and summate (ie, the force varies with the contraction time of the motor unit and the rate at which the action potentials are evoked). At lower rates of stimulation, the ripples in the tetanus denote the peaks of individual twitches (Figure 31–2A). The peak force achieved during a tetanic contraction varies as a sigmoidal function of action potential rate, with the shape of the curve depending on the contraction time of the motor unit (Figure 31–2B). Maximal force is reached at lower action potential rates for slow-contracting motor units than the rates needed to achieve maximal force in fast-contracting units.

The functional properties of motor units vary across the population and between muscles. At one end of the distribution, motor units have long twitch contraction times and produce small forces, but are less fatigable. At the other end of the distribution, motor units have short contraction times, produce large forces, and are

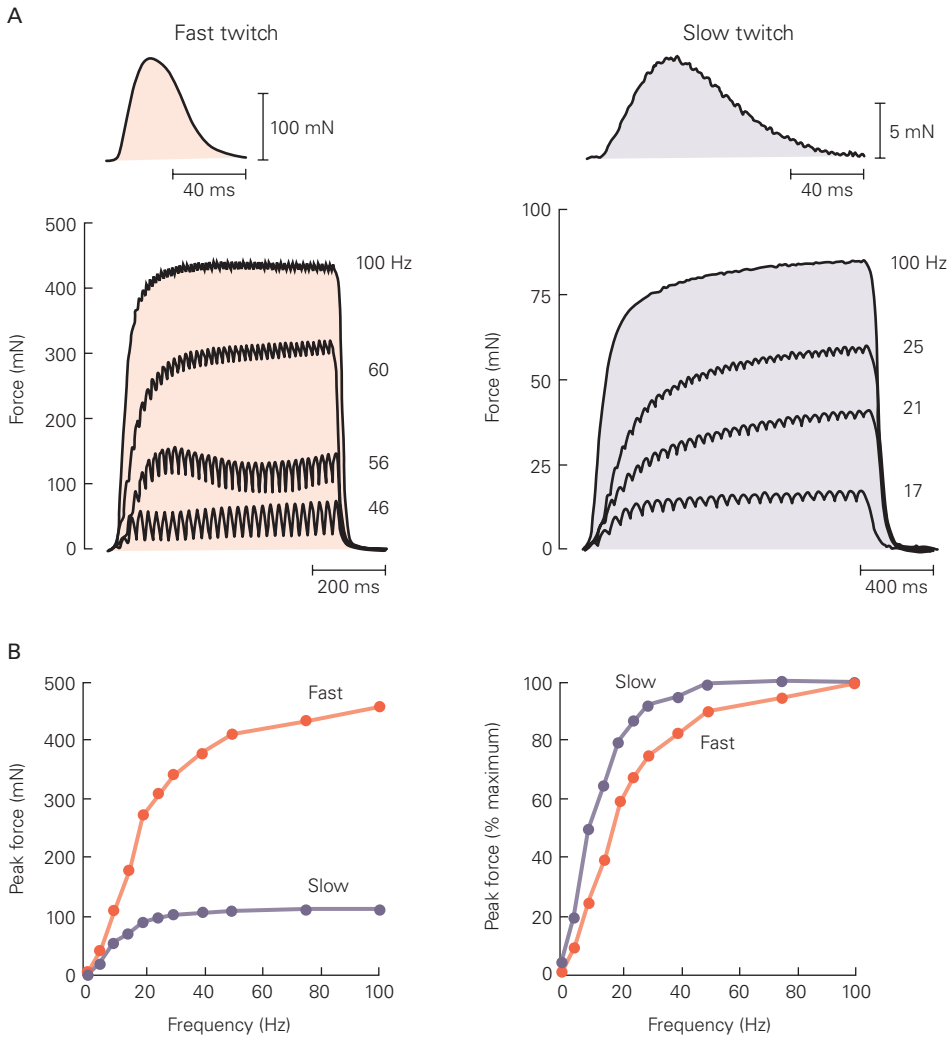


Figure 31–2 The force exerted by a motor unit varies with the rate at which its neuron generates action potentials.

A. Traces show the forces exerted by fast- and slow-contracting motor units in response to a single action potential (**top trace**) and a series of action potentials (set of **four traces below**). The time to the peak twitch force, or contraction time, is briefer in the faster unit. The rates of the action potentials used to evoke the tetanic contractions range from 17 to 100 Hz in the slow-contracting unit to 46 to 100 Hz in the fast-contracting unit. The peak tetanic force evoked by 100-Hz stimulation is greater for the fast-contracting unit. Note the different force scales for the two sets of traces. (Adapted, with permission, from Botterman, Iwamoto, and Gonyea 1986; adapted from Fuglevand, Macefield, and Bigland-Ritchie 1999; and Macefield, Fuglevand, and Bigland-Ritchie 1996.)

B. Relation between peak force and the rate of action potentials for fast- and slow-contracting motor units. The absolute force (*left plot*) is greater for the fast-contracting motor unit at all frequencies. At lower stimulus rates (*right plot*), the force evoked in the slow-contracting motor unit (longer contraction time) sums to a greater relative force (percent of peak force) than in the fast-contracting motor unit (shorter contraction time).

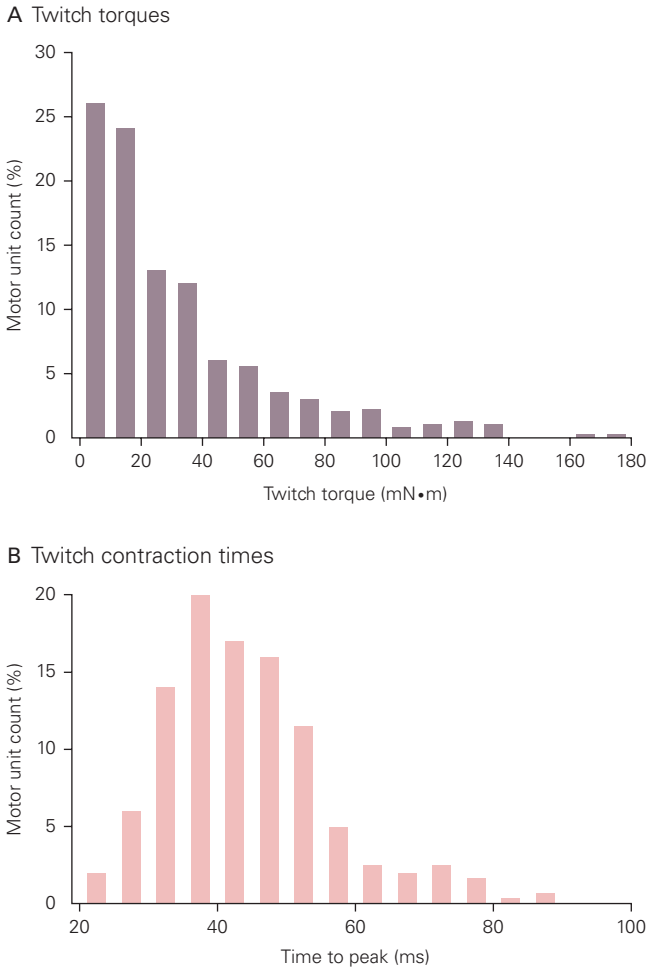


Figure 31–3 Most human motor units produce low forces and have intermediate contraction times. (Reproduced, with permission, from Van Cutsem et al. 1997. © Canadian Science Publishing.)

A. Distribution of twitch torques for 528 motor units in the tibialis anterior muscle obtained from 10 subjects.

B. Distribution of twitch contraction times for 528 motor units in the tibialis anterior muscle.

more fatigable. The order in which motor units are recruited during a voluntary contraction begins with the slow-contracting, low-force units and proceeds up to the fast-contracting, high-force units. As observed by Jacques Duchateau and colleagues, most motor units in humans produce low forces and have intermediate contraction times (Figure 31–3).

The range of contractile properties exhibited by motor units is partly attributable to differences in the structural specializations and metabolic properties of muscle fibers. One commonly used scheme to characterize muscle fibers is based on their reactivity to histochemical assays for the enzyme myosin adenosine triphosphatase (ATPase), which is used as an index of contractile speed. Histochemical stains for myosin ATPase can identify two types of muscle fibers: type I (low levels of myosin ATPase) and type II (high levels of myosin ATPase). Slow-contracting motor units contain type I muscle fibers, and fast-contracting units include type II fibers. The type II fibers can be further classified as being less fatigable (type IIa) or more fatigable (type IIb, IIx, or IId), due to the association between myosin ATPase content and the relative abundance of oxidative enzymes. Another commonly used scheme distinguishes muscle fibers on the basis of genetically defined isoforms of the myosin heavy chain (MHC). Muscle fibers in slow-contracting motor units express MHC-I, those in the less fatigable fast-contracting units express MHC-IIA, and those in the more fatigable fast-contracting units express MHC-IIX.

In actuality, the contractile properties of single muscle fibers are less distinct than the two classification schemes suggest (Figure 31–4). In addition to the variability in the contractile properties of each type of muscle fiber (MHC-I, -IIA, or -IIX), some muscle fibers co-express more than one MHC isoform. Such hybrid muscle fibers exhibit contractile properties that are intermediate between the muscle fibers that compose a

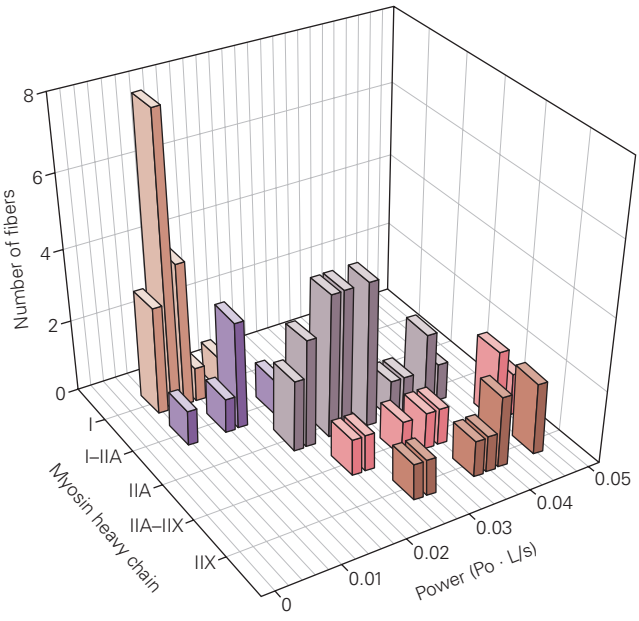


Figure 31–4 The contractile properties of muscle fiber types are distributed continuously. Peak power produced by segments of single muscle fibers from the vastus lateralis muscle with different types of myosin heavy chain (MHC) isoforms. Two types of hybrid fibers (I-IIA and IIA-IIX) contain isoforms of both types of MHCs. Power is calculated as the product of peak tetanic force (P_o) and maximal shortening velocity (segment length per second [L/s]). (Adapted, with permission, from Bottinelli et al. 1996. Copyright © 1996 The Physiological Society.)

single isoform. The relative proportion of hybrid fibers in a muscle increases with age. As with the distribution of contractile properties across motor units (Figure 31–3), the distribution across individual muscle fibers is also continuous, from slow to fast contracting and from least to most powerful (Figure 31–4).

Physical Activity Can Alter Motor Unit Properties

Alterations in habitual levels of physical activity can influence the three contractile properties of motor units (contraction speed, maximal force, and fatigability). A decrease in muscle activity, such as occurs with aging, bed rest, limb immobilization, or space flight, reduces the maximal capabilities of all three properties. The effects of increased physical activity vary with the intensity and duration of the activity. Brief sets of strong contractions performed a few times each week can increase motor unit force (strength training); brief sets of rapid contractions performed a few times each week can increase motor unit discharge rate (power training); and prolonged periods of weaker contractions can reduce motor unit fatigability (endurance training).

Changes in the contractile properties of motor units involve adaptations in the structural specializations and biochemical properties of muscle fibers. The improvement in contraction speed caused by power training, for example, is associated with an increase in the maximal shortening velocity of a muscle fiber caused by an increase in the quantity of myosin ATPase in the fiber. Similarly, the increase in maximal force is associated with the enlarged size and increased intrinsic force capacity of the muscle fibers produced by an increase in the number and density of the contractile proteins.

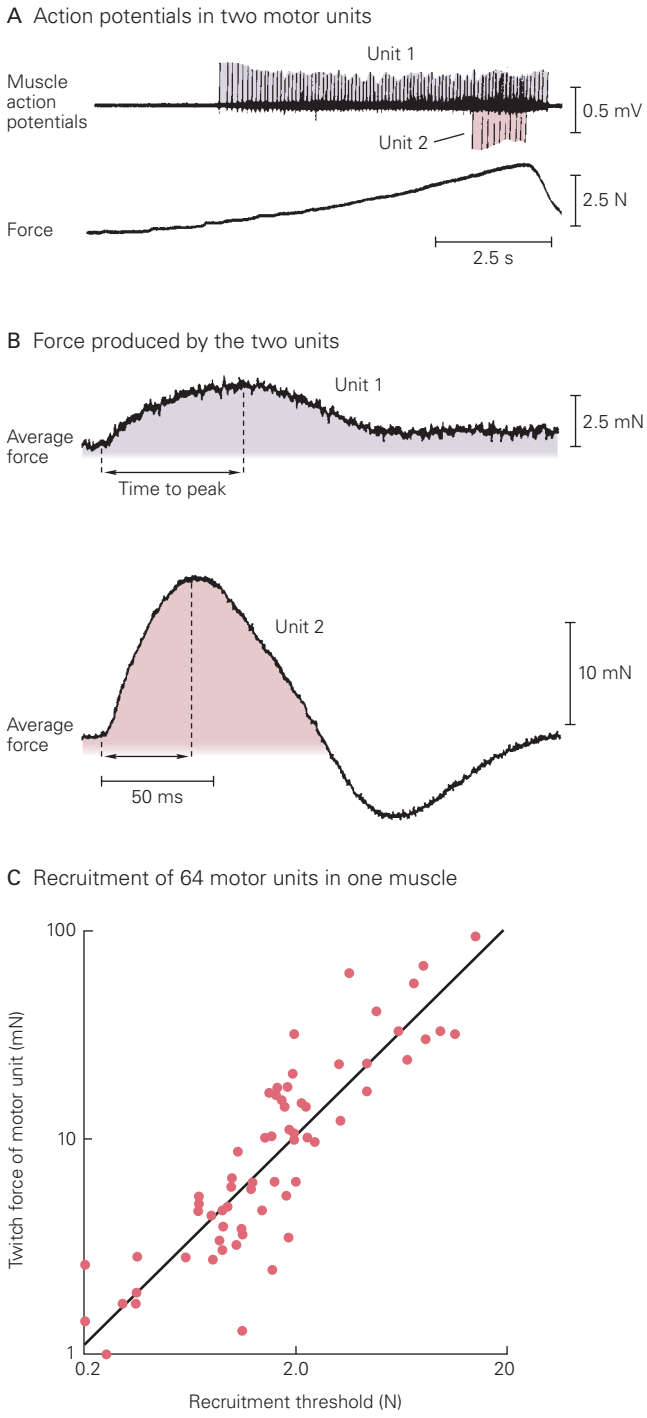
In contrast, decreases in the fatigability of a muscle fiber can be caused by many different adaptations, such as increases in capillary density, number of mitochondria, efficiency of the processes involved in activating the contractile proteins (excitation-contraction coupling), and oxidative capacity of the muscle fibers. Although the adaptive capabilities of muscle fibers decline with age, the muscles remain responsive to exercise even at 90 years of age.

Despite the efficacy of strength, power, and endurance training in altering the contractile properties of muscle fibers, these training regimens have little effect on the composition of a muscle's fibers. Although several weeks of exercise can change the relative proportion of type IIA and IIX fibers, it produces no change in the proportion of type I fibers. All fiber types adapt in response to exercise, although to varying extents depending on the type of exercise. For example, strength training of leg muscles for 2 to 3 months can increase the cross-sectional area of type I fibers by 0% to 20% and of type II fibers by 20% to 60%, increase the proportion of type IIa fibers by approximately 10%, and decrease the proportion of type IIx fibers by a similar amount. Furthermore, endurance training may increase the enzyme activities of oxidative metabolic pathways without noticeable changes in the proportions of type I and type II fibers, but the relative proportions of type IIa and IIx fibers do change as a function of the duration of each exercise session. Conversely, although several weeks of bed rest or limb immobilization do not change the proportions of fiber types in a muscle, they do decrease the size and intrinsic force capacity of muscle fibers. Adaptations in fiber type properties and proportions in turn alter the distribution of contractile properties in muscle fibers (Figure 31–4) and motor units (Figure 31–3).

Although physical activity has little influence on the proportion of type I fibers in a muscle, more substantial interventions can have an effect. Space flight, for example, exposes muscles to a sustained decrease in gravity that reduces the proportion of type I fibers in some leg muscles and decreases contractile properties. Similarly, surgically changing the nerve that innervates a muscle alters the pattern of activation and eventually causes the muscle to exhibit properties similar to those of the muscle that was originally innervated by the transplanted nerve. Connecting a nerve that originally innervated a rapidly contracting leg muscle to a slowly contracting leg muscle, for example, will cause the slower muscle to become more like a faster muscle. In contrast, a history of performing powerful contractions with leg muscles is associated with a modest reduction in the proportion of type I fibers, a marked increase in the proportion of type IIx fibers, and a huge increase in the power that can be produced by the type IIa and IIx fibers.

Muscle Force Is Controlled by the Recruitment and Discharge Rate of Motor Units

The force exerted by a muscle during a contraction depends on the number of motor units that are activated and the rate at which each of the active motor neurons discharges action potentials. Force is increased during a muscle contraction by the activation of additional motor units, which are recruited progressively from the weakest to the strongest (Figure 31–5). A motor unit's recruitment threshold is the force during the contraction at which the motor unit is activated. Muscle force decreases gradually by terminating the activity of motor units in the reverse order from strongest to weakest.



The order in which motor units are recruited is highly correlated with several indices of motor unit size, including the size of the motor neuron cell bodies, the diameter and conduction velocity of the axons, and the amount of force that the muscle fibers can exert. Because individual sources of synaptic input are broadly distributed across most neurons in a motor nucleus, the orderly recruitment of motor neurons is not accomplished by the sequential activation of different sets of synaptic inputs that target specific motor neurons. Rather, recruitment order is determined by intrinsic differences in the responsiveness of individual motor neurons to relatively uniform synaptic input.

One of these factors is the anatomical size of a neuron's soma and dendrites. Smaller neurons have a higher input resistance (R_{in}) to current and, due to Ohm's law ($\Delta V_m = I_{syn} \times R_{in}$), experience a greater change in membrane potential (ΔV_m) in response to a given synaptic current (I_{syn}). Consequently, increases in the net excitatory input to a motor nucleus cause the levels of depolarization to reach threshold in an ascending order of motor neuron size: Contraction force is increased by recruiting the smallest motor neuron first and the largest motor neuron last (Figure 31–6). This effect is known as the size principle of motor neuron recruitment, a concept enunciated by Elwood Henneman in 1957.

The size principle has two important consequences for the control of movement by the nervous system. First, the sequence of motor neuron recruitment is determined by the properties of the spinal neurons and not by supraspinal regions of the nervous system. This means that the brain cannot selectively activate specific motor units. Second, the axons arising from small motor neurons are thinner than those associated with

Figure 31–5 (Left) Motor units that exert low forces are recruited before those that exert greater forces. (Adapted, with permission, from Desmedt and Godaux 1977; Milner-Brown, Stein, and Yemm 1973. Copyright © 1973 The Physiological Society.)

A. Action potentials in two motor units were recorded concurrently with a single intramuscular electrode while the subject gradually increased muscle force. Motor unit 1 began discharging action potentials near the beginning of the voluntary contraction, and its discharge rate increased during the contraction. Motor unit 2 began discharging action potentials near the end of the contraction.

B. Average twitch forces for motor units 1 and 2 as extracted with an averaging procedure during the voluntary contraction.

C. The plot shows the net muscle forces at which 64 motor units in a hand muscle of one person were recruited (recruitment threshold) during a voluntary contraction relative to the twitch forces of the individual motor units.

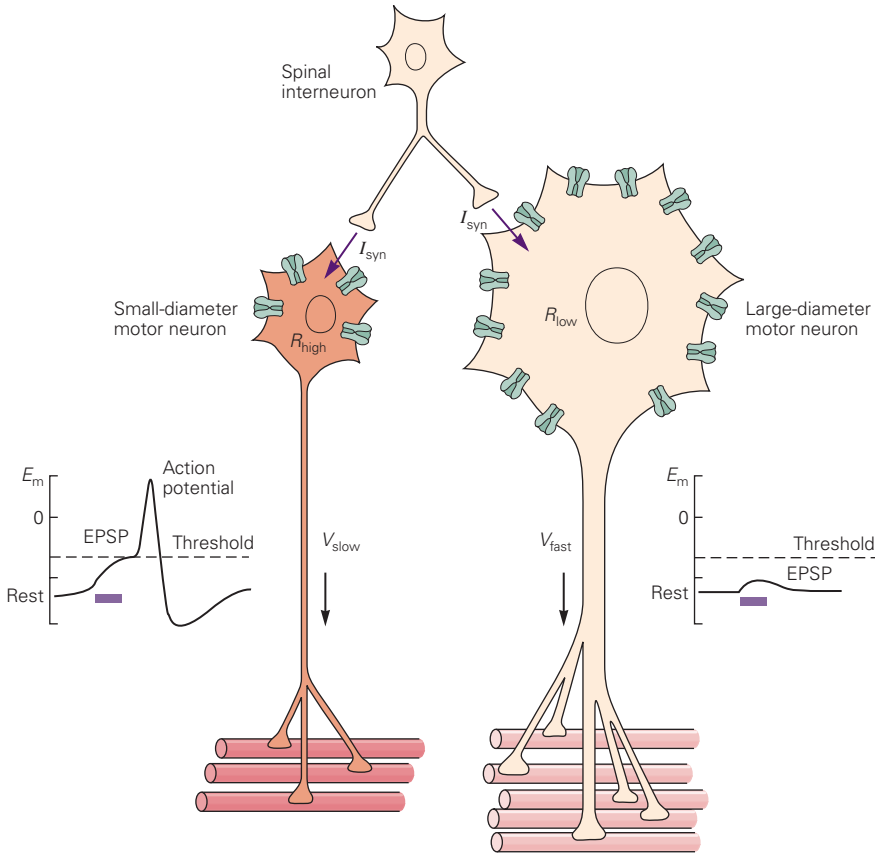


Figure 31–6 The size principle of motor neuron recruitment. Two motor neurons of different sizes have the same resting membrane potential (V_r) and receive the same excitatory synaptic current (I_{syn}) from a spinal interneuron. Because the small motor neuron has a smaller surface area, it has fewer parallel ion channels and therefore a higher input resistance (R_{high}). According to Ohm's law ($V = IR$), I_{syn} in the small neuron produces a large excitatory postsynaptic potential (**EPSP**) that reaches threshold, resulting in the discharge of an action potential. However, the axon of the small motor neuron has a small diameter and thus conducts the action potential at a relatively low velocity (V_{slow}) and to fewer muscle fibers. In contrast, the large motor neuron has a larger surface area, which results in a lower transmembrane resistance (R_{low}) and a smaller EPSP that does not reach threshold in response to I_{syn}; however, when synaptic input does reach threshold, the action potential is conducted relatively rapidly (V_{fast}) (Chapter 9).

large motor neurons and innervate fewer muscle fibers. Because the number of muscle fibers innervated by a motor neuron is a key determinant of motor unit force, motor units are activated in order of increasing strength, so the earliest recruited motor units are the weakest ones.

As suggested by Edgar Adrian in the 1920s, the muscle force at which the last motor unit in a motor nucleus is recruited varies between muscles. In some hand muscles, all the motor units have been recruited when the force reaches approximately 60% of maximum during a slow muscle contraction. In the biceps brachii, deltoid, and tibialis anterior muscles, recruitment continues up to approximately 85% of the maximal force. Beyond the upper limit of motor unit recruitment, changes in muscle force depend solely on variations in the rate at which motor neurons generate action potentials. Over most of the operating range of a muscle, the force it exerts depends on concurrent changes in discharge rate and the number of active motor units (Figure 31–7). Except at low forces, however, variation in

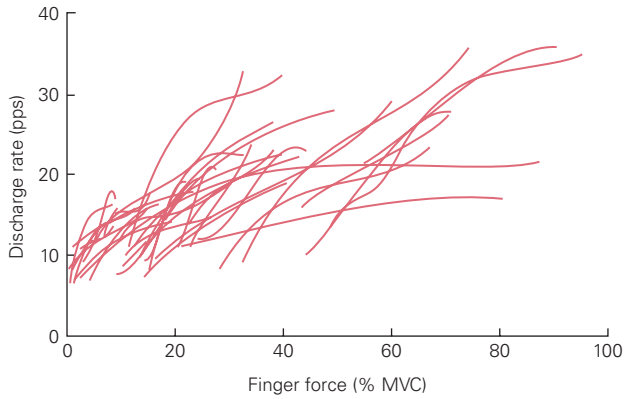


Figure 31–7 Muscle force can be adjusted by varying the number of active motor units and their discharge rate. Each line shows the discharge rate (pulses per second [**pps**]) for a single motor unit in a hand muscle over a range of finger forces (maximal voluntary contraction [**MVC**]). The finger force was produced by the action of a single hand muscle. The leftmost point of each line indicates the threshold force at which the motor unit is recruited, whereas the rightmost point corresponds to the peak force at which the motor unit could be identified. The range of discharge rates was often less for motor units with lower recruitment thresholds. Increases in finger force were produced by concurrent increases in discharge rate and the number of activated motor units. (Adapted, with permission, from Moritz et al. 2005.)

discharge rate has a greater influence on muscle force than does changes in the number of active motor units.

The order in which motor units are recruited does not change with contraction speed. Due to the time involved in excitation-contraction coupling, faster contractions require the action potential for each motor unit to be generated earlier than during a slow contraction. As a result of this adjustment, the upper limit of motor unit recruitment during the fastest muscle contractions is approximately 40% of maximum. Consequently, it is possible to manipulate the rate at which motor units are recruited by varying contraction speed.

The Input–Output Properties of Motor Neurons Are Modified by Input From the Brain Stem

The discharge rate of motor neurons depends on the magnitude of the depolarization generated by excitatory inputs and the intrinsic membrane properties of the motor neurons in the spinal cord. These properties can be profoundly modified by input from monoaminergic neurons in the brain stem (Chapter 40). In the absence of this input, the dendrites of motor neurons passively transmit synaptic current to the cell body, resulting in a modest depolarization that immediately ceases when the input stops. Under these conditions, the relation between input current and discharge rate is linear over a wide range.

The input–output relation becomes nonlinear, however, when the monoamines serotonin and norepinephrine induce a huge increase in conductance by activating L-type Ca^{2+} channels that are located on the dendrites of the motor neurons. The resulting inward Ca^{2+} currents can enhance synaptic currents by three- to five-fold (Figure 31–8). In an active motor neuron, this augmented current can sustain an elevated discharge rate after a brief depolarizing input has ended, a behavior known as *self-sustained firing*. A subsequent brief inhibitory input, such as from a spinal reflex pathway, can terminate such self-sustained firing.

Because the properties of motor neurons are strongly influenced by monoamines, the excitability of the pool of motor neurons innervating a single muscle is partly under control of the brain stem. In the awake state, moderate levels of monoaminergic input to the motor neurons of slowly contracting motor units promote self-sustained firing. This is probably the source of the sustained force exerted by slower motor units to maintain posture (Chapter 36). Conversely, the withdrawal of monoaminergic drive during sleep decreases excitability and helps ensure a relaxed motor state. Thus, monoaminergic input from the brain stem can adjust the gain of the motor unit pool to meet the demands of different tasks. This flexibility does not compromise the size principle of orderly recruitment because the threshold for activation of the persistent inward currents is lowest in the motor neurons of slower contracting motor units, which are the first recruited even in the absence of monoamines.

Muscle Force Depends on the Structure of Muscle

Muscle force depends not only on the amount of motor neuron activity but also on the arrangement of the fibers in the muscle. Because movement involves the controlled variation of muscle force, the nervous system must take into account the structure of muscle to achieve specific movements.

The Sarcomere Is the Basic Organizational Unit of Contractile Proteins

Individual muscles contain thousands of fibers that vary from 1 to 50 mm in length and from 10 to 60 µm in diameter. The variation in fiber dimensions reflects differences in the quantity of contractile protein. Despite this quantitative variation, the organization of contractile proteins is similar in all muscle fibers. The proteins are arranged in repeating sets of thick and thin filaments, each set known as a *sarcomere* (Figure 31–9). The in vivo length of a sarcomere, which is bounded by Z disks, ranges from 1.5 to 3.5 µm within and across muscles. Sarcomeres are arranged in series to form a *myofibril*, and the myofibrils are aligned in parallel to form a muscle fiber (myocyte).

The force that each sarcomere can generate arises from the interaction of the contractile thick and thin filaments. The thick filament consists of several hundred myosin molecules arranged in a structured sequence. Each myosin molecule comprises paired coiled-coil domains that terminate in a pair of globular heads. The myosin molecules in the two halves of a thick filament point in opposite directions and are progressively displaced so that the heads, which extend away from the filament, protrude around the thick filament (Figure 31–9C). The thick filament is anchored in the middle of the sarcomere by the protein titin, which connects each end of the thick filament with neighboring strands of actin in the thin filament and with the Z-disc. To maximize the interaction between the globular heads of myosin and the thin filaments, six thin filaments surround each thick filament.

The primary components of the thin filament are two helical strands of fibrous F-actin, each of which

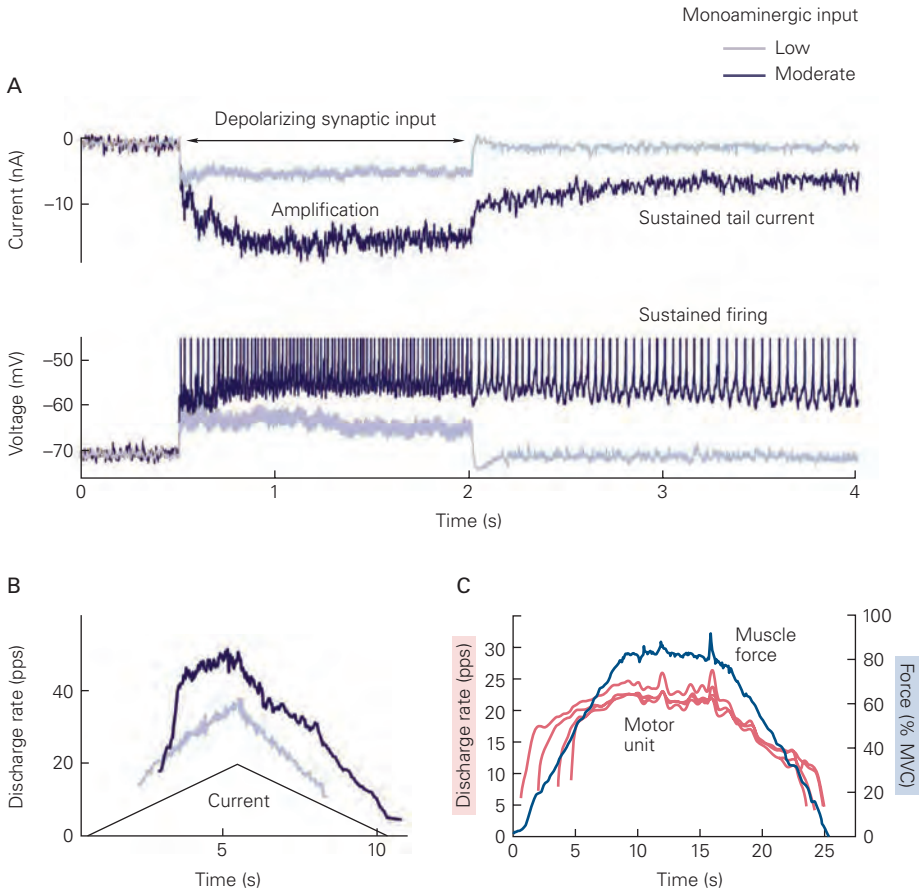


Figure 31–8 **Monoaminergic input enhances the excitability of motor neurons.** (Part **A**, adapted, with permission, of Heckman et al. 2009. Copyright © 2009 International Federation of Clinical Neurophysiology; Part **B**, data from CJ Heckman; Part **C**, adapted, with permission, from Erim et al. 1996. Copyright © 1996 John Wiley & Sons, Inc.)

A. Membrane currents and potentials in spinal motor neurons of adult cats that were either deeply anesthetized (low monoaminergic drive) or decerebrate (moderate monoaminergic drive). When monoaminergic input is absent or low, a brief excitatory input produces an equally brief synaptic current during voltage clamp (**upper record**). This current is not sufficient to bring the membrane potential of the neuron to threshold for generating action potentials in the unclamped condition (**lower record**). The same brief excitatory input during moderate levels of monoaminergic input activates a persistent inward current in the dendrites, which amplifies the excitatory synaptic current and decays slowly following cessation of synaptic input (**upper record**). This persistent inward current causes a high discharge rate during the input and sustains a lesser discharge rate after the input ceases (**lower record**). A brief inhibitory input will return the neuron to its resting state.

B. High levels of monoaminergic input to a motor neuron give rise to a persistent inward current in response to injected current, resulting in a much greater discharge rate for a given amount of current.

C. The **blue** trace represents the force exerted by the dorsiflexor muscle during a contraction that gradually increased to 80% of maximal voluntary isometric contraction (**MVC**) force in a human subject. Each of the four **pink** traces indicates the change in the rate at which a single motor unit discharged action potentials during the contraction. The leftmost point (start) of each of these four traces shows the time when the motor unit was recruited, and the rightmost point (end) denotes the time at which the motor neuron stopped discharging action potentials. The rapid increase in discharge rate during the increase in muscle force is similar to the change in rate observed in the presence of moderate levels of monoaminergic input (see part **B**).

contains approximately 200 actin monomers. Superimposed on F-actin are tropomyosin and troponin, proteins that control the interaction between actin and myosin. Tropomyosin consists of two coiled strands that lie in the groove of the F-actin helix; troponin is a small molecular complex that is attached to tropomyosin at regular intervals (Figure 31–9C).

The thin filaments are anchored to the Z disk at each end of the sarcomere, whereas the thick filaments occupy the middle of the sarcomere (Figure 31–9B). This organization accounts for the alternating light and dark bands of striated muscle. The light band contains only thin filaments, whereas the dark band contains both thick and thin filaments. When a muscle is

activated, the width of the light band decreases but the width of the dark band does not change, suggesting that the thick and thin filaments slide relative to one another during a contraction. This led to the *sliding filament hypothesis* of muscle contraction proposed by A. F. Huxley and H. E. Huxley in the 1950s.

The sliding of the thick and thin filaments is triggered by the release of Ca^{2+} from within the sarcoplasm of a muscle fiber in response to an action potential that travels along the fiber's membrane, the sarcolemma. Varying the amount of Ca^{2+} in the sarcoplasm controls the interaction between the thick and thin filaments. The Ca^{2+} concentration in the sarcoplasm is kept low under resting conditions by active pumping of Ca^{2+} into the sarcoplasmic reticulum, a network of longitudinal tubules and chambers of smooth endoplasmic reticulum. Calcium is stored in the terminal cisternae, which are located next to intracellular extensions of the sarcolemma known as transverse tubules (T-tubules). The transverse tubules, terminal cisternae, and sarcoplasmic reticulum constitute an activation system that transforms an action potential into the sliding of the thick and thin filaments (Figure 31–9A).

As an action potential propagates along the sarcolemma, it invades the transverse tubules and causes the rapid release of Ca^{2+} from the terminal cisternae into the sarcoplasm. Once in the sarcoplasm, Ca^{2+} diffuses among the filaments and binds reversibly to troponin, which results in the displacement of the troponin–tropomyosin complex and enables the sliding of the thick and thin filaments. Because a single action potential does not release enough Ca^{2+} to bind all available troponin sites in skeletal muscle, the strength of a contraction increases with the action potential rate.

The sliding of the filaments depends on mechanical work performed by the globular heads of myosin, work that uses chemical energy contained in adenosine triphosphate (ATP). The actions of the myosin heads are regulated by the *cross-bridge cycle*, a sequence of detachment, activation, and attachment (Figure 31–10). In each cycle, a globular head undergoes a displacement of 5 to 10 nm. Contractile activity continues as long as Ca^{2+} and ATP are present in the cytoplasm in sufficient amounts.

Once the contractile proteins have been activated by the release of Ca^{2+}, sarcomere length may increase, remain the same, or decrease depending on the magnitude of the load against which the muscle is acting. The force generated by an activated sarcomere when its length does not change or decreases can be explained by the cross-bridge cycle involving the thick and thin filaments. When the length of the activated sarcomere increases, however, the force developed by the extension of titin adds significantly to the sarcomere force. The force produced by titin during the stretch of an activated sarcomere is augmented by its ability to increase stiffness, which is accomplished when titin binds Ca^{2+} and then attaches at specific locations on actin to reduce the length that it can be stretched. The force produced by activated sarcomeres therefore depends on the interactions of three filaments (actin, myosin, and titin).

Noncontractile Elements Provide Essential Structural Support

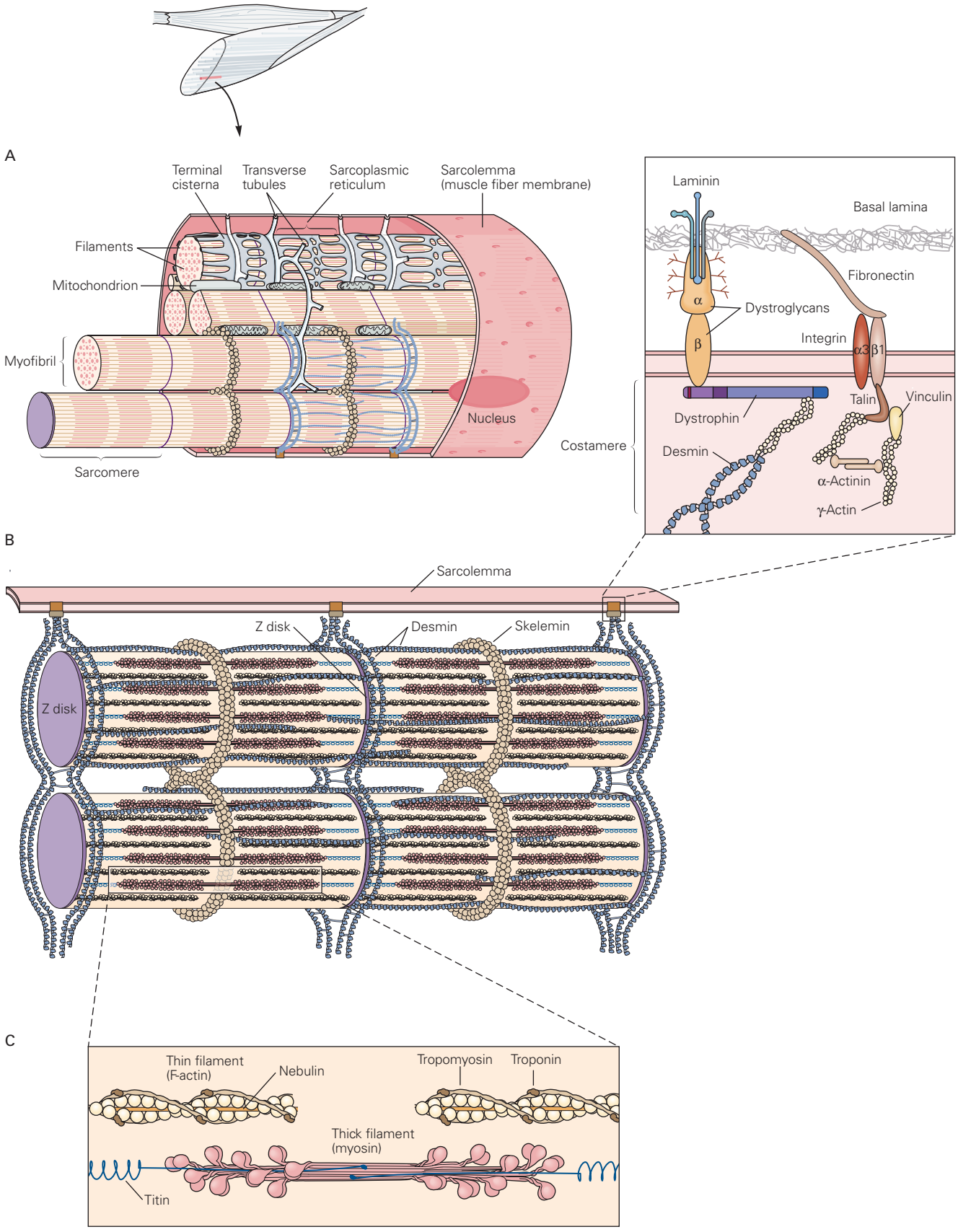
Structural elements of the muscle fiber maintain the alignment of the contractile proteins within the fiber and facilitate the transmission of force from the sarcomeres to the skeleton. A network of proteins (nebulin, titin) maintains the orientation of the thick and thin filaments within the sarcomere, whereas other proteins (desmin, skelemins) constrain the lateral alignment of the myofibrils (Figure 31–9B). These proteins contribute to the elasticity of muscle and maintain the appropriate alignment of cellular structures when the muscle acts against an external load.

Although some of the force generated by the cross bridges is transmitted along the sarcomeres in series, most of it travels laterally from the thin filaments to an extracellular matrix that surrounds each muscle fiber, through a group of transmembrane and membrane-associated proteins called a *costamere* (see inset for Figure 31–9B). The lateral transmission of force follows two pathways through the costamere, one through a dystrophin–glycoprotein complex and the other through vinculin and members of the integrin family. Mutations of genes that encode components of the dystrophin–glycoprotein complex cause muscular dystrophies in humans, which are associated with substantial decreases in muscle force.

Contractile Force Depends on Muscle Fiber Activation, Length, and Velocity

The force that a muscle fiber can exert depends on the number of cross bridges formed and the force produced by each cross bridge. These two factors are influenced by the Ca^{2+} concentration in the sarcoplasm, the amount of overlap between the thick and thin filaments, and the velocity with which the thick and thin filaments slide past one another.

The influx of Ca^{2+} that activates formation of the cross bridges is transitory because continuous pump activity quickly returns Ca^{2+} to the sarcoplasmic reticulum. The release and reuptake of Ca^{2+} in response to a single action potential occurs so quickly that only some


A
Terminal cisterna
Transverse tubules
Sarcoplasmic reticulum
Sarcolemma (muscle fiber membrane)
Filaments
Mitochondrion
Myofibril
Nucleus
Sarcomere
Laminin
Basal lamina
Fibronectin
α
Dystroglycans
β
Integrin
α3β1
Talin
Vinculin
Dystrophin
Costamere
Desmin
α-Actinin
γ-Actin
B
Sarcolemma
Z disk
Desmin
Skelemin
Z disk
C
Thin filament (F-actin)
Nebulin
Tropomyosin
Troponin
Thick filament (myosin)
Titin