MUSCULOSKELETAL

Section I - Neurotransmission

I. Corticospinal Tract and Alpha Motor Neurons (Figure 9.1)

A. The descending corticospinal tract synapses on alpha motor neurons in the ventral horn of the spinal cord.

B. Descending axons of the corticospinal tract release ACh into the synaptic cleft which binds ACh receptors of an alpha motor neuron.

C. Binding of ACh to the postsynaptic cleft causes Na^+ influx and K^+ efflux resulting in alpha motor neuron depolarization.

D. Depolarization reaches the axon hillock and voltage-sensitive sodium channels open, depolarizing this region of the neuron.

E. Depolarization in the axon hillock causes voltage-sensitive Ca^{2+} channels to open.

F. Ca^{2+} influx allows neurotransmitter vesicles within the alpha motor neuron to fuse to the cell membrane and enter the synaptic cleft.

II. Muscle Stimulation (Figure 9.1)

A. Neurotransmitter vesicles in the presynaptic terminals release acetylcholine (ACh) into the synaptic cleft.

B. Nicotinic ACh receptors of the postsynaptic cleft within skeletal muscle tissue facilitate Na^+ and K^+ exchange.

C. Binding of ACh to the receptors causes Na^+ to enter the cell and K^+ to leave the cell resulting in depolarization.

D. Voltage gated Na^+ channels then open resulting in additional depolarization.

E. The muscle cell membrane (sarcolemma) contains deep invaginations that extend into the muscle fiber which are called T-tubules.

F. T-tubules are an extension of the extracellular space and contain L-type voltage-gated calcium channels that open when intracellular Na^+ concentrations rise resulting in depolarization.

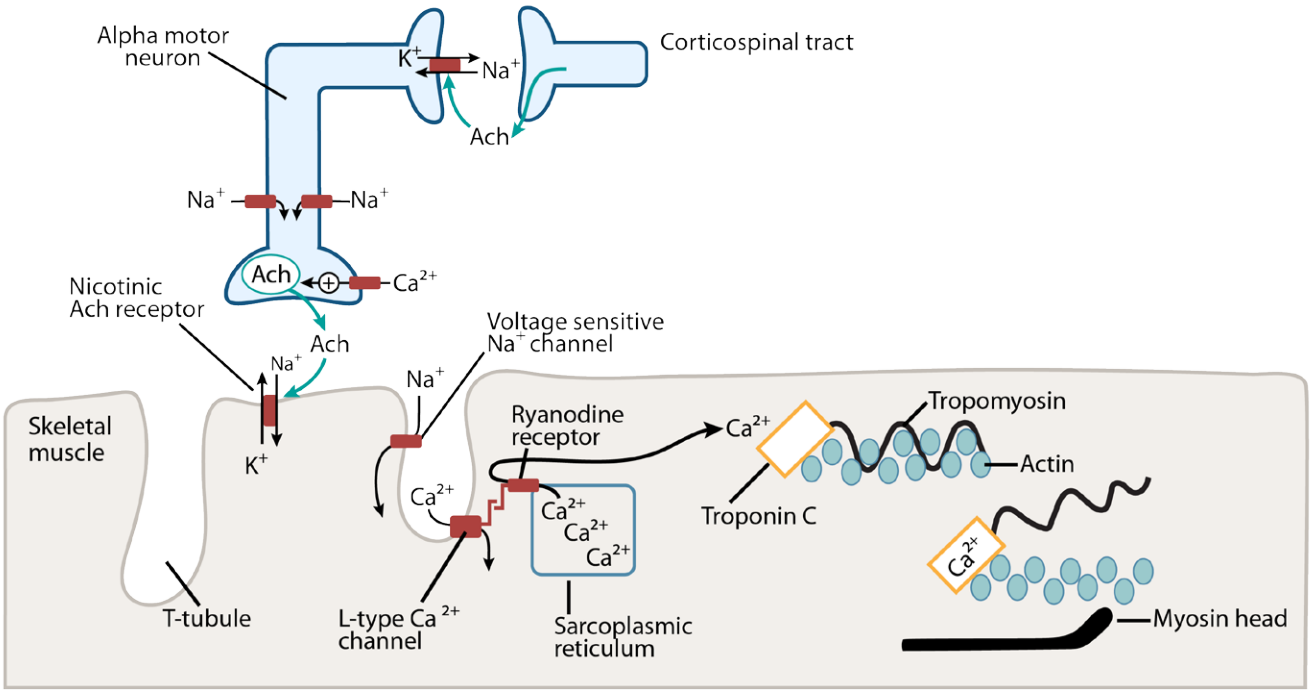


Figure 9.1 - Neurotransmission

G. The expansive distribution of T-tubules allows the entire muscle fiber to contract uniformly because it allows the depolarizing signal to reach all of the myofibrils at the same.

H. Ca^{2+} enters the cell through L-type Ca^{2+} channels, but the release of Ca^{2+} from the sarcoplasmic reticulum (SR) is not directly dependent upon Ca^{2+}. Rather, the L-type Ca^{2+} channel mechanically interacts with the ryanodine receptors resulting in SR release of Ca^{2+}.

I. Ca^{2+} release from the SR results in increased cytosolic Ca^{2+} which binds to troponin C.

J. Troponin C moves tropomyosin from actin allowing myosin to bind actin and cause muscle contraction.

K. After contraction the Ca^{2+}-ATPase pump (SERCA) actively pumps intracellular Ca^{2+} into the SR which allows intracellular Ca^{2+} concentrations to be kept low.

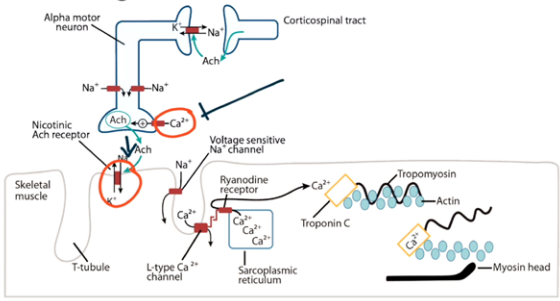
1. Within the SR is a Ca^{2+}-binding protein called calsequestrin → allowing the SR to store Ca^{2+}

REVIEW QUESTIONS

1. A new experimental drug is known to inhibit voltage-sensitive Ca^{2+} channels in the alpha motor neuron. How will this drug likely alter skeletal muscle activity?

- **The calcium channels described are responsible for inducing acetylcholine release into the synaptic cleft → stimulation of the postsynaptic sodium-potassium channel → muscle contraction**
- **Blockage of the calcium channels → ↓ skeletal muscle activity**

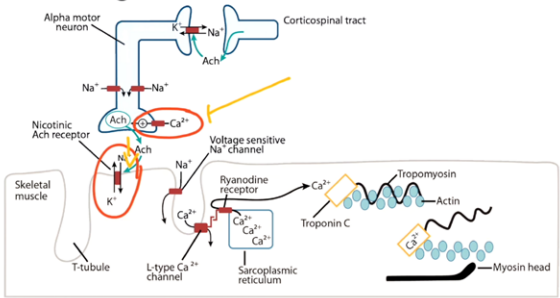
Figure 9.1 - Neurotransmission



2. A 66-year-old with a 50 pack-year smoking history presents with generalized muscle weakness. He states that it is worse in the morning but gets better throughout the day. What is the underlying explanation for the muscle weakness?

- **This patient has small cell lung cancer → Lambert-Eaton syndrome (paraneoplastic syndrome that results in antibodies against the presynaptic calcium channels)**

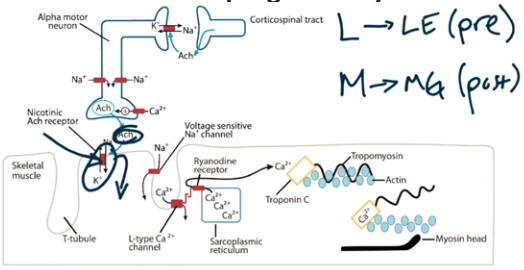
Figure 9.1 - Neurotransmission



REVIEW QUESTIONS

3. Why does myasthenia gravis result in progressive weakening of muscles with repetitive use?

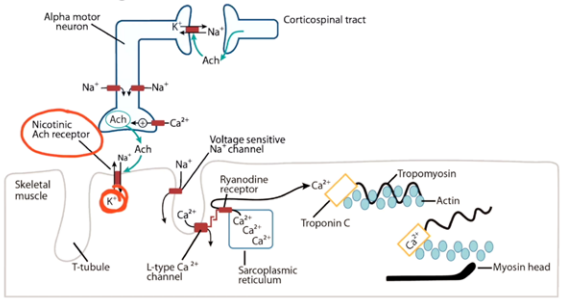
- **Myasthenia gravis → antibodies against the postsynaptic acetylcholine receptors**
- **Dysfunctional receptors → excessive endocytosis**
- **Initially, the acetylcholine binds the few receptors that are available and results in a strong muscle contraction**
- **However, as more acetylcholine is released there are no more available receptors so the muscle becomes progressively weaker**



4. A 67-year-old female is being intubated for a hip replacement surgery. The anesthesiologist suddenly notices that she develops hyperkalemia. What drug was likely used to assist with the intubation that resulted in the hyperkalemia?

- **Succinylcholine (activates the nicotinic acetylcholine receptor → sustained efflux of potassium)**

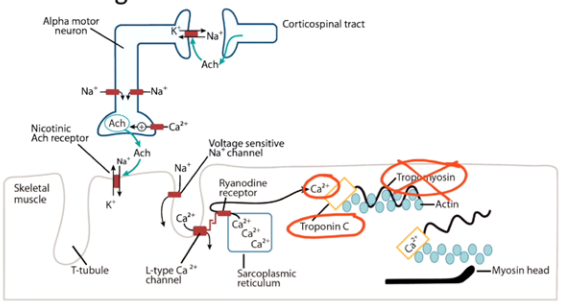
Figure 9.1 - Neurotransmission



5. The skeletal muscle of a knockout mouse is able to contract despite total depletion of intracellular skeletal muscle calcium concentrations. What protein defect most likely explains the finding?

- **Tropomyosin**
- **This protein normally prevents actin from binding myosin and is released from actin in the presence of calcium**
- **If calcium is not needed for muscle contraction, then tropomyosin must be defective**

Figure 9.1 - Neurotransmission



6. A 47-year-old male is administered an inhaled anesthetic and suddenly develops intense muscle contractions. What molecular abnormality explains the sudden change?

- **Inhaled anesthetics can cause malignant hyperthermia (autosomal dominant disorder → mutations in the ryanodine receptor → excessive release of calcium into the cytosol → intense muscle contractions)**

desflurane / isoflurane → malignant hyperthermia

Figure 9.1 - Neurotransmission