

Lecture 10. Ionic Mechanisms of Synaptic Excitation

Dr. Bruce Johnson

Recommended Reading

Watch Video 10-1: V_{Rev} for one ion

Be able to explain the following figures from Bear et al. (read associated text if necessary): p.115, Fig 5.4; p.120, Fig. 5.9; p. 127, Box 5.4; p.128, Fig. 5.15.

Learning Objectives

1. To understand the basic mechanisms of chemical synaptic transmission
2. To understand how Ohm's Law can be used to calculate the current flowing through the transmitter receptors at an excitatory synapse.
3. To understand the concept of the reversal potential of a synaptic event and how it can be used to determine whether a fast synapse is excitatory or inhibitory

Lecture Outline

1. Actions of acetylcholine (ACh) at the vertebrate neuromuscular junction (NMJ).
 - Structure of the NMJ
 - Structure of the nicotinic ACh receptor
2. Determination of V_{Rev} for a receptor permeant to only one ion (video)
 - Variation of the post-synaptic membrane potential while evoking pre-synaptic release: point at which the direction of the EPSP voltage change flips = V_{Rev}.
3. V_{Rev} at the real NMJ: receptor permeant to more than one ion
 - V_{Rev} is the balance where the sum of all currents flowing through the receptor channel add to zero
 - Is the point the EPSP AIMS towards, for a conductance increase EPSP
 - At the vertebrate NMJ:
 - $V_{Rev} = [(pNa/pK)[Na]_{out} + [K]_{out}] / [(pNa/pK)[Na]_{in} + [K]_{in}]$
 - Proof by altering concentrations of extracellular Na⁺ and K⁺

4. V_{Rev} is a property of individual ligand-gated ion channels (receptors), not the neuron: can see with single channel recordings
5. The actions of ACh are excitatory because V_{Rev} is more depolarized than the spike threshold.
6. The specificity of the response to a neurotransmitter is a function of which receptor it binds to, not the transmitter: each transmitter can bind to a variety of different receptors, with different properties.

Study Questions

1. You are studying a synapse from the purple neuron onto the brown neuron in the Peanut-Butter-and-Jellyfish (PBJ-Fish), an odd animal from the South Pacific coral islands. This animal has an unusual distribution of ions in its extracellular and intracellular space, as you can see here:

Ion	Extracellular (mM)	Intracellular (mM)
Na^+	20	150
K^+	150	20
Cl^-	120	24

Using the methods that the Takeuchis developed, you wish to test the hypothesis that this synaptic current is carried by both sodium and potassium, and the channels are three times as permeant to sodium as to potassium (i.e., synaptic $g_{\text{Na}}/g_{\text{K}} = 3$).

- a. What is your estimate of the reversal potential of this synaptic current, using the ionic concentrations above? Show your calculations.
 - b. When the purple cell is stimulated, would the brown cell depolarize, hyperpolarize or not change from its resting potential of -45 mV ? Explain your answer.
 - c. If the threshold for spike initiation is -35 mV , is this synapse excitatory or inhibitory?
2. The Nernst potentials for different ions in a given cell are as follows:

$$E_{Na} = +55 \text{ mV}$$

$$E_K = -80 \text{ mV}$$

$$E_{Cl} = -60 \text{ mV}$$

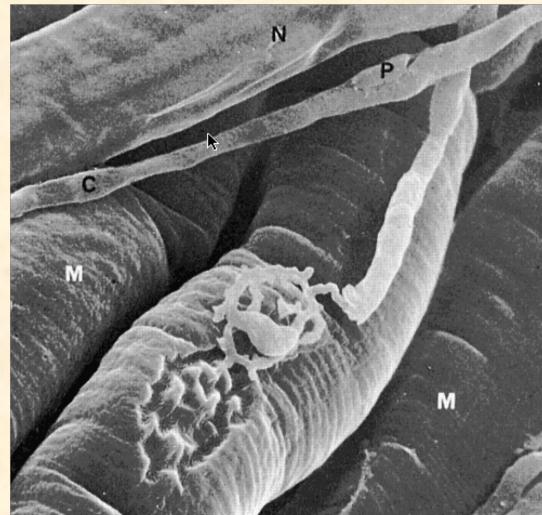
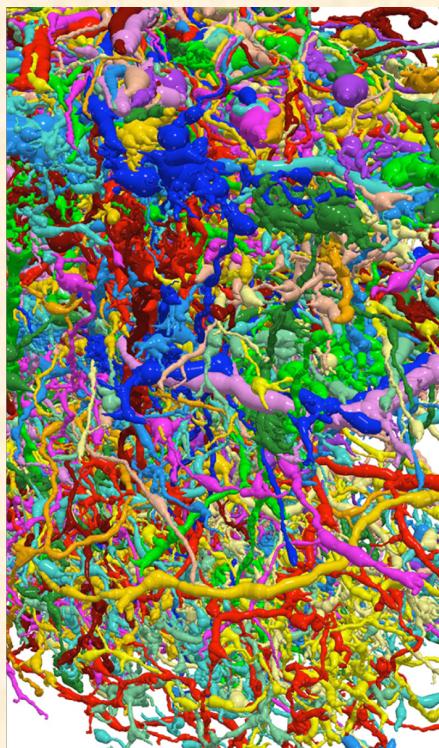
$$E_{Ca} = +150 \text{ mV}$$

If the reversal potential of a given ion channel is -70 mV, and you know that the ion channel allows Cl^- to flow through it, then which of the following statements must be true.

- a) The channel is also permeable to Ca
 - b) The channel is not permeable to any other ions aside from Cl
 - c) The channel is also permeable to K
 - d) The channel is also permeable to Na
3. Why is knowledge of the reversal potential useful for neurobiologists?

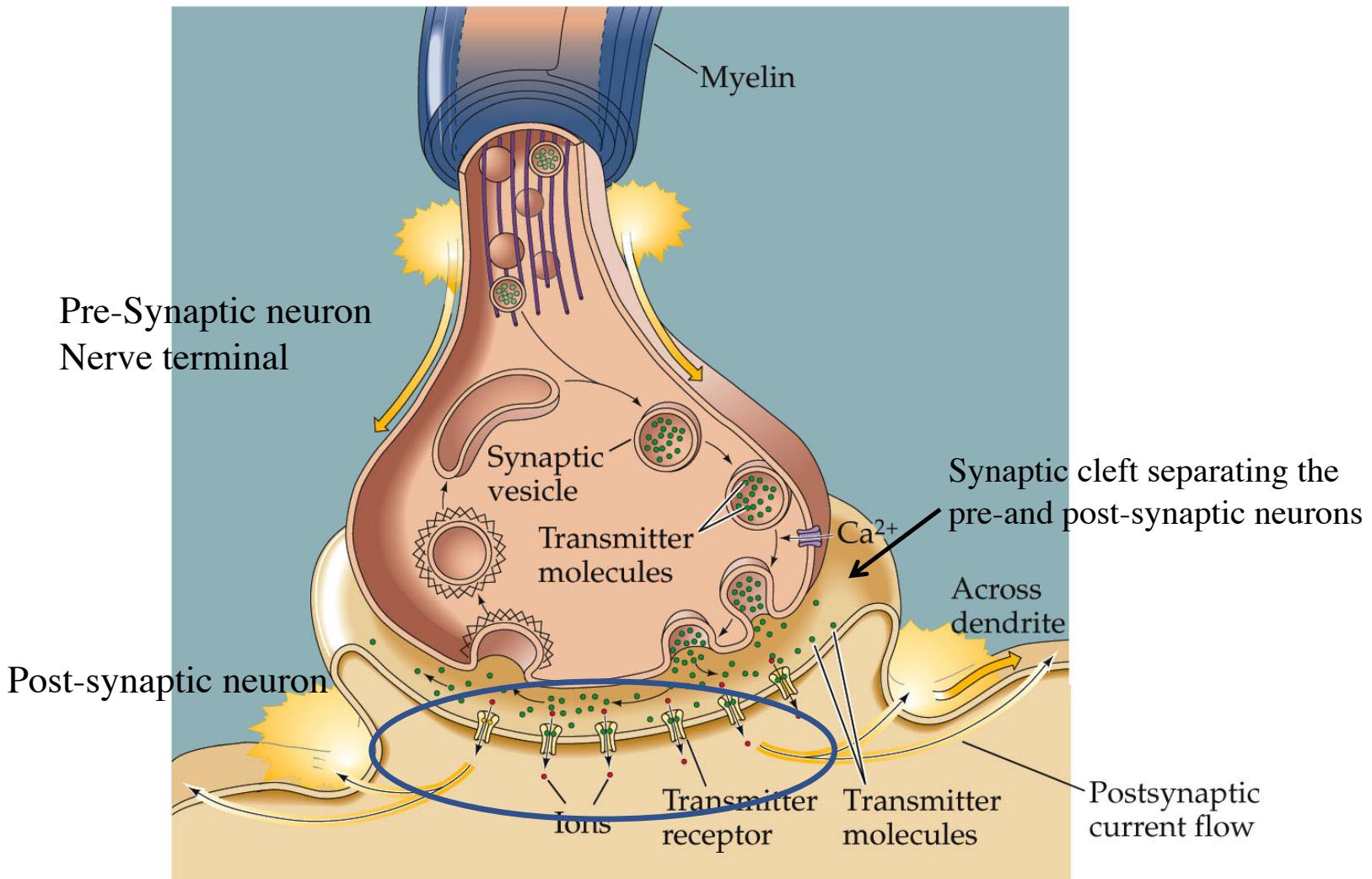
Lecture 10: Ionic Mechanisms of Synaptic Excitation

Bruce Johnson (brj1)



[https://www.youtube.com/watch?
v=mItV4rC57kM](https://www.youtube.com/watch?v=mItV4rC57kM)

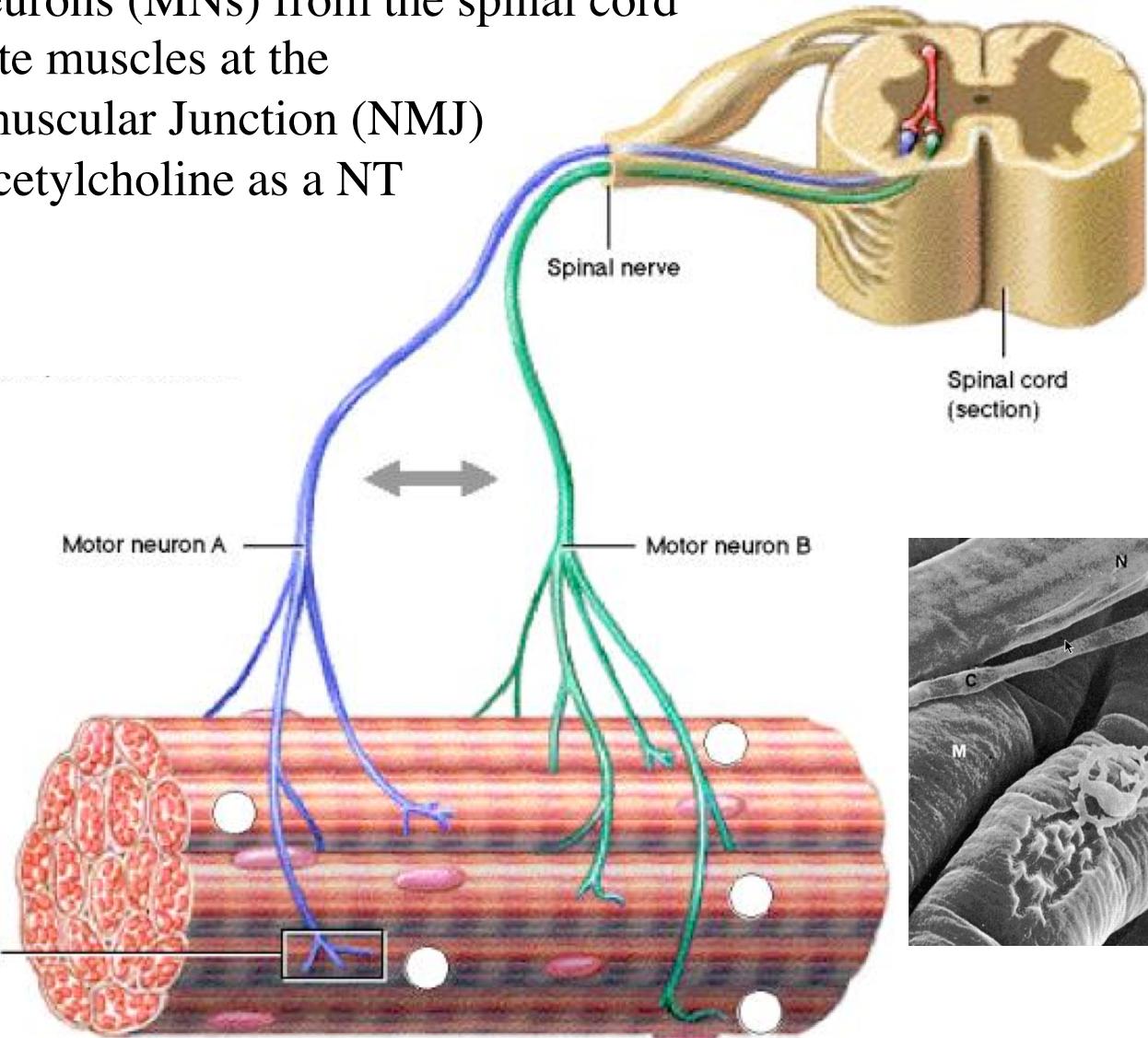
Overview of Chemical Synapses



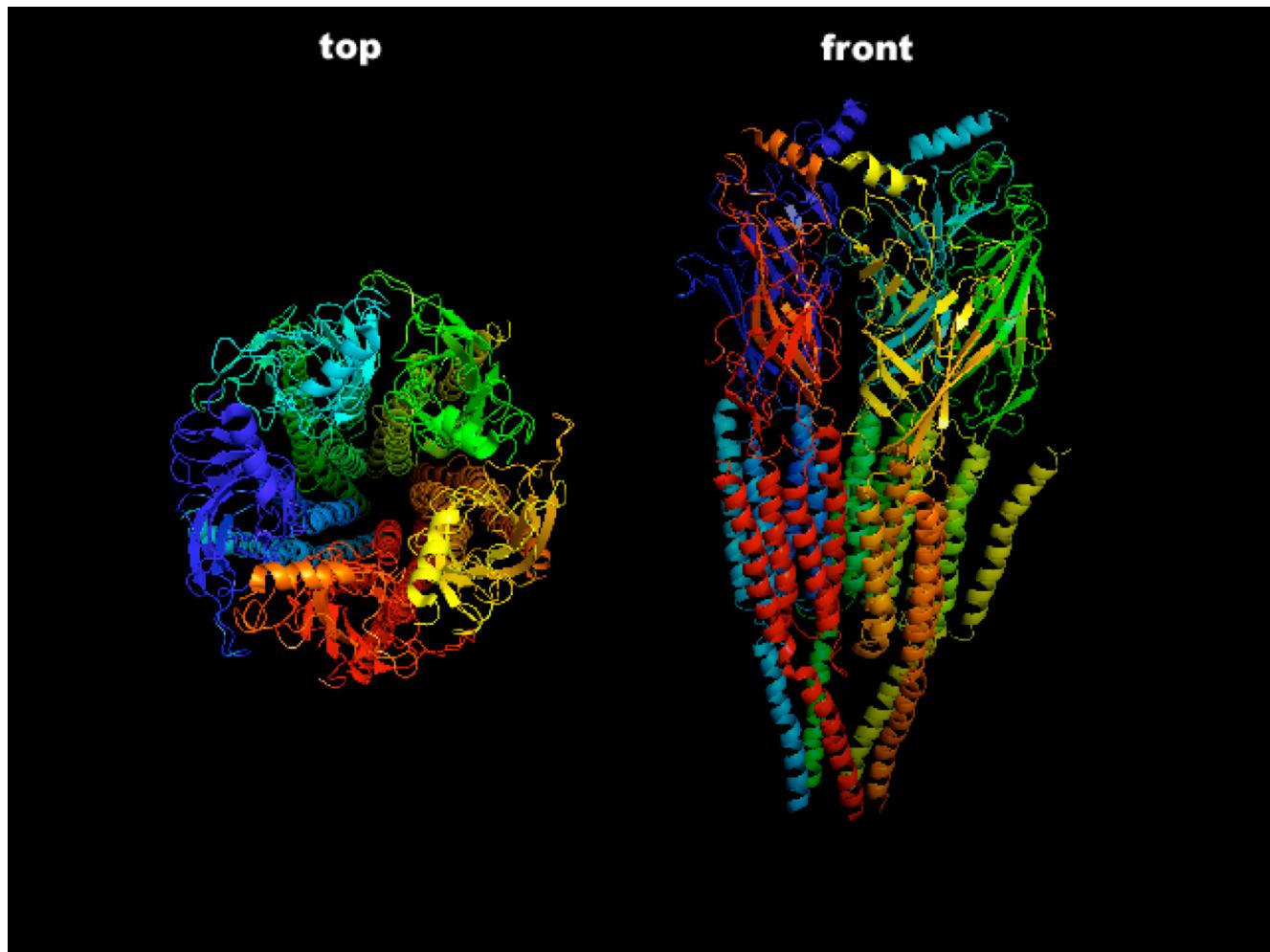
Goals for today

- Understand the steps in post-synaptic activation of neurons
- Discuss the concept of the reversal potential for a synapse and how it helps define excitatory and inhibitory synapses
- Review the concept of the driving force which combines the chemical and electrical gradients that push ions one way or another across the membrane
- Understand the ionic basis of acetylcholine synapses

Motoneurons (MNs) from the spinal cord innervate muscles at the Neuromuscular Junction (NMJ) using acetylcholine as a NT

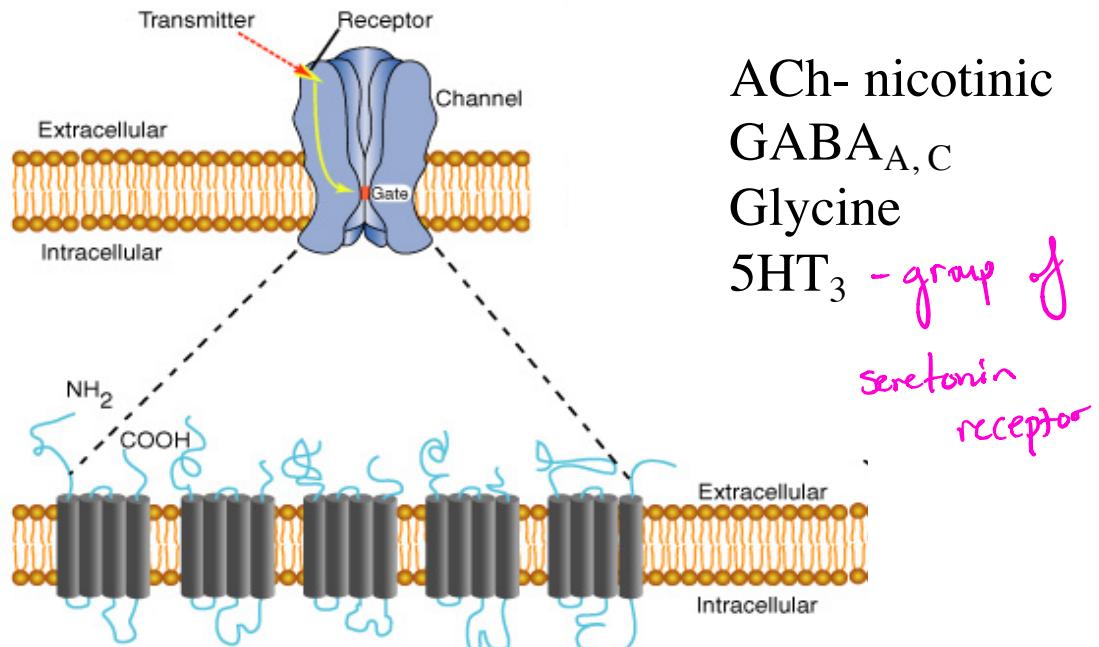


Nicotinic AChR from *Torpedo californica*:



Receptor families suggest similar evolutionary origins

Ionotropic Receptor Family



Video 10-1: Reversal potential for an ion channel permeable to a single ion

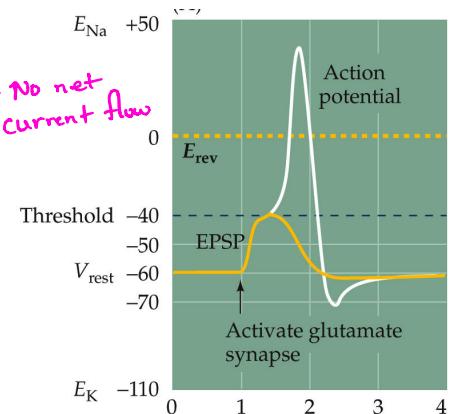
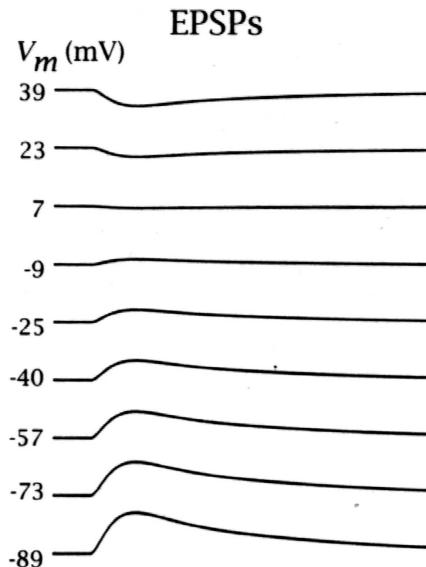
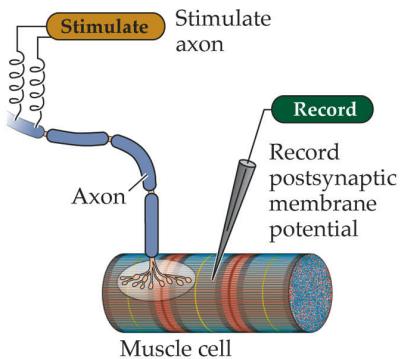
Major concepts:


$$G = \frac{1}{R}$$

- 1) Reversal potential: the voltage towards which the current aims for a conductance increase = $R \downarrow$ synaptic event, where sum of currents flowing through the receptor channel adds to zero.
- 2) Driving force: the energy which pushes ion flow in one direction or another

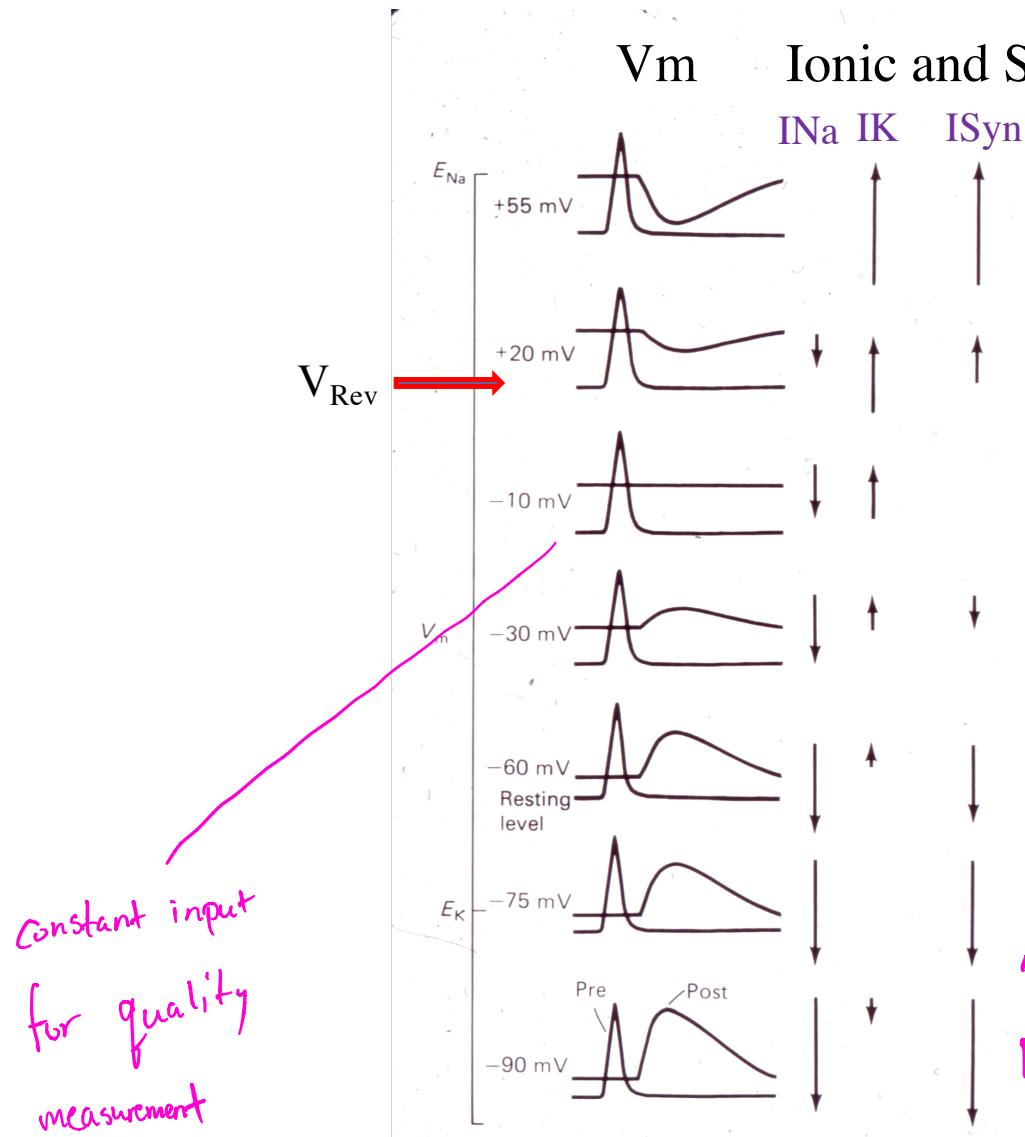
Postsynaptic Response

**Excitation: Conductance increase (resistance decrease):
Channels in membrane open**



Membrane potential goes towards V_{rev} (Equil. Pot)

V_m Ionic and Synaptic I



$$V_{syn} = I_{syn} \times R_{in}$$

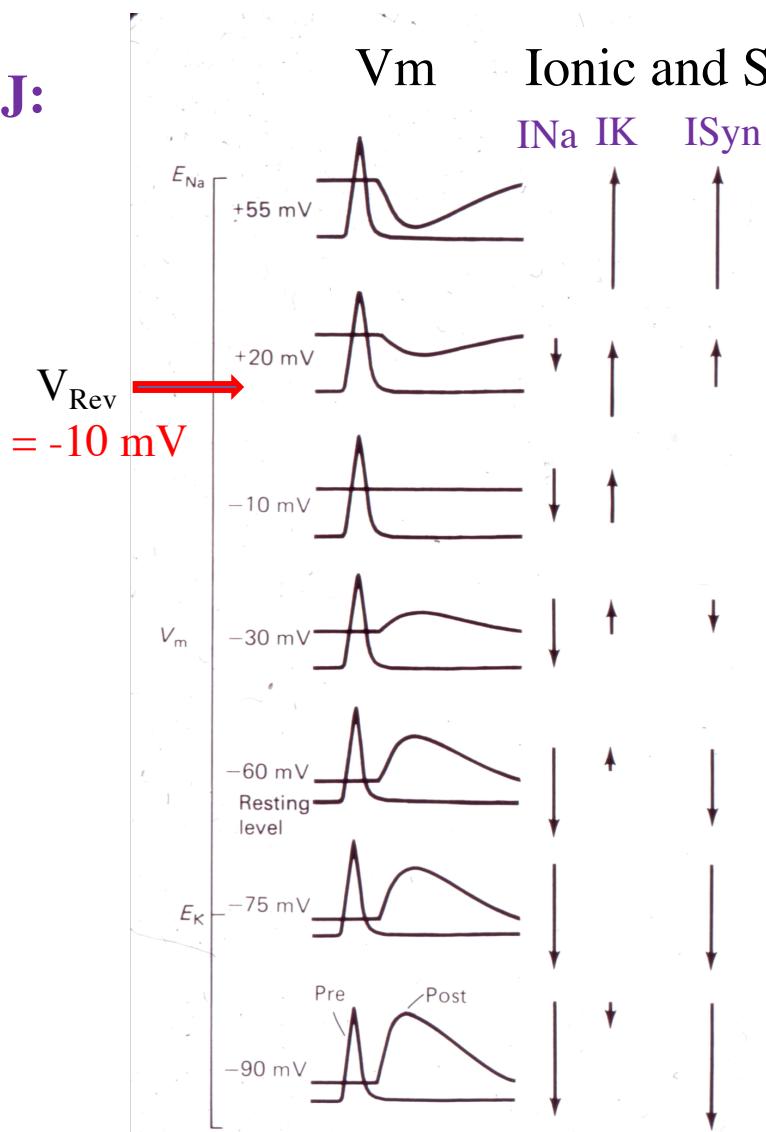
$$I_{syn} = (R_{in})^{-1} \times V_{syn}$$

$$I_{syn} = g_{syn} \times (V_m - V_{Rev})$$

Driving Force:
 $V_m - V_{Rev}$

"ion channels can have mixed selectivity"

Real NMJ:

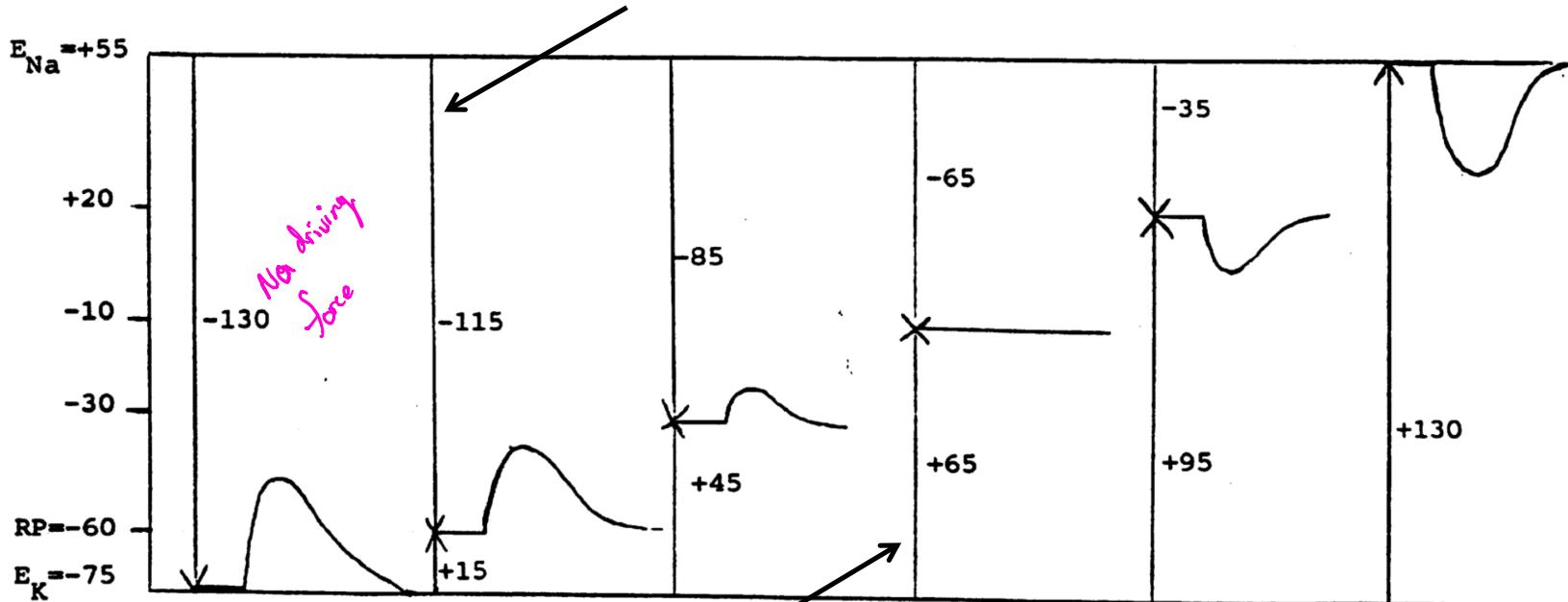


Ionic and Synaptic I

Takeuchi hypothesis:
The AChR channel is
EQUALLY permeant
to Na^+ and K^+

Driving Force:
 $V_m - V_{Rev}$

Driving force for sodium: ($V_m - E_{Na}$)



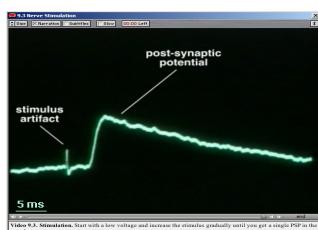
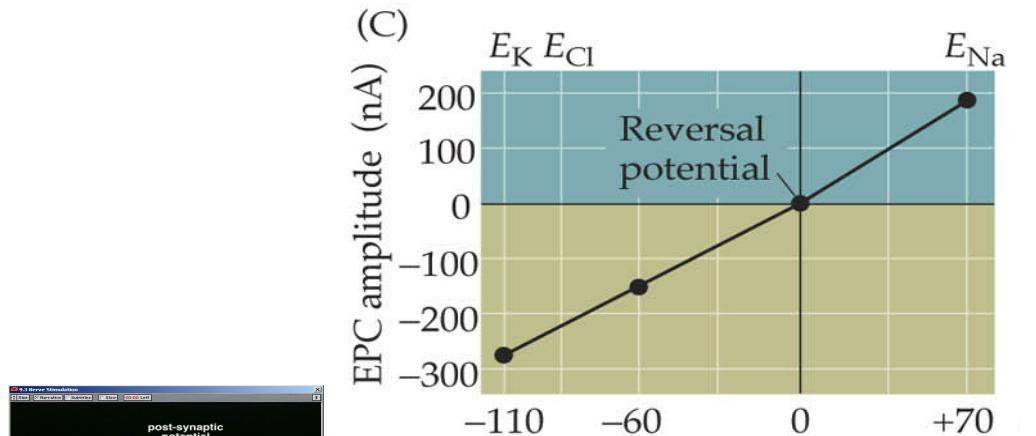
Driving force for potassium ($V_m - E_K$)

Conductance change due to multiple ions

Goldman
Equation

7. Goldman Equation

$$V_m = \frac{RT}{F} \ln \frac{P_K [K]_o + P_{Na} [Na]_o}{P_K [K]_i + P_{Na} [Na]_i}$$



Postsynaptic membrane potential (mV)

Why a depolarization?

Correct calculation of V_{Rev} from the Goldman equation:

$$V_{\text{Rev}} = 58 \log \frac{(P_{\text{Na}}/P_K) [Na]_{\text{out}} + [K]_{\text{out}}}{(P_{\text{Na}}/P_K) [Na]_{\text{in}} + [K]_{\text{in}}}$$

P_{Na}/P_K is the relative permeability of the AChR for Na relative to K

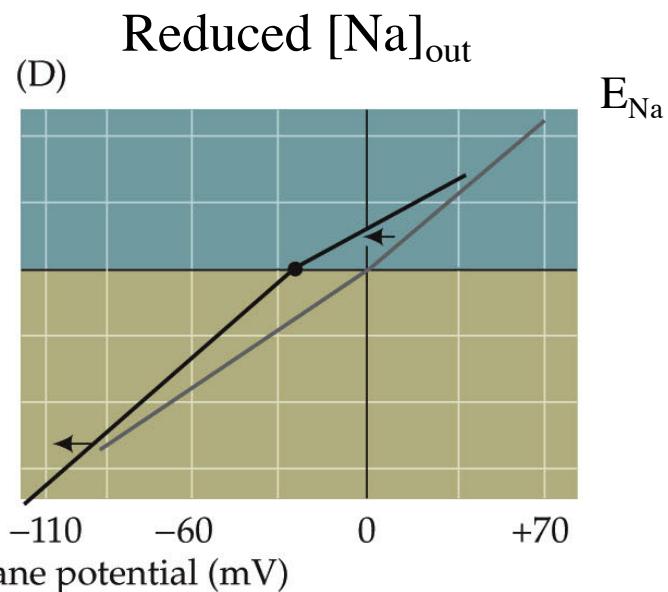
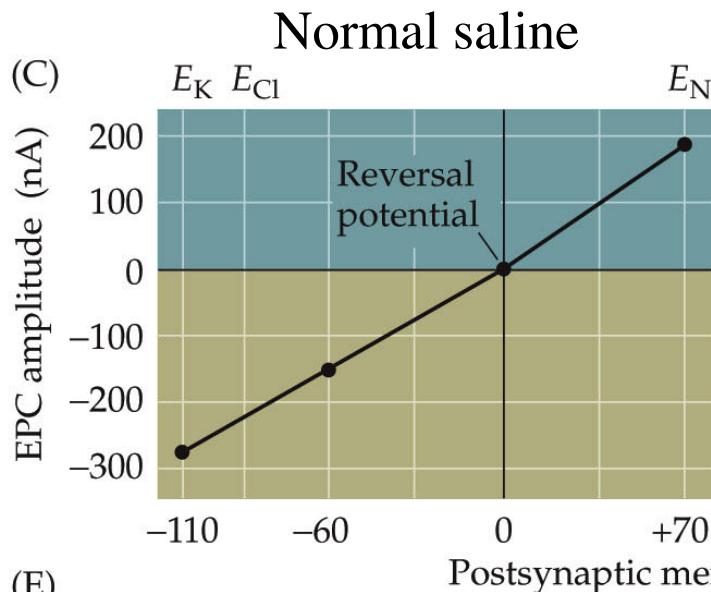
Real $P_{\text{Na}}/P_K = 1.29$

Na worth
"30° more" than K

V_{rev} depends only on (P_{Na}/P_K) , and ion concentrations

if it's not -1 gotta think a lit

Effects of changing extracellular Na and K on V_{Rev}



$$V_{\text{Rev}} = 58 \log \frac{(P_{\text{Na}}/P_{\text{K}}) [Na]_{\text{out}} + [K]_{\text{out}}}{(P_{\text{Na}}/P_{\text{K}}) [Na]_{\text{in}} + [K]_{\text{in}}}$$

Correct calculation of V_{Rev} from the Goldman equation:

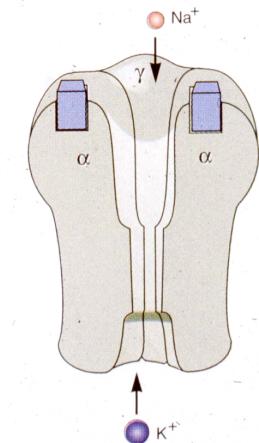
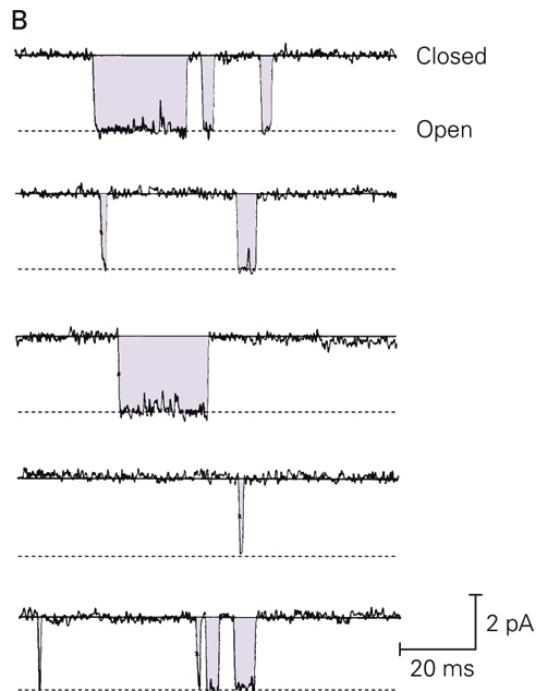
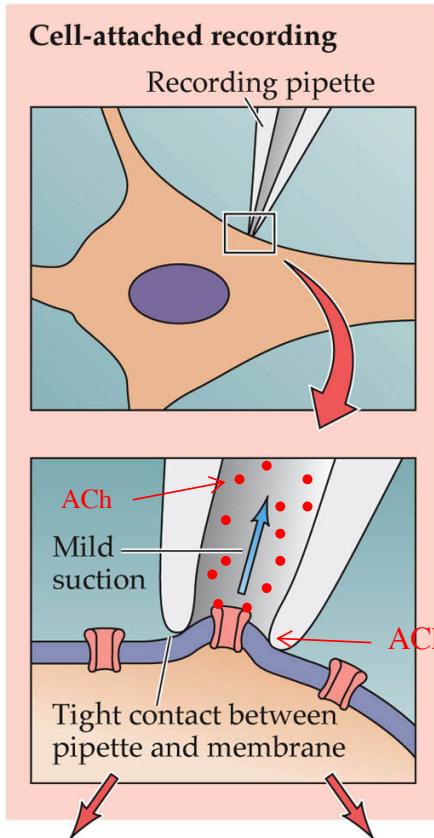
$$V_{\text{Rev}} = 58 \log \frac{(P_{\text{Na}}/P_{\text{K}}) [Na]_{\text{out}} + [K]_{\text{out}}}{(P_{\text{Na}}/P_{\text{K}}) [Na]_{\text{in}} + [K]_{\text{in}}}$$

$P_{\text{Na}}/P_{\text{K}}$ is the relative permeability of the AChR for Na and K

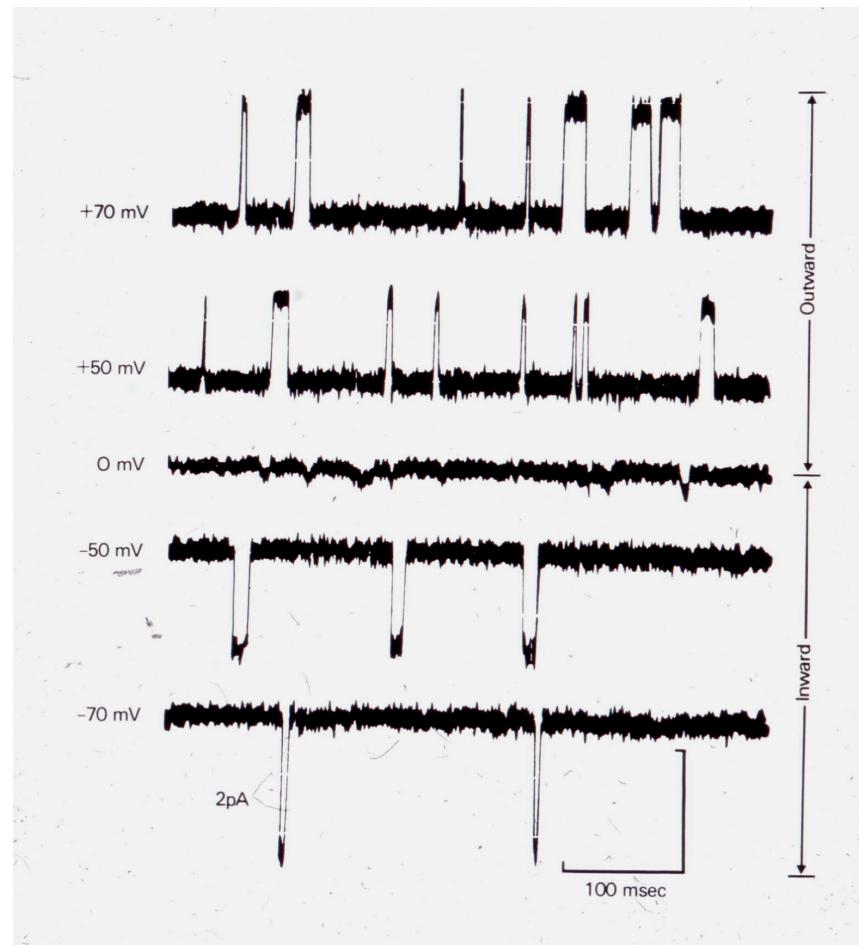
Real V_{rev} is near 0 mV, so $(P_{\text{Na}}/P_{\text{K}}) = 1.29$

V_{rev} depends only on $(P_{\text{Na}}/P_{\text{K}})$, E_{Na} and E_{K}

Single channel recordings from ACh receptor



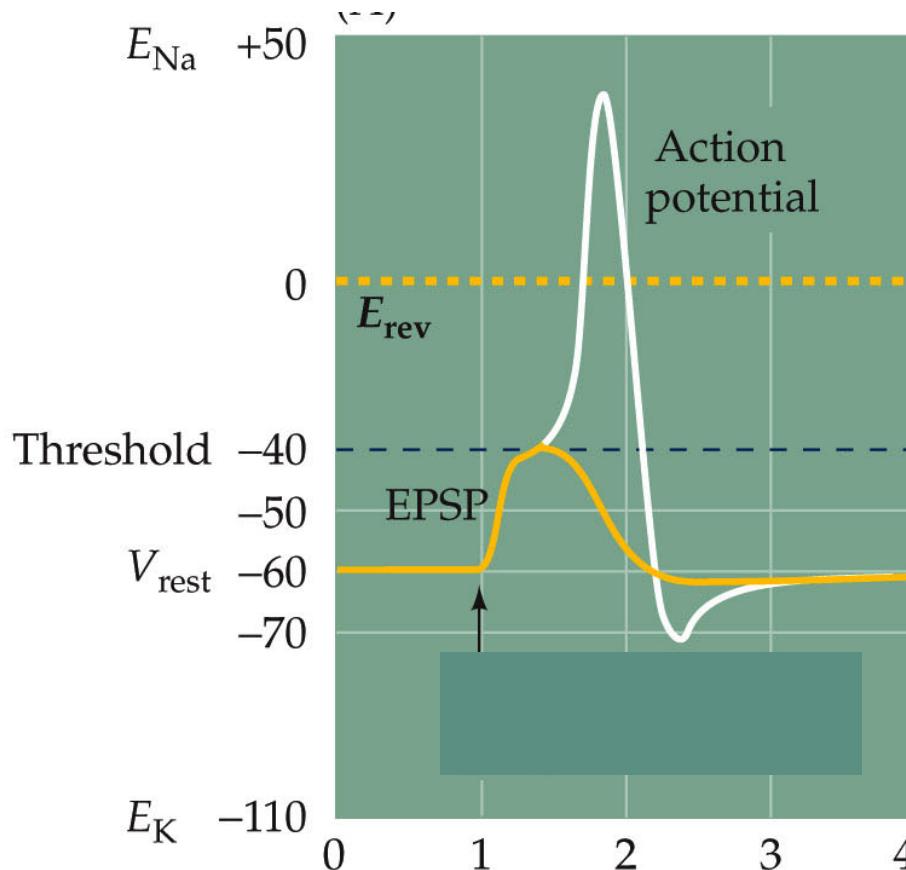
Single channel recordings of AChRs reverse near 0 mV



Conclusions:

1. Why is the AChR an excitatory receptor?

V_{rev} is more depolarized than $V_{threshold}$, so would try to evoke an AP

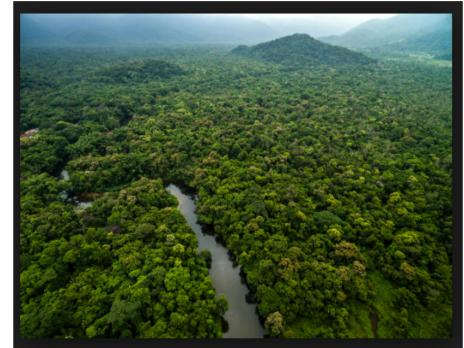


a depolarizing synapse is considered excitatory

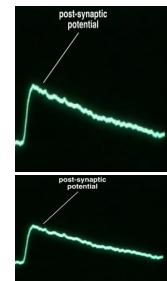
Conclusions, cont.

2. The V_{rev} is a characteristic of the ACh receptor, not the neuron: each transmitter receptor has its own V_{rev} , based on its molecular structure of the receptor's channel
3. The channel in the ACh receptor is not related to the voltage-sensitive channels we discussed earlier.
4. The specificity of the response is a function of the receptor, not the neurotransmitter.

Hit by a poison dart in the Amazon! Neuroscientists rush to determine site of synaptic action



Epsp amp
\ down



MUSCULAR WEAKNESS → MUSCLE CONTRACTIONS NORMAL

symptom

PATIENT 1

physiology shows

REDUCED EPSPS AND MEPPS

indicates

PRE-SYNAPTIC INDICATORS

but check

POSTSYNAPTIC PROBLEM

Mepp Amp down
frequency same



HYPER-ESTERASE

check by

TITRATE ESTERASE BLOCK

FAST DESENSITIZATION

check

DESENSITIZATION TIME COURSE

DECREASED R-INPUT

check with

IV PLOT

APPLIED TRANSMITTER

check with

APPLIED TRANSMITTER

v-IR

Curare