

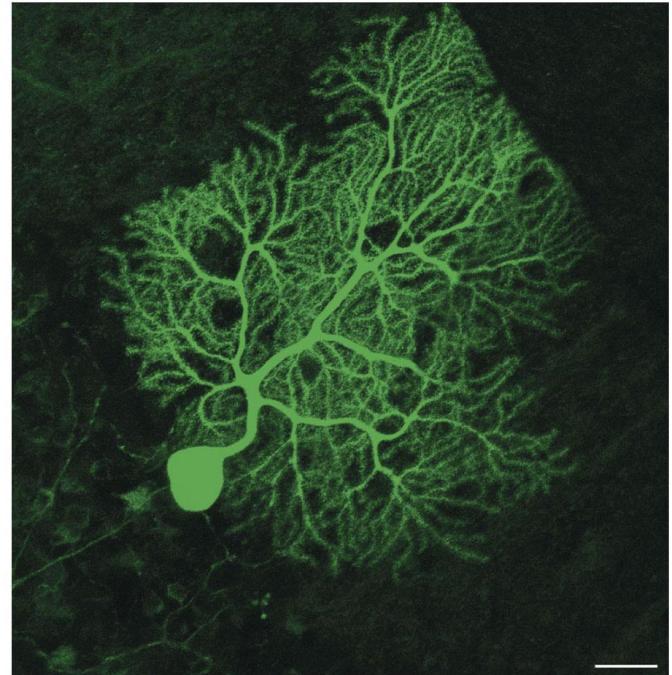
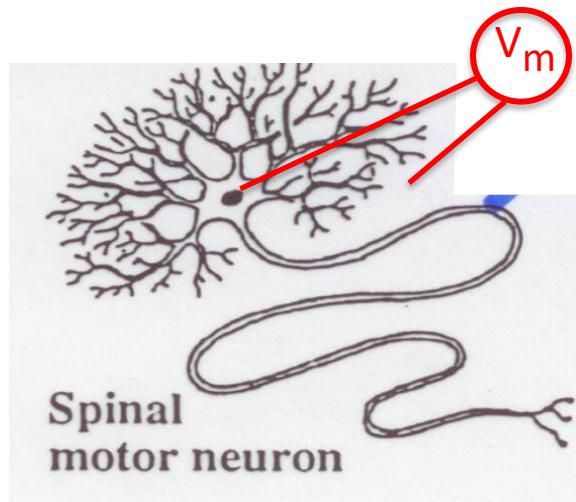
Neuroscience Graduate Program

Boot Camp 2020

Jing Wang and Stefan Leutgeb

Biophysics Overview

The membrane potential of neurons

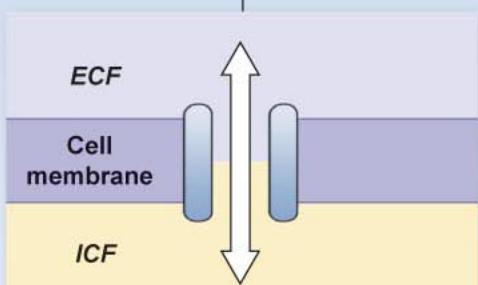


Membrane potential is the voltage measured across the cell membrane; it is represented as V_m

In electrophysiological recordings, the extracellular fluid is assigned a charge that is 0 (i.e., ground).

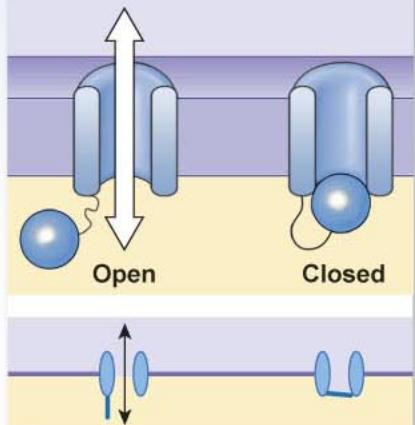
MEMBRANE TRANSPORTERS

Channel proteins create a water-filled pore

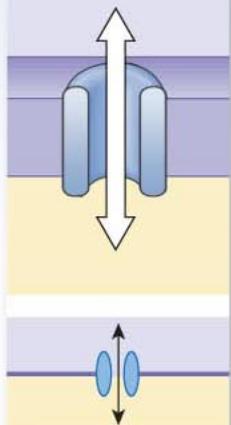


can be classified

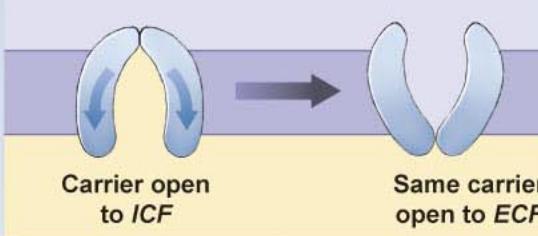
Gated channels



Open channels



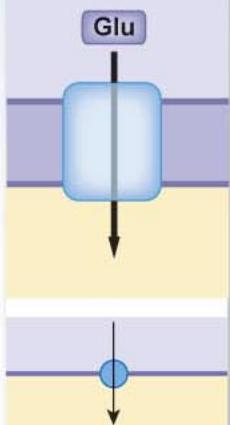
Carrier proteins never form an open channel between the two sides of the membrane



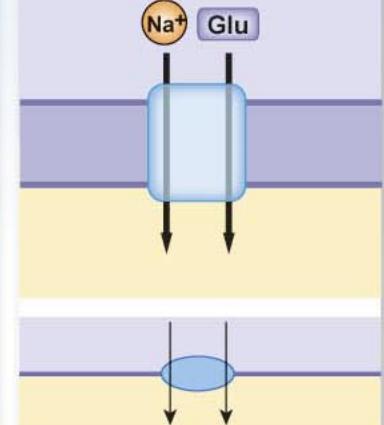
can be classified

Cotransporters

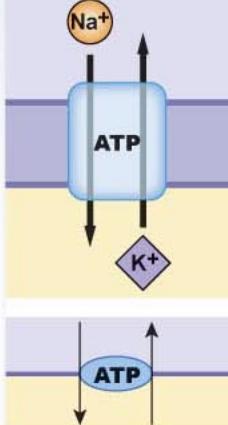
Uniport carriers



Symport carriers



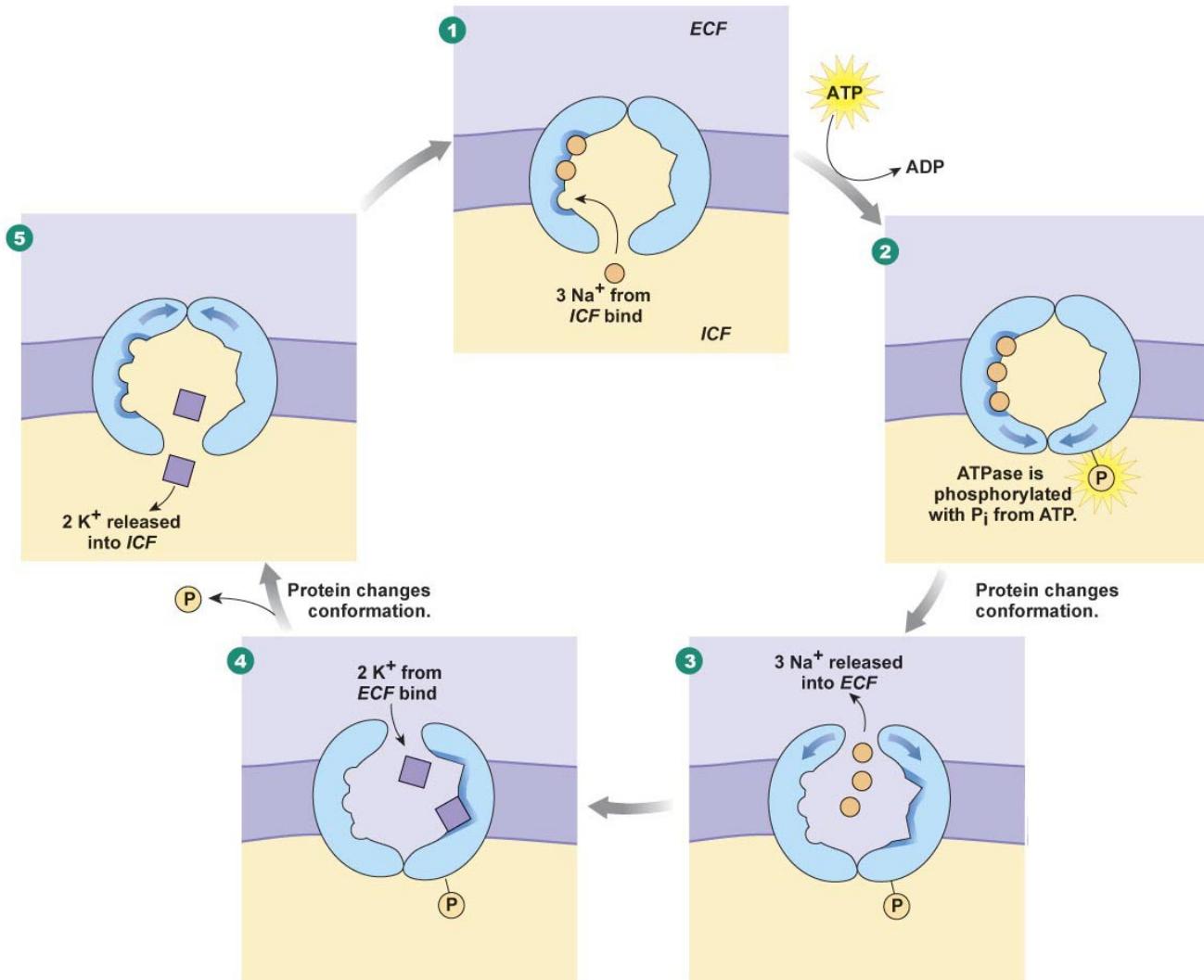
Antiport carriers



Channel proteins/Ion channels

- channel proteins create a water-filled pore
- Na⁺ channels, K⁺ channels, Ca⁺⁺ channels, Cl⁻ channels
monovalent cation channels, cation channels
- the ease with which ions flow through a channel is called **conductance**, facilitated diffusion
- **open channels** or pores are usually open
leak channels
- **gated channels** open and close in response to signals
 - (a) mechanically gated ion channels
physical forces, i.e., stretch, pressure
 - (b) chemically gated ion channels (**nicotinic, muscarinic, ...**)
extracellular and intracellular ligands
 - (c) voltage-gated ion channels
cell's membrane potential

Carrier proteins/sodium-potassium pump

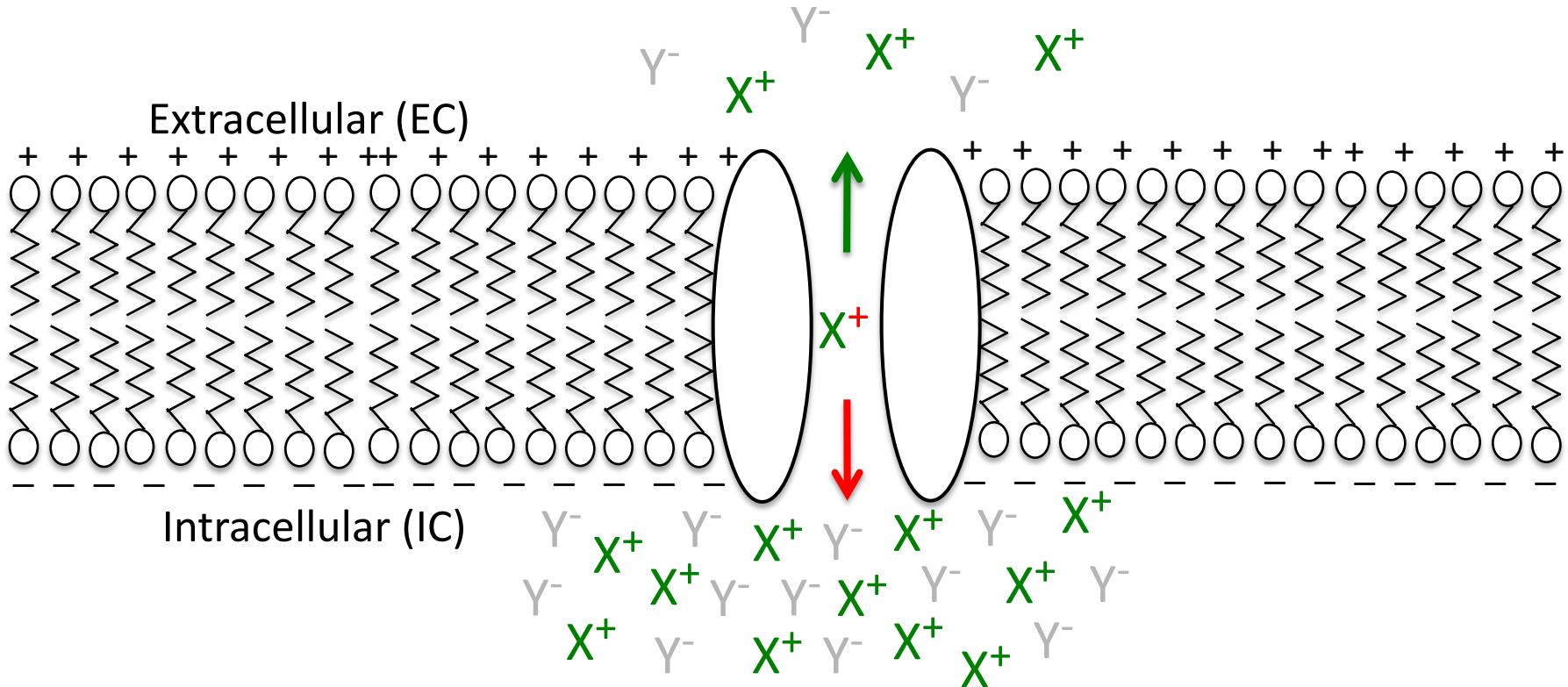


The origin of the membrane potential

The inside-negative resting membrane potential is generated by

- A) the imbalance from pumping 3 positive Na ion out while pumping only 2 positive K ions into the cell
- B) by letting K⁺ freely move between the inside and outside of the cell
- C) by pumping Na⁺ out of the cell while the more negatively charged proteins than positive ions remain in the cell

Forces acting on an ion (X^+) in a channel permeable only to that ion



Force toward EC: chemical concentration gradient = $RT \ln \frac{[X]_{\text{out}}}{[X]_{\text{in}}}$

Force toward IC: electrical concentration gradient = $z_x F V_m$

At equilibrium, the forces are equal: $RT \ln \frac{[X]_{\text{out}}}{[X]_{\text{in}}} = z_x F V_m$

At equilibrium, the forces are equal: $RT \ln \frac{[X]_{\text{out}}}{[X]_{\text{in}}} = z_x F V_m$

Solve for V_m : $V_m = \frac{RT}{z_x F} \ln \frac{[X]_{\text{out}}}{[X]_{\text{in}}} = E_x$

This is the **Nernst Equation**

- the equilibrium V_m gets a special name E_x which is called “the X equilibrium potential”
(the potential at which ion X is at equilibrium)

The Nernst Equation is usually written in log to the base 10 rather than ln, and the constants are lumped together. At 25 °C:

$$E_x = \frac{59 \text{ mV}}{z} \log \frac{[X]_{\text{out}}}{[X]_{\text{in}}}$$

TABLE 8-2

Ion Concentrations and Equilibrium Potentials

ION	EXTRACELLULAR FLUID (mM)	INTRACELLULAR FLUID (mM)	E_{ion} AT 37° C
K ⁺	5 mM (normal range: 3.5–5)	150 mM	-90 mV
Na ⁺	145 mM (normal range: 135–145)	15 mM	+60 mV
Cl ⁻	108 mM (normal range: 100–108)	10 mM (range: 5–15)	-63 mV
Ca ²⁺	1 mM	0.0001 mM	see Concept Check question 6

$$E_{Na} = \frac{59}{z} \log \frac{[X]_{out}}{[X]_{in}}$$

$$E_{Na} = \frac{59}{+1} \log \frac{150}{15}$$

$$E_{Na} = \frac{59}{+1} \log 10 \quad \log 10 = 1$$

$$E_{Na} = +59 \text{ mV}$$

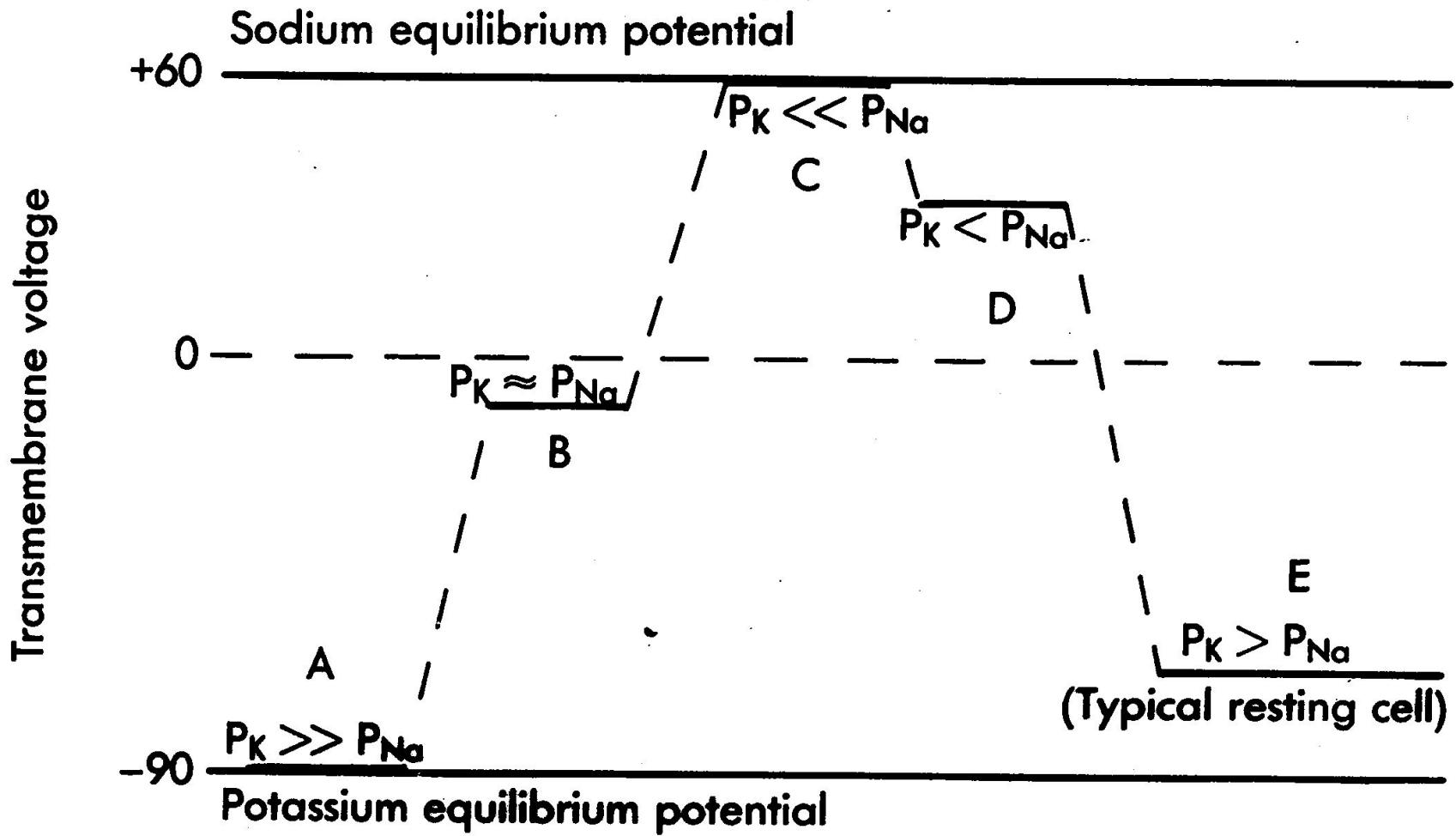
Equilibrium potential is the potential when the net flow of an ion is zero.

Resting membrane potential is the potential when the net current flow in and out of a cell is zero.

Reversal potential is the potential when the net current flow through a channel reverses. The net current is zero at the reversal potential.

If a channel is only permeable to a single type of ion (e.g., K⁺), its reversal potential is equal to the equilibrium potential for the ion.

If a cell has only ion channels open that are permeable to a single ion (e.g., K⁺) the resting membrane potential is equal to the equilibrium potential for the ion.



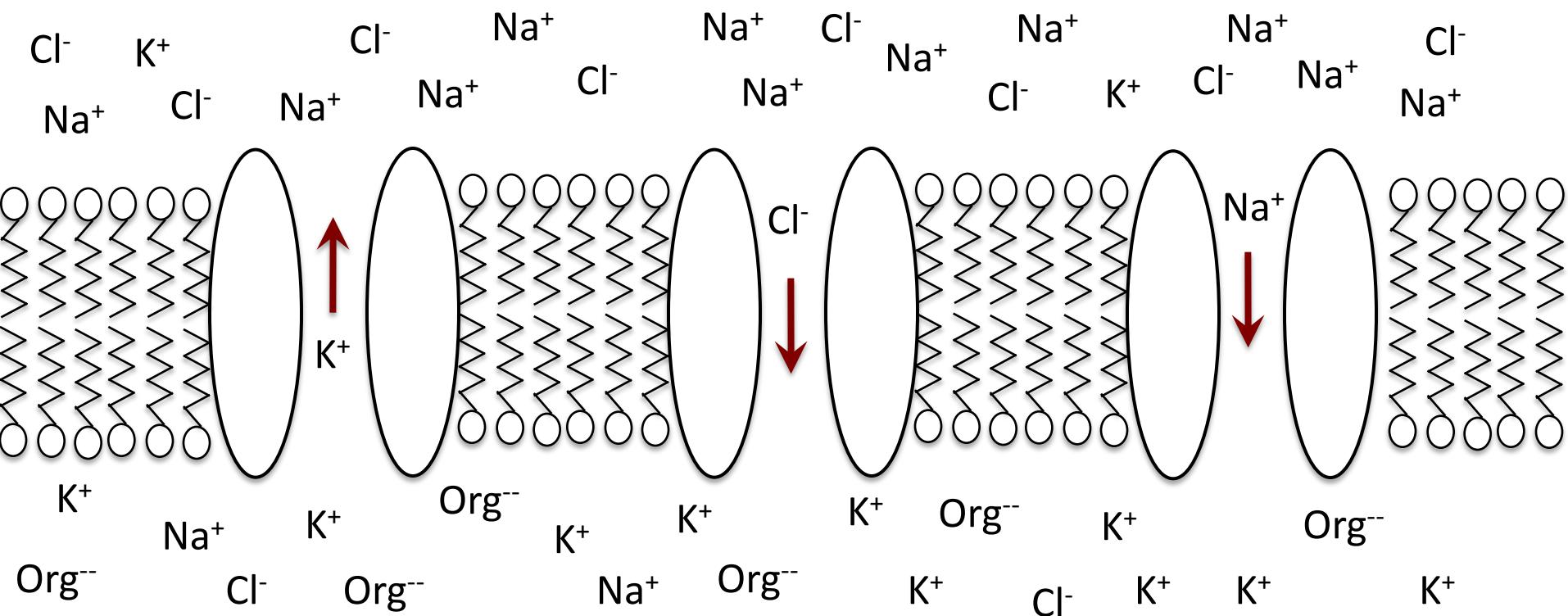
Note: Permeabilities (P_x) are used for the Goldman equation; conductances (G_x) are used for the resting potential equation. For present purposes, they are equivalent.

More channels ...

If Na^+ channels suddenly open and K^+ channels close, which one is reached first and which is reached at equilibrium

- A) Na^+ ions flow until the membrane potential reaches 0 mV
- B) Na^+ ions flow until the Na^+ concentration inside and outside of the cell is equal.
- C) Na^+ ions flow until the Na^+ equilibrium potential is reached

Three major ions determine the membrane potential at rest:



Resting potential (V_m) is a combination of the 3 equilibrium potentials:

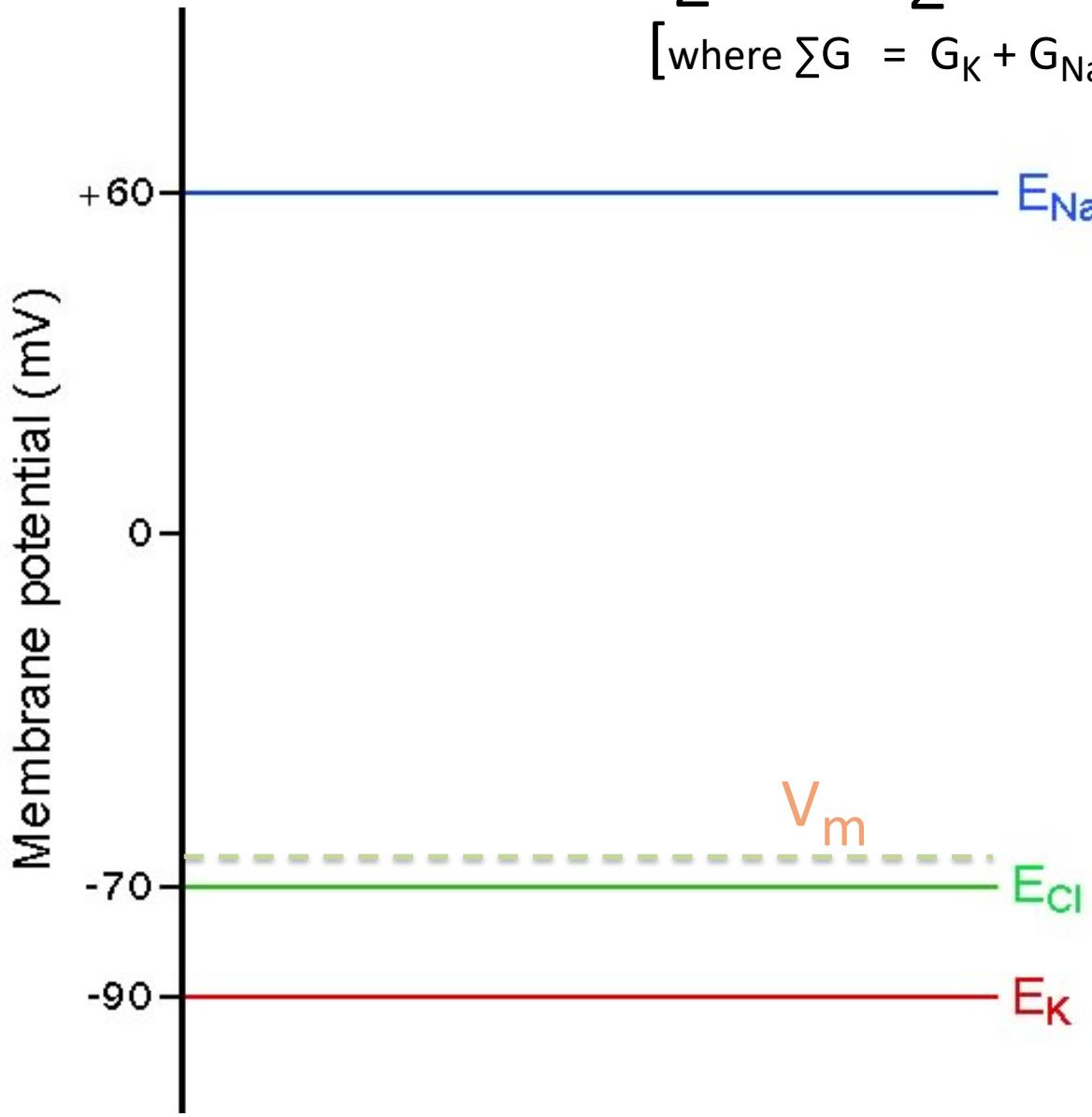
$$V_m = \frac{G_K}{\sum G} E_K + \frac{G_{Na}}{\sum G} E_{Na} + \frac{G_{Cl}}{\sum G} E_{Cl}$$

[where $\sum G = G_K + G_{Na} + G_{Cl}$]

More ion types? Just add more terms.

$$\text{Resting potential} = V_m = \frac{G_K}{\sum G} E_K + \frac{G_{Na}}{\sum G} E_{Na} + \frac{G_{Cl}}{\sum G} E_{Cl}$$

[where $\sum G = G_K + G_{Na} + G_{Cl}$]



If: $G_K = 80 \text{ nS}$
 $G_{Na} = 15 \text{ nS}$
 $G_{Cl} = 5 \text{ nS}$

then:

$$V_m = -66.5 \text{ mV}$$

and:

$$I_{Na} = -1897.5 \text{ pA}$$

$$I_{Cl} = +17.5 \text{ pA}$$

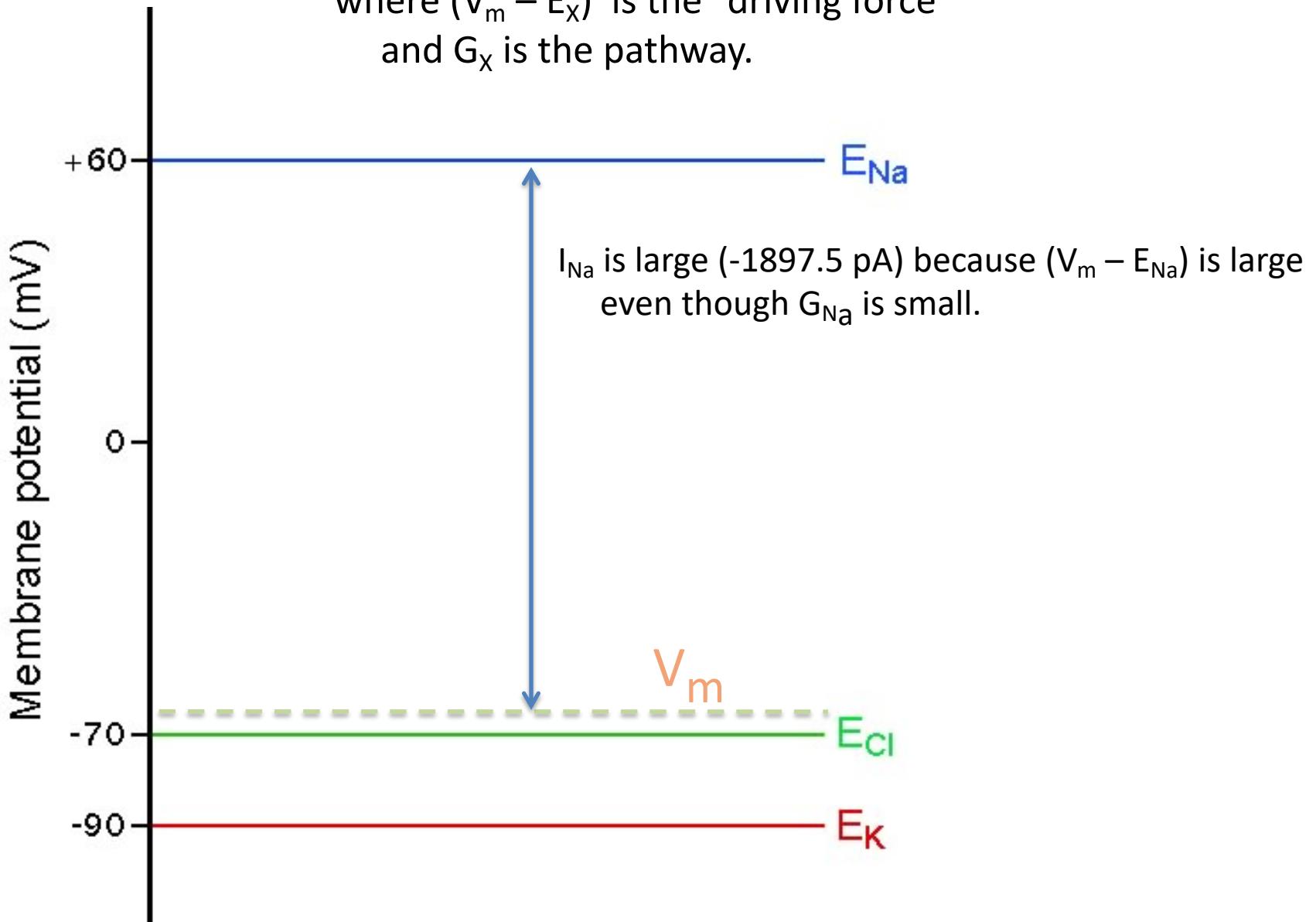
$$I_K = +1880 \text{ pA}$$

[using: $I_x = (V_m - E_x) G_x$]

$$I_x = (V_m - E_x) G_x$$

Na⁺ current

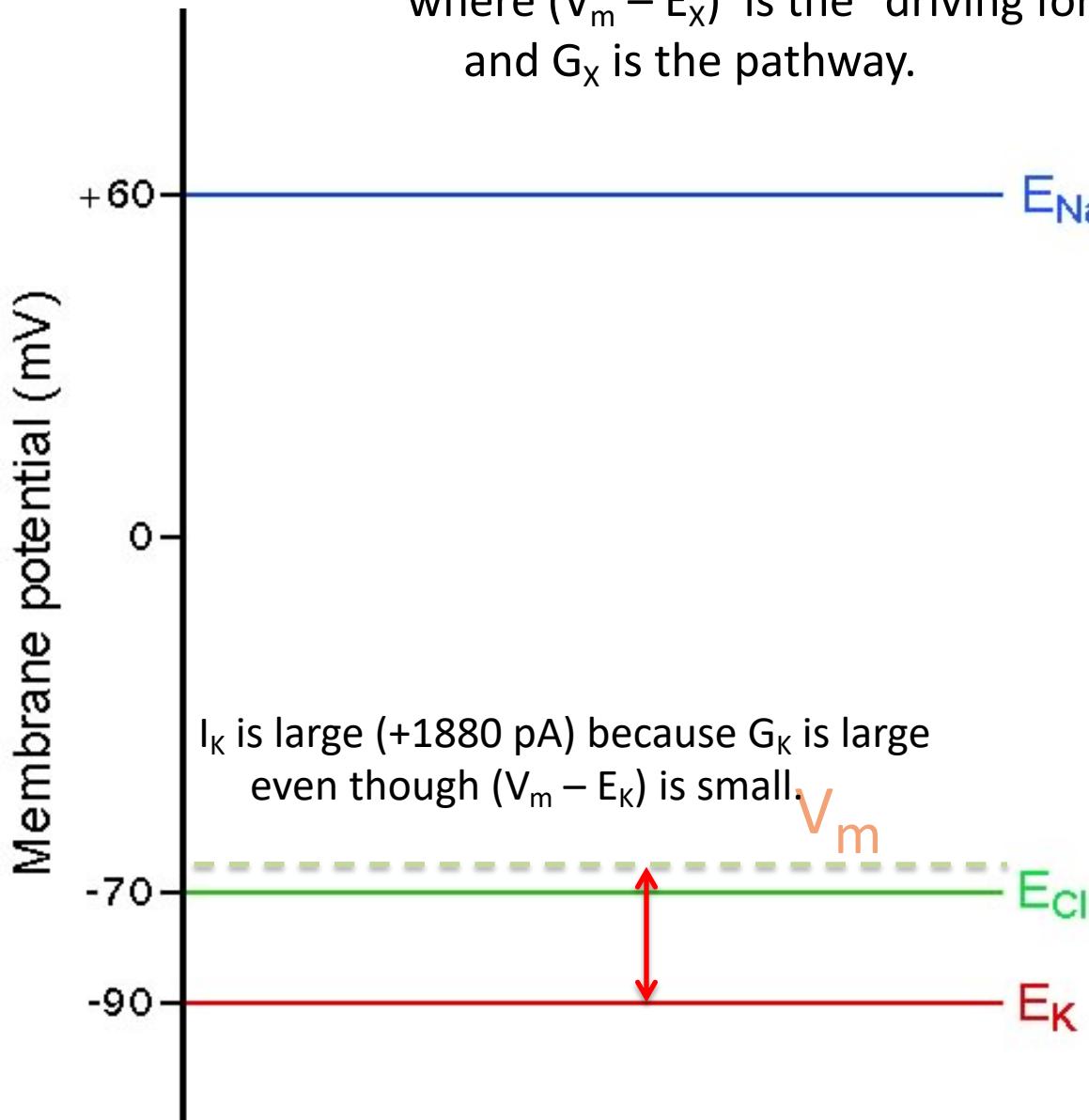
where $(V_m - E_x)$ is the “driving force”
and G_x is the pathway.



$$I_x = (V_m - E_x) G_x$$

K+ current

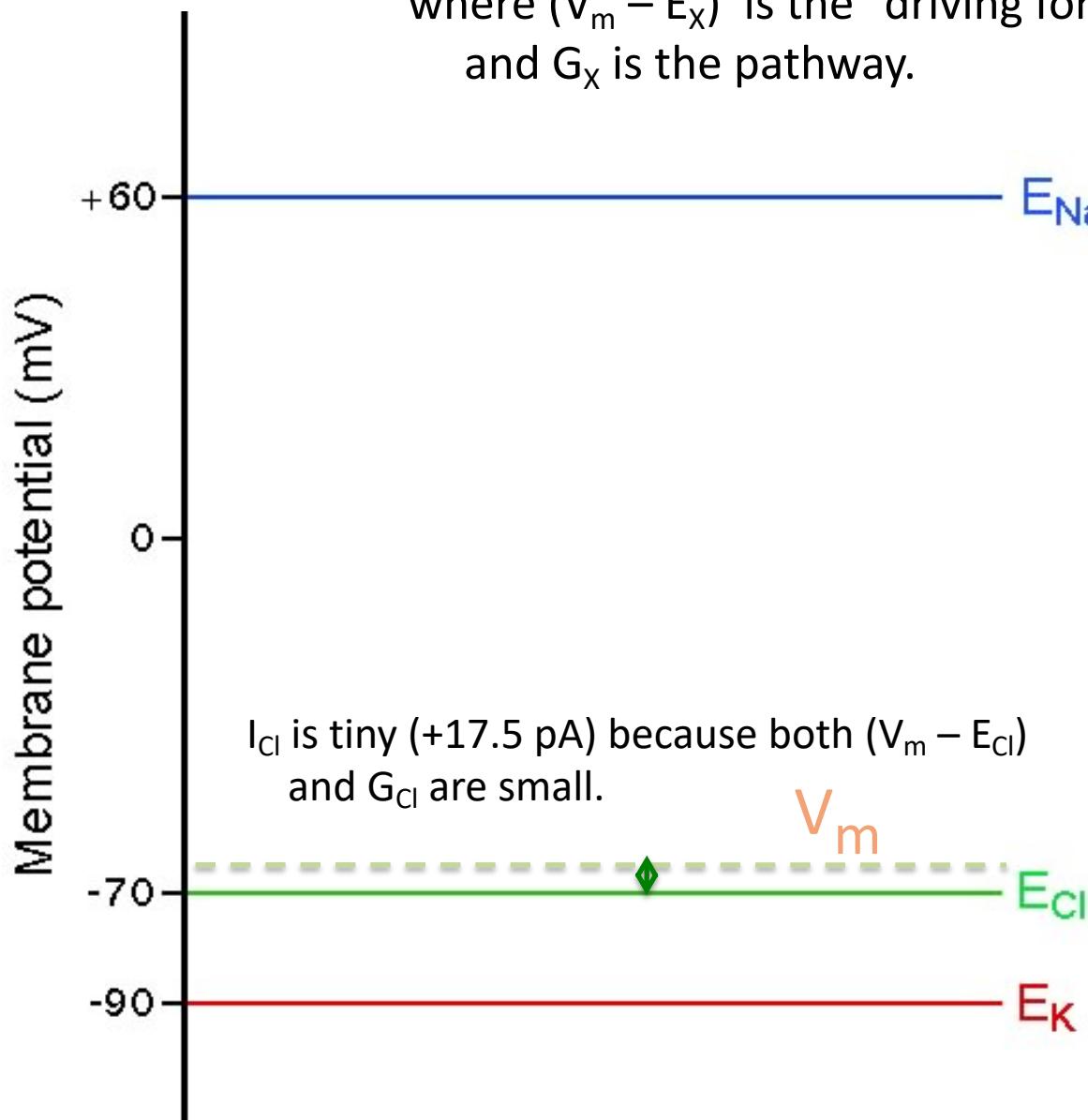
where $(V_m - E_x)$ is the “driving force”
and G_x is the pathway.



Cl⁻ current

$$I_x = (V_m - E_x) G_x$$

where $(V_m - E_x)$ is the “driving force”
and G_x is the pathway.



Equations

Ohm's Law:

$$V = IR, I = V/R$$

Nernst equation:

$$E_x = \frac{RT}{z_x F} \ln \frac{[X]_{\text{out}}}{[X]_{\text{in}}}$$

Nernst equation:

$$E_x = \frac{61}{z_x} \log \frac{[X]_{\text{out}}}{[X]_{\text{in}}}$$

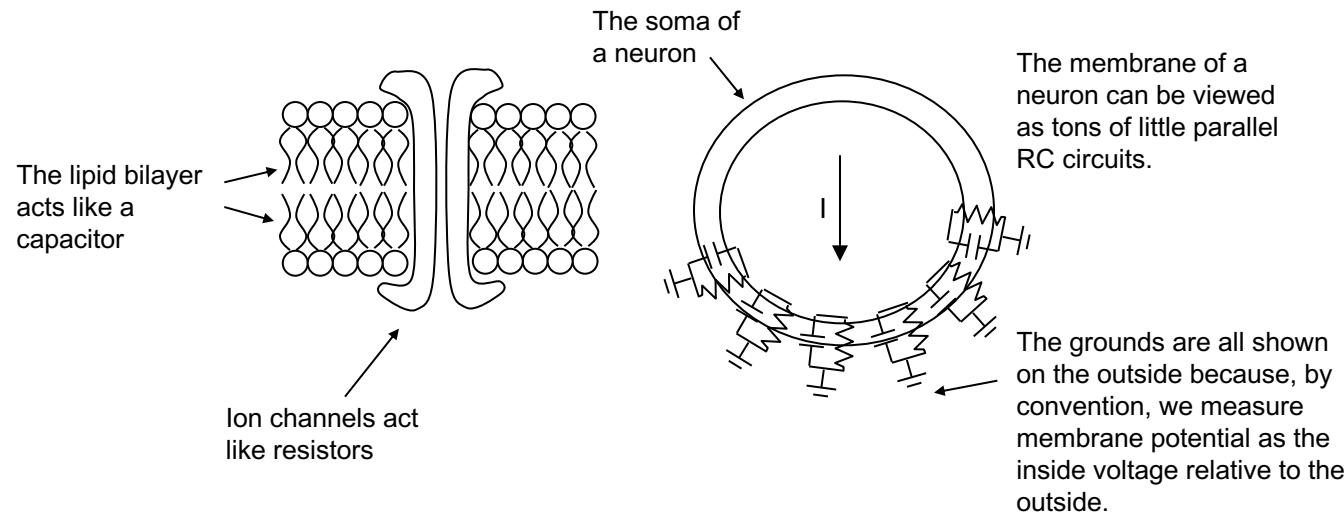
Resting potential = $V_m = \frac{G_K}{\sum G} E_K + \frac{G_{Na}}{\sum G} E_{Na} + \frac{G_{Cl}}{\sum G} E_{Cl}$

[where $\sum G = G_K + G_{Na} + G_{Cl}$]

Force-pathway equation:

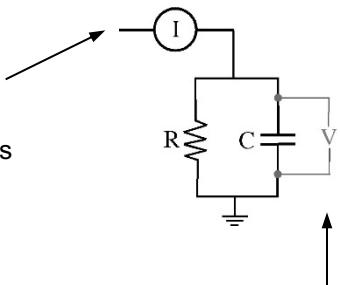
$$I_x = (V_m - E_x) G, G = 1/R$$

The cell membrane adds capacitance



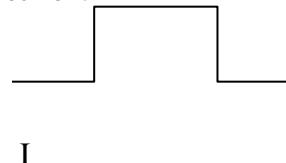
RC circuits

This means current is going into the circuit

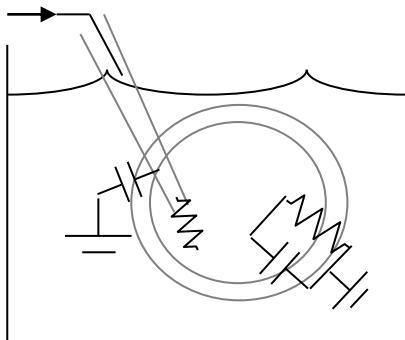
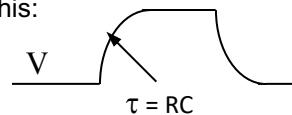


This means that voltage is being measured across the capacitor.
(NB: The voltage is the same across every element of a parallel circuit, so the same voltage drops across the resistor.)

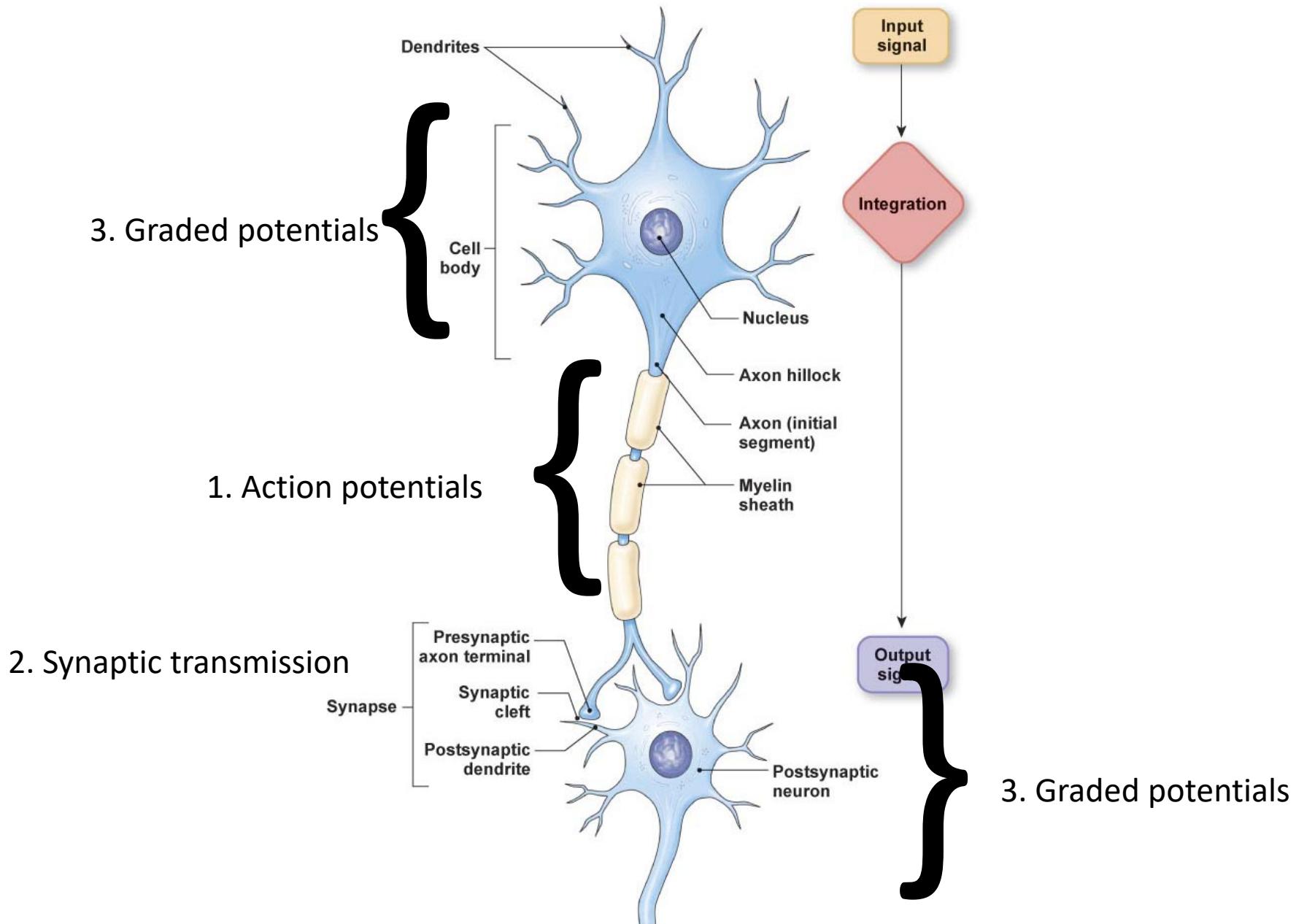
In this circuit, a current step like this:



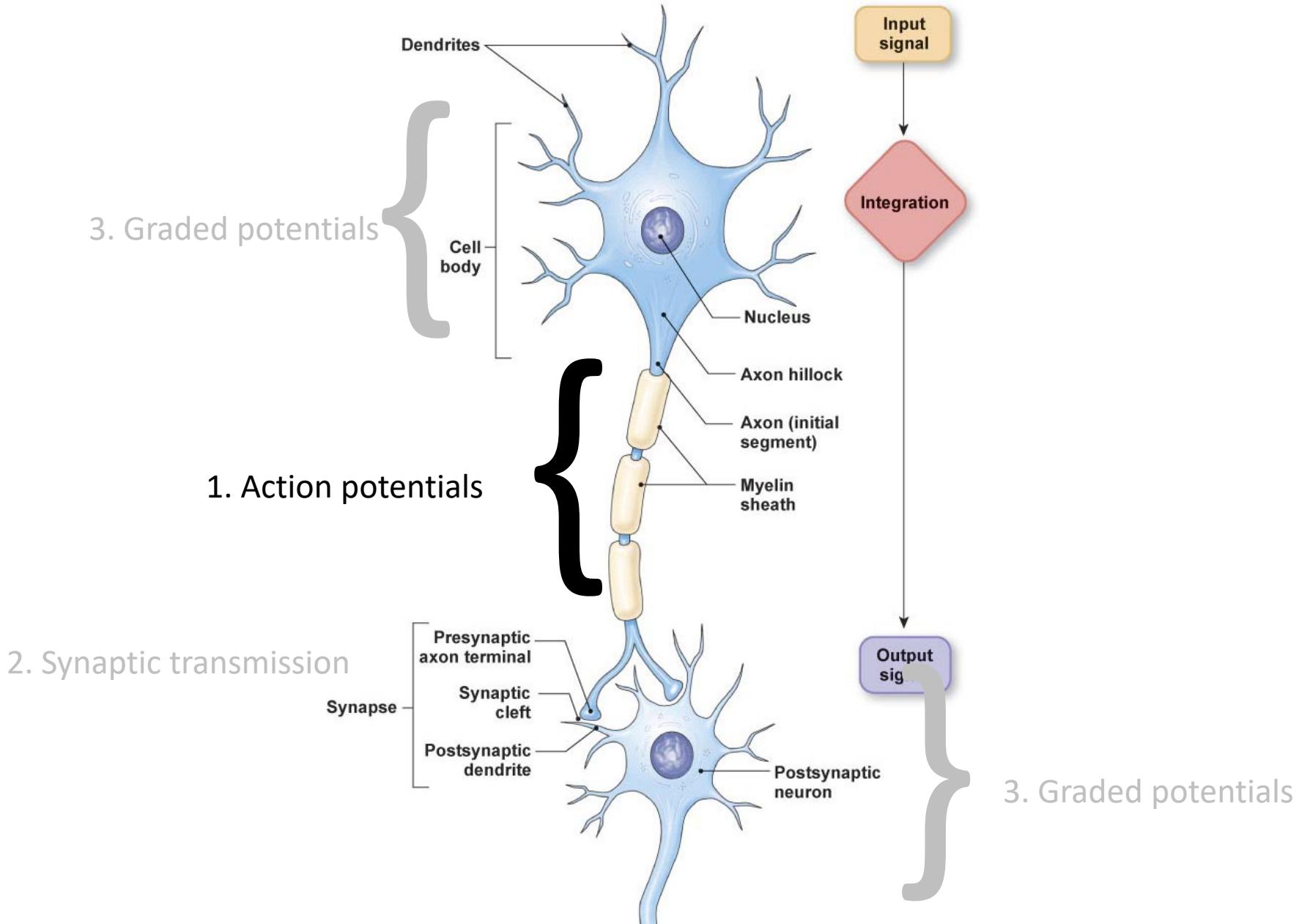
produces a voltage response like this:



Different types of propagation/transmission

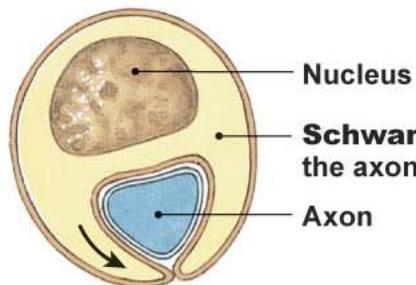


Different types of propagation/transmission

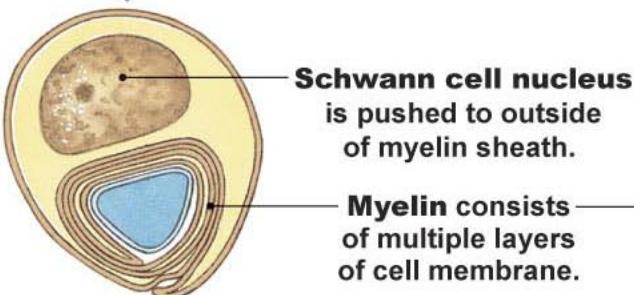
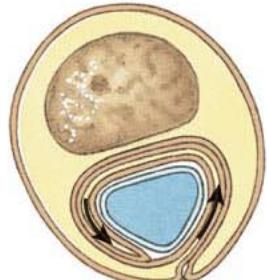


Peripheral neurons are myelinated by Schwann cells

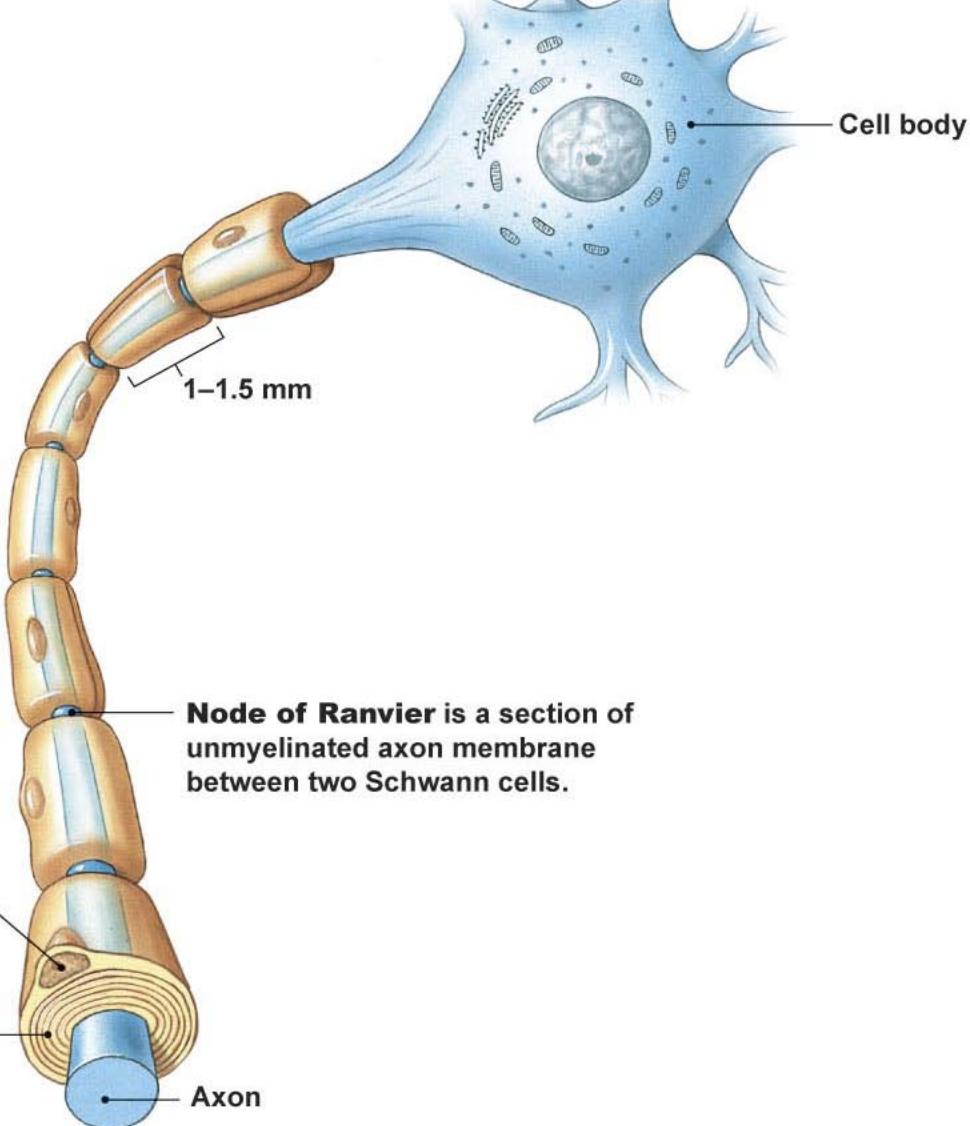
Central neurons are myelinated by oligodendrocytes



Nucleus
Schwann cell wraps around the axon many times.
Axon



(a) Myelin formation in the peripheral nervous system

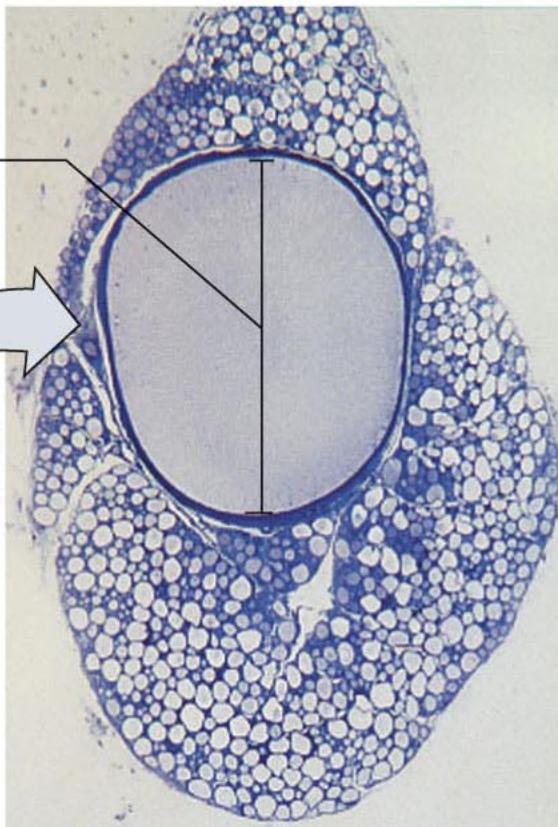


(b) Each Schwann cell forms myelin around a small segment of one axon.

Myelination allows for rapid propagation at a small axon diameter

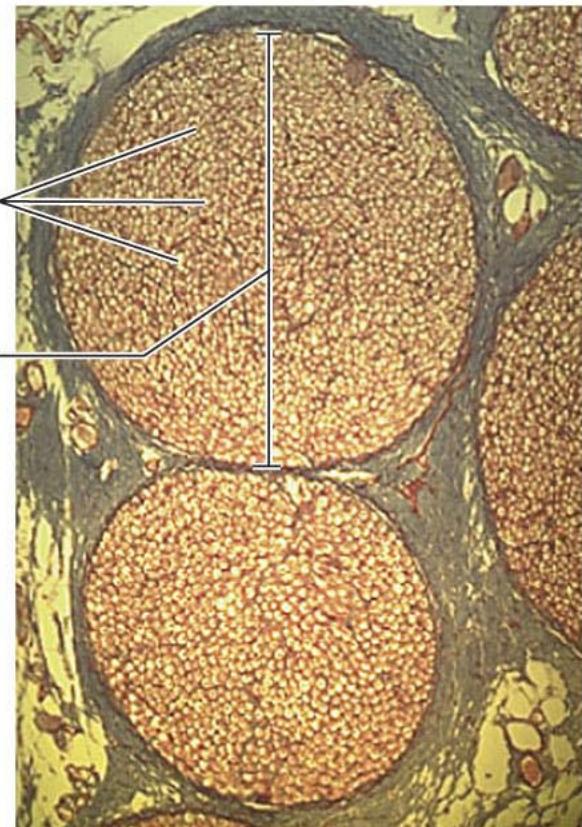
Squid giant axon

One giant axon from
a squid is 0.8 mm in
diameter

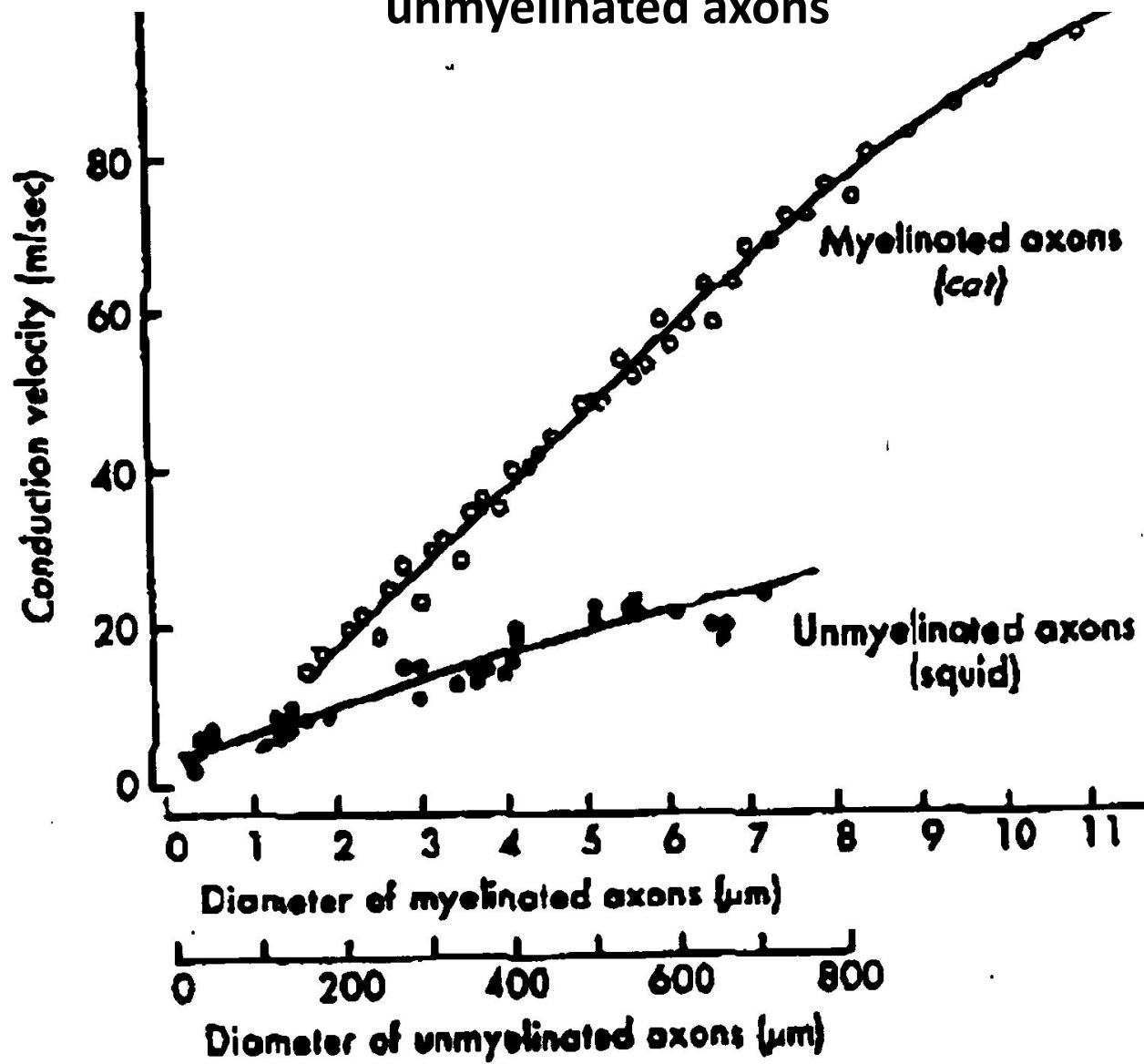


Axons

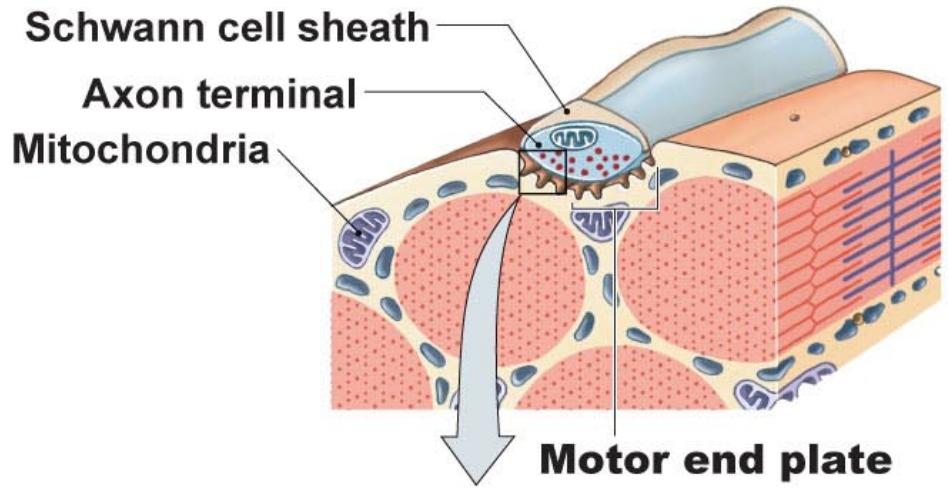
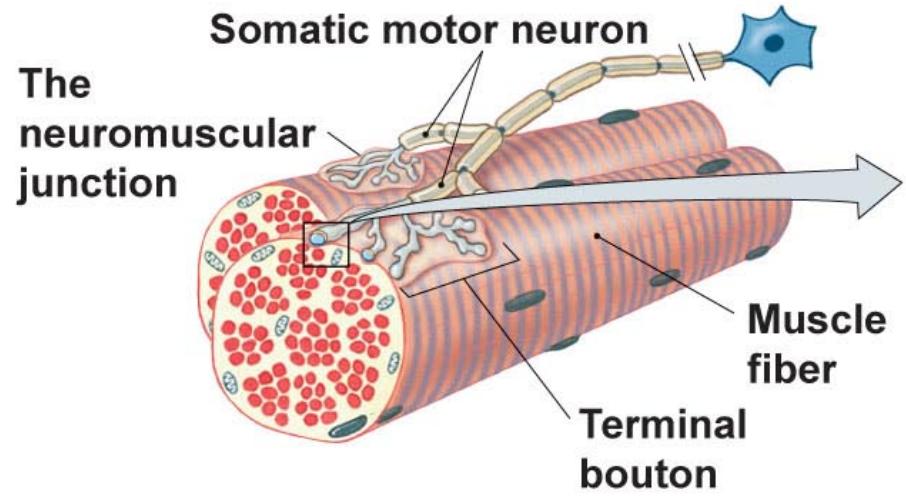
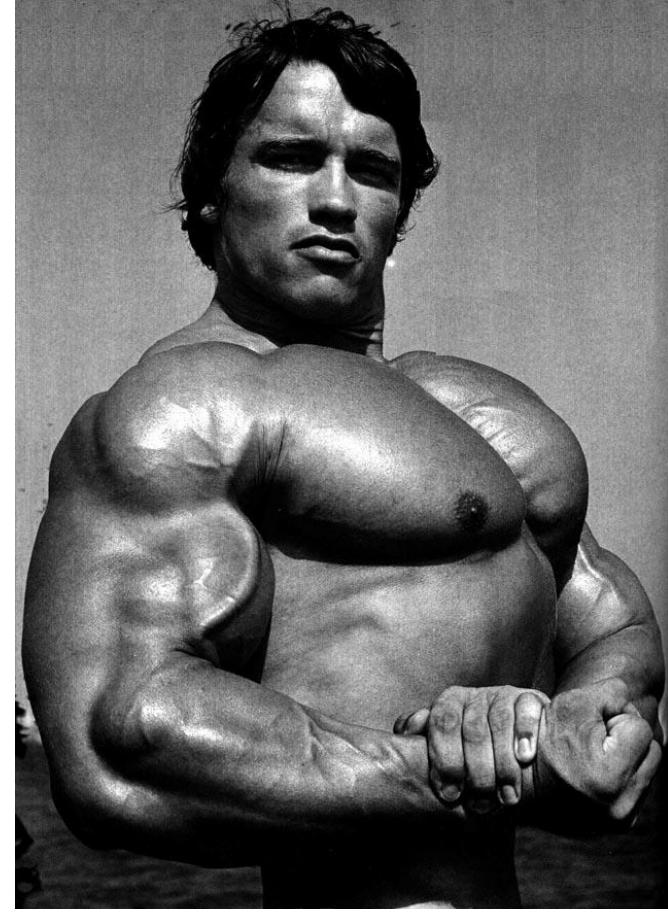
Nerve



Comparison of conduction velocity between myelinated and unmyelinated axons

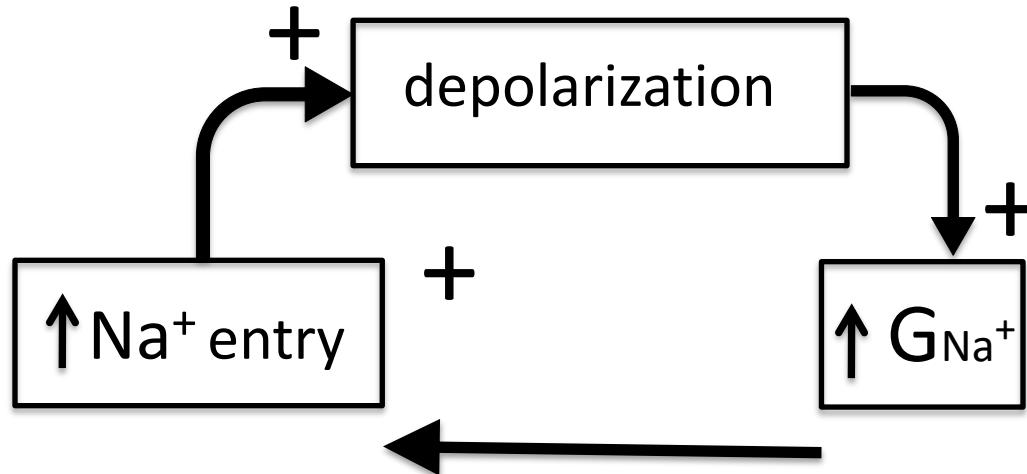


Resting membrane potential and action potentials in muscle cells



Two types of ion channels for action potential propagation

Voltage-gated Na^+ channels:

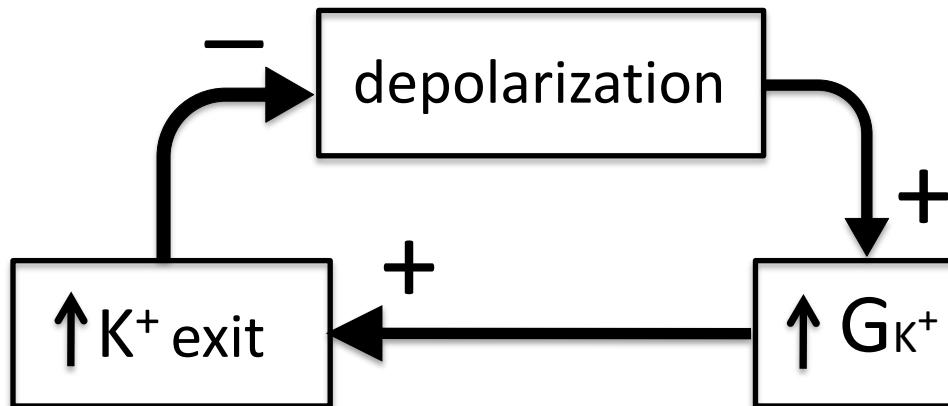


Positive feedback

- depolarizes cell to its maximum value

$$[E_{\text{Na}}]$$

Voltage-gated K^+ channels:

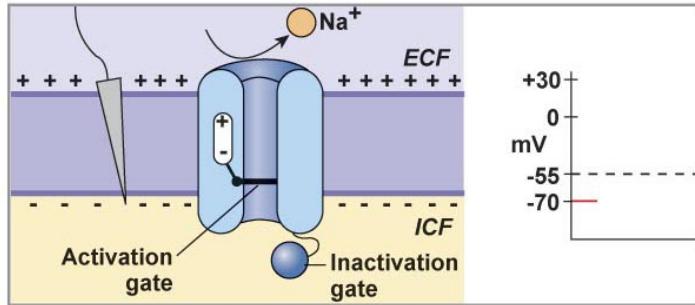


Negative feedback

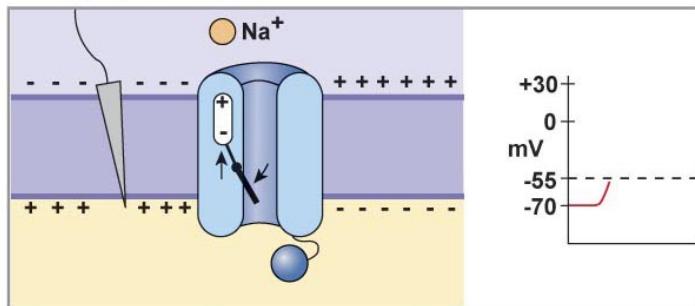
- returns to resting potential

$$[V_m]$$

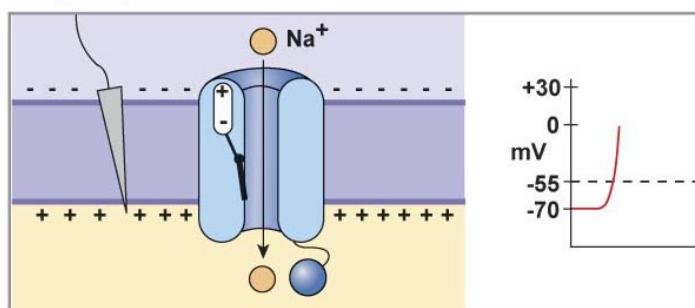
The positive feedback is terminated by the inactivation gate



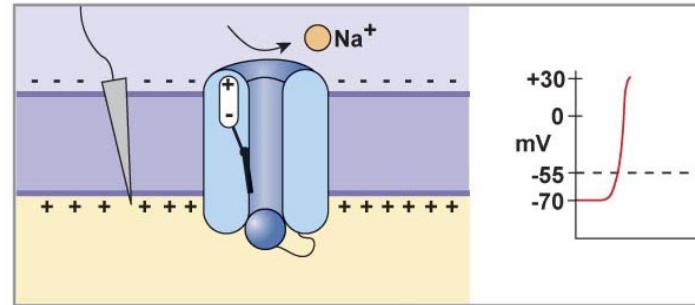
(a) At the resting membrane potential, the activation gate closes the channel.



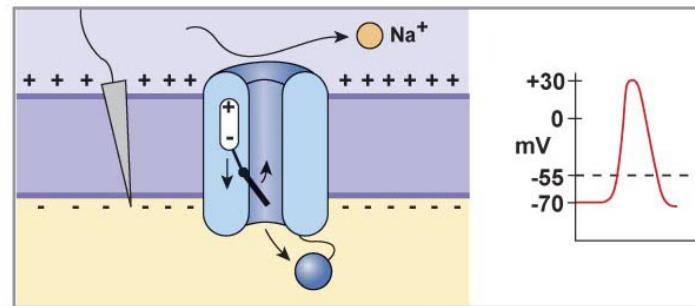
(b) Depolarizing stimulus arrives at the channel. Activation gate opens.



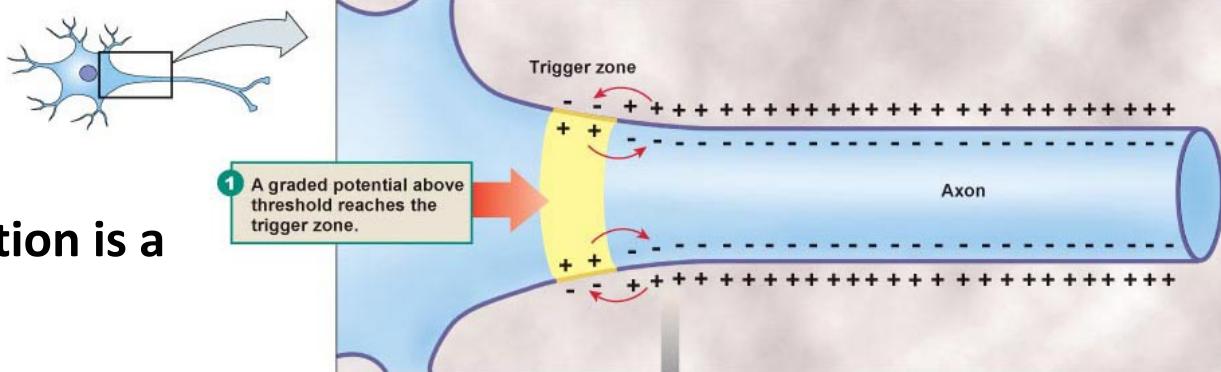
(c) With activation gate open, Na^+ enters the cell.



(d) Inactivation gate closes and Na^+ entry stops.

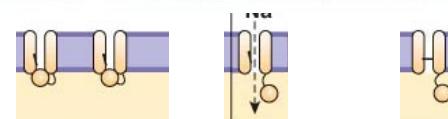
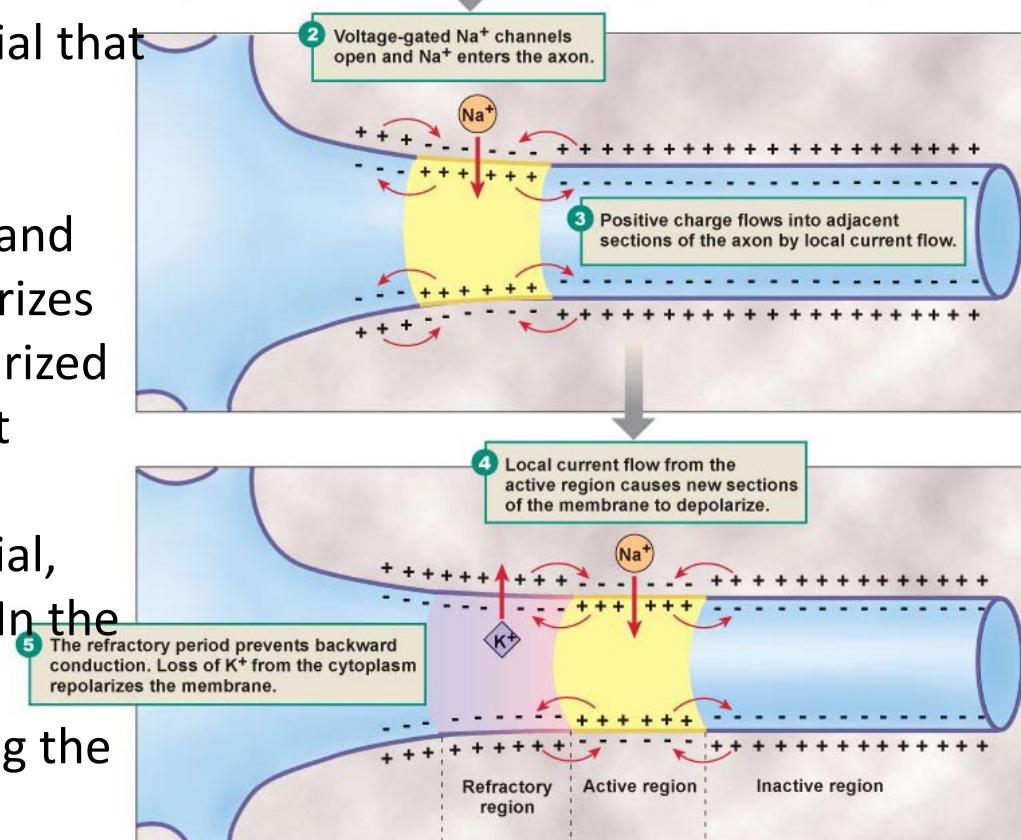


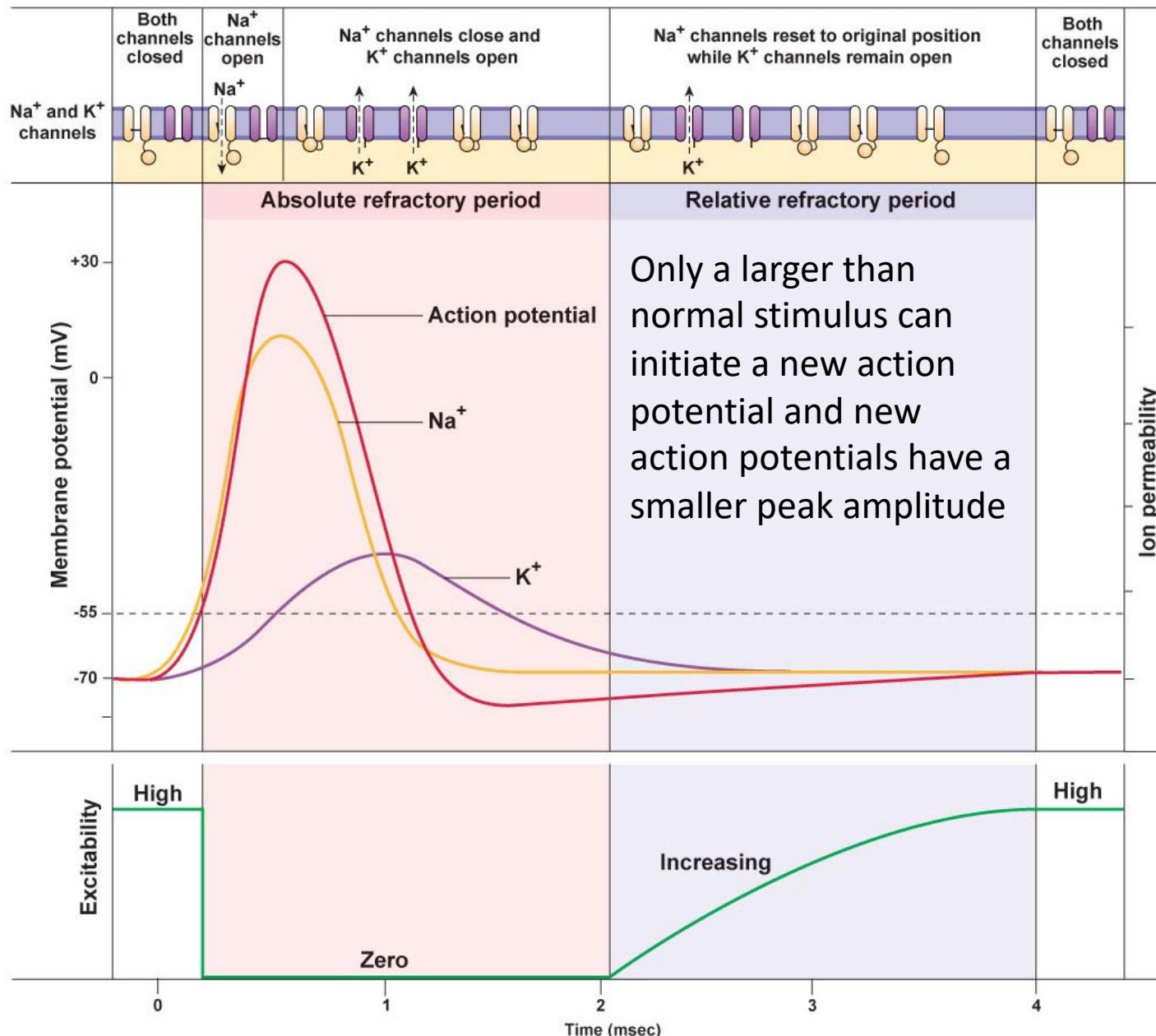
(e) During repolarization caused by K^+ leaving the cell, the two gates reset to their original positions.



Action potential propagation is a 'domino effect'.

1. The stimulus is a graded potential that enters the trigger zone
2. The depolarization opens Na^+ channels, Na^+ enters the axon, and the axon initial segment depolarizes
3. Positive charge from the depolarized trigger zone spreads to adjacent sections of the membrane
4. In advance of the action potential, the process continues with (2). In the wake of the action potential, inactivated sodium channels bring the process to an end.





ACTION POTENTIAL INITIATION

If an action potential is initiated half-way between the cell body and the action terminal, it travels

- A) towards the cell body
- B) towards the axon terminal
- C) towards the cell body and the axon terminal
- D) neither towards the cell body and nor towards the axon terminal because it cannot propagate.

Different types of propagation/transmission

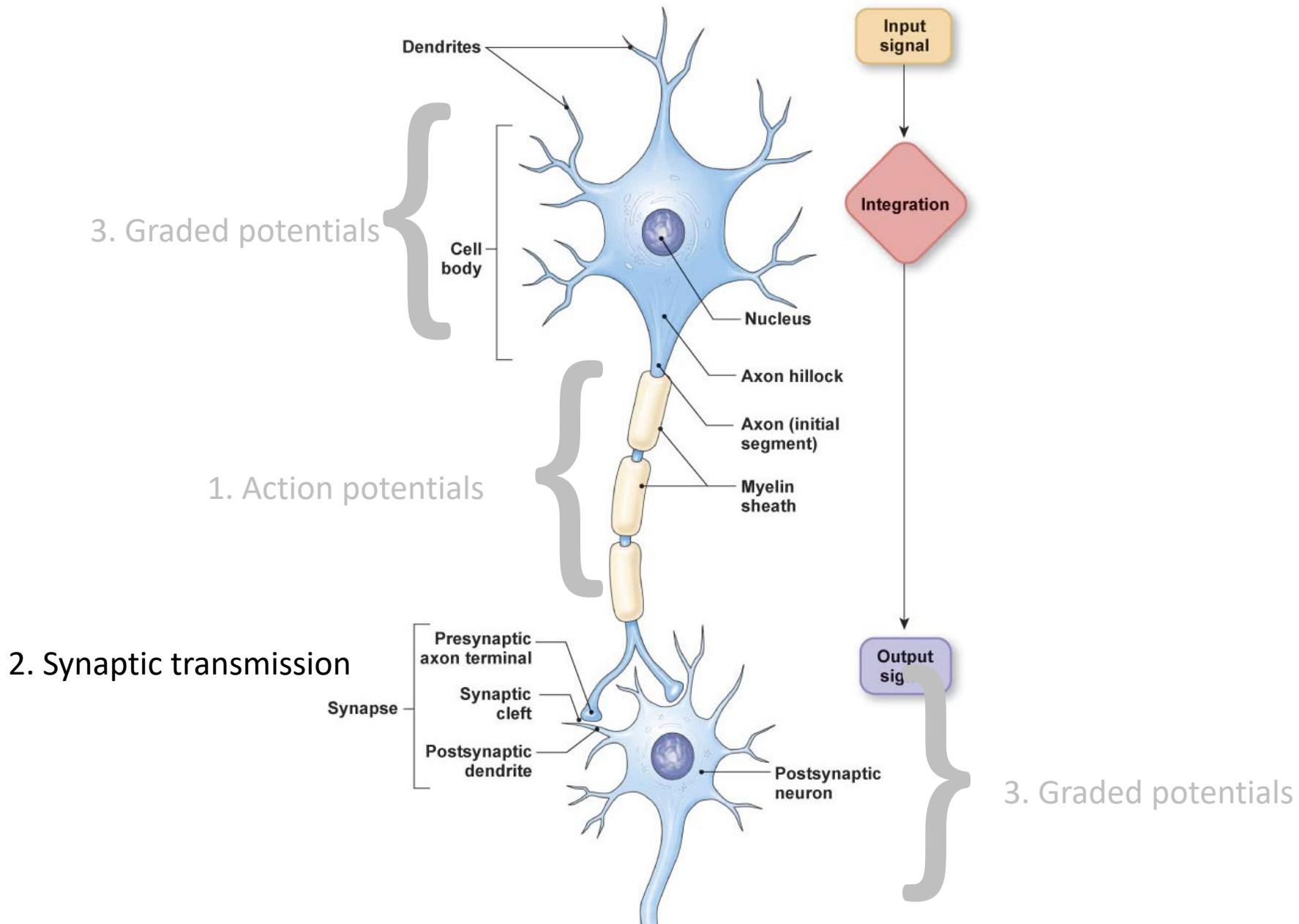
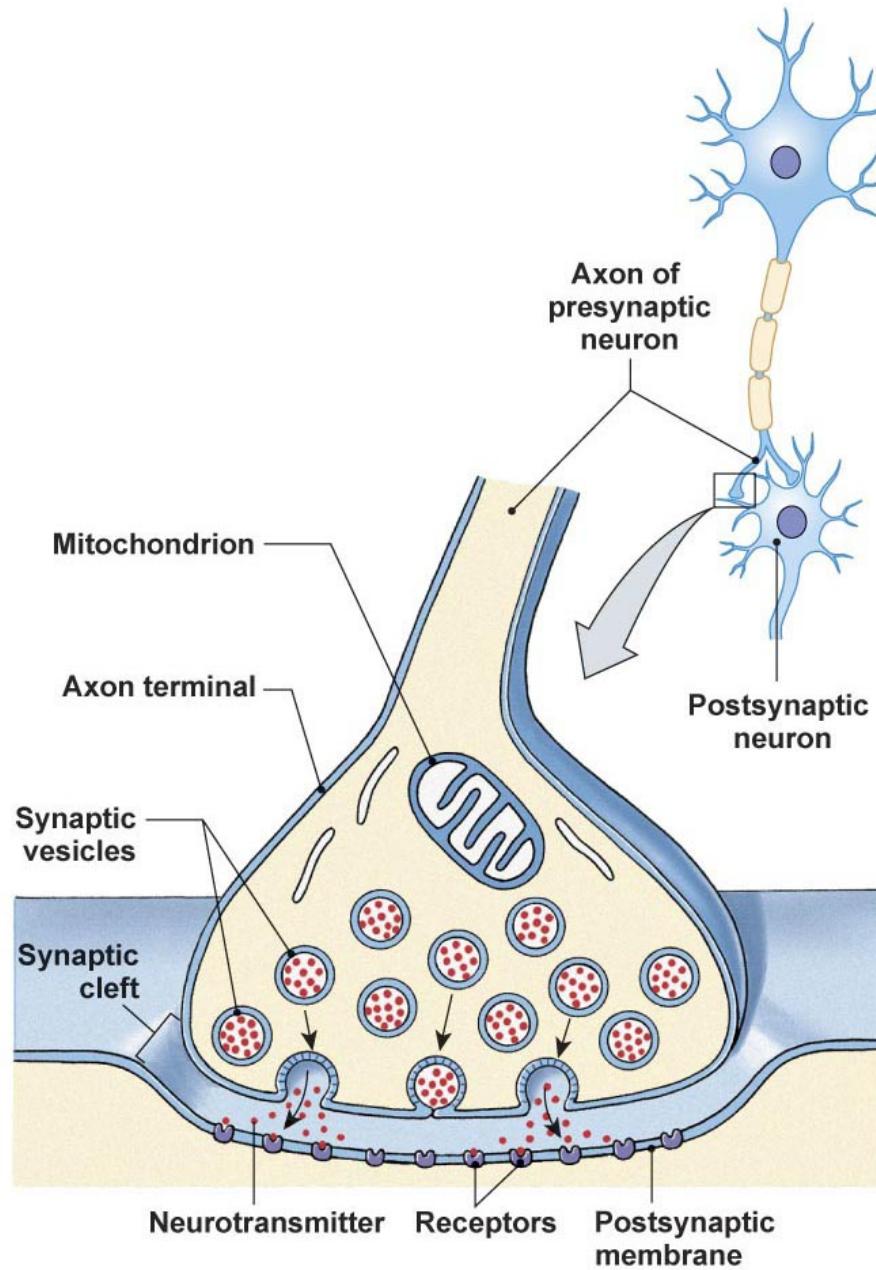
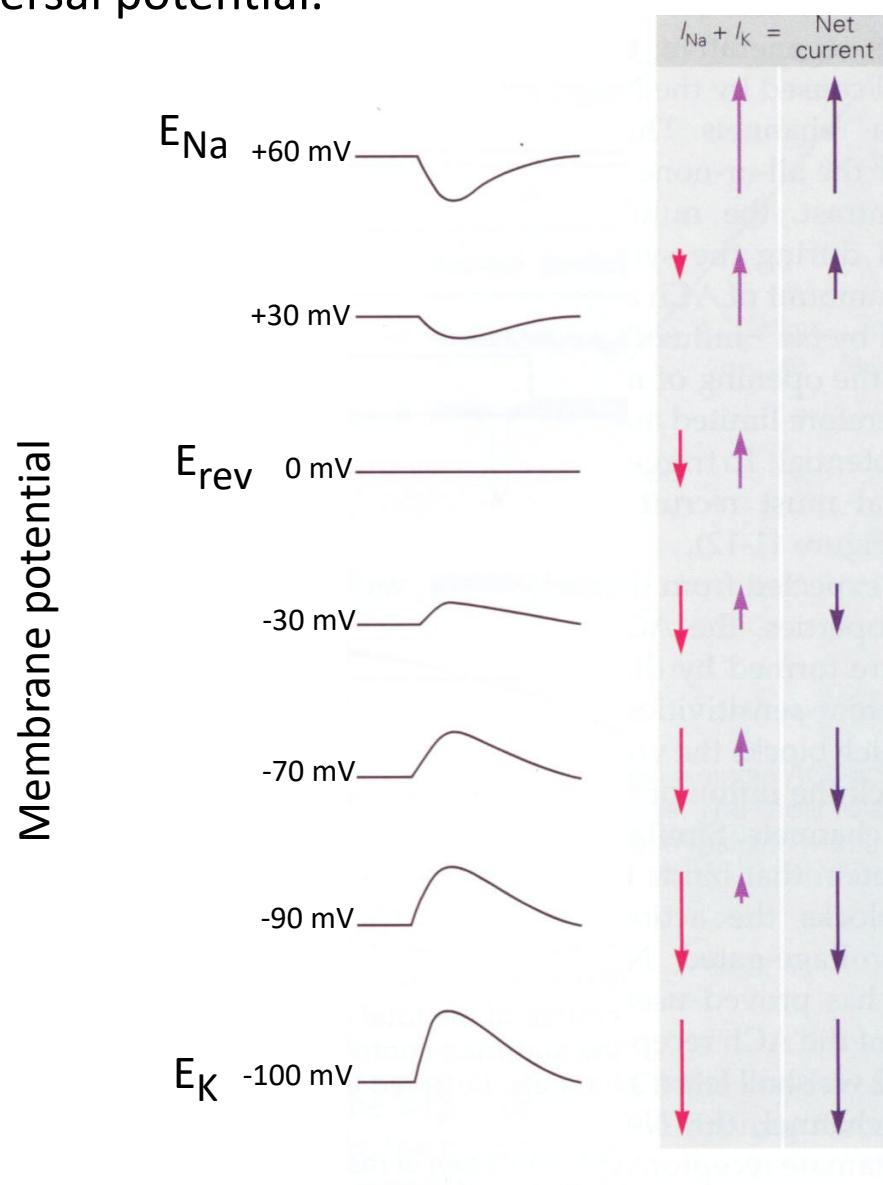


Figure 8-19
see also Fig. 8-20



Reversal potential is the potential when the net current flow through a channel reverses.

The net current is zero at the reversal potential.



If the channel is only permeable to a single type of ion (e.g., K^+) the reversal potential is equal to the equilibrium potential for the ion

Seven classes of neurotransmitters (neurocrines)

(1) Acetylcholine

(2) Amines (**made from amino acids, amino acid derivatives**)

Dopamine (dopaminergic), Norepinephrine (noradrenergic), Epinephrine (adrenergic); made from tyrosine

Serotonin; made from tryptophan

Histamine; made from histidine

(3) Amino Acids

Glutamate

Aspartate

Gamma-aminobutyric acid (GABA)

Glycine

(4) Purines

Adenosine

(5) Gases

NO (nitric oxide)

(6) Peptides

(7) Lipids

Eicosanoids; ligands for the cannabinoid receptor

Examples of receptor types

Acetylcholine

Nicotinic (ionotropic; monovalent cation channels)

Muscarinic (metabotropic; coupled to G-proteins and linked to second messenger systems), e.g., opens K⁺ channel AND/OR opens Cl⁻ channel

Norepinephrine (noradrenergic)

Alpha-receptors (metabotropic; coupled to G-proteins and linked to second messenger systems)

alpha 1 – activate phospholipase C, increase in inositol triphosphate (IP3) and diacylglycerol (DAG)

alpha 2 – inhibit adenylyl cyclase, decrease in cAMP

Beta-receptors (metabotropic; coupled to G-proteins and linked to second messenger systems) – increase in cAMP

Glutamate

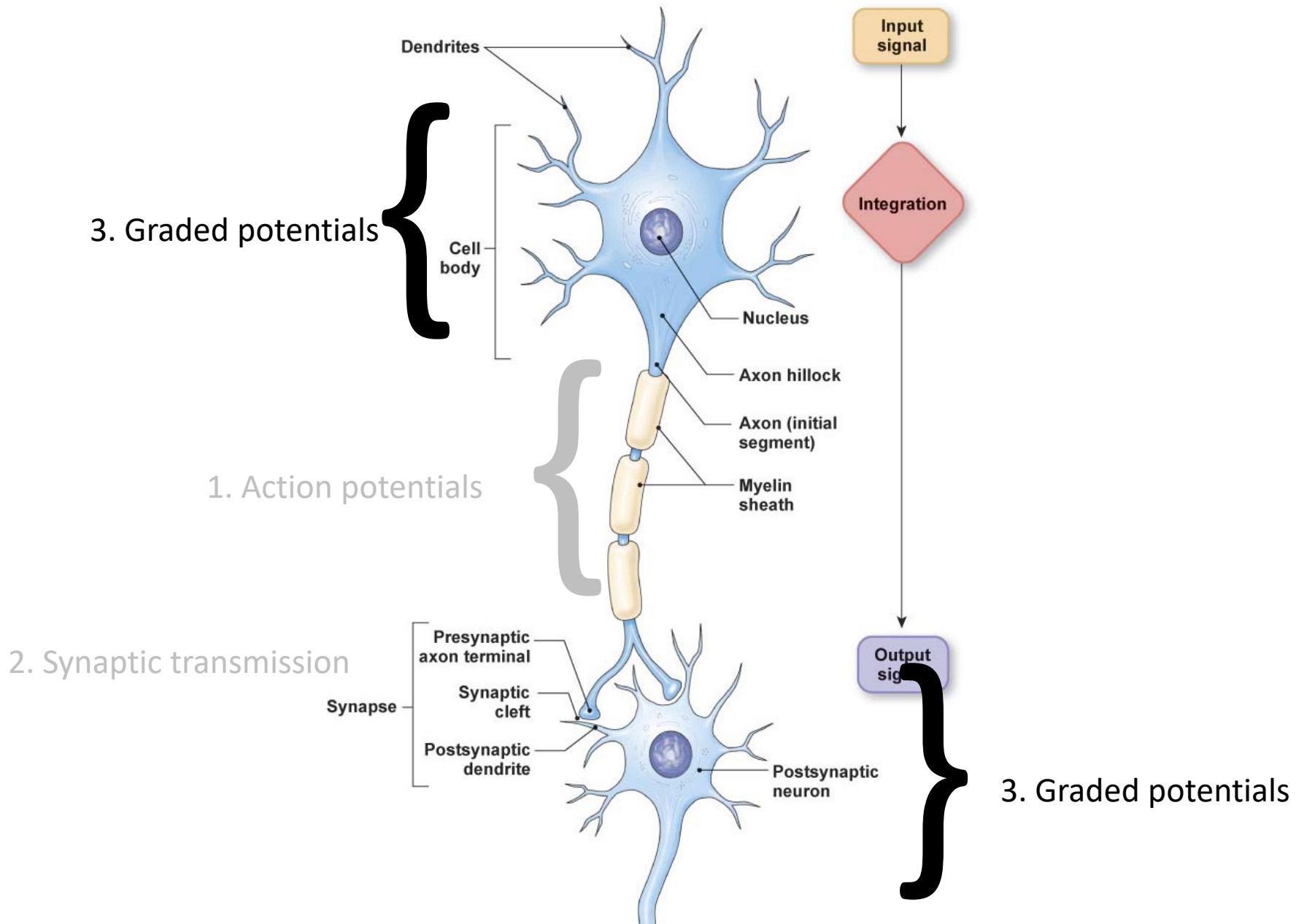
Metabotropic glutamate receptors (G-protein coupled receptors)

Ionotropic glutamate receptors

AMPA-receptors (ligand gated monovalent cation channels)

NMDA-receptors (cation channels; **require both glutamate binding and a change in membrane potential**; blocked by Mg⁺⁺ at resting membrane potentials)

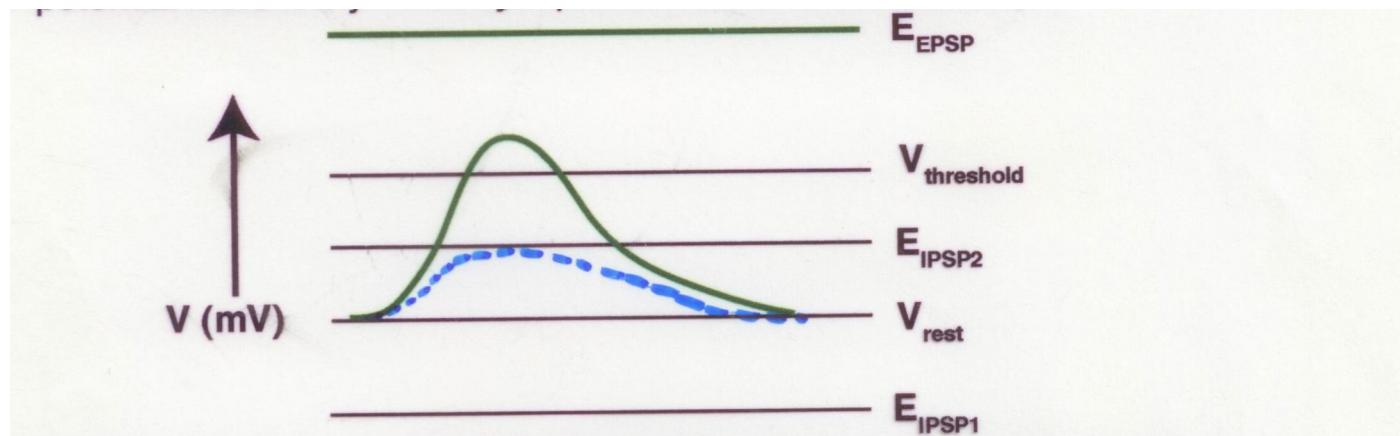
Different types of propagation/transmission



Postsynaptic potentials depend on the channels that are opened

Monovalent cation channel, Excitatory:

Reversal potential (E_{EPSP}) is more positive than the threshold potential ($V_{threshold}$)

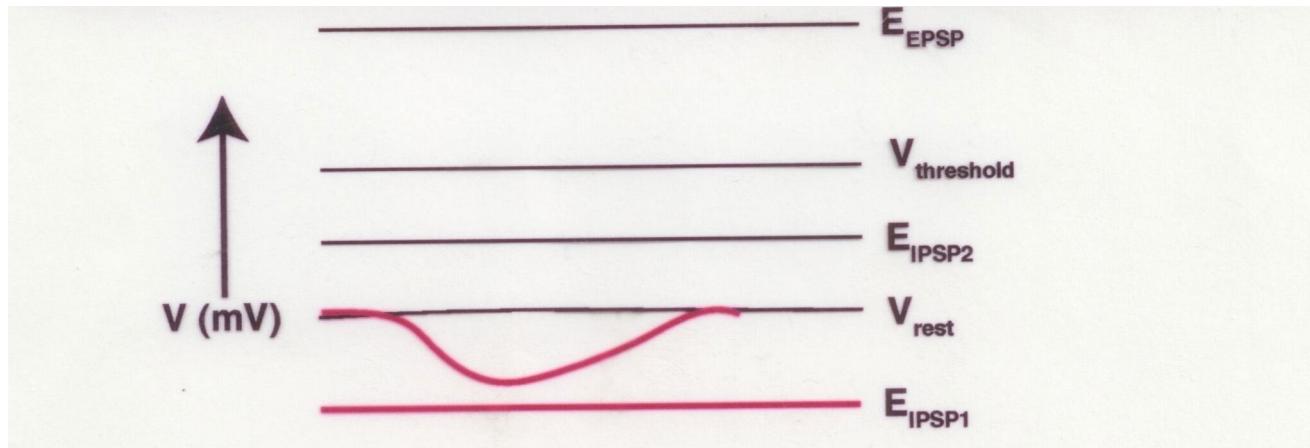


Green line: excitatory PSP (EPSP), depolarizing

Postsynaptic potentials depend on the channels that are opened

K⁺ channel, inhibitory:

Reversal potential (E_{IPSP}) is more negative than the threshold potential ($V_{threshold}$)

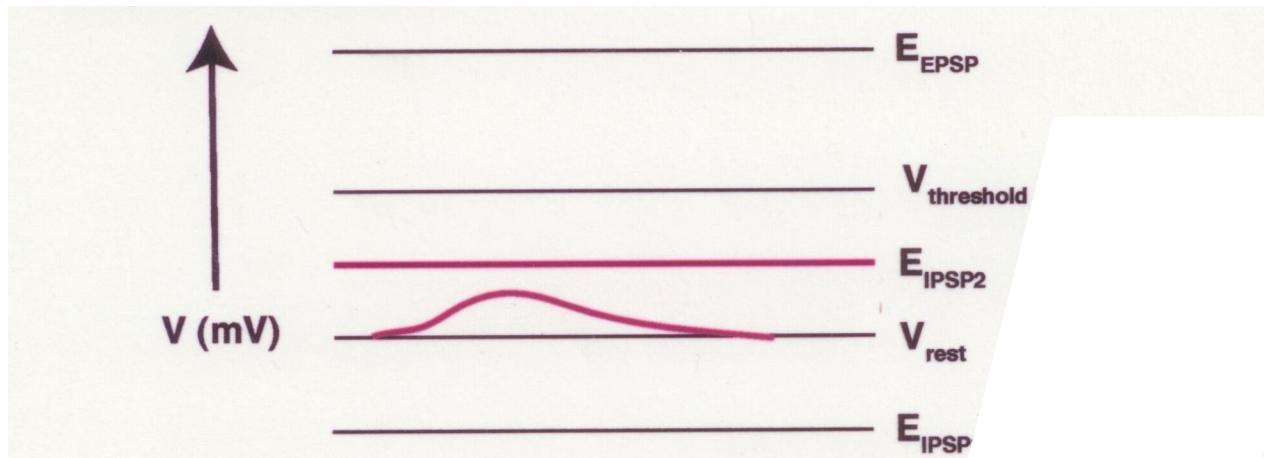


Red line: inhibitory PSP (IPSP), hyperpolarizing

Postsynaptic potentials depend on the channels that are opened

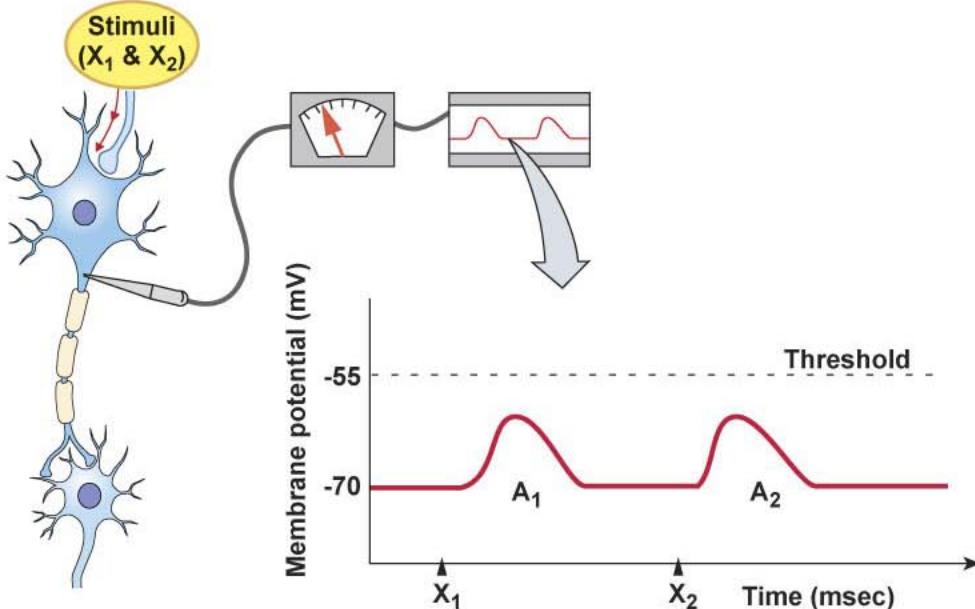
Cl⁻ channel, inhibitory:

Reversal potential (E_{IPSP}) is more negative than the threshold potential ($V_{threshold}$)

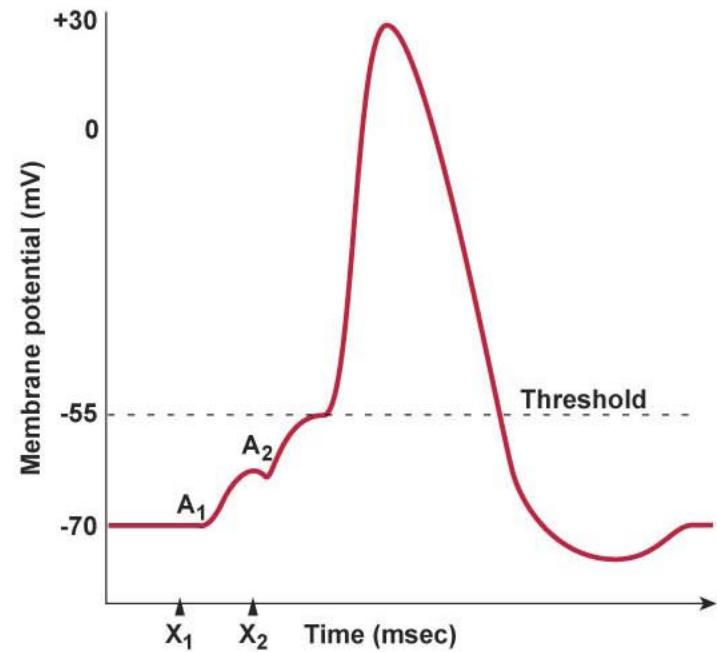


Red line: inhibitory PSP (IPSP), ?polarizing

Successive PSPs at the same synapse can combine to result in a summed PSP



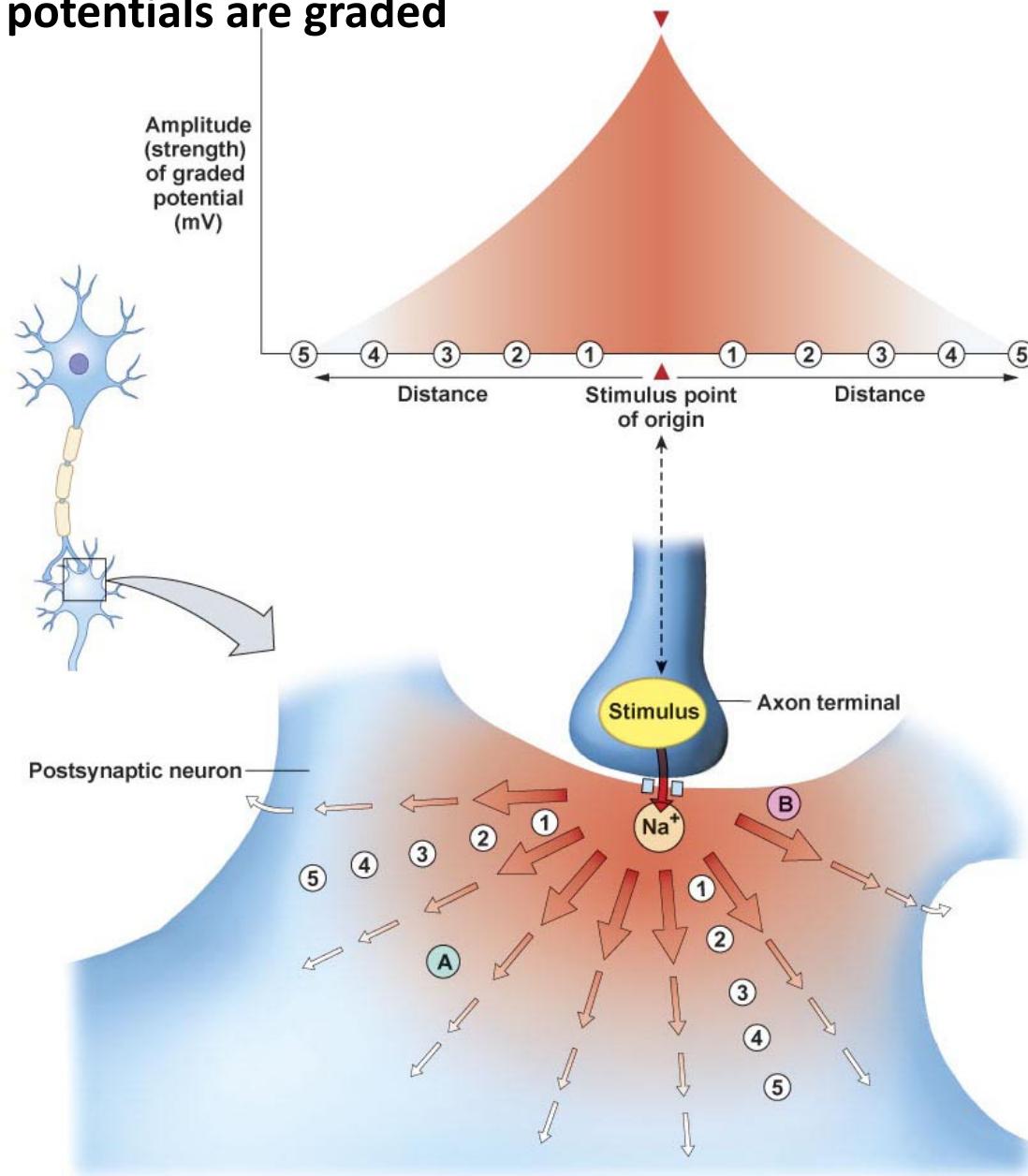
(a) No summation. Two subthreshold graded potentials will not initiate an action potential if they are far apart in time.



(b) Summation causing action potential. If two subthreshold potentials arrive at the trigger zone within a short period of time, they may sum and initiate an action potential.

Figure 8-24

Postsynaptic potentials are graded



Simultaneous PSP at different synapses combine to result in a summed PSP

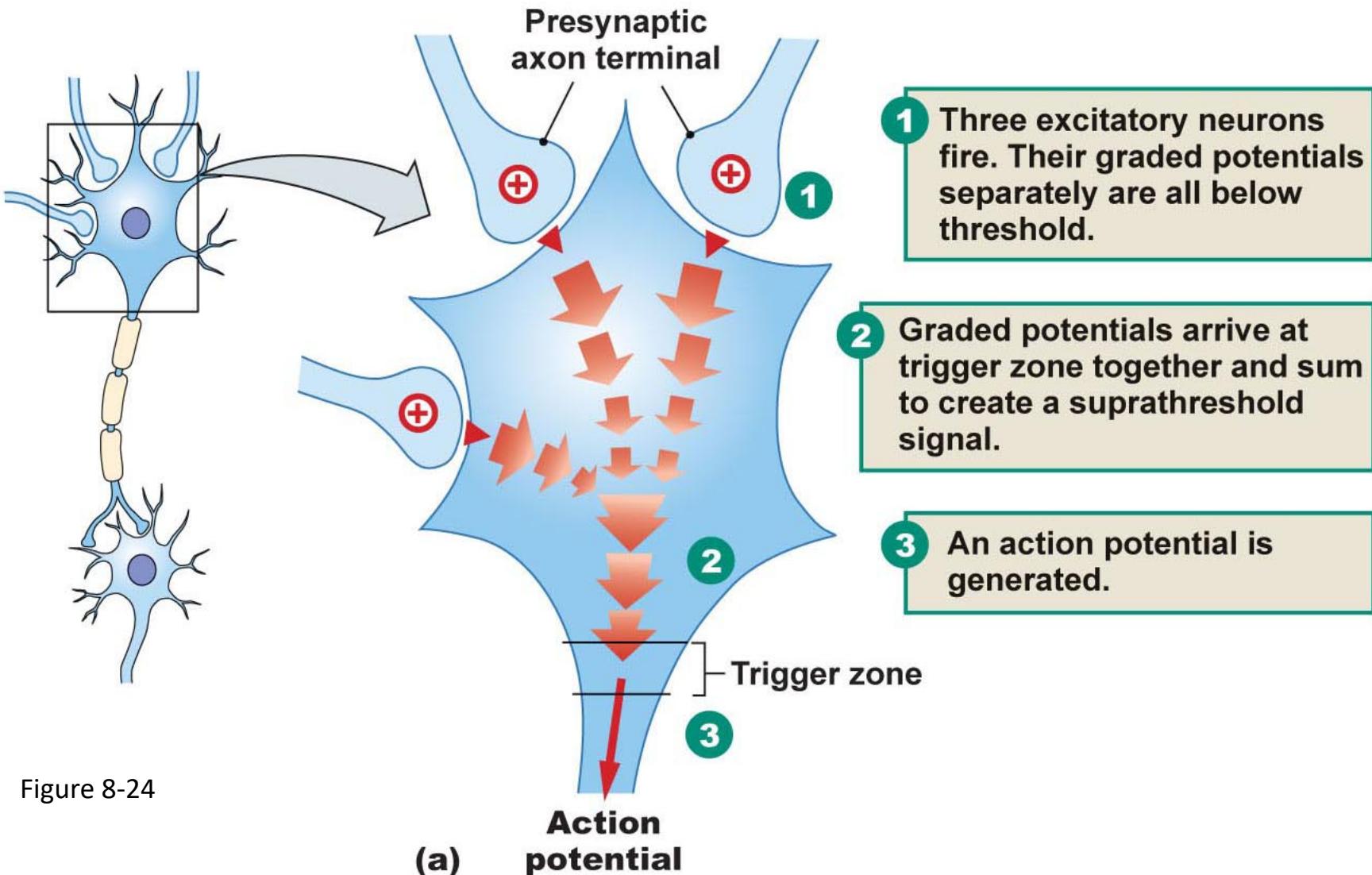
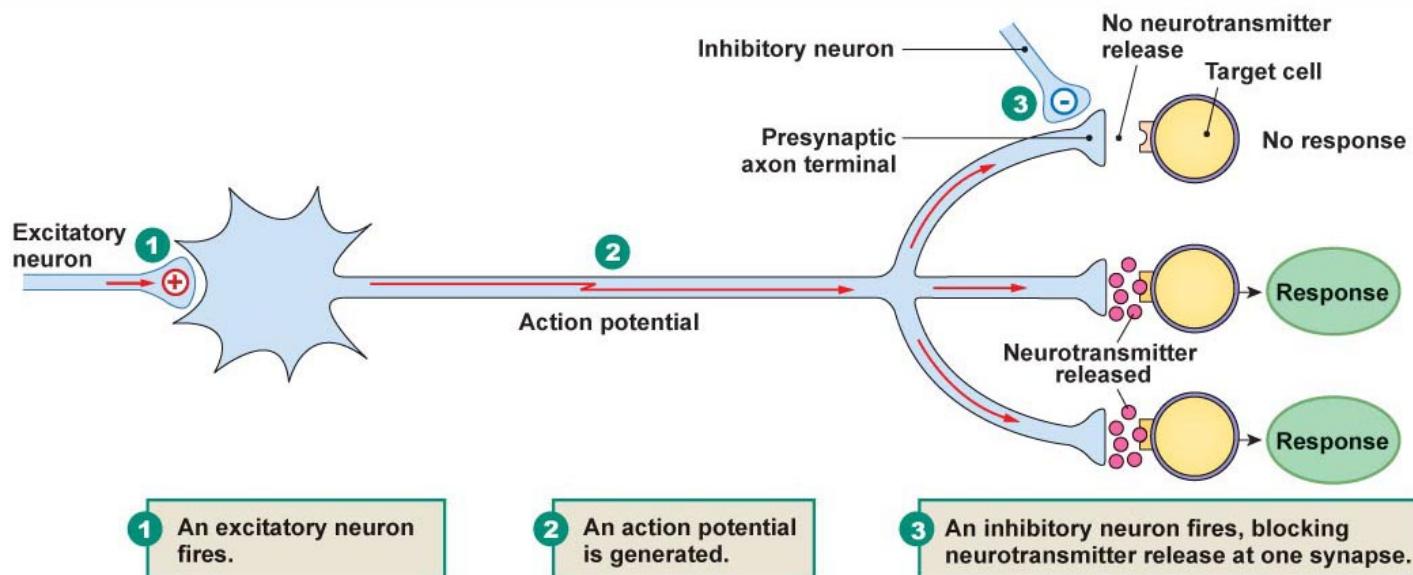


Figure 8-24

Inhibitory PSPs subtract from the excitatory PSPs

(a) Presynaptic inhibition



(b) Postsynaptic inhibition

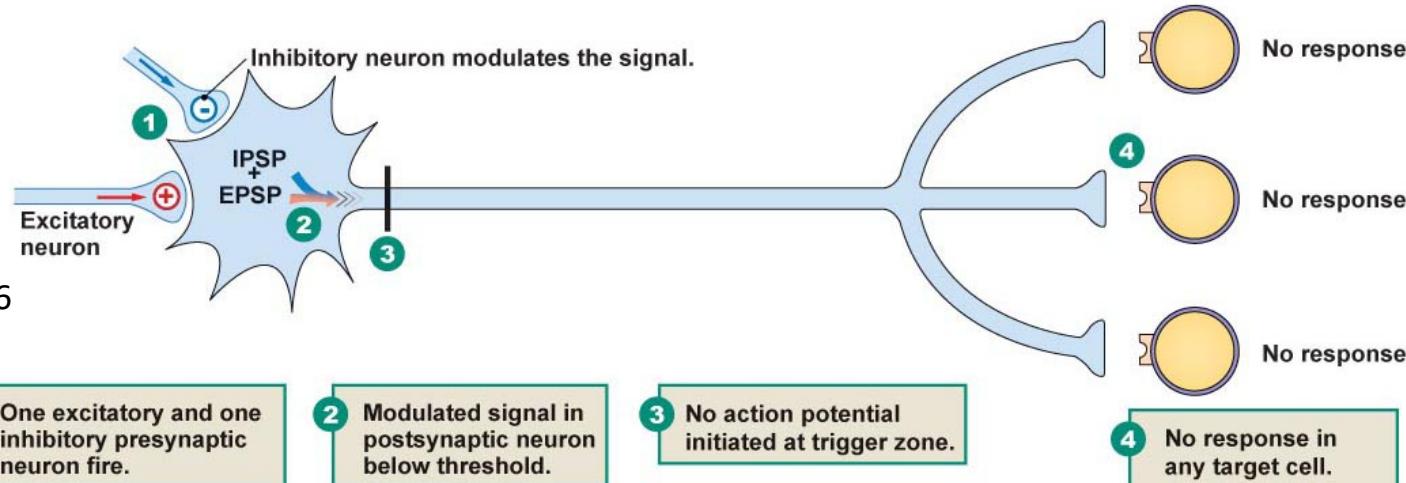


Figure 8-26