A 32-year-old woman presents to her primary care physician’s office with difficulty chewing food. She states that when she eats certain foods that require a significant amount of chewing (meat), her jaw muscles become weak and “tired.” After a period of rest, her jaw muscles regain their strength until she eats again. The patient is diagnosed with myasthenia gravis and is started on neostigmine, an acetylcholinesterase (AChE) inhibitor.

- What effect would an AChE inhibitor have at the neuromuscular junction?

- How would a large reduction in extracellular [Ca\(^{2+}\)] affect synaptic transmission at the neuromuscular junction?

- What is the ionic mechanism that underlies the endplate potential (EPP) produced by acetylcholine (ACh) release?
ANSWERS TO CASE 4: SYNAPTIC POTENTIALS

Summary: A 32-year-old woman is diagnosed with myasthenia gravis and is being treated with neostigmine.

◆ **Effect of AChE inhibitor:** Blocks the degradation of ACh, causing an increase in the endplate potential, and prolongs the action of ACh at the motor endplate.

◆ **Effect of reducing \([\text{Ca}^{2+}]_o\):** Reduces \(\text{Ca}^{2+}\)-dependent exocytosis of ACh from vesicles in the presynaptic terminal.

◆ **Ionic mechanism of EPP:** ACh opens ligand-gated channels that are equally permeable to \(\text{Na}^+\) and \(\text{K}^+\). The net effect is depolarization that reaches action potential threshold in the muscle cell.

CLINICAL CORRELATION

Myasthenia gravis is a neuromuscular disease with classic symptoms of weakness and fatigue of skeletal muscles. Myasthenia gravis is seen more commonly in females, with peak incidence at 20 to 30 years of age. Men have a peak of incidence at around 50 to 60 years of age. The underlying pathophysiology is the development of antibodies to peripheral ACh receptors. The release of ACh remains normal, but because of the reduction in the number of receptors, the EPP is reduced and may fail to reach threshold for muscle action potentials. This is most likely to occur during repetitive firing and twitch summation because ACh release decreases during repetitive activity, and if the EPP is reduced to begin with, it will fall below the action potential threshold more rapidly. This reduces twitch summation, causing weakness and fatigue, and explains the classic symptoms of myasthenia gravis: muscle weakness that increases with repetitive muscle use (eg, chewing) and partially recovers with rest. Treatment with AChE inhibitors decreases the degradation of ACh, thus enhancing and prolonging each EPP, increasing twitch summation and reducing weakness.

APPROACH TO SYNAPTIC POTENTIALS

Objectives

1. Understand the physiology of the neuromuscular junction.
2. Understand the synaptic physiology within the nervous system.

Definitions

**Endplate potential (EPP):** The excitatory postsynaptic potential (EPSP) at the neuromuscular junction caused by the opening by ACh of nicotinic ACh receptors in the muscle endplate.
**Inhibitory synapses:** Synapses in which neurotransmitter release produces an inhibitory postsynaptic potential (IPSP) that reduces the ability of the postsynaptic cell to fire action potentials.

**Ionotropic receptor:** A receptor that is also an ion channel and therefore produces a change in membrane potential when binding of a neurotransmitter opens (or, in some cases, closes) the channel.

**Metabotropic receptor:** A receptor that is linked by signal transduction pathways to potentially diverse cellular responses, including effects on ion channels (not directly linked to the receptor), neurotransmitter release, and gene transcription.

**DISCUSSION**

The **neuromuscular junction** is the synapse between a motor neuron and a skeletal muscle cell. Although it shares basic functions with other chemical synapses, the neuromuscular junction has unique features that ensure that each **EPP is large** enough to exceed the action potential threshold in the muscle cell. At the endplate, the motor neuron axon arborizes into numerous terminal boutons that contain large numbers of ACh-filled vesicles. ACh is synthesized in the boutons from choline and acetylcoenzyme A by choline acetyltransferase. ACh then is pumped into the vesicles by a specific ACh-H\(^+\) exchanger. The boutons lie over junctional folds in the postsynaptic membrane that contain nicotinic ACh receptors closely apposed to presynaptic active zones. The basal lamina between the presynaptic and postsynaptic membranes contains a high concentration of the degradative enzyme AChE.

Synaptic transmission begins when an action potential propagates from the main axon into the endplate. Consequent **depolarization** of the bouton opens voltage-gated Ca\(^{2+}\) channels, producing an **influx of Ca\(^{2+}\)** that then binds to specific proteins that cause fusion of vesicles with the plasma membrane and **exocytosis of ACh.** The ACh diffuses across the synaptic cleft. Binding of ACh to nicotinic ACh receptors on the junctional folds causes the ligand-gated channels to open in an **all-or-none** fashion. The channels are equally permeable to Na\(^+\), which flows into the cell, and to K\(^+\), which flows out of the cell. The combined Na\(^+\) and K\(^+\) current depolarizes the muscle cell from its resting potential (\(~ \sim −80 \text{ mV}\)) to the threshold for the action potential (\(~ \sim −50 \text{ mV}\)), with the resulting action potential propagating across the entire muscle cell. Because both Na\(^+\) (which has a very positive equilibrium potential, E\(_{Na}\)) and K\(^+\) (which has a very negative equilibrium potential, E\(_K\)) flow through the ACh-gated channels at the endplate, the **reversal potential** (defined as the potential where the sum of the inward Na\(^+\) and outward K\(^+\) current through the open channels is 0) is close to 0 mV, which is approximately halfway between E\(_{Na}\) and E\(_K\). If resting
membrane potential is more negative than the reversal potential, ACh produces a **depolarizing** change in membrane potential, becoming less negative. If resting membrane potential is more positive than the reversal potential, ACh produces a **hyperpolarizing** change in membrane potential, becoming more negative. The **nicotinic ACh receptor is an ionotropic receptor**: a receptor protein that is itself an ion channel. Postsynaptic potentials mediated by a ligand, such as ACh, binding to an inotropic receptor have very brief durations (tens of milliseconds). The duration of the EPP is limited by rapid hydrolysis of ACh by AChE and by diffusion of ACh away from the active zones. At other synapses, such as those utilizing glutamate, dopamine, norepinephrine (NE), serotonin, γ-aminobutyric acid (GABA), or glycine as a neurotransmitter, active reuptake by high-affinity systems involving Na⁺ cotransport is also important for removing the neurotransmitter rapidly.

Chemical transmission at other synapses also involves **Ca²⁺-dependent exocytosis** of neurotransmitters but can differ in the neurotransmitter released, the receptors bound by the neurotransmitter, the ions involved in mediating the postsynaptic response, and whether metabolic responses are involved. Within the **central nervous system (CNS)**, excitatory synapses often utilize **glutamate** as a neurotransmitter, and this opens channels like those in the neuromuscular junction that are permeable to both Na⁺ and K⁺. The reversal potential of these synapses is also close to 0 mV. However, individual excitatory postsynaptic potentials (EPSPs) at central synapses are much smaller than the EPP (<1 mV vs. >40 mV) because each action potential releases only one or a few vesicles rather than the 100 or so vesicles released at the endplate. Activation of neurons depends on **temporal summation** of many small EPSPs arriving at a high frequency from the same presynaptic neuron and on **spatial summation** of small EPSPs arriving simultaneously from many presynaptic neurons. In contrast, only a single presynaptic neuron synapses with each muscle cell, every EPP reaches action potential threshold (producing a twitch), and temporal summation of EPPs does not occur (instead, temporal summation of twitches is important).

The **nervous system** has numerous **inhibitory synapses**, most of which utilize GABA or glycine as a neurotransmitter. Inhibitory ligand-gated channels often are **selectively permeable to Cl⁻**, which usually has an equilibrium potential slightly negative to the resting potential of the neuron. Opening Cl⁻ channels at inhibitory synapses produces an inhibitory postsynaptic potential (IPSP) that opposes the depolarizing effects of simultaneously released excitatory neurotransmitters. The nervous system also has **modulatory synapses** in which a neurotransmitter such as glutamate, ACh, dopamine, NE, serotonin, or a neuropeptide binds to metabotropic receptors that can be coupled by G proteins to enzymes, such as adenyl cyclase or phospholipase C, that activate cell signaling cascades, which then may alter neuronal function in various ways for periods that can range from seconds to weeks or longer and may contribute to the formation and storage of memories.
COMPREHENSION QUESTIONS

[4.1] Which of the following enzymes catalyzes the synthesis of ACh?
A. Acetyl-coenzyme A
B. Acetylcholinesterase (AChE)
C. Acetylcholine-H+ (ACh-H+ ) exchanger
D. Amino acid decarboxylase
E. Choline acetyltransferase

[4.2] Which of the following is the most common action of γ-aminobutyric acid (GABA):
A. Opening channels permeable to Cl−
B. Opening channels permeable to Ca2+
C. Opening channels permeable to Na+ and K+
D. Closing channels permeable to Na+
E. Closing channels permeable to Cl− and K+

[4.3] Which of the following statements distinguishes excitatory chemical synapses in the brain from the neuromuscular junction?
A. Excitation is produced by ligand-gated channels.
B. Ligand-gated channels increase permeability to both Na+ and K+.
C. Postsynaptic action potentials are triggered when a sufficient number of voltage-gated Na+ channels are opened by an EPP or by summing EPSPs.
D. Temporal summation and spatial summation onto the postsynaptic cell increase the likelihood that a postsynaptic action potential will be evoked.
E. The synaptic reversal potential is close to 0 mV.

Answers

[4.1] E. Choline acetyltransferase synthesizes ACh from choline and acetyl-coenzyme A. The ACh is transported into the vesicle by the ACh-H+ exchanger, and after release it is hydrolyzed by AChE to acetate and choline.

[4.2] A. GABA and glycine are the most important inhibitory neurotransmitters and produce their most common inhibitory effects by opening Cl− channels and producing a current that often causes a slight hyperpolarization and always tends to clamp the neuron close to its resting potential.

[4.3] D. In contrast to other neuronal synapses, the individual EPSPs (or EPPs) at the neuromuscular junction are normally much larger than is required to evoke an action potential, and so temporal summation does not increase the probability of firing (although high-frequency firing of the motor neuron does lead to summation of twitches and to tetanization). All the other features listed are shared by the neuromuscular junction and excitatory chemical synapses in the brain.
**PHYSIOLOGY PEARLS**

- Chemical synaptic transmission begins when an action potential depolarizes a presynaptic terminal sufficiently to open voltage-gated Ca\(^{2+}\) channels and thus trigger Ca\(^{2+}\)-dependent exocytosis of neurotransmitter.
- ACh at the neuromuscular junction and glutamate at central excitatory synapses bind to receptors on ligand-gated channels that are equally permeable to Na\(^+\) and K\(^+\).
- The duration of brief postsynaptic potentials mediated by ionotropic receptors is limited by enzymatic degradation of neurotransmitter, its diffusion away from the active zones and its active transport into the terminal and nearby cells.
- An individual EPP at the neuromuscular junction is very large (>40 mV) and reliably reaches the action potential threshold. Temporal and spatial summation is unnecessary and does not occur at the neuromuscular junction.
- In myasthenia gravis, the EPP is reduced by an autoimmune response to the ACh receptor and often fails to reach threshold during repetitive firing.
- Individual EPSPs in the CNS are very small (<1 mV) and require the summation of many separate EPSPs (temporal and/or spatial summation) to reach the action potential threshold.
- Inhibitory synapses utilize GABA or glycine and often open ligand-gated channels that are selective for Cl\(^-\), which usually has an equilibrium potential that is slightly more hyperpolarized than is the resting potential. Opening these channels opposes the depolarizing effects of excitatory synapses that are active at the same time.
- In many modulatory synapses, neurotransmitter binds to metabotropic receptors that are coupled via G proteins to cell-signaling cascades, which can produce neuronal alterations ranging in duration from tens of seconds to weeks or longer.

**REFERENCES**


Moczydlowski, EG. Synaptic transmission in the nervous system. Ibid pp. 295-324.