Presynaptic action potential

EPSP in postsynaptic neuron

Ca²⁺ current in presynaptic neuron

Presynaptic inhibition

Presynaptic facilitation

FIGURE 6–10 **Effects of presynaptic inhibition and facilitation on the action potential and the Ca²⁺ current in the presynaptic neuron and the EPSP in the postsynaptic neuron.** In each case, the solid lines are the controls and the dashed lines the records obtained during inhibition or facilitation. Presynaptic inhibition occurs when activation of presynaptic receptors increases Cl⁻ conductance which decreases the size of the action potential. This reduces Ca²⁺ entry and thus the amount of excitatory transmitter released. Presynaptic facilitation is produced when the action potential is prolonged and the Ca²⁺ channels are open for a longer duration. (Modified from Kandel ER, Schwartz JH, Jessell TM [editors]: *Principles of Neural Science,* 4th ed. McGraw-Hill, 2000.)

inhibition). For instance, a spinal motor neuron emits a recurrent collateral that synapses with an inhibitory interneuron, which then terminates on the cell body of the spinal neuron and other spinal motor neurons (**Figure 6–11**). This particular inhibitory neuron is sometimes called a **Renshaw cell** after its discoverer. Impulses generated in the motor neuron activate the inhibitory interneuron to secrete the inhibitory neurotransmitter **glycine,** and this reduces or stops the discharge of the motor neuron. Similar inhibition via recurrent collaterals is seen in the cerebral cortex and limbic system. Presynaptic inhibition due to descending pathways that terminate on afferent pathways in the dorsal horn may be involved in the gating of pain transmission.

Another type of inhibition is seen in the cerebellum. In this part of the brain, stimulation of basket cells produces IPSPs in the Purkinje cells. However, the basket cells and the Purkinje cells are excited by the same parallel-fiber excitatory input (see Chapter 12). This arrangement, which has been called feed-forward inhibition, presumably limits the duration of the excitation produced by any given afferent volley.
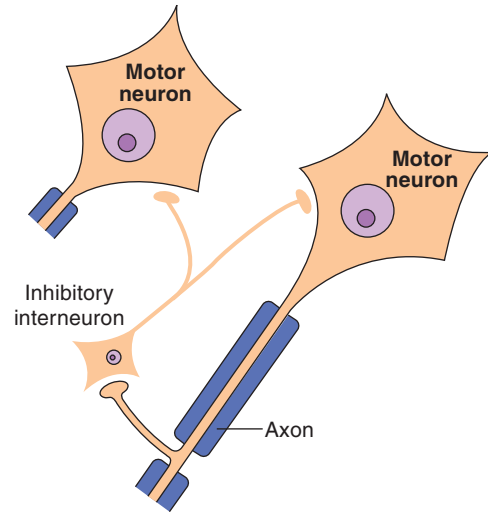

FIGURE 6–11 **Negative feedback inhibition of a spinal motor neuron via an inhibitory interneuron.** The axon of a spinal motor neuron has a recurrent collateral that synapses on an inhibitory interneuron that terminates on the cell body of the same and other motor neurons. The inhibitory interneuron is called a Renshaw cell and its neurotransmitter is glycine.

NEUROMUSCULAR TRANSMISSION

NEUROMUSCULAR JUNCTION

As the axon supplying a skeletal muscle fiber approaches its termination, it loses its myelin sheath and divides into a number of terminal boutons (**Figure 6–12**). The terminal contains many small, clear vesicles that contain acetylcholine, the transmitter at these junctions. The endings fit into **junctional folds,** which are depressions in the **motor end plate,** the thickened portion of the muscle membrane at the junction. The space between the nerve and the thickened muscle membrane is comparable to the synaptic cleft at neuron-to-neuron synapses. The whole structure is known as the **neuromuscular junction.** Only one nerve fiber ends on each end plate, with no convergence of multiple inputs.

SEQUENCE OF EVENTS DURING TRANSMISSION

The events occurring during transmission of impulses from the motor nerve to the muscle are somewhat similar to those occurring at neuron-to-neuron synapses (**Figure 6–13**). The impulse arriving in the end of the motor neuron increases the permeability of its endings to Ca²⁺. Ca²⁺ enters the endings and triggers a marked increase in exocytosis of the acetylcholine-containing synaptic vesicles. The acetylcholine diffuses to nicotinic cholinergic (N$_M$) receptors that are concentrated at the tops of the junctional folds of the membrane of the motor end plate. Binding of acetylcholine to these receptors increases
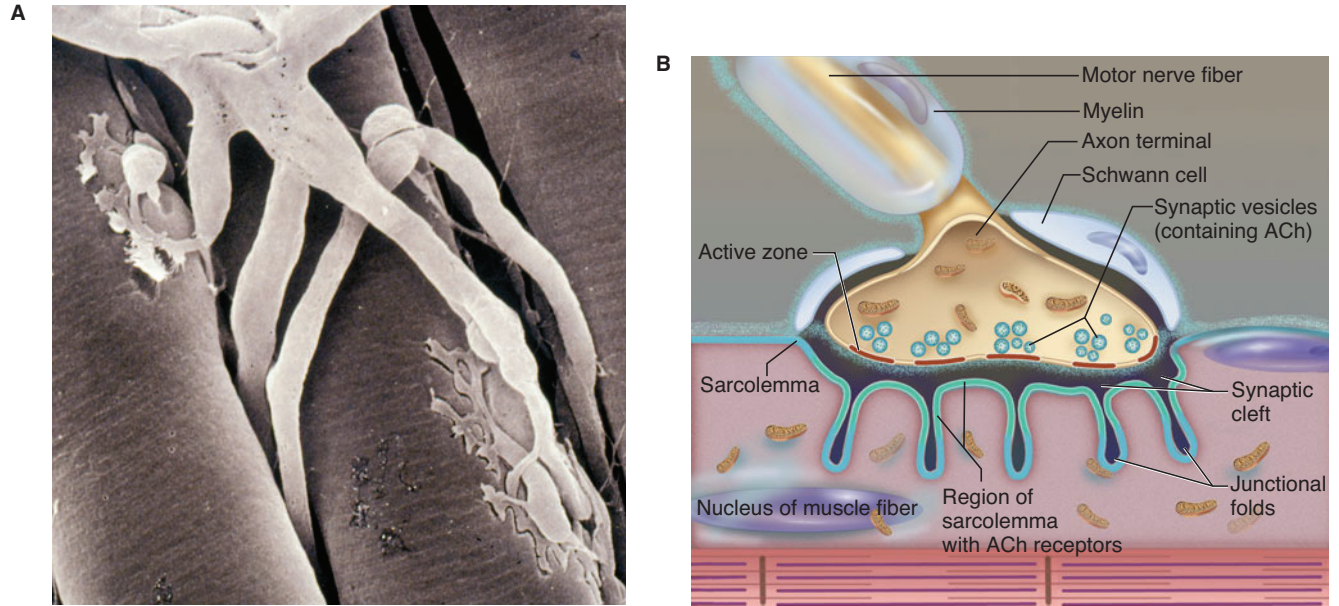
A

B

Motor nerve fiber
Myelin
Axon terminal
Schwann cell
Synaptic vesicles
(containing ACh)
Active zone
Sarcolemma
Synaptic
cleft
Junctional
folds
Nucleus of muscle fiber   Region of
sarcolemma
with ACh receptors

FIGURE 6–12 **The neuromuscular junction. A)** Scanning electronmicrograph showing branching of motor axons with terminals embedded in grooves in the muscle fiber's surface. **B)** Structure of a neuromuscular junction. (From Widmaier EP, Raff H, Strang KT: *Vanders Human Physiology.* McGraw-Hill, 2008.)
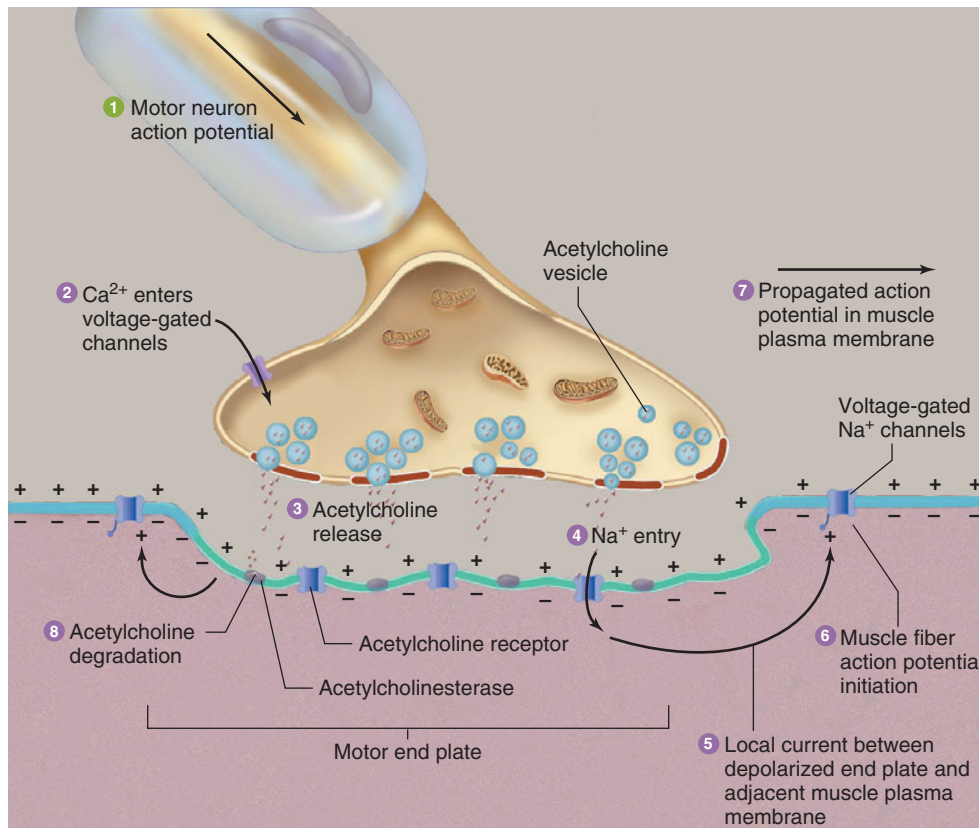
1 Motor neuron
action potential

Acetylcholine
vesicle

2 Ca²⁺ enters
voltage-gated
channels

7 Propagated action
potential in muscle
plasma membrane

Voltage-gated
Na⁺ channels

3 Acetylcholine
release

4 Na⁺ entry

6 Muscle fiber
action potential
initiation

8 Acetylcholine
degradation

Acetylcholine receptor

Acetylcholinesterase

Motor end plate

5 Local current between
depolarized end plate and
adjacent muscle plasma
membrane

FIGURE 6–13 **Events at the neuromuscular junction that lead to an action potential in the muscle fiber plasma membrane.** The impulse arriving in the end of the motor neuron increases the permeability of its endings to Ca^{2+} which enters the endings and triggers exocytosis of the acetylcholine (ACh)-containing synaptic vesicles. ACh diffuses and binds to nicotinic cholinergic (N_M) receptors in the motor end plate which increases Na^+ and K^+ conductance. The resultant influx of Na^+ produces the end plate potential. The current sink created by this local potential depolarizes the adjacent muscle membrane to its firing level. Action potentials are generated on either side of the end plate and are conducted away from the end plate in both directions along the muscle fiber and the muscle contracts. ACh is then removed from the synaptic cleft by acetylcholinesterase. (From Widmaier EP, Raff H, Strang KT: *Vanders Human Physiology.* McGraw-Hill, 2008.)

the Na^+ and K^+ conductance, and the resultant influx of Na^+ produces a depolarizing potential, the **end plate potential.** The current sink created by this local potential depolarizes the adjacent muscle membrane to its firing level. Action potentials are generated on either side of the end plate and are conducted away from the end plate in both directions along the muscle fiber. The muscle action potential, in turn, initiates muscle contraction, as described in Chapter 5. Acetylcholine is then removed from the synaptic cleft by acetylcholinesterase, which is present in high concentration at the neuromuscular junction.

An average human end plate contains about 15–40 million acetylcholine receptors. Each nerve impulse releases acetylcholine from about 60 synaptic vesicles, and each vesicle contains about 10,000 molecules of the neurotransmitter. This amount is enough to activate about 10 times the number of N_M receptors needed to produce a full end plate potential. Therefore, a propagated action potential in the muscle is regularly produced, and this large response obscures the end plate potential. However, the end plate potential can be seen if the 10-fold safety factor is overcome and the potential is reduced to a size that is insufficient to activate the adjacent muscle membrane. This can be accomplished by administration of small doses of curare, a drug that competes with acetylcholine for binding to N_M receptors. The response is then recorded only at the end plate region and decreases exponentially away from it. Under these conditions, end plate potentials can be shown to undergo temporal summation.

QUANTAL RELEASE OF TRANSMITTER

Small quanta (packets) of acetylcholine are released randomly from the nerve cell membrane at rest. Each produces a minute depolarizing spike called a **miniature end plate potential,** which is about 0.5 mV in amplitude. The size of the quanta of acetylcholine released in this way varies directly with the Ca^{2+} concentration and inversely with the Mg^{2+} concentration at the end plate. When a nerve impulse reaches the ending, the number of quanta released increases by several orders of magnitude, and the result is the large end plate potential that exceeds the firing level of the muscle fiber. Quantal release of acetylcholine similar to that seen at the myoneural junction has been observed at other cholinergic synapses, and quantal release of other transmitters occurs at noradrenergic, glutamatergic, and other synaptic junctions. Two diseases of the neuromuscular junction, myasthenia gravis and Lambert-Eaton syndrome, are described in **Clinical Box 6–2** and **Clinical Box 6–3**, respectively.

CLINICAL BOX 6–2

Myasthenia Gravis

Myasthenia gravis is a serious and sometimes fatal disease in which skeletal muscles are weak and tire easily. It occurs in 25 to 125 of every 1 million people worldwide and can occur at any age but seems to have a bimodal distribution, with peak occurrences in individuals in their 20s (mainly women) and 60s (mainly men). It is caused by the formation of circulating antibodies to the muscle type of **nicotinic cholinergic receptors.** These antibodies destroy some of the receptors and bind others to neighboring receptors, triggering their removal by endocytosis. Normally, the number of quanta released from the motor nerve terminal declines with successive repetitive stimuli. In myasthenia gravis, neuromuscular transmission fails at these low levels of quantal release. This leads to the major clinical feature of the disease, muscle fatigue with sustained or repeated activity. There are two major forms of the disease. In one form, the extraocular muscles are primarily affected. In the second form, there is a generalized skeletal muscle weakness. In severe cases, all muscles, including the diaphragm, can become weak and respiratory failure and death can ensue. The major structural abnormality in myasthenia gravis is the appearance of sparse, shallow, and abnormally wide or absent synaptic clefts in the motor end plate. Studies show that the postsynaptic membrane has a reduced response to acetylcholine and a 70–90% decrease in the number of receptors per end plate in affected muscles. Patients with mysathenia gravis have a greater than normal tendency to also have rheumatoid arthritis, systemic lupus erythematosus, and polymyositis. About 30% of mysathenia gravis patients have a maternal relative with an autoimmune disorder. These associations suggest that individuals with myasthenia gravis share a genetic predisposition to autoimmune disease. The thymus may play a role in the pathogenesis of the disease by supplying helper T cells sensitized against thymic proteins that cross-react with acetylcholine receptors. In most patients, the thymus is hyperplastic; and 10–15% have a thymoma.

THERAPEUTIC HIGHLIGHTS

Muscle weakness due to myasthenia gravis improves after a period of rest or after administration of an **acetylcholinesterase inhibitor** such as **neostigmine** or **pyridostigmine.** Cholinesterase inhibitors prevent metabolism of acetylcholine and can thus compensate for the normal decline in released neurotransmitters during repeated stimulation. **Immunosuppressive drugs** (eg, **prednisone, azathioprine,** or **cyclosporine**) can suppress antibody production and have been shown to improve muscle strength in some patients with myasthenia gravis. **Thymectomy** is indicated especially if a thymoma is suspected in the development of myasthenia gravis. Even in those without thymoma, thymectomy induces remission in 35% and improves symptoms in another 45% of patients.

CLINICAL BOX 6–3

Lambert–Eaton Syndrome

In a relatively rare condition called **Lambert–Eaton Syndrome (LEMS),** muscle weakness is caused by an autoimmune attack against one of the voltage-gated Ca^{2+} channels in the nerve endings at the neuromuscular junction. This decreases the normal Ca^{2+} influx that causes acetylcholine release. The incidence of LEMS in the U.S. is about 1 case per 100,000 people; it is usually an adult-onset disease that appears to have a similar occurrence in men and women. Proximal muscles of the lower extremities are primarily affected, producing a waddling gait and difficulty raising the arms. Repetitive stimulation of the motor nerve facilitates accumulation of Ca^{2+} in the nerve terminal and increases acetylcholine release, leading to an increase in muscle strength. This is in contrast to myasthenia gravis in which symptoms are exacerbated by repetitive stimulation. About 40% of patients with LEMS also have cancer, especially small cell cancer of the lung. One theory is that antibodies that have been produced to attack the cancer cells may also attack Ca^{2+} channels, leading to LEMS. LEMS has also been associated with lymphosarcoma, malignant thymoma, and cancer of the breast, stomach, colon, prostate, bladder, kidney, or gall

bladder. Clinical signs usually precede the diagnosis of cancer. A syndrome similar to LEMS can occur after the use of **aminoglycoside antibiotics,** which also impair Ca^{2+} channel function.

THERAPEUTIC HIGHLIGHTS

Since there is a high comorbidity with small cell lung cancer, the first treatment strategy is to determine whether the individual also has cancer and, if so, to treat that appropriately. In patients without cancer, **immunotherapy** is initiated. **Prednisone** administration, **plasmapheresis,** and **intravenous immunoglobulin** are some examples of effective therapies for LEMS. Also, the use of **aminopyridines** facilitates the release of acetylcholine in the neuromuscular junction and can improve muscle strength in LEMS patients. This class of drugs causes blockade of presynaptic K^+ channels and promote activation of voltage-gated Ca^{2+} channels. Acetylcholinesterase inhibitors can be used but often do not ameliorate the symptoms of LEMS.

NERVE ENDINGS IN SMOOTH & CARDIAC MUSCLE

The postganglionic neurons in the various smooth muscles that have been studied in detail branch extensively and come in close contact with the muscle cells (**Figure 6–14**). Some of these nerve fibers contain clear vesicles and are cholinergic, whereas others contain the characteristic dense-core vesicles that contain norepinephrine. There are no recognizable end plates or other postsynaptic specializations. The nerve fibers run along the membranes of the muscle cells and sometimes groove their surfaces. The multiple branches of the noradrenergic and, presumably, the cholinergic neurons are beaded with enlargements (**varicosities**) and contain synaptic vesicles (Figure 6–14). In noradrenergic neurons, the varicosities are about 5 μm apart, with up to 20,000 varicosities per neuron. Transmitter is apparently liberated at each varicosity, that is, at many locations along each axon. This arrangement permits one neuron to innervate many effector cells. The type of contact in which a neuron forms a synapse on the surface of another neuron or a smooth muscle cell and then passes on to make similar contacts with other cells is called a **synapse en passant.**

In the heart, cholinergic and noradrenergic nerve fibers end on the sinoatrial node, the atrioventricular node, and the bundle of His (see Chapter 29). Noradrenergic fibers also innervate the ventricular muscle. The exact nature of the

endings on nodal tissue is not known. In the ventricle, the contacts between the noradrenergic fibers and the cardiac muscle fibers resemble those found in smooth muscle.

JUNCTIONAL POTENTIALS

In smooth muscles in which noradrenergic discharge is excitatory, stimulation of the noradrenergic nerves produces discrete partial depolarizations that look like small end plate potentials and are called **excitatory junction potentials (EJPs).** These potentials summate with repeated stimuli. Similar EJPs are seen in tissues excited by cholinergic discharges. In tissues inhibited by noradrenergic stimuli, hyperpolarizing **inhibitory junction potentials (IJPs)** are produced by stimulation of the noradrenergic nerves. Junctional potentials spread electrotonically.

DENERVATION SUPERSENSITIVITY

When the motor nerve to skeletal muscle is cut and allowed to degenerate, the muscle gradually becomes extremely sensitive to acetylcholine. This is called **denervation hypersensitivity** or **supersensitivity.** Normally nicotinic receptors are located only in the vicinity of the motor end plate where the axon of the motor nerve terminates. When the motor nerve is severed,
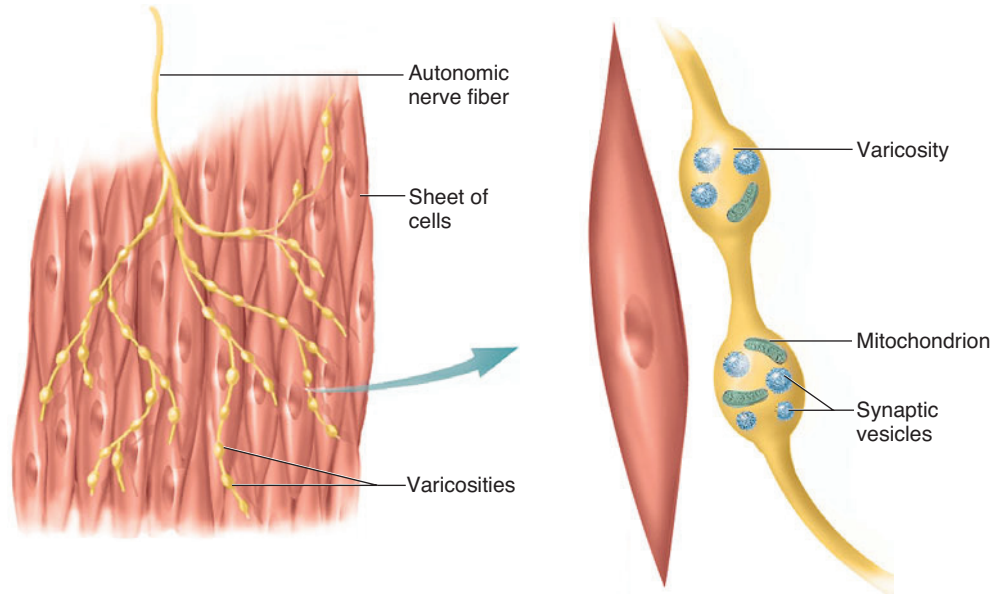
FIGURE 6–14 Endings of postganglionic autonomic neurons on smooth muscle. The nerve fibers run along the membranes of the smooth muscle cells and sometimes groove their surfaces. The multiple branches of postganglionic neurons are beaded with enlargements (varicosities) and contain synaptic vesicles. Neurotransmitter is released from the varicosities and diffuses to receptors on smooth muscle cell plasma membranes. (From Widmaier EP, Raff H, Strang KT: *Vanders Human Physiology.* McGraw-Hill, 2008.)

there is a marked proliferation of nicotinic receptors over a wide region of the neuromuscular junction. Denervation supersensitivity also occurs at autonomic junctions. Smooth muscle, unlike skeletal muscle, does not atrophy when denervated, but it becomes hyperresponsive to the chemical mediator that normally activates it. This hyperresponsiveness can be demonstrated by using pharmacological tools rather than actual nerve section. Prolonged use of a drug such as reserpine can be used to deplete transmitter stores and prevent the target organ from being exposed to norepinephrine for an extended period. Once the drug usage is stopped, smooth muscle and cardiac muscle will be supersensitive to subsequent release of the neurotransmitter.

The reactions triggered by section of an axon are summarized in **Figure 6–15**. Hypersensitivity of the postsynaptic structure to the transmitter previously secreted by the axon endings is a general phenomenon, largely due to the synthesis or activation of more receptors. Both orthograde degeneration **(wallerian degeneration)** and retrograde degeneration of the axon stump to the nearest collateral **(sustaining collateral)** will occur. There are a series of changes in the cell body that leads to a decrease in Nissl substance **(chromatolysis).** The nerve then starts to regrow, with multiple small branches projecting along the path the axon previously followed **(regenerative sprouting).** Axons sometimes grow back to their original targets, especially in locations like the neuromuscular junction. However, nerve regeneration is generally limited because axons often become entangled in the area of tissue damage at the site where they were disrupted. This difficulty has been reduced by administration of **neurotrophins** (see Chapter 4).

Denervation hypersensitivity has multiple causes. As noted in Chapter 2, a deficiency of a given chemical messenger generally produces an upregulation of its receptors. Another factor is a lack of reuptake of secreted neurotransmitters.
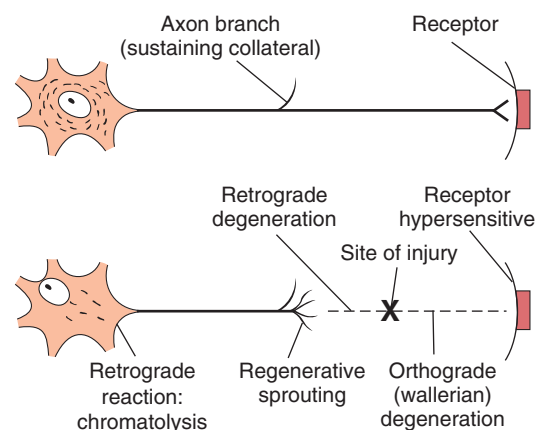

FIGURE 6–15 Summary of changes occurring in a neuron and the structure it innervates when its axon is crushed or cut at the point marked X. Hypersensitivity of the postsynaptic structure to the transmitter previously secreted by the axon occurs largely due to the synthesis or activation of more receptors. There is both orthograde (wallerian) degeneration from the point of damage to the terminal and retrograde degeneration of the axon stump to the nearest collateral (sustaining collateral). Changes also occur in the cell body, including chromatolysis. The nerve starts to regrow, with multiple small branches projecting along the path the axon previously followed (regenerative sprouting).

CHAPTER SUMMARY

- The terminals of the presynaptic fibers have enlargements called terminal boutons or synaptic knobs. The presynaptic terminal is separated from the postsynaptic structure by a synaptic cleft. The postsynaptic membrane contains neurotransmitter receptors and usually a postsynaptic thickening called the postsynaptic density.

- At chemical synapses, an impulse in the presynaptic axon causes secretion of a neurotransmitter that diffuses across the synaptic cleft and binds to postsynaptic receptors, triggering events that open or close channels in the membrane of the postsynaptic cell. At electrical synapses, the membranes of the presynaptic and postsynaptic neurons come close together, and gap junctions form low-resistance bridges through which ions pass with relative ease from one neuron to the next.

- An EPSP is produced by depolarization of the postsynaptic cell after a latency of 0.5 ms; the excitatory transmitter opens Na^+ or Ca^{2+} ion channels in the postsynaptic membrane, producing an inward current. An IPSP is produced by a hyperpolarization of the postsynaptic cell; it can be produced by a localized increase in Cl^- transport. Slow EPSPs and IPSPs occur after a latency of 100–500 ms in autonomic ganglia, cardiac, and smooth muscle, and cortical neurons. The slow EPSPs are due to decreases in K^+ conductance, and the slow IPSPs are due to increases in K^+ conductance.

- Postsynaptic inhibition during the course of an IPSP is called direct inhibition. Indirect inhibition is due to the effects of previous postsynaptic neuron discharge; for example, the postsynaptic cell cannot be activated during its refractory period. Presynaptic inhibition is a process mediated by neurons whose terminals are on excitatory endings, forming axoaxonal synapses; in response to activation of the presynaptic terminal. Activation of the presynaptic receptors can increase Cl^- conductance, decreasing the size of the action potentials reaching the excitatory ending, and reducing Ca^{2+} entry and the amount of excitatory transmitter released.

- The axon terminal of motor neurons synapses on the motor end plate on the skeletal muscle membrane to form the neuromuscular junction. The impulse arriving in the motor nerve terminal leads to the entry of Ca^{2+} which triggers the exocytosis of the acetylcholine-containing synaptic vesicles. The acetylcholine diffuses and binds to nicotinic cholinergic receptors on the motor end plate, causing an increase in Na^+ and K^+ conductance; the influx of Na^+ induces the end plate potential and subsequent depolarization of the adjacent muscle membrane. Action potentials are generated and conducted along the muscle fiber, leading in turn to muscle contraction.

- When a nerve is damaged and then degenerates, the postsynaptic structure gradually becomes extremely sensitive to the transmitter released by the nerve. This is called denervation hypersensitivity or supersensitivity.

MULTIPLE-CHOICE QUESTIONS

For all questions, select the single best answer unless otherwise directed.

1. Which of the following electrophysiological events is correctly paired with the change in ionic currents causing the event?
   A. Fast inhibitory postsynaptic potentials (IPSPs) and closing of Cl^- channels.
   B. Fast excitatory postsynaptic potentials (EPSPs) and an increase in Ca^{2+} conductance.
   C. End plate potential and an increase in Na^+ conductance.
   D. Presynaptic inhibition and closure of voltage-gated K^+ channels.
   E. Slow EPSPs and an increase in K^+ conductance.

2. Which of the following physiological processes is not correctly paired with a structure?
   A. Electrical transmission : gap junction
   B. Negative feedback inhibition : Renshaw cell
   C. Synaptic vesicle docking and fusion : presynaptic nerve terminal
   D. End plate potential : muscarinic cholinergic receptor
   E. Action potential generation : initial segment

3. Initiation of an action potential in skeletal muscle
   A. requires spatial facilitation.
   B. requires temporal facilitation.
   C. is inhibited by a high concentration of Ca^{2+} at the neuromuscular junction.
   D. requires the release of norepinephrine.
   E. requires the release of acetylcholine.

4. A 35-year-old woman sees her physician to report muscle weakness in the extraocular eye muscles and muscles of the extremities. She states that she feels fine when she gets up in the morning, but the weakness begins soon after she becomes active. The weakness is improved by rest. Sensation appears normal. The physician treats her with an anticholinesterase inhibitor, and she notes immediate return of muscle strength. Her physician diagnoses her with
   A. Lambert–Eaton syndrome.
   B. myasthenia gravis.
   C. multiple sclerosis.
   D. Parkinson disease.
   E. muscular dystrophy.

5. A 55-year-old female had an autonomic neuropathy which disrupted the sympathetic nerve supply to the pupillary dilator muscle of her right eye. While having her eyes examined, the ophthalmologist placed phenylephrine in her eyes. The right eye became much more dilated than the left eye. This suggests that
   A. the sympathetic nerve to the right eye had regenerated.
   B. the parasympathetic nerve supply to the right eye remained intact and compensated for the loss of the sympathetic nerve.
   C. phenylephrine blocked the pupillary constrictor muscle of the right eye.
   D. denervation supersensitivity had developed.
   E. the left eye also had nerve damage and so was not responding as expected.