



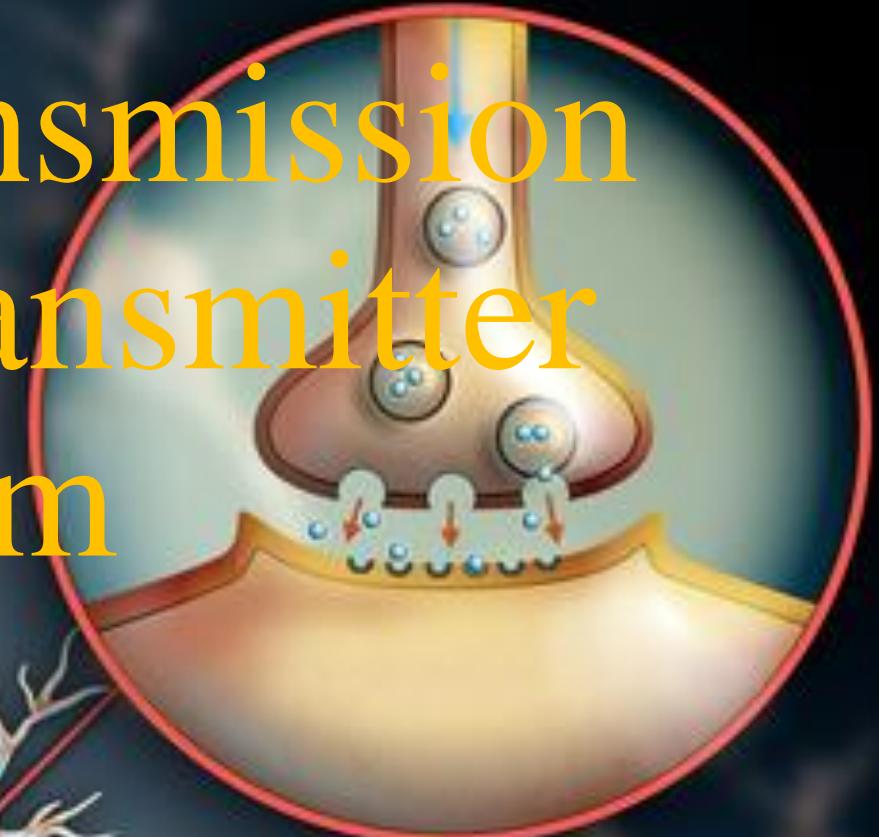
Introduction to Cognitive Neuroscience

Lecture Synaptic transmission and neurotransmitter system

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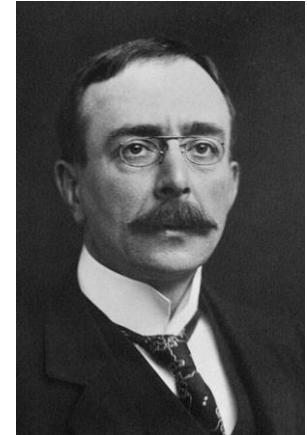
Synaptic transmission and neurotransmitter system



Synaptic transmission



- The **process of information transfer** at a synapse is called **synaptic transmission**
- **Charles Sherrington** by the **end of the nineteenth century**, recognized that transfer of information from one neuron to another occurs at specialized sites of contact, named synapses
- The actions of **psychoactive drugs**, the **causes of mental disorders**, the **neural bases of learning and memory** - indeed, all the operations of the nervous system- **cannot be understood** without knowledge of synaptic transmission.
- Both **electrical and chemical** transmission involve in information transmission

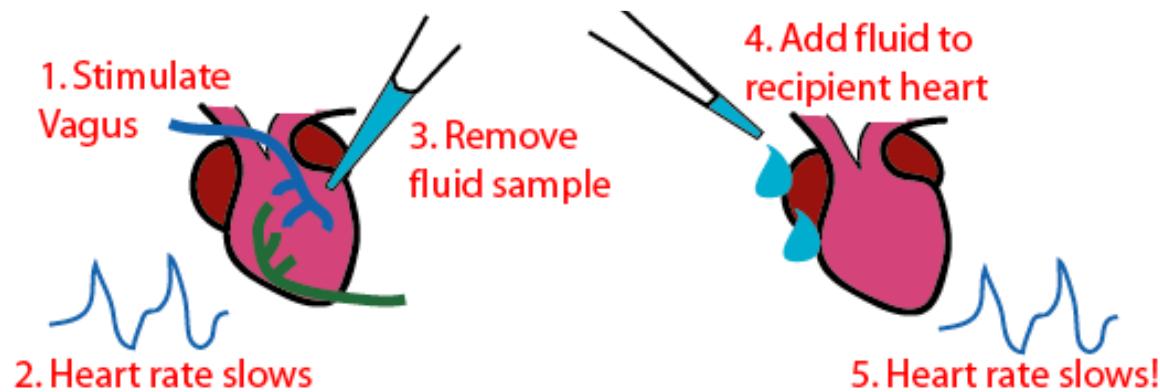


1857-1952 (aged 94)



Otto Loewi and Vagusstoff

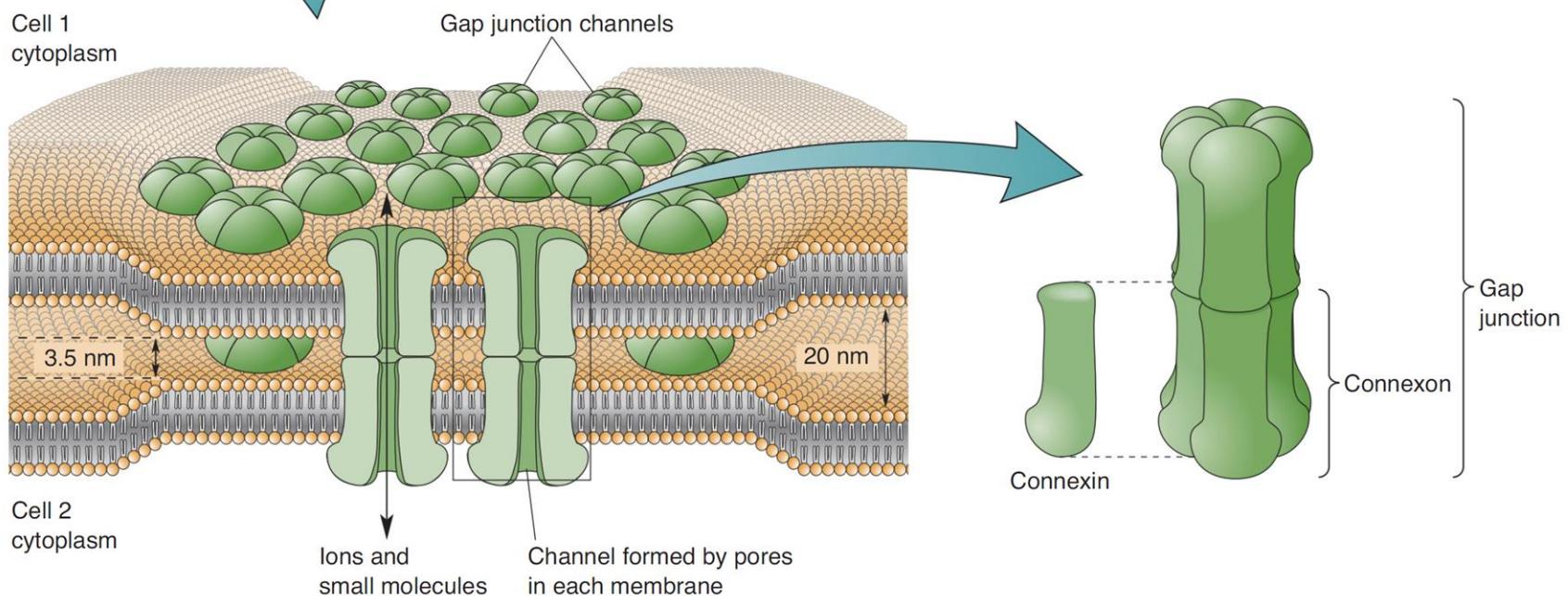
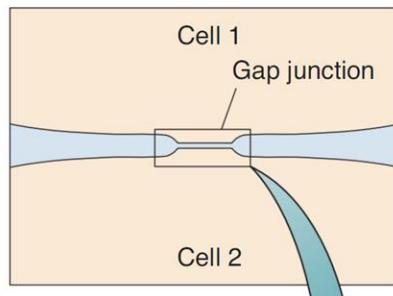
- In Austria in the 1920s, showed that synaptic transmission between **nerve and heart** is chemically mediated.
- Chemical transmission of the nervous impulse was **conclusively proved**
- The **active compound**, which Loewi called *vagusstoff*, turned out to be **acetylcholine**





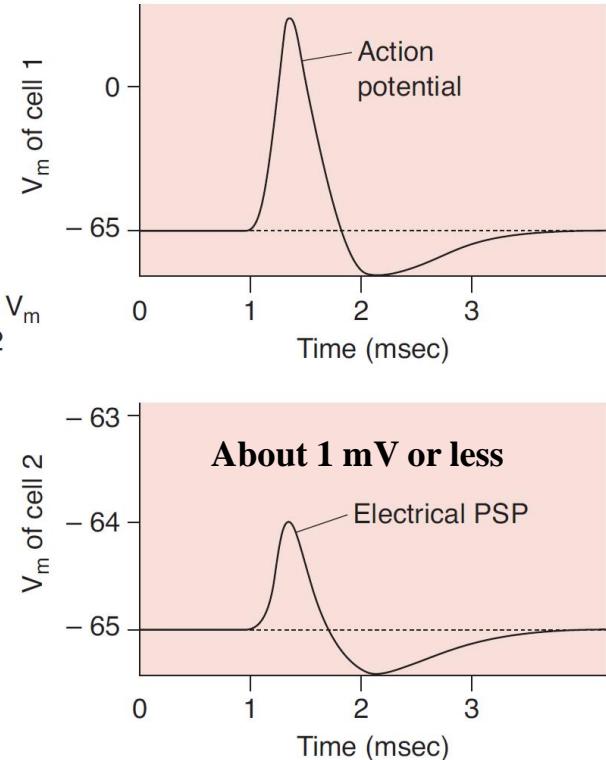
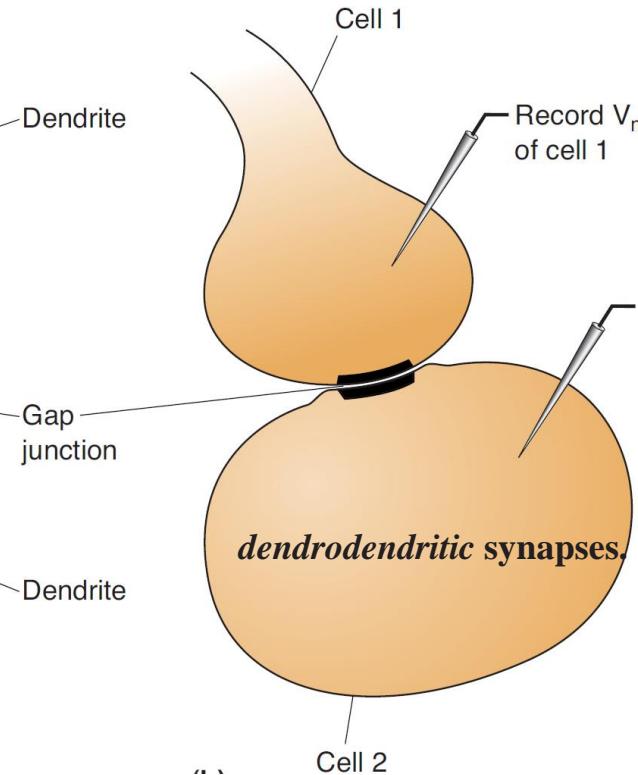
Gap junctions; Electrical Synapses

- The **membranes of two** cells are **separated** by only **about 3 nm**
- Its diameter is about **1–2 nm**
- Electrical synapses are **bidirectional**
- Cells connected by gap junctions are said to be **electrically coupled**
- It is quick and used in neural pathways **mediating escape reflexes**





In mammalian CNS, an **action potential generated** in one neuron **causes a small amount** of ionic current to flow through gap junction channels into a second neuron, **inducing an electrical PSP (post synaptic potential)**



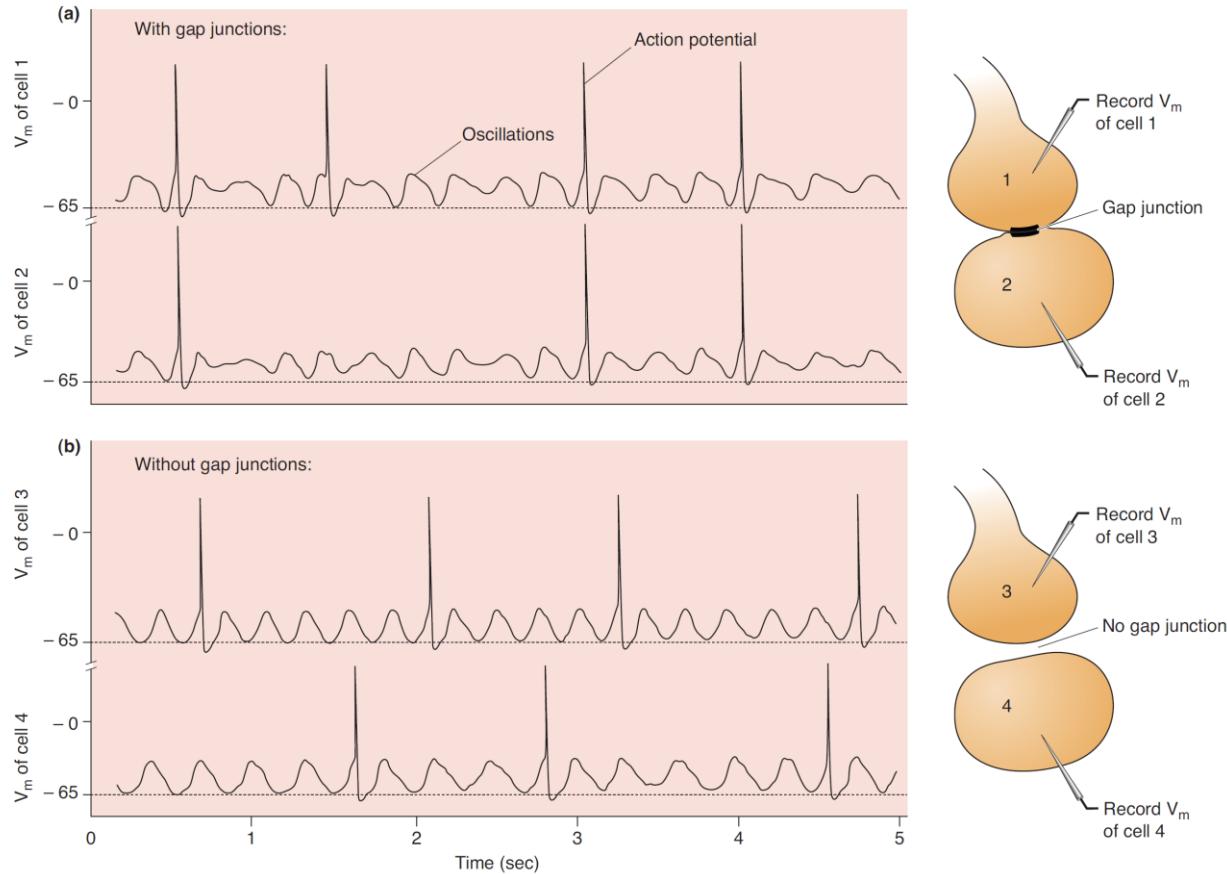


Why is there gap junction in mammals

- The **speed** of electrical transmission
- Ability to **synchronize** neural activity by **reciprocal** action and transmission **of sub-threshold voltages**.
- Gap junctions **allow neighboring cells to share both electrical and chemical signals** that may help **coordinate their growth and maturation**.
- Gap junctions also **interconnect many non-neural cells**, including glia, epithelial cells, smooth and cardiac muscle cells, liver cells, and some glandular cells.



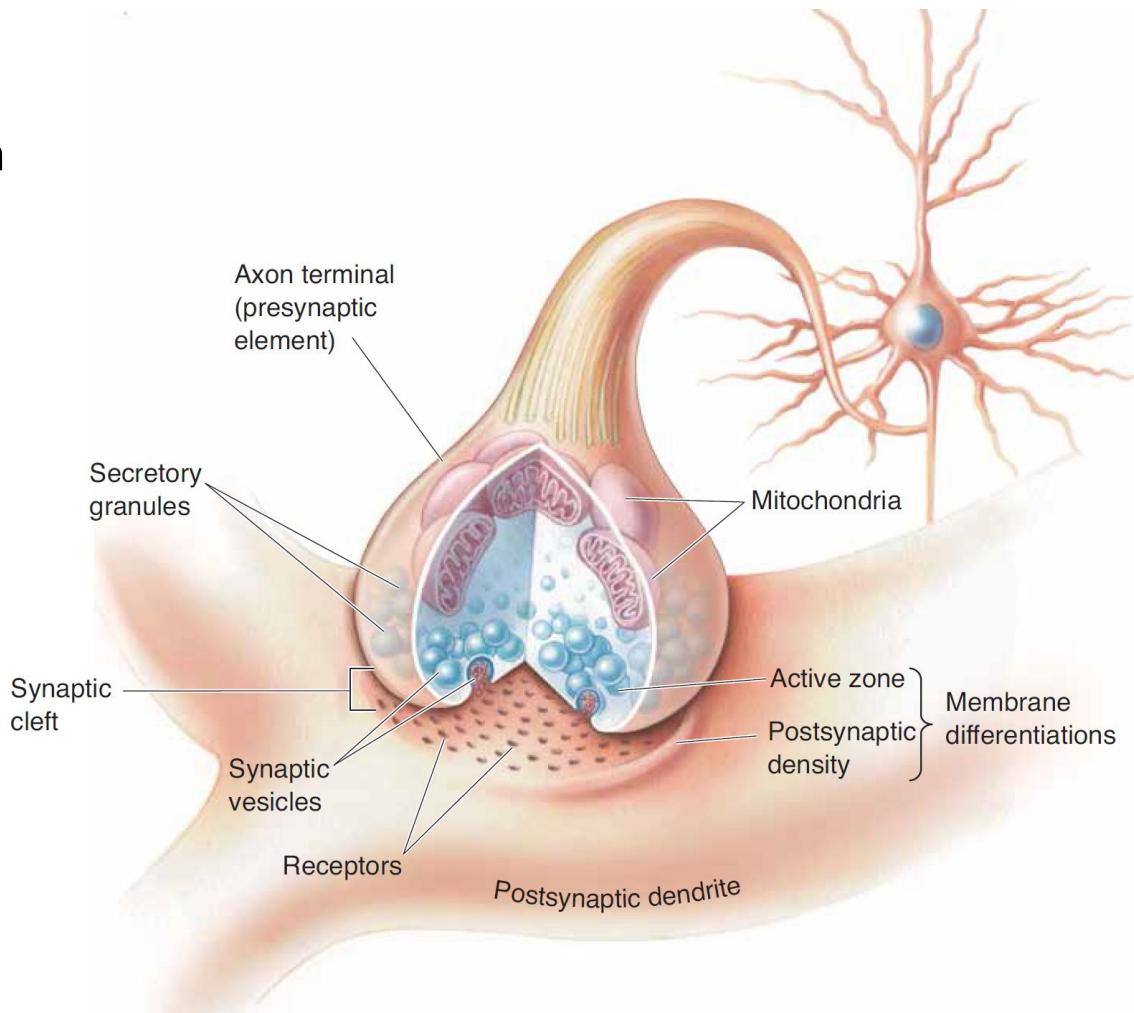
Electrical synapses can help neurons to synchronize their activity





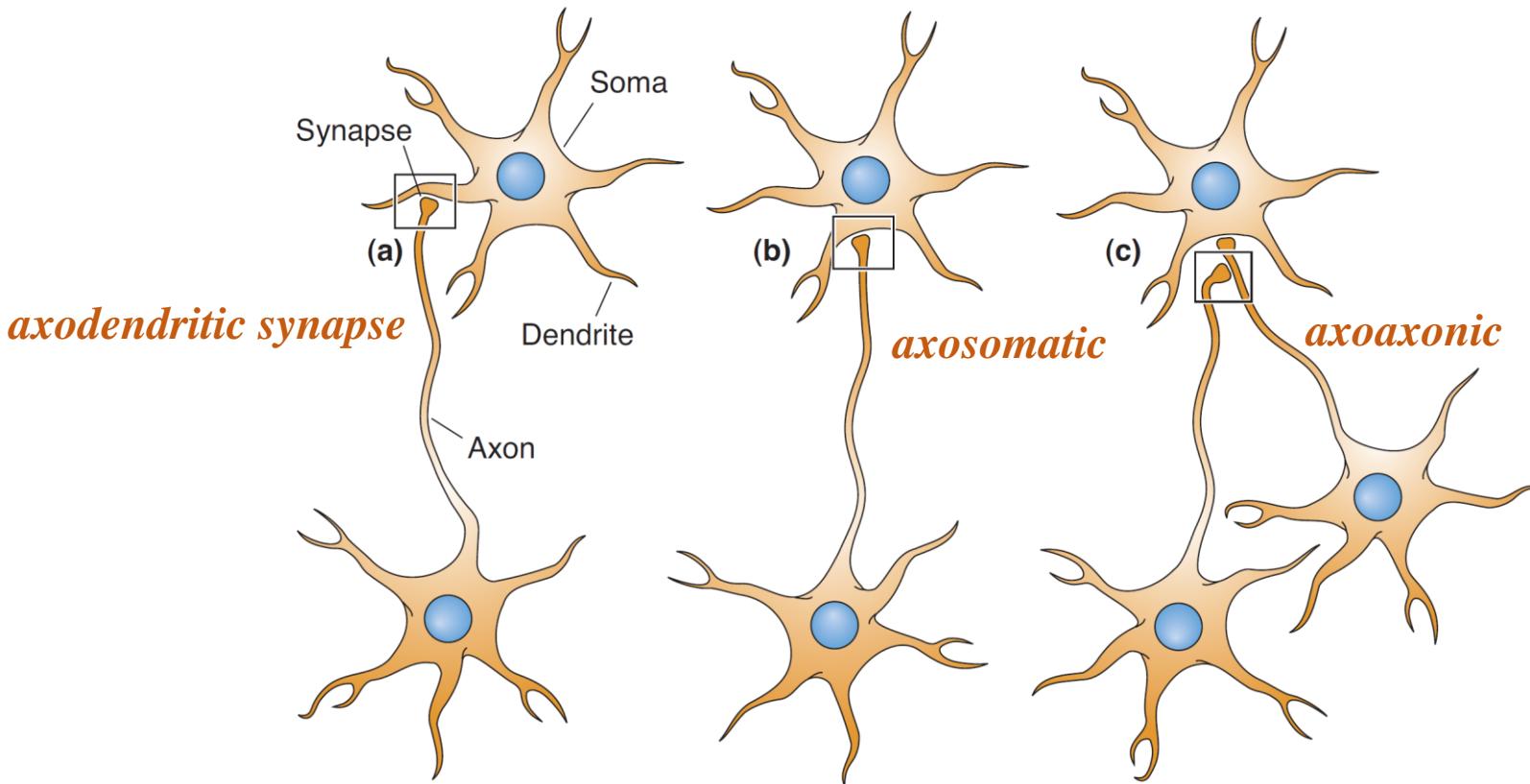
Chemical Synapses

- Most synaptic transmission in the **mature human nervous system** is chemical
- **Synaptic cleft** width: is **20–50 nm (10 times)** the width of the separation at **gap junctions**)
- Vesicles store neurotransmitter





Synaptic arrangements in the CNS

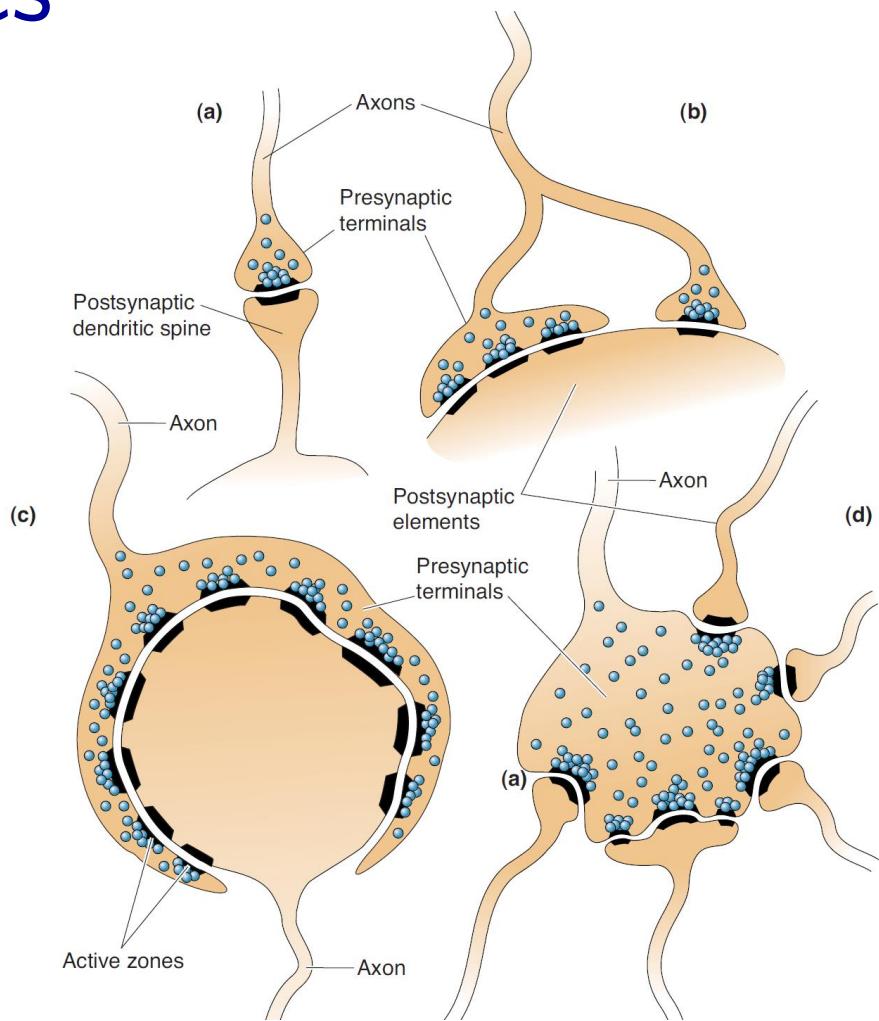


Sometimes dendrites form synapses with one another; these are called **dendrodendritic** synapses.



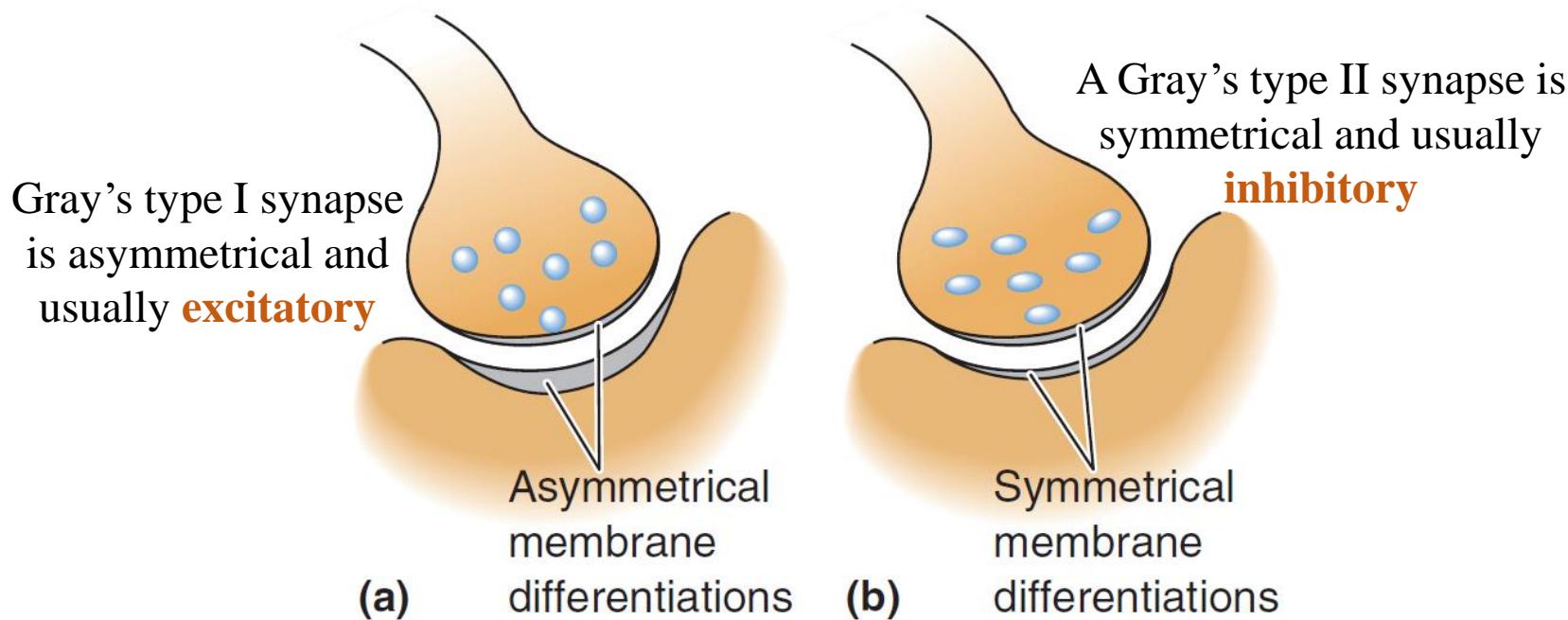
Various shapes and sizes of CNS synapses

- (a) **Axospinous** synapse
 - Presynaptic terminals can be recognized by their many **vesicles**
- (b) An axon branches to form **two presynaptic** terminals, one larger than the other
- (c) An **unusually large** axon terminal contacts and surrounds a postsynaptic soma.
- (d) An unusually large presynaptic axon terminal contacts five postsynaptic **dendritic spines**

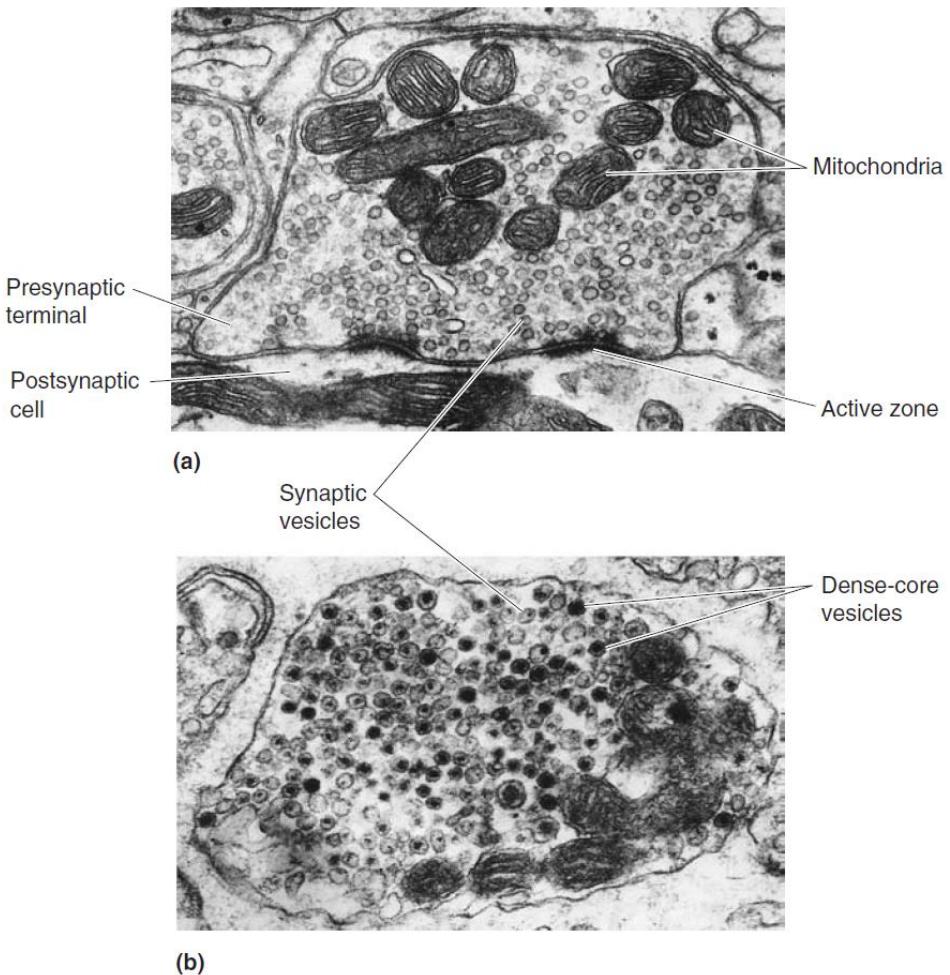




Two categories of CNS synaptic membrane differentiations



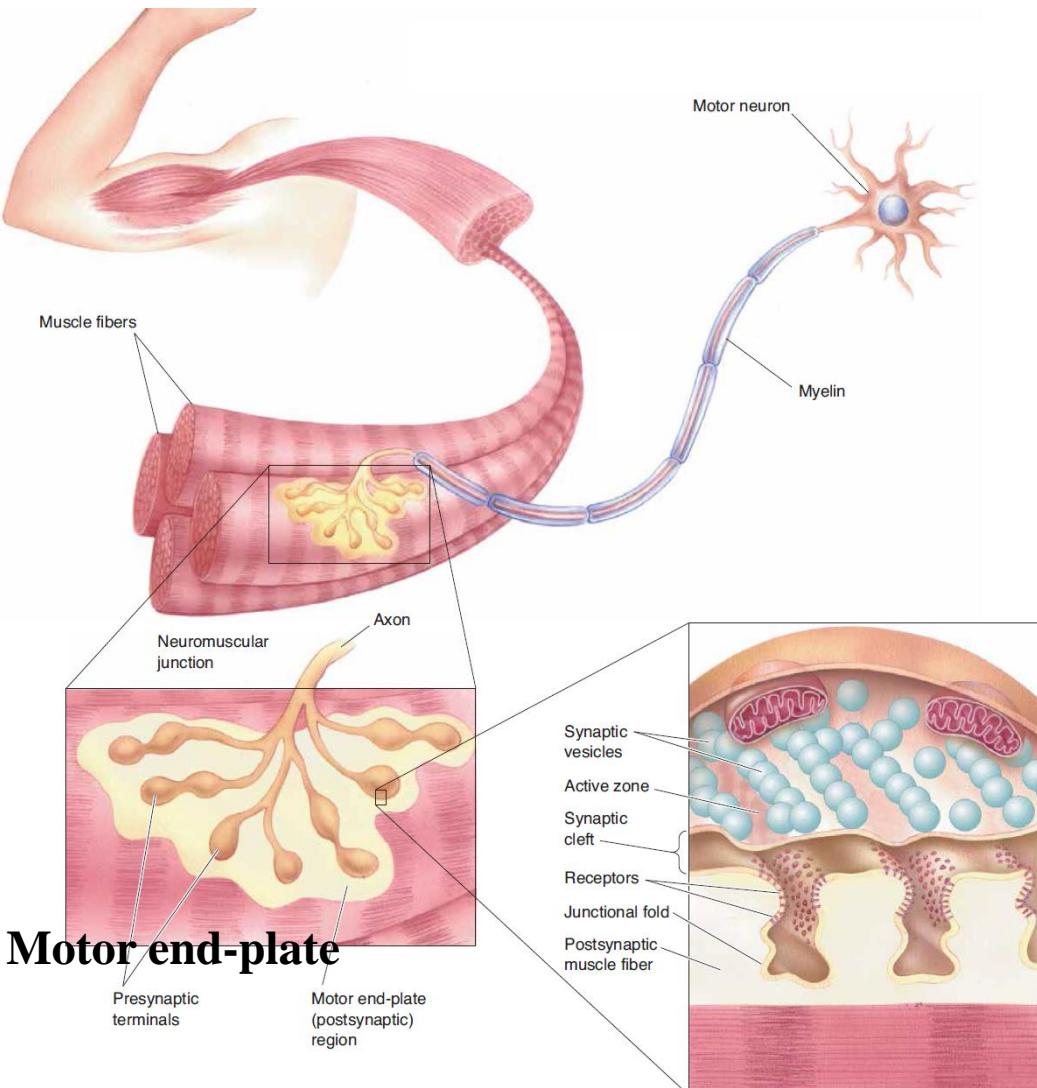
Chemical synapses, as seen with the electron microscope.





The Neuromuscular Junction.

- Synapses **outside** the CNS
- It is one of **the largest** synapses
- The **presynaptic** terminal contains a large number of active zones
- **More accessible** to researchers than CNS synapses, much of what we know about the mechanisms was first established here

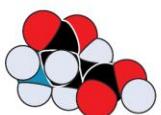
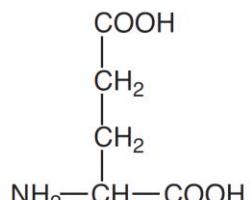




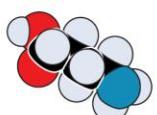
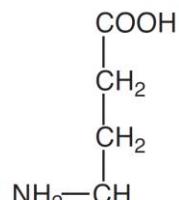
Principles of chemical synaptic transmission

- A **complex process** for release and reuptake of neurotransmitter so **no wonder** physiologists initially were **skeptical** about the existence of **chemical synapses** in the brain!
- **Three** chemical categories:
 - (1) ***amino acids***
 - (2) ***amines*** *Small organic molecules, in synaptic vesicles*
 - (3) ***peptides*** *Large molecules, chains of amino acids, in secretory granules*
- Speed of synaptic transmission:
 - **Fast** mediated by the **amino acids** ($\sim 10\text{--}100$ msec)
 - **Slower** are mediated by all three chemical categories (~ 100 ms – minutes)

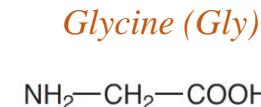
Amino Acids



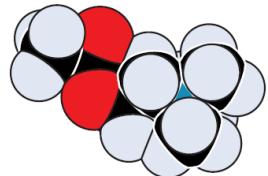
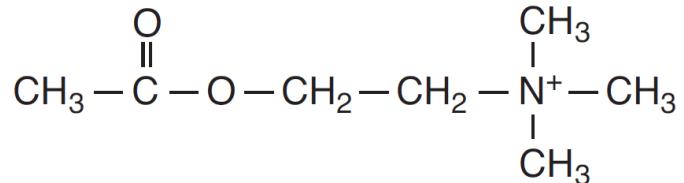
Glutamate (Glu)



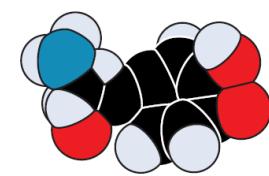
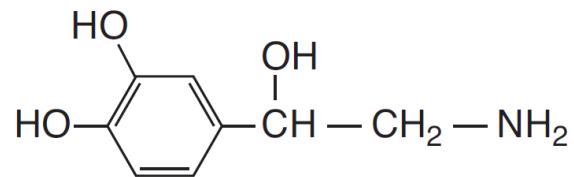
Gamma-aminobutyric acid (GABA)



Amines

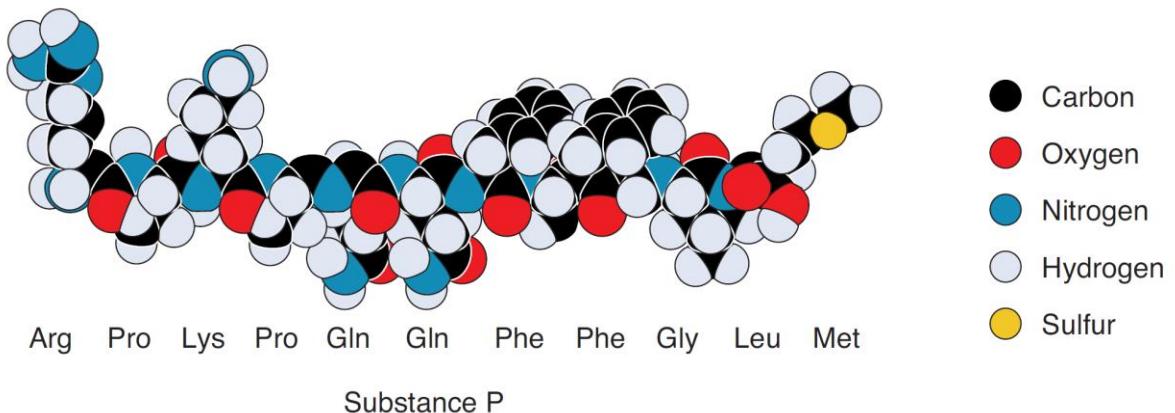


Acetylcholine (ACh)



Norepinephrine (NE)

Peptides

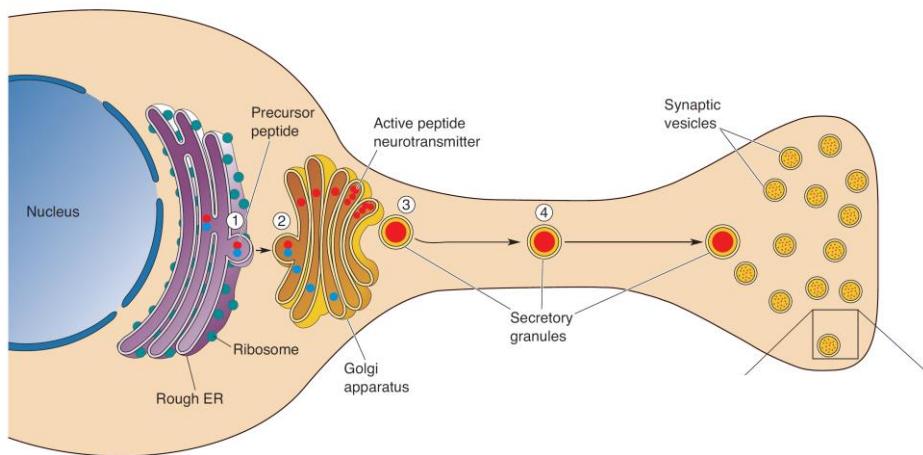


Amino Acids	Amines	Peptides
Gamma-aminobutyric acid (GABA)	Acetylcholine (ACh)	Cholecystokinin (CCK)
Glutamate (Glu)	Dopamine (DA)	Dynorphin
Glycine (Gly)	Epinephrine	Enkephalins (Enk)
	Histamine	<i>N</i> -acetylaspartylglutamate (NAAG)
	Norepinephrine (NE)	Neuropeptide Y
	Serotonin (5-HT)	Somatostatin
		Substance P
		Thyrotropin-releasing hormone
		Vasoactive intestinal polypeptide (VIP)



Neurotransmitter Synthesis and Storage

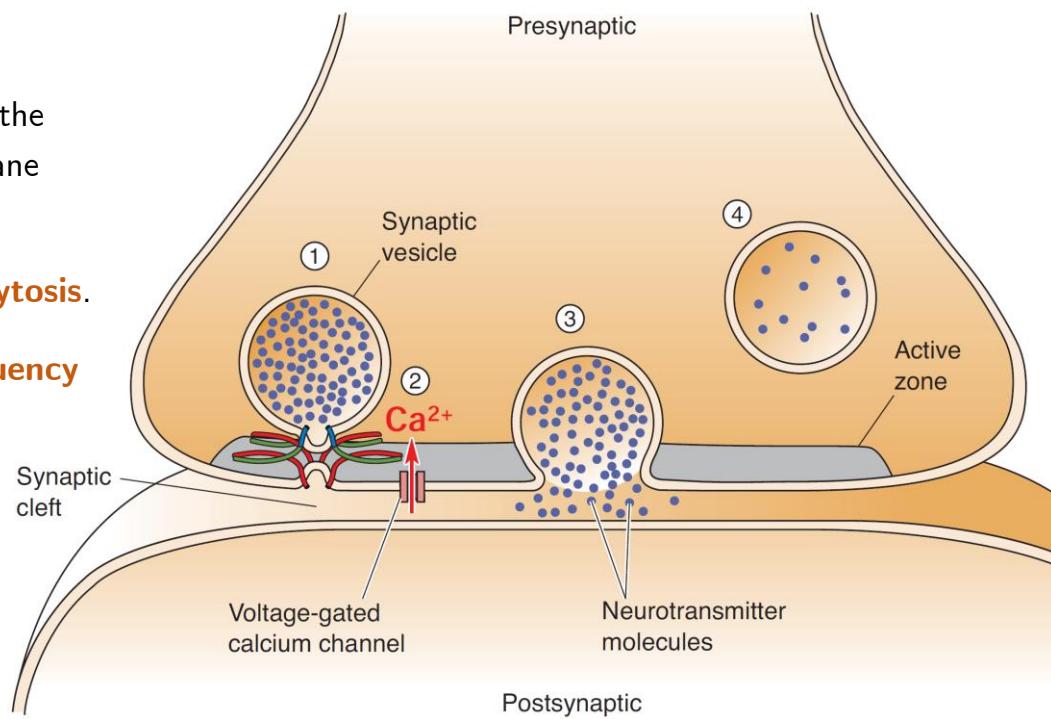
- **Glutamate** and **glycine** are among the **20 amino acids** consequently, they are abundant in all cells of the body
- **GABA** and the **amines** are made only by the neurons that release them. These neurons **contain specific enzymes that synthesize** the neurotransmitters



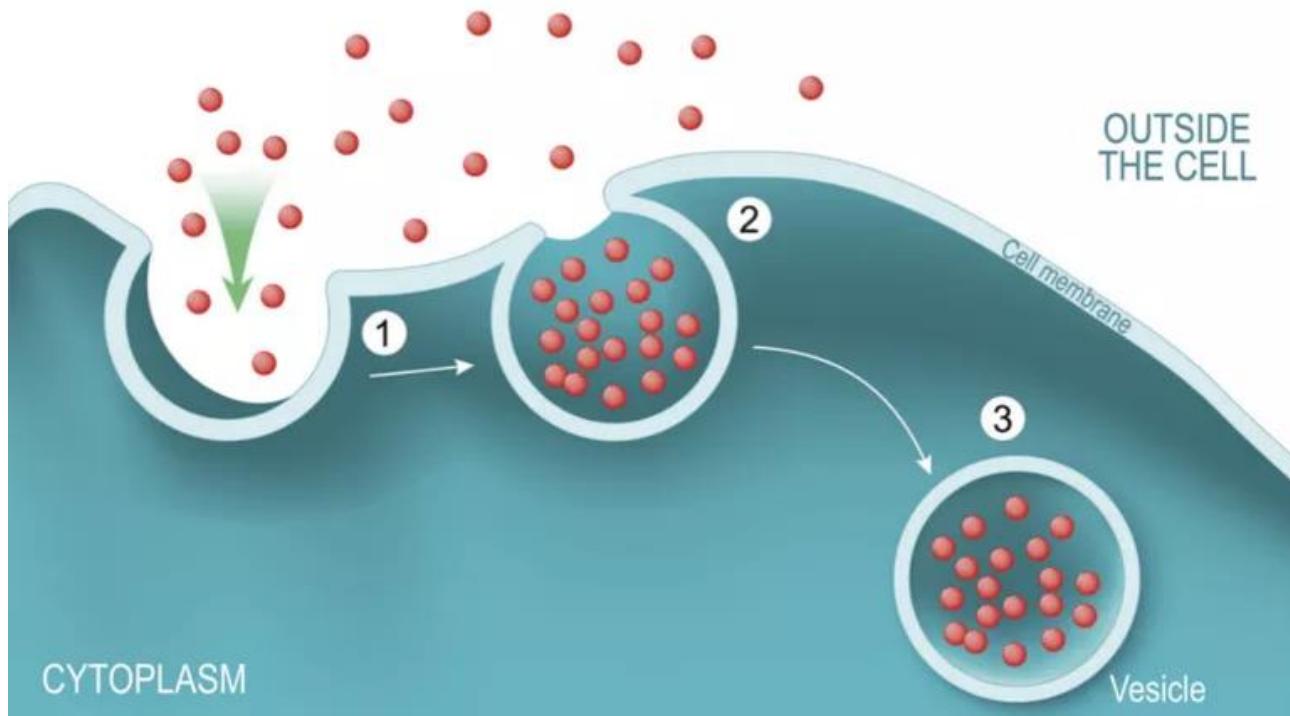


The release of neurotransmitter by exocytosis

- ① A **synaptic vesicle** loaded with neurotransmitter, in response to
- ② An **influx of Ca^2** through **voltage-gated calcium channels**
- ③ **Releases its contents within 0.2 msec** into the synaptic cleft by the fusion of the vesicle membrane with the presynaptic membrane, and
- ④ Is eventually **recycled** by the process of **endocytosis**.
- Release of **peptides** generally requires **high-frequency trains of action** (taking **50 msec** or more)

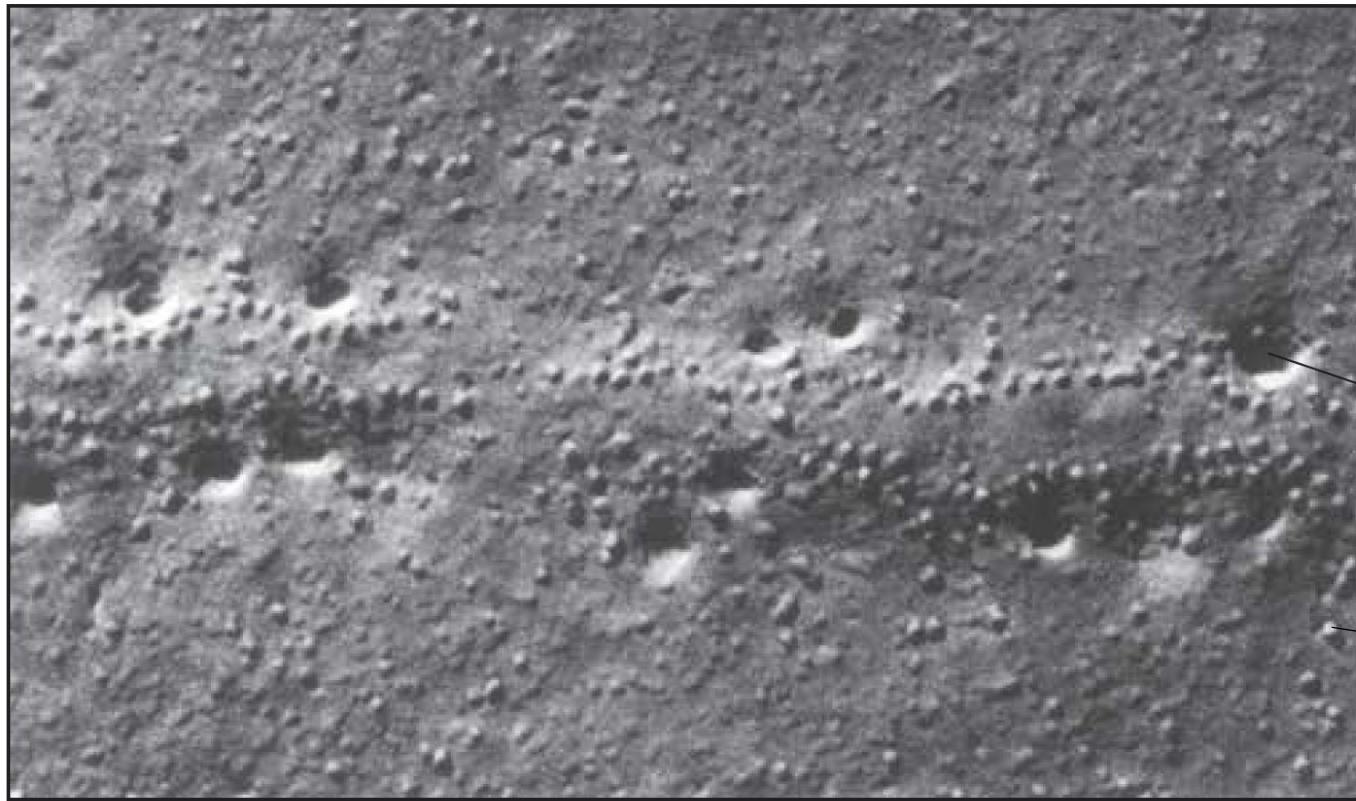


Endocytosis



<https://www.thoughtco.com/what-is-endocytosis-4163670>

Neuromuscular junction in frog



Exocytotic
fusion
pore

calcium
channels

Neurotransmitter receptors

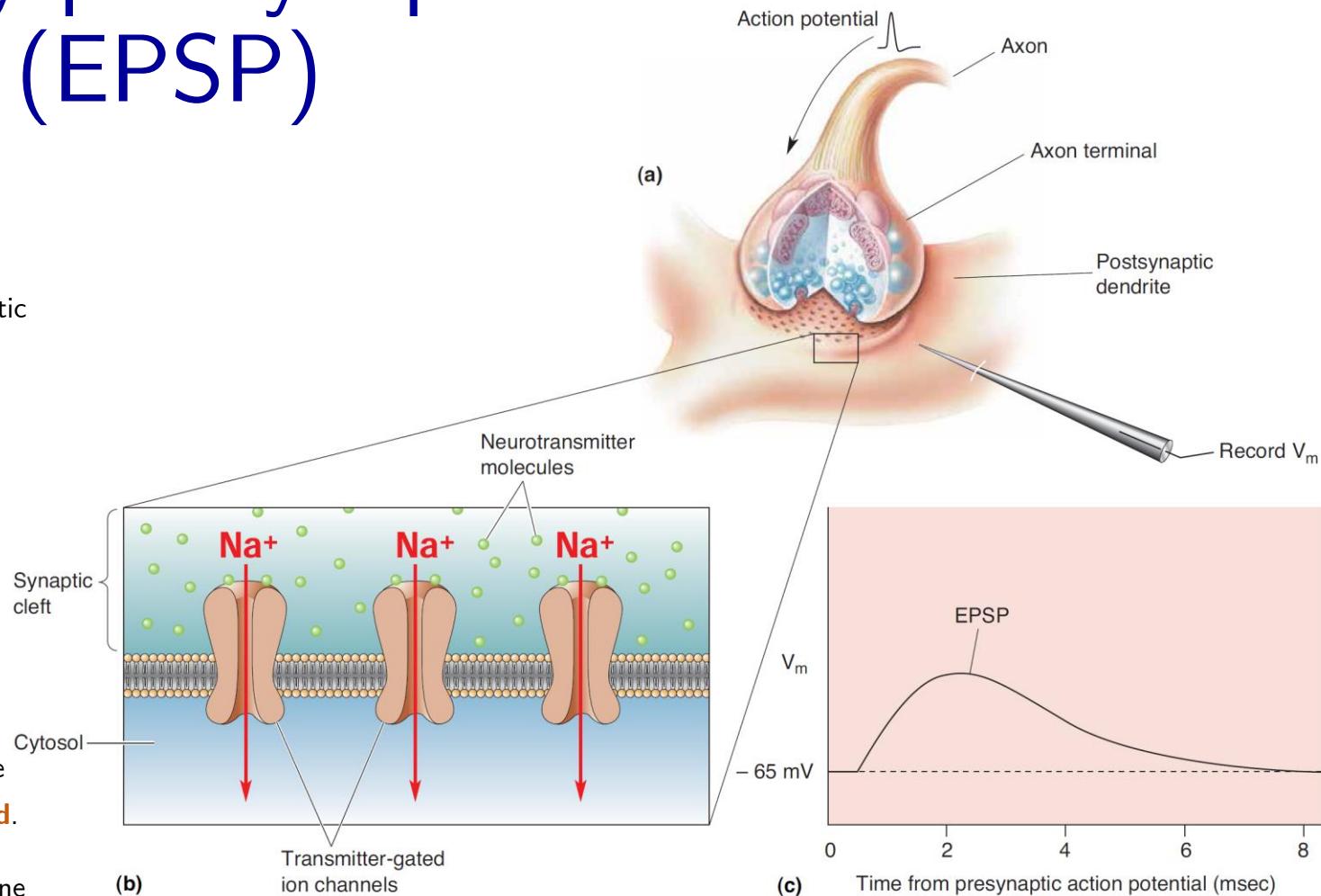


- There are well over **100 different** neurotransmitter receptors
- **Binding of neurotransmitter** to the receptor is like inserting a **key in a lock**; this causes **conformational changes in the protein**
- They can be classified into two types:
 - **Transmitter-gated ion channels**
 - **G-protein-coupled receptors**



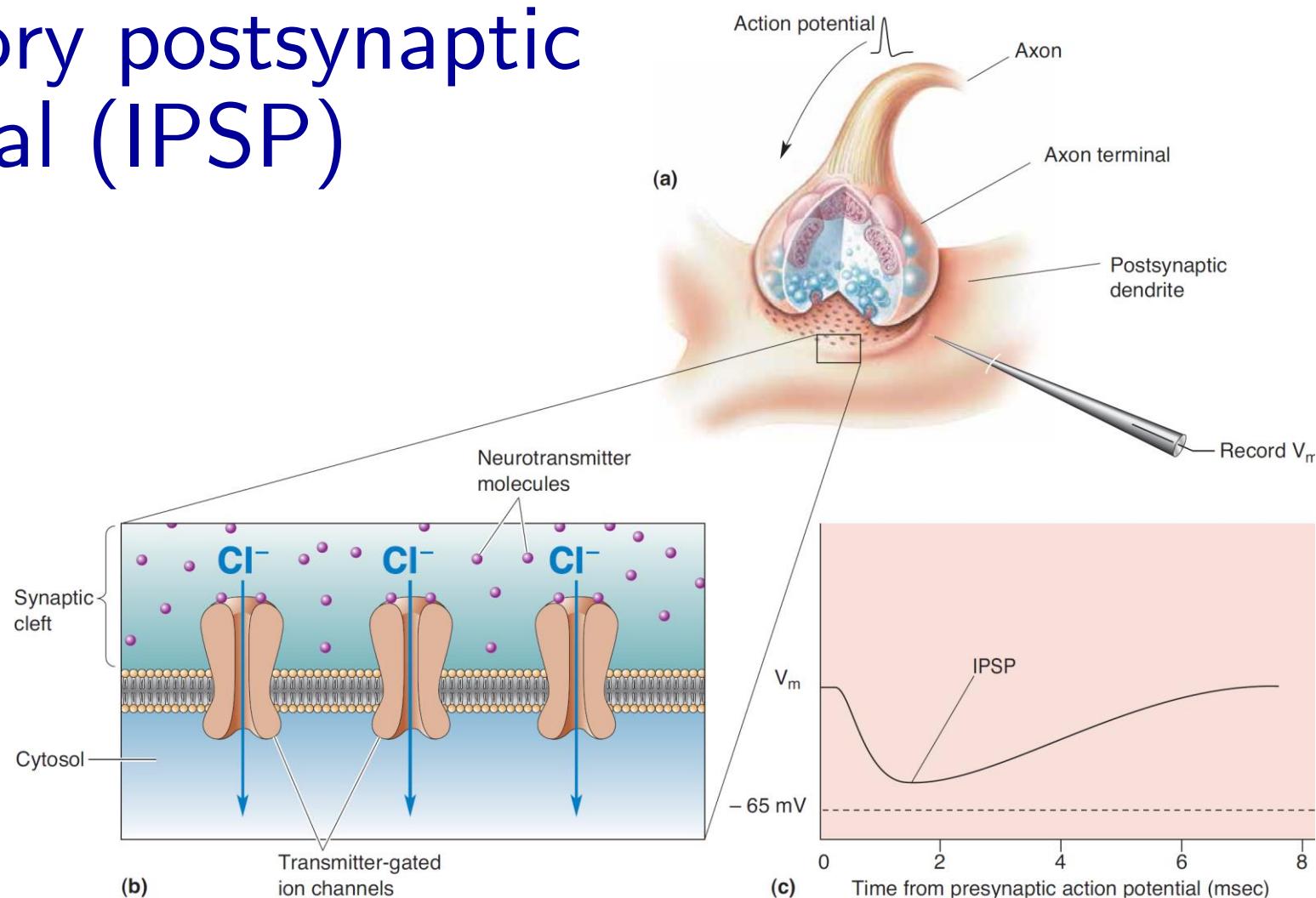
The generation of an excitatory postsynaptic potential (EPSP)

- (a) An action potential arriving in the presynaptic terminal causes the release of neurotransmitter.
- (b) The molecules bind to transmitter-gated ion channels. Na enters the postsynaptic cell through the open channels, the membrane will become depolarized.
- (c) Change in membrane potential

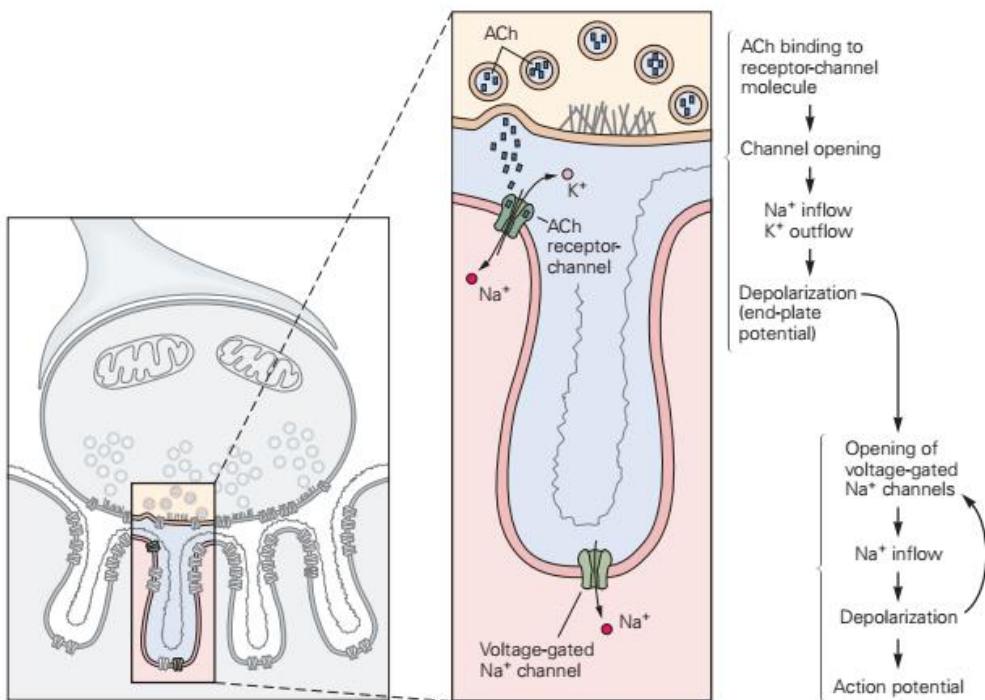




The generation of an Inhibitory postsynaptic potential (IPSP)



The depolarization resulting from the opening of ACh receptor-channels at the end-plate opens voltage-gated Na⁺ channels.



G-protein-coupled receptors, slower, longer lasting, and much more diverse

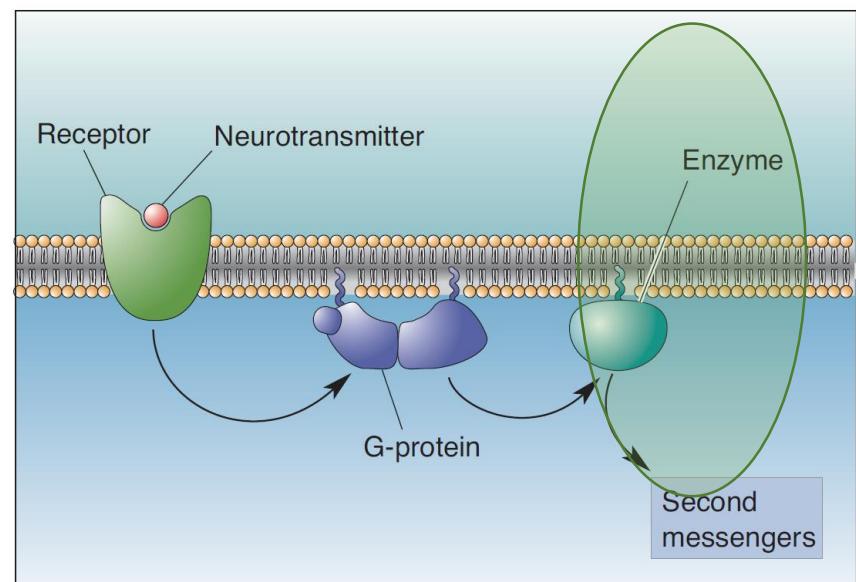
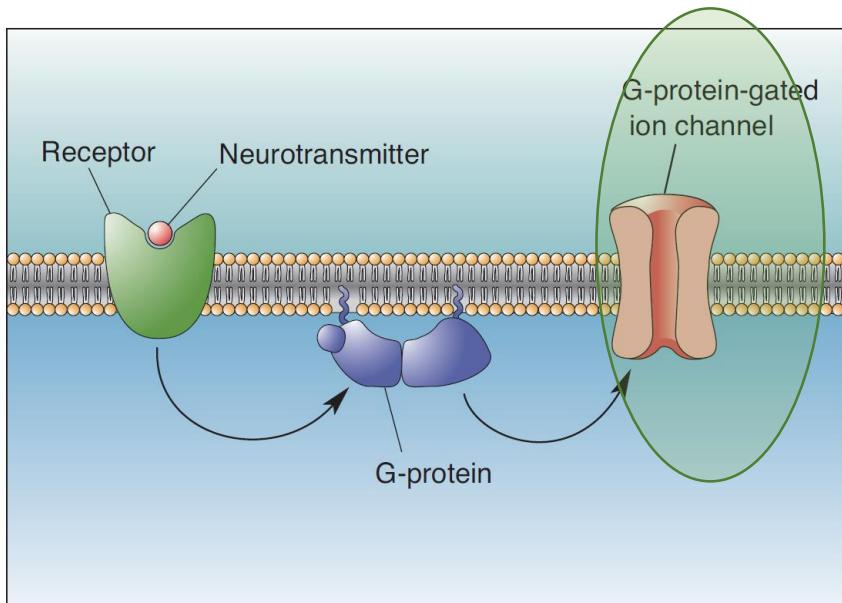


- This involves **three** steps:
 - 1. Neurotransmitter molecules **bind** to receptor proteins
 - 2. The receptor proteins activate small proteins, called **G-proteins** ,
 - 3. The activated G-proteins activate “effector” proteins
- **Effector proteins** can be:
 - G-protein-gated ion channels in the membrane
 - **Enzymes that synthesize** molecules called **second messengers**. Second messengers can activate additional enzymes in the cytosol
- G-protein-coupled receptors can trigger **widespread metabolic effects**, they are often referred to as **metabotropic receptors** .
- The **same neurotransmitter** can have **different postsynaptic actions**, depending on what **receptors** it binds to.



G-protein-coupled receptors

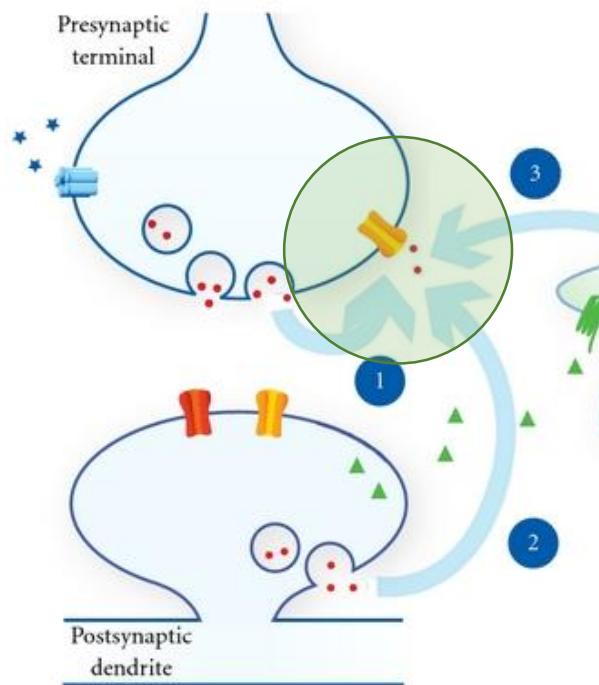
- **Effector proteins** can be:
 - G-protein-gated ion channels in the membrane
 - Enzymes that synthesize molecules called **second messengers** Second messengers can activate additional enzymes in the cytosol that



Autoreceptors



- **Presynaptic receptors**
- They are sensitive to the **neurotransmitter** released by the **presynaptic terminal**
- **Some functions:**
 - **Inhibition** of neurotransmitter release
 - In some cases, **neurotransmitter synthesis**.
 - Presynaptic terminal **regulation**
 - **Reduce release** when the concentration of neurotransmitter in the synaptic cleft gets too high



Neurotransmitter Recovery and Degradation



- **Simple diffusion** of the transmitter molecules away from the synapse
- For most of the **amino acid and amine neurotransmitters**, diffusion is aided by mechanism named **reuptake**
- **Reuptake occurs** by the action of **specific neurotransmitter transporter proteins** located in the presynaptic membrane.
 - Inside the cytosol of the terminal, the transmitters may be **enzymatically destroyed**, or **they may be reloaded** into synaptic vesicles.
- **Transporters** also exist in the **membranes of glia** surrounding the synapse,
- Neurotransmitter action can also **be terminated by enzymatic destruction** in the synaptic cleft (e.g. ACh at the neuromuscular junction)
- **High concentrations** of **ACh** after several seconds leads to a process called **desensitization**

Neuropharmacology



- Each of the **steps of synaptic transmission** we have discussed so far, including: **neurotransmitter synthesis, loading into synaptic vesicles, exocytosis, binding and activation of receptors, reuptake, and degradation, is chemical**, and therefore can be affected by **specific drugs and toxins**
- **Receptor antagonists:**
 - **Inhibitors of neurotransmitter receptors**, called, bind to the receptors and block (antagonize) the normal action of the transmitter
 - **Curare** an arrow-tip poison traditionally used by South American Indians
 - Curare binds tightly to the **ACh receptors on skeletal muscle** cells and blocks the actions of ACh,
- **Receptor agonists:**
 - **Mimic the actions** of the naturally occurring neurotransmitter
 - **Nicotine binds** to, and activates, the **ACh receptors** in skeletal muscle
- **Defective neurotransmission** is believed to be the **root** cause of a large number of **neurological and psychiatric** disorders



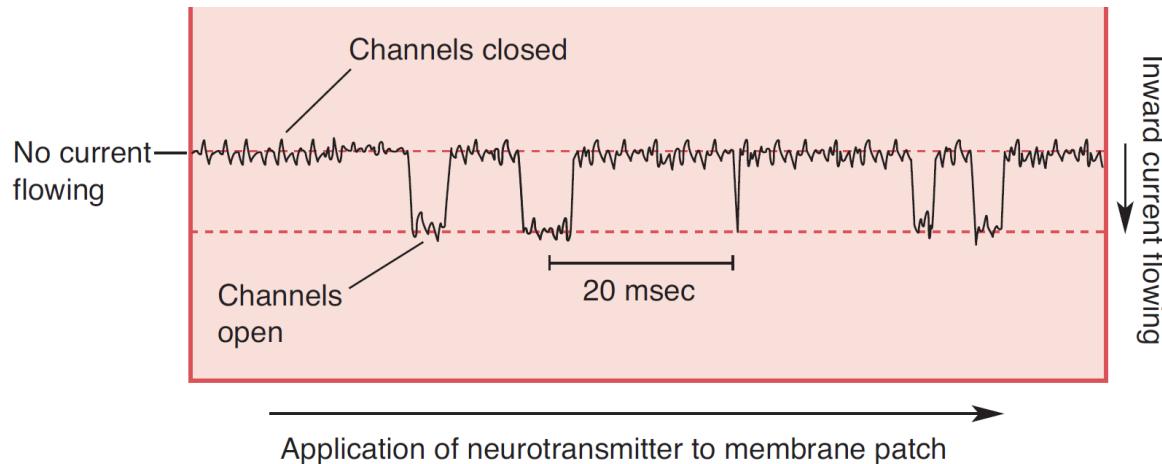
Principles of synaptic integration

Synaptic integration is the process by which multiple synaptic potentials combine within one postsynaptic neuron



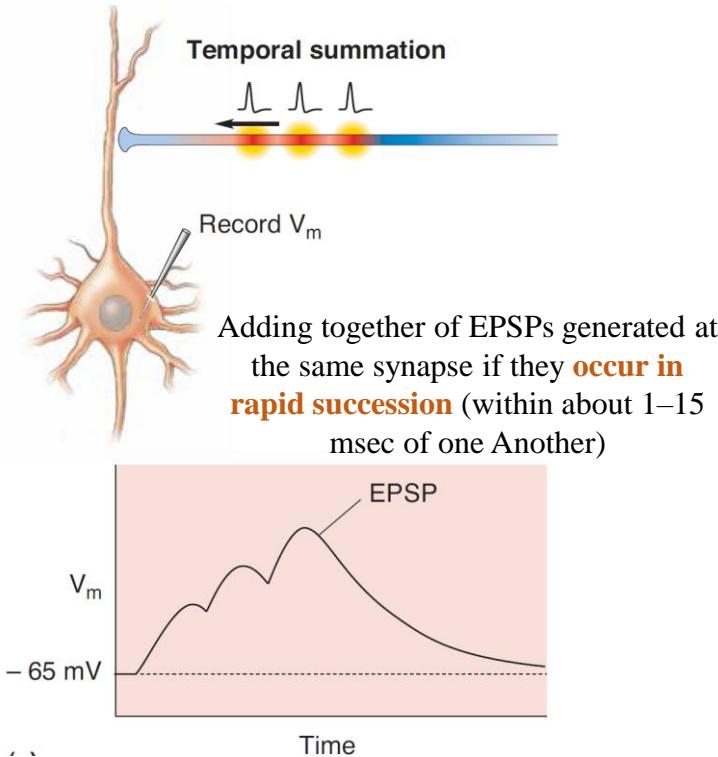
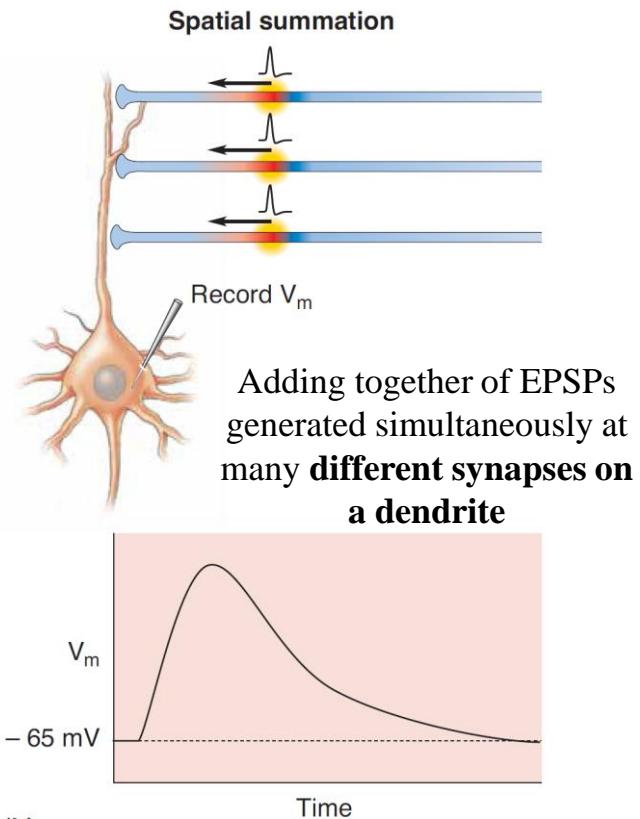
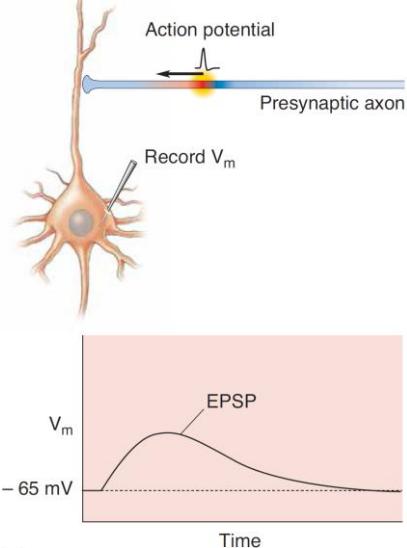
Quantal Analysis of EPSPs

- The **amplitude of the postsynaptic EPSP** is some multiple of the response to the **contents of a single vesicle**
- The **quantum**: reflects the number of **transmitter molecules** in a single synaptic **vesicle** and the number of postsynaptic **receptors** available at the synapse.
- This **tiny** response to vesicle exocytose is a **miniature postsynaptic potential**, often called simply a **mini**. Mini in CNS is about a few **tenths of a millivolt**





EPSP summation



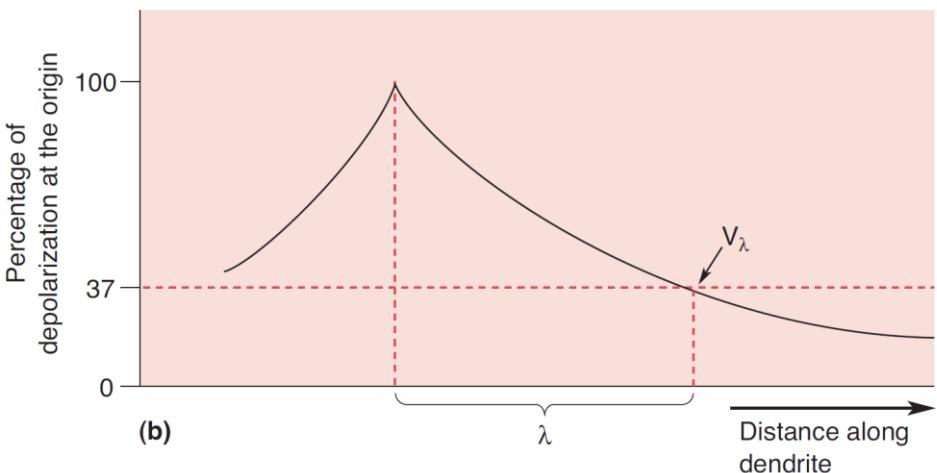
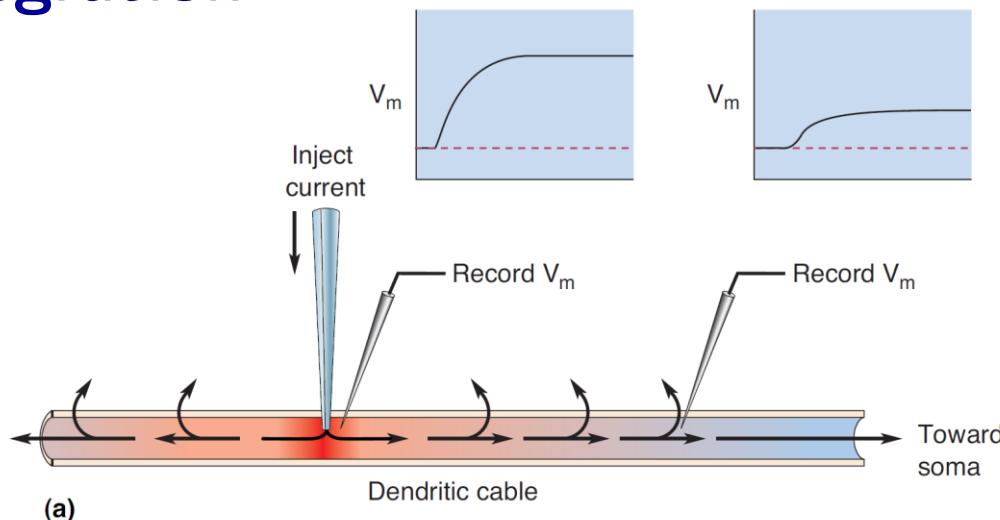


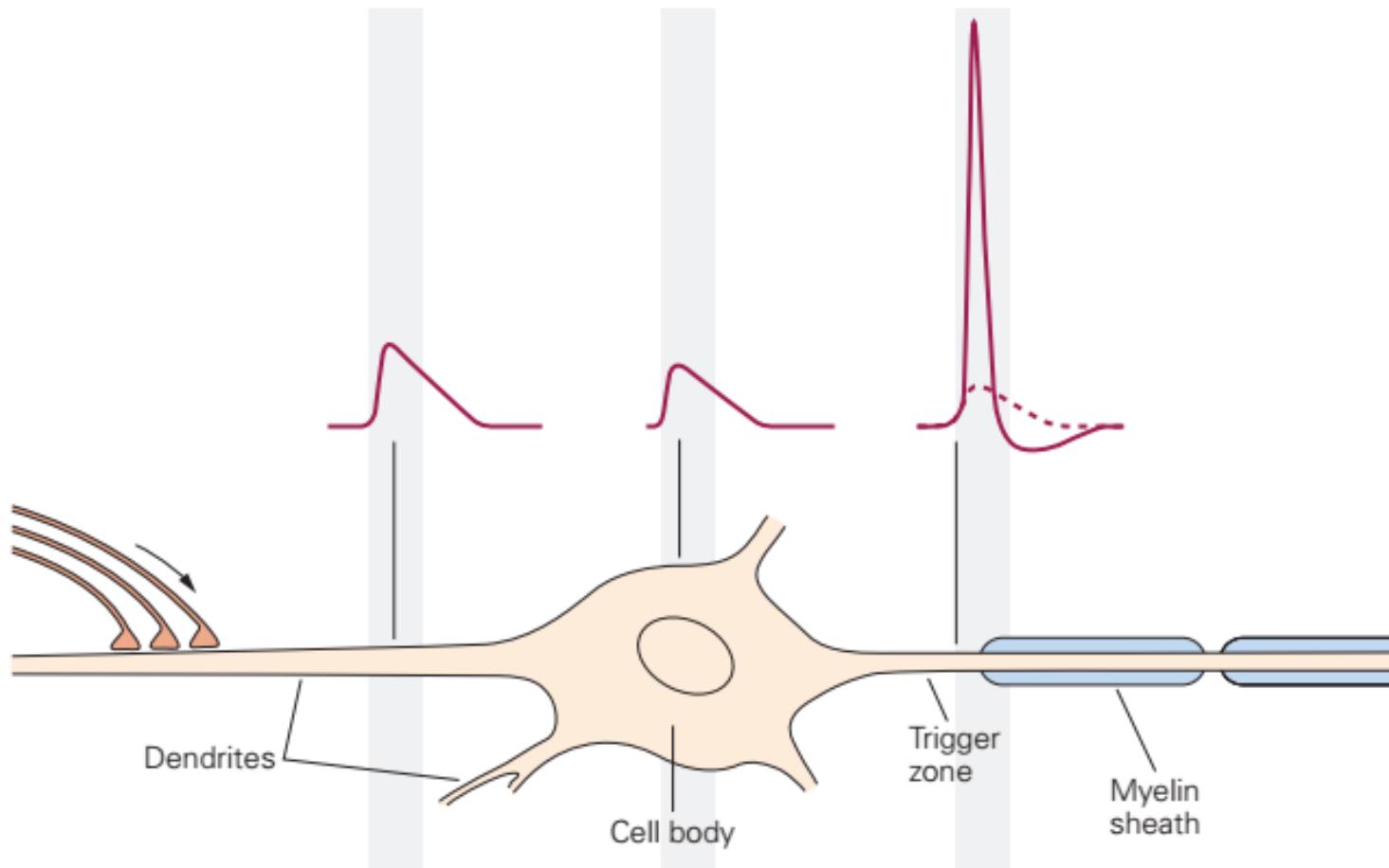
The contribution of dendritic properties to synaptic integration

- **Passive** simple cable equations (it lacks voltage-gated channels)
- Synaptic current will flow farther down a **wide dendrite (low r_a)** with **few open** membrane channels (**high r_m**)
- **Excitable Dendrites:** A variety of neurons have dendrites with significant numbers of voltage-gated sodium

$$\Delta V(x) = \Delta V_0 e^{-x/\lambda},$$

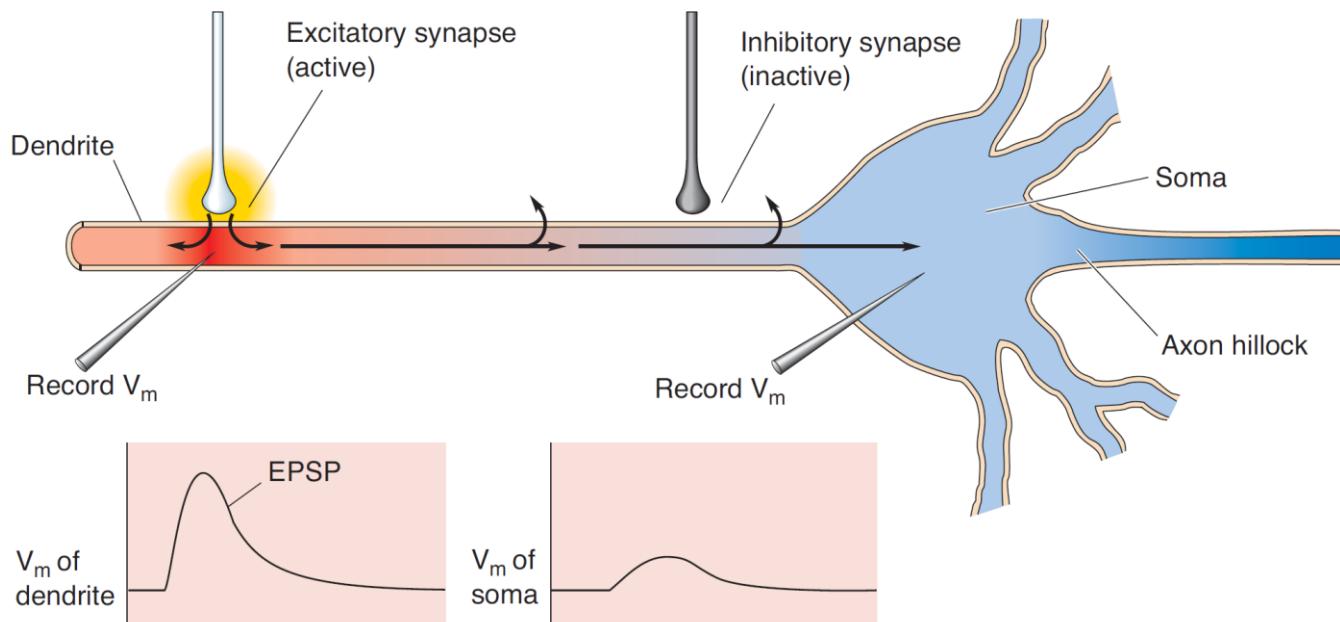
$$\lambda = \sqrt{(r_m / r_a)}.$$





IPSPs

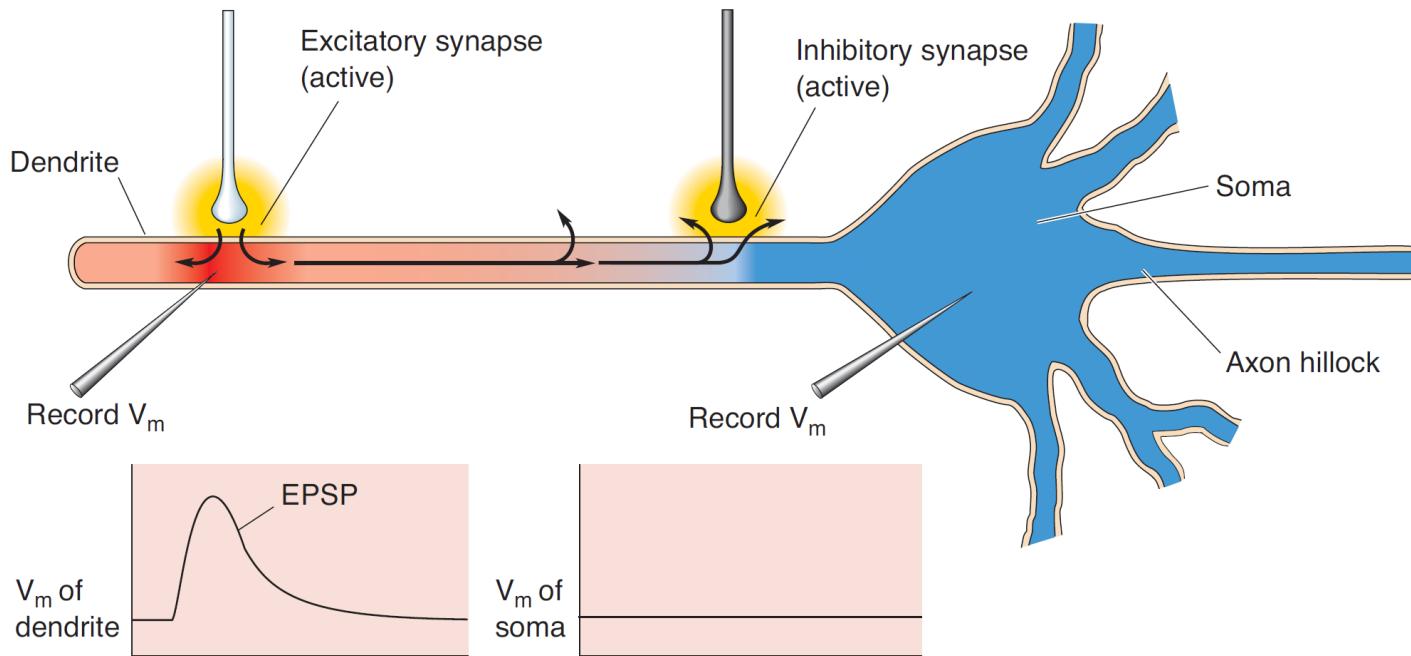
- Similar **mechanism** with epsp but
 - Bind **different neurotransmitters** (either **GABA or glycine**)
 - Different **ions to pass through** their channels (E_{Cl} , about -65 mv)





Shunting Inhibition

- Inhibitory and excitatory inputs are **stimulated together**, the depolarizing current **leaks out before it reaches the soma**
- Shunting inhibition acts to drastically reduce r_m and consequently λ (like black hole)





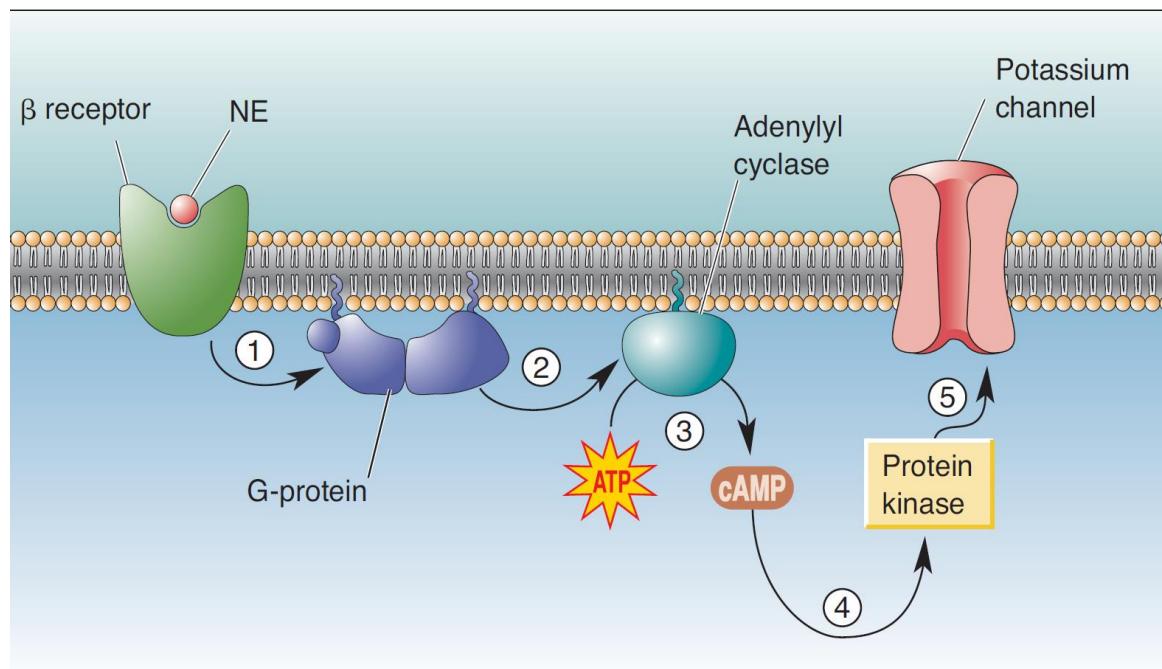
The Geometry of Excitatory and Inhibitory Synapses

- **Inhibitory synapses:**
 - GABA or glycine
 - Gray's type II (symmetric)
 - on many neurons are found **clustered on the soma and near the axon hillock**, where they are in an **especially powerful position to influence** the activity of the postsynaptic neuron
- excitatory synapses:
 - Glutamate
 - Gray's type I

Modulation



- It does not cause any dramatic effects on the neuron (direct production of psp's)
- For example NE produces **little change in membrane potential** but greatly increases the **response produced by another neurotransmitter** at an excitatory synapse
- cAMP in a different cell type with different enzymes may produce functionally opposite changes in the excitability of cells





Elements of neurotransmitter systems

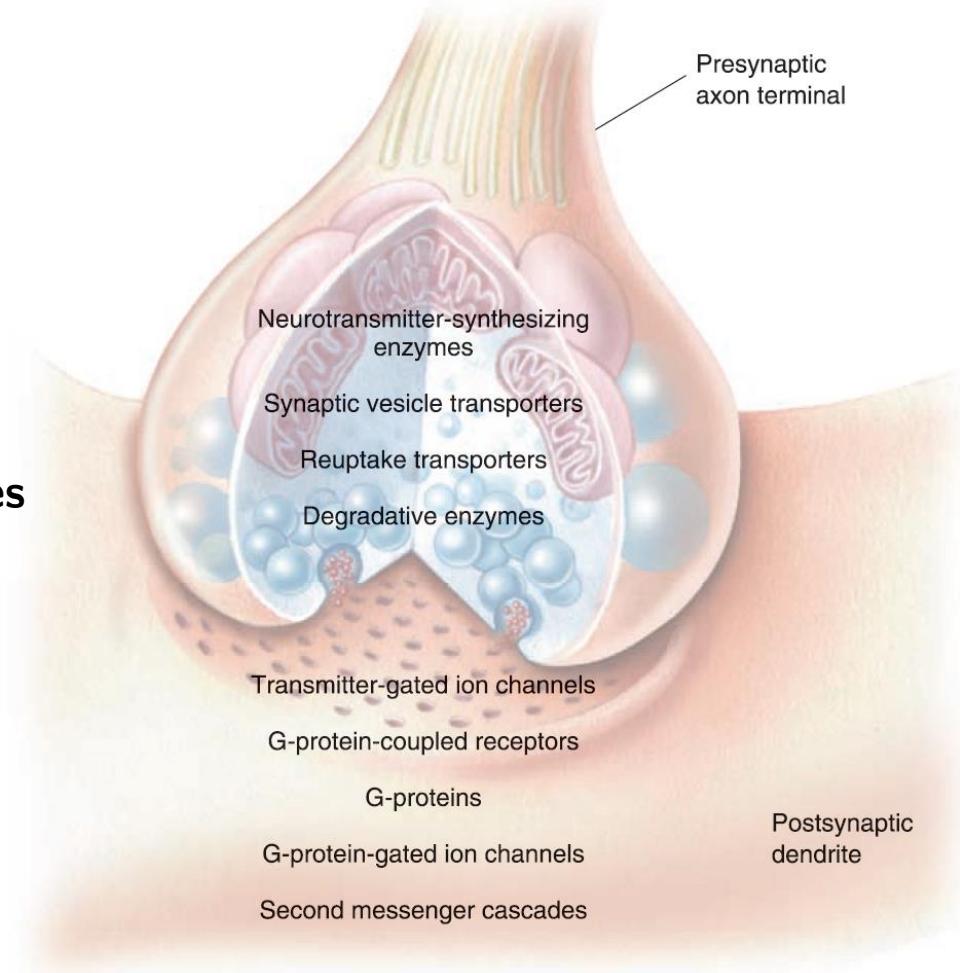
Amino acids, amines, and peptides

Glutamatergic

GABAergic

Peptidergic

suffix *-ergic* used to identify the various
neurotransmitter systems



Localization of Transmitters



- First step in studying neurotransmitter system is to show that the molecule is, in fact, **localized** in, and **synthesized** by, particular neurons

immunocytochemistry

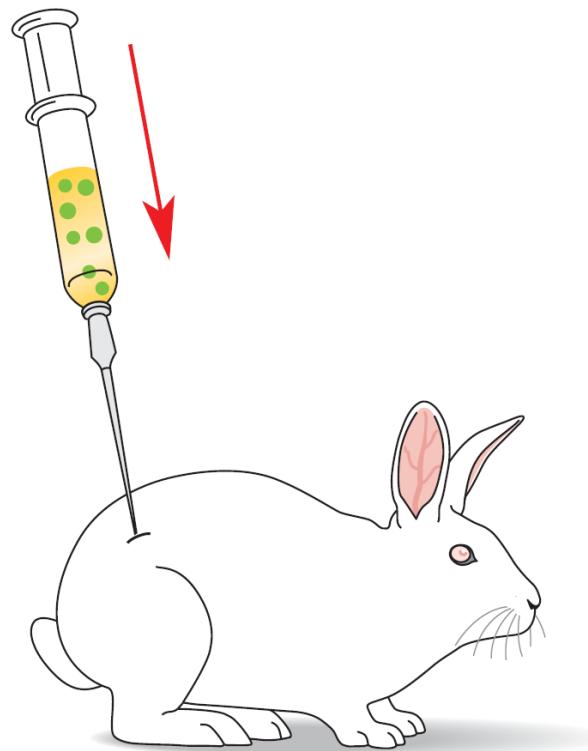


- It is used to **anatomically localize particular molecules** to particular cells.
- Neurotransmitter (or other substances) **is injected into the bloodstream**
- **Immune system** response is the generation of **large proteins** called **antibodies**. Antibodies can **bind tightly to specific** sites on the foreign molecule
- When these labeled antibodies are **applied to a section of brain tissue**, they will color just those cells that **contain the transmitter candidate**

- **Immunohistochemistry.**

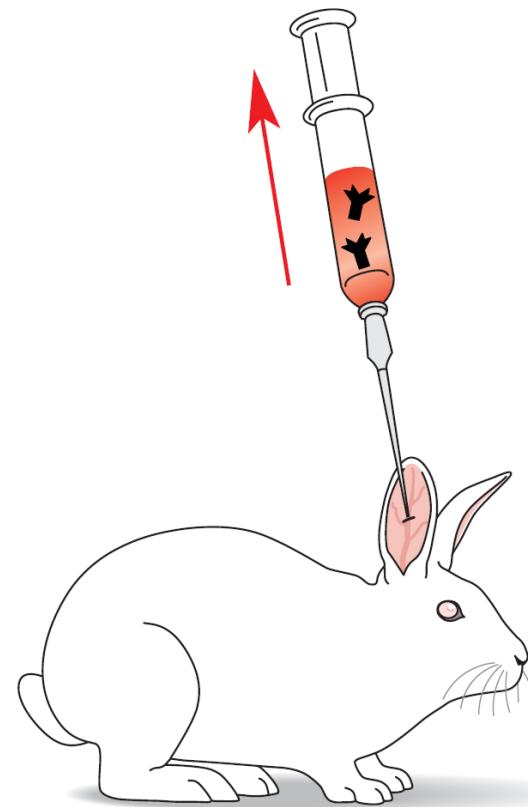
This method uses **labeled antibodies** to identify the location of molecules within cells.

- (a) The **molecule** of interest (a neurotransmitter candidate) is injected into an animal, causing an **immune response** and the generation of antibodies.



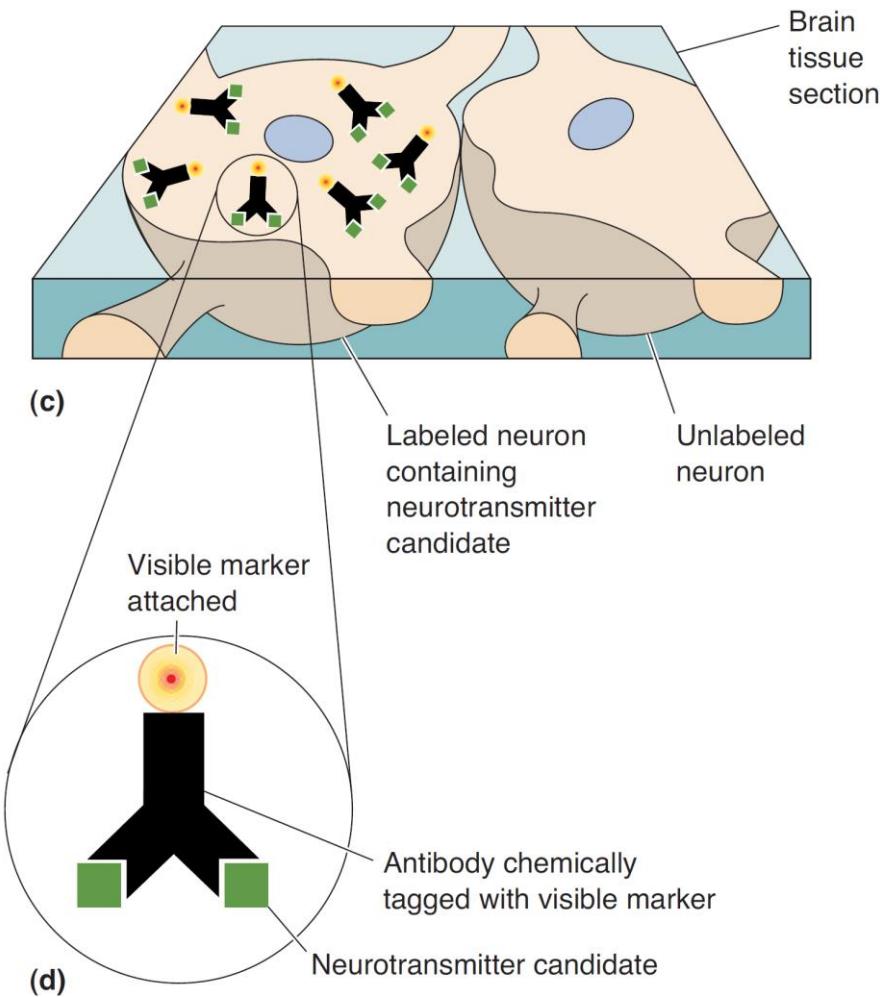
(a) Inject neurotransmitter candidate

- (b) Blood is withdrawn from the animal, and the antibodies are isolated from the serum.



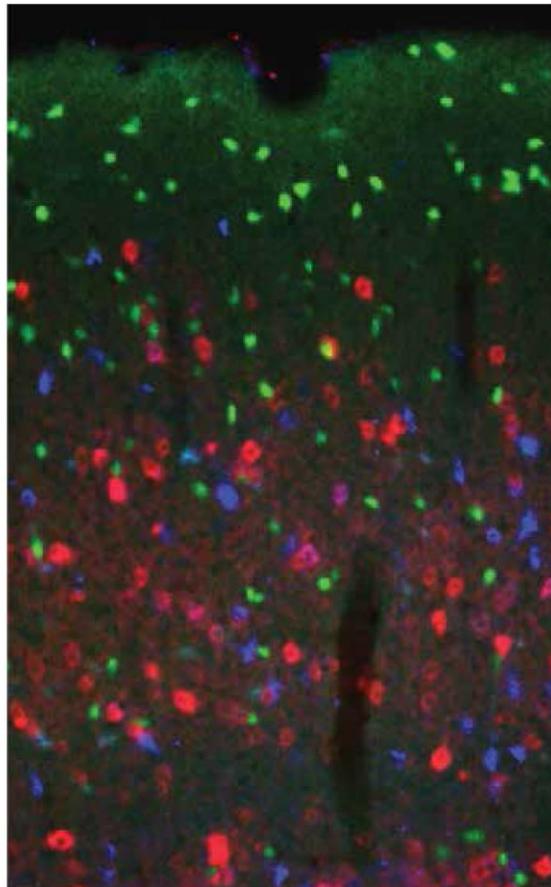
(b) Withdraw specific antibodies from ear vein

- (c) The antibodies are **tagged** with a **visible marker** and applied to sections of brain tissue. The antibodies **label only those cells that contain the neurotransmitter candidate.**
- (d) A close-up of the complex that includes the **neurotransmitter candidates, an antibody, and its visible marker.**





(a)



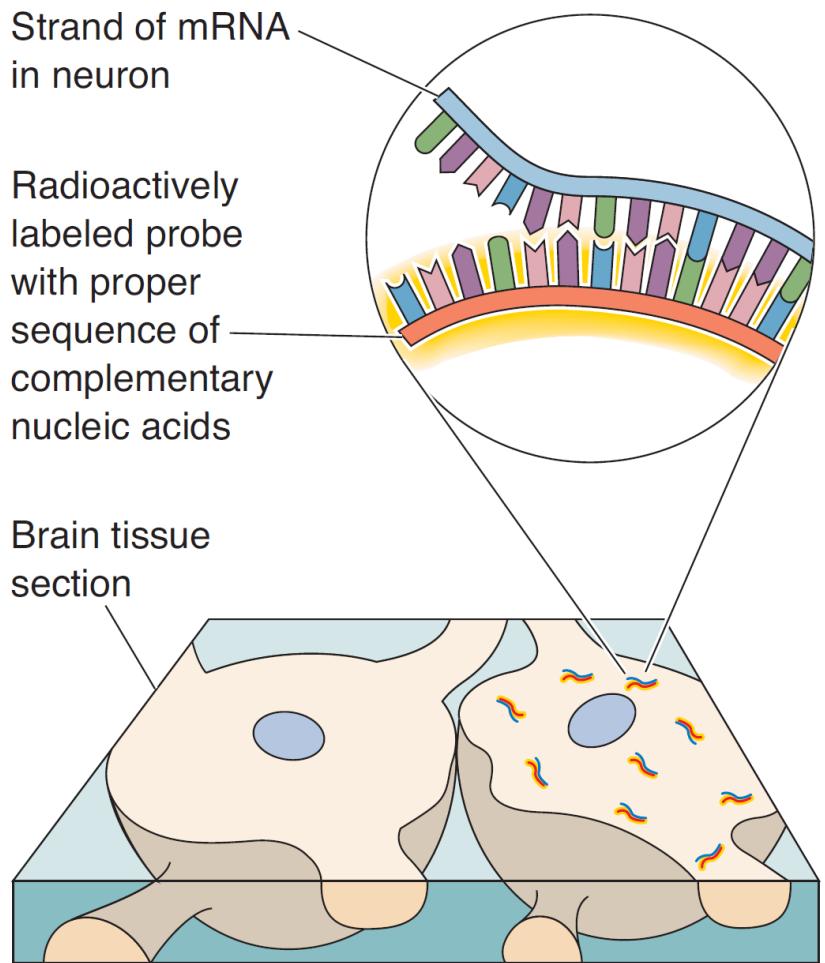
(b)

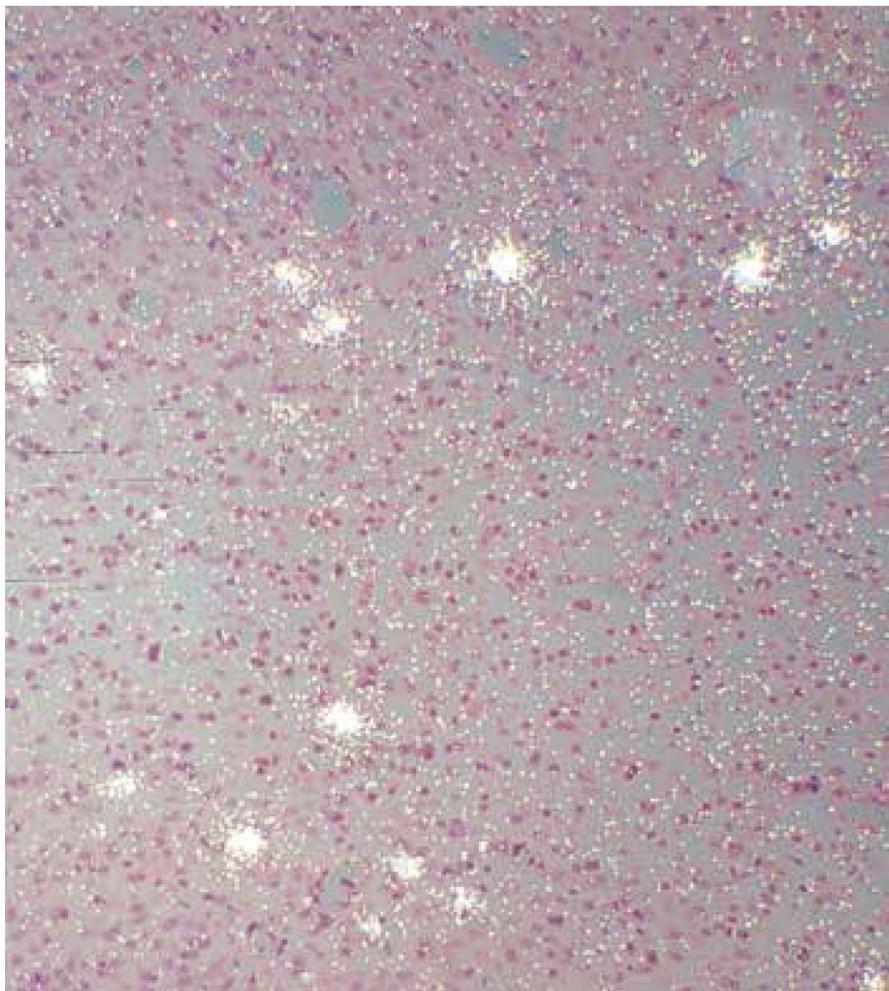
Immunohistochemical localization of proteins in neurons. (a) A neuron in the cerebral cortex labeled with antibodies that bind to a peptide neurotransmitter. (Source: Courtesy of Dr. Y. Amitai and S. L. Patrick.) (b) Three distinct types of neurons in the cerebral cortex, each labeled with a different antibody tagged with a differently colored fluorescent marker (green, red, and blue). (Source: Courtesy of Dr. S.J. Cruikshank and S.L. Patrick.) The image in a is shown at a higher magnification than that in b.



In situ hybridization

- **Strands** of mRNA consist of **nucleotides arranged** in a **specific sequence**.
- Each nucleotide will stick to one other **complementary** nucleotide.
- A **synthetic probe** is constructed containing **a sequence of complementary nucleotides** that will allow it to stick to the **mRNA**.
- If the probe is labeled, the location of cells containing the **mRNA will be revealed**.



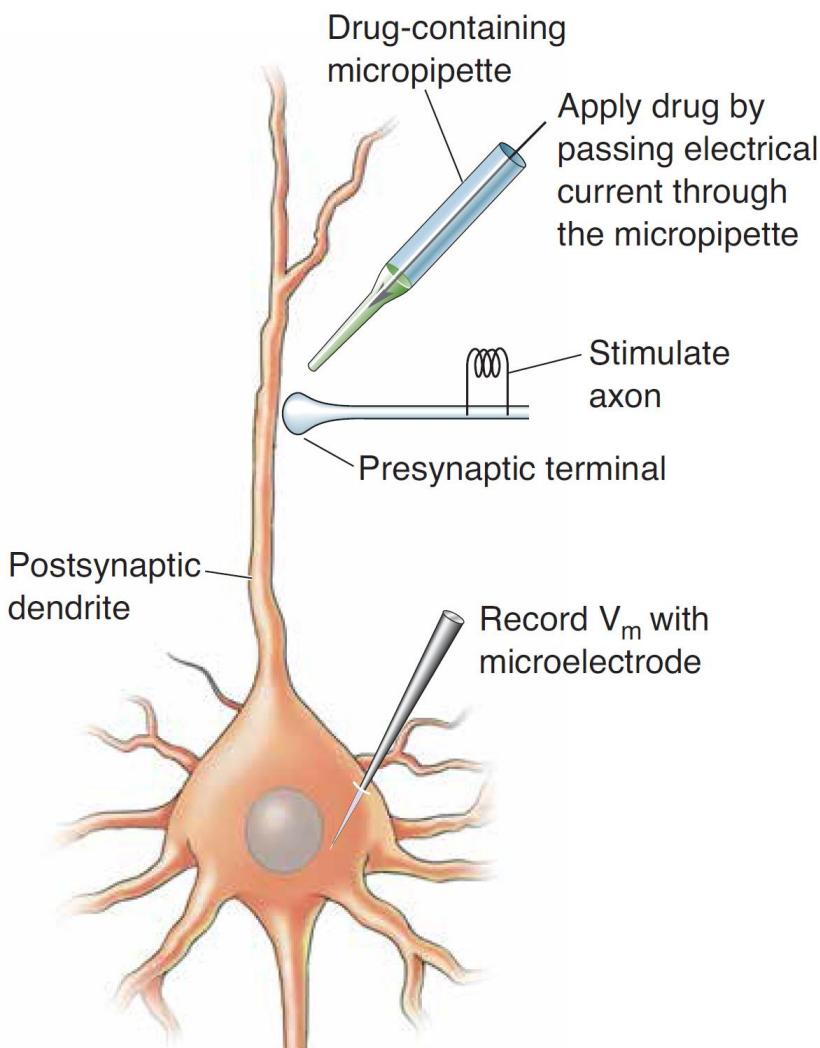


***In situ* hybridization of the mRNA for a peptide neurotransmitter in neurons, visualized with autoradiography.** Only neurons with the proper mRNA are labeled, visible here as clusters of white dots. (Source: Courtesy of Dr. S. H. C. Hendry.)

Studying Transmitter Release



- General approach helped **Loewi and Dale** identify **ACh** as a transmitter
- For CNS **using brain slices** that are kept alive ***in vitro*** and testing bathing solution
- Microiontophoresis:**
 - It use to apply drugs or neurotransmitter candidates in **very small amounts to the surface of neurons** by passing electrical current through the pipette.
 - Neurotransmitter candidates **dissolved** in solutions that will cause them to acquire **a net electrical charge**
 - The responses generated **by the drug** can be compared to those **generated by synaptic stimulation**





Receptors; Neuropharmacological Analysis.

- One neurotransmitter can **bind to many different receptors**
- Based on agonists and antagonists; **selective drugs have been extremely useful** for categorizing receptor subclasses
- **Dale's principle:**
 - The idea that a neuron has only one neurotransmitter is often called
- Many **peptide-containing neurons** **violate** Dale's principle
- **Co-transmitters:**
 - When **two or more transmitters** are released from one **nerve terminal**
- Most neurons seem to release only a single Neurotransmitter
- **Receptor subtype:**
 - Each of the **different receptors** a neurotransmitter **binds** to it.
 - ACh acts on two different cholinergic **receptor subtypes** : One type is present **in skeletal muscle**, and the other is in **heart muscle**



Neurotransmitters, some receptors, and their pharmacology

Neurotransmitter	Receptor Subtype	Agonist	Antagonist
Acetylcholine (ACh)	Nicotinic receptor	Nicotine	Curare
	Muscarinic receptor	Muscarine	Atropine
Norepinephrine (NE)	α receptor	Phenylephrine	Phenoxybenzamine
	β receptor	Isoproterenol	Propranolol
Glutamate (Glu)	AMPA	AMPA	CNQX
	NMDA	NMDA	AP5
GABA	GABA _A	Muscimol	Bicuculline
	GABA _B	Baclofen	Phaclofen
ATP	P2X	ATP	Suramin
Adenosine	A type	Adenosine	Caffeine



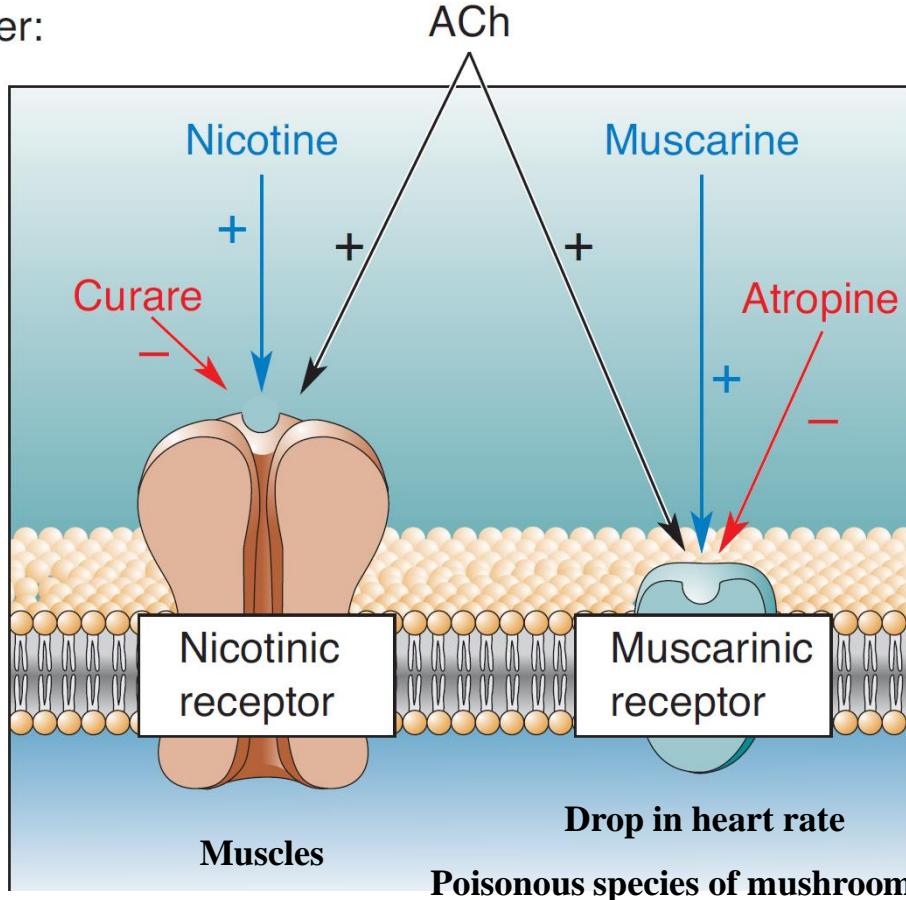
The neuropharmacology of cholinergic synaptic transmission

Neurotransmitter:

Agonists:

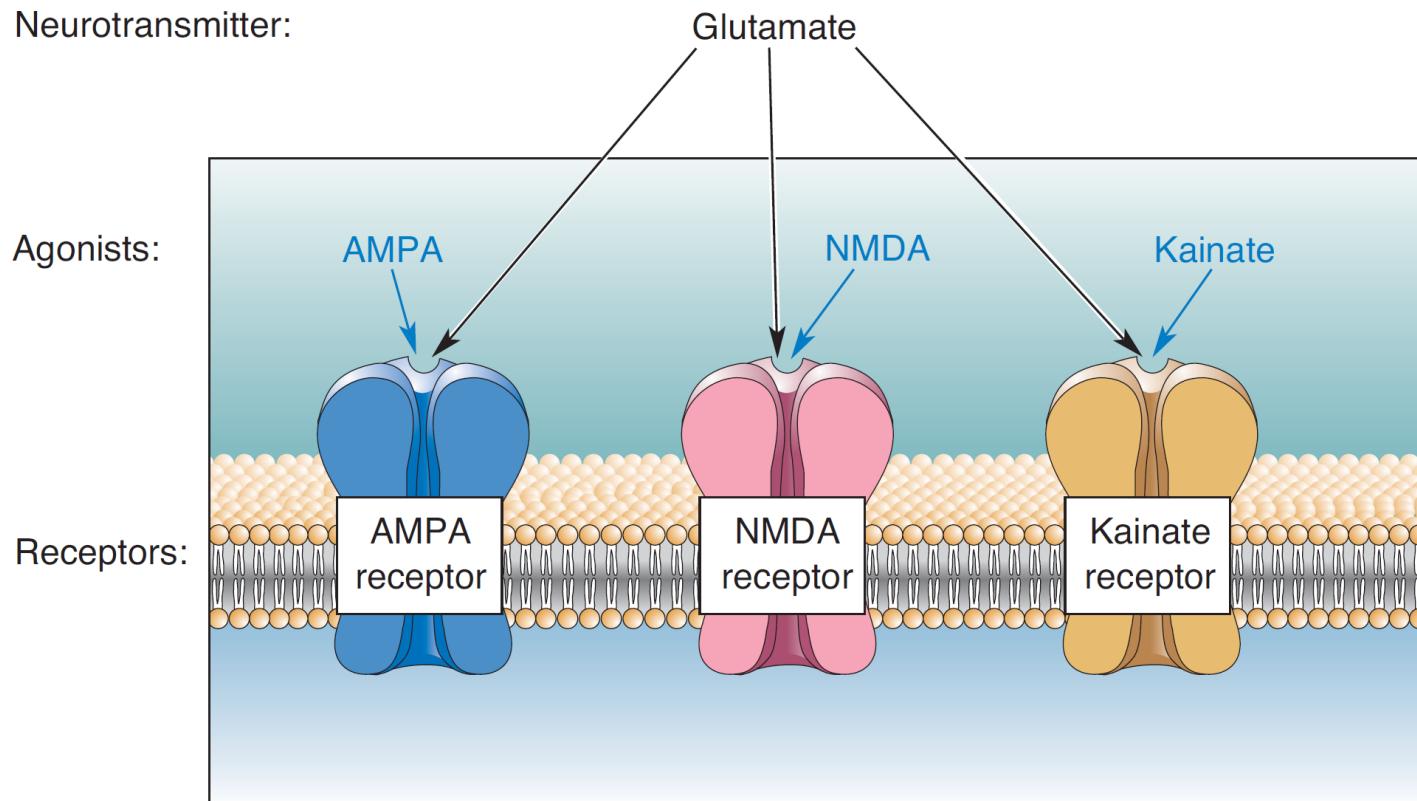
Antagonists:

Receptors:





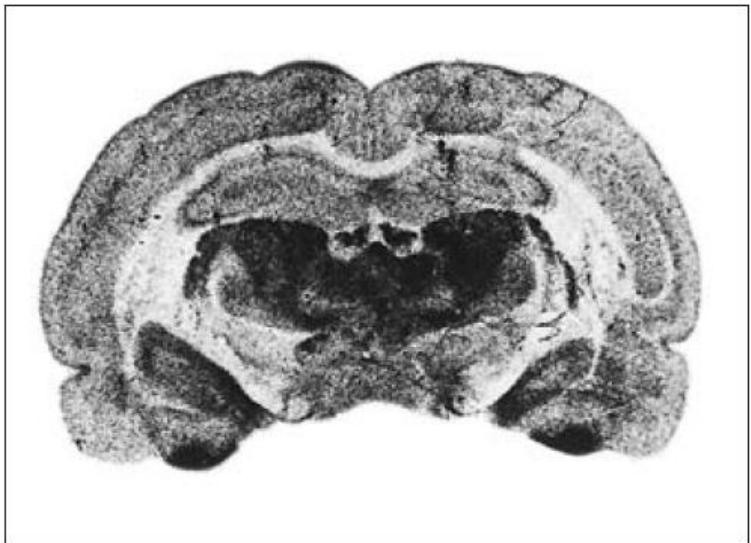
The neuropharmacology of glutamatergic synaptic transmission





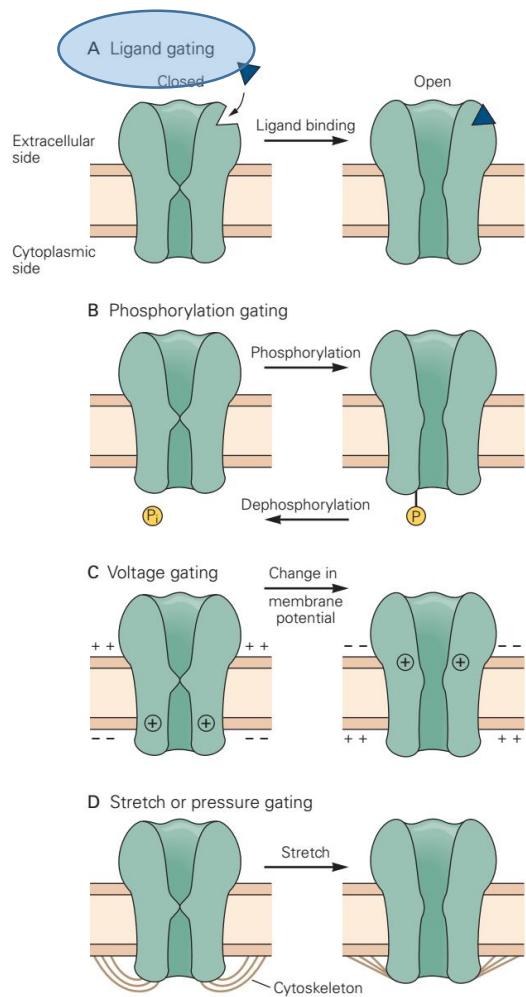
Ligand-binding method

- Any **chemical compound** that binds to a specific site on a receptor is called a ***ligand***
- Using **radioactively labeled** ligands
- Ligand for a receptor can be an **agonist**, an **antagonist** or the chemical **neurotransmitter** itself
- Mapping the **anatomical distribution of different neurotransmitter** receptors in the brain

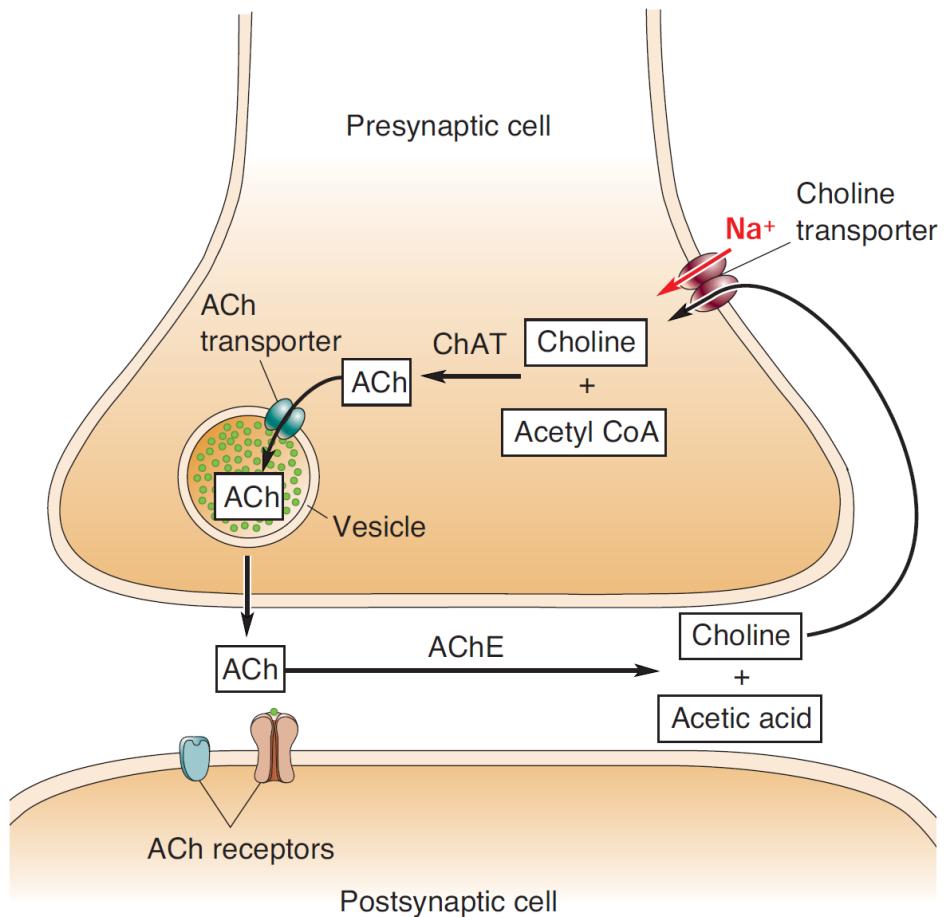


Opiate receptor binding to a slice of rat brain. Special film was exposed to a brain section that had radioactive opiate receptor ligands bound to it. The dark regions contain more receptors. (Source: Snyder, 1986, p. 44.)

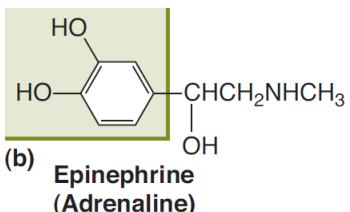
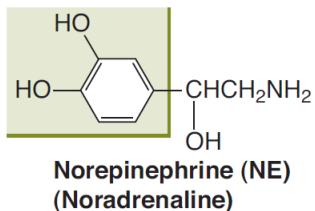
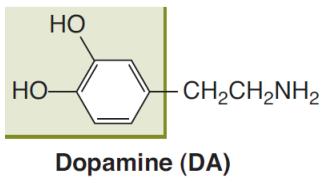
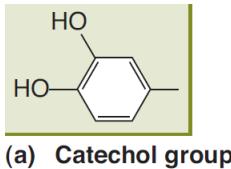
Several types of stimuli control the opening and closing of ion channels.



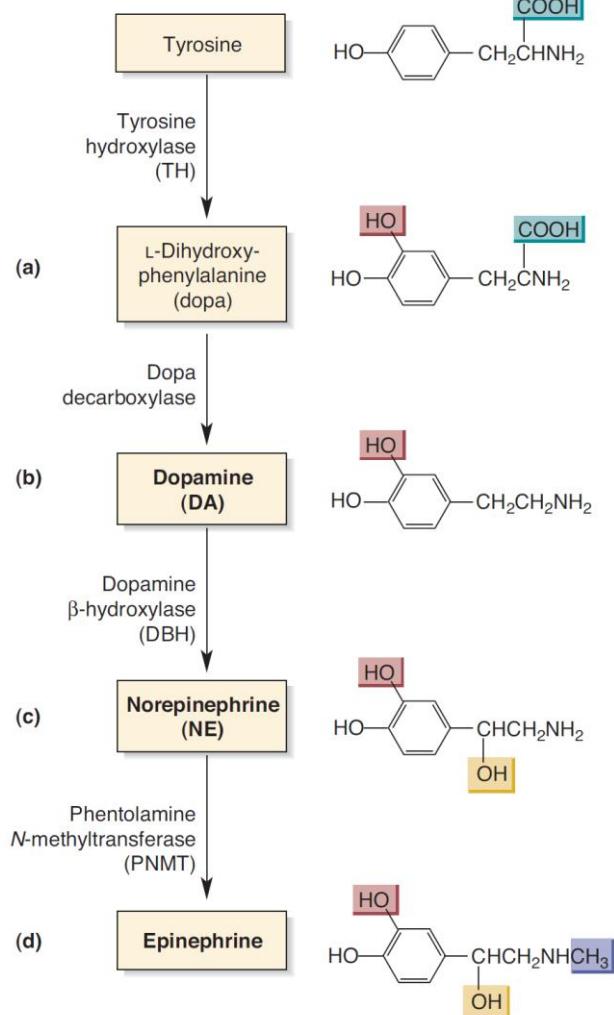
Neurotransmitter chemistry; The life cycle of ACh



Catecholaminergic Neurons



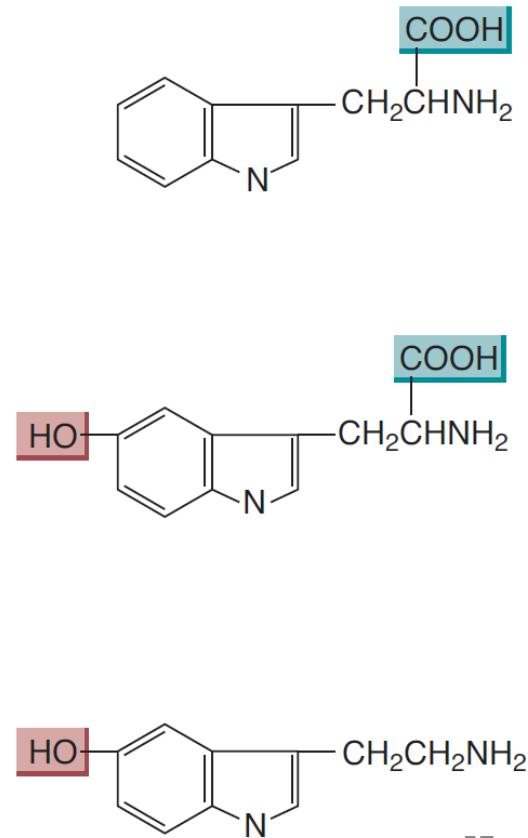
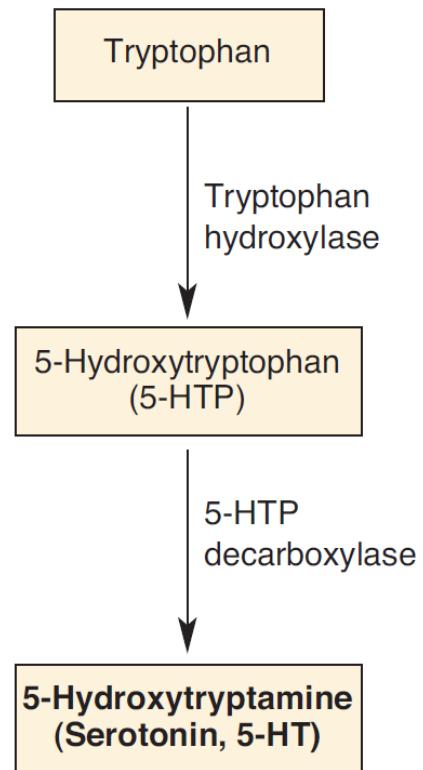
- The actions of catecholamines in the synaptic cleft are **terminated by selective uptake** of the neurotransmitters back into the axon terminal **via Na-dependent transporters**.
- It is **slower** than Ach
- They synthesize from **tyrosine**



Serotonergic Neurons

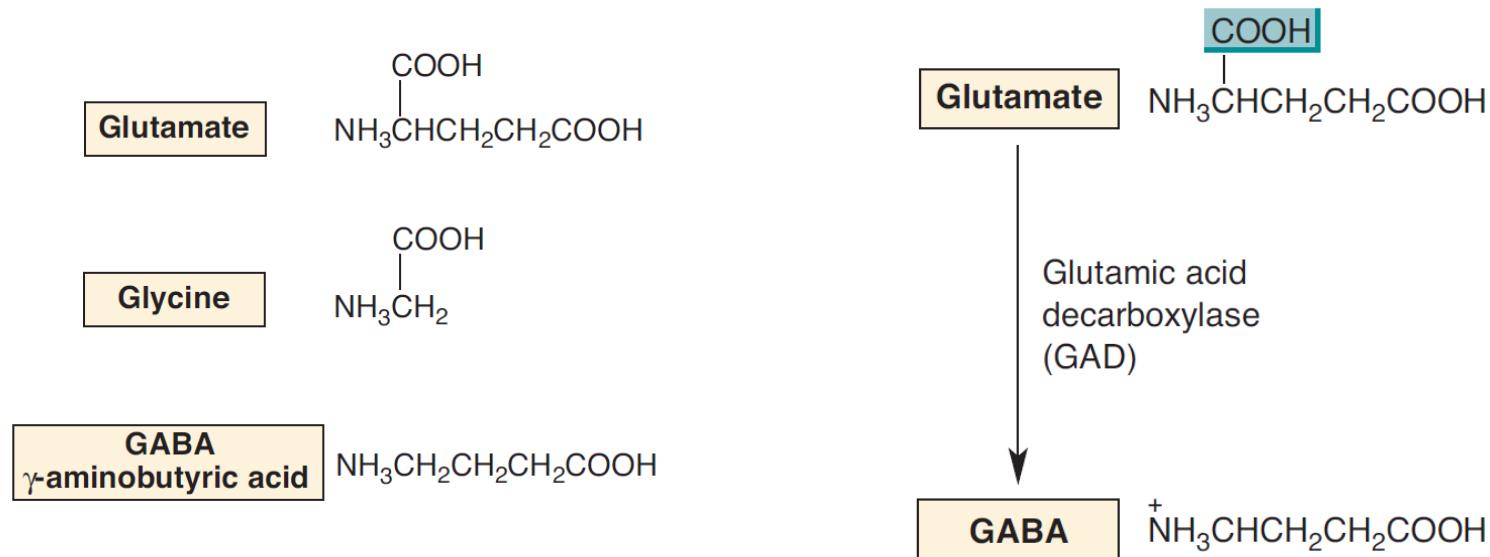


- Regulate **mood**, **emotional behavior**, and **sleep**.
- Several clinically useful antidepressant drugs, including **fluoxetine** (trade name Prozac), are **selective inhibitors of serotonin reuptake**.





The amino acid neurotransmitters

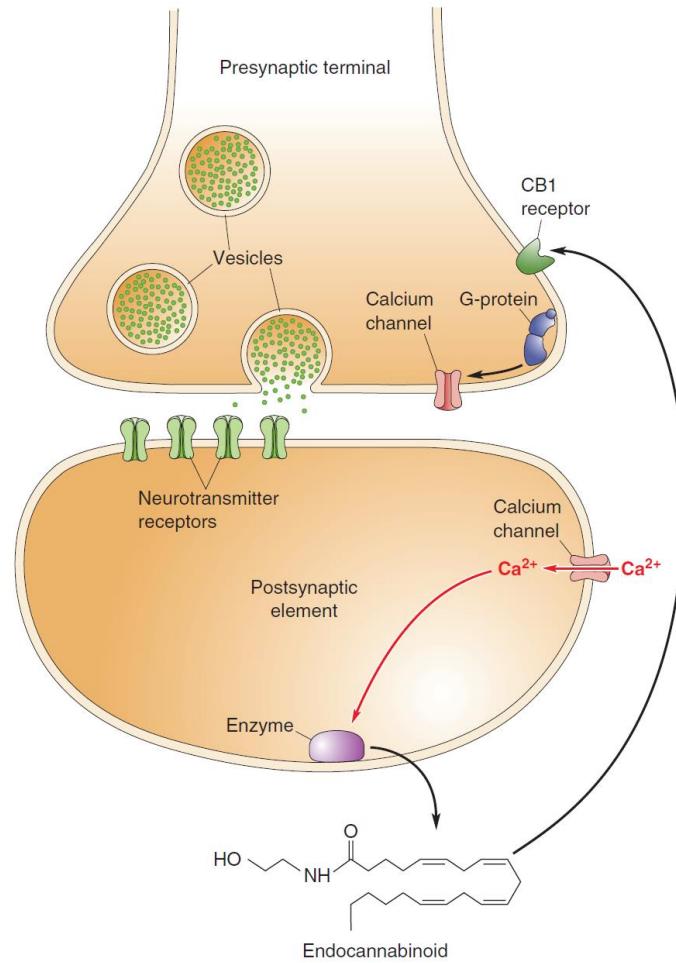


The synthesis of GABA from glutamate.

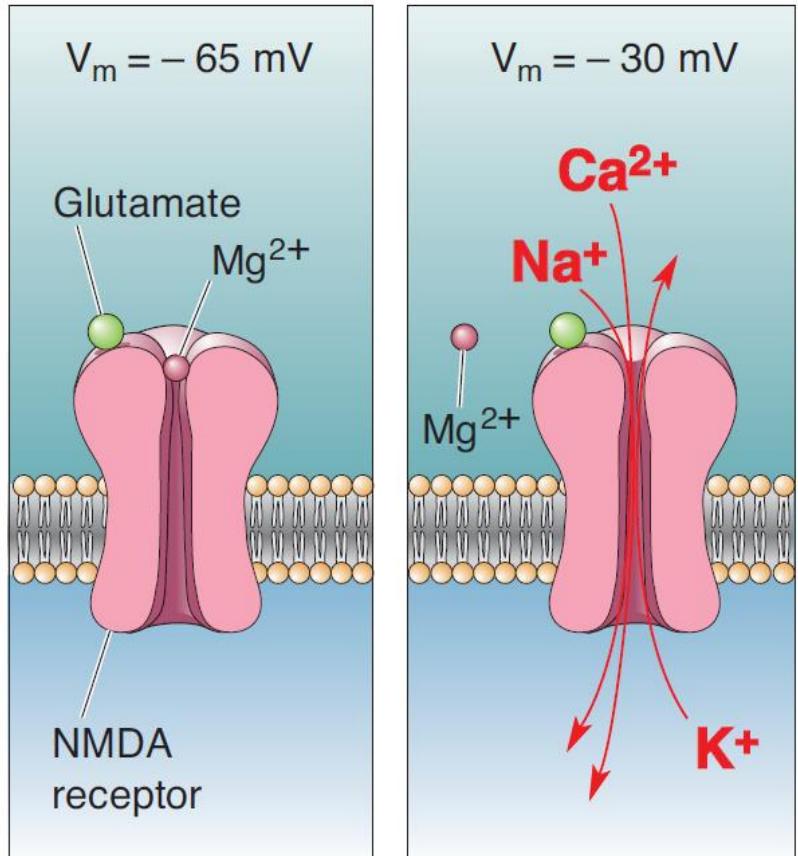


Endocannabinoids

- Can be released from **postsynaptic** neurons and act on presynaptic terminals
- Communication in this direction, from “post” to “pre,” is called **retrograde signaling**;
- **Retrograde messengers:** kind of feedback system
- **Vigorous firing of action** potentials in the **postsynaptic neuron** causes voltage-gated calcium channels to open
- [Ca²⁺] then somehow stimulates the **synthesis of endocannabinoid** molecules
- CB1 receptors are G-protein-coupled receptors, and their main effect is often to **reduce the opening of presynaptic calcium channels**



Inward ionic current through the NMDA-gated channel. (a) Glutamate alone causes the channel to open, but at the resting membrane potential, the pore becomes blocked by Mg^{2+} . (b) Depolarization of the membrane relieves the Mg^{2+} block and allows Na^+ and Ca^{2+} to enter.



(a) Glutamate

(b) Glutamate and depolarization

- **Synaptic inhibition** must be tightly regulated in the brain.
 - **Too much causes a loss of consciousness** and coma;
 - **Too little leads to a seizure.**
- modulatory binding sites of **GABA_A** receptor:
 - Benzodiazepines
 - Barbiturates
 - Ethanol
- **Benzodiazepines** increase the **frequency of channel openings**, while **barbiturates** increase the **duration of channel openings**

