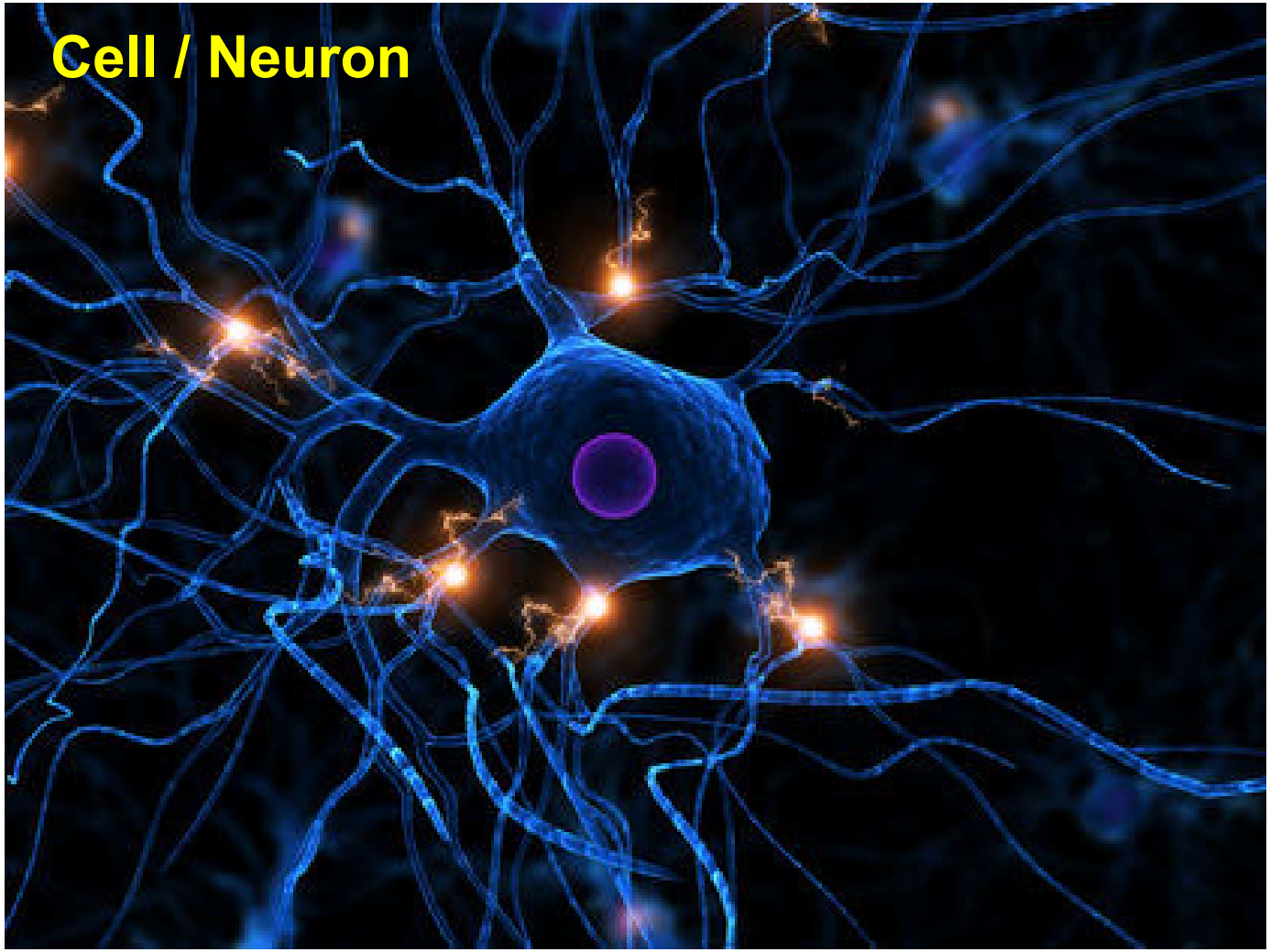
Introduction

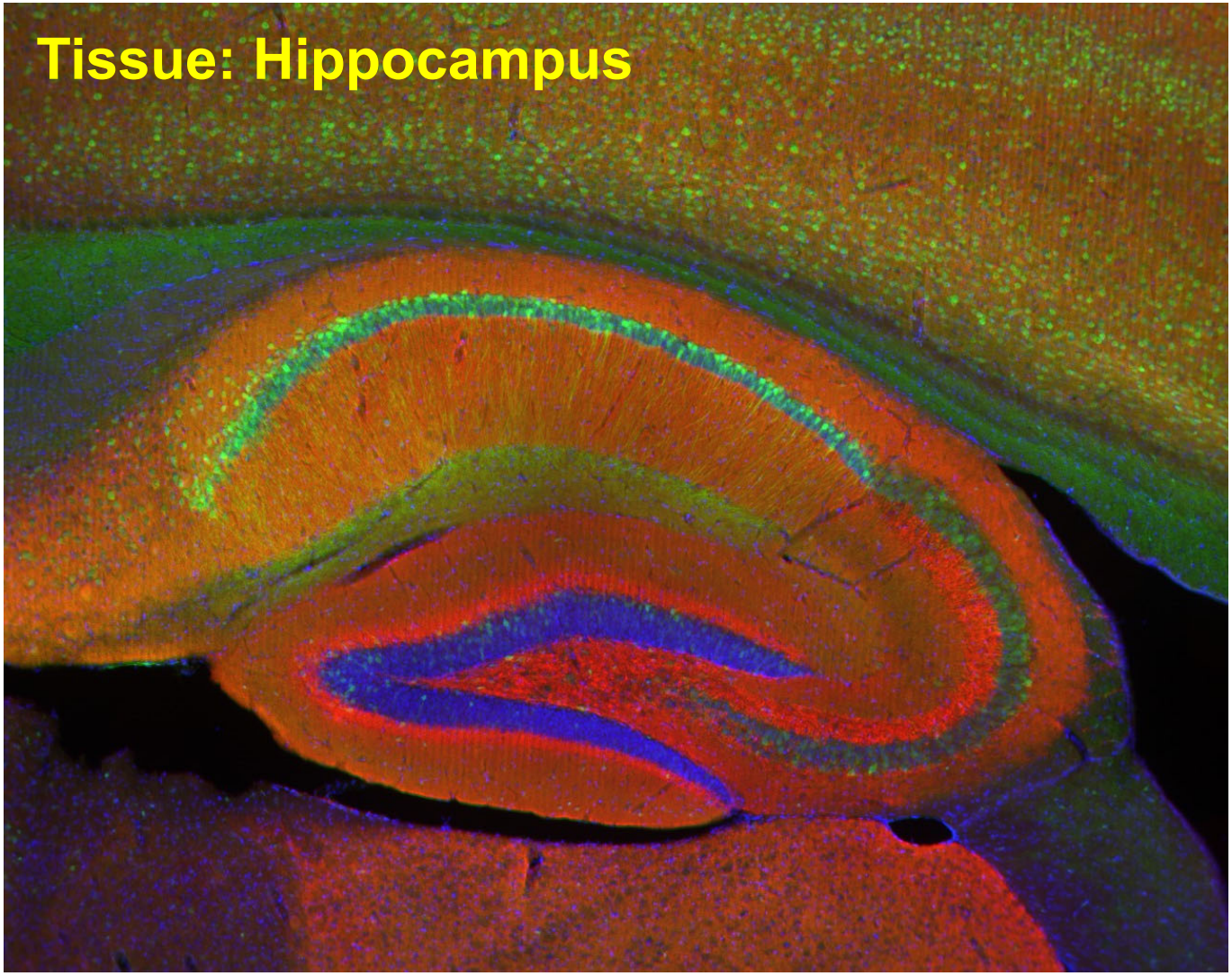
- Our brain is made up of many chemicals working together in a highly-controlled manner.
- All the activities in our brain are based on chemical reactions.
- Neurotransmitters in synapse are endogenous chemicals that enable signal transmission in the brain.

Neuron

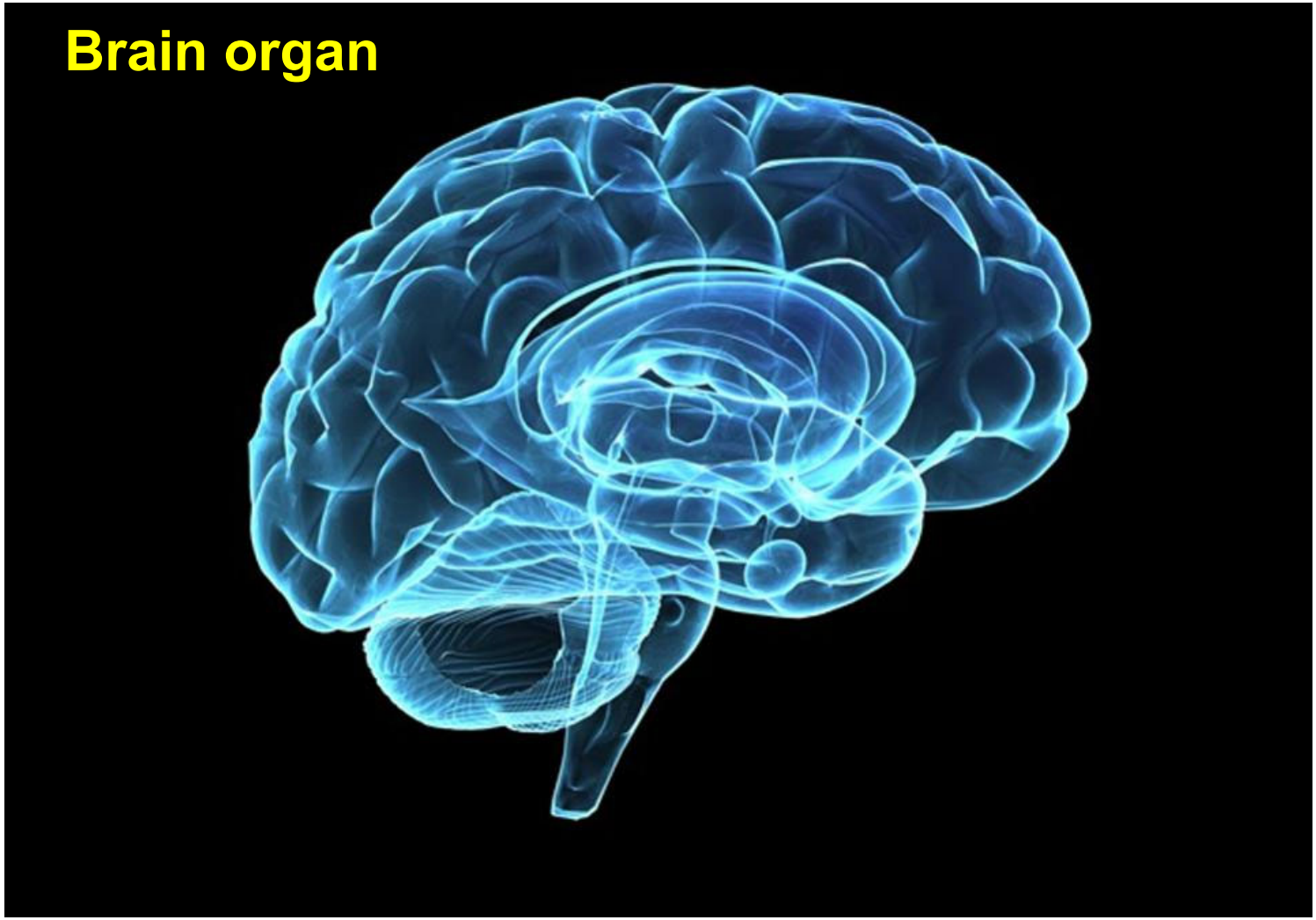


Synapse between neurons

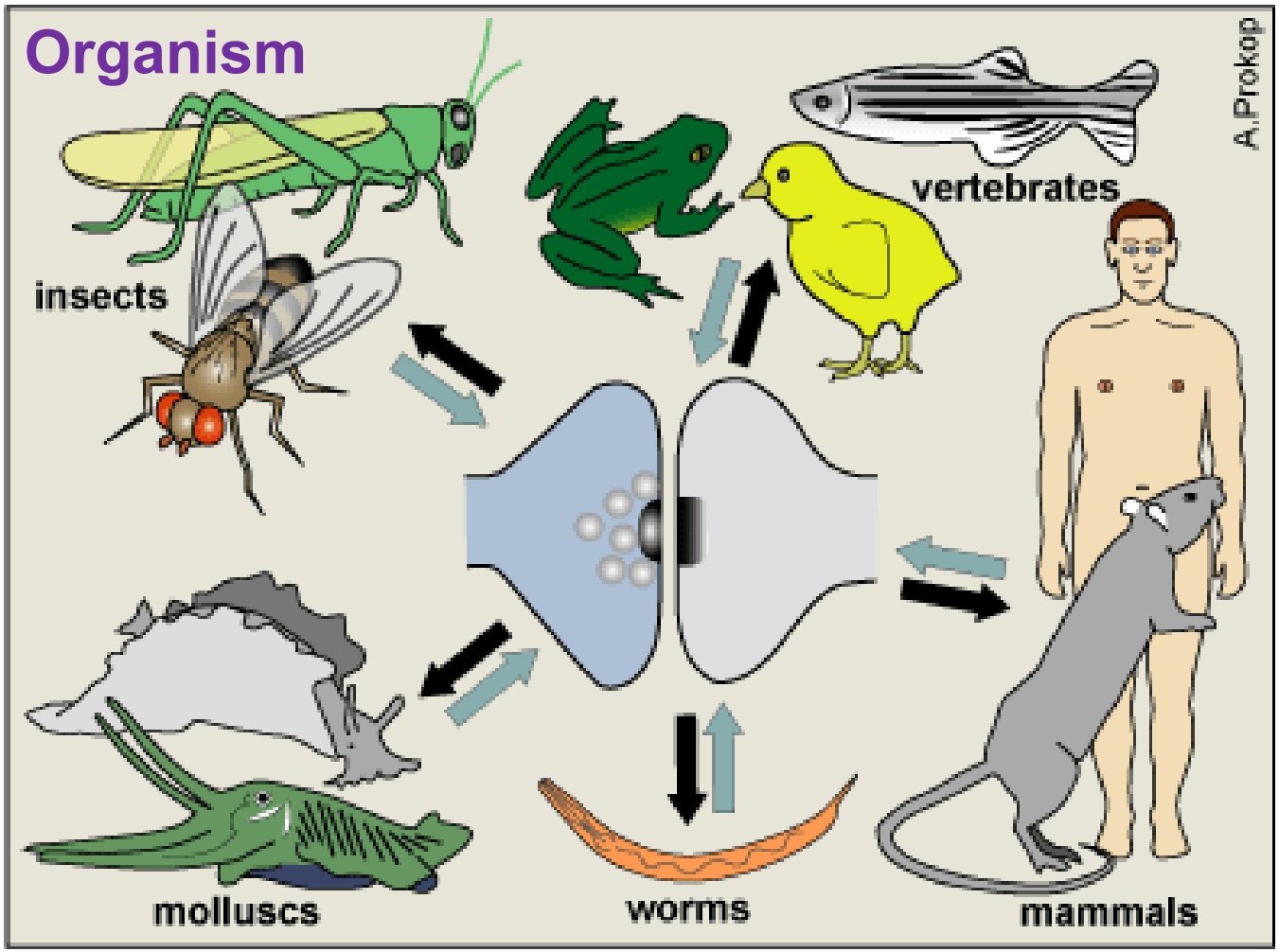
Brain tissue



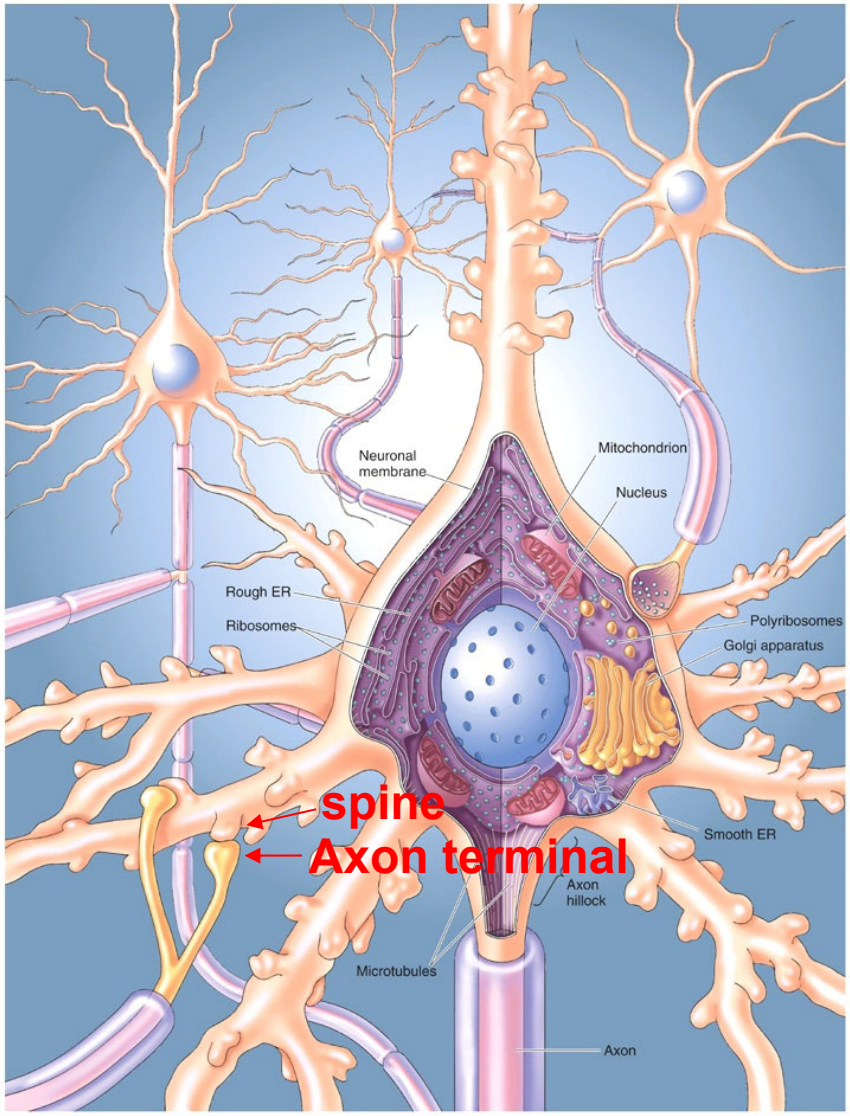
Brain



Synapse determines distinct behaviors



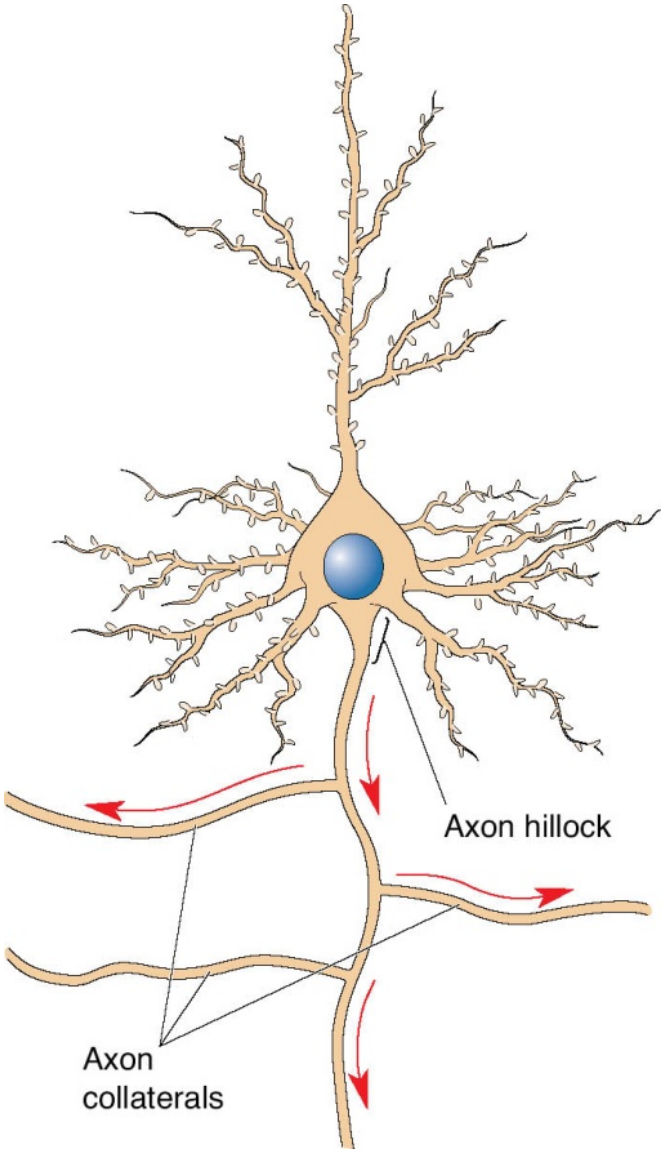
The Prototypical Neuron



- Soma: Signal Integration
  Protein (channels/receptors) synthesis
- Axon: Signal output
  Axon hillock (or axon initial segment)
  Axon terminal
- Dendrite: Signal input
  Spines

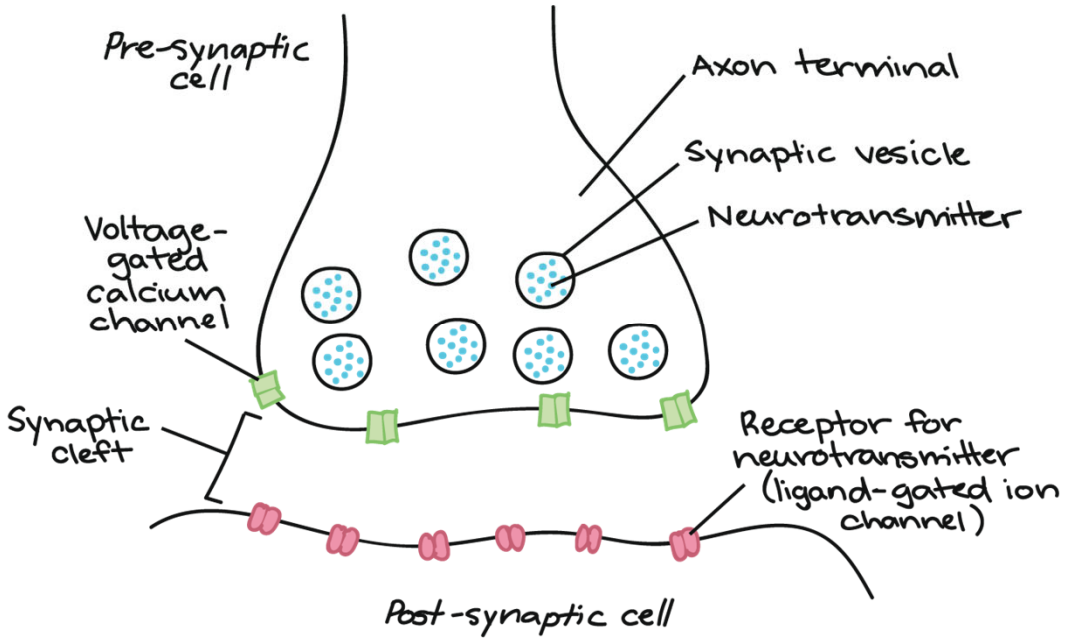
The Prototypical Neuron: Axon

- The axon
  - Axon hillock (beginning) / Axon initial segment
  - Axon trunk and collaterals
  - Axon terminal (presynaptic)



The Prototypical Neuron: Axon terminal

- The axon terminal
  - Differences between axon terminal and axon trunk
    - Presence of synaptic vesicles in terminal
    - Abundance of membrane proteins (channels and receptors) in terminal



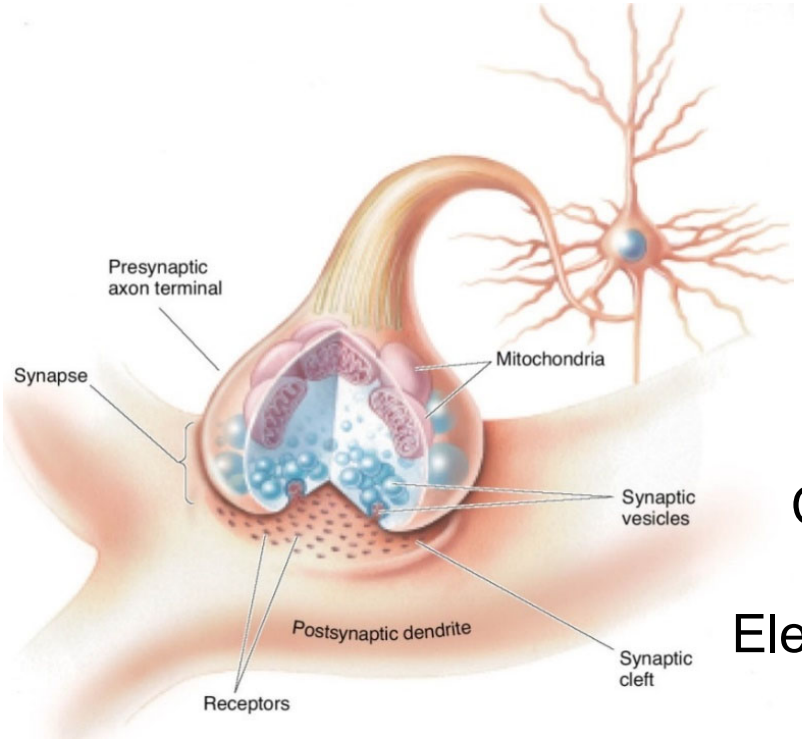
The Prototypical Neuron: Spines on dendrites

- Dendrites
  - "Antennae" of neurons
  - Dendritic tree
  - Synapse has membrane proteins (channels and receptors)
  - Dendritic spines contain postsynaptic receptors (usually receives signals from axon terminal)

Dendrites

Spines

The Prototypical Neuron: Synapse



Electrical signal (Axon terminal)

↓

Chemical signal (Synaptic vesicle)

↓

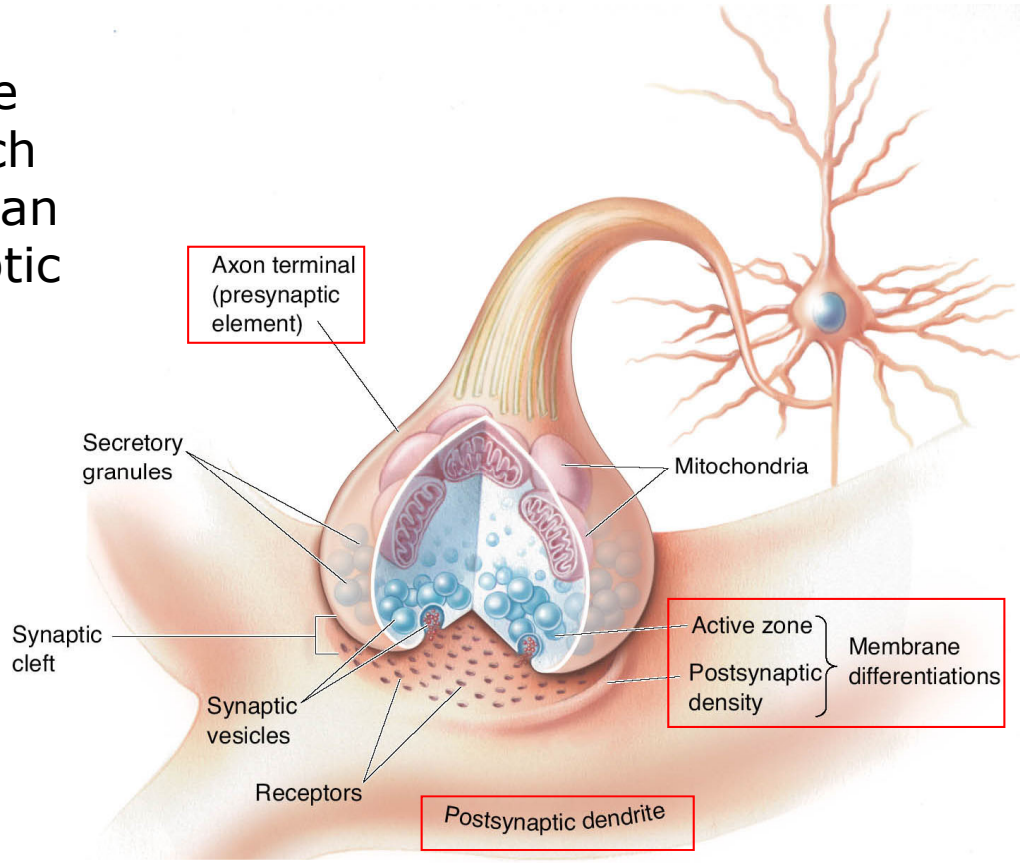
Electrical signal (postsynaptic receptor)

- The synapse
  - Synaptic transmission by interaction of presynaptic neurotransmitter release with postsynaptic receptors
  - Electrical-to-chemical-to-electrical transformation
  - Synaptic transmission dysfunction leads to brain disorders

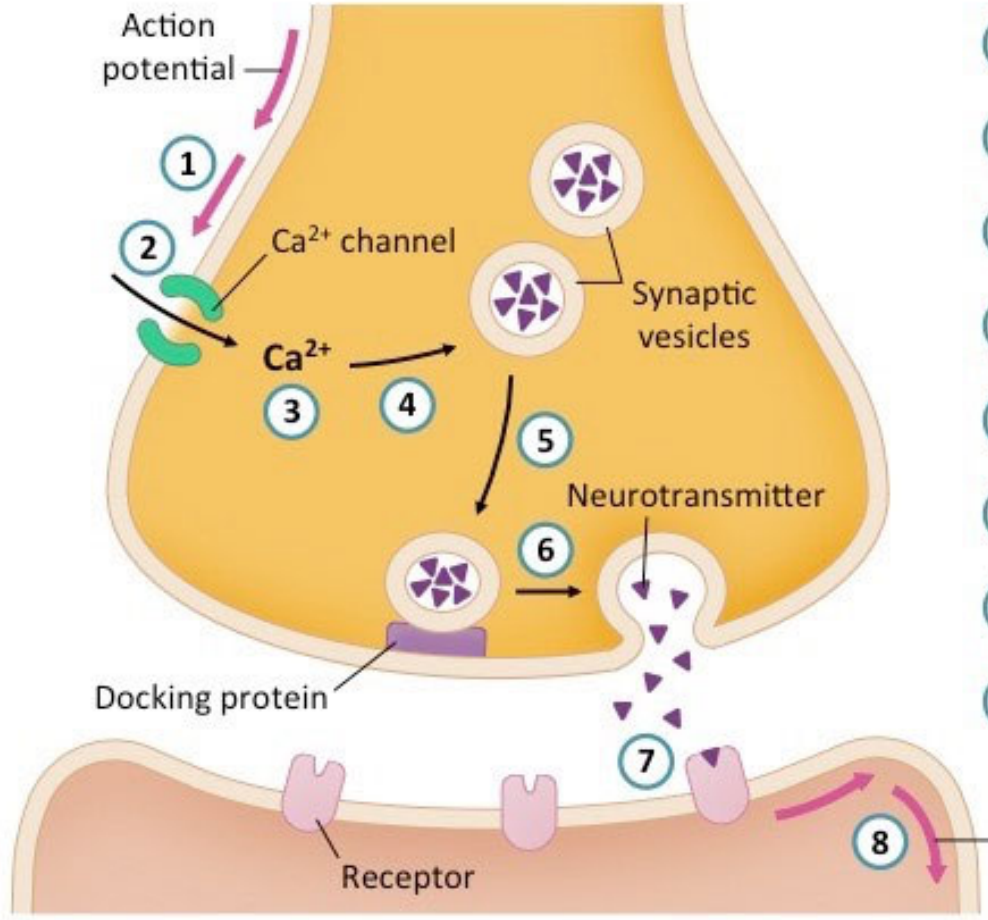
Synapse structures

- Axon terminal: typically contains dozens of membrane-bounded sphere and synaptic vesicles.

- Postsynaptic density contains the neurotransmitter receptors, which convert the chemical signal into an electrical signal in the postsynaptic neuron.



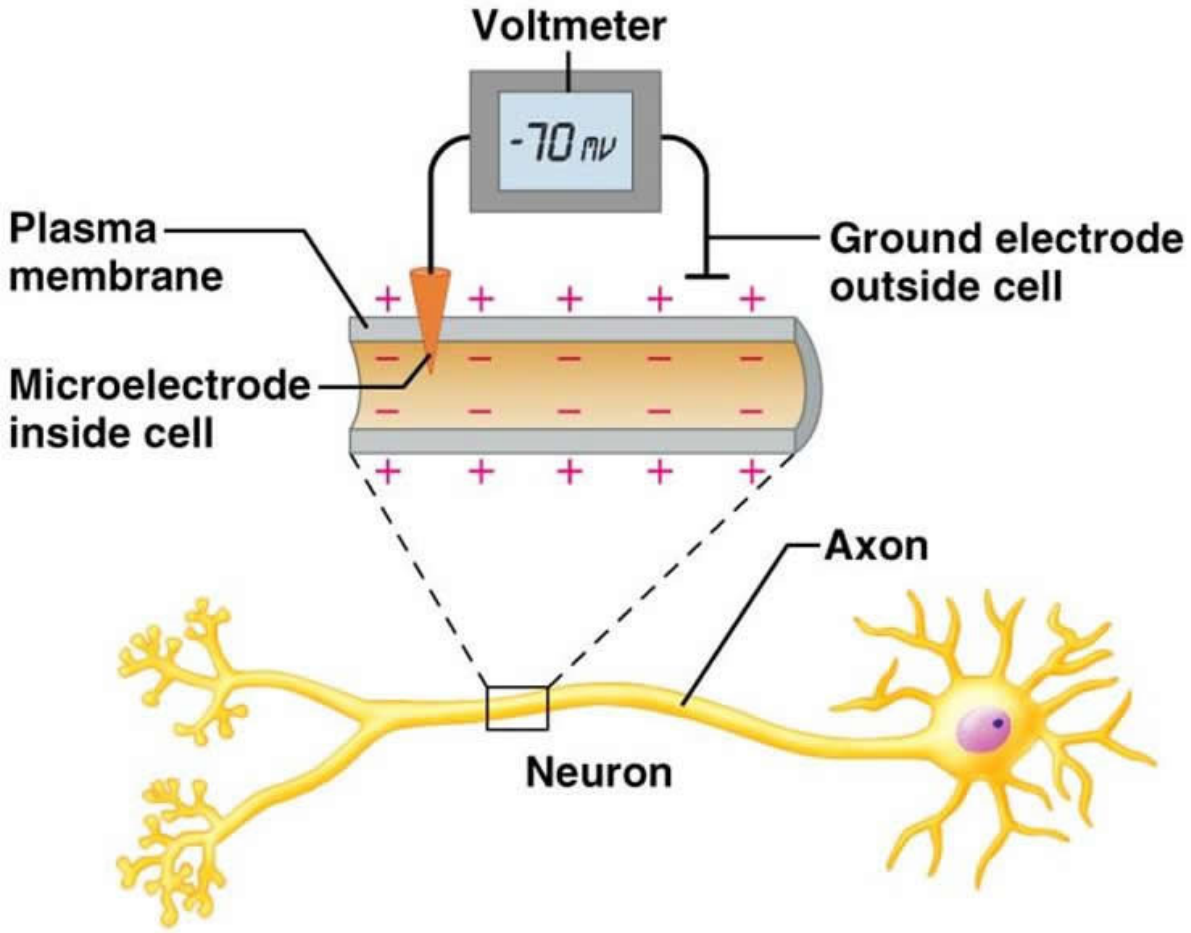
Neurotransmitter release



1. Action potential arrives at axon terminal
2. Voltage-gated Ca^{2+} channels open
3. Ca^{2+} enters the presynaptic neuron
4. Ca^{2+} signals to neurotransmitter vesicles
5. Vesicles move to the membrane and dock
6. Neurotransmitters released via exocytosis
7. Neurotransmitters bind to receptors
8. Signal initiated in postsynaptic cell

http://ib.bioninja.com.au/standard-level/topic-6-human-physiology/65-neurons-and-synapses/synaptic-transfer.html

Ions and Electrical Currents



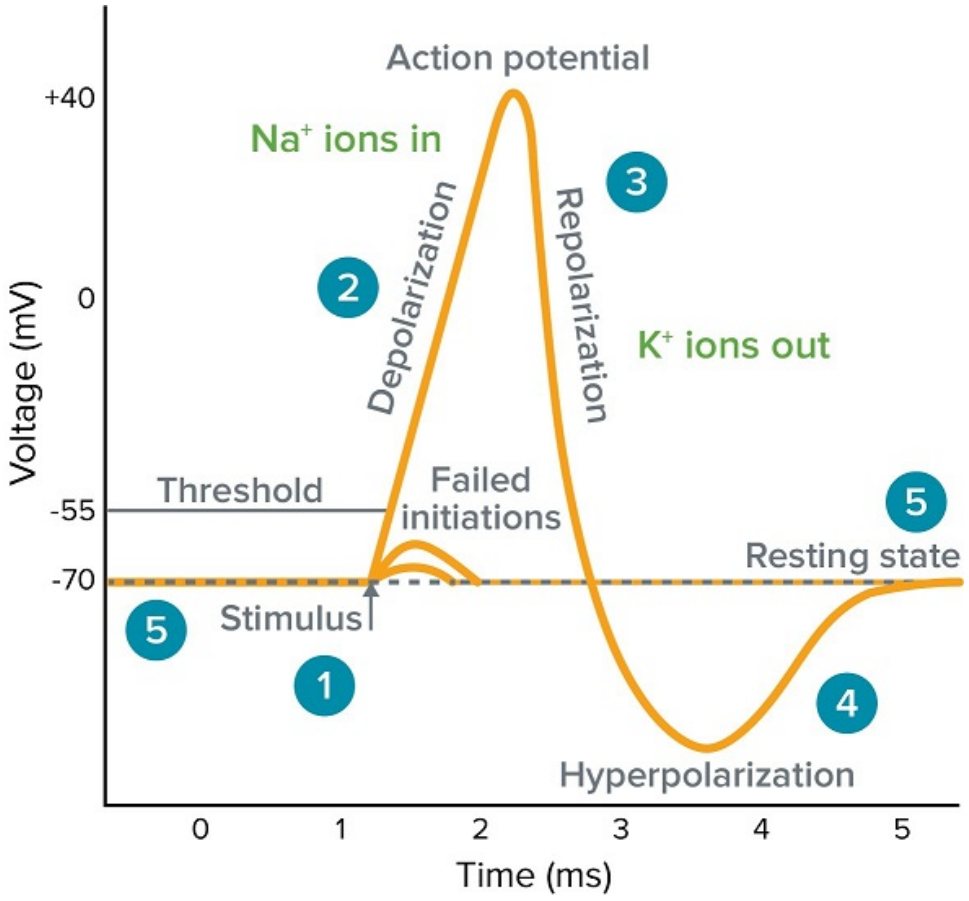
The movement of electrically charged ions that are dissolved in water is the basis of electrical currents in nerve cells.

Electrochemical gradients & equilibrium potentials

		Excitation	Inhibition	Excitation	Inhibition
		Na^+	K^+	Ca^{2+}	Cl^-
Extracellular concentration (mM)		**145**	4	**1.5**	**123**
Equilibrium potential (mV)		+67	−98	+129	−90
Intracellular concentration (mM)		12	**155**	10^{-4}	4.2

e.g., mammalian skeletal muscle cells

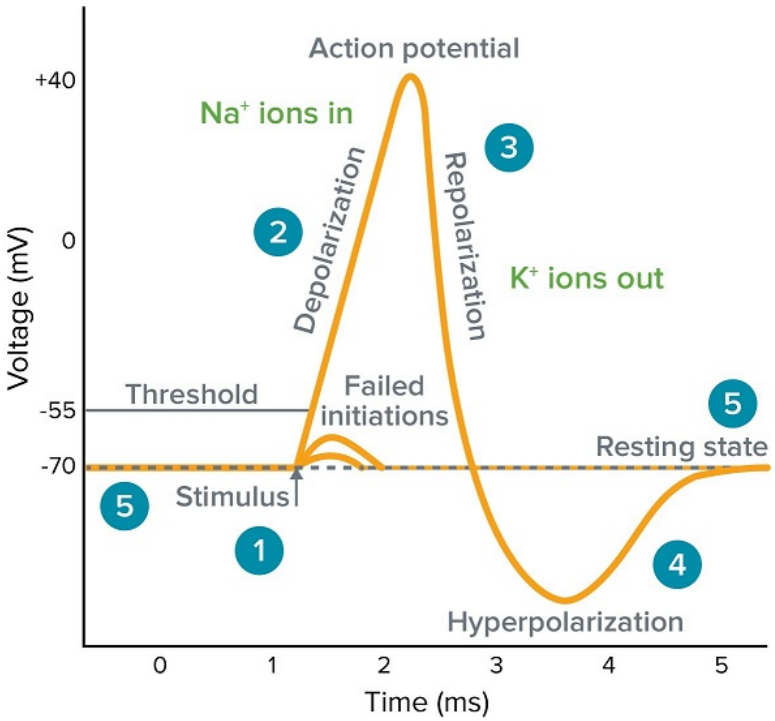
Action potential is a short-lasting event in which the electrical membrane potential rapidly rises and falls



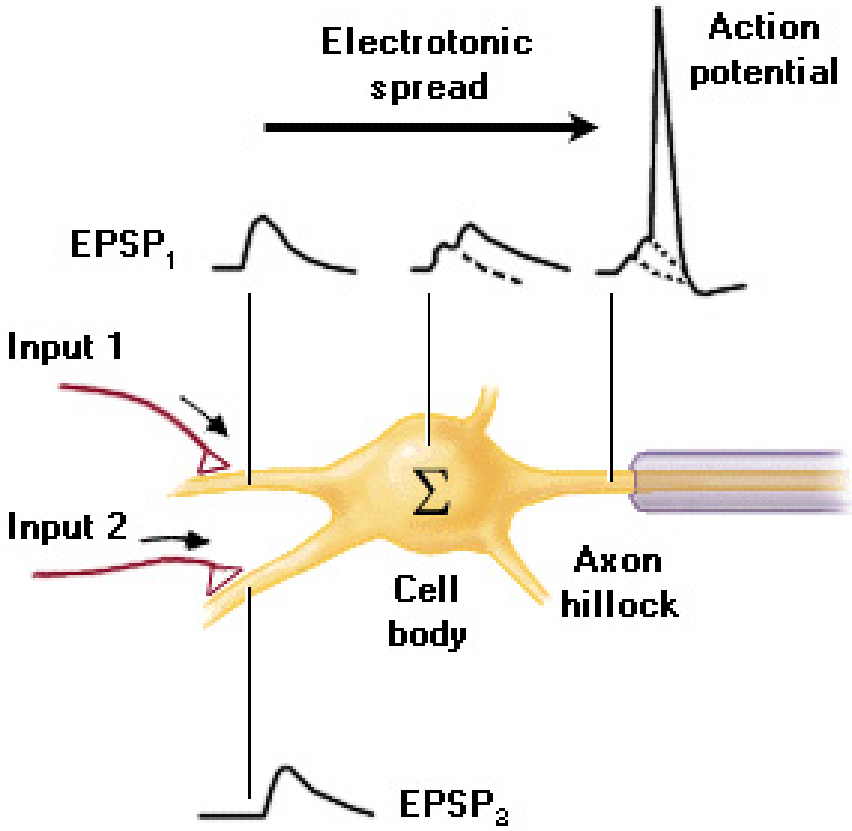
1, stimulus (or synaptic input)
2, depolarization
3, repolarization
4, hyperpolarization
5, Resting state

Action potentials vs synaptic potentials

Action potentials



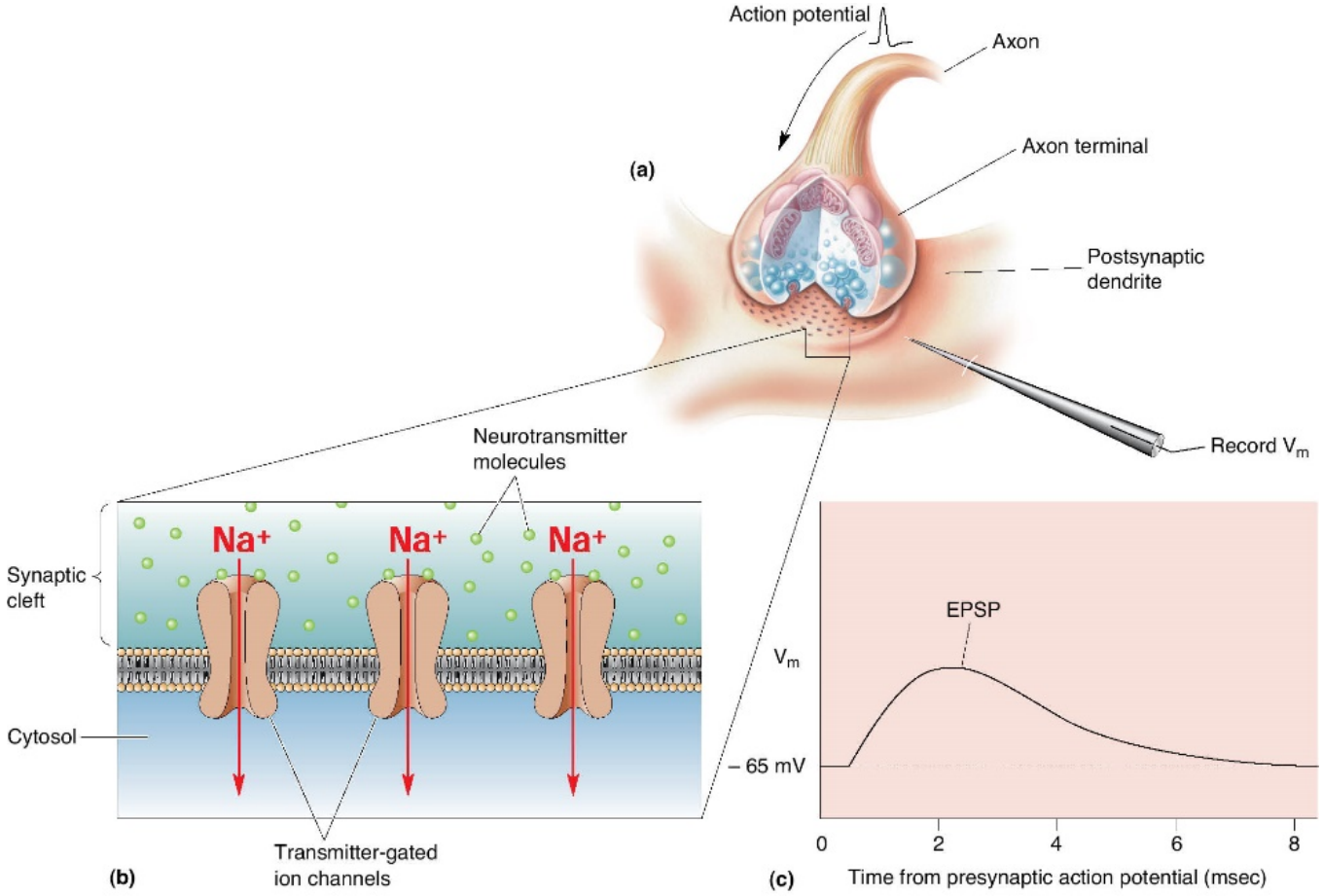
Synaptic potentials



EPSP: excitatory postsynaptic potential

Excitatory postsynaptic potentials

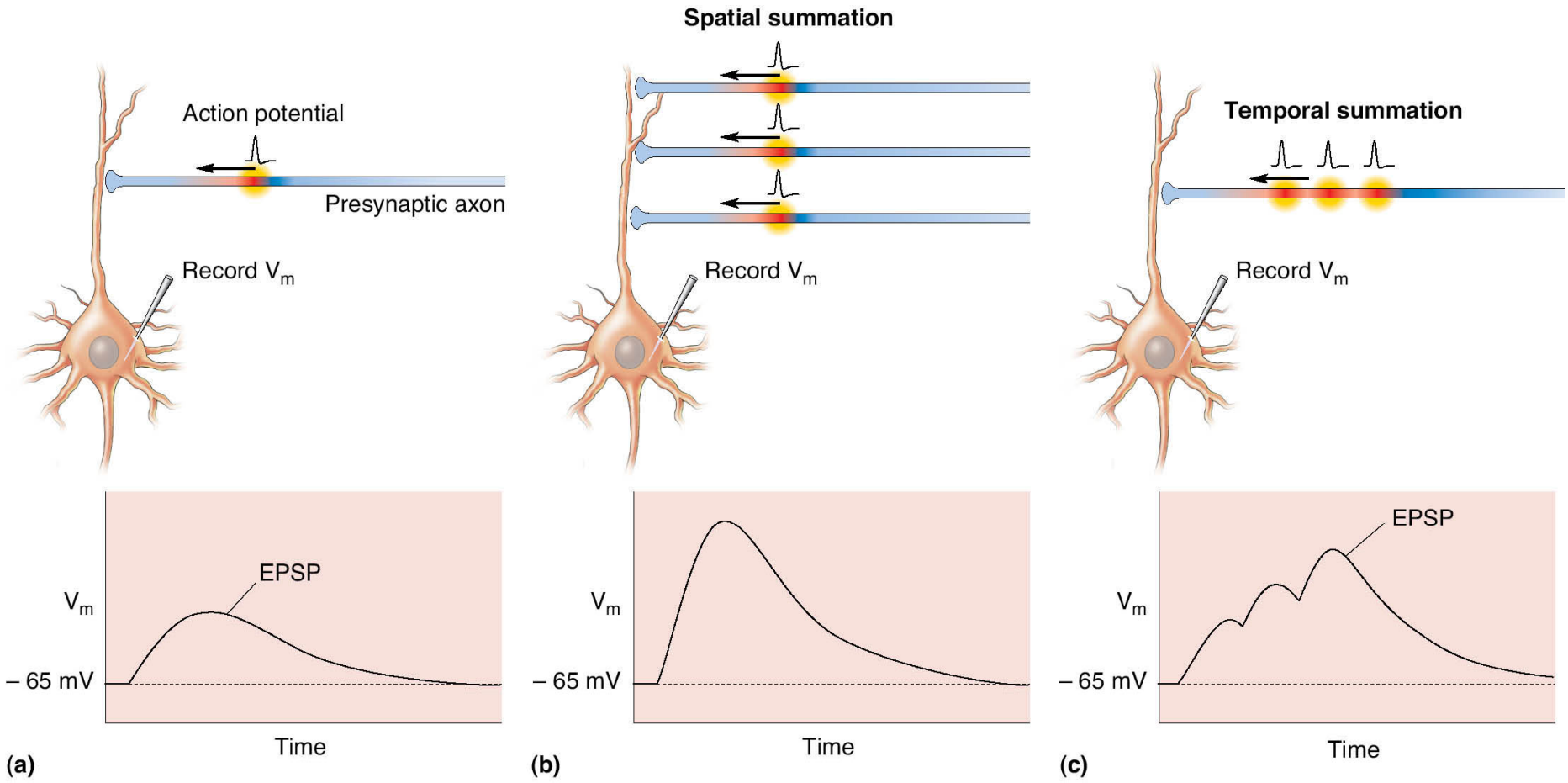
- EPSP (excitatory postsynaptic potential): transient postsynaptic membrane depolarization caused by presynaptic release of an excitatory neurotransmitter (e.g. Glutamate, Acetylcholine)



Synaptic Integration

- Process by which multiple synaptic potentials combine within one postsynaptic neuron
- Most CNS neurons receive thousands of synaptic inputs.
- EPSP summation
  - Allows neurons to perform sophisticated computations
  - EPSPs add together to produce significant postsynaptic depolarization
  - Spatial summation: EPSPs generate simultaneously at different sites
  - Temporal summation: EPSPs generated at same synapse in rapid succession

Spatial and temporal summation of EPSPs

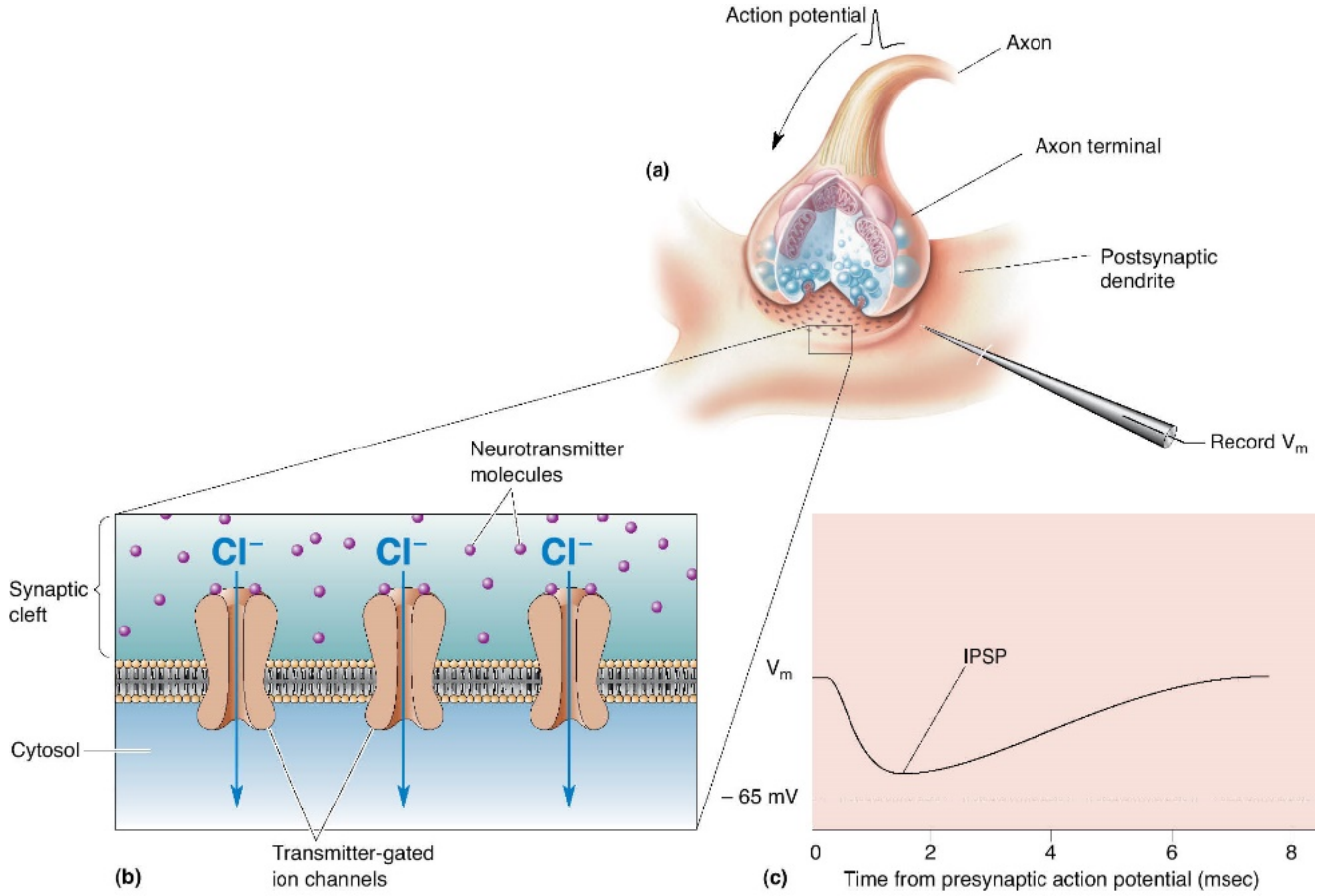


Inhibition

- Not all synapses are excitatory.
- Action of inhibitory synapses—Take membrane potential away from action potential threshold.
- Inhibitory synapses exert powerful control over neuron output.

Inhibitory postsynaptic potentials

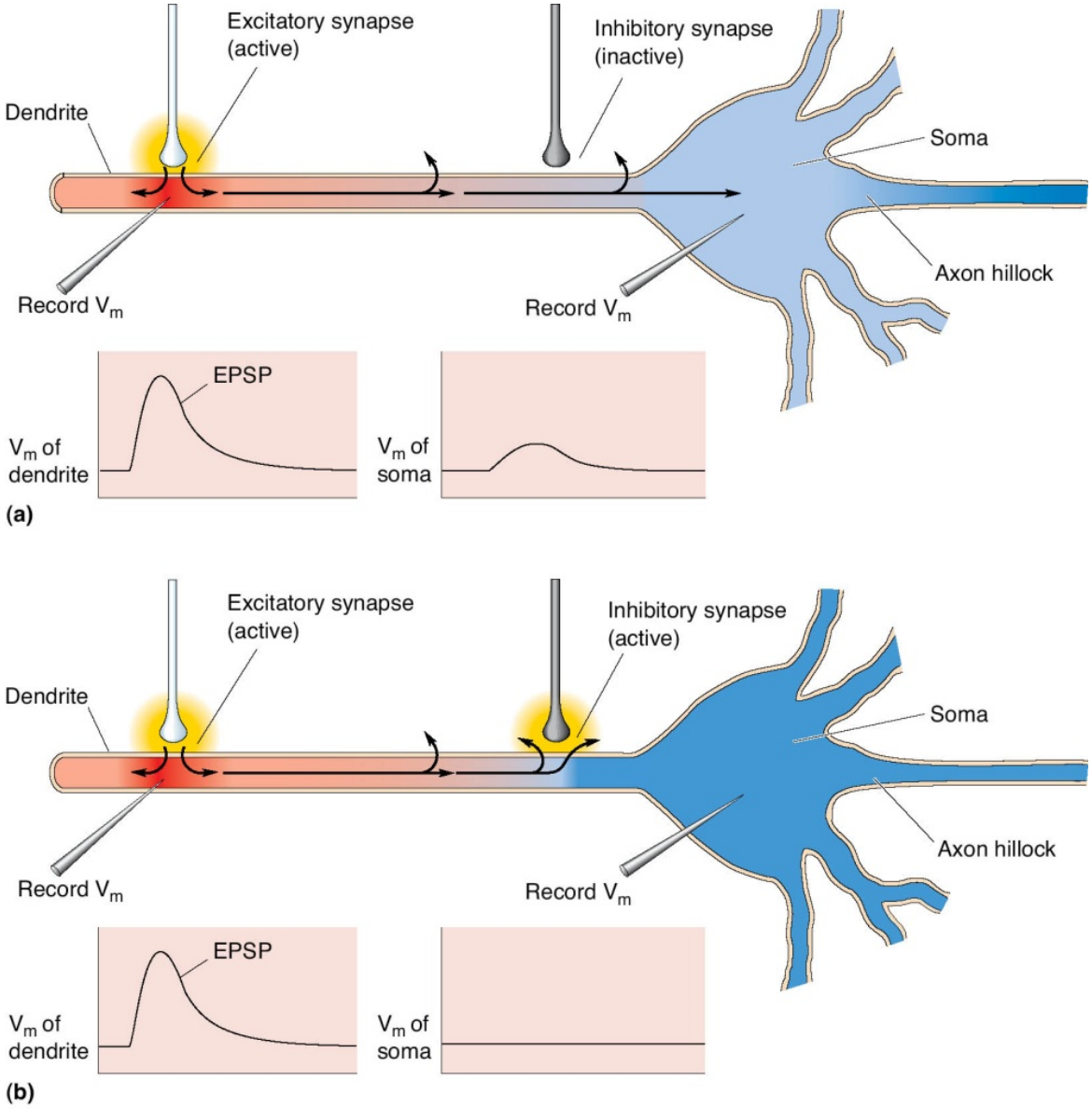
- IPSP (inhibitory postsynaptic potential): transient postsynaptic membrane hyperpolarization caused by presynaptic release of an inhibitory neurotransmitter (e.g. GABA, Glycine)



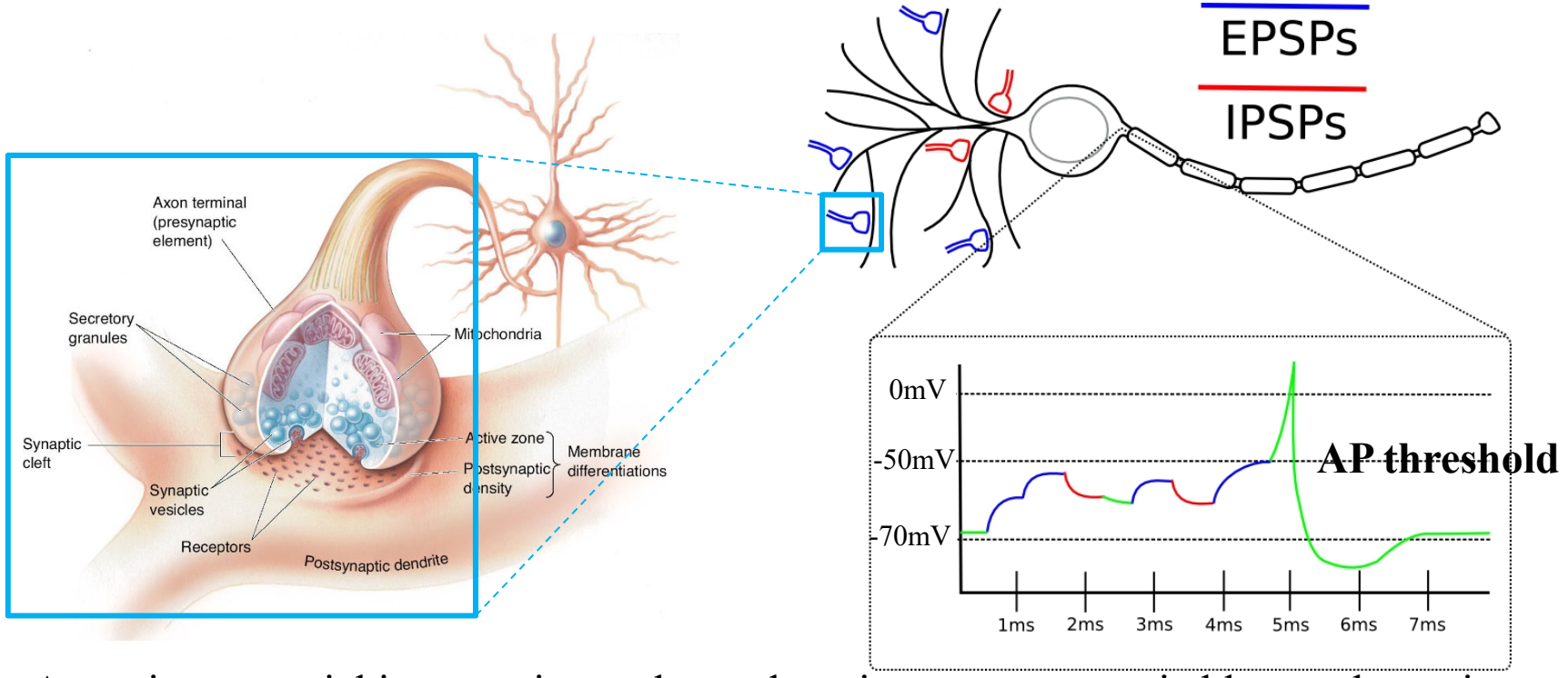
IPSPs and Shunting Inhibition

- Excitatory vs. inhibitory synapses: bind different neurotransmitters, allow different ions to pass through receptors
- Membrane potential less negative than ~−70 mV = hyperpolarizing IPSP
- Shunting inhibition: Synapse acts as an electrical shunt, preventing the current from flowing from the dendrites to the axon.

Shunting Inhibition

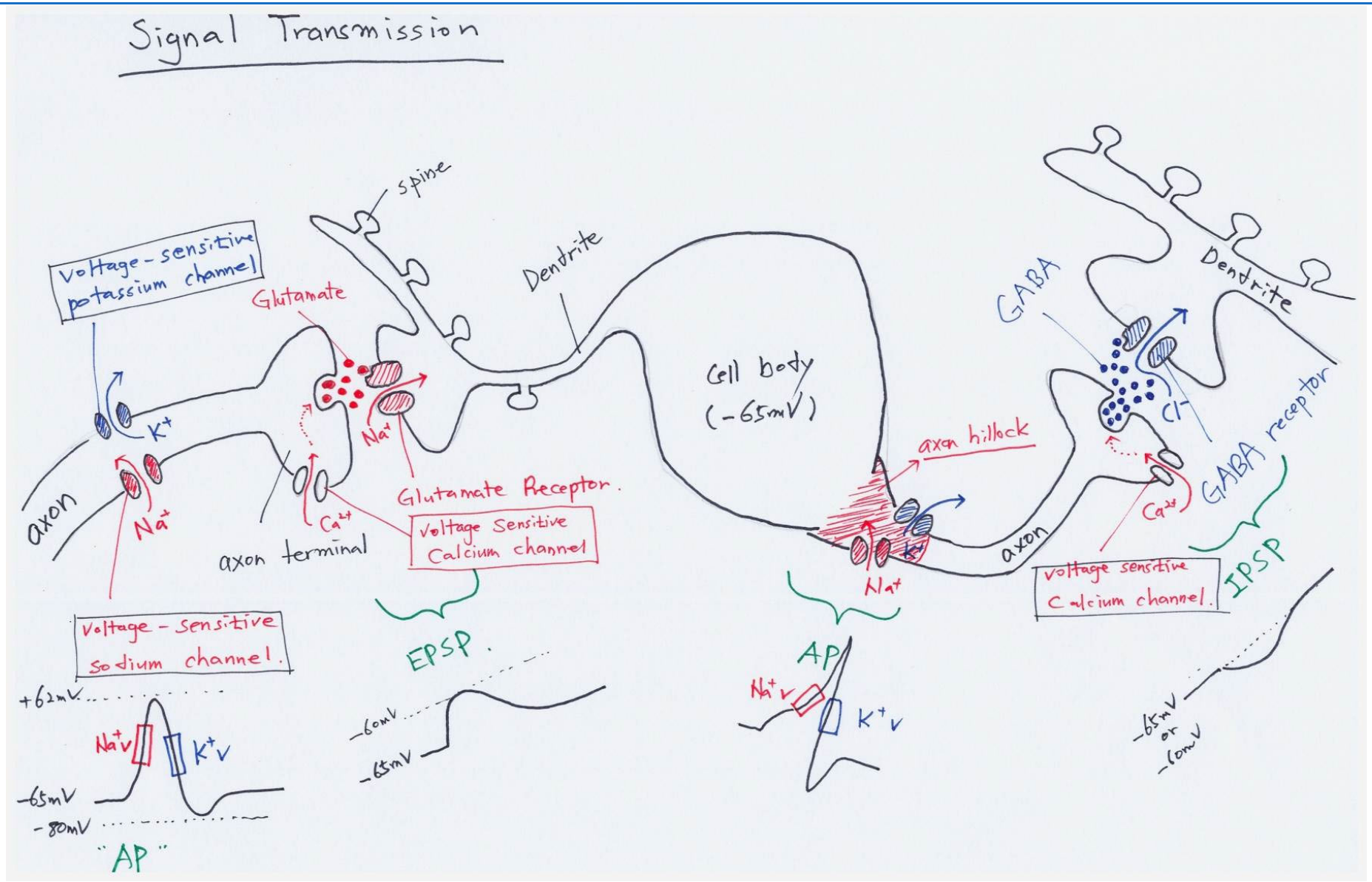


AP vs EPSP (IPSP)

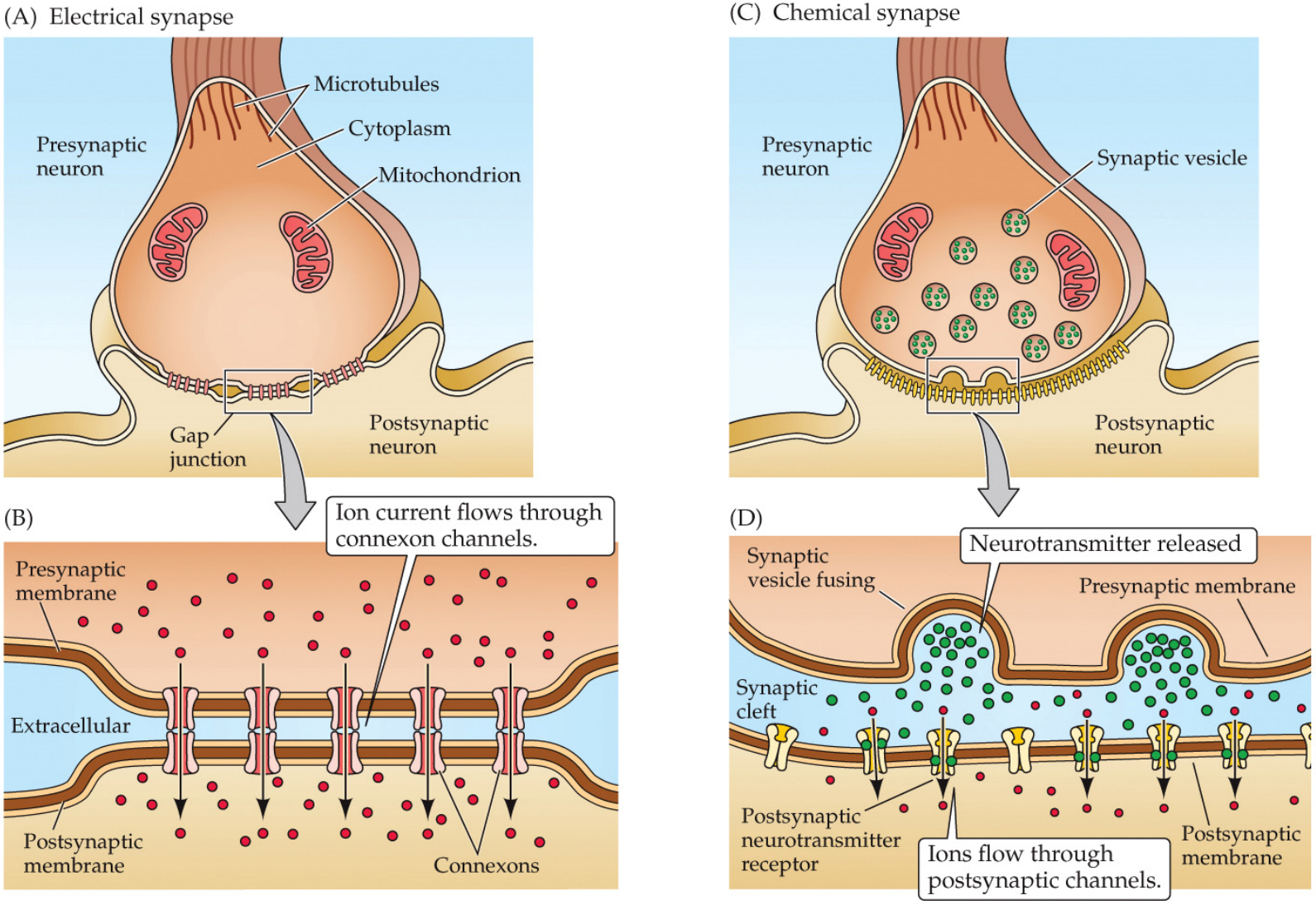


- An action potential is a transient voltage alteration across an excitable membrane in excitable cells (e.g. neurons, skeletal, cardiac, smooth muscle cells, neuroendocrine cells) generated by the activity of voltage-gated ion channels.
- Excitatory postsynaptic potentials are a temporary depolarization of postsynaptic membrane caused by the flow of positively charged ions into the postsynaptic cell as a result of opening of ligand-sensitive channels/receptors, making the neuron more likely to fire an action potential.

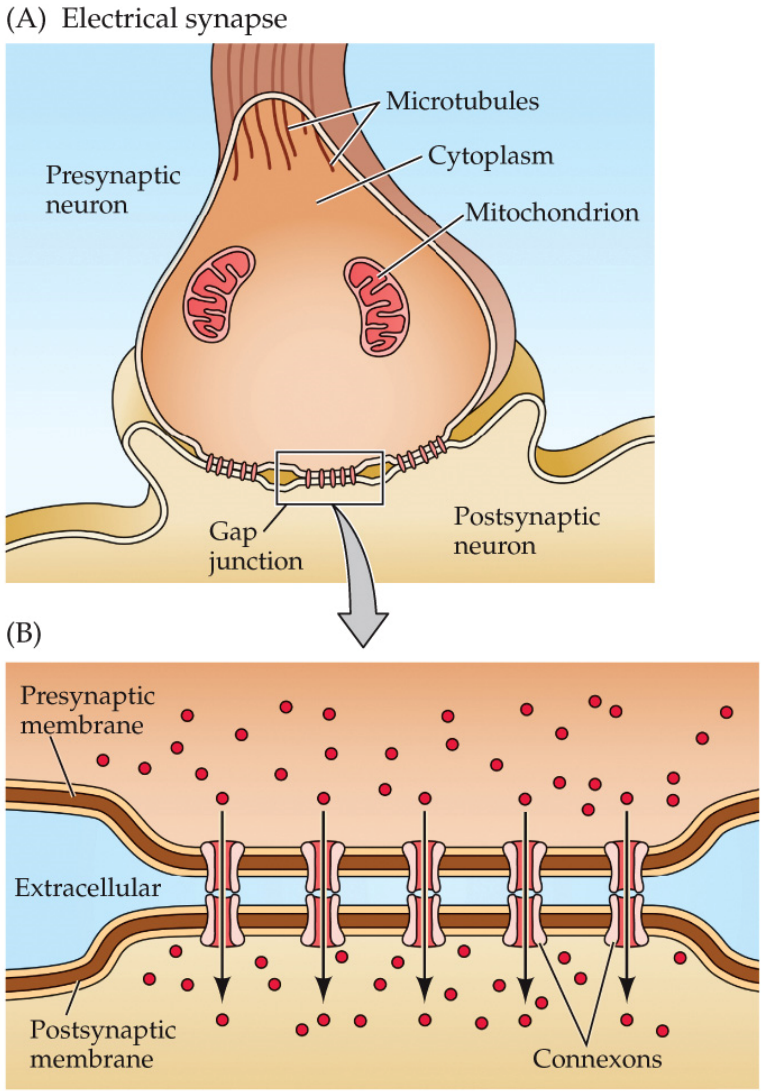
Signal transmission by AP & synaptic potentials



Electrical and chemical synapses differ fundamentally in their transmission mechanisms



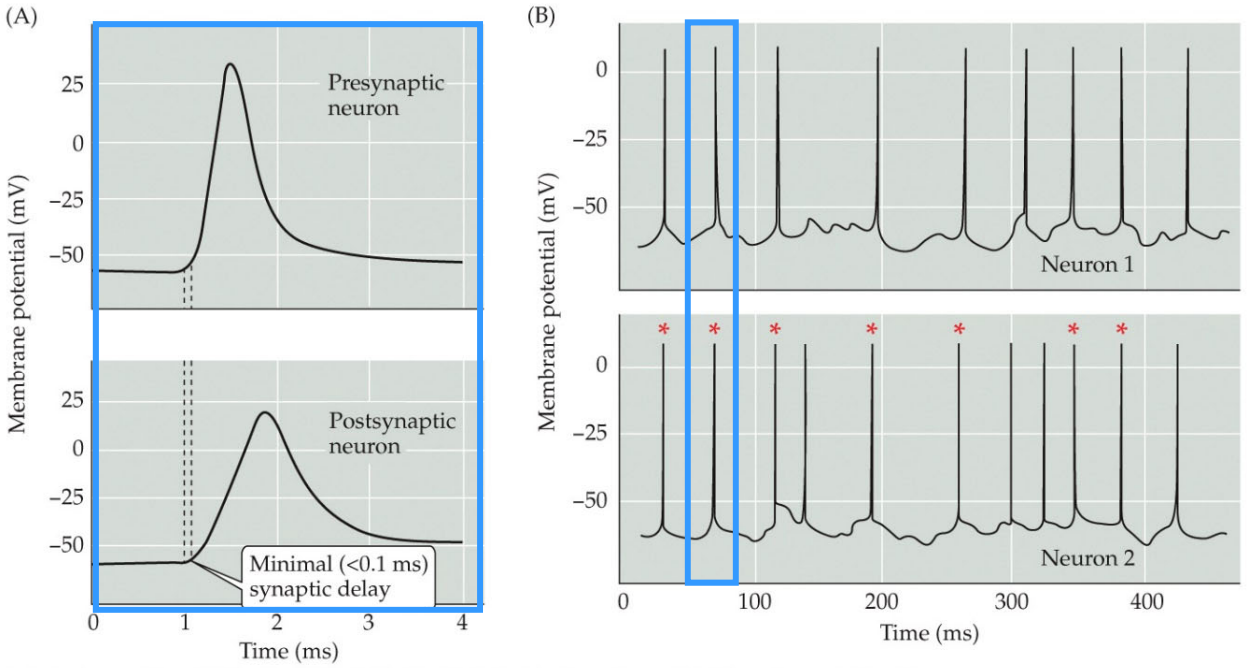
Electrical synapses: Gap Junction



(A) At electrical synapses, gap junctions occur between pre- and postsynaptic membranes.

(B) Gap junctions contain connexon channels that permit current to flow passively from the presynaptic cell to the postsynaptic cell.

Function of gap junctions at electrical synapses



A after Furshpan and Potter (1959) *J. Physiol.* (Lond.) 145: 289–324. B after Beierlein and Connors (2000) *Nature Neurosci.* 3: 904–910.

***NEUROSCIENCE 6e*, Figure 5.3**

(Advantages of electrical synapses)

1. Rapid transmission
2. Bidirectional for electrical synapses vs unidirectional for chemical synapses
3. Facilitation of synchronized activities
4. Direct mediation of intracellular signalling via second messenger (e.g. Na^+, Ca^{2+}, cAMP, IP_3, sugar, inorganic ions, amino acids, nucleotides, and so on)

Neuropharmacology

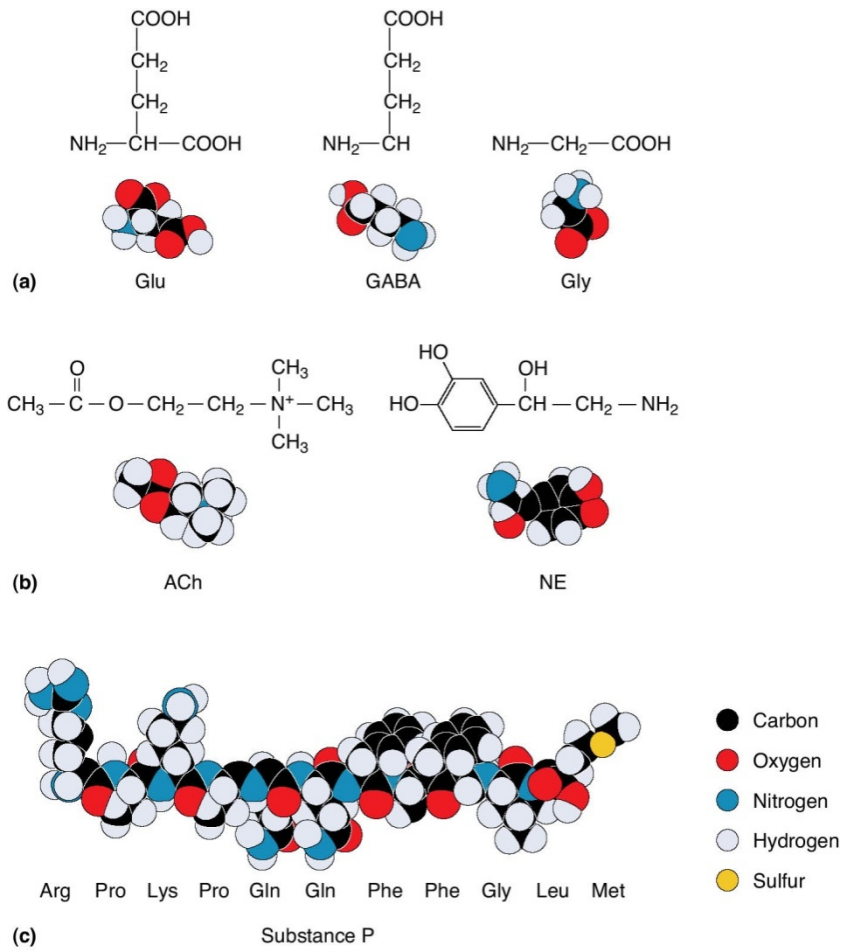
- Study of effects of drugs on nervous system
- Receptor antagonists: inhibitors of neurotransmitter receptors
  - Example: curare (ACh antagonist)
- Receptor agonists: mimic actions of naturally occurring neurotransmitters
  - Example: nicotine (ACh agonist)
- Defective neurotransmission: root cause of neurological and psychiatric disorders

Neurotransmitter categories

- Amino acids: small organic molecules (**glutamate**, glycine, **GABA**)

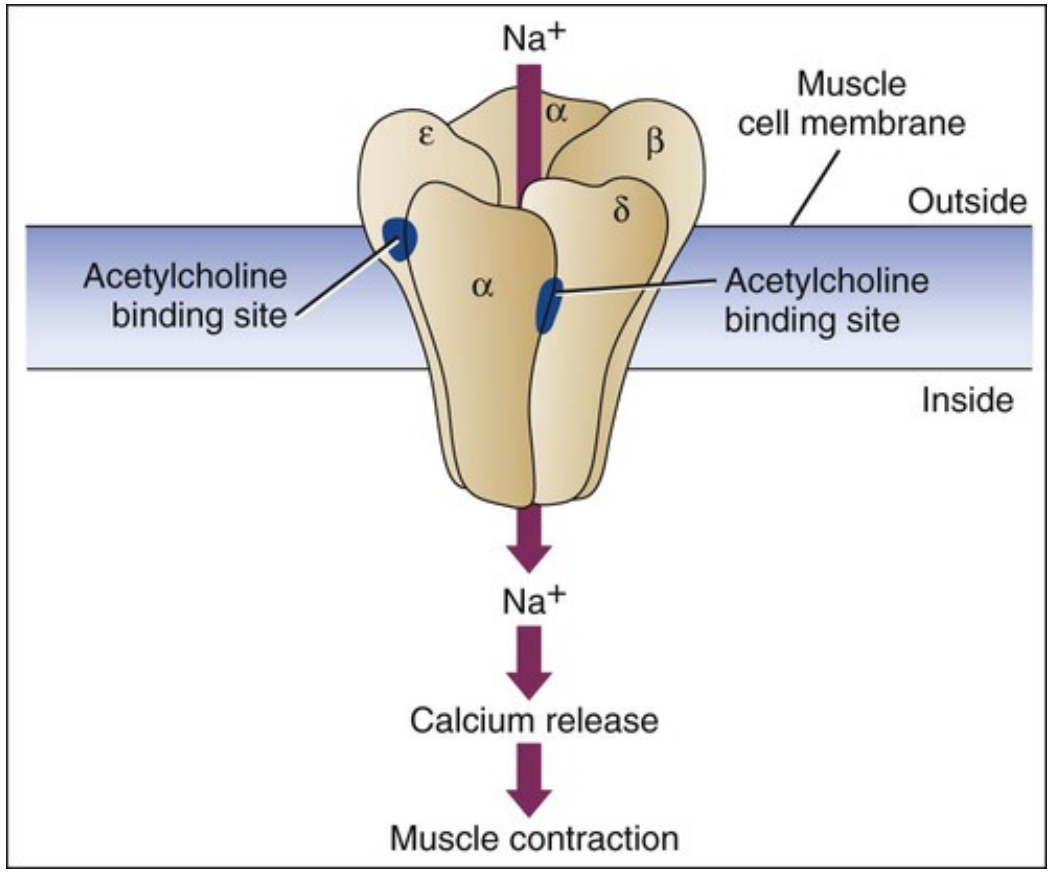
- Amines: small organic molecules—vesicles (dopamine (DA), **acetylcholine (Ach),** histamine, Norepinephrine (NE), Serotonin (5-HT))

- Peptides: large molecules, stored in and released from secretory granules. (substance P, Cholecystokinin (CCK), Neuropeptide Y, somatostatin, Vasoactive intestinal polypeptide (VIP)).



The Acetyl-Choline Receptor (AChR): Ionotropic receptor

- The AChR is a transmembrane protein
- It binds two ACh molecules
- The receptor is a ligand gated ion channel
- ACh binding causes a shape change that allows Na^+ to pass through the channel



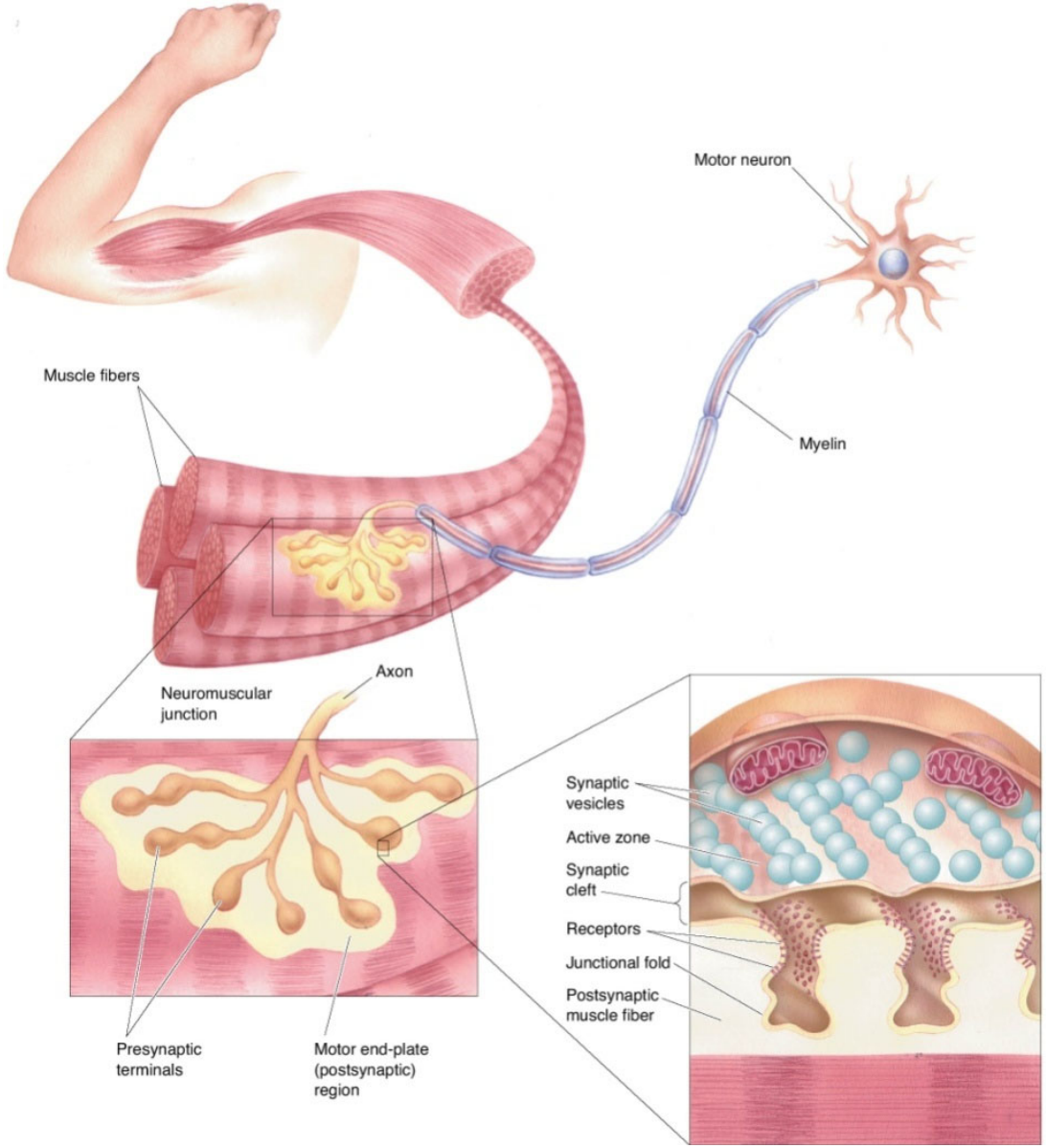
Many poisons are Neurotoxins

Most of them work by interfering with control of muscle contractions

They cause death because they stop the heart and lungs by the deficit of neural functions.

The point where your muscles and nervous system meet is called the

neuromuscular junction (NMJ)



Signals sent from your central nervous system to the NMJ tell muscles to move

The synapses at the NMJ use a neurotransmitter called acetylcholine

Many neurotoxins make it impossible for the neurone to fire its electrical signal

Venomous snake; spider venom;
poison arrow frogs; scorpion stings etc…

Many neurotoxins make it impossible for the neurone to fire its electrical signal

Cobratoxin blocks acetylcholine receptors

Acetylcholine can't bind to its receptors, so the neuronal signals that control your muscles are blocked; your muscles are paralysed

Left untreated, a bite from an Indian Cobra can kill in just 1 hour

Bacteria toxin: Botox

Botulinum toxin (Botox) is a neurotoxin produced by bacteria called *Clostridium Botulinum*

It is used medically to treat muscle spasms and cosmetically to reduce wrinkles

It works by preventing vesicles containing neurotransmitter from fusing with the presynaptic membrane.

This means acetylcholine isn't released at the neuromuscular junction, so muscles are paralysed

Plant toxin: Curare

Curare is used by some indigenous South American tribes for poison darts and poison arrows

It comes from the curare plant

Curare paralyses muscles by blocking acetylcholine receptors

It was one of the first chemicals used as a muscle relaxant in anaesthesia; at the right does, it has medical uses.

Fish Toxin

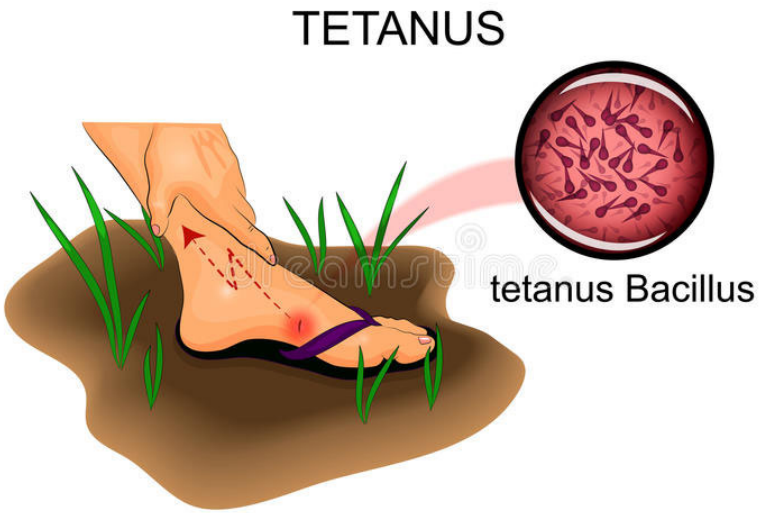
One puffer fish (Fugu) contains enough neurotoxin (Tetrodotoxin, TTX) to kill 30 people

Fugu can only be prepared by specially trained chefs who carefully remove all the parts of the fish that contain the poison

There is no known antidote

Puffer fish for sale at Kuromon Ichiba market, Osaka, Japan

Bacteria toxin: Tetanospasmin



Tetanus is caused by the neurotoxin tetanospasmin which comes from a bacterium called *Clostridium tetani and* inhibits the release of GABA.

It causes poisoning by interfering muscle contractions; Muscles become very sensitive to stimulation and instead contracting and then releasing, they go into spasm

Synaptic Neurotoxins