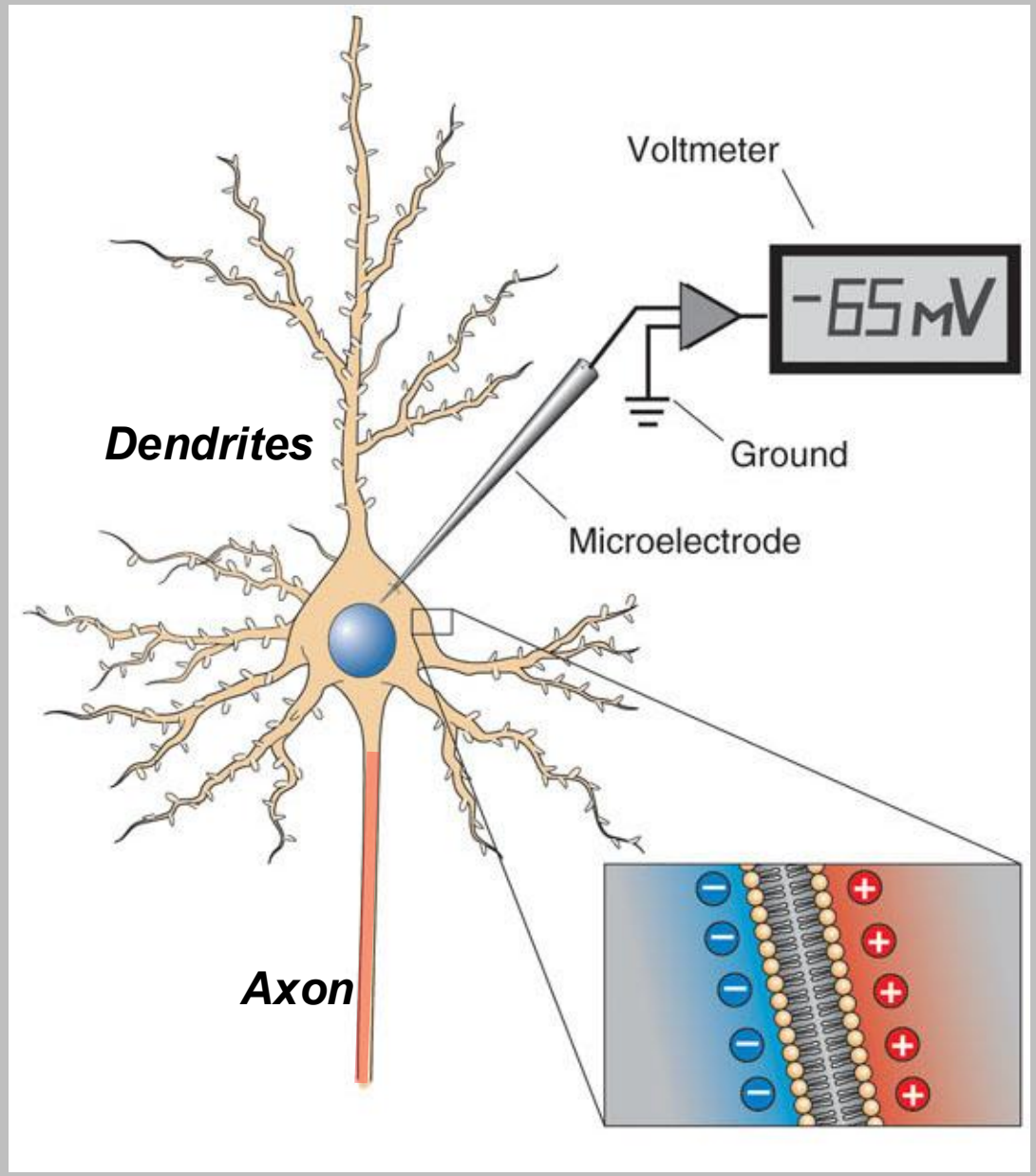
Neuronal resting membrane potential (rVm)

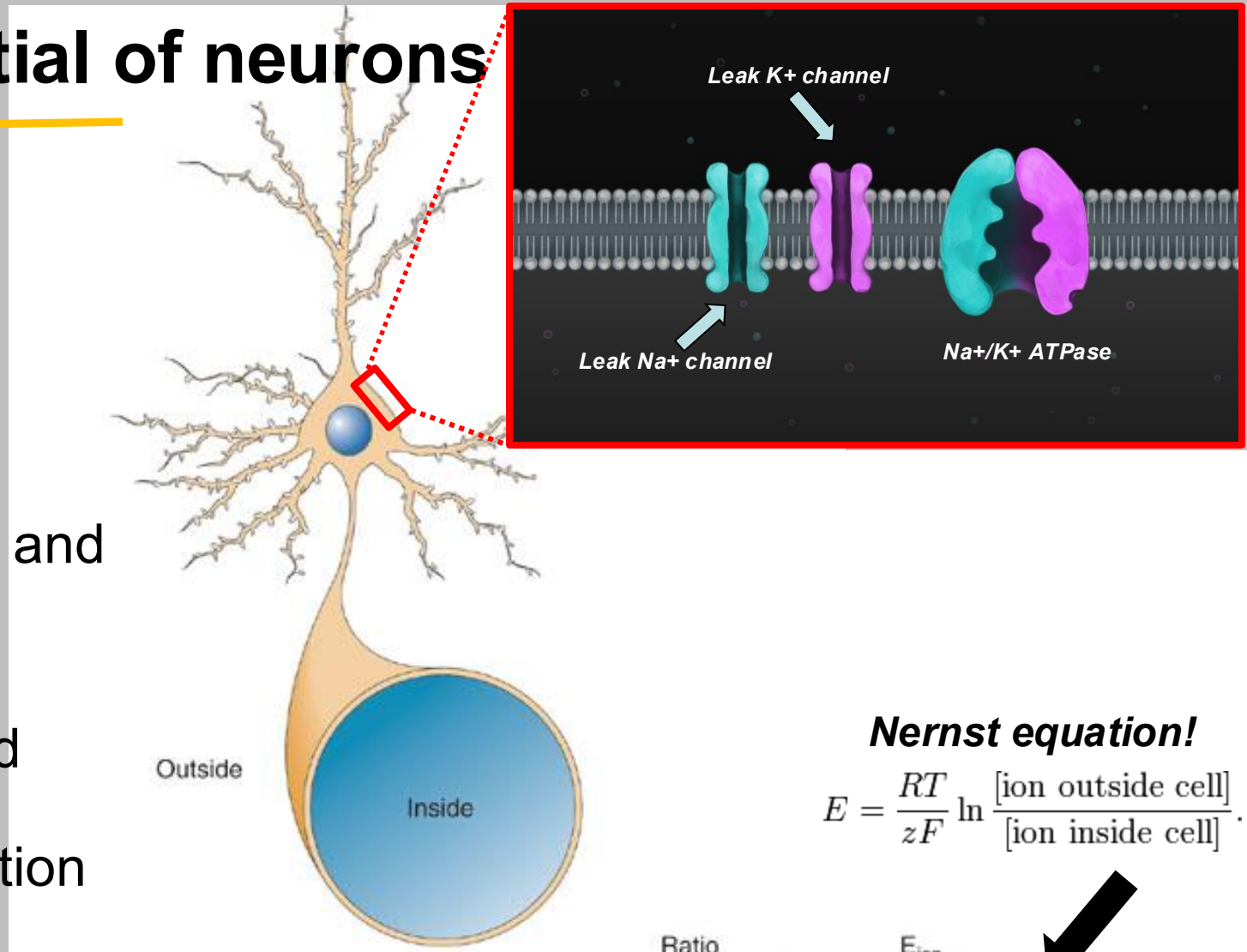
- Neuronal membrane changes, electric activity, and synaptic connections creates behavior!
- rVm of neuron is “hyperpolarized” (more negative) relative to the extracellular side.
- rVm is ~ -65mV in many central neurons but can vary by +/-15mV.
- Membrane potential physiology also important to understand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

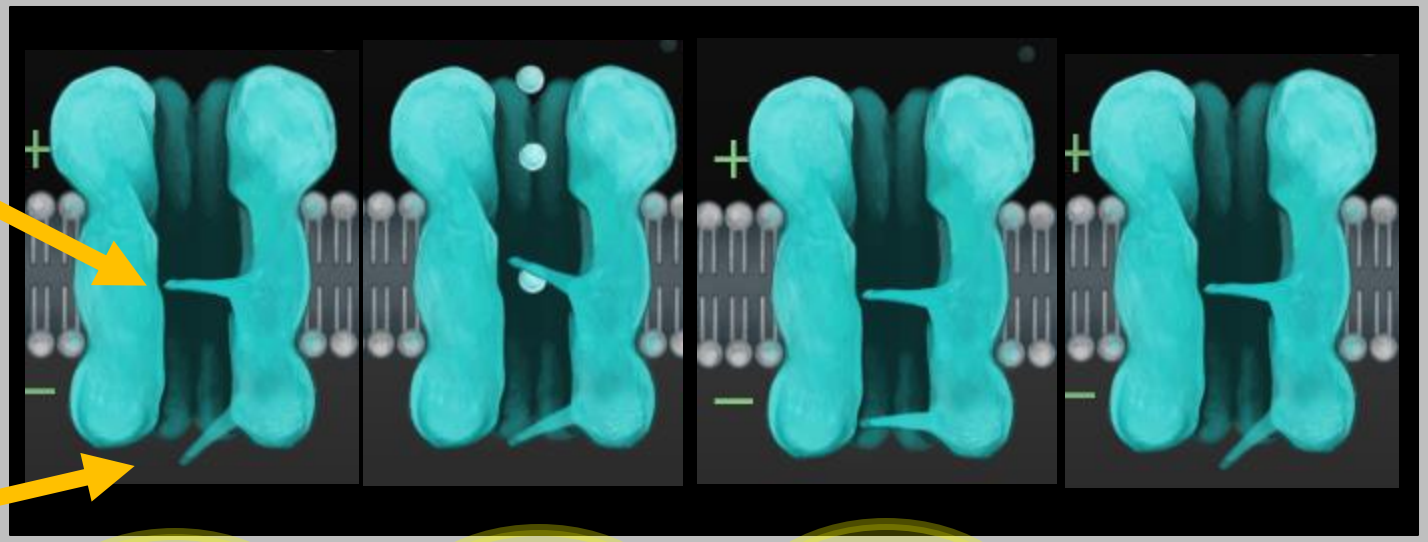
$$E = \frac{RT}{zF} \ln \frac{[\text{ion outside cell}]}{[\text{ion inside cell}]}.$$

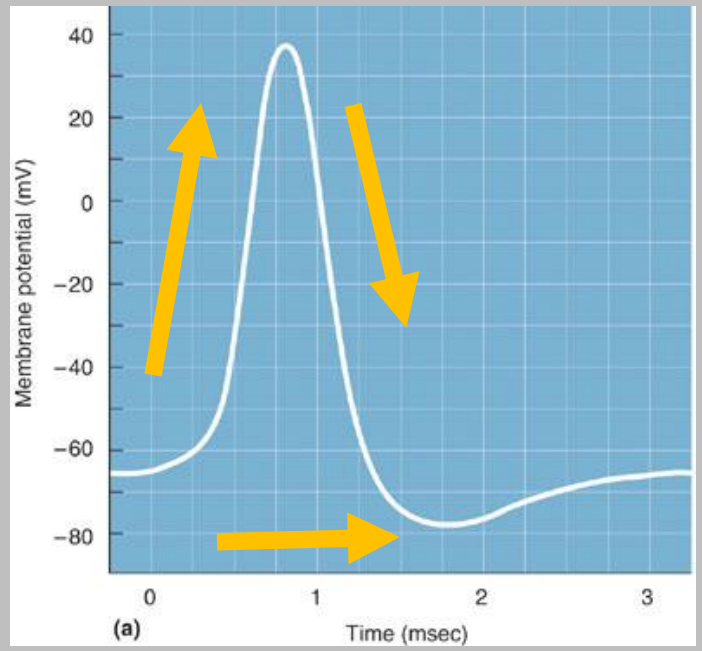
Outside		Inside		Ratio Outside:Inside	E_{ion} (at 37°C)
$[K^+]_o$	= 5 mM	$[K^+]_i$	= 100 mM	1:20	−80 mV
$[Na^+]_o$	= 150 mM	$[Na^+]_i$	= 15 mM	10:1	62 mV
$[Ca^{2+}]_o$	= 2 mM	$[Ca^{2+}]_i$	= 0.0002 mM	10,000:1	123 mV
$[Cl^-]_o$	= 150 mM	$[Cl^-]_i$	= 13 mM	11.5:1	−65 mV

Voltage-gated sodium channel inactivaton

"Pore" or Activation gate

Inactivation gate



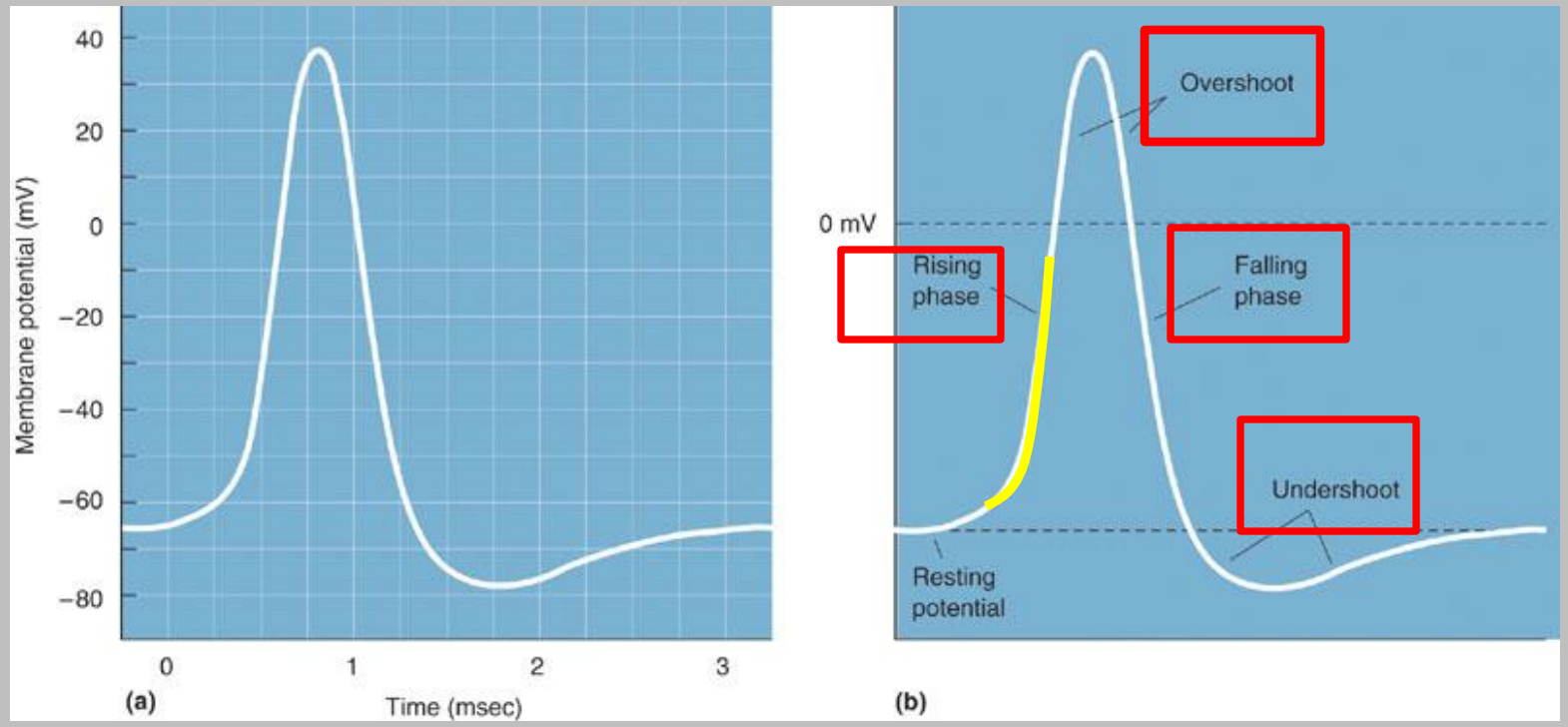


Closed channel ***Open channel*** ***Inactivated channel*** ***Closed channel***

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

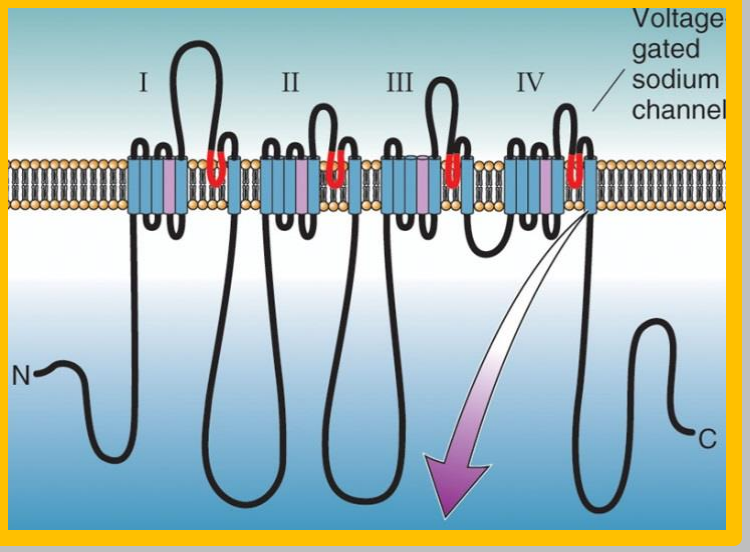
Saxitoxin

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

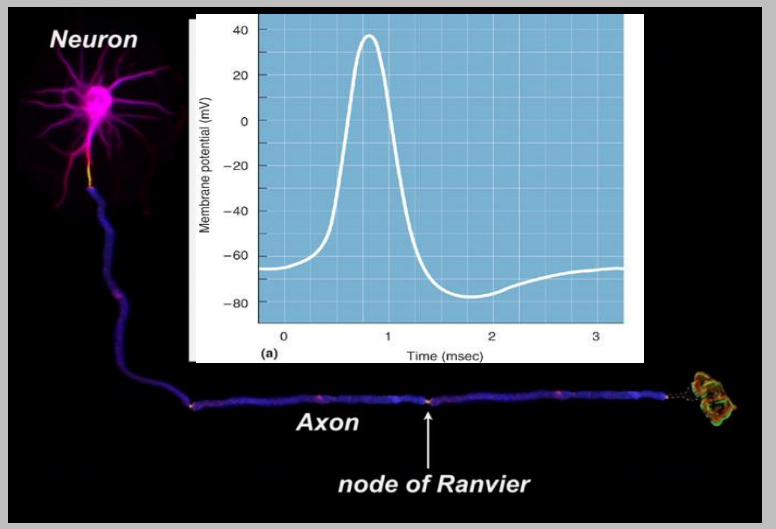
α-dendrotoxin

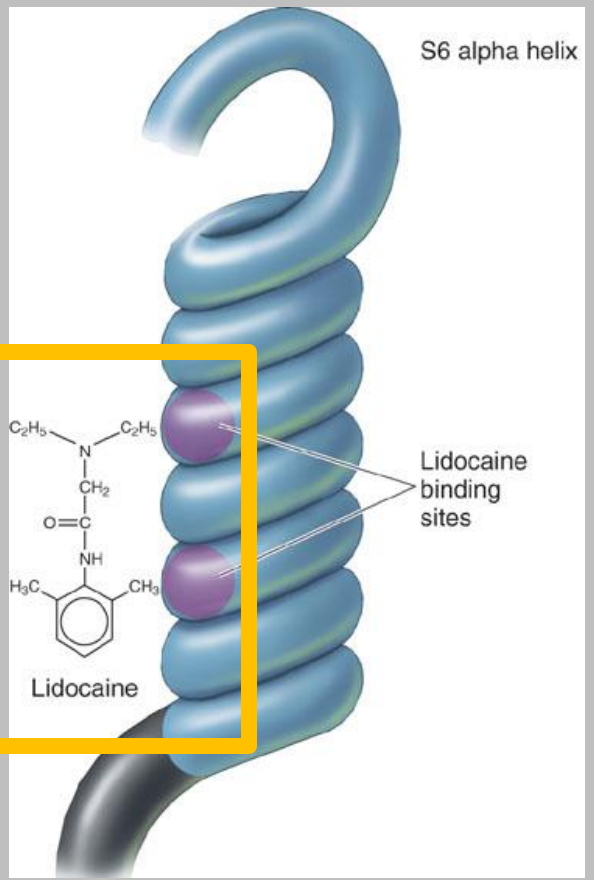
- potent potassium channel blocker (Kv1)
- found in venom of the green mamba Dendroaspis angusticeps
- prolongs action potentials affecting neuro and cardiovascular function

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

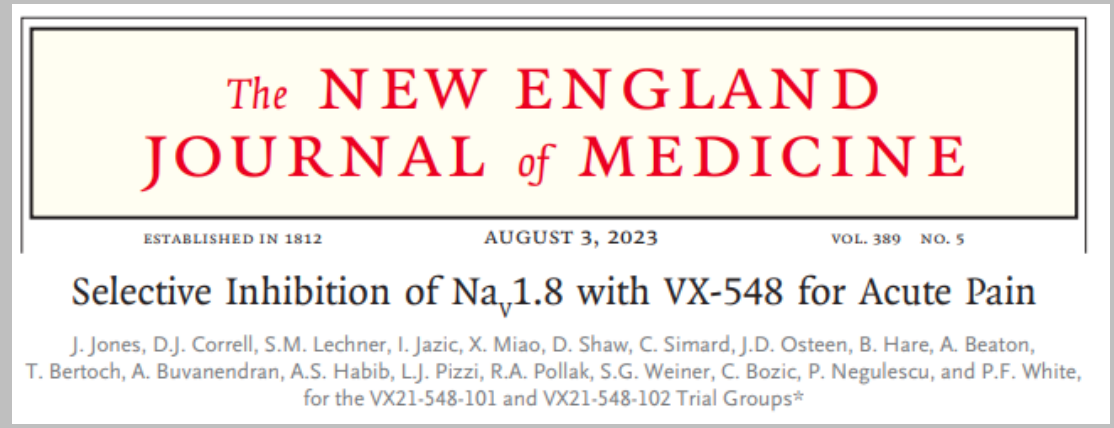




Targeting VG Na channels for the treatment of pain (ex. after surgery).

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.

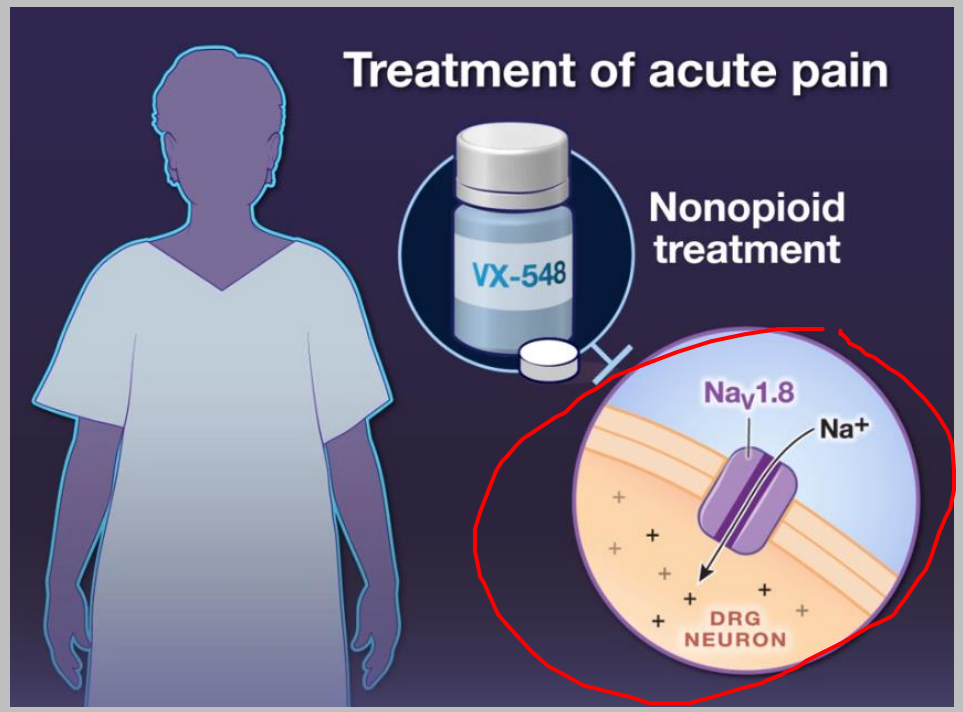

The NEW ENGLAND JOURNAL of MEDICINE

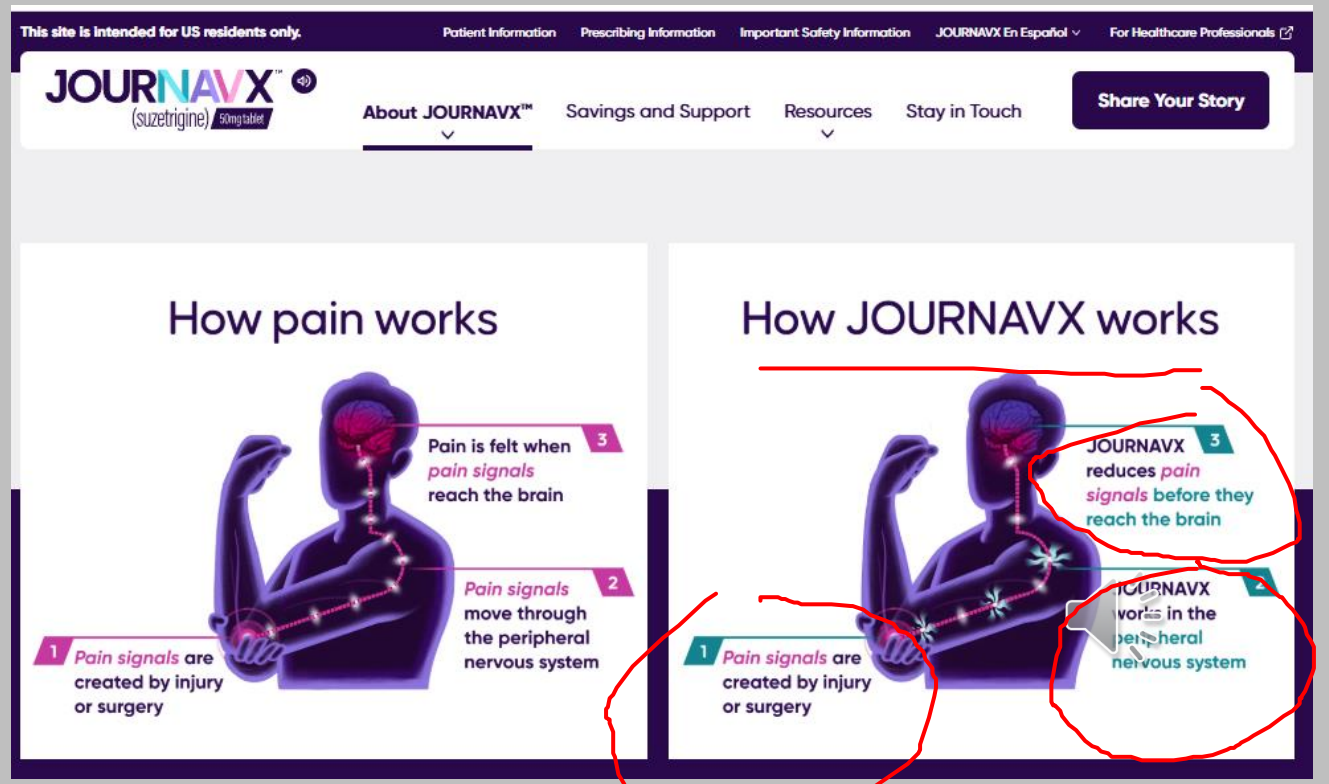
ESTABLISHED IN 1812 AUGUST 3, 2023 VOL. 389 NO. 5

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*

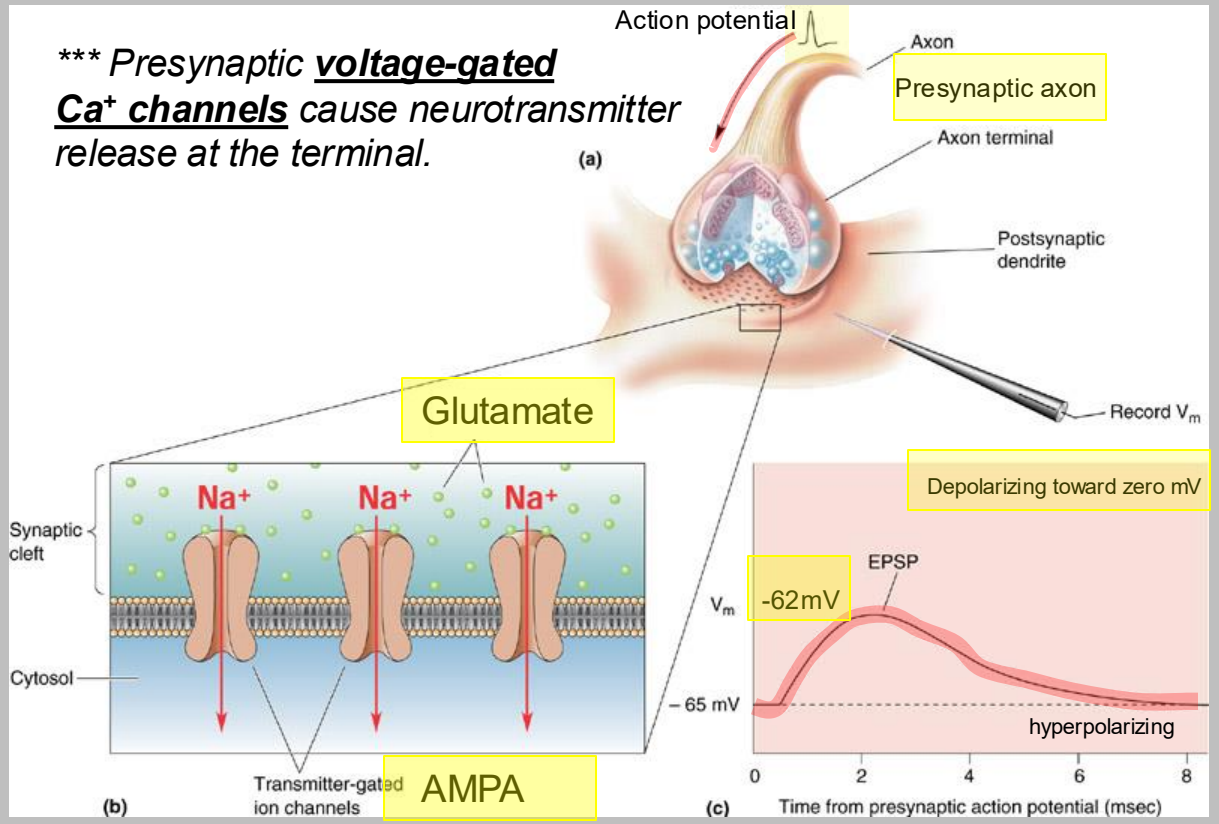
VX-548 now called suzetrigine (Journavx)

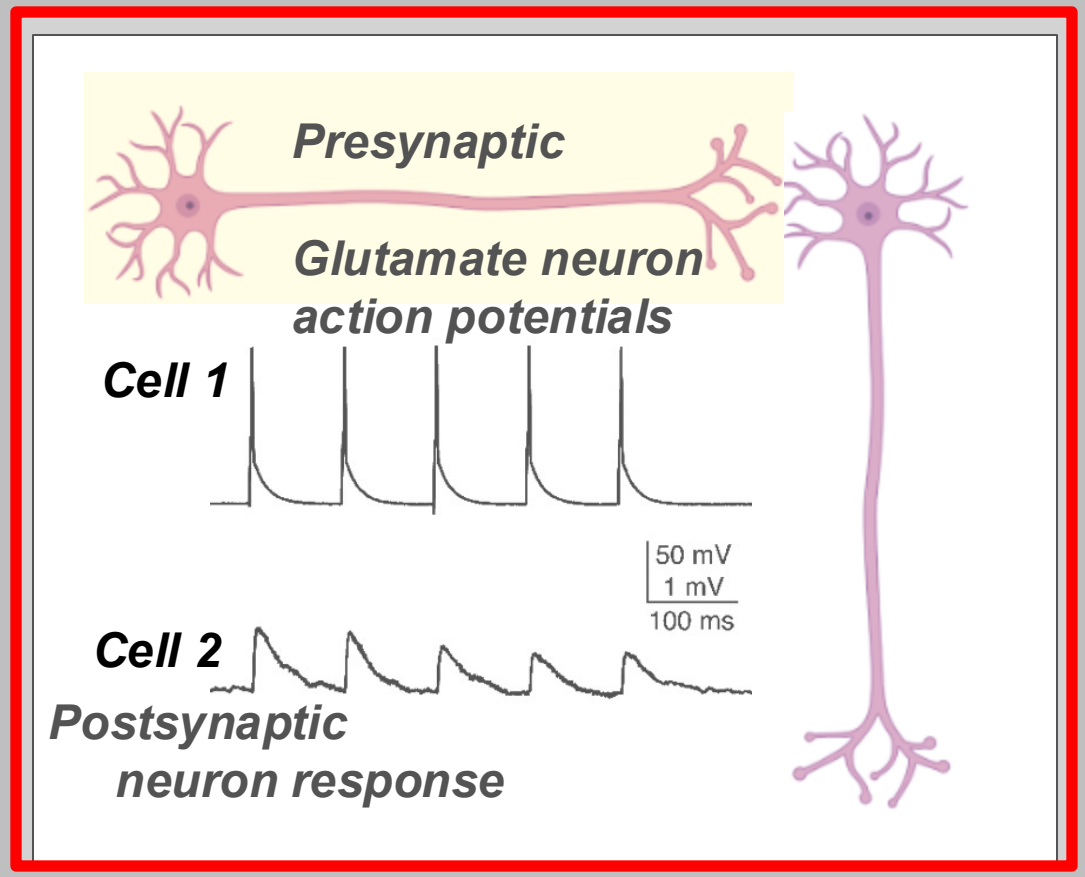




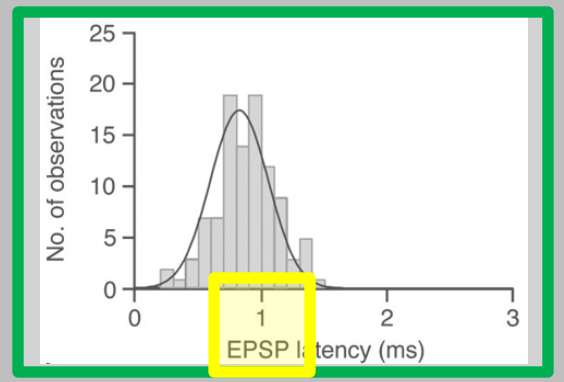
https://www.journavx.com/how-journavx-works

Glutamate synapses depolarize the postsynaptic neuron





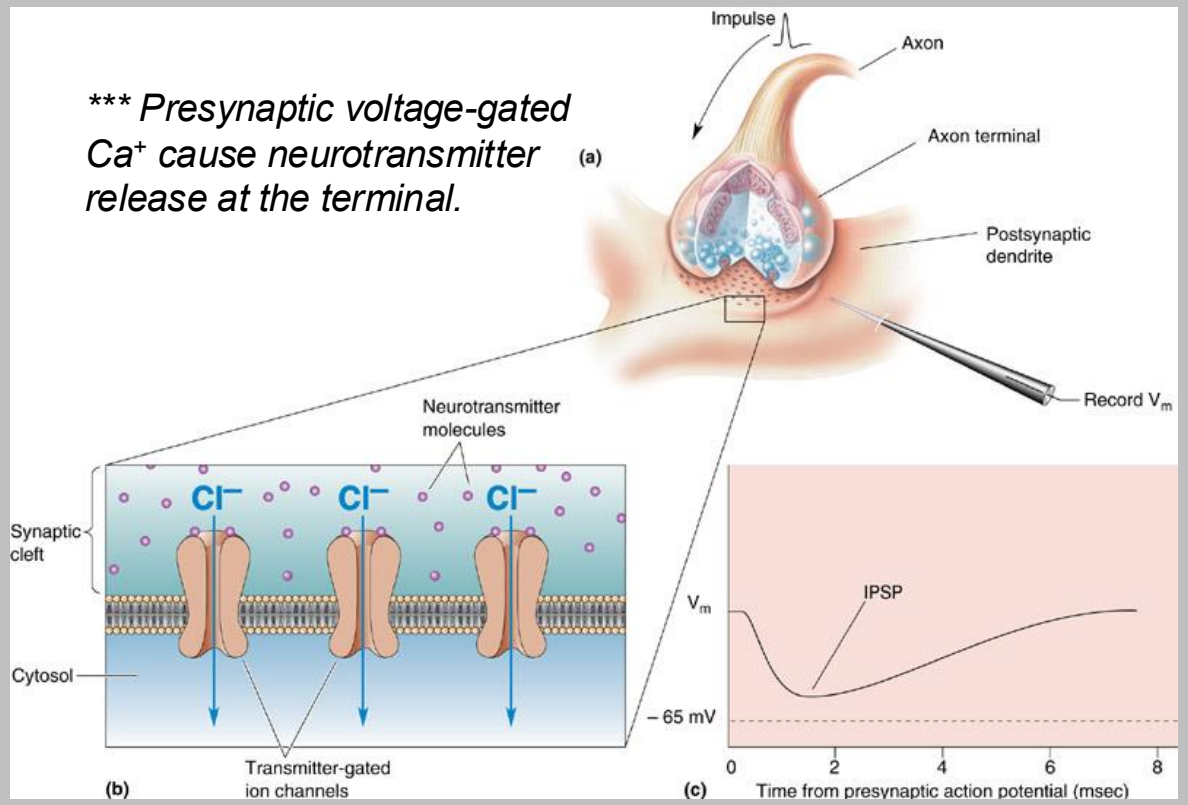
- *AP induced release of Glutamate into cleft*
- *Ionotropic glutamate receptors (AMPA) have a Na+ pore. Glu binding opens channel and Na+ rushes into the cell (some K+ out of the cell).*
- *Depolarizes postsynaptic neuron which might contribute to AP generation in postsynaptic neuron.*

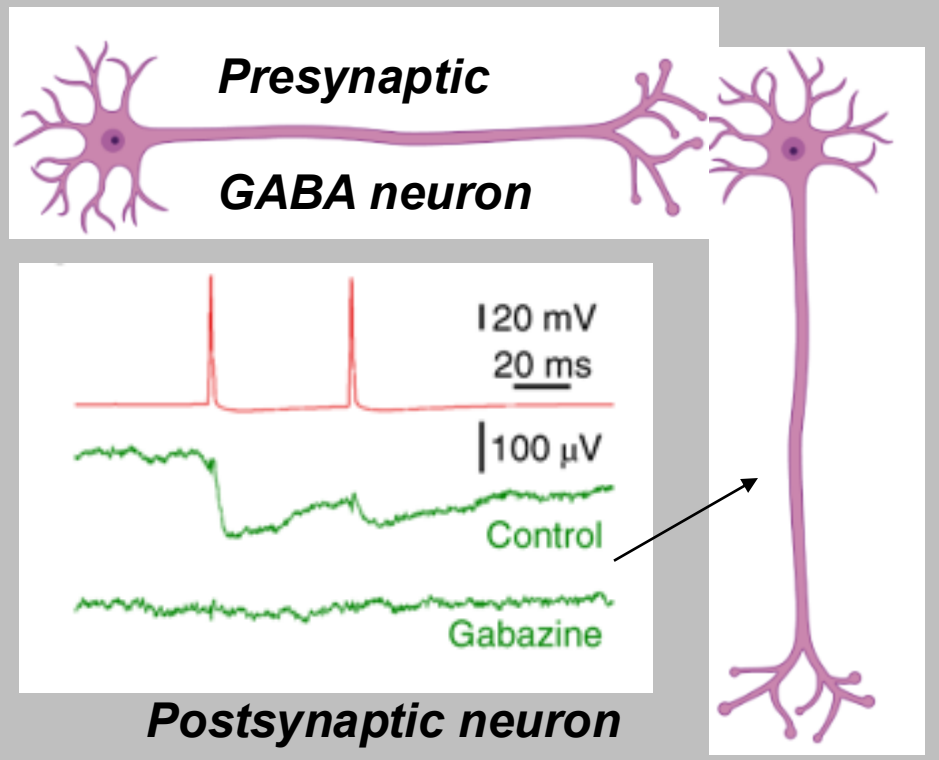


Feldmeyer et al. 2005

GABA synapses hyperpolarize the postsynaptic neuron

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





Postsynaptic neuron response

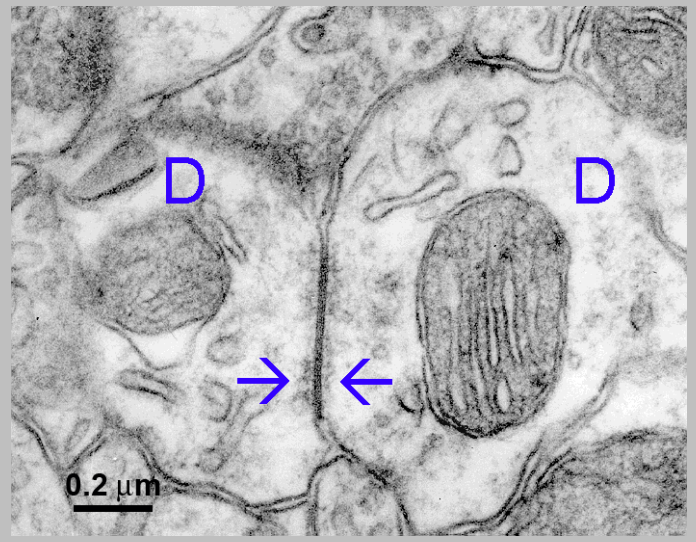
- *AP induced release of GABA*
- *Ionotropic $GABA_A$ receptors have a Cl- pore.*
-*Cl- rushes into the cell due to concentration gradient*
- *Make it harder for the postsynaptic neuron to fire APs*

Boldog et. al 2018

Neurons are connected to one another at the synapse

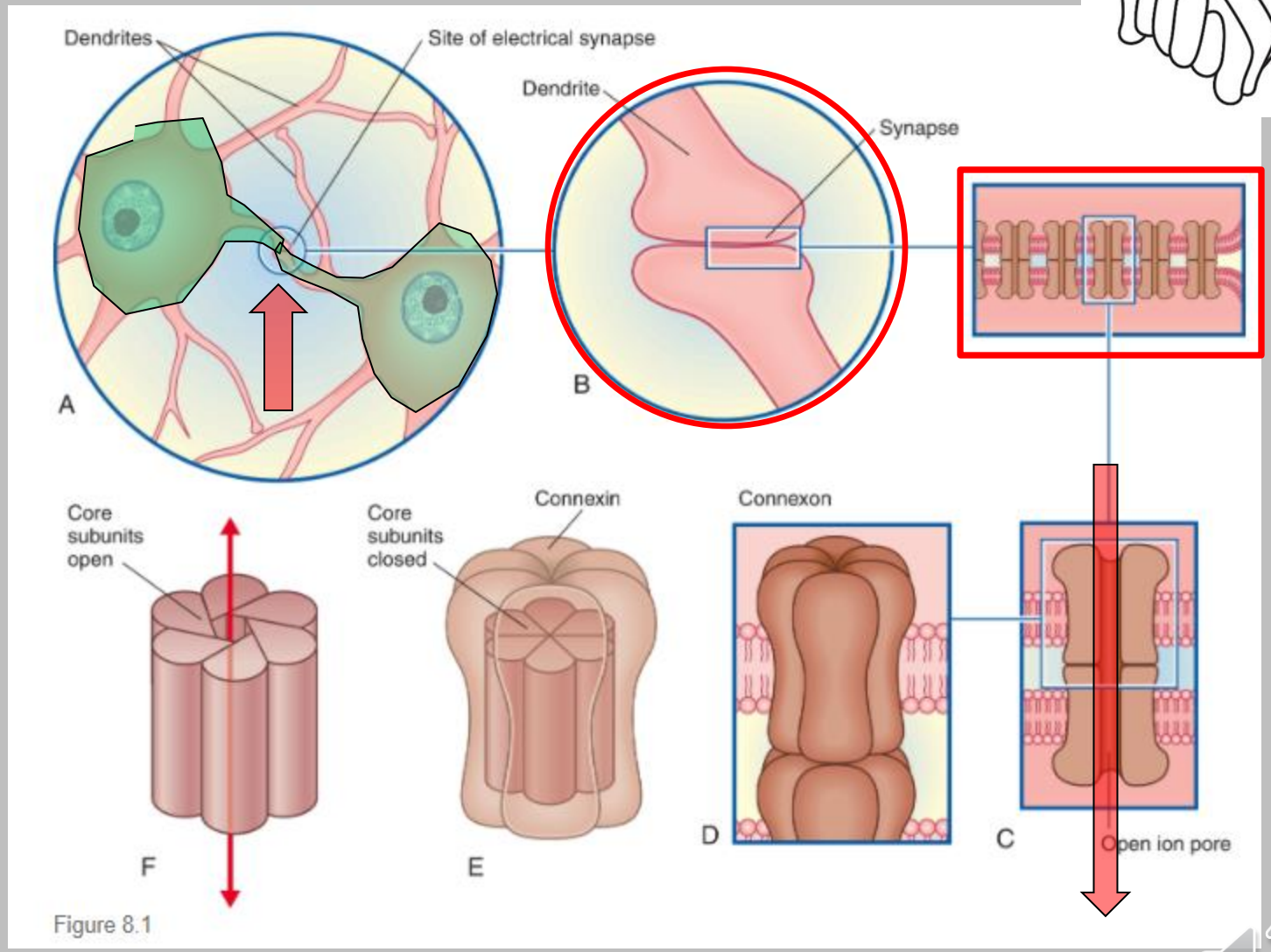
- the site where neurons functionally communicate with one another

Electrical synapses:
Gap junctions/Connexons



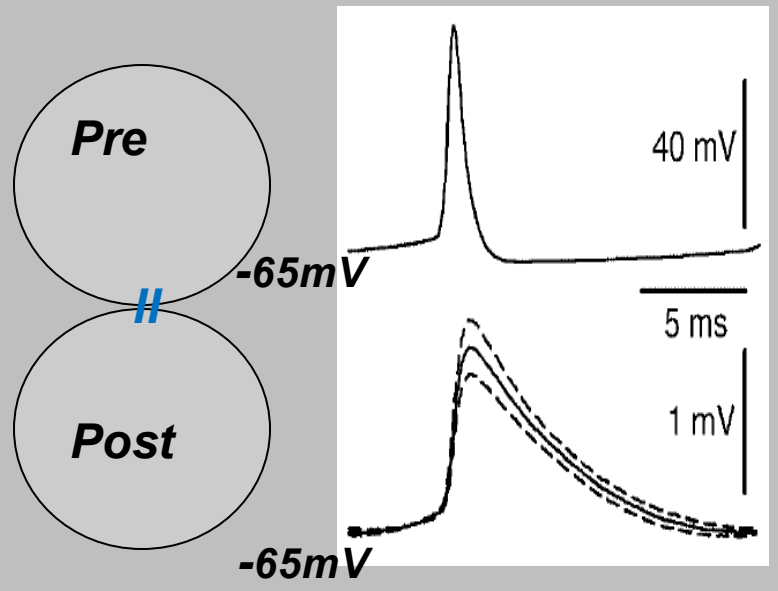
Direct ion & small molecule flow from one neuron to the other. Usually bidirectional.

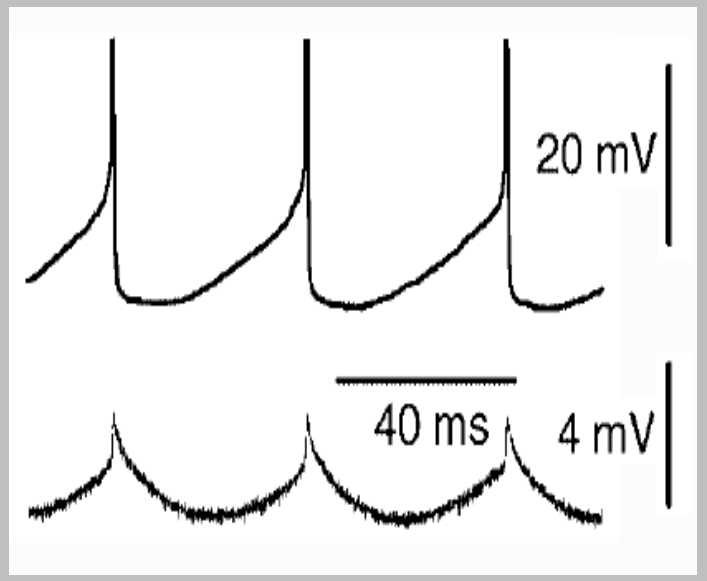
Certain connexins expressed specific cell types.
~30 disease due to connexin gene mutations



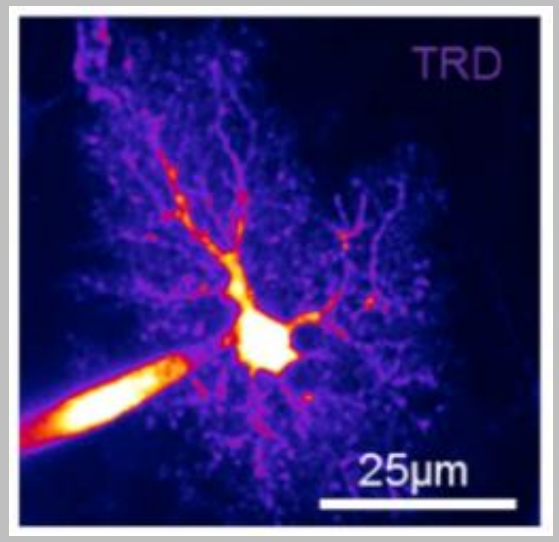
•*E Mtui MD, G Gruener MD, MBA and P Dockery BSc, PhD*
• *Fitzgerald's Clinical Neuroanatomy and Neuroscience, 8; 85-101*

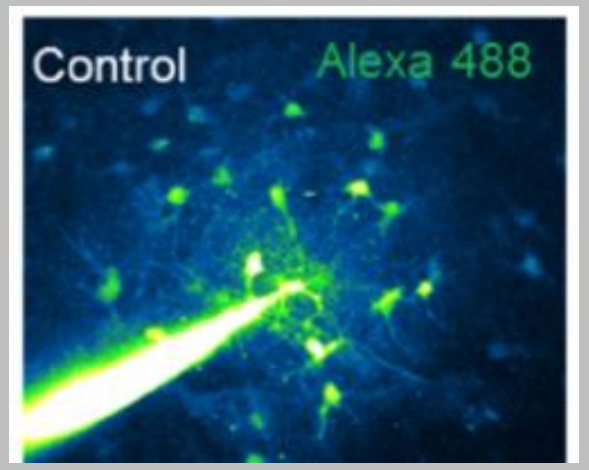
Gap junctions/Electrical synapses: no neurotransmitter used





Connors & Long 2004

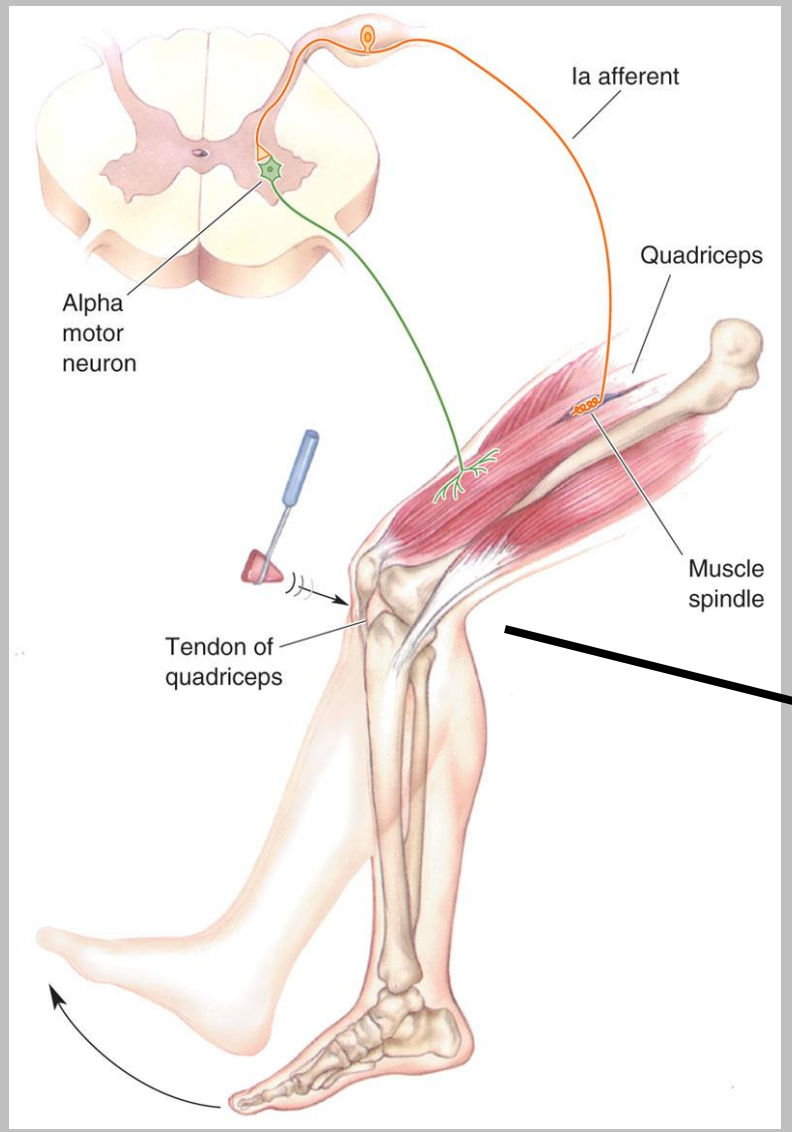




- ***Gap junctions allow direct ion & small molecule flow from one neuron to the other which can depolarize or hyperpolarize the postsynaptic neuron***
- ***Amplitude attenuation of currents***
- ***Usually bidirectional***
- ***Fastest type of neural communication <1ms***
- ***Can depolarize neurons***

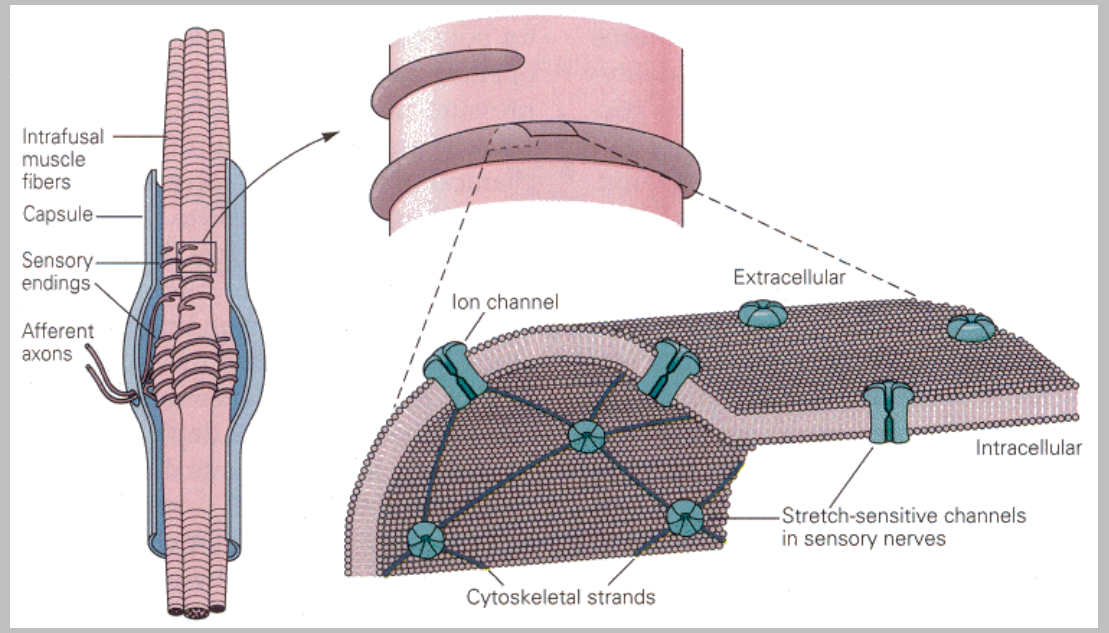
Breithausen et al. Glia 2019
https://doi.org/10.1002/glia.23751

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

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

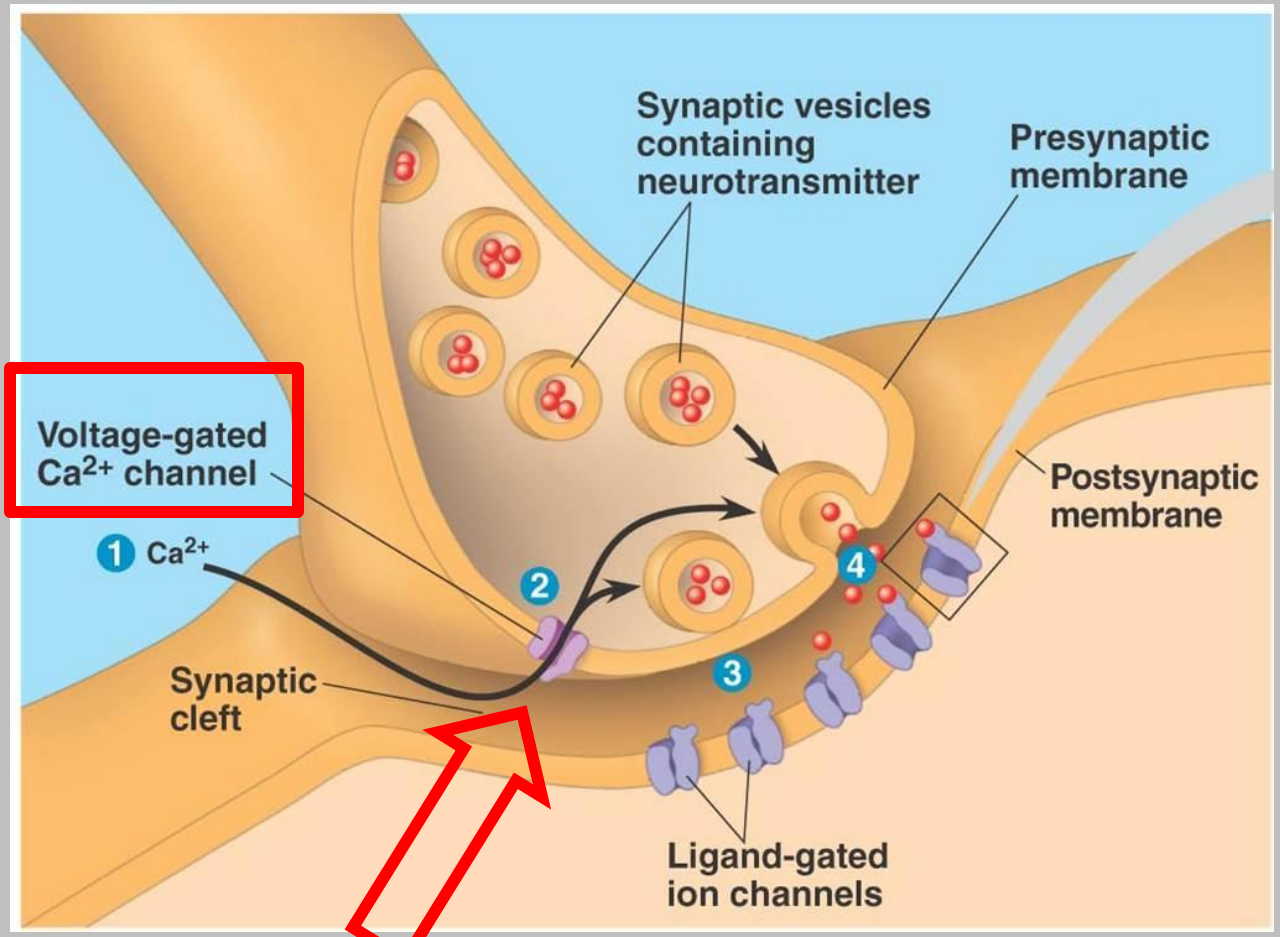
<u>Synaptic cleft</u>
- *Neurotransmitter breakdown*

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

Synaptic mechanisms of disease

Lambert-Eaton Syndrome:

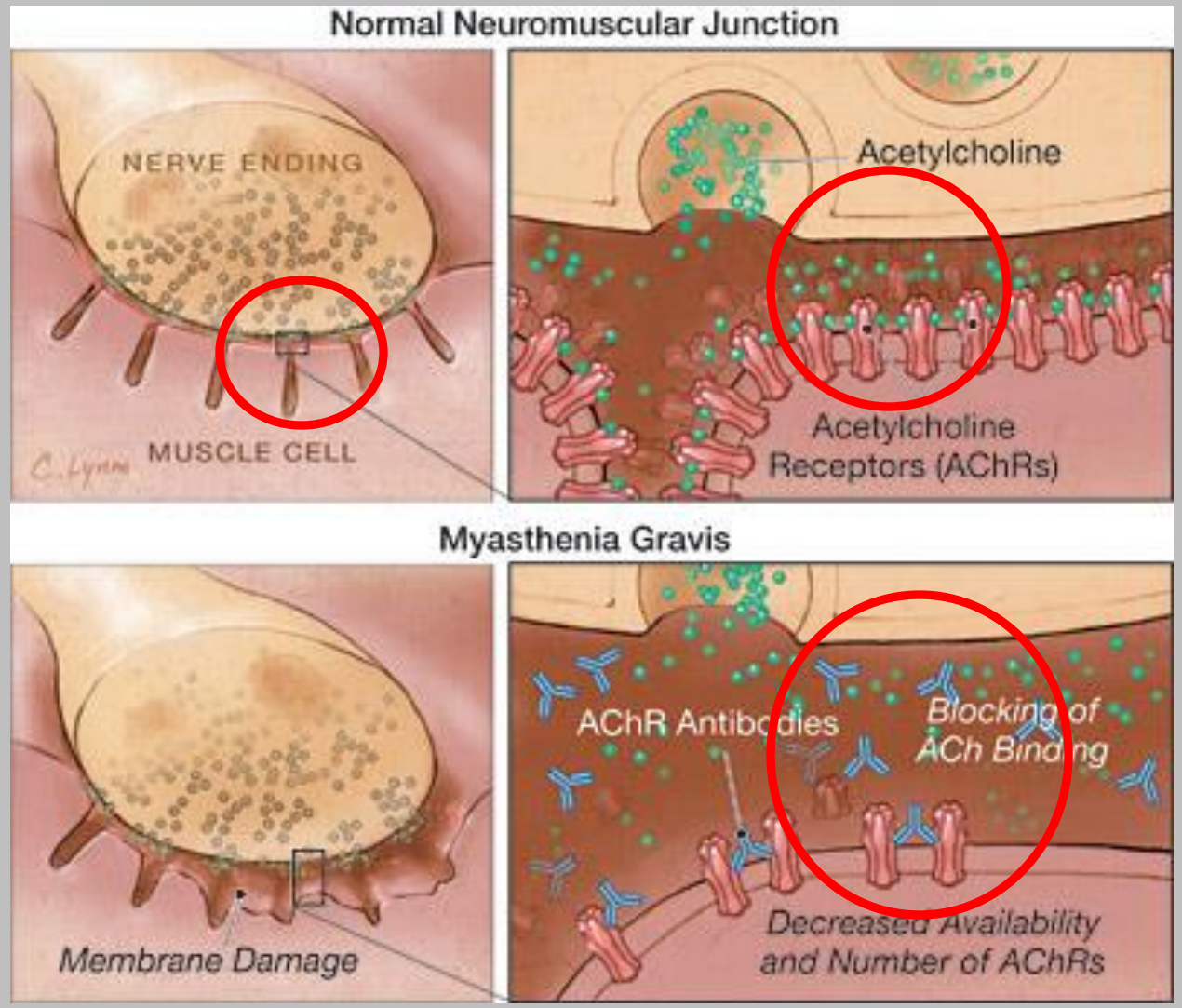
Auto-immune Disease of VGCC at the NMJ



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