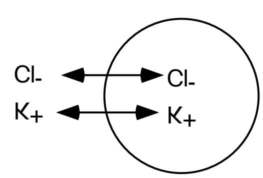
Membrane Potentials, Action Potentials, and Synaptic Transmission

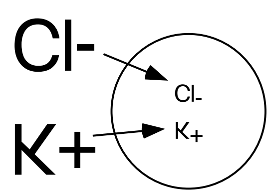
Core Curriculum II

Spring 2015

Membrane Potential

Example 1: K^+, Cl^- equally permeant
no charge imbalance, so V_m=0

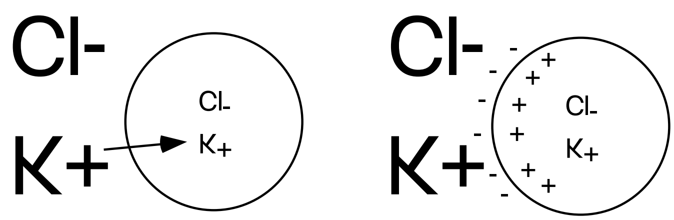




Membrane Potential

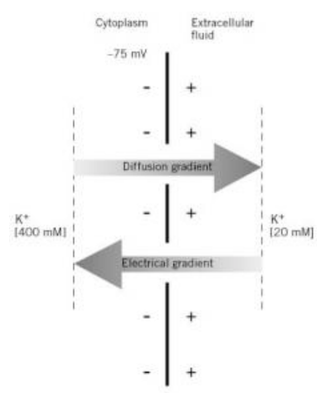
Example 2: only K^+ is permeant

Charge imbalance is set up, leading to a membrane potential (positive inside)



Membrane Potential

- Concentration gradient makes K^+ "want" to leave cell



Membrane Potential

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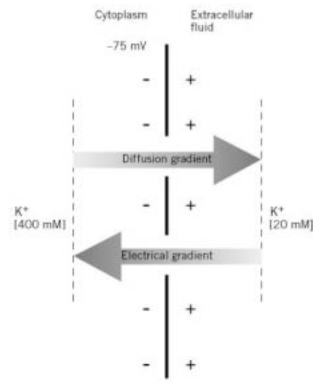
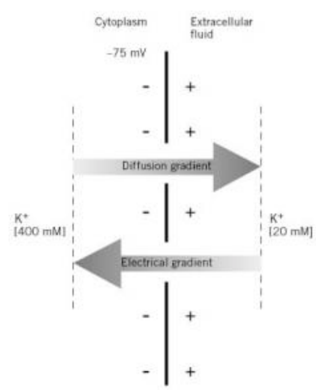
- Electrical gradient makes K^+ "want" to enter cell



Membrane Potential

- Concentration gradient makes K^+ "want" to leave cell
- Electrical gradient makes K^+ "want" to enter cell
- At equilibrium these forces balance out and there is no net movement



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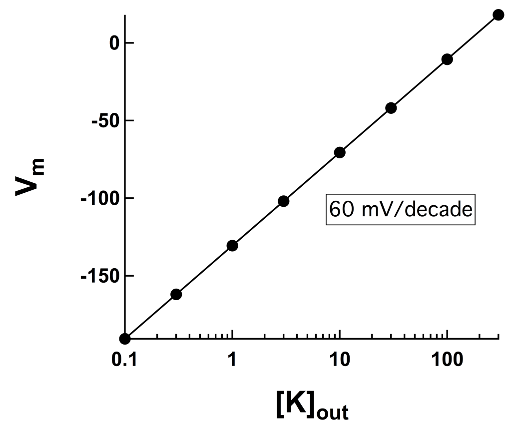
- Membrane potential set up exactly counterbalances the diffusion-driven movement of ions across the membrane
- There will be no <u>net</u> movement of ions across the membrane
- This membrane potential is often termed a *diffusion potential, equilibrium potential,* or *Nernst potential*

Nernst Potential

$$E_x = -\frac{RT}{zF}\ln\frac{[X_i]}{[X_o]}$$

$$E_x = \frac{-60mV}{z}\log\frac{[X_i]}{[X_o]}$$

Nernst Potential



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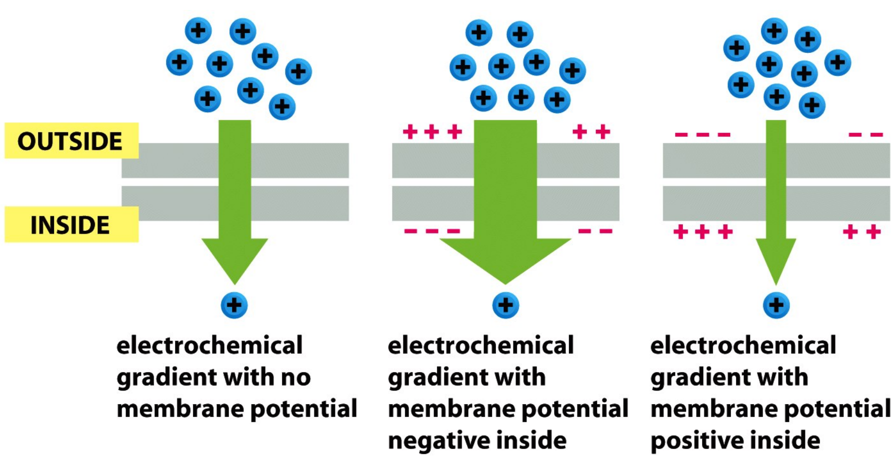
- $I_x = g_x(V_m - E_x)$ $[g_x \alpha P_x]$
- Because the charge affects things, we often refer to an "electrochemical gradient"

Driving Force



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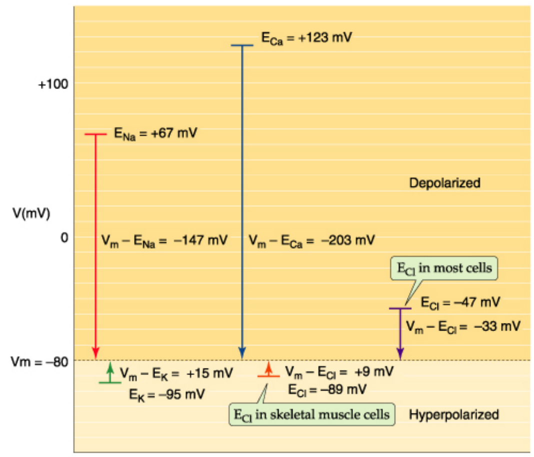

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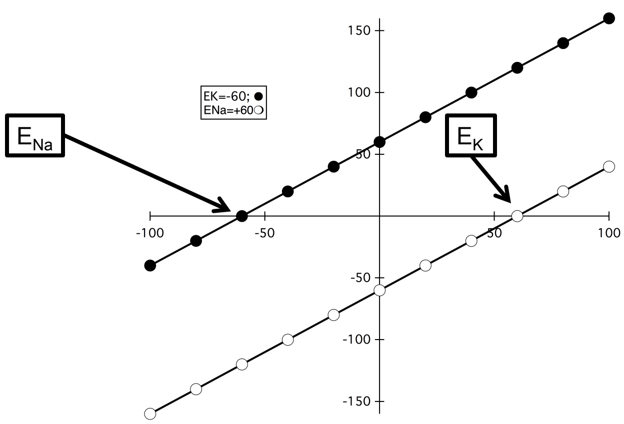

What is V_m if there is more than 1 permeant ion?

- Most cells have permeability to more than 1 ion

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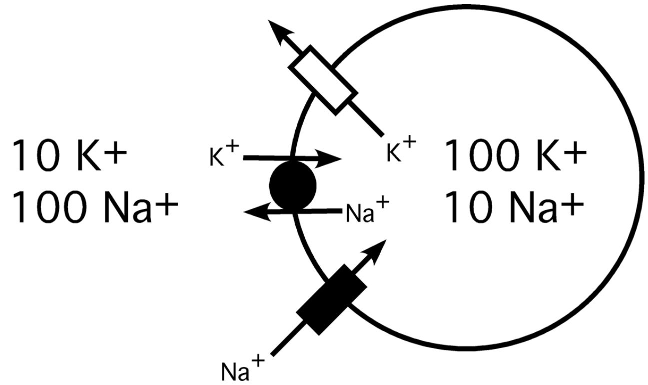
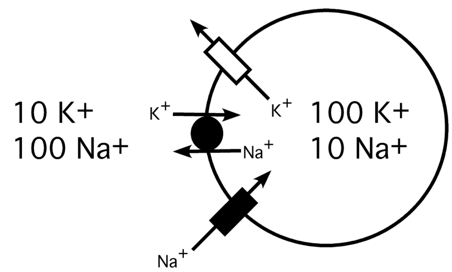
- Most cells have permeability to more than 1 ion
- Consider the following situation
  - Membrane permeable to K^+ and Na^+
  - Ion gradients set up by a pump (assume 1:1 stoichiometry)

What is V_m if there is more than 1 permeant ion?



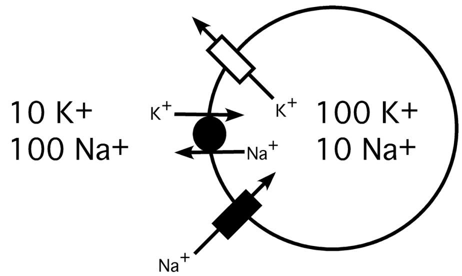
Case 1: K^+ and Na^+ are equally permeant

The Na^+ gradient is equal and opposite to the K^+ gradient, and Na^+ and K^+ can leak in at the same rate that they are pumped out, maintaining the gradients. Under these conditions, the diffusion of K^+ across the membrane is equal and opposite to the diffusion of Na^+, so nothing has to be done to conserve electroneutrality. NO V_m NEEDS TO BE SET UP.



Case 2: P_K does not equal P_{Na}

If $P_K > P_{Na}$ the pumping rate does not equal the leak rate for both ions, and more K^+ leaks out than Na^+ leaks in. Electroneutrality would be violated, and a V_m will be set up to counteract the excess leakage of K^+. The V_m set up should decrease K^+ exit and increase Na^+ entry until the rates are equal.



Case 2: P_K does not equal P_{Na}

Two extremes:

- P_K >>>>>>> P_{Na} ((P_{Na}/P_K) ~0)
  - This is essentially a purely K^+-selective membrane, so $V_m = E_K$

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  - This is essentially a purely Na^+-selective membrane, so $V_m = E_{na}$

Goldman-Hodgkin-Katz Equation gives the explicit relationship

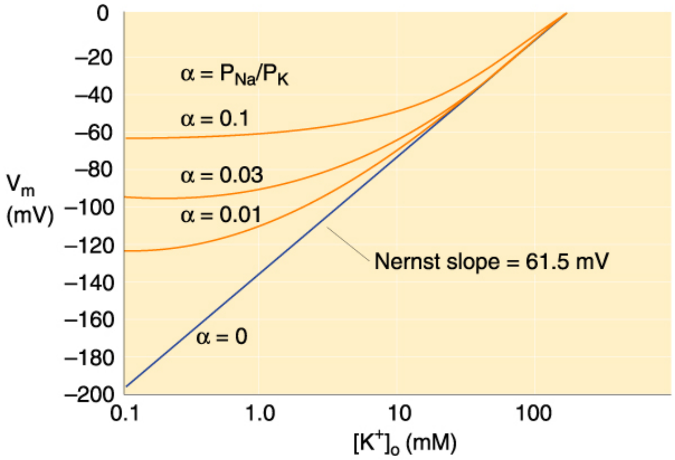
GHK Equation

$$V_m = -60 \log \frac{[K^+]_i + \alpha[Na^+]_i}{[K^+]_o + \alpha[Na^+]_o}$$

$\alpha = (P_{Na}/P_K)$

(can add other terms for additional ions)

GHK Equation



V_m as a function of $[K^+]_{out}$

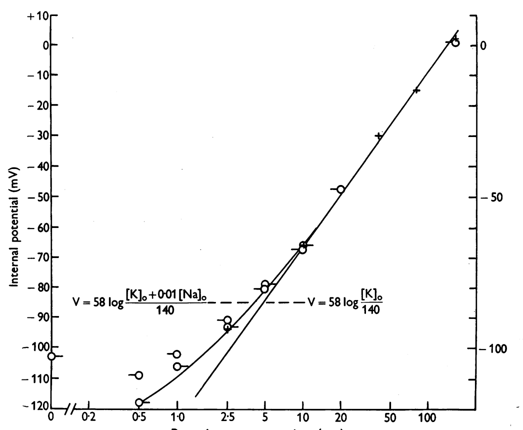


Fig. 5. Relation between membrane potential and log[K] when using chloride-free sulphate solutions containing 8 mM-$CaSO_4$. Crosses are potentials measured after equilibrating for 10–60 min; circles are potentials measured 20–60 sec after a sudden change in concentration, –○ after increase in $[K]_o$, ○– after decrease in $[K]_o$. With the exception of the right-hand point, all solutions were of the same ionic strength as Ringer's fluid and had concentrations intermediate between *D* and *E* of Table 1. The right-hand point was obtained with solution *H* and the potassium concentration has been corrected on the graph for the difference in ionic strength. Semi-log. scale; average data on seven fibres.

Hodgkin and Horowicz, 1959

To Get a Membrane Potential You Need:

- Selective permeability (i.e., $\alpha \neq 1$)
  - Note: it is the *relative* ionic permeability(*i.e.*, α) rather than the absolute ionic permeability (P_{Na}, P_K) that matters

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- Ion gradients (set up by ion pumps like the Na/K ATPase)

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- This change is termed an *action potential*

Action Potentials

- Transient change in membrane potential

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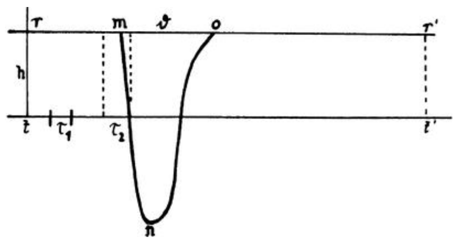
- Transient change in membrane potential
- 1st measured in 1868 by Julius Bernstein using extracellular electrodes
  - Did not know actual value of membrane potential or its changes – just that it changed



Bernstein, J (1868) *Pflugers Archiv* 1:173

Action Potentials

Bernstein proposed that the membrane was permeable to K^+ at rest (CORRECT!), and that an AP was a transient breakdown of selectivity to create a non-selective membrane

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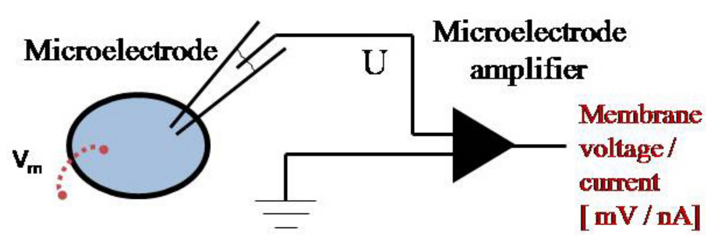
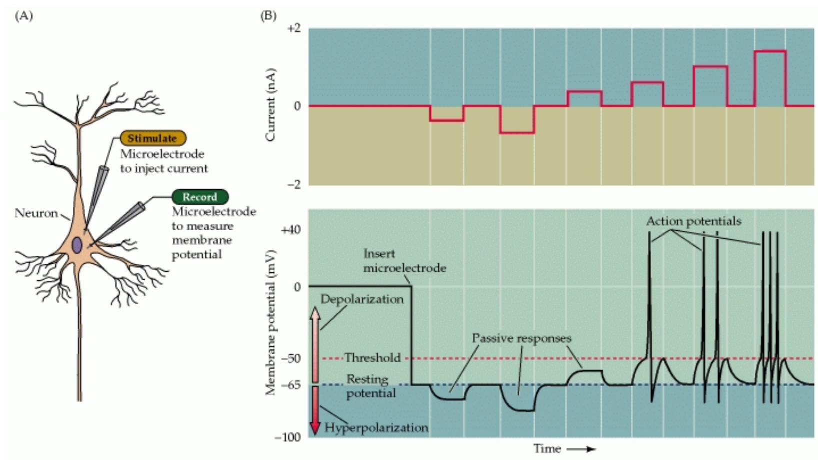
- Means that the peak of the AP = 0 mV
- Invention of intracellular electrodes in the 1930's allowed measurement of true V_m values

Intracellular Recording



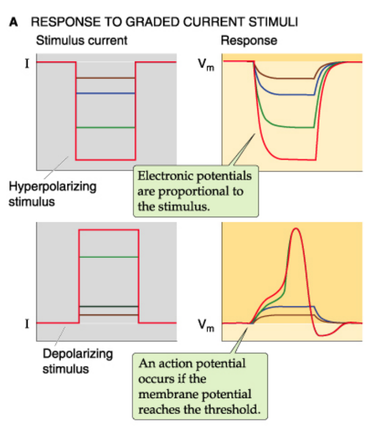
Action Potential



Purves et al *Neuroscience*, Sinauer Associates

APs are all-or-none

For a given set of conditions (ion concentrations, etc) APs are of constant amplitude



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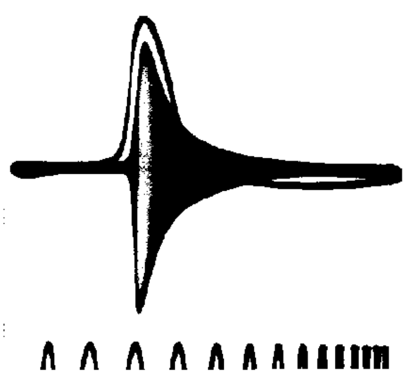
- Changes in V_m can then reflect a change in α or ion gradients
- In reality, changes in ion gradients cannot occur fast enough, so AP's reflect a change in α

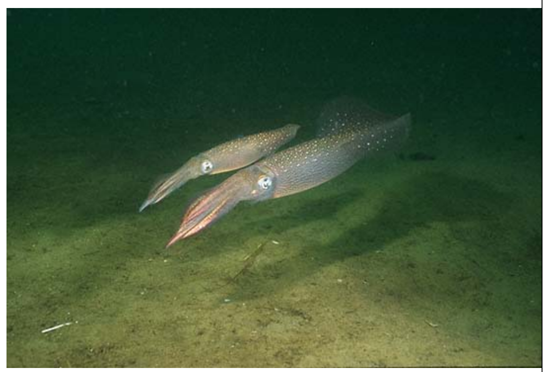
Ionic Basis of APs



- 1938: KS Cole demonstrated that there was an increase in membrane conductance during a squid giant axon AP (Cole and Curtis (1939) *J Gen Physiol* 22:649-670)

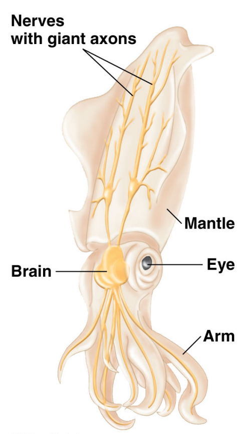
Ionic Basis of APs

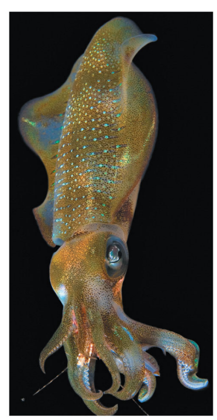
- 1940's-1950's: Hodgkin and Huxley (and sometimes Katz) carried out a series of experiments using squid giant axon to examine the processes that take place during an action potential



Squid Giant Axon

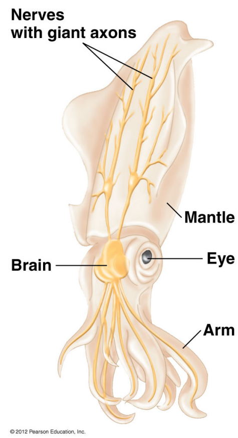
- A large axon of 1-2 mm diameter that controls the fast escape mechanism of the squid

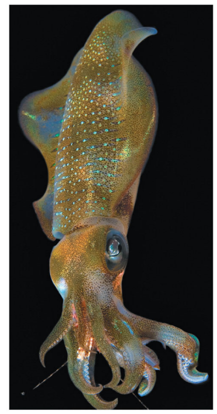




Squid Giant Axon

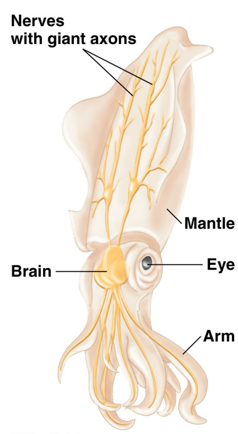
- A large axon of 1-2 mm diameter that controls the fast escape mechanism of the squid
- So large, it was originally thought to be a blood vessel

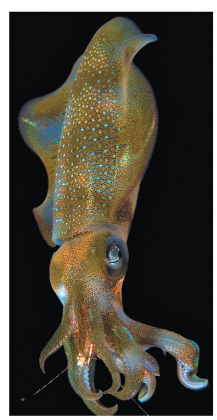




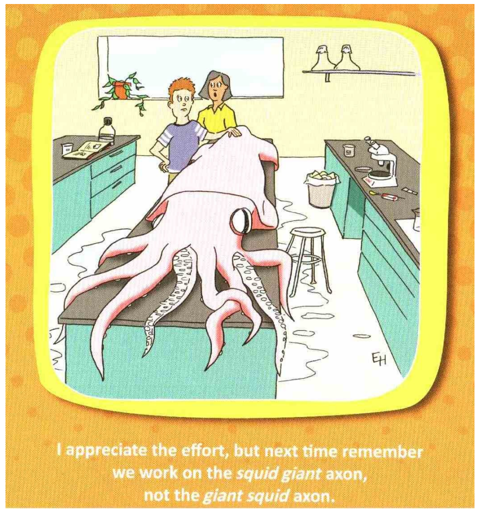
Squid Giant Axon

- A large axon of 1-2 mm diameter that controls the fast escape mechanism of the squid
- So large, it was originally thought to be a blood vessel
- Large size and geometry allowed manipulations such as axial electrodes that are impossible in smaller nerves



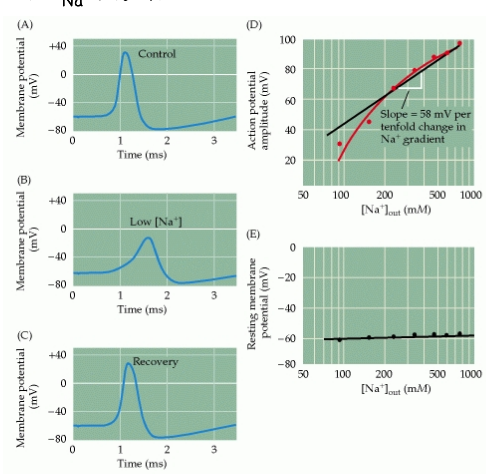


…not to be confused with an axon from a giant squid…



Ionic Basis of APs

Hodgkin and Katz showed in 1949 that AP peak depended on $[Na]_o$, like E_{Na} should



Purves et al *Neuroscience*, Sinauer Associates

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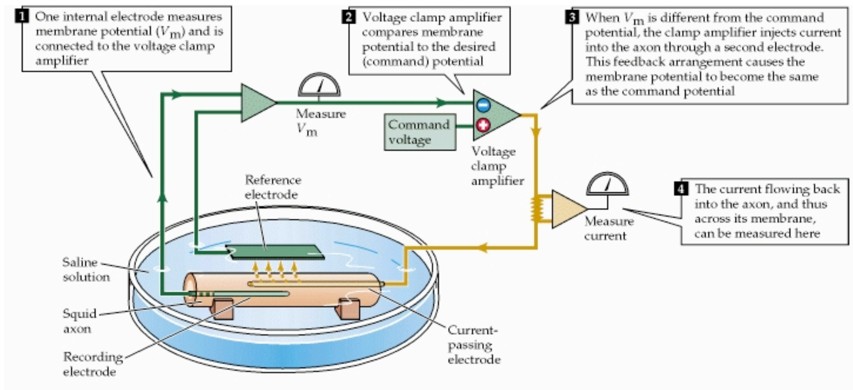
- Hodgkin and Huxley analyzed the time- and voltage-dependence of the currents using the **voltage-clamp**

Voltage Clamp



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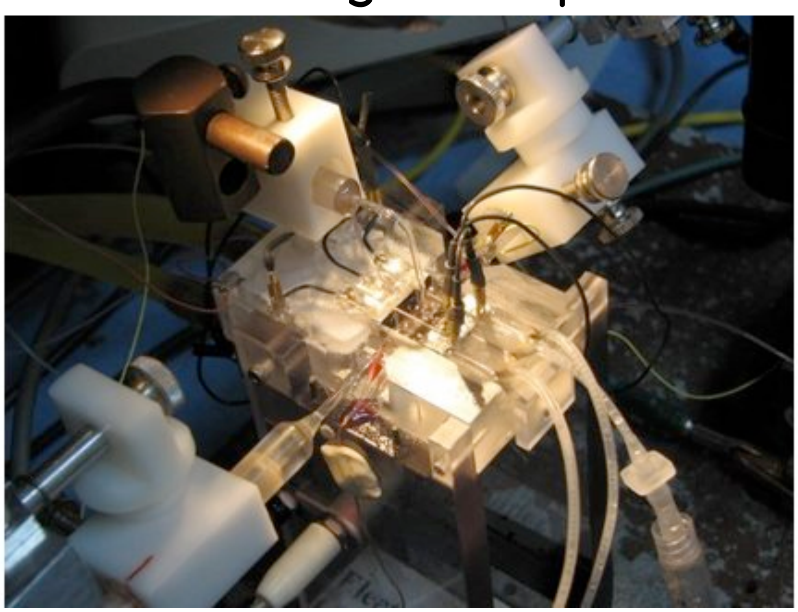
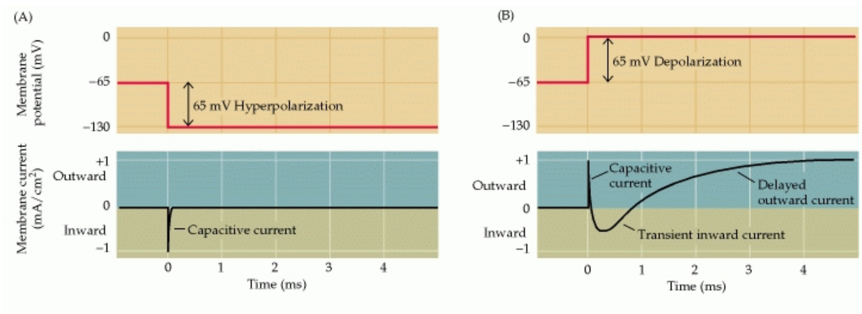
Voltage Clamp

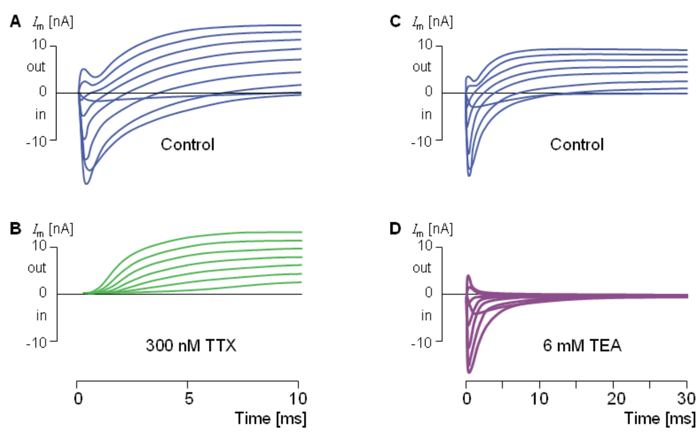


Voltage-Clamp Currents



- Purves et al *Neuroscience*, Sinauer Associates

Ionic Basis of APs



www.bem.fi/book/04/04x/0409x.htm

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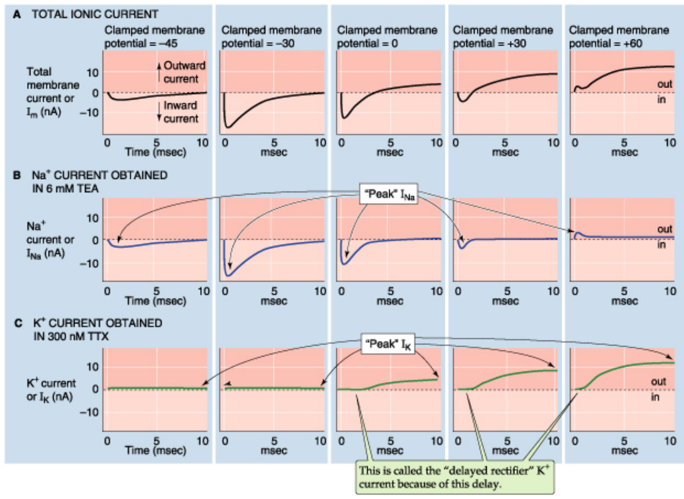

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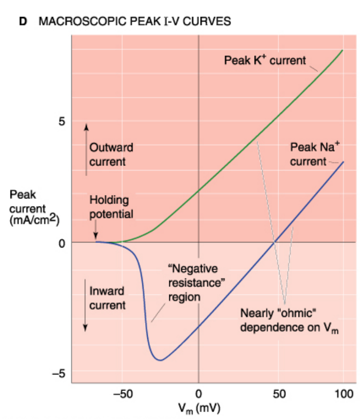
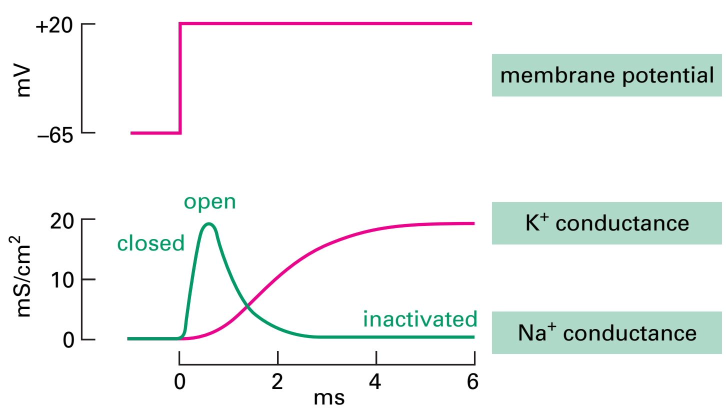


Properties of Ionic Conductances



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- Na^+ conductance
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- Na^{+} conductance
  - Voltage dependent
  - Rapid gating
  - inactivates
- K^{+} conductance
  - Voltage dependent
  - Slower gating ("delayed rectifier")
  - No inactivation

Reconstruction of the Action Potential

- Hodgkin and Huxley analyzed the voltage and time dependence of the Na^{+} and K^{+} permeability pathways.

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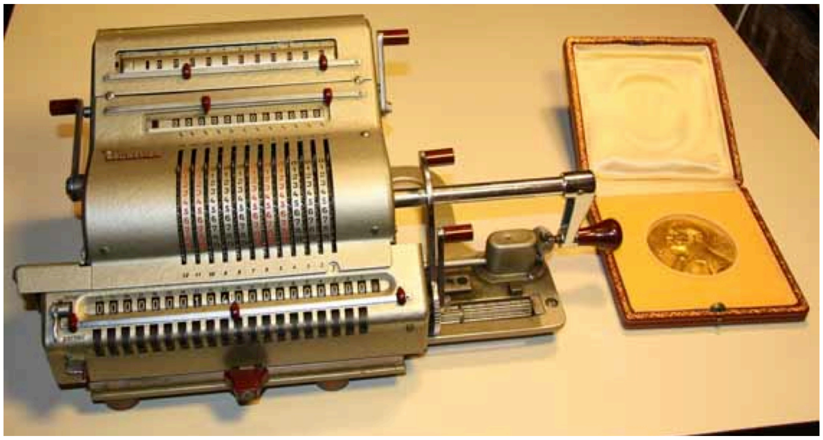
- Hodgkin and Huxley analyzed the voltage and time dependence of the Na^+ and K^+ permeability pathways.
- Using these properties, they created a kinetic model of the gating of these two pathways

- Using this model, they simulated an action potential. Note: All calculations were done using a hand-cranked calculator. It took three weeks to calculate a propagated AP!

Reconstruction of the Action Potential



Hodgkin-Huxley Equations

$$I = C_M \frac{dV}{dT} + \bar{g}_K n^4 (V - V_K) + \bar{g}_{Na} m^3 h (V - V_{Na}) + \bar{g}_l (V - V_l)$$

$$\frac{dn}{dt} = \alpha_n (1 - n) - \beta_n n$$

$$\frac{dm}{dt} = \alpha_m (1 - m) - B_m m$$

$$\frac{dh}{dt} = \alpha_h (1 - h) - \beta_h h$$

$$\alpha_n = \frac{0.01(V + 10)}{e^{\frac{V-10}{10}} - 1}$$

$$\beta_n = 0.125 e^{(V/80)}$$

$$\alpha_m = \frac{0.1(V + 25)}{e^{\frac{V+25}{10}} - 1}$$

$$\beta_m = 4 e^{(V/18)}$$

$$\alpha_h = 0.07 e^{\frac{V}{20}}$$

$$\beta_h = \frac{1}{e^{\frac{V+30}{10}} + 1}$$

Reconstructed AP

J. Physiol. (1952) 117, 500–544

A QUANTITATIVE DESCRIPTION OF MEMBRANE CURRENT AND ITS APPLICATION TO CONDUCTION AND EXCITATION IN NERVE

By A. L. HODGKIN and A. F. HUXLEY
From the Physiological Laboratory, University of Cambridge

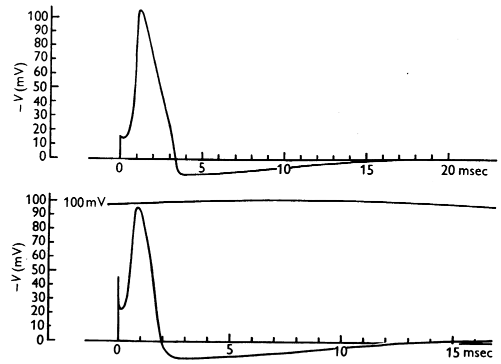


Fig. 13. Upper curve: solution of eqn. (26) for initial depolarization of 15 mV, calculated for 6° C. Lower curve: tracing of membrane action potential recorded at 9·1° C (axon 14). The vertical scales are the same in both curves (apart from curvature in the lower record). The horizontal scales differ by a factor appropriate to the temperature difference.

Permeability Pathways=Ion Channels

- The permeability pathways are discrete transmembrane proteins that undergo voltage-driven conformational changes.

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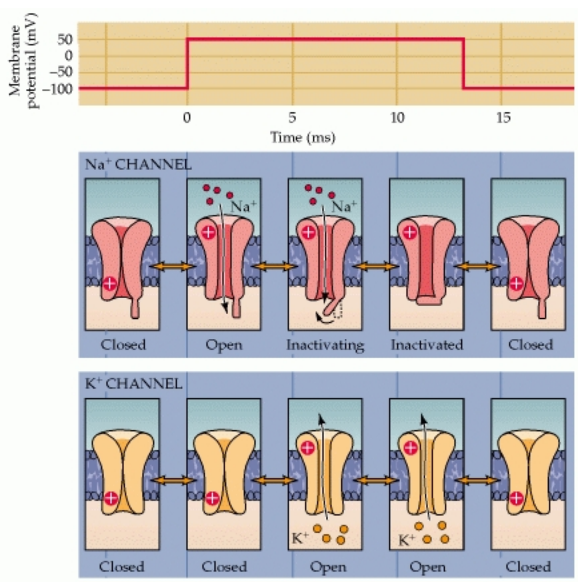
- Upon forming the OPEN state of the channel, an ion-selective transmembrane pore is formed and the ion travels down its electrochemical gradient.

Voltage-gated Ion Channels



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Voltage-gated Ion Channels

- The currents that Hodgkin and Huxley recorded are the summation of the activity of the zillions of channels present in the cell membrane.

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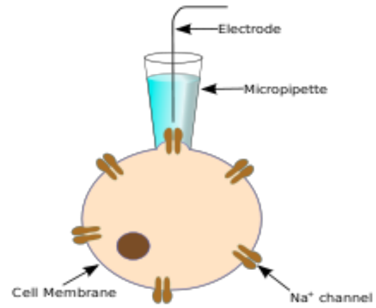
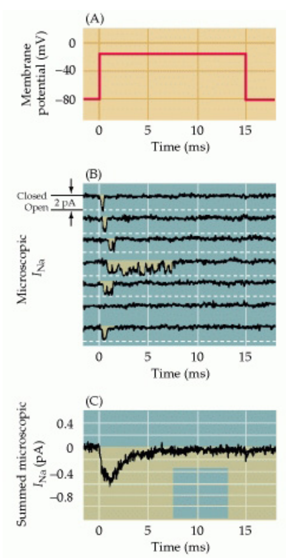
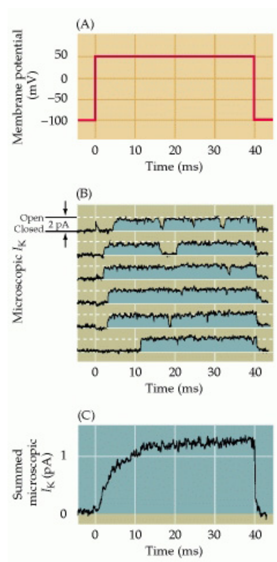
- It is possible to record the activity of a single ion channel

Single Channel Recording



Single Na⁺ and K⁺ channels

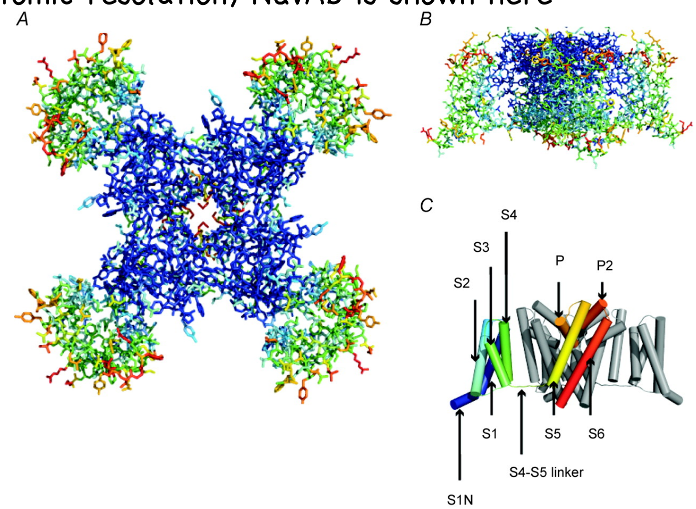




Purves et al *Neuroscience*, Sinauer Associates

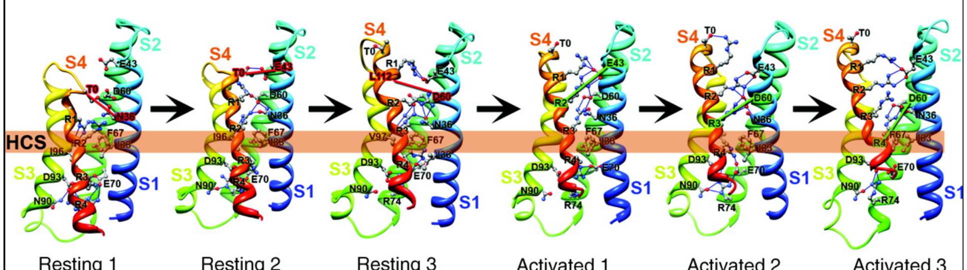
Voltage-gated Ion Channels

The structures of a number of channels are known to atomic resolution; NavAb is shown here



Voltage-gated Ion Channels

S4 helix is the voltage sensor; it moves in response to a change in transmembrane voltage



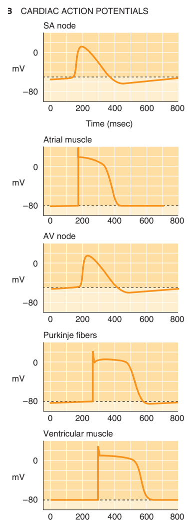
Ionic Basis of AP's: SUMMARY

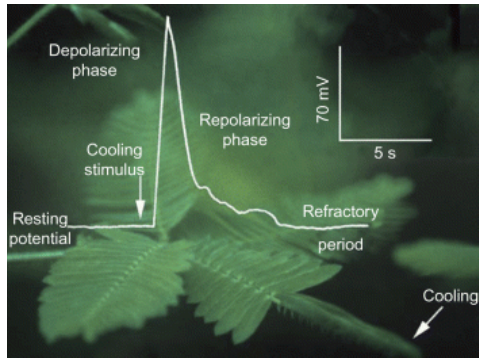
- AP is the transient cycling of membrane permeability

Ionic Basis of AP's: SUMMARY

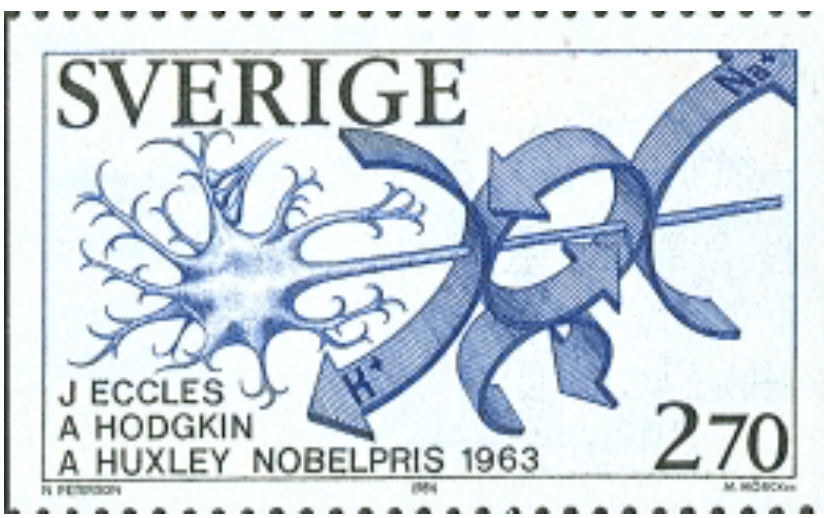
- AP is the transient cycling of membrane permeability
- Applies to all AP's
  - Conductances and time courses of conductance change may vary, but every AP is still a cyclic change in permeability

Ionic Basis of APs





Ionic Basis of APs



Synaptic Transmission

- How do APs get started?

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- Experimentally, a shock can elicit an AP, but this is not the physiological stimulus

Synaptic Transmission

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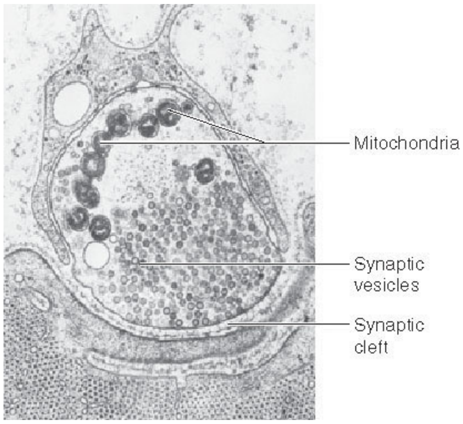
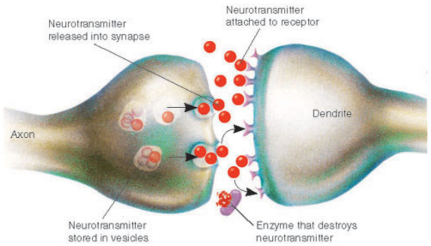
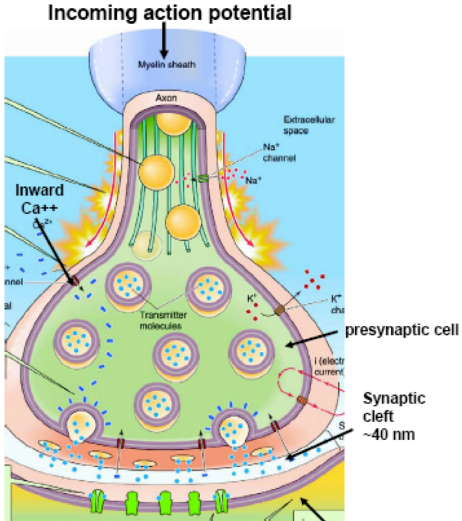
- Experimentally, a shock can elicit an AP, but this is not the physiological stimulus
- Point of initiation is at the **synapse**, where two excitable cells come together

The Synapse





Chemical Synaptic Transmission



B&B, Fig. 8-2

1. Action potential arrives at pre-synaptic terminus and depolarizes V-sensitive Ca++ channels, causing influx of Ca++
2. Ca++ triggers synaptic vesicles loaded with NT to fuse at pre-synaptic membrane and exocytose NT into cleft
3. Rapid diffusion of NT across cleft to postsynaptic side
4. NT binds to, and activates, postsynaptic receptors which in-turn activate the post-synaptic cell
5. Process is terminated by (i) enzymatic degradation of NT, (ii) re-uptake of NT into presynaptic terminal, or (iii) diffusion of NT away from synapse

-- B&B pgs 206-207

Synaptic Transmission

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Synaptic Transmission

- Release of neurotransmitter from the pre-synaptic cell results in a change in membrane potential of the post-synaptic cell
- Excitatory synapse: depolarization results, causing postsynaptic cell to pass threshold, eliciting an AP
- Inhibitory synapse: hyperpolarization results, preventing AP
- Basic mechanism worked out by Bernard Katz and colleagues using the frog neuromuscular junction

Synaptic transmission

Excitatory transmitters increase nonselective cation permeability, making $\alpha \rightarrow 1$, leading to depolarization

Synaptic transmission

Excitatory transmitters increase nonselective cation permeability, making $\alpha \rightarrow 1$, leading to depolarization

Inhibitory transmitters increase anion permeability, making $V_m \rightarrow E_{Cl}$, which is around -80 mV; makes it harder to depolarize membrane

Synaptic Transmission

Excitatory transmitters

- Acetylcholine (ACh)
- Serotonin (5-HT)
- glutamate

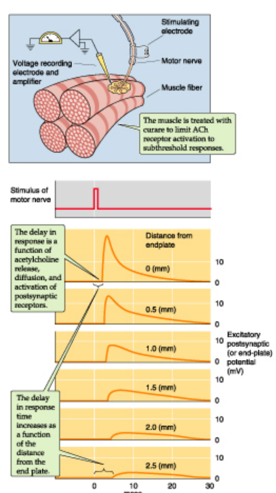
Synaptic Transmission

Excitatory transmitters
- Acetylcholine (ACh)
- Serotonin (5-HT)
- glutamate

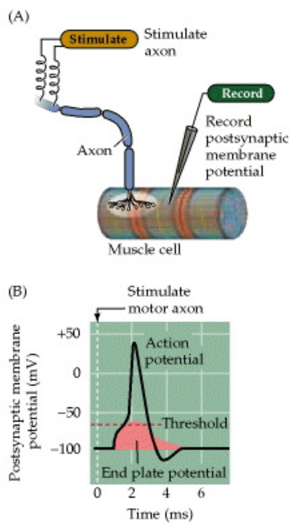
Inhibitory transmitters
- γ-amino butyric acid (GABA)
- glycine

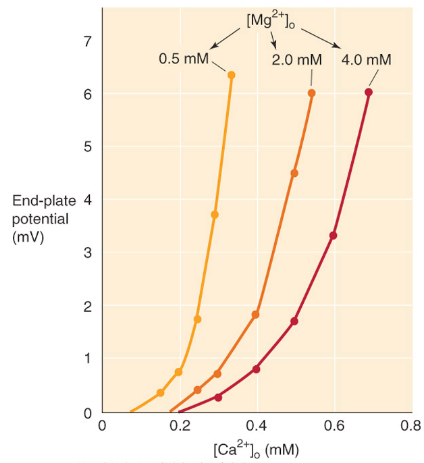
Katz: Neuromuscular Junction

Response to stimulus is highly localized



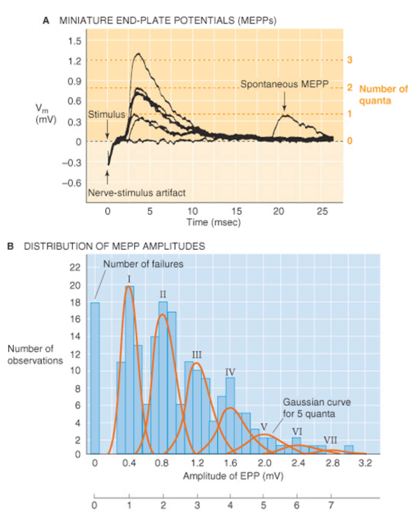
Katz: Neuromuscular Junction





Purves et al *Neuroscience*, Sinauer Associates

Katz: Quantal release of ACh



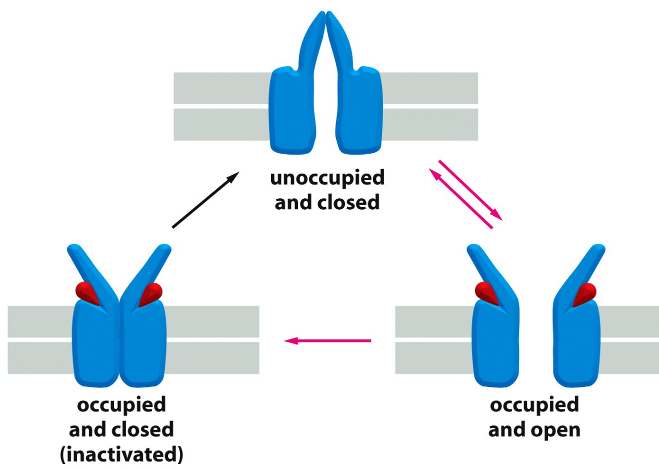
Neuromuscular Junction

- ACh interacts with the nicotinic acetylcholine receptor (AChR)

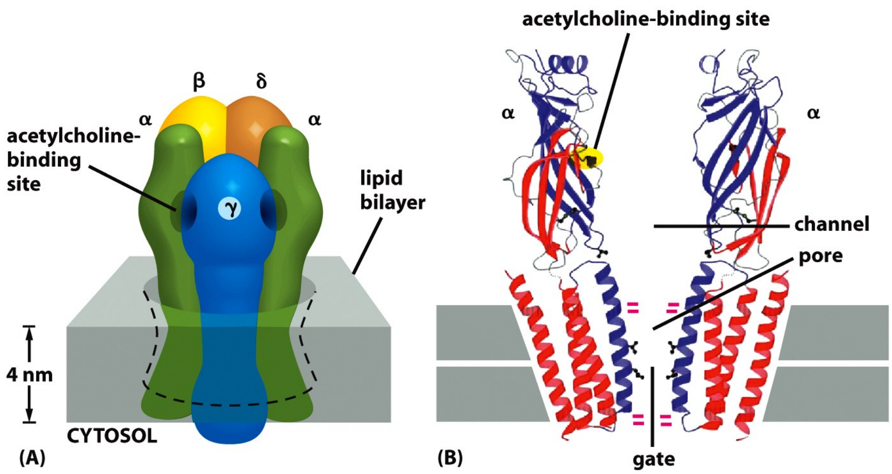
Neuromuscular Junction

- ACh interacts with the nicotinic acetylcholine receptor (AChR)
- The AChR is a transmembrane protein that undergoes a conformational change in the presence of ACh, opening a cation-selective transmembrane pore.

AChR

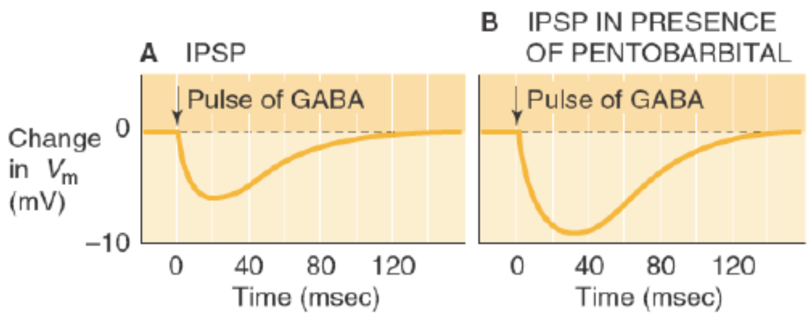

unoccupied
and closed
occupied
and closed
(inactivated)
occupied
and open

AChR


β
δ
α
α
acetylcholine-
binding
site
γ
lipid
bilayer
4 nm
CYTOSOL
(A)
acetylcholine-binding site
α
α
channel
pore
gate
(B)

What About Inhibitory Transmitters?

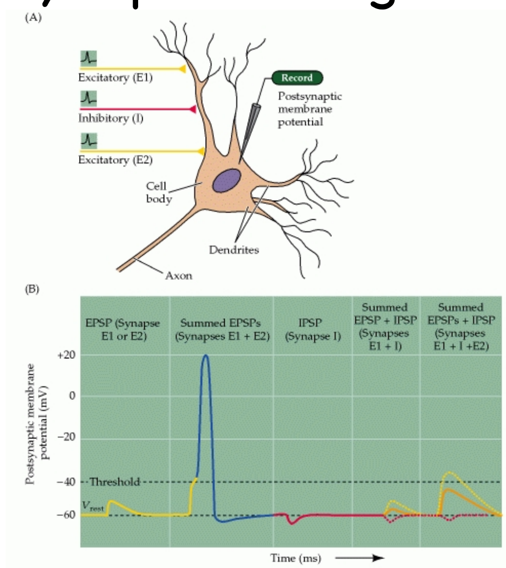
Inhibitory transmitters drive V_m to E_{Cl}, which is either at the resting potential or more negative. The response is called an inhibitory postsynaptic potential (IPSP)



Why have both excitatory and inhibitory responses?

Most neurons have both excitatory and inhibitory responses. Since the only output of an excitable cell is an all-or-none action potential, multiple inputs allow integration of responses.

Synaptic Integration



Purves et al *Neuroscience*, Sinauer Associates

Synaptic Transmission