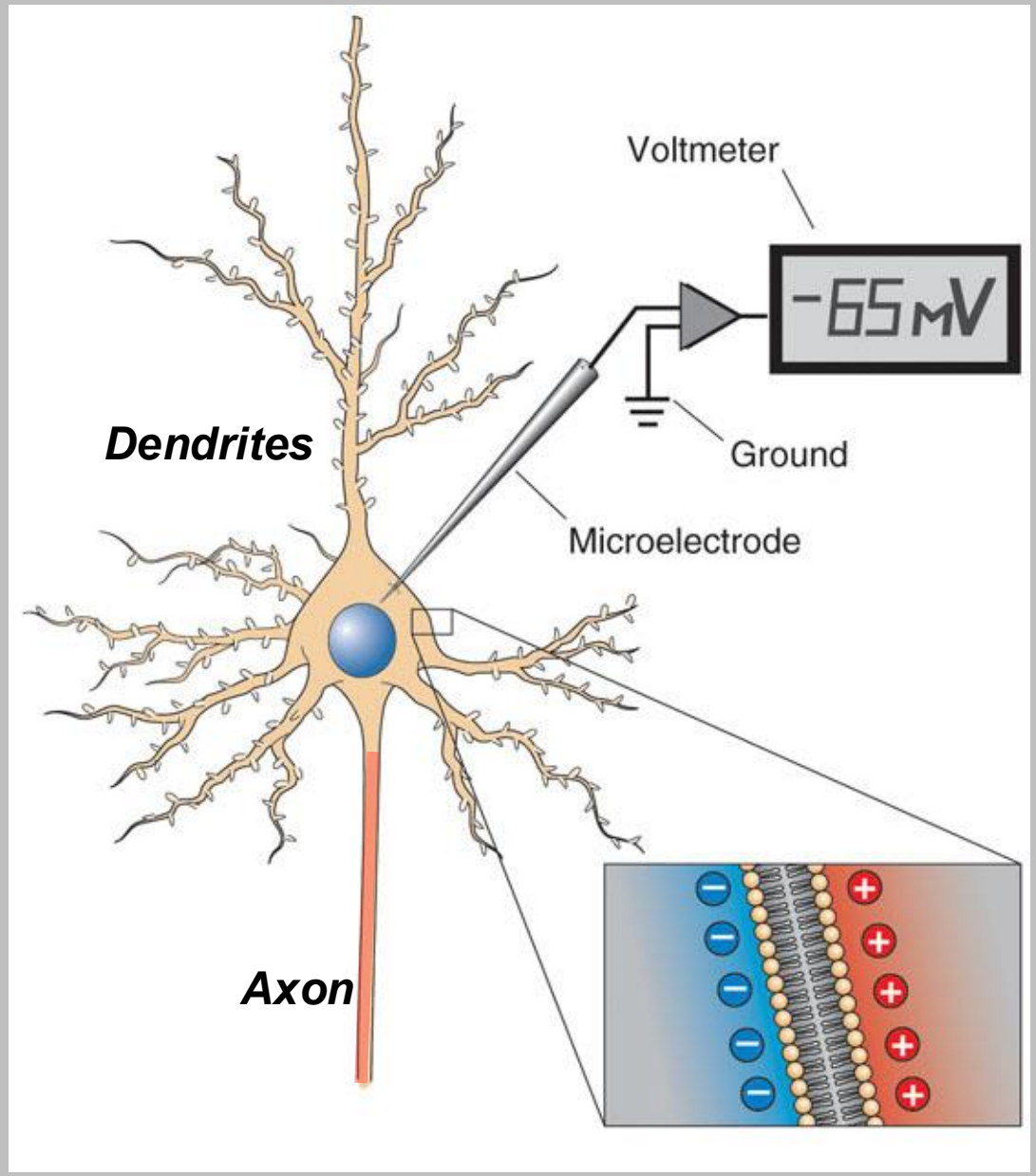
Session objectives

- Students will be able to describe how different ionic conductances create the resting membrane potential of neurons.
- Students will be able to describe how different ionic conductances generate an action potential as well as the different phases of the action potential
- Students will be able to describe the anatomy and physiology of chemical and electric synapses.
- Students will be able to describe the major steps that characterize synaptic transmission beginning with an action potential in the presynaptic neuron to depolarization or hyperpolarization in the postsynaptic neuron
- Students will be able to describe several examples of the clinical relevance of ion channels and synaptic transmission.

Neuronal resting membrane potential (rVm)

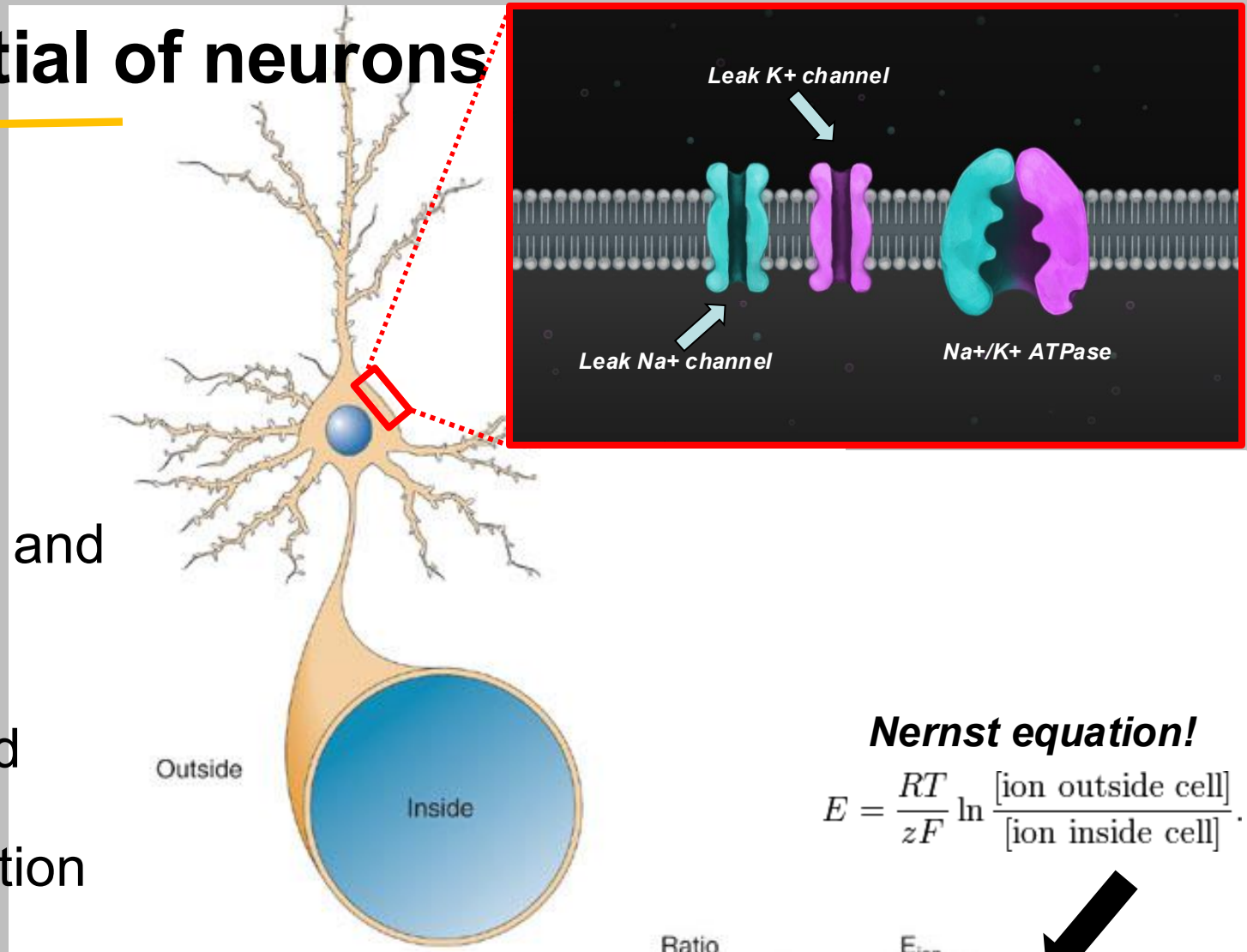
- Neuronal membrane changes, electric activity, and synaptic connections creates behavior!
- rVm of neuron is “hyperpolarized” (more negative) relative to the extracellular side.
- rVm is ~ -65mV in many central neurons but can vary by +/-15mV.
- Membrane potential physiology also important to understand cardiovascular function.



Resting membrane potential of neurons

- Hyperpolarized rVm is established by…

- 1] Na/K pump ->> <u>3Na^+ out / 2K^+ in</u>
- 2] membrane channels selectively permeable to certain ions “leak” K+ and “leak” Na+ channels.
- 40X more “leak” K than “leak” Na
- 3] unequal concentration of charged ions present in the intra vs. extracellular space determine direction and extent of ion flow.

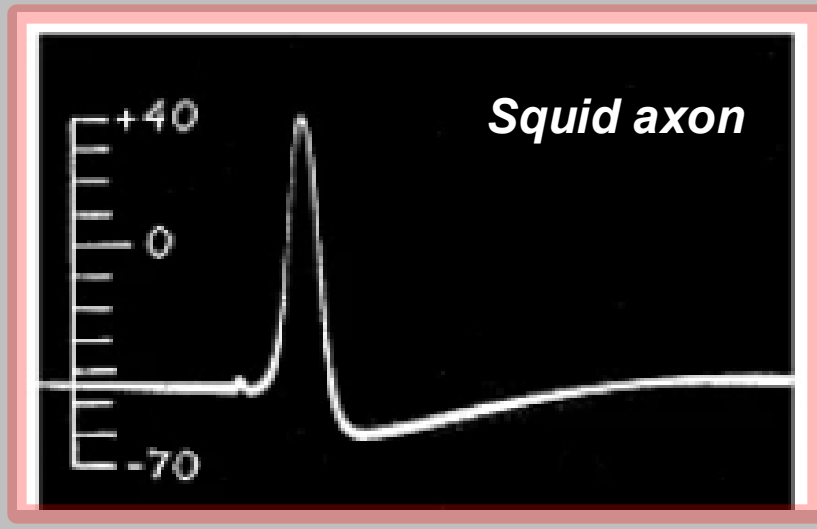


Nernst equation!

$$E = \frac{RT}{zF} \ln \frac{[\text{ion outside cell}]}{[\text{ion inside cell}]}.$$

Outside		Inside		Ratio Outside:Inside	E_{ion} (at 37°C)
$[K^+]_o$	= 5 mM	$[K^+]_i$	= 100 mM	1:20	−80 mV
$[Na^+]_o$	= 150 mM	$[Na^+]_i$	= 15 mM	10:1	62 mV
$[Ca^{2+}]_o$	= 2 mM	$[Ca^{2+}]_i$	= 0.0002 mM	10,000:1	123 mV
$[Cl^-]_o$	= 150 mM	$[Cl^-]_i$	= 13 mM	11.5:1	−65 mV

Action Potentials (APs)



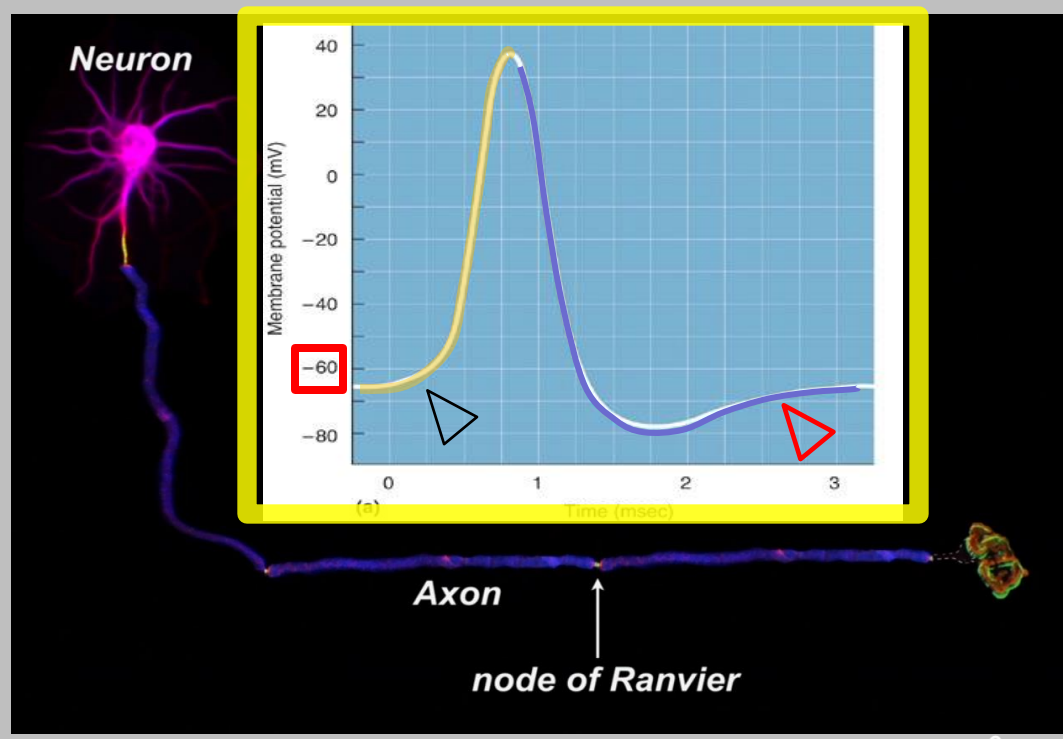
APs are the information carrying electrical signal of neurons about the external world, motor commands, emotions, etc.

Neurons have a threshold for AP generation – depolarization to ~-40mV then… bang!

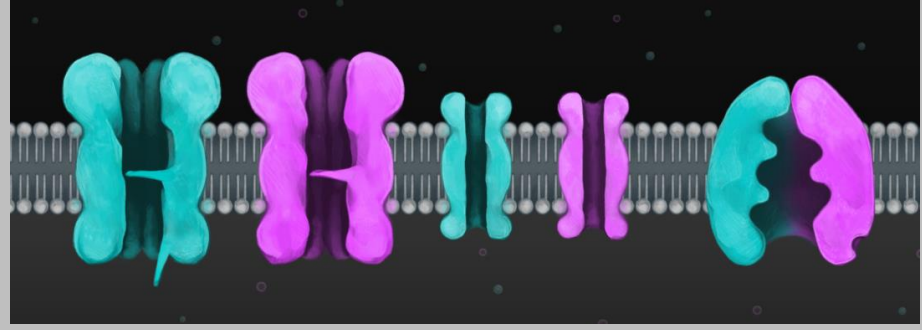
What determines the AP threshold? – the "voltage-gating" of voltage-gated Na+ channels (activation voltage ~-40mV)

APs are generated by the activation of voltage-gated Na+ and K+ channels.

Travel down the axon and cause neurotransmitter release which is used to communicate across neuronal connections (synaptic transmission).



Action potential simulation: https://neuromembrane.ualberta.ca/



ACTION POTENTIAL
Simulation

LEAK CHANNELS

Relative Permeability

Na+ K+

Net Conductance (mS)

NA+ CHANNEL

Conductance (mS)

Reverse Potential 0.0 mV

Inactivation Gate

TTX Neurotoxin

K+ CHANNEL

Conductance (mS)

Reverse Potential 0.0 mV

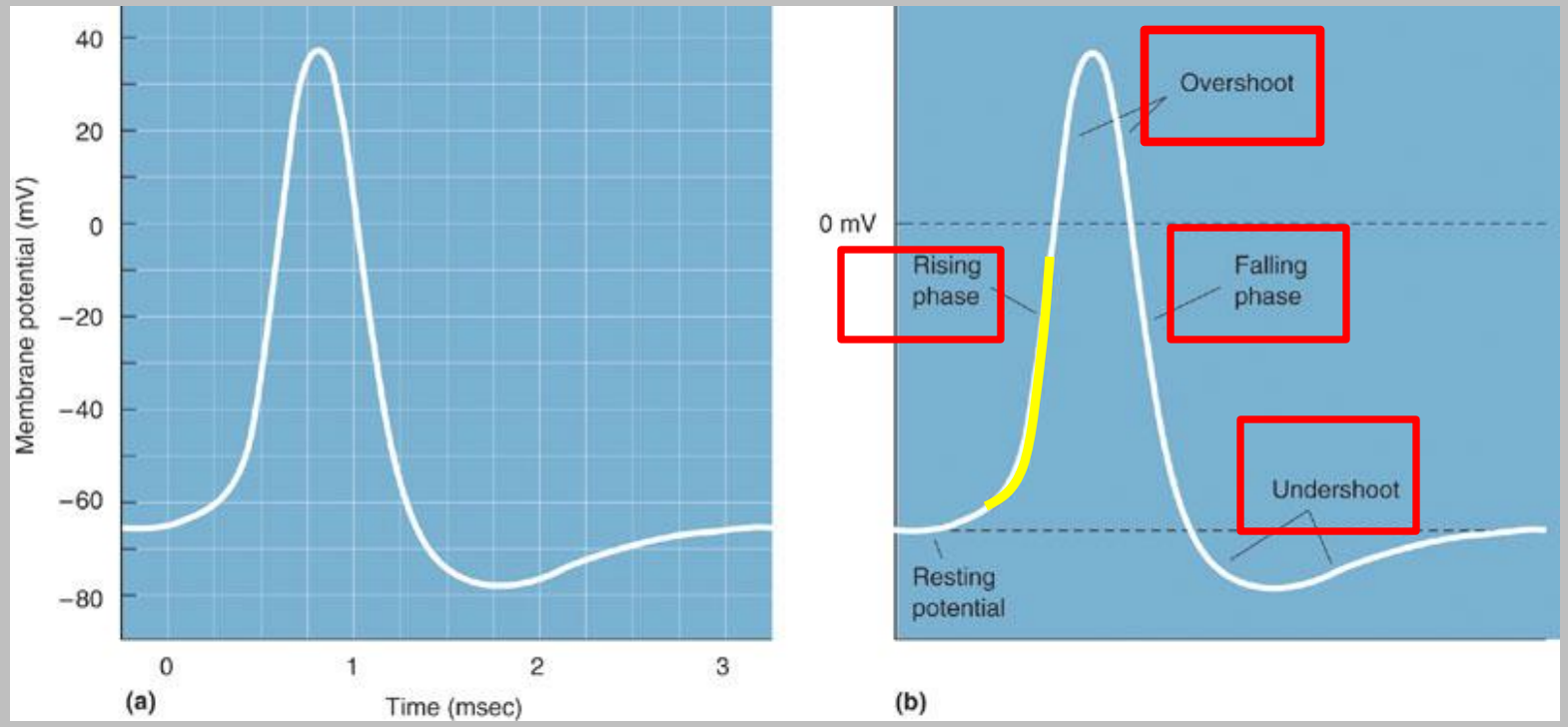
MEMBRANE SETTINGS

CONCENTRATION SETTINGS

EXTERNAL CURRENT

CREATE SIMULATION

4 Phases of the AP



- 1. Rising phase = initial rapid ***depolarization*** – opening of **voltage-gated** Na+ channels
- 2. Overshoot = portion of the AP that is depolarized > 0mV – opening, closing, inactivation of Na+ channels and opening of K+ channels.
- 3. Falling phase = rapid ***hyperpolarization*** – opening of **voltage gated** K+ channels
- 4. Undershoot = portion of AP that is hyperpolarized past resting Vm toward (EK+, -80mV) - closing of K+ channels.

Clinical correlates: Mechanisms of neurotoxins

Tetrodotoxin (TTX)

- potent sodium channel blocker
- found in symbiotic bacteria in Pufferfish eg. genus *Lagocephalus*
- eaten in small amounts causes tingling and numbness of the mouth.
- eaten in large amounts can cause limb weakness, respiratory failure and cardiac arrest
- symptom onset varies from immediately to ~15mins

Saxitoxin

- potent sodium channel blocker
- produced by dinoflagellates found in shellfish
- causes "paralytic shellfish poisoning“
- similar symptoms as in TTX poisoning

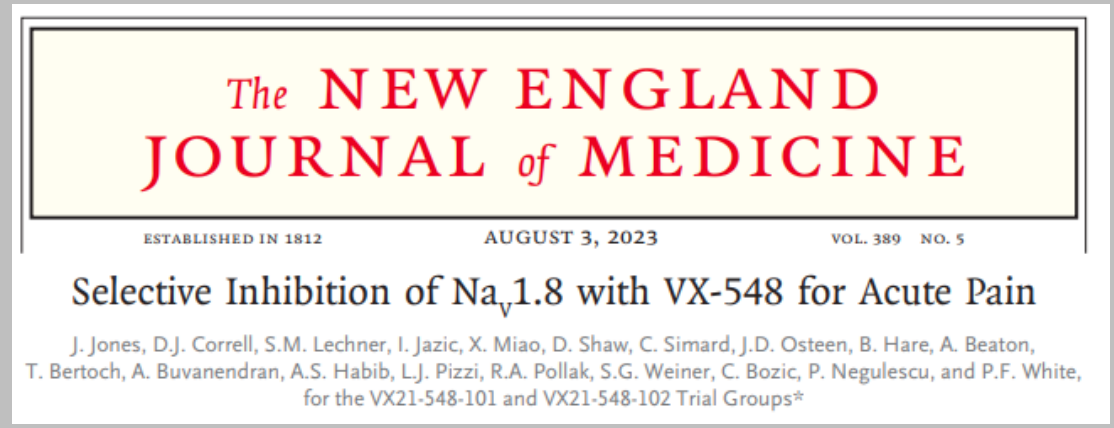
α-dendrotoxin

- potent potassium channel blocker (Kv1)
- found in venom of the green mamba Dendroaspis angusticeps
- prolongs action potentials affecting neuro and cardiovascular function

Targeting VG Na channels for the treatment of pain (ex. after surgery).

Block action potentials in peripheral neurons (DRGs) carrying pain info to brain.

DRGs express voltage gated Na+ channel (Nav1.8) that is not found in central neurons.

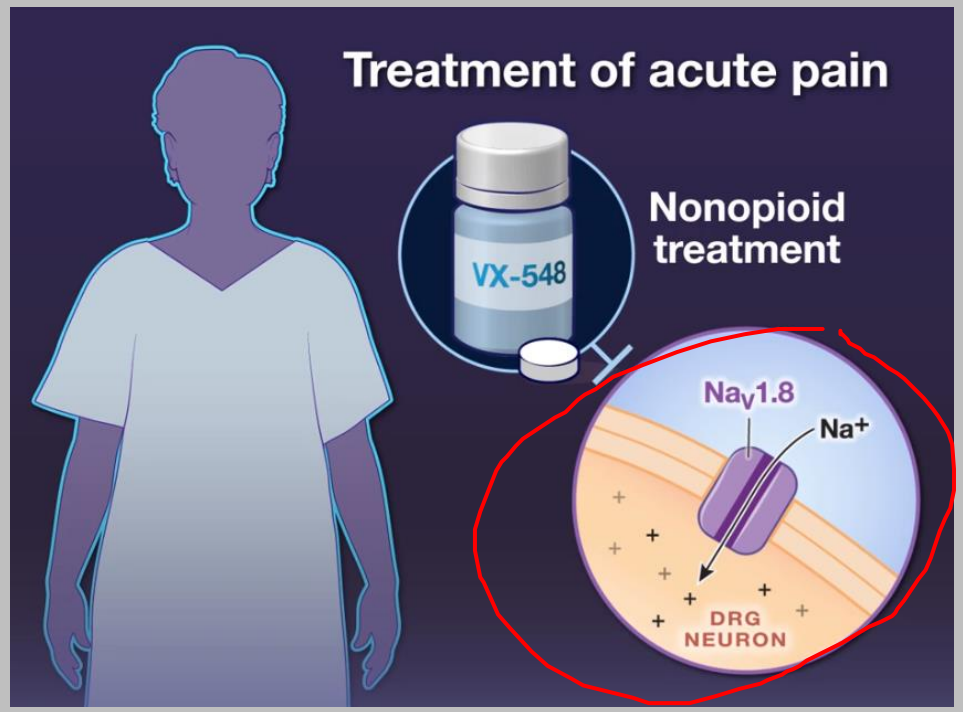

The NEW ENGLAND JOURNAL of MEDICINE

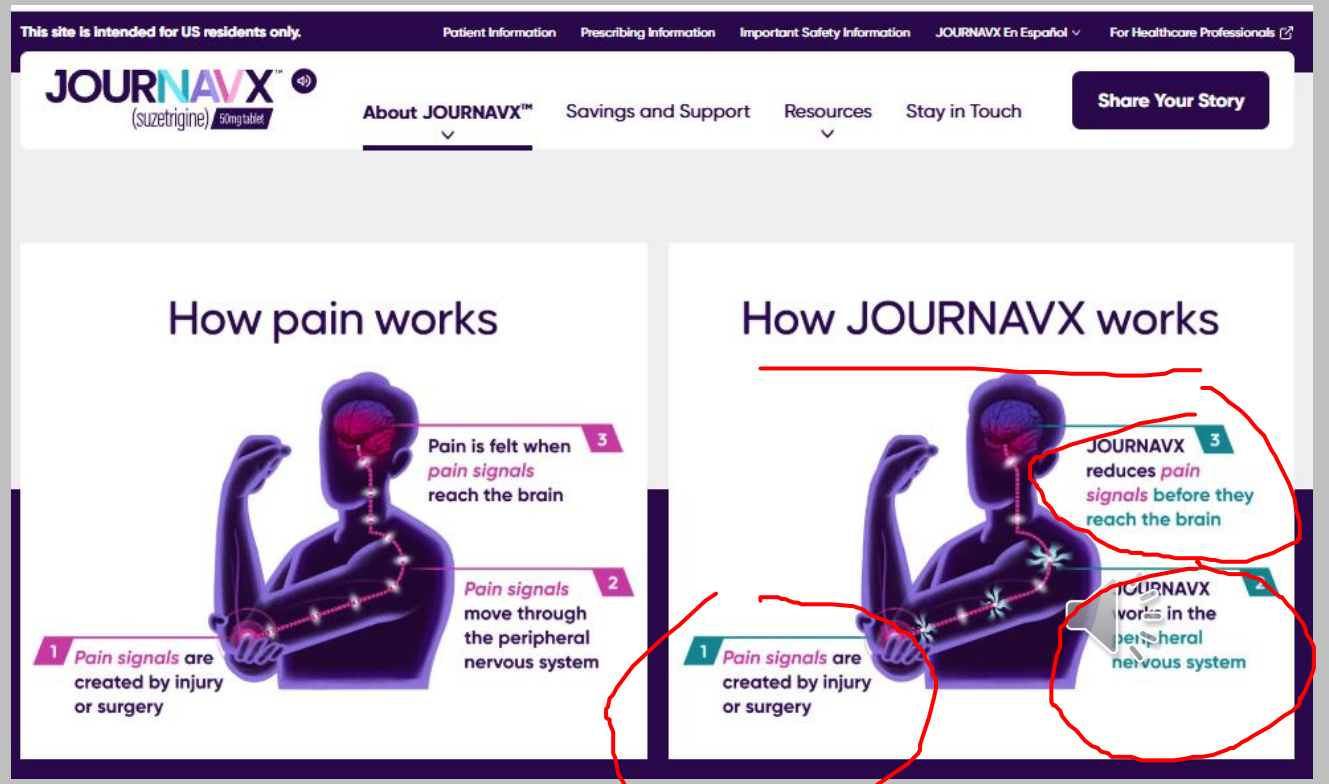
ESTABLISHED IN 1812 AUGUST 3, 2023 VOL. 389 NO. 5

Selective Inhibition of $Na_V1.8$ with VX-548 for Acute Pain

J. Jones, D.J. Correll, S.M. Lechner, I. Jazic, X. Miao, D. Shaw, C. Simard, J.D. Osteen, B. Hare, A. Beaton, T. Bertoch, A. Buvanendran, A.S. Habib, L.J. Pizzi, R.A. Pollak, S.G. Weiner, C. Bozic, P. Negulescu, and P.F. White, for the VX21-548-101 and VX21-548-102 Trial Groups*

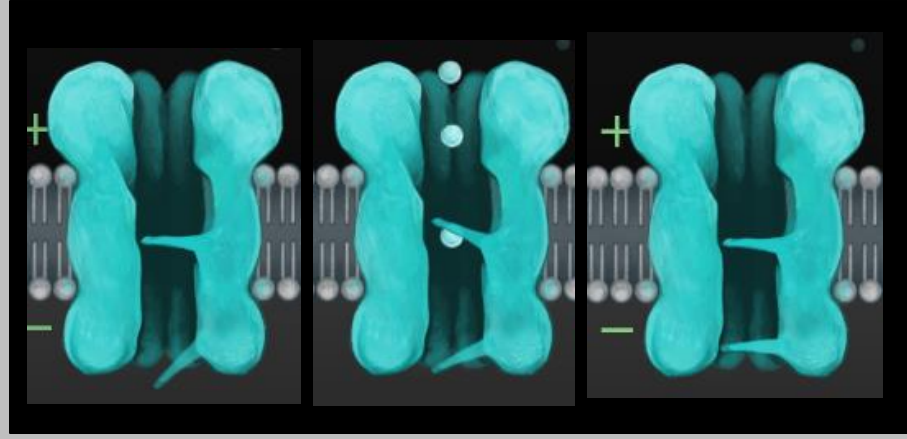
VX-548 now called suzetrigine (Journavx)





https://www.journavx.com/how-journavx-works

VG Sodium channel gene mutations in PNS cause pain syndromes

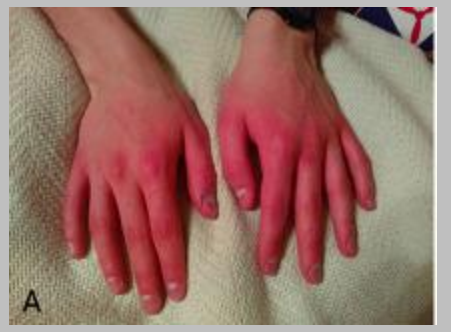


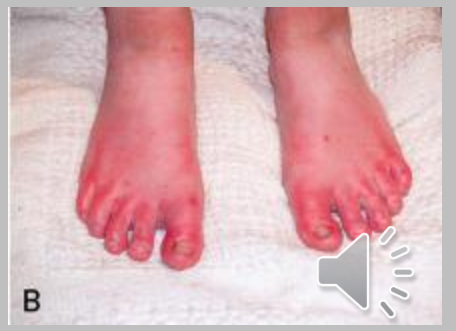
- Mutations can change channel function **increasing** activity –

too many action potentials, abnormal pain signals sent to CNS

1] Inherited Primary Erythromelalgia (Nav1.8) rare syndrome of intermittently **red, hot, painful extremities**. Usually affects the lower extremities (predominantly the feet) but may also involve the upper extremities (predominantly hands) and rarely involves the face. Symptoms present in the first two decades of life.

2] Familial Episodic Pain Syndrome (Nav1.7) also rare and characterized by intense, recurrent pain attacks, which often subside with age. Autonomic symptoms include excessive sweating, palpitations, and breathing difficulties. Pain can be in more proximal areas such as shoulders, chest, knees.





https://www.mayoclinicproceedings.org/article/S0025-6196%2822%2900498-0/fulltext

- Mutations can changes channel function **reducing** activity –

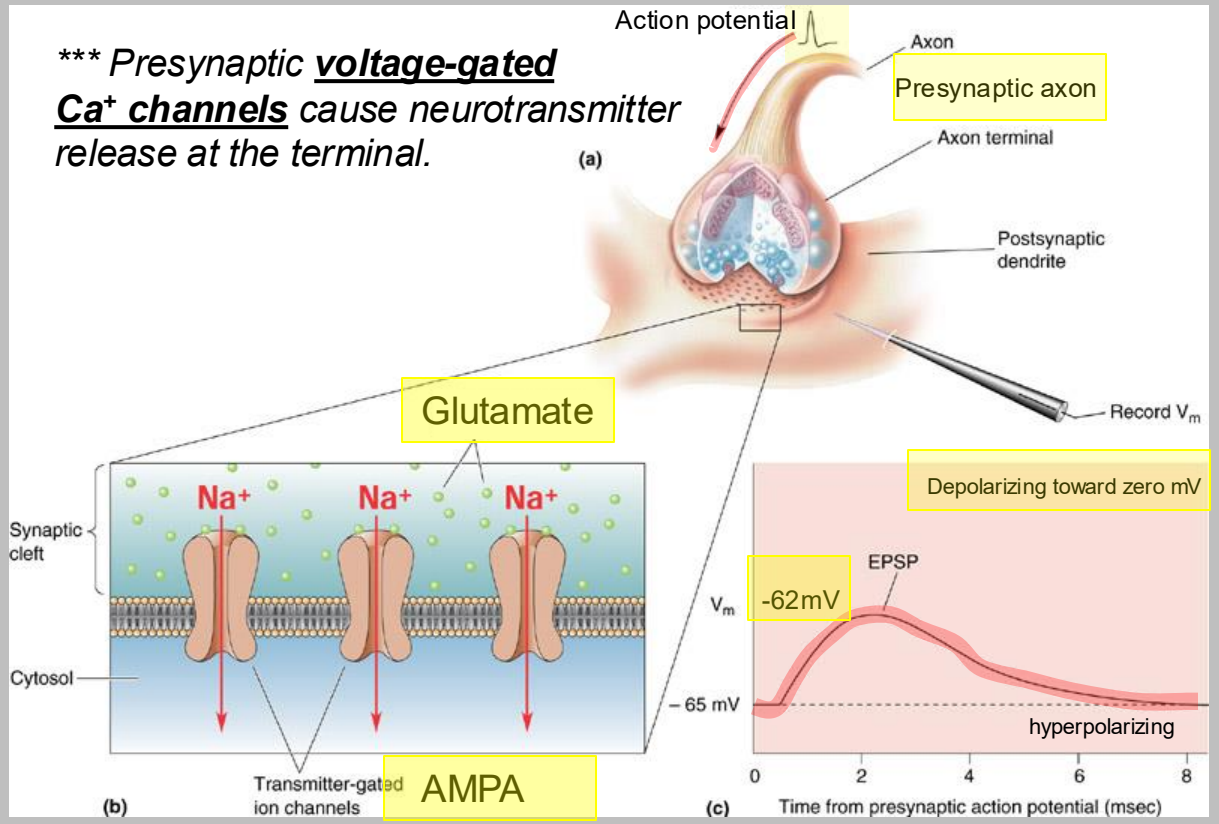
too few action potentials, reduced pain signals sent to CNS

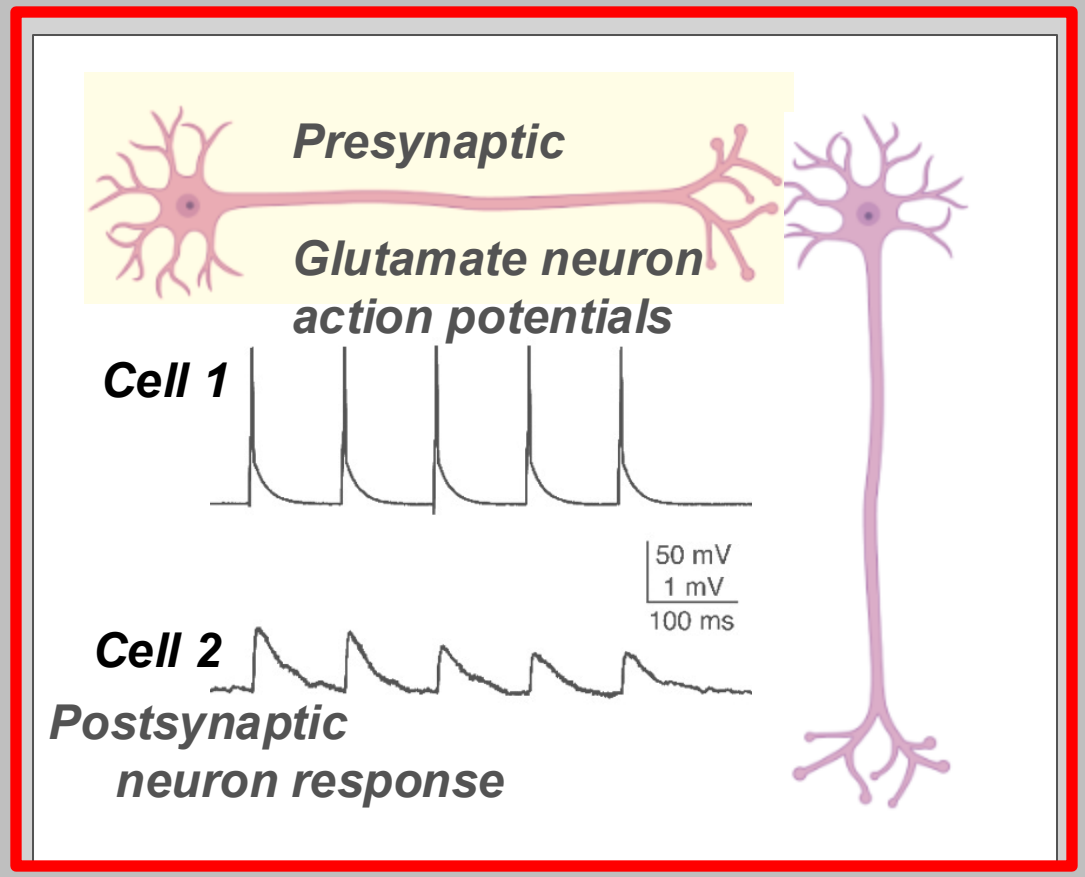
1] Congenital Pain Insensitivtiy/ Congenital Analgesia (Nav1.7) condition characterized by the (near) complete absence of pain perception typically associated with noxious stimuli. Patients have painless injuries beginning in infancy but otherwise normal sensory modalities.

Conclusions (Part 2):

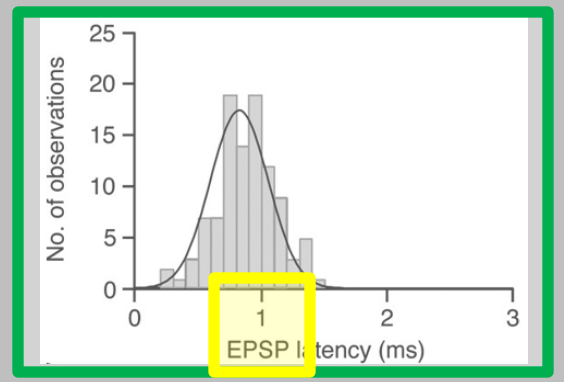
- The neuronal membrane contains voltage-gated Na+ and K+ channels that contribute to the generation of the action potential
- The action potential has distinct phases which are produced by the sequential opening and closing of Na+ and K+ channels
- Action potential generation can be modified by ion channel blockers such as TTX and lidocaine and Journavx.
- Gene mutations affecting voltage gated Na+ channels produce pain syndromes

Glutamate synapses depolarize the postsynaptic neuron



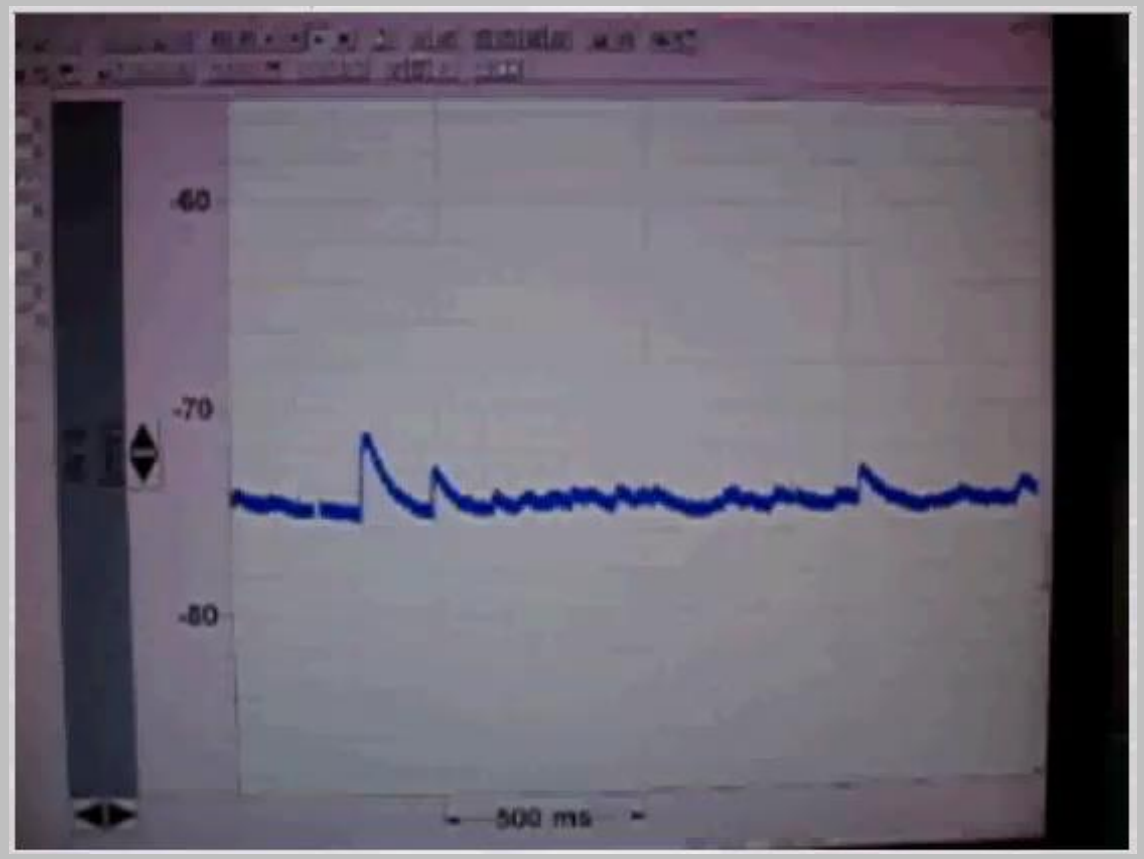


- *AP induced release of Glutamate into cleft*
- *Ionotropic glutamate receptors (AMPA) have a Na+ pore. Glu binding opens channel and Na+ rushes into the cell (some K+ out of the cell).*
- *Depolarizes postsynaptic neuron which might contribute to AP generation in postsynaptic neuron.*



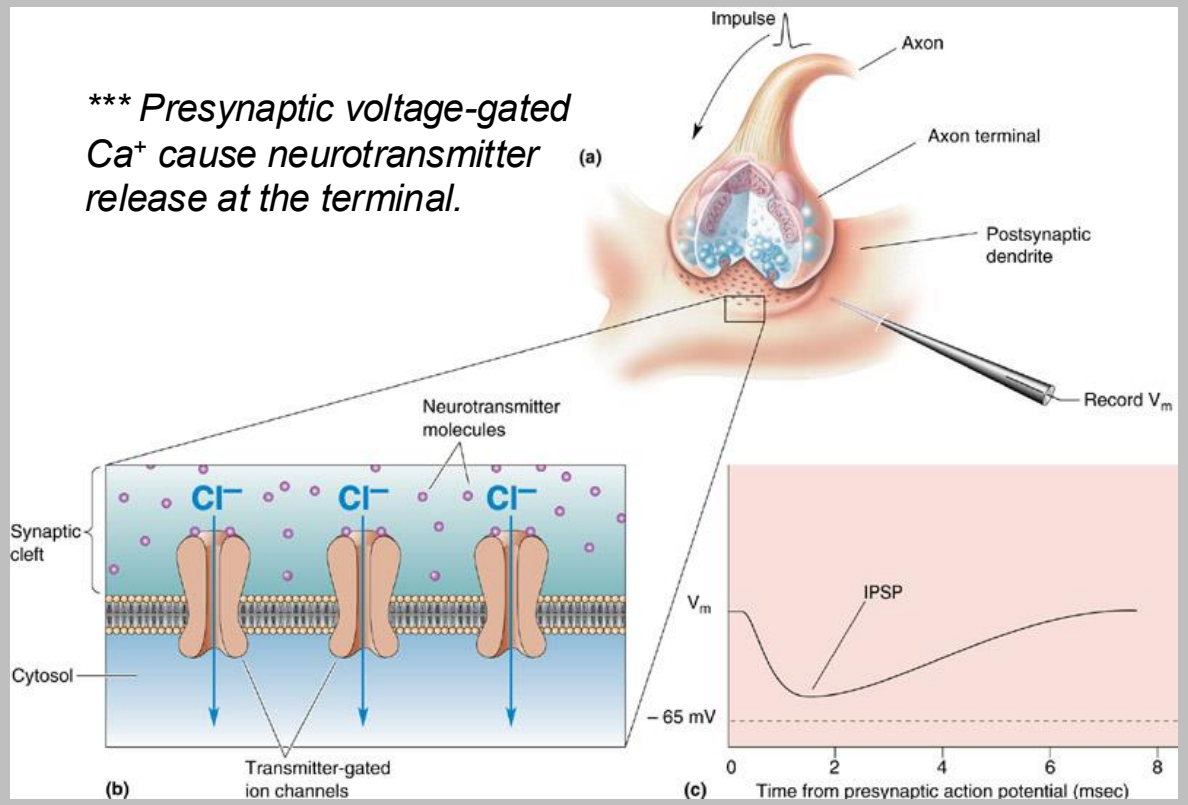
Feldmeyer et al. 2005

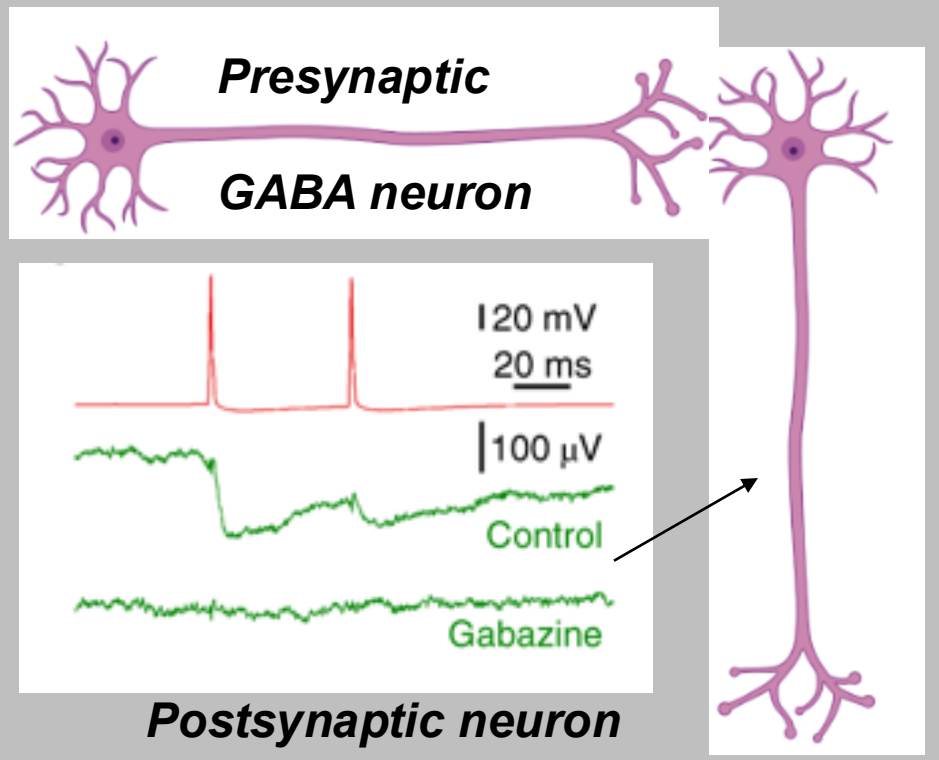
Excitatory postsynaptic potentials- EPSPs



GABA synapses hyperpolarize the postsynaptic neuron

*** Presynaptic voltage-gated Ca^{+} cause neurotransmitter release at the terminal.



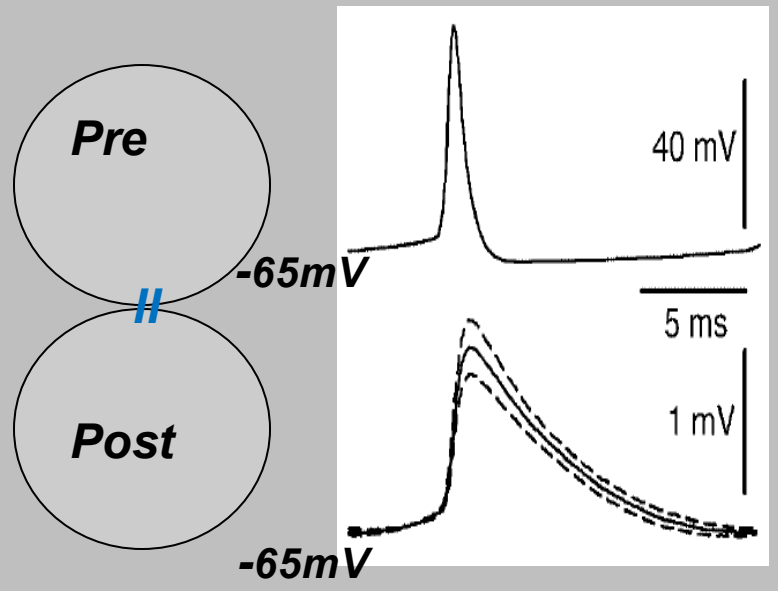


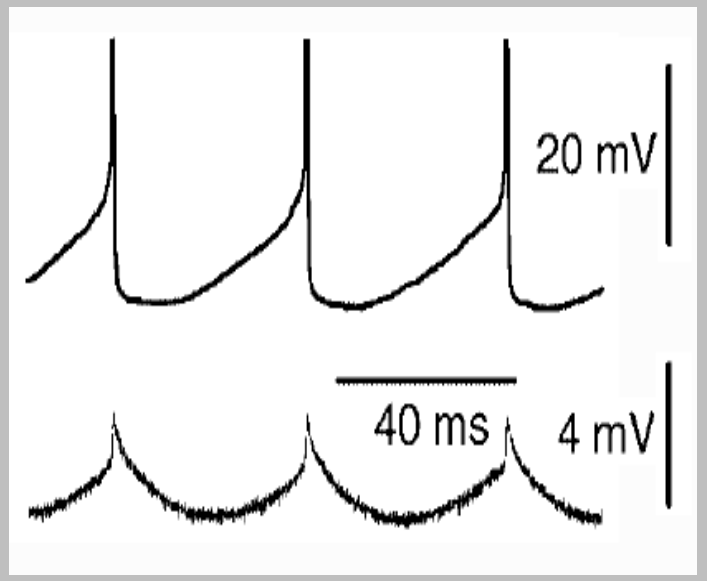
Postsynaptic neuron response

- *AP induced release of GABA*
- *Ionotropic $GABA_A$ receptors have a Cl- pore.*
-*Cl- rushes into the cell due to concentration gradient*
- *Make it harder for the postsynaptic neuron to fire APs*

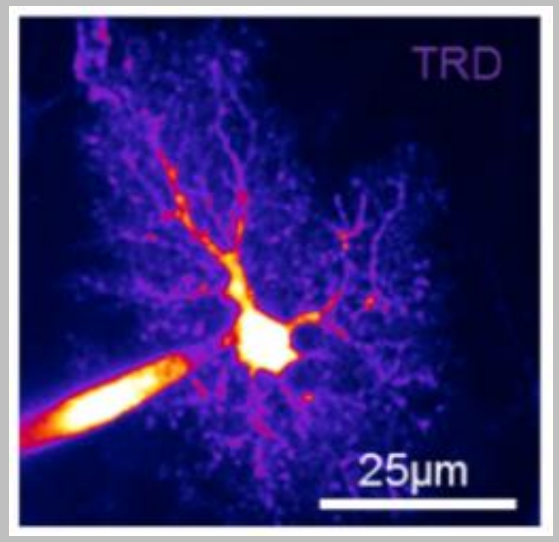
Boldog et. al 2018

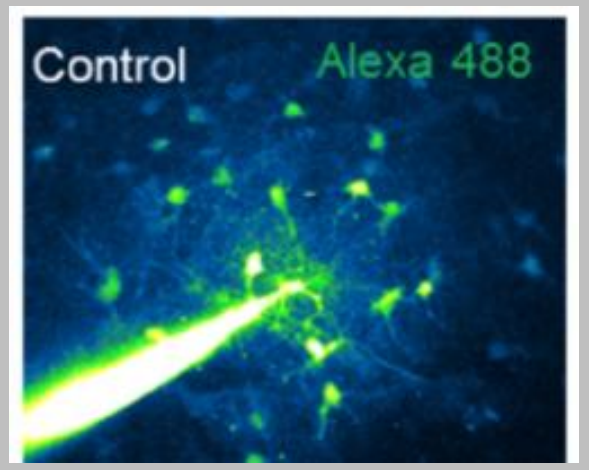
Gap junctions/Electrical synapses: no neurotransmitter used





Connors & Long 2004

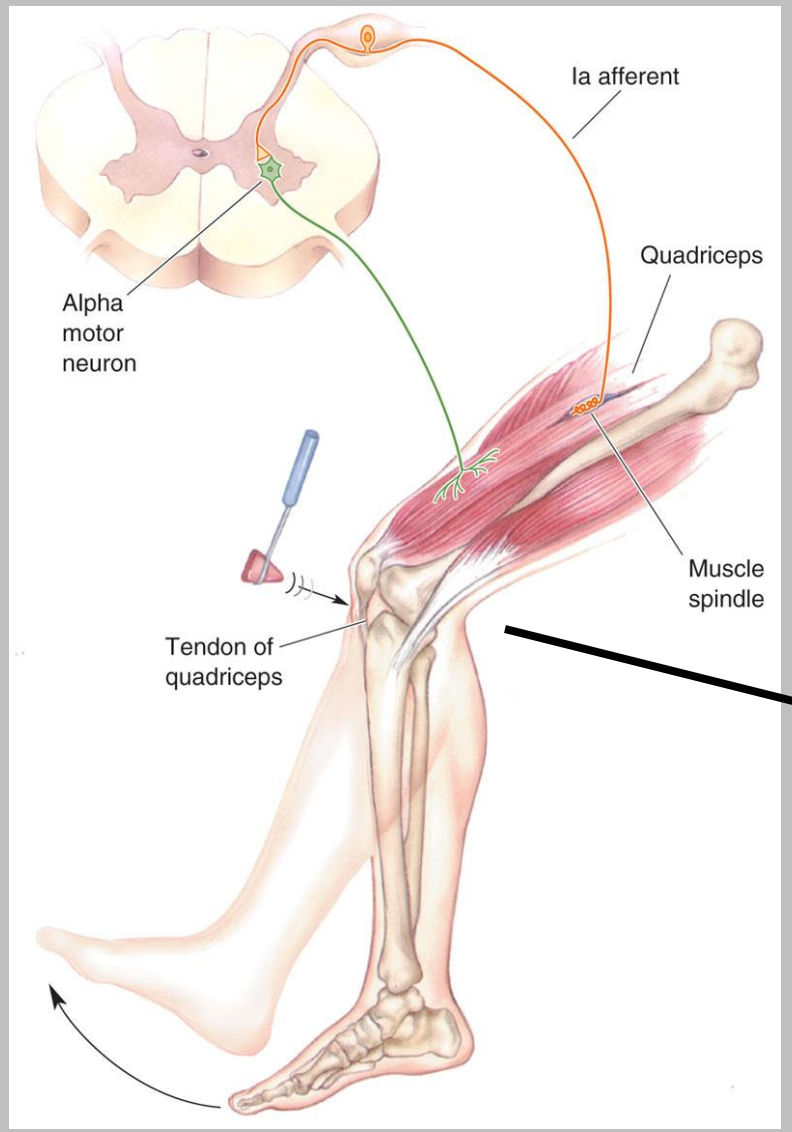




- ***Gap junctions allow direct ion & small molecule flow from one neuron to the other which can depolarize or hyperpolarize the postsynaptic neuron***
- ***Amplitude attenuation of currents***
- ***Usually bidirectional***
- ***Fastest type of neural communication <1ms***
- ***Can depolarize neurons***

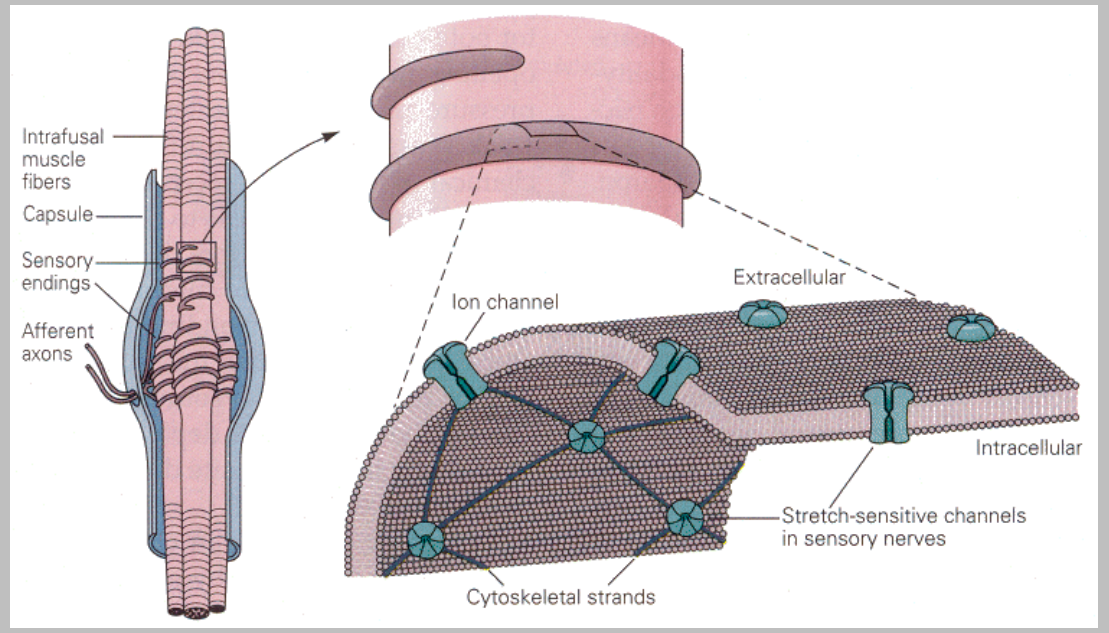
Breithausen et al. Glia 2019
https://doi.org/10.1002/glia.23751

Patellar-tendon reflex:
Great example of how neuronal connections and synaptic physiology creates behavior! Sensation & movement response



Sensory pathway:
Stretch-sensitive channels on 1a axons depolarize neuron and open voltage gated Na+ channels causing AP.

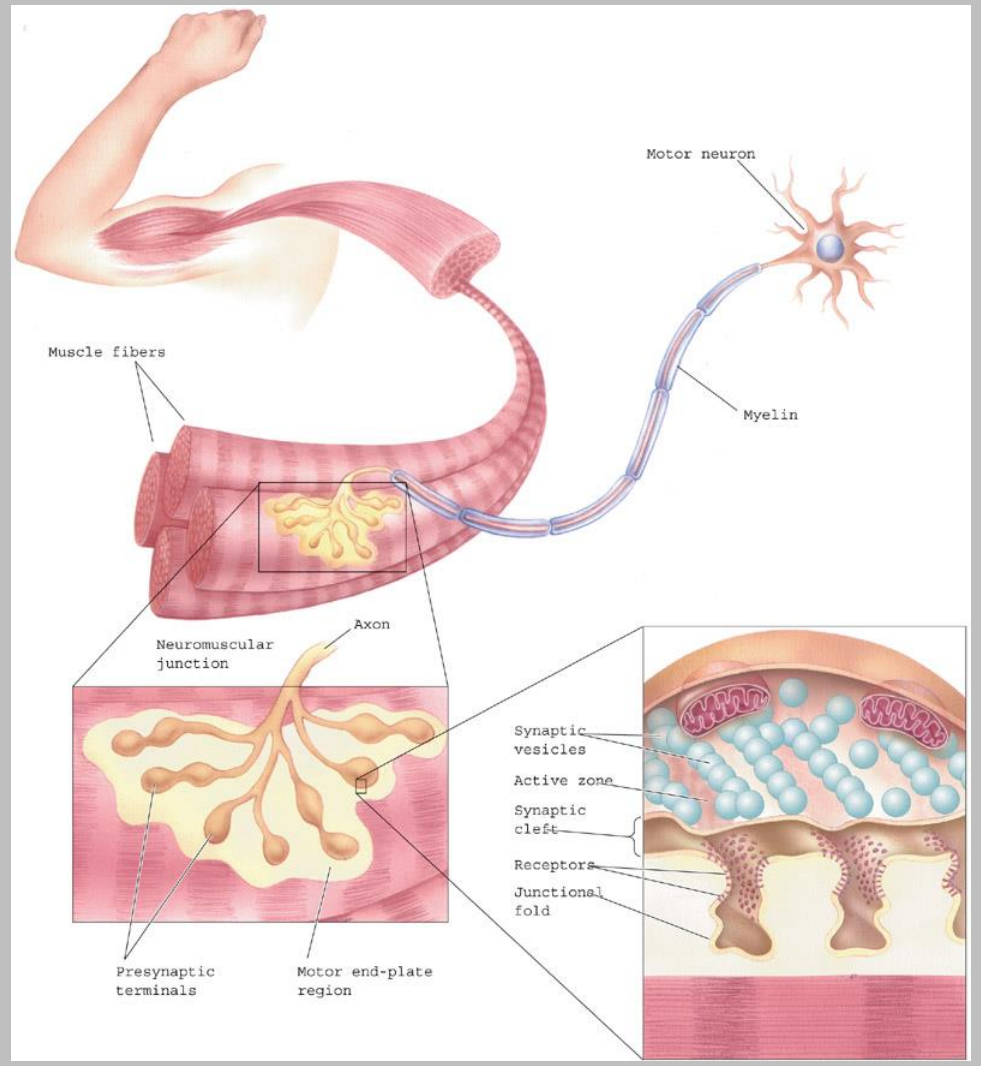
Motor pathway:
1a neuron synapses on motor neuron and releases Glu.
Motor neuron fires an AP and releases Ach at quad muscle causing contraction.

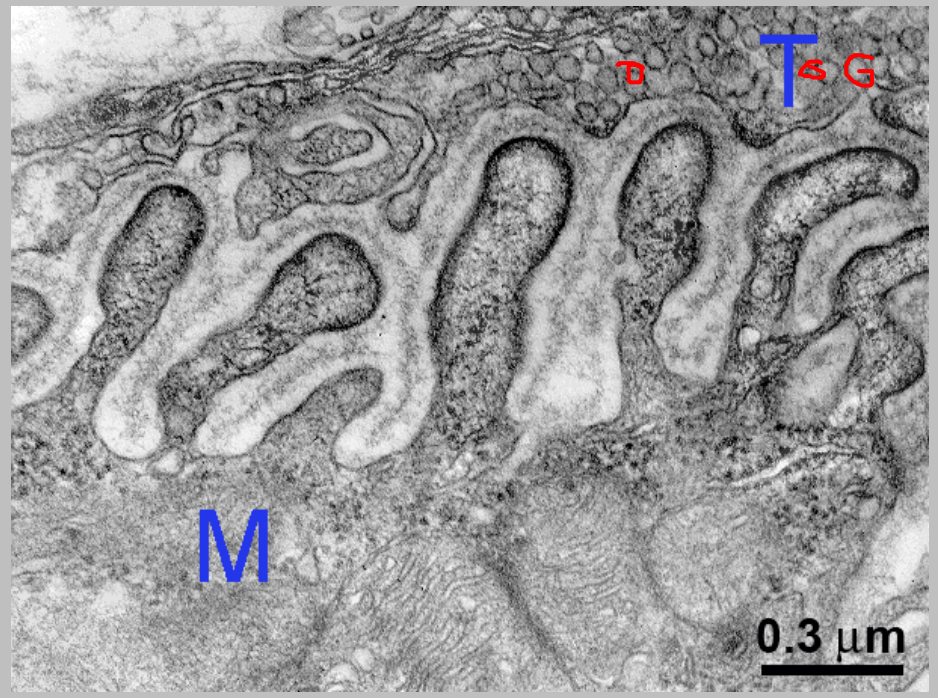


Synaptic Transmission & Behavior:

Neuromuscular synapse/junction

- synapse formed by motor neuron with a muscle fiber.





Synaptic transmission

<u>Presynaptic</u>
- *Resting membrane potential*
- *Action potential generation*
- *Neurotransmitter synthesis*
- *Vesicle packaging of neurotransmitter*
- *Axonal calcium channels*
- *Reuptake of transmitter*

<u>Synaptic cleft</u>
- *Neurotransmitter breakdown*

<u>Postsynaptic</u>
- *Postsynaptic transmitter receptors*
  Ionotropic/metabotropic

Synaptic mechanisms of disease

Conclusions (Part 3):

- Neurons are connect to one another via chemical and electrical synapses
- The postsynaptic effect of a given neurotransmitter will depend on the type of transmitter itself as well as the type of receptor found on the postsynaptic neuron (ionotropic vs. metabotropic)
- All of the players (neurons, channels, myelin, transmitters, etc) involved in synaptic transmission are vulnerable to perturbation in disease and are drug-able targets for therapy.