light work. However, during heavy exercise, the anaerobic glycolysis continues in parallel, leading to an accumulation of lactic acid (and ensuing acidosis) and other metabolites such as inorganic phosphate (Pᵢ), which limits exercise duration (see Sect. 45.7). As long as anaerobic processes continue, muscle keeps accumulating an oxygen debt for two reasons. Since CrP is depleted to low concentrations, it needs to be reconstituted after exercise. This occurs through phosphorylation by ATP (Lohmann reaction), which can only proceed when enough ATP is generated by oxidative phosphorylation during recovery. This portion of the oxygen debt may amount to as much as 41. An even greater amount (up to 201) may be contributed, under heavy exercise, by the production and oxygen-dependent elimination of lactate in liver and heart [78].

**Aerobic Exercise.** Long-term exercise is only possible under aerobic conditions, under which glucose and fatty acids are metabolized via the citric acid cycle [1]. The body’s adipose tissues constitute a long-term fat store on the order of 300,000kJ [58]. The glycogen content of skeletal muscle is not sufficient to supply the required amounts of glucose; instead together with the fatty acids, these have to be delivered via the circulation. The same applies for the required oxygen, because 16 mol O₂ is needed for the production of 1 mol ATP and there is only a small reserve bound to myoglobin (about 0.4 l for a few seconds of maximal exercise [58]). These forms of exercise then require adjustments of circulatory, cardiac, and respiratory functions (see Chap. 108). A stationary equilibrium between the production and breakdown of ATP must be reached in order not to let the system be run down during fatigue (see below). ATP and CrP concentrations are therefore fairly constant (approximately 5 mmol/l and 30 mmol/l, respectively).

**Other Reactions.** There are, of course, numerous other biochemical reactions in muscle (e.g., [47]). Given the fact that, when going from rest to full activity, a muscle in-
increases its energy turnover 20- to 100-fold or more (see below), 65%–80% of the ATP used in an isometric tetanus is split by the actomyosin ATPase involved in contractility and its on-off control [47]. Distinct, but lesser reactions include the following [47]:

- (Na⁺-K⁺) pump activity, using about 10% of the isometric ATP hydrolysis rate
- Ca²⁺ pump activity in the sarcoplasmic reticulum, estimated to account for approximately 20%–35% of the ATP used in maintained isometric tetanus
- Phosphorylation of myosin light chains LC₇, using about 5% of the ATP in a 5-s tetanus at 0°C [5,6].

### 45.7 Muscle Fatigue

Muscle fatigue is a phenomenon of immense practical importance in normal individuals, particularly in physically demanding occupations and in athletic competition, as well as in patients with various types of disorders affecting the CNS or peripheral neuromuscular apparatus. Whereas the first part of this statement is common everyday experience, the latter is not as evident because other phenomena and symptoms often supersede fatigue. However, in patients with upper motoneuron disease, for example after stroke, multiple sclerosis, and spinal cord injury, the fatiguability of the tibial anterior muscle is enhanced, probably resulting from conversion of many fatigue-resistant into fatigable muscle units after prolonged disuse [61,66], although there are reports to the contrary (see [29]). In addition, in the rare, but particularly interesting cases of mitochondrial myopathies leading to lactacidosis [27], symptoms of severe exhaustion, weakness, and muscle fatigue during exercise are predominant features. Muscle fatigue is also an important limiting factor in situations when functional electrical stimulation (FES) is used to help restore motor function following neurological damage, e.g., in paraplegics (for references see [11]). Despite its ubiquity, the mechanisms contributing to muscle fatigue have not yet been fully elucidated (e.g., [29,34,85,91]). This is due not only to the lack of a unanimously accepted definition (see [9,15,20,29]), but also to the fact that multiple processes are involved, encompassing various mechanisms at different levels, from higher-order CNS structures to electrical and biochemical alterations within muscle fibers (e.g., [21,29]). Muscle fatigue may be defined as “... any reduction in the force-generating capacity (measured by the maximum voluntary contraction), regardless of the task performed” [10]. It should be noted that decline in force production capacity is usually accompanied by a reduction of contraction and relaxation speed, resulting in a loss of power [91]. These changes during fatigue have very different time courses depending on the experimental protocols used. Thus, during continuous high-frequency stimulation, fatigue develops rapidly, and the underlying mechanisms have a specific pattern (high-frequency fatigue). In relative terms, force declines much more slowly during maximal voluntary contractions, which is primarily due to neural compensatory mechanisms (see Chap. 50). Similarly, slow changes occur during repeated intermittent tetanic stimulation [91]. Fatigue develops more dramatically during dynamic exercise involving shortening contractions than during isometric contractions [55]. Differences are also apparent for the recovery phase, indicating that different mechanisms induce fatigue. For example, after long-lasting, low-frequency tetanic stimulation, force remains depressed over long periods (low-frequency fatigue) [91]. Muscle fatigue is therefore a multi-faceted phenomenon.

The major sites at which fatigue may develop can be summarized as follows [8,37]:

- Inputs to higher motor centers
- Inputs to lower motoneurons in brainstem and spinal cord
- Motoneuron excitability
- Neuromuscular end plate
- Excitability of the sarcolemma
- Excitation–contraction coupling
- Contractile mechanisms
- Metabolic energy supply.

The relative importance of these sites for muscle fatigue has been debated for a century [34,91]. However, as noted, muscle fatigue is a multifactorial process, and therefore the relative importance of the multiple factors and potential sites involved likely depends on the fiber-type composition of the contracting muscle(s), the intensity, type, and duration of muscle activity, and the state of training and fitness [34]. This even applies to changes, during fatigue, in processes beyond the neuromuscular junction (the last four items in the above list), which are believed to be the primary sites of genuine muscle fatigue. Thus, fatigue can result from:

- Metabolic changes
- Disturbances in excitation–contraction coupling
- Changes in cross-bridge function
- Muscle injury.

**Metabolic Factors** [15,34,55,91]. When a muscle is maximally activated from rest, its metabolic rate increases dramatically, this increase being specific to animal species, muscle fiber type, and form of exercise. Thus, the ratio of maximal to basal metabolic rate may vary from approximately 20 in slow mammalian muscle to approximately 500 or more in fast frog muscle [91]. This causes changes in intra- and extracellular metabolite and ion concentrations which may influence muscle fiber function. Factors influencing changes include preparation, type of fatiguing stimulation, aerobic versus anaerobic conditions, isometric versus shortening contractions [55,62]:

- Intracellular ATP concentration does not change considerably, because ATP is immediately reconstituted
through the Lohmann reaction (see above); typical changes are from 6 to 4.6 mmol/l [62]; as a consequence, CrP may change from approximately 30 mmol/l to 12 mmol/l, where the change is greater in dynamic than isometric exercise [55].

- As a consequence of increased CrP breakdown, creatine and inorganic phosphate P; concentrations increase; P; typically increases from 5 to 25 mmol/l [62], where the increase is larger in dynamic (shortening) than isometric contractions [55].

- In the absence of sufficient oxygen (particularly during strong contractions occurring blood flow, i.e., greater than 30% maximal voluntary contraction), pyruvate is metabolized to lactic acid, leading to intra- and extracellular acidosis; the pH typically decreases from about 7.0 to 6.5 [62], this change again being greater in dynamic than in isometric contractions [55].

- Changes in intra- and extracellular Na⁺ and K⁺ concentrations during prolonged (in particular high-frequency) activation; of major importance is the fact that the extracellular K⁺ concentration may rise from approximately 5 mmol/l to 10 mmol/l or more [63]; this may lead to significant depolarization of the sarcotubular [80].

- Decreases in sarcoplasmic free Ca²⁺ concentration, which may have a number of causes.

- Rise in sarcoplasmic Mg²⁺ concentration, which may inhibit Ca²⁺ release from the sarcoplasmic reticulum [91].

- Glycogenolysis and glycolysis increase; after long-lasting exercise at moderate to high work loads, glycogen becomes depleted, and this lack may contribute to fatigue although the precise mechanisms is not known.

Some of these changes may affect various processes involved in excitation–contraction coupling and force production (see below).

**Disturbances in Excitation—contraction Coupling.** Such disturbances (see Fig. 45.5) may result from the following [34,91]:

- Altered excitability of the sarcotubular and/or T-tubular system (Fig. 45.5, sites 1 and 2)

- Impaired coupling between T-tubular charge sensor and sarcoplasmic Ca²⁺ release channel (Fig. 45.5, site 3)

- Inhibition of the sarcoplasmic Ca²⁺ release channel (Fig. 45.5, site 4)

- Depression of Ca²⁺ reuptake into the sarcoplasmic reticulum (Fig. 45.5, site 5).

According to the membrane hypothesis of muscle fatigue, the action potential conduction along the sarcotubular and into the T tubules is compromised [34,91]. During ongoing high-frequency stimulation (high-frequency fatigue), K⁺ may accumulate and Na⁺ may be depleted extracellularly, and vice versa intracellularly. These changes in ionic gradients may lead to depolarization, inactivation of Na⁺ channels, reduction in action potential amplitude and conduction velocity, and spike broadening. An indirect sign of action potential changes is a shift of the EMG power spectrum to lower frequencies [23]. Due to diffusion restrictions, this effect is particularly pronounced in the deeper regions of the T tubules so that the action potential may fail to invade them completely. The effect may be enhanced by a metabolically induced failure of the sarcotubular (Na⁺-K⁺) pump to maintain the ionic gradient due to increased extracellular K⁺ concentration and membrane K⁺ conductance. All the above changes decrease Ca²⁺ release from the sarcoplasmic reticulum, especially in interior regions of the muscle fiber. However, during moderate activation, these effects may be mitigated by an increased rate of the sarcotubular (Na⁺-K⁺) pump; the electrogenticity of this pump also counteract depolarization [63]. Since ionic gradients are rapidly reestablished within 1–2 s of rest, this hypothesis cannot account for the slow recovery of other forms of fatigue [34].

In other forms of fatigue (e.g., during intermittent tetanic stimulation), action potential conduction appears to be unimpaired. Here, the coupling between the T-tubular voltage sensors and Ca²⁺ release from the sarcoplasmic reticulum may be disturbed. Possible reasons for this include the following [91]:

- Desensitization of voltage sensors to depolarization

- Desensitization of Ca²⁺ release channels to voltage sensor signals

- Reduction of Ca²⁺ channel opening probability.

While there is as yet no indication that the tubular charge sensors are sensitive to metabolites, the sarcoplasmic Ca²⁺ release channels might be. Low ATP concentration slows Ca²⁺ release, but ATP does not change much during fatigue. IP₃ may have a role, but this is not yet clear.

Another cause of fatigue may be inhibition of the sarcoplasmic Ca²⁺ release channel, possibly caused by an increase in intracellular H⁺ concentration. It has been found for some time that lactic acid is produced during strong muscular activity, particularly by fast-contracting fibers. However, it is now believed that not lactic acid per se, but the associated increase in H⁺ concentration is responsible for fatigue. Low pH has been shown to have a number of depressant effects on the Ca²⁺ induced force production, from sarcoplasmic Ca²⁺ release to the number of active cross-bridges during high-force contraction [34]. In addition, during high-force activity, P; increases intracellularly and inhibits a number of processes. High-energy phosphates (ATP and CrP) do not appear to play an important role.

There is also some indication that sarcoplasmic Ca²⁺ reuptake by the ATP-dependent pump is reduced by metabolites, which would result in a diminished Ca²⁺ content of the sarcoplasmic reticulum and reduced Ca²⁺ release upon activation.

**Changes in Cross-Bridge Function.** The Ca²⁺ sensitivity of the myofibrils may be reduced due to the following factors [91]:

- Desensitization of voltage sensors to depolarization

- Desensitization of Ca²⁺ release channels to voltage sensor signals

- Reduction of Ca²⁺ channel opening probability.
• Competition of $H^+$ for $Ca^{2+}$ binding sites on troponin C
• Reduction of $Ca^{2+}$ sensitivity by increased $P_i$

These changes are expressed by a shift of the sigmoidal $[Ca^{2+}]$–force relation (see Chap. 46) to higher $Ca^{2+}$ concentrations. Moreover, the maximal $Ca^{2+}$-activated force is reduced by intracellular $pH$ decreases and $P_i$ increases, most of this reduction being due to a decrease in force production per cross-bridge. For example, a fall in $pH$ from 7.0 to 6.5 and an increase in $P_i$ to 15 mmol/l depress maximum force to 50% [62].

**Muscle Injury.** Prolonged endurance and high-force exercise may result in structural changes in muscle such as disrupted sarcomeres and swollen sarcoplasmic reticula and mitochondria. This may lead to functional impairment, although the precise mechanism is not known [34]. These various factors may play different roles under different circumstances. This implies that there is most likely no single cause of muscle fatigue, but a plethora of causes. Whatever the causes responsible for muscle fatigue, such fatigue poses a problem to the CNS in organizing movement and posture. This issue will be dealt with in Chap. 50.

**45.9 Conclusions**

The following conclusions may be drawn:

• Skeletal muscles move skeletal segments with respect to each other or hold them in place. In either case, they generate force by means of a “contractile” apparatus.
• In addition to force, two further outputs are of importance during muscle contraction: electrical excitation, as measured by the EMG, and heat, as readily apparent from everyday experience. The EMG is used in a number of ways in research and the diagnosis of neurological diseases. Heat production is less significant in the clinical context, but poses a serious problem for thermoregulation.
• Elucidation of the anatomy and physiology of the contractile apparatus has been a matter of intense research for about 150 years. The structure of the molecules involved in the contraction process is now well known (myosin, actin, troponin and tropomyosin). The interaction of myosin and actin filaments during the contraction process is assumed to take place according to the sliding filament theory, i.e., the elongated myosin and actin filaments slide past each other while the myosin heads cyclically bind to the actin filaments.
• The molecular mechanisms underlying the contractile process result in a number of properties peculiar to macroscopic muscle. Muscle contraction can take various forms depending on the activation (excitation) patterns, muscle, length, and its change. A single activation results in a twitch, repetitive activation in more or less fused contractions (added twitches) depending on the temporal spacing of the activations. Activation history-dependent effects are reflected in nonlinear phenomena such as twitch potentiation and the catch-like property. The forces produced depend on the length of muscle, yielding characteristic nonlinear tension–length relationships, and on the velocity of shortening or lengthening, yielding nonlinear force–velocity relationships.
• Metabolism is closely coupled to muscle performance. Only part of the chemical energy available in the form of high-energy phosphates can be converted into mechanical work, the rest being dissipated as heat. Various portions of heat associated with different subprocesses of the contraction can be distinguished: activation heat, maintenance heat, shortening heat, and recovery heat. The ultimate chemical driving reaction is the breakdown of ATP, whose reconstitution may take various forms:
  • rephosphorylation by CrP, anaerobic glycolysis, or aerobic respiration (oxidative phosphorylation). The parts played by these three processes vary depending on the nature of muscle exercise.
• Muscle fatigue is a multifactorial process occurring at a number of different sites, whose relative importance depends on the type, intensity, and duration of contraction.

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