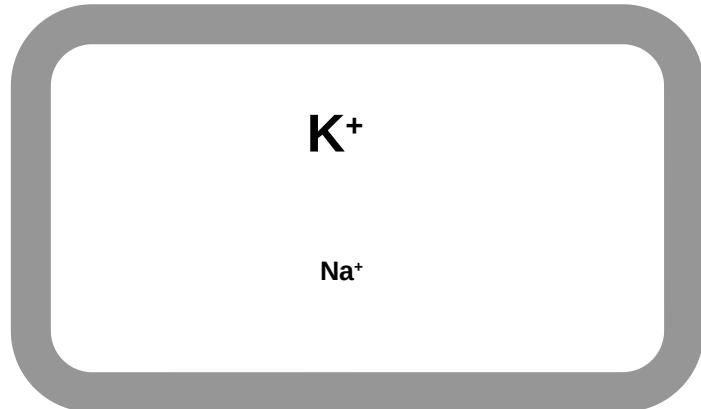


# Motor and Sensory

Lecture 3

$K^+$ 

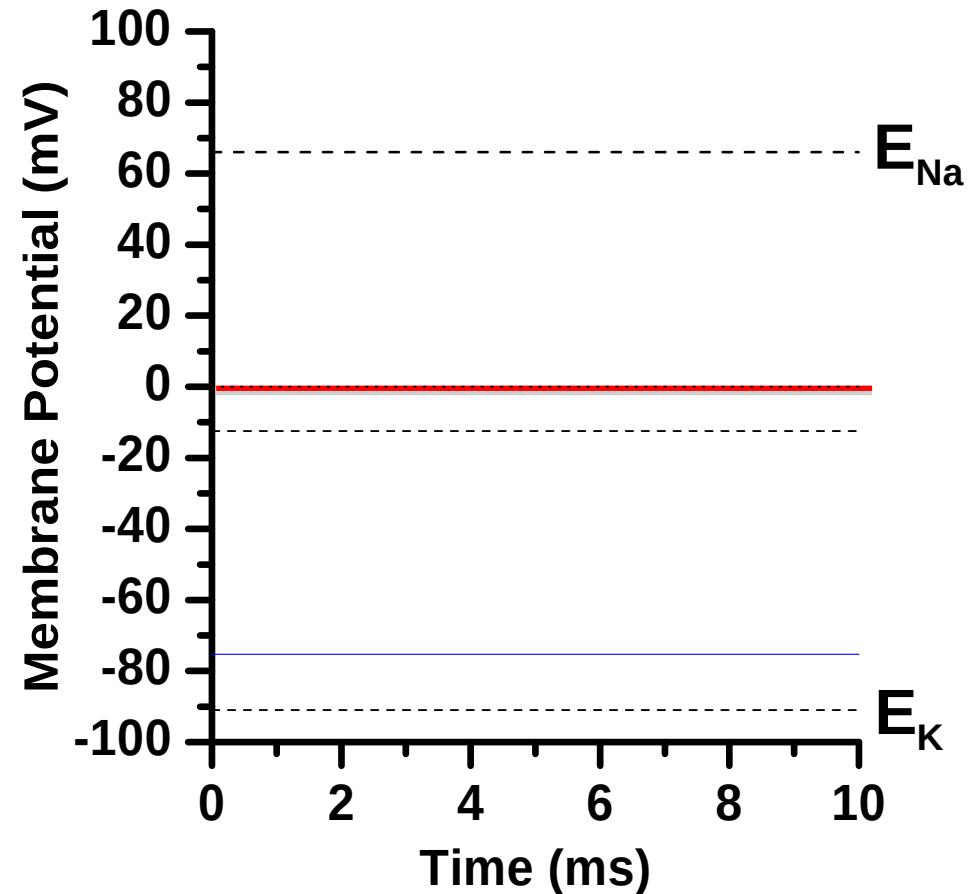
$$V_m = E_{Na} (G_{Na}/G_m) + E_K (G_K/G_m)$$

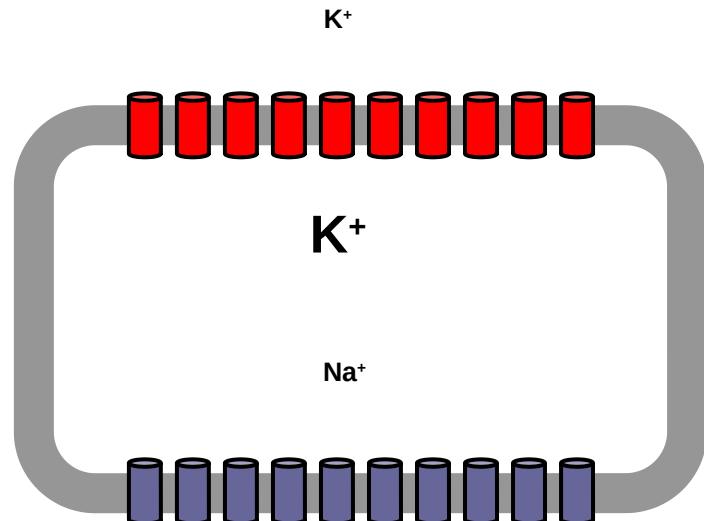
 $Na^+$ 

No ion channels

$$G_{Na}/G_m = 0 \quad G_K/G_m = 0$$

$$V_m = 0 \text{ mV}$$





**ion channels are closed**

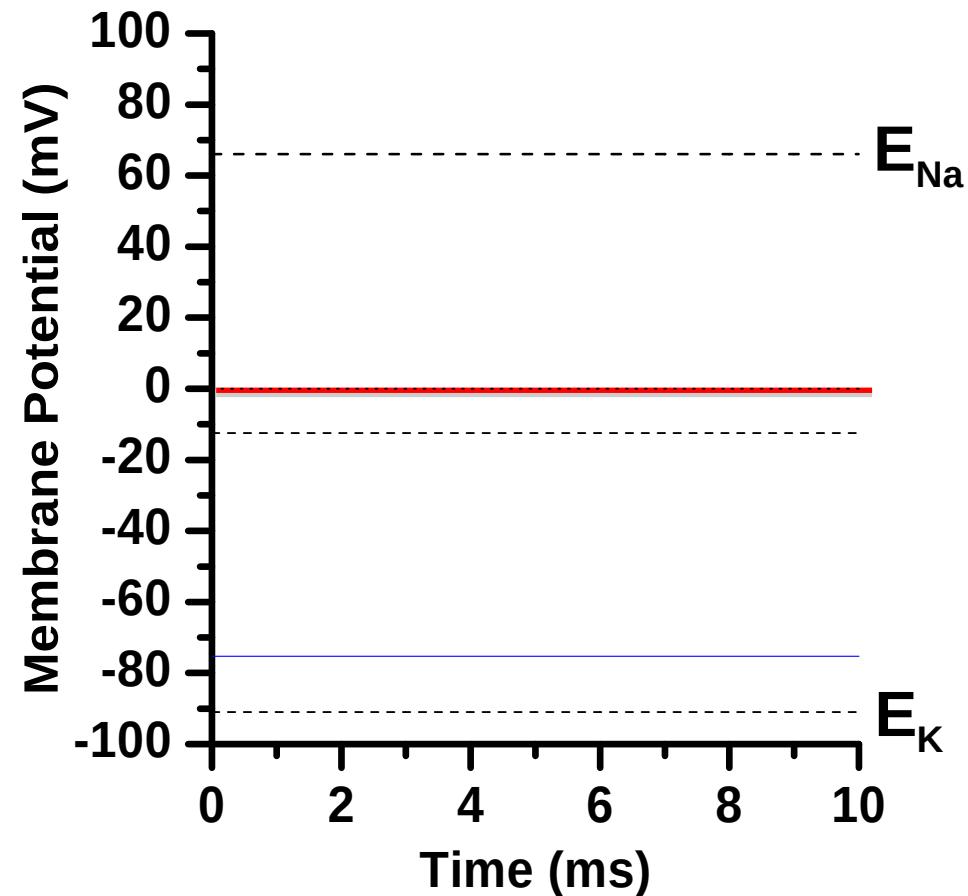


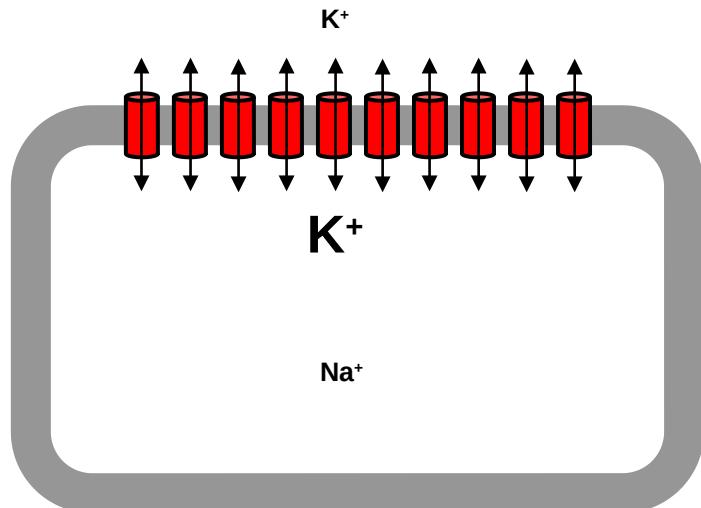
$G_x \propto \# \text{ open channels}$

$$V_m = E_{Na} (G_{Na}/G_m) + E_K (G_K/G_m)$$

$$G_{Na}/G_m = 0 \quad G_K/G_m = 0$$

$$V_m = 0 \text{ mV}$$





**$K^+$  channels are open**

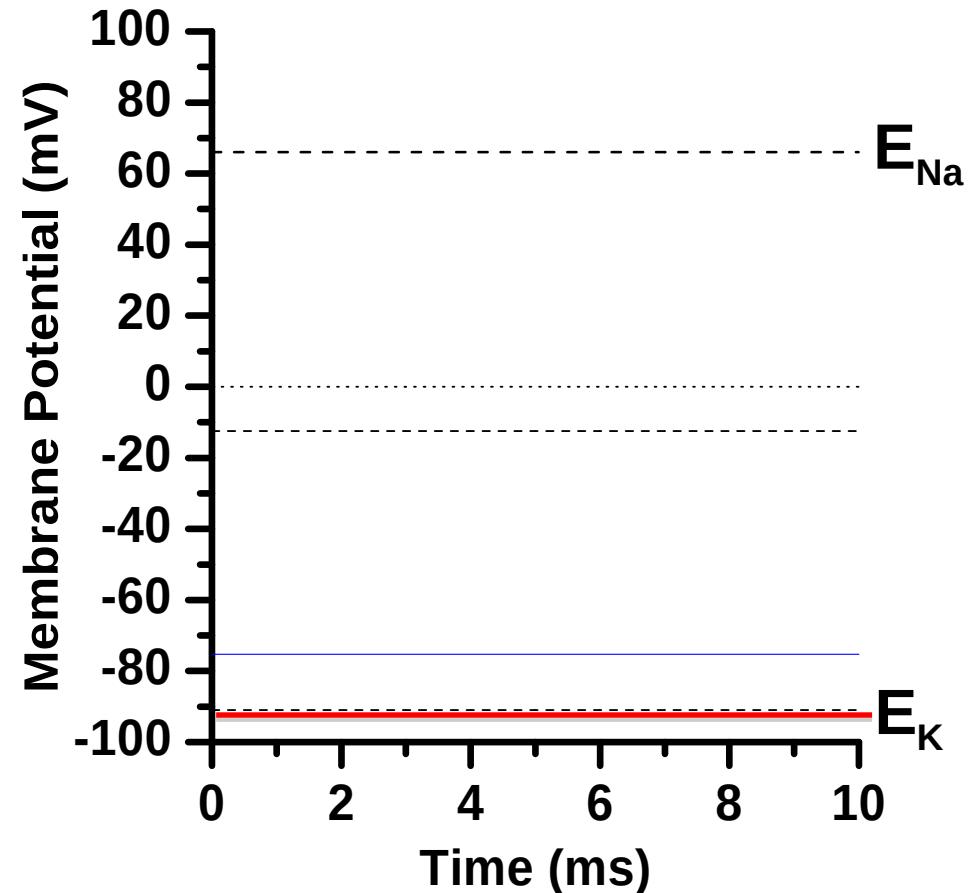


$G_x \alpha$  # open channels

$$V_m = E_{Na} (G_{Na}/G_m) + E_K (G_K/G_m)$$

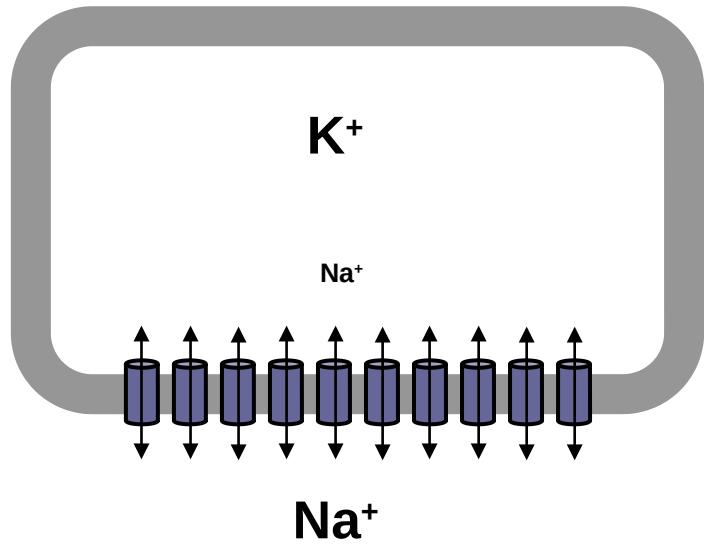
$$G_{Na}/G_m = 0 \quad G_K/G_m = 1$$

$$V_m = (+66)(0) + (-91)(1) = -91 \text{ mV}$$



$K^+$ 

$$V_m = E_{Na} (G_{Na}/G_m) + E_K (G_K/G_m)$$



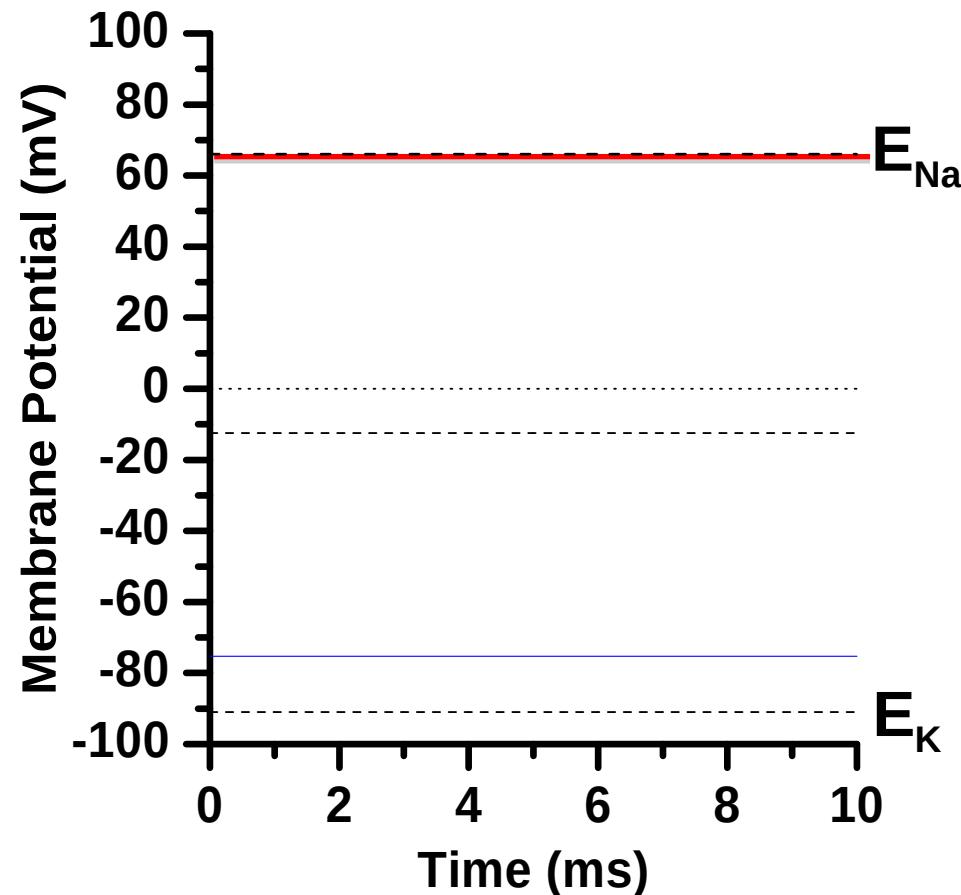
$Na^+$  channels are open

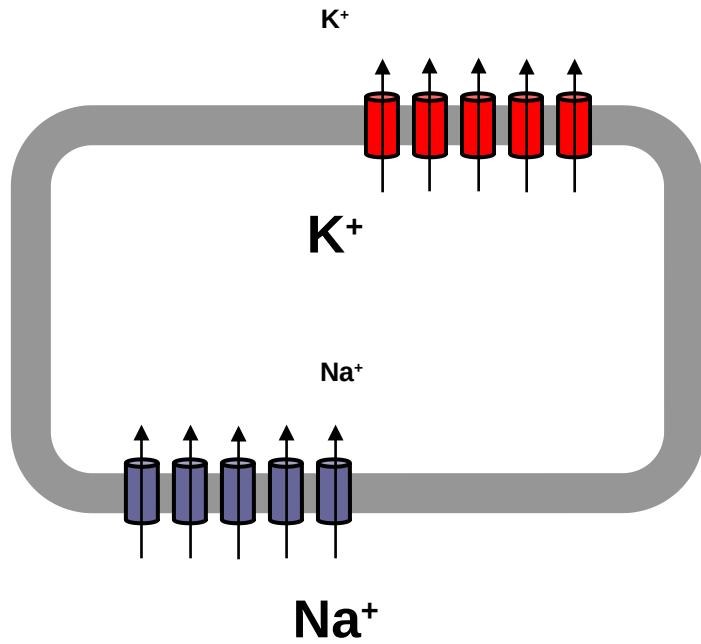


$G_x \alpha$  # open channels

$$G_{Na}/G_m = 1 \quad G_K/G_m = 0$$

$$V_m = (+66)(1) + (-91)(0) = +66 \text{ mV}$$





$Na^+$  &  $K^+$  channels are open

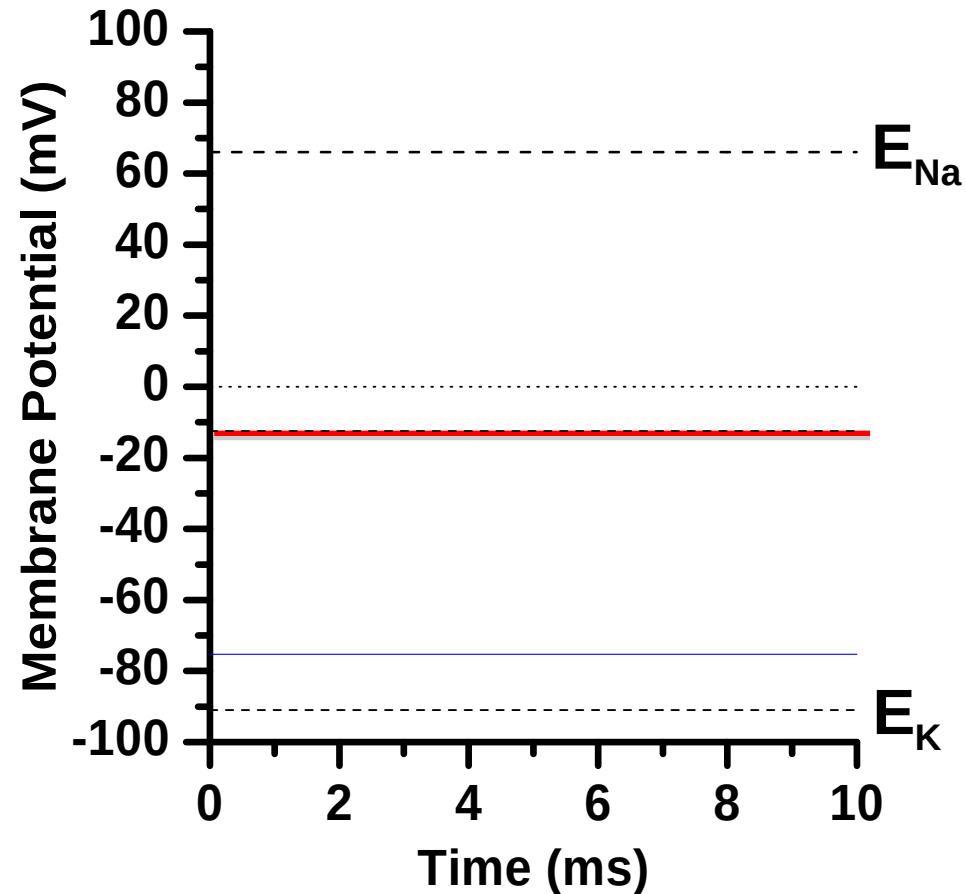


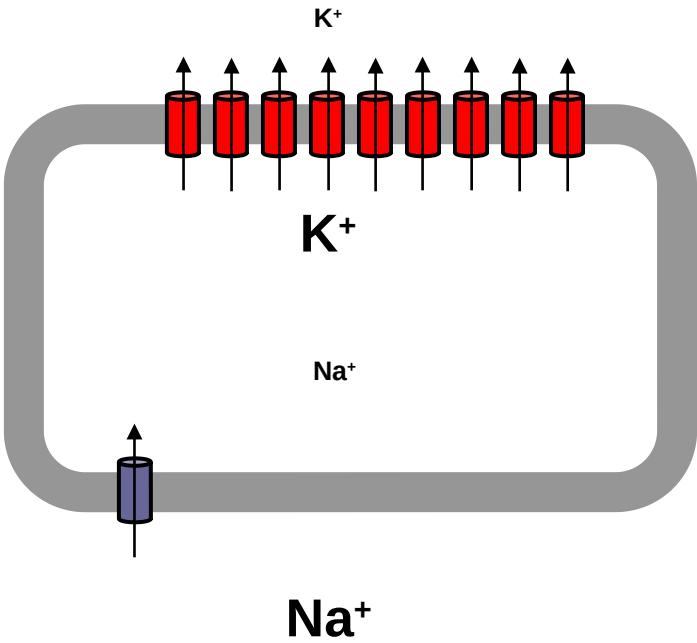
$G_x \alpha$  # open channels

$$V_m = E_{Na} (G_{Na}/G_m) + E_K (G_K/G_m)$$

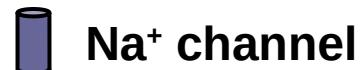
$$G_{Na}/G_m = 0.5 \quad G_K/G_m = 0.5$$

$$V_m = (E_{Na} + E_K) / 2 = -12.5 \text{ mV}$$





$Na^+$  &  $K^+$  channels are open

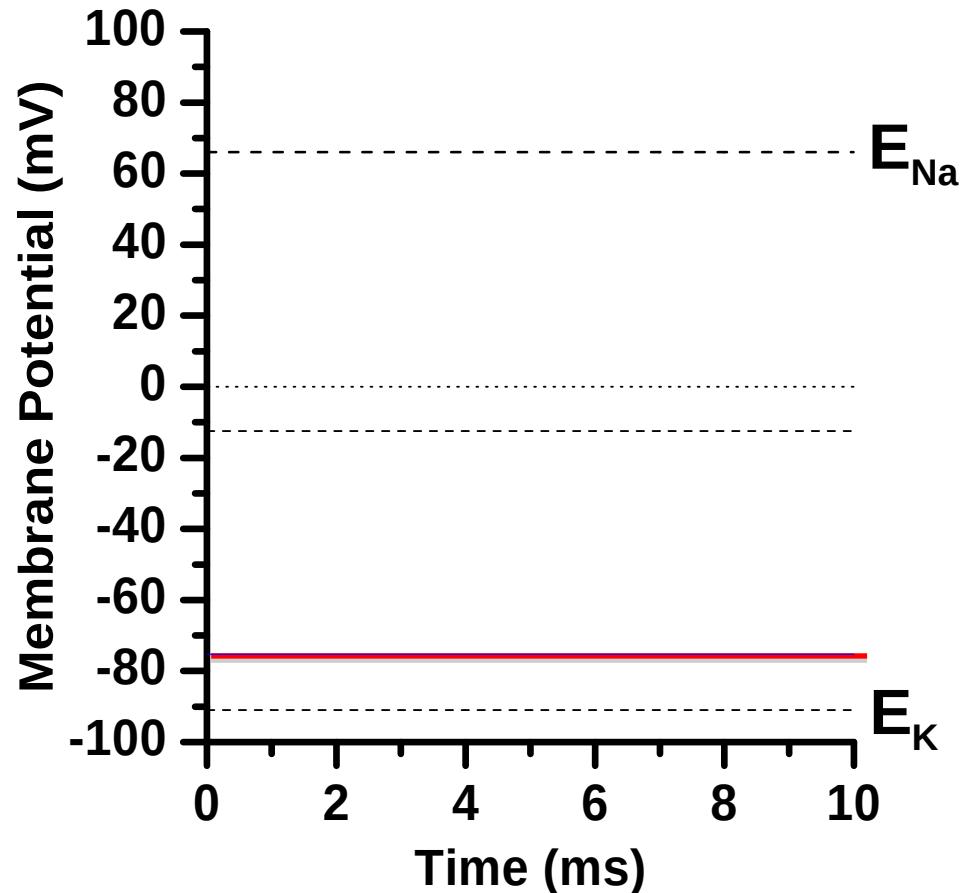


$G_x \alpha$  # open channels

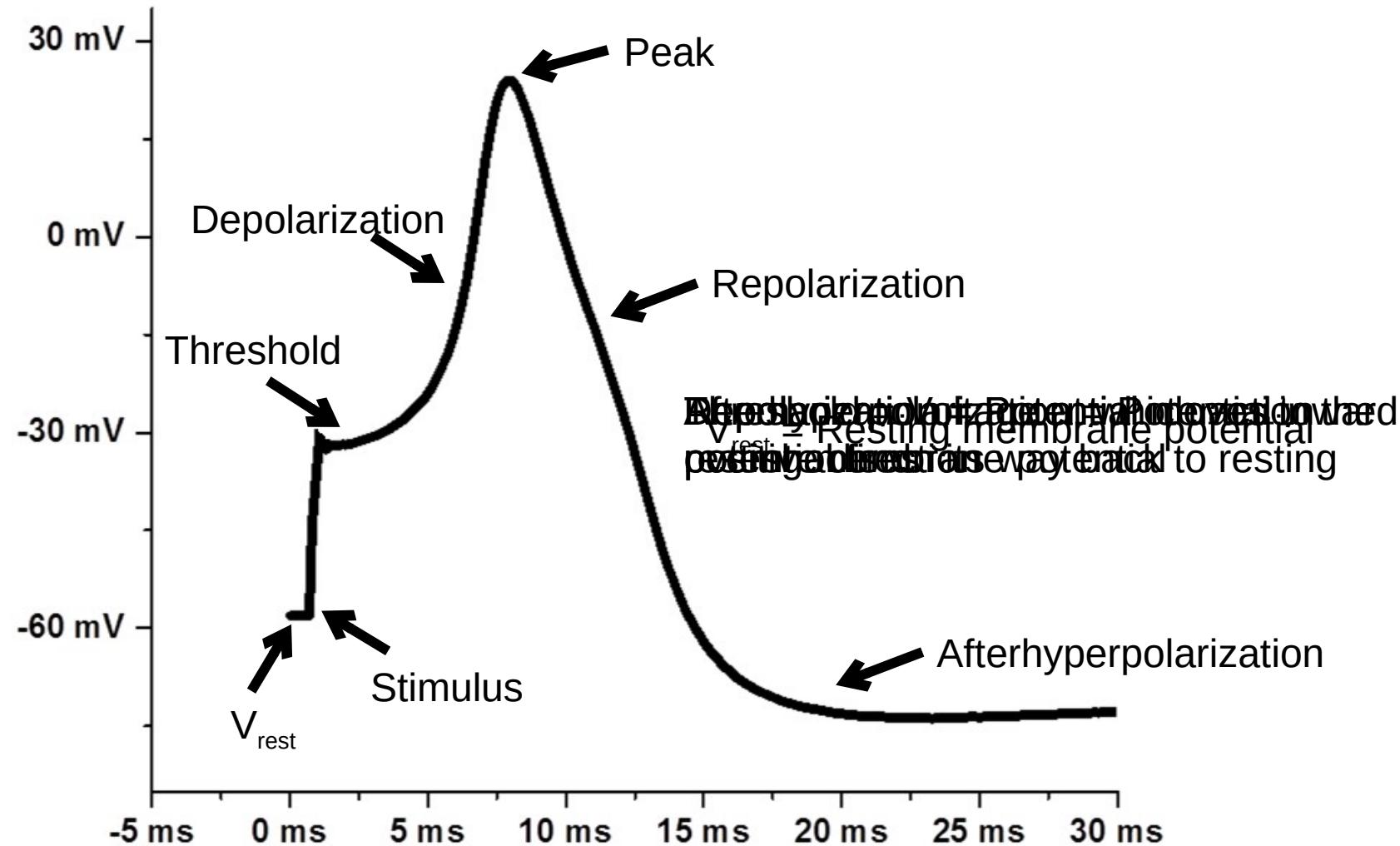
$$V_m = E_{Na} (G_{Na}/G_m) + E_K (G_K/G_m)$$

$$G_{Na}/G_m = 0.1 \quad G_K/G_m = 0.9$$

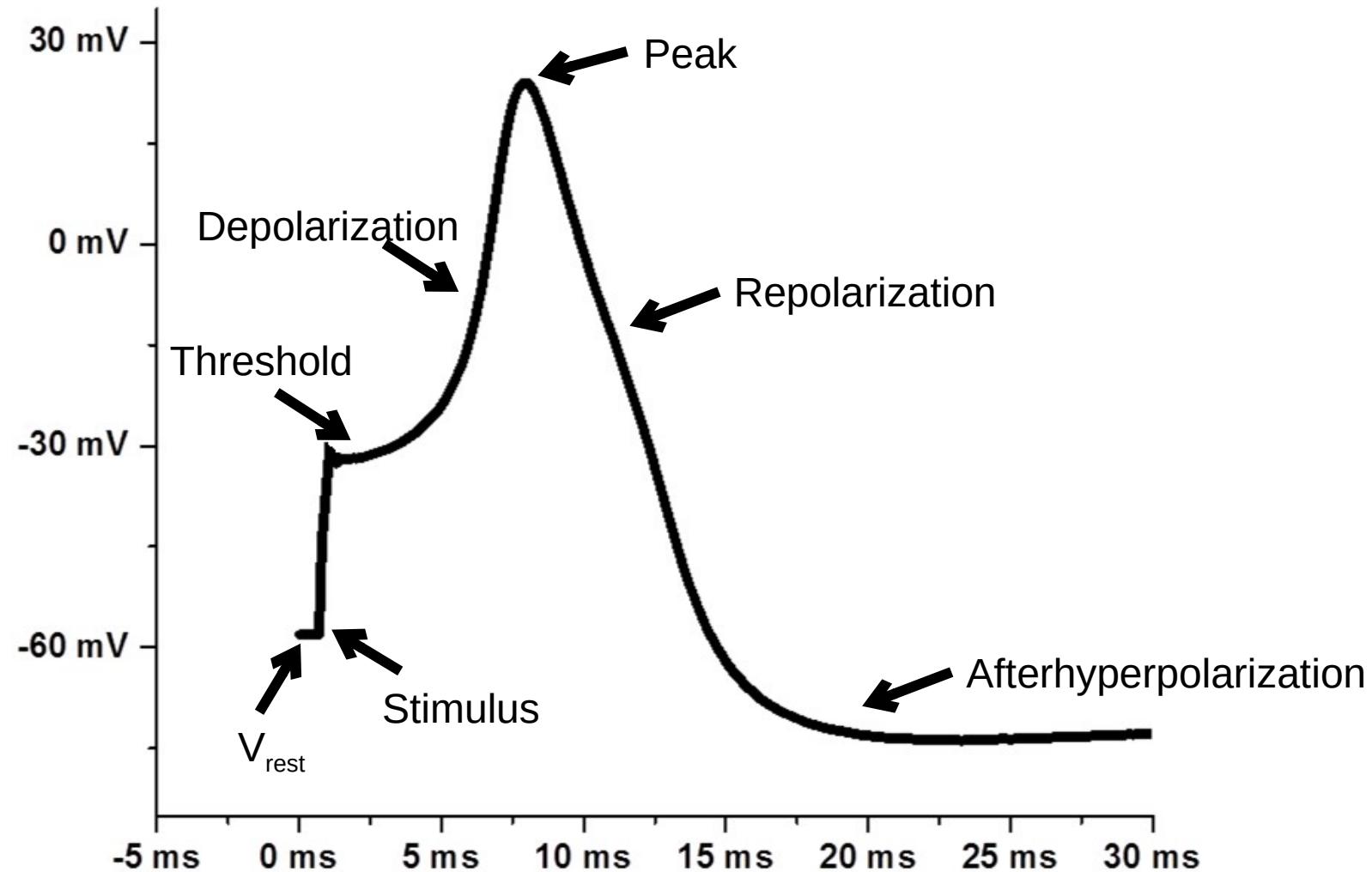
$$V_m = (+66)(0.1) + (-91)(0.9) = -75.3 \text{ mV}$$



# The Action Potential Waveform



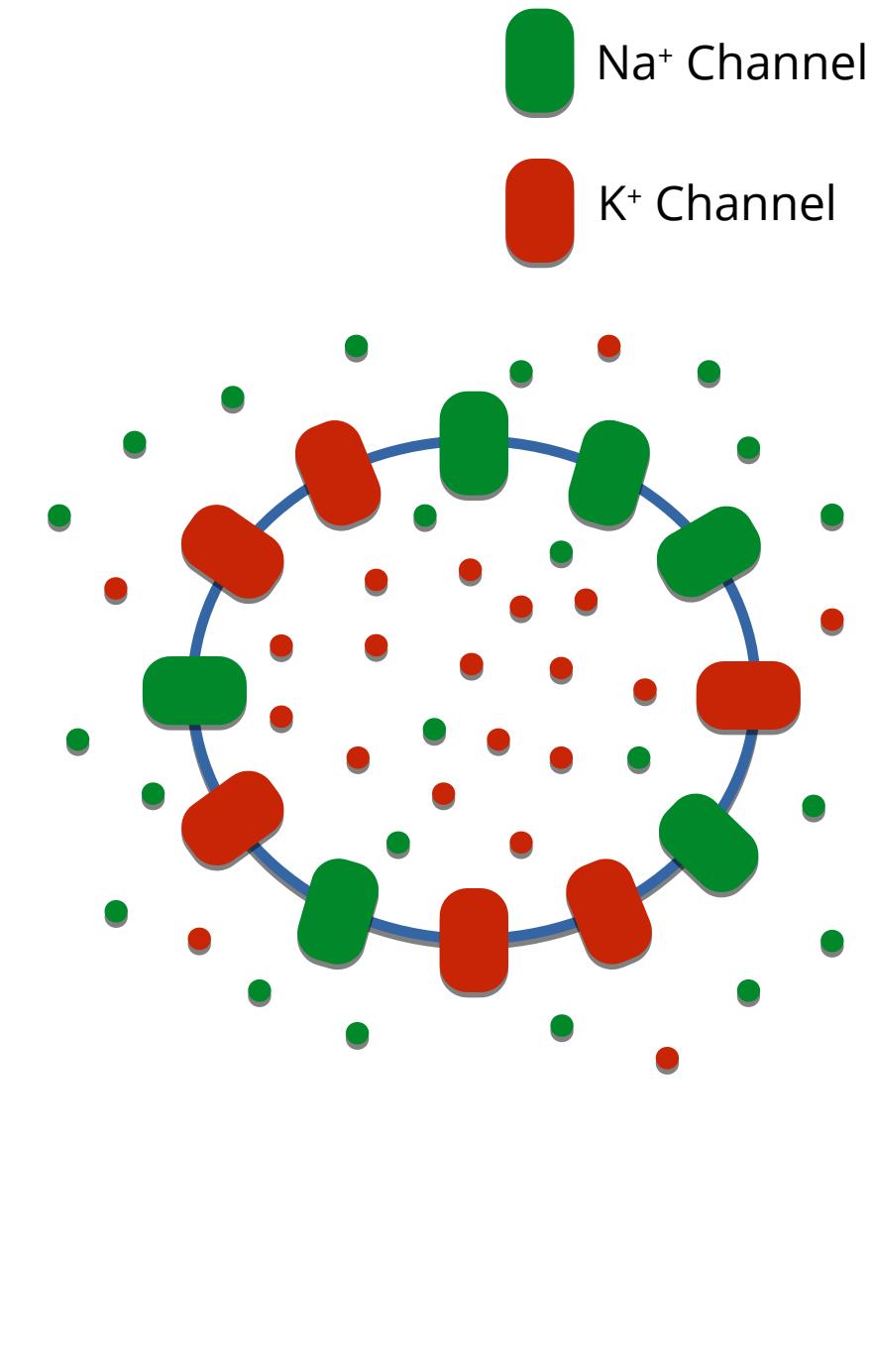
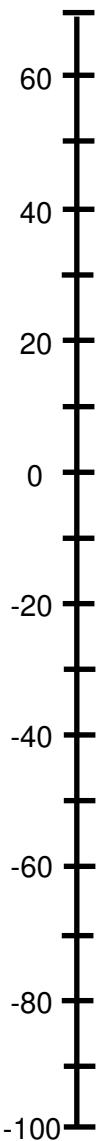
# The Action Potential Waveform



# Defining terms

- $V_{rest}$  = Resting membrane potential
- Threshold = Voltage at which action potential fires (point of no return)
- Depolarization = Potential moves in the positive direction
- Repolarization = Potential moves toward resting membrane potential
- Afterhyperpolarization = Potential overshoots on its way back to resting

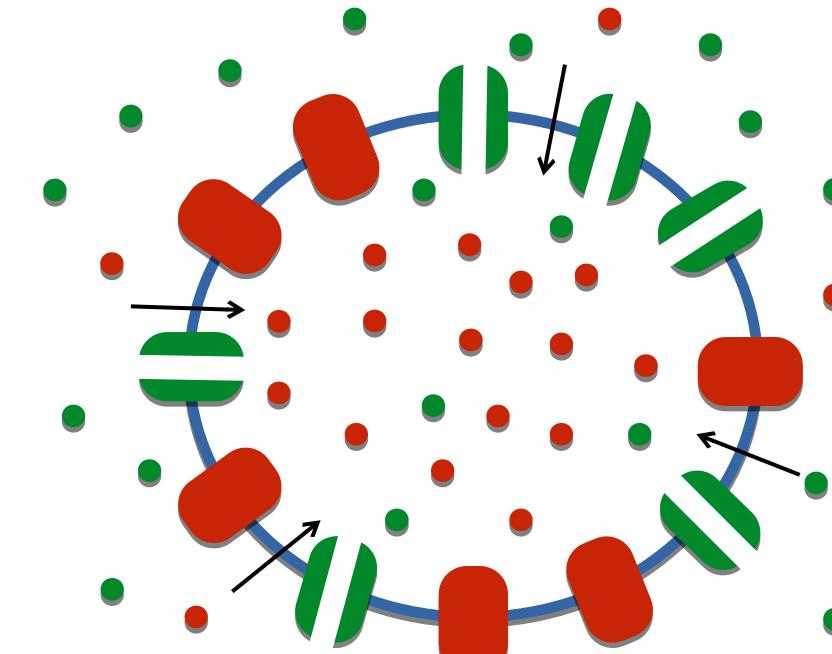
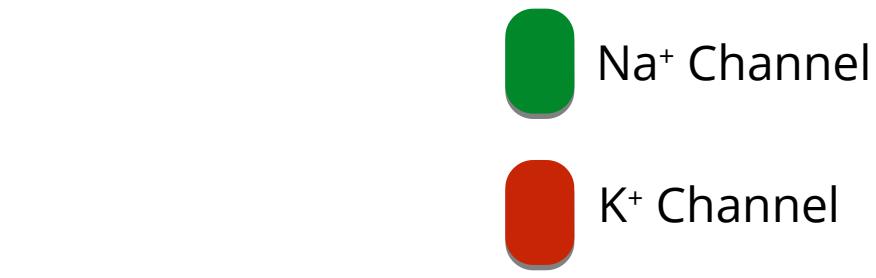
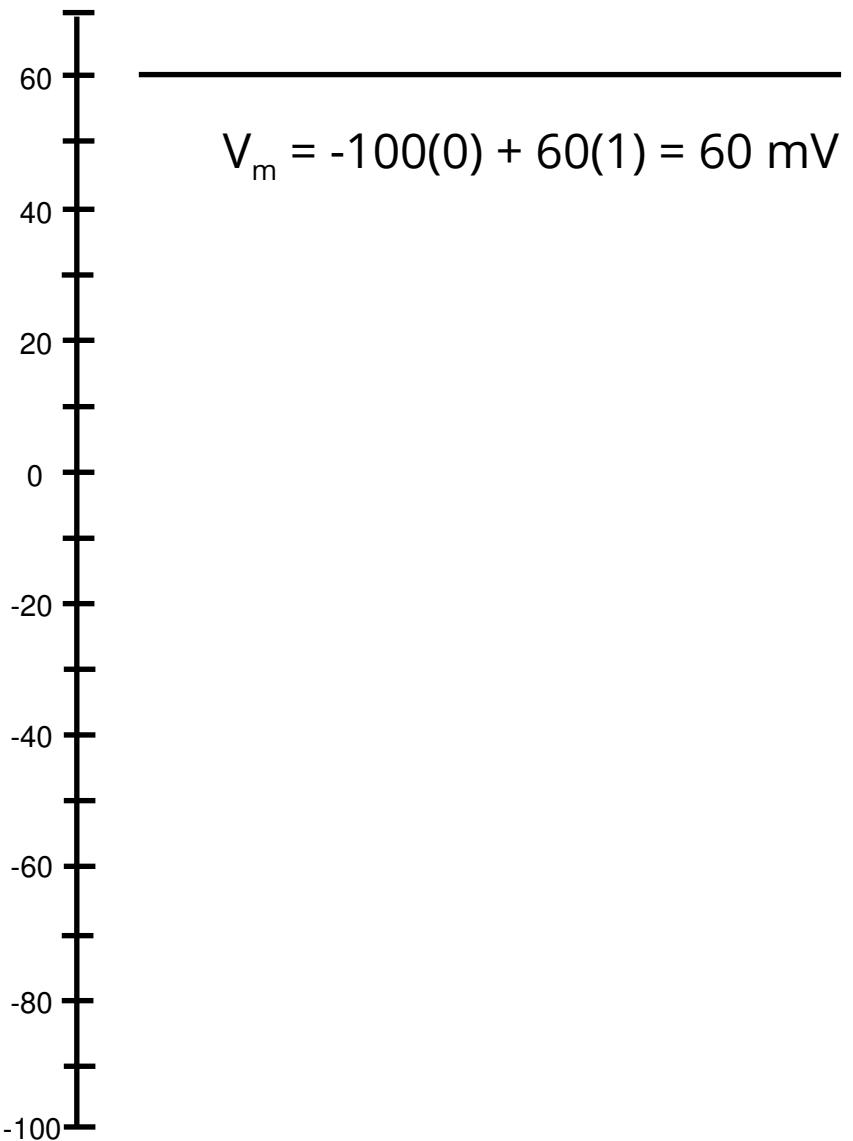
# Membrane Potential



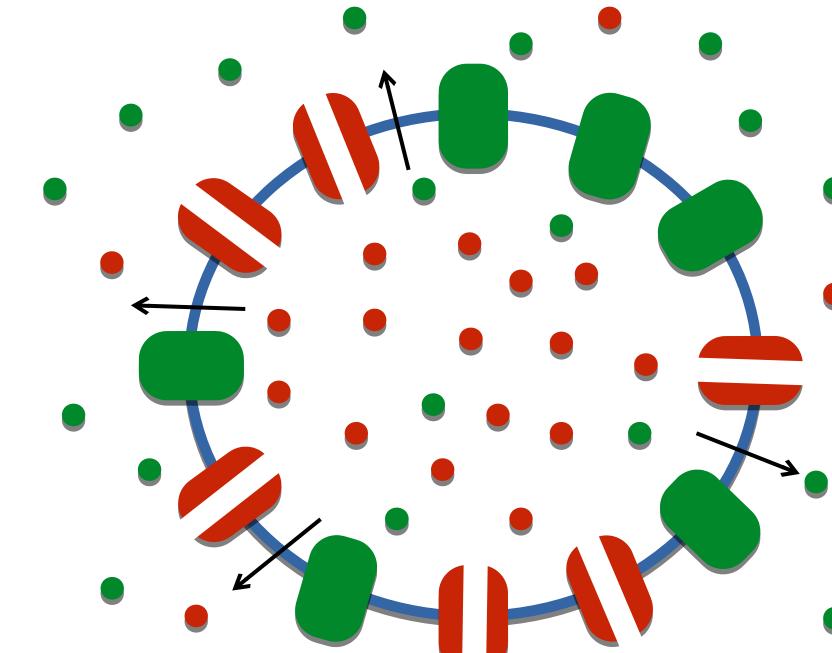
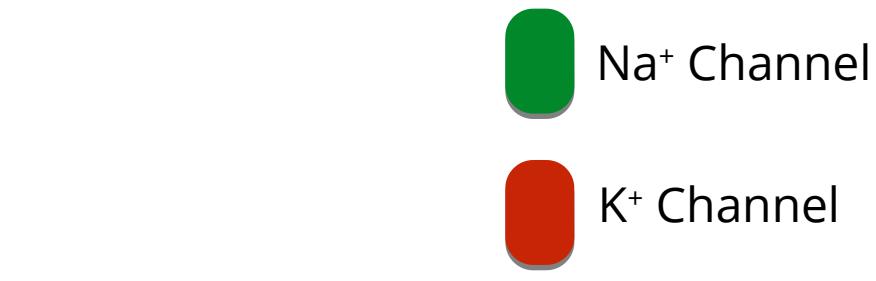
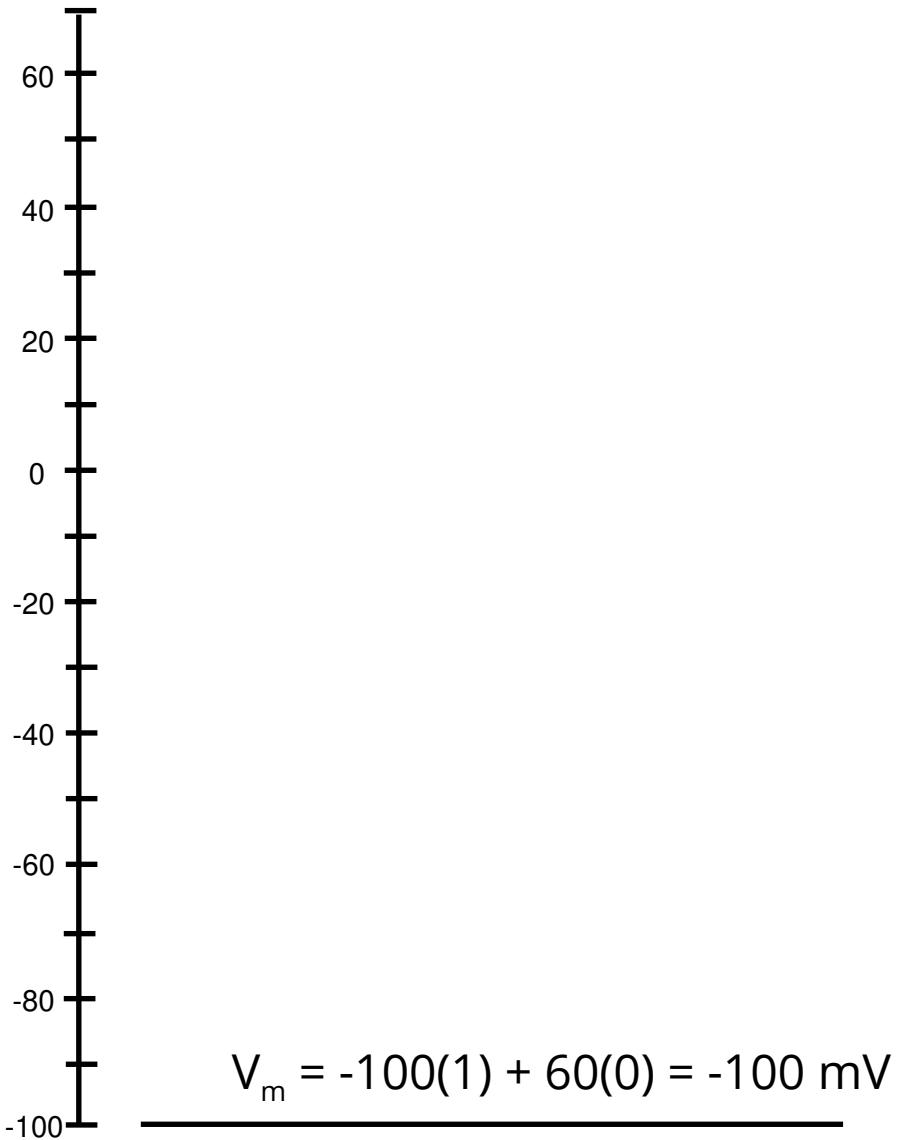
$\text{Na}^+$  Channel

$\text{K}^+$  Channel

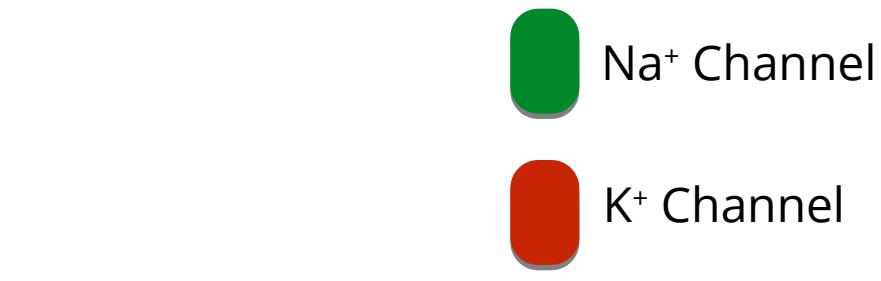
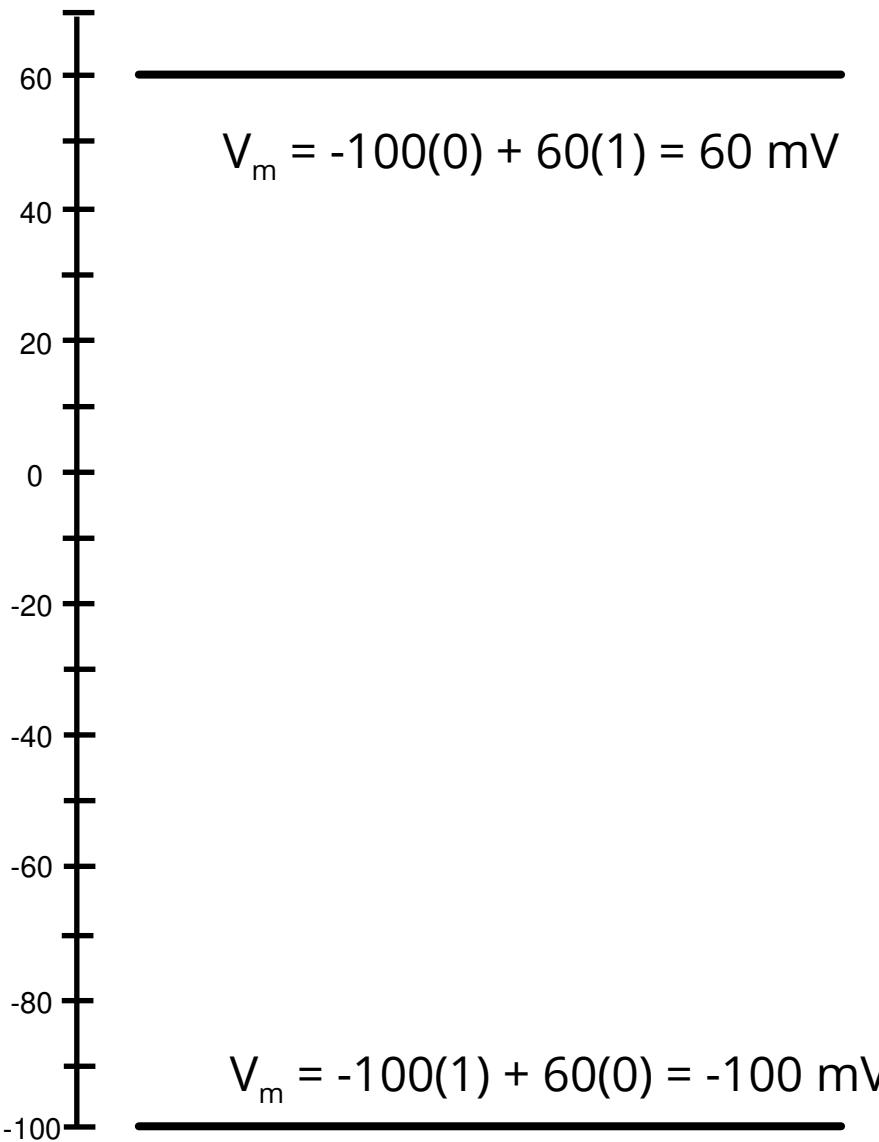
# Membrane Potential



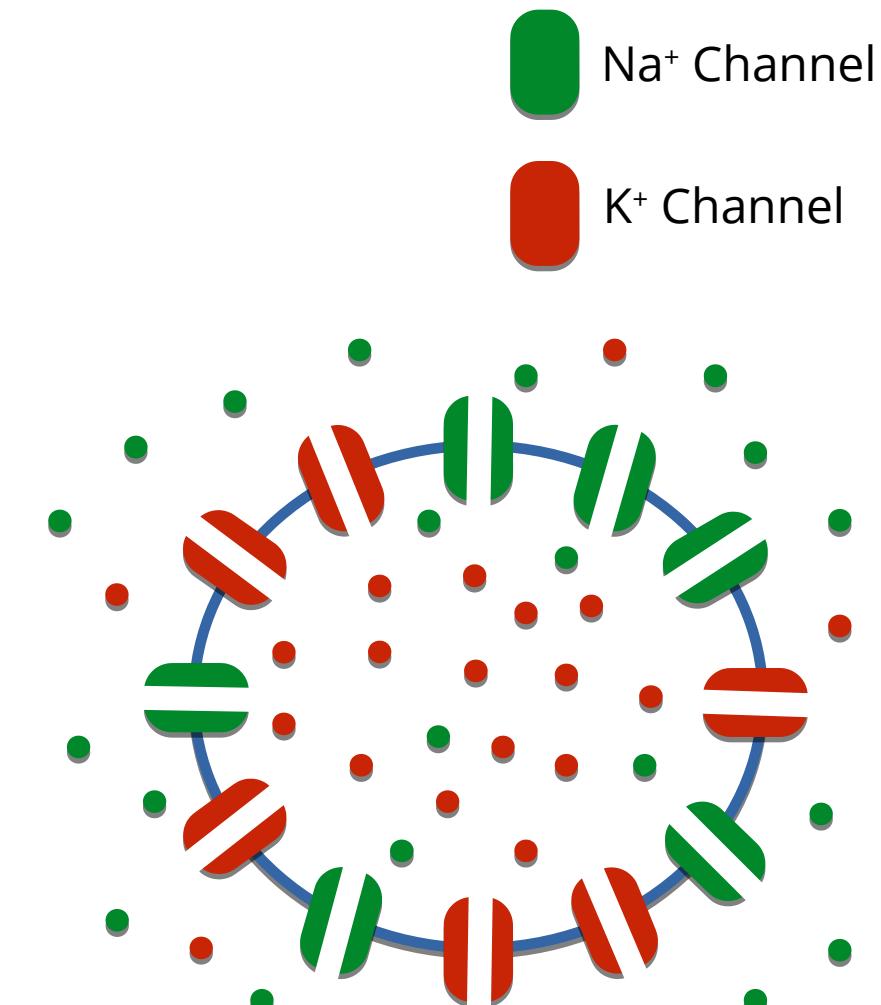
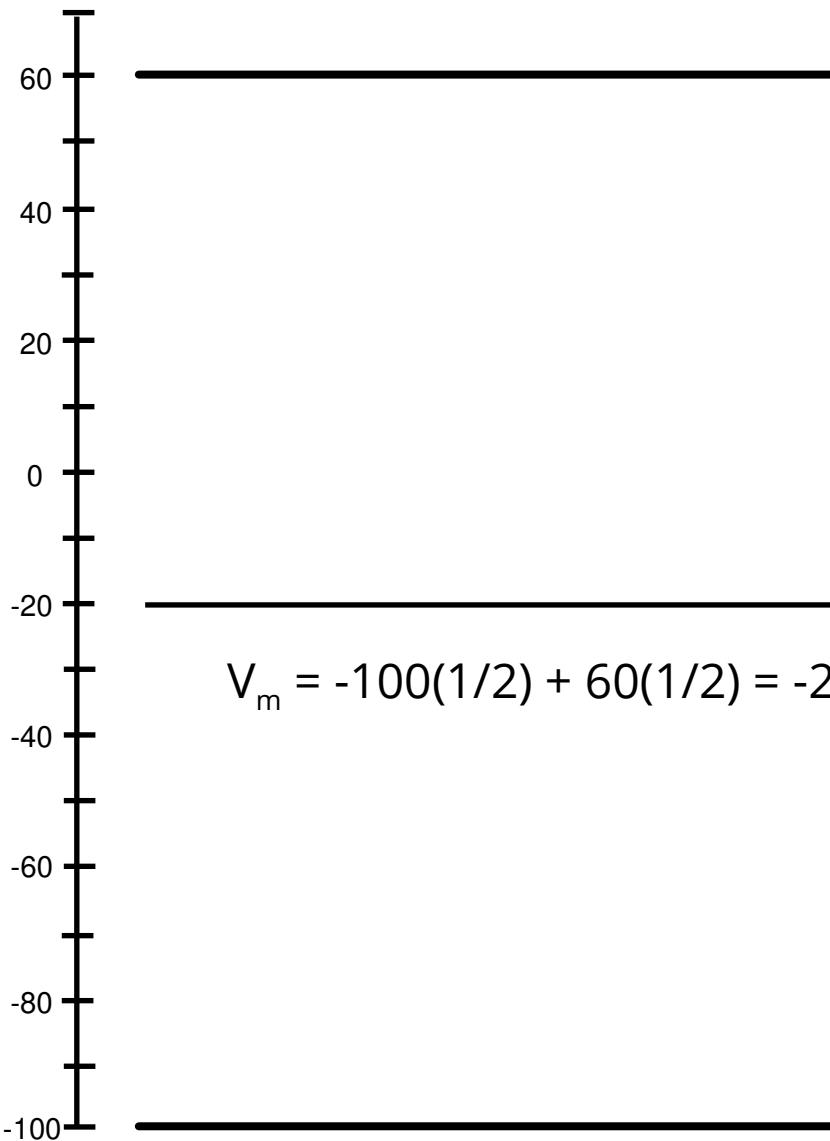
# Membrane Potential



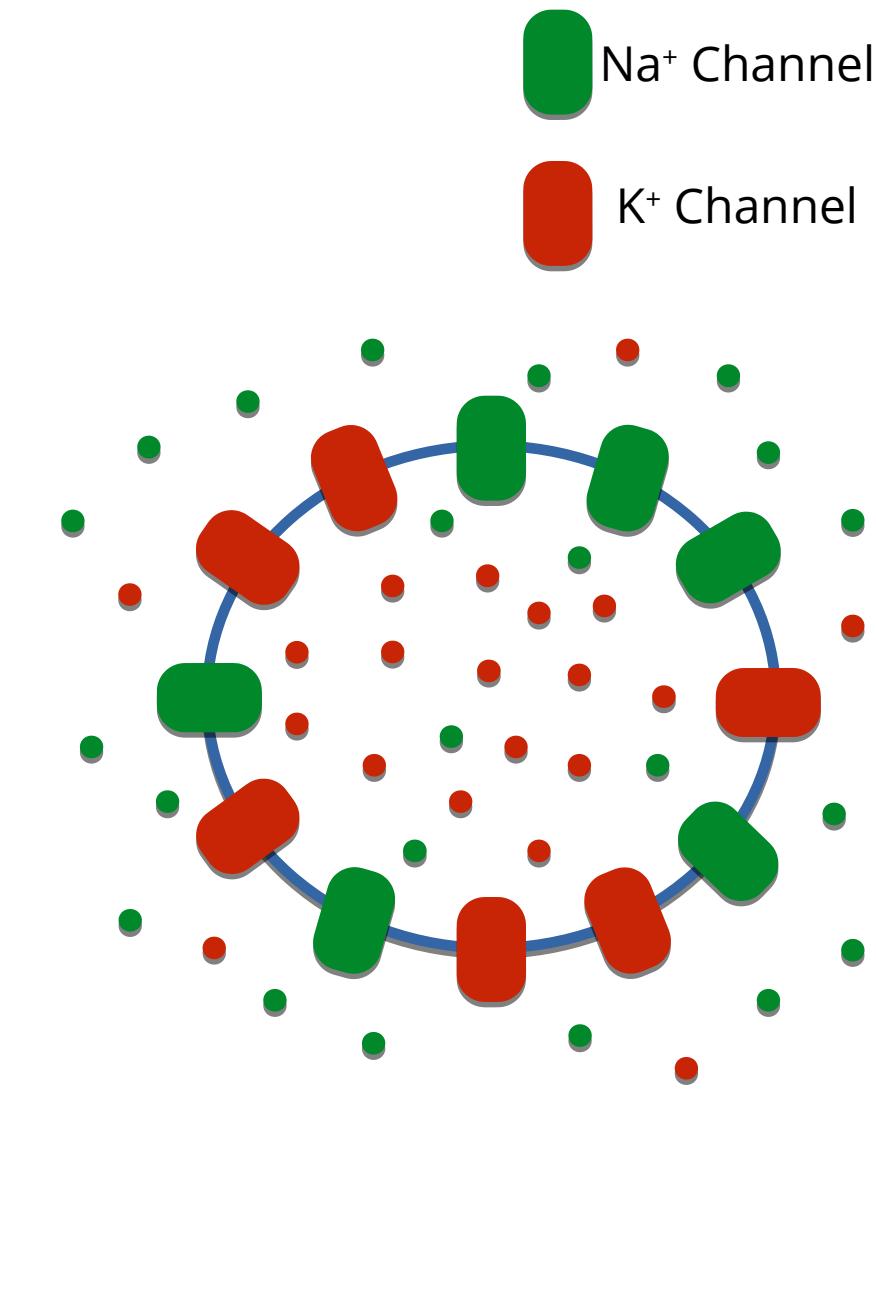
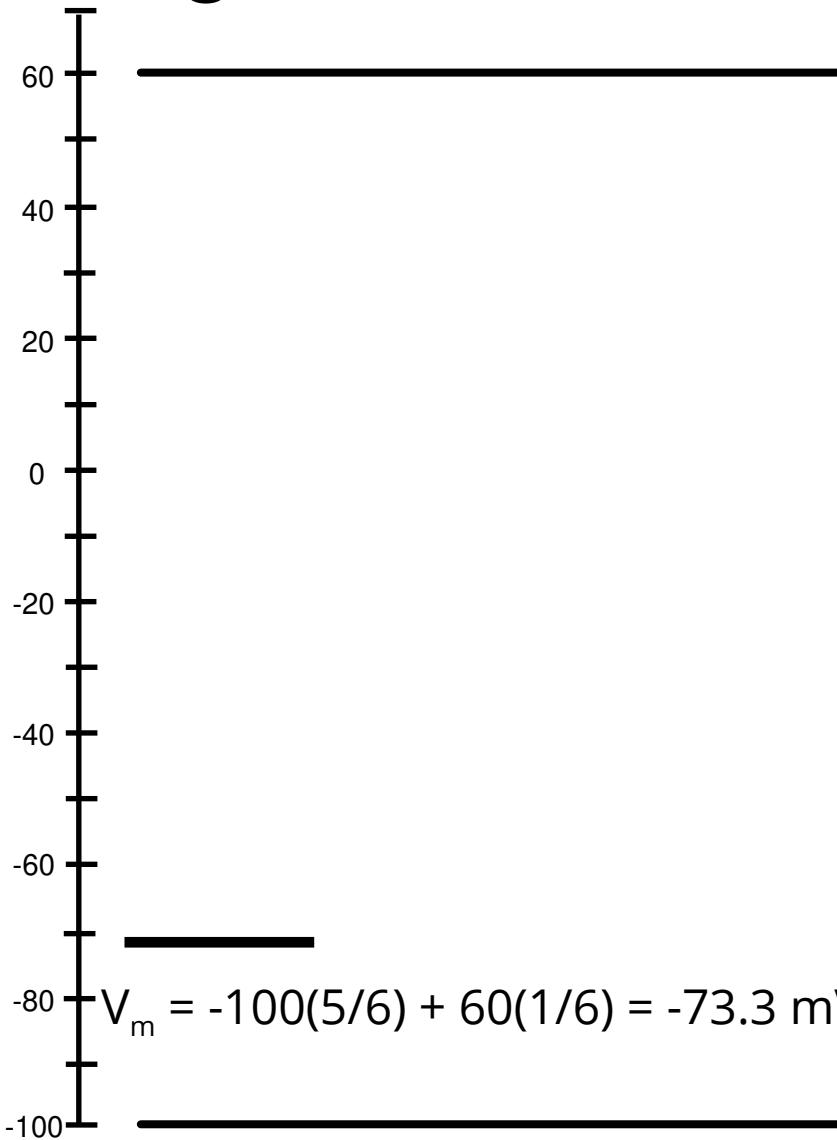
# Membrane Potential



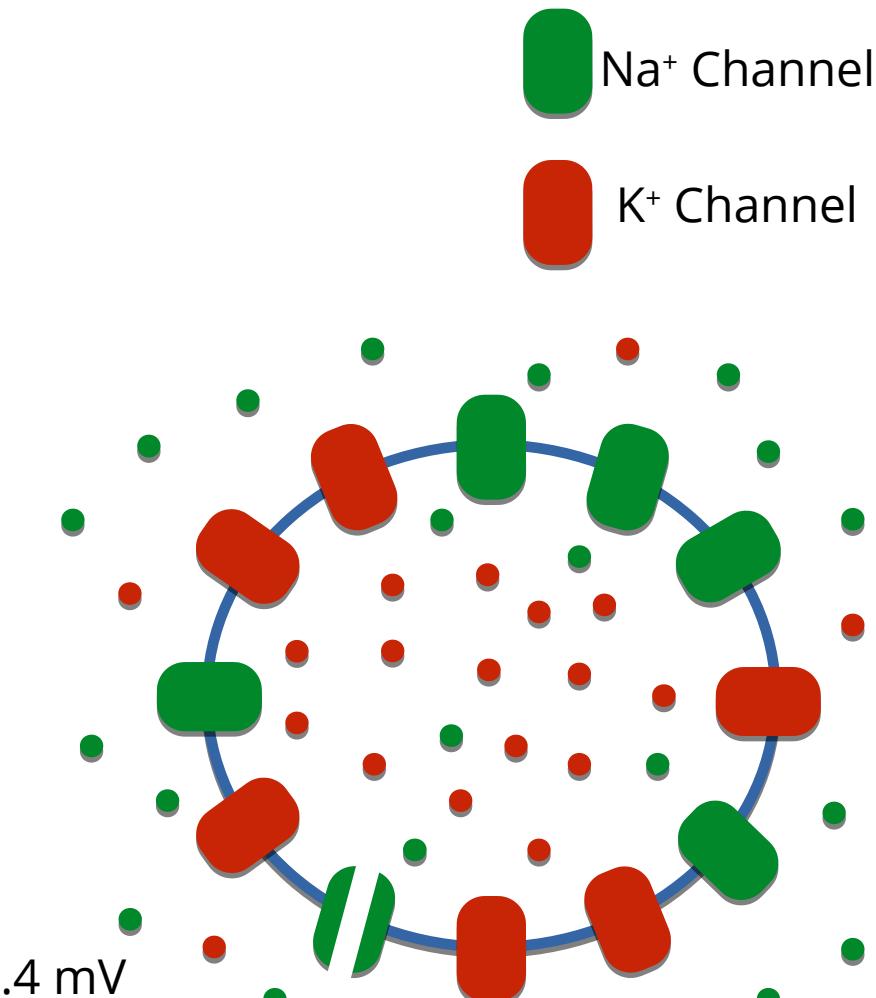
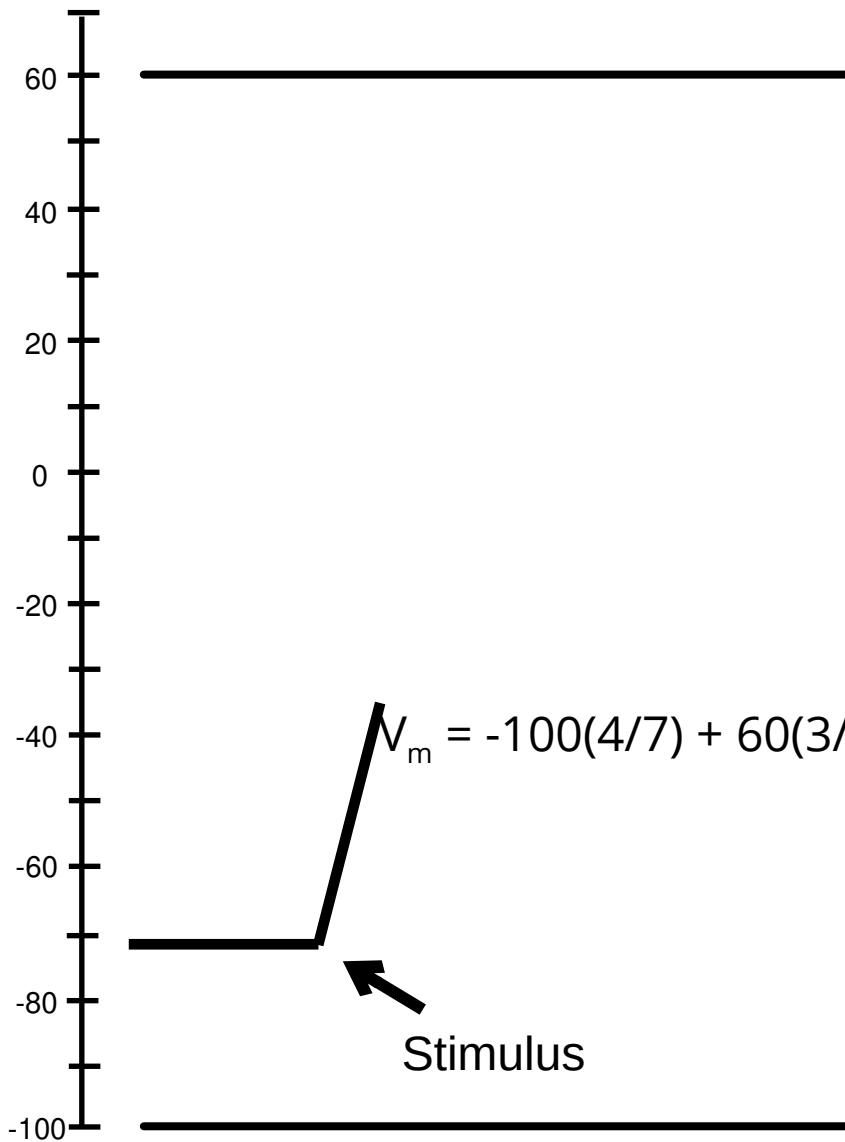
# Membrane Potential



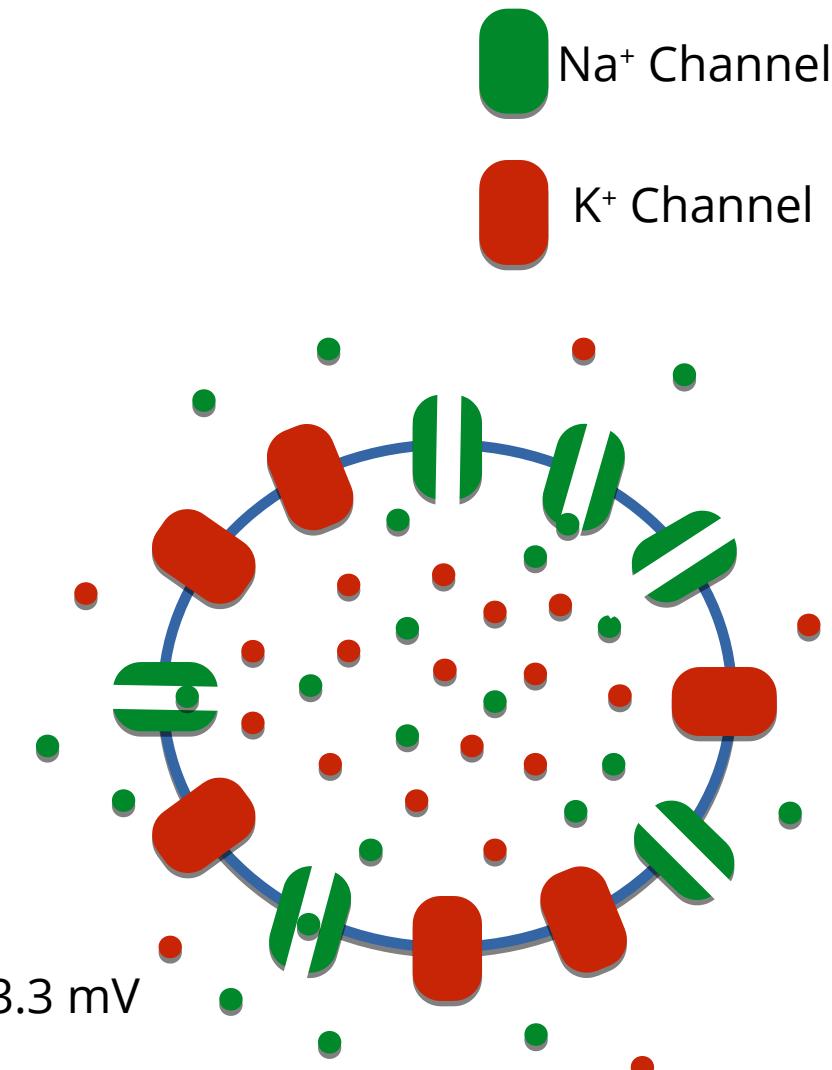
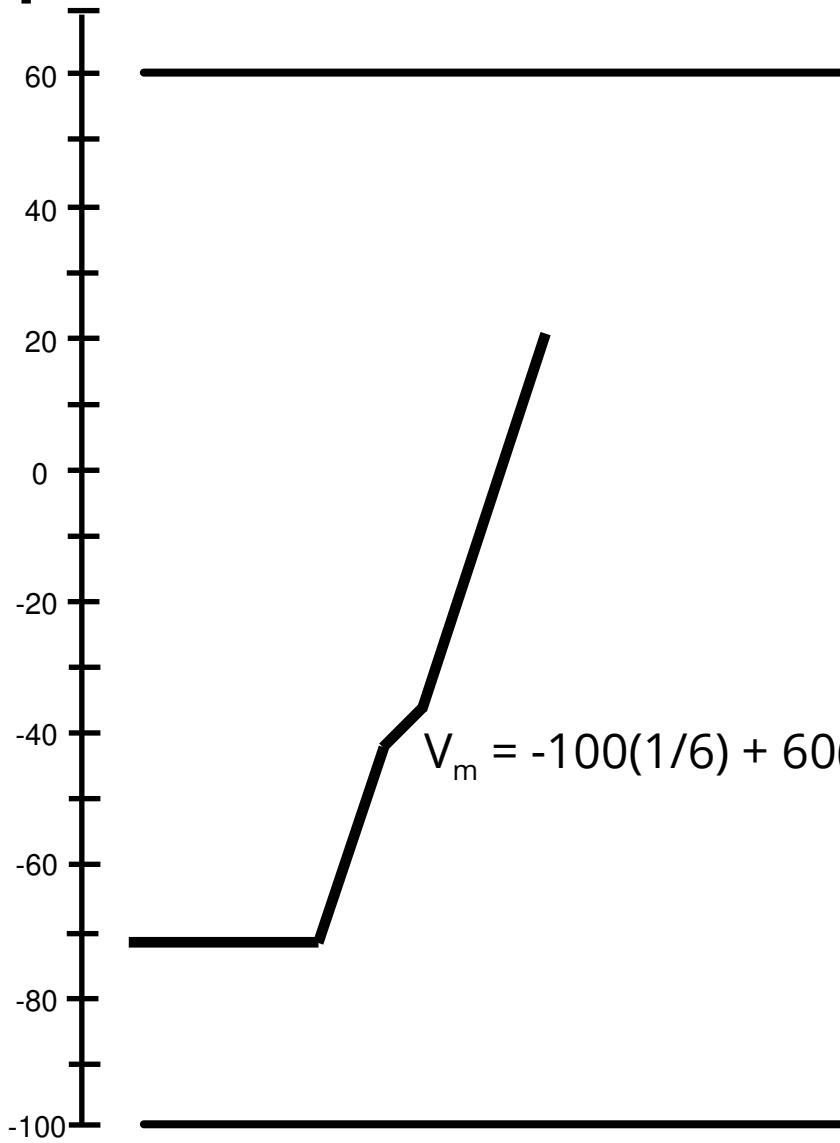
# Resting



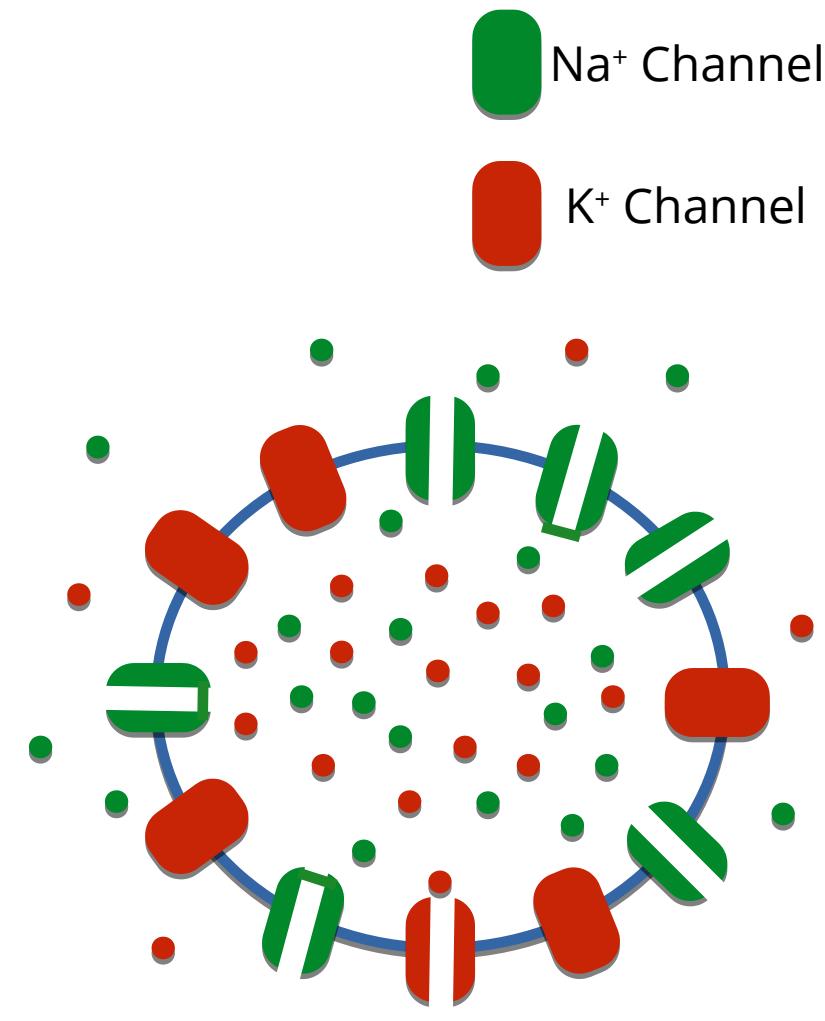
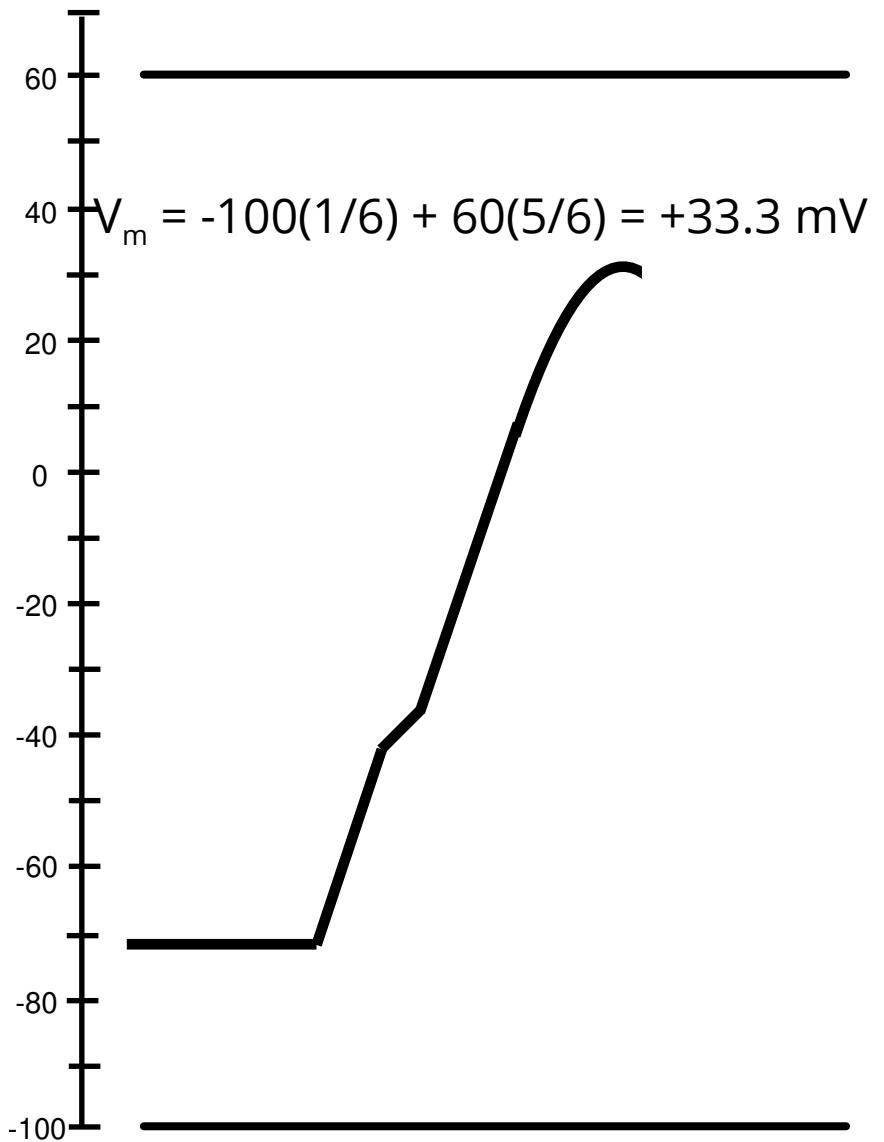
# Threshold



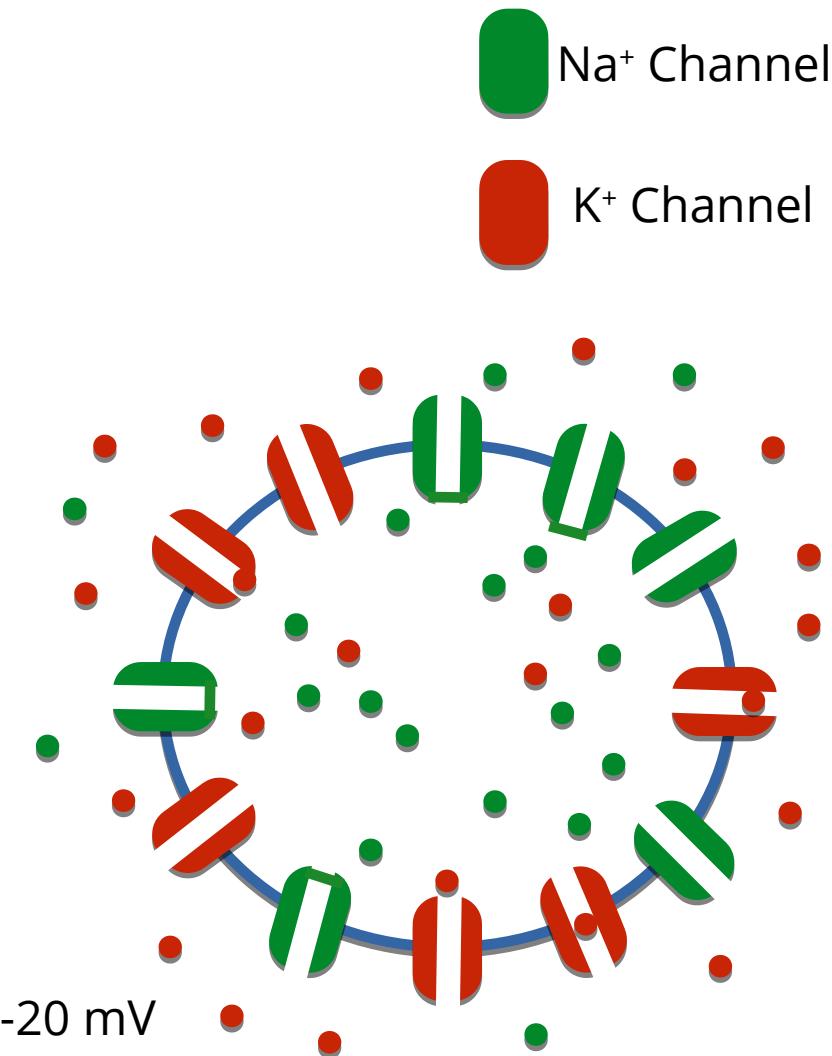
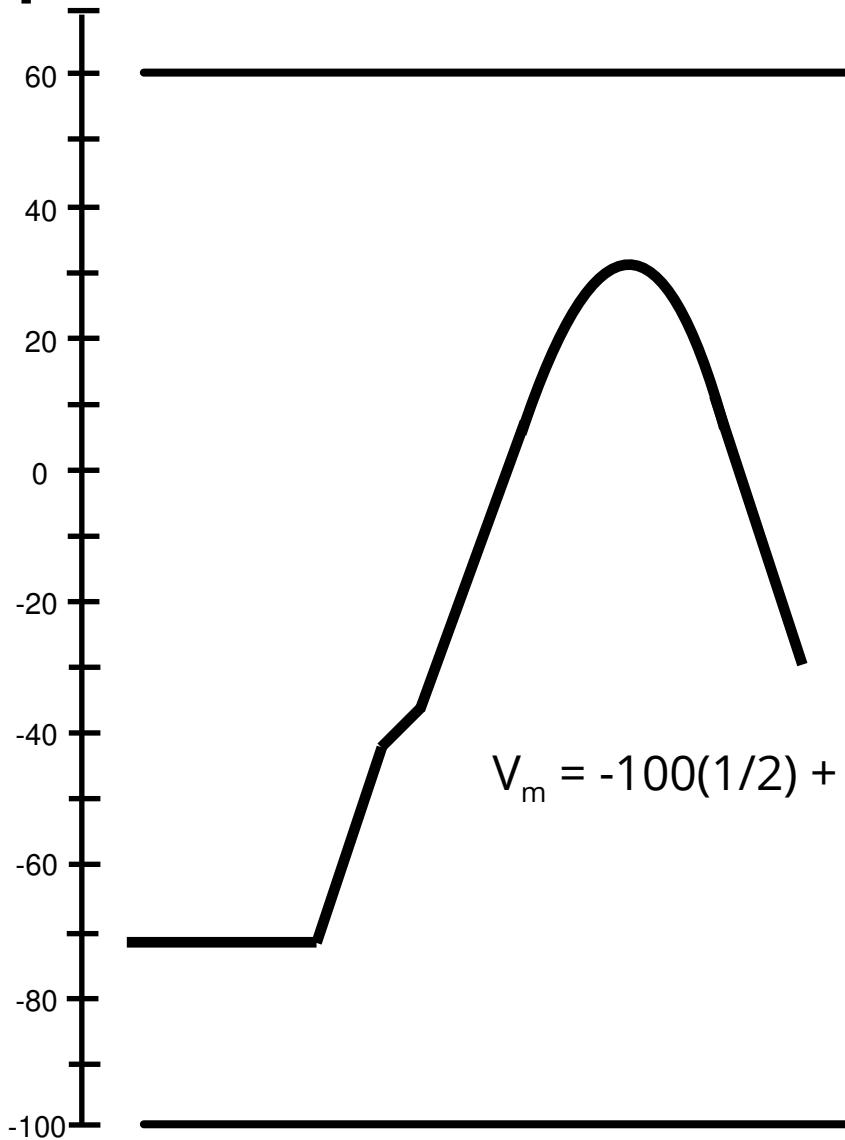
# Depolarization



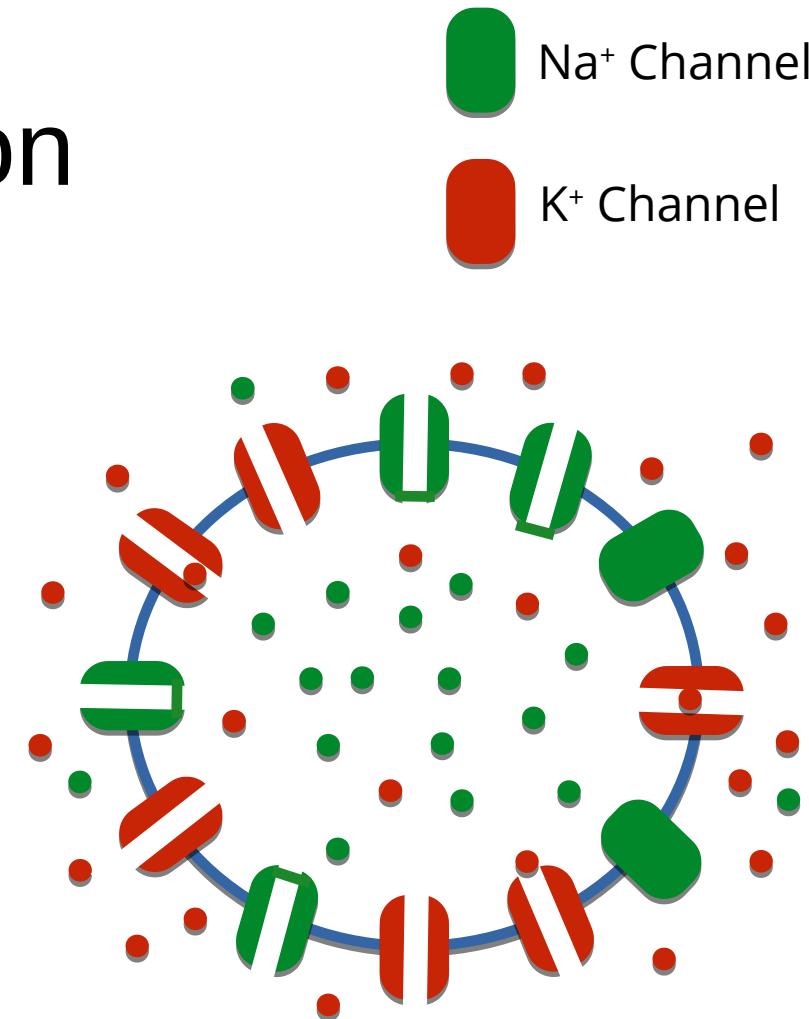
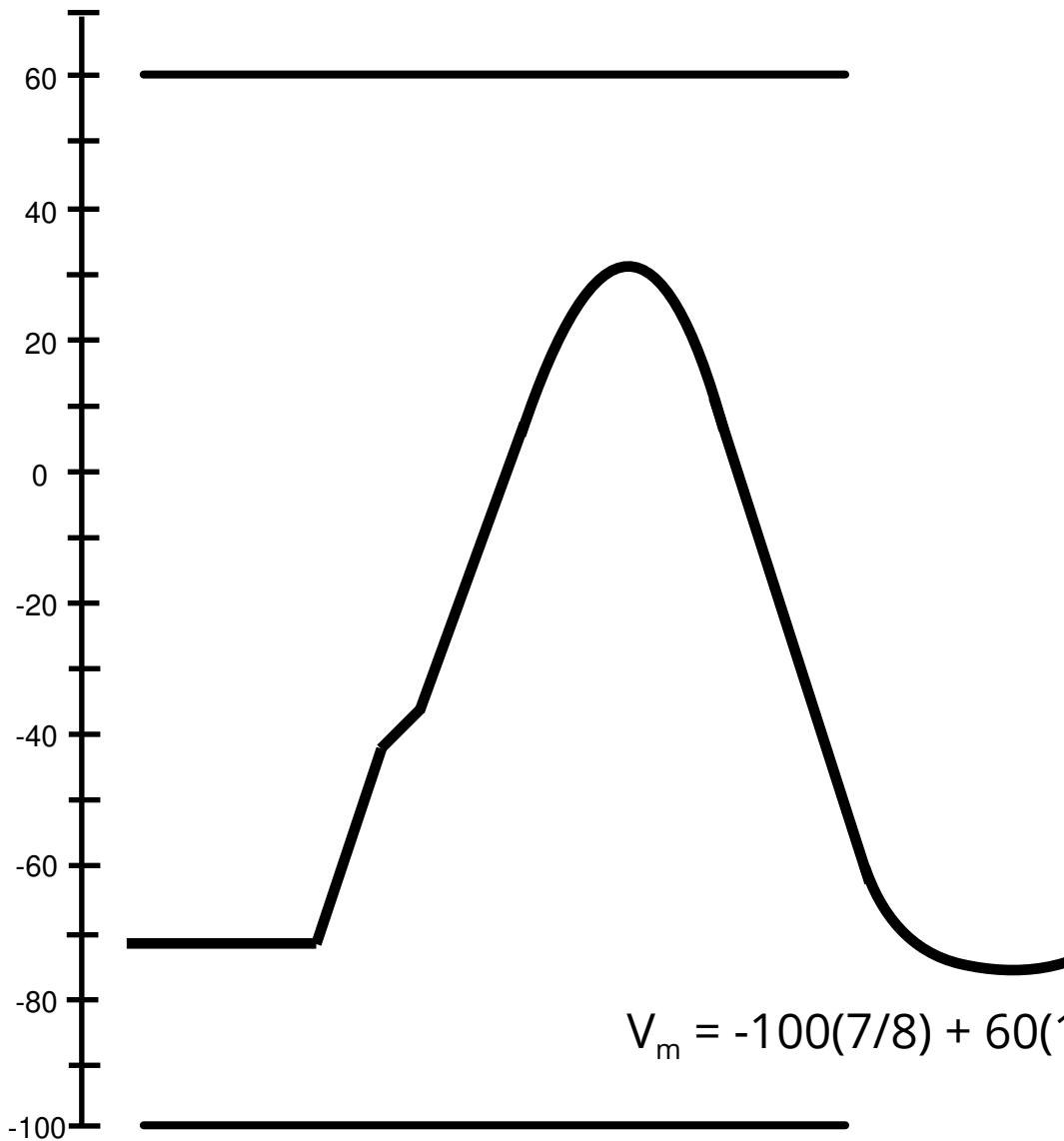
# Peak



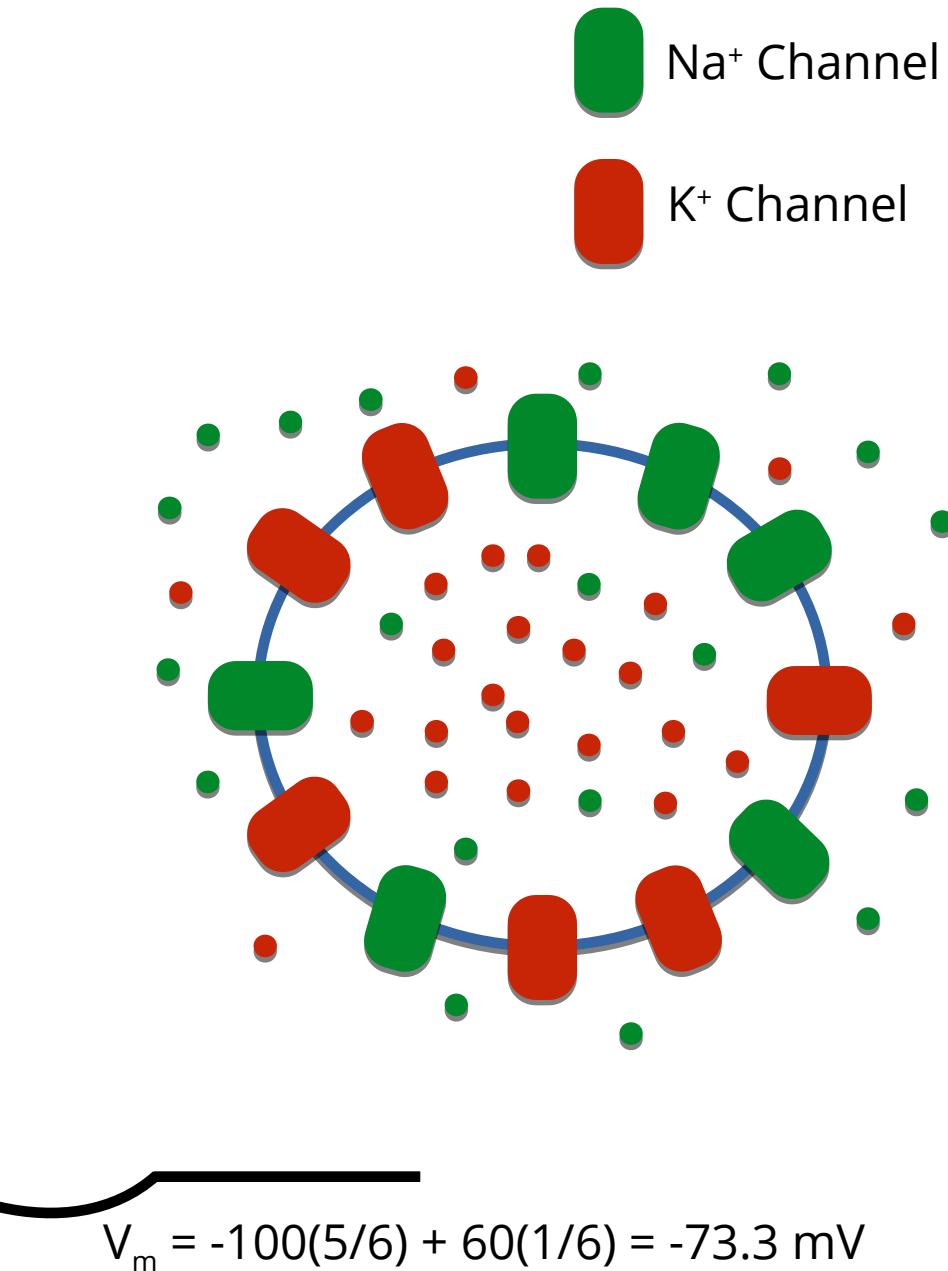
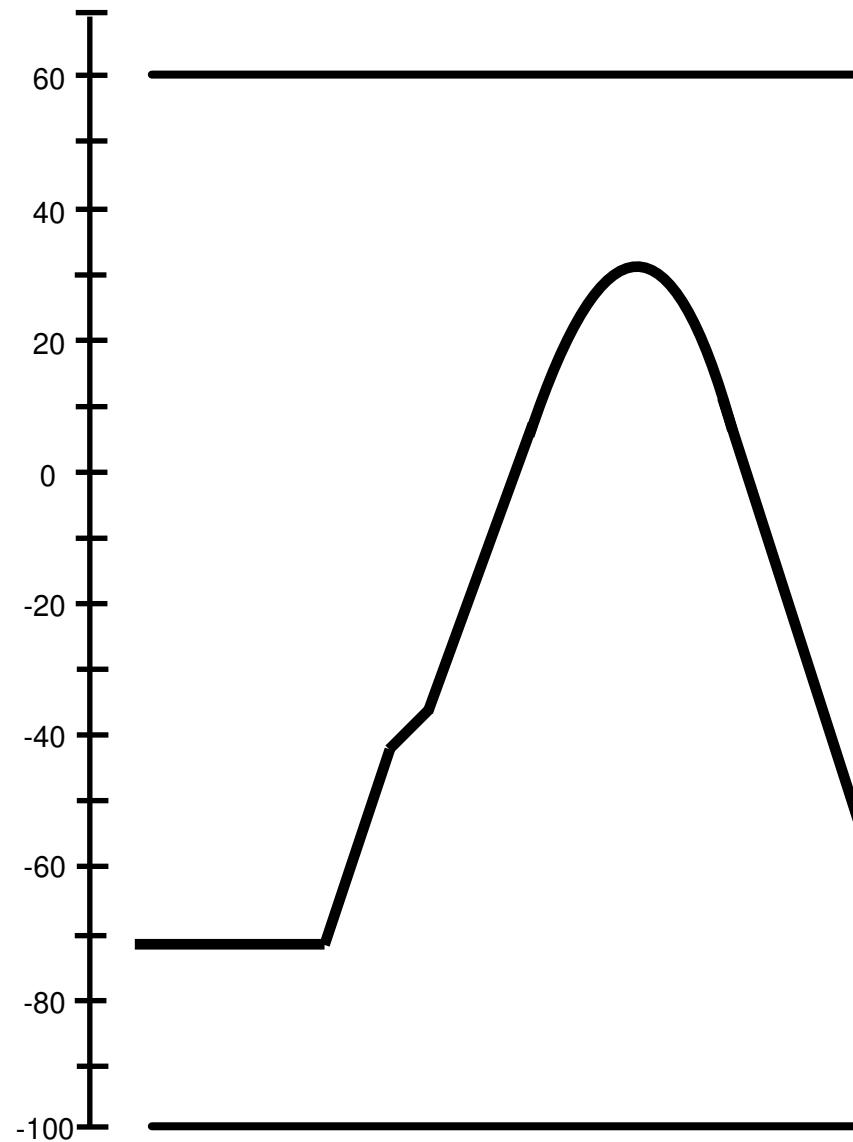
# Repolarization



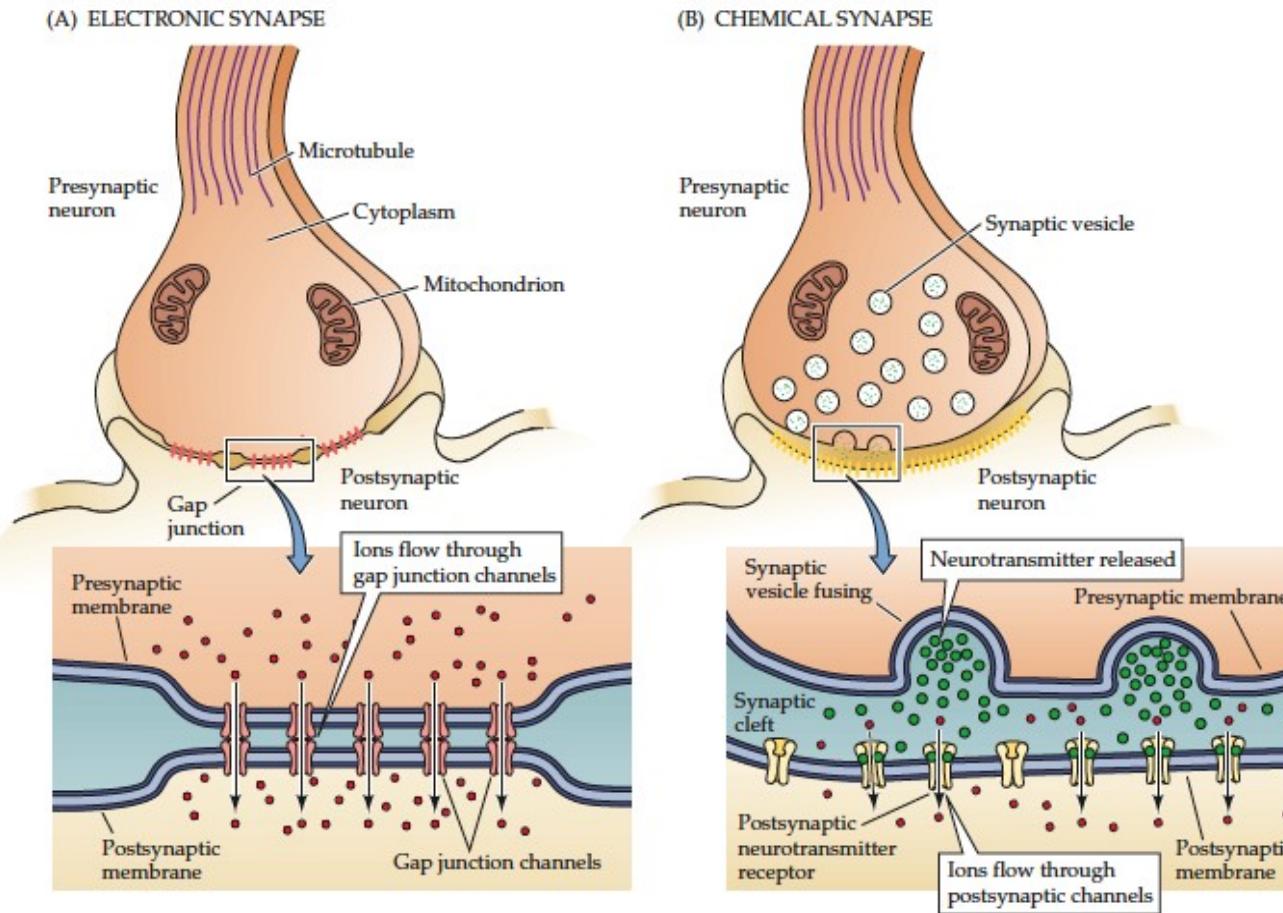
# Afterhyperpolarization



# Return to Rest

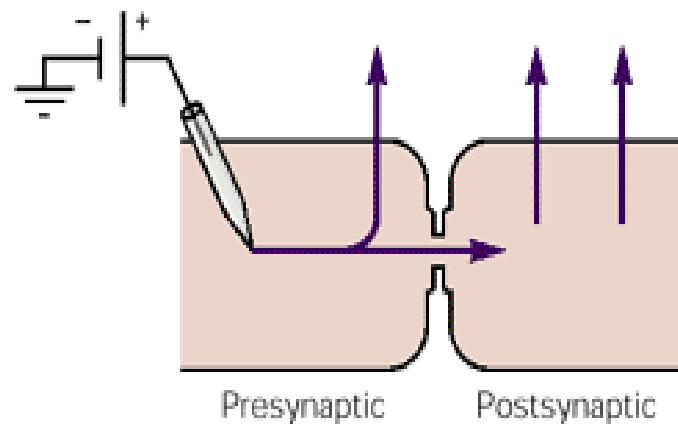


# Properties of Electrical and Chemical Synapses

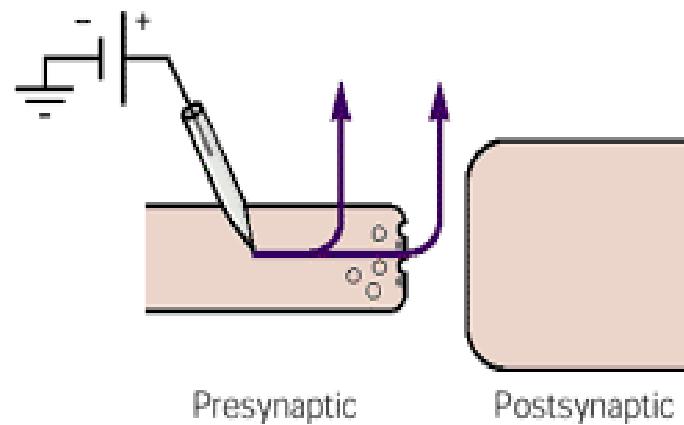


## Current flows differently at electrical and chemical synapses

A Current flow at electrical synapses

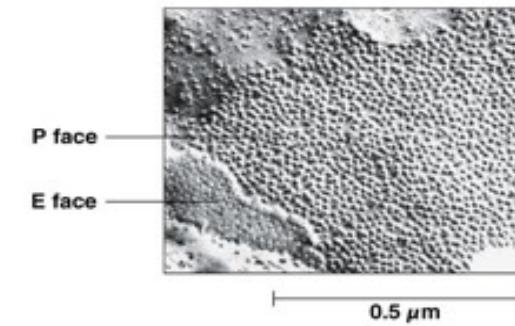
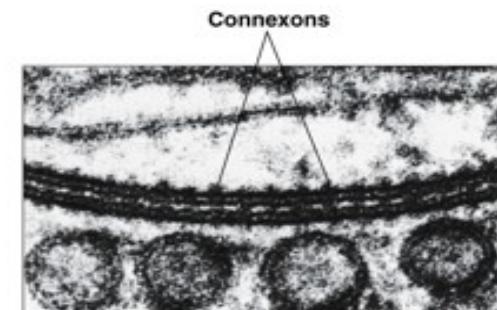
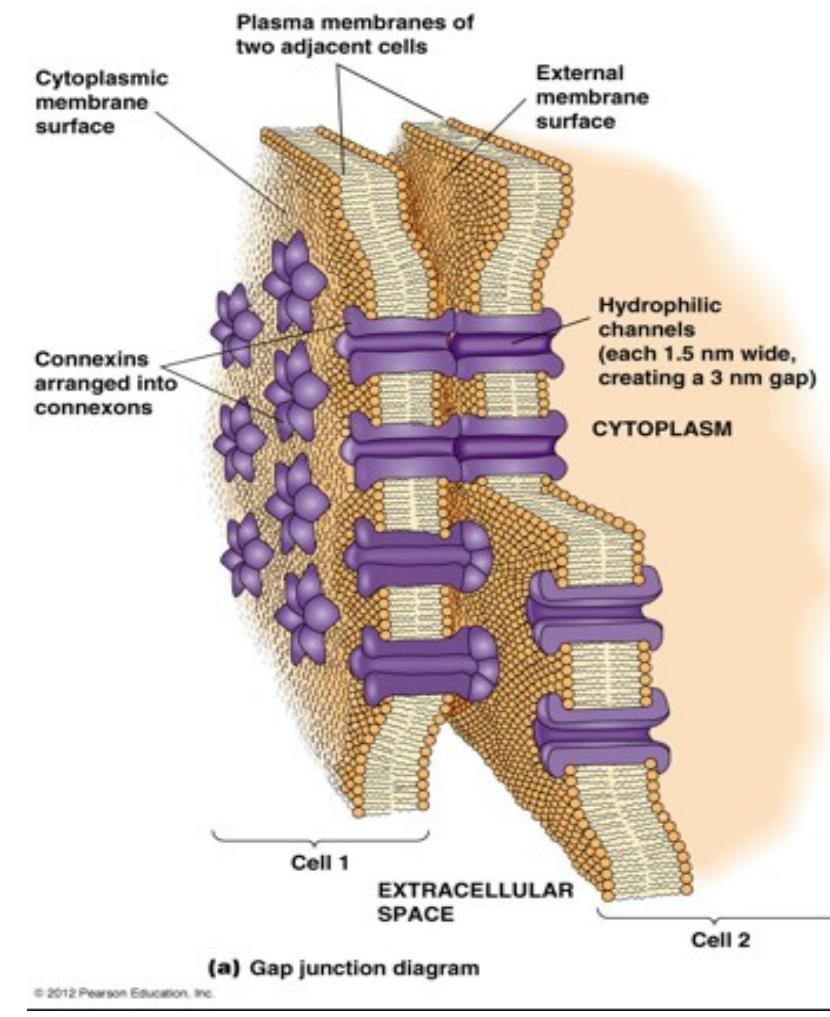


B Current flow at chemical synapses



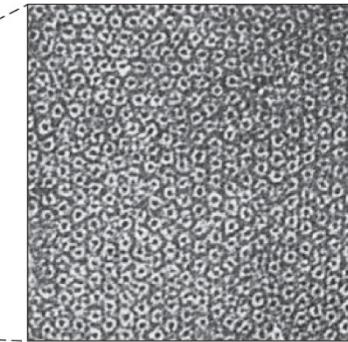
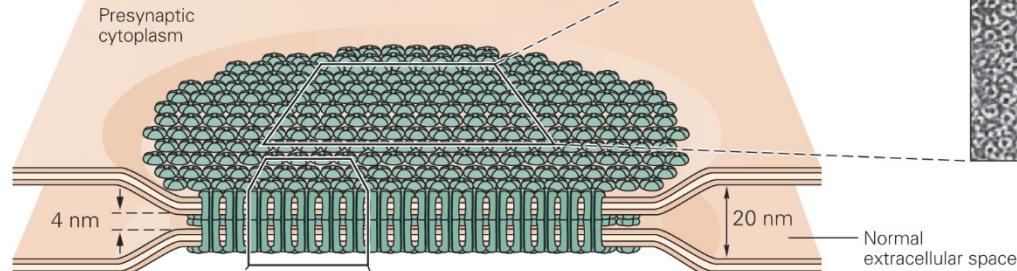
Principles of Neuroscience 5<sup>th</sup> Ed, Kandel et al

## Electrical connections: Gap Junctions

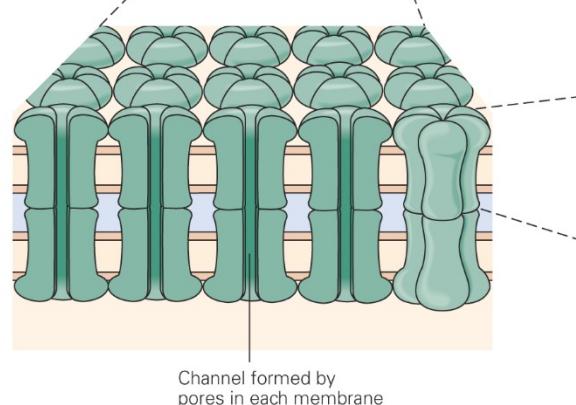


## Electrical connections: Gap Junctions formed by connexins

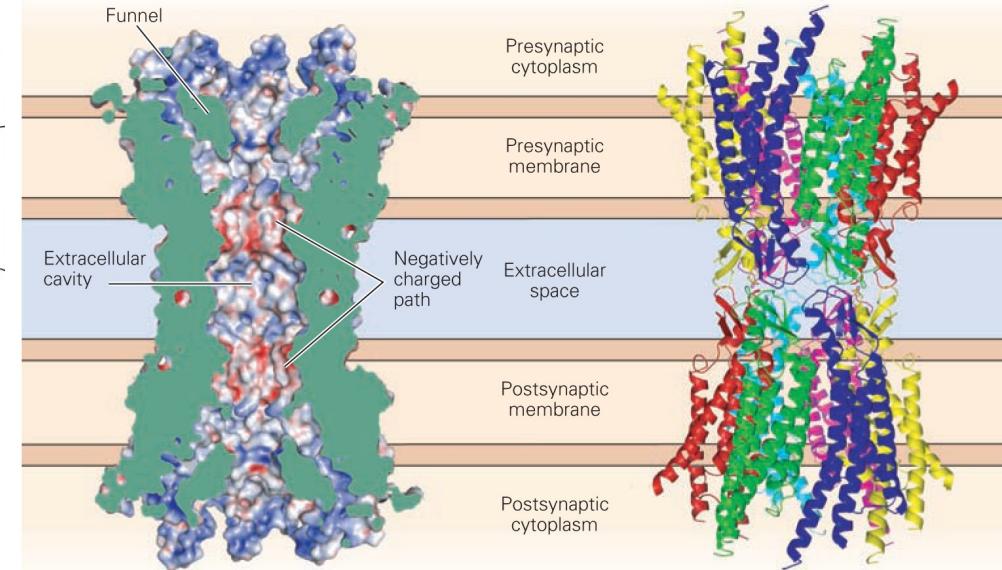
A



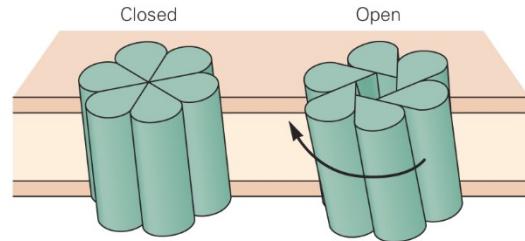
B



B



D

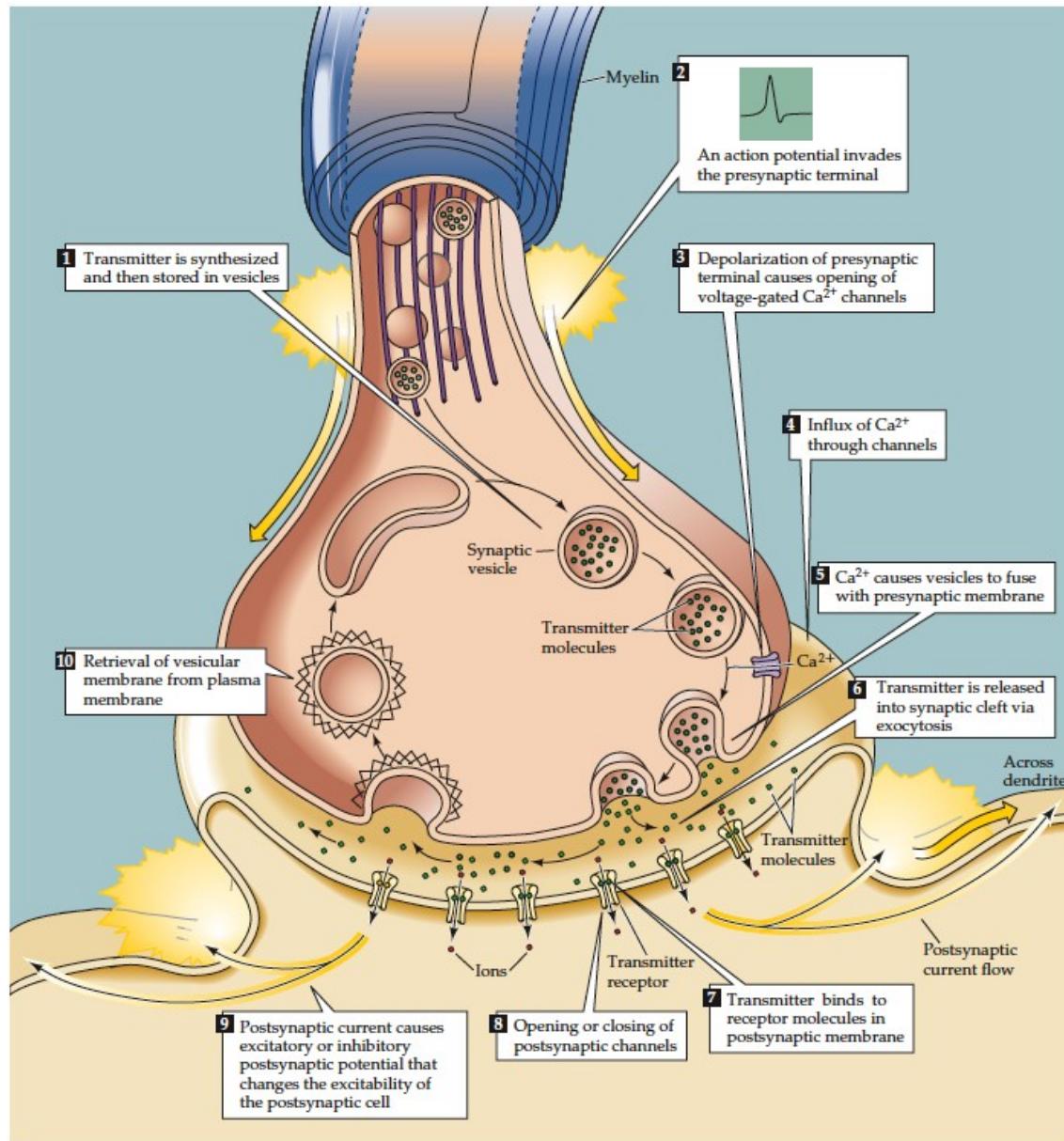


## Electrical connections: Diseases

There is some association between mutations in these genes and human disease such as epilepsy and Charcot–Marie–Tooth disease, a peripheral demyelinating disorder resulting from defects in a specific connexin - Cx32.



## Chemical synapses: Asymmetric morphology



J. E. Heuser and T. S. Reese

## Defining a compound as a neurotransmitter

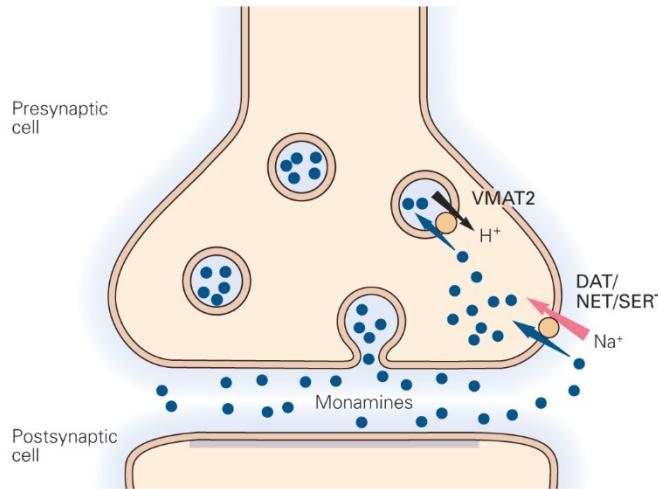
1. Must be synthesized by the presynaptic neuron.
2. Must be present in the presynaptic terminal and release to act on the postsynaptic neuron.
3. When applied exogenously (i.e., drug), it mimics the action of the endogenously released transmitter, activating the same ion channels or 2nd-messenger systems.
4. A specific mechanism exists for removing it from its site of action (usually the synaptic cleft)



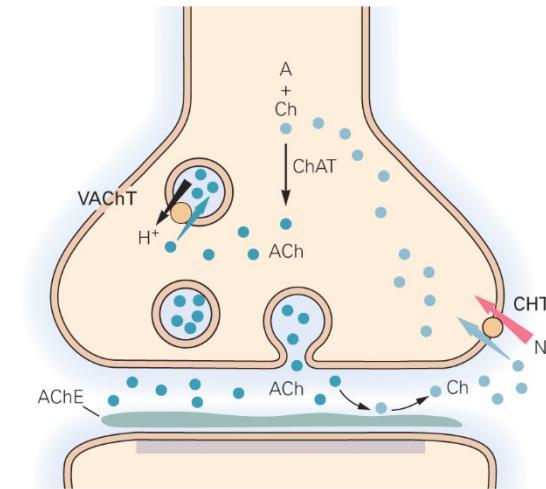
J. E. Heuser and T. S. Reese

# Neurotransmitter: Must be synthesized by the presynaptic neuron

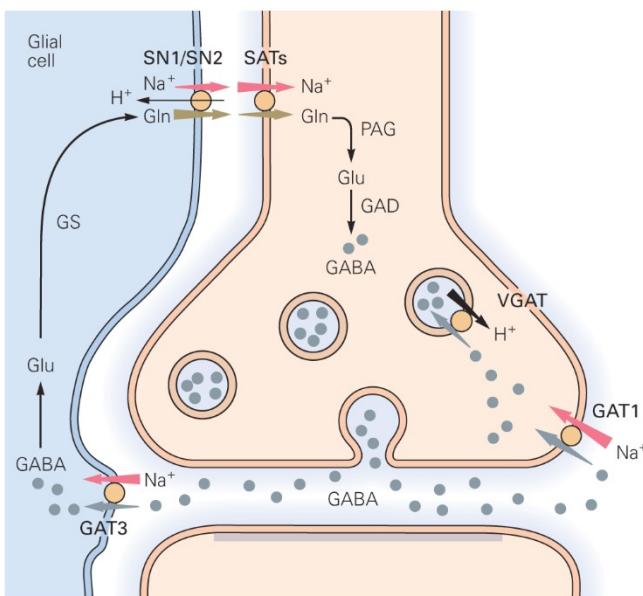
A Monoamines



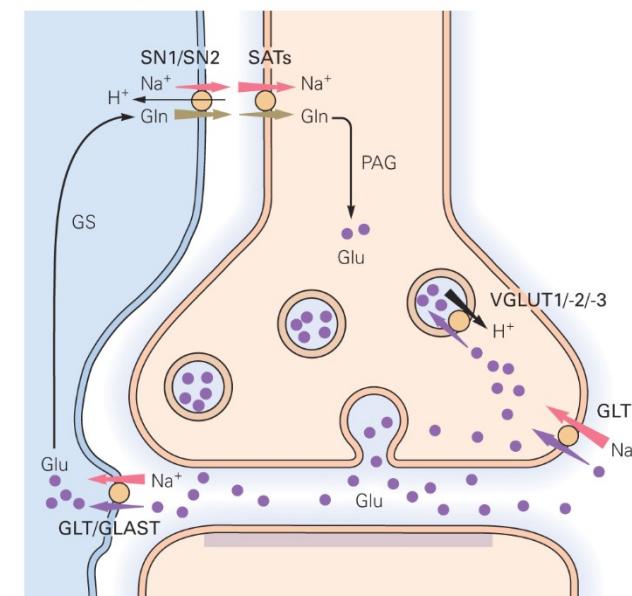
B Acetylcholine



C GABA



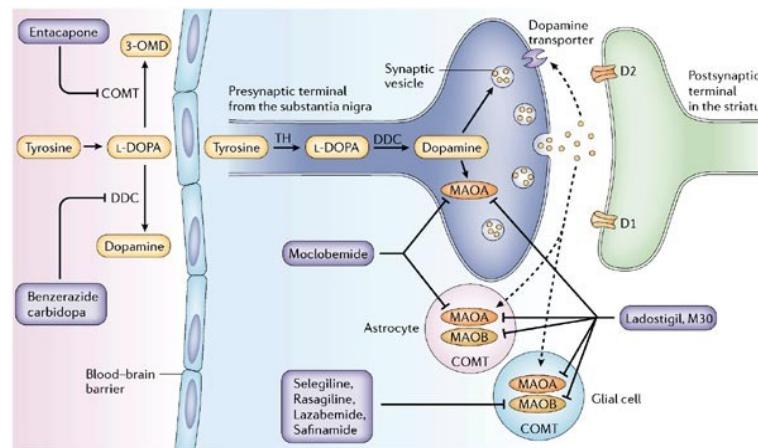
D Mediate glutamate



Neurotransmitter: Must be synthesized by the presynaptic neuron

Diseases of NT synthesis –  
Extremely rare disorders

Tyrosine Hydroxylase (TH) deficiency (also known as Recessive Dopa-Responsive Dystonia) is a rare metabolic disorder characterized by the lack of the enzyme involved in converting the amino acid tyrosine to LDopa. The neurotransmitters dopamine, norepinephrine, epinephrine (collectively known as catecholamines) and serotonin are deficient in the central nervous system and periphery.



## Release of NT from presynaptic terminal: Neurotransmission requires multiple steps

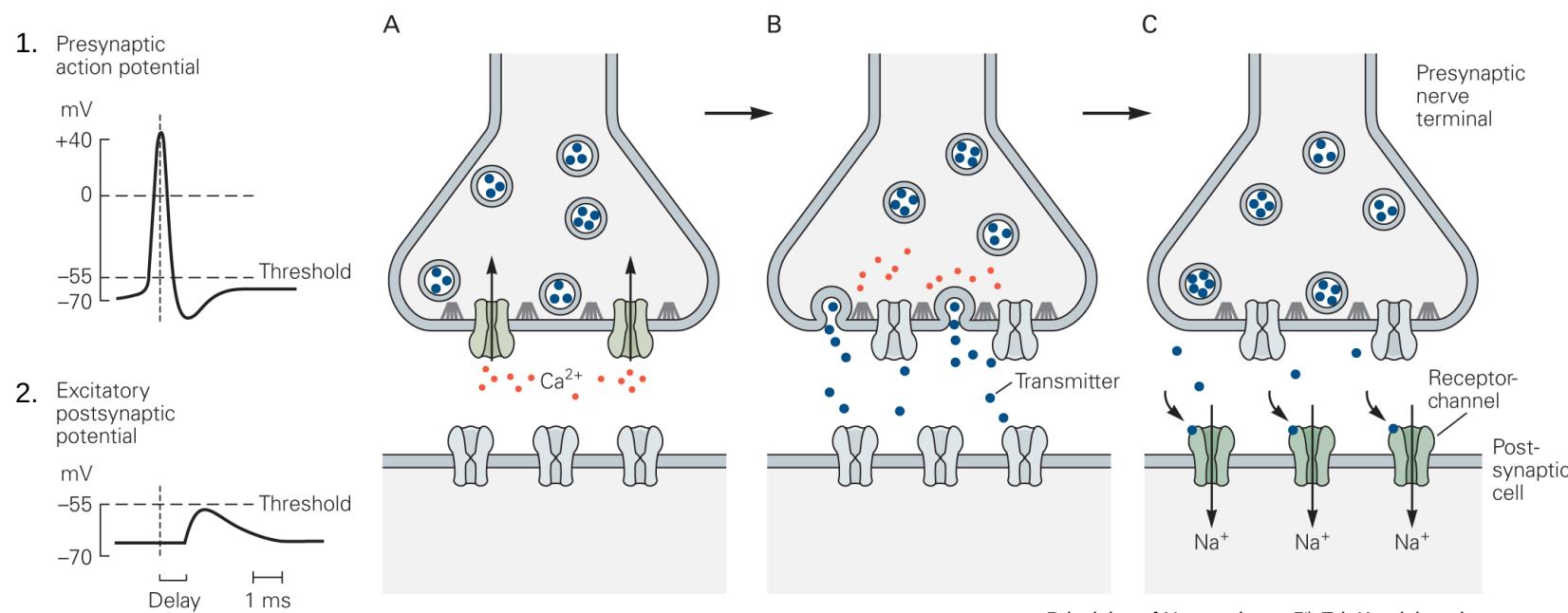
### 1. Action potential invasion

A. Calcium influx

B. Vesicle fusion and transmitter release

C. Postsynaptic receptor activation

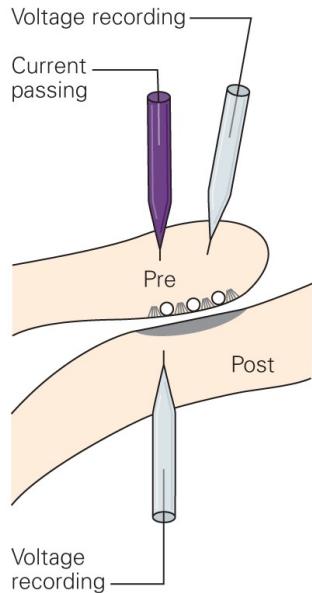
### 2. Postsynaptic potential change



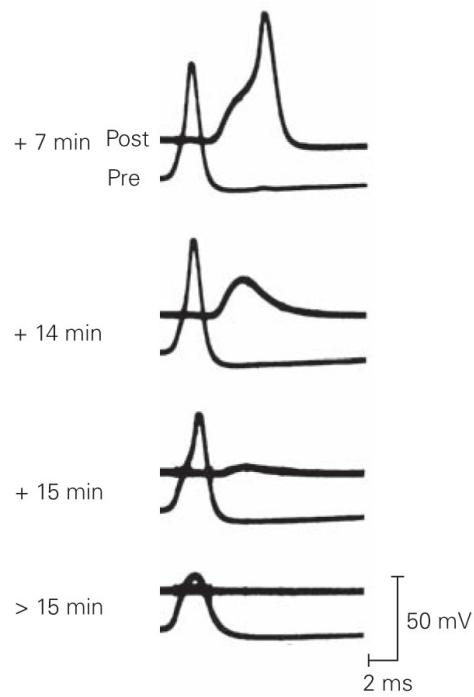
Principles of Neuroscience 5<sup>th</sup> Ed, Kandel et al

## Release of NT from presynaptic terminal: Presynaptic depolarization is required

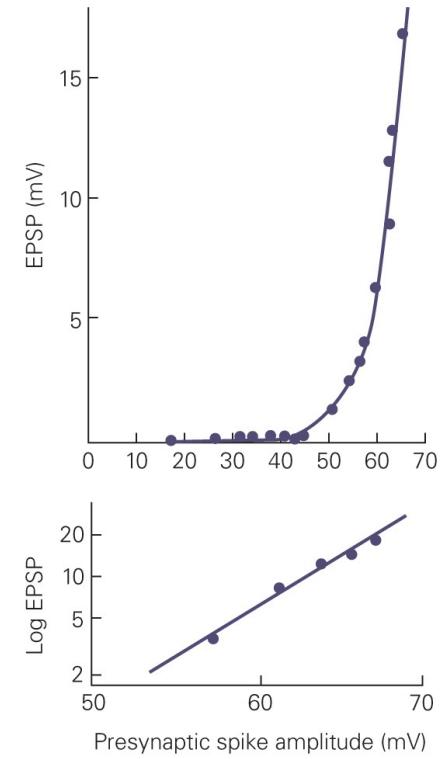
A Experimental setup



B Potentials when  $\text{Na}^+$  channels are progressively blocked by TTX

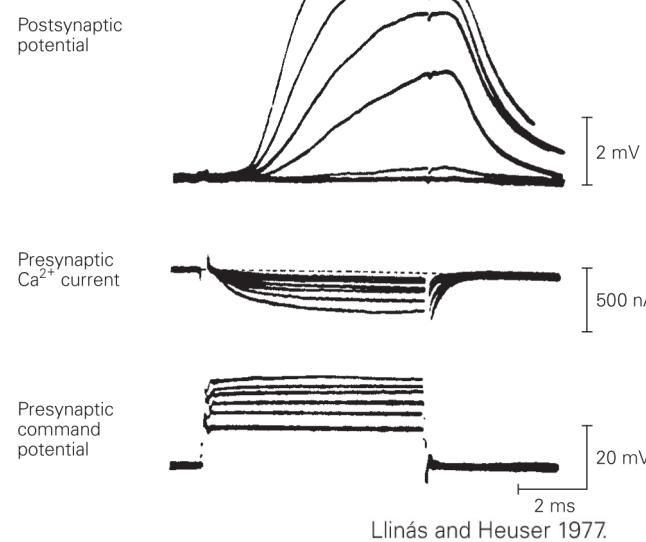


C Input-output curve of postsynaptic response



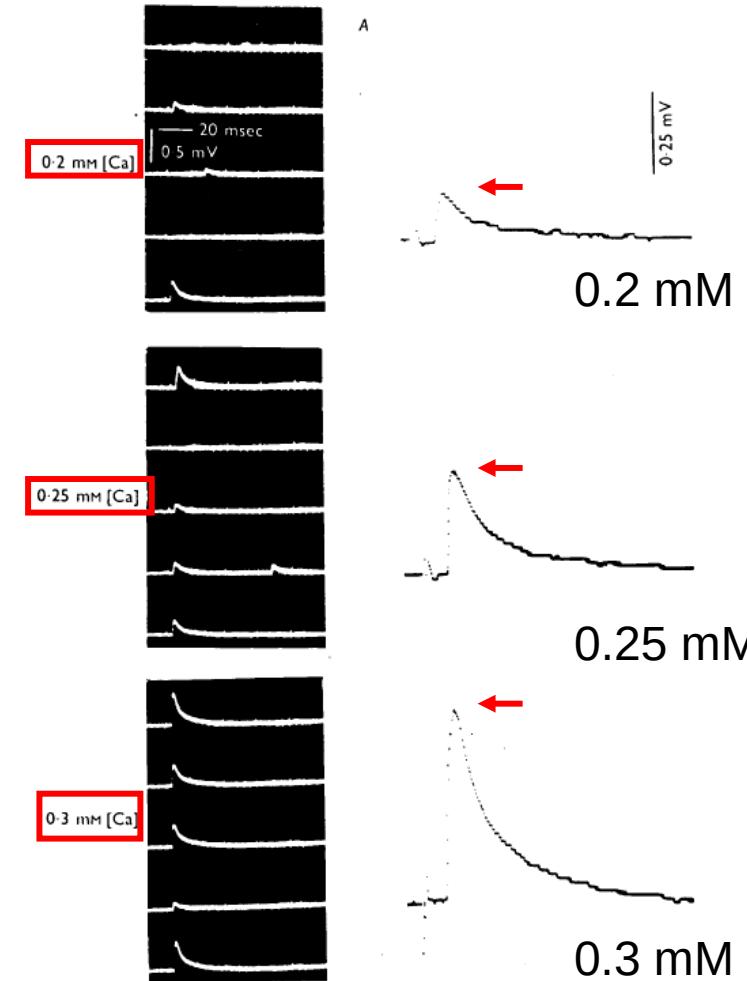
## Release of NT from presynaptic terminal: Calcium influx

**Ca<sup>2+</sup> entry into the axon terminal rapidly triggers exocytosis by binding to a “calcium sensor” for release**



Release depends on [Ca]<sub>Ext</sub>

more calcium = more release



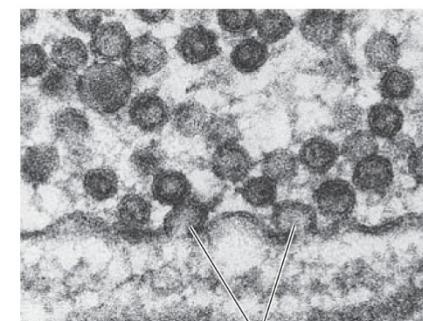
Dodge & Rahamimoff, 1966

# Synaptic transmission relies on the precise control of synaptic vesicle trafficking

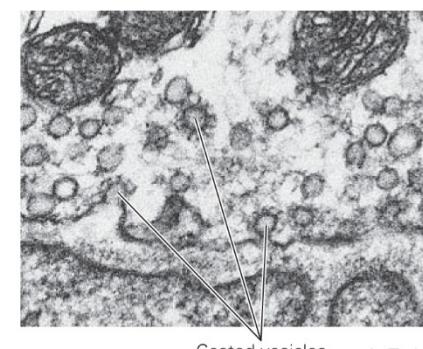
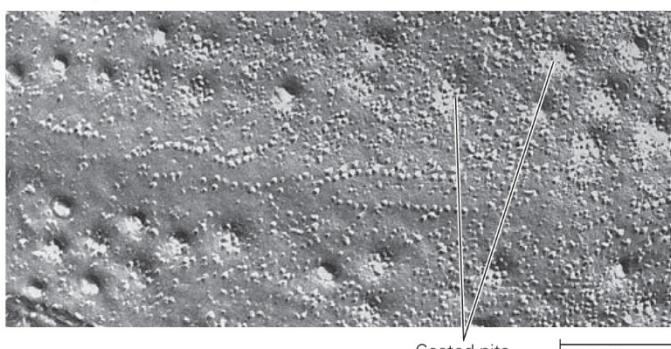
A Cell membrane at synapse



B Exocytosis



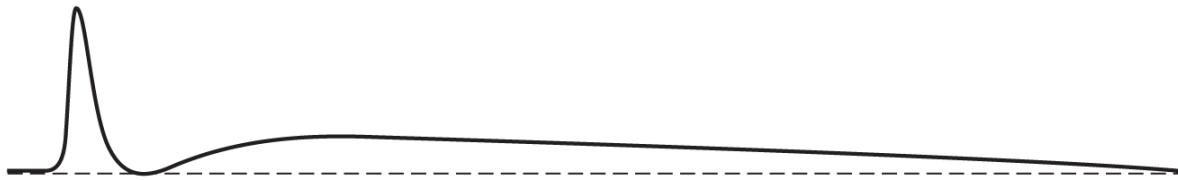
C Endocytosis



J. E. Heuser and T. S. Reese

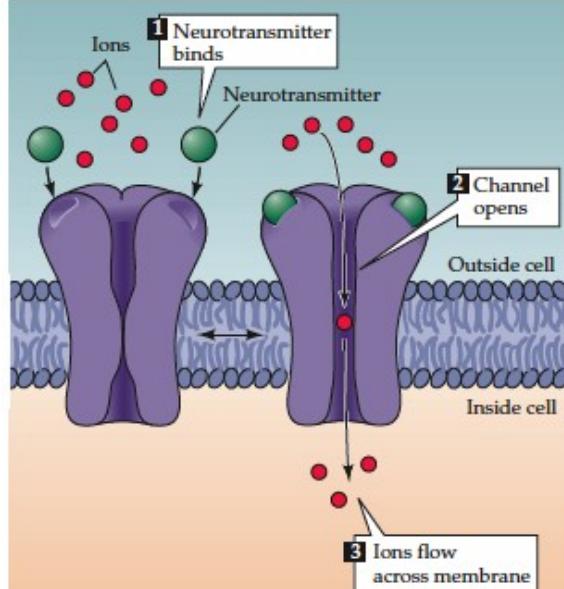
## Postsynaptic receptor activation

Fast EPSP

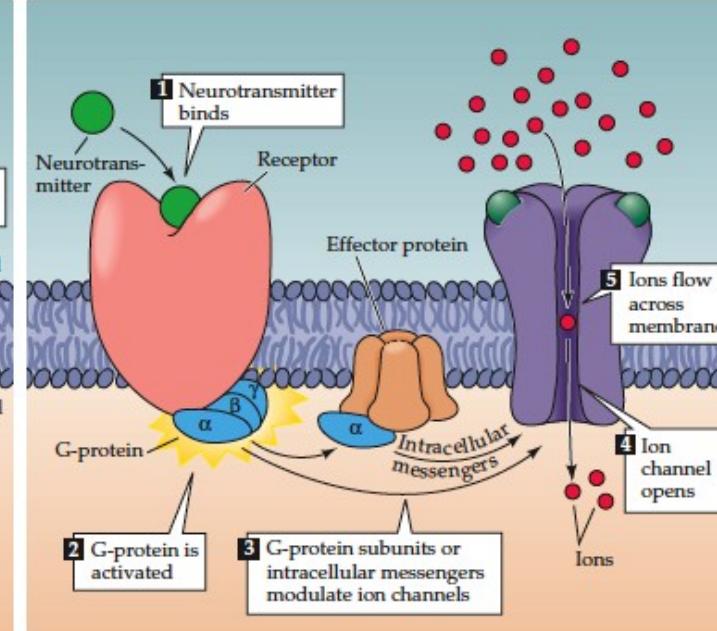


Slow EPSP

(A) Ligand-gated ion channels

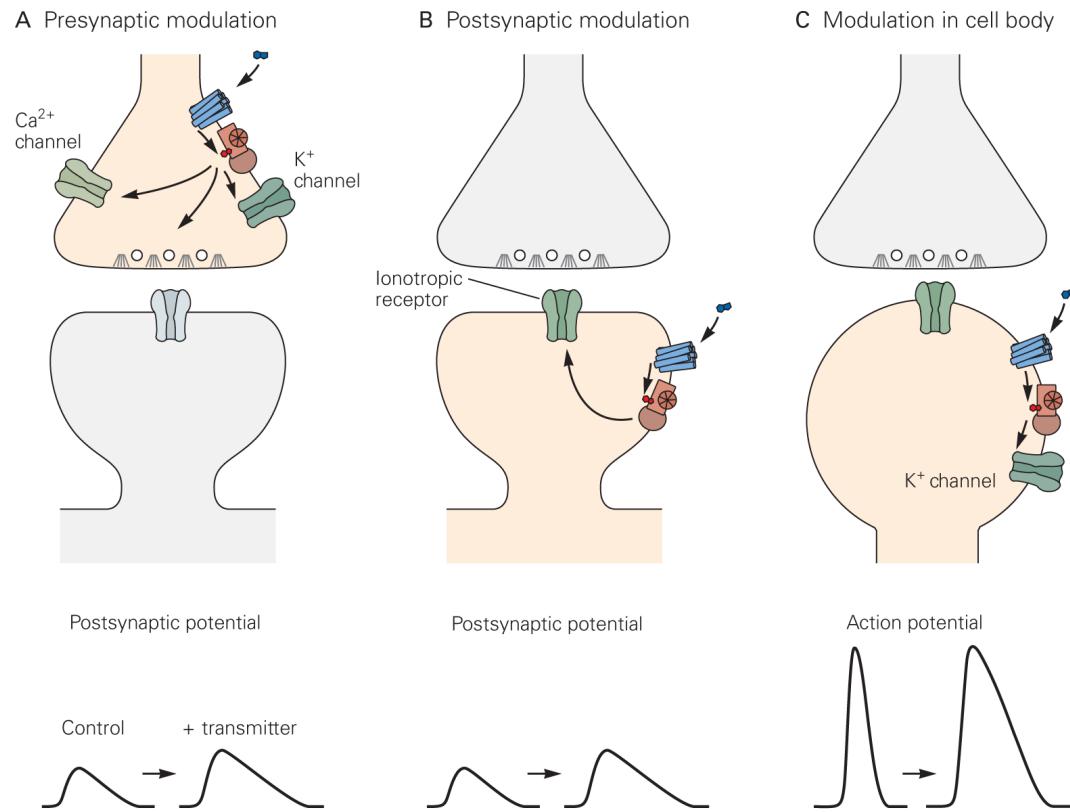


(B) G-protein-coupled receptors

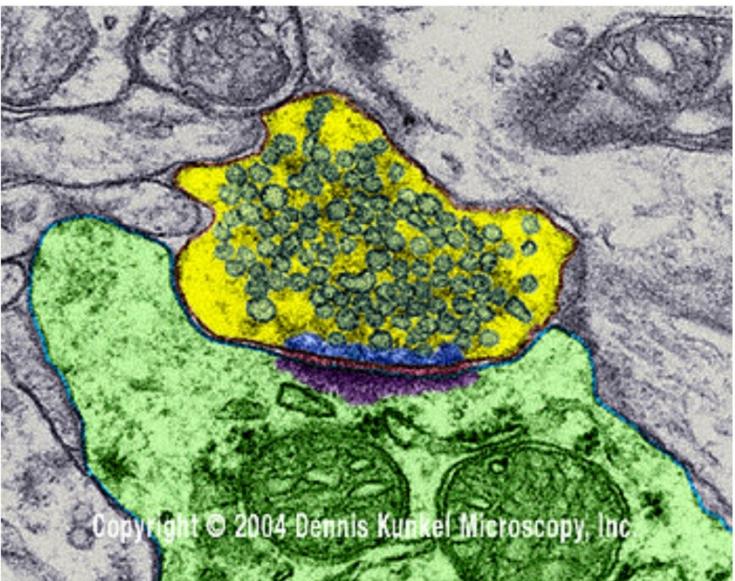


Neuroscience 4th Ed, Purves et al

## Functions of second messenger modulation



Principles of Neuroscience 5<sup>th</sup> Ed, Kandel et al



In the brain synapses are tightly packed with other cells and surrounding glia. The processes of astrocytes are intimately associated with both presynaptic and postsynaptic elements and play important roles in modulating plasticity of synapses and removing and recycling neurotransmitter that is released from the presynaptic terminal.

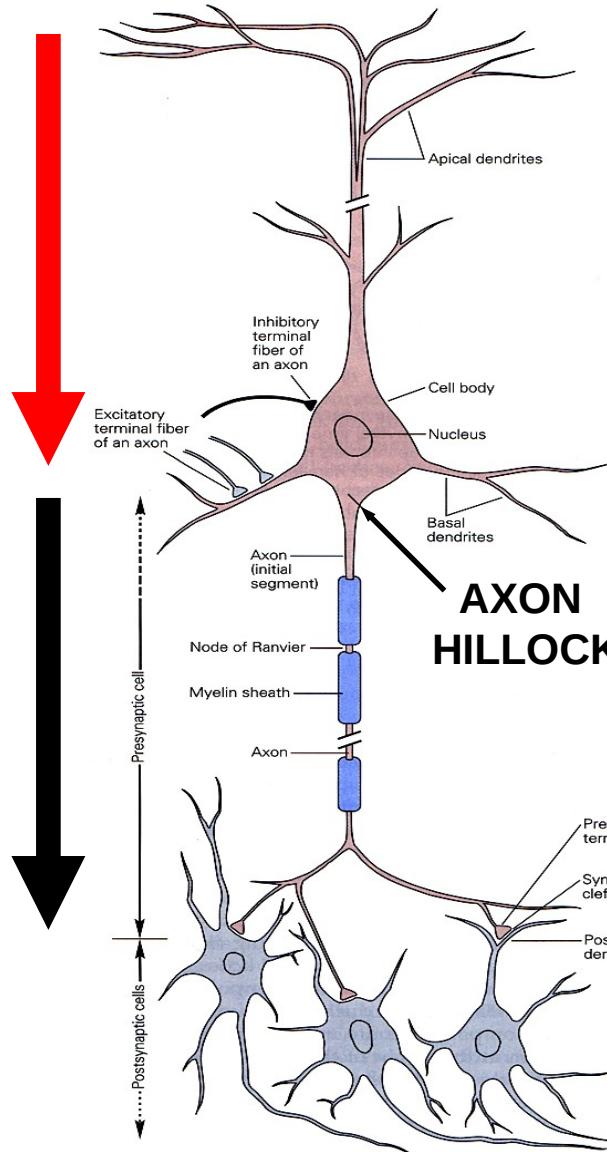
# Synapses mediate flow of Electrical Signals in the CNS

Passive signaling is governed by the electrical and geometrical properties of the cell.

Resting ion channels influence passive signaling

Active signaling is mainly governed by the biophysical properties of voltage-gated ion channels

Kandel et al. Principles of Neural Science, 1995



Electrotonic potentials depend on passive signaling

EPSPs (excitatory postsynaptic potentials) and IPSPs (inhibitory postsynaptic potentials) spread passively along the dendrites

The action potential underlies active electrical propagation along the axon

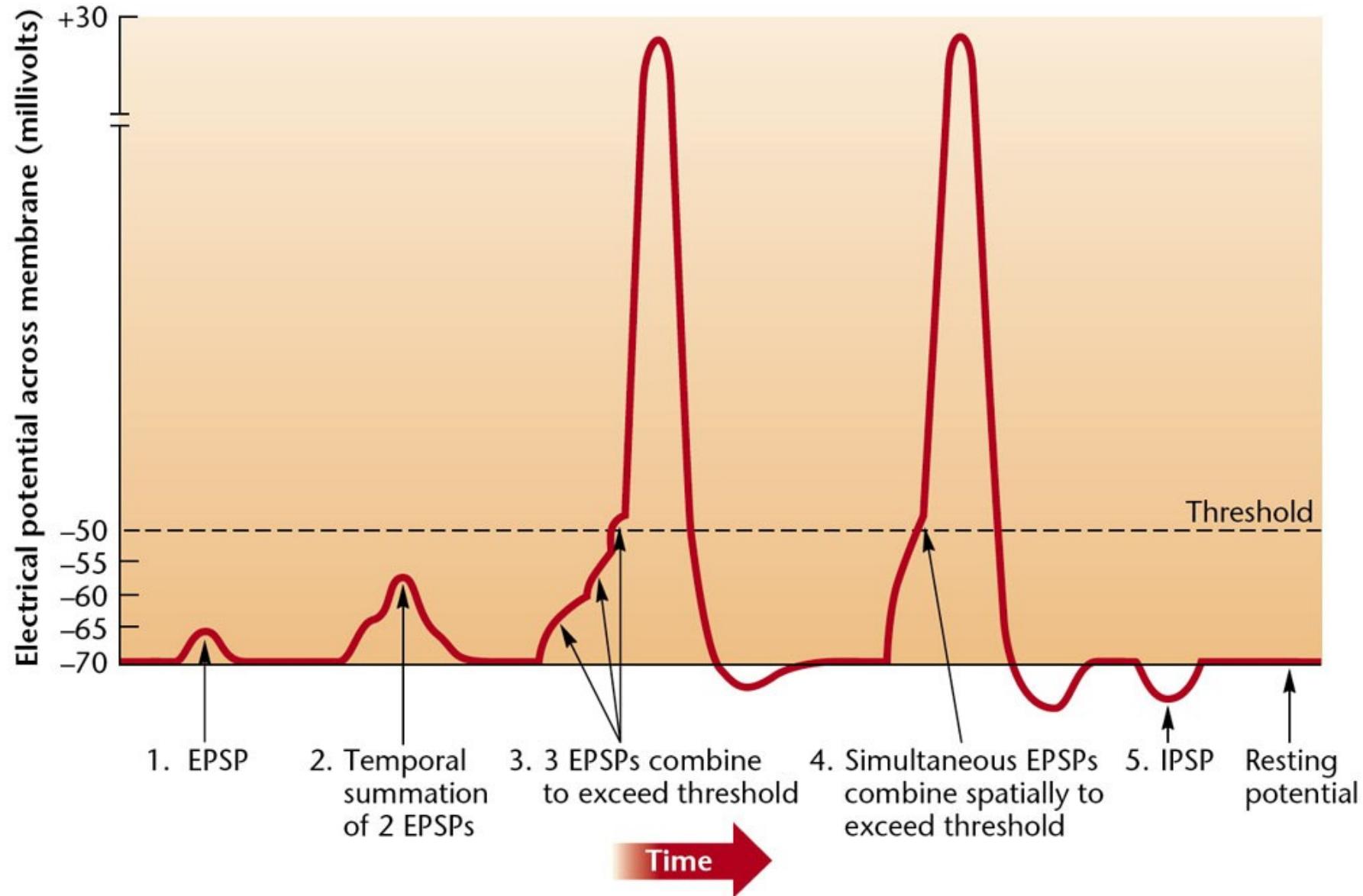
**CHEMICAL SYNAPTIC TRANSMISSION**

# Properties of some major neurotransmitters

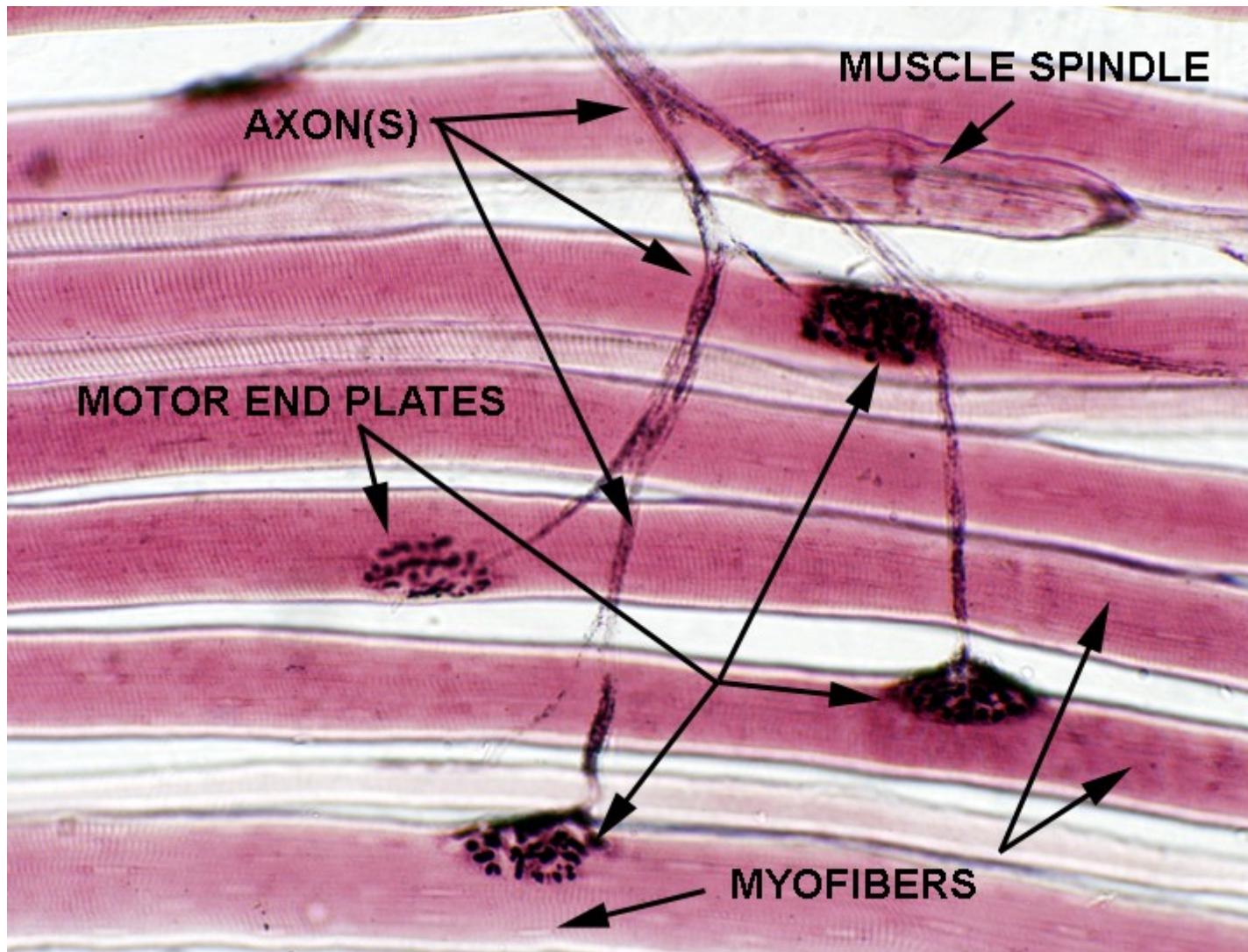
Neurotransmitters	Postsynaptic cleft	Precursors	A. Small molecules
Ach (Acetylcholine)	Excitatory	Choline + Acetyl CoA	Class I Acetylcholine
Glutamate	Excitatory	Glutamine	Class II: The Amines Norepinephrine Epinephrine
GABA	Inhibitory	Glutamate	Dopamine Serotonin Histamine
Glycine	Inhibitory	Serine	Class III: Amino Acids Gamma-aminobutyric acid (GABA) Glycine Glutamate Aspartate
Catecholamines • Epinephrine • Norepinephrine • Dopamine	Excitatory Excitatory Both Excitatory and Inhibitory	Tyrosine	Class IV Nitric oxide (NO)
Serotonin (5-HT)	Inhibitory(mostly) Excitatory	Tryptophan	B. Large molecules
Histamine	Excitatory	Histidine	• Neuropeptides (Substance P, Endorphins, Insulin, Glucagon etc)
ATP	Excitatory	ADP	
Neuropeptides	Excitatory and Inhibitory	Amino acids	

How do they change the RMP????

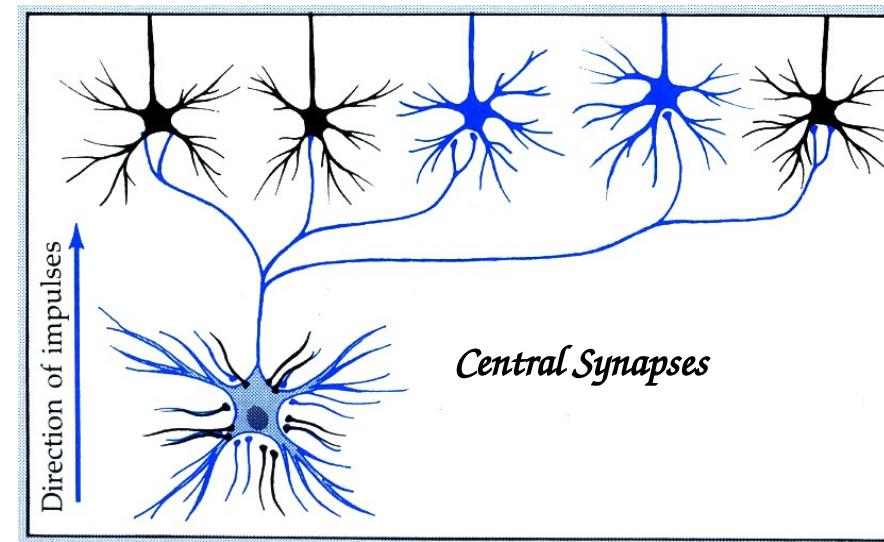
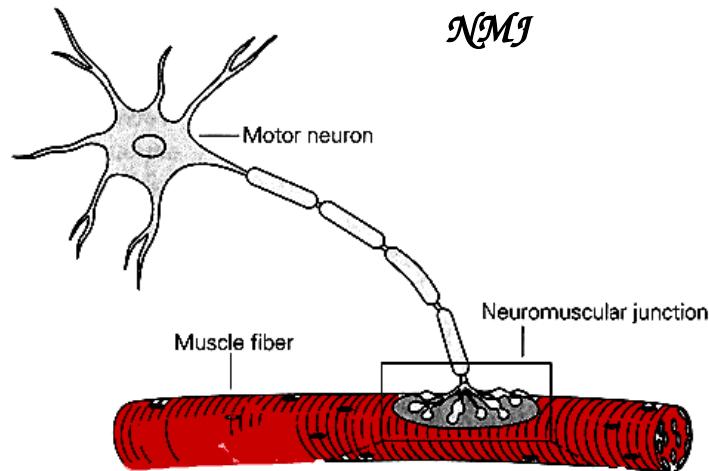
# How do they change the RMP????



## A single synapse is made on each adult muscle fiber



# Differences between the Neuromuscular Junction and Central Synapses



Kandel, Schwartz & Jessel, Principles of Neural Science  
Fig. 11-1; Fig. 11-2

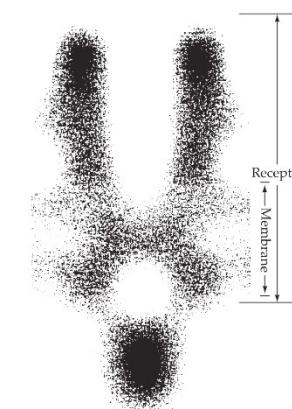
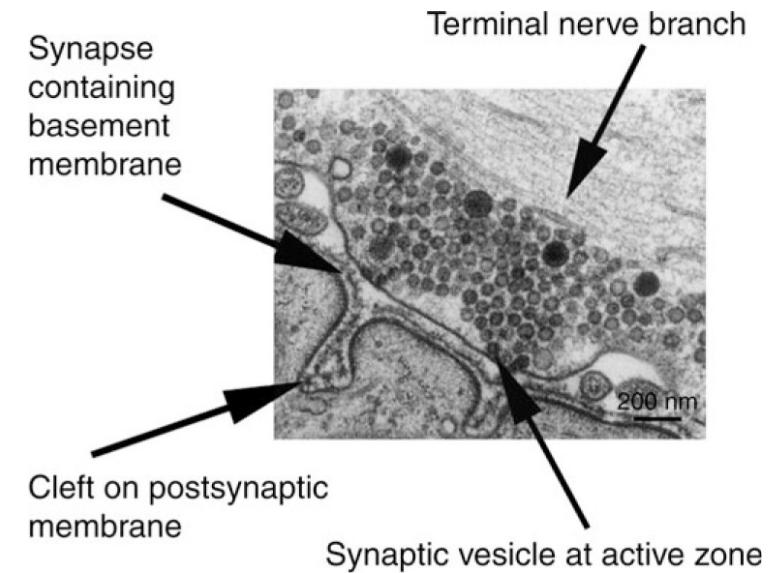
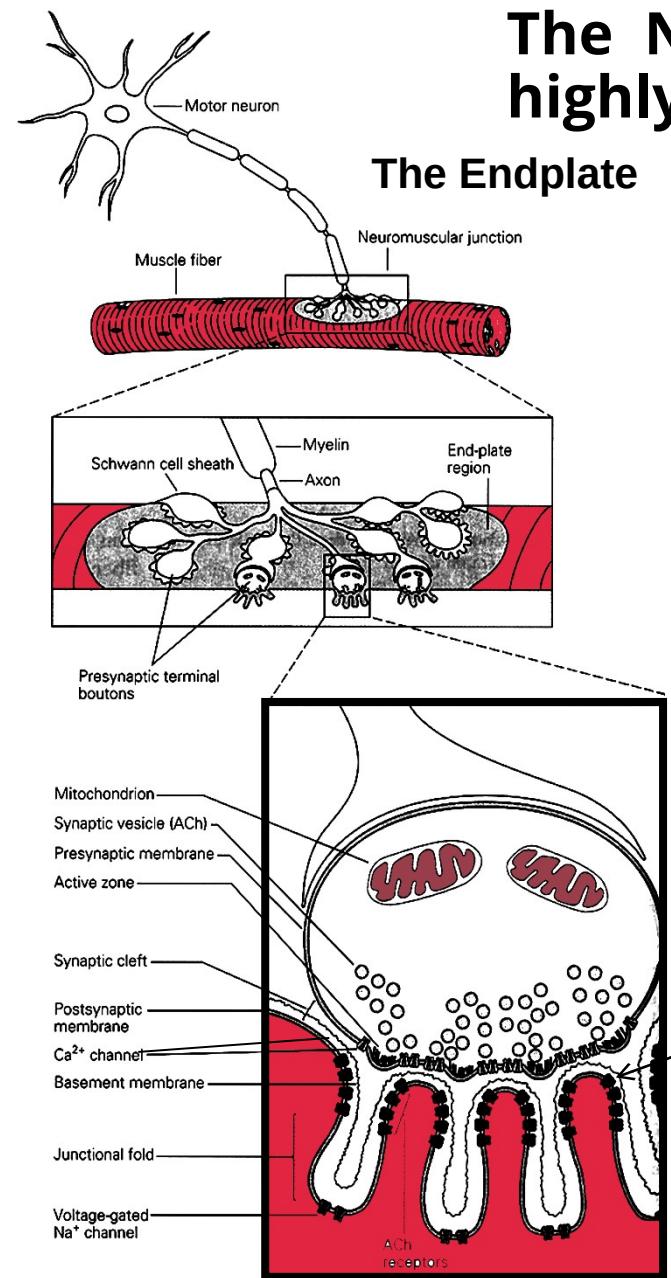
Kuffler, Nicholls and Martin, From Neuron to Brain  
Chap. 9, Fig. 7

## **Signaling at the Neuromuscular Junction against Signaling in Central Neurons**

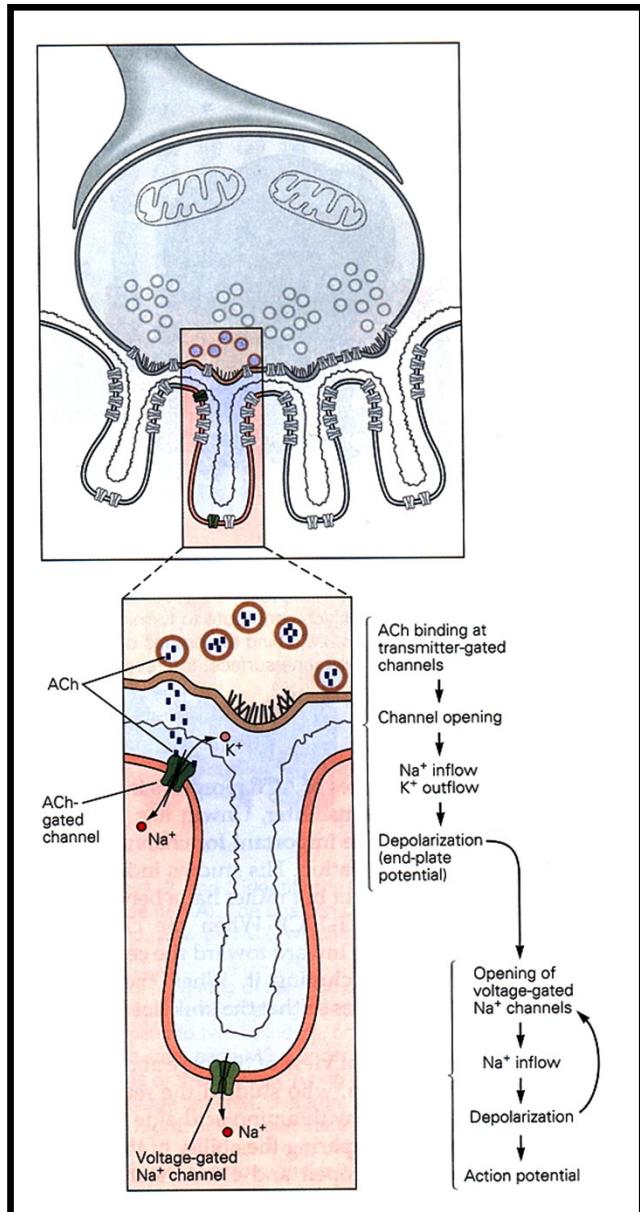
	<b>Neuromuscular Junction</b>	<b>Central Neuron</b>
<b>Number of synaptic connections per cell</b>	Innervated by one motoneuron	Innervated by many neurons
<b>Type of input</b>	Excitatory (in vertebrates)	Excitatory and inhibitory
<b>Variety of neurotransmitters</b>	One only (Ach). Ligand gated ion channel	Many (Ach, GABA, Gly, Glu, etc.). Ligand gated ion channels or metabotropic
<b>Effectiveness of an individual synaptic contact.</b>	Very effective. One action potential > one synaptic potential > muscle excitation.	Modestly effective. Many synaptic potentials (50-100) are necessary to fire an action potential.

Typically, a neuronal EPSP is 0.2 – 0.4 mV. Approximately, 10 mV are necessary to cross the action potential threshold.

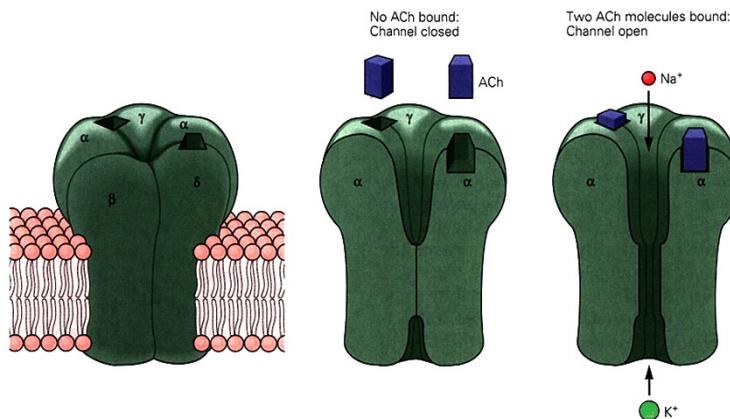
# The Neuromuscular Junction is highly organized



Toyoshima and Unwin, 1990



## Acetylcholine Receptor (AchR) mediates synaptic transmission at the NMJ

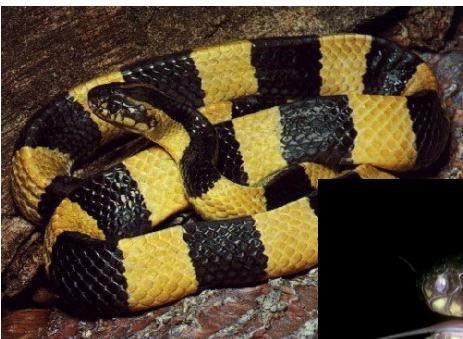


**Binding of two molecules of Ach to the receptor induces a conformational change that opens a non-selective cationic channel. The resulting current is responsible for the depolarizing muscle endplate potential**

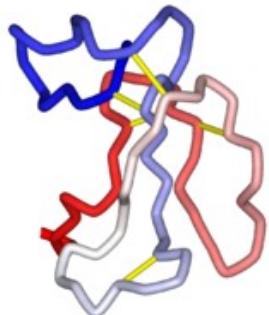
*Kandel, Schwartz and Jessel.  
Principles of Neural Science, McGraw Hill, 2000*

# Many natural toxins target the NMJ

## Banded krait *Bungarus fasciatus*



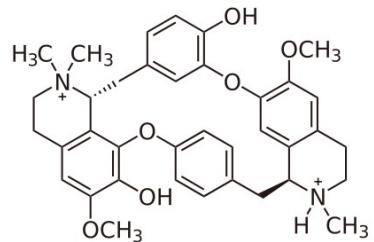
## *$\alpha$ -Bungarotoxin*



## *Ultrahigh affinity antagonist of the nAChR*



## *Strychnos toxifera*



*d*-tubocurare  
competitive antagonist of nAChR

## *Curare*

## *Indigenous hunters Amazon jungle*



## *Blowgun*

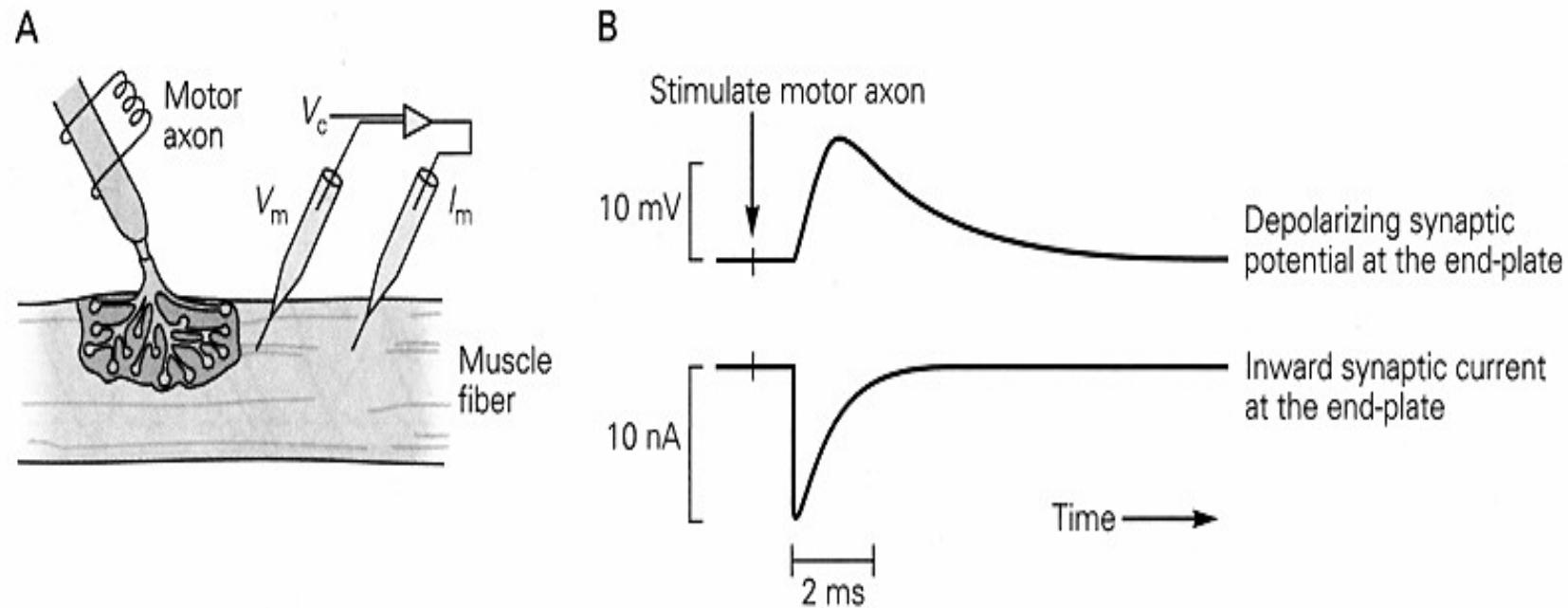


## *Poison darts*

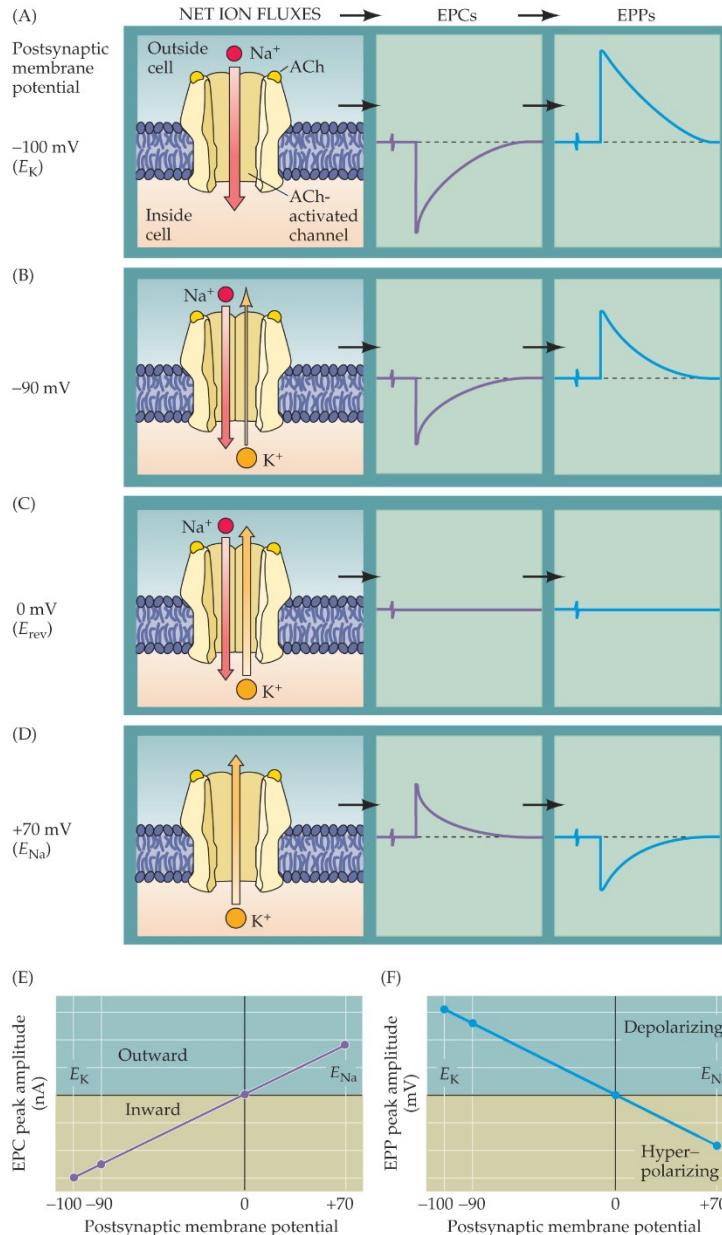
**Why synaptic transmission at the NMJ?  
The synapse is small and the muscle is  
fiber large**



# The EPP and the corresponding endplate current (EPC)



# The EPP is excitatory



## Synaptic current at various levels of $V_m$

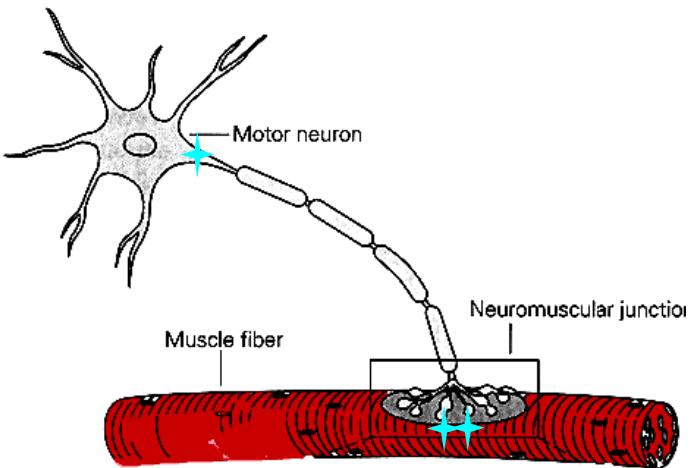
At  $\sim 0 \text{ mV}$  there is no observable net synaptic current (panel B). The influx of  $\text{Na}^+$  is exactly equal to the efflux of  $\text{K}^+$  (steady-state).

Thus, this  $E_{\text{EPP}}$  is the *Reversal Potential* of the synaptic current at the endplate.

An  $E_{\text{EPP}} = 0$  indicates a slightly  $\text{Na}^+$ -selective channel

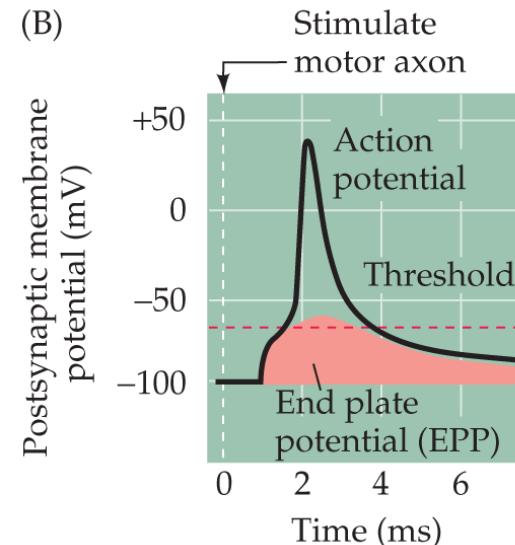
*Purves, Augustine, Fitzpatrick, Hall,  
LaMantia, McNamara and Williams,  
Neuroscience, 2004*

# NMJ has a high safety factor



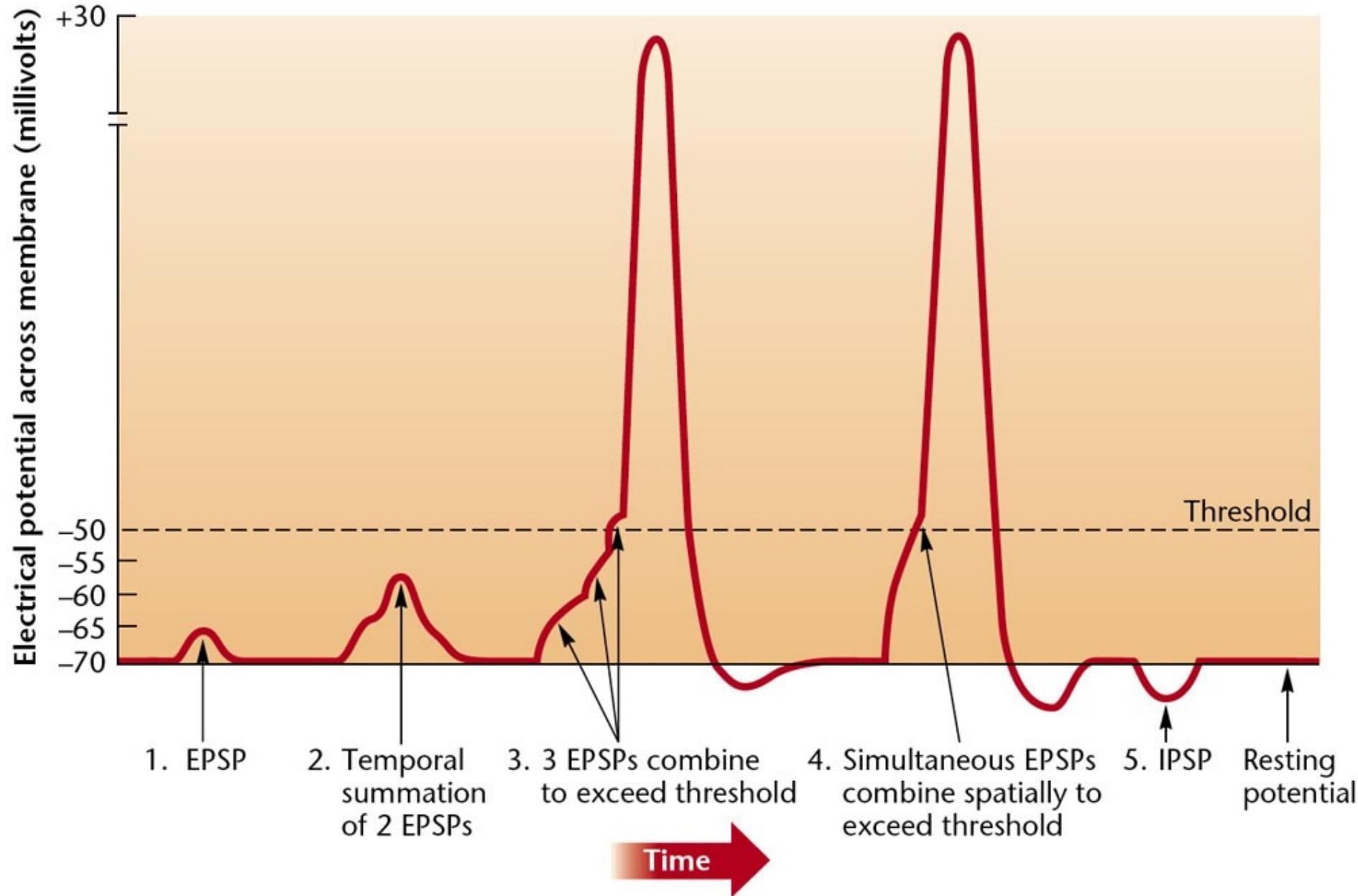
NMJ  
Highly effective  
High safety factor

One MN AP > muscle excitation (AP) > contraction



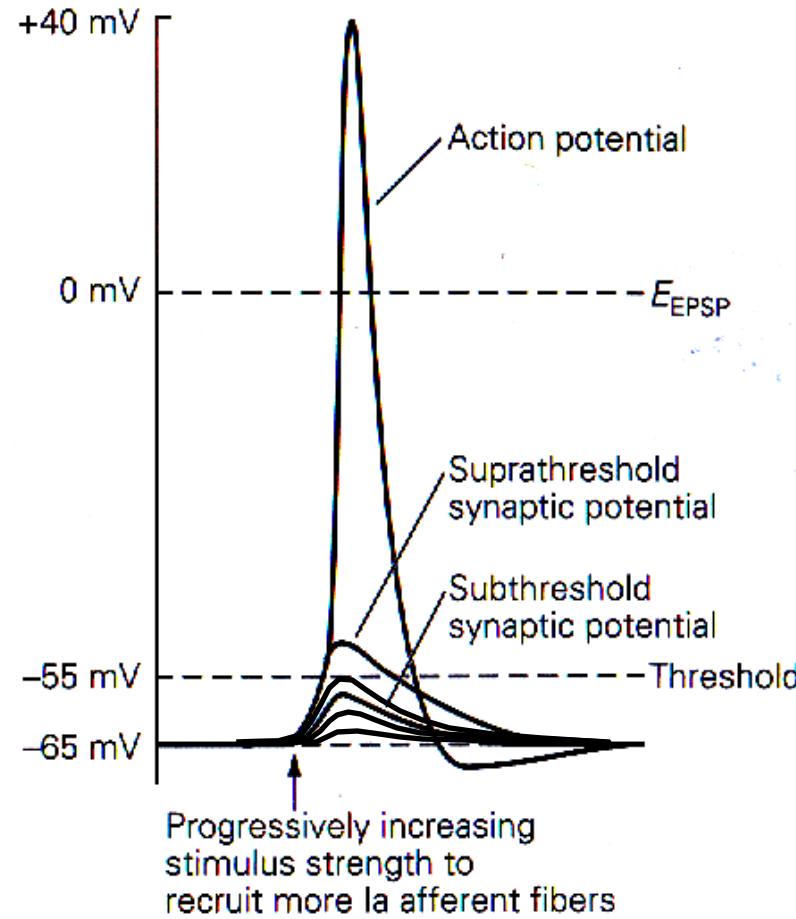
Purves, Augustine, Fitzpatrick, Hall,  
LaMantia, McNamara and Williams,  
Neuroscience, 2004

The EPP at the NMJ always crosses the muscle AP threshold

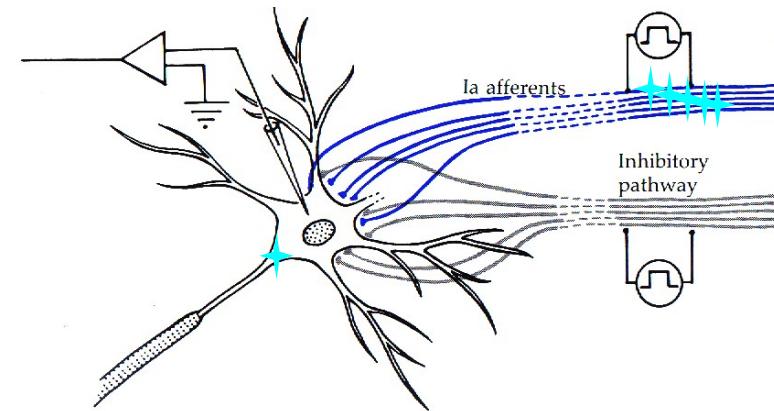


# Central synapses have a low safety factor

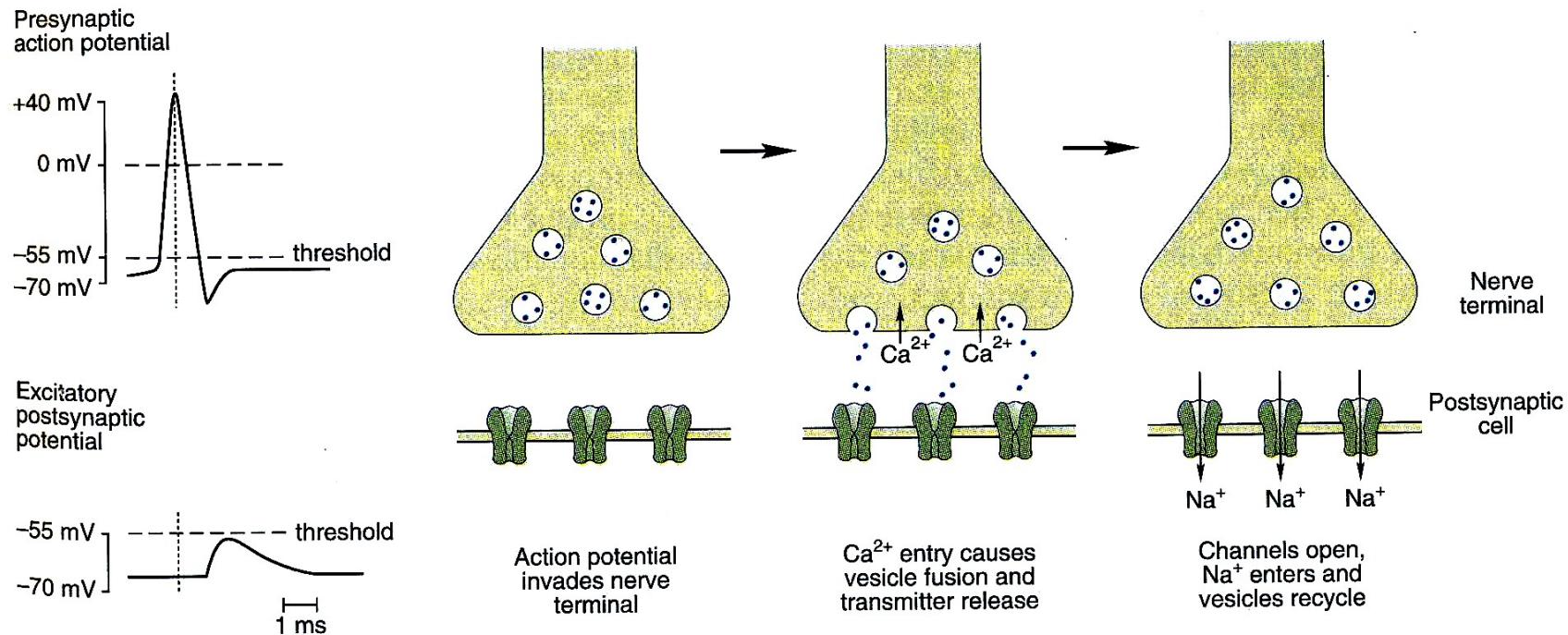
B Excitatory synaptic actions



*Central Synapses  
Not so effective  
Low safety factor*



# The Calcium Hypothesis of Synaptic Transmission



## *The NMJ Pioneers*



Top: Steve, John Eccles, and Bernard Katz in Australia ca. 1941. Bottom:  
Steve, Katz, and Eccles ca. 1975.

*Steve Kuffler  
left  
Bernard Katz\*  
Center*

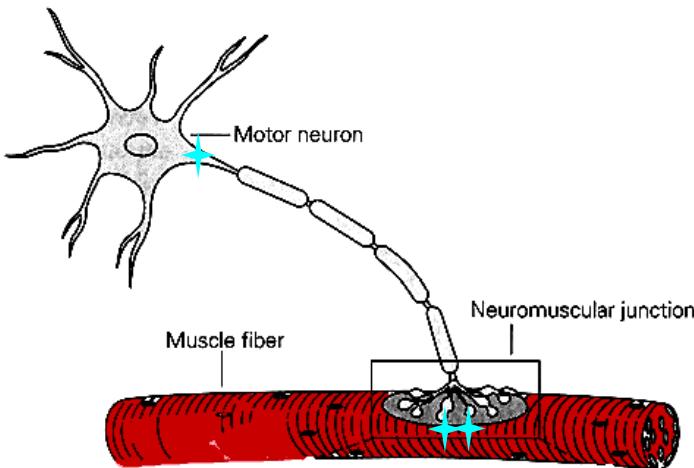
*\*Nobel Prize in Medicine, 1970*

*Famous co-workers:*

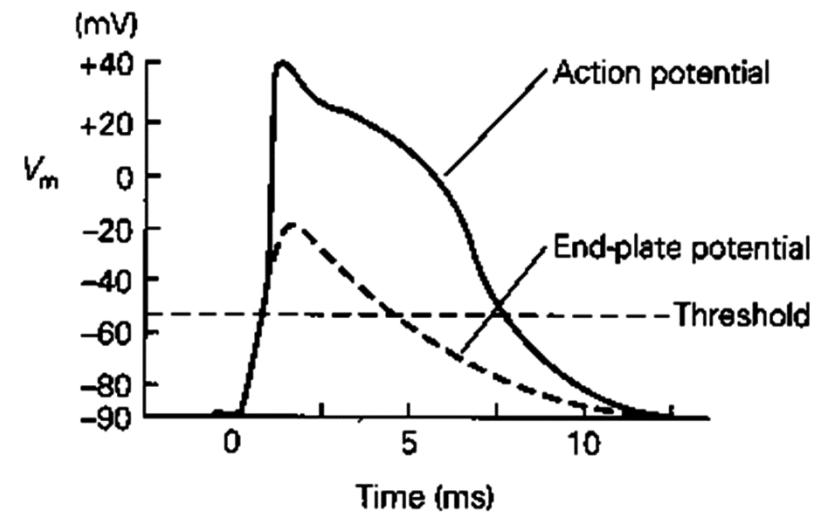
*Paul Fatt  
Jose Del Castillo  
Ricardo Miledi*

# Toning down muscle excitation with curare

## A competitive antagonist of the AchR

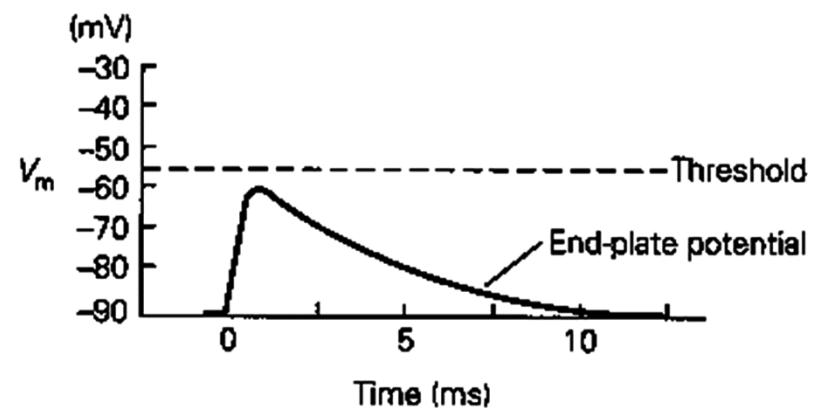


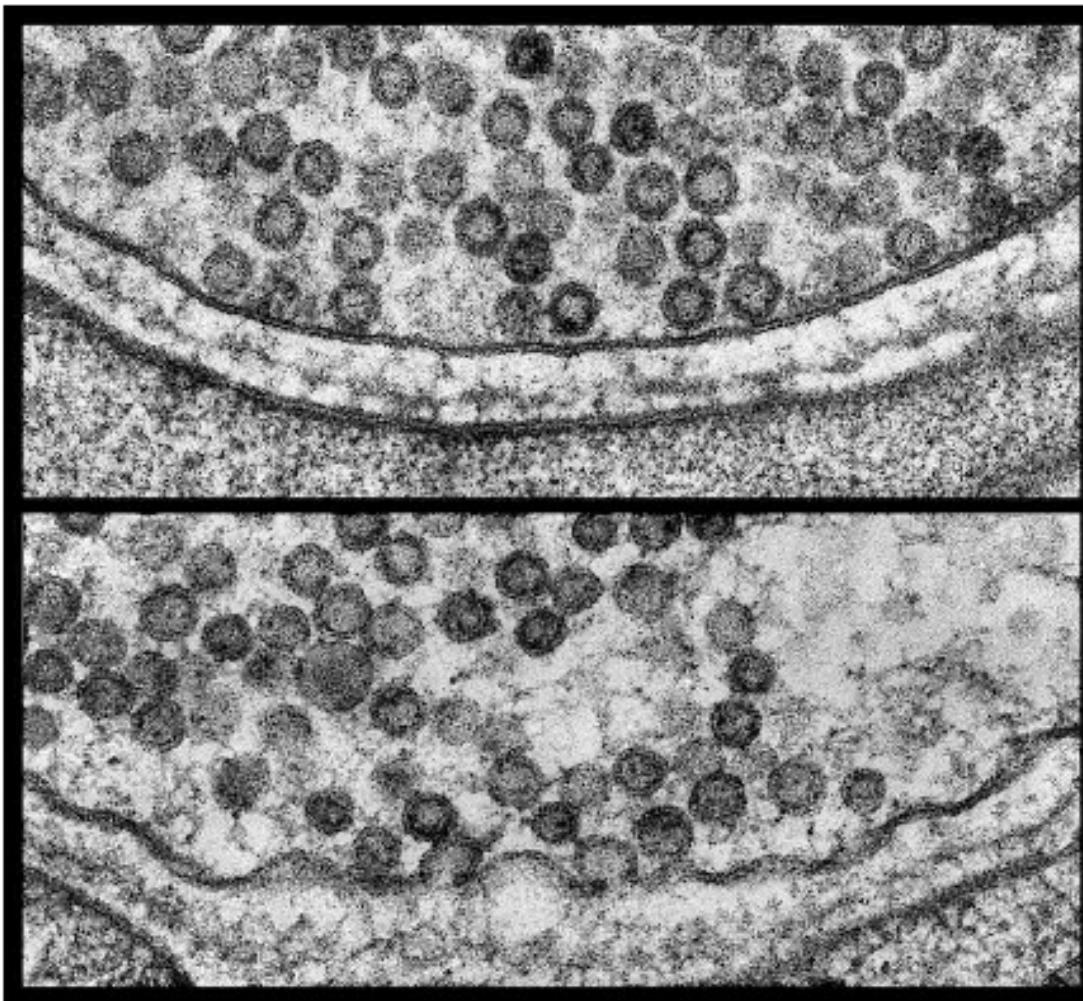
**A Normal**



The EPP is transient because Acetylcholinesterase (AchE), a very fast enzyme present in the synaptic cleft destroys Ach.

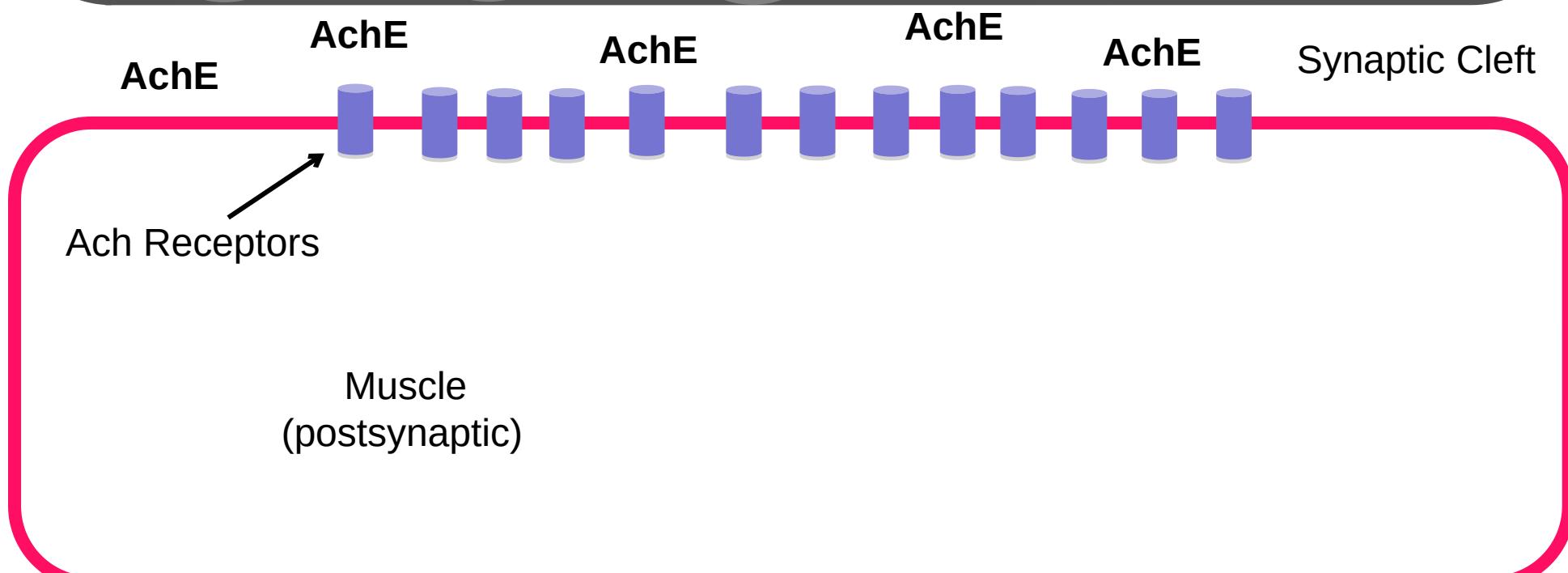
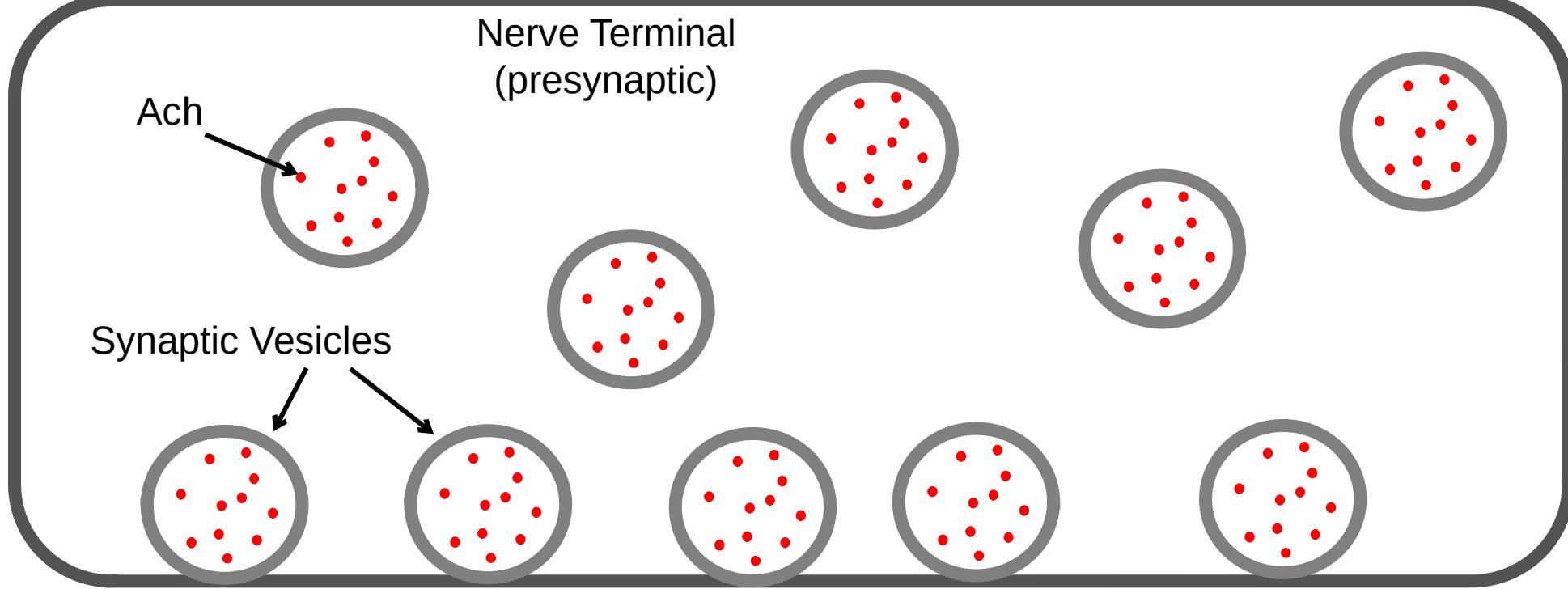
**B With curare**

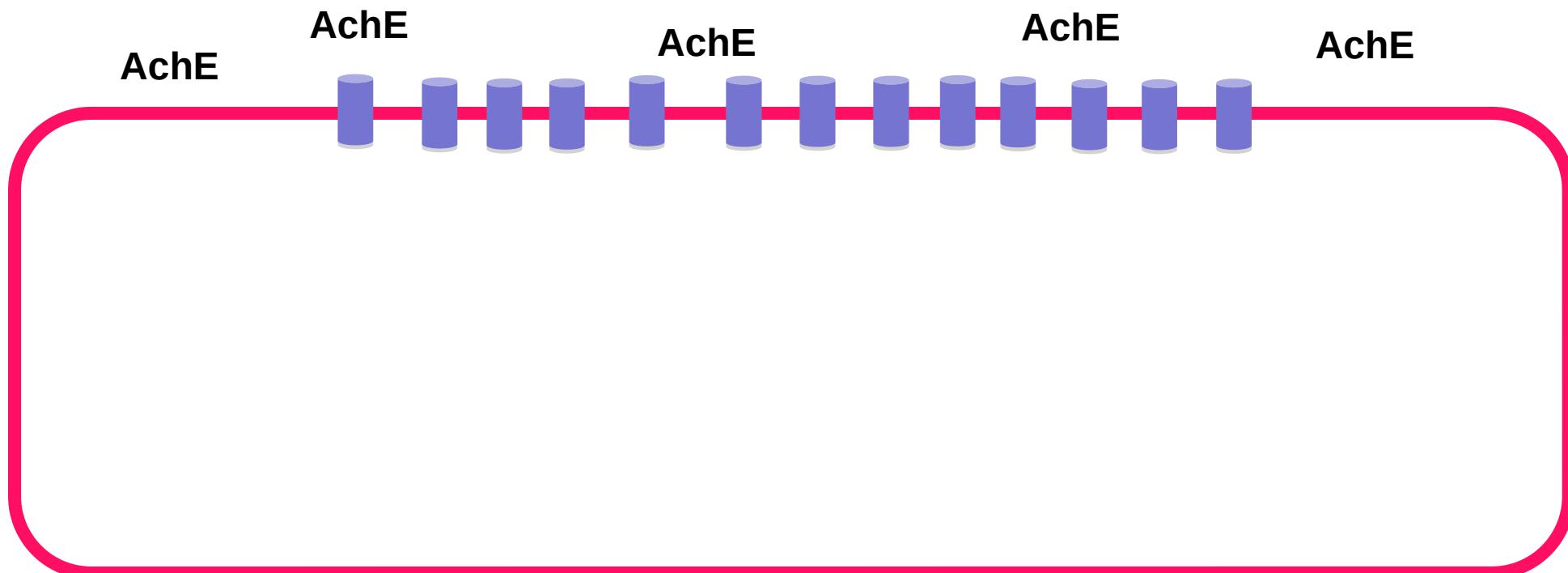
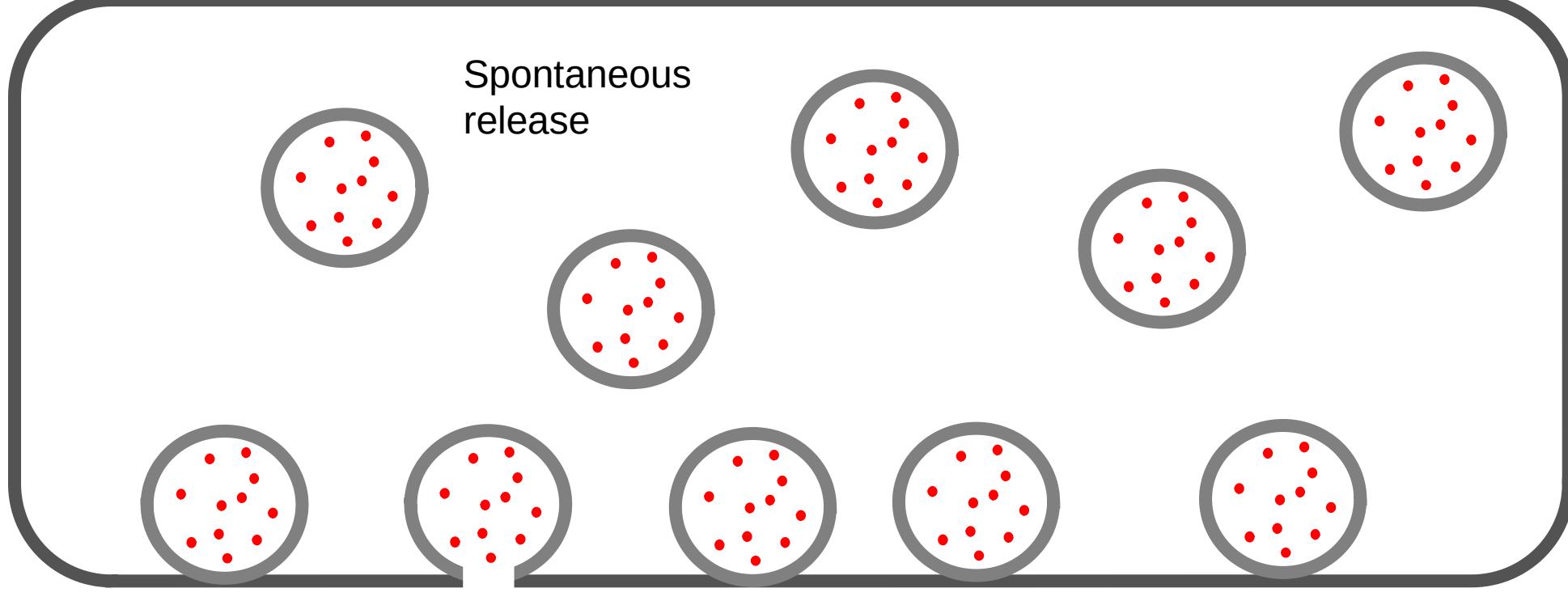


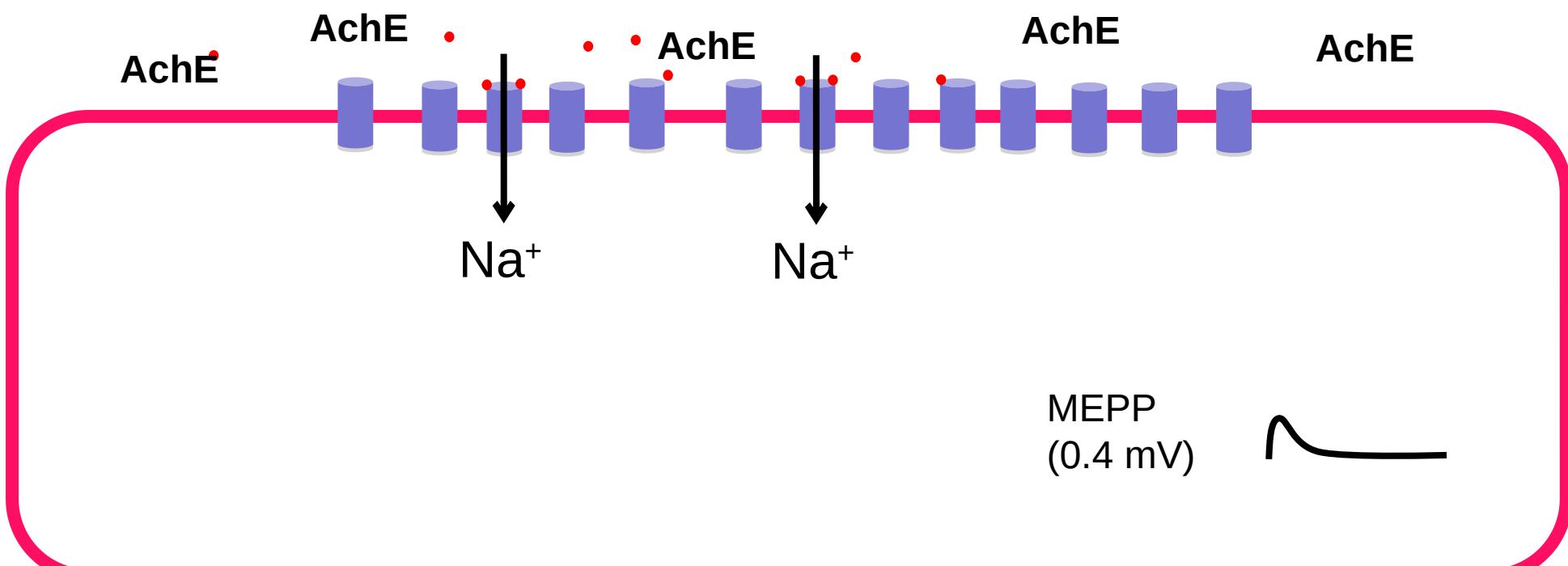
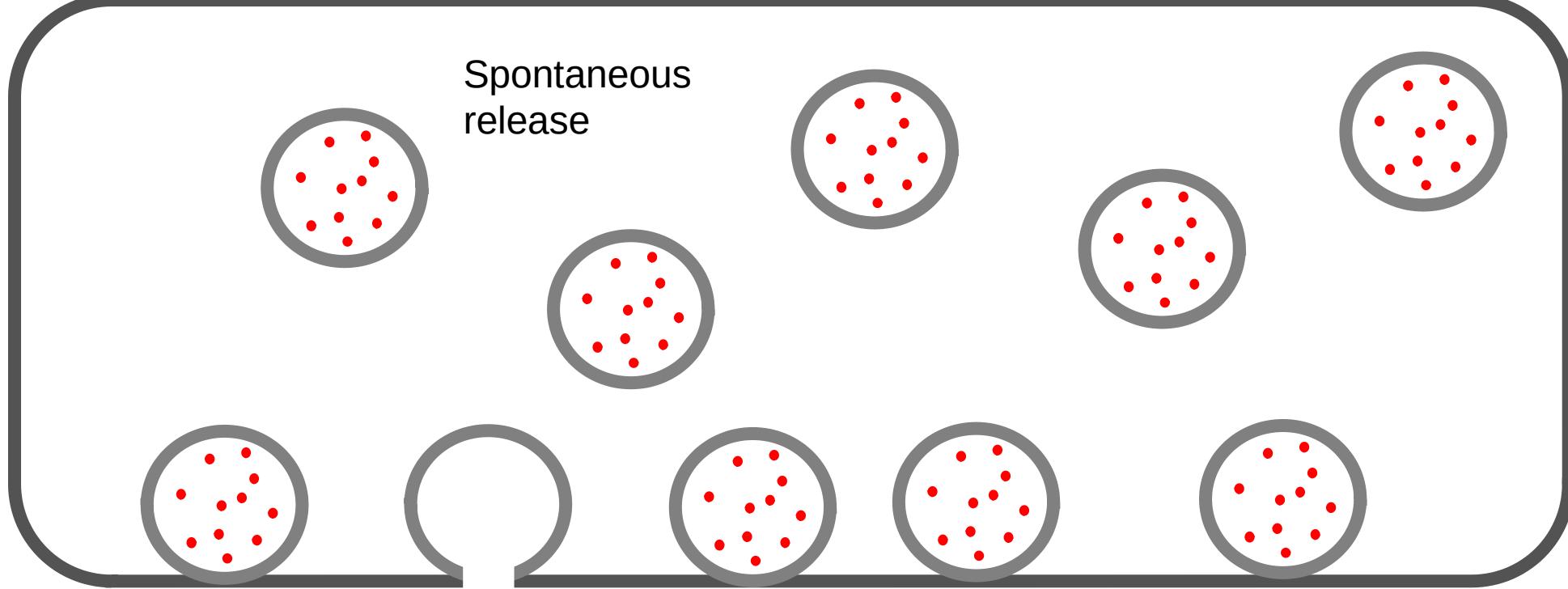


Release of acetylcholine  
at presynaptic plasma  
membrane

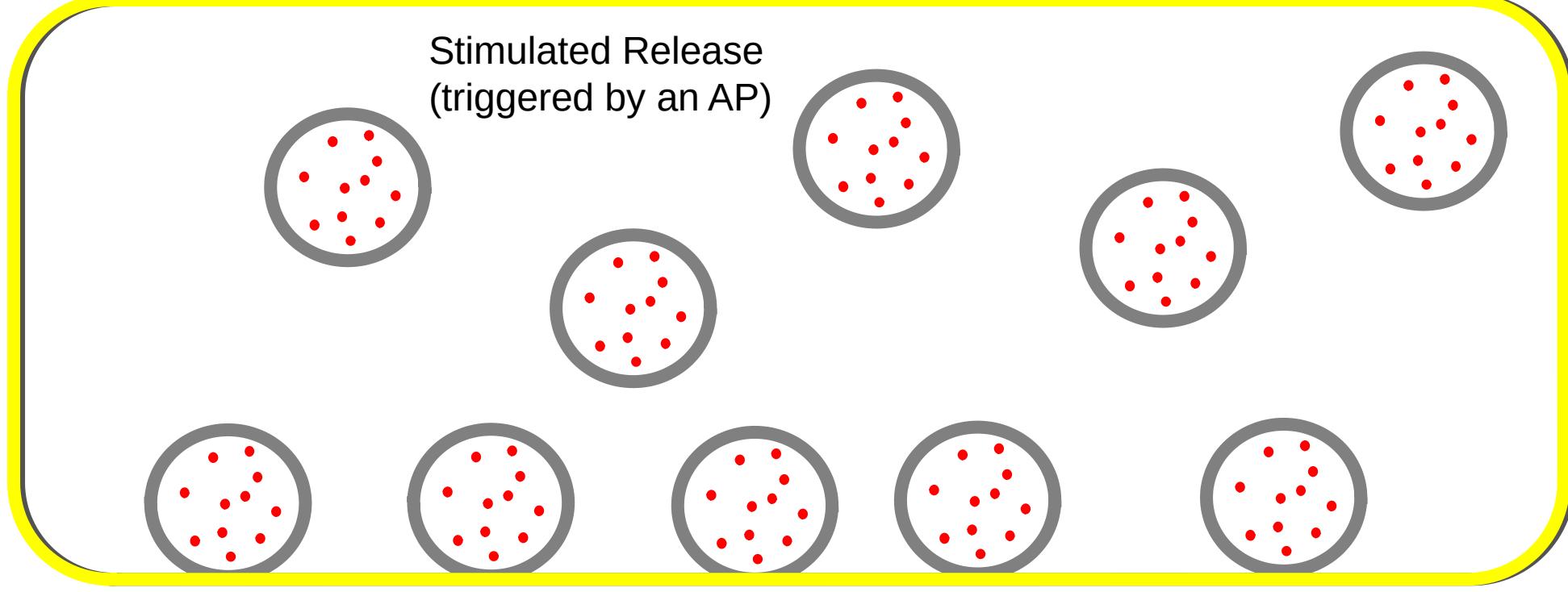
Heuser, 1975

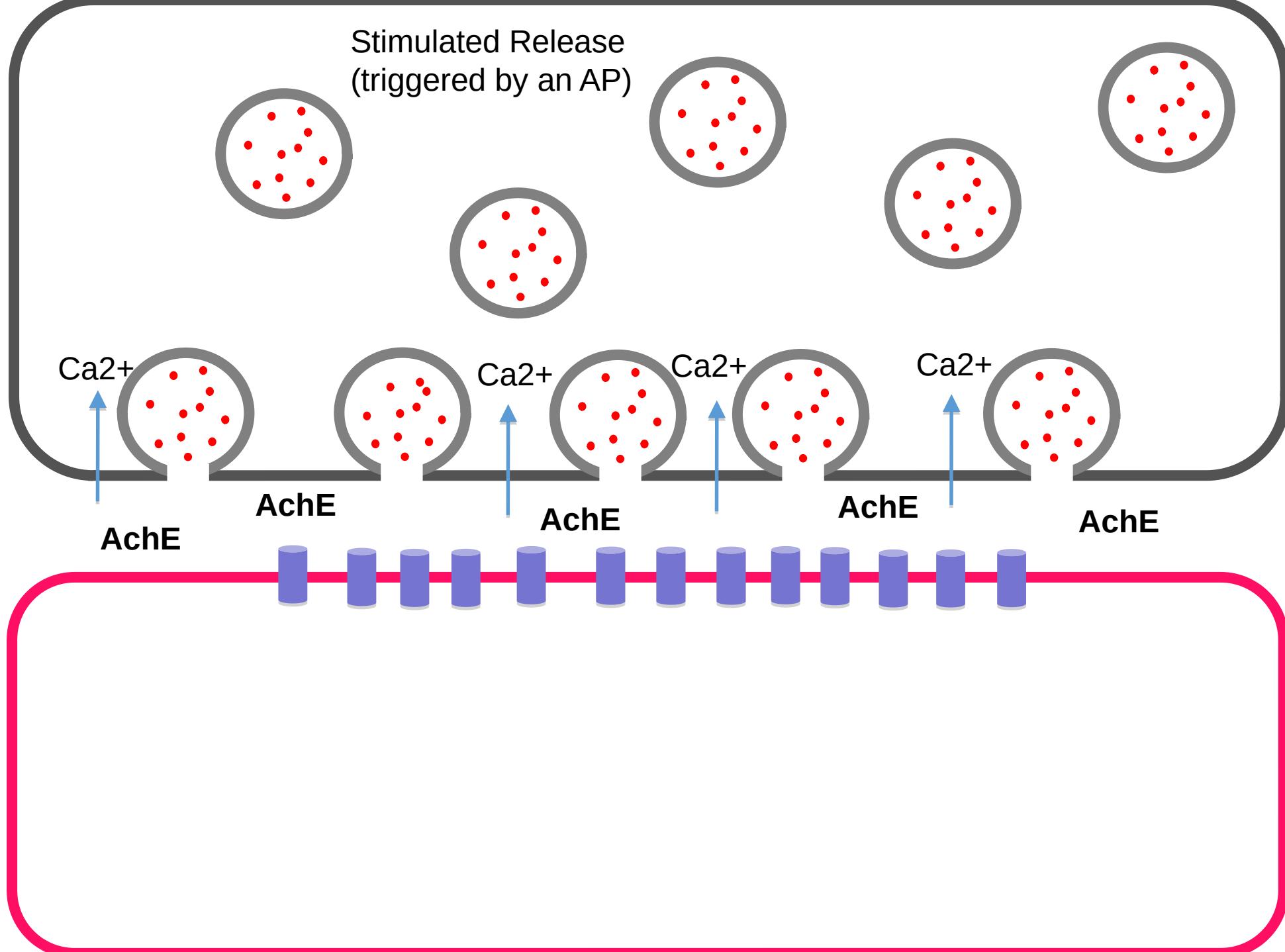


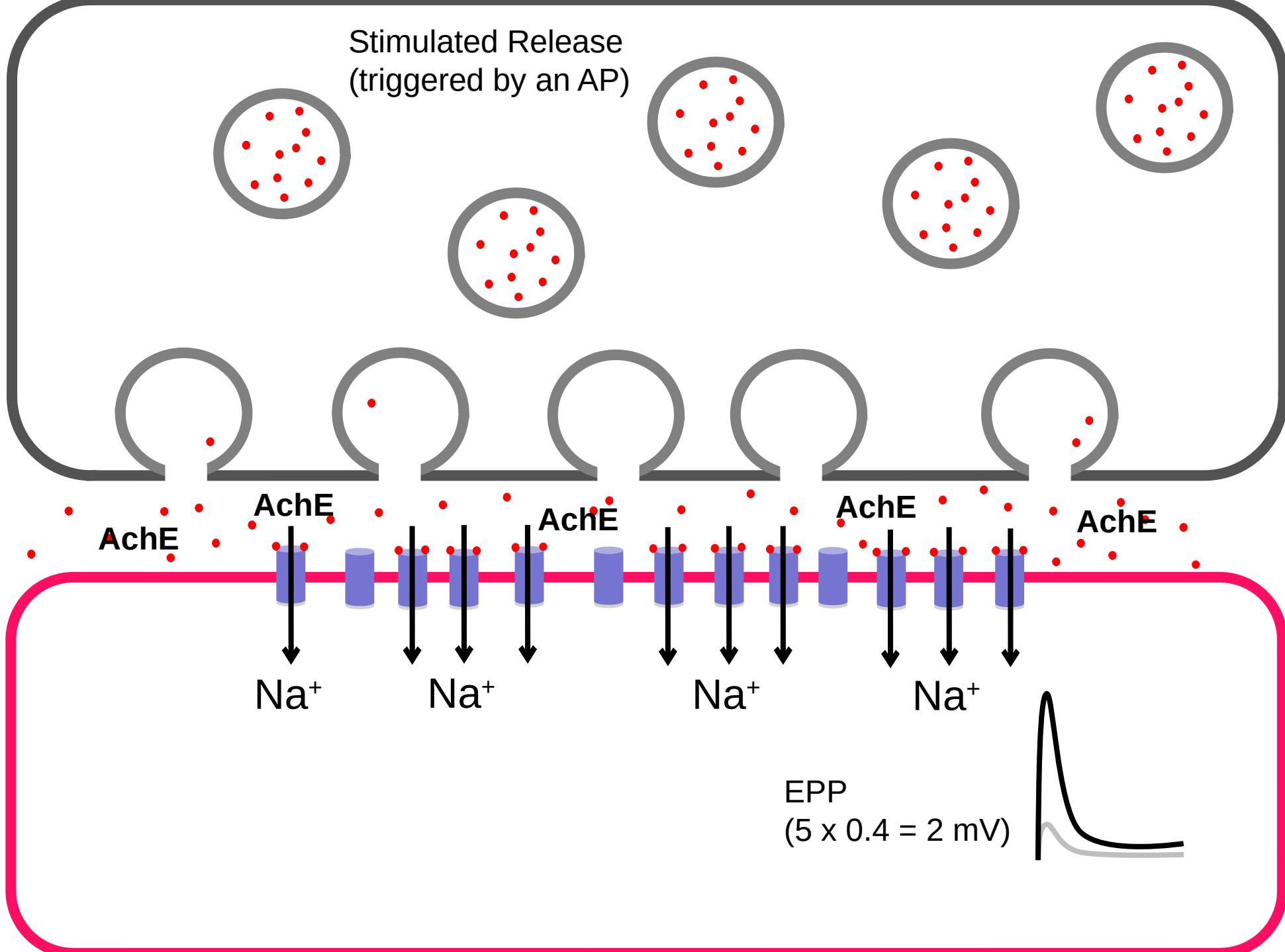




Stimulated Release  
(triggered by an AP)







# NMJ diseases

## Myasthenia Gravis

### (postsynaptic)

Autoimmune, acquired channelopathy  
(ptosis – “lazy eye”)

Myasthenia – Fatigue and Recovery Test ‘Simpson plus’



Toyka, K. V. Neurology 2006;67:1524

NEUROLOGY

jameslindlibrary.org



**Walker MB (1934). Treatment of myasthenia gravis with physostigmine**  
**Lancet 1:1200-1201**

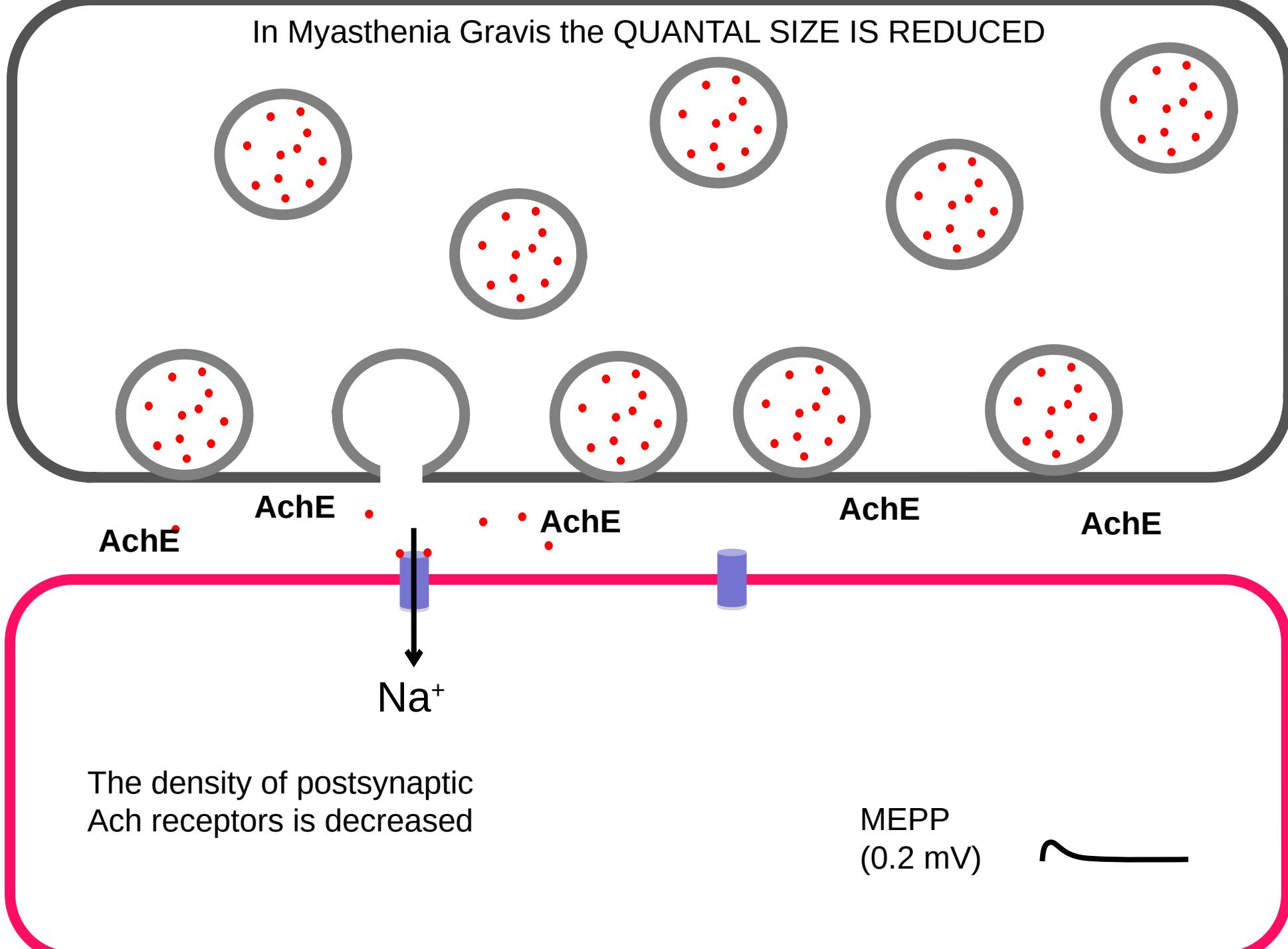
*Physostigmine inhibits acetylcholinesterase*

(-)                    (+)



Before injection the patient cannot raise her left eyelid. Thirty minutes after it the eye is fully open. (The photographs are reproduced from a cinematograph film and are reversed left for right.)

## In Myasthenia Gravis the QUANTAL SIZE IS REDUCED



# NMJ Diseases

## Botulism

(presynaptic)

14 year old with botulism



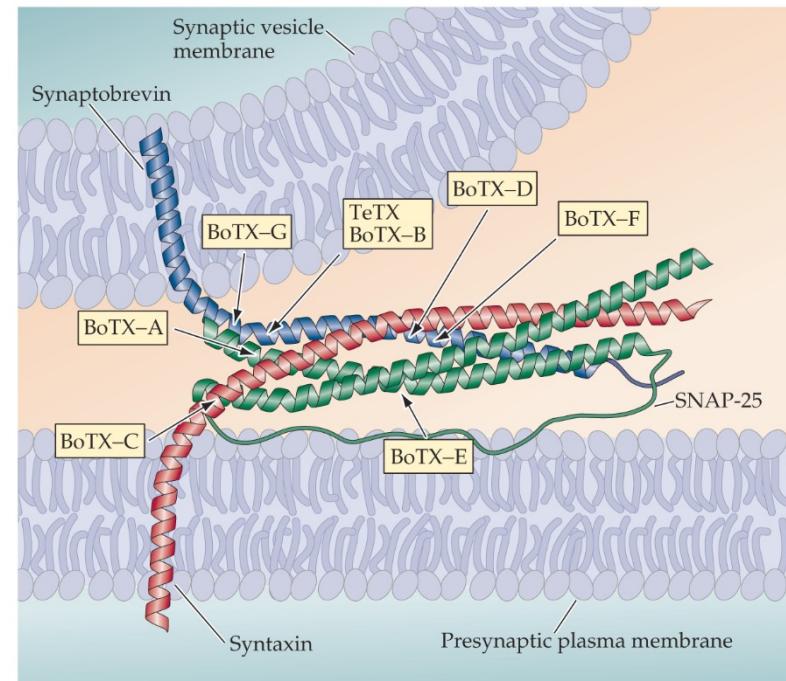
Botulinum toxin is a neurotoxin produced by the bacterium *Clostridium botulinum*. Perhaps the most toxic protein known ( $LD_{50} = 0.005 - 0.05 \text{ mg / kg}$ ). It occurs in contaminated food.

Botulinum toxin specifically cleaves SNARE proteins and, thereby, prevents docking and fusion of synaptic vesicles with the presynaptic membrane during excitation of the synaptic terminal at the muscle endplate.

<http://en.wikipedia.org/wiki/Botulism>

# Botulism (presynaptic)

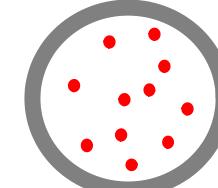
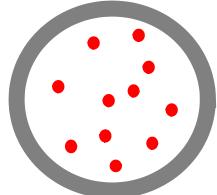
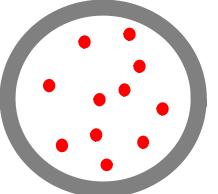
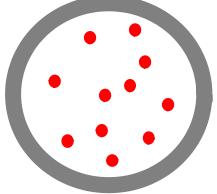
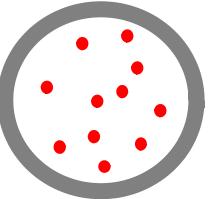
Syndrome	Comments
Foodborne botulism	Caused by ingestion of food contaminated by <i>Clostridium</i> spores or with toxin produced under anaerobic conditions (e.g. home canning). Nausea, vomiting, and abdominal pain occur within ~36 h. Autonomic dysfunction (blurred vision, diplopia, bradycardia, and hypotension) followed by descending flaccid paralysis occur
Wound botulism	Results from contamination of surgical or other wounds. Recently commonly seen in drug abusers injecting 'black tar' heroin subcutaneously ('skin-popping'). Incubation period 4–14 days. Similar presentation to foodborne botulism without GI symptoms
Infant botulism	Result of absorption of toxin produced within GI tract of children >1 yr old. Classically <i>Clostridium</i> spores ingested in infected honey
Adult infectious botulism	Similar aetiology to infant botulism. Usually seen after GI tract surgery or antimicrobial therapy
Inadvertent botulism	Follows accidental overdose or accidental i.v. injection of botulinum toxin during the treatment of movement disorders (e.g. focal dystonia)



Purves, Augustine, Fitzpatrick, Hall,  
LaMantia, McNamara and Williams,  
Neuroscience, 2004

Botulinum toxin inhibits stimulated presynaptic release

Botulinum  
toxin



AchE

AchE

AchE

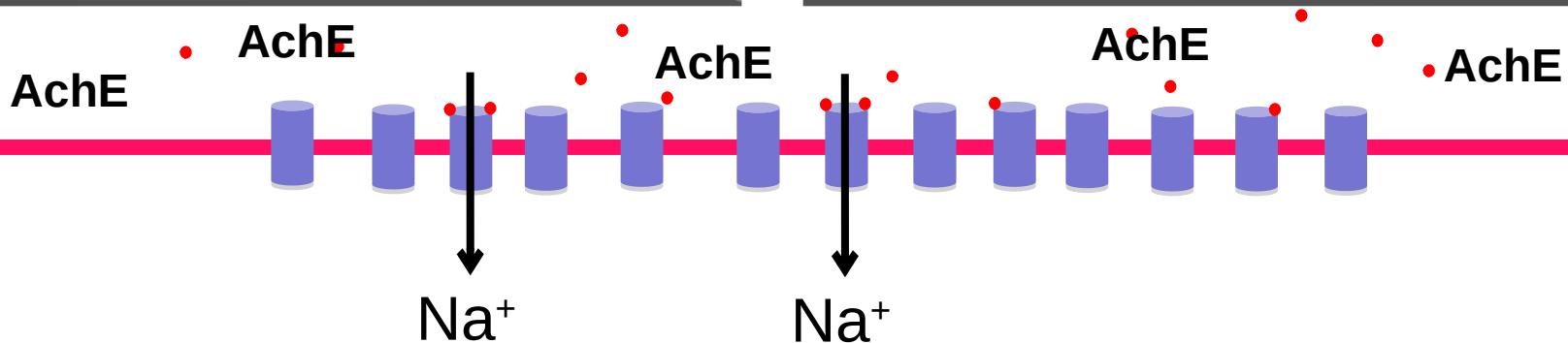
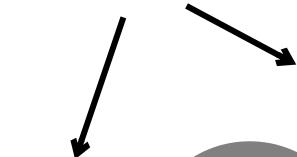
AchE

AchE



## In Botulism the QUANTUM CONTENT IS REDUCED

Botulinum toxin



The average # of quanta evoked  
by a presynaptic AP is reduced

The EPP is reduced

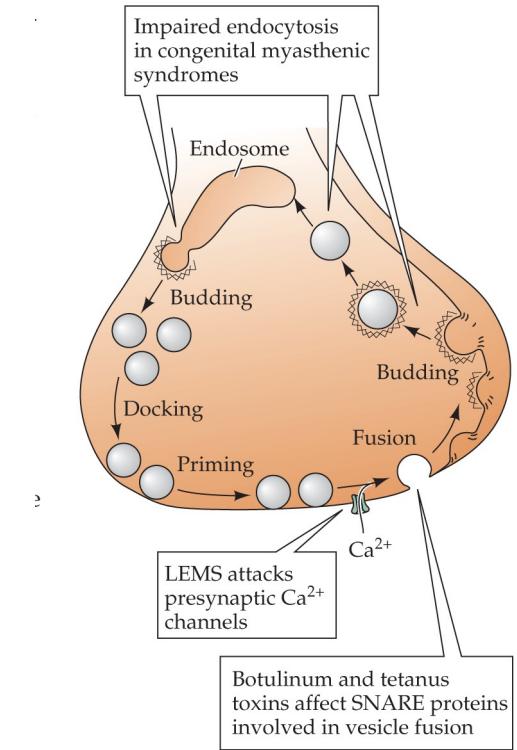


# Disruption of synaptic vesicle release



## *Clostridium tetani*

- Anaerobic soil bacterium
- Responsible for 350,000 cases/year of tetanus (spastic paralysis) worldwide
- Tetanus toxin blocks release of inhibitory neurotransmitters from the presynaptic membranes; Cleaves v-Snare (synaptobrevin, VAMP2)



Purves, Augustine, Fitzpatrick, Hall,  
LaMantia, McNamara and Williams,  
Neuroscience, 2004