Behavioral Neuroscience A
5: Neurotransmitters

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https://youtu.be/hQ_Nm6sILT8

Lecture Video at above link.

Today’s aim

Last week, we learned how signals propagate electrically *inside* neural cells.

How are signals communicated *between* neural cells ***chemically***?

Today's Topics

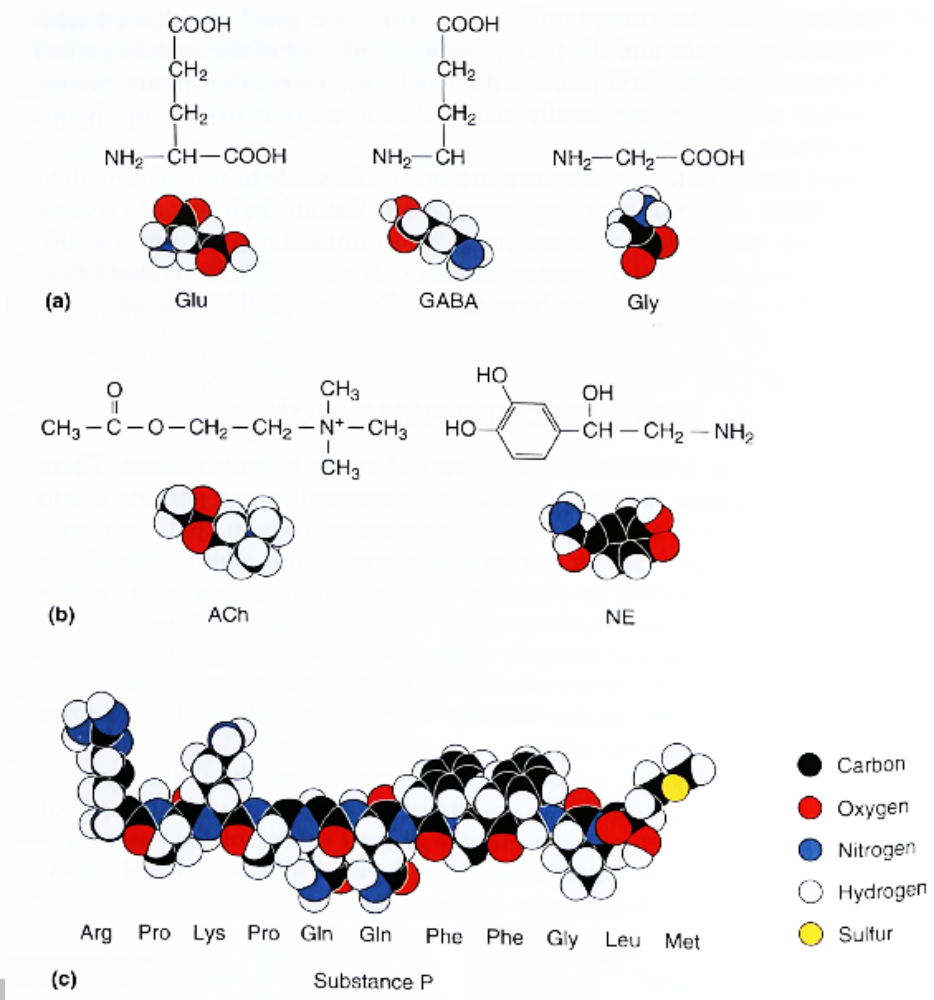
Neurotransmitters, drugs, and hormones

1) Synaptic transmission

2) Neurotransmitters

3) Schizophrenia and dopamine

4) Electrical synapses: gap junctions



Synaptic Transmission is Chemical

Otto Loewi (1873-1961)

(Aus dem pharmakologischen Institut der Universität Graz.)

Über humorale Übertragbarkeit der Herznervenwirkung.

I. Mitteilung.

Von

O. Loewi.

(Ausgeführt mit Unterstützung der Fürst Liechtenstein-Spende.)

(Mit 5 Textabbildungen.)

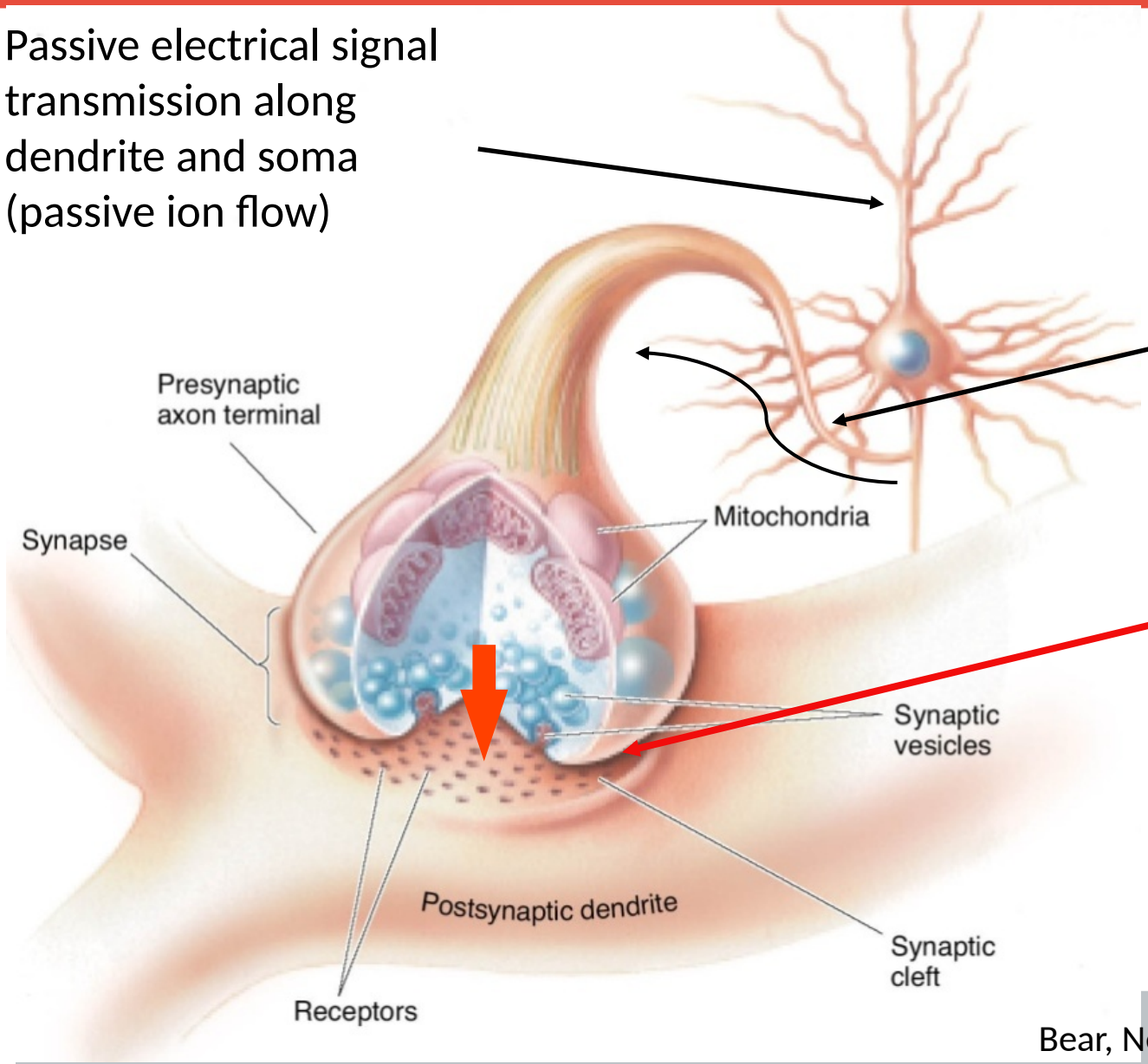
(Eingegangen am 20. März 1921.)

Otto Loewi reported in 1921 that synaptic transmission between vagus nerve and heart (vagal activity slows the heart) is chemical: he stimulated the vagus nerve of an isolated frog heart electrically which led to a slowing of the heart beat.
He then took the solution in which the heart was bathed to another frog heart which again slowed due to some chemical (acetylcholine) in the solution.

Electrical and Chemical Signals in Brain

Passive electrical signal transmission along dendrite and soma (passive ion flow)

Active electrical signal transmission along axon (action potential)



Chemical signal transmission across synapse

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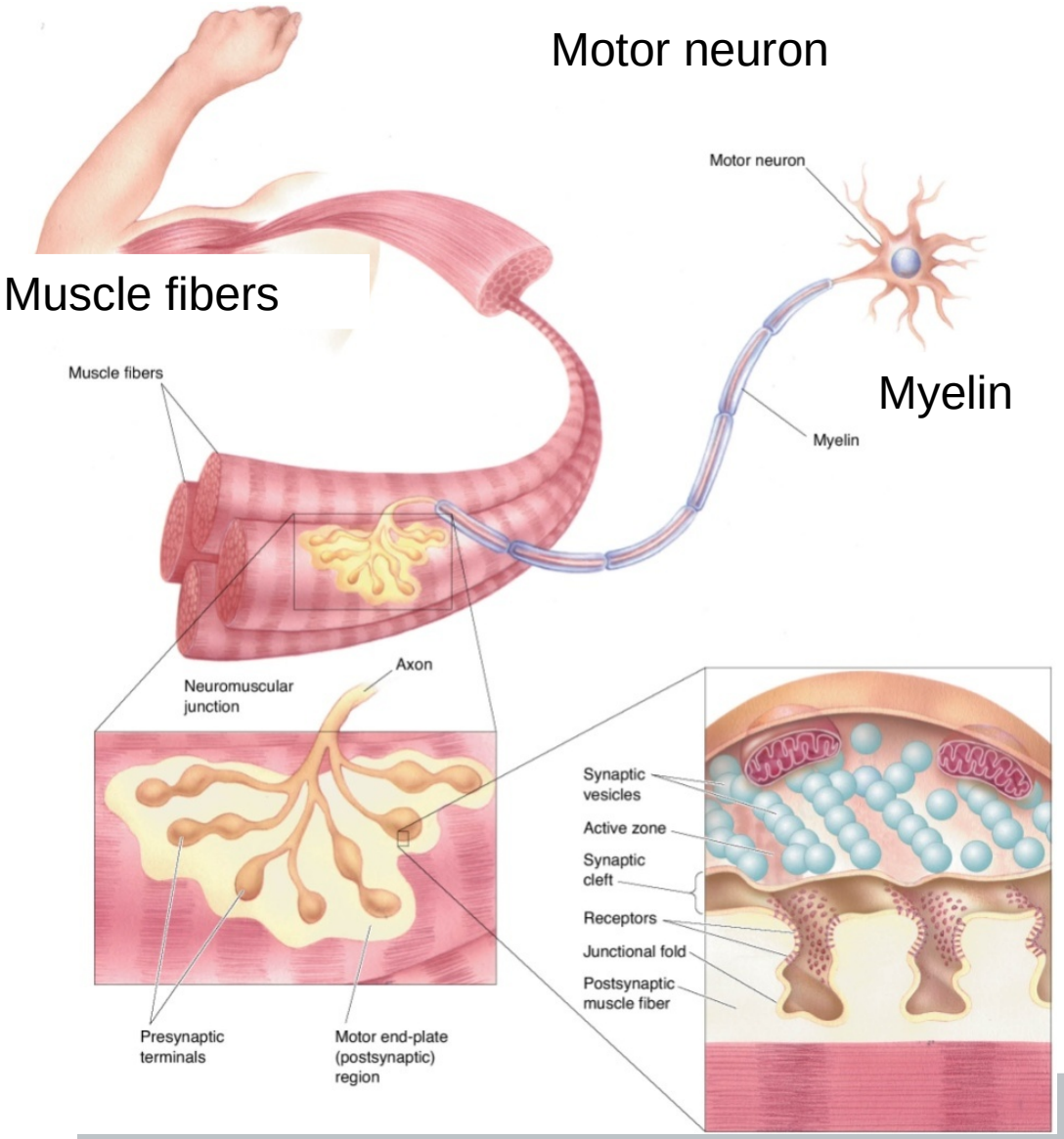
Neuromuscular Junction



The neuromuscular junction (link between motor neuron and muscle) is a special synapse covering a wide area, using the neurotransmitter acetylcholine for chemical transmission (cholinergic).

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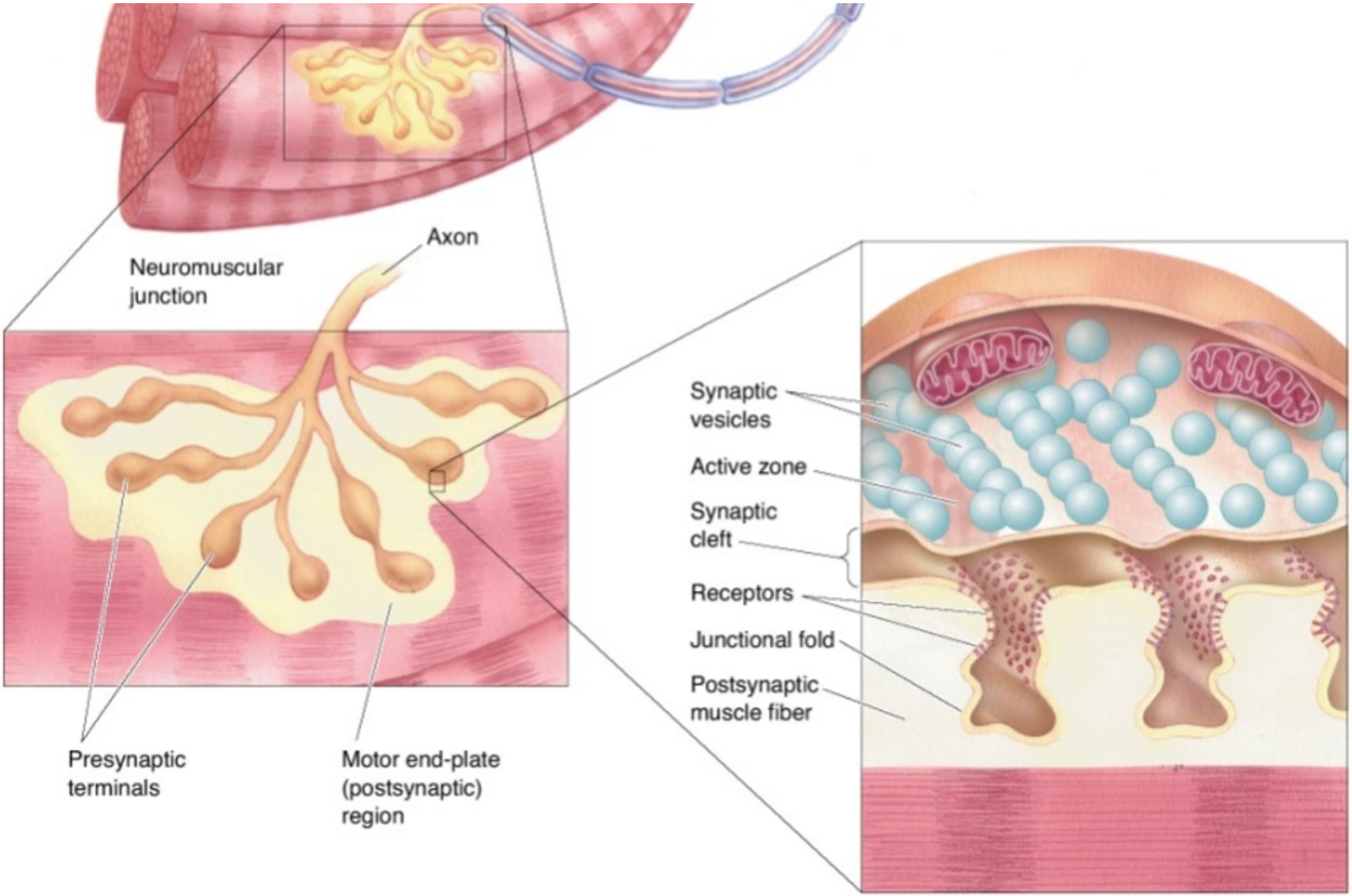
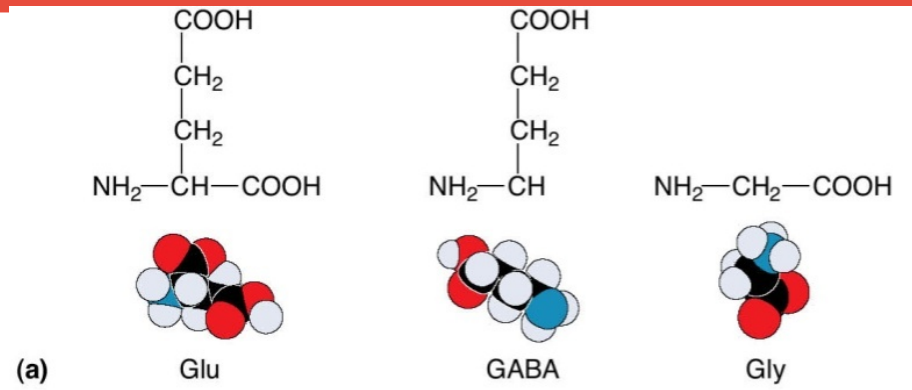
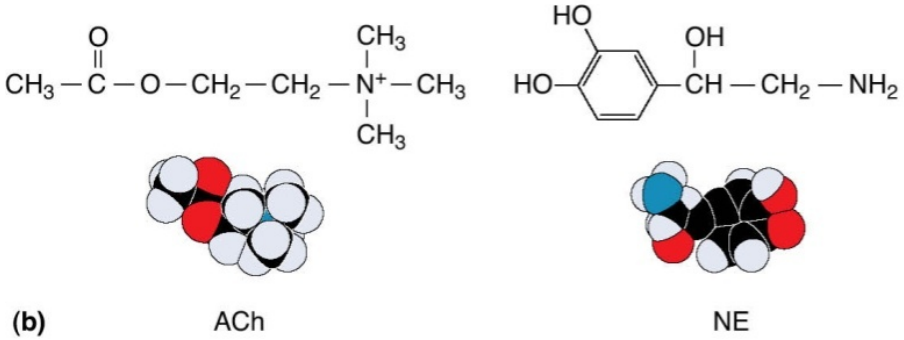
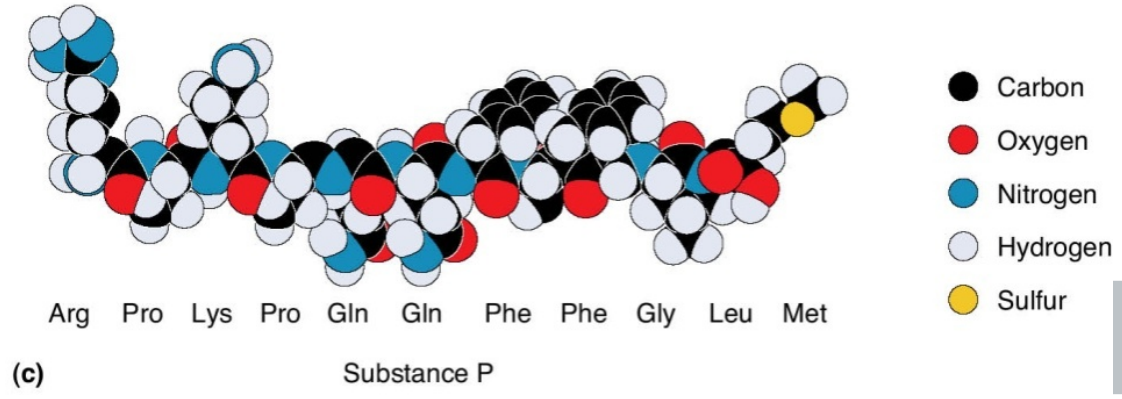
Neuromuscular junction



Man types of neurotransmitters







a) Amino acids:

- Glutamate (Glu)
- γ-aminobutyric acid (GABA)
- Glycine (Gly)

b) Amines:

- Acetylcholine (ACh)
- Norepinephrine (NE)

c) Peptides:

- Substance P

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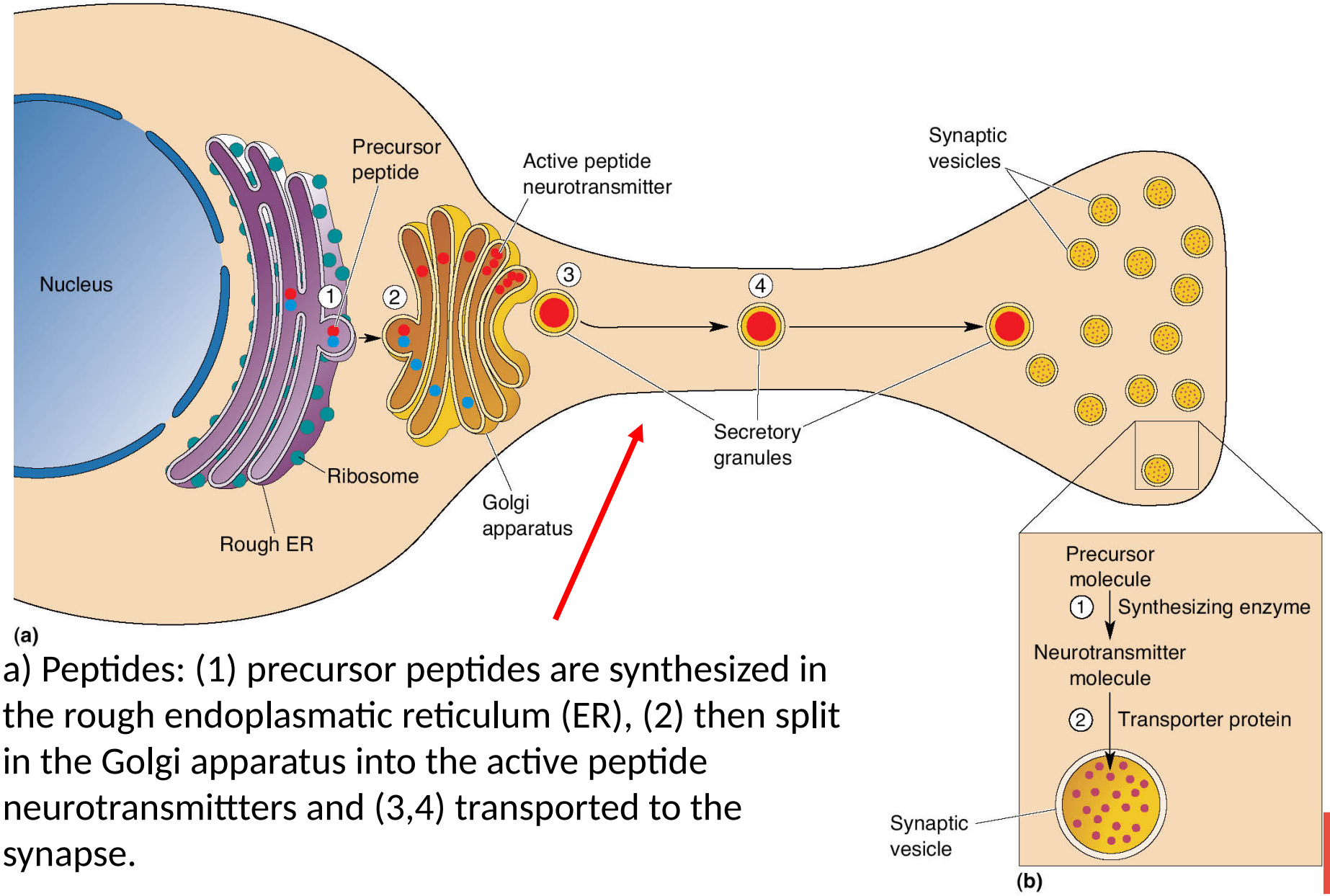
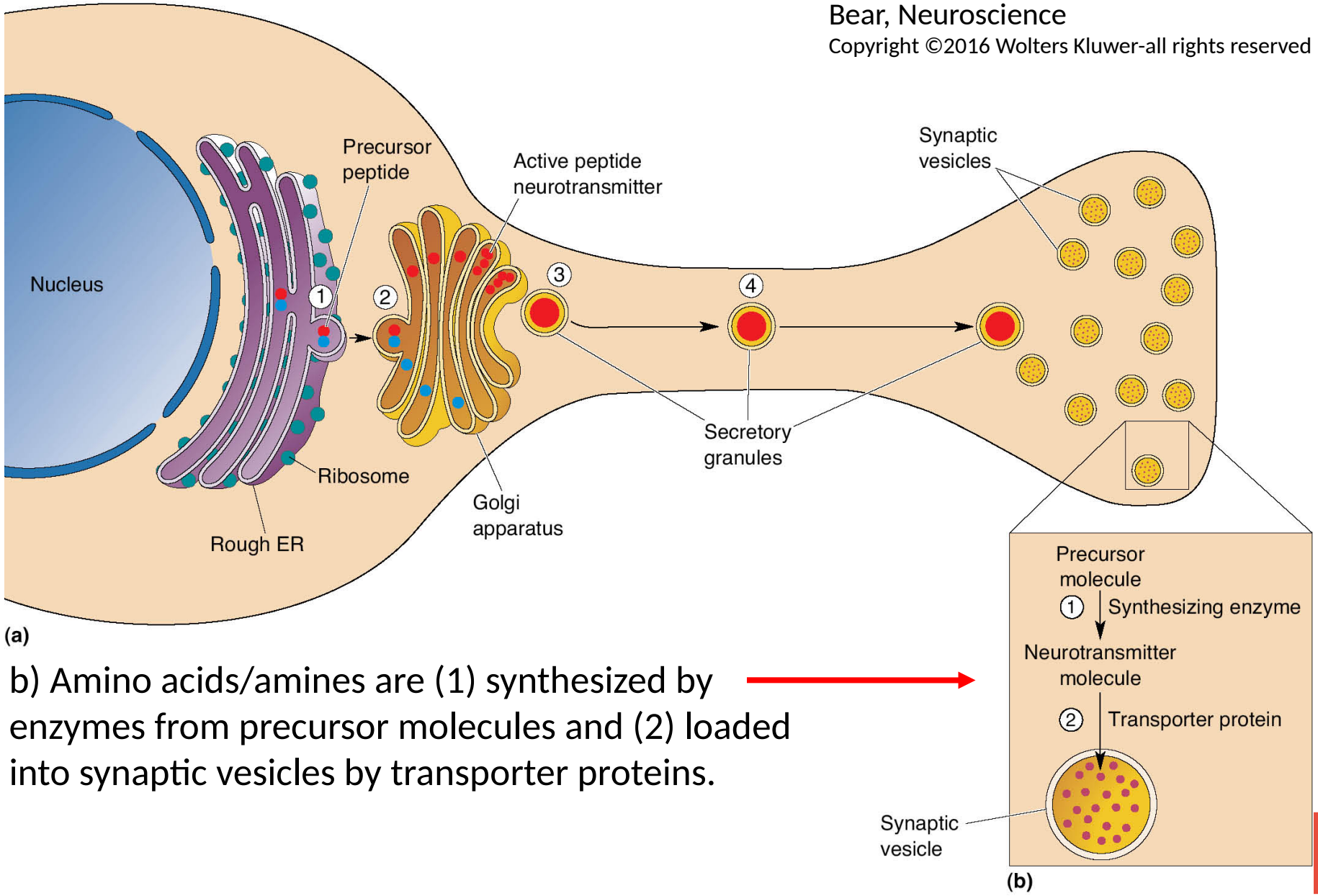
Synthesis (1)



a) Peptides: (1) precursor peptides are synthesized in the rough endoplasmatic reticulum (ER), (2) then split in the Golgi apparatus into the active peptide neurotransmittters and (3,4) transported to the synapse.

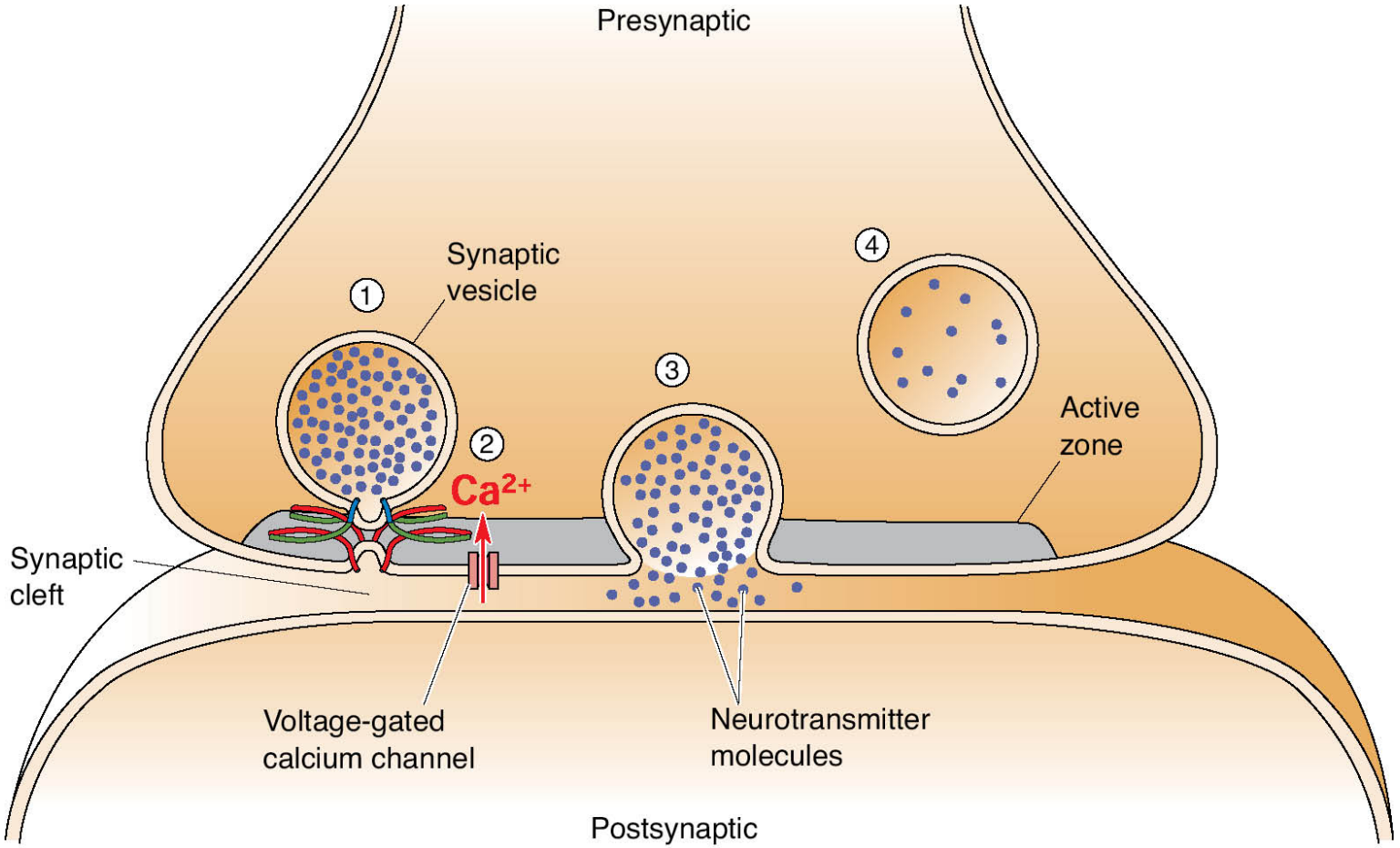
Synthesis (2)



b) Amino acids/amines are (1) synthesized by enzymes from precursor molecules and (2) loaded into synaptic vesicles by transporter proteins.

Exocytosis

(1) Neurotransmitter is released (3) from synaptic vesicles when (2) voltage-gates calcium channels open and allow an influx of Ca^{2+} ions.



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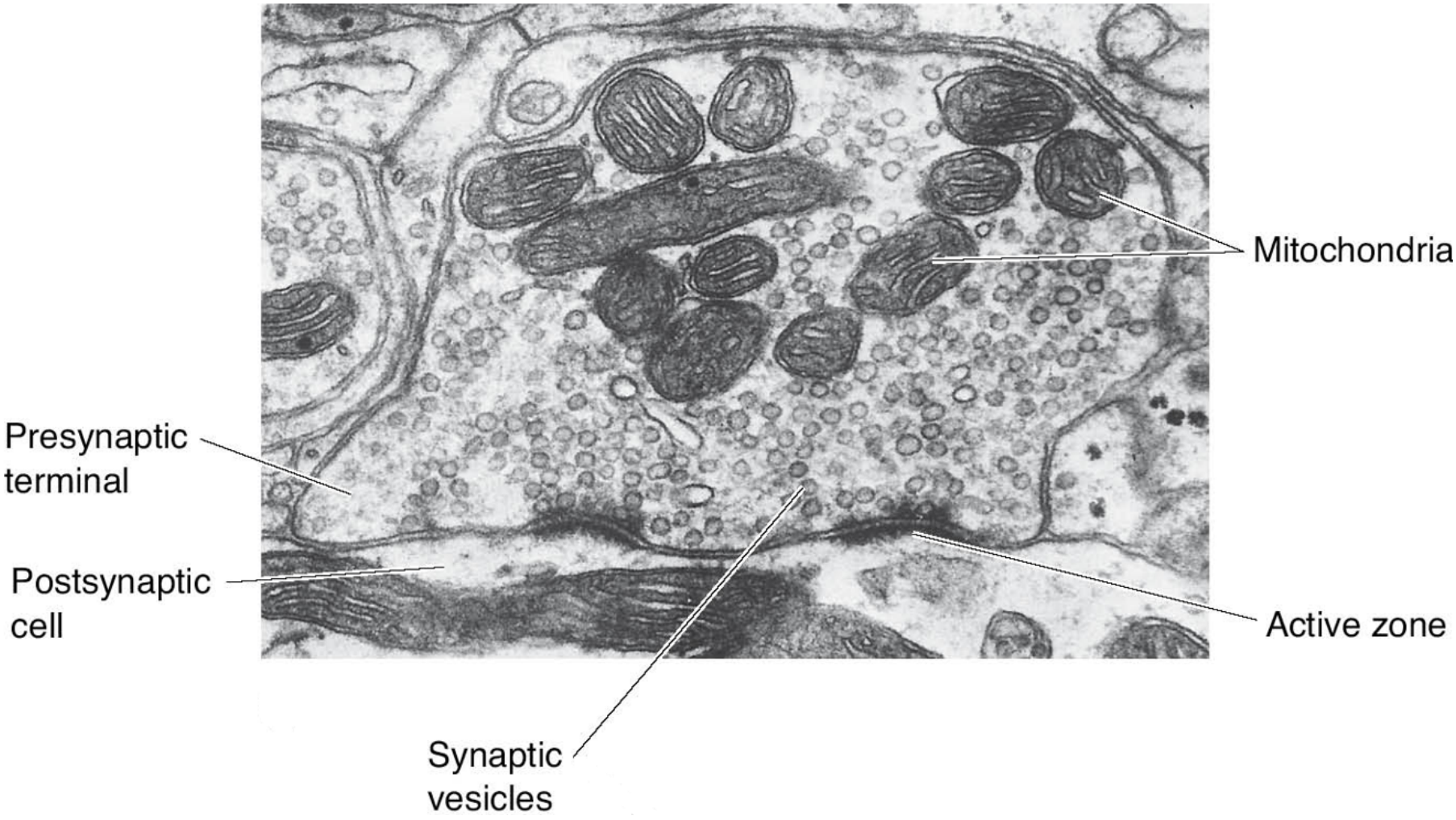
CNS Synapse – Electron Microscope

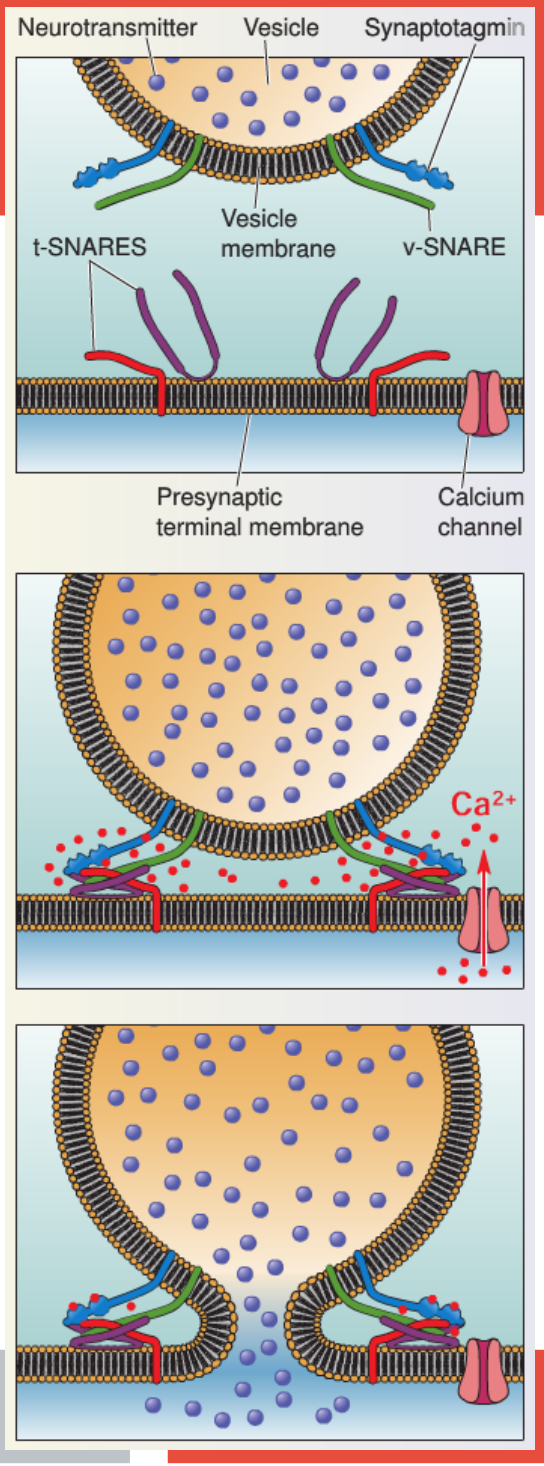


Exocytosis

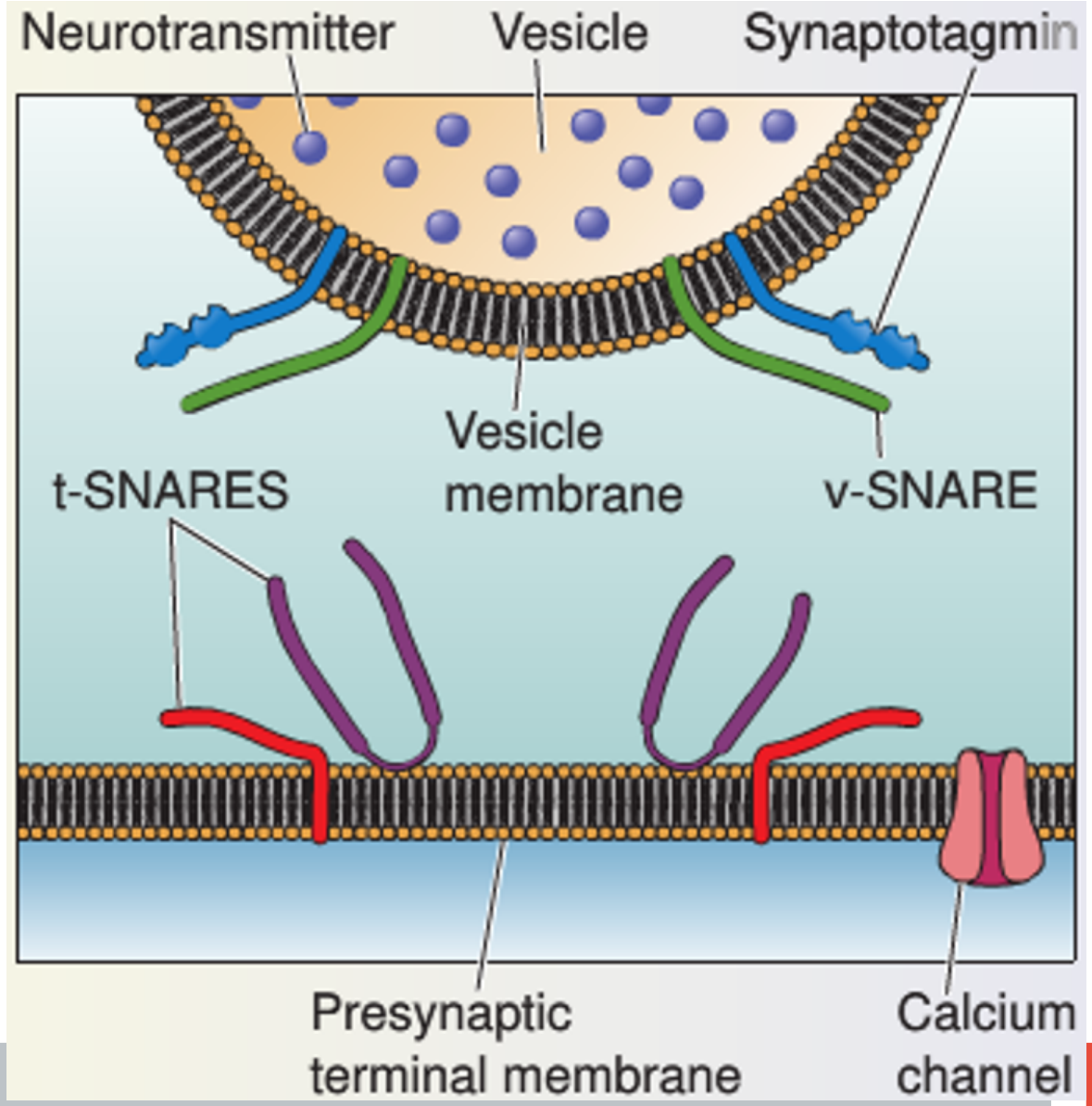
Proteins called SNARES support the binding and fusion of cell membranes.

Docking of the synaptic vesicle to the membrane is supported by a bond between t-SNARES (cell membrane) and v-SNARES (vesicle).

When Ca^{2+} ions enter the cell, they bind to the vesicle protein synaptotagmin (in blue) which triggers membrane fusion and neurotransmitter release.



Exocytosis (3)

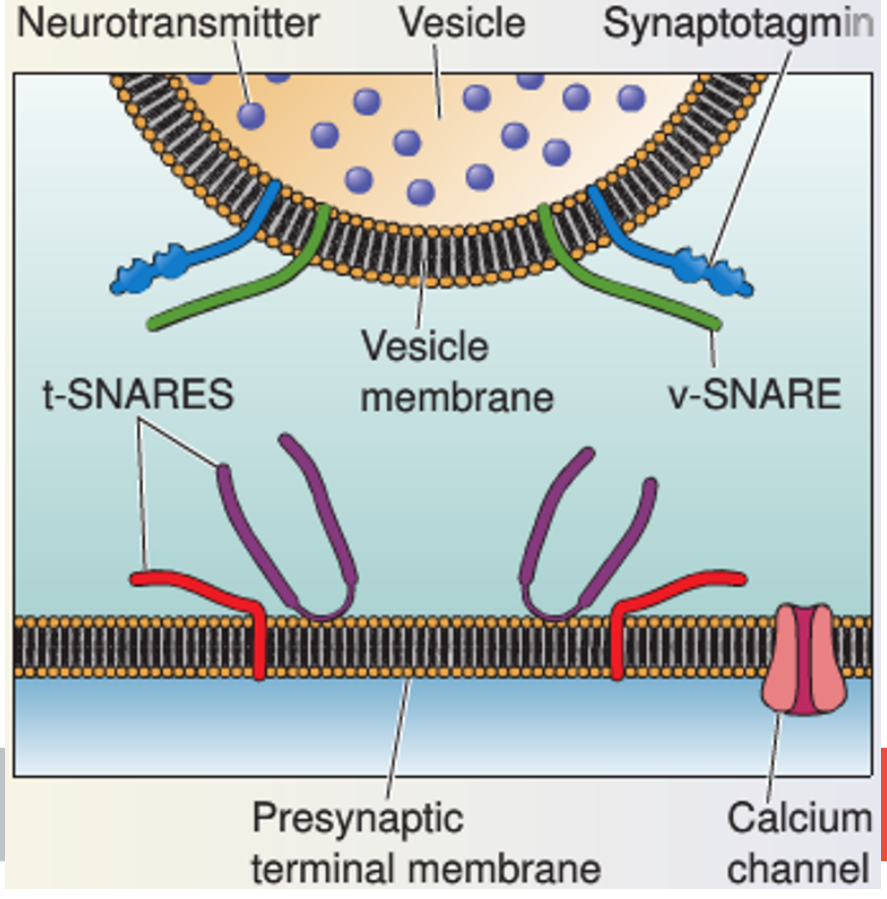


Poisons affecting exocytosis

Two examples of bacterial poisons that affect the process of exocytosis:

Botulinum toxin produced by Clostridium botulinum (often foodborne, often canned products) affects the SNARE proteins of neuromuscular junctions which use acetylcholine for transmission. Thus acetylcholine cannot be secreted and muscles are paralyzed.

Tetanus poison (tetanospasmin) produced by the bacterium Clostridum tetani (often found in soil or animal feces) affects the SNARE proteins of vesicles in inhibitory GABA neurons. This leads to reduced inhibition of motor neurons and spasms.



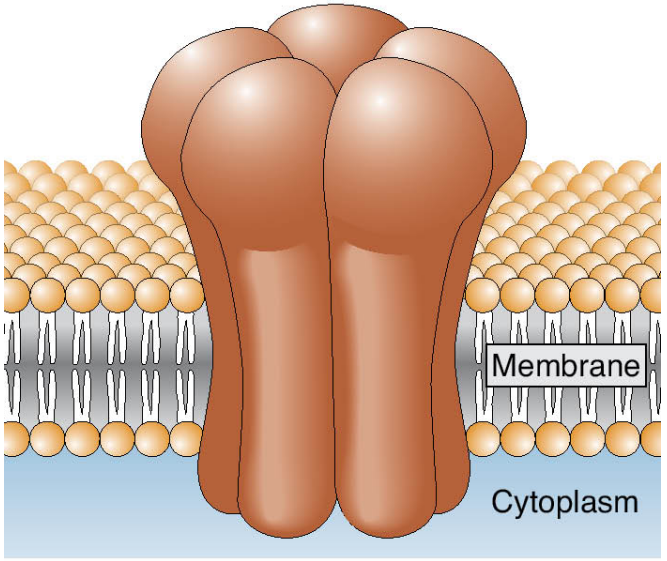
Transmitter-gated ion channels

(or ligand-gated ion channels)

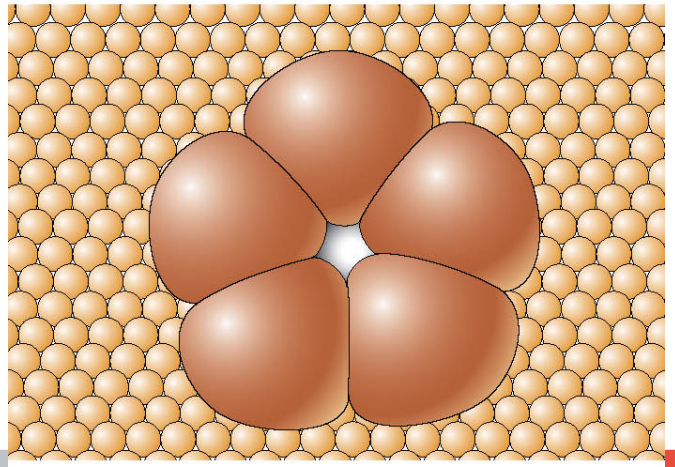
The effect of the neurotransmitter is mediated by postsynaptic membrane receptors.

Transmitter-gated ion channels respond to binding with a neurotransmitter by opening.
→ Ions can flow, e.g., Na^+ ions into the cell (into the cytoplasm).

The image shows the shape of an acetylcholine channel.

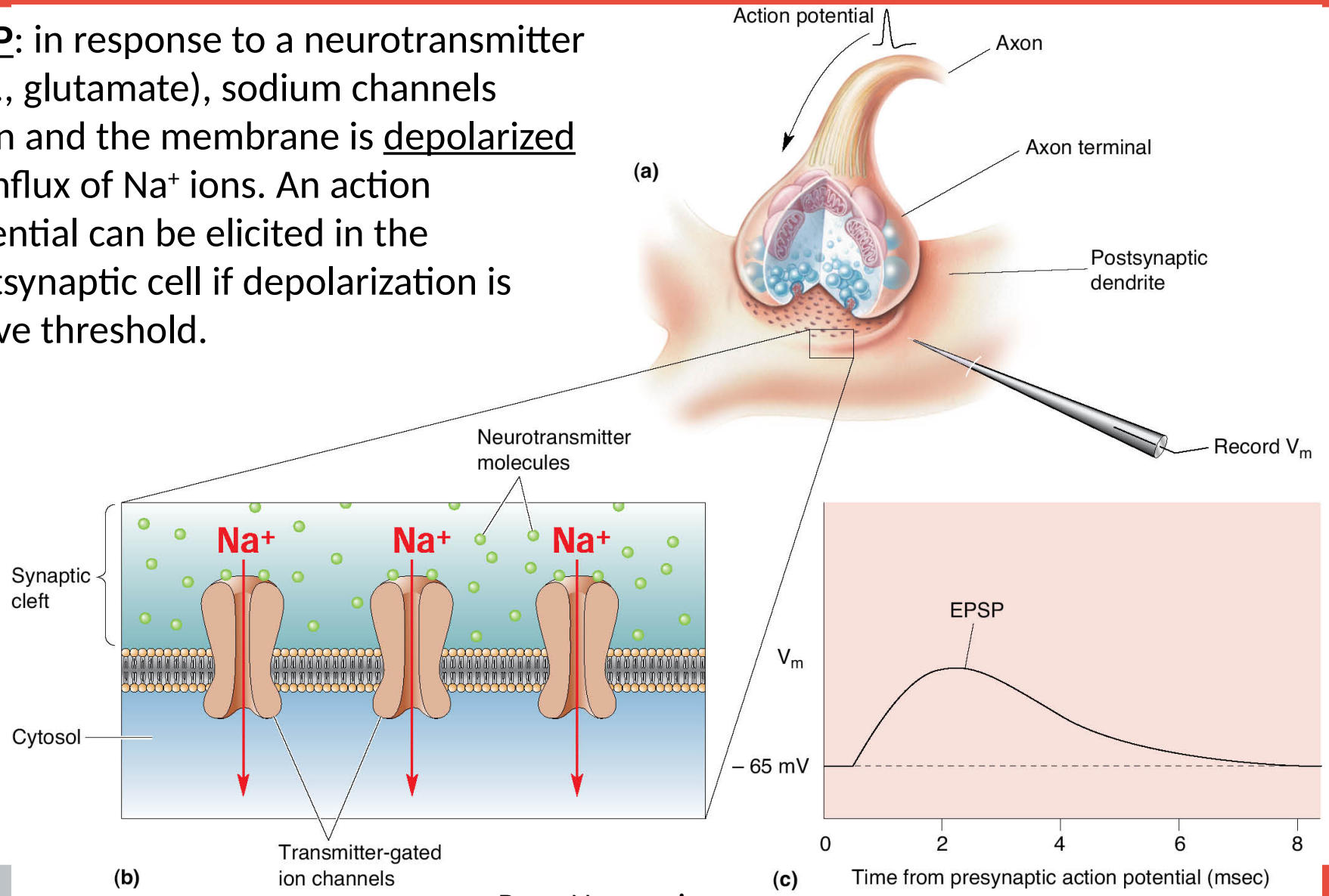


(a)


(b)

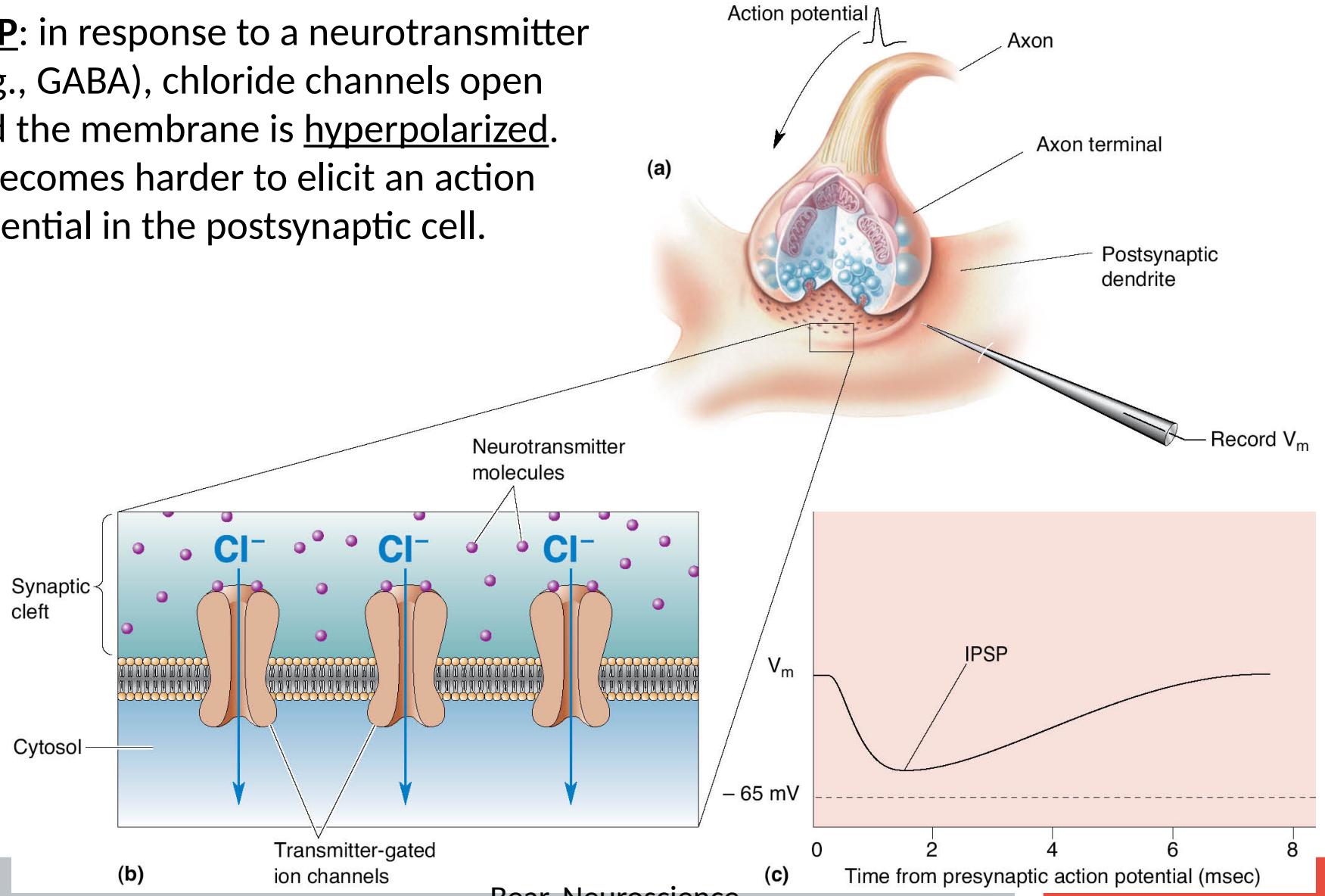
Excitatory Post-Synaptic Potential

EPSP: in response to a neurotransmitter (e.g., glutamate), sodium channels open and the membrane is depolarized by influx of Na^+ ions. An action potential can be elicited in the postsynaptic cell if depolarization is above threshold.



Inhibitory Post-Synaptic Potential

IPSP: in response to a neurotransmitter (e.g., GABA), chloride channels open and the membrane is hyperpolarized. It becomes harder to elicit an action potential in the postsynaptic cell.

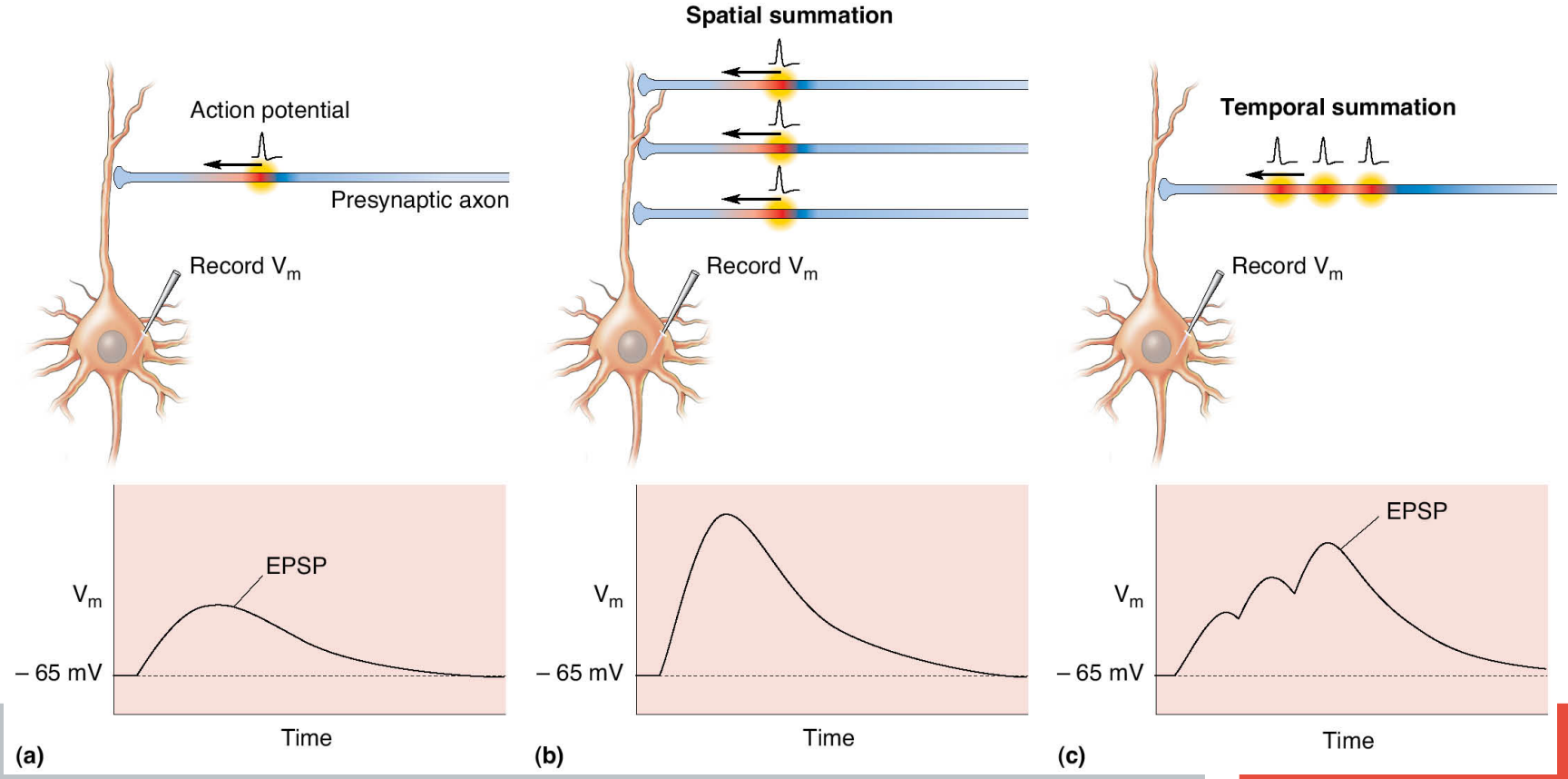


Temporal/Spatial Summation

The excitatory postsynaptic potential (EPSP) elicited by a single synapse if often not enough to trigger a postsynaptic action potential.

EPSPs from many synapses active at the same time can be sufficient:
Spatial summation

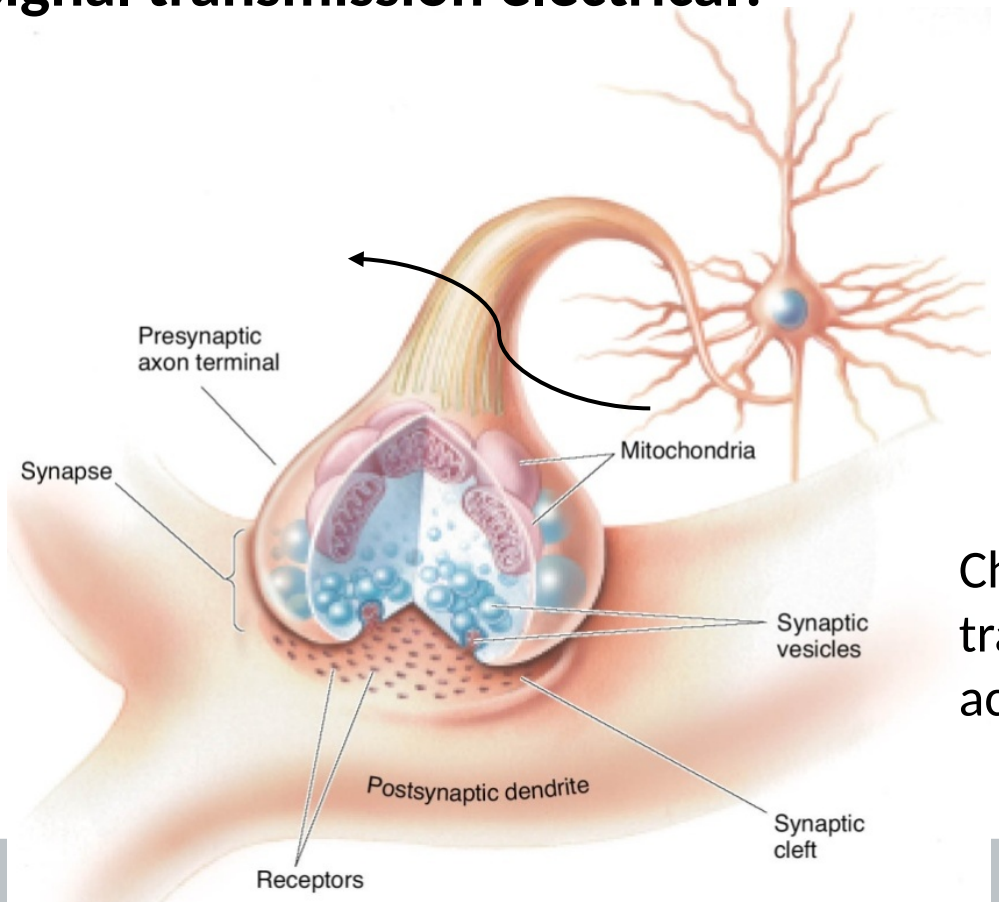
Many EPSPs from the same synapse, but in fast sequence can be sufficient:
Temporal summation



Question

Chemical signal transmission is rather slow (more than 0.3ms, but mostly 1-5ms for the 20-50nm across the synaptic cleft).

Why is not all signal transmission electrical?



Electrical signal transmission along axon (action potential)

Chemical signal transmission across synapse

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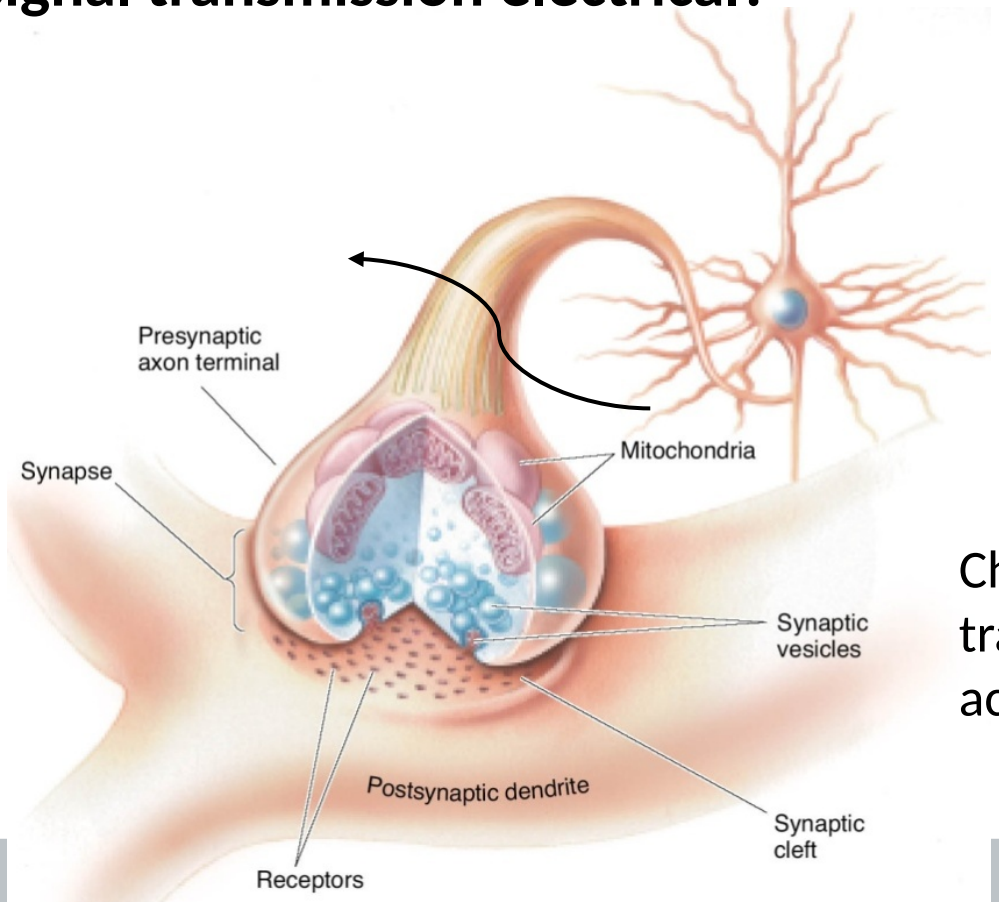
Question

Hint: You can't change the sign, or the time course…

Why is not all signal transmission electrical?

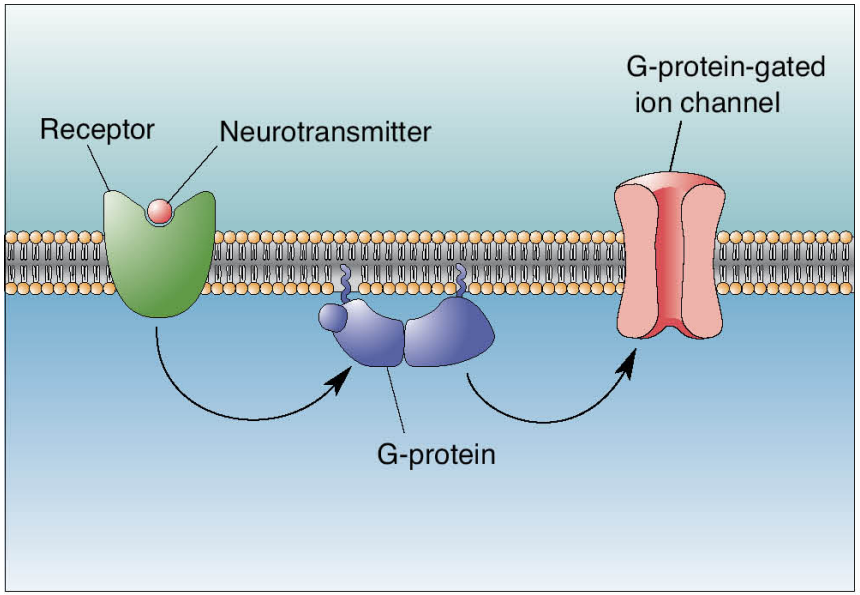


Electrical
signal transmission
along axon
(action potential)

Chemical signal
transmission
across synapse

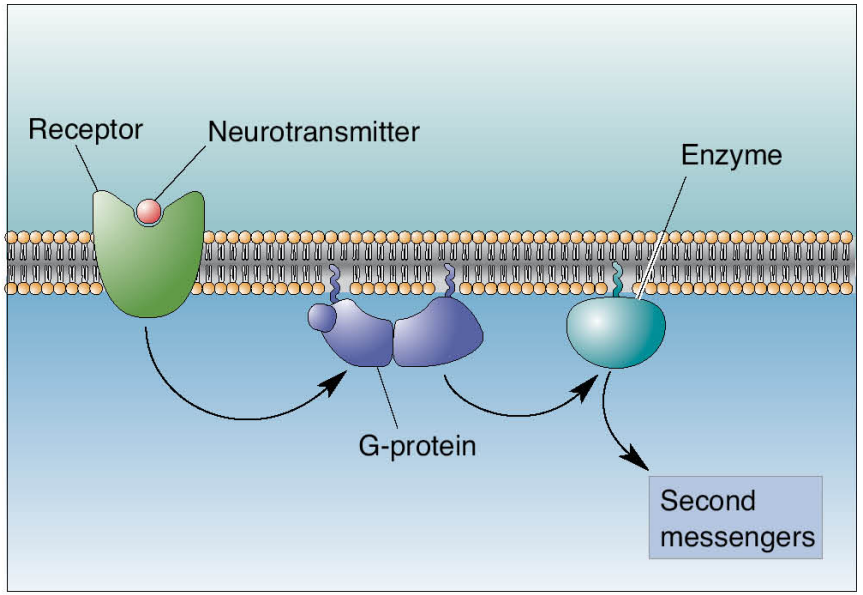
G-Protein Coupled Receptors (GPCR)

G-protein coupled-receptors (post-synaptic) act slower than transmitter-gated ion channels: a neurotransmitter binds to a receptor, the receptor activates a G-protein, which can move along the cell membrane. The G-protein activates effector proteins:



(a)

a) The effector protein can be an ion channel which opens after activation by the G-protein.



(b)

b) The effector protein can be an enzyme that synthesizes a second messenger.

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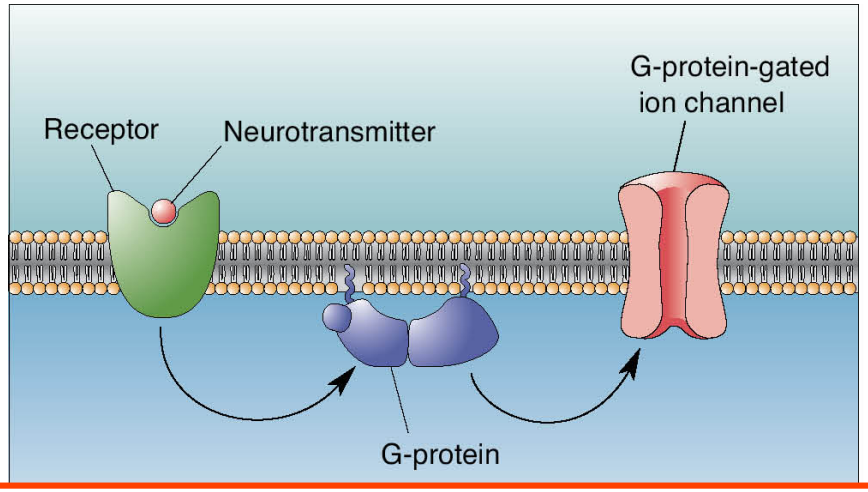
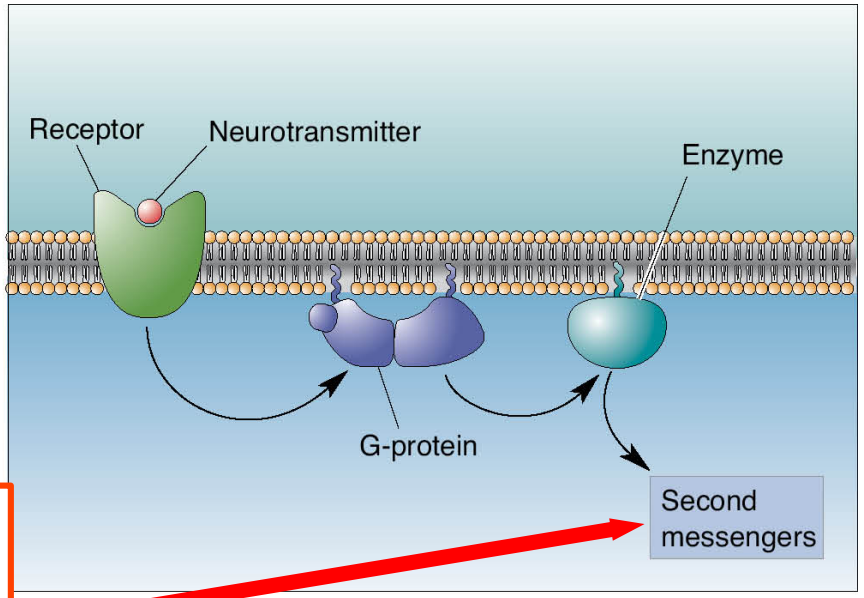
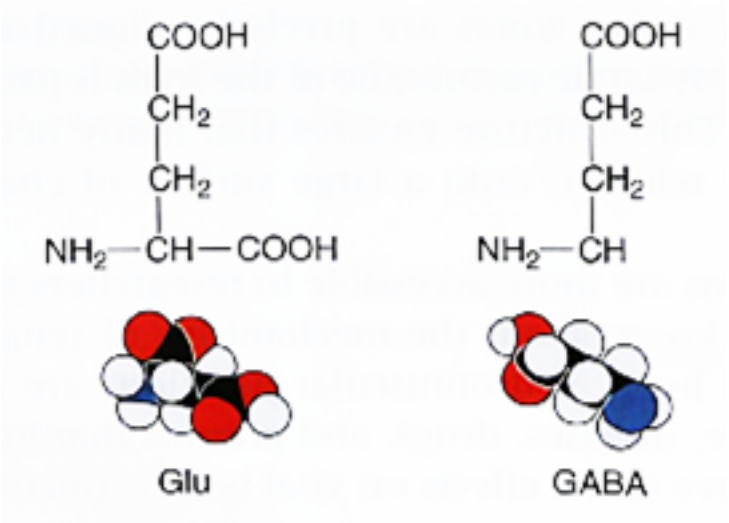




This in turn can activate other enzymes or alter cellular metabolism (can also affect ion channel function-> e.g., learning).

b) The effector protein can be an enzyme that synthesizes a second messenger.

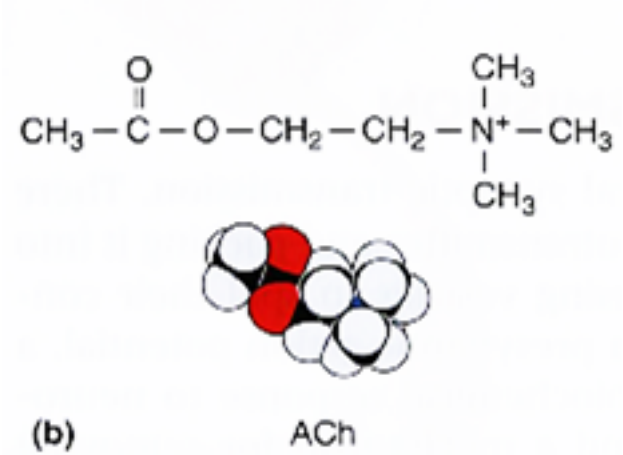
Some specific neurotransmitters



Amino Acids

Glutamate (Glu): major excitatory neurotransmitter in the brain

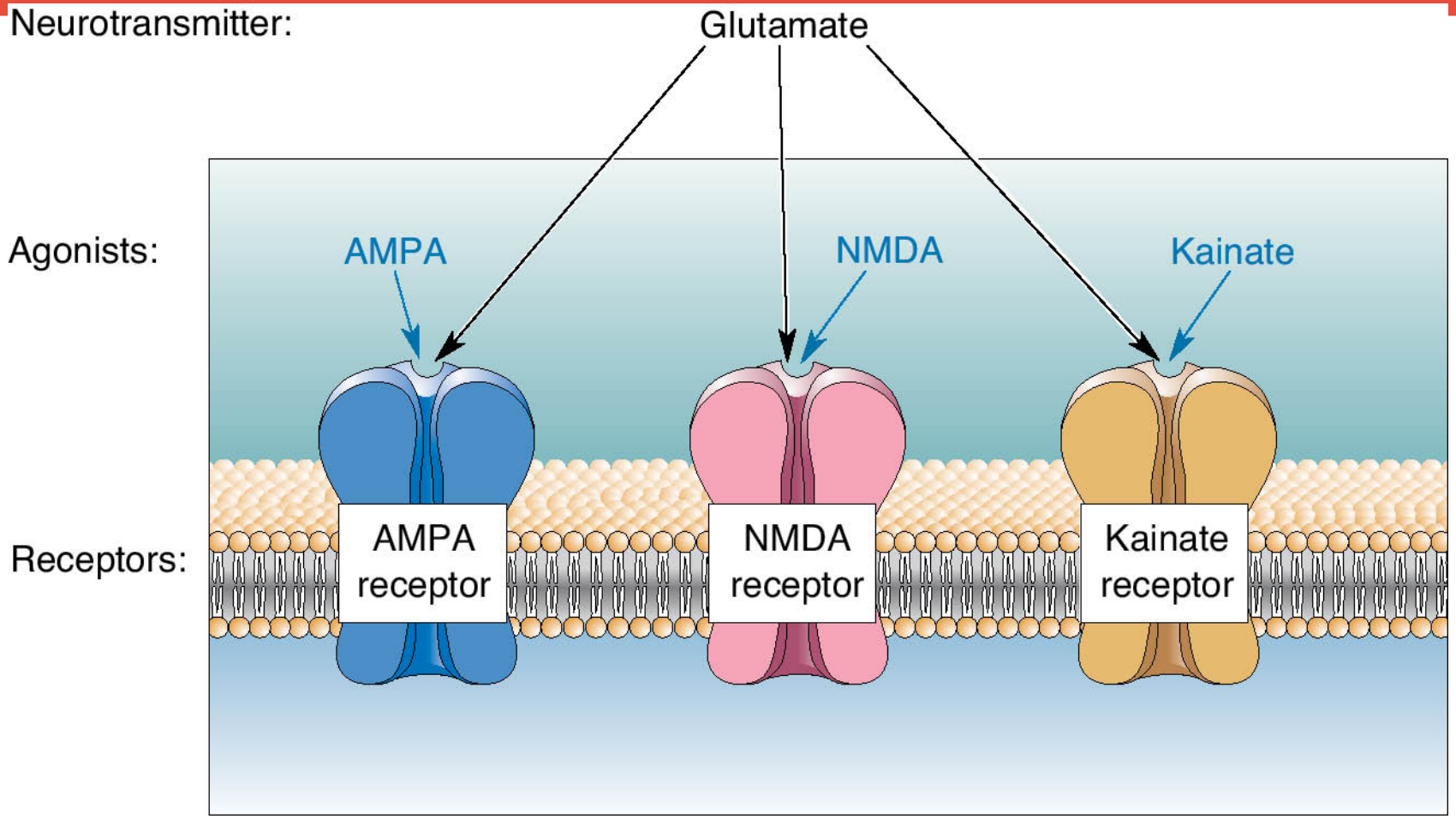
γ-aminobutyric acid (GABA) : major inhibitory neurotransmitter in the brain



Amine:

Acetylcholine (ACh): neuromuscular junction and throughout the brain as modulatory cholinergic system

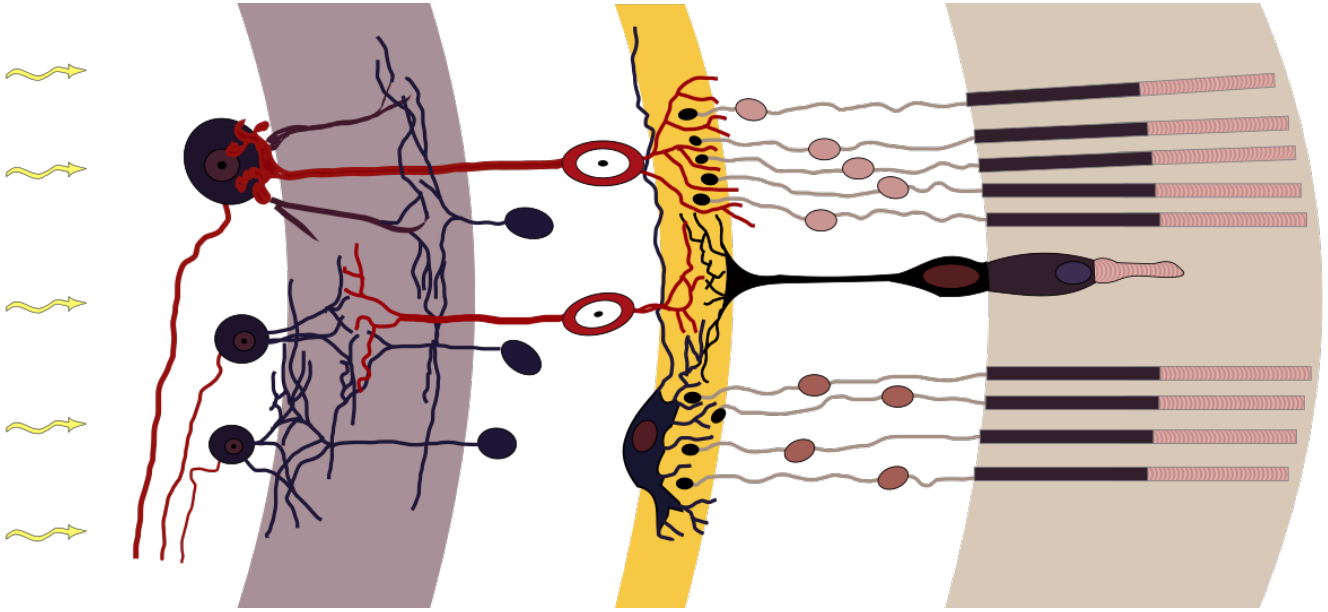
Different receptors for *same* transmitter



Glutamate is the most wide-spread excitatory neurotransmitter in the CNS. The receptors have different subtypes named by the chemicals that act as agonists (activate the receptor).

Different receptors for same transmitter

Sometimes, receptors can even reverse the effect (from EPSP → IPSP).



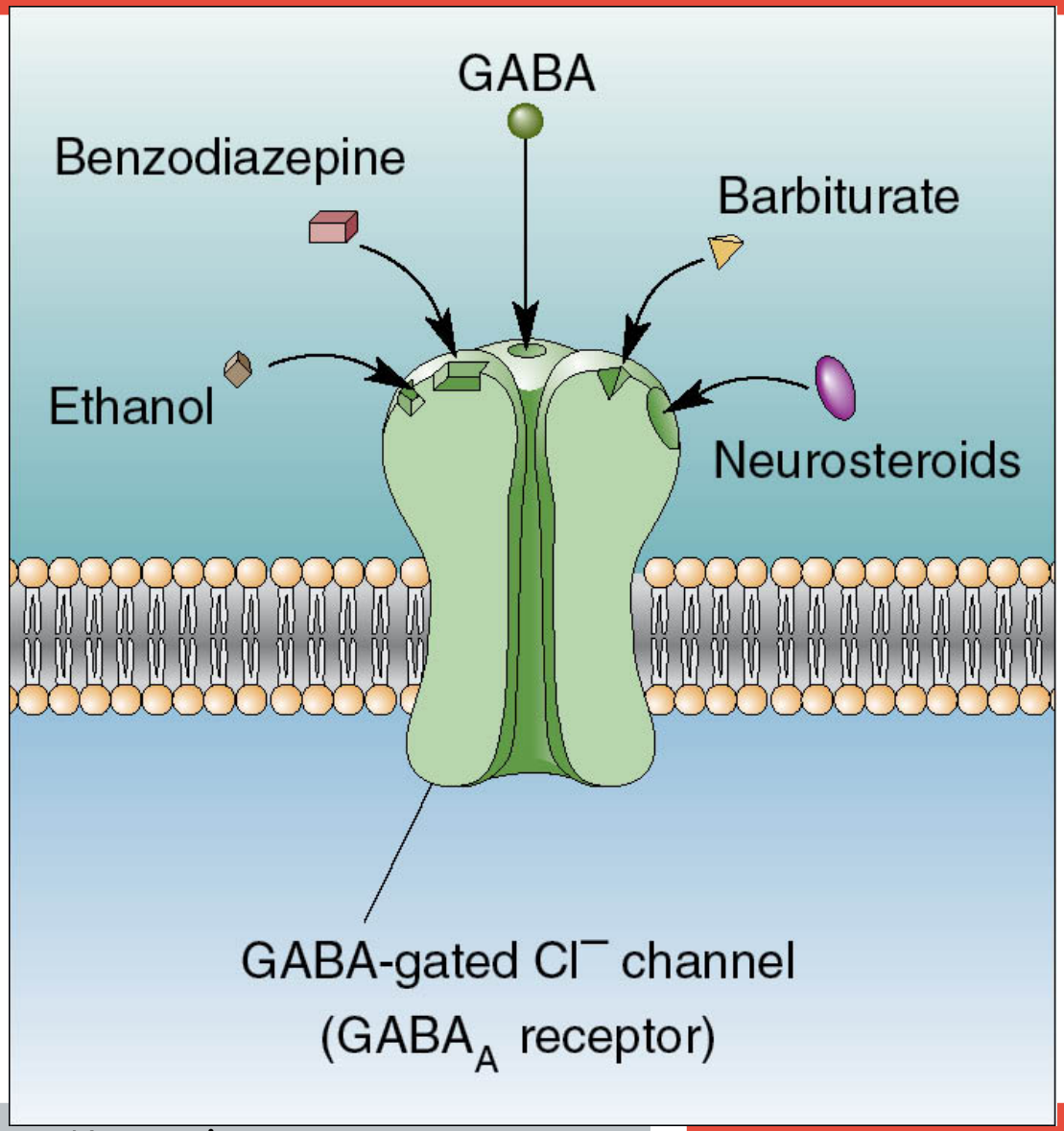
Bipolar cells in the retina are of two types:
ON: express *mGluR6* glutamate receptor, which couples negatively to nonselective cation channel (causes hyperpolarization IPSP)
OFF: express *AMPA/kainate* glutamate receptors (causes depolarization EPSP)

Different GABA receptors

GABA is the main inhibitory neurotransmitter in the CNS. Glycine is more dominant in the spinal cord and brain stem (also CNS). They both gate a Cl^- channel.

Ethanol/alcohol enhances the function of the $GABA_A$ receptor (inhibition).

Benzodiazepines (such as diazepam) and barbiturates act as CNS depressants (to treat anxiety or seizures) because they also enhance inhibition by GABA.



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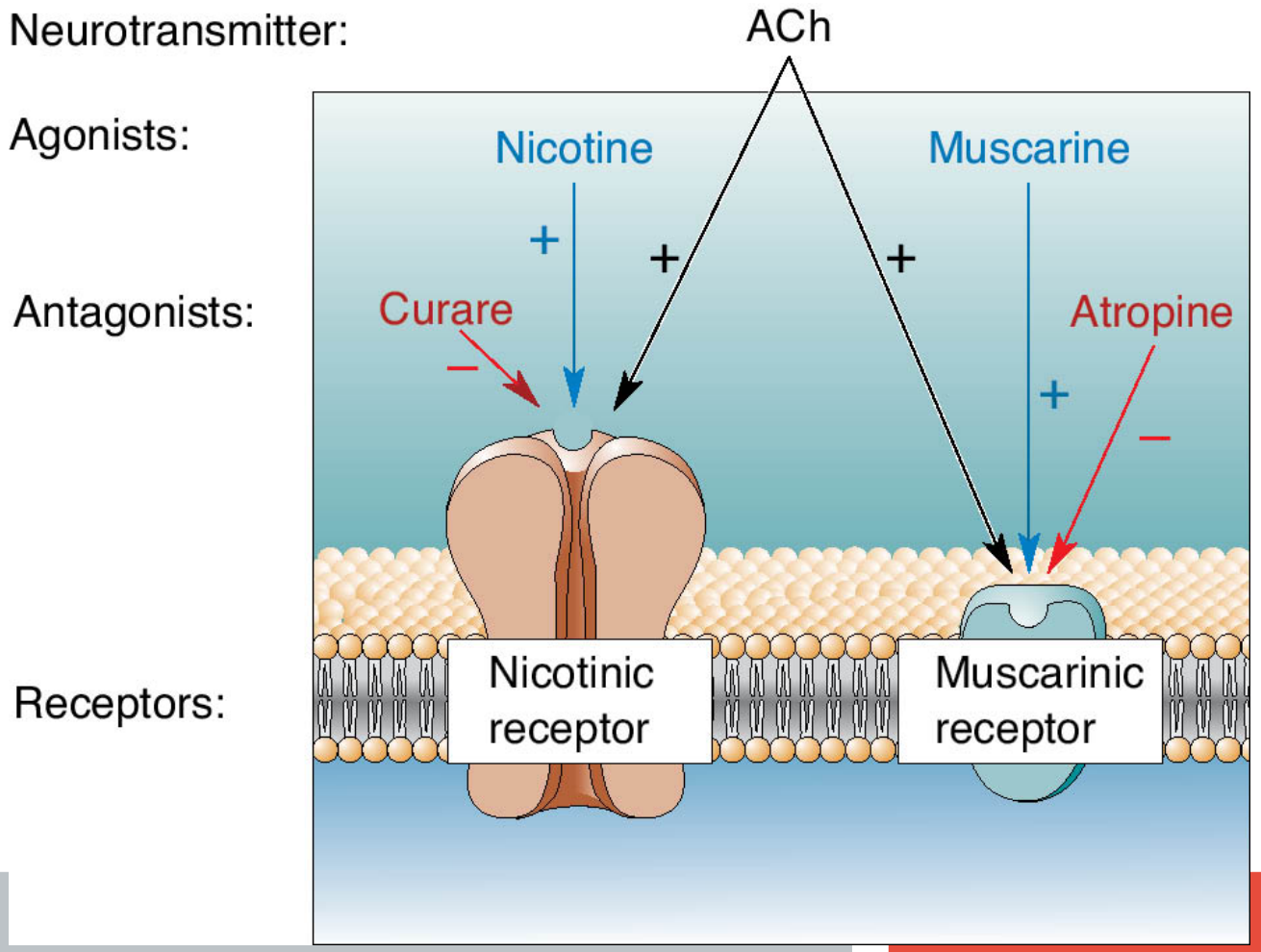
Different ACh receptors

Acetylcholine (ACh) receptors have two subtypes: nicotinic receptors mainly in skeletal muscles, muscarinic receptors, e.g., for slowing the heart.

Nicotinic receptor: nicotine activates it, the arrow-tip poison curare inhibits it.

Muscarinic receptor: the mushroom poison muscarine activates it, the plant poison atropine inhibits it.



Life cycle of ACh in synapse

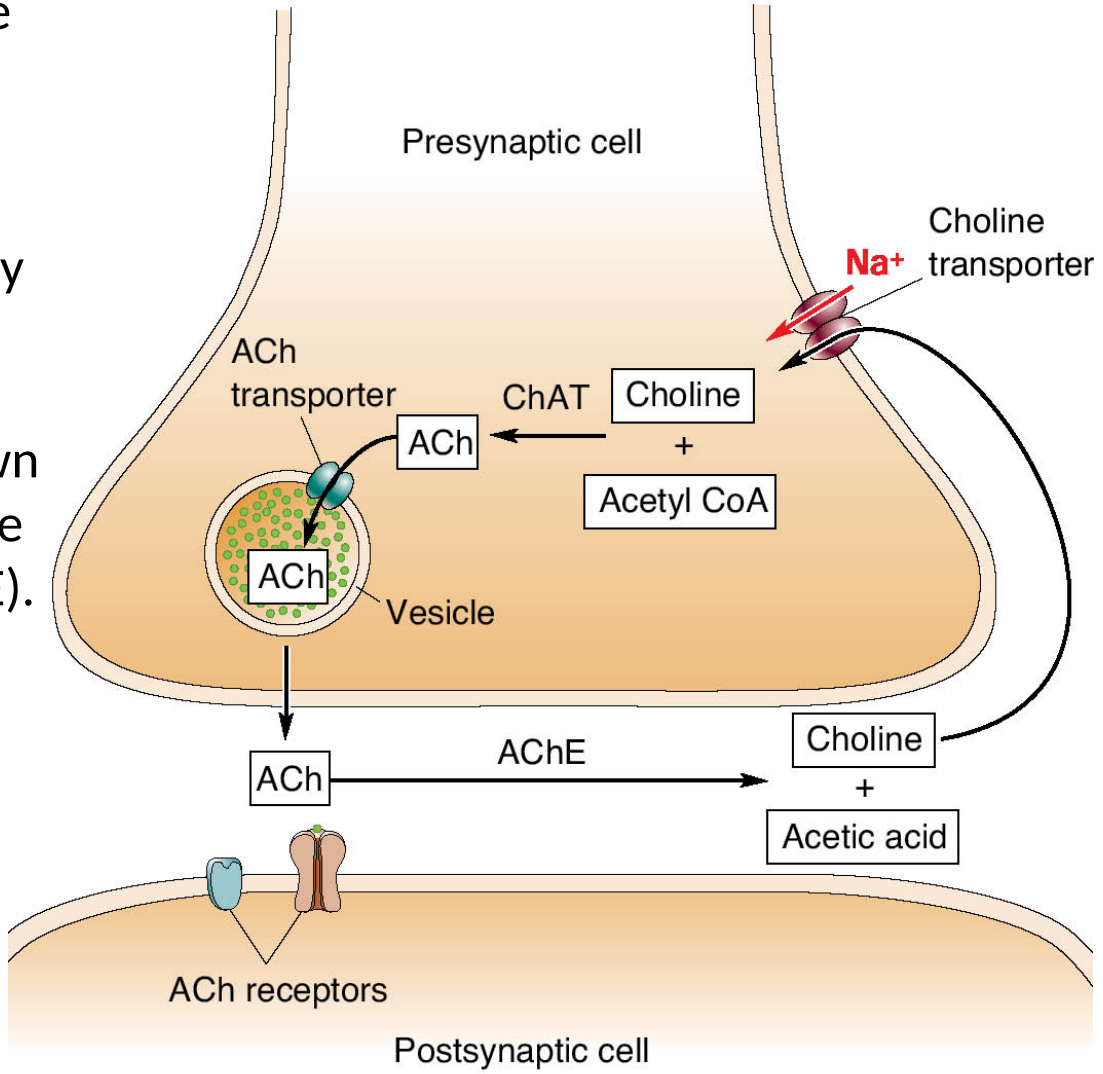
ACh is synthesized with the enzyme choline acetyltransferase (ChAT) from choline and acetyl CoA.

It is then concentrated in vesicles by an ACh transporter.

After exocytosis, ACh is broken down into choline and acetic acid with the enzyme acetylcholinesterase (AChE).

Choline is taken up from the extracellular fluid by a choline transporter.

Many poisons and drugs affect these recycling pipelines of ACh and other neurotransmitters.



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Choline is taken up extracellular fluid b transporter.

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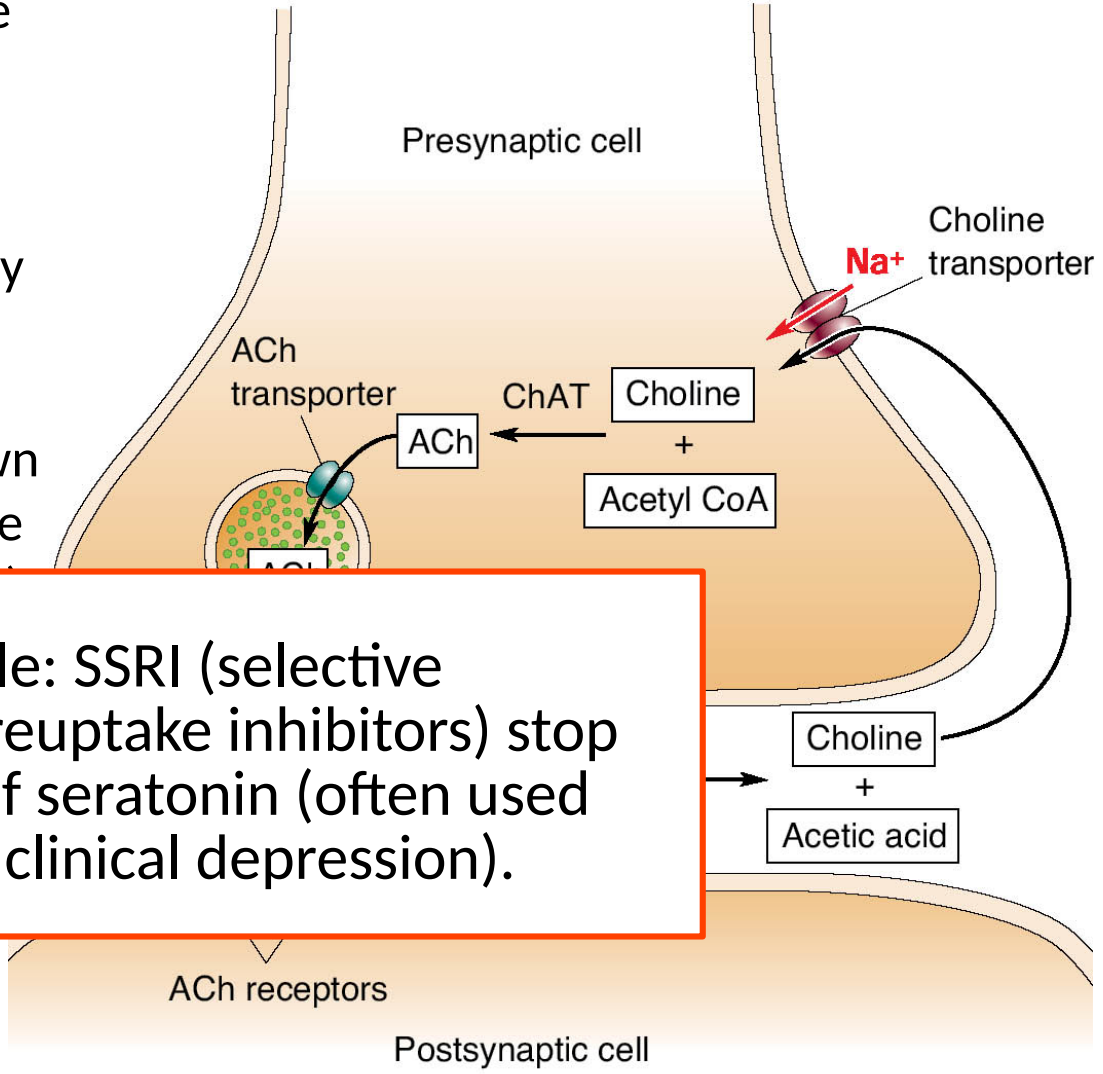


For example: SSRI (selective seratonin reuptake inhibitors) stop reuptake of seratonin (often used in treating clinical depression).

Schizophrenia (and Dopamine – DA)

Severe psychiatric disease that affects around 0.4-0.8 % of the general population.

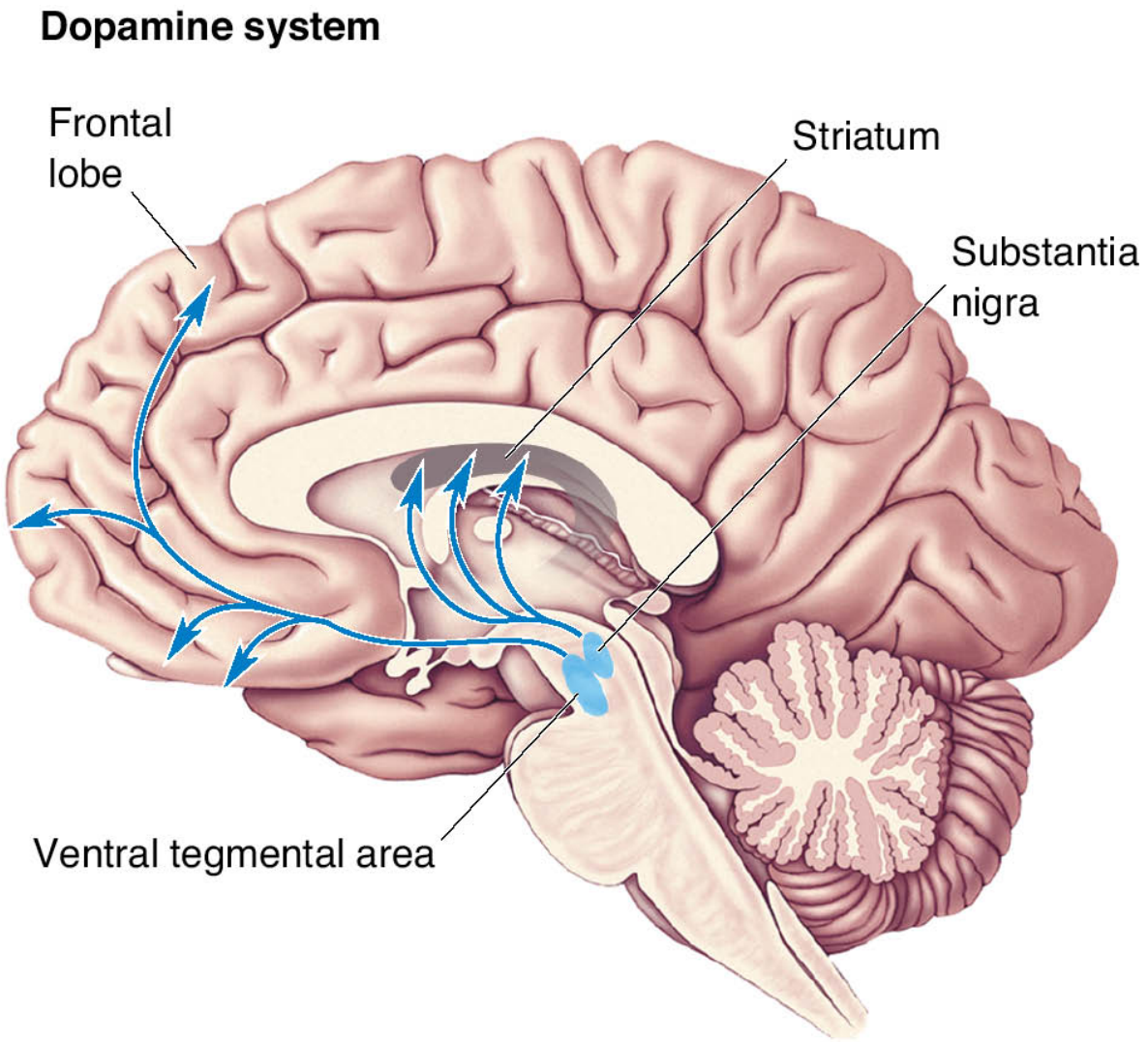
Positive Symptoms:	hallucinations, delusions, disorganized speech, disorganized/catatonic behavior
Negative Symptoms :	Flat affect, lack of pleasure, initiative, communication

Heritability is high, identical twins share the diagnosis in around 48% of the cases, fraternal twins in 17%. More than 100 gene loci have been associated with the risk of schizophrenia. Recently, a gene called C4 involved in immune function and brain development has been associated with schizophrenia risk (Sekar et al., Nature, 2016).

Dopamine in Schizophrenia

Neuroleptic drugs like chlorpromazine and haloperidol (developed in the 1950s) act as an antagonist to D_2 (Dopamine) receptors: they block these receptors.

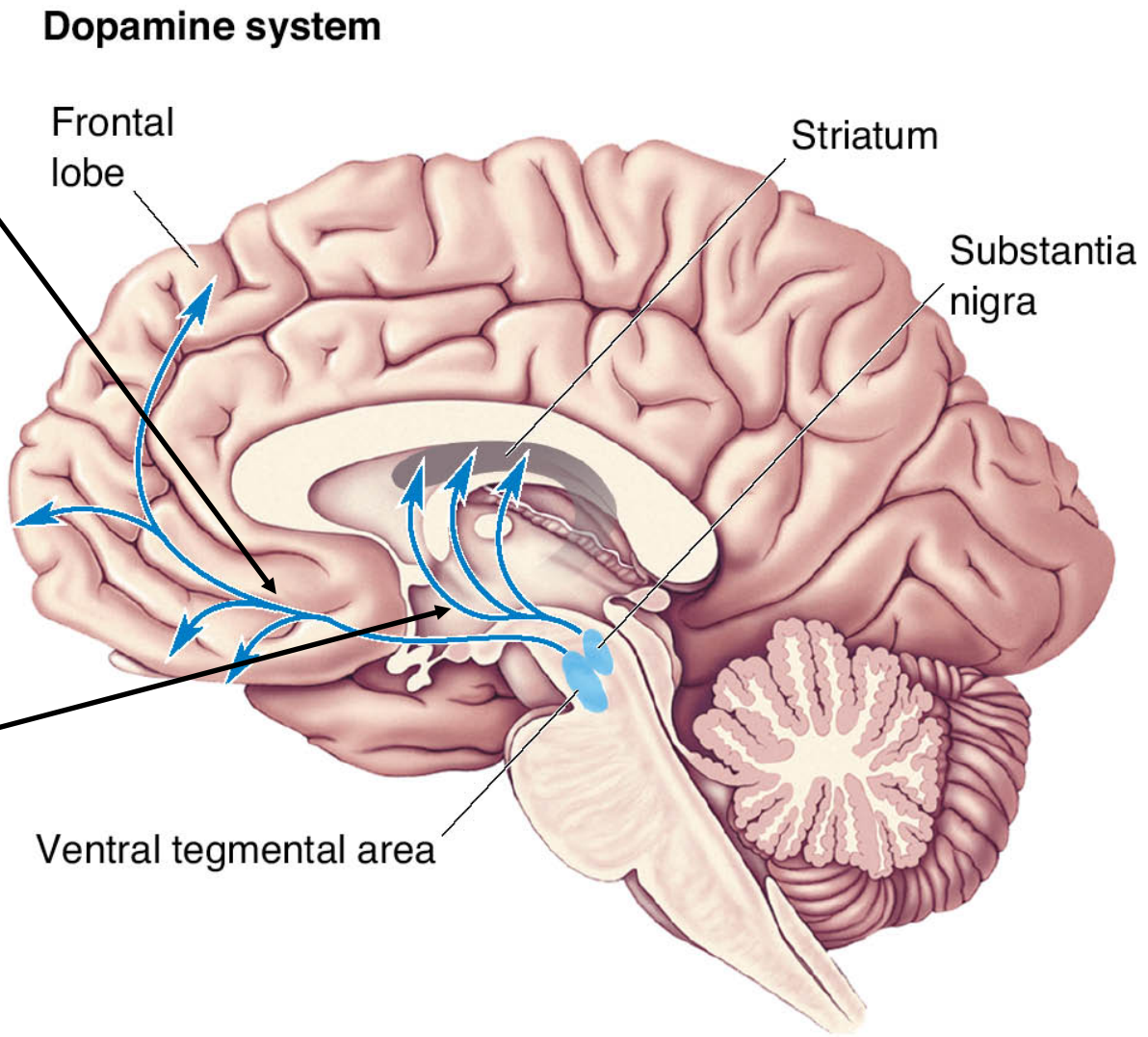
They improve the positive symptoms (reduce hallucinations, delusions, and disorganized speech/behavior).



DA and Schizophrenia

The effects of neuroleptic drugs mainly involve the mesocorticolimbic dopamine system.

However, they also have severe side effects: Parkinsonism, i.e., Parkinson's disease like symptoms (tremor, rigidity, slowness of movement).
That is because they also affect the nigrostriatal dopamine pathway.



Advantage of Schizophrenia (creativity?)

The romantic German poet Friedrich Hölderlin (1770-1843) suffered from a mental disorder (even though it is impossible to do a retrospective diagnosis) and spent half his life in the Hölderlin tower in Tübingen.

Is there a link between schizophrenia and creativity in the arts?

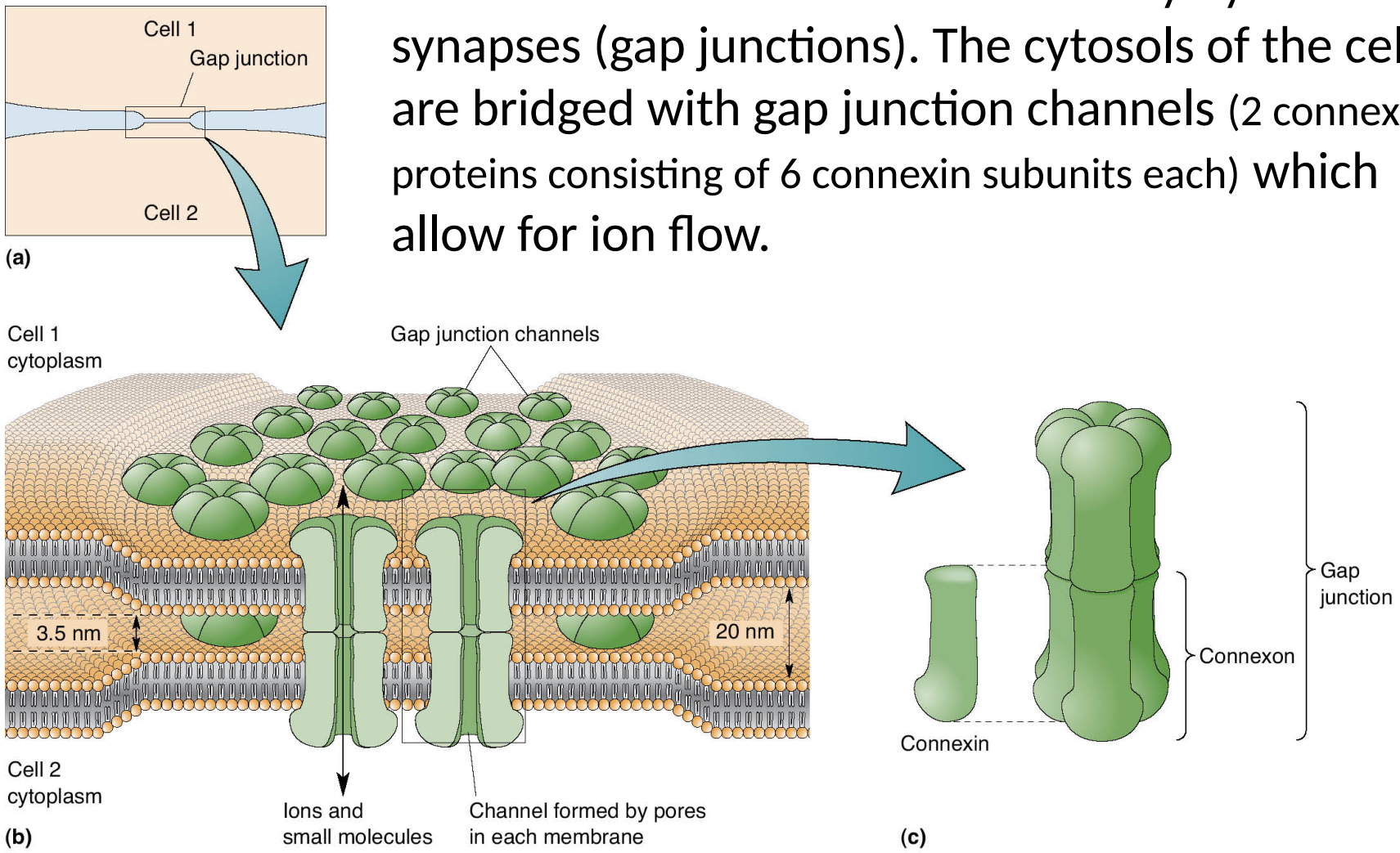
A recent study (Power et al., Nature Neuroscience, 2015) tested in a large sample of Icelanders (n=86292) whether there is an association between polygenic risk scores for schizophrenia and creativity (working as an artist such as musician, dancer, visual artist).

A significant (but small) association was found, with polygenic risk scores for schizophrenia explaining about 0.24% of the variance of creativity.

(polygenic risk scores: predicting risk by taking into account multiple genetic variants)

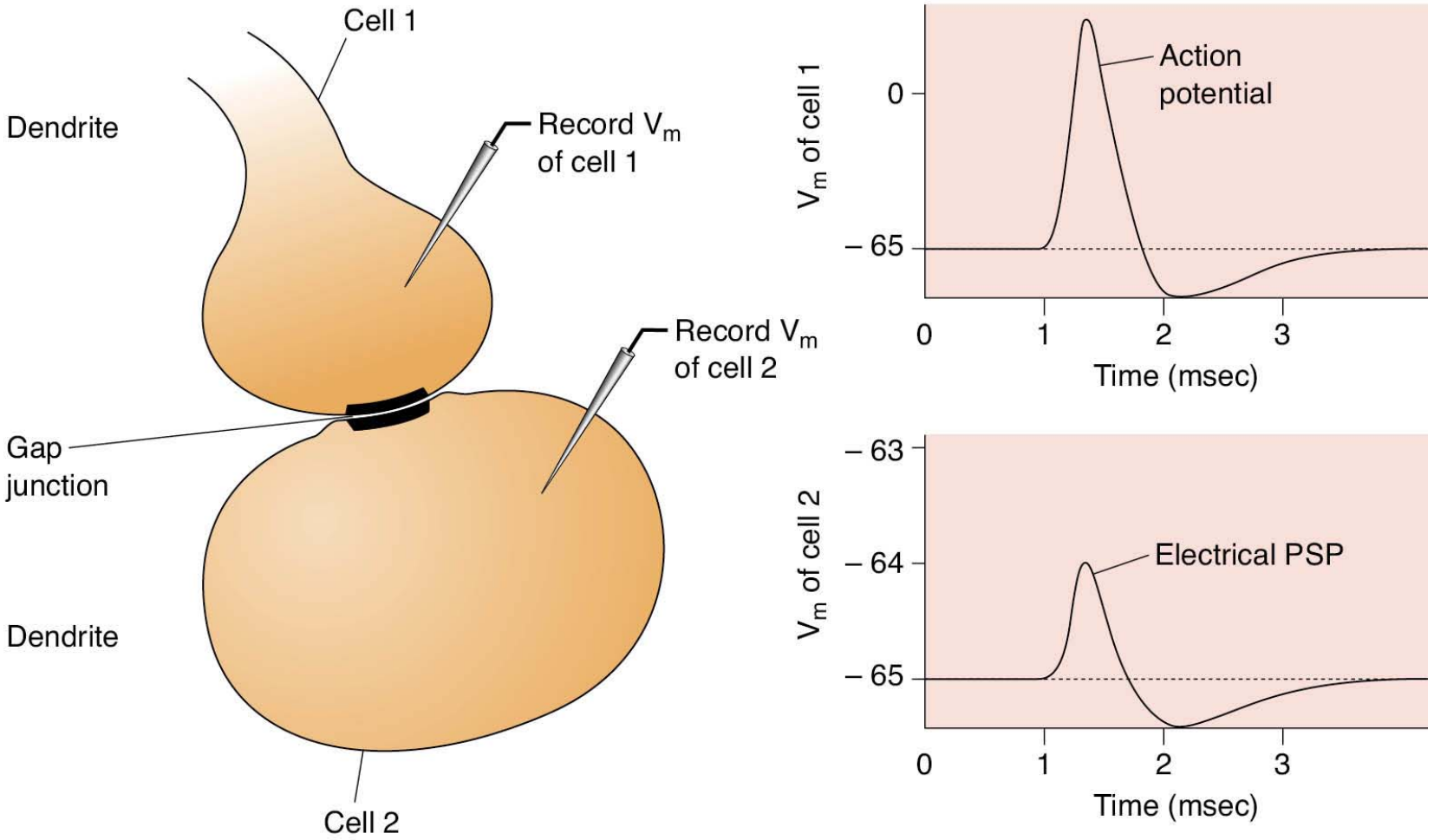
Electrical Synapses (Gap Junctions)

Some neurons are connected directly by electrical synapses (gap junctions). The cytosols of the cells are bridged with gap junction channels (2 connexon proteins consisting of 6 connexin subunits each) which allow for ion flow.



Gap Junctions

Action potentials in one cell will result in electrical postsynaptic potentials (PSP) that can trigger an action potential (if above threshold).



Summary

Neural information processing
Neurotransmitters and drugs

- The brain transmits information
  - electrically (membrane potential, ion flow, action potentials)
  - chemically (synaptic transmission)
  - electrically (gap junctions)
  - chemically (hormones)

- The synapse is the place of action for many drugs (therapeutic and recreational).