2.Transmission of Impulses from Neurons to Skeletal Muscle Fibers: The Neuromuscular Junction

Skeletal muscle fibers are innervated by large, myelin- ated nerve fibers that originate in motoneurons of the spinal cord. Each nerve fiber normally stimulates three fibers to several hundred skeletal muscle fibers. The nerve ending makes a junction, called the neuromuscu- lar junction, and the action potential in the muscle fiber travels in both directions toward the muscle fiber ends.

Secretion of Acetylcholine by the Nerve Terminals (p. 83)

When a Nerve Impulse Reaches the Neuromuscular Junction, Vesicles Containing Acetylcholine Are Released into the Synaptic Space. On the inside surface of the neural membrane are linear dense bars. To the side of each dense bar are voltage-gated calcium channels. When the action potential spreads over the nerve terminal, these channels open allowing calcium ions to diffuse into the terminal. The calcium ions are believed to exert an attractive influence on the acetylcholine vesicles, drawing them adjacent to the dense bars. Some of the vesicles fuse with the neural membrane and empty their acetylcholine into the synaptic space via the process of exocytosis. **Acetylcholine Opens Acetylcholine-Gated Ion Channels on the Postsynaptic Membrane.** Acetylcholine-gated cation channels are located on the muscle membrane immediately below the dense bar areas. When two acetylcholine molecules attach to the channel receptors, a conformational change opens the channel. The principal effect of opening the acetylcholine-gated channels is to allow large numbers of sodium ions to pour into the inside of the muscle fiber, carrying with them large numbers of positive charges. This effect creates a local potential change at the muscle fiber membrane called the end-plate potential. In turn, this end-plate potential normally leads to opening of voltage-gated sodium channels, which initiate an action potential at the muscle membrane and thus causes muscle contraction.

Acetylcholine Released into the Synaptic Space Is Destroyed by Acetylcholinesterase or Simply Diffuses Away. The acetylcholine, once released into the synaptic space, continues to activate the acetylcholine receptors for as long as it remains in the space. Most of the acetylcholine is destroyed by the enzyme acetylcholinesterase. A small amount diffuses out of the synaptic space. The short period during which the acetylcholine remains in the synaptic space—a few milliseconds at most—is always sufficient to excite the muscle fiber under normal conditions.

Acetylcholine Produces an End-Plate Potential That Excites the Skeletal Muscle Fiber. The movement of sodium ions into the muscle fiber causes the internal membrane potential in the local area of the end-plate to increase in the positive direction as much as 50 to 75 millivolts, creating a local potential called the end-plate potential. The end-plate potential created by acetylcho- line stimulation is normally far greater than that necessary to initiate an action potential in the muscle fiber. **Drugs That Enhance or Block Transmission at the Neuromuscular Junction (p. 86)**

Drugs Can Affect the Neuromuscular Junction by Having Acetylcholine-Like Actions, Blocking Neuromuscular Transmission, and Inactivating Acetylcholinesterase

• Drugs that have acetylcholine-like actions. Many compounds, including methacholine, carbachol, and nicotine, have the same effect on the muscle fiber as does acetylcholine. The difference between these drugs and acetylcholine is that they are not destroyed by cholinesterase, or they are destroyed slowly.

• Drugs that block neuromuscular transmission. A group of drugs known as the curariform drugs can prevent passage of impulses from the end-plate into the muscle. Thus d-tubocurarine competes with acetylcholine for the acetylcholine receptor sites, so the acetylcho- line generated by the end-plate cannot increase the permeability of the muscle membrane acetylcholine channels sufficiently to initiate an action potential.

• Drugs that inactivate acetylcholinesterase. Three par- ticularly well-known drugs—neostigmine, physostig- mine, and diisopropyl fluorophosphate—inactivate acetylcholinesterase. As a result, acetylcholine levels increase with successive nerve impulses, causing large amounts of acetylcholine to accumulate and then repetitively stimulate the muscle fiber.

Neostigmine and physostigmine last up to several hours. Diisopropyl fluorophosphate, which has potential military use as a powerful “nerve” gas poi- son, inactivates acetylcholinesterase for weeks.

Myasthenia Gravis Causes Muscle Paralysis

Paralysis Occurs Because of the Inability of the Neuro- muscular Junctions to Transmit Signals from the Nerve Fibers to the Muscle Fibers. Pathologically, myasthenia gravis is thought to be an autoimmune disease in which patients have developed antibodies against their own acetylcholine-gated ion channels. The end-plate potentials that occur in the muscle fibers are too weak to initiate opening of voltage-gated sodium channels so that muscle fiber depolarization does not occur. If the disease is sufficiently intense, the patient dies of paralysis—in particular, paralysis of the respiratory muscles. The disease usually can be ameliorated by administration of neostigmine or another anticholinesterase drug. This treatment allows acetylcholine to accumulate in the synaptic cleft.