14

Diseases of the Nerve and Motor Unit

… to move things is all that mankind can do, for such the sole executant is muscle, whether in whispering a syllable or in felling a forest.

Charles Sherrington, 1924

The major consequence of the elaborate information processing that takes place in the brain is the contraction of skeletal muscles. Indeed, animals are distinguishable from plants by their ability to make precise, goal-directed movements of their body parts. As we shall see in Chapter 16, the problem of deciding when and how to move is, to a large degree, the driving force behind the evolution of the nervous system.

In all but the most primitive animals, specialized muscle cells generate movement. There are three general types of muscles: Smooth muscle is used primarily for internal actions such as peristalsis and control of blood flow; cardiac muscle is used exclusively for pumping blood; and skeletal muscle is used primarily for moving bones. In this chapter we examine a variety of neurological disorders in mammals that affect movement by altering action potential conduction in a motor nerve, synaptic transmission from nerve to muscle, or muscle contraction itself.

In 1925 Charles Sherrington introduced the term *motor unit* to designate the basic unit of motor function—a motor neuron and the group of muscle fibers it innervates (see Chapter 34). The number of muscle fibers innervated by a single motor neuron varies widely throughout the body, depending on the dexterity of the movements controlled and the mass of the

body part to be moved. Thus motor units with fewer than 100 muscle fibers finely control eye movements, whereas in the leg a single motor unit contains up to 1,000 muscle fibers. In each case all the muscles innervated by a motor unit are of the same type. Moreover, motor units are recruited in a fixed order for both voluntary and reflex movements. The smallest motor units are the first to be recruited, joined later by larger units as muscle force increases.

The motor unit is a common target of disease. The distinguishing features of diseases of the motor unit vary depending on which functional component is primarily affected: (1) the cell body of the motor or sensory neuron, (2) the corresponding axons, (3) the neuromuscular junction (the synapse between the motor axon and muscle), or (4) the muscle fibers that are innervated by the motor neuron. Accordingly, disorders of the motor unit have traditionally been classified as motor neuron diseases, peripheral neuropathies, disorders of the neuromuscular junction, or primary muscle diseases (myopathies) (Figure 14–1).

Peripheral neuropathies arise from abnormal function of motor neurons or their axons, leading to weakness of movement. Most peripheral neuropathies also involve sensory neurons, leading to problems in sensation. In some rare motor neuron diseases the motor neurons and motor tracts in the spinal cord degenerate but sensory nerves are spared. In *myopathies* weakness is caused by degeneration of the muscles with little or no change in motor neurons. In neuromuscular junction diseases alterations in the synapse lead to weakness that may be intermittent. Clinical and laboratory studies usually allow one to distinguish disorders of peripheral nerves from those of the neuromuscular junction or muscle (see Postscript to this chapter).

Disorders of the Peripheral Nerve, Neuromuscular Junction, and Muscle Can Be Distinguished Clinically

When a peripheral nerve is cut, the muscles innervated by that nerve immediately become paralyzed and then waste progressively. Because the nerve carries sensory as well as motor fibers, sensation in the area innervated by the nerve is also lost and tendon reflexes are lost immediately. The term *atrophy* (literally, lack of nourishment) refers to the wasting away of a once-normal muscle. Because of historical usage *atrophy* appears in the names of several diseases that are now regarded as neurogenic.

The main symptoms of the myopathies often include difficulty in walking or lifting. Other, less common symptoms include inability of the muscle to relax (myotonia), cramps, pain (myalgia), or the appearance in the urine of the heme-containing protein that gives muscle its red color (myoglobinuria). The muscular dystrophies are myopathies with special characteristics: The diseases are inherited, all symptoms are caused by

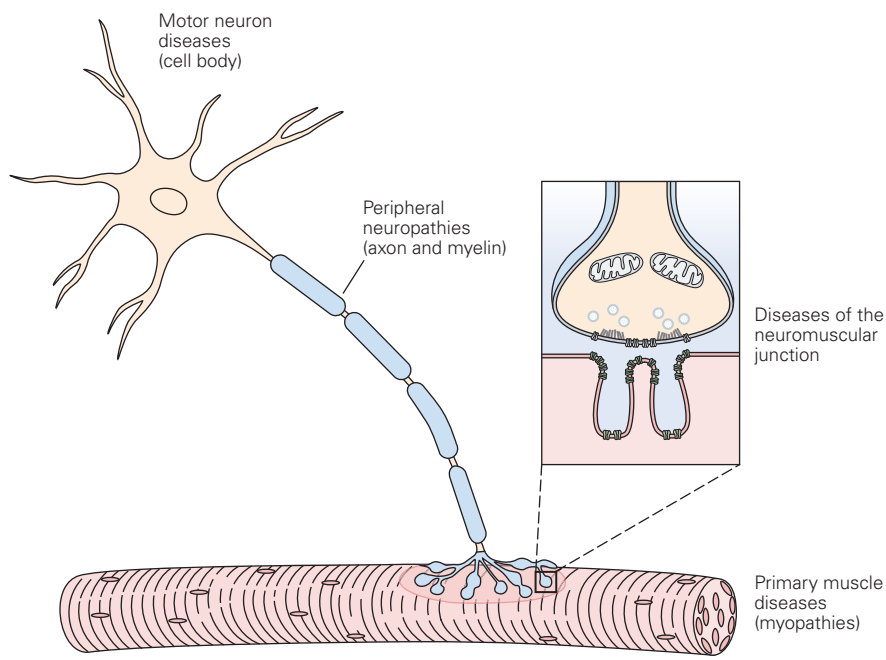


Figure 14–1 Classification of the four types of motor unit disorders is based on the part of the motor unit that is affected.

weakness, the weakness becomes progressively more severe, and signs of degeneration and regeneration are seen histologically.

Distinguishing neurogenic and myopathic diseases may be difficult because both produce weakness of muscle. Classification and differential diagnosis of these diseases involve both clinical and laboratory criteria. As a first approximation, weakness of the distal limbs most often indicates a neurogenic disorder, whereas proximal limb weakness signals a myopathy. *Fasciculations*—twitches of muscle that are visible through the skin—are often signs of neurogenic diseases. They result from involuntary but synchronous contractions of all muscle fibers in a motor unit. *Fibrillations*—spontaneous contractions of single muscle fibers—can also be signs of on going denervation of muscle. Fibrillations are not visible but can be recorded with an electromyogram (EMG). The electrical record of a fibrillation is a low-amplitude potential that reflects electrical activity in a single muscle cell. Electrophysiological studies suggest that fasciculations arise in the motor nerve terminal.

In diagnosing motor neuron disorders, clinical neurologists distinguish between lower and upper motor neurons. *Lower motor neurons* are motor neurons of the spinal cord and brain stem that directly innervate skeletal muscles. *Upper motor neurons* are neurons in the premotor cortex that issue commands for movements to the lower motor neurons through their axons in the corticospinal (pyramidal) tract. The distinction between upper and lower motor neurons is important clinically because diseases involving each class of neurons produce distinctive symptoms. Disorders of lower motor neurons cause atrophy, fasciculations, decreased muscle tone, and loss of tendon reflexes; disorders of upper motor neurons and their axons result in spasticity, overactive tendon reflexes, and an abnormal plantar extensor reflex (the Babinski sign).

The primary symptom of disorders of the neuromuscular junction is weakness; in some neuromuscular junction diseases this weakness is quite variable even during the course of a single day.

A Variety of Diseases Target Motor Neurons and Peripheral Nerves

Motor Neuron Diseases Do Not Affect Sensory Neurons

The best-known disorder of motor neurons is amyotrophic lateral sclerosis (Lou Gehrig disease). *Amyotrophy* is another word for neurogenic atrophy of muscle; *lateral sclerosis* refers to the hardness felt when the pathologist examines the spinal cord at autopsy. This hardness results from the proliferation of astrocytes and scarring of the lateral columns of the spinal cord caused by degeneration of the corticospinal tracts. Some motor neurons are spared, notably those supplying ocular muscles and those involved in voluntary control of bladder sphincters.

The symptoms of amyotrophic lateral sclerosis (ALS) usually start with painless weakness of the arms or legs. Typically the patient, often a man in his 40s or 50s, discovers that he has trouble in executing fine movements of the hands; typing, playing the piano, playing baseball, fingering coins, or working with tools all become awkward.

Most cases of ALS involve both upper and lower motor neurons. Thus the typical weakness of the hand is associated with wasting of the small muscles of the hands and feet and fasciculations of the muscles of the forearm and upper arm. These signs of lower motor neuron disease are often associated with hyperreflexia, an increase in tendon reflexes characteristic of corticospinal upper motor neuron disease.

The cause of most (95%) cases of ALS is unknown; the disease is progressive and ultimately affects muscles of respiration. There is no effective treatment for this fatal condition.

Approximately 10% of cases are inherited as dominant traits. Of these, approximately 25% arise from mutations in the gene encoding the protein copper/zinc cytosolic superoxide dismutase, or SOD1. The fact that this form of the disease is dominantly inherited suggests that the disorder arises from some acquired toxic property of the mutant SOD1 protein. This is underscored by the observation that nearly all mutations causing this form of ALS are missense changes that substitute one or more amino acids in the wild-type, normal protein. The exact neurotoxic property of the mutant enzyme remains unclear.

Strikingly, mice and rats that have high levels of the mutant SOD1 develop an adult-onset form of motor neuron disease that leads to death. By contrast, mice expressing equivalently high levels of normal SOD1 do not develop paralysis. These findings are consistent with the concept that the mutant molecule has acquired one or more forms of cytotoxicity. As with other aspects of normal and abnormal functions of the brain and spinal cord, mouse models of motor neuron disease have proven highly instructive for the study of potential treatments as well as the molecular pathogenesis of the disease.

There are other variants of motor neuron disease. The first symptoms may be restricted to muscles

innervated by cranial nerves, with resulting dysarthria (difficulty speaking) and dysphagia (difficulty swallowing). When cranial symptoms occur alone, the syndrome is called progressive bulbar palsy. (The term *bulb* is used interchangeably with *pons,* the structure at the base of the brain where motor neurons that innervate the face and swallowing muscles reside, and *palsy* means weakness.) If only lower motor neurons are involved, the syndrome is called progressive spinal muscular atrophy.

Progressive spinal muscular atrophy is a developmental disorder of motor neurons and is characterized by weakness, wasting, loss of reflexes, and fasciculations. Most cases arise in infants and are caused by recessively inherited mutations in the gene encoding a protein called survival motor neuron or SMN. Some rare cases begin in late childhood or even early adulthood. The SMN protein is implicated in the trafficking of RNA in and out of the nucleus and in the formation of complexes that are important in RNA splicing. In humans the SMN locus on chromosome 5 has two almost identical copies of the SMN gene. One produces a full length SMN protein, whereas the second expresses a small amount of full-length SMN and a shortened SMN. The loss of full-length SMN from mutations at the main locus can be mitigated to some degree by the shortened SMN protein expressed at the second locus.

Amyotrophic lateral sclerosis and its variants are restricted to motor neurons; they do not affect sensory neurons or autonomic neurons. The acute viral disease poliomyelitis is also confined to motor neurons. These diseases illustrate dramatically the individuality of nerve cells and the principle of selective vulnerability. The basis of this selectivity is, in general, not understood.

Diseases of Peripheral Nerves Affect Conduction of the Action Potential

Diseases of peripheral nerves may affect either axons or myelin. Because motor and sensory axons are bundled together in the same peripheral nerves, disorders of peripheral nerves usually affect both motor and sensory functions. Some patients with peripheral neuropathy report abnormal, frequently unpleasant, sensory experiences similar to the sensations felt after local anesthesia for dental work. These sensations are variously called numbness, pins-and-needles, or tingling. When the sensations occur spontaneously without an external sensory stimulus they are called paresthesias.

Patients with paresthesias usually have impaired perception of cutaneous sensations (pain and temperature), often because the small myelinated fibers that carry these sensations are selectively affected. Proprioceptive sensations (position and vibration) may be lost without loss of cutaneous sensation. Lack of pain perception may lead to injuries. The sensory disorders are more prominent distally (called a glove-and-stocking pattern), possibly because the distal portions of the nerves are most remote from the cell body and therefore most susceptible to disorders that interfere with axonal transport of essential metabolites and proteins.

Peripheral neuropathy is first manifested by weakness that is usually distal. Tendon reflexes are usually depressed or lost, fasciculation is seen only rarely, and wasting does not ensue unless the weakness has been present for many weeks.

Neuropathies may be either acute or chronic. The best-known acute neuropathy is Guillain-Barré syndrome. Most cases follow respiratory infection or infectious diarrhea, but the syndrome may occur without preceding illness. The condition may be mild or so severe that mechanical ventilation is required. Cranial nerves may be affected, leading to paralysis of ocular, facial, and oropharyngeal muscles. The disorder is attributed to an autoimmune attack on peripheral nerves by circulating antibodies. It is treated by removing the offending antibodies by infusions of gamma globulin and plasmapheresis. The blood is removed from a patient, cells are separated from plasma which has the antibodies, and the cells alone are returned to the patient.

The chronic neuropathies vary from the mildest manifestations to incapacitating or even fatal conditions. There are many varieties, including genetic diseases (acute intermittent porphyria, Charcot-Marie-Tooth disease), metabolic disorders (diabetes, vitamin B_{12} deficiency), intoxication (lead), nutritional disorders (alcoholism, thiamine deficiency), carcinomas (especially carcinoma of the lung), and immunological disorders (plasma cell diseases, amyloidosis). Some chronic disorders, such as neuropathy caused by vitamin B_{12} deficiency in pernicious anemia, are amenable to therapy.

In addition to being acute or chronic, neuropathies may be categorized as demyelinating (in which the myelin sheath breaks down) or axonal (in which the axon is affected). In demyelinating neuropathies, as might be expected from the role of the myelin sheath in saltatory conduction, conduction velocity is slowed because the axons have lost myelin (discussed below). In axonal neuropathies the myelin sheath is not affected and conduction velocity is normal.

Axonal and demyelinating neuropathies may lead to positive or negative symptoms and signs. The negative signs consist of weakness or paralysis, loss of

tendon reflexes, and impaired sensation resulting from loss of motor and sensory nerves. The positive symptoms of peripheral neuropathies consist of paresthesias that arise from abnormal impulse activity in sensory fibers, and either spontaneous activity of injured nerve fibers or electrical interaction (cross-talk) between abnormal axons, a process called *ephaptic transmission* to distinguish it from normal synaptic transmission. For unknown reasons damaged nerves also become hyperexcitable. Lightly tapping the site of injury can evoke a burst of unpleasant sensations in the region over which the nerve is distributed.

Negative symptoms, which have been studied more thoroughly than positive symptoms, can be attributed to three basic mechanisms: conduction block, slowed conduction, and impaired ability to conduct impulses at higher frequencies. Conduction block was first recognized in 1876 when the German neurologist Wilhelm Erb observed that stimulation of an injured peripheral nerve below the site of injury evoked a muscle response, whereas stimulation above the site of injury produced no response. He concluded that the lesion blocked conduction of impulses of central origin, even when the segment of the nerve distal to the lesion was still functional. Later studies confirmed this conclusion by showing that selective application of diphtheria and other toxins produces conduction block by causing demyelination only at the site of application.

Why does demyelination produce nerve block and how does it lead to slowing of conduction velocity? As discussed in Chapter 6, conduction velocity is much more rapid in myelinated fibers than in unmyelinated axons for two reasons. First, there is a direct relationship between conduction velocity and axon diameter, and myelinated axons tend to be larger in diameter. Second, membrane capacitance in the myelinated regions of the axon is less than at the unmyelinated nodes of Ranvier, greatly speeding up the rate of depolarization and thus conduction. In contrast, when an action potential propagates along long stretches of demyelinated axon it becomes severely attenuated.

When myelination is disrupted by disease, the action potentials in different axons of a nerve begin to conduct at slightly different velocities. As a result, the nerve loses its normal synchrony of conduction in response to a single stimulus (measurement of conduction velocities in peripheral nerves is described in Figure 14–2). This slowing and loss of synchrony are thought to account for some early clinical signs of demyelinating neuropathy. For example, functions that normally depend on the arrival of synchronous bursts of neural activity, such as tendon reflexes and vibratory sensation, are lost soon after the onset of a chronic neuropathy. As demyelination becomes more severe, conduction becomes blocked. Conduction failure may be intermittent, occurring only at high frequencies of neural firing, or complete.

The Molecular Bases of Some Inherited Peripheral Neuropathies Have Been Defined

Myelin proteins have been found to be affected in some demyelinating hereditary peripheral neuropathies, termed Charcot-Marie-Tooth disease. As in other peripheral neuropathies, muscle weakness and wasting, loss of reflexes, and loss of sensation in the distal parts of the limbs characterize the condition. These symptoms appear in childhood or adolescence and are slowly progressive.

One form (type 1) has the features of a demyelinating neuropathy. Conduction in peripheral nerves is slow, with histological evidence of demyelination followed by remyelination. Sometimes the remyelination leads to gross hypertrophy of the nerves. Type 1 disorders are inexorably progressive, without remissions or exacerbations. Another form (type 2) has normal nerve conduction velocity and is considered an axonal neuropathy without demyelination. Both types 1 and 2 are inherited as autosomal dominant diseases.

In the 1990s the genetic defects in these conditions began to be localized. The type 1 disease was attributed to mutations on two different chromosomes (locus heterogeneity). A more common form (type 1A) was linked to chromosome 17, whereas a less common form (1B) was localized to chromosome 1. To a remarkable degree the genes at these loci have been directly implicated in myelin physiology (Figure 14–3). Type 1A involves a defect in peripheral myelin protein 22, and type 1B the myelin protein P_0. Moreover, as discussed in Chapter 8, an X-linked form of demyelinating neuropathy occurs because of mutations in the gene expressing connexin-32, a subunit of the gap-junction channels that interconnect myelin folds near the nodes of Ranvier (Figure 14–3B). Still other genes have been implicated in inherited demyelination.

Some proteins implicated in axonal neuropathies are identified in Figure 14–4 and Table 14–1. Genes encoding the neurofilament light subunit and an axonal motor protein related to kinesin, which is important for transport along microtubules, are mutated in two types of axonal neuropathies. Defects in these genes are associated with peripheral neuropathies with prominent weakness. The mechanisms by which genes alter axonal function in other axonal neuropathies are less evident.

As noted earlier, a wide range of problems other than genetic mutations lead to peripheral neuropathies. Particularly striking are nerve defects associated with the presence of autoantibodies directed against ion channels in distal peripheral nerves. For example, some individuals with motor unit instability (cramps and fasciculations), as well as sustained or exaggerated muscle contractions caused by hyperexcitability of motor nerves, have serum antibodies directed against one or more axonal voltage-gated K^+ channels. The prevailing view is that binding the autoantibodies to the channels reduces K^+ conductance and thereby depolarizes the axon, leading to augmented and sustained firing of the distal motor nerve and associated muscle contractions. Alterations in ion channel function underlie a variety of neurological disorders, as in acquired disorders of channels in the neuromuscular junction and inherited defects in voltage-gated channels in muscle (discussed below).

Diseases of the Neuromuscular Junction Have Multiple Causes

Many diseases involve disruption of chemical transmission between neurons and their target cells. By analyzing such abnormalities researchers have learned a great deal about the mechanisms underlying normal synaptic transmission as well as disorders caused by dysfunction at the synapse.

Diseases that disrupt transmission at the neuromuscular junction fall into two broad categories:

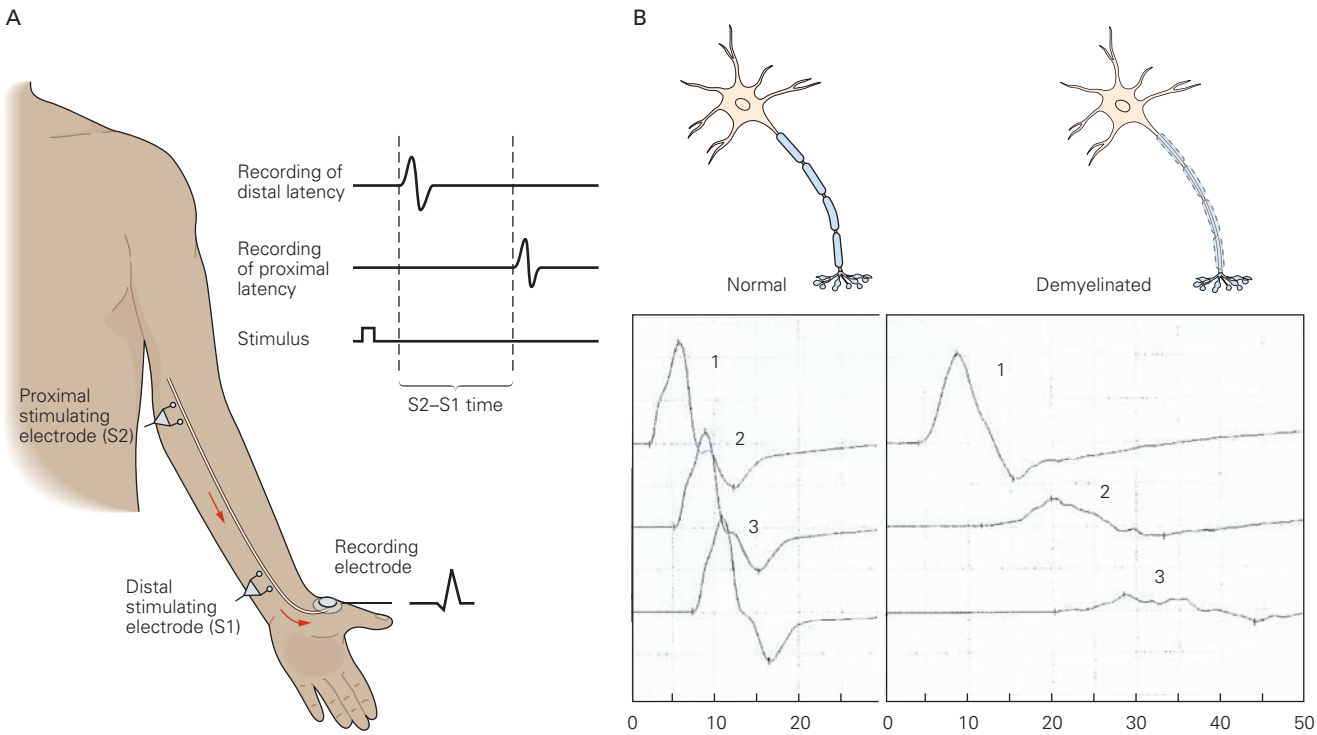


Figure 14–2 Measurement of motor nerve conduction velocity.

A. A shock is applied through a proximal (S2) or distal (S1) stimulating electrode, and the extracellular action potential is measured by the recording electrode. The time it takes the action potential to propagate from S2 to the muscle (t_{S2}) is the proximal latency; the time from S1 to the muscle (t_{S1}) is the distal latency. The distance between S1 and S2 divided by ($t_{S2} - t_{S1}$) gives the conduction velocity.

B. The waveforms of motor nerve action potentials are recorded in the thumb muscles after stimulation of the motor nerve at the wrist (**1**), just below the elbow (**2**), and just above the elbow (**3**). The action potentials from a normal nerve have the same waveforms regardless of the site of stimulation. They are distinguished only by the longer time period required for the waveform to develop as the site of the stimulus is moved up the arm (away from the recording site). When the motor nerve is demyelinated just distal to the elbow but above the wrist, the motor nerve action potential is normal when stimulation occurs at the wrist (**1**) but delayed and desynchronized when stimulation is proximal to the nerve lesion (**2, 3**). (Reproduced, with permission, from Bromberg 2002.)

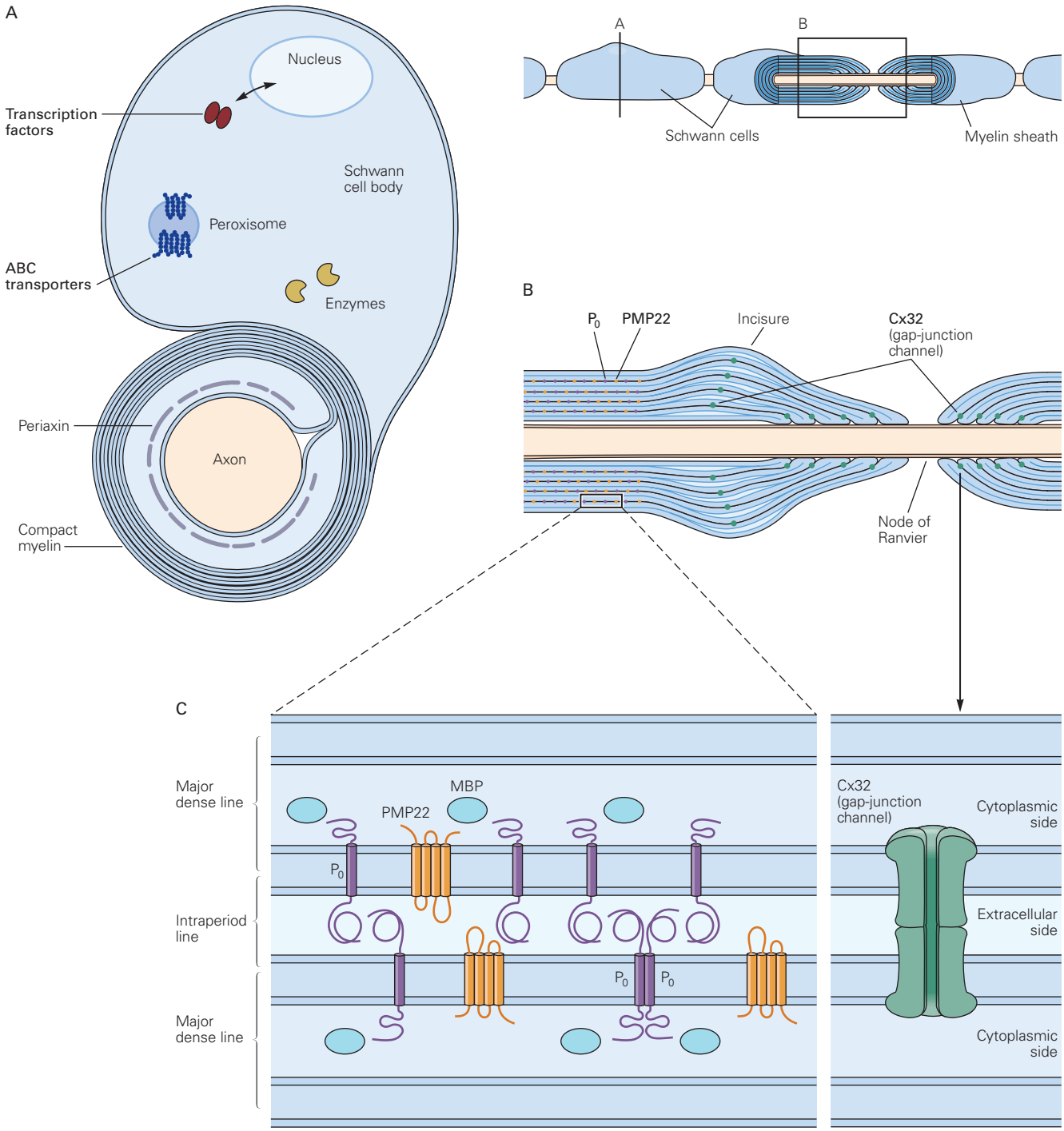


Figure 14–3 Genetic defects in components of myelin cause demyelinating neuropathies.

A. Myelin production and function in the Schwann cell are adversely affected by multiple genetic defects including abnormalities in transcription factors, ABC (*ATP-b*inding *c*assette) transporters in peroxisomes, and multiple proteins implicated in organizing myelin. In compact myelin thin processes of Schwann cells are tightly wrapped around an axon. Viewed microscopically at high power, the site of apposition of the intracellular faces of the Schwann cell membrane appears as a dense line, whereas the apposed extracellular faces are described as the *intraperiod line* (see definition in part C). (Adapted, with permission, from Lupiski 1998.)

B. Peripheral axons are wrapped in myelin, which is compact and tight except near the nodes of Ranvier and at focal sites described as "incisures" by Schmidt and Lanterman. (Adapted, with permission, from Lupiski 1998.)

C. The rim of cytoplasm, in which myelin basic protein (MBP) is located, defines the major dense line, whereas the thin layer of residual extracellular space defines the intraperiod line. Three myelin-associated proteins are defective in three different demyelinating neuropathies: P_0 (Dejerine-Sottas infantile neuropathy), peripheral myelin protein or PMP22 (Charcot-Marie-Tooth neuropathy type 1), and connexin-32 or Cx32 (X-linked Charcot-Marie-Tooth neuropathy). Mutations in PMP22 and P_0 genes adversely affect the organization of compact myelin. (Adapted, with permission, from Brown and Amato 2002.)

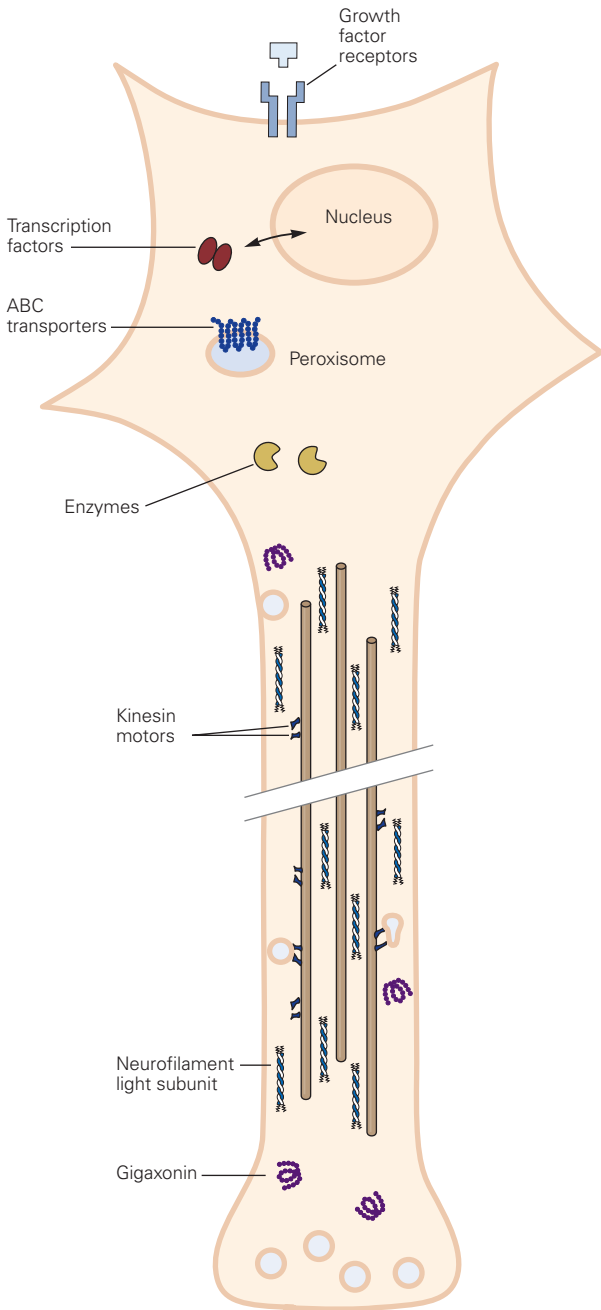


Figure 14–4 Genetic defects in a number of cell constituents cause axonal neuropathies. These include defects in receptors for growth factors, ABC (ATP-binding cassette) transporters in peroxisomes, cytosolic enzymes, microtubule motor proteins like the kinesins, neurofilament proteins, and other structural proteins such as gigaxonin. (Adapted, with permission, from Brown and Amato 2002.)

those that affect the presynaptic terminal and those that primarily involve the postsynaptic membrane. In both categories the most intensively studied cases are autoimmune and inherited defects in critical synaptic proteins.

Myasthenia Gravis Is the Best Studied Example of a Neuromuscular Junction Disease

The most common and extensively studied disease affecting synaptic transmission is myasthenia gravis, a disorder at the neuromuscular junction in skeletal muscle. Myasthenia gravis (the term means severe weakness of muscle) has two major forms. The most prevalent is the autoimmune form. The second is congenital and heritable; it is not an autoimmune disorder and is heterogeneous. Fewer than 500 cases have been identified, but analysis of the congenital syndromes has provided information about the organization and function of the human neuromuscular junction. This form is discussed later in the chapter.

In autoimmune myasthenia gravis antibodies are produced against the nicotinic acetylcholine (ACh) receptor in muscle. These antibodies interfere with synaptic transmission by reducing the number of functional receptors or by impeding the interaction of ACh with its receptors. As a result, communication between the

Table 14–1 Representative Inherited Disorders of Peripheral Nerves

Site of primary defect	Protein	Disease
Myelin	Proteolipid myelin protein 22	Charcot-Marie-Tooth disease (CMT)
	Proteolipid protein P_0	Infantile CMT (Dejerine-Sottas neuropathy)
	Connexin-32	X-linked CMT
Axon	Kinesin KIF1Bβ motor protein	Motor predominant neuropathy
	Heat shock protein 27	Motor predominant neuropathy
	Neurofilament light subunit	Motor predominant neuropathy
	Tyrosine kinase A receptor	Congenital sensory neuropathy
	ABC 1 transporter	Tangier disease
	Transthyretin	Amyloid neuropathy

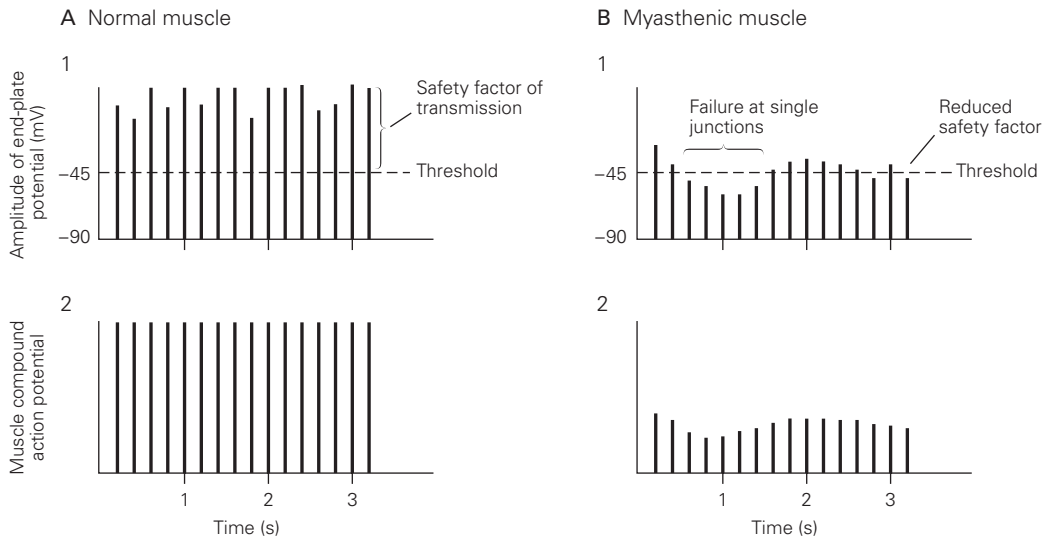


Figure 14–5 Synaptic transmission at the neuromuscular junction fails in myasthenia gravis. (Reproduced, with permission, from Lisak and Barchi 1982.)

A. In the normal neuromuscular junction the amplitude of the end-plate potential is so large that all fluctuations in the potential occur well above the threshold for an action potential. That is, there is a large safety factor in synaptic transmission (1). Therefore, during repetitive stimulation of the motor nerve the amplitude of the compound action potentials, representing the action potentials in all muscle fibers innervated by the nerve, is constant and invariant (2).

B. In the myasthenic neuromuscular junction postsynaptic changes reduce the amplitude of the end-plate potential so that under optimal circumstances the end-plate potential may be just sufficient to produce a muscle action potential. Fluctuations in transmitter release that normally accompany repeated stimulation now cause the end-plate potential to drop below this threshold, leading to conduction failure at that synapse (1). The amplitude of the compound action potentials in the muscle declines progressively and shows only a small and variable recovery (2).

motor neuron and the skeletal muscle becomes weakened. This weakness has four special characteristics:

1. It almost always affects cranial muscles—eyelids, eye muscles, and oropharyngeal muscles—as well as limb muscles.
2. The severity of symptoms varies in the course of a single day, from day to day, or over longer periods (giving rise to periods of remission or exacerbation), making myasthenia gravis unlike most other diseases of muscle or nerve.
3. There are no conventional clinical or electromyographic signs of denervation.
4. The weakness is reversed by drugs that inhibit acetylcholinesterase, the enzyme that degrades ACh.

Myasthenia gravis is a disorder of neuromuscular transmission. When a motor nerve is stimulated at rates of 2 to 5 per second, the amplitude of the compound action potential evoked in normal human muscle remains constant. In myasthenia gravis the amplitude decreases rapidly. This abnormality resembles the pattern induced in normal muscle by *d*-tubocurarine (the active compound in curare), which blocks nicotinic ACh receptors and inhibits the action of ACh at the neuromuscular junction. Neostigmine (Prostigmin), which inhibits acetylcholinesterase and thus prolongs the action of ACh at the neuromuscular junction, reverses the decrease in amplitude of evoked compound action potentials in myasthenic patients (Figure 14–5).

The decrease in the compound muscle action potential in response to repetitive stimulation of the motor nerve mirrors the clinical symptom of fatigability in myasthenia. For example, when patients are asked to look upward in a sustained gaze, the eyelids tire after several seconds and droop downward (ptosis). Like decremental responses on electromyography, this fatigability and drooping reverse after treatment with inhibitors of acetylcholinesterase (Figure 14–6).

Approximately 15% of adult patients with myasthenia have benign tumors of the thymus (thymomas). As the symptoms in myasthenic patients are often improved by removal of these tumors, some element of the thymoma may stimulate autoimmune

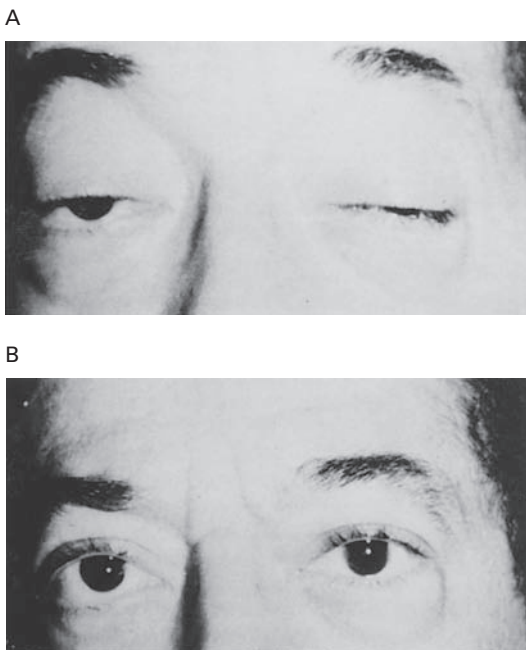


Figure 14–6 Myasthenia gravis often selectively affects the cranial muscles. (Reproduced, with permission, from Rowland, Hoefer, and Aranow 1960.)

A. Severe drooping of the eyelids, or ptosis, is characteristic of myasthenia gravis. This patient also could not move his eyes to look to either side.

B. One minute after an intravenous injection of 10 mg edrophonium, an inhibitor of acetylcholinesterase, both eyes are open and can be moved freely. The inhibition of acetylcholinesterase prolongs the action of ACh in the synaptic cleft, thus compensating for the reduced number of ACh receptors in the muscle (see Figure 14–7).

pathology. Indeed, myasthenia gravis often affects people who have other autoimmune diseases, such as rheumatoid arthritis, systemic lupus erythematosus, or Graves disease (hyperthyroidism).

The modern concept of myasthenia emerged with the isolation and characterization of the nicotinic ACh receptor. In 1973 Douglas Fambrough and Daniel Drachman, using radioactive α-bungarotoxin to label the receptor in human end-plates, found fewer binding sites in myasthenic muscle than in controls. In addition, morphological studies revealed a smoothing of the junctional folds, the site of receptor localization (Figure 14–7).

That same year James Patrick and Jon Lindstrom demonstrated in rabbits that the generation of antireceptor antibodies was accompanied by the onset of myasthenia-like symptoms when they injected animals with nicotinic ACh receptors purified from eel electroplax (which is related to the skeletal muscles of higher vertebrates). The weakness was reversed by the cholinesterase inhibitors neostigmine or edrophonium. As in humans with myasthenia gravis, the animals were abnormally sensitive to neuromuscular blocking agents such as curare, and the evoked compound action potentials in muscle decreased with repetitive stimulation. It was later found that a similar syndrome could be induced in mice and other mammals by immunization with nicotinic ACh receptor protein (Figure 14–8).

By 1975 all the essential characteristics of the human disease had been reproduced in experimental

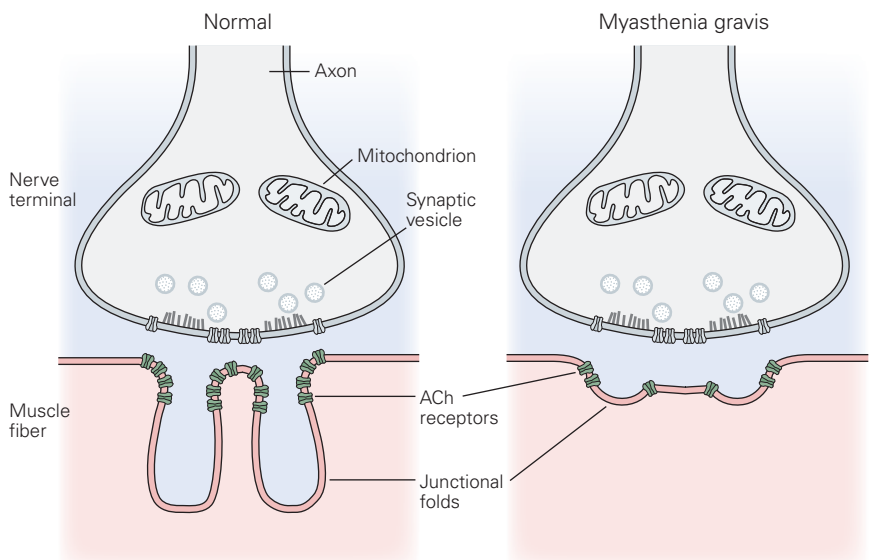
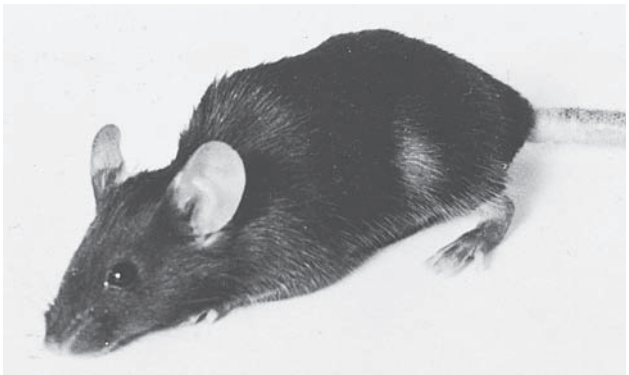


Figure 14–7 Morphological abnormalities of the neuromuscular junction in myasthenia gravis. At the neuromuscular junction ACh is released by exocytosis of synaptic vesicles at active zones in the nerve terminal. Acetylcholine flows across the synaptic cleft to reach receptors that are concentrated at the peaks of junctional folds. Acetylcholinesterase in the cleft rapidly terminates transmission by hydrolyzing ACh. The myasthenic neuromuscular junction has a reduced number of ACh receptors, simplified synaptic folds, and a widened synaptic space, but a normal nerve terminal.

A



B

Figure 14–8 The posture of a myasthenic mouse improves after treatment with neostigmine. To produce the syndrome the mouse was immunized with 15 µg of purified nicotinic ACh receptor protein. (Reproduced, with permission, from Berman and Patrick 1980.)

A. Before treatment the mouse is inactive.

B. The mouse is standing 12 minutes after receiving an intraperitoneal injection of 37.5 µg/kg neostigmine bromide, which inhibits acetylcholinesterase and thus increases the availability of ACh in the synaptic cleft of the neuromuscular junction.

autoimmune myasthenia gravis in mice, rabbits, and monkeys. After experimental myasthenia gravis was characterized, antibodies directed against nicotinic ACh receptors were found in the serum of many patients with myasthenia. How do these immunological observations account for the characteristic decrease in the response of myasthenic muscle to repeated stimulation?

An action potential in a motor axon normally releases enough ACh to induce a large excitatory end-plate potential with an amplitude of approximately 70 to 80 mV relative to the resting potential of –90 mV (see Chapter 9). Thus the normal end-plate potential is greater than the threshold needed to initiate an action potential, approximately –45 mV. In normal muscle the difference between the threshold and the actual end-plate potential amplitude—the safety factor—is therefore quite large (Figure 14–5A). In fact, in many muscles the amount of ACh released during synaptic transmission can be reduced to as little as 25% of normal before it fails to initiate an action potential.

A reduction in the density of ACh receptors, as in myasthenia, reduces the probability that a molecule of ACh will find a receptor before it is hydrolyzed by the enzyme acetylcholinesterase. In addition, in myasthenia the geometry of the end-plate is also disturbed. The normal infolding at the junctional folds is reduced and the synaptic cleft is enlarged (Figure 14–7). These morphological changes promote diffusion of ACh away from the synaptic cleft and thus further reduce the probability of ACh interacting with the few remaining functional receptors. As a result, the amplitude of the end-plate potential is reduced to the point where it is barely above threshold (Figure 14–5B).

Thus in myasthenia synaptic transmission is readily blocked even though the vesicles in the presynaptic terminals contain normal amounts of ACh and the process of transmitter release is intact. Both the physiological abnormality (the decremental response) and the clinical symptoms (muscle weakness) are partially reversed by drugs that inhibit acetylcholinesterase (Figures 14–6 and 14–8).

How do antibodies cause the symptoms of myasthenia? The antibodies do not simply occupy the site of ACh binding. Rather, they appear to react with epitopes elsewhere on the receptor molecule. This increases the destruction of nicotinic ACh receptors, probably because myasthenic antibodies bind and cross-link the receptors, triggering their degradation (Figure 14–9). In addition, some myasthenic antibodies bind proteins of the complement cascade of the immune system, causing lysis of the postsynaptic membrane.

Despite the evidence documenting the primary role of antibodies against the nicotinic ACh receptor in myasthenia, approximately one-fifth of patients with myasthenia, including some who respond to antiimmune therapy like plasmapheresis, do not have these antibodies. Instead, most of these patients have antibodies against another postsynaptic protein, known as MuSK (*mu*scle-*s*pecific Trk-related receptor with a *k*ringle domain). MuSK is a receptor tyrosine kinase that interacts with agrin, a protein released from the motor nerve terminal that helps to organize the nicotinic ACh receptors into clusters at the neuromuscular junction.

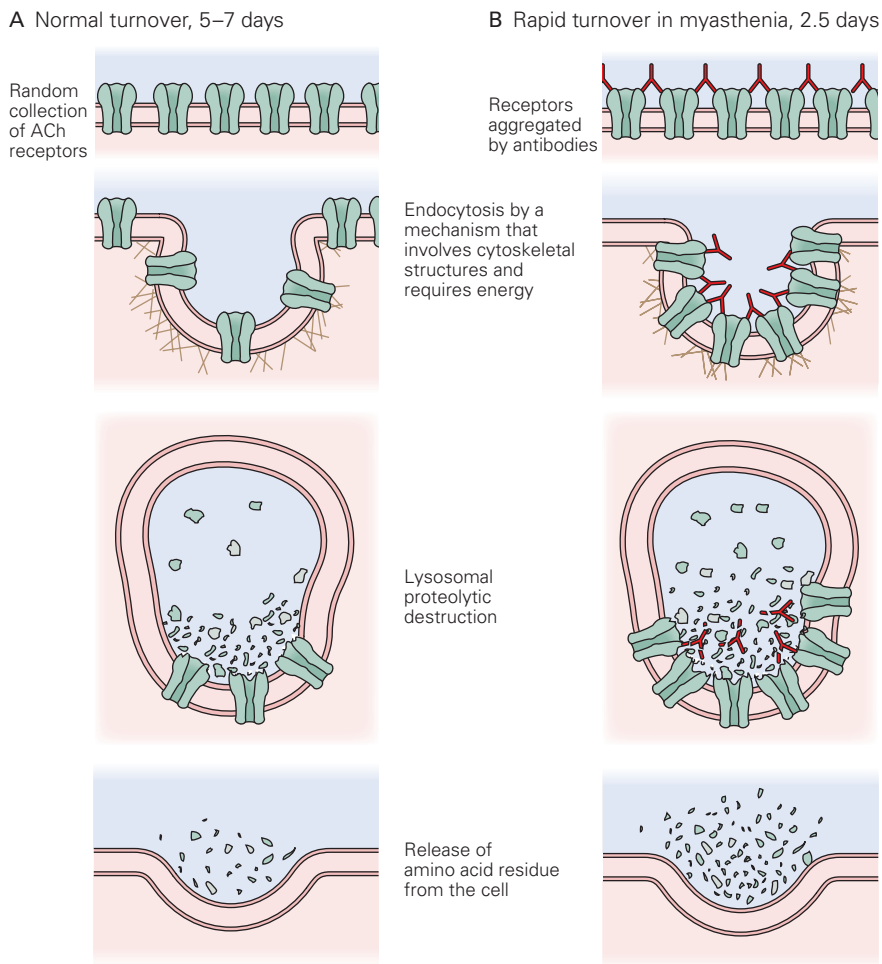


Figure 14–9 Turnover of ACh receptors increases in myasthenia. (Adapted, with permission, from Lindstrom 1983, and Drachman 1983.)

A. Normal turnover of randomly spaced ACh receptors takes places every 5 to 7 days.

B. In myasthenia gravis and experimental myasthenia gravis, the cross-linking of ACh receptors by antibodies facilitates endocytosis and the phagocytic destruction of the receptors, which leads to a two- to threefold increase in the rate of receptor turnover. Binding of antireceptor antibody activates the complement cascade, which is involved in focal lysis of the postsynaptic membrane. This focal lysis is probably primarily responsible for the characteristic morphological alterations of postsynaptic membranes in myasthenia (see Figure 14–7).

It appears to be functionally important both during development and in the adult. Although the adverse effects of the anti-MuSK antibodies have not yet been defined, the antibodies block some of the normal clustering of the nicotinic ACh receptors following the interaction of agrin with MuSK.

Treatment of Myasthenia Targets the Physiological Effects and Autoimmune Pathogenesis of the Disease

Anticholinesterases, especially pyridostigmine, provide symptomatic relief, but the treatment is rarely complete and does not alter the basic disease. Immunosuppressive therapies include corticosteroids and azathioprine or related drugs that suppress antibody synthesis.

Plasmapheresis—removing the plasma and the antibodies to the nicotinic ACh receptors or to MuSK—often ameliorates symptoms within days or a few weeks, as does infusion of immunoglobulin.

Although the benefit is transient, it may be sufficient to prepare a patient for thymectomy or to support the patient through more severe episodes. Intravenous administration of immunoglobulins also reduces the titer of antibodies to the nicotinic ACh receptor and to MuSK by mechanisms that are unclear.

There Are Two Distinct Congenital Forms of Myasthenia Gravis

There are two distinct types of myasthenia in which symptoms may be present from birth. In neonatal myasthenic syndrome the mother herself has autoimmune myasthenia that is transmitted passively to the newborn via the immune system. By contrast, in congenital myasthenia the infant has an inherited defect in some component of the neuromuscular junction,

rather than an autoimmune disease, and thus does not have serum antibodies to the nicotinic ACh receptor or MuSK.

Congenital myasthenic syndromes fall into three broad groups based on the site of the defect in the neuromuscular synapse: presynaptic, synaptic cleft, and postsynaptic forms. Clinical features common to these disorders include a positive family history, weakness with easy fatigability (present since infancy), drooping of the eyelids (ptosis), a decremental response to repetitive stimulation on electromyography, and negative screening for anti-nicotinic ACh receptor antibodies. A striking feature of many of these diseases is the subnormal development of the skeletal muscles, reflecting the fact that normal function at the neuromuscular synapse is required to maintain normal muscle bulk.

In one presynaptic form of congenital myasthenia the enzyme choline acetyltransferase is absent or reduced in the distal motor terminal. This enzyme is essential for the synthesis of ACh from choline and acetyl coenzyme A (see Chapter 13). In its absence the synthesis of ACh is impaired. The result is weakness that usually begins in infancy or early childhood. In another presynaptic form of congenital myasthenia the number of quanta of ACh released after an action potential is less than normal. The molecular basis for this defect is unknown.

Congenital myasthenia may also result from the absence of acetylcholinesterase in the synaptic cleft. In this circumstance end-plate potentials and miniature end-plate potentials are not small, as in autoimmune myasthenia, but are rather markedly prolonged, which may explain the repetitive response of the evoked muscle potential in those patients. Cytochemical studies indicate that ACh-esterase is absent from the basement membranes. At the same time, nicotinic ACh receptors are preserved.

The physiological consequence of ACh-esterase deficiency is sustained action of ACh on the end-plate and ultimately the development of an end-plate myopathy. This myopathy indicates that skeletal muscle can react adversely to excessive electrical stimulation at the neuromuscular junction. In treating this disorder it is critical to avoid using agents like inhibitors of ACh-esterase that can increase firing in the end-plate and thereby exacerbate the muscle weakness.

Most congenital myasthenia cases are caused by primary mutations in the genes encoding different subunits of the nicotinic ACh receptor. The *slow channel syndrome* is characterized by prominent limb weakness but little weakness of cranial muscles (the reverse of the pattern usually seen in autoimmune myasthenia, where muscles of the eyes and oropharynx are almost always affected). End-plate currents are slow to decay and channel opening is abnormally long. The mutations probably act both by increasing the affinity of the nicotinic ACh receptor for ACh, thereby prolonging the effects of this transmitter, and by directly slowing the channel closing rate. In some instances quinidine is effective therapy for slow channel syndrome because it blocks the open receptor-channel. As in ACh-esterase mutations, the end-plate degenerates because of excessive postsynaptic stimulation, and thus anticholinesterase medications are potentially dangerous.

In the *fast channel syndrome* a different set of mutations in one or more subunits of the nicotinic ACh receptor leads to an accelerated rate of channel closing and end-plate current decay. The fast channel syndrome may respond either to acetylcholinesterase inhibitors or to 3,4-diaminopyridine, which increases presynaptic firing and ACh quantal release, probably by blocking a presynaptic K^+ conductance.

Lambert-Eaton Syndrome and Botulism Are Two Other Disorders of Neuromuscular Transmission

Some patients with cancer, especially small-cell cancer of the lung, have a syndrome of proximal limb weakness and a neuromuscular disorder with characteristics that are the opposite of those seen in myasthenia gravis. Instead of a decline in synaptic response to repetitive nerve stimulation, the amplitude of the evoked potential increases; that is, neuromuscular transmission is facilitated. The first postsynaptic potential is abnormally small, and subsequent responses increase in amplitude so that the final summated potential is two to four times the amplitude of the first potential.

This disorder, *Lambert-Eaton syndrome,* is attributed to the action of antibodies against voltage-gated Ca^{2+} channels in the presynaptic terminals. It is thought that these antibodies react with an antigen in the channels, degrading the channels as the antibody-antigen complex is internalized. Calcium channels similar to those in presynaptic terminals are found in cultured cells from the small-cell carcinoma of the lung; development of antibodies against these antigens in the tumor might be followed by pathogenic action against nerve terminals, another kind of molecular mimicry.

A facilitating neuromuscular block also occurs in human botulism, because the botulinum toxin also impairs release of ACh from nerve terminals. Both botulism and Lambert-Eaton syndrome are ameliorated by administration of calcium gluconate or guanidine, agents that promote the release of ACh. These drugs are less effective than immunosuppressive treatments

for long-term control of Lambert-Eaton syndrome, which is chronic. However, botulism is transient, and if the patient is kept alive during the acute phase by treating symptoms, the disorder disappears in weeks as the infection is controlled and botulinum toxin is inactivated.

Diseases of Skeletal Muscle Can Be Inherited or Acquired

The weakness seen in any myopathy is usually attributed to degeneration of muscle fibers. At first the missing fibers are replaced by regeneration of new fibers. Ultimately, however, renewal cannot keep pace and fibers are lost progressively. This leads to compound potentials of brief duration and reduced amplitude in the motor unit. The decreased number of functioning muscle fibers accounts for the diminished strength. Skeletal muscle diseases are conveniently divided into those that are inherited and those that appear to be acquired.

Dermatomyositis Exemplifies Acquired Myopathy

The prototype of an acquired myopathy is dermatomyositis, defined by two clinical features: rash and myopathy. The rash has a predilection for the face, chest, and extensor surfaces of joints, including the fingers. The myopathic weakness primarily affects proximal limb muscles. Both rash and weakness usually appear simultaneously and become worse in a matter of weeks. The weakness may be mild or life-threatening.

This disorder affects children or adults. Approximately 10% of adult patients have malignant tumors. Although the pathogenesis is unknown, dermatomyositis is thought to be an autoimmune disorder of small intramuscular blood vessels.

Muscular Dystrophies Are the Most Common Inherited Myopathies

The best-known inherited muscle diseases are the muscular dystrophies; several major types are distinguished by clinical and genetic patterns. Some types are characterized by weakness alone (Duchenne, facioscapulohumeral and limb girdle dystrophies); others have additional clinical features (such as the myotonic muscular dystrophies). Most are recessively inherited and begin in early childhood (Duchenne, Becker, and limb girdle dystrophy); less frequently, the dystrophies are dominantly inherited (facioscapulohumeral or myotonic dystrophy). In the limb-girdle dystrophies progressive weakness of the proximal limbs is a cardinal trait. In the myotonic muscular dystrophies progressive weakness is accompanied by severe muscle stiffness.

Duchenne muscular dystrophy affects only males because it is transmitted as an X-linked recessive trait. It starts in early childhood and progresses relatively rapidly, so patients are in wheelchairs by age 12 years and usually die in their third decade. This dystrophy is caused by mutations that severely reduce levels of dystrophin, a skeletal muscle protein that apparently confers tensile strength to the muscle cell. In a related inherited muscle disorder known as *Becker muscular dystrophy,* dystrophin is present but is either abnormal in size or reduced in quantity (approximately 10%). Becker dystrophy is thus much milder; individuals with Becker dystrophy typically are able to walk well into adulthood, albeit with weakness of the proximal leg and arm muscles.

The dystrophin gene is the second largest human gene, spanning approximately 2.5 million base pairs, or 1% of the X chromosome and 0.1% of the total human genome. It contains at least 79 exons that encode a 14-kb mRNA. The inferred amino acid sequence of the dystrophin protein suggests a rod-like structure and a molecular weight of 427,000, with domains similar to those of two cytoskeletal proteins, alpha-actinin and spectrin. Dystrophin is localized to the inner surface of the plasma membrane. The amino terminus of dystrophin is linked to cytoskeletal actin, whereas the carboxy terminus is linked to the extracellular matrix by transmembrane proteins (Figure 14–10).

Most boys with Duchenne muscular dystrophy have a deletion in the dystrophin gene; approximately a third have point mutations. In both cases the mutations introduce premature stop codons in the mutant RNA transcripts that prevent synthesis of full-length dystrophin. Becker dystrophy is also caused by deletions and missense mutations, but the mutations do not introduce stop codons. The resulting dystrophin protein is nearly normal in length and can at least partially substitute for normal dystrophin (Figure 14–11).

The discovery of the affected gene product in Duchenne muscular dystrophy by Louis Kunkel in the mid-1980s was rapidly followed by the discovery of numerous other novel muscle proteins, some with an intimate relationship to dystrophin. As a result, the primary genetic and protein defects underlying most major muscular dystrophies have now been identified (Table 14–2). Thus it may be more constructive now to change the system of classifying the dystrophies to one based on the component of the muscle cell that is implicated. Most of the dystrophies, best represented

Table 14–2 Representative Muscular Dystrophies

Site of primary defect	Protein	Disease
Extracellular matrix	Collagen VI α1, α2, and α3	Bethlem myopathy
	Merosin laminin α2-subunit	Congenital myopathy
Transmembrane	α-sarcoglycan	LGMD-2D
	β-sarcoglycan	LGMD-2E
	χ-sarcoglycan	LGMD-2C
	σ-sarcoglycan	LGMD-2F
	Dysferlin	LGMD-2B, Miyoshi myopathy
	Caveolin-3	LGMD-1C, rippling muscle disease
	α7-integrin	Congenital myopathy
	Na^+ channel	Hyperkalemic paralysis
	Ca^{2+} channel	Hypokalemic paralysis
	Cl^- channel	Myotonia congenita
	XK protein	McLeod syndrome
Submembrane	Dystrophin	Duchenne, Becker dystrophies
Sarcomere/myofibrils	Tropomyosin B	Nemaline rod myopathy
	Calpain	LGMD-2A
	Titin	Distal (Udd) dystrophy
	Nebulin	Nemaline rod myopathy
	Telethonin	LGMD-2G
	Skeletal muscle actin	Nemaline rod myopathy
	Troponin	Nemaline rod myopathy
Cytoplasm	Desmin	Desmin storage myopathy
	αβ-crystallin	Distal myofibrillar myopathy
	Selenoprotein	Rigid spine syndrome
	Plectin	Epidermolysis bullosa simplex
Sarcoplasmic reticulum	Ryanodine receptor	Central core disease, malignant hyperthermia
	SERCA1	Brody myopathy
Nucleus	Emerin	Emery-Dreifuss dystrophy
	Lamin A/C	Emery-Dreifuss dystrophy
	Poly A binding protein, repeat	Oculopharyngeal dystrophy
Enzymes/miscellaneous	Myotonin kinase, CTG repeat	Myotonic dystrophy
	Zinc finger 9, CCTG repeat	Proximal myotonic dystrophy
	Epimerase	Inclusion body myositis
	Myotubularin	Myotubular myopathy
	Chorein	Chorea-acanthocytosis
Golgi apparatus	Fukutin	Fukuyama congenital dystrophy
	Fukutin-related peptide	Limb-girdle dystrophy
	POMT1	Congenital muscular dystrophy
	POMGnT1	Congenital muscular dystrophy

LGMD, limb-girdle muscular dystrophy.

by dystrophin deficiency, are believed to arise because of accelerated muscle injury and breakdown. A small group, associated with deficiency of the protein dysferlin, is a consequence of slower repair of muscle membrane after injury (Figure 14–10).

Many of these disorders are characterized by slowly progressive weakness of the proximal arms and legs and thus are limb-girdle dystrophies. Most are recessively inherited; mutations in both copies of a particular gene prevent expression of the normal protein product and thus lead to loss of function of that protein.

Primary genetic defects in a diverse group of skeletal muscle proteins lead to the limb-girdle phenotype (Table 14–2) in which weakness is prominent in the torso and in proximal muscles of the arms and legs. Why this pattern of degeneration is so common is unknown, especially because the affected proteins are expressed in both distal and proximal muscles. The pattern likely reflects muscle use. The proximal muscles are, on average, more subject to low-level but chronic contractile activity because they serve as antigravity muscles.

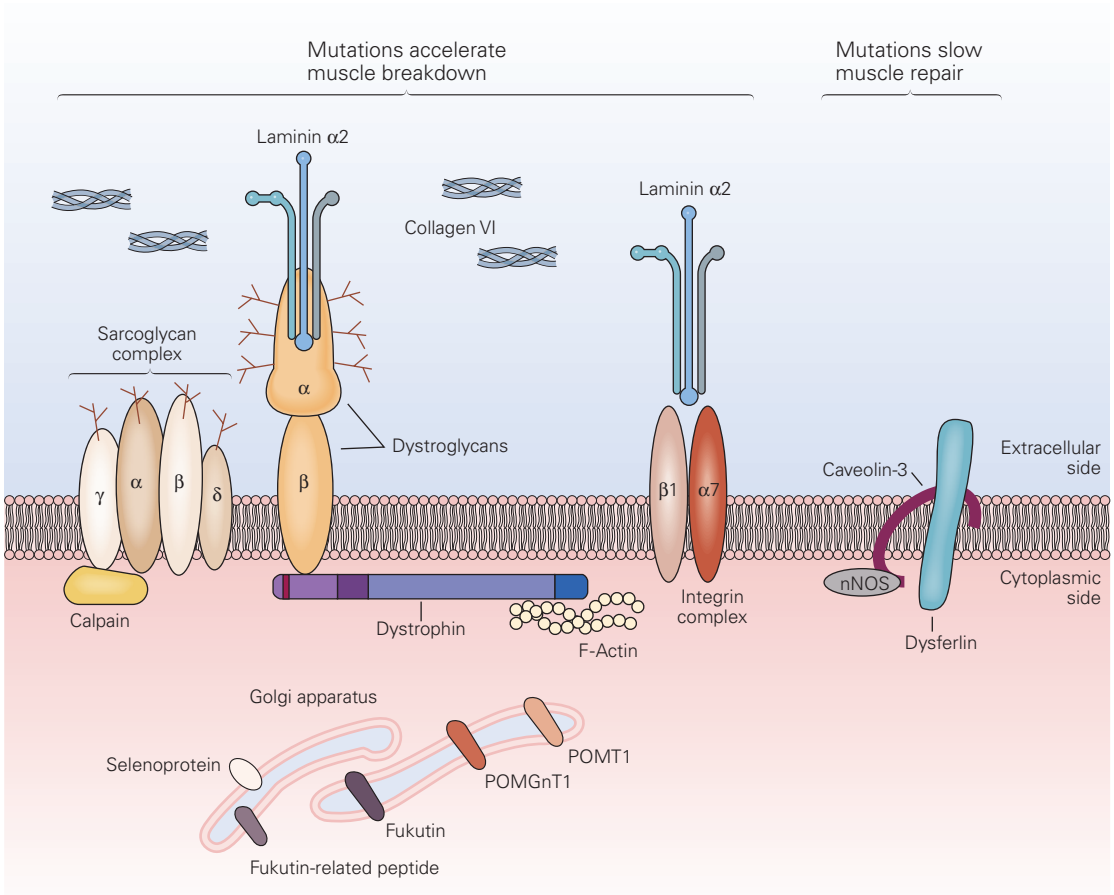


Figure 14–10 **In muscular dystrophy mutant proteins either weaken the muscle cell membrane or slow its repair after injury.** For example, a deficiency of dystrophin, a submembrane protein, causes Duchenne muscular dystrophy. Dystrophin interacts with complexes of other membrane proteins that are mutant in other dystrophies, including the dystroglycans and the sarcoglycans, which are closely associated with extracellular proteins such as laminin α2 and collagen. Several other proteins that are normally present in the Golgi apparatus and essential for adding sugar groups to membrane proteins are found to be mutant in different forms of muscular dystrophy. These include POMT1 (protein *O*-mannosyl transferase 1), POMGnT1 (protein *O*-mannosyl β1,2-*N*-acetylglucosaminyl transferase), fukutin, fukutin-related peptide, and a selenoprotein. Dysferlin, which is mutated in still other dystrophies, is involved in the repair of skeletal muscle membrane after injury. (Modified, with permission, from Brown and Mendell 2005.)

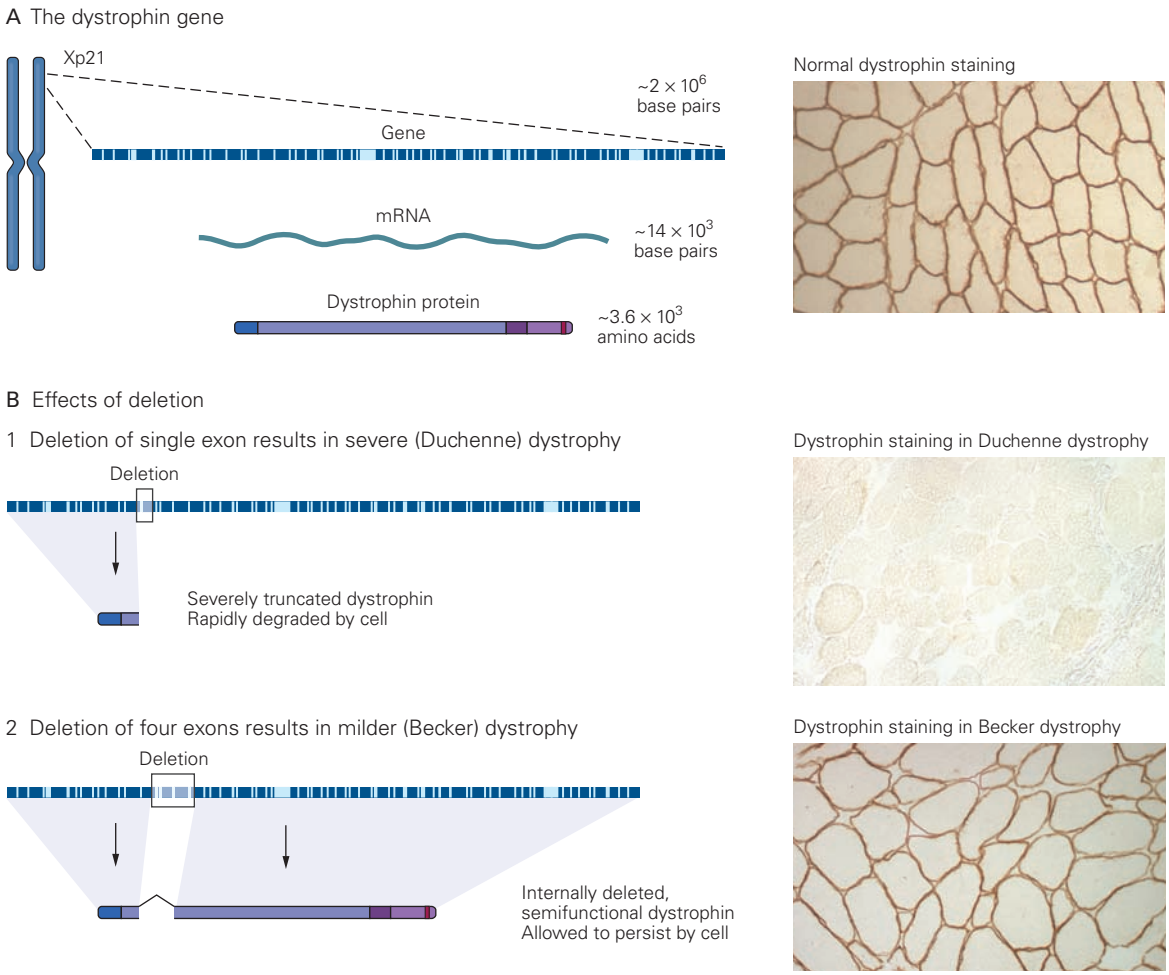


Figure 14–11 Two forms of muscular dystrophy are caused by deletion mutations in the dystrophin gene. (Adapted, with permission, from Hoffman and Kunkel 1989; photos, reproduced with permission, from Arthur P. Hays.)

A. The relative position of the dystrophin gene within the Xp21 region of the X chromosome. An enlargement of this locus shows the 65 exons (**light blue**) and introns (**dark blue**) defining the gene with approximately 2.0×10^6 base pairs. Transcription of the gene gives rise to mRNA (approximately 14×10^3 base pairs), and translation of this mRNA gives rise to the protein dystrophin (mol wt 427,000). Expression of dystrophin in a normal muscle is shown in an immunoperoxidase stain photo at right.

B. A deletion of genomic DNA encompassing only a single exon results in the clinically severe Duchenne muscular dystrophy. A larger deletion encompassing four exons results in the clinically milder Becker muscular dystrophy. In both cases the gene is transcribed into mRNA, and the exons flanking the deletion are spliced together. **1.** If a single exon is deleted and a nonintegral set of codons is missing, the borders of neighboring exons may not match, causing the translational reading frame to shift. As a result, incorrect amino acids are inserted into the growing polypeptide chain until an abnormal stop codon is reached, causing premature termination of the protein. The truncated protein may be unstable, may fail to be localized in the membrane, or may fail to bind to glycoproteins. Functional dystrophin is then almost totally absent. A muscle biopsy of Duchenne dystrophy (right) shows no detectable immunoreactive dystrophin. **2.** If the deletion is larger but an integral number of codons are deleted, the reading frame can be maintained in the mRNA. This produces a dystrophin molecule with an internal deletion but intact ends. Although the protein is smaller than normal and may be present in less than normal amounts, some muscle function is preserved. Immunoperoxidase staining of dystrophin is minimally reduced in a muscle biopsy of Becker dystrophy (right).

Myotonic dystrophy has several distinctive features, including an autosomal inheritance pattern, weakness that is predominantly distal, involvement of nonmuscle tissues, and striking muscle stiffness (myotonia). The stiffness is induced by excessive electrical discharges of the muscle membrane associated with voluntary muscle contractions or percussive or electrical stimulation of the muscle. It is most intense with the first few movements after a period of rest and improves with continued muscular activity (*warm-up* phenomenon). Typical features are difficulty relaxing the grip of a handshake for several seconds, difficulty opening the eyelids after forceful squinting, or stiffness in the legs with the first few steps after rising from a chair.

Electromyography demonstrates that the muscle cell membrane is electrically hyperexcitable; after a contraction, bursts of repetitive action potentials wax and wane in amplitude and frequency (20–100 Hz) over several seconds and thereby delay relaxation (Figure 14–12A). This sustained contraction is truly independent of nerve supply because it persists after blockade of either the incoming motor nerve impulse or neuromuscular transmission with agents such as curare.

The symptoms are not confined to muscles. Almost all patients have cataracts; affected men commonly have testicular atrophy and baldness and often develop cardiac conduction system defects that lead to irregularities in the heartbeat. The primary genetic defect is a dominantly transmitted expansion of a triplet of base pairs (CTG) in a noncoding region of a gene (myotonin kinase) on chromosome 19. RNA transcripts of the expanded CTG segments accumulate in the nucleus and alter splicing of several critical genes, including the gene for a Cl^- channel, ClC-1 (see Chapter 5). Loss of function of this channel leads to excessive electrical activity in skeletal muscle and, as a consequence, myotonia. As discussed below, direct mutations in the same Cl^- channel gene can lead to a similar abnormal pattern of muscle activity.

Some Inherited Diseases of Skeletal Muscle Arise from Genetic Defects in Voltage-Gated Ion Channels

The normal electrical excitability of skeletal muscle is essential to the rapid and nearly synchronous contraction of an entire muscle fiber. The depolarizing end-plate potential at the neuromuscular junction triggers an action potential that propagates longitudinally along the surface of the muscle fiber and radially inward along the transverse tubules, invaginations of the fiber membrane that come into close apposition with the sarcoplasmic reticulum (see Chapter 34).

Depolarization of the transverse tubules induces a conformational change in L-type voltage-gated Ca^{2+} channels. The conformational change is directly transmitted to a particular class of Ca^{2+} release channels (ryanodine receptors) in the sarcoplasmic reticulum, causing the channels to open. The release of Ca^{2+} from the sarcoplasmic reticulum raises myoplasmic Ca^{2+} and thus activates ATP-dependent movement of actin-myosin filaments.

Normally, one action potential is generated in a muscle fiber for each end-plate potential. Repolarization of the muscle action potential depends on inactivation of Na^+ channels and the opening of delayed-rectifier voltage-gated K^+ channels similar to those in axons. In addition, Cl^- influx through the ClC-1 channels is important in maintaining the normal negative resting potential. Mutations in any one of these channels contribute to inherited muscle disease.

Periodic Paralysis Is Associated with Altered Muscle Excitability and Abnormal Levels of Serum Potassium

The electrical coupling of the end-plate potential to depolarization of the transverse tubules is disrupted in several inherited diseases of muscle. These disorders reflect a variety of defects in excitability ranging from complete failure of action potential generation to prolonged bursts of repetitive discharges in response to a single stimulus (Figure 14–12). The derangements of muscle fiber excitability are transient and result in *periodic paralysis.* Between episodes muscle function is normal. These are rare diseases of skeletal muscle, with a prevalence of 1 per 100,000 or less. Inheritance is autosomal dominant, except for one form of myotonia.

Weakness may be so severe during an attack of periodic paralysis that a patient is bedridden for hours, unable to raise an arm or leg off the bed. Fortunately, during such attacks the muscles of respiration and swallowing are spared, so life-threatening respiratory arrest does not occur. Attack frequency is variable from almost daily to only a few episodes in a lifetime. Consciousness and sensation are not impaired.

During an attack the resting potential of affected muscles is depolarized from a normal value of –90 mV to approximately –60 mV. At this depolarized potential most Na^+ channels are inactivated, rendering the muscle fiber chronically refractory and thus unable to generate action potentials. Recovery of strength occurs spontaneously and is associated with repolarization to a resting potential within a few millivolts of normal and recovery of excitability.

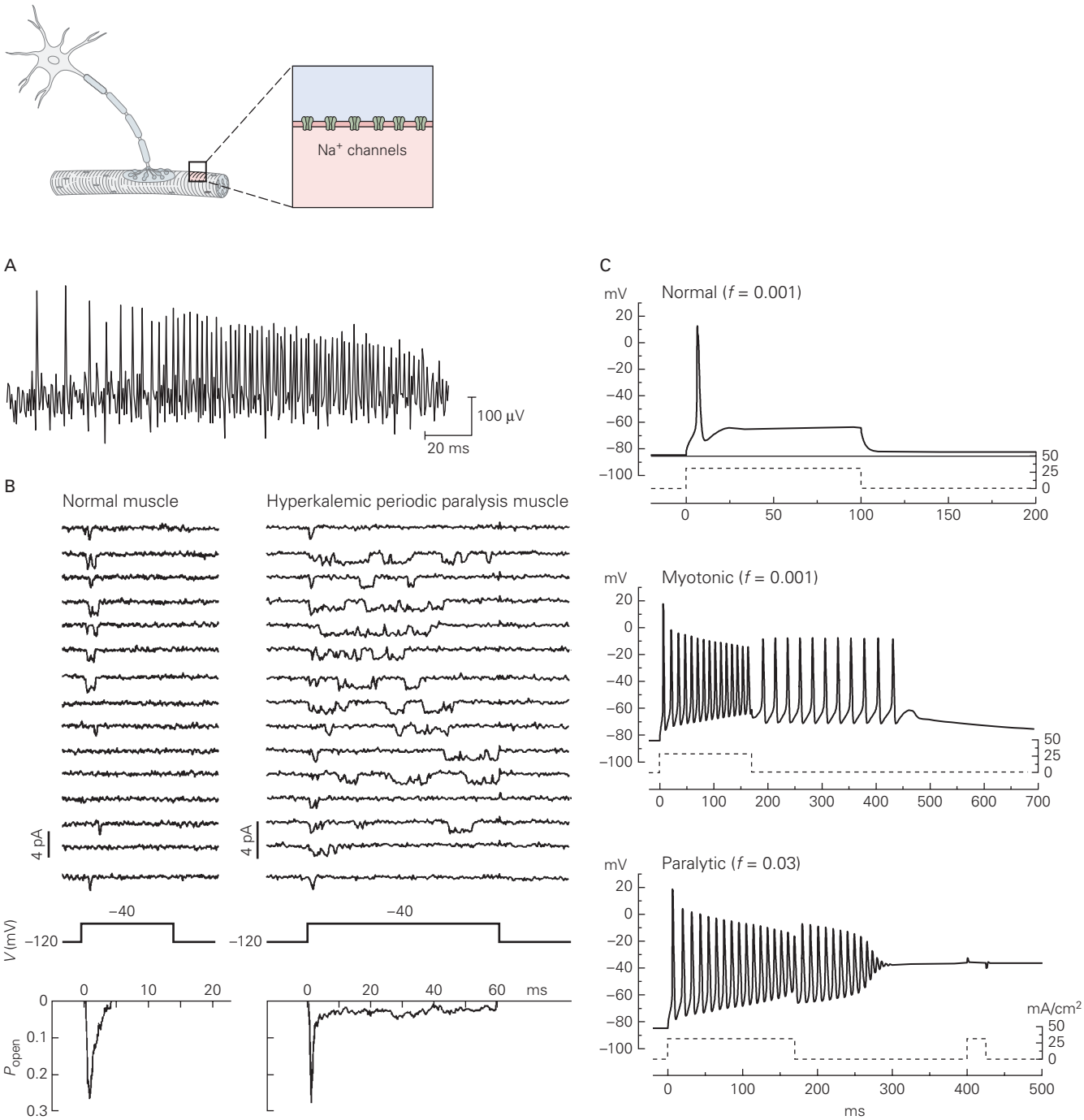


Figure 14–12 Myotonia or paralysis may result from impaired inactivation of Na^+ channels in skeletal muscle.

A. The electrical signature of myotonia (muscle stiffness) is a rapid burst of action potentials in response to a single stimulus. The action potentials, shown here from extracellular recordings, vary in amplitude and wax and wane in frequency. Such a burst may be triggered by a voluntary muscle contraction or a mechanical stimulus such as percussion of the muscle.

B. Cell-attached patch recordings from cultured human muscle cells. In normal muscle the Na^+ channels open early and briefly in response to a voltage-clamp depolarization from –120 mV to –40 mV. In muscle from patients with hyperkalemic periodic paralysis (M1592V Na^+ channel mutation) the prolonged openings and reopenings indicate impaired inactivation. The probability of channel opening (obtained by averaging individual records) remains elevated in the hyperkalemic muscle following inactivation. (Reproduced, with permission, from Cannon, Brown, and Corey 1991.)

C. Even modest disruption of Na^+ channel inactivation is sufficient to produce bursts of myotonic discharges or depolarization-induced loss of excitability. These computer simulation records show muscle voltage in response to an injected depolarizing current (**dashed line**). The fraction of mutant channels that actually fails to inactivate normally (*f*) varies within a population over time. In these simulations *f* was varied from normal to values appropriate for myotonic or paralytic muscle. (Reproduced, with permission, from Cannon, Brown, and Corey 1993.)

Two variants of periodic paralysis have been delineated. Hyperkalemic periodic paralysis attacks occur during periods of high venous K^+ (6.0 mM or higher versus normal levels of 3.5–4.5 mM). Ingesting foods with high K^+ content such as bananas or fruit juice may trigger an attack. Conversely, hypokalemic periodic paralysis presents as episodic weakness in association with low blood K^+ (2.5 mM or lower). Affected muscle is paradoxically depolarized in the setting of reduced extracellular K^+, which shifts the reversal potential for K^+ to more negative values. Both forms are inherited as autosomal dominant traits.

Genetic analyses have demonstrated that hyperkalemic periodic paralysis is caused by missense mutations in a gene that encodes the pore-forming subunit of a voltage-gated Na^+ channel expressed in skeletal muscle. Inactivation of mutant Na^+ channels is disrupted. Subtle defects of inactivation produce myotonia; more pronounced changes result in chronic depolarization and loss of excitability with paralysis (Figure 14–12B, C). Hypokalemic paralysis is usually caused by mutations in a gene that encodes the main subunit of a voltage-sensitive Ca^{2+} channel in skeletal muscle. Andersen's syndrome, a rare form of periodic paralysis characterized by weakness, developmental defects, and cardiac irritability, is caused by primary mutations in the gene for an inward-rectifying K^+ channel important for establishing the resting potential (Figure 14–13).

In myotonia congenita muscle stiffness is present from birth and is not progressive. Unlike myotonic dystrophy there is no muscle wasting, permanent muscle weakness, or other organ involvement. Myotonia congenita is a consequence of mutations in the gene coding for the ClC-1 Cl^- channel in skeletal muscle membrane. The resultant decrease in Cl^- influx leads to membrane depolarization and repetitive firing. The disease is inherited as a dominant, semidominant, or recessive trait.

An Overall View

Studies of the diseases of the peripheral nervous system represent a powerful synergy between clinical and basic neuroscience and the fruitful interaction of both approaches with molecular genetics and molecular immunology. Progress in the last decade in defining the molecular basis for these disorders has been extraordinary. Molecular genetic analyses of most disorders inherited as Mendelian traits, beginning only with clinical data in affected families and DNA from family members, have led to the description of causative defects in muscle and nerve proteins.

In some diseases, such as primary muscular dystrophies and inherited neuropathies, little is known about the normal function of the newly discovered disease genes. Thus, the investigation of these diseases has generated new opportunities to learn about the basic molecular and cellular biology of nerve and muscle. In other diseases, such as familial amyotrophic lateral sclerosis and the ion channel diseases, the disease genes and proteins have previously been identified and studied extensively; there is already a large body of biological and biophysical information on which to base further studies.

Also remarkable is the convergence of the discovery of the primary gene defects in the inherited nerve and muscle disorders with new technologies for manipulating the DNA of mice. We now have mouse models of the human diseases with precisely defined genetic defects (using transgenes to over express specific mutant proteins or gene knock-out technology to disrupt the function of proteins). These are already proving invaluable for the analysis of the function of novel proteins, the mechanism of disease evolution, and studies of new treatment strategies.

In general, the development of new therapies for these disorders has lagged behind discovery of

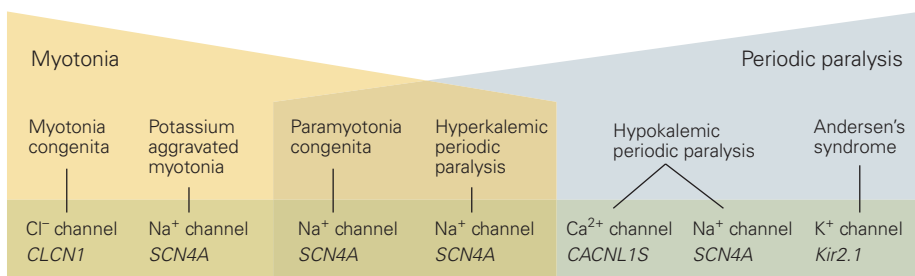


Figure 14–13 The myotonias and periodic paralyses are caused by mutations in genes for diverse voltage-gated ion channels in the skeletal muscle membrane. Some channel disorders are characterized only by myotonia, some only by periodic paralysis, and some by myotonia and paralysis. Some clinical disorders (eg, hypokalemic periodic paralysis) may arise from defects in different channels in different individuals.

the offending genetic or immune defects. The best exception to this generalization is myasthenia gravis; anti-immune therapies have dramatically reduced myasthenia mortality. Converting new molecular insights from other neuromuscular diseases into effective treatments will be a central challenge for clinical neuroscience in the next decade.

The primary therapy for recessively inherited, loss-of-function diseases will ultimately be some form of replacement of the missing protein; the use of viral-mediated gene therapy has already been explored in a pilot study of adults with a sarcoglycan deficiency. It is conceivable that newer methods to replace the missing proteins will not require viral delivery systems.

A major therapeutic challenge across all of human genetics is how to treat the dominantly inherited diseases in which the primary pathology involves cytotoxic effects of the gene mutations. Exciting strategies are evolving to inactivate the mutant allele. These include developing small molecules and proteins that inactivate the promoters for the genes and infusing either antisense oligonucleotides or inhibitory RNA molecules to inactivate the RNA templates made from the genes. Moreover, as the cellular pathways activated by the mutant genes and proteins become known, more downstream targets for the development of more conventional drug therapies will be identified.

For all these reasons we can be optimistic that the molecular analysis of these neuromuscular disorders will continue to illuminate important neurobiological principles in the neuromuscular system while at the same time opening new avenues for primary treatments of these often devastating diseases.

Postscript: Diagnosis of Motor Unit Disorders Is Aided by Laboratory Criteria

When the sole manifestation of a disease is limb weakness (with no fasciculation or upper motor neuron signs) clinical criteria may be insufficient to distinguish neurogenic and myopathic diseases. To assist in this differentiation, clinicians rely on several laboratory tests: measurement of muscle enzyme activity in serum, electromyography and nerve conduction studies, muscle biopsy, and DNA analysis.

One test that helps distinguish myopathic from neurogenic diseases is the measurement of serum enzyme activities. The sarcoplasm of muscle is rich in soluble enzymes that are normally found in low concentrations in the serum. In many muscle diseases the concentration of these sarcoplasmic enzymes in serum is elevated, presumably because the diseases affect the integrity of surface membranes of the muscle that ordinarily keep soluble enzymes within the sarcoplasm. The enzyme activity most commonly used for diagnosing myopathy is creatine kinase, an enzyme that phosphorylates creatine and is important in the energy metabolism of muscle.

Some abnormalities can be diagnosed by electromyography, a clinical procedure in which a small needle is inserted into a muscle to record extracellularly the electrical activity of several neighboring motor units. Three specific measurements are important: spontaneous activity at rest, the number of motor units under voluntary control, and the duration and amplitude of action potentials in each motor unit.

In normal muscle there is usually no activity outside the end-plate in the muscle at rest. During a weak voluntary contraction a series of motor unit potentials is recorded as different motor units become recruited. In fully active normal muscles these potentials overlap in an interference pattern so that it is impossible to identify single potentials (Figure 14–14A). Normal values have been established for the amplitude and duration of motor unit potentials. The amplitude of the motor unit potential is determined by the number of muscle fibers within the motor unit.

In neurogenic disease the partially denervated muscle is spontaneously active even at rest. The muscle may still contract in response to voluntary motor commands; but because some motor axons have been lost, the number of motor units under voluntary control is smaller than normal. During a maximal voluntary contraction the loss of motor units is evident in the EMG, which shows a discrete pattern of motor unit potentials instead of the profuse interference pattern for normal muscles (Figure 14–14B).

In recently denervated muscle the EMG may also show fibrillation potentials, low-amplitude electrical potentials that correspond to the firing of a single muscle fiber. As the neurogenic disease progresses, the amplitude and duration of individual motor unit potentials may increase, because the remaining axons give off small branches that innervate the muscle fibers denervated by the loss of other axons. Accordingly, surviving motor units contain more than the normal number of muscle fibers.

In myopathic diseases there is no activity in the muscle at rest and no change in the number of motor units firing during a contraction. But because there are fewer surviving muscle fibers in each motor unit, the motor unit potentials are of shorter duration and smaller in amplitude (Figure 14–14C).

The conduction velocities of peripheral motor axons can also be measured through electrical stimulation and recording (see Figure 14–2). The conduction

velocity of motor axons is slowed in demyelinating neuropathies but is normal in neuropathies without demyelination (axonal neuropathies).

The histochemical appearance of muscle in a biopsy can provide a useful diagnostic tool. Human muscle fibers are identified by histochemical reactions as type I or type II, which respectively are either aerobic (enriched for oxidative enzymes) or anaerobic (abundant glycolytic enzymes) (see Chapter 34). All muscle fibers innervated by a single motor neuron are of the

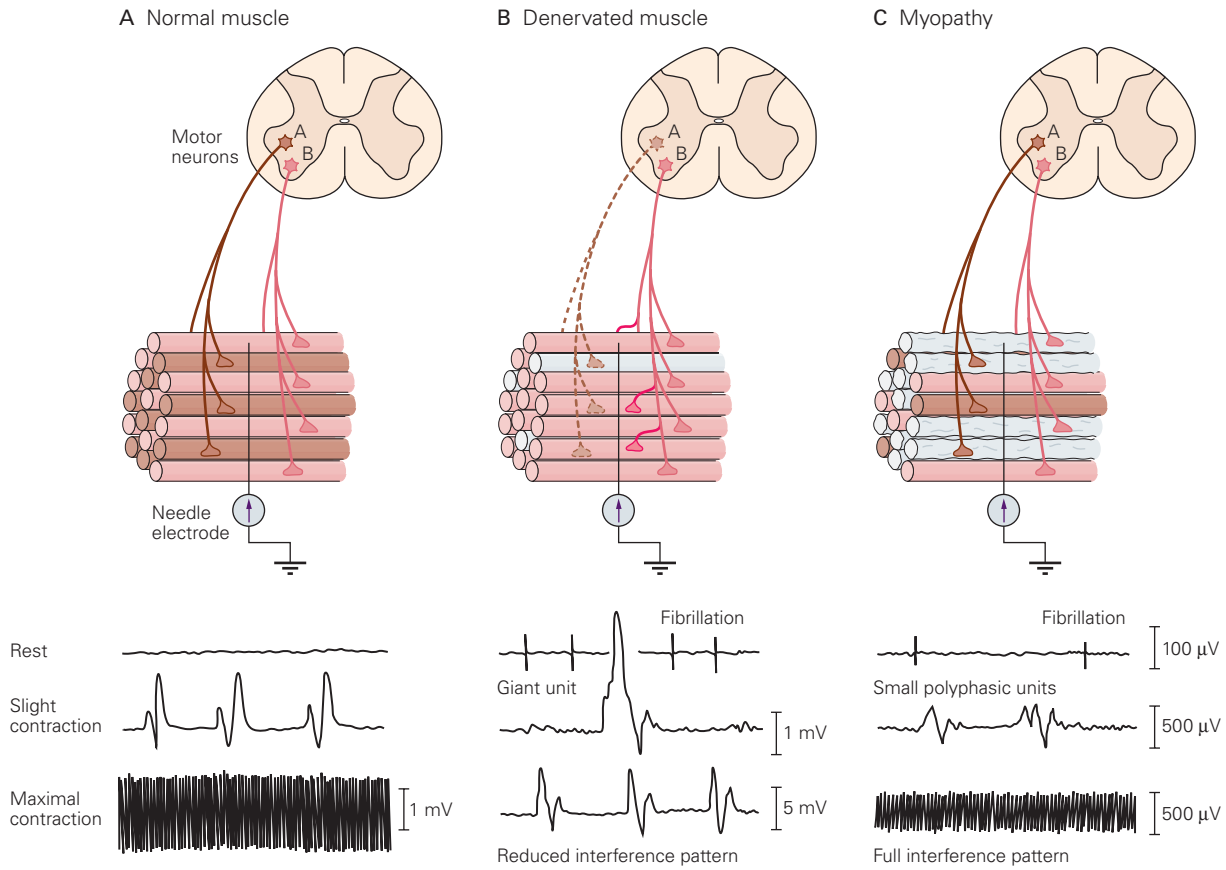


Figure 14–14 Neurogenic and myopathic diseases have different effects on the motor unit.

A. A motor unit potential is recorded by inserting a needle electrode into the muscle. The muscle fibers innervated by a single motor neuron are not usually adjacent to one another, yet the highly effective transmission at the neuromuscular junction ensures that each muscle fiber innervated by the same neuron will generate an action potential and contract in response to an action potential in the motor neuron. Activation of one or a few motor neurons produces a simple extracellular voltage signal and a small contraction (middle trace). A larger contraction activates a greater number of motor neurons and a larger number of muscle fibers, producing a strong contraction (lower trace). The extracellular voltage signal is more complex. Interference from the extracellular currents through the large number of muscle fibers, which are activated at slightly different times by the large number of motor neurons.

B. When motor neurons are diseased, the number of motor units under voluntary control is reduced. The muscle fibers supplied by the degenerating motor neuron (cell A) become denervated and atrophic. However, the surviving neuron (cell B) sprouts axonal branches that reinnervate some of the denervated muscle fibers. The electromyogram shows larger than normal motor unit potentials (middle trace) because the surviving motor neuron innervates more than the usual number of muscle fibers (it also innervates formerly denervated fibers). Axons of the surviving motor neuron fire spontaneously even at rest, giving rise to fasciculations, another characteristic of motor neuron disease. Single denervated fibers also fire spontaneously, producing fibrillations (top trace). Under conditions of maximal contraction the interference pattern is reduced (lower trace) because muscle fiber action potentials are more synchronized due to the reduced number of motor neuron inputs.

C. When muscle is diseased the number of muscle fibers in each motor unit is reduced. Some muscle fibers innervated by the two motor neurons shrink and become nonfunctional. In the electromyogram the motor unit potentials do not decrease in number but are smaller and of shorter duration than normal.

Table 14–3 Differential Diagnosis of Disorders of the Motor Unit

Finding	Nerve	Neuromuscular junction	Muscle
Clinical			
Weakness	++	+	++
Wasting	++	–	+
Fasciculations	+	–	–
Cramps	+	–	+/–
Sensory loss	+/–	–	–
Hyperreflexia, Babinski	+ (ALS)	–	–
Laboratory			
Elevated serum CPK	–	–	++
Elevated cerebrospinal fluid protein	+/–	–	–
Slowed nerve conduction	+	–	–
Response to repetitive stimulation	Normal	Decremental (MG) Incremental (LEMS)	Normal
Electromyography			
Fibrillation, fasciculation	++	–	+/–
Duration of potentials	Increased	Normal	Decreased
Amplitude of potentials	Increased	Normal	Decreased
Muscle Biopsy			
Isolated fiber atrophy	++	Normal	+/–
Grouped fiber atrophy	++	Normal	Normal
Muscle necrosis	Normal	Normal	++

ALS, amyotrophic lateral sclerosis; CPK, creatine phosphokinase; LEMS, Lambert-Eaton myasthenic syndrome; MG, myasthenia gravis.

same histochemical type. However, the muscle fibers of one motor unit are normally interspersed among the muscle fibers of other motor units. Enzyme stains of a cross section of healthy muscle show that oxidative or glycolytic fibers are intermixed in a *checkerboard* pattern.

In chronic neurogenic diseases the muscle innervated by a dying motor neuron becomes atrophic and some muscle fibers disappear. Axons of surviving neurons tend to sprout and reinnervate some of the nearby remaining muscle fibers. Because the motor neuron determines the biochemical properties of a muscle fiber, the reinnervated muscle fibers assume the histochemical properties of the innervating neuron. As a result, the fibers of a muscle in neurogenic disease become clustered by type (a pattern called *fiber-type grouping*).

If the disease is progressive and the neurons in the surviving motor units also become affected, atrophy occurs in groups of adjacent muscle fibers belonging to the same histochemical type, a process called *group atrophy.* In contrast, the muscle fibers in myopathic diseases are affected in a more or less random fashion. Sometimes an inflammatory cellular response is evident and sometimes there is prominent infiltration of the muscle by fat and connective tissue.

The main clinical and laboratory features used for the differential diagnosis of diseases of the motor unit are listed in Table 14–3.

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