NEW YORK INSTITUTE OF TECHNOLOGY

College of Osteopathic Medicine

# Class of 2029
# Physiology of Neurons & Synapses


- Raddy L. Ramos, PhD
- Assoc. Prof, Biomedical Sciences
- Email with questions or to set up a meeting: rramos02@nyit.edu

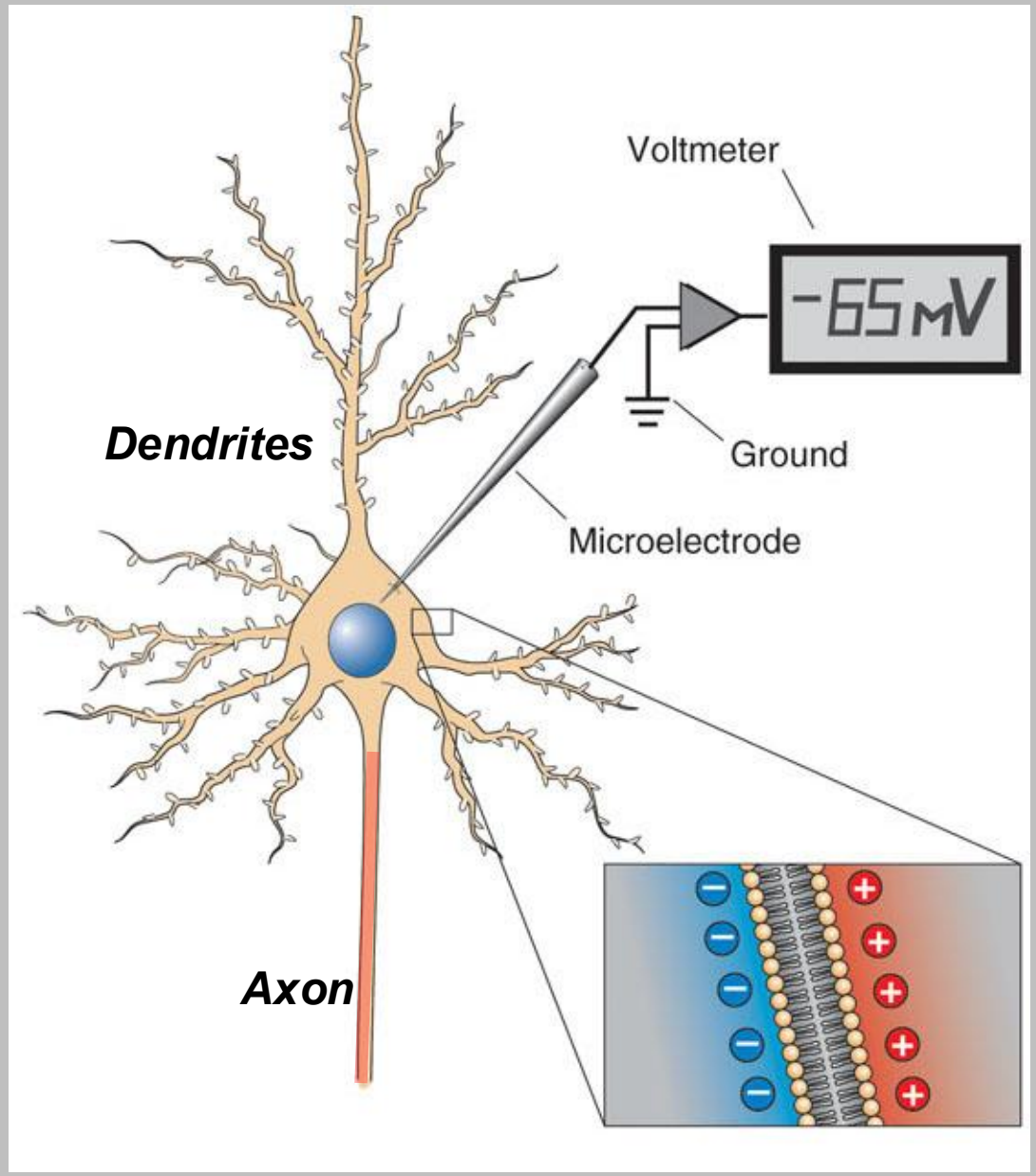

Do.
Make.
Heal.
Innovate.
Reinvent the Future.

# 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)

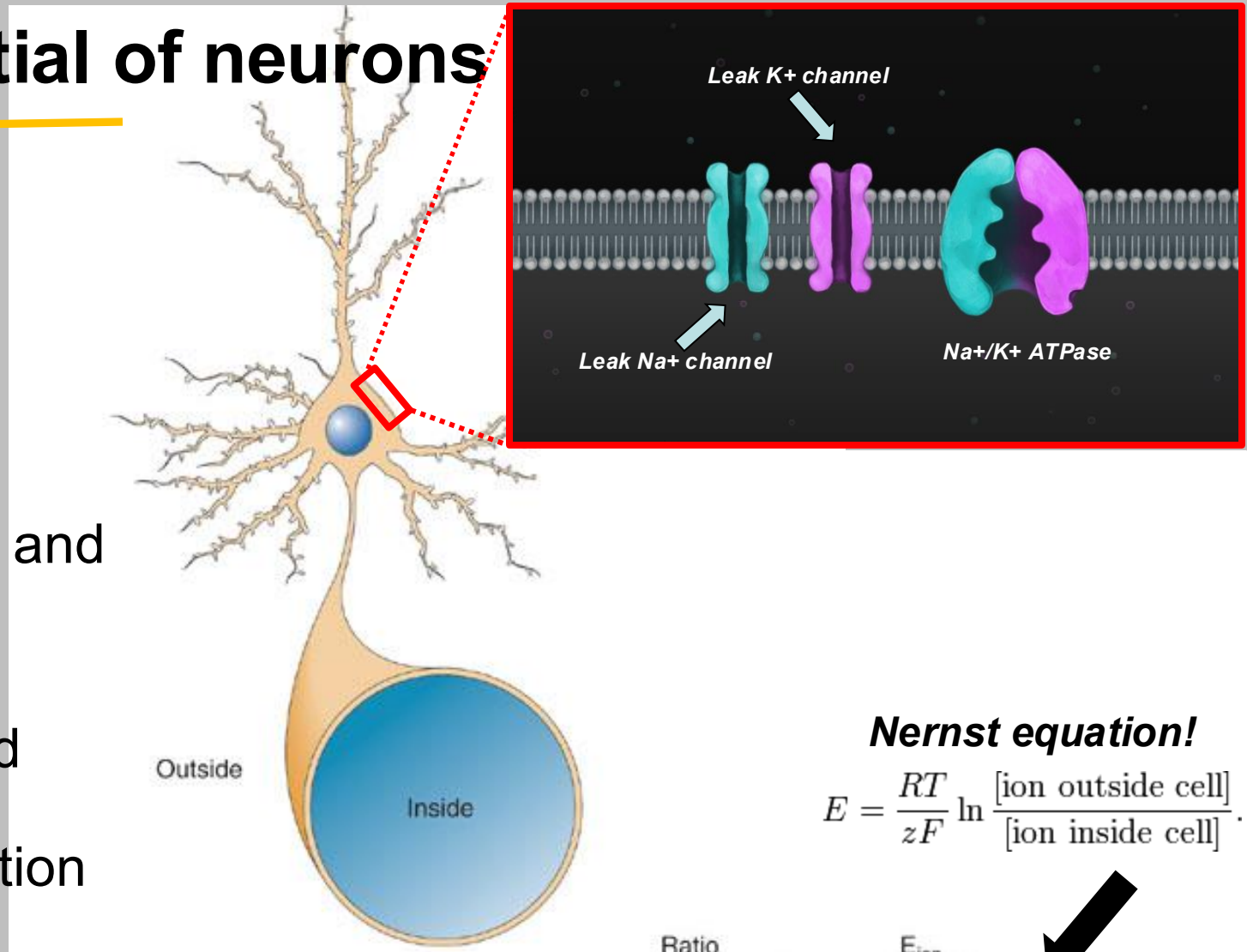
- Neuronal membrane changes, electric activity, and synaptic connections creates behavior!
- rVm of neuron is “hyperpolarized” (more negative) relative to the extracellular side.
- rVm is ~ -65mV in many central neurons but can vary by +/-15mV.
- Membrane potential physiology also important to understand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



# Resting membrane potential of neurons

- Hyperpolarized rVm is established by…

- 1] Na/K pump ->> <u>3$Na^+$ out / 2$K^+$ 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.



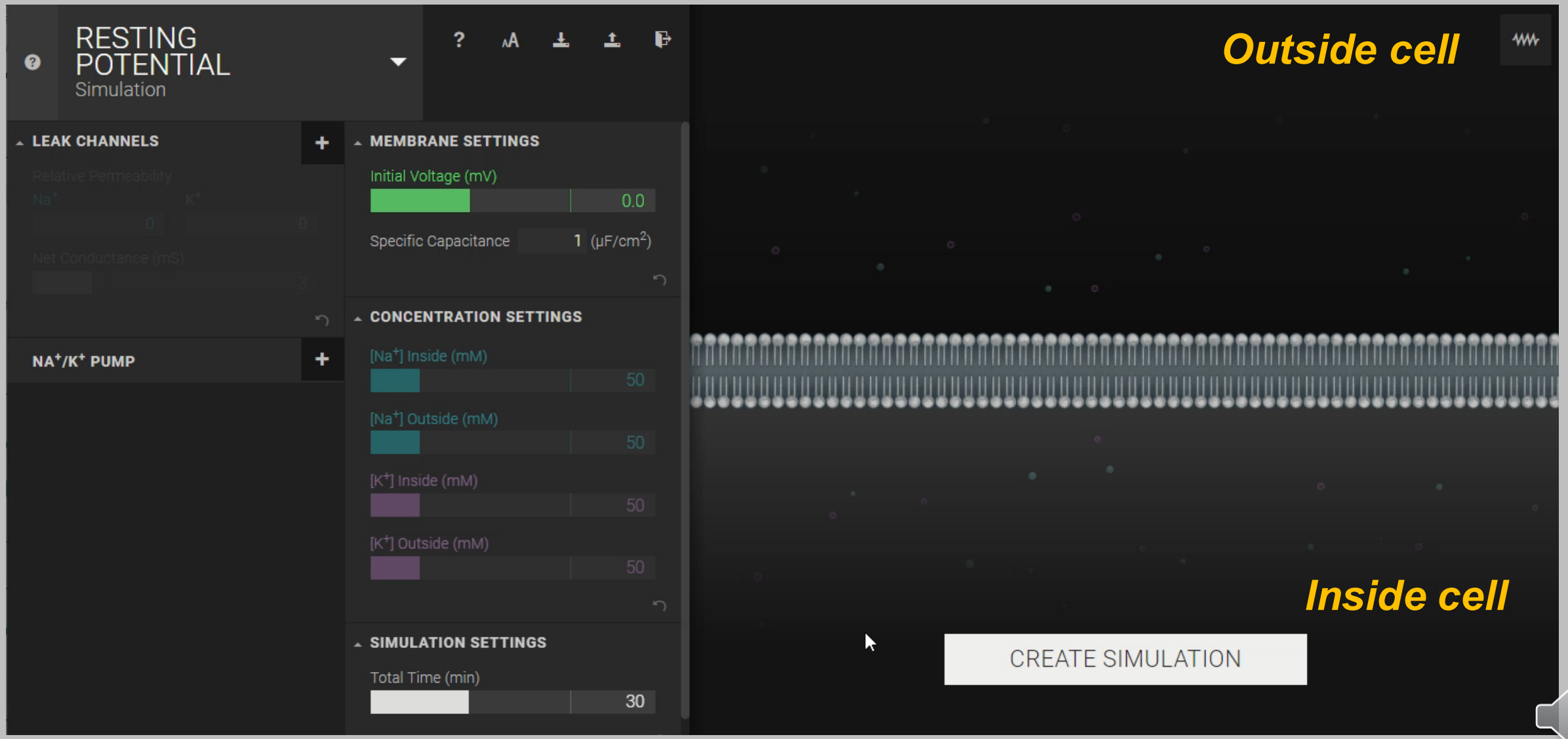

***Nernst equation!***

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

| 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 |

# Resting membrane potential simulation:

https://neuromembrane.ualberta.ca/



# Leak $K^+$ channels contribute the most but not entirely to the rVm (-65mV)

- If the $K^+$ channels contributed the sole ionic conductance at rest then rVm would be equal to $E_K$ ($^-$80mV)
- The rVm is more depolarized than $E_K$
- Leak $Na^+$ channels also contribute to rVm.
- The relative permeability of $K^+$:$Na^+$ is approx 40:1.
- Thus rVm is closest to $E_{K+}$ compared to other ions

| Outside | Inside | Ratio Outside:Inside | $E_{ion}$ (at 37°C) |
|---|---|---|---|
| $[K^+]_o$ = 5 mM | $[K^+]_i$ = 100 mM | 1:20 | −80 mV |
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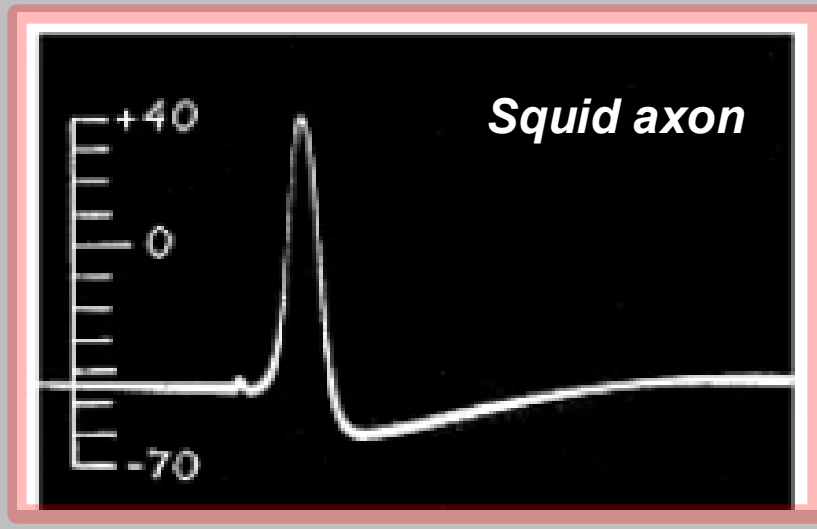
| $[Cl^-]_o$ = 150 mM | $[Cl^-]_i$ = 13 mM | 11.5:1 | −65 mV |

# Conclusions (Part 1):

- Neurons exhibit a negative resting membrane potential due to…
- Na/K pump
- Membrane channels selectively permeable to certain ions especially leak K+ (minimal leak Na+ channels)
- 40:1 permeability ratio between K+ vs Na+ leak channels
- Unequal concentration of charged ions present in the intra vs. extracellular space determine direction and extent of ion flow and membrane potential change.

# Action Potentials (APs)



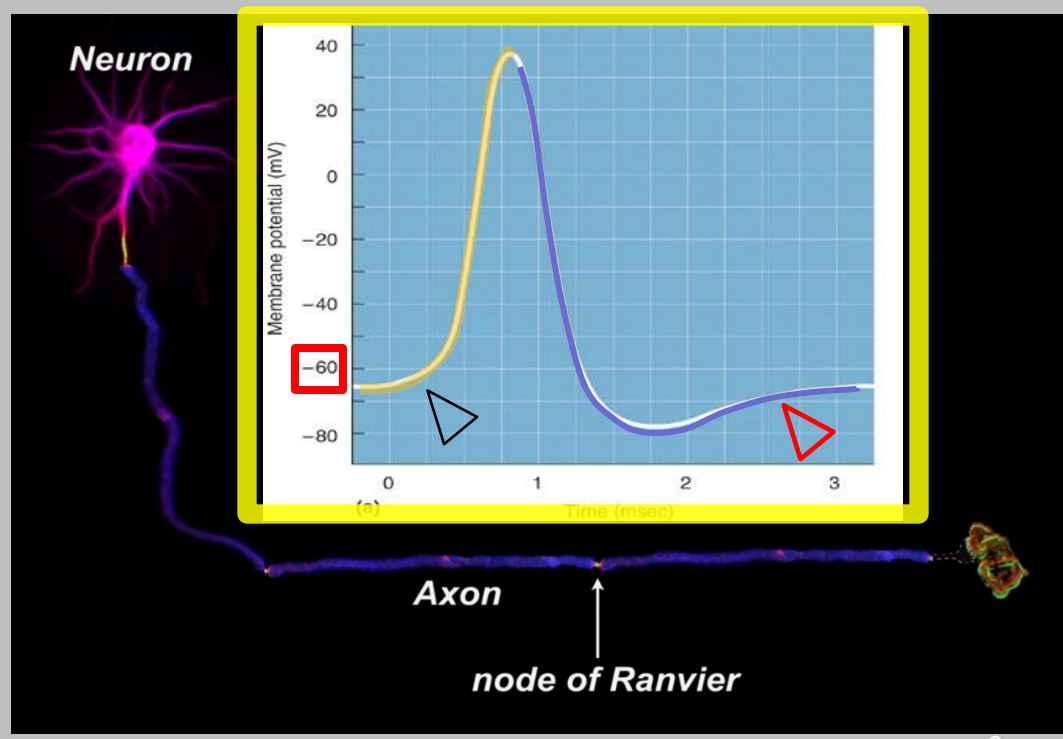

*APs are the information carrying electrical signal of neurons about the external world, motor commands, emotions, etc.*

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

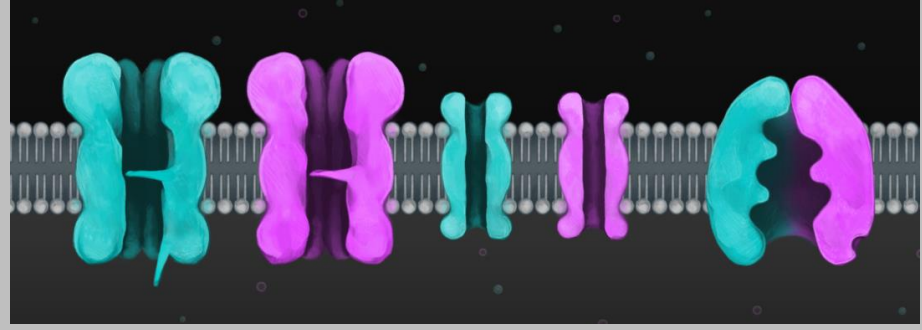
*What determines the AP threshold? – the "voltage-gating" of voltage-gated Na+ channels (activation voltage ~-40mV)*

*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

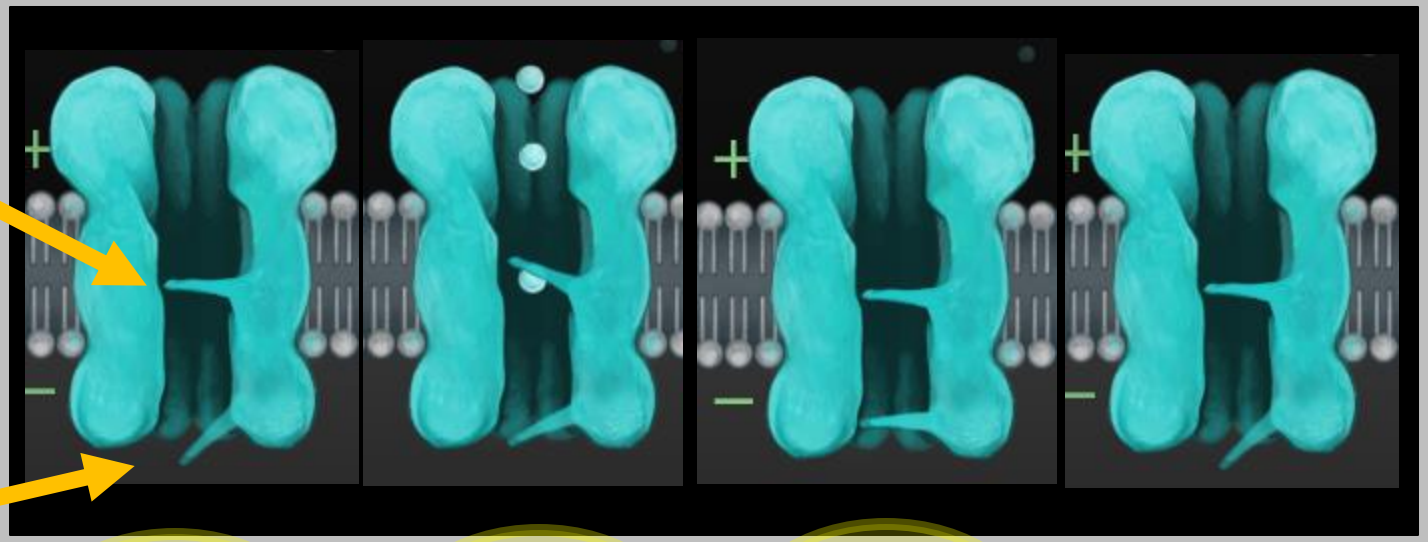
EXTERNAL CURRENT

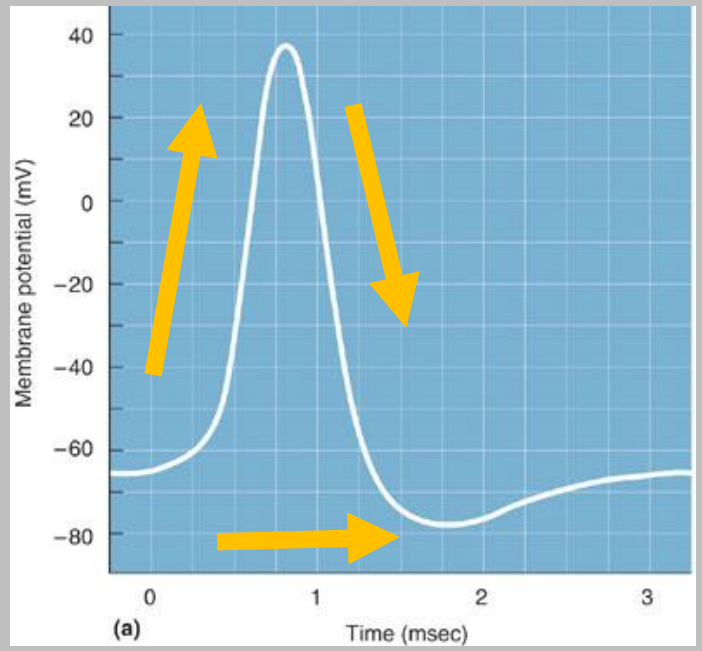
CREATE SIMULATION

# Voltage-gated sodium channel inactivaton

***"Pore" or Activation gate***

***Inactivation gate***



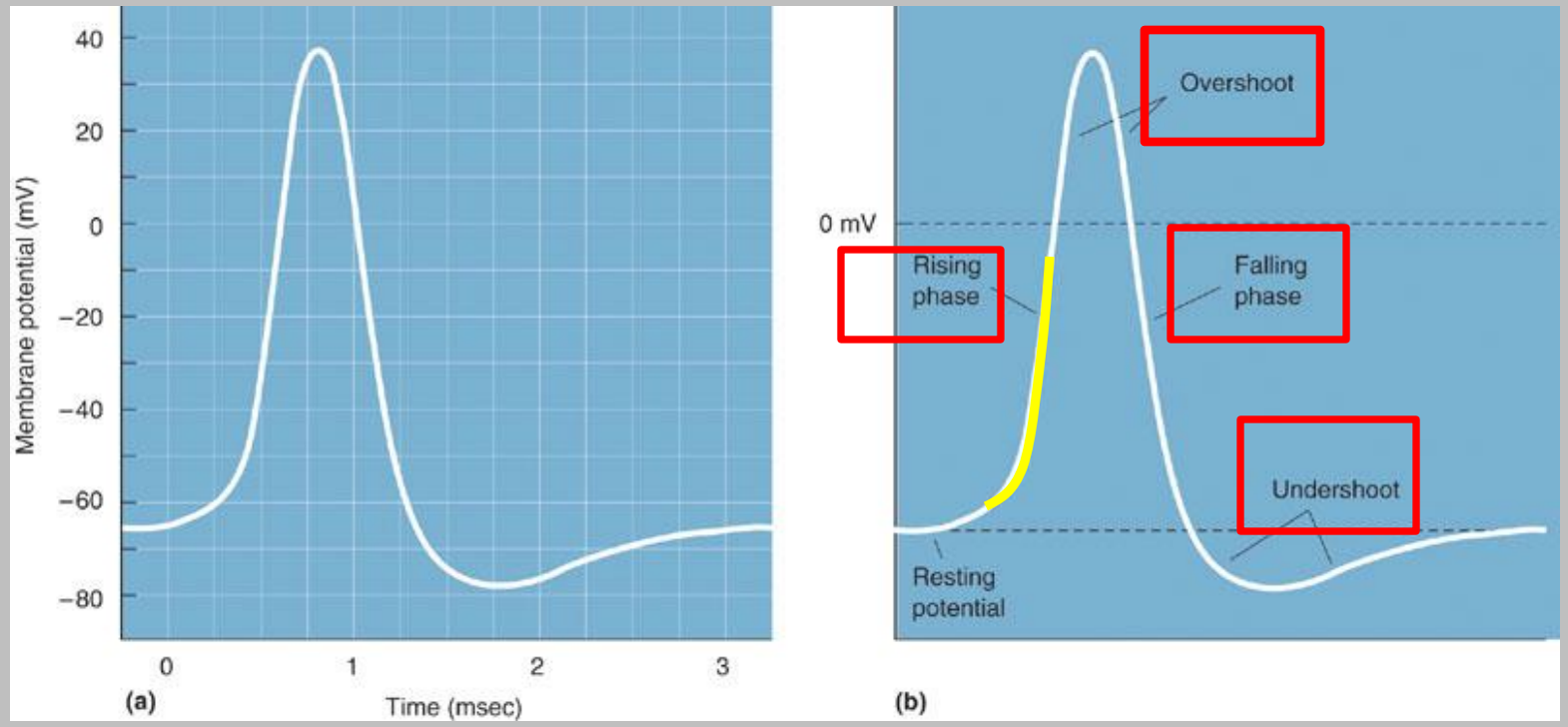




***Closed channel*** ***Open channel*** ***Inactivated channel*** ***Closed channel***

***Membrane potential : Rest - depolarized - repolarize - rest***

*Channel inactivation is produced by a separate part of the protein – "known as the inactivation gate"*
*Genetic mutations that affect the "inactivation gate" result in channels being open for too long – EPILEPSY!*
*Drugs have been developed to modify channel inactivation – speed up or slow down inactivation.*

# 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

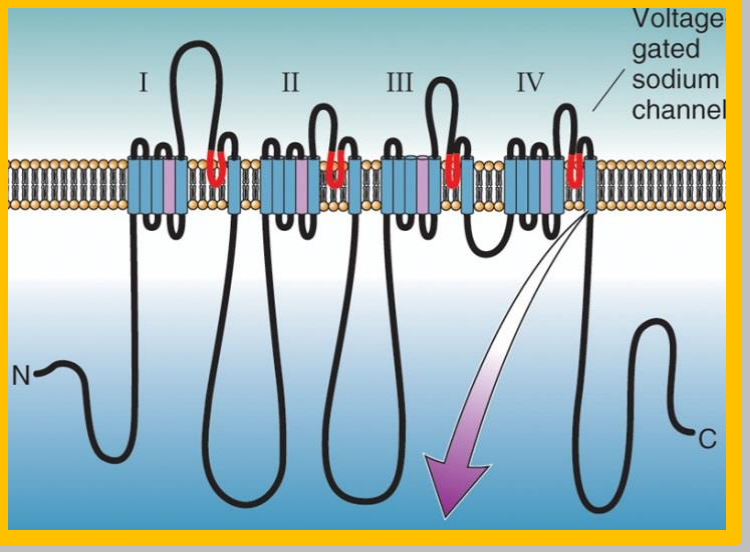
Saxitoxin

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

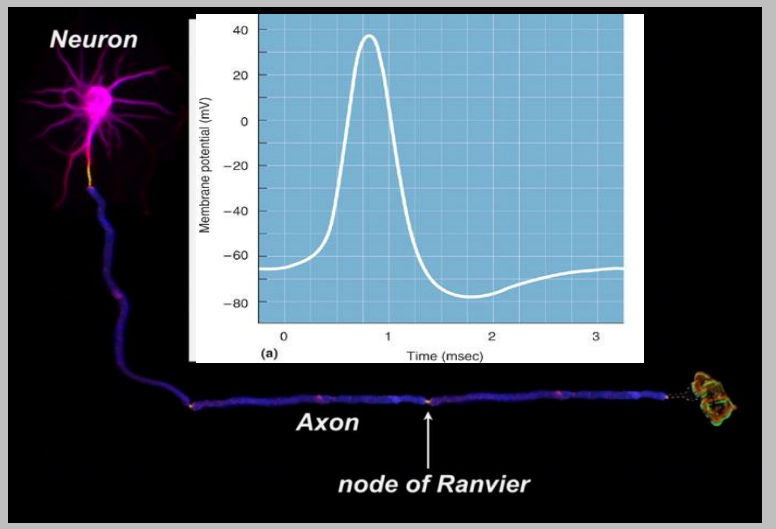
α-dendrotoxin

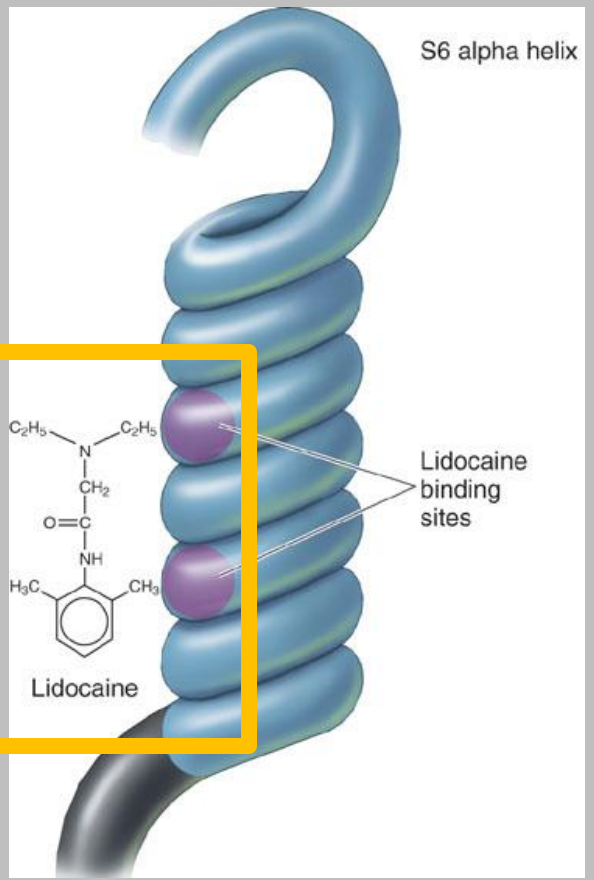
- potent potassium channel blocker (Kv1)
- found in venom of the green mamba Dendroaspis angusticeps
- prolongs action potentials affecting neuro and cardiovascular function

# Mechanism of drug action: Lidocaine




- local anesthetic used for a variety of applications
- Sodium channel blocker
- can be applied topically as a cream
- can be injected directly into nerve, tissue, CSF



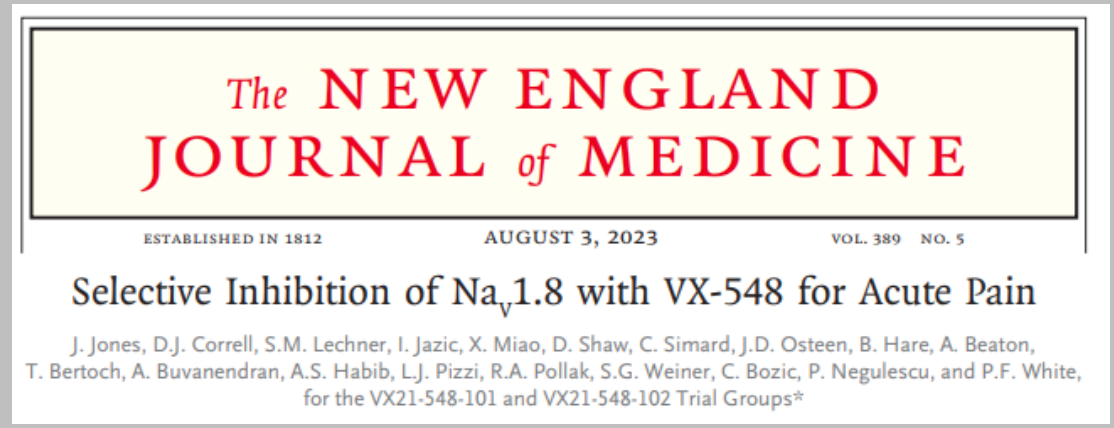





**Targeting VG Na channels for the treatment of pain (ex. after surgery).**

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.

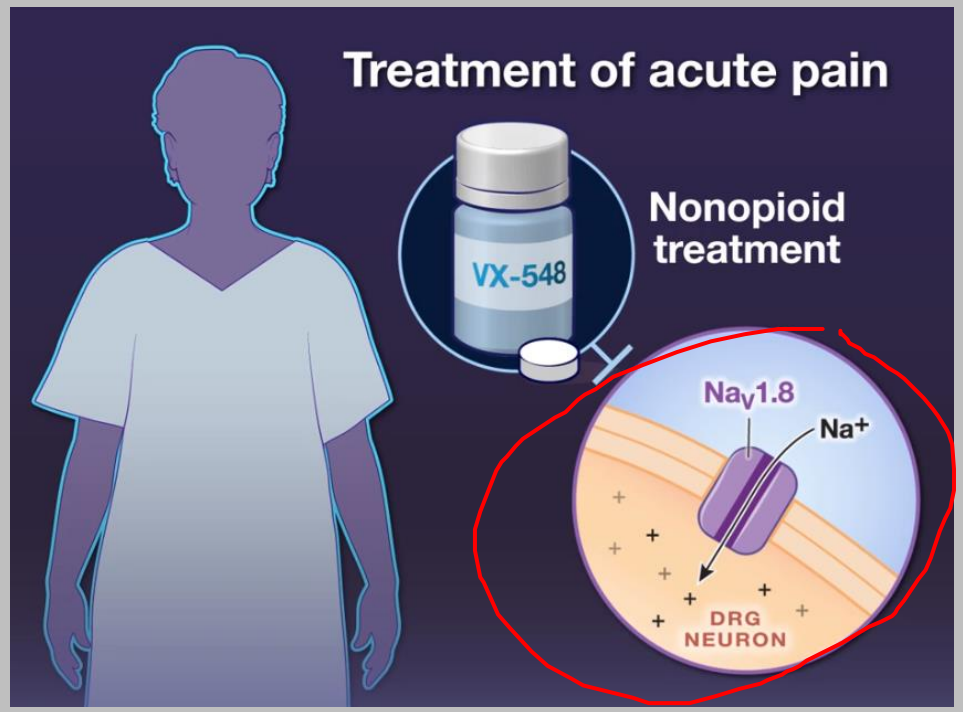

The NEW ENGLAND JOURNAL of MEDICINE

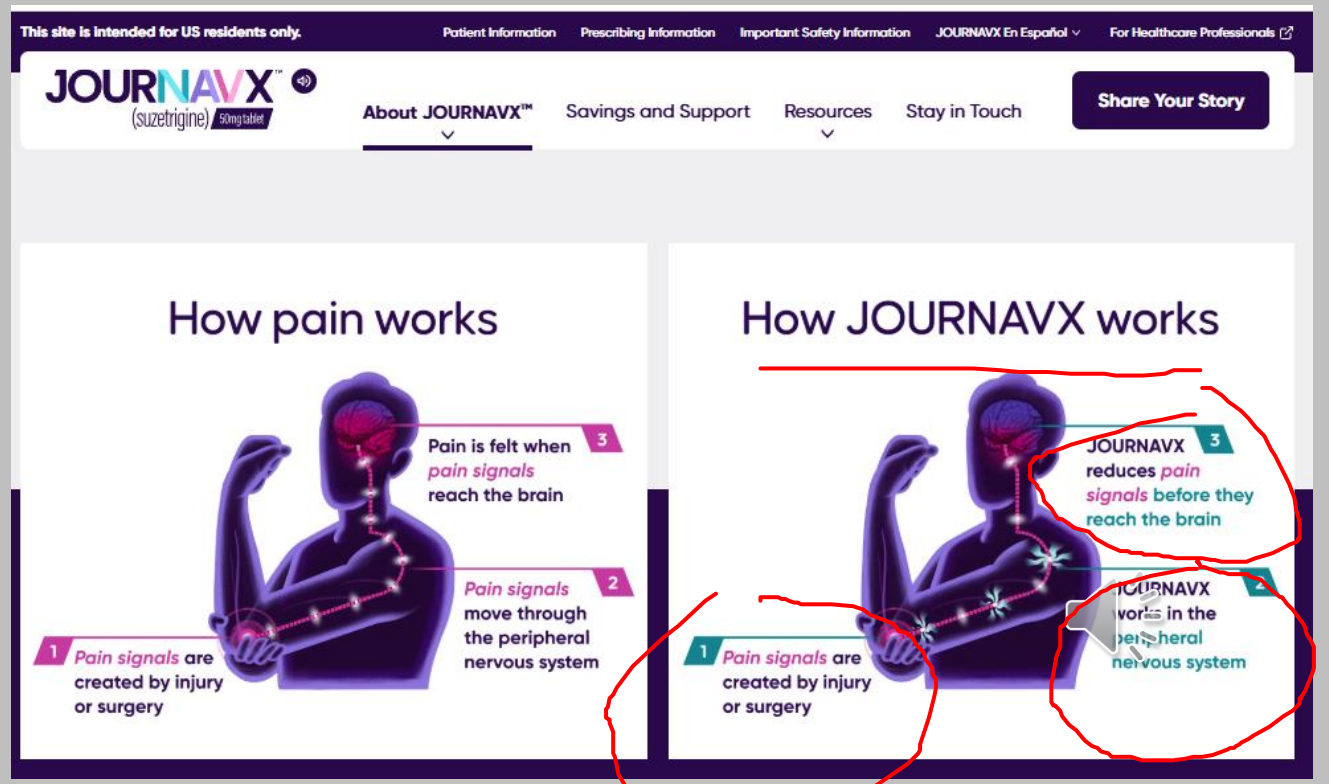
ESTABLISHED IN 1812 AUGUST 3, 2023 VOL. 389 NO. 5

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*

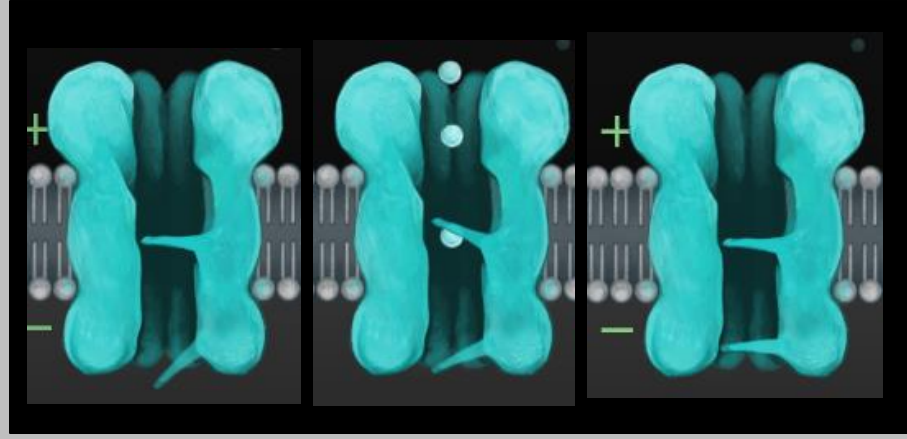
***VX-548 now called suzetrigine (Journavx)***




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

# VG Sodium channel gene mutations in PNS cause pain syndromes

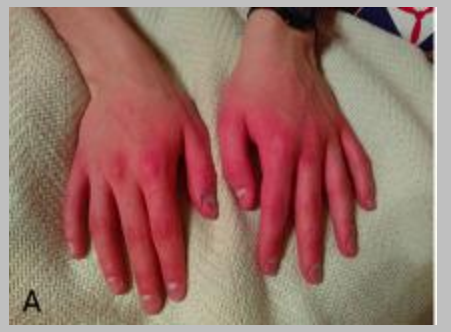


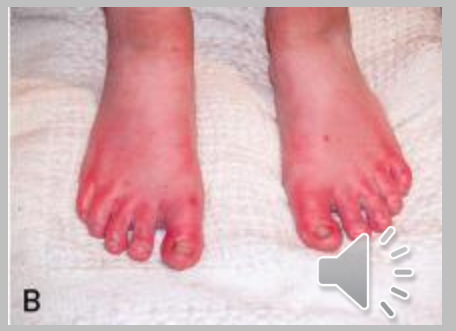
- Mutations can change channel function **increasing** activity –

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.

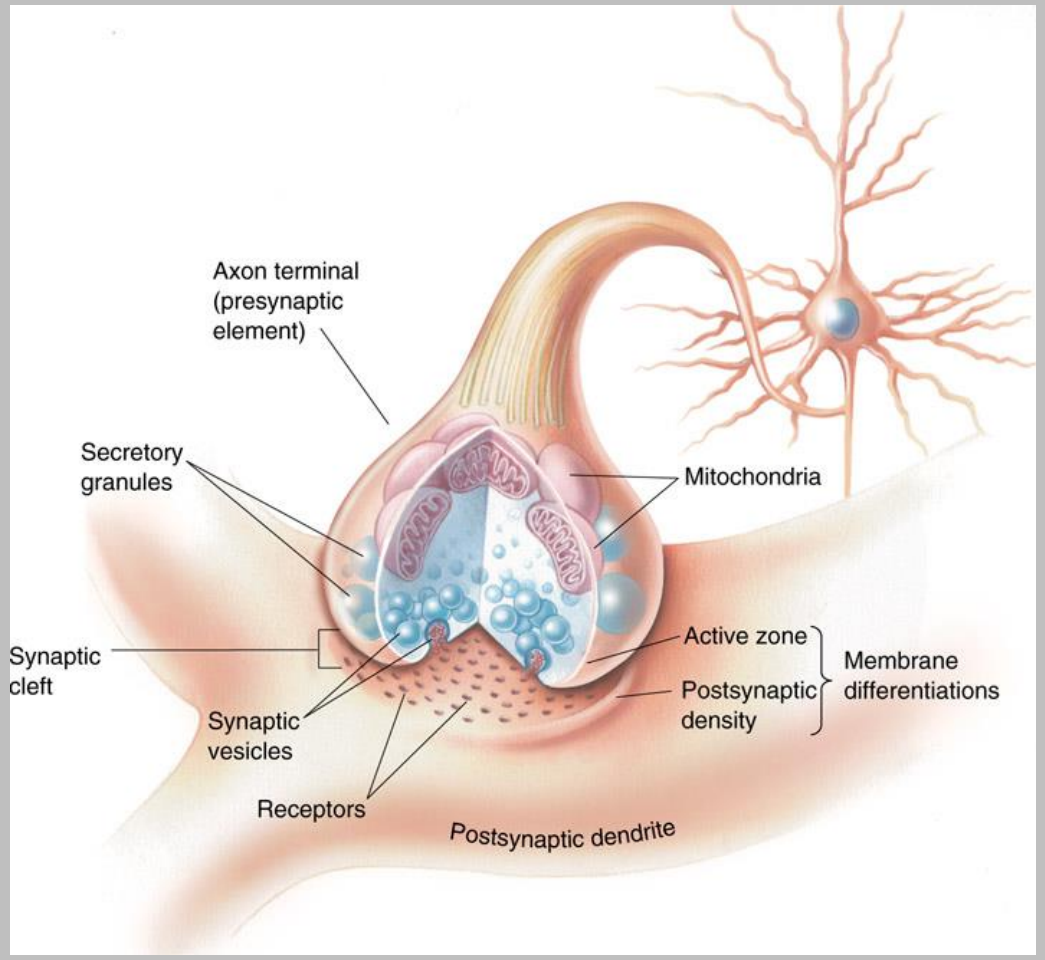
# Conclusions (Part 2):

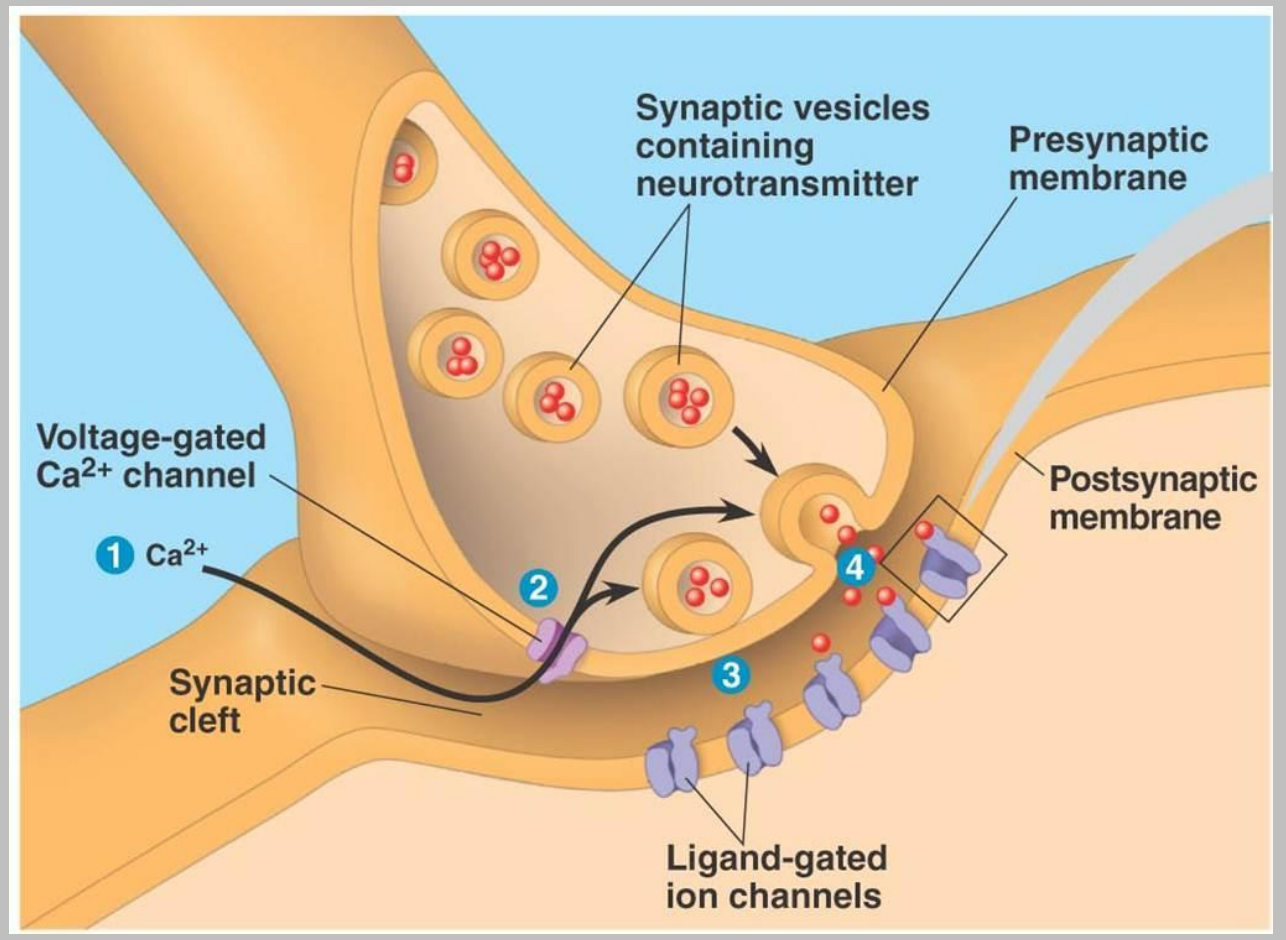
- The neuronal membrane contains voltage-gated Na+ and K+ channels that contribute to the generation of the action potential
- The action potential has distinct phases which are produced by the sequential opening and closing of Na+ and K+ channels
- Action potential generation can be modified by ion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

# Neurons are connected to one another at the synapse

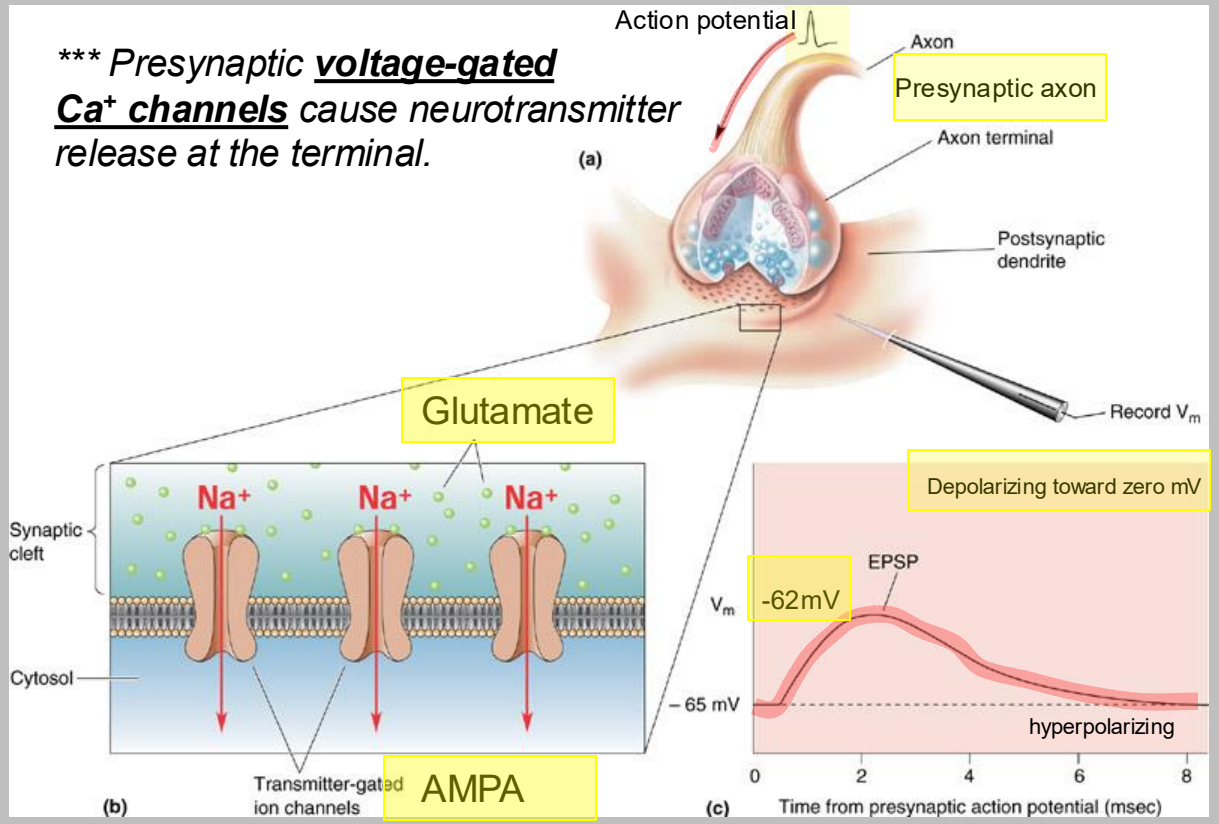
*- the site where neurons functionally communicate with one another*

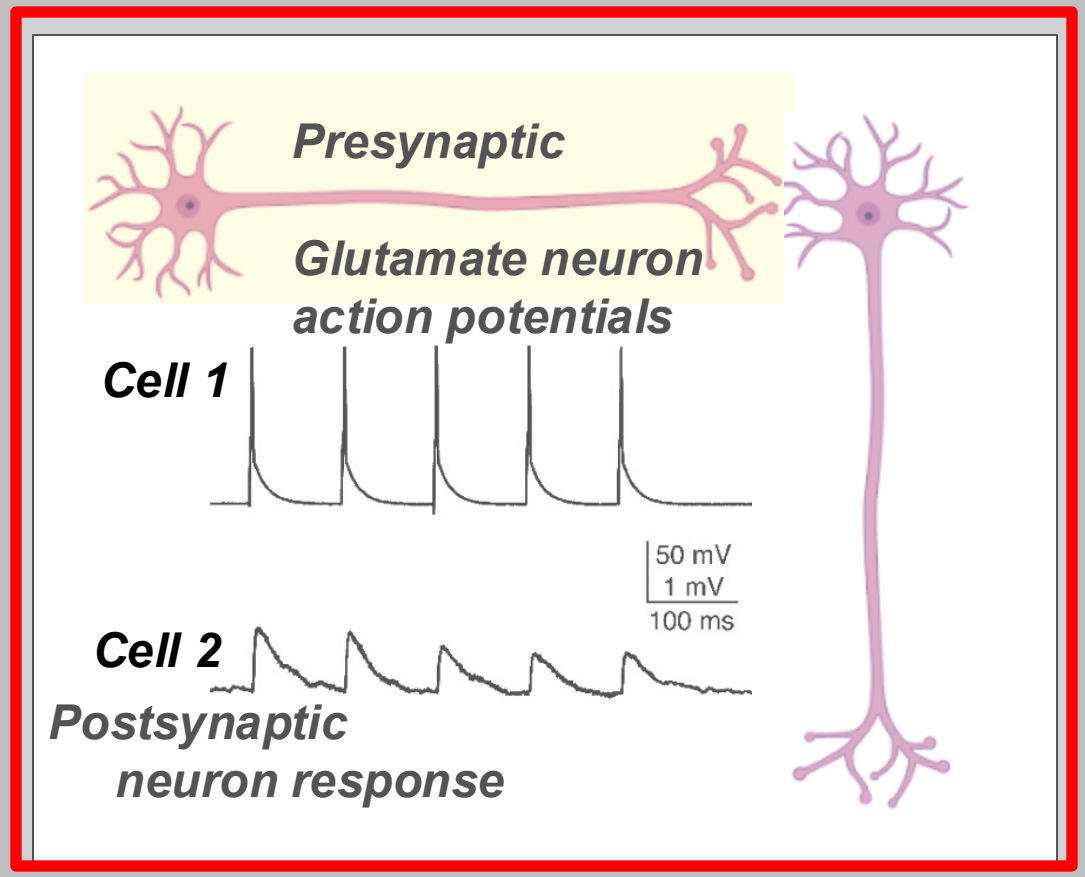
## *Chemical synapses & neurotransmitter release*



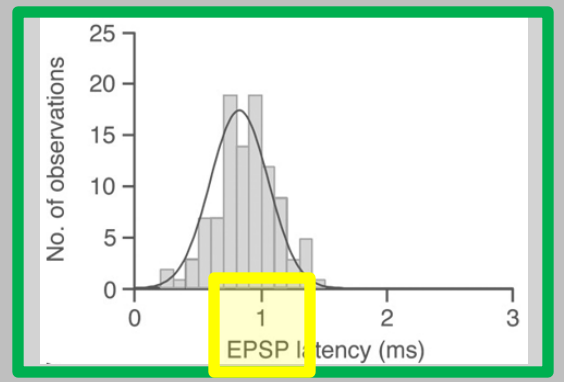



# Glutamate synapses depolarize the postsynaptic neuron



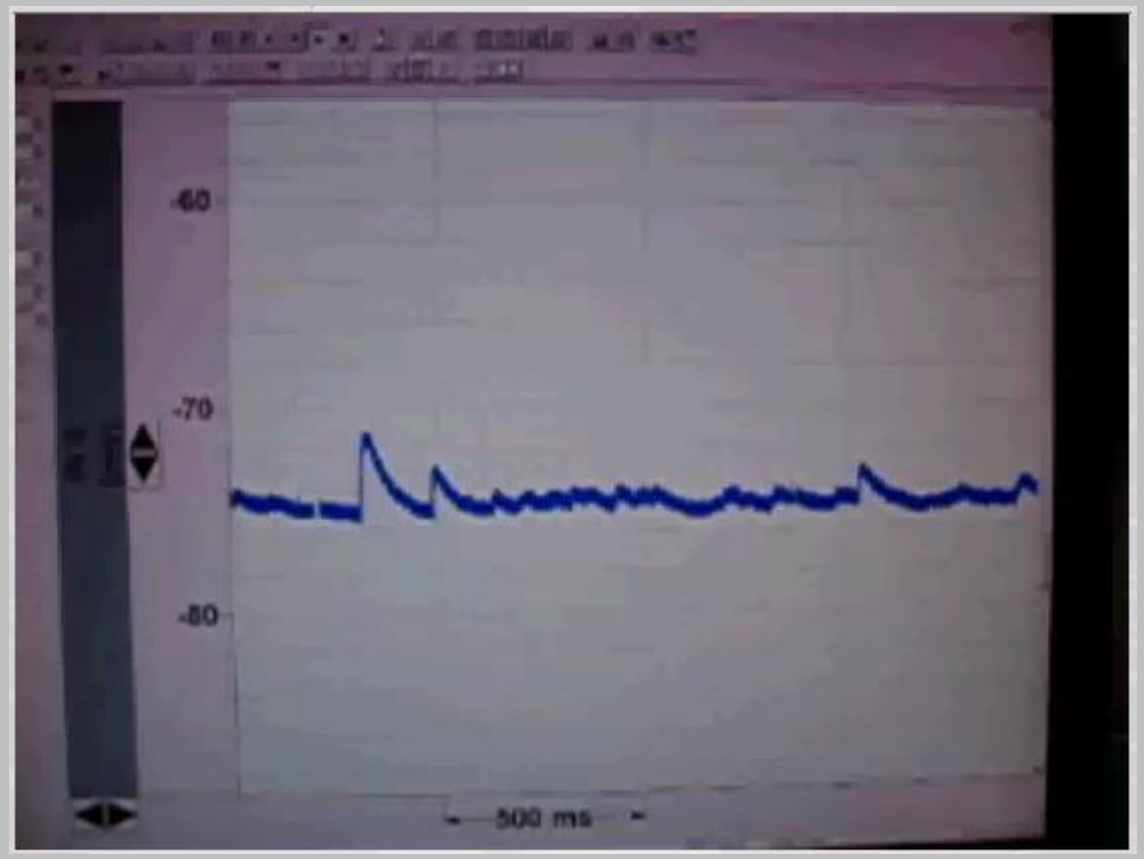




- *AP induced release of Glutamate into cleft*
- *Ionotropic glutamate receptors (AMPA) have a Na+ pore. Glu binding opens channel and Na+ rushes into the cell (some K+ out of the cell).*
- *Depolarizes postsynaptic neuron which might contribute to AP generation in postsynaptic neuron.*



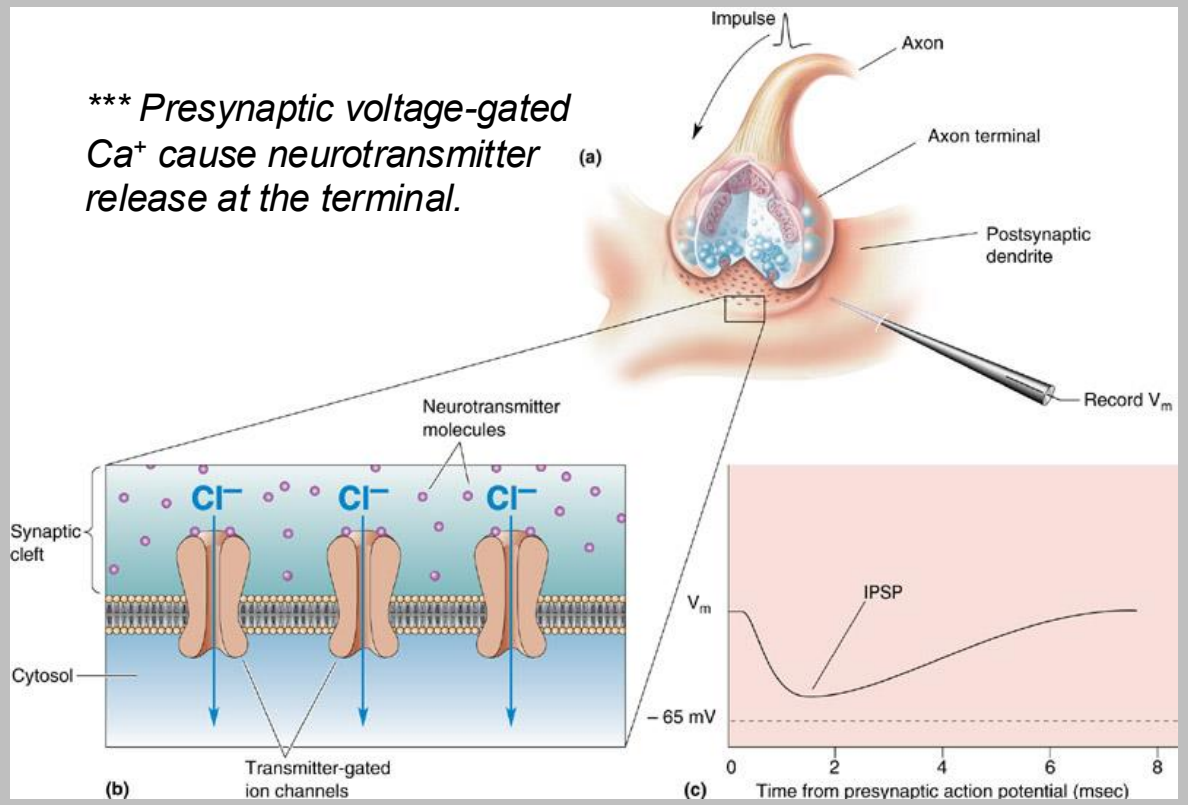

*Feldmeyer et al. 2005*

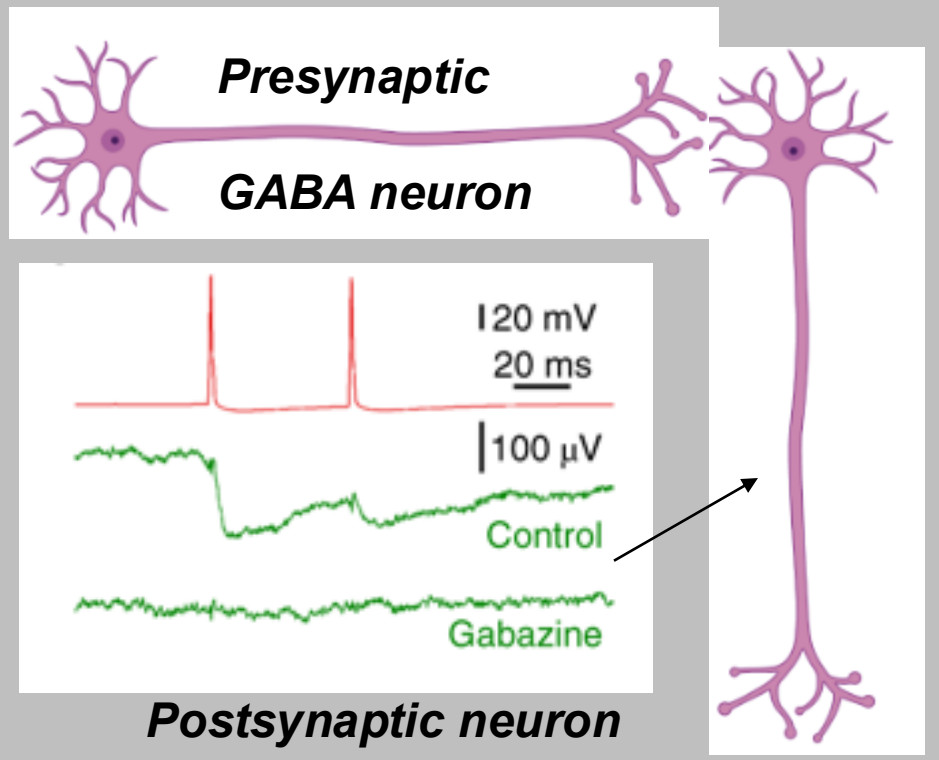
# Excitatory postsynaptic potentials- EPSPs



# GABA synapses hyperpolarize the postsynaptic neuron

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




***Postsynaptic neuron response***

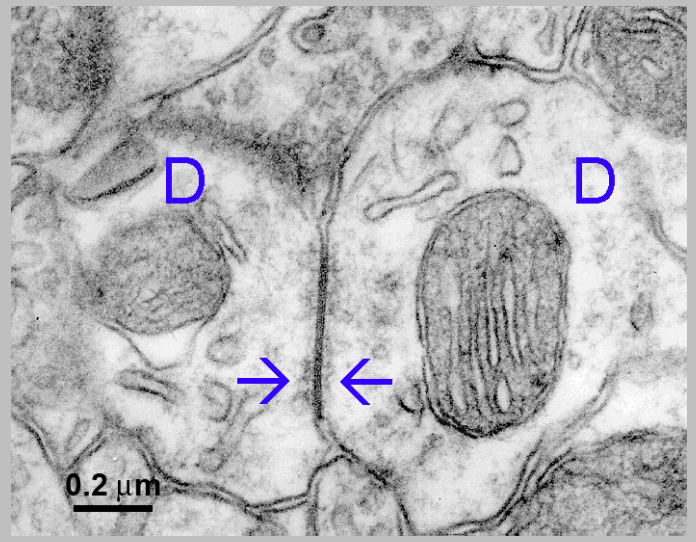
- *AP induced release of GABA*
- *Ionotropic $GABA_A$ receptors have a Cl- pore.*
-*Cl- rushes into the cell due to concentration gradient*
- *Make it harder for the postsynaptic neuron to fire APs*

*Boldog et. al 2018*

# *Neurons are connected to one another at the synapse*

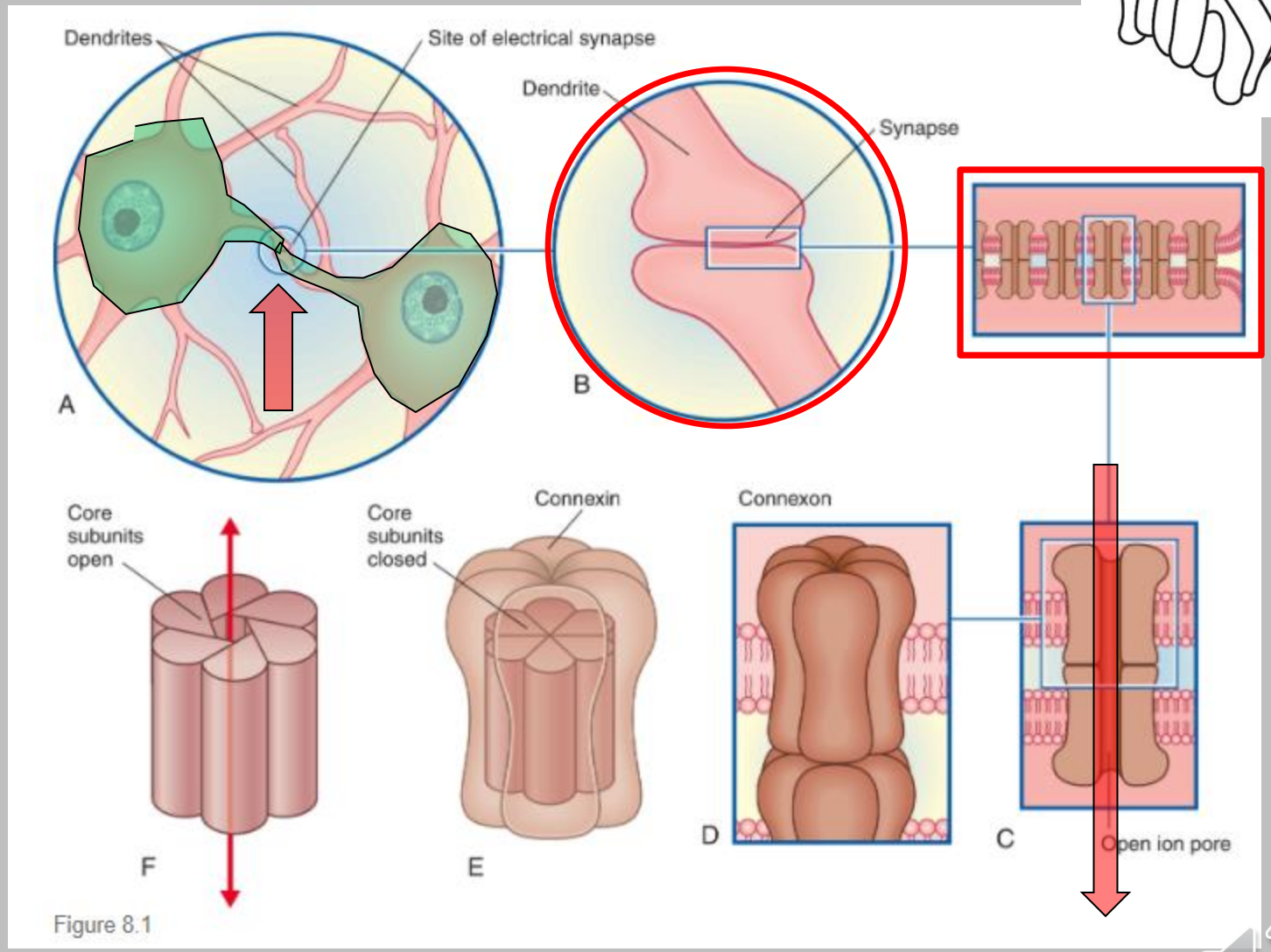
***- the site where neurons functionally communicate with one another***

Electrical synapses:
Gap junctions/Connexons




***Direct ion & small molecule flow from one neuron to the other. Usually bidirectional.***

***Certain connexins expressed specific cell types.***
***~30 disease due to connexin gene mutations***

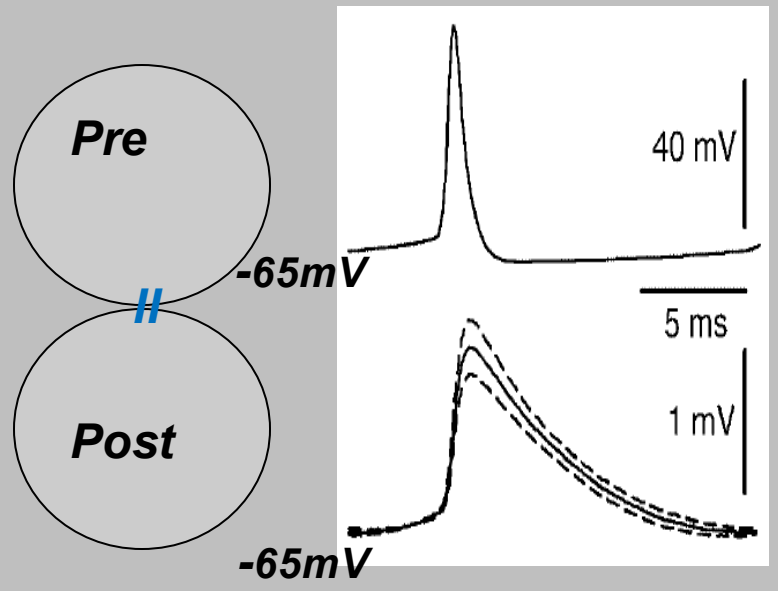


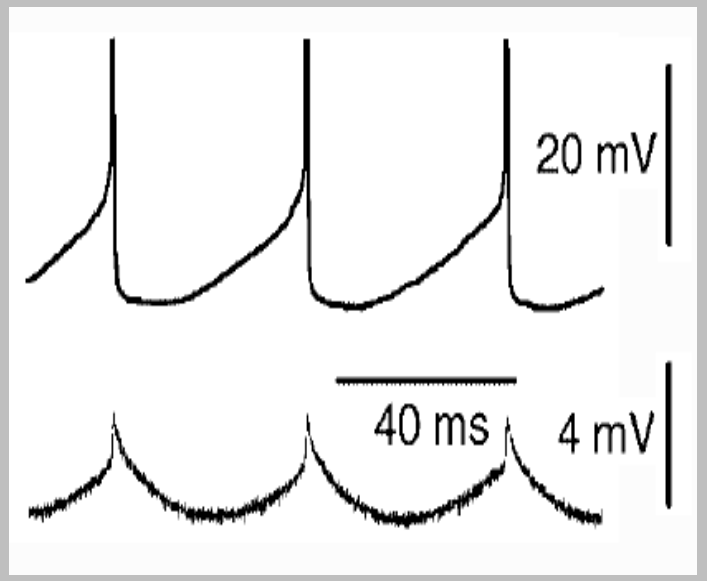




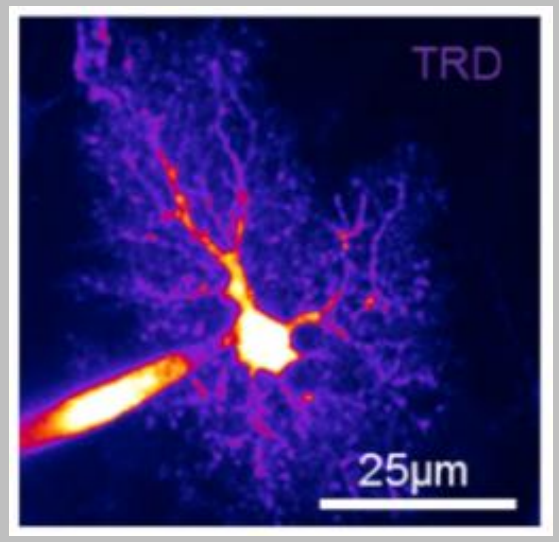
•*E Mtui MD, G Gruener MD, MBA and P Dockery BSc, PhD*
• *Fitzgerald's Clinical Neuroanatomy and Neuroscience, 8; 85-101*

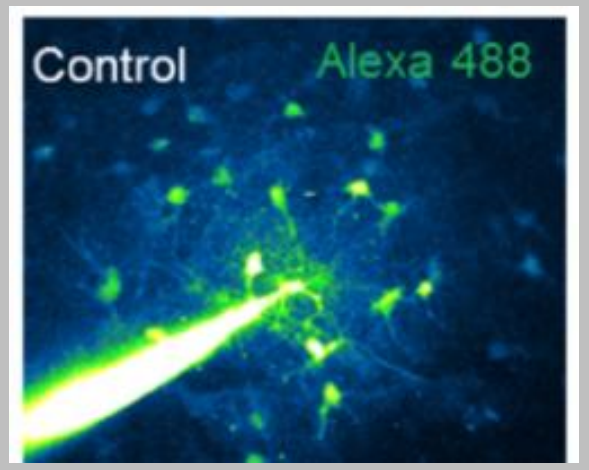
# Gap junctions/Electrical synapses: no neurotransmitter used




*Connors & Long 2004*

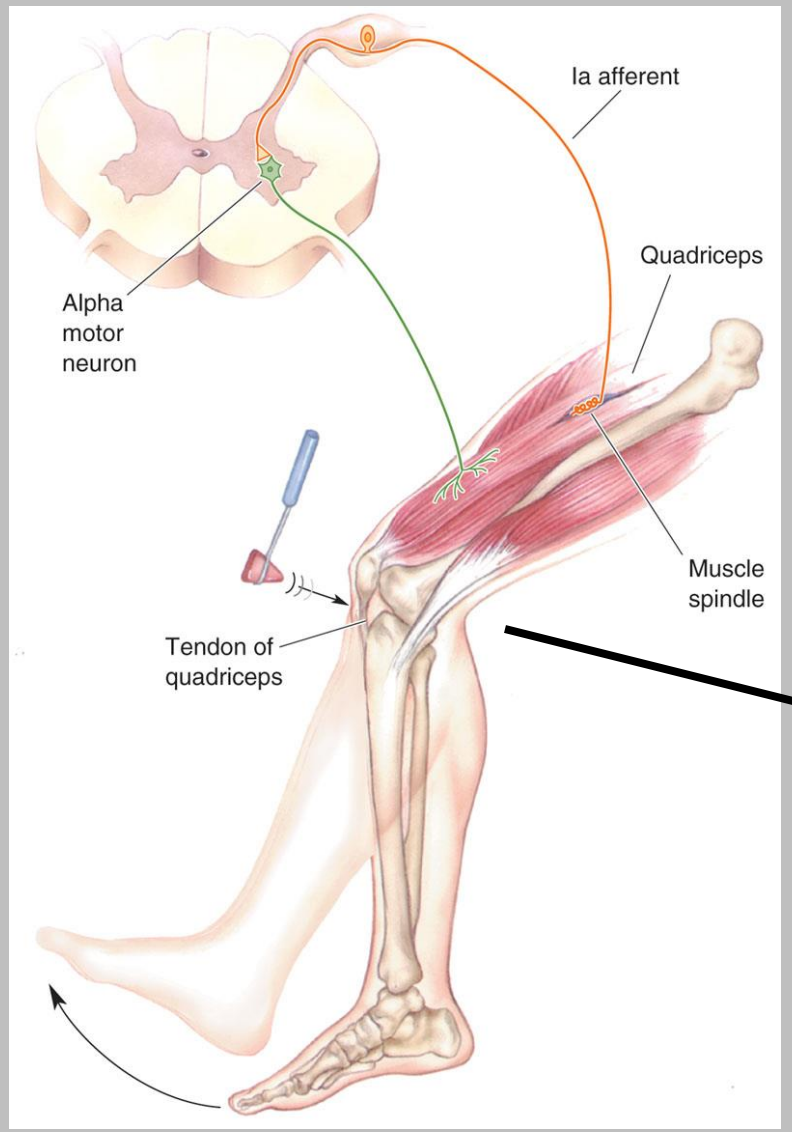



- ***Gap junctions allow direct ion & small molecule flow from one neuron to the other which can depolarize or hyperpolarize the postsynaptic neuron***
- ***Amplitude attenuation of currents***
- ***Usually bidirectional***
- ***Fastest type of neural communication <1ms***
- ***Can depolarize neurons***

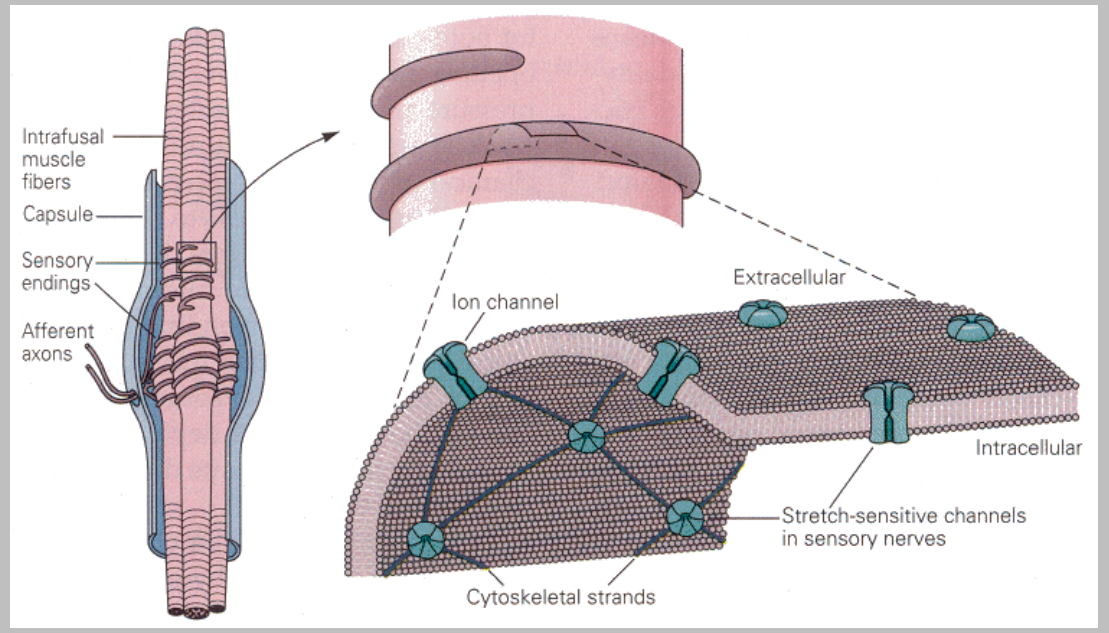
*Breithausen et al. Glia 2019*
*https://doi.org/10.1002/glia.23751*

# 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.*

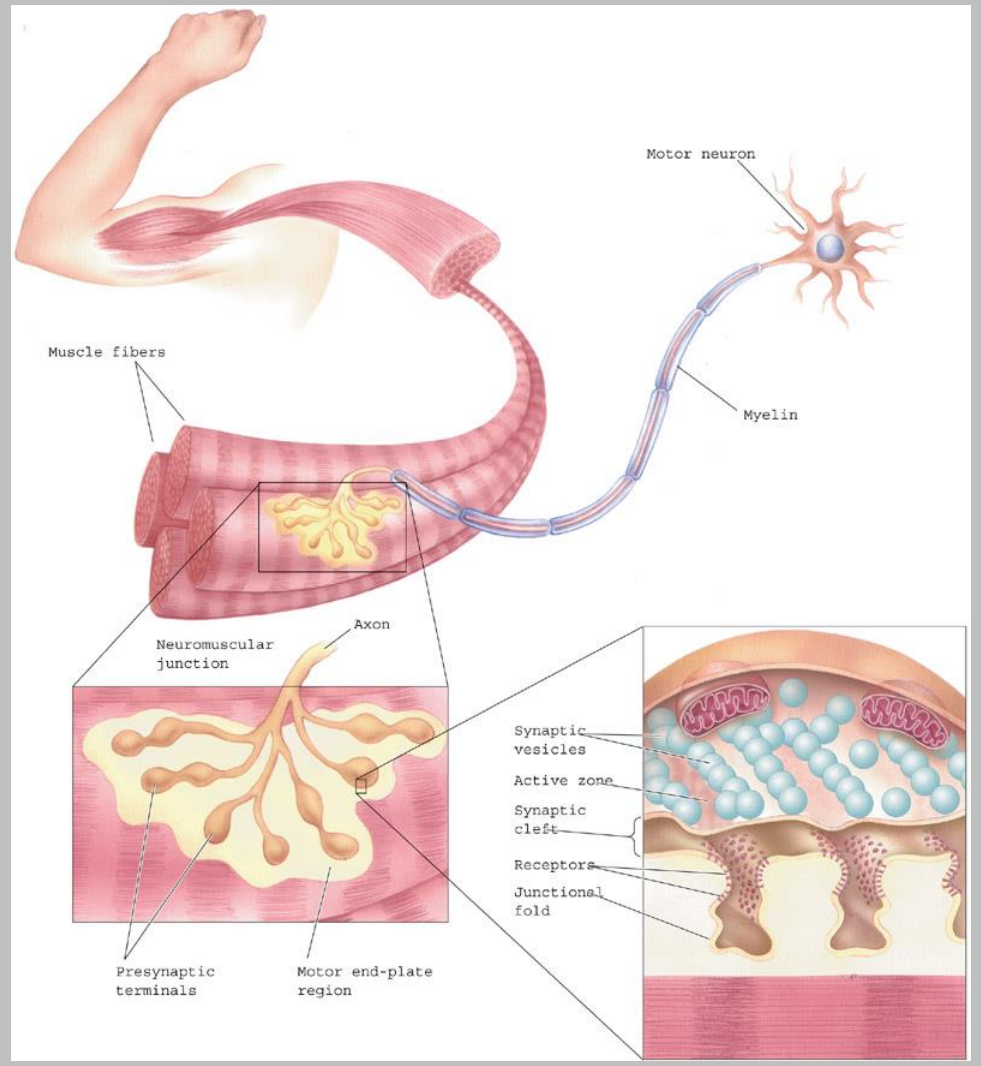
*Motor pathway:*
*1a neuron synapses on motor neuron and releases Glu.*
*Motor neuron fires an AP and releases Ach at quad muscle causing contraction.*

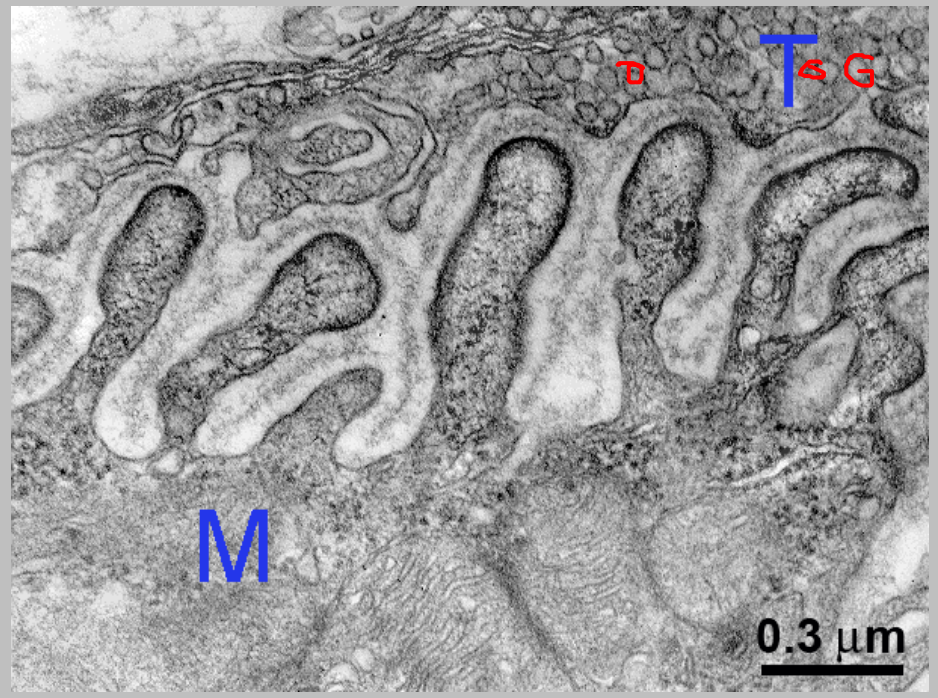


# Synaptic Transmission & Behavior:

## Neuromuscular synapse/junction

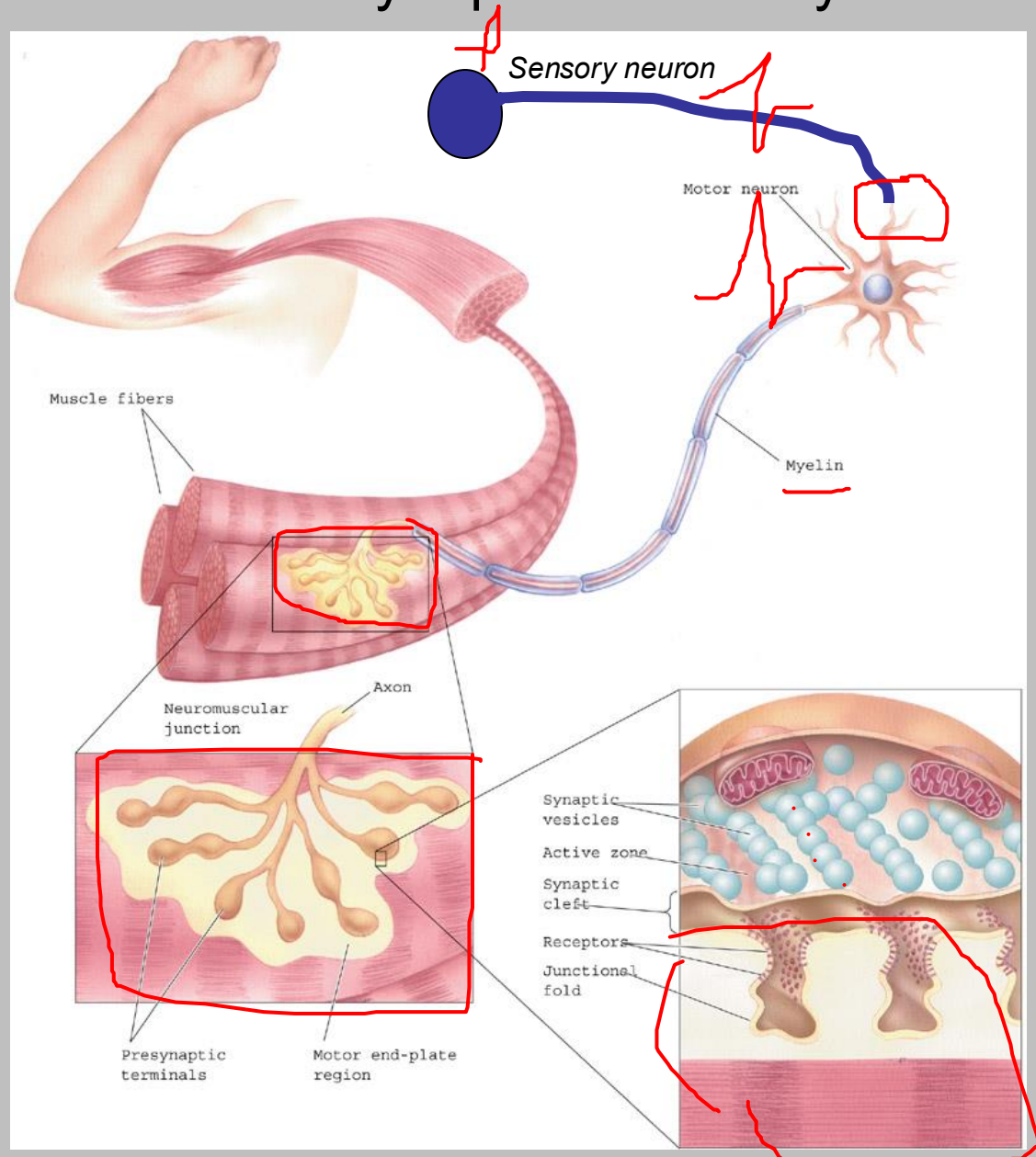
- synapse formed by motor neuron with a muscle fiber.

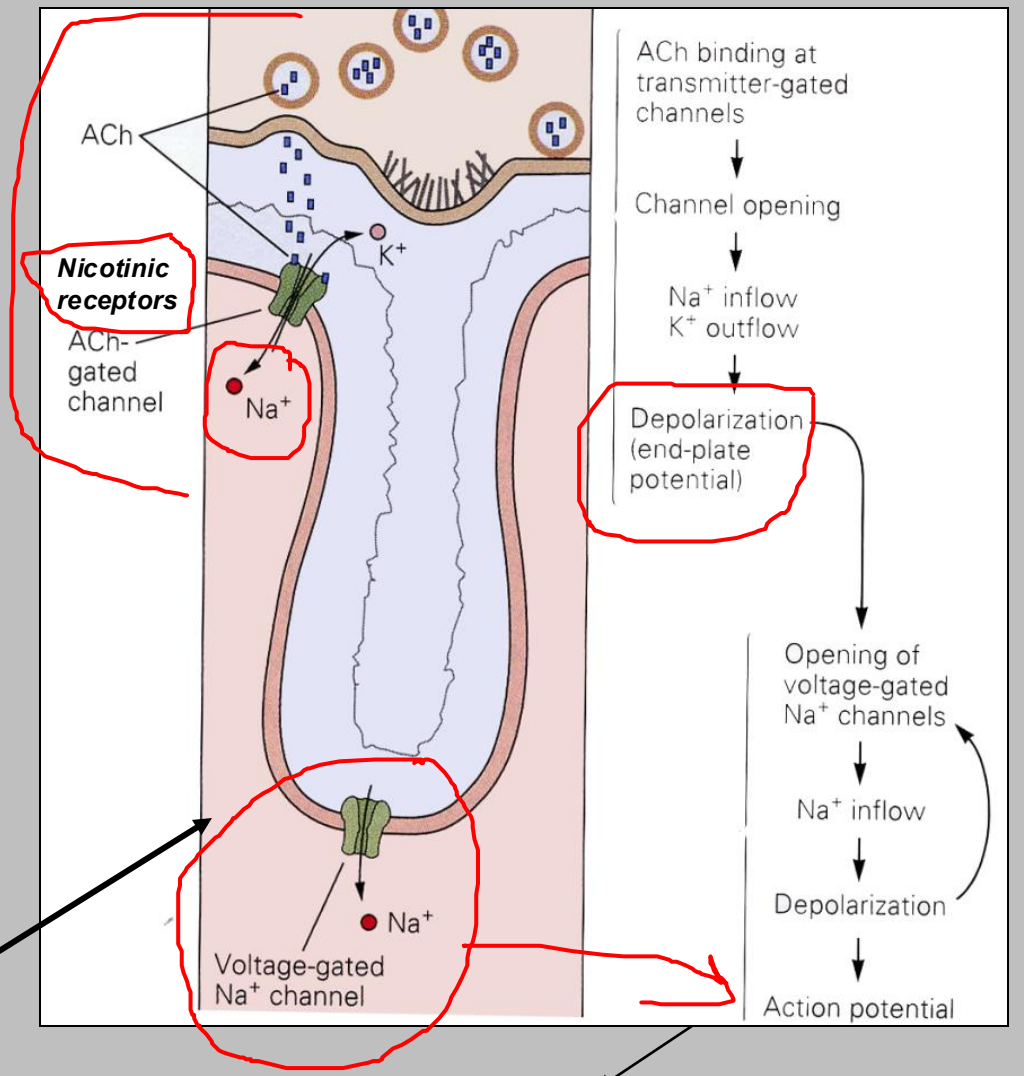


# Neuromuscular synapse/junction

- synapse formed by motor neuron with a muscle fiber.




*Muscle contraction & behavior!*

# *Synaptic transmission*

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

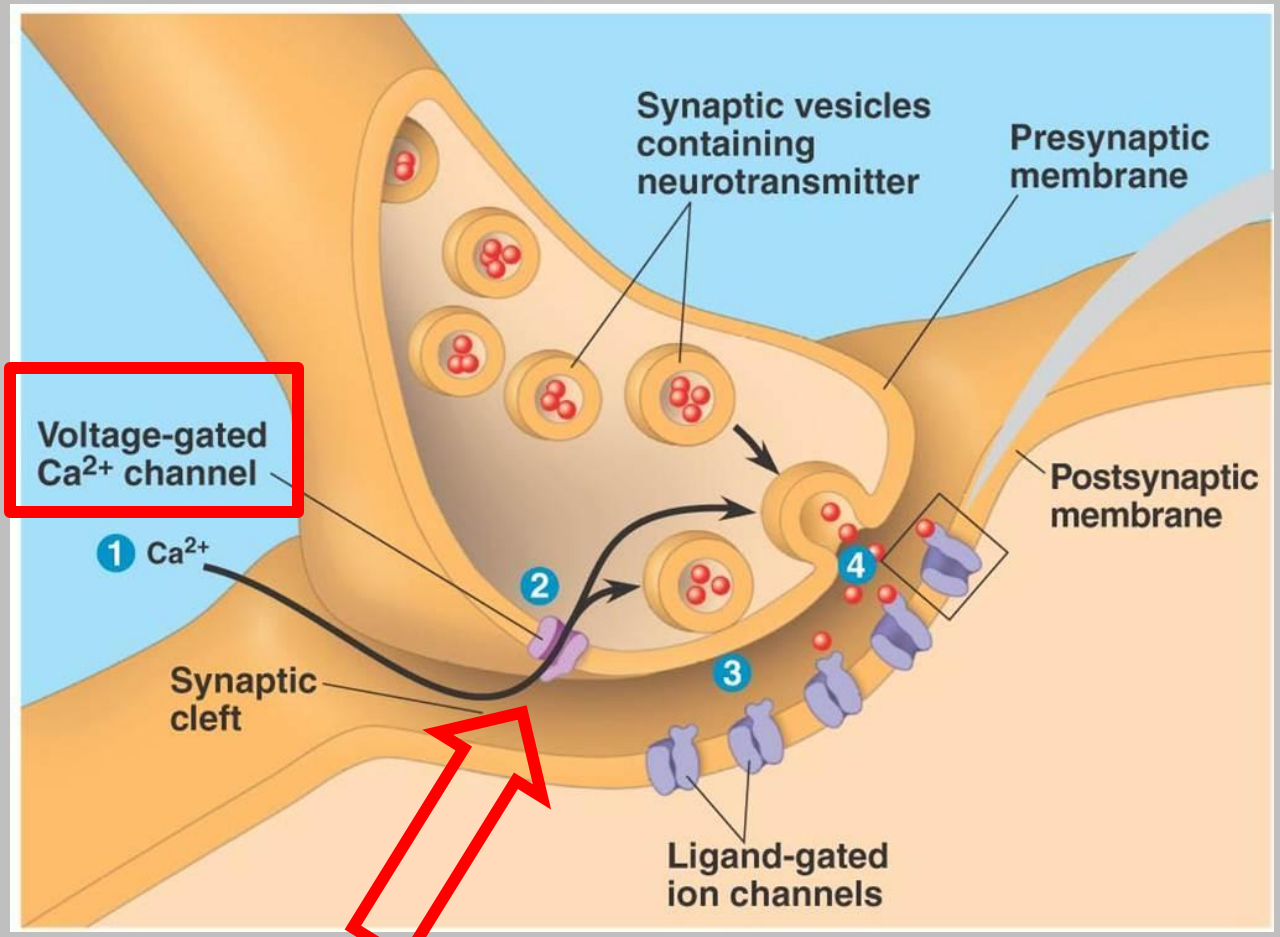
*<u>Synaptic cleft</u>*
- *Neurotransmitter breakdown*

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

*Synaptic mechanisms of disease*

# Lambert-Eaton Syndrome:

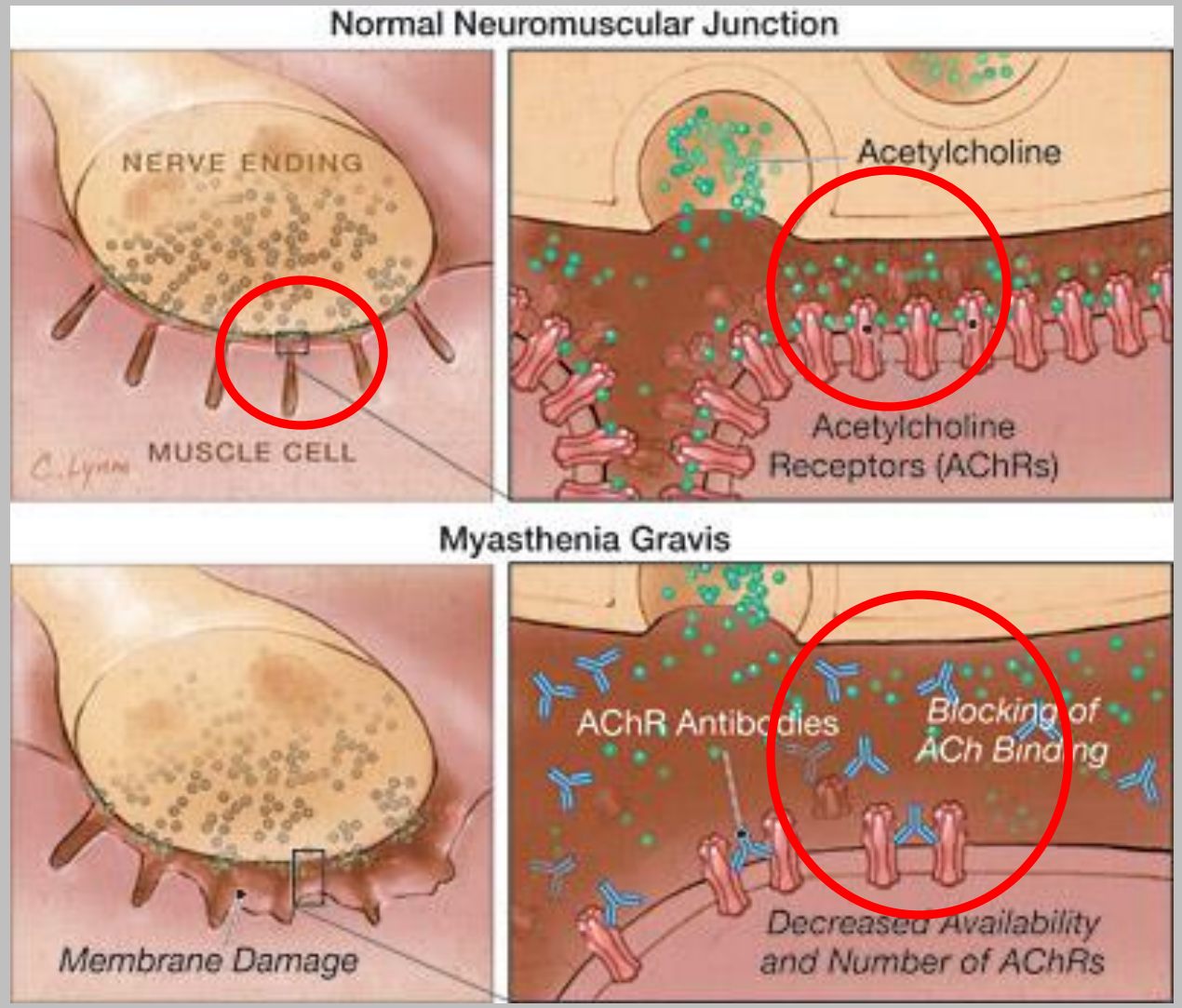
## Auto-immune Disease of VGCC at the NMJ




***Auto-antibodies to VG Ca channel***

- Autoimmune disease characterized by the production <u>of antibodies against voltage gated calcium channels (VGCC) present in NMJ</u>
- Symptoms include muscle weakness throughout body especially limbs & face and autonomic symptoms.
- Weak muscles (weakness is often relieved for a short time after exercise or exertion)
- Trouble walking, climbing stairs or getting up from a chair, Tingling sensation in the hands or feet
- Eyelid drooping, Fatigue, Dry mouth or dry eyes
- Trouble speaking and swallowing
- Trouble breathing, Bladder and bowel changes
- Erectile dysfunction, Decreased sweating
- Weight loss
- Some pharmacological immunological treatments available to modulate VGCC function

# Myasthenia Gravis:
## Disease of AchR at the NMJ




AChR autoantibodies

- Autoimmune disease characterized by the production of antibodies against AchR
- Symptoms include muscle weakness throughout body especially limbs and face.
- Some pharmacological and immunological treatments available

*New drug on the market: Vyvgart (FDA 2021)*


*https://vyvgarthcp.com/gmg/about/moa*

# 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.

# Lecture Feedback Form:

https://comresearchdata.nyit.edu/redcap/surveys/?s=HRCY448FWYXREL4R