Force Generation for Locomotion of Vertebrates: Skeletal Muscle Overview

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Abstract—**Locomotion is essential for vertebrate survival. Forces required for movement are generated by skeletal muscle. Skeletal muscle shortening and/or force generation occur via parallel sliding of two protein filaments: actin and myosin. This is driven by cross-bridge cycling, where elementary length changes of 5.3 nm and unitary forces of 1.7 pN are fueled by conversion of chemical energy, stored in the form of ATP, into a change in myosin protein configuration.**

The range of force and length changes of a muscle are determined by factors such as muscle cross section, fiber angle, tendon attachment and lever geometry, but also by the metabolic pathways available for ATP synthesis and by enzymes involved in cross-bridge cycling. Regardless of structural differences, muscle mechanical activity is affected by the extent of actin and myosin filament overlap, and force output can be graded by selective recruitment of motor units and/or by variation of force output from individual units.

The cost of locomotion is further determined by the environment and form of movement. Swimming is the most cost-effective form of translocation whereas terrestrial movement is the most expensive. Still, the energy efficiency of vertebrate skeletal muscle activity is up to 0.45, and this complex system will inevitably serve as a reference point for novel actuator technologies.

Keywords—**muscle structure, muscle function, force regulation**

I. Introduction

Locomotion is a vital function for vertebrates, required for systems maintenance, regeneration, reproduction and protection. This includes not only translocation, but also the postural basis for stance and stability.

The foundation for the build-up and regulation of force for locomotion is provided by skeletal muscle. Other muscle types exist, such as smooth and cardiac muscle, but are not addressed.

II. Structure of Skeletal Muscle

Skeletal muscle is made up of anatomically distinct units, which are attached to bones (via tendons) or other muscles (via ligaments) to support specialized movement. In the human, there are 630 distinct muscles, which make up 40% of total body weight.

Individual muscles are composed of fascicles – assemblies of muscle fibers that are surrounded by a connective tissue sheath that can span the entire length of a muscle (Fig. 1A/B/C). Each fiber (diameter between 10 and 100 μm) is one single cell, which is usually multi-nucleated, and whose

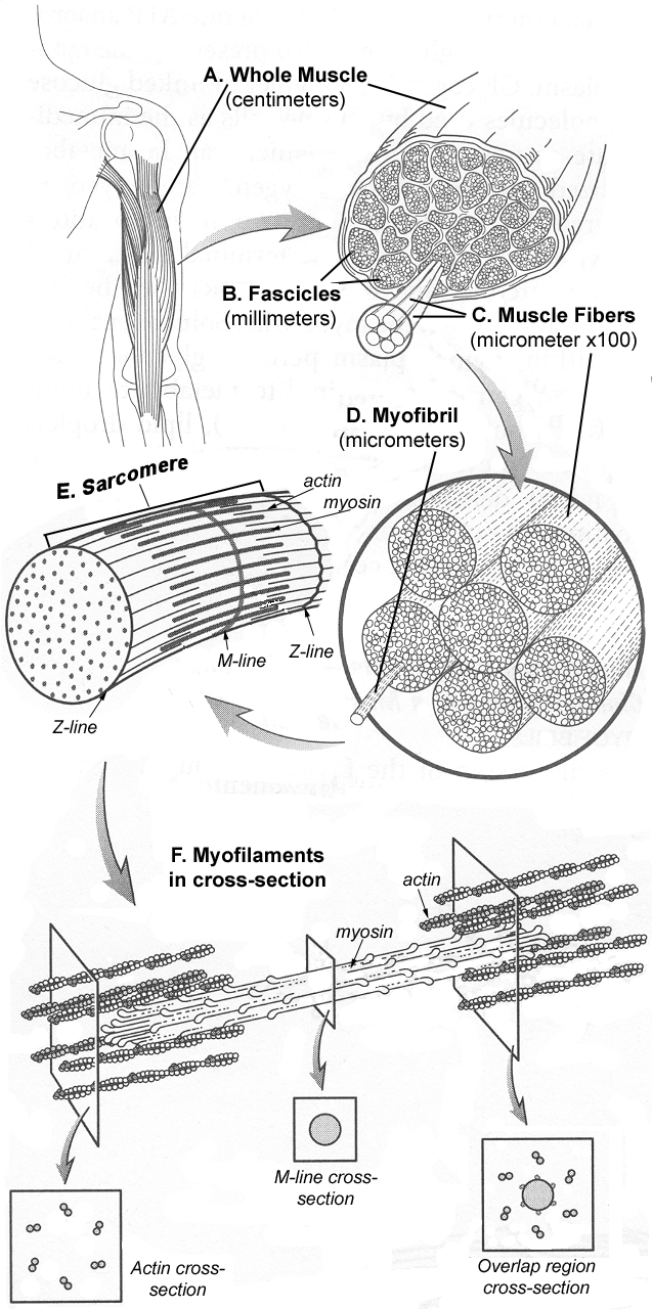

Fig. 1. Organization of skeletal muscle, with approximate diameters in parentheses. (After Lieber RL: Skeletal Muscle Structure, Function, & Plasticity, 2nd ed. Baltimore: Lippincott Williams & Wilkins, 2002, *Permission pending.*)

Supported by the UK Medical Research Council. P. Kohl is a Royal Society Research Fellow.

cytosol is confined by a single membrane called the sarcolemma. Glycogen, a chief energy provider for skeletal muscle contraction, is stored in conjunction with this membrane. The sarcolemma protrudes into the muscle fiber at regular intervals forming transverse tubules (t-tubules). T-tubules provide an important pathway for electrical signals from the surface to the core of the cell, where they abut the cisterns of the sarcoplasmic reticulum (SR), the intracellular Ca^{2+} store of muscle cells.

Fibers contain densely packed regular bundles of myofibrils, the contractile units of muscle. Myofibrils are made up of thick (myosin, diameter 15 nm) and thin (actin, diameter 5 nm) protein myofilaments. These myofilaments are arranged in a hexagonal pattern and interdigitate (Fig. 1F). In man, each myofibril contains approximately 1,500 myosin and 3,000 actin filaments [1]. Myofibrils (and therefore myofilaments) are organized in highly structured sarcomeres (Figs. 1E and 2).

The regular packing of myofibrils in the sarcomere gives rise to the typical cross-striation of skeletal muscle, as the region of the sarcomere that contains the (thick) myosin filaments is optically more dense (Anisotropic: A-band) than the remainder of the sarcomere that contains only the (thin) actin filaments (Isotropic: I-band). The center of the I-band is marked by a narrow dark line, referred to as the Z-line (Zwischen, German for 'in between'). The distance between two Z-lines is the sarcomere length (~2.5 μm at rest). Z-lines provide the anchor point for actin filaments, which extend on both sides of each Z-line.

Actin filaments (each ~1.0 μm long) consist of two intertwined pearl necklace-like chains composed of globular actin molecules (the pearls, where myosin will bind), tropomyosin (the chain, which covers the binding sites for myosin), and troponin (where Ca^{2+} will bind to displace tropomyosin and enable actin-myosin bonding, see below).

Myosin filaments (~1.6 μm long) consist of several hundred myosin molecules that are each around 0.15 μm long [2], and have the appearance of a daffodil (before flowering). Individual molecules are connected by their 'stems', with the bud 'head' sticking out to the sides of the assembled filament, as in a tightly wrapped bunch of flowers. Assembly of the complete myosin filament is such that two bunches are connected stem-to-stem, so that both end regions of a myosin filament contain myosin bud heads (where the myosin molecules at opposite ends of the filament have reverse orientation). The centre part of the filament is smooth (no myosin heads) and interlinked with neighboring myosin filaments of the same sarcomere at the M-line (Mittel, German for 'middle'; Figs. 1F and 2).

Myofibrils also contain mitochondria (the 'power station' of the cell), often arranged in parallel with individual sarcomeres (Fig. 2).

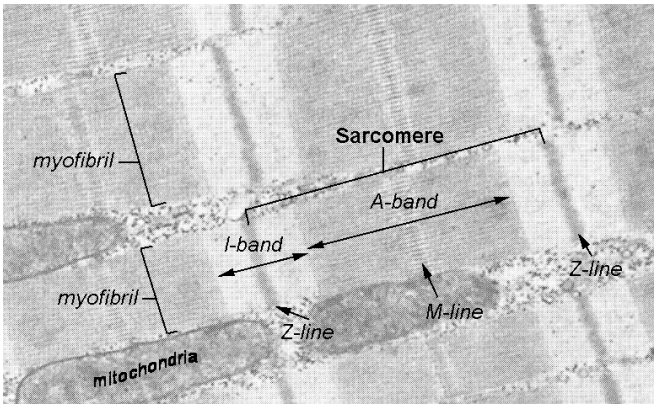

Fig. 2. Human skeletal muscle sarcomere structure. Myosin is attached to the M-line, while actin is attached at the Z-lines. During contraction, cross-bridge cycling pulls the Z-lines towards the M-line. (From [1], pp. 69, with permission from Elsevier.)

III. Physiology – The Pathway to Contraction

A. Excitation-contraction coupling overview

Every individual muscle fiber is innervated by a single motor neuron, although a motor neuron controls more than one fiber (with the number depending on the precision of movement afforded). This group of fibers and its controlling neuron is called a motor unit.

Contraction is initiated by an electrical impulse (somewhat paradoxically called an 'action potential', AP) of neural origin (i.e. originating in the brain or spinal cord) that reaches all muscle fibers within a motor unit via the corresponding motor neuron. Subsequent to neuro-muscular transmission, the AP travels along the sarcolemma of each muscle fiber and proceeds into the t-tubules. The t-tubular electrical signal causes release of Ca^{2+} from the adjacent SR. As a result, the cytosolic or intracellular ('free') Ca^{2+} concentration ($[Ca^{2+}]_i$) in the cell increases by two to three orders of magnitude from a resting value of 0.01 μM to a peak value of 1-10 μM [3]. Ca^{2+} binds to troponin on the actin filament, displacing the tropomyosin chain to expose the binding sites for myosin, thereby allowing actin and myosin to interact. Ca^{2+} regulation of contractile force in vertebrate striated muscle is exerted primarily through effects on the thin filament, by modulating cross-bridge binding to actin, as reviewed in [4]. The dependence of force production on Ca^{2+} is shown schematically in Fig. 3A.

In the presence of ATP (adenosine triphosphate), the key biological energy molecule, actin and myosin filaments will slide past each other, driven by cross-bridge cycling (see below). This causes an increase of force and, provided that the external load is less than the maximal force development of the contractile apparatus, shortening of the sarcomere. In either case, the mechanical event is known (again, somewhat paradoxically) as a 'contraction': 'isometric' if constant length, 'isotonic' if constant force. It should be noted that realistic movements are probably never either of these two 'pure' forms - rather a complicated mix of them and eccentric (lengthening) contractions.

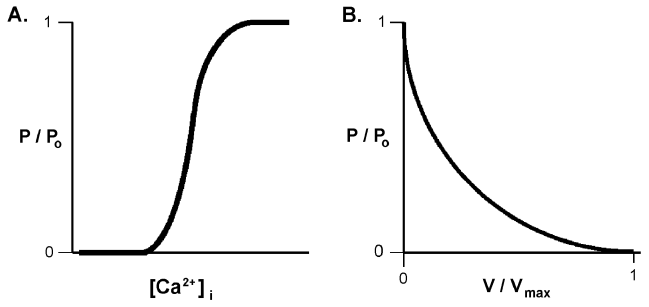

Fig. 3. A: Schematic representation of isometric force production (normalized to its maximum value: P_o) as a function of cytosolic Ca^{2+} concentration. B: Relative force versus relative velocity (V/V_{max}).

The AP-induced increase in $[Ca^{2+}]_i$ is counteracted by re-uptake of Ca^{2+} into the SR. This is also an energy consuming process that requires ATP. In the absence of maintained electrical stimulation, $[Ca^{2+}]_i$ decreases to its resting level, which prevents further formation of new actin-myosin bonds. A single contraction followed by relaxation is called a 'twitch'.

B. Sliding filament theory

Neither the thick nor the thin filaments changes length when resting muscle length is altered, whereas sarcomere length (the distance between adjacent pairs of Z-lines) can vary from a minimum of about 1.5 μm to a maximum of about 3.5 μm. Hence, as muscle length varies, only the length of the I-band changes (A-band length is invariant). This fundamental observation, made independently by AF Huxley [5] and HE Huxley [6] in 1954, underpins the 'sliding filament theory' of muscle contraction.

In 1957, AF Huxley [7] proffered a mathematical model of muscle contraction that postulated the existence of 'cross-bridges' extending from the thick filaments that could interact with binding sites on the thin filaments. In this model, thermal agitation (Brownian motion) and displacement-dependent rate constants ensure that a myosin cross-bridge has a high probability of binding favorably to actin. Cross-bridge binding instantaneously gives rise to a Hookean elasticity, causing the thin filament to slide with respect to the thick filament. The opposite polarity of myosin cross-bridges at the M-line ensures that the thin filaments on either side are pulled toward one-another. Since the thin filaments attach to adjacent Z-lines, the resulting force acts to diminish I-band (and, hence sarcomere) length. Huxley's mathematical model accurately simulated the experimentally observed (hyperbolic) dependence of contractile velocity on force development (Fig. 3B).

C. Cross-bridge cycling

Cross-bridge cycling is the fundamental mechanism by which the myosin heads pulling on the actin filaments cause the sarcomere to shorten at a load-dependent velocity. At any given time, the force developed by the muscle thus depends on the external load (Fig. 3B), and the number of cross-bridges that are active. The latter, in turn, depends on the $[Ca^{2+}]_i$ (Fig. 3A) as well as sarcomere length (see Fig. 6, below).

Cross-bridge cycling begins when excitation-contraction coupling causes a sufficient rise in $[Ca^{2+}]_i$. Through the interaction of Ca^{2+}, troponin and tropomyosin, actin and myosin form a 'cross-bridge' bond (Fig. 4D). Utilizing the chemical energy provided by the hydrolysis of ATP, the myosin head bends, thereby pulling actin towards the centre of the myosin molecule in the so-called 'power stroke' (Fig. 4E). Each complete cross-bridge cycle utilizes one ATP molecule and creates up to 1.7 pN of force [8] and up to 5.3 nm of displacement [9].

Subsequent to the power stroke, the actin-myosin complex is in a 'rigor' state and not actively producing force. In the absence of ATP, the proteins would remain coupled (Fig. 4A), causing muscle stiffening (which, in dead muscle tissue, is called *rigor mortis*). However, under physiological conditions, ATP binds to myosin, breaking the bond between it and actin (Fig. 4B), thereby preparing the cross-bridge either for attachment to a distal actin site, if contractile velocity is non-zero (A_{n+1}; Fig. 4C), or for re-attachment to the same actin site, if the contraction is isometric. Note that, in either case, the power stroke is associated with release of the ATP hydrolysis products (ADP and P_i).

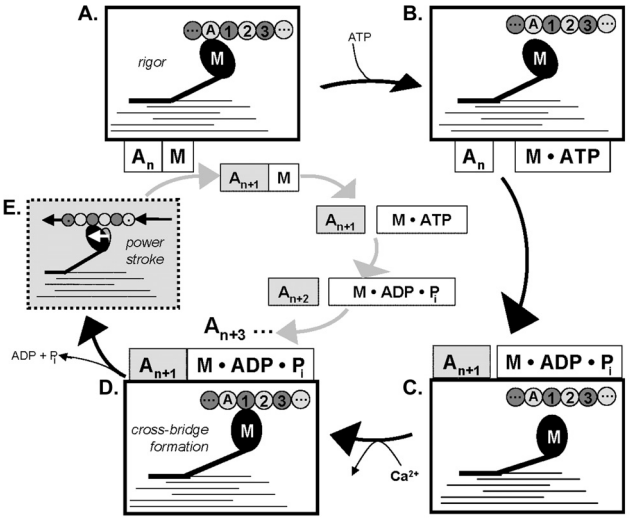

Fig. 4. Stages of the cross-bridge cycle. A: myosin head (M) strongly bound to actin (A_n), which – in the absence of ATP – creates a rigor state. B: ATP binds to myosin and relieves its bond to A_n. C: hydrolysis of ATP rotates the myosin head, which is now facing an actin binding site (A_{n+1}) that is further to the 'right' of the original one. D: addition of Ca^{2+} removes inactivation of actin binding site to allow formation of cross-bridge between M and A_{n+1}. E: release of hydrolysis products (ADP and P_i) generates the 'power stroke'. Gray arrows denote subsequent cycles involving the same M but, provided that shortening ensues, different actin monomers: A_{n+2}, A_{n+3}, … (for details, see text).

Cross-bridge cycling continues for as long as the concentration of Ca^{2+} remains high and the chemical energy of ATP hydrolysis exceeds the elastic energy of the cross-bridge bond. Muscle shortening, on the other hand, is prevented whenever the load exceeds the muscle's maximal isometric force (P_o) or if the myosin filaments reach the Z-lines. Whereas different cross-bridges within each sarcomere attach and re-attach at the same rates, they do so asynchronously. (This is similar to the action of multiple people pulling hand-over-hand on a rope.)

It is important to note that muscles may only actively shorten, not lengthen. Myosin molecules are unable to 'push' actin away from the center of the myosin molecule to lengthen the sarcomere. Lengthening therefore requires opposing forces, such as those provided passively by tissue elasticity (see Fig. 6, below) or gravity, or actively by antagonistic muscles (i.e. those with an opposing action at a joint).

For further detail on the molecular mechanisms of muscle contraction see [10].

IV. Generation and Regulation of Force

A. Tetanic tension

A key mechanism controlling force in skeletal muscle is AP frequency. Since AP duration is much shorter than a typical muscle twitch, additional APs can reach the fiber before it has relaxed (i.e. before $[Ca^{2+}]_i$ has returned to resting value). Re-stimulation of a fiber under these conditions leads to cumulative amplification of $[Ca^{2+}]_i$. This amplification will cause a summation of force (called 'temporal summation'). In Fig. 5, this occurs at stimulation frequencies above 5 Hz.

If the interval between APs is less than 1/3 of the duration of a twitch (ranging from 10 to 50 ms, depending on muscle type and excitability [3]), individual twitches will fuse. Complete fusion is called a 'tetanus'- a maintained powerful contraction. During a tetanic contraction, the muscle operates on the plateau region of the force-Ca^{2+} relationship (Fig. 3A).

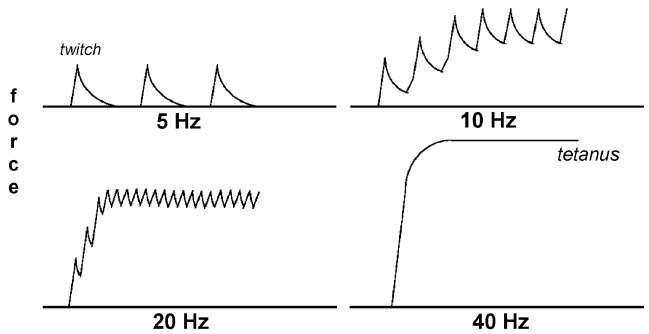

Fig. 5. Gradation of force by temporal summation. Increased frequency of electrical stimulation raises force of contraction, and at 40 Hz, this fiber responds with a fully fused tetanus (sustained peak force). For details, see text.

Upon cessation of electrical stimulation (and provided that ATP is sufficiently abundant), $[Ca^{2+}]_i$ is reduced by the re-uptake of Ca^{2+} into the SR, and force declines to its resting value.

B. Controlled movements (gradation of tension)

Tetanic tension development is best suited for large-scale manipulation rather than delicate movements, as the absolute amount of tension generated may fluctuate considerably. Controlled, graded tension, in particular in a dynamic setting, is more effectively achieved through selective recruitment of motor units.

Motor units differ in the number of fibers they contain. Units with fewer fibers are normally involved in precision movement, while those with larger numbers support movements that require high force output. Motor neurons of the muscles in the human larynx, for example, innervate as few as 2 to 3 muscle fibers for voice control, while the motor neurons of the gastrocnemius (calf muscle) can innervate up to 2,000 fibers for synchronized force development.

Most muscles have a wide range of motor unit sizes. Smaller units are generally recruited first for lesser movements or those that require precise fine-tuning. As the requirement for force increases, both the number and the size of recruited motor units increase, with the largest units being activated last.

The fibers of individual motor units are evenly dispersed within the muscle, which provides for uniform contraction and more even force distribution (reducing peak tension in any single area of a muscle).

C. Structural effects on force development (architecture)

Muscle cross-sectional area provides a good indication of maximum force output. A larger cross-sectional area indicates more fibers, or fibers with a larger diameter, both of which translate into larger numbers of parallel sarcomeres and, hence, a bigger area for cross-bridge formation. Maximum contractile strength is about 3 to 4 kg per cm^2 of muscle cross-section (300-400 kPa) [11]. Muscle can increase in size (hypertrophy) with repeated use, fostering an effective adaptive response of the biological system to external requirements.

In addition to the influence of cross-sectional area, muscle force is affected by the arrangement of muscle fibers. In parallel fibered muscles, fiber direction is parallel to the main axis of force development, so fascicle length and muscle length are equal. In contrast, unipennate fibers run at a 'pennation angle' (usually between 0° and 30°) to the force axis, so fascicle length and muscle length are unequal. (Bipennate muscles have fibers that attach to a tendon in the middle of the muscle, and multipennate muscles are those with multiple tendon attachments and fiber angles.) Whereas unipennate muscles commonly have larger cross-sections,

the net force contributed by their individual fibers is reduced by the cosine of the pennation angle.

Effective force output and contractile velocity are further affected by the position of tendon attachments to bones (relative to neighboring joints). The mechanical advantage of the resulting lever systems influences both force output and fine control of movement.

D. Length-tension relationship

As detailed above, force output is determined by the number of active cross-bridges, which is dictated by sarcomere length. Sarcomere length is directly related to the amount of overlap between actin and myosin filaments, which, in turn, determines the number of cross-bridges that may maximally be formed at any time. The highest active tension can be generated when all myosin heads (at either end of the myosin molecule) face actin binding sites (b-c, Fig. 6). This is the case when sarcomere length in skeletal muscle is around 2.25-2.5 μm [12].

If muscle fibers are stretched beyond this point, the myosin heads that are close to the M-line will no longer overlap the actin filaments (d, Fig. 6) and thus cannot contribute to active force generation. In the extreme of excessive stretch, at around 3.5 μm [12], actin and myosin filaments will have no overlap (e, Fig. 6). Cross-bridges cannot form and no shortening or tension may be actively generated.

When sarcomere length is less than about 2.25 μm (a-b, Fig. 6), interaction of opposite actin filaments disturbs the hexagonal arrangement required for optimal cross-bridge formation, and maximum tension development is reduced. At a sarcomere length of about 1.67 μm, myosin filaments will begin to encounter the Z-lines, causing a further decrease in active tension generation [12] (a, Fig. 6).

The length of a sarcomere that optimizes force production, L_o, is thus in the mid-region near 2.25 μm (b, Fig. 6), and pre-setting muscles to this length maximizes force output. A comprehensive analysis of sarcomere length changes by Burkholder and Lieber [13] found that most muscles operate over a surprisingly narrow range: 94 ± 13% of L_o.

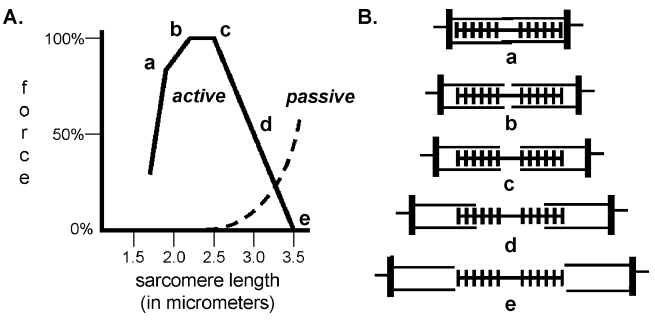

Fig. 6. Sarcomere length-tension relationships as measured in a single fiber (data from [5]). A: piecewise linear nature of the active force-length relationship. Dashed curve denotes force-extension relation of resting muscle. B: sarcomere structural interpretation of panel A.

Skeletal muscle is characterized by showing negligible resting (passive) force at sarcomere lengths less than L_o. Above L_o, passive force rises quasi-exponentially with sarcomere length (dashed curve, Fig. 6A). This behavior is largely attributable to the elastic characteristics of extracellular components – especially the connective tissue that envelops individual fibers, fascicles and the whole muscle (Fig. 1).

E. Isotonic force-velocity relationship

As stated earlier, the amount of force generated also depends on the velocity of muscle shortening (Fig. 3A). Faster movements will not permit as much force output as those with a lower velocity. This occurs because the rates of cross-bridge attachment, detachment and re-attachment are chemically limited by the enzymatic activity of the actin-activated myosin ATPase. The number of active cross-bridges at any time is thus reduced during fast movements of any given muscle. In addition, there are different myosin ATPase isoforms, which differentiate various muscle types with their individual characteristic peak cross-bridge cycling rates [14].

F. Co-activation

In vivo, muscles do not normally contract in isolation, but in groups that support either optimized force development, stability of movement, or an extended range of motion. These may be muscles of close proximity with comparable locomotory potential (agonists), muscles that attach to opposite sides of a joint and afford balanced motion (antagonist), or even muscles that are fairly far removed from the active focus, for example, to adjust posture or thrust. This, again, is precisely regulated to match the requirement for movement, and to allow for highly specialized and flexible motion.

G. Muscle tone

Even in the absence of overt activity, muscles have a certain tautness. This is called ‘muscle tone’ and arises from low frequency action potentials generated within the nervous system. The maintenance of tone (like that of posture) is thus an energy consuming process.

V. Skeletal Muscle Energetics

A. Efficiency of skeletal muscle

Efficiency is defined as the power output divided by the power input. The peak thermodynamic efficiency of muscle is around 0.45, based on input of the high-energy fuel ATP.

This value drops to about half that level when the cost of conversion of dietary substrates into high-energy storage compounds is taken into account [2].

This figure still ignores the anabolic costs of muscle fiber synthesis, maintenance or repair (normal turnover rates are such that the contractile protein of active muscle is totally replaced every 2-4 weeks). Such costs are usually attributed to 'resting' or 'basal' metabolism.

B. Metabolic pathways

The obligatory energy substrate that skeletal muscle utilizes is ATP, which, when broken down into ADP and P_i, releases up to 50 kJ per mole of chemical energy [15]. ATP is needed to fuel cross-bridge cycling, but also to pump Ca^{2+} back into the SR (where one ATP is needed to transport two Ca^{2+} ions against their concentration gradient) and to maintain a suitable electro-chemical environment for normal AP propagation.

The ATP concentration in skeletal muscle is about 4 mM, which is enough to enable contraction for only several seconds [1] or less (since ATP turnover increases linearly with force production [16]). To maintain contraction and force output beyond such a limited period, ATP must be constantly replenished. The immediate source of replenishment is creatine phosphate (CrP), which is present in muscle cells at a concentration of about 20 mM - sufficient to sustain only another 10-20 s of contraction. Glucose serves as the main metabolic source for ATP re-synthesis in muscle; it arises from blood glucose, muscle glycogen, or liver glycogen.

The synthesis of ATP from glucose occurs by two main pathways: oxidative phosphorylation and glycolysis. As the name suggests, oxidative phosphorylation requires oxygen (and takes place in the mitochondria), while glycolysis does not (it takes place anaerobically in the cytoplasm).

Aerobic ATP synthesis is more efficient than anaerobic synthesis, yielding 36 ATP from one molecule of glucose, compared to only 2 ATP via the glycolytic pathway. Force can be maintained with aerobic ATP synthesis for an extended period of time, providing there is an adequate supply of nutrients.

Besides its lower relative ATP production, another disadvantage of glycolysis is that it produces lactic acid, which cannot be metabolized by skeletal muscle and will therefore decrease pH, causing inhibition of cross-bridge formation. Contraction based on ATP arising solely from the glycolytic pathway can therefore maintain maximum force for only around one minute.

Despite these disadvantages, the cycle of glycolysis is 2.5 times faster than oxidative phosphorylation, which allows this pathway to serve a vital role in muscle function. It allows peak power output that exceeds the energetic limits set by restrictions in oxygen supply (the rate of which is limited by the transport capacity of respiratory and circulatory systems). The 'oxygen debt' developed in the process of glycolytic phosphorylation (oxygen is the only eradicator of the by-products of anaerobic metabolism) must, however, be compensated after the end of a period of heavy work. This causes increased respiratory rates and metabolic utilization of lactate in the heart and liver.

Oxidative phosphorylation, therefore, supports the majority of sustained locomotory activities, while anaerobic glycolysis is used for activities that require brief periods of large power output.

C. Fiber types

Muscle fibers can be categorized by their dominant metabolic pathway for ATP synthesis. There are three main types (easily identified by their color): slow oxidative fibers – type I (red), fast oxidative / glycolytic – type IIA (pink), and fast glycolytic – type IIB (white).

The different fiber colors are related to their content of myoglobin, the oxygen store of muscle cells. Myoglobin, which is red in appearance, is present in particularly high concentration in slow oxidative fibers (which also contain more mitochondria). Most of these fibers tend to be in small motor units and are recruited early during muscle activity. Fast glycolytic cells, in contrast, have very low levels of myoglobin and mitochondria, and large motor unit size. Fast oxidative / glycolytic fibers have mixed properties.

Within a motor unit, fiber types are consistent. Most vertebrates will have a mix of fiber types in individual skeletal muscles. An exception to this rule is fish, which have distinct and well-defined bands of white or red fibers (making them an interesting model for experimental work).

D. Fatigue

Prolonged contraction decreases force output, leading to fatigue (divided into peripheral and central components). Peripheral fatigue is caused primarily by processes within the muscle fiber itself, most prominently depletion of substrates and accumulation of their by-products. Changes in pH, osmotic pressure, and muscle temperature all contribute to peripheral fatigue. Because of the glycolytic effects on pH, type II fibers are 'fast-fatigueable', while type I, fibers are considered 'fatigue-resistant' (and are thus important for maintaining posture).

Central fatigue is of neuronal origin, with factors such as decreased motivation or alertness causing a reduction in AP frequency to motor neurons (although the extent and mechanisms of effects by the nervous system are less well understood). For detailed reviews on central and peripheral fatigue, see [17] and [18].

E. External factors affecting locomotion energy

The energetic cost of locomotion is influenced not only by internal factors, but also by the external environment. The surrounding medium (i.e. air or water) affects the

energy requirement for locomotion via pressure, friction, buoyancy, etc. Air provides the environment with least resistance to locomotion, but lacks the buoyancy of water to provide structural support. Since temperature also affects energy requirements for locomotion and body maintenance, the thermal conductance of the surrounding medium influences overall energy cost. When comparing the energy cost of locomotion (identified as the difference between total and basal energy requirement, the latter being the energy needed to maintain the body at rest), it has been found that terrestrial locomotion requires the highest energy, costing four times that of flying, and more than eight times that of swimming [19].

In spite of the pronounced differences in environment, locomotory design, and energy requirements in various vertebrates, similar top speeds of *horizontal* locomotion (28 to 30 ms^{-1}) are found in representatives of terrestrial (cheetah), swimming (sailfish), and flying (peregrine falcon) vertebrates.

VI. Conclusion

Properties of biological force generators for locomotion have been well investigated in many vertebrates and, in the context of novel actuator technologies, may serve as a yard-stick for design and assessment.

Acknowledgments

We thank Patricia J. Cooper for her helpful comments.

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