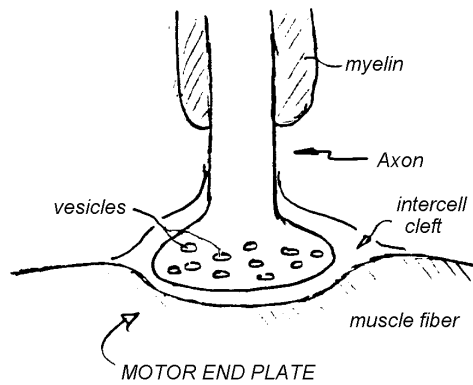


INTRODUCTION

A. Intercellular Transmission across Synapses

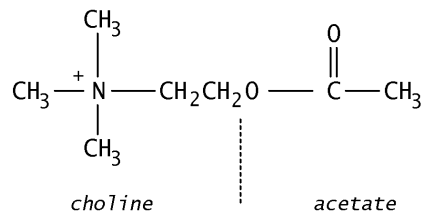
1. Types of cells connected
 - a. neuron-neuron
 - b. neuron-secretory gland
 - c. neuron-muscle cell
 - 1) skeletal muscle (somatic muscle)
 - 2) cardiac muscle
 - 3) smooth muscle
 - d. other: e.g. neuron-adipose tissue cell
2. Mechanisms of synaptic transmission
 - a. electrical, by current flow across intercellular low resistance junctions (gap junctions); rare in mammals
 - b. release of a chemical (transmitter, neurotransmitter)

B. Functional Anatomy of the Nerve-Skeletal Muscle Junction (neuromuscular junction, myoneural junction)



Note: the neurons innervating skeletal muscle cells have large, myelinated axons; their cell bodies are in the CNS; they are termed alpha motoneurons because of their function and size

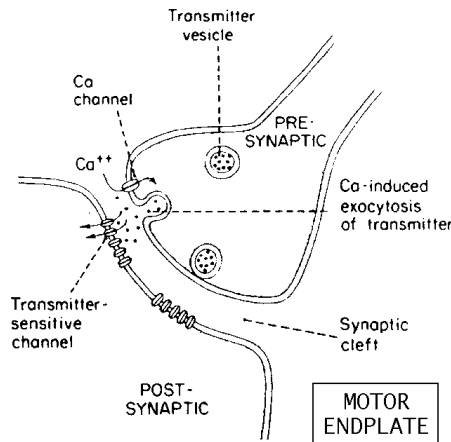
Note: vesicles contain acetylcholine (ACh); similar amount in each vesicle



Note: the junction between the axon termination and the muscle cell motor end plate is termed a synapse; the axon ending is termed presynaptic; the muscle cell end plate is termed postsynaptic

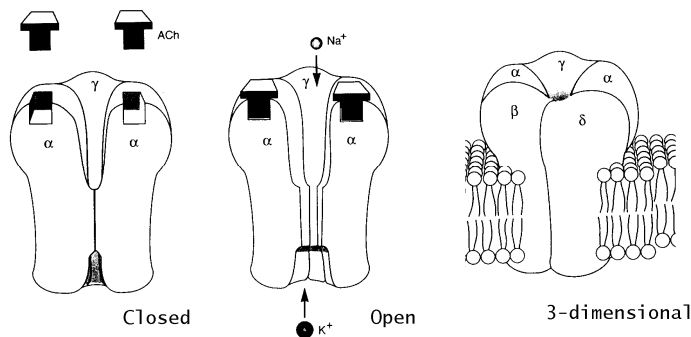
TRANSMISSION SEQUENCE

- A. Nerve axon action potential arrives at endplate, transiently depolarizing the axon terminal and then dying out
- B. Axon terminal depolarization opens calcium ion channels briefly, permitting Ca^{++} to diffuse into the axon terminal
- C. Increased intracellular Ca^{++} leads to exocytosis of some of the Ach-containing vesicles, which discharge their Ach into the intercellular cleft



- D. ACh diffuses to muscle fiber endplate region; diffusion is rapid because the distance is short
- E. ACh attaches to binding site on muscle fiber (ACh Receptor); binding site on nonspecific small ion channels, and causes the channels to open

Notes: (1) these channels are ACh sensitive, not voltage sensitive
(2) ACh channel confined mainly to endplate region of the muscle fiber

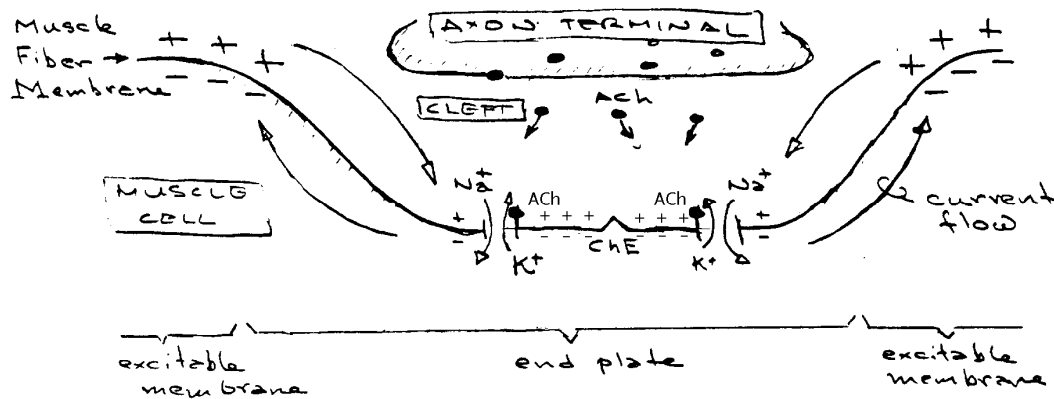


TRANSMISSION SEQUENCE (continued)

F. Na^+ diffuses into the muscle cell, causing endplate depolarization,

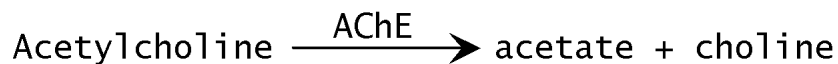
1. The depolarization is termed the endplate potential (epp)
2. The epp is a local, non-propagated depolarization
3. No action potential is generated by the ACh-sensitive channels, since they are not voltage sensitive

G. Endplate potential spreads passively to the nearby muscle fiber membrane, which does contain voltage gated channels (as in other excitable membranes), depolarizing the membrane to threshold and initiating a muscle cell AP



H. The AP is propagated along the muscle fiber membrane, inducing muscle fiber contraction

I. ACh in the cleft region is destroyed by acetylcholine esterase (AChE)



1. Destruction is rapid, before a second AP can be initiated
2. Choline is taken back up into the nerve terminal, to be reused in ACh synthesis

NOTES:

1. The net effect of this sequence is to generate a single muscle fiber AP for each nerve axon AP (one-to-one transmission)
2. Skeletal muscle contraction is completely controlled by its nervous innervation (not by endocrines, not autogenic, etc.)

PATHOPHYSIOLOGY

A. ACh Release Block

1. botulinum toxin (Botox)
 - a. produced by anaerobic microorganism clostridium botulinum
 - b. interferes with Ca^{++} activated ACh release
 - c. extremely potent: lethal dose 10^{-7} gm

B. Reduced muscle endplate sensitivity to ACh

1. Curare and similar neuro-muscular blocking agents.
 - a. attach to ACh site on endplate, but do not cause channel to open and prevent ACh from binding
 - b. termed competitive antagonists of ACh
2. Myasthenia gravis (usually an autoimmune disease)
 - a. due to reduced number of ACh endplate receptors
 - b. characterized by easy fatigability
 - c. treatment: administer anti-acetylcholine-esterase agent
3. Occupation of ACh receptors by depolarizing agents (depolarizing blockers)
 - a. same action as ACh on permeability
 - b. not attacked by AChE
 - c. surrounding muscle fiber membrane remains refractory

E. Anti Acetylcholine Esterase Agents

1. Example: di-isopropylfluorophosphate (DFP) -- nerve gas
2. Causes depolarization block

F. Increase Excitability

1. Myotonia: difficulty in relaxing muscles after contraction; frequently due to defects in muscle ion channels ("channelopathy") due to generation of several muscle APs for each motoneuron AP