A few questions on the content of the previous lecture

slido

.... can be either excitatory or inhibitory, while .... are all-or-none

ⓘ Start presenting to display the poll results on this slide.

slido

At rest, there is more .... outside the cell, and more ... inside the cell

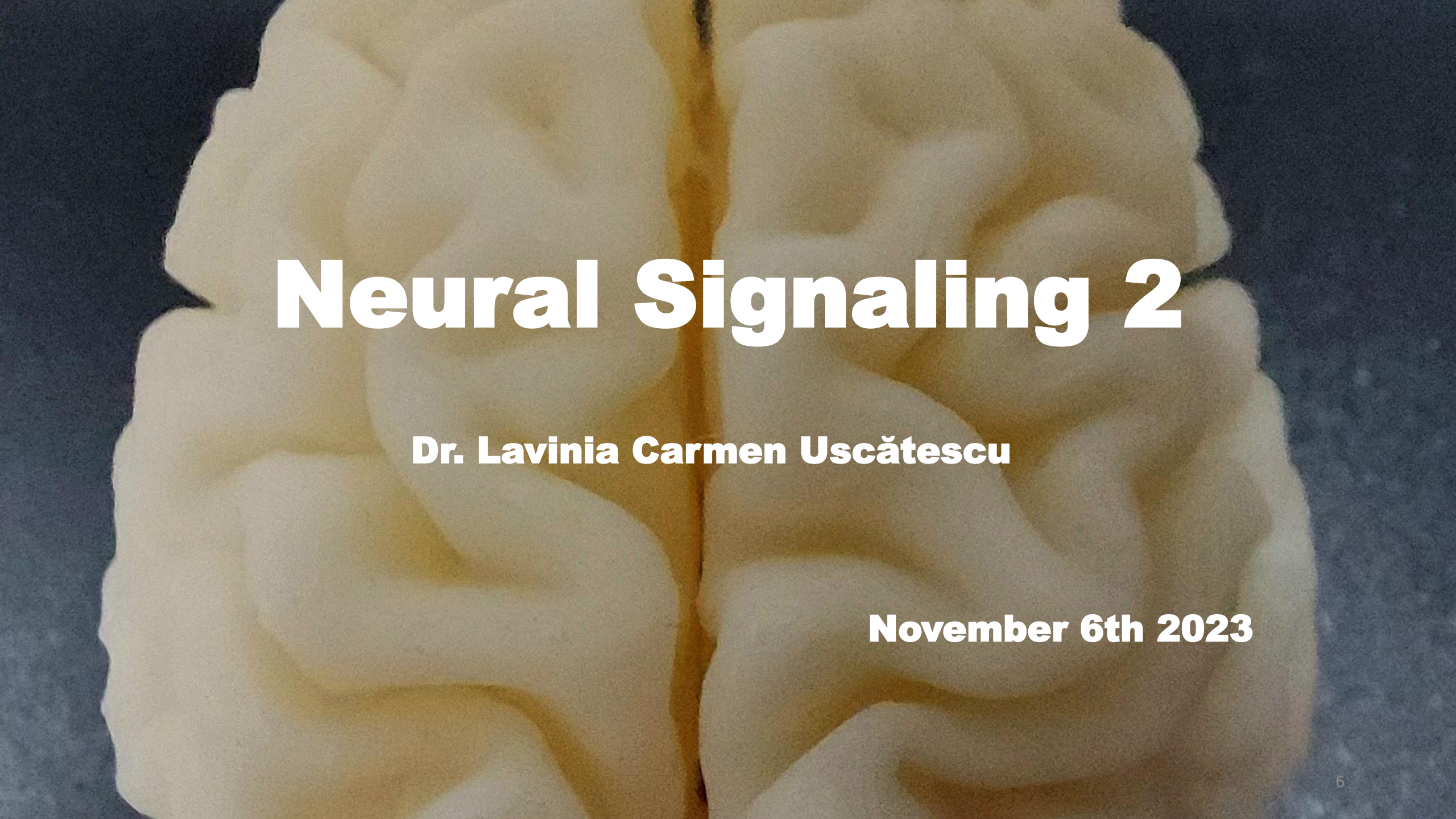
ⓘ Start presenting to display the poll results on this slide.

slido

The sodium-potassium pump works to ... (choose all that apply)

ⓘ Start presenting to display the poll results on this slide.

Any questions/remarks before we begin today’s lecture?



Neural Signaling 2

Dr. Lavinia Carmen Uscătescu

November 6th 2023

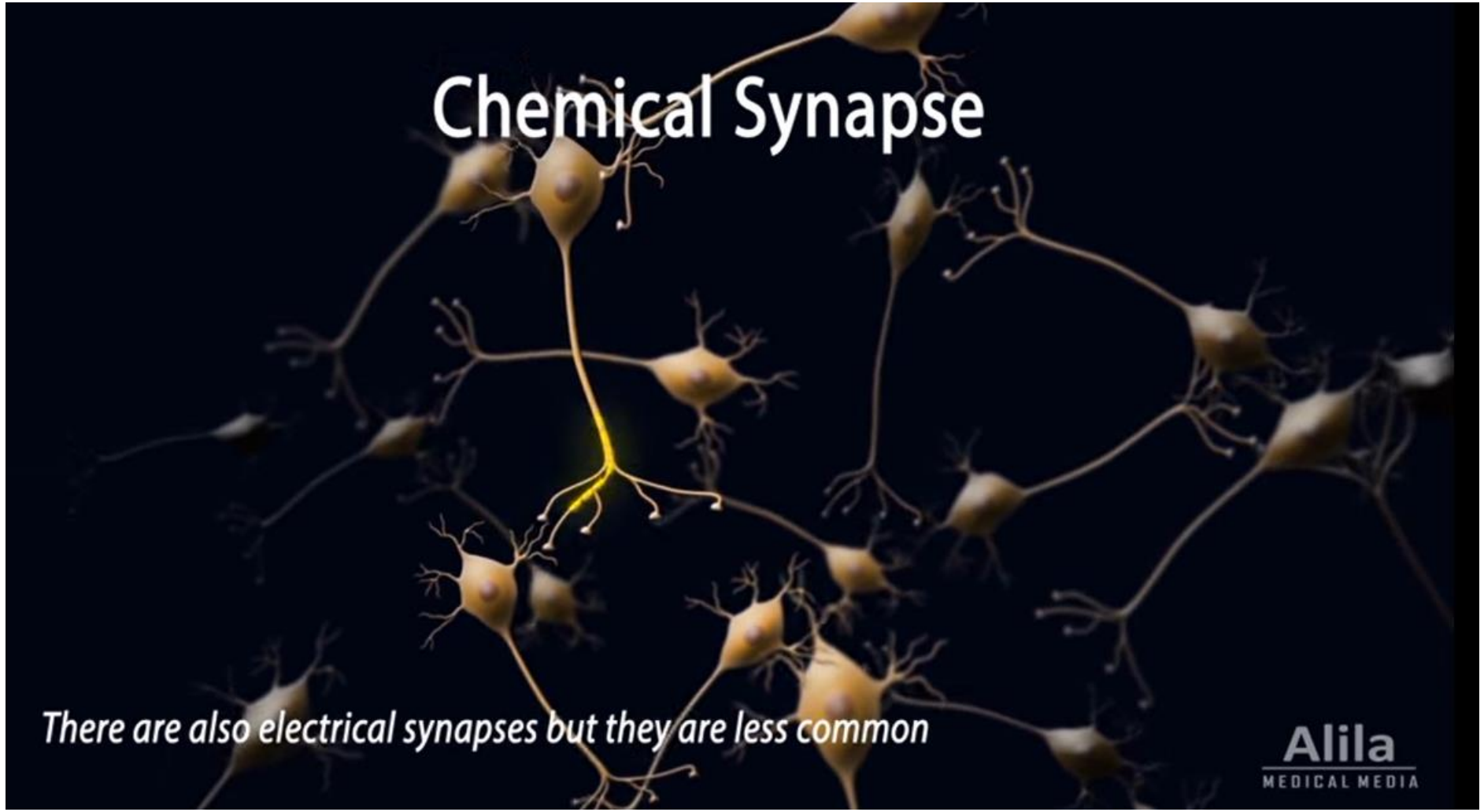
What you can gain from this lecture

- Knowledge about neuronal signal transmission, both electrical and chemical
- Essential vocabulary to characterize synaptic transmission
- Knowledge about important historical moments that marked the characterization of synaptic transmission

Outline

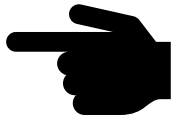
1. Overview
2. Electrical synapses
3. Chemical synapses

Let’s first set the stage for today’s lecture



https://www.youtube.com/watch?v=cZwb8zqAPXc&t=6s

Neuronal communication = an **electrochemical** event

The **movement of the action potential** down the axon = **electrical**  the focus of last week's lecture

the focus of today's lecture

The **movement of the neurotransmitters** across the synaptic space = **chemical**

*Note however that **most, but not all synapses are chemical**; **some are electrical**. These are faster than the chemical ones and occur when two neurons communicate via **gap junctions**.*

Overview

The term "**synapse**" was coined

nature › books received › article

Published: 06 June 1907

The Integrative Action of the Nervous System

Nature **76**, 122 (1907) | Cite this article

1611 Accesses | **2** Citations | Metrics

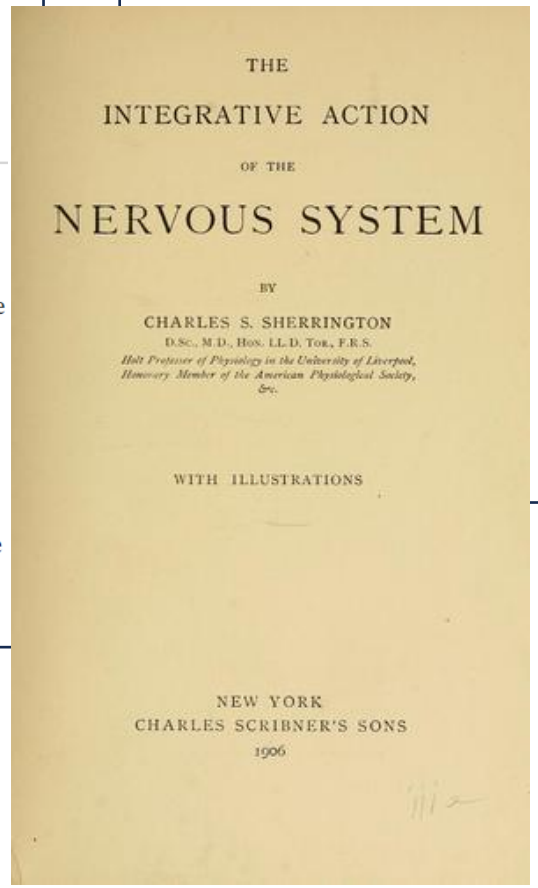
Abstract

THE unravelling of the arrangement and complications of the nervous system has always been of great interest not only to physiologists, but also to mankind in general. The specially human attributes which distinguish our species from the rest of the Mammalia have at least an intimate connection with the superior development of the central nervous system, and we have therefore a peculiar interest in tracing the methods by which this complexity is of advantage to the individual.

The Integrative Action of the Nervous System.

By Dr. C. S. Sherrington Pp. xvi + 411. (London: Archibald Constable and Co., Ltd., 1906.) Price 16*s*. net.

https://www.nature.com/articles/076122a0



The Nobel Prize in Physiology or Medicine 1932

Sir Charles Sherrington
Edgar Adrian

Share this

Sir Charles Sherrington
Facts

Photo from the Nobel Foundation archive.

Sir Charles Scott Sherrington
The Nobel Prize in Physiology or Medicine 1932

Born: 27 November 1857, London, United Kingdom

Died: 4 March 1952, Eastbourne, United Kingdom

Affiliation at the time of the award: University of Oxford, Oxford, United Kingdom

Prize motivation: "for their discoveries regarding the functions of neurons"

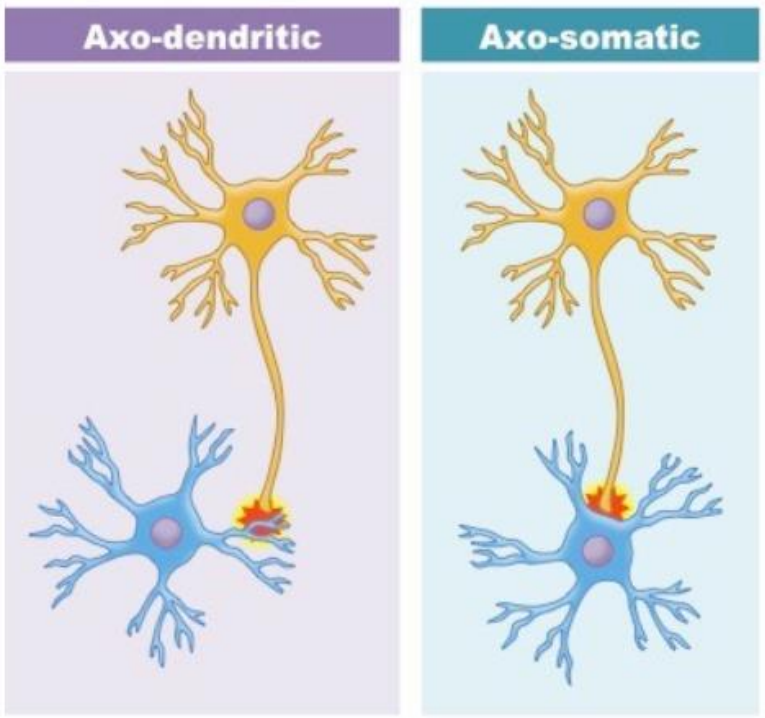
Prize share: 1/2

https://www.nobelprize.org/prizes/medicine/1932/sherrington/facts/

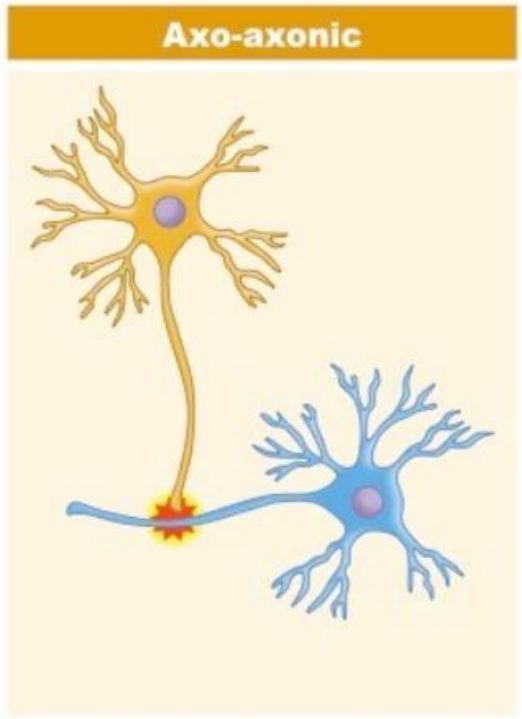
synapse *= specialized point of contact between two neurons =>* ***synaptic transmission***

image source: https://tinyurl.com/j3fepws7

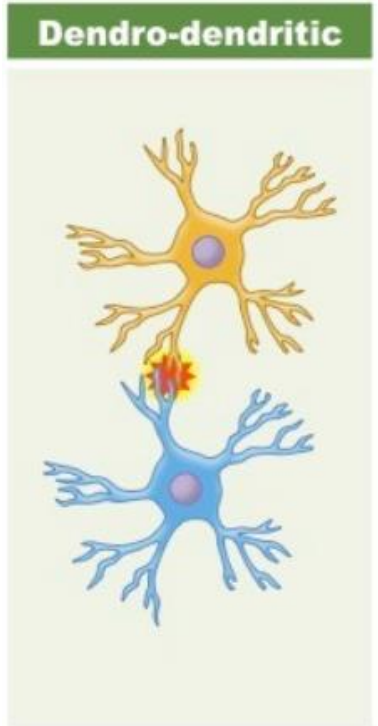
Types of synapses



Axodendritic and Axosomatic synapses are the most common.



Axoaxonic synapses can mediate *presynaptic facilitation and inhibition*.

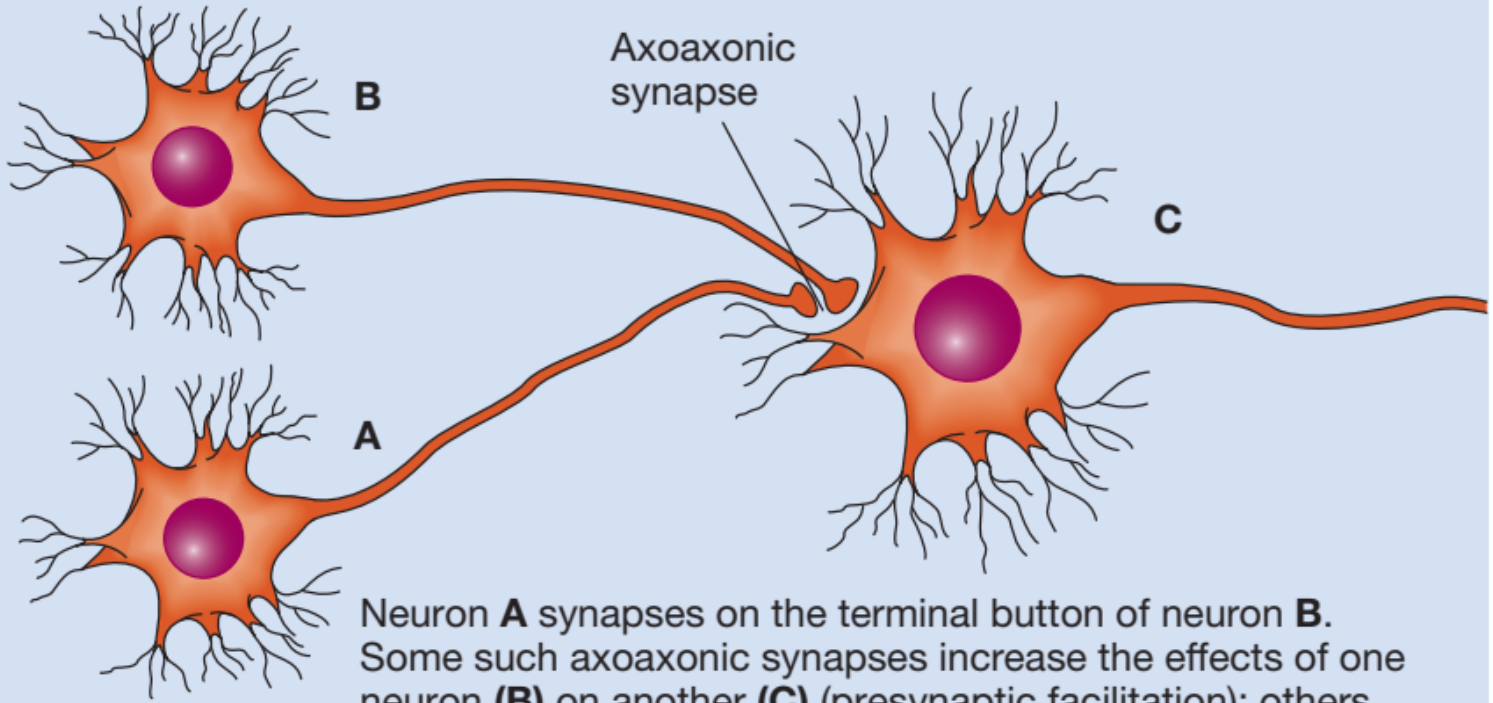


Dendrodendritic synapses can transmit signals in either direction.

image source: https://tinyurl.com/3ajwtapn

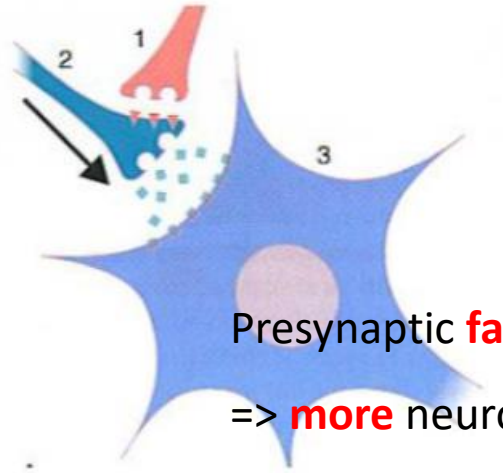
Presynaptic **facilitation** and **inhibition**

Figure 4.8 Presynaptic facilitation and inhibition.



Neuron **A** synapses on the terminal button of neuron **B**. Some such axoaxonic synapses increase the effects of one neuron **(B)** on another **(C)** (presynaptic facilitation); others decrease the effects of one neuron **(B)** on another **(C)** (presynaptic inhibition). The advantage of presynaptic facilitation and inhibition is that they selectively influence single synapses, rather than the entire neuron.

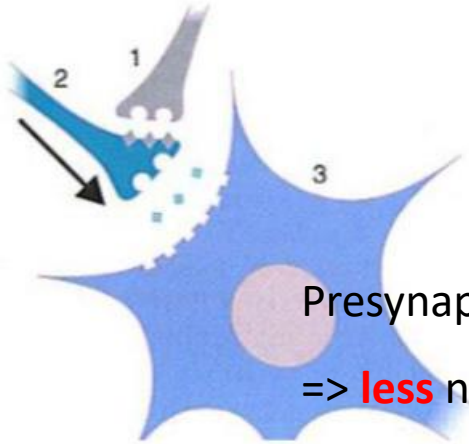
Pinel & Barnes, (2021), p. 108



Presynaptic **facilitation**

=> **more** neurotransmitter

is released



Presynaptic **inhibition**

=> **less** neurotransmitter

is released

Image source: https://tinyurl.com/3wf4uurt

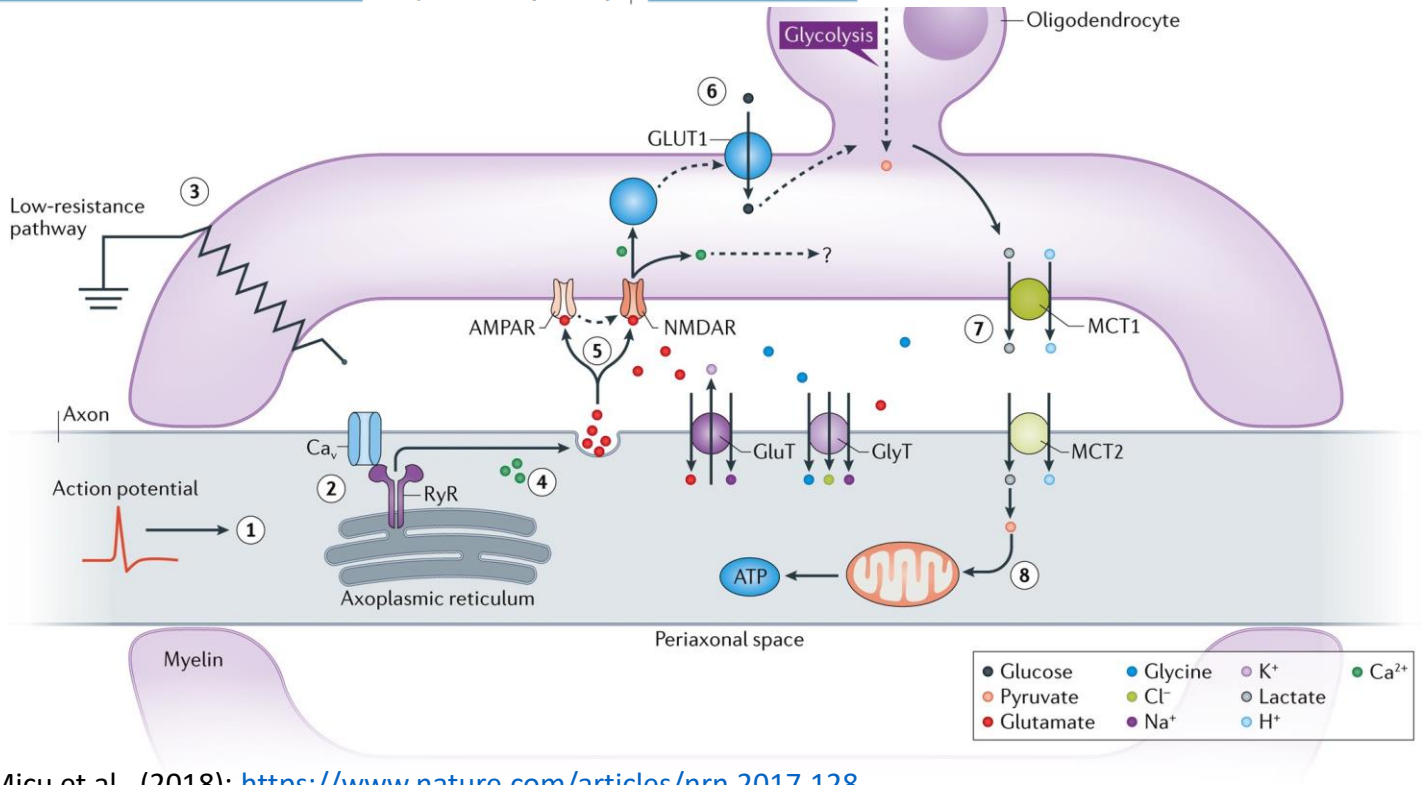
Axomyelinic synapses

Published: 09 November 2017

Axo-myelinic neurotransmission: a novel mode of cell signalling in the central nervous system

Ileana Micu, Jason R. Plemel, Andrew V. Caprariello, Klaus-Armin Nave & Peter K. Stys

Nature Reviews Neuroscience **19**, 49–58 (2018) | Cite this article



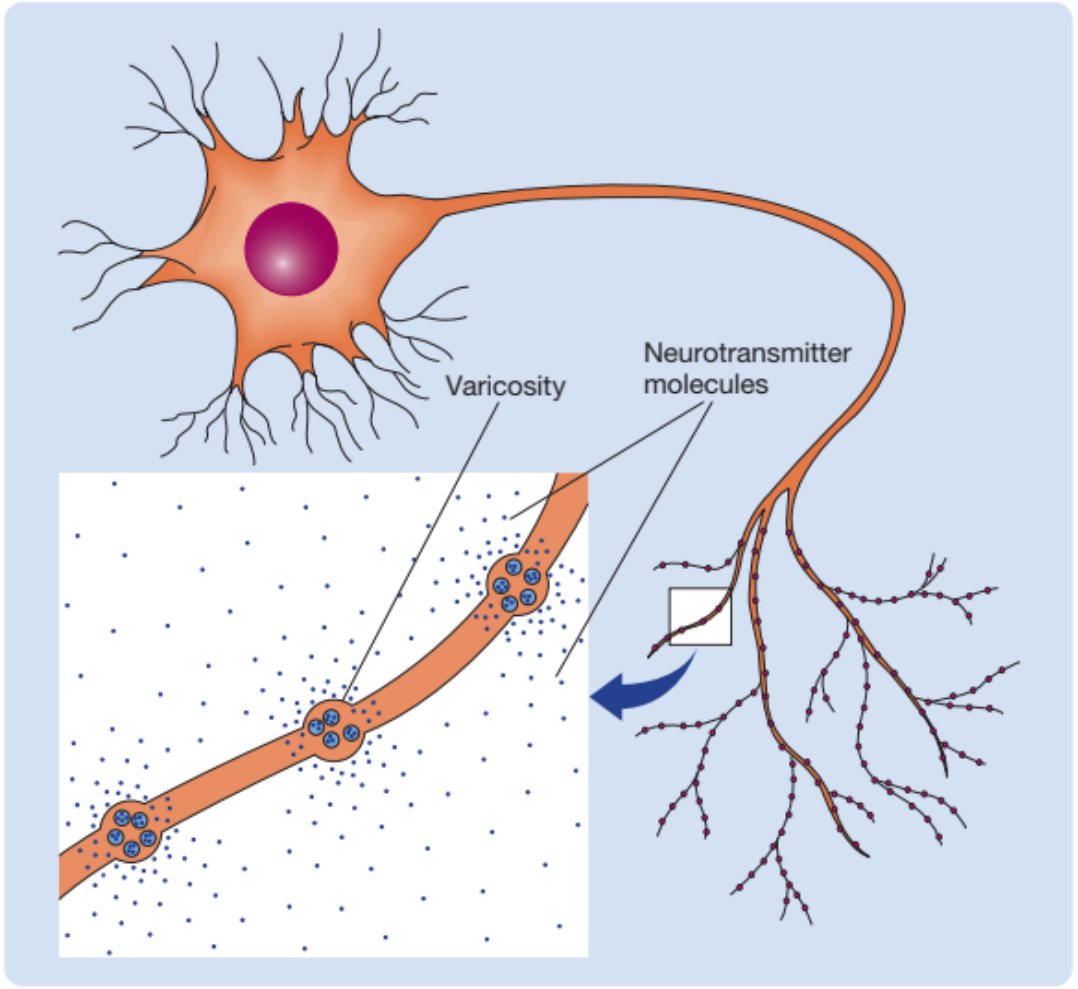
Micu et al., (2018): https://www.nature.com/articles/nrn.2017.128

Once thought to be a mostly inert layer of insulation around axons, myelin is now considered to play an active and dynamic role in the preservation and maintenance of axonal structure and function[1,2]. We had previously reported the presence of NMDA receptors (NMDARs) in CNS myelin that were activated by reverse Na^+-dependent glutamate and glycine transport during chemically induced ischaemia in white matter[3,4]. These results suggested that NMDARs expressed on myelin have a physiological purpose and could represent the receiving end of a potential, synapse-like, chemically dependent signalling interaction between the axon and its myelin sheath[5]. The mechanisms underlying the communication between axon and adjacent myelin membranes were unknown, but recently, studies have emerged that begin to shed light on the molecular architecture of this putative 'axo-myelinic synapse' (AMS), how it responds under normal (rather than pathological) conditions[6] and its potential physiological roles[1,6]. Technical

**N-methyl-D-aspartate (NMDA) receptor is a receptor of glutamate, the primary excitatory neurotransmitter in the human brain*

Directed v. **nondirected** synapses

Figure 4.9 One example of nondirected neurotransmitter release. Some neurons release neurotransmitter molecules diffusely from varicosities along the axon and its branches.



Pinel & Barnes, (2021), p. 108

directed synapses

synapses whose site of neurotransmitter release and site of neurotransmitter reception are in close proximity

nondirected synapses

synapses whose site of neurotransmitter release is at some distance from the site of reception

Electrical v. **chemical** synapses at a glance

Type of synapse	Electrical	Chemical
Distance between pre- and post-synaptic cell membranes	4 nm	20 - 40 nm **1 nm = 10^{-9} m (one billionth of a meter)*
Cytoplasmic continuity between pre- and post-synaptic cells	Yes	No
Ultrastructural components	Gap-junction channels	Presynaptic vesicles and active zones; postsynaptic receptors
Agent of transmission	Ion current	Chemical transmitter
Synaptic delay	Virtually absent	Significant; at least 0.3 ms, usually 1 – 5 ms or longer
Direction of transmission	Usually bidirectional	Unidirectional

based on Kandel et al., (2021), p. 242

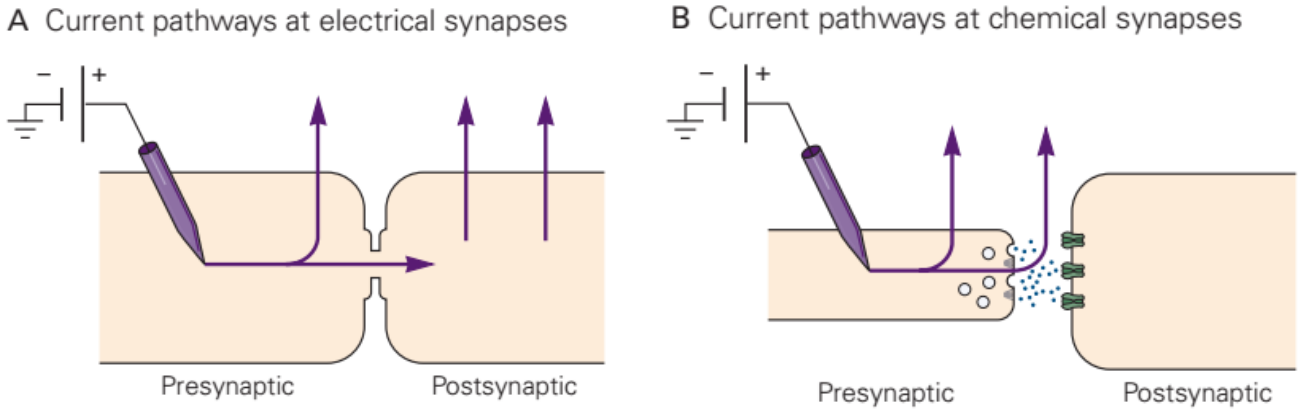


Figure 11–1 Functional properties of electrical and chemical synapses.

A. At an electrical synapse, some current injected into the presynaptic cell escapes through resting (nongated) ion channels in the cell membrane. However, some current also enters the postsynaptic cell through gap-junction channels that connect the cytoplasm of the pre- and postsynaptic cells and that provide a low-resistance (high-conductance) pathway for electrical current.

B. At chemical synapses, all current injected into the presynaptic cell escapes into the extracellular fluid. However, the resulting depolarization of the presynaptic cell membrane can produce an action potential that causes the release of neurotransmitter molecules that bind receptors on the postsynaptic cell. This binding opens ion channels that initiate a change in membrane potential in the postsynaptic cell.

Kandel et al., (2021), p. 243

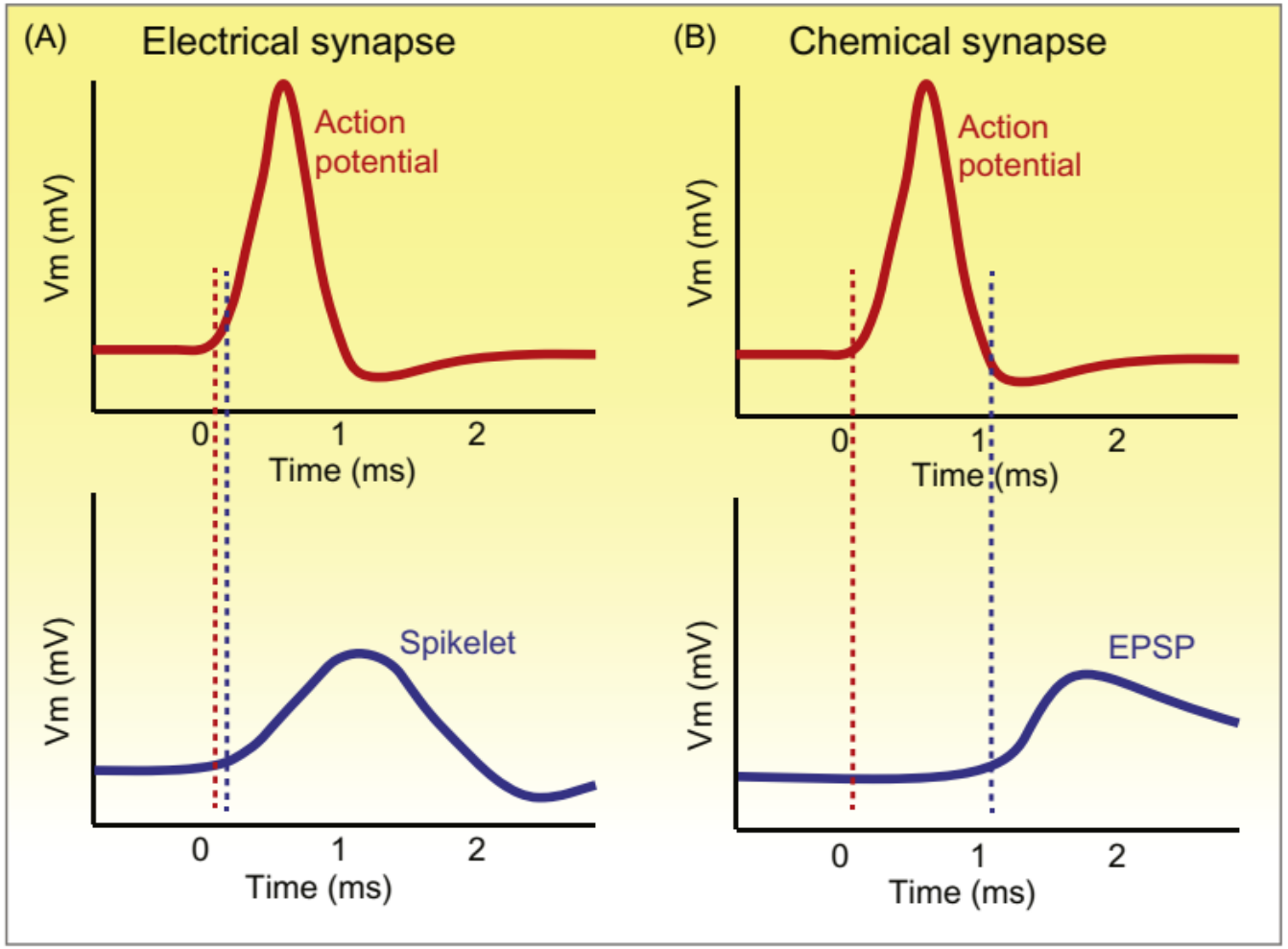


FIGURE 5.10 **Synaptic delays at electrical and chemical synapses.** Synaptic transmission through a gap junction has essentially no synaptic delay (~0.1 ms), compared to a typical chemical synapse, which can have up to a 1–2 ms synaptic delay (see Chapters 6–8). (A) An action potential in the presynaptic neuron (top) leads, with little to no synaptic delay, to a small "spikelet" (spike-like depolarization) in the postsynaptic neuron when an electrical synapse connects these two cells. (B) An action potential in the presynaptic neuron leads, with about a 1 ms synaptic delay, to an excitatory postsynaptic potential (EPSP) in the postsynaptic neuron when a chemical synapse connects these two cells.

Meriney & Fanselow, (2019), p. 75

Electrical synapses

First functional characterization: Edwin Furshpan, David Potter, and Akira Watanabe

J. Physiol. (1959) 145, 289–325

TRANSMISSION AT THE GIANT MOTOR SYNAPSES OF THE CRAYFISH

BY E. J. FURSHPAN* AND D. D. POTTER*

From the Biophysics Department, University College London

(*Received* 30 *July* 1958)

https://pubmed.ncbi.nlm.nih.gov/13642302/

Indications for the existence of electrical synapses in neuronal tissue were first made evident by Harry Grundfest's group and by Furshpan and Potter (1959), who demonstrated that signal transmission between segments of the cord giant fibers in crustaceans and at the giant cord-motor synapses of the crayfish was electrically mediated. Although this form of transmission

Pfaff, Volkow & Rubenstein, (2022), p. 790

Jpn J Physiol. 1958 Dec 20;8(4):305-18. doi: 10.2170/jjphysiol.8.305.

The interaction of electrical activity among neurons of lobster cardiac ganglion

A WATANABE

PMID: 13620382 DOI: 10.2170/jjphysiol.8.305

https://pubmed.ncbi.nlm.nih.gov/13620382/

mammalian brain, one estimates the same proportion of synapses that are electrical. When focusing on the issue of functional relevance of neuronal gap junction, the seminal proposals about electrical synapses made more than 50 years ago by Akira Watanabe are still gospel. On the basis of his observation that in the cardiac ganglion of the Japanese lobster neurons are coupled electrically, he drew the following conclusions: (1) ionic current can pass directly from cell to cell; (2) electrical synapses possess low-pass filter characteristics, meaning that slow fluctuations of membrane voltage are mediated more efficiently between the cells than are fast events such as action potentials; and (3) that synchronization of neurons is a paramount feature of electrical connections because membrane potential oscillations appeared coordinated among neurons. A fine example that these functional properties can be extended

Pfaff, Volkow & Rubenstein, (2022), p. 807

Anatomy of an electrical synapse

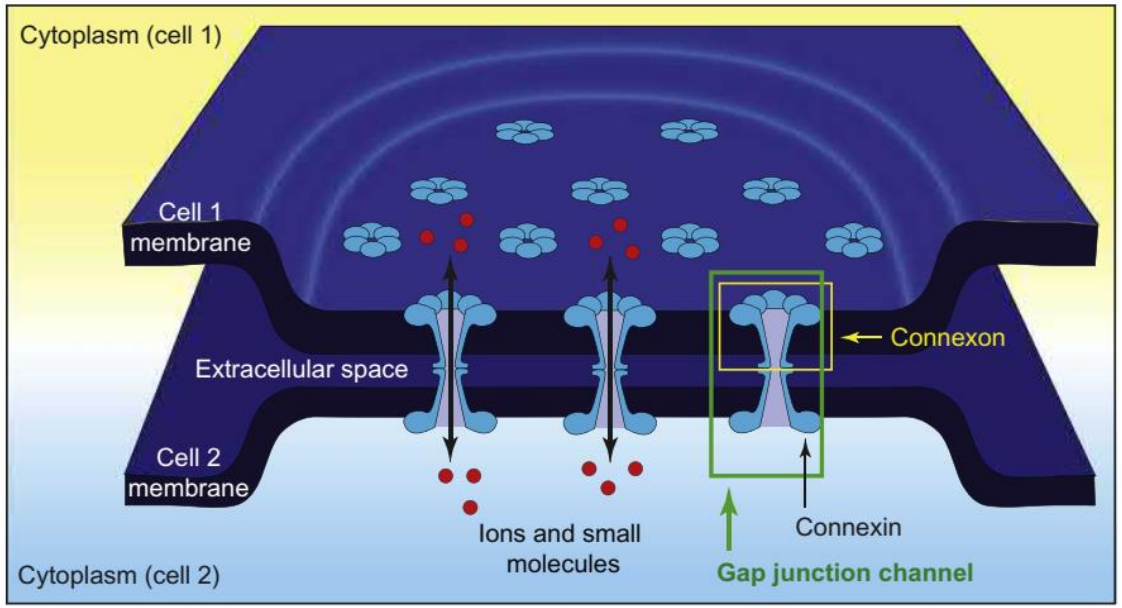


FIGURE 5.5 Diagram of a gap junction. **Six connexin subunits** (light blue) come together to form **one connexon** (yellow box), and many connexons are embedded in the synaptic membrane of both cells (1 and 2) at the **gap junction**. **One connexon from each cell comes together to form a complete gap junction channel** (green box) **with a pore in its center**. The gap junction channels can pass **ions and small molecules** from the cytoplasm of one cell into the cytoplasm of another.

Meriney & Fanselow, (2019), p. 70

gap junction

specialized formation of intercellular channels, or protein pores, that form a complex with regulatory proteins

connexon

a hemichannel (i.e., half a gap junction)

connexin

protein subunit of a connexon; each connexon is composed of 6 connexin subunits => connexons are hexamers

New connexins are produced **in the cell body** and are transported to the site of gap junction formation, which can be in the cell body or other locations within neurons. They are then **inserted** into the plasma membrane and **aligned** with the connexins of opposing **hemichannels** synthesized by the coupled neighboring cell.

The mammalian genome codes for about **20 different connexin proteins**. In the adult nervous system, specific types of connexins are expressed in neurons, while others appear to be present in glia.

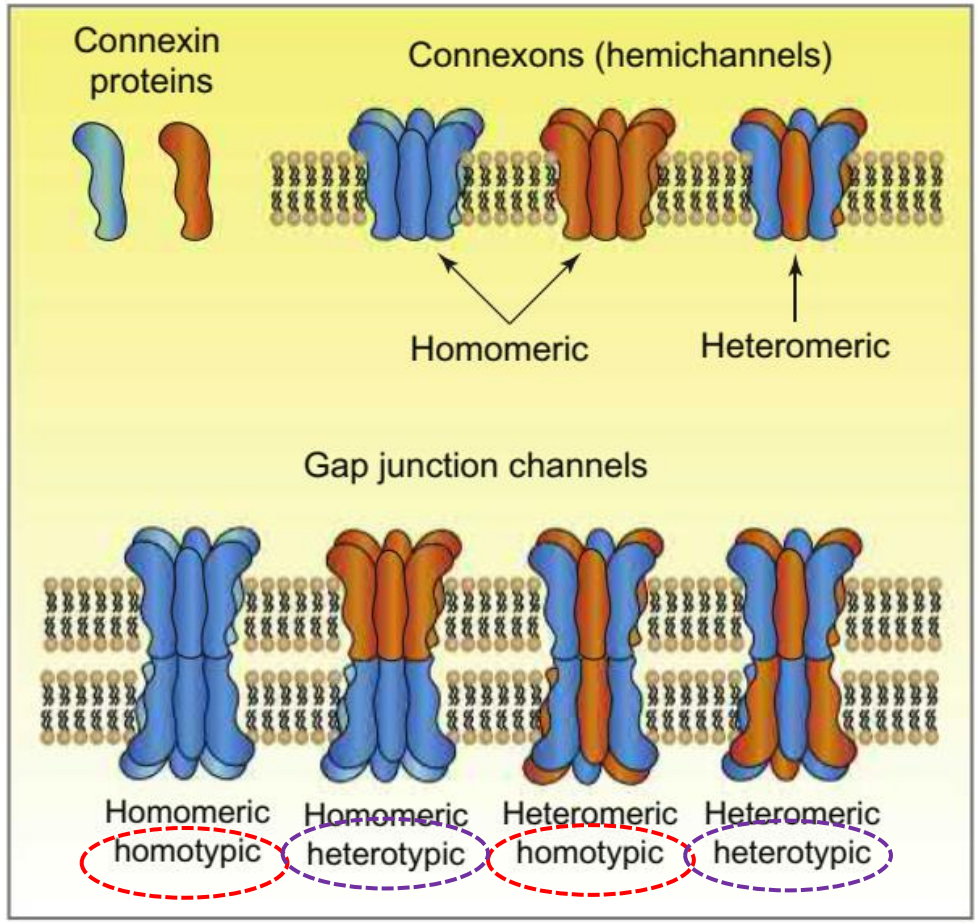
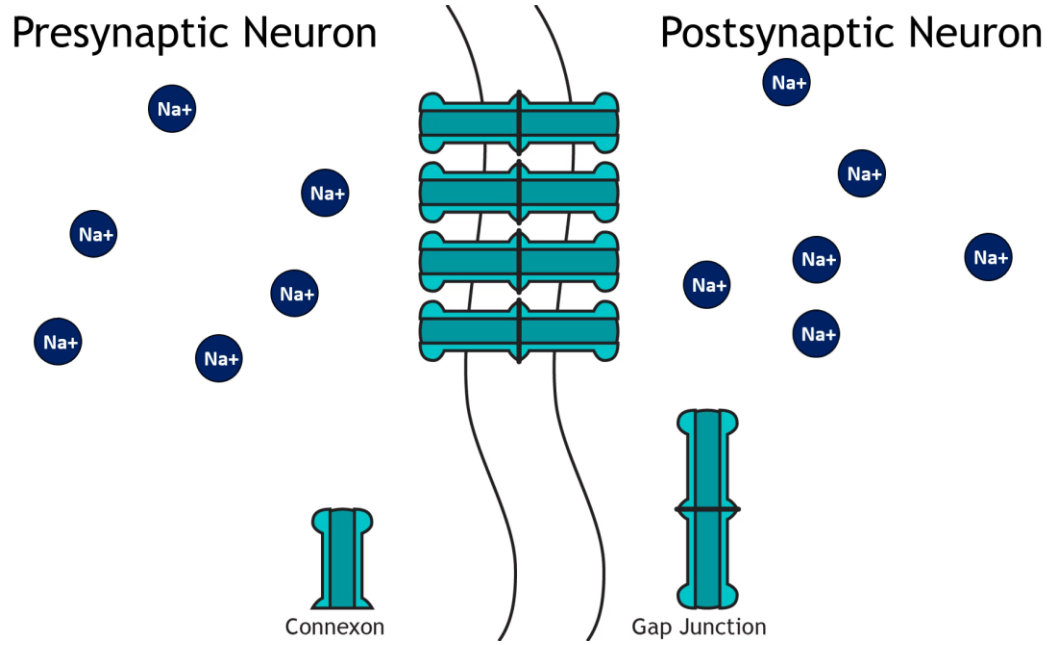
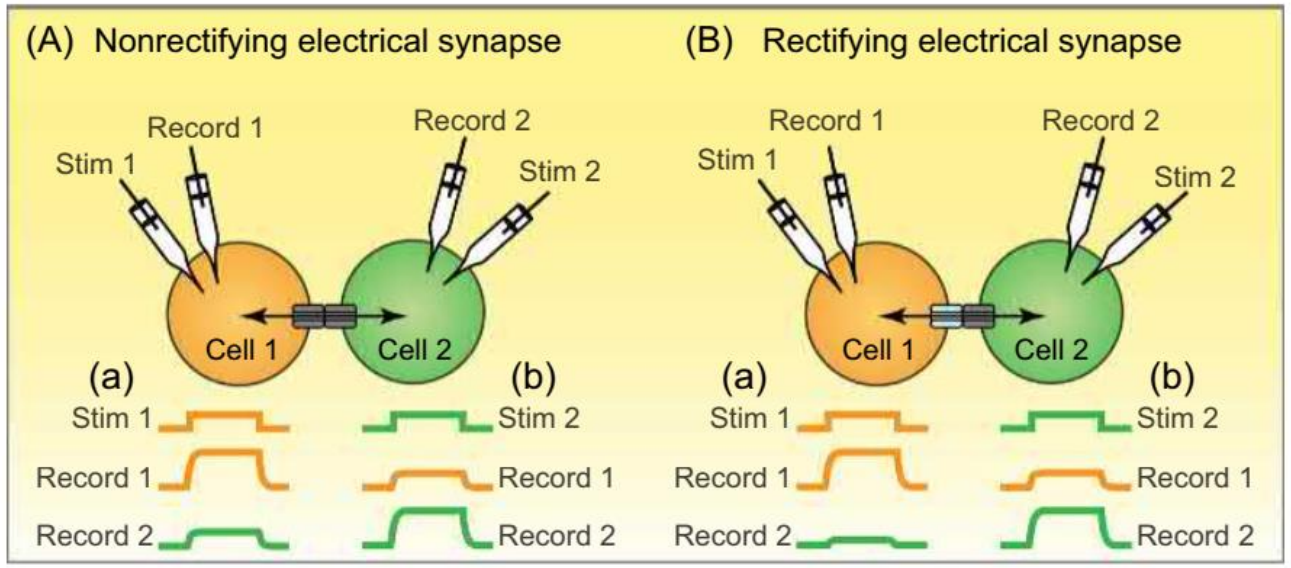


FIGURE 5.6 **The formation of connexon channels from connexin protein subunits.** Each cell assembles a connexon hemichannel from six individual connexin proteins (top). Connexons can be assembled using six proteins of the same subtype (homomeric), or a mix of different proteins (heteromeric). Then, two hemichannels come together (one from each cell that will be electrically coupled) to form the final gap junction channel (bottom). These gap junction channels can be mixed and matched with connexons from each cell to form a variety of gap junction channel types.

Meriney & Fanselow, (2019), p. 71





Meriney & Fanselow, (2019), p. 72

https://openbooks.lib.msu.edu/neuroscience/chapter/synapse-structure/

Electrical synapses are usually **bidirectional**

=> **nonrectifying**

These gap junction channels are **homotypic**

A minority of electrical synapses pass current preferentially in **one direction**

=> **rectifying**

These gap junction channels are **heterotypic**

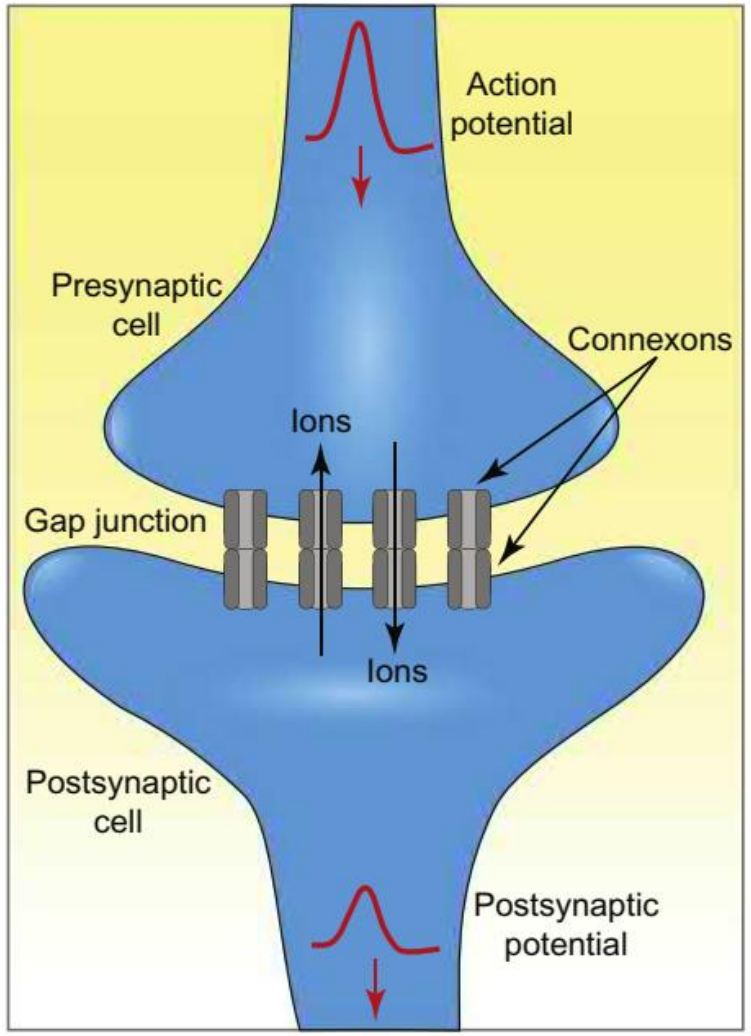


FIGURE 5.8 **The transfer of an electrical potential from a presynaptic cell to a postsynaptic cell through connexon channels.** An action potential in the presynaptic cell (*upper red trace*) results in a smaller depolarization in the postsynaptic cell (*lower red trace*). The ions that pass through gap junctions result in current flux that affects membrane potential.

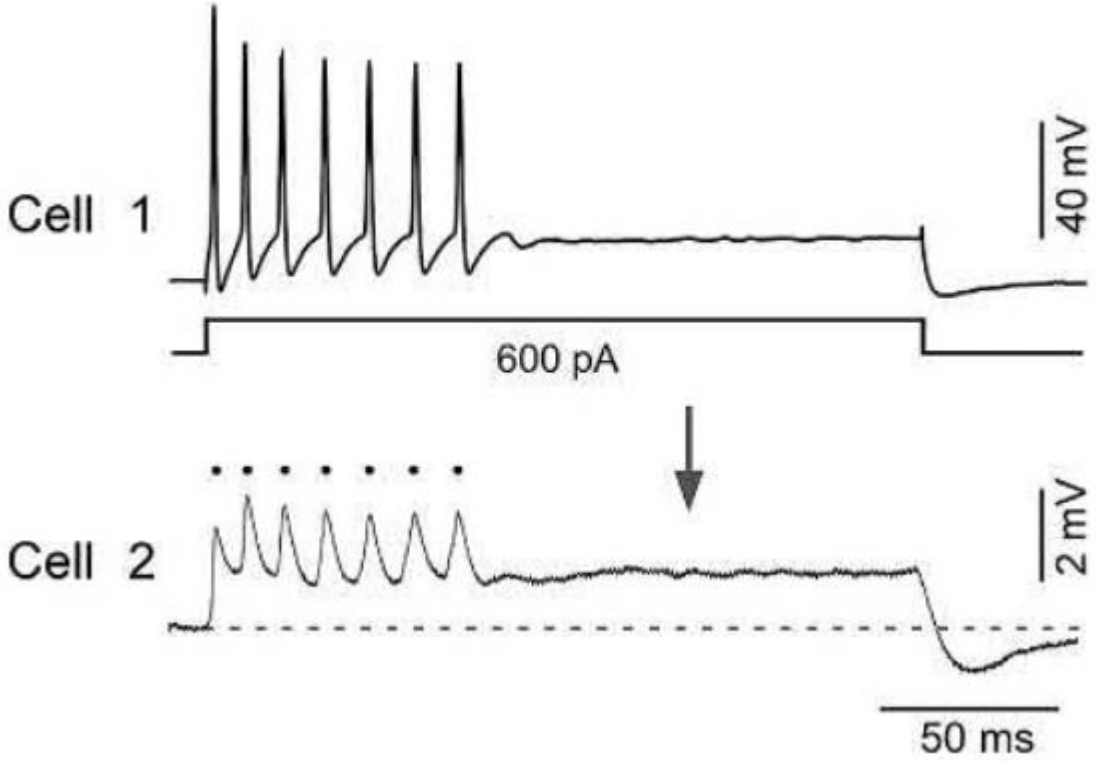


FIGURE 5.9 **Conduction of action potential signals in one cell through a gap junction to a second cell.** When a depolarizing current injection (600 pA square step) is given to cell 1 via an electrode, that cell fires action potentials (*top trace*). The depolarizations resulting from each of the action potentials in cell 1 cause small "spikelets" in cell 2 (indicated by the dot above each spikelet). These spikelets ride on top of a small, constant depolarization (*arrow*) that is also seen in cell 1 in response to the current injection. Note the difference in the voltage scale bar when comparing top and bottom traces. *Source: Adapted from Curti, S., Hoge, G., Nagy, J.I., Pereda, A.E., 2012. Synergy between electrical coupling and membrane properties promotes strong synchronization of neurons of the mesencephalic trigeminal nucleus. J. Neurosci. 32, 4341–4359 (Curti et al., 2012).*

Meriney & Fanselow, (2019), p. 74

1 pA (picoampere) = 10^{-12} amperes

***Volts** and **amperes** are **measures of electricity**. **A volt is the unit of electric potential difference**, or the size of the force that sends the electrons through a circuit. **An ampere is the unit used to measure electric current**. Current is a count of the number of electrons flowing through a circuit.*

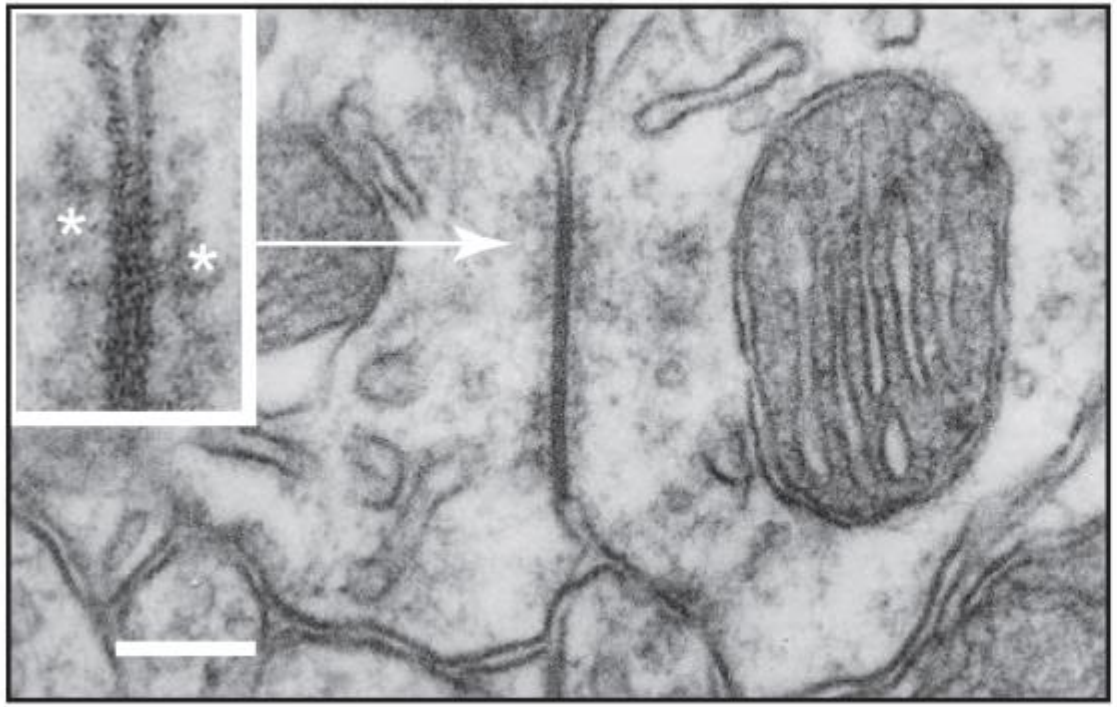


FIGURE 5.4 **Electron micrograph of a neuronal gap junction (*arrow*) between two dendrites in the mouse neocortex.** Gap junctions are characterized by a short distance between the plasma membranes of the two connected cells. Scale bar = 200 nm. Arrow points to the gap junction in the image that is enlarged in the inset. This enlargement more clearly reveals the presence of electron-dense material (*asterisks*) in the cytoplasm on each side of the gap junction. *Source: From Atlas of ultrastructural neurocytology. <http://synapseweb.clm.utexas.edu/atlas>; J. Spacek contributor. SynapseWeb, Kristen, M. Harris, P.I. <http://synapseweb.clm.utexas.edu/>.*

Meriney & Fanselow, (2019), p. 69

"[…] electron micrographs reveal **electron-dense material** inside both cells at the site of the electrical synapses, which is thought to represent a collection of **scaffolding and modulatory proteins associated with the gap junction, akin to the pre- and postsynaptic densities that are present at chemical synapses**."

Meriney & Fanselow, (2019), p. 69

Brief summary

Electrical synapses are **strongest** when they contain **many gap junction channels** and the **postsynaptic cell is smaller** than the presynaptic cell.

In most cases, a presynaptic action potential will only depolarize the postsynaptic cell slightly, causing a **subthreshold depolarization** (i.e., **spikelet**), rather than generating an action potential.

Electrical synapses are **mostly bidirectional** (i.e., **nonrectifying**) if the gap junction channel is **homotypic**. Some electrical synapses conduct current preferentially in one direction (i.e., **rectifying**) if the gap junction channel is **heterotypic**.

Electrical synapses are almost instantaneous (~ 0.1 ms).

They are **widespread in early stages of brain development**, before chemical synapses mature (more so than in the adult brain). They are common in invertebrate and nonmammalian nervous systems, but infrequent in mammals except **between neuroglial cells**.

Chemical synapses

First functional characterization

Singapore Med J. 2014 Jan; 55(1): 3–4.
doi: 10.11622/smedj.2014002

Otto Loewi (1873–1961): Dreamer and Nobel laureate

Alli N McCoy, MD.PhD[1] and Yong Siang Tan, MD, JD[2]

Ironically, Otto Loewi is better known for the way in which he came upon the idea that won him the Nobel Prize than for the discovery itself. Loewi's prize-winning experiment came to him in a dream. According to Loewi, "*The night before Easter Sunday of [1920] I awoke, turned on the light and jotted down a few notes on a tiny slip of thin paper. Then I fell asleep again. It occurred to me at 6.00 o'clock in the morning that during the night I had written down something important, but I was unable to decipher the scrawl. The next night, at 3.00 o'clock, the idea returned. It was the design of an experiment to determine whether or not the hypothesis of chemical transmission that I had uttered 17 years ago was correct. I got up immediately, went to the laboratory, and performed a simple experiment on a frog heart according to the nocturnal design.*"

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4291908/

The Nobel Prize in Physiology or Medicine 1936

Sir Henry Dale
Otto Loewi

Otto Loewi
Facts

Photo from the Nobel Foundation archive.

Otto Loewi
The Nobel Prize in Physiology or Medicine 1936

Born: 3 June 1873, Frankfurt-on-the-Main, Germany

Died: 25 December 1961, New York, NY, USA

Affiliation at the time of the award: Graz University, Graz, Austria

Prize motivation: "for their discoveries relating to chemical transmission of nerve impulses"

Prize share: 1/2

https://www.nobelprize.org/prizes/medicine/1936/loewi/facts/

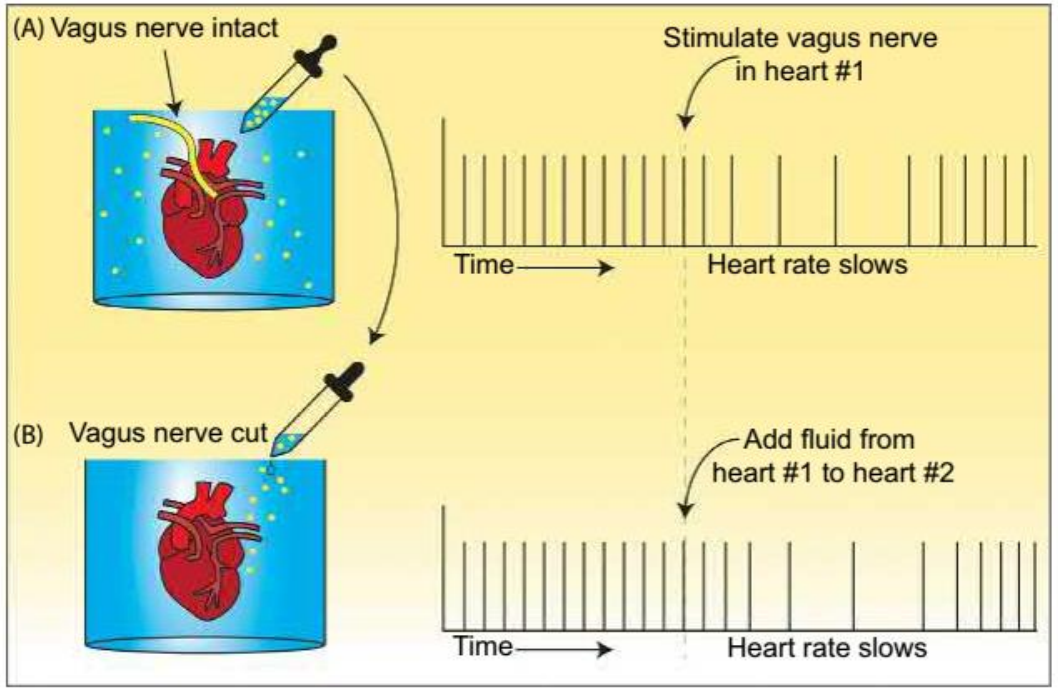


FIGURE 16.2 **Schematic diagram of Löwi's two-heart experiment.** Diagram of a dissected heart suspended in Ringer's solution, with the vagus nerve intact (A). The heart continues to beat, as indicated by the vertical lines on the graph to the right. When Löwi stimulated the vagus nerve, the heart rate slowed. Löwi then transferred some of the solution from the chamber containing the heart with the intact vagus nerve (A) to a chamber containing a second heart which had no vagus nerve (B). When he did so, the second heart also slowed, indicating that a diffusible substance from the solution around the first heart affected the rate of contraction of the second heart. This diffusible substance is acetylcholine.

Meriney & Fanselow, (2019), p. 348

**There's one vagus nerve on each side of the body, which runs from the lower part of the brain through the neck to the chest and stomach. It is part of the parasympathetic nervous system, and controls, among other functions, heart rate.*

*In his experiment, Loewi put **two frog hearts** in separate chambers. These were bathed in **Ringer's solution**, the composition of which is similar to the extracellular solution surrounding the frog heart in vivo, which kept the heart alive and able to beat. In one of these hearts, the vagus nerve remained **intact**, and in the second, it was **removed**. Loewi **stimulated** the vagus nerve on the first heart for several minutes, which, as expected, caused **the heart rate to slow**. When he transferred some of the Ringer's solution surrounding the first heart to the chamber containing the second heart, it too started to beat more slowly, **without having a functioning vagus** nerve at all. These results suggested that when the vagus nerve on the first heart was stimulated, a **chemical must have been released** into the solution surrounding the first heart that was responsible for slowing the heart rate. Loewi did not know the identity of the chemical that had been released by stimulation of the vagus nerve, so he referred to it as "**Vagusstoff**," German for "vagus substance." We now know that this chemical is the transmitter acetylcholine.*

Neurotransmitters

Over 100 types of **neurotransmitters** enabling diverse chemical signalling.

neuropeptides/peptide neurotransmitters

large molecules (3 to 36 amino acids)

e.g., oxytocin and vasopressin

(1) **synthesized in the cell body** and transported to the terminal => slower release

(2) a single neuron can synthesize and release **more than one** neuropeptide

small-molecule neurotransmitters

(a) acetylcholine

(b) monoamines

- histamine
- catecholamines (dopamine, norepinephrine, and epinephrine)
- indolamines (serotonin)

(c) soluble gases (nitric oxide)

(d) amino-acids (GABA, glycine, glutamate)

(1) **synthesized and stored in the terminal** => fast release

(2) a single neuron typically synthesizes and releases **only one** small-molecule neurotransmitter

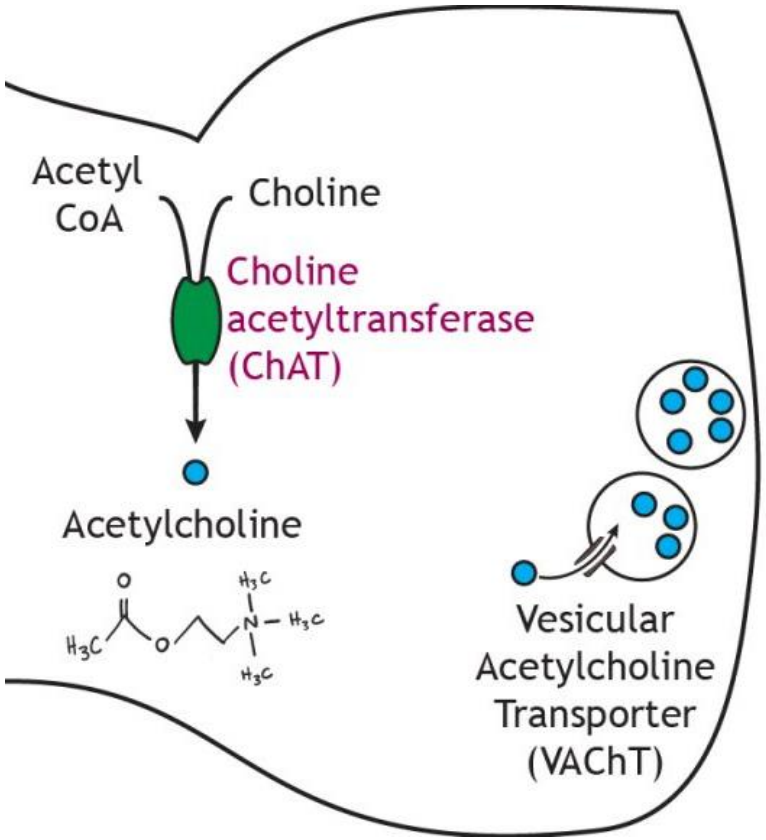
A molecule can be called a neurotransmitter if:

(1) it is **synthesized** within in the presynaptic neuron;

(2) it is **released** by the presynaptic neuron in response to stimulation;

(3) when applied experimentally, it must cause the **same effect** in the postsynaptic neuron as when it is released by a presynaptic neuron.

Acetylcholine (ACh)



A **small-molecule** transmitter.

Synthesized from **acetyl coenzyme A (acetyl CoA)** and **choline** via the enzyme **choline acetyltransferase**.

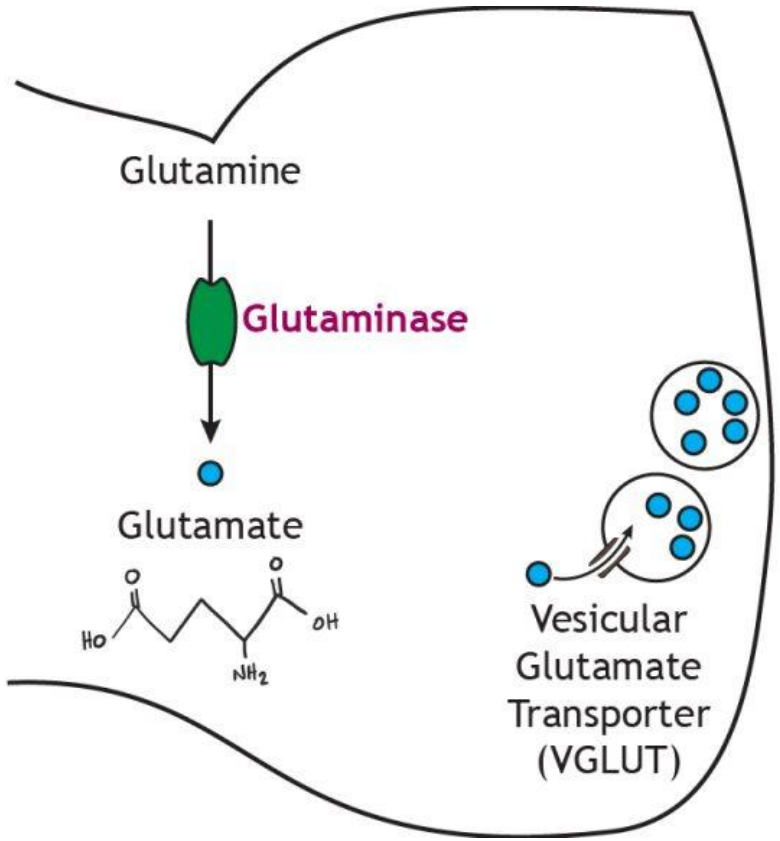
Acetylcholine is **packaged** into vesicles for storage in the terminal via the **vesicular acetylcholine transporter (VAChT).**

Best known for its role at the **neuromuscular junction**

(i.e, the synapse between a motor neuron and a muscle fiber).

https://openbooks.lib.msu.edu/neuroscience/chapter/neurotransmitter-synthesis-and-storage/

Glutamate (Glu)



An **amino-acid** transmitter.

The primary **excitatory** neurotransmitter in the brain.

Synthesized from g**lutamine** via the enzyme **glutaminase**.

Glutamate is **packaged** into vesicles for storage via the **vesicular glutamate transporter.**

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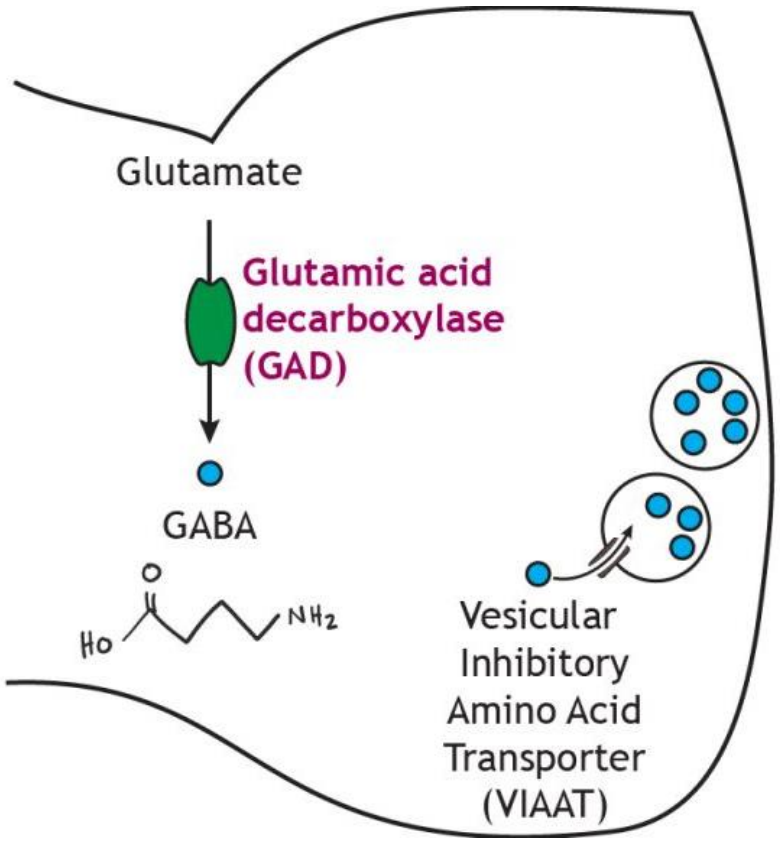
γ-Aminobutyric acid (GABA)



An **amino-acid** transmitter.

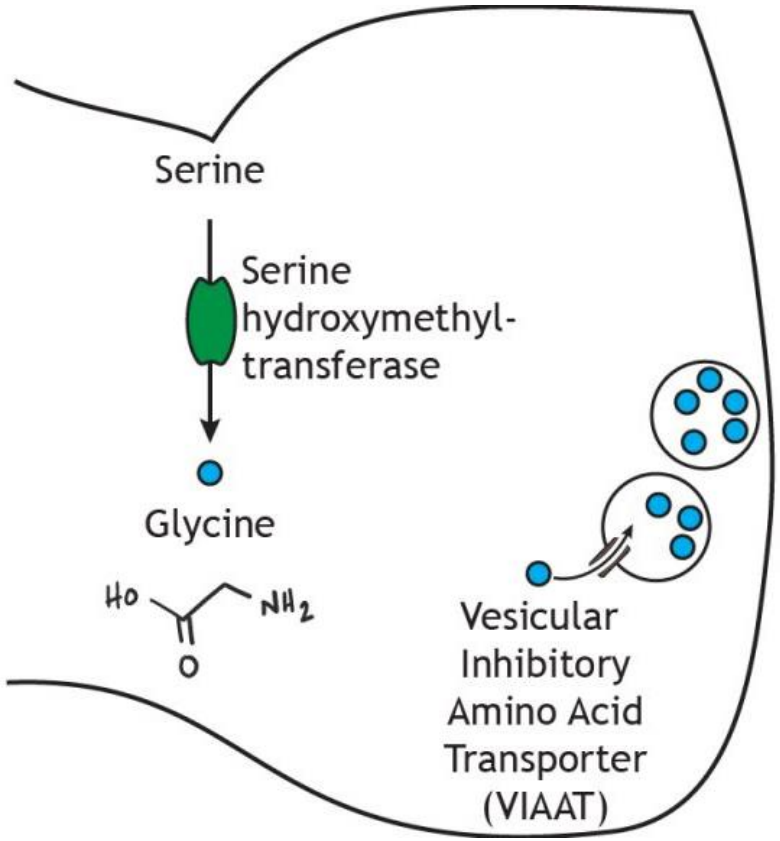
The primary **inhibitory** neurotransmitter in the brain.

Synthesized from **glutamate** via the enzyme **glutamic acid decarboxylase**.

GABA is **packaged** into vesicles for storage via the **vesicular inhibitory amino acid transporter.**

https://openbooks.lib.msu.edu/neuroscience/chapter/neurotransmitter-synthesis-and-storage/

Glycine (Gly)



An **amino-acid inhibitory** transmitter.

More common in the **spinal cord** than in the brain.

Synthesized from **serine** via the enzyme **serine hydroxymethyltransferase**.

Glycine is **packaged** into vesicles for storage via the **vesicular inhibitory amino acid transporter.**

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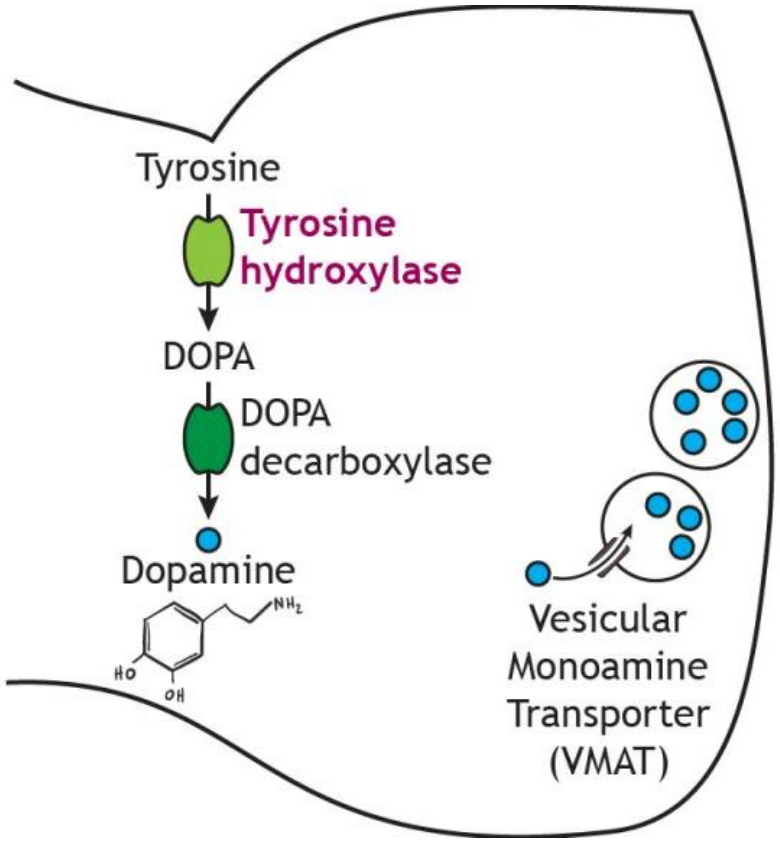
Dopamine (DA)



A **catecholamine** transmitter.

Best known for its roles in **reward** and **movement**.

Synthesized in a two-steps process: (1) **tyrosine** is converted into **DOPA** via **tyrosine hydroxylase**, and (2) DOPA is converted into **dopamine** via **DOPA decarboxylase**.

Dopamine is **packaged** into vesicles for storage via the **vesicular monoamine transporter.**

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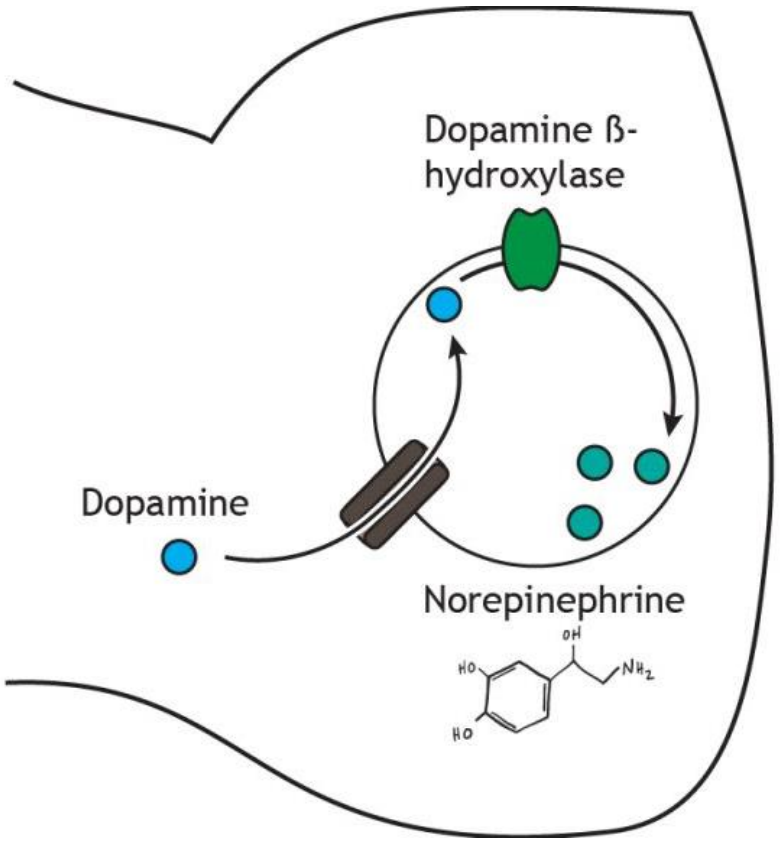
Norepinephrine/Noradrenaline (NE)



A **catecholamine** transmitter.

Important for the fight-or-flight response (increases **alertness, arousal,** and **attention**).

Synthesized from **dopamine**, after the dopamine has been packaged into vesicles, via a membrane-bound enzyme called **dopamine beta-hydroxylase**.

Therefore, unlike the other small molecule neurotransmitters, norepinephrine is synthesized **within the vesicles**, not in the cytoplasm => **no additional packaging** is necessary.

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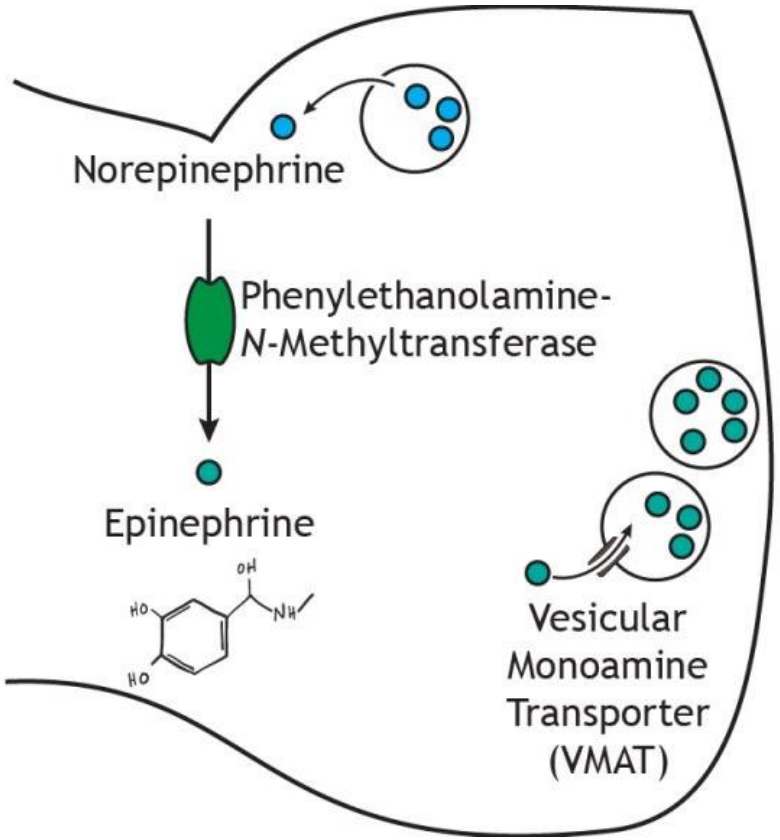
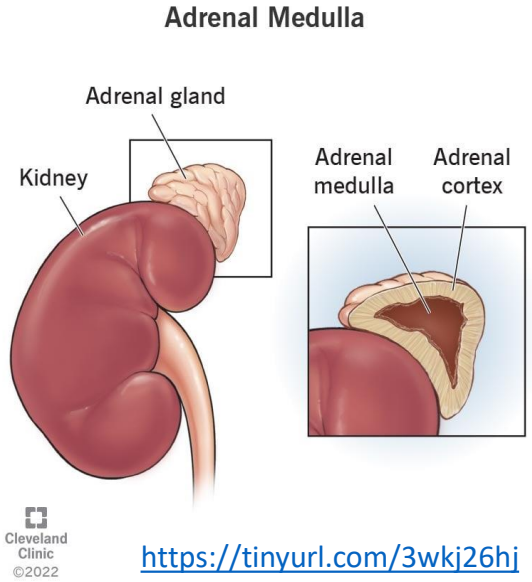
Epinephrine/Adrenaline (EPI)



A **catecholamine** transmitter (often considered a **hormone** rather than a neurotransmitter).

Primarily released by the **adrenal medulla** (i.e., the inner part of an adrenal gland).

It is used as a neurotransmitter in only a **small number** of neurons.



https://tinyurl.com/3wkj26hj

Important for the fight-or-flight response (increased vascular smooth muscle contraction, pupillary dilator muscle contraction, and intestinal sphincter muscle contraction).

Synthesized from **norepinephrine** via enzyme **phenylethanolamine-N-methyltransferase** (i.e., requires norepinephrine to exit the vesicles where it was synthesized).

Epinephrine is **packaged** into vesicles for storage via the **vesicular monoamine transporter.**

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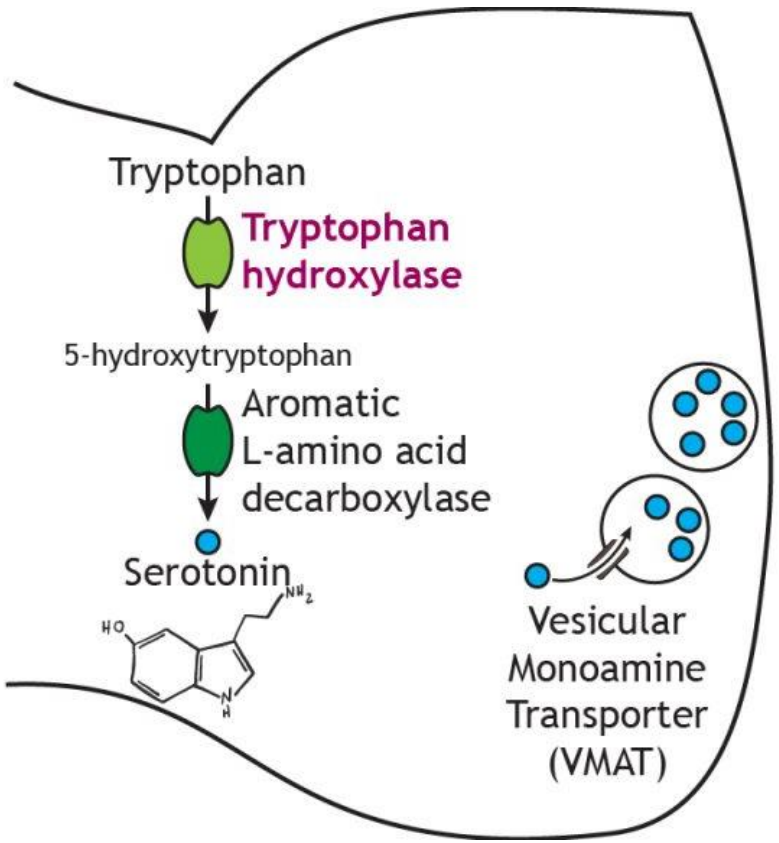
Serotonin/5-hydroxytryptamine (5-HT)



An **indolamine** transmitter.

Best known for its role in mood regulation.

Synthesized in a two-steps process: (1) **tryptophan** is converted into **5-hydroxytryptophan** by **tryptophan hydroxylase**, and (2) **5-hydroxytryptophan** is converted into serotonin by **aromatic L-amino acid decarboxylase**.

Serotonin is **packaged** into vesicles for storage via the **vesicular monoamine transporter.**

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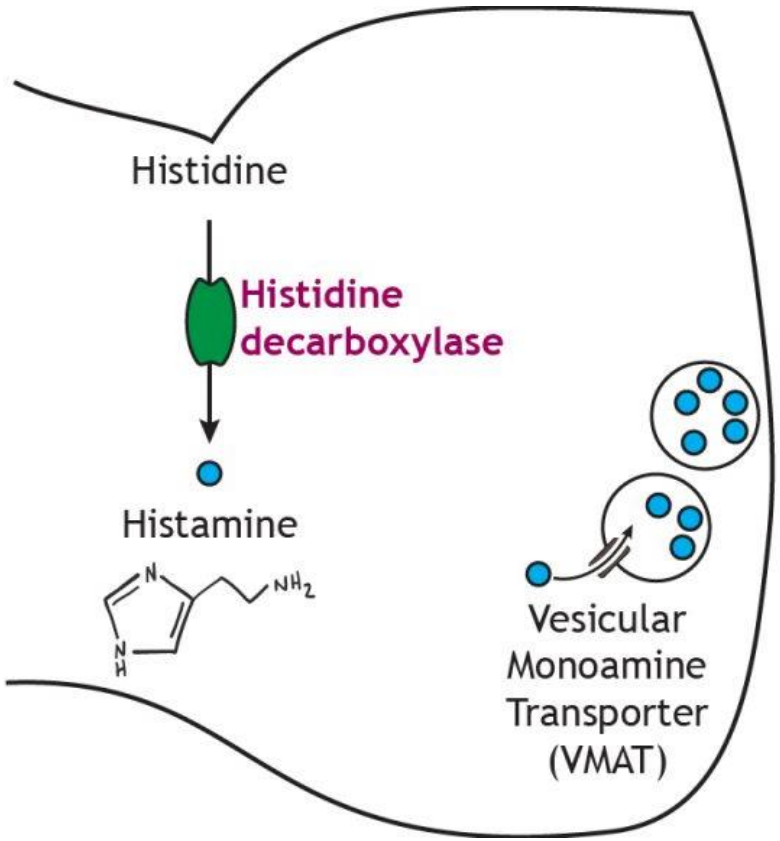
Histamine



A **monoamine** transmitter (neither catecholamine, nor indolamine).

In the CNS, it is a **wake-promoting and rapid eye movement (REM) sleep–suppressing** neurotransmitter. Can also act as a **neuromodulator**.

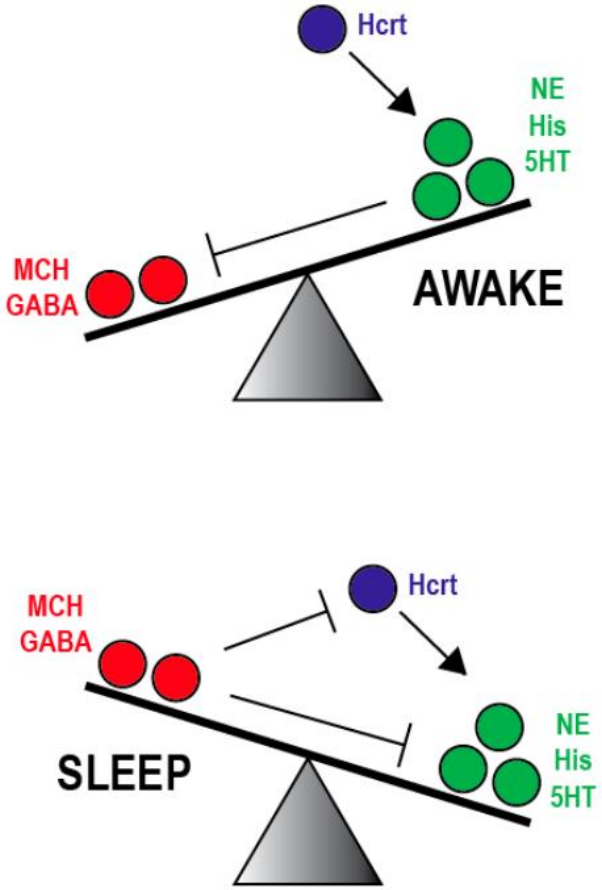
Synthesized from **histidine** via **histidine decarboxylase**.

Histamine is **packaged** into vesicles for storage via the **vesicular monoamine transporter.**

https://openbooks.lib.msu.edu/neuroscience/chapter/neurotransmitter-synthesis-and-storage/

Neuromodulators

The alphabet soup of some commonly studied neuromodulators. *5HT, serotonin; ACh, acetylcholine; CST, cortistatin; DA, dopamine; Hcrt, hypocretin; His, histamine; MCH, melanin-concentrating hormone; NE, norepinephrine; NPS, neuropeptide S.*



The role of neuromodulators in sleep/wake transitions. *The balance between wakefulness and sleep is thought to depend upon a balance of activity in different neuromodulatory systems. NE, His, 5HT, and other systems tend to be active during wakefulness, with Hcrt exerting an excitatory tone on these systems. Other systems, such as the MCH system and populations of GABAergic nuclei are more active during sleep. The precise contribution of individual neuronal populations to sleep/wake states is relatively unknown.*

All CNS neurons that produce neuromodulators also release traditional neurotransmitters.

The small molecule **ACh** functions as a neurotransmitter in the PNS and as a neuromodulator in the CNS.

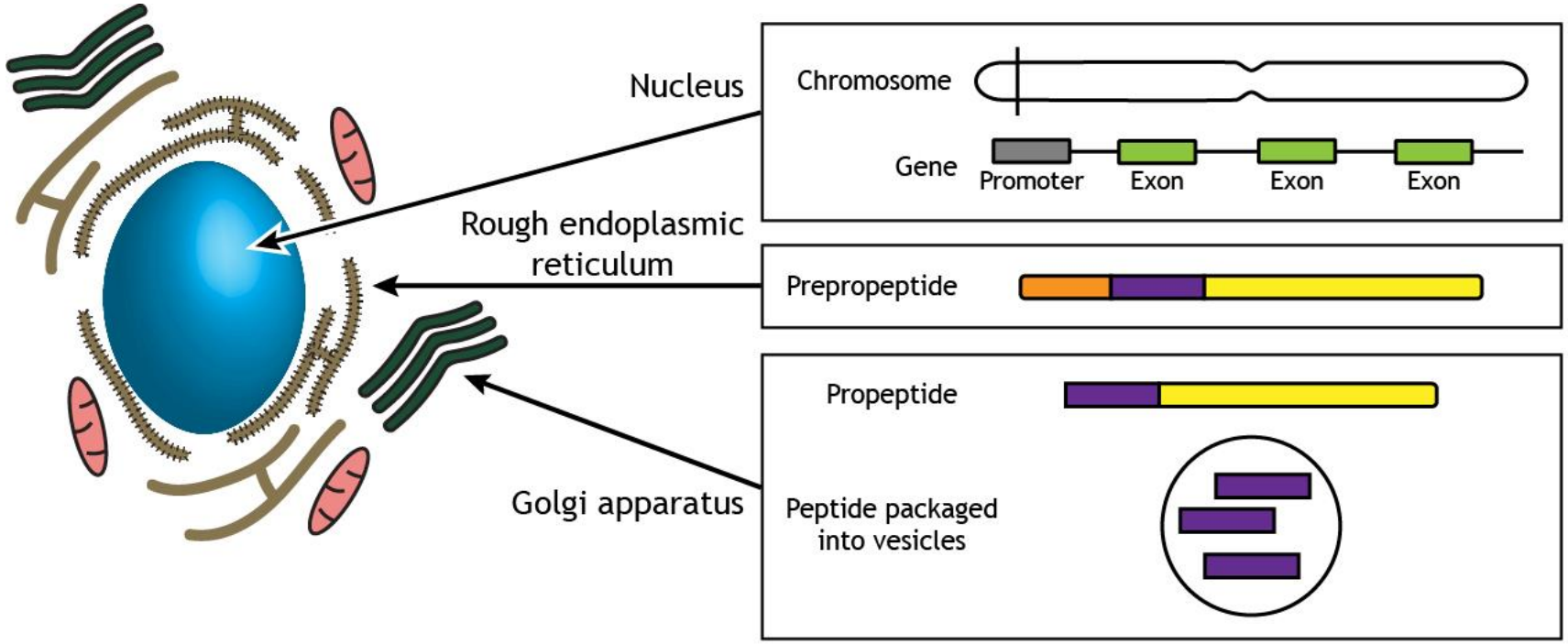
the Decea Lab: https://tinyurl.com/yrt96ham

neuromodulators

project diffusely throughout the nervous system, and modulate the response of postsynaptic neurons to traditional neurotransmitters

5HT serotonin
ACh acetylcholine
CST cortistatin
DA dopamine
Hcrt hypocretin
His histamine
MCH melanin-concentrating hormone
NE norepinephrine
NPS neuropeptide S
GABA gamma aminobutyric acid

Neuropeptide synthesis



Neuropeptides are **synthesized** from **mRNA** into **peptide chains** made from **amino-acids**. In most cases, a larger **precursor molecule** called the **prepropeptide** is translated into the original amino acid sequence in the rough endoplasmic reticulum. The prepropeptide is processed further to the **propeptide** stage. The remaining processing and **packaging** of the final **neuropeptide** into a **vesicle** occurs in the Golgi apparatus. The peptides are packaged into vesicles that are significantly larger that the vesicles that store the small molecule transmitters. These large vesicles must then move from the soma to the terminal.

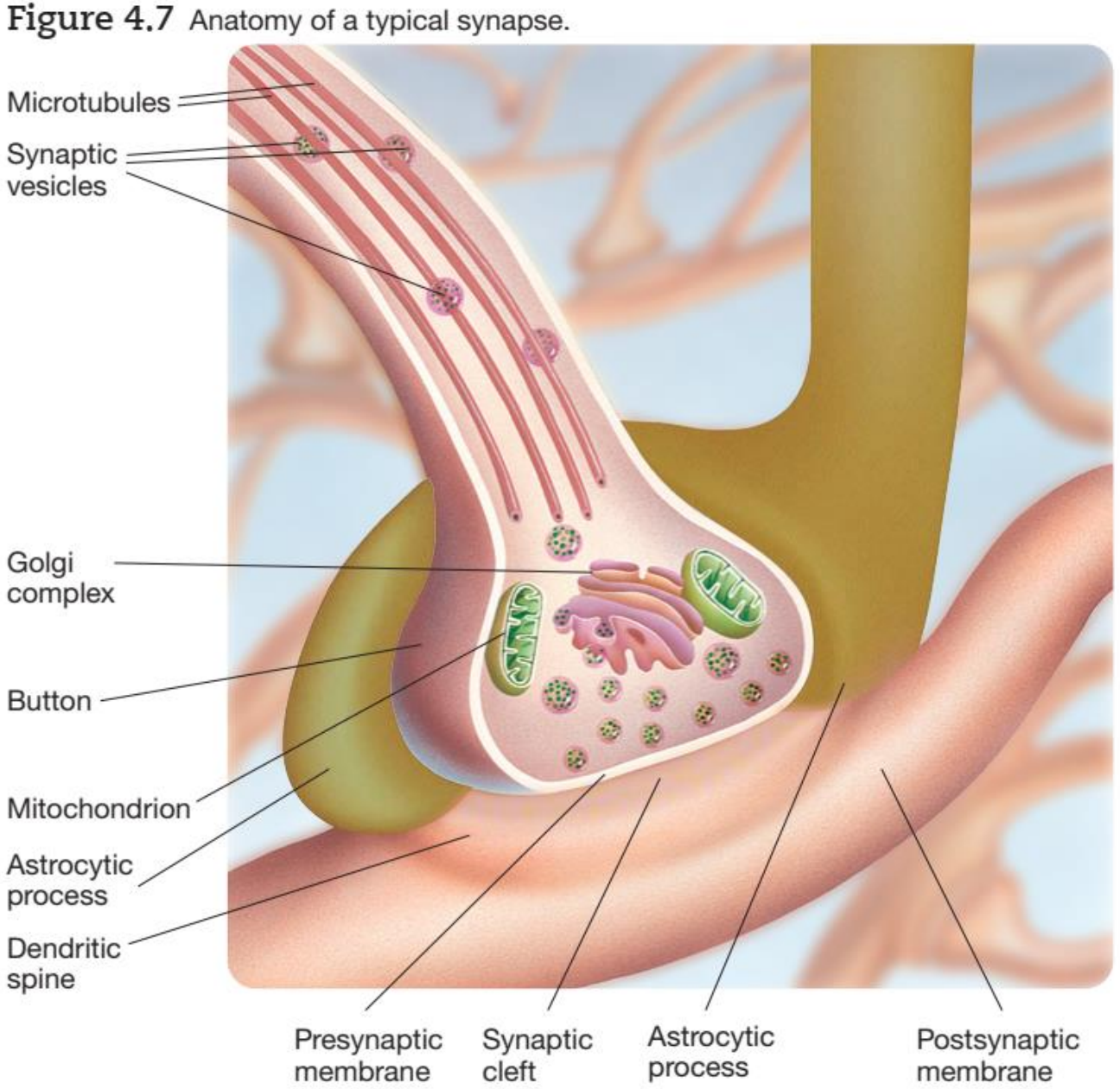
https://openbooks.lib.msu.edu/neuroscience/chapter/neurotransmitter-synthesis-and-storage/

Anatomy of a chemical synapse

Small-molecule neurotransmitters are typically synthesized in the cytoplasm of the **terminal button** and packaged in synaptic vesicles by the **button's Golgi complex**. These vesicles are stored in clusters next to the presynaptic membrane.

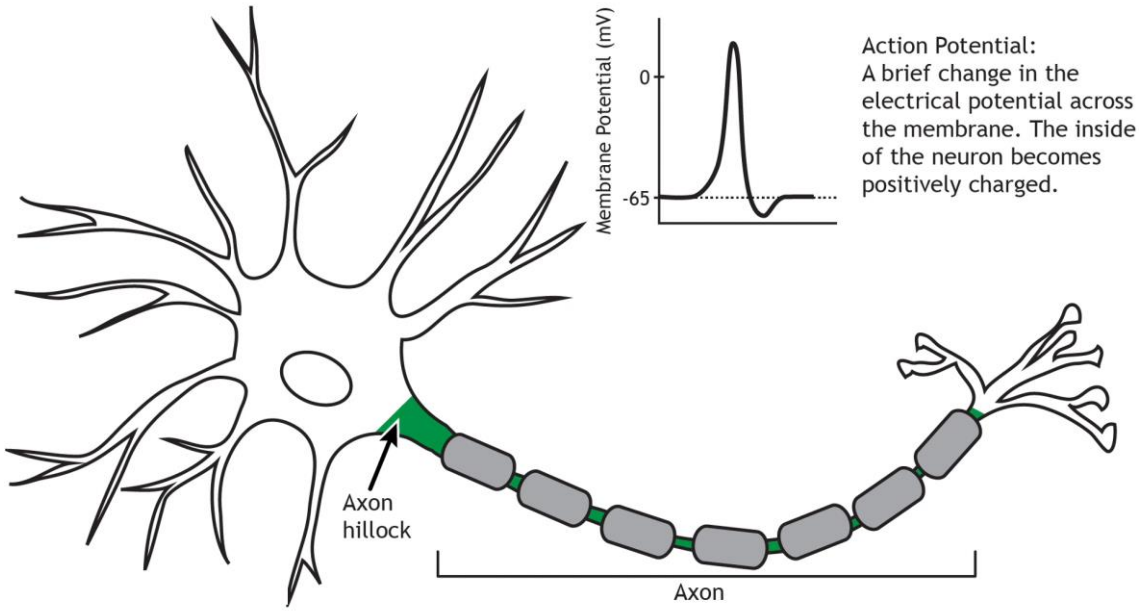
Neuropeptides, like other proteins, are assembled in the cytoplasm of the cell body on **ribosomes**; they are then packaged in vesicles by the **cell body's Golgi complex** and transported by **microtubules** to the terminal buttons.

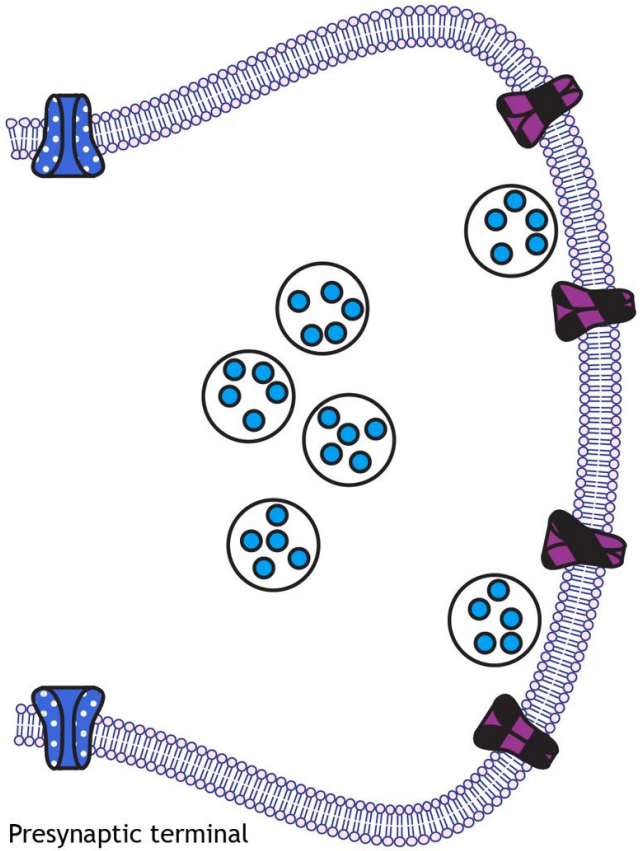
These vesicles are larger than those containing small-molecule neurotransmitters, and they do not usually cluster around the presynaptic membrane.



Pinel & Barnes, (2021), p. 109

Steps of a chemical synaptic transmission



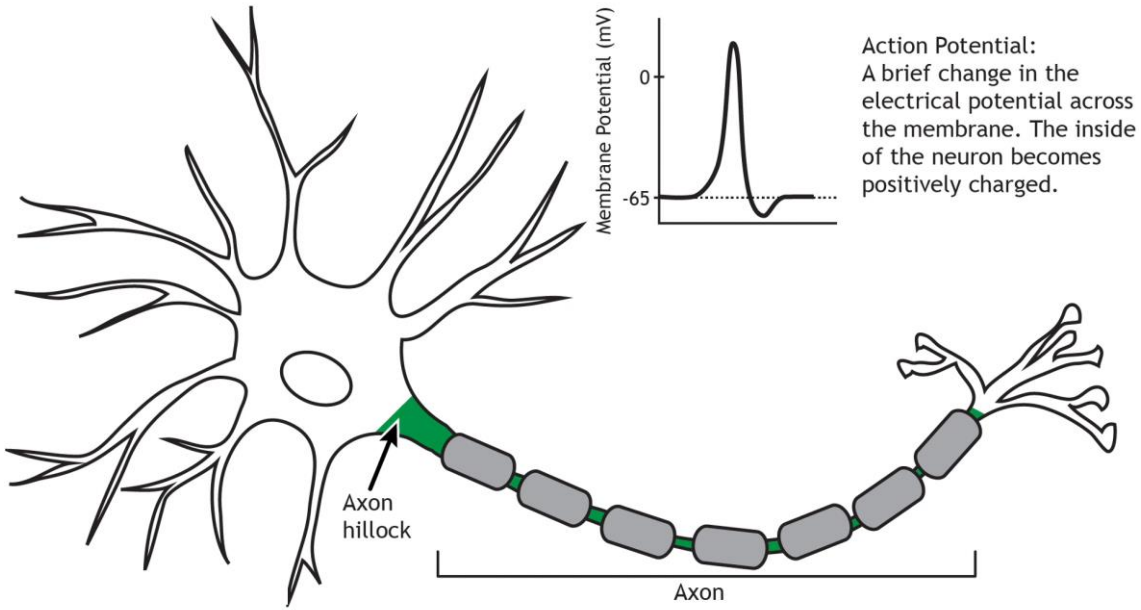


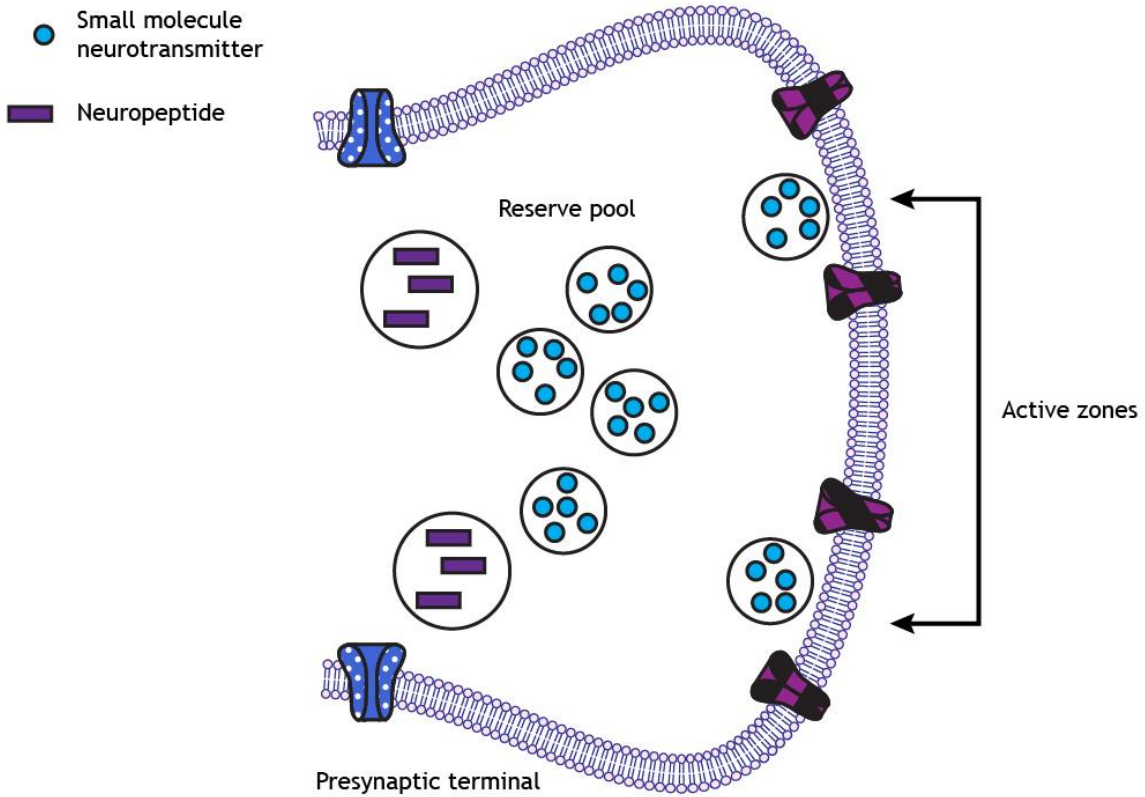
(1) The action potential **depolarizes** the neuronal membrane and travels towards the **synaptic terminal**.

(2) An influx of Na^+ ions depolarized the terminal => voltage-gated Ca^+ channels open => influx of calcium.

https://openbooks.lib.msu.edu/neuroscience/chapter/neurotransmitter-release/

Steps of a chemical synaptic transmission



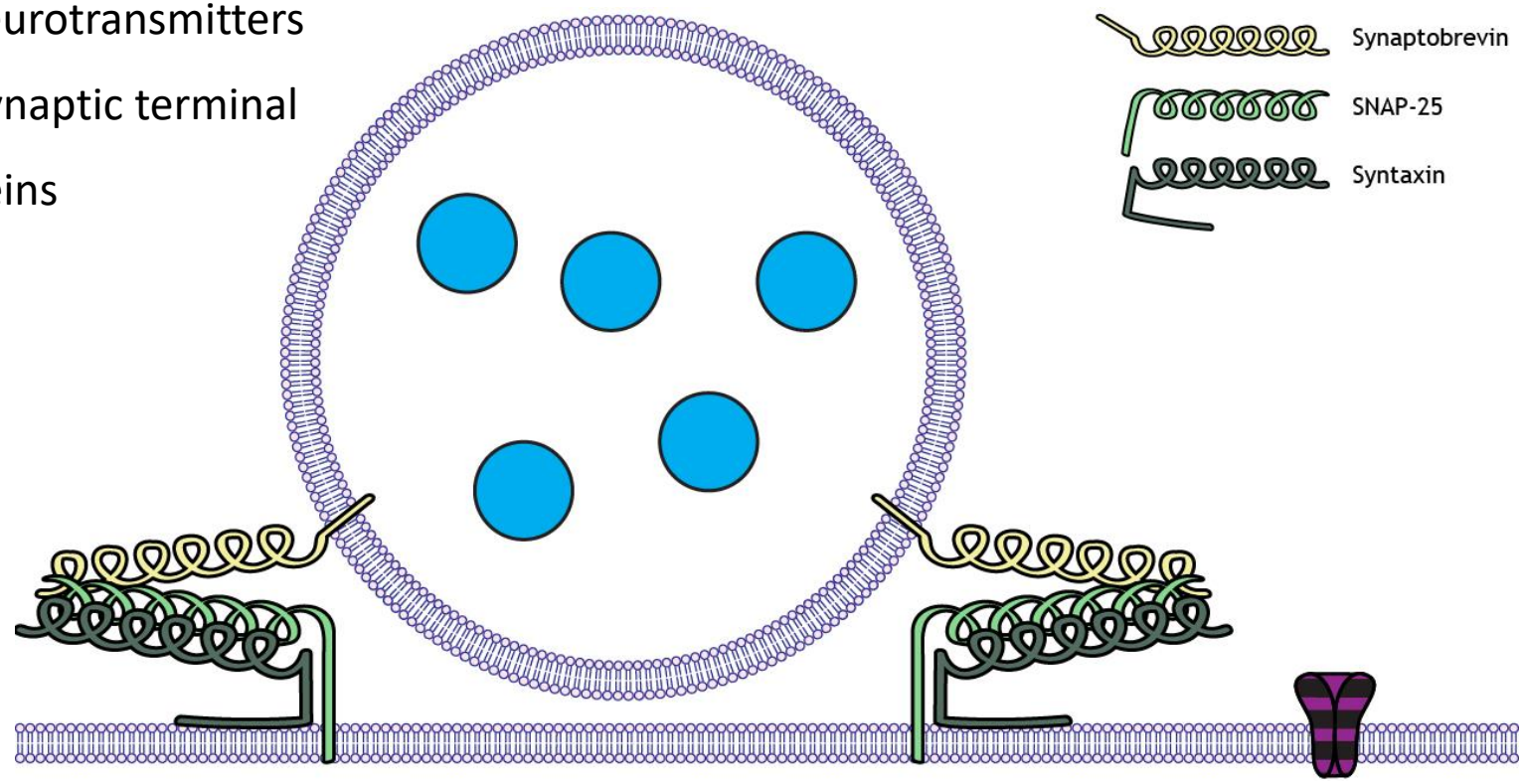


(1) The action potential **depolarizes** the neuronal membrane and travels towards the **synaptic terminal**.

https://openbooks.lib.msu.edu/neuroscience/chapter/neurotransmitter-release/

(2) An influx of Na^+ ions **depolarizes** the terminal => voltage-gated **Ca^+ channels open** => influx of calcium. Ca^+ channels are concentrated around the **active zone**, where small-molecule neurotransmitters are released.

(3) The vesicles containing small-molecule neurotransmitters are **docked** at the active zone, onto the presynaptic terminal membrane via three membrane-bound proteins called **SNARE proteins**.



Synaptobrevin (a **v**-SNARE)
located on the **V**esicular membrane

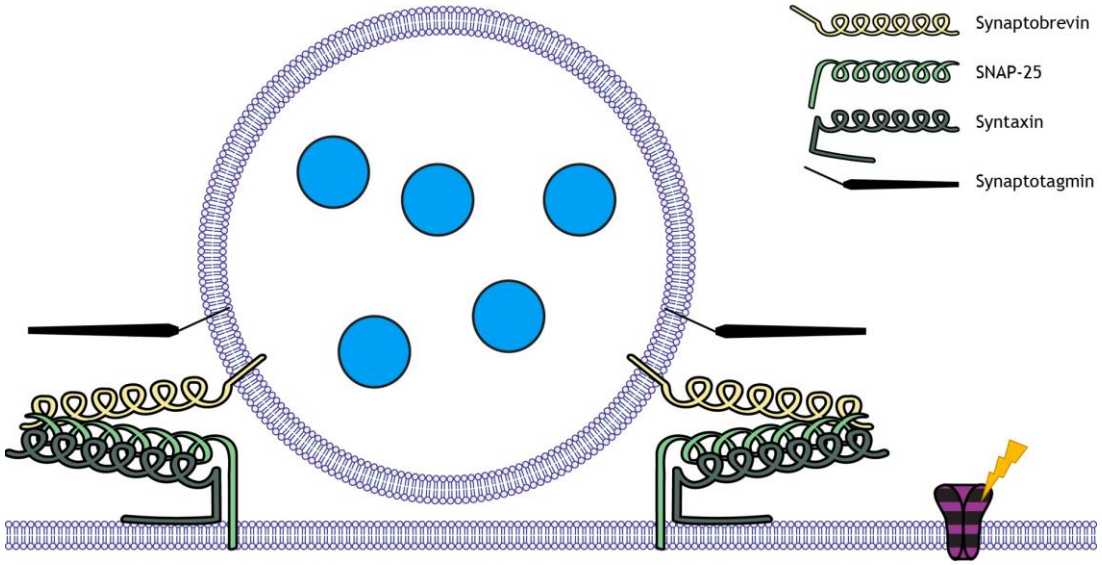
Syntaxin and **SNAP-25** (**t**-SNARES)
located on the **t**erminal membrane
(i.e., the **T**arget membrane)

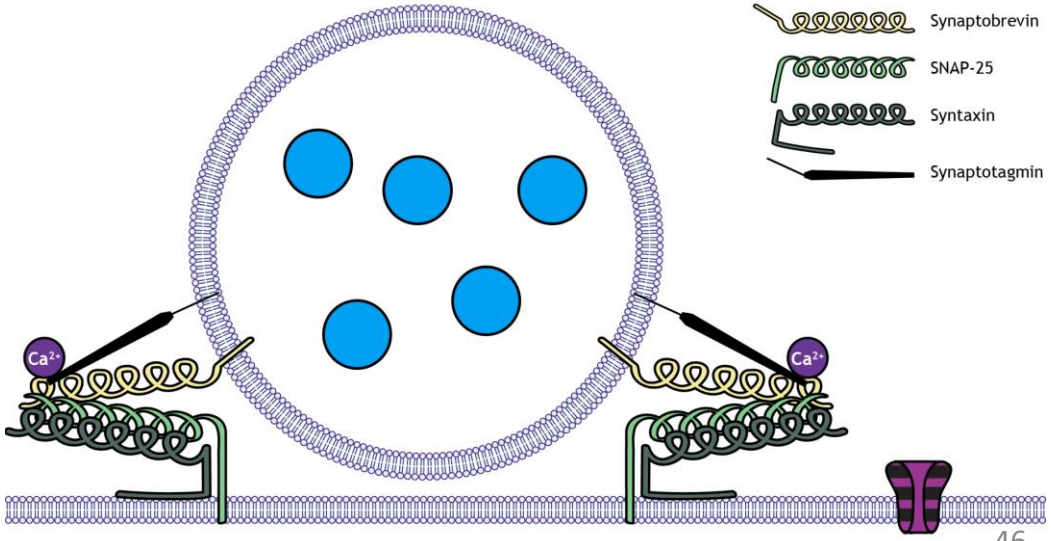
https://openbooks.lib.msu.edu/neuroscience/chapter/neurotransmitter-release/

(4) **Exocytosis** (release of neurotransmitter into the **synaptic cleft**) => two steps:

(a) **Synaptotagmin** is another vesicle-bound protein which is **sensitive to calcium** => when calcium is present at the active zone, it **interacts with the SNARE proteins** => the first step toward **exocytosis** of the synaptic vesicle.

(b) The synaptic vesicle membrane **fuses** with the presynaptic terminal membrane, **exocytosis** occurs, and the neurotransmitters **released**.



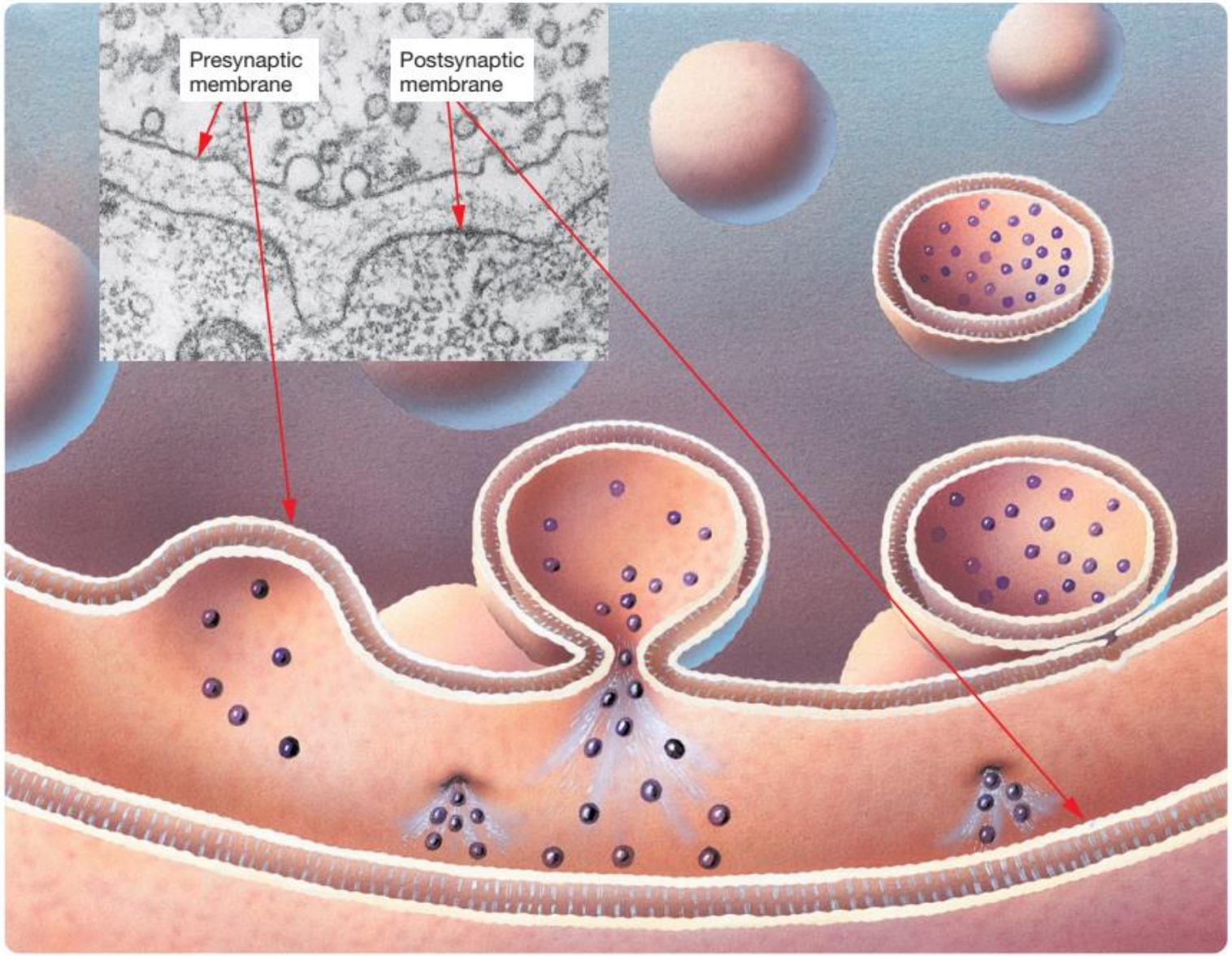


https://openbooks.lib.msu.edu/neuroscience/chapter/neurotransmitter-release/

(5) After exocytosis of the transmitter molecules, the neurotransmitters released into the synaptic cleft bind to the **receptors** located on the postsynaptic membrane.

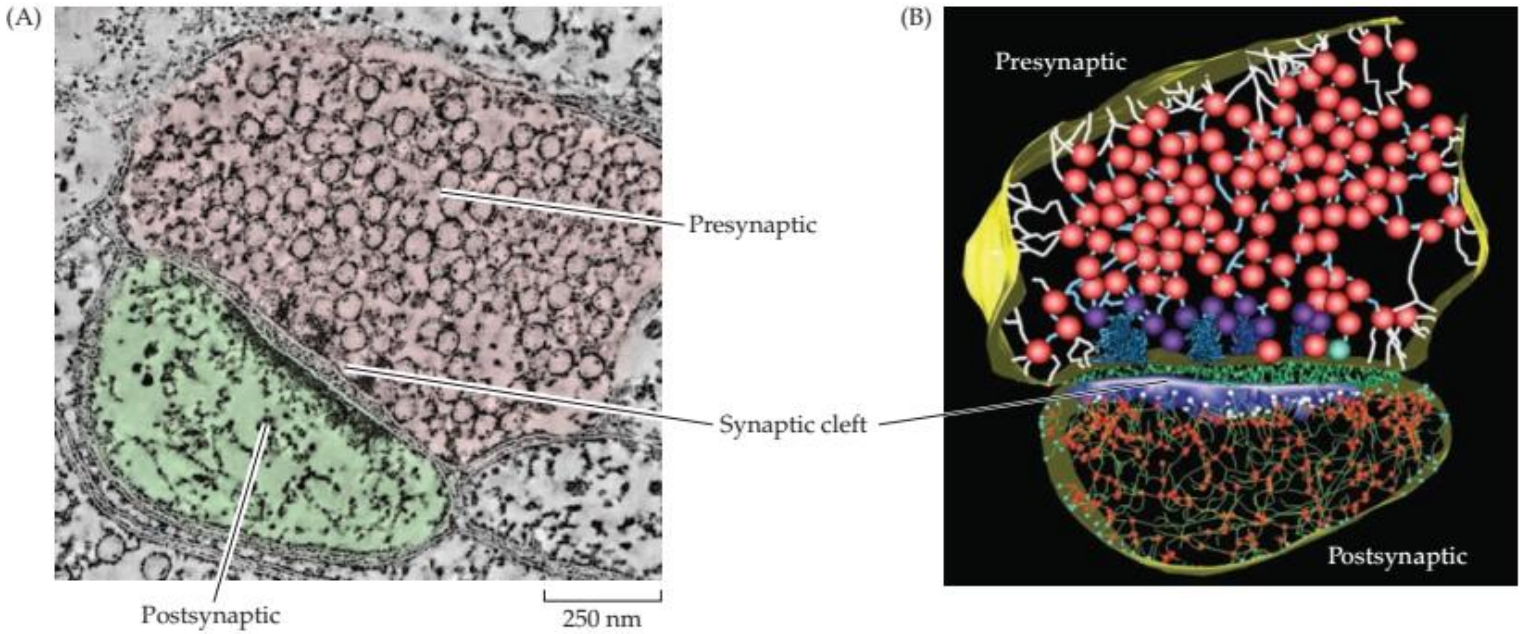
Receptors fall into two main categories: **ligand-gated channels** (also **ionotropic-** or **neurotransmitter-gated**), and **G-protein coupled receptors** (also **metabotropic receptors**), which are *guanosine-triphosphate–sensitive proteins*.

Figure 4.10 Schematic illustration of exocytosis.



Don W. Fawcett/Science Source

Pinel & Barnes, (2021), p. 110



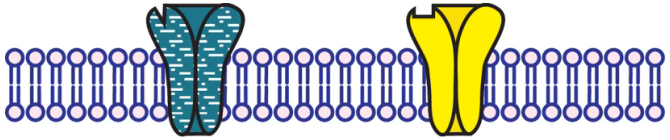
Purves et al., (2018), p. 90

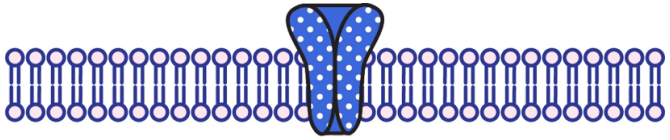
◀ **FIGURE 5.4 Structure and function of chemical synapses.** (A) Structure of a chemical synapse in the cerebral cortex. A presynaptic terminal (pink) forms a synapse with a postsynaptic dendrite (green). (B) Three-dimensional reconstruction of the synapse shown in (A). Inside the presynaptic terminal, spheres indicate synaptic vesicles at various stages of their trafficking cycle, linear elements indicate intracellular filaments, and dark blue indicates dense projections associated with the active zone. Inside the postsynaptic neuron, the blue structure is the postsynaptic density, green structures represent filaments, red spheres indicate points where the filaments branch. Green material within the synaptic cleft indicates structures of unknown function. (C) Sequence of events involved in transmission at a typical chemical synapse. (A,B from Burette et al., 2012.)

Ligand-gated channels

Primarily located along the dendrites or cell body.

Ligand-gated channels require a specific molecule, such as a neurotransmitter, to **bind** to the receptor to cause the channel to open and allow ion flow.





Neurotransmitters and receptors fit together like a **lock and key**; only certain neurotransmitters are able to bind to and open certain receptors.

Glutamate

Ligand-gated channels

GABA

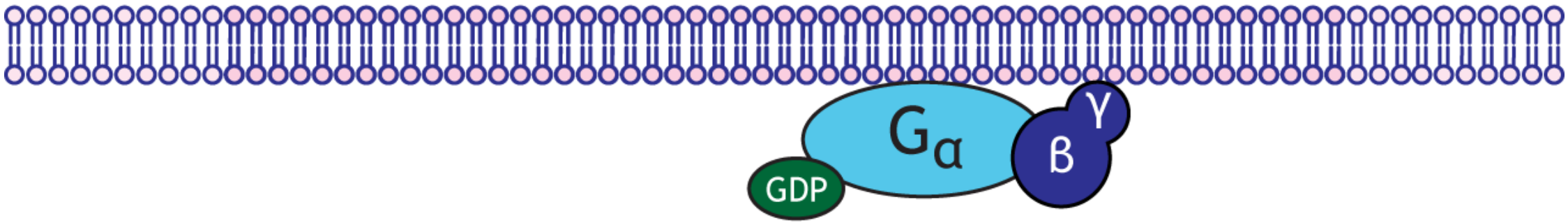
Voltage-gated channels

https://openbooks.lib.msu.edu/neuroscience/chapter/neurotransmitter-action-ionotropic-receptors/

G-protein coupled receptors (GPCR)

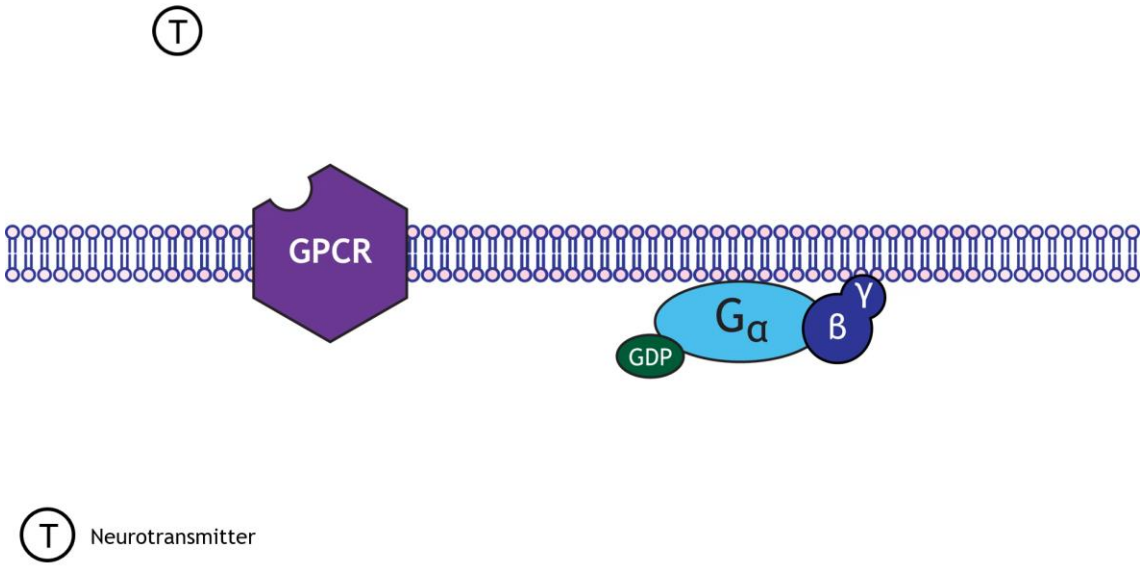
Can be present anywhere along the neuron if there is a synapse (not just along the dendrites or cell body).

They are more **prevalent** than ionotropic receptors, and their effects are **slower** to develop, **longer-lasting**, more **diffuse**, and more **varied**.



G-proteins are enzymes with **three subunits**: **alpha**, **beta**, and **gamma**. In the **resting state** of the G-protein complex, the **alpha subunit is bound to a GDP** (i.e., *guanosine diphosphate*) molecule. There are **multiple types of alpha subunits**, and each initiate **different cellular cascades** in the neuron.

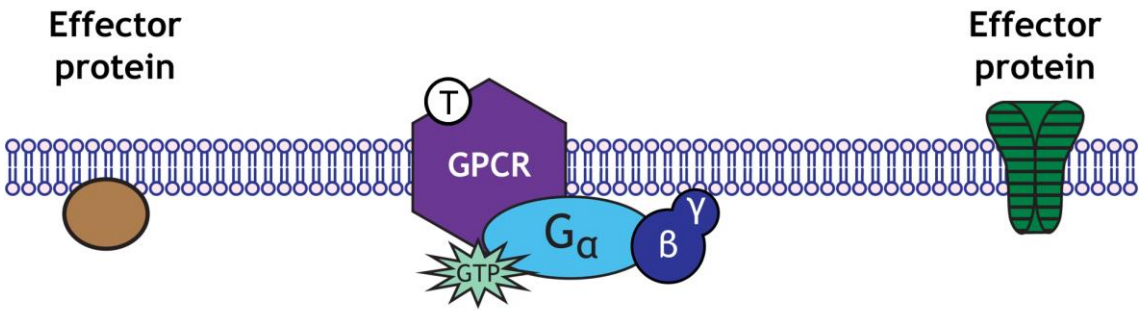
https://openbooks.lib.msu.edu/neuroscience/chapter/neurotransmitter-action-g-protein-coupled-receptors/



Neurotransmitter **binds** to a GPCR => the receptor **interacts** with an inactivated G-protein complex.

The complex that binds is **specific** to the receptor; **different** metabotropic receptors for the same neurotransmitter can have **different** effects in the cell due to which G-protein binds.

Once coupled to the receptor, the GDP molecule is **exchanged** for a GTP molecule, and the G-protein becomes **activated**.



After activation, the G-protein complex will **separate** into the **alpha-GTP subunit** and the **beta-gamma subunit**. Both components can alter the function of **effector proteins** in the cell. Effector protein functions can range from **altering ion permeability** across the membrane by opening ion channels to initiating **second messenger cascades**. Second messenger cascades can have long-term, widespread, and diverse cellular effects including activation of cellular enzymes or altering gene transcription.

Brief clarification of **second messenger cascades**

Neurotransmitters are considered to be the **first messengers**.

A second messenger diffuses through the cytoplasm and may influence the activities of the neuron in a variety of ways, e.g., it may enter the nucleus and bind to the DNA, thereby influencing **genetic expression**.
Thus, a neurotransmitter's binding to a metabotropic receptor can have **radical, long-lasting effects**.

Furthermore, there is now evidence that **ionotropic** receptors **can** also produce second messengers that can have enduring effects (see Pinel & Barnes, 2021, p. 111, and the references therein).

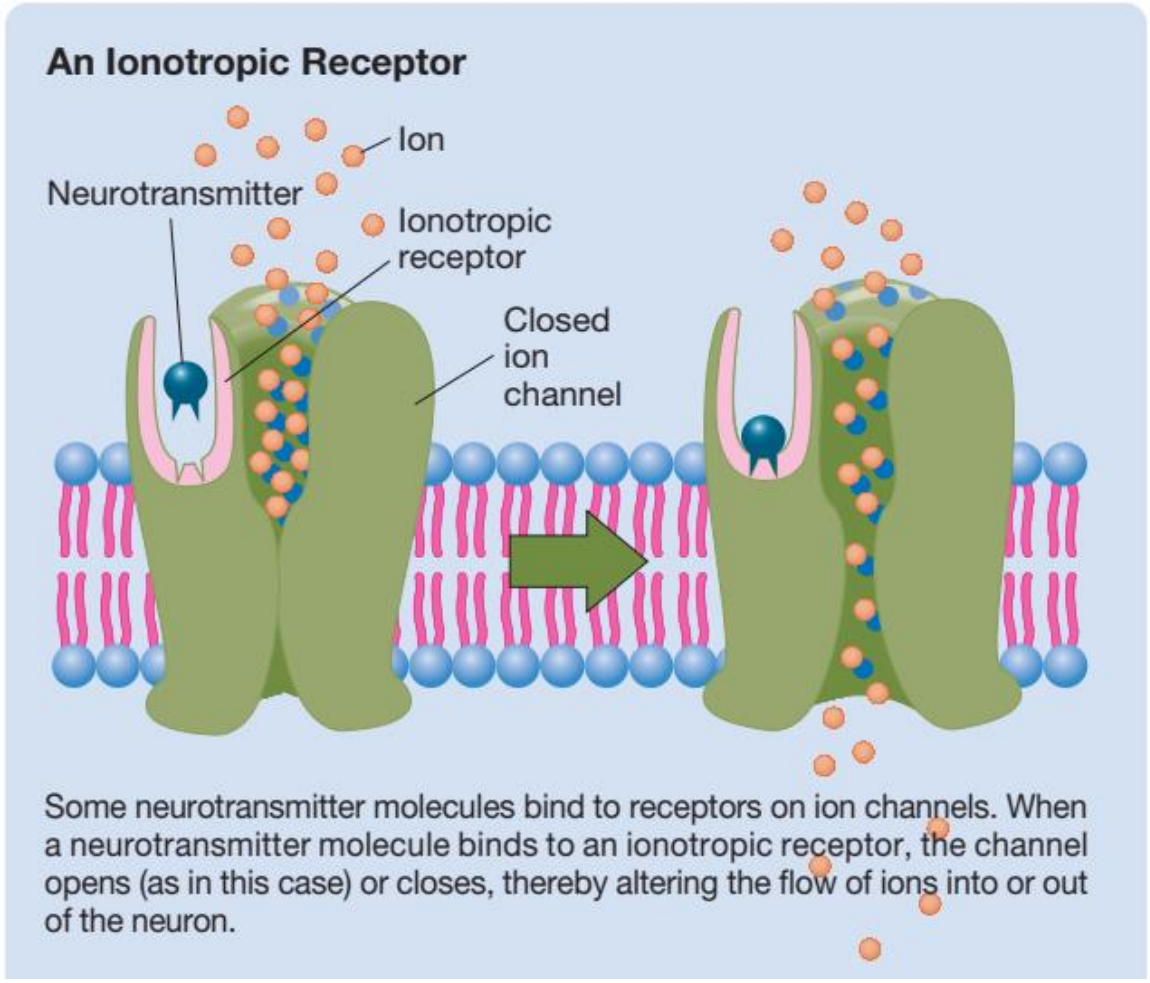
Brief clarification of the different effects of small-molecule v. neuropeptide transmitters

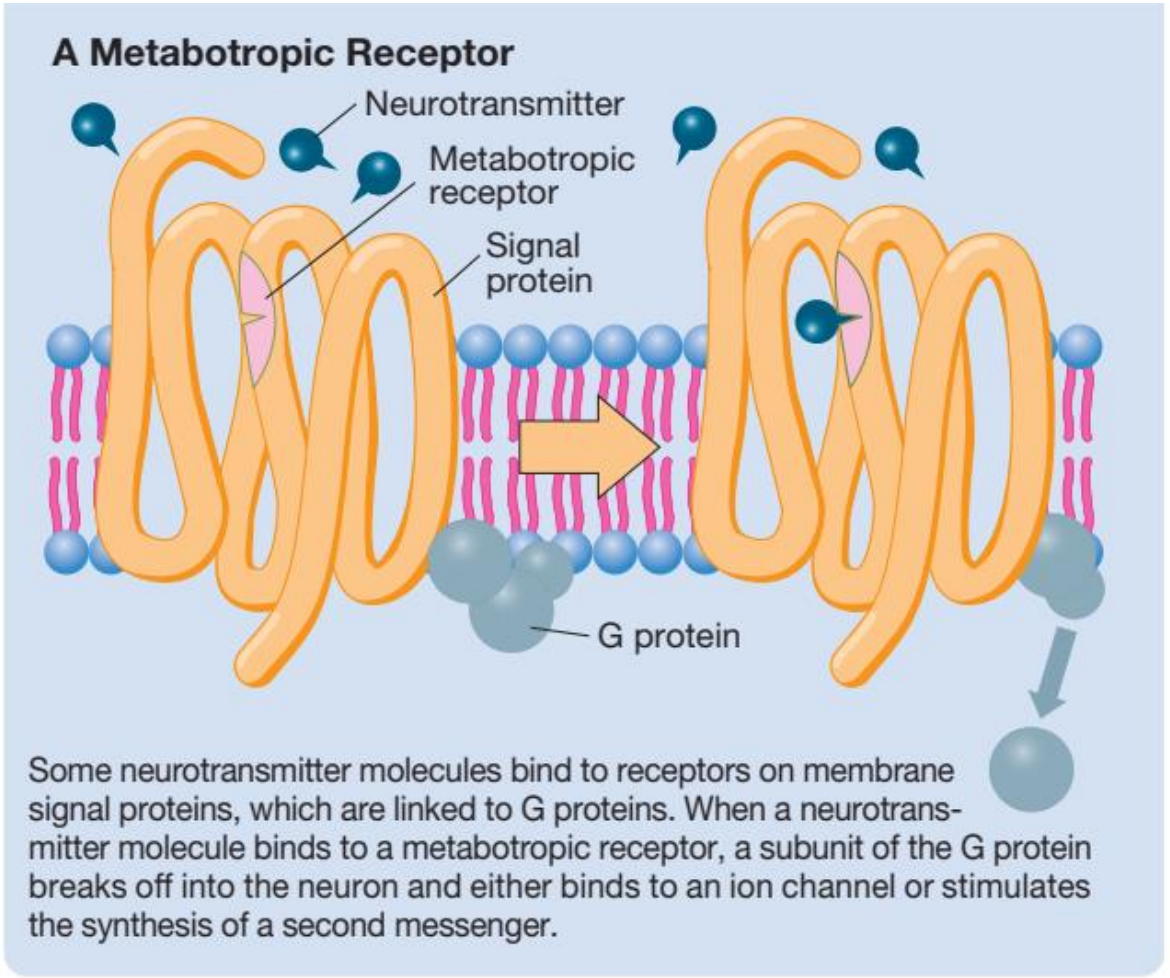
Differences between small-molecule and peptide neurotransmitters in **patterns of release and receptor binding** suggest that they serve different functions.

Small molecule neurotransmitters tend to be **released into directed synapses** and to activate either ionotropic receptors or metabotropic receptors that act **directly on ion channels** => the function of small-molecule neurotransmitters appears to be the transmission of **rapid, brief** excitatory or inhibitory signals to adjacent cells.

In contrast, **neuropeptides** tend to **be released diffusely**, and virtually all bind to **metabotropic receptors** that act through **second messengers** => the function of neuropeptides appears to be the transmission of **slow, diffuse, long-lasting** signals (Pinel & Barnes, 2021, p. 111).

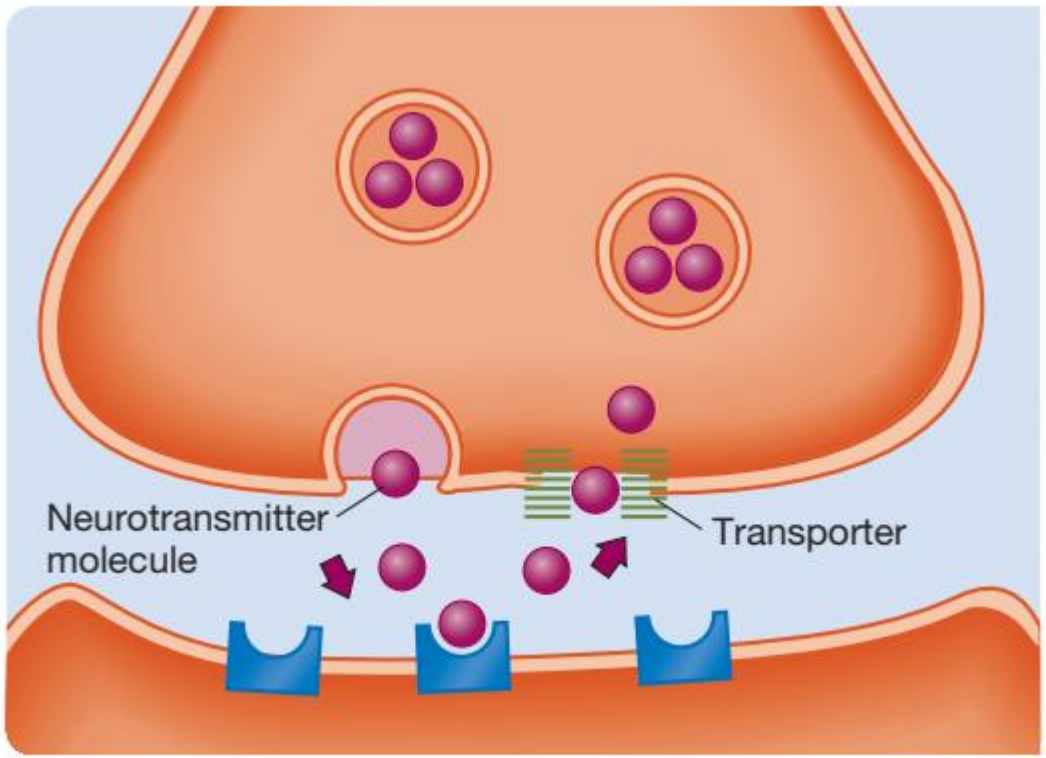
Briefly: **ionotropic** v. **metabotropic** receptors





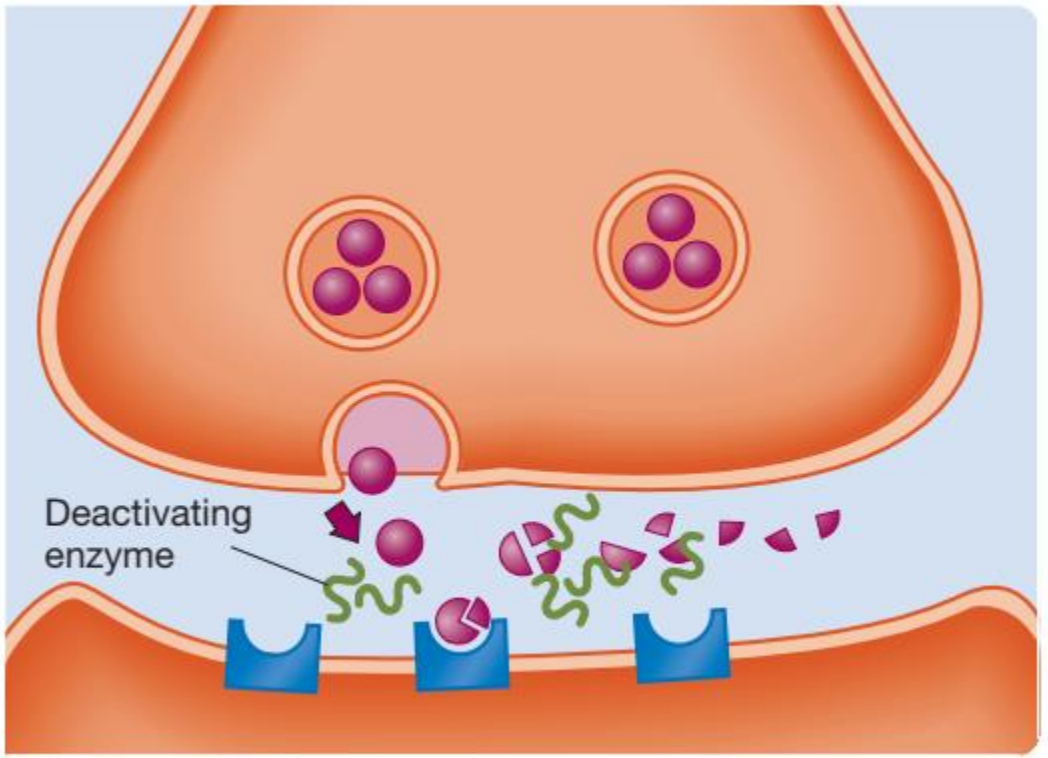
Pinel & Barnes, (2021), p. 111

(6) Termination of neurotransmitter action through (a) **reuptake** or (b) **enzymatic degradation**



Reuptake

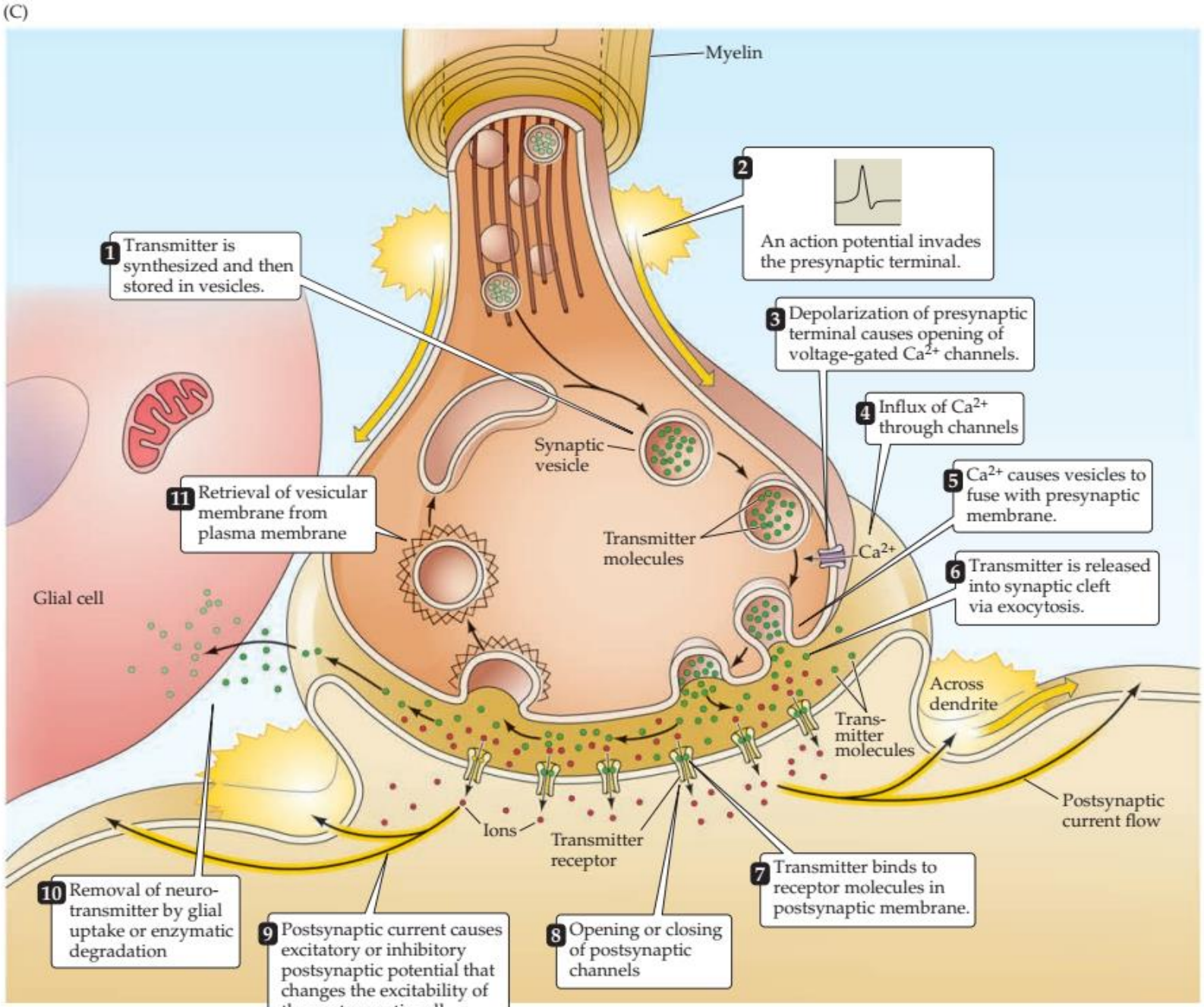
Pinel & Barnes, (2021), p. 112



Enzymatic Degradation

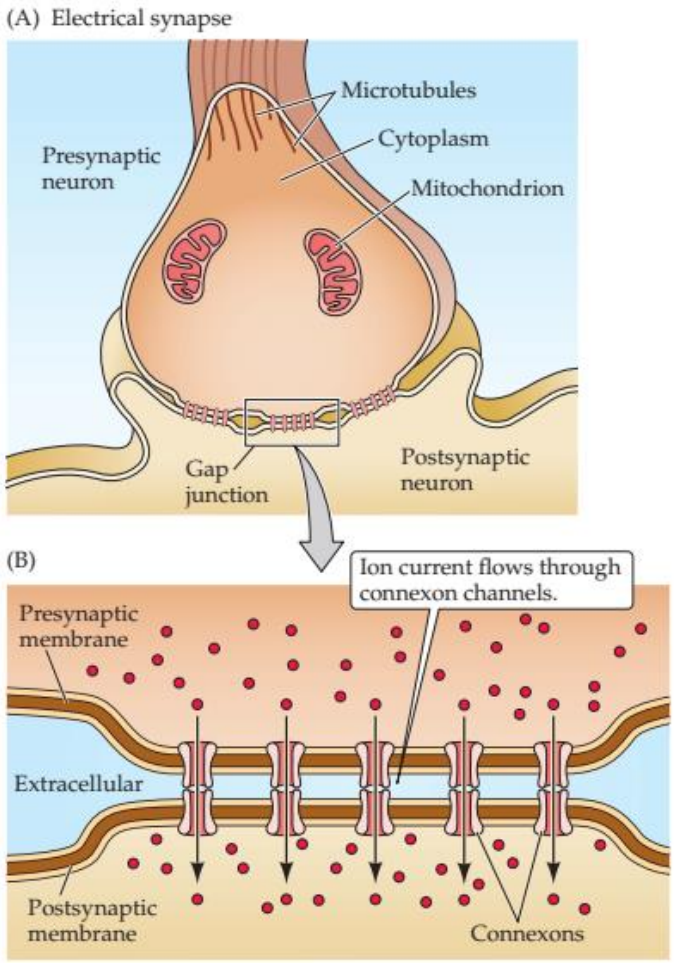
Most common; neurotransmitters are transported back into the presynaptic terminal.

Specialized enzymes degrade the neurotransmitter (e.g., acetylcholinesterase degrades Ach)



Purves et al., (2018), p. 90

Briefly: **electrical** v. **chemical** synapses



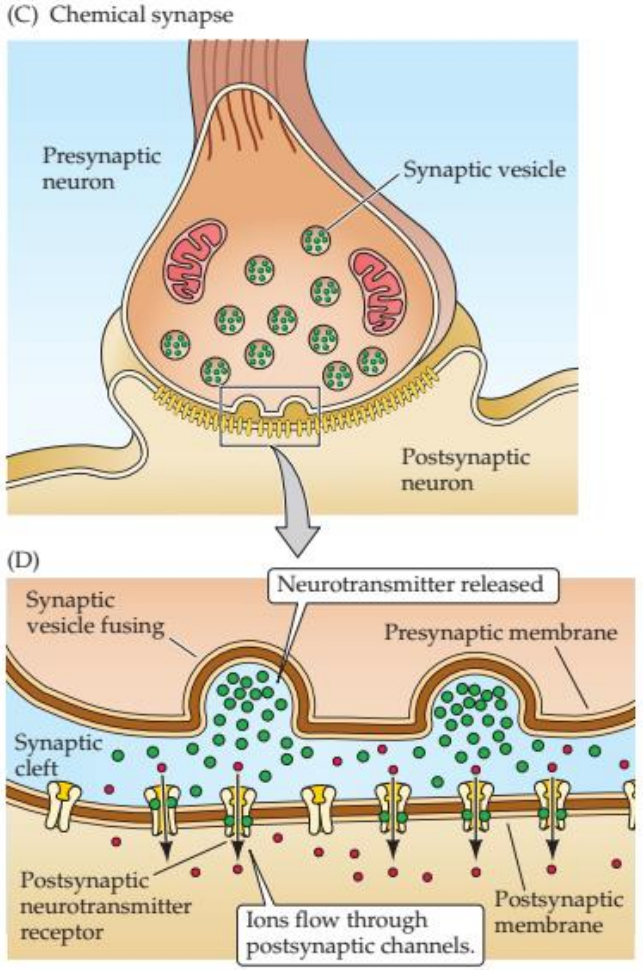
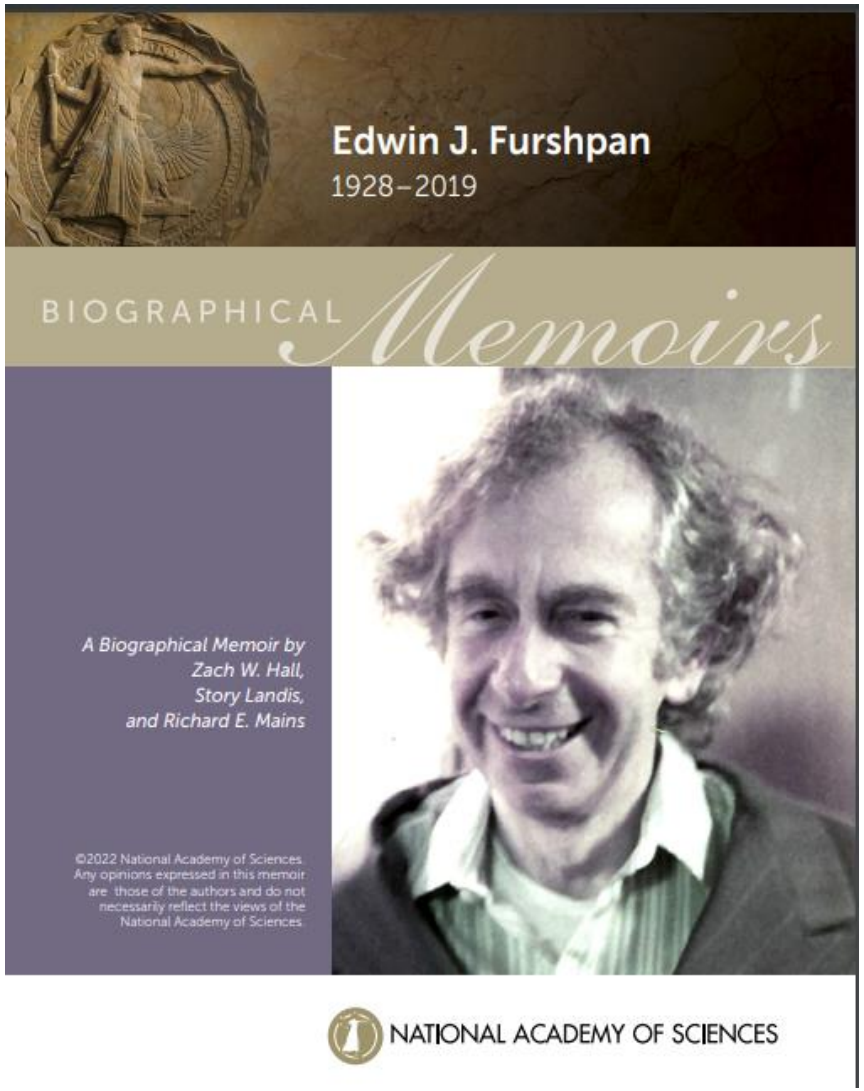
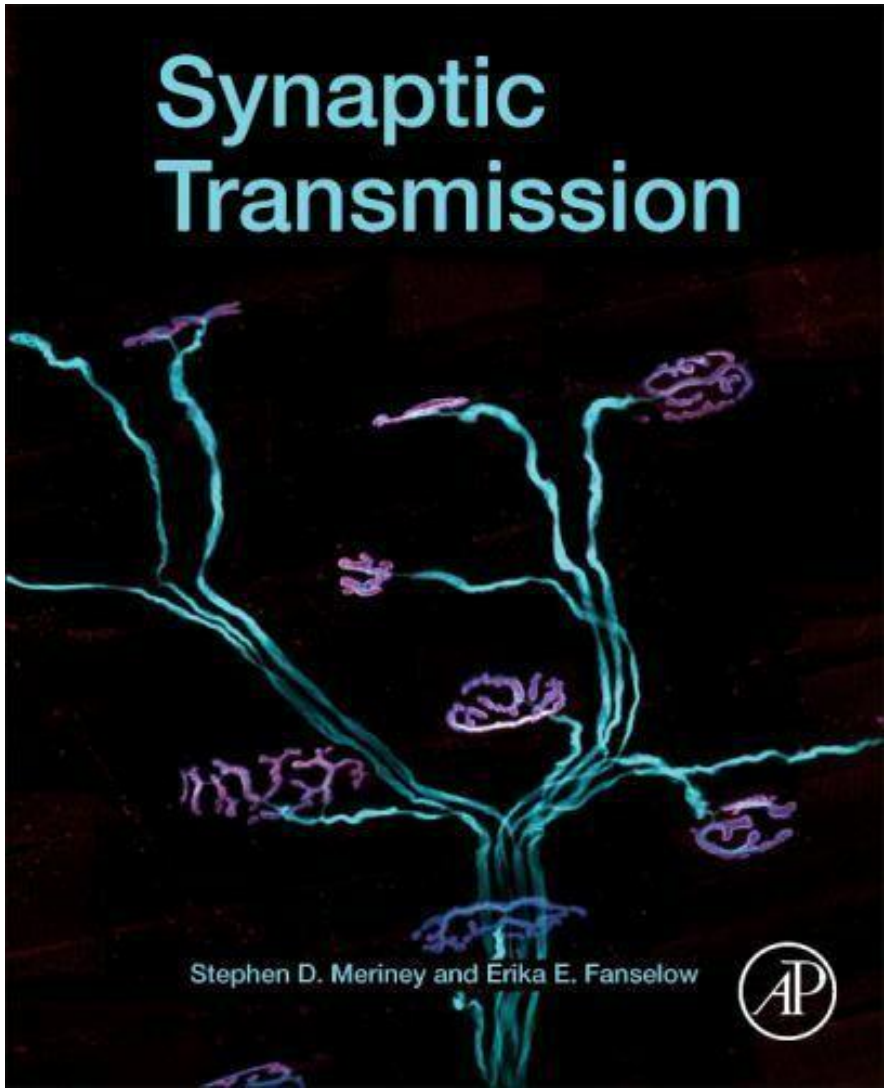


FIGURE 5.1 Electrical and chemical synapses differ fundamentally in their transmission mechanisms. (A) At electrical synapses, gap junctions occur between pre- and postsynaptic membranes. (B) Gap junctions contain connexon channels that permit current to flow passively from the presynaptic cell to the postsynaptic cell. (C) At chemical synapses, there is no intercellular continuity, and thus no direct flow of current from pre- to postsynaptic cell. (D) Synaptic current flows across the postsynaptic membrane only in response to the secretion of neurotransmitters, which open or close postsynaptic ion channels after binding to receptor molecules on the postsynaptic membrane.

Purves et al., (2018), p. 86

Further reading





https://tinyurl.com/kb8h2cm6

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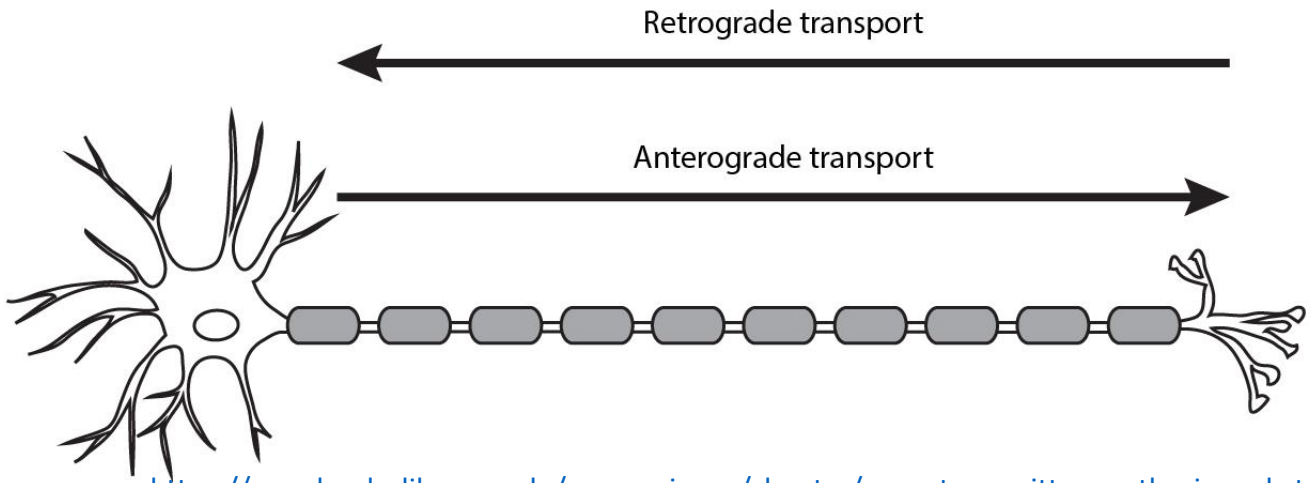
Science. 2019 Oct 11; 366(6462): eaaw9997.
doi: 10.1126/science.aaw9997

Axonal transport: Driving synaptic function

Pedro Guedes-Dias[1,2] and Erika L. F. Holzbaur[1,*]



https://openbooks.lib.msu.edu/neuroscience/chapter/neurotransmitter-synthesis-and-storage/

Abstract

Go to: ▸

The intracellular transport system in neurons is specialized to an extraordinary degree, enabling the delivery of critical cargo to sites in axons or dendrites that are far removed from the cell center. Vesicles formed in the cell body are actively transported by kinesin motors along axonal microtubules to presynaptic sites that can be located over a meter away. Both growth factors and degradative vesicles carrying aged organelles or aggregated proteins take the opposite route, driven by dynein motors. Distance is not the only challenge; precise delivery of cargos to sites of need must also be accomplished. For example, localized delivery of presynaptic components to hundreds of thousands of '*en passant*' synapses distributed along the length of a single axon in some neuronal subtypes provides a layer of complexity that must be successfully navigated to maintain synaptic transmission. Here, we review recent advances in the field of axonal transport with a focus on conceptual developments, and highlight our growing quantitative understanding of neuronal trafficking and its role in maintaining the synaptic function that underlies higher cognitive processes such as learning and memory.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6996143/

Cold Spring Harb Perspect Biol. 2016 Aug; 8(8): a005926.
doi: 10.1101/cshperspect.a005926

PMCID: PMC4968160
PMID: 27481708

Second Messengers

Alexandra C. Newton,[1] Martin D. Bootman,[2] and John D. Scott[3]

Abstract

Go to: ▸

Second messengers are small molecules and ions that relay signals received by cell-surface receptors to effector proteins. They include a wide variety of chemical species and have diverse properties that allow them to signal within membranes (e.g., hydrophobic molecules such as lipids and lipid derivatives), within the cytosol (e.g., polar molecules such as nucleotides and ions), or between the two (e.g., gases and free radicals). Second messengers are typically present at low concentrations in resting cells and can be rapidly produced or released when cells are stimulated. The levels of second messengers are exquisitely controlled temporally and spatially, and, during signaling, enzymatic reactions or opening of ion channels ensure that they are highly amplified. These messengers then diffuse rapidly from the source and bind to target proteins to alter their properties (activity, localization, stability, etc.) to propagate signaling.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4968160/

Further resources

FOUNDATIONS OF NEUROSCIENCE

https://openbooks.lib.msu.edu/neuroscience/chapter/neurotransmitter-clearance/

13.

NEUROTRANSMITTER CLEARANCE

Acetylcholine

Acetylcholine action is terminated by acetylcholinesterase, an enzyme present in the synaptic cleft. Acetylcholinesterase degrades acetylcholine into choline and acetate molecules. Choline is then transported back into the presynaptic terminal and used in the synthesis of new acetylcholine.

Neurotransmitter
Receptor

Glutamate

e action is terminated by two mechanisms. Reuptake of glutamate molecules presynaptic terminal can occur, or glutamate can be transported into nearby . The excitatory amino acid transporters are sodium co-transporters and use m electrochemical gradient to drive neurotransmitter transport. Within glial amate is converted into glutamine by glutamine synthetase. Glutamine is sported out of the glial cell and back into the presynaptic terminal for use in utamate synthesis. If glutamate is transported back into the presynaptic ter- can be repackaged in synaptic vesicles.

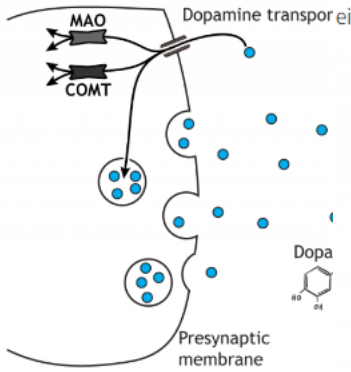
GABA and Glycine

Like glutamate, GABA and glycine action are terminated by either reuptake into the presynaptic terminal and packaging in synaptic vesicles or through transport into glial cells where breakdown can occur. The GABA and glycine transporter also use the sodium electrochemical gradient to drive the movement of the transmitter across the membrane.

Dopamine

Dopamine action is terminated by reuptake into the presynaptic terminal via the dopamine transporter (DAT). Once inside the cell, actions of either monoamine oxidase (MAO) or cat or it is repackaged into vesicles.

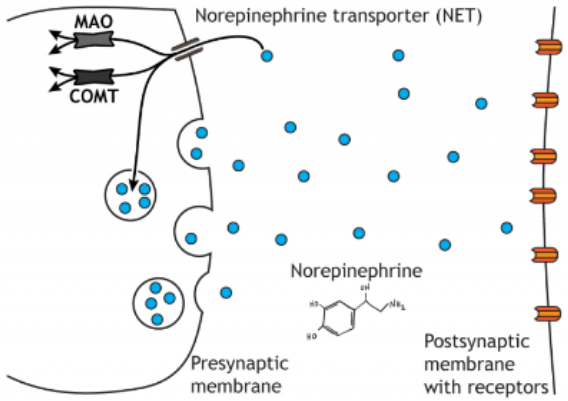
Neurotransmitter
Receptor



Norepinephrine

Norepinephrine follows the same pathway as dopamine. Reuptake into the presynap terminal occurs via the norepinephrine transporter (NET), and then the transmitter is either degraded within the cell by MAO or COMT or repackaged into synaptic vesicles

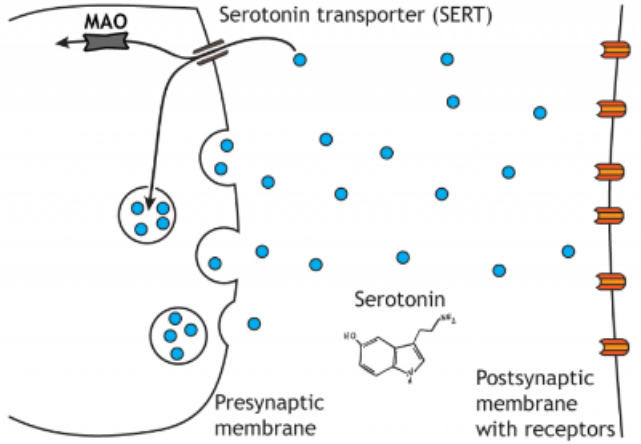
Neurotransmitter
Receptor



Serotonin

Like the other monoamines, serotonin is transported back into the presynaptic terminal via the serotonin transporter (SERT). The difference between serotonin and the catecholamines dopamine and norepinephrine is that monoamine oxidase is the only enzyme used for degradation.

Neurotransmitter
Receptor



In continuation of lecture 4

Perspective | Published: 19 October 2023

A conceptual framework for astrocyte function

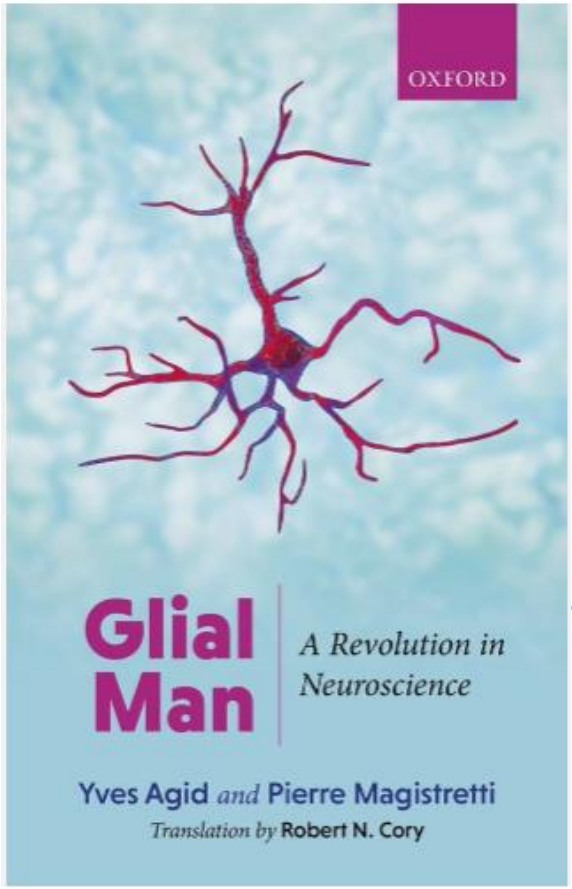
Ciaran Murphy-Royal, ShiNung Ching & Thomas Papouin

Nature Neuroscience **26**, 1848–1856 (2023) | Cite this article

Abstract

The participation of astrocytes in brain computation was hypothesized in 1992, coinciding with the discovery that these cells display a form of intracellular Ca^{2+} signaling sensitive to neuroactive molecules. This finding fostered conceptual leaps crystalized around the idea that astrocytes, once thought to be passive, participate actively in brain signaling and outputs. A multitude of disparate roles of astrocytes has since emerged, but their meaningful integration has been muddied by the lack of consensus and models of how we conceive the functional position of these cells in brain circuitry. In this Perspective, we propose an intuitive, data-driven and transferable conceptual framework we coin 'contextual guidance'. It describes astrocytes as 'contextual gates' that shape neural circuitry in an adaptive, state-dependent fashion. This paradigm provides fresh perspectives on principles of astrocyte signaling and its relevance to brain function, which could spur new experimental avenues, including in computational space.

https://www.nature.com/articles/s41593-023-01448-8



Contents

In continuation of lecture 4

New center will target glial cells to treat neurological diseases

Case Western Reserve University has established an Institute for Glial Sciences to advance research of glial cells and their critical role in the health and diseases of the nervous systems, including multiple sclerosis, Alzheimer's, pediatric leukodystrophies, autism spectrum disorders, Parkinson's disease and cancer.

Housed within **Case Western Reserve School of Medicine's** Department of Genetics and Genome Sciences, the new institute will be directed by **Paul Tesar**, the Dr. Donald and Ruth Weber Goodman Professor of Innovative Therapeutics. The institute will focus on three nervous systems: the central, peripheral and enteric.

Paul Tesar

https://tinyurl.com/yvnz9kwa