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Physiology

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This section outlines the general principles in physiology, including topics within neuromuscular physiology, movement disorders, neuroimmunology, and epilepsy. The section on neuromuscular physiology focuses on electrophysiology, neuromuscular junction disorders, and autonomic disorders. In the movement disorders section, the anatomy of the basal ganglia is discussed. The pathophysiology of multiple sclerosis and other autoimmune disorders is discussed in the neuroimmunology section. The section on epilepsy covers basics topics of the electroencephalogram (EEG).

Neuromuscular Physiology

Electrophysiology of Synaptic Transmission

The motor unit is composed of the motor neuron, motor axon, neuromuscular junction (NMJ), and muscle. Voluntary movement is initiated by neurons in the motor cortex resulting in activation of the spinal motor neurons. An action potential originating at the proximal segment of the spinal motor axon then propagates from one node of Ranvier to the following node until it reaches the presynaptic nerve terminal. At the NMJ, acetylcholine is released from the presynaptic membrane and traverses the synaptic cleft to bind to the acetylcholine receptor (AchR) on the postsynaptic membrane; this activates the mechanisms that ultimately result in muscle contraction. This section describes the anatomy of the NMJ and the electrophysiologic studies available clinically to evaluate patients suspected of having an NMJ disorder.

The NMJ consists of three principal components: the presynaptic region (motor nerve terminal), the synaptic cleft, and the postsynaptic region on the muscle membrane. The proteins located in the presynaptic terminal function to optimize binding of the synaptic vesicles to the presynaptic membrane and release of the acetylcholine contained in the vesicles.

Acetylcholine is the neurotransmitter of the NMJ, synthesized from choline and acetyl-coenzyme A by the enzyme choline acetyltransferase, and stored in synaptic vesicle. Each synaptic vesicle contains approximately 10,000 acetylcholine molecules; all the acetylcholine within one vesicle is called a quantum. At rest, individual vesicles spontaneously bind to the presynaptic membrane and release their quanta of acetylcholine; these travel across the synaptic cleft to bind to the AchR on the postsynaptic membrane.

Depolarization of the postsynaptic membrane that occurs as a result of spontaneous release of acetylcholine is known as a miniature end-plate potential. For the synaptic vesicles to

be released, synaptobrevin on the synaptic vesicle membrane first binds to a complex of proteins, syntaxin-1 and synaptic vesicle–associated protein 25 (SNAP-25), in a process called docking. Docking occurs in the region of the motor nerve terminal membrane called an active zone. Active zones are release sites located directly across from the AchR on the sarcolemmal membrane. There are approximately 1,000 to 2,000 active zones per nerve terminal. The complex of synaptobrevin, syntaxin-1, and SNAP-25 (also known as the *SNARE proteins*) places the synaptic vesicle near the presynaptic membrane.

When the action potential propagating along the motor axon reaches the nerve terminal, the P/Q-type calcium channel becomes active and allows an influx of calcium ions into the presynaptic nerve terminal. This increase in calcium concentration is sensed by synaptotagmin, another protein on the synaptic vesicle membrane, which binds to the SNARE proteins and facilitates the process of fusing the synaptic vesicle membrane to the nerve terminal membrane to release acetylcholine.

The synaptic cleft is a 50-nm space between the nerve terminal and the sarcolemmal membrane. The basal lamina that spans this extracellular space contains acetylcholinesterase along with several other proteins important for regulating postsynaptic proteins. In the NMJ, acetylcholinesterase has a collagen tail that attaches to the synaptic basal lamina. This collagen domain is encoded by the *COLQ* gene; a mutation in this gene is one of the causes of congenital myasthenic syndrome. When acetylcholine is released into the synaptic cleft, its activities are limited by diffusion out of the cleft and hydrolysis to choline and acetate by acetylcholinesterase. The choline product is then transported back into the nerve terminal for recycling to synthesize new acetylcholine molecules.

Sample Question 1

Which of the following changes in vital signs upon standing is considered a diagnostic criterion for postural orthostatic tachycardia syndrome in adults?

A. increase in heart rate by 10 beats/minute
B. increase in heart rate by 20 beats/minute
C. increase in heart rate by 30 beats/minute
D. decrease in systolic blood pressure by 20 mm Hg
E. decrease in diastolic blood pressure by 10 mm Hg

Sample Question 2

A 20-year-old woman describes a variety of nocturnal events characterized by arousal from sleep and unusual behavior, including arms flailing, torso rocking, and screaming that lasts 30 seconds to 1 minute followed by a return to sleep. When the patient awakens in the morning, she does not remember the events in question. During a 5-day stay in the epilepsy monitoring unit for spell classification, four typical events with the same phenomena were observed. Her EEG during these events, as well as interictally, showed no epileptiform discharges. Which of the following is the most likely explanation for these events?

A. psychogenic nonepileptic seizures
B. typical non-REM–related sleep disorder
C. circadian rhythm sleep-wake disorder
D. focal seizures with impaired awareness that cannot be captured on standard scalp EEG
E. a manifestation related to obstructive sleep apnea

Sample Question 3

A 34-year-old woman who presents for evaluation of abnormal involuntary movements has been treated for anxiety, dysphoria, and irritability over the past 2 years. She has never taken antipsychotic medications but has somewhat responded to a 6-month course of citalopram 20 mg daily. She has no family history of neurologic disease, but her father had a history of depression and alcohol abuse and committed suicide at age 40 years. Examination reveals irregular, rapid, dance-like movements of the extremities, and genetic testing shows 41 CAG repeats in the HTT gene. Which of the following statements about the underlying basal ganglia pathophysiology of the patient's condition is true?

A. Degeneration of striatal neurons has caused decreased activity in the direct pathway.
B. There is increased inhibition of the external globus pallidus.
C. There is a net effect of hypoactivity of the thalamocortical projections out of the basal ganglia.
D. Striatal medium spiny neurons containing enkephalin are more vulnerable to degeneration.
E. Tonic activity of the internal globus pallidus is disinhibited.