Case 7

Myasthenia Gravis: Neuromuscular Transmission

Wendy Chu is a 23-year-old photographer for a busy local newspaper. Over the last 8 months, she experienced “strange” symptoms. She had severe eyestrain when she read for longer than 15 minutes. She became tired when she chewed her food, brushed her teeth, or dried her hair; and she had extreme fatigue on the job. Despite her strong work ethic, Wendy had to excuse herself from several “shoots” because she simply could not carry the heavy equipment. Wendy is not a complainer, but she began to worry about these vague symptoms.

She was evaluated by her physician, who suspected myasthenia gravis. While awaiting the results of a serum antibody test, the physician initiated a trial of pyridostigmine, an acetylcholinesterase inhibitor. Wendy immediately felt better while taking the drug; her strength returned to almost normal. Meanwhile, the results of the antibody test were positive, confirming the diagnosis of myasthenia gravis.

QUESTIONS

1. What steps are involved in neuromuscular transmission?

2. What antibody was measured in Wendy’s serum? Against what protein is this antibody directed?

3. Using your description of neuromuscular transmission, explain why severe muscle weakness (e.g., ocular, jaw) occurs in myasthenia gravis.

4. Why does pyridostigmine, an acetylcholinesterase inhibitor, improve muscle strength in myasthenia gravis?

5. Consider the following drugs that act at various steps in neuromuscular transmission. What is the action of each drug, and which drugs are contraindicated in myasthenia gravis?
   - Botulinus toxin
   - Curare
   - Neostigmine
   - Hemicholinium
ANSWERS AND EXPLANATIONS

1. **Neuromuscular transmission** is the process whereby an action potential in a motoneuron produces an action potential in the muscle fibers that it innervates. The steps in neuromuscular transmission, shown in Figure 1-11, are as follows: (1) An action potential is propagated down the motoneuron until the presynaptic terminal is depolarized. (2) Depolarization of the presynaptic terminal causes voltage-gated Ca\(^{2+}\) channels to open, and Ca\(^{2+}\) flows into the nerve terminal. (3) Uptake of Ca\(^{2+}\) into the nerve terminal causes exocytosis of stored acetylcholine (ACh) into the synaptic cleft. (4) ACh diffuses across the synaptic cleft to the muscle end plate, where it binds to **nicotinic ACh receptors** (AChR). (5) The nicotinic AChR is also an ion channel for Na\(^+\) and K\(^+\). When ACh binds to the receptor, the channel opens. (6) Opening of the channel causes both Na\(^+\) and K\(^+\) to flow down their respective electrochemical gradients. As a result, depolarization occurs. (7) This depolarization, called the **end plate potential**, spreads to neighboring regions of the muscle fiber. (8) Finally, the muscle fibers are depolarized to threshold and fire action potentials. Through this elaborate sequence of events, an action potential in the motoneuron causes an action potential in the muscle fibers that it innervates.

![Figure 1-11 Steps in neuromuscular transmission. The numbers correspond to the steps discussed in the text. ACh, acetylcholine; AChR, ACh receptor.](image)

2. Wendy’s physician suspected myasthenia gravis and measured serum levels of an antibody to the **nicotinic AChR**. Accordingly, the antibody is called AChR-ab.

3. In myasthenia gravis, abnormal antibodies to AChR (AChR-ab) are produced, circulate in the blood, and bind to nicotinic receptors on the muscle end plates. When antibodies are bound to AChR, the receptors are not available to be activated by ACh that is released physiologically from motoneurons. Thus, while normal action potentials occur in the motoneurons and ACh is released normally, the ACh cannot cause depolarization of muscle end plates. Without depolarization of muscle end plates, there can be no action potentials or contraction in the muscle.

4. After ACh binds to and activates AChR on the muscle end plate, it is degraded by acetylcholinesterase, an enzyme that is also present on the muscle end plate. This degradative step, whose byproducts are choline and acetate, terminates the action of ACh on the muscle fiber. Choline is taken up into the motoneuron terminal and recycled into the synthesis of more ACh.

   Pyridostigmine is an **acetylcholinesterase inhibitor** that binds to acetylcholinesterase and thereby prevents binding and degradation of ACh at the muscle end plate. In the treatment of myasthenia gravis, pyridostigmine prevents degradation of ACh, increasing its synaptic concentration and prolonging its action. The longer the muscle end plate is exposed to high concentrations of ACh, the greater the likelihood that action potentials and contraction in the muscle will occur.
5. In principle, any drug that interferes with any step in neuromuscular transmission is contraindicated in myasthenia gravis. **Botulinus toxin** blocks the release of ACh from motoneuron terminals, and therefore, causes total blockade of neuromuscular transmission; it is contraindicated in myasthenia gravis. **Curare**, a competitive inhibitor of ACh for the AChR on the muscle end plate, prevents depolarization of the muscle fiber; it is contraindicated. **Neostigmine** is an acetylcholinesterase inhibitor that is related to pyridostigmine and is used to treat myasthenia gravis by preventing ACh degradation. **Hemicholinium** blocks the reuptake of choline into motoneuron terminals, thereby depleting stores of ACh; it is contraindicated.