INTRODUCTION TO NEUROSCIENCE

UNIT NATS 6001

Lecture 3b- Communication mechanisms in the nervous system

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Neuronal communication

What happens once the action potential arrive to the axon terminal?

How information transmitted between two neurons?

Neuronal communication

Objectives

Synapses (anatomical and functional perspectives)

Electrical and Chemical transmission

Direct and indirect synaptic transmission

The vesicle cycle

Neurotransmitters

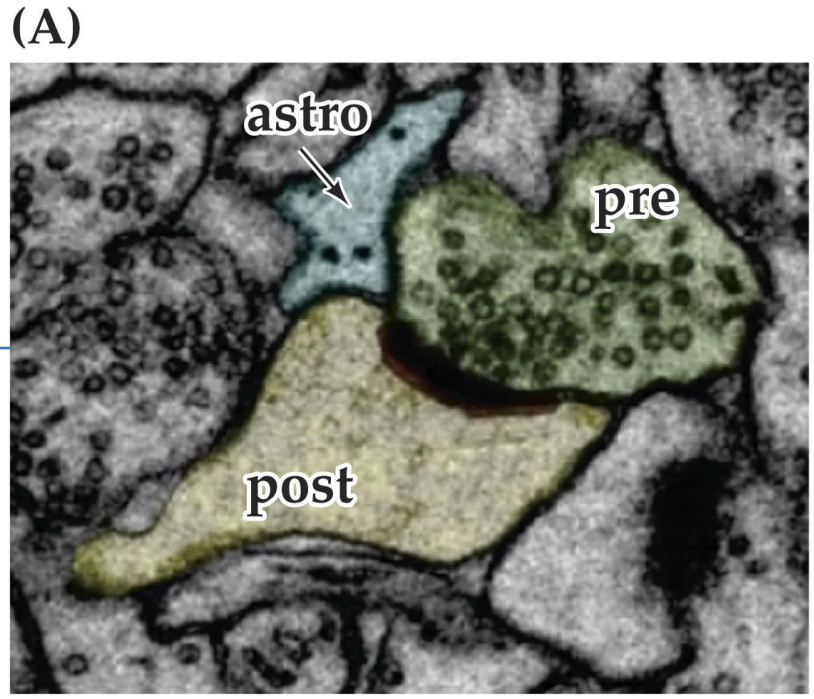
Neuronal communication

How information is transmitted between two neurons?

In the nervous system, information is transmitted through a special structure called ***Synapse***

Synapse – point of contact between neurons and their target (neurons / muscles/ glands), used to transfer signals.

A ***tripartite synapse*** made out of a presynaptic axon terminal, a postsynaptic dendrite and an astrocyte that wrap the synapse



NEUROSCIENCE 5e, Box 5C (Part 1)

Neuronal communication

Historical perspective-

One of the most intriguing questions during the last century was how neurons transmit information with high speed?

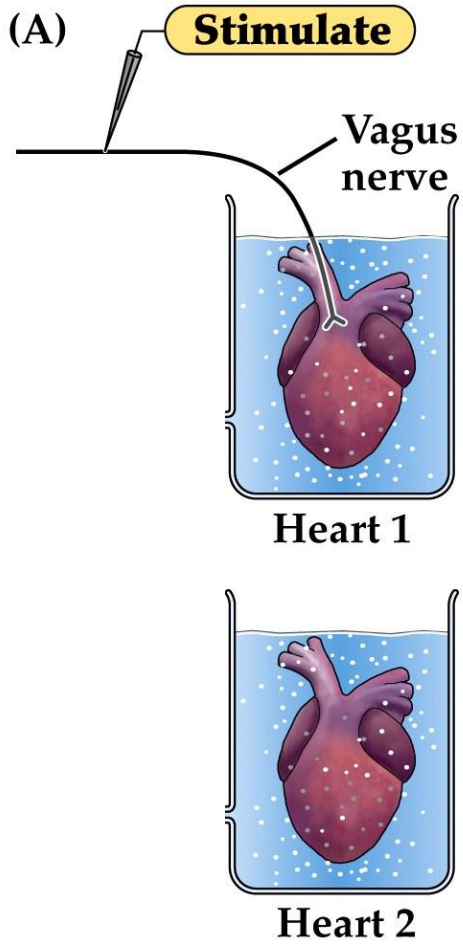
The common hypothesis claimed that electrical currents in the presynaptic terminal spread ***passively*** to the postsynaptic cell (***electrical transmission***).

The opposing hypothesis claimed that the information was transmitted by the local release and action of a chemical substance (***chemical transmission***, not very popular till 1950)

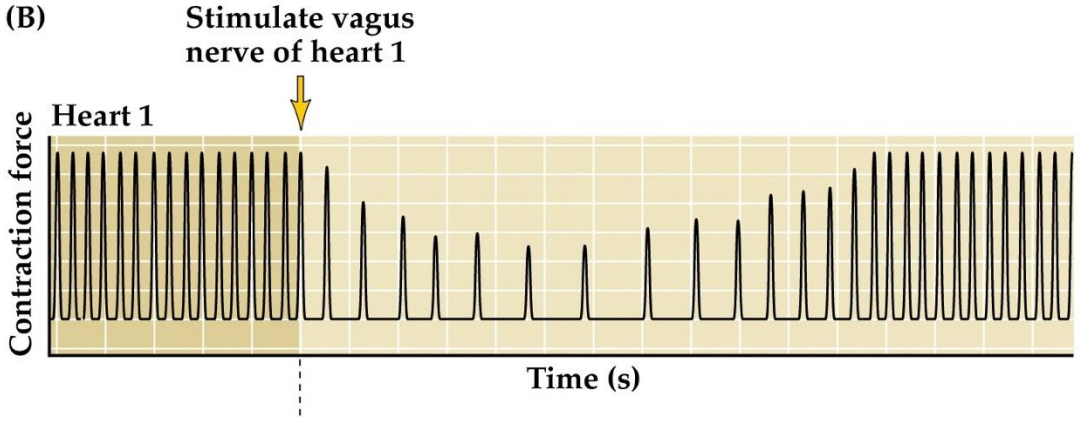
The reality is that the neurons transmit information **through both mechanisms**

Neuronal communication early days

To prove the existence of ***chemical transmission, Otto Loewi*** performed this experiment:



- He took two hearts (frog), perfused them in a solution and monitored there heart beats
- Than he stimulate the Vagus nerve of the first heart and found that the heart rate decreased.

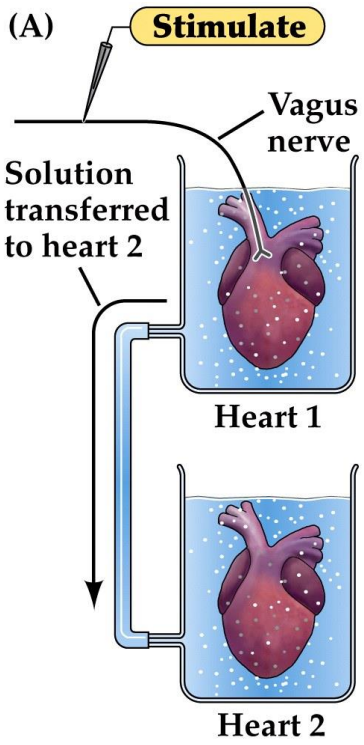


NEUROSCIENCE 5e, Figure 5.4 (Part 1)

Neuronal communication

When he circulated the solution of the first heart with the second, he saw that the second heart followed the response of the first one.

He concluded that the transmission of information between the Vagus nerve and the heart must be ***chemical.***



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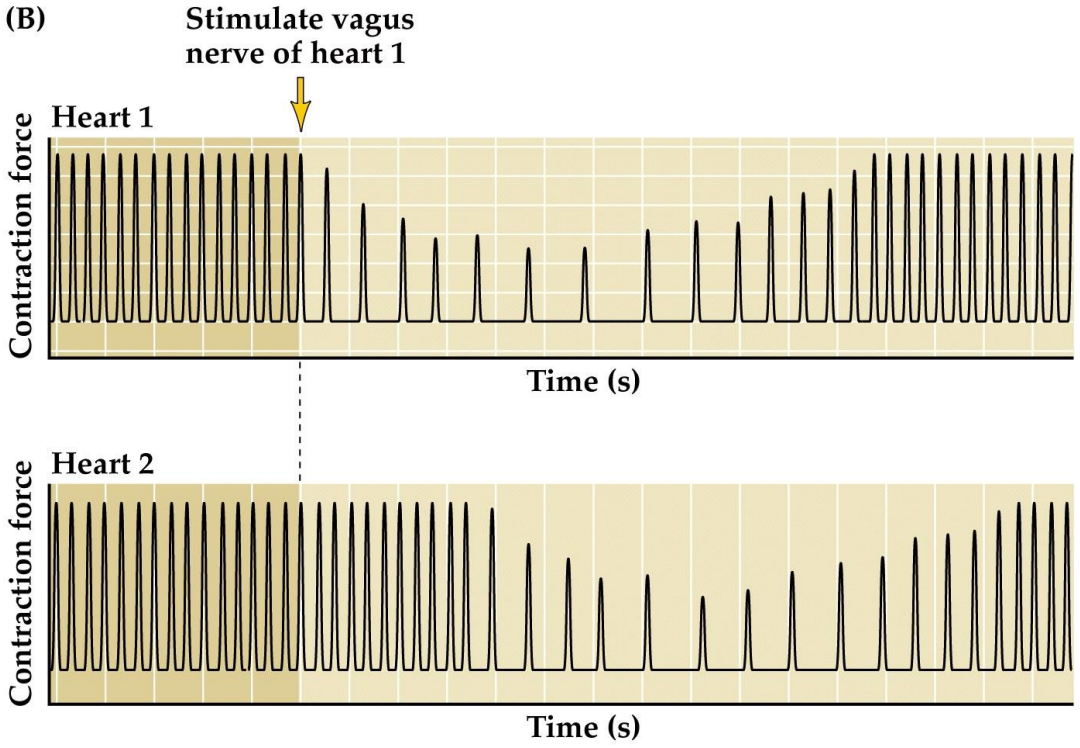
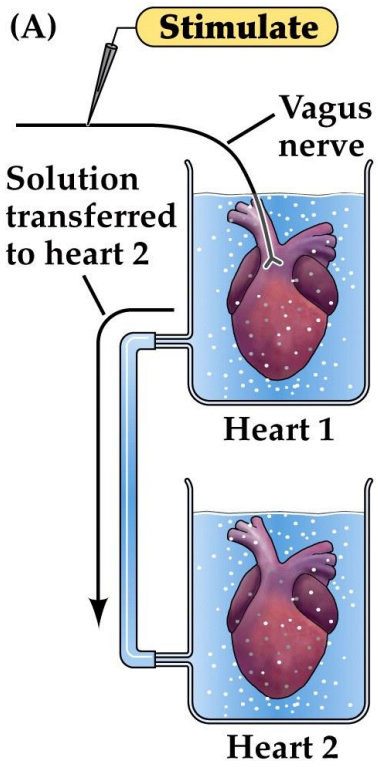


NEUROSCIENCE 5e, Figure 5.4 (Part 2)

Neuronal communication

So what really happened in this experiment?



NEUROSCIENCE 5e, Figure 5.4 (Part 1)

The stimulation of the Vagus nerve, lead to a release of a substance, which Loewi called ***"Vagus substance"*** – later shown to be Acetylcholine (ACh)

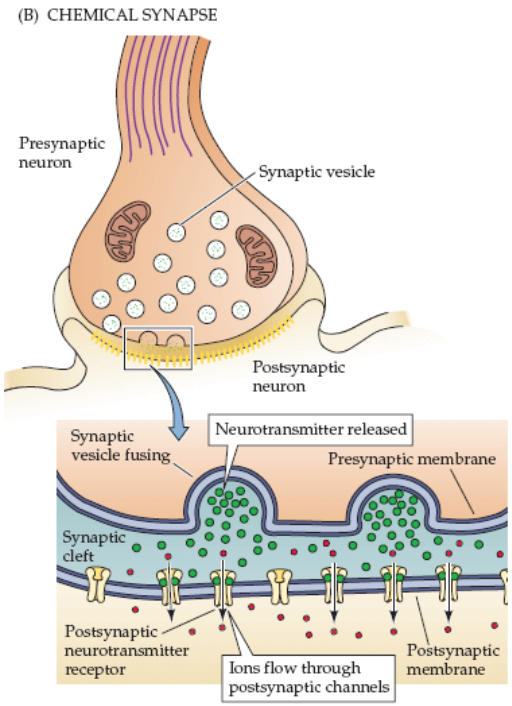
ACh spread in the first heart perfusion and from there to the next perfusion, in which it impact the second heart beating.

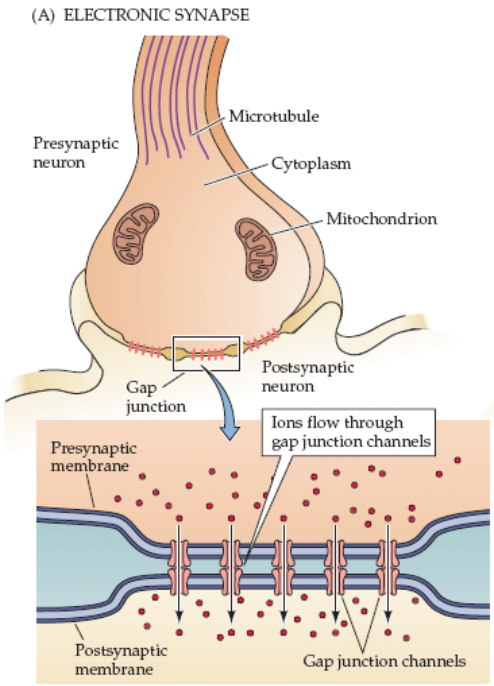
Therefore, information ***can*** be transmitted through chemical agents.

Mechanisms for synaptic transmission

We have two types of synaptic transmission in the nervous system:

- ***Chemical transmission*** through ***chemical synapses*** (most common)
- ***Electrical transmission*** through ***electrical synapses***



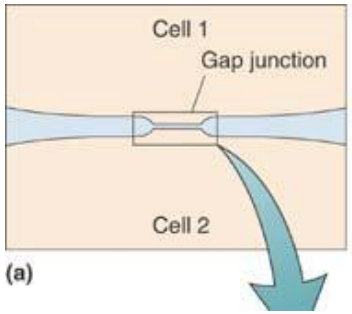


Mechanisms for synaptic transmission

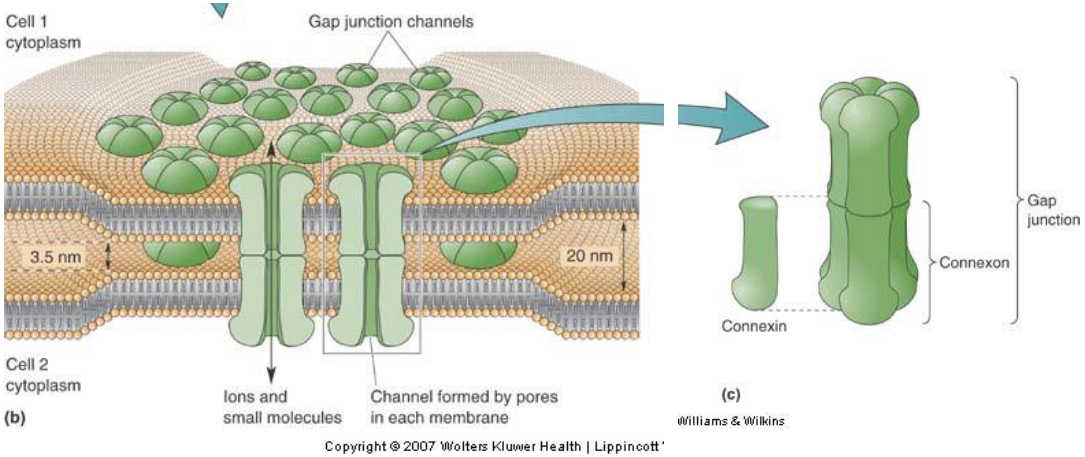
Lets have a close look on each type

Electrical Synapses

Electrical transmission is the direct transfer of ***ionic current*** from one cell to the other through ***Gap Junctions***



- The membranes of two cells are held together by clusters of ***connexins***
- ***Connexon -*** A channel formed by six connexins
- Two ***connexons*** combine to from a gap junction channel, which allows ions to pass from one cell to the other



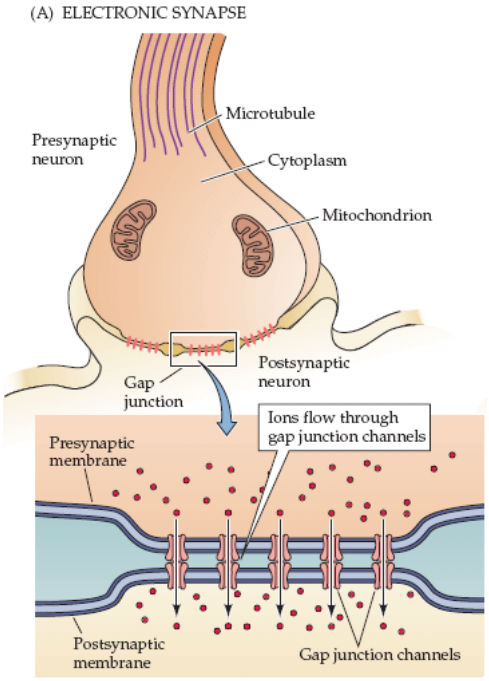
Pore is 1-2 nm wide : large enough for all the major cellular ions and many small organic molecules to pass

Electrical Synapses

Why we have electrical transmission?

- Amplification of signal, as it allow to synchronize electrical activity among populations of neurons (e.g. inhibitory neurons form an inhibitory network).

- Fast response to coordinate the activity of group of neurons (e.g. escape reflex in Crayfish)



Electrical Synapses

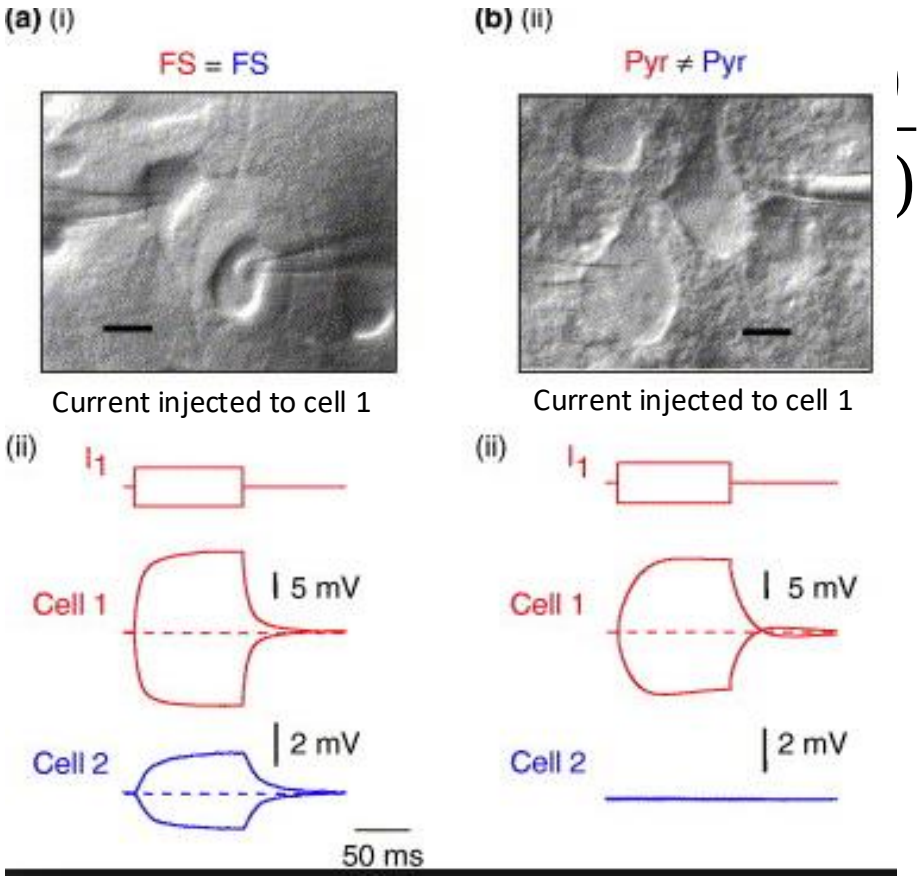
Characteristics of electrical synapses:

- ***Wide pore*** size (1-2 nm) that allow the transport of large molecules.
- Mostly ***bidirectional*** – as current can flow in either direction across the gap junction according to the potential difference (although sometimes unidirectional).
- ***Fast transmission***, as no involvement of vesicular release (0.2 ms).
- The channels opening can be ***regulated*** through calcium and phosphorylation.
- In electrical synapses, the response is ***always of the same sign*** as the source *(**depolarization** of the pre-synaptic membrane will always induce a **depolarization** in the post-synaptic membrane, and vice versa for hyperpolarization).*
- Have a ***coupling ratio*** – the degree of electrical coupling between two cells

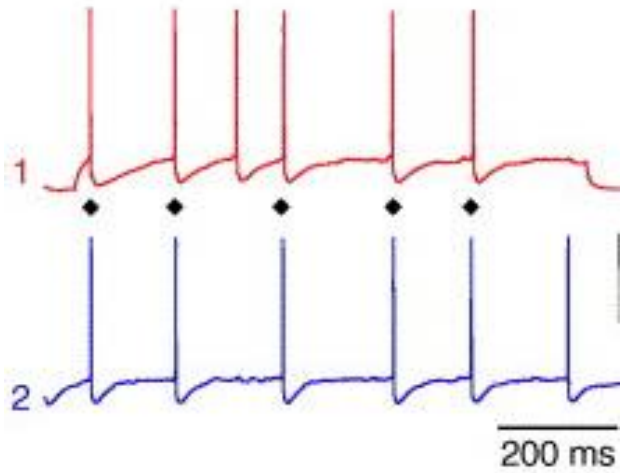
Electrical Synapses coupling coefficient

A Coupling ratio describe the ***connection strength*** of the synapse

Example – ***CC*** of 1:5 means that the voltage change in the postsynaptic cell (V_2)is a fifth of the voltage in the presynaptic cell (V_1).



$$\frac{\quad}{\quad} = 0.2$$



Hestrin et al, 2005

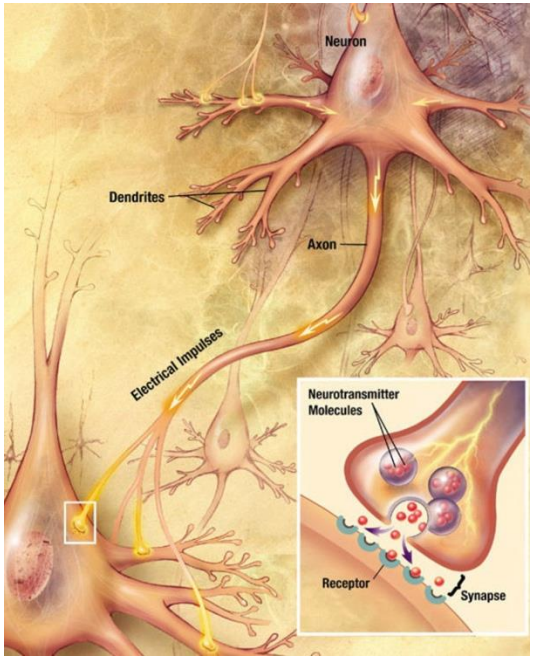
Chemical synapses

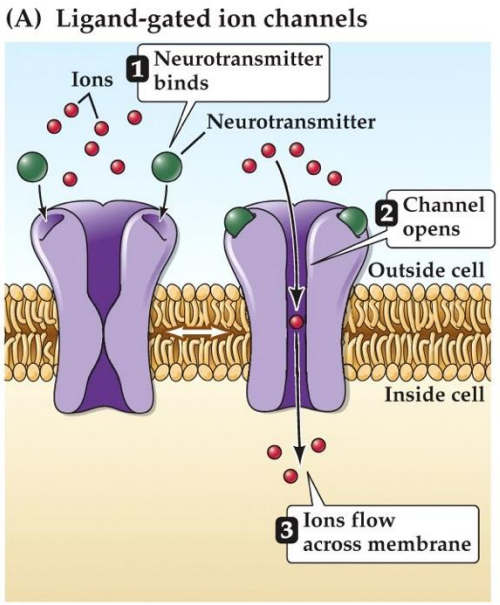
In chemical synapses,

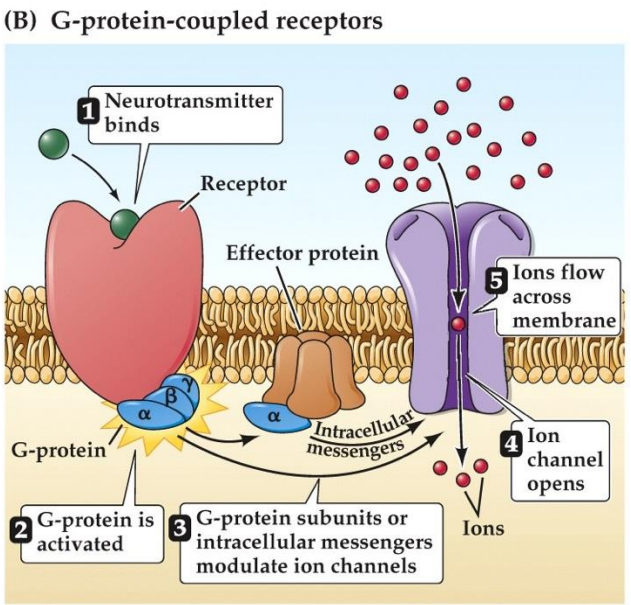
A ***neurotransmitter*** is released from a presynaptic ***vesicle*** and bind to a postsynaptic ***receptor.***

If the ***receptor*** is an ion channel ***(inotropic receptors)***, it will open and initiate an ion influx or efflux out of the postsynaptic cell (***Direct transmission)***

If the ***receptor*** is not an ion channel (***metabotropic receptors***), it will lead to a cascade of second messengers which will ultimately modulate ion channels (***indirect transmission***)



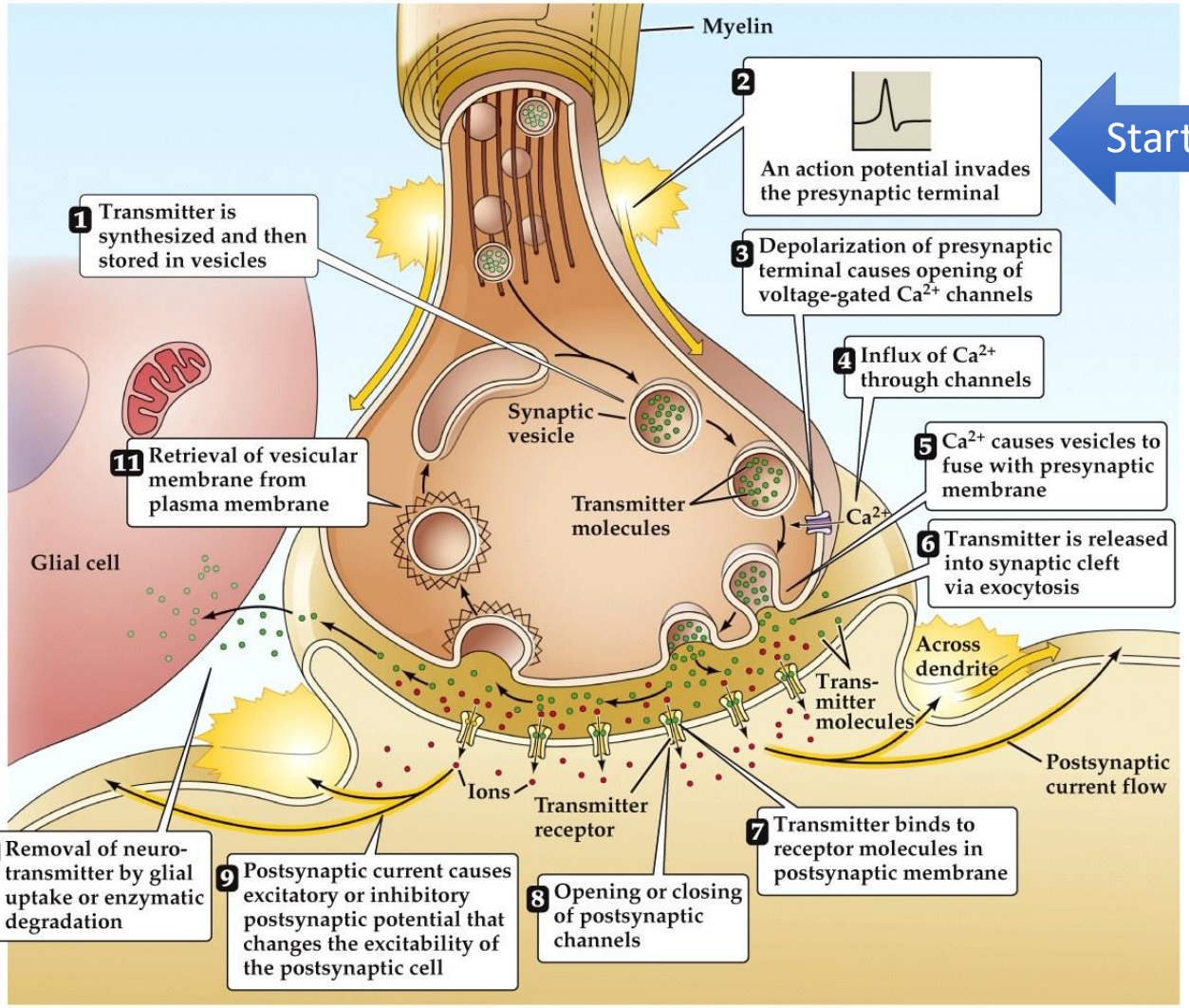




***NEUROSCIENCE 5e,* Figure 5.16**

Chemical synapses Direct transmission

Direct transmission starts with an action potential…



***NEUROSCIENCE 5e*, Figure 5.3**

Chemical synapses Direct transmission

The activation of the ***inotropic receptors*** will ultimately lead to ion flux that can lead to either ***excitation*** or ***inhibition***.

Excitation – a process which increase the probability of initiating an action potential in the postsynaptic cell. An excitatory event will increase the ***excitability*** of the membrane (usually ***depolarizing*** the membrane potential).

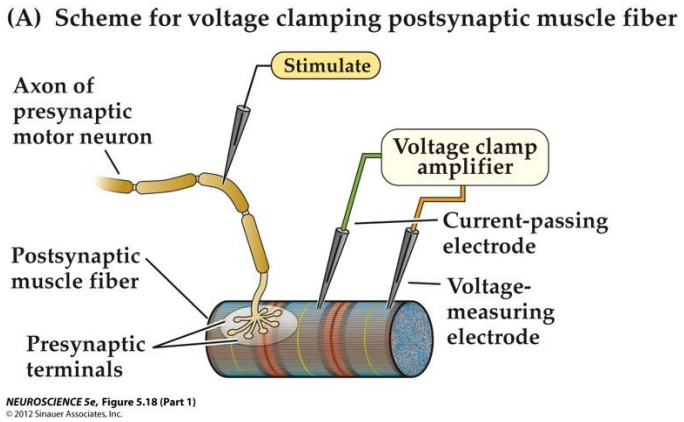
Inhibition – a process which decrease the ***excitability*** of the membrane (and therefor the probability to produce action potential), either by hyperpolarizing the membrane potential, or shunting excitatory currents.

Excitability – a qualitative characteristic of the membrane, which describe the potential to produce an action potential. Defined as $1/I_{Rheobase}$

$I_{Rheobase}$ - the minimal current needed to elicit an action potential at infinite time (>x5 time constant)

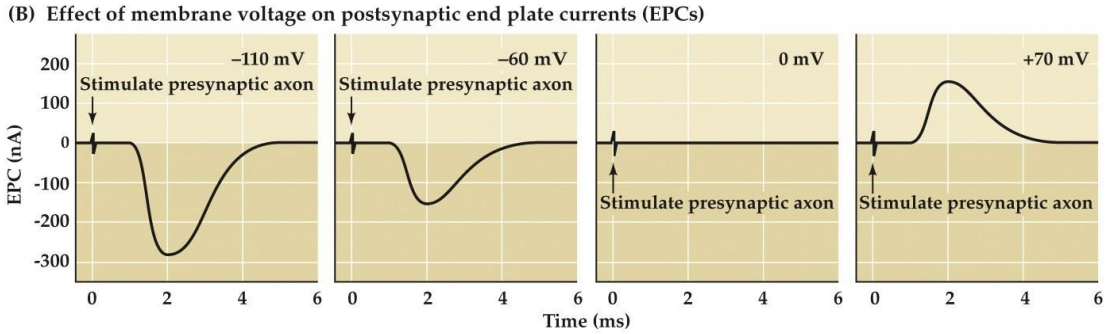
Chemical synapses Direct transmission

To get a better understanding about the postsynaptic potentials, lets look on the synaptic transmission in the neuromuscular junction



A two-electrode voltage clamp setup, enable to clamp the voltage and record the current going through the membrane

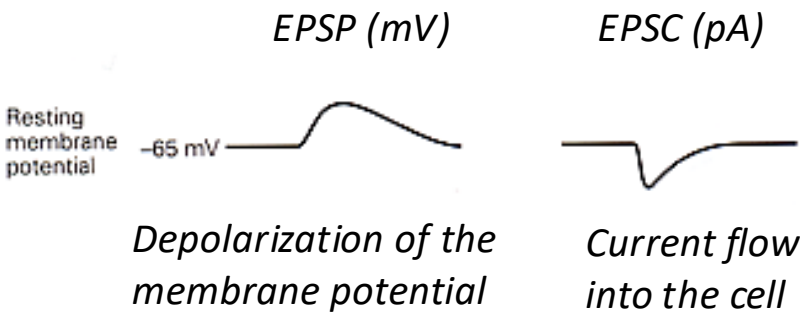
Following stimulation of an action potential in the presynaptic terminal, there is a change in the membrane current of the postsynaptic cell, called ***Excitatory postsynaptic current (EPC)***



Chemical synapses Direct transmission

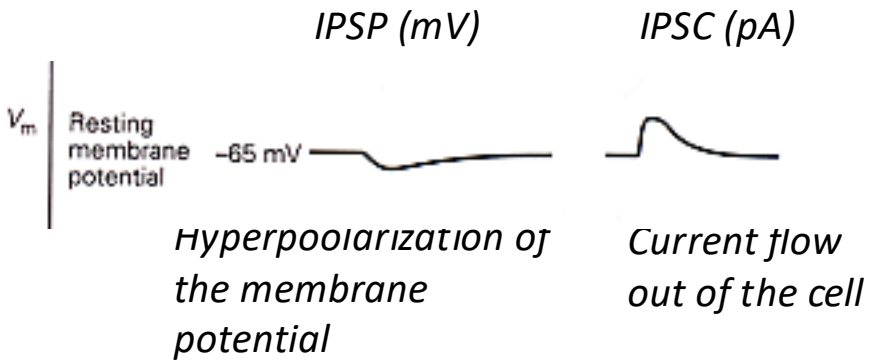
The change in the membrane potential can be either ***excitatory*** or ***inhibitory***

An excitatory current/potential is called ***Excitatory post Synaptic Potential/Current (EPSP/EPSC)***



Chemical synapses Direct transmission

An inhibitory current/potential is called ***Inhibitory post Synaptic Potential/Current (IPSP/IPSC)***



Chemical synapses Direct transmission

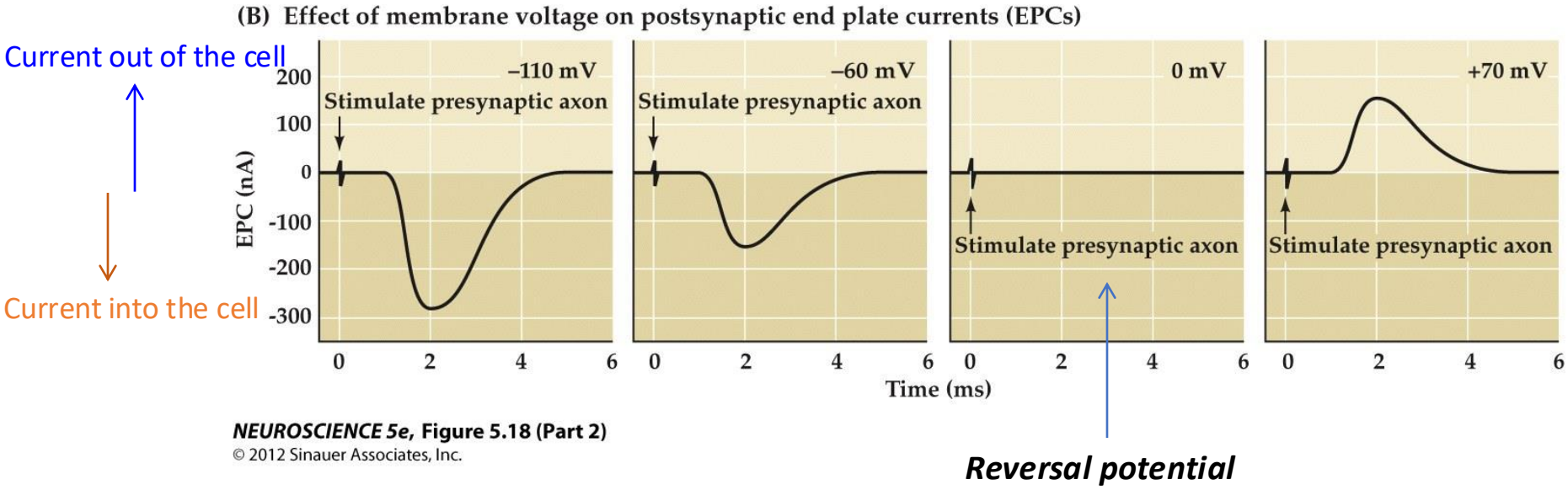
Does all depolarizing synaptic potentials are excitatory and hyperpolarizing are inhibitory?

No, it depends on the ***synaptic reversal potential***

Chemical synapses Direct transmission

The ***synaptic reversal potential*** is the membrane potential in which the current flowing through the synaptic channels equal to zero. Further depolarization will result in a current flow to the opposite direction.

The current amplitude is voltage dependent, as it decrease with depolarization of the membrane potential



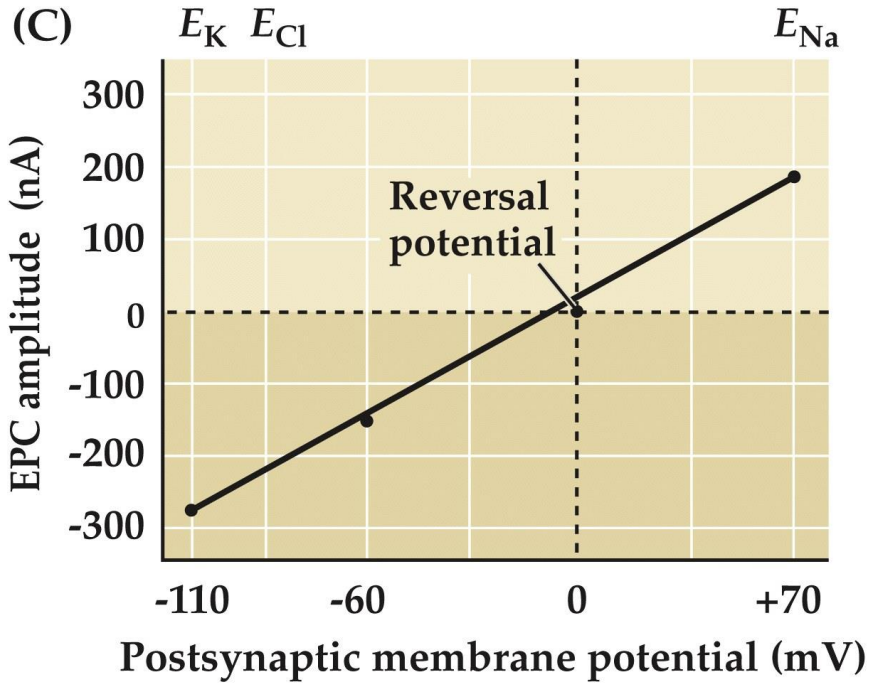
***NEUROSCIENCE 5e*, Figure 5.18 (Part 2)**

Once the net current flow into the cell is ***reversed*** to a current out of the cell, we can say that the synapse is in it's reversal potential.

Chemical synapses Direct transmission

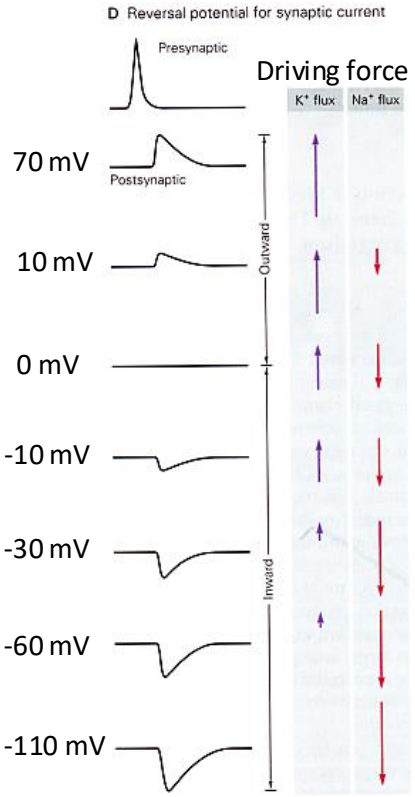
Per definition,
the reversal potential is the membrane potential where the I-V slope cross the O current.

An I-V curve



NEUROSCIENCE 5e, Figure 5.18 (Part 3)

Can be measured experimentally



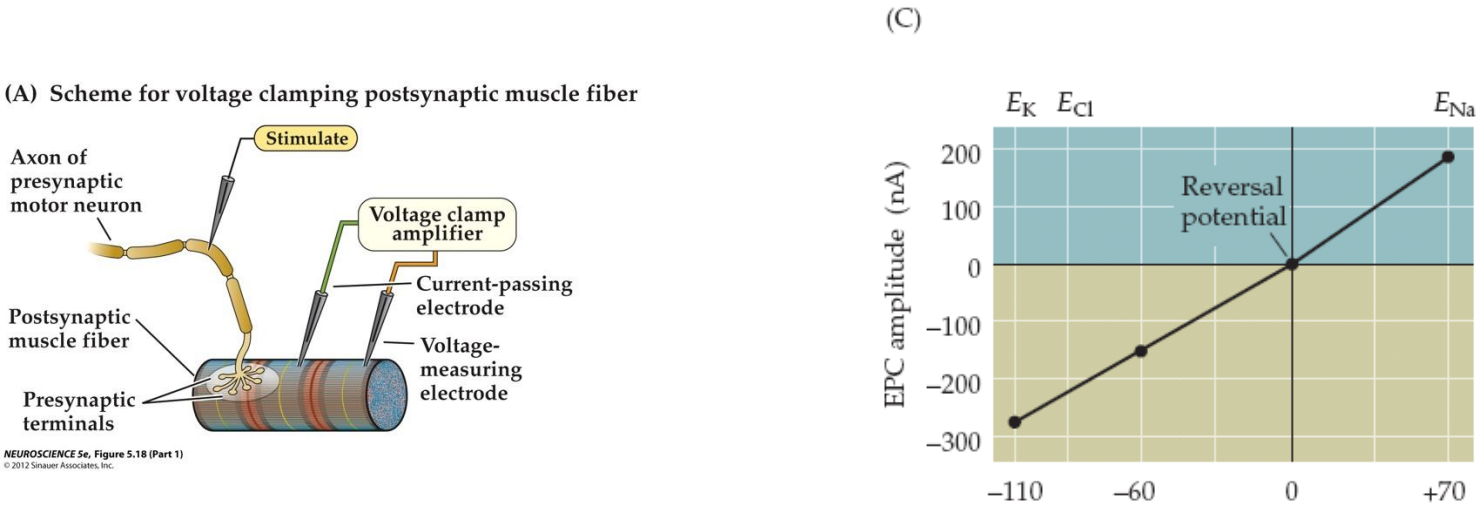
Chemical synapses Direct transmission

What determine the synaptic reversal potential?

Chemical synapses Direct transmission

Let's go back to the neuromuscular junction experiment…

Following synaptic stimulation and establishment of the ***reversal potential***, we changing the external Na^+ and K^+ concentration.

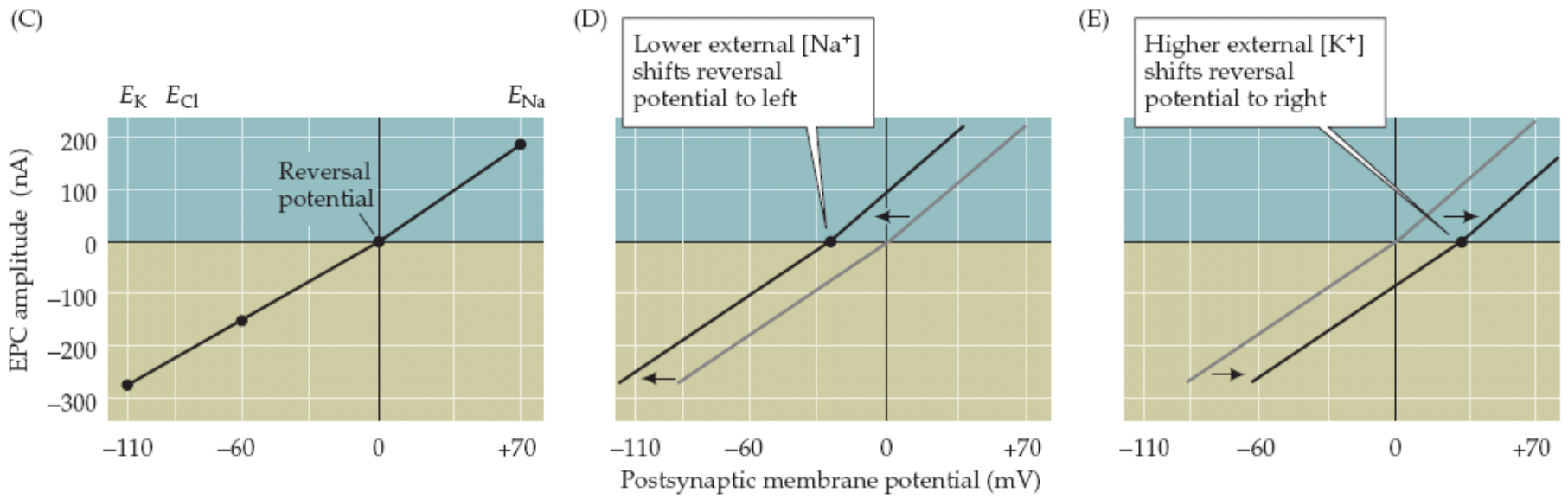


***NEUROSCIENCE 5e*, Figure 5.18 (Part 2)**

Chemical synapses Direct transmission

Changing the external concentration of Na^+ or K^+ shift the ***IV slope*** and therefore the ***synaptic reversal potential***. Why?

Changing the external concentration impact the equilibrium (Nernst) potential of the specific ion.



Because these specific synaptic channels conduct both Na^+ and K^+ , both ions can impact the reversal potential of the synapse.

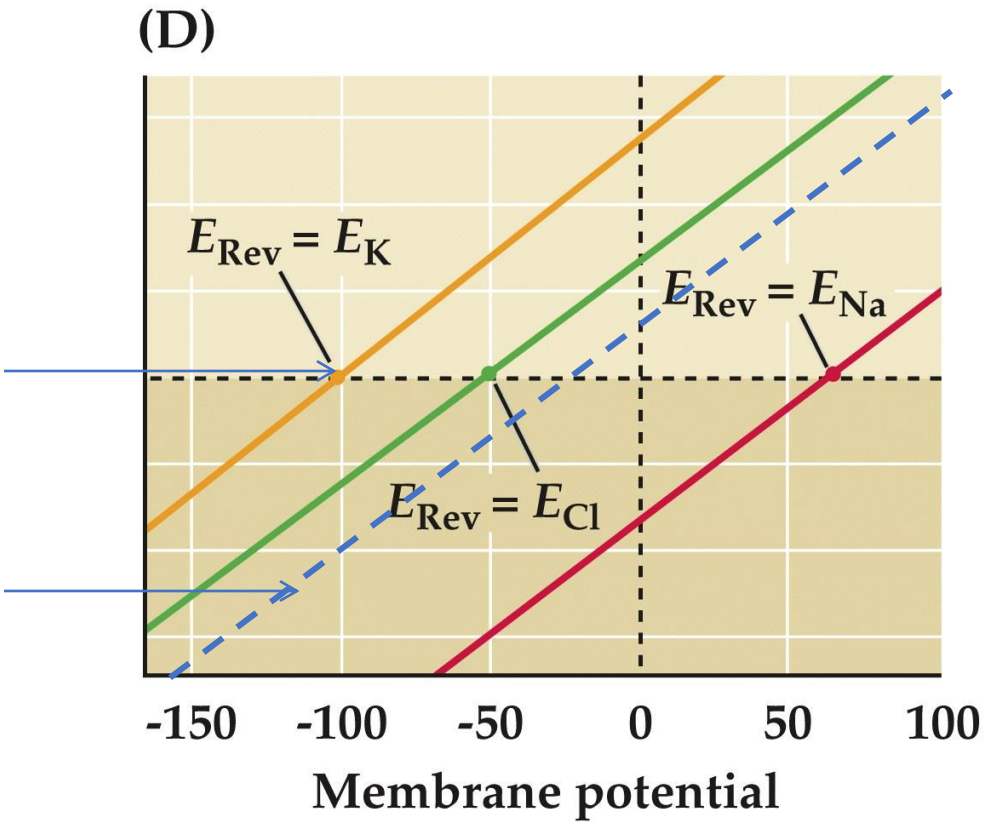
Chemical synapses Direct transmission

The reversal potential depends on the ***Nernst potential*** of the ions that pass through the synaptic channel.

When a membrane is permeable to ***more than one ion***, than the synaptic reversal potential will be the ***average Nernst potential of their relative conductances***.

Reversal potentials of synapses that conduct only one type of ions

If the synapse is conducting more than one ion (Na & K+)



NEUROSCIENCE 5e, Figure 5.18 (Part 4)

Chemical synapses Direct transmission

Sample questions:

What will be the synaptic reversal potential (V_s) of a synapse that is ***equally*** permeable to Na^+ and K^+ ions?

E_{Na} = +40 mV
E_K= -100 mV

$$Vs = \frac{g_{Na} * E_{Na} + g_K * E_K}{g_K + g_{Na}} = \frac{0.5 * 40 + 0.5 * -(100)}{0.5 + 0.5} = -30mV$$

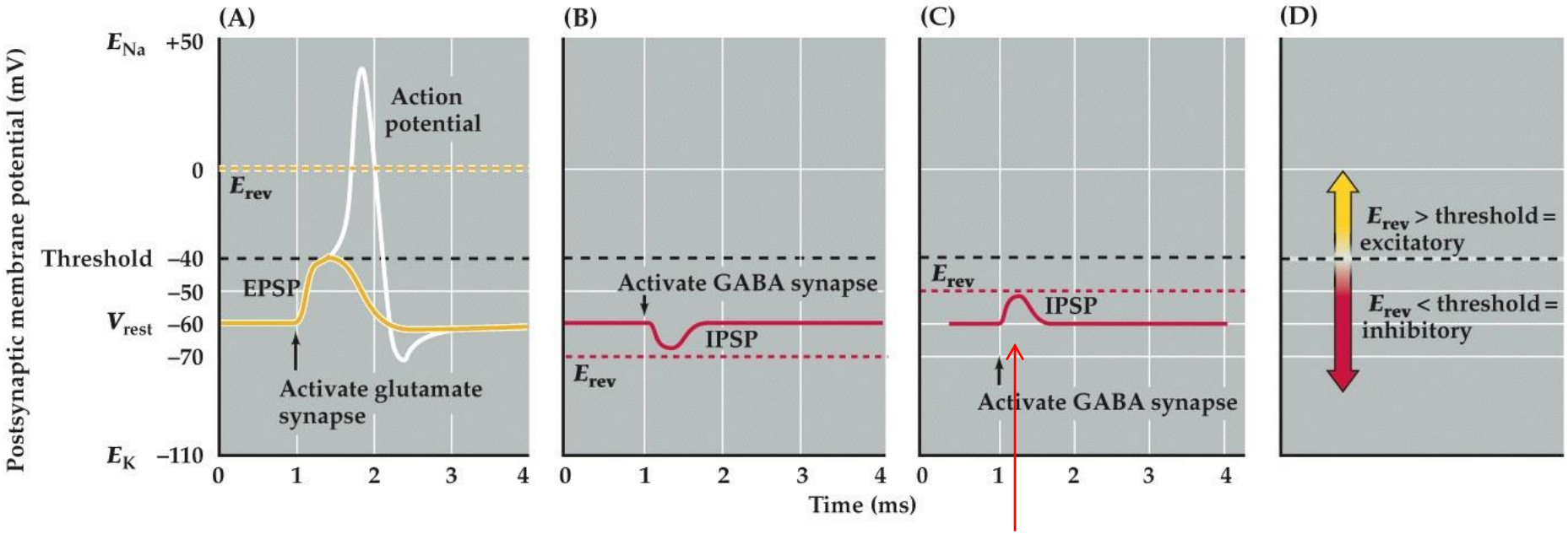
The significance of the reversal potential is that it gives us information about the currents that flowing through a synapse.

Chemical synapses Direct transmission

How can we determine if a synapse is inhibitory or excitatory?

Chemical synapses Direct transmission

Whenever the ***synaptic reversal potential*** is more ***positive*** (depolarized) than the threshold for action potential, we refer to it as an ***excitatory synapse***



What about this one?

Whenever the synaptic reversal potential is more ***negative*** (hyperpolarized) than the threshold for action potential, we refer to it as an ***inhibitory synapse***

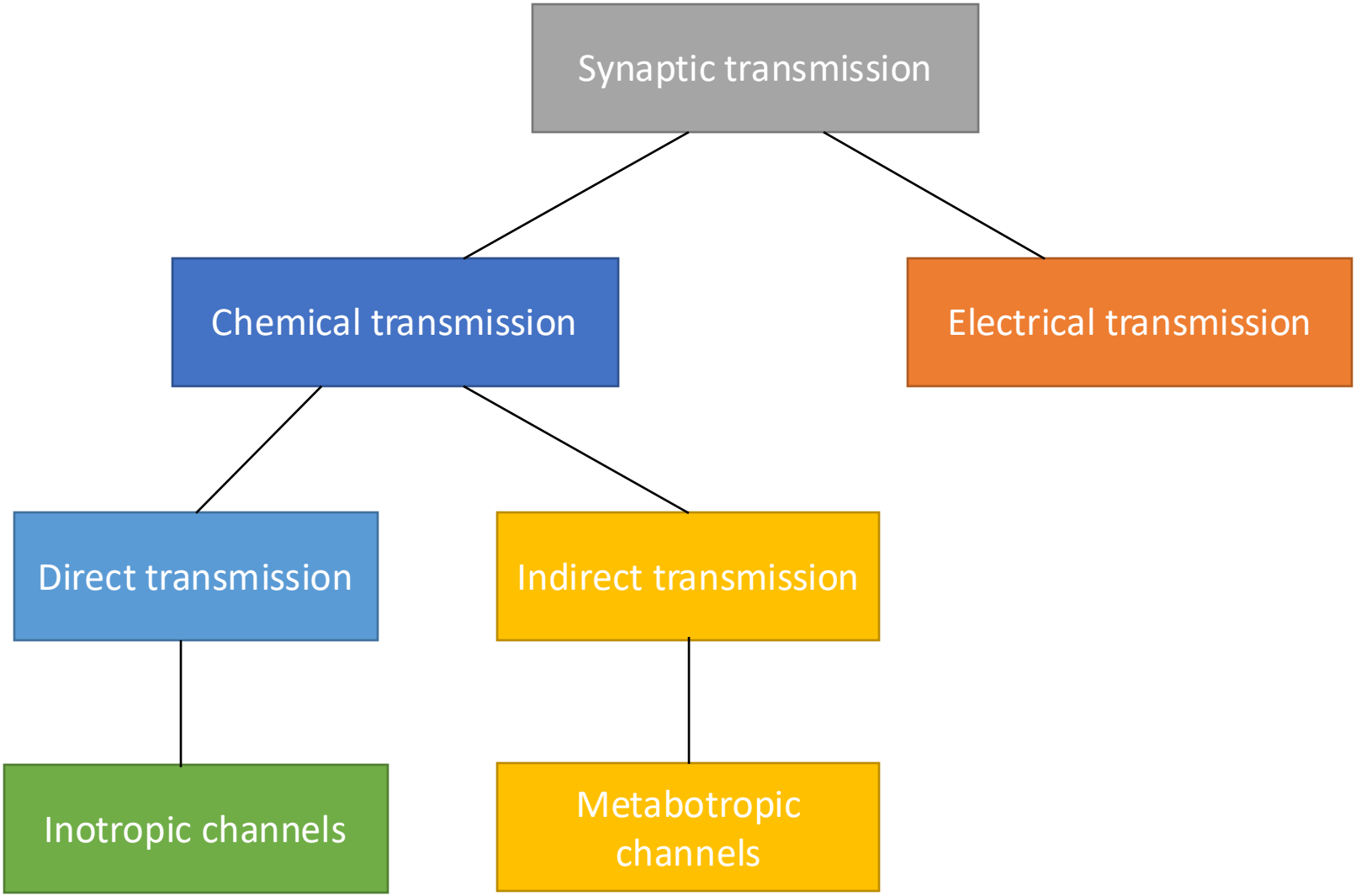
Chemical synapses summary

- ***Direct transmission*** is mediated by inotropic receptors, which are the target ion channels

- During direct transmission, the ***signal is terminated*** once the neurotransmitter is removed from the synapse.

Synapses summary

Synapse – point of contact between a neuron and their target (neurons / muscles/ glands), used to transfer signals.



Comparison between chemical and electrical synapses

	Property	Electrical synapses	Chemical synapses
1.	Distance between pre- and postsynaptic cell membranes	3.5 nm	30–50 nm
2.	Cytoplasmic continuity between pre- and postsynaptic cells	Yes	No
3.	Ultrastructural components	Gap junction channels	Presynaptic active zones and vesicles; postsynaptic receptors
4.	Agent of transmission	Ionic current	Chemical transmitter
5.	Synaptic delay	Virtually absent	Significant: at least 0.3 ms, usually 1–5 ms or longer
6.	Direction of transmission	Usually bidirectional	Unidirectional

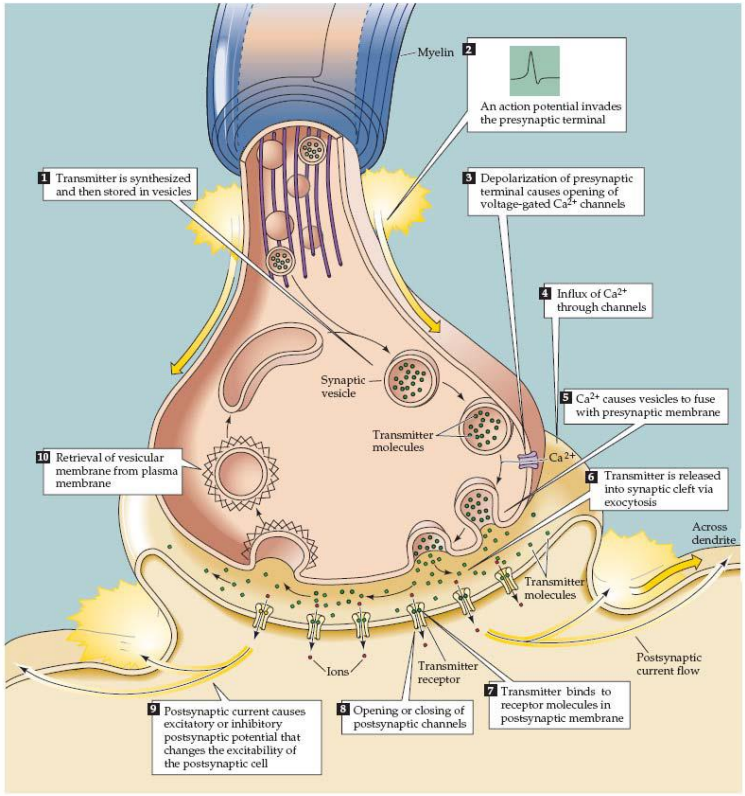
Synaptic Vesicles

The vesicle cycle

Synaptic Vesicles

Vesicles are small sacs filled with ***neurotransmitters*** that are released at the synapse through exocytosis

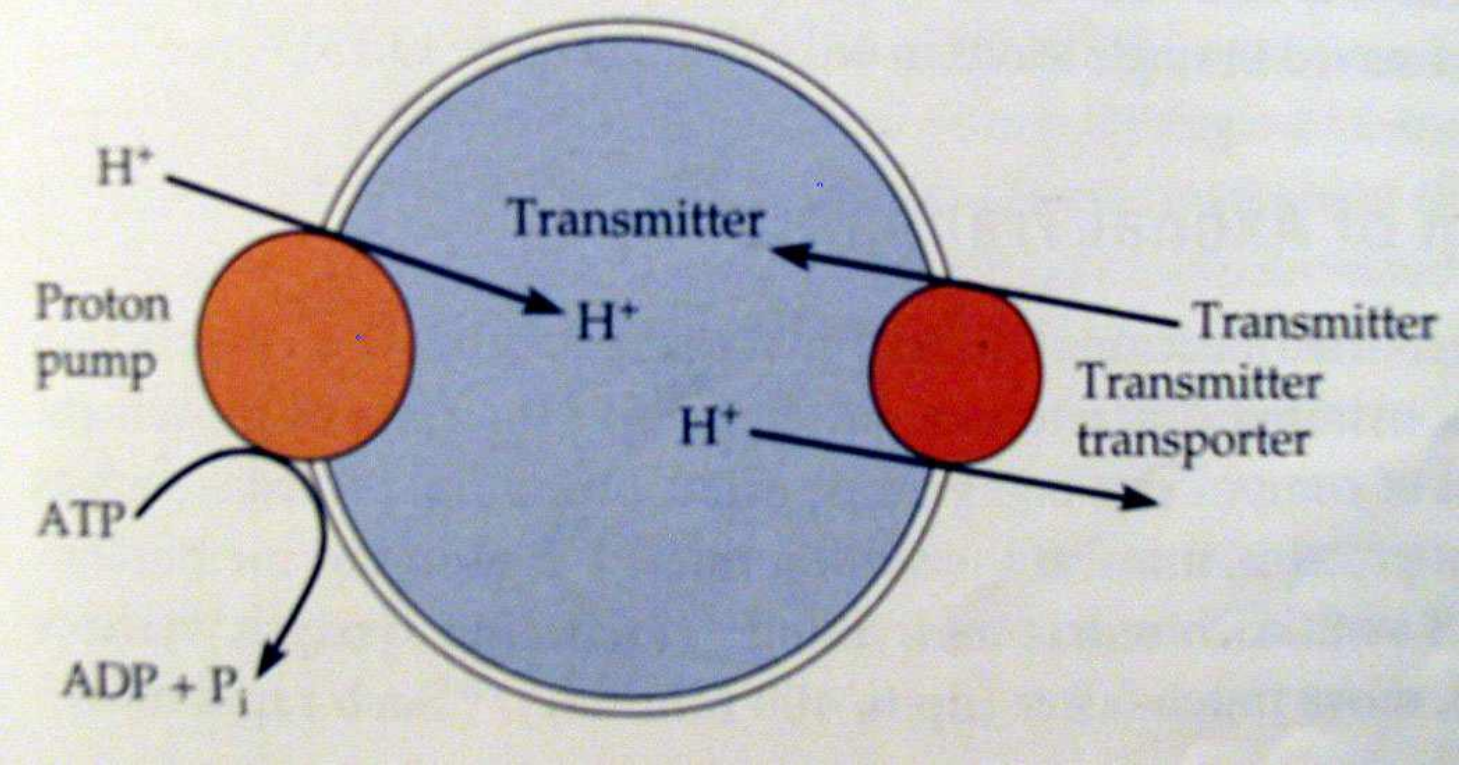
Vesicles are constantly created by the cell. They expressed ***transport proteins (proton pumps)*** that involve in neurotransmitters ***uptake*** and ***trafficking proteins*** that participate in the vesicle exocytosis, endocytosis and recycling.



Neurotransmitter loading into the vesicle

Neurotransmitter ***packaging*** is made through ***vesicular transporters*** that use a the ***H^+ gradient*** as an energy source.

The ***proton gradient*** is build up by a proton pump (ATPase), hence the pH in the vesicle is very acidic (pH 5.5) compared to the cytoplasm (pH 7.2-7.4)



Synaptic vesicle cycle

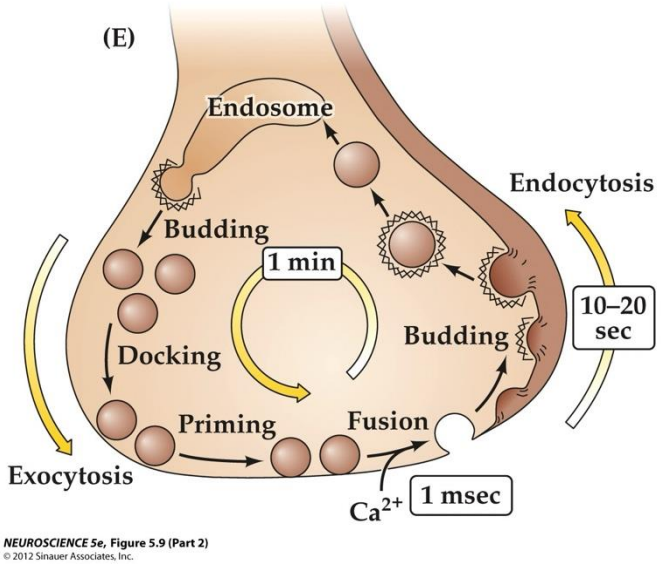
The Synaptic vesicle cycle start with ***fusion*** of the vesicle with the cell membrane following action potential.

Following ***fusion***, there is a ***budding*** process, which is a formation of new vesicles through endocytosis

Following the budding process, the vesicles are filled with neurotransmitters, and than join to a cluster called the ***reserve pool***, in till they need to participate in neurotransmitter release again.

The vesicles are moving from the reserve pool, and ***docking*** at the ***active zone***

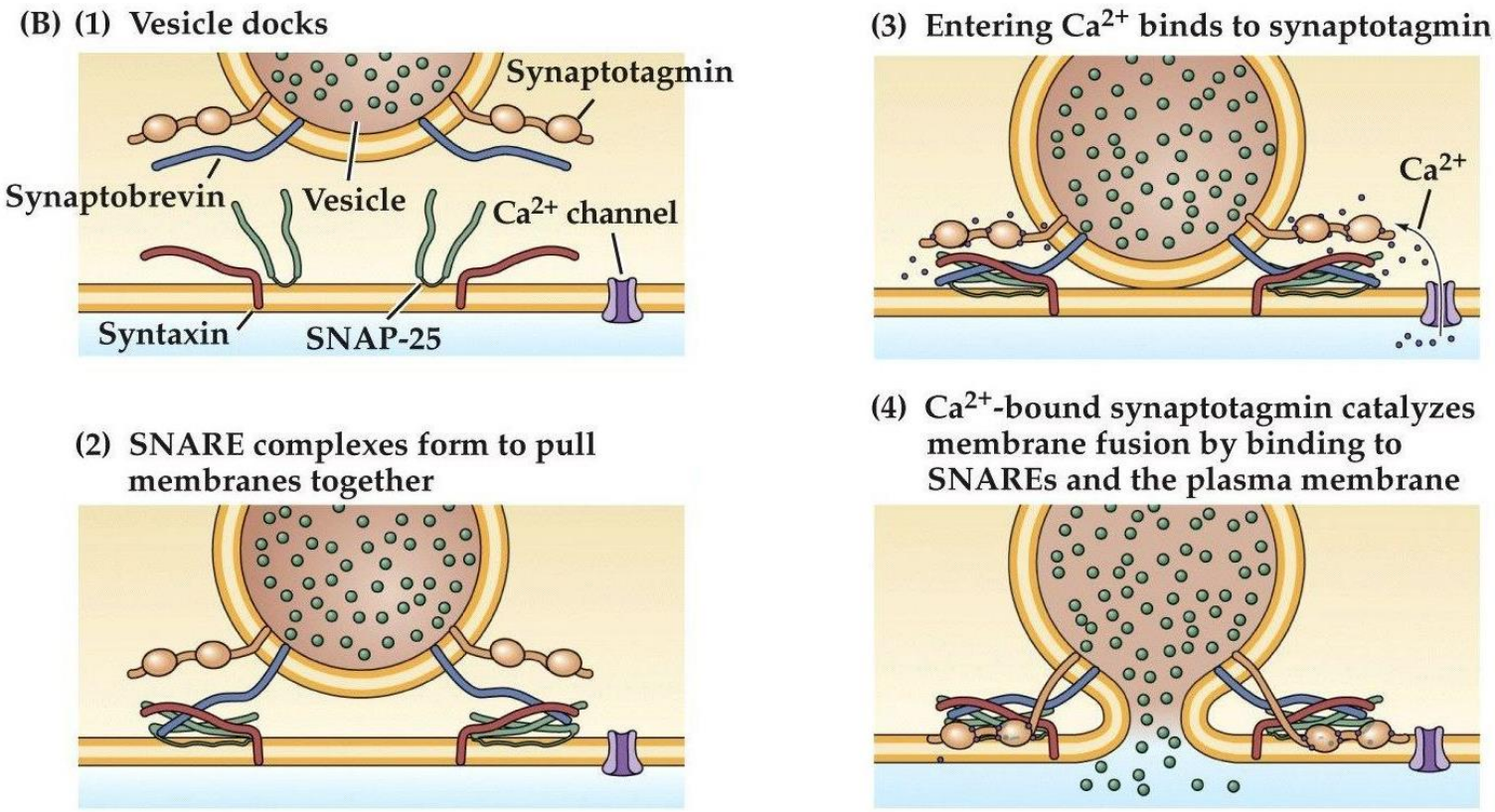
Docked vesicles undergo a ***priming*** reaction that makes them competent for Ca^{2+} triggering



NEUROSCIENCE 5e, Figure 5.9 (Part 2)

Synaptic vesicle cycle

Zooming into the docking and priming processes



***NEUROSCIENCE 5e*, Figure 5.14 (Part 2)**

What are

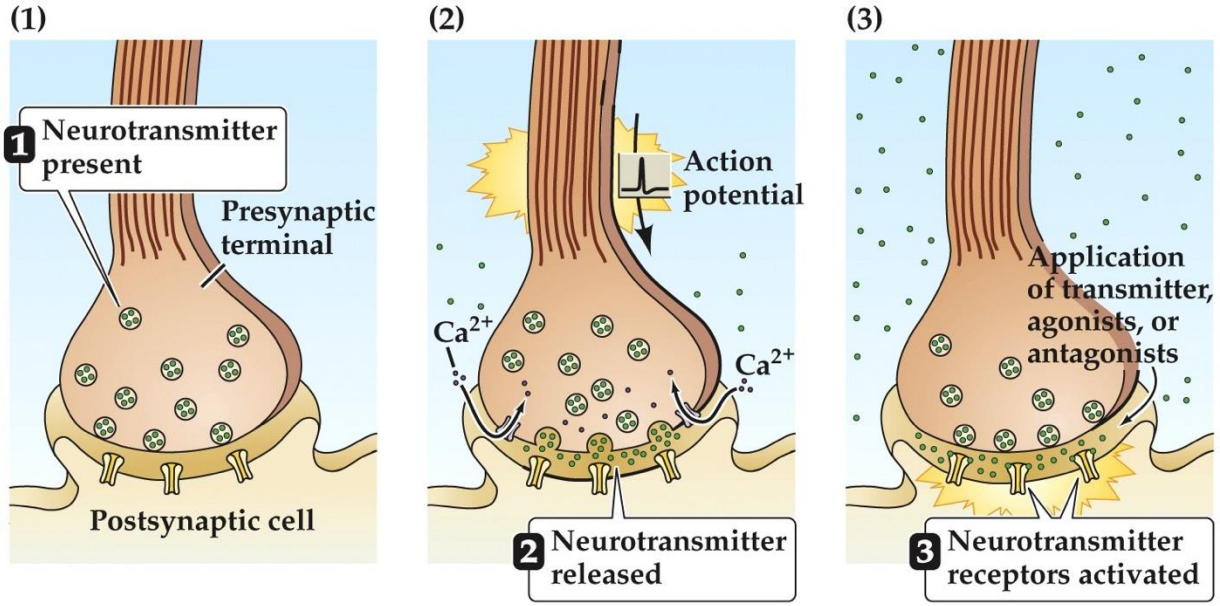
Neurotransmitters

Neurotransmitters

Neurotransmitter is a chemical agent acting as a messenger between communicating neurons

<u>There are three criteria that define a neurotransmitter:</u>

1. Must be ***present*** within the presynaptic neuron
2. Must be ***released*** in response to presynaptic depolarization, and the release must be ca^{2+} dependent
3. Must have ***specific receptors*** on the postsynaptic cell

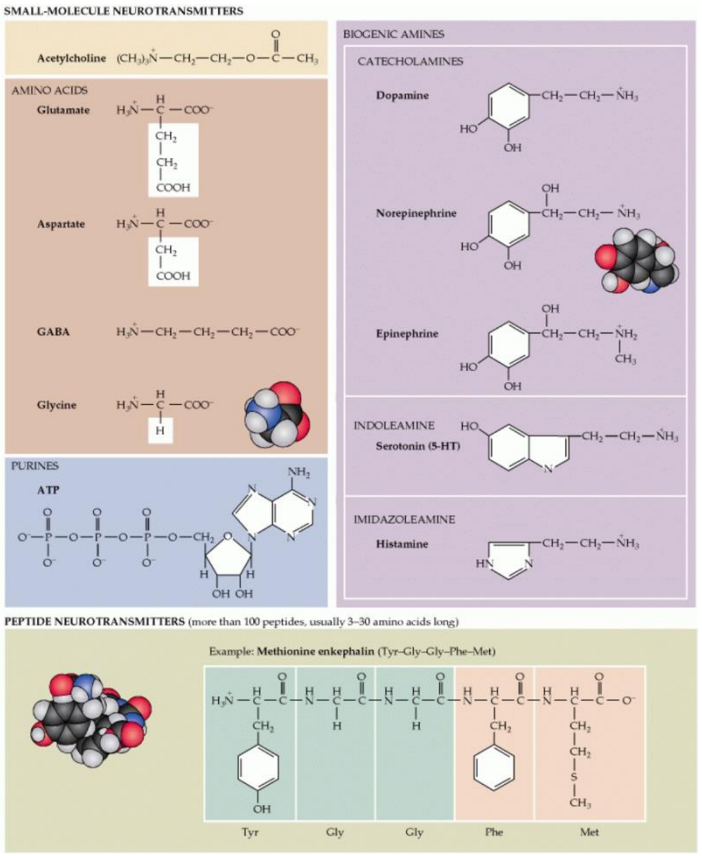


NEUROSCIENCE 5e, Box 5A

Neurotransmitters

There are more than 100 neurotransmitters in the nervous system, which divided to two main categories: ***Small molecule neurotransmitters*** and ***neuropeptides***

Neuropeptides –large transmitter molecules (3-36 amino acids)
Small molecule neurotransmitters – usually an individual amino acid (Glutamate; GABA)

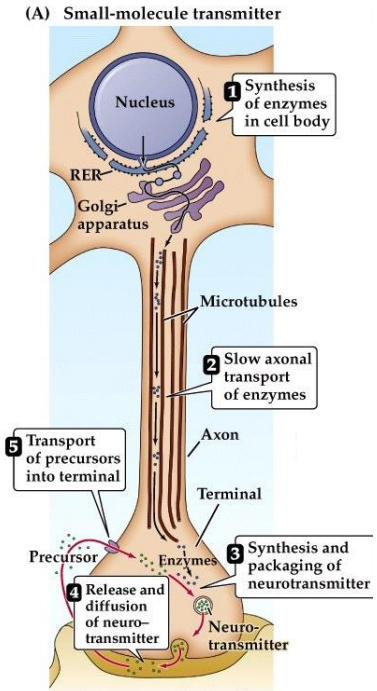


Neurotransmitters Synthesis

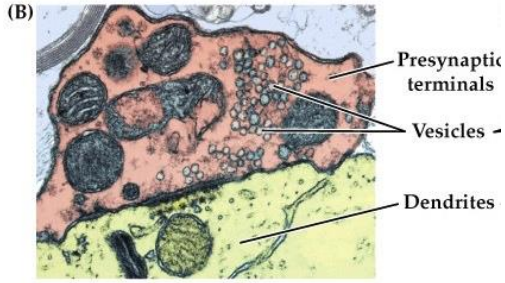
The ***synthesis, packaging, release*** and ***degradation*** of neurotransmitters are highly regulated to achieve the desired level of neurotransmitters.

Synthesis of ***small molecule*** neurotransmitters occurs ***locally*** within the presynaptic terminal by ***enzymes*** arriving from the soma.

The enzymes synthesize the neurotransmitters in the ***presynaptic cytoplasm***, which are than loaded to the vesicle (with ***clear center***) by ***transporters*** that located on the ***vesicle membrane***.

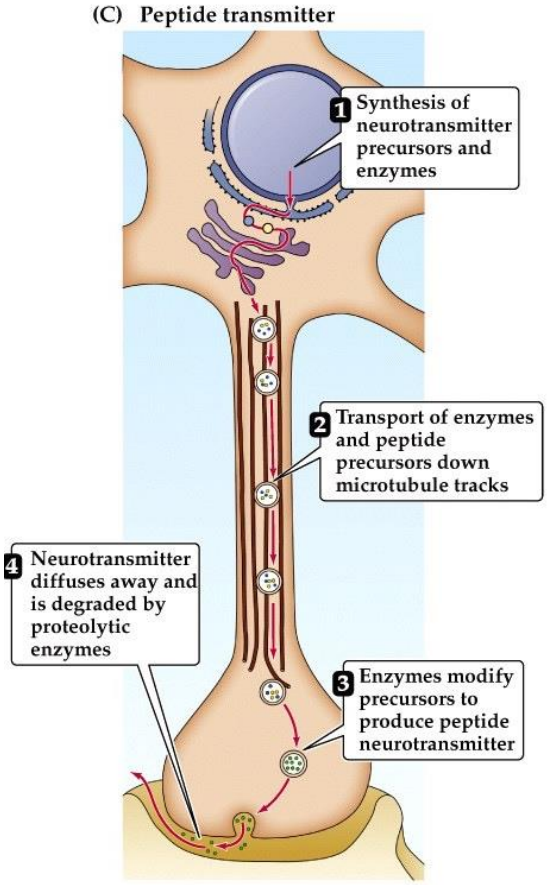


Small clear core vesicles

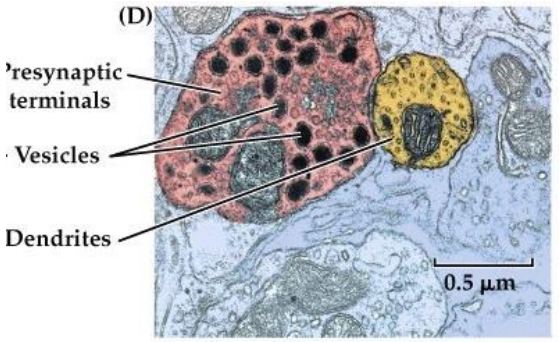


Neurotransmitters Synthesis

Synthesis of ***neuropeptides*** occurs ***distally*** -in the soma, and than they are transported to the synaptic terminal through fast axonal transport (400 mm/day).



Large dense-core vesicles

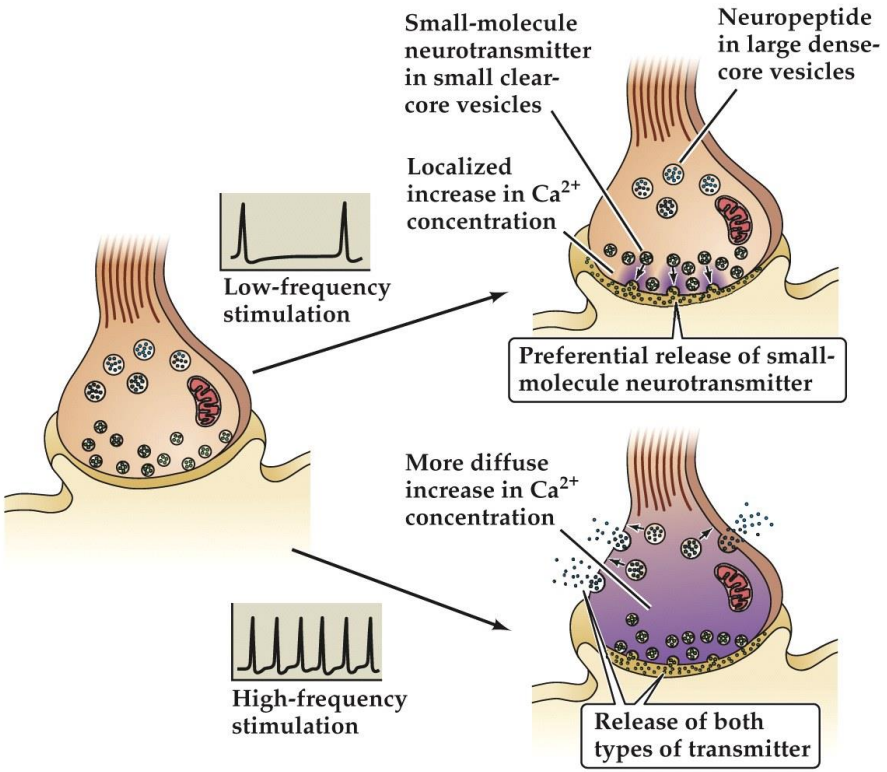


Synaptic Vesicles *Co-transmission*

Till recently it was believed that a given neuron can produce only one type of neurotransmitter.

There is evidence that neurons can synthesize and release two or more types of neurotransmitters, released in a mechanism called co-transmission.

When two types of neurotransmitters located within the same terminal, their individual release will be dependent on the synaptic activity – ***low frequency- small vesicles,*** while ***high frequency- all vesicles.***



***NEUROSCIENCE 5e*, Figure 5.12**

Neurotransmitters

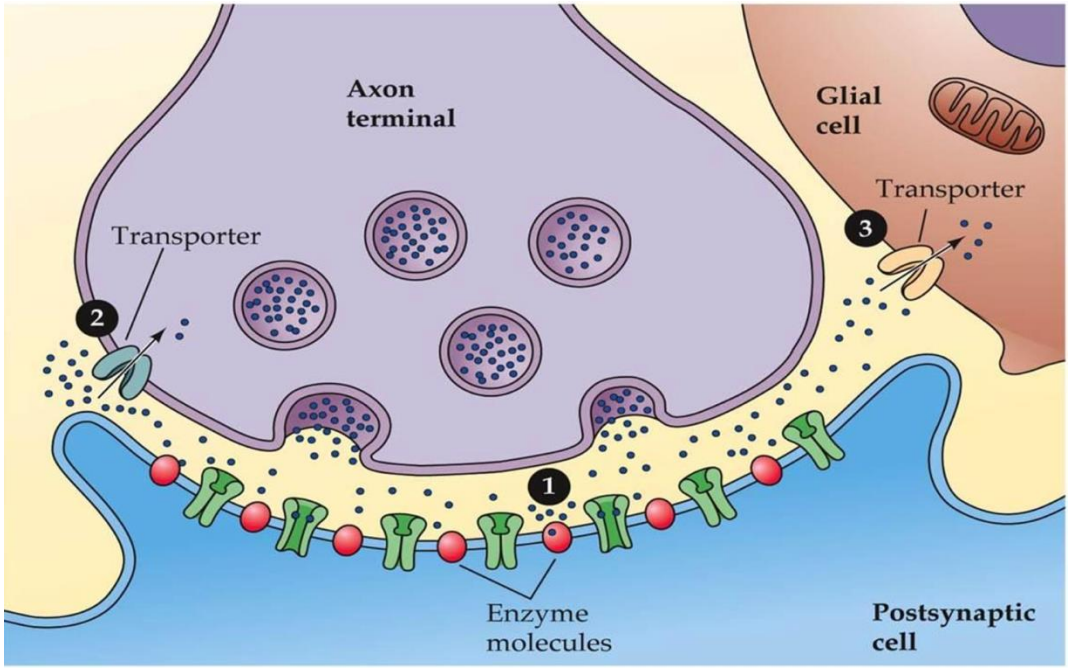
How the synaptic signal is terminated?

Neurotransmitters Reuptake

After activating their postsynaptic receptors, the neurotransmitters are ***removed*** from the ***synaptic cleft*** to allow a new cycle of synaptic transmission.

The removal of neurotransmitters can be by means of a ***diffusion away*** from the receptors and ***reuptake*** to the presynaptic terminals (or astrocytes) or ***degradation*** by synaptic enzymes.

Abnormalities in the function of neurotransmission can lead to neurological and psychological disorders. Therefore many ***neuropharmacological*** therapies are based on drugs that affect the neurotransmitter systems (receptors; transporters, etc..).



Neurotransmitters

Close-up

on the main neurotransmitters
in the nervous system

Postsynaptic receptors

Definitions:

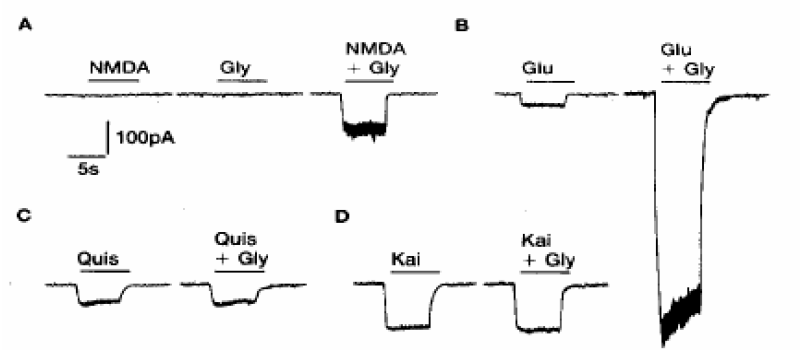
Agonist – a chemical substance that bind to the receptor and activate it

Endogenic agonist – the natural agonist of a receptor

Partial agonist – an agonist that activate the receptor with low efficiency

Co-agonist – a substance that bind to another binding site on the receptor and enhance the activation of the agonist

Antagonist – a chemical substance that bind to the receptor and prevent it's activation by agonists



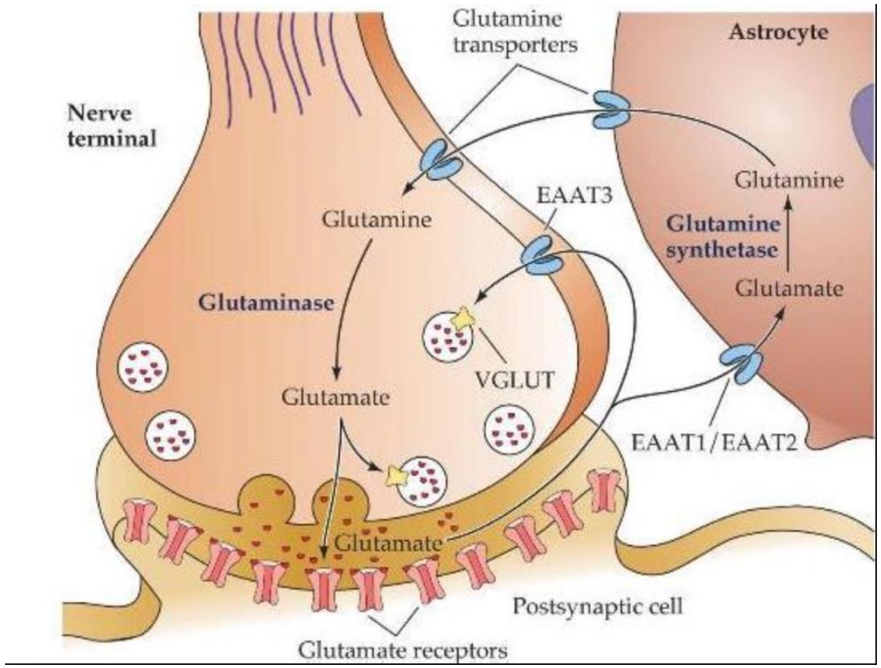
Main Neurotransmitters Glutamate

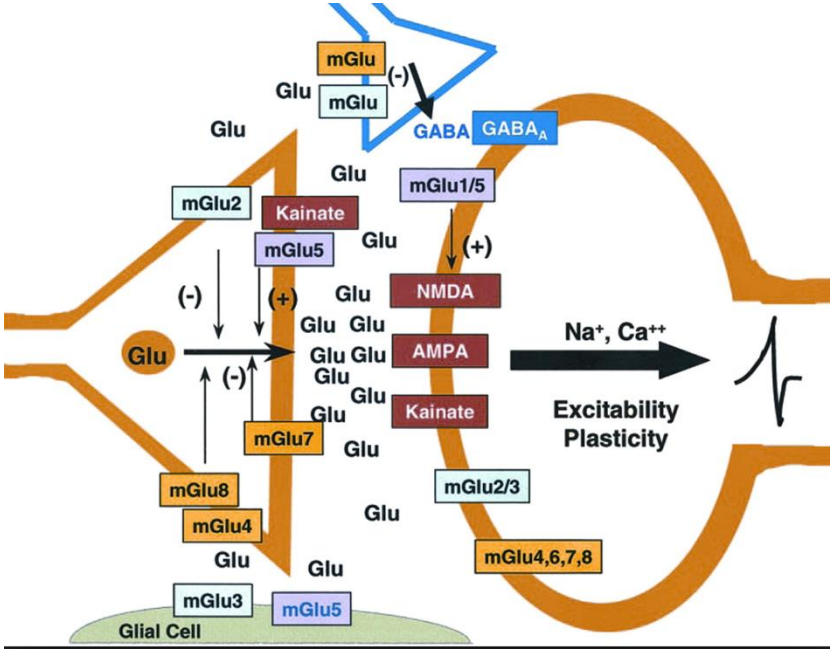
Glutamate (Amino acid) is the main ***excitatory*** neurotransmitter in the CNS. About half of all synapses in the brain release ***glutamate.***

It is synthesize from ***Glutamine*** by the enzyme ***Glutaminase*** and than packed into vesicles by ***VGLUT*** (vesicular glutamate transporter)

Glutamate is removed from the synaptic cleft by the excitatory amino acid transportes ***(EAAT)*** into the presynaptic terminal or to the neighboring ***astrocytes***, where it metabolized back to ***Glutamine***

Activate both ionotropic receptors (***AMPA, Kainate*** and ***NMDA)*** and metabotropic receptors ***(mGlur)***



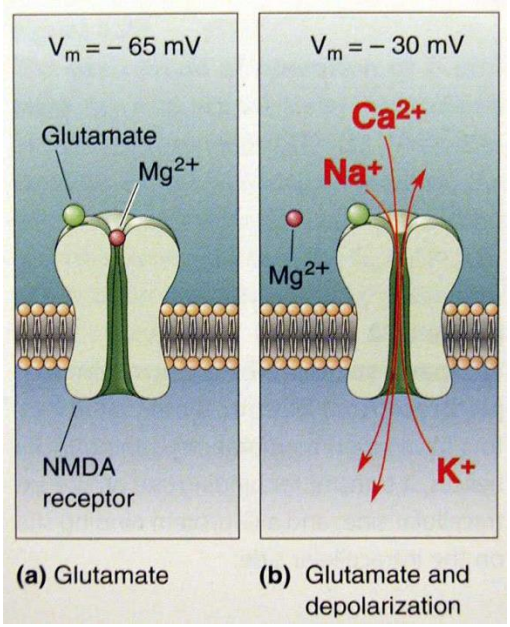


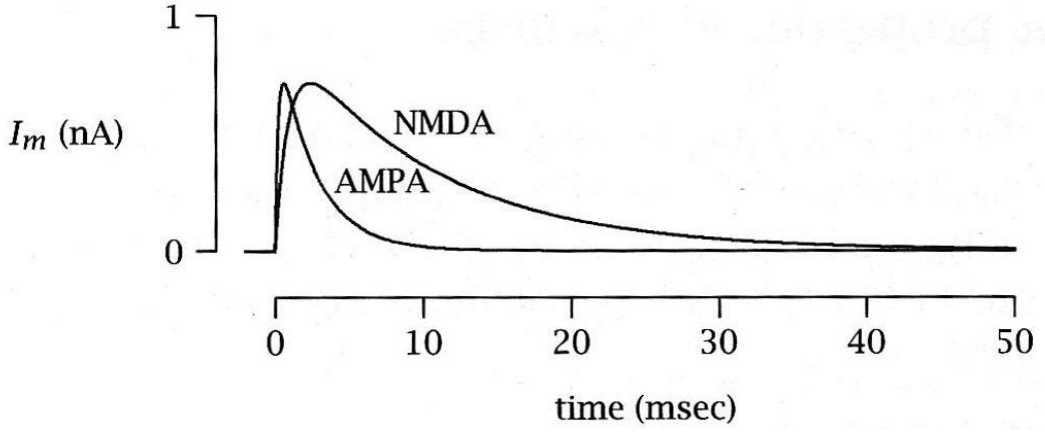
NMDA receptor

A Unique glutamate receptor that is both ***ligand gated*** and ***voltage gated***, which is involved in many synaptic plasticity processes

NMDA receptor activation require the attachment of ***Glutamate ion*** as well as ***depolarization***, which remove the Mg^{2+} ion that blocks the pore

NMDA current kinetics is ***slower*** than other glutamatergic receptors and result in significant ***increase of intracellular calcium*** that participate in many metabolic processes that are essential for ***synaptic plasticity***





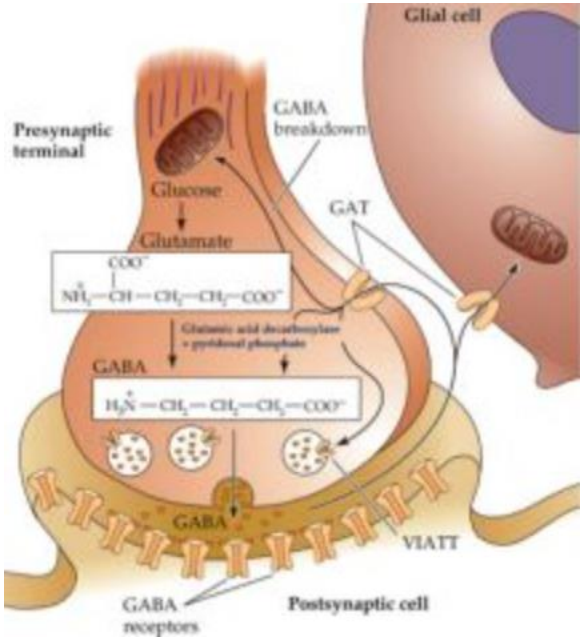
Main Neurotransmitters GABA

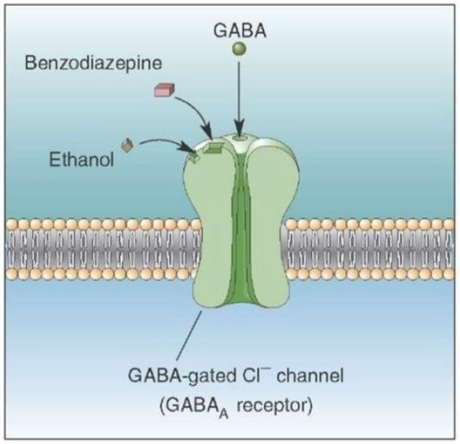
GABA (γ-aminobutyricacid) is the main ***inhibitory*** neurotransmitter in the CNS, used by a third of all synapses.

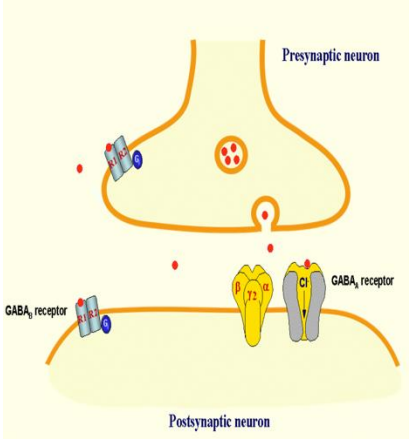
It is synthesized from ***Glutamate*** by the enzyme ***Glutamic acid decarboxylase (GAD)*** which is expressed exclusively in ***GABAergic*** neurons, and than packed into vesicles by ***a vesicular inhibitory amino acid transporter (VIAAT)***

GABA is removed from the synaptic cleft by ***GABA transporters (GAT)*** and than degraded

Activate both ionotropic receptors (***$GABA_a$*** ;Cl^- channel***)*** and metabotropic receptors ***($GABA_b$;*** K^+ efflux***)***







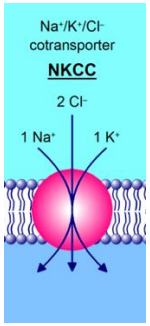
Main Neurotransmitters GABA

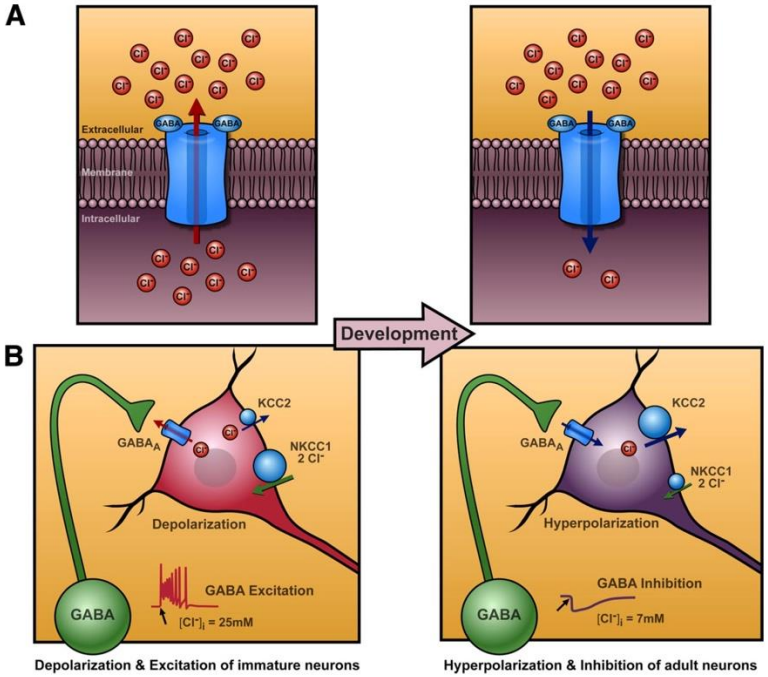
During ***development***, GABA is an ***excitatory*** neurotransmitter that excite it's target cells.

This is due to the fact that during development, the intracellular Cl^- concentration is very high, as it is controlled by the ***$Na^+/K^+/Cl^-$ cotransporter***, that pumps Cl^- into the cell.

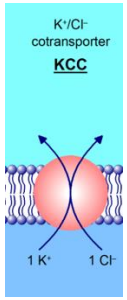
As the neurons continue to develop, they express the ***K^+/Cl^-*** cotransporter that pumps ***Cl^-*** out of the neurons and maintain a low Cl^- concentration.

*During development, GABA activation lead to **depolarization** as Cl- leaving the cell according to the driving force*





*In mature neurons, GABA activation lead to **hyperpolarization** as Cl- getting into the cell according to the driving force*



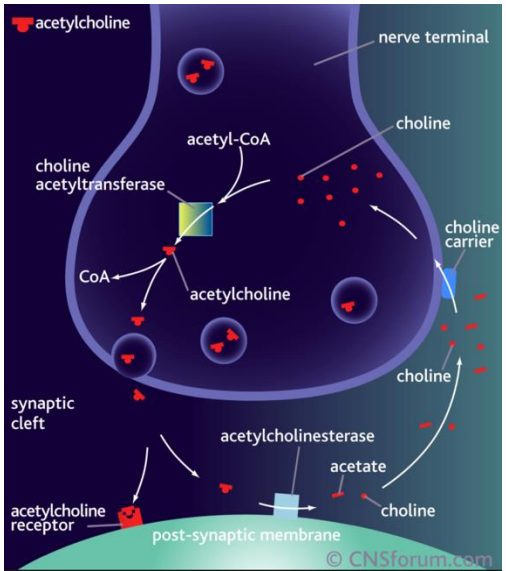
Acetylcholine

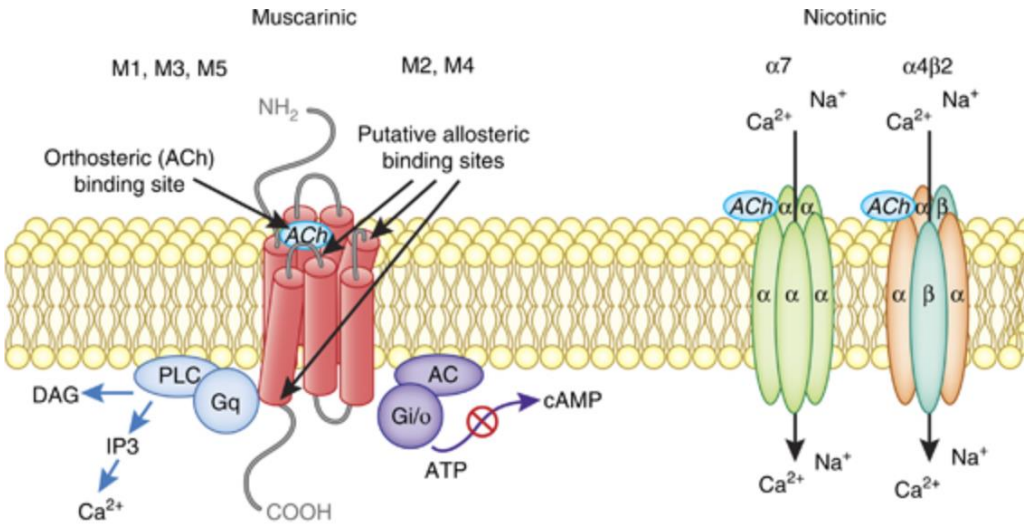
Acetylcholine (***ACh)*** is the first substance identified as neurotransmitter. It has an ***excitatory*** impact on the target cell and expressed in both CNS and PNS.

ACh is synthesized from ***Acetyl CoA*** and ***Choline*** by the enzyme ***Choline Acetyl transferase (CAT),*** and loaded to vesicles by the vesicular ACh transporter ***VAChT***.

ACh action on the postsynaptic receptors is terminated by the enzyme ***acetylcholine esterase*** (***AChE),*** which hydrolyze ***ACh*** in the synaptic cleft.

Activate ionotropic receptors (***nicotinic acetylcholine receptors; nAChR),*** and metabotropic receptors (***muscarinic acetylcholine receptors; mAChR***)

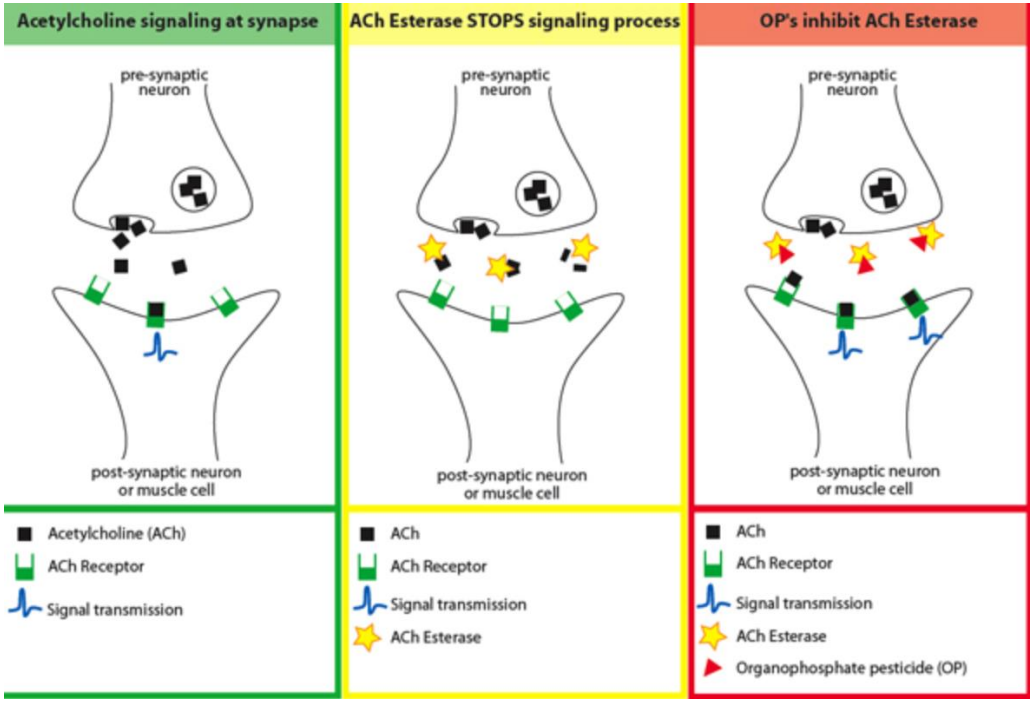


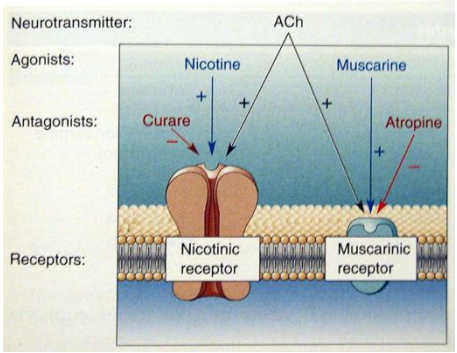


Acetylcholine

Organophosphates (also known as ***nerve gas***) can inhibit the enzyme ***AChE***, which result in accumulation of ***ACh*** at the synapse and constant depolarization and activation that paralyze the neuromuscular junction. ***Atropine*** can save you, why? ***Antagonist to ACh receptors***

Organophosphates are very popular ***insecticides***



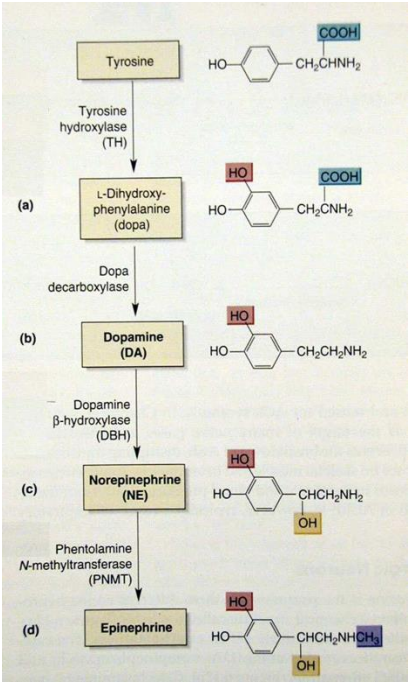


Biogenic Amines

Part of the ***small molecule neurotransmitters***, active in both PNS and CNS as modulatory neurotransmitters (through metabotropic receptors).

There are 5 biogenic amines:

Three catecholamine's - ***Dopamine***, ***Norepinephrine*** (also named Noradrenaline) and ***Epinephrine*** (Adrenalin), which are synthesized from the amino acid ***Tyrosine.***



Dopamine is synthesized from DOPA by the enzyme DOPA decarboxylase, and is involved in coordination of body movements as well as in ***motivation***, ***reward*** and ***reinforcement***.

Norepinephrine is synthesized from ***Dopamine*** and involved in sleep, wakefulness and attention behavior. Very common in the PNS, and act as a stimulating agent through metabotropic receptors.

Biogenic Amines

Other Biogenic amines are:

Histamine – mediate arousal and attention through the activation of metabotropic receptors.

Serotonin – synthesized from the amino acid ***tryptophan.*** Involved in regulation of sleep and wakefulness as well as on anxiety and depression. Many antidepressant drugs are selective serotonin reuptake inhibitors (***SSRI***) that inhibit the transport of serotonin from the synapse.

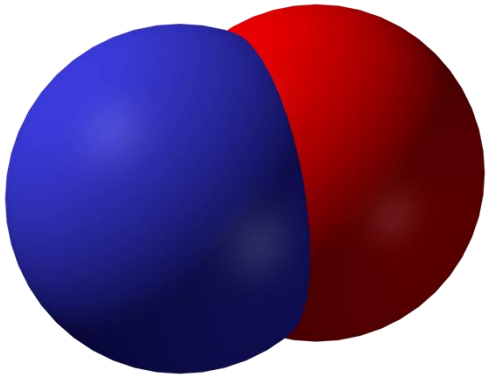
As serotonin is ***endogenic antagonist*** to ***K^+ channels***, it lead to ***widening*** of the presynaptic action potential and ***augmentation*** of the vesicular exocytosis.

Retrograde messengers

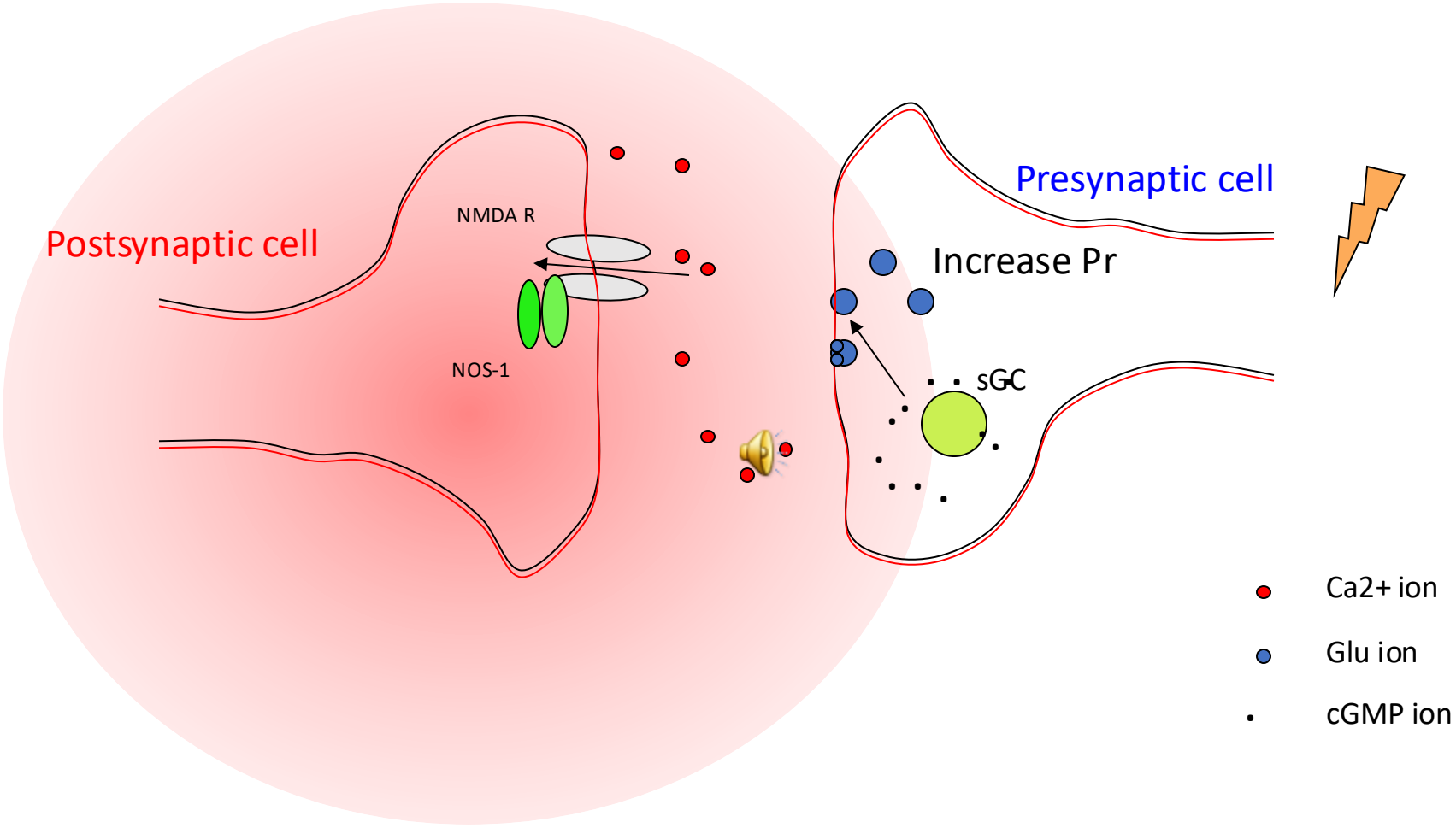
Unconditional neurotransmitters that send information in the ***opposite*** direction, from the dendritic spine to the presynaptic axon terminal. Involved in processes of synaptic plasticity.

One of the most famous retrograde messengers is ***Nitric Oxide*** (***NO***) which is a gas molecule that synthesized by the enzyme Nitric Oxide Synthase (***NOS***), which is regulated by calcium influx.

Once generated, ***NO*** diffuse from the production site to the target proteins through the neuronal membrane and activate the protein ***Guanylyl cyclase*** to synthesize ***cGMP***.



Nitric Oxide as a retrograde messenger



Further reading

From neuron to brain – chapters 4,8 “Ion channels and signaling”
Neuroscience – chapters 1, 2