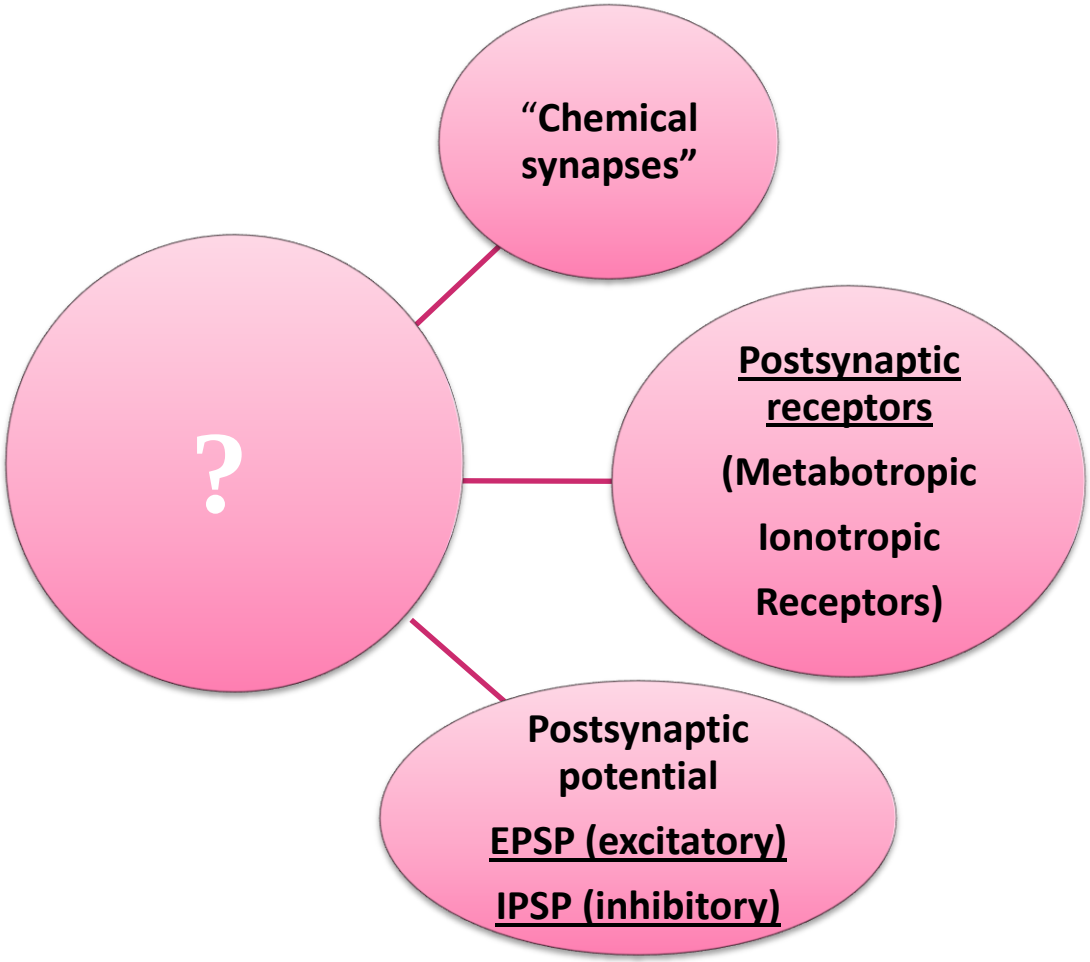
# STRUCTURE AND FUNCTION OF THE SYNAPSE

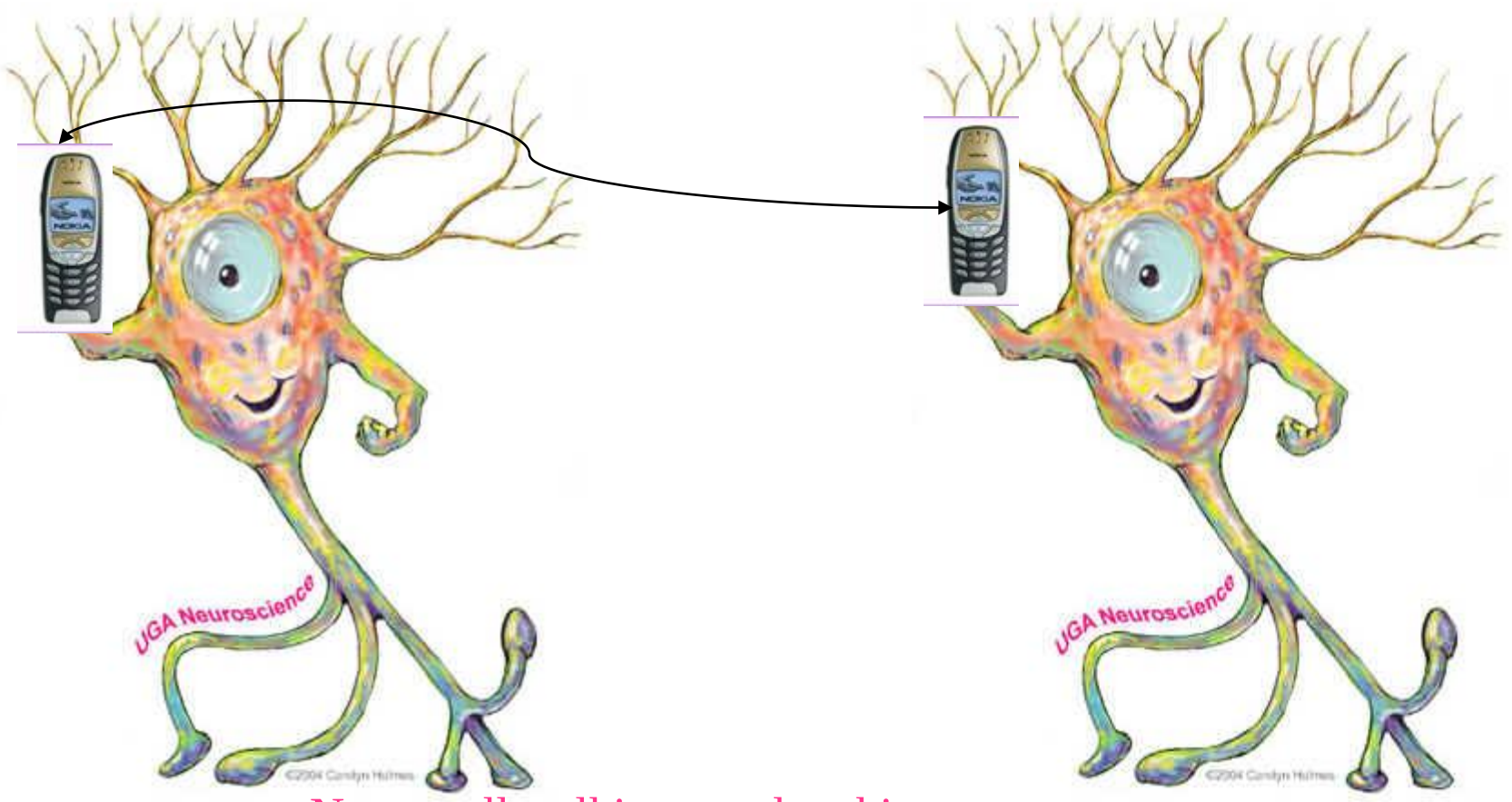
Basic neuroscience

2013

# What we are going to talk about?



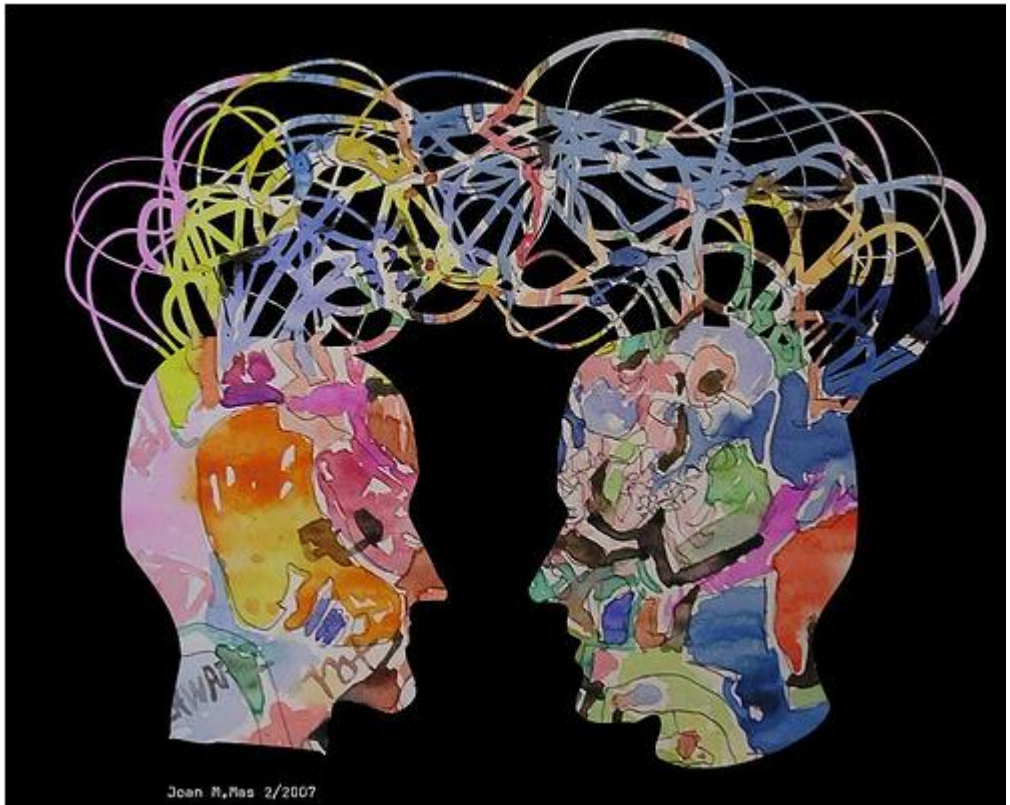
# We will learn how neurons comunicate with each other?




Nerve cells talking - and making sense

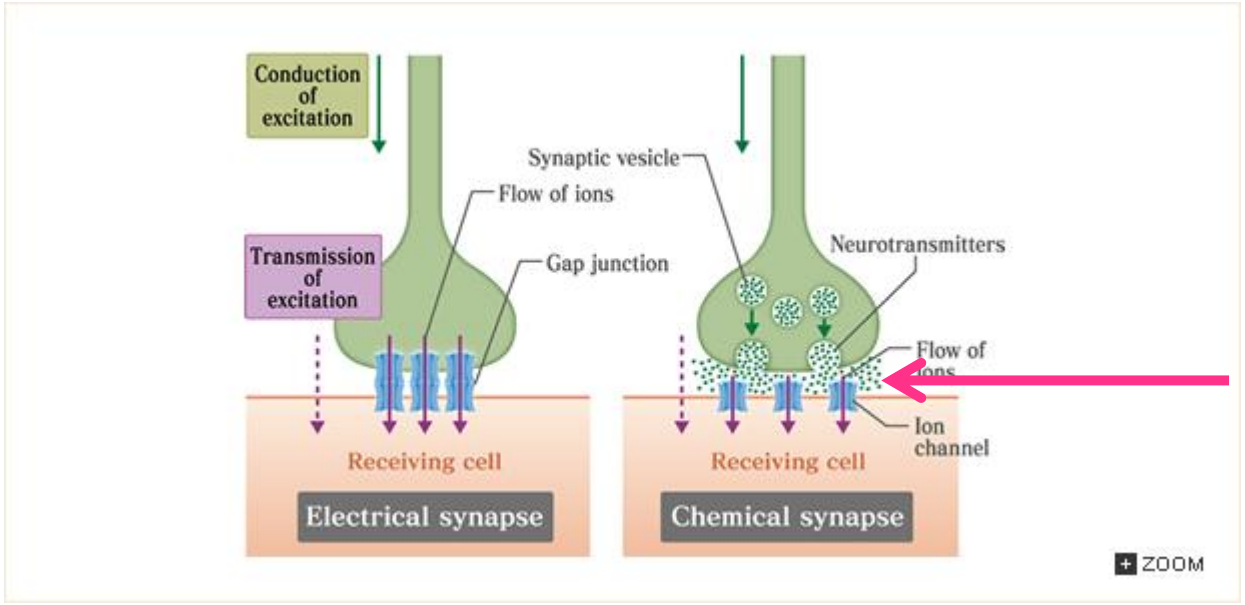
# What’s the point?

- To understand how do we communicate to each other
- To understand the information transfer within the motor, sensory and other systems such as higher brain functions, learning, aging, sleeping etc.



- Average neuron forms and receives abut 1000 synaptic connections
- Human brain contains $10^{11}$ neurons
- $10^{14}$ synaptic connectins are formed in the brain

# Electrical vs chemical synapses

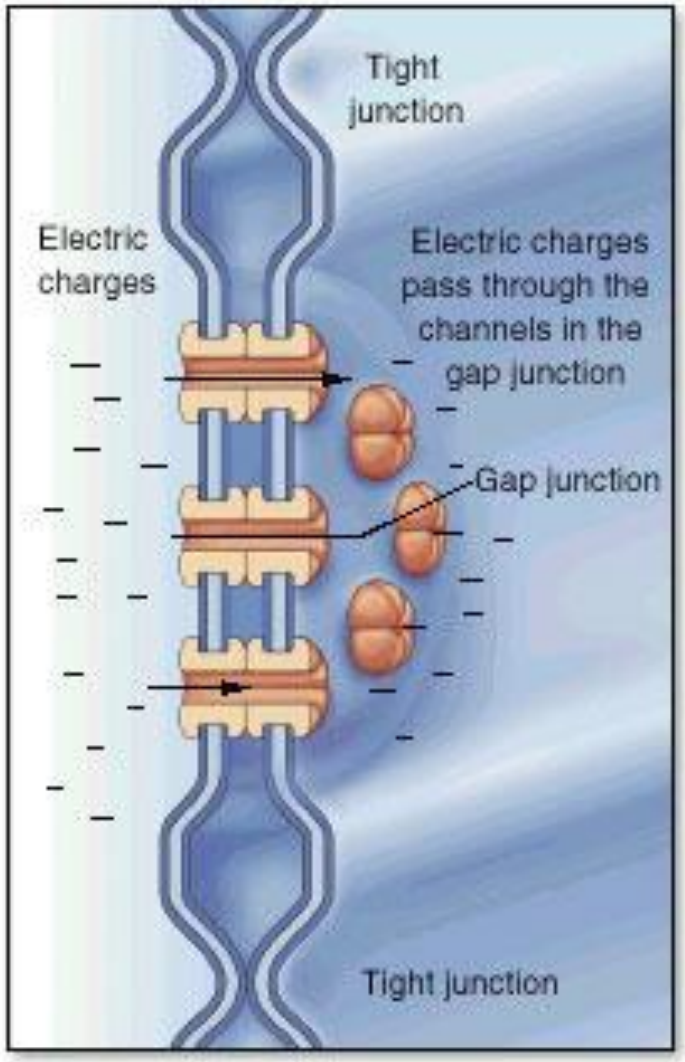



Synaptic cleft

# Electrical synapse

- Ion channels connects presynaptic and postsynaptic cell
- Current fllows directly from presyanptic to postsynaptic neuron
- Lasts less than 0.1 msec
- Rectifying or unidirectionaly synapses
- Nonrectifying or bidirectional synapses (most in the mammalian CNS)

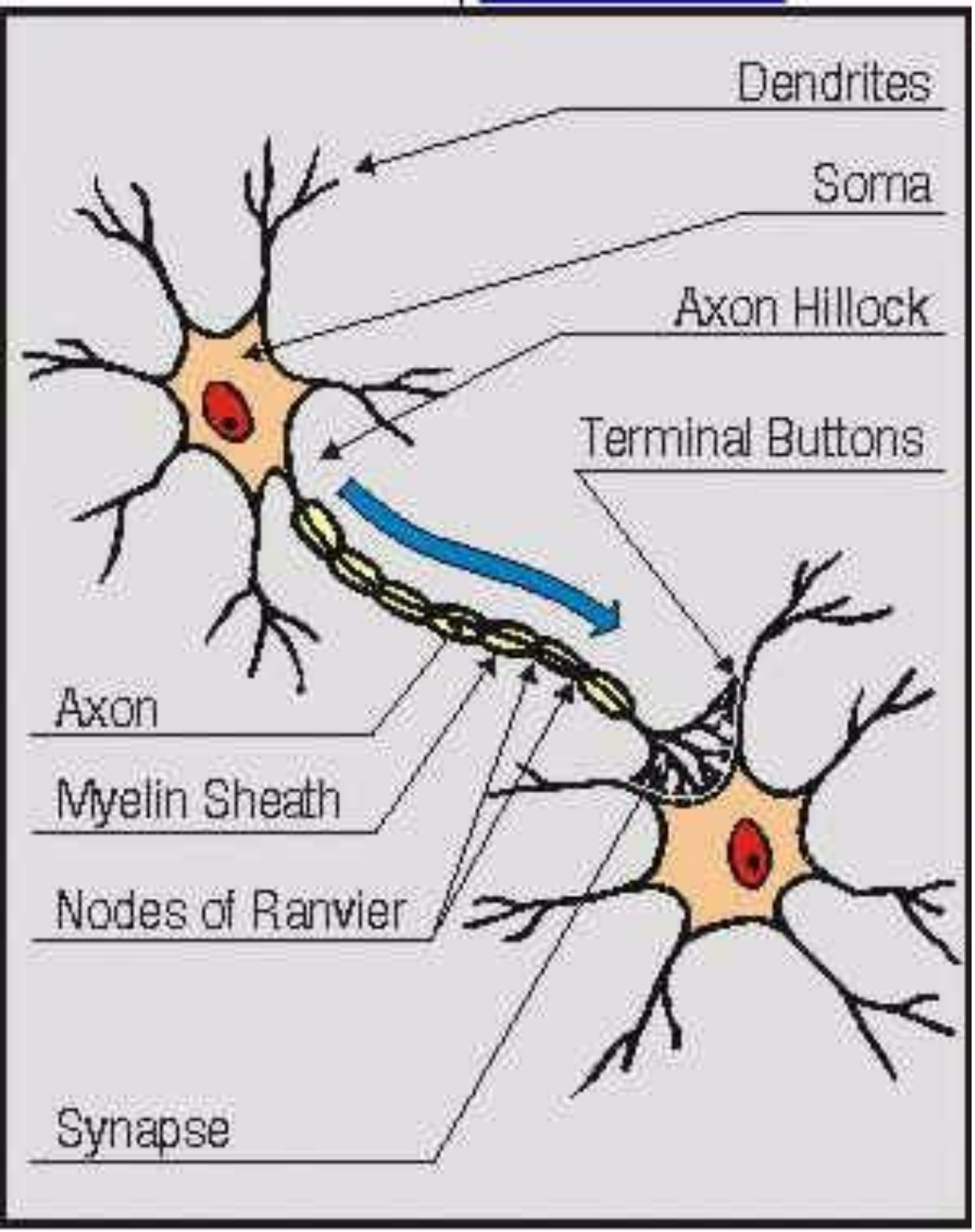
# Electrical synapse




Gap junction channels are Formed by two hemichannels:

a) **Presynaptic connexon**
b) **Postsynaptic connexon**

Each connexon is composed of **Six subunits** called **connexins**




## **Chemical Synapse** :

Functional synapse connects two neurons: There are three major structures:

1. presynaptic element
2. synaptic cleft
3. postsynaptic element

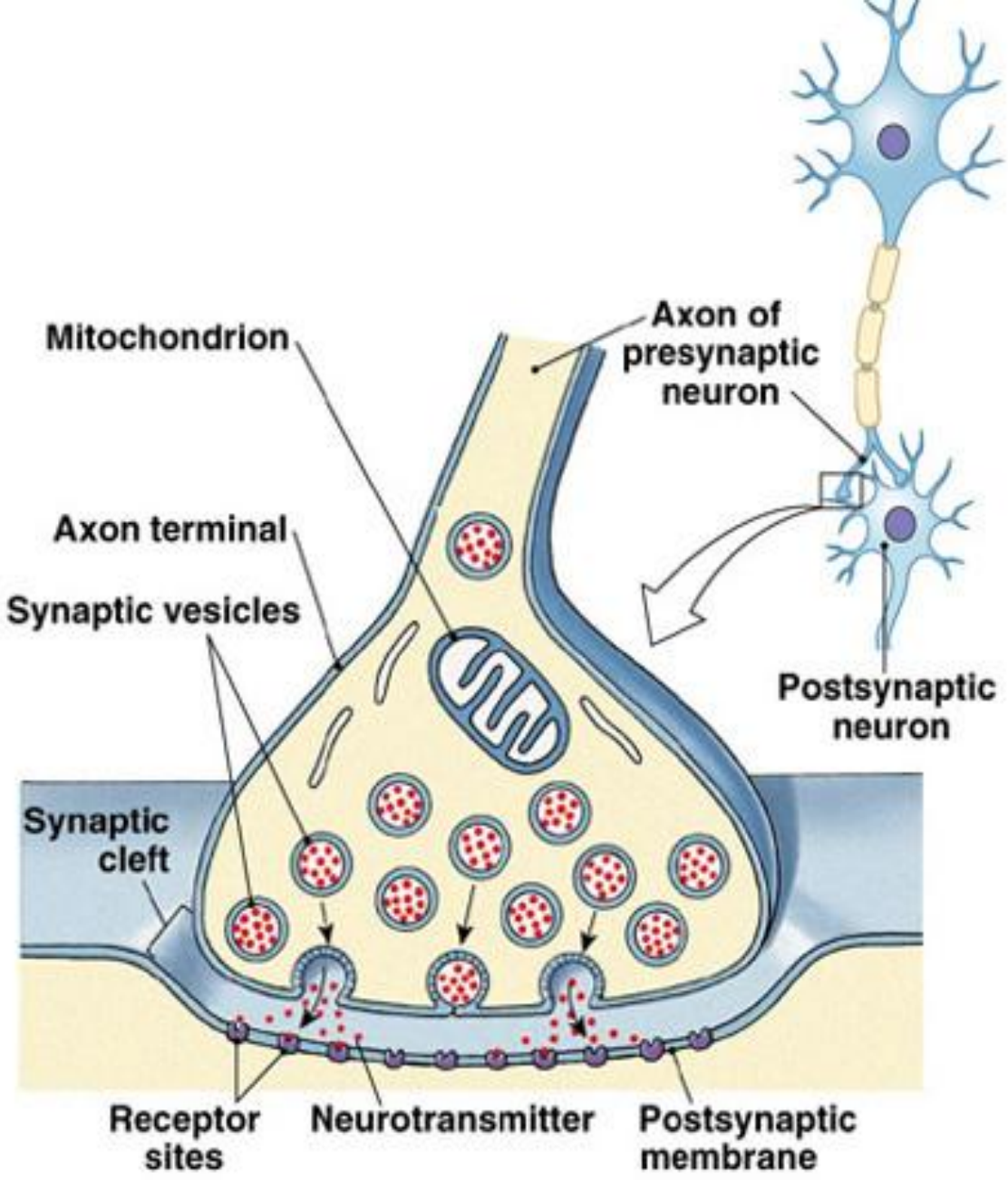



Fig. 8-20

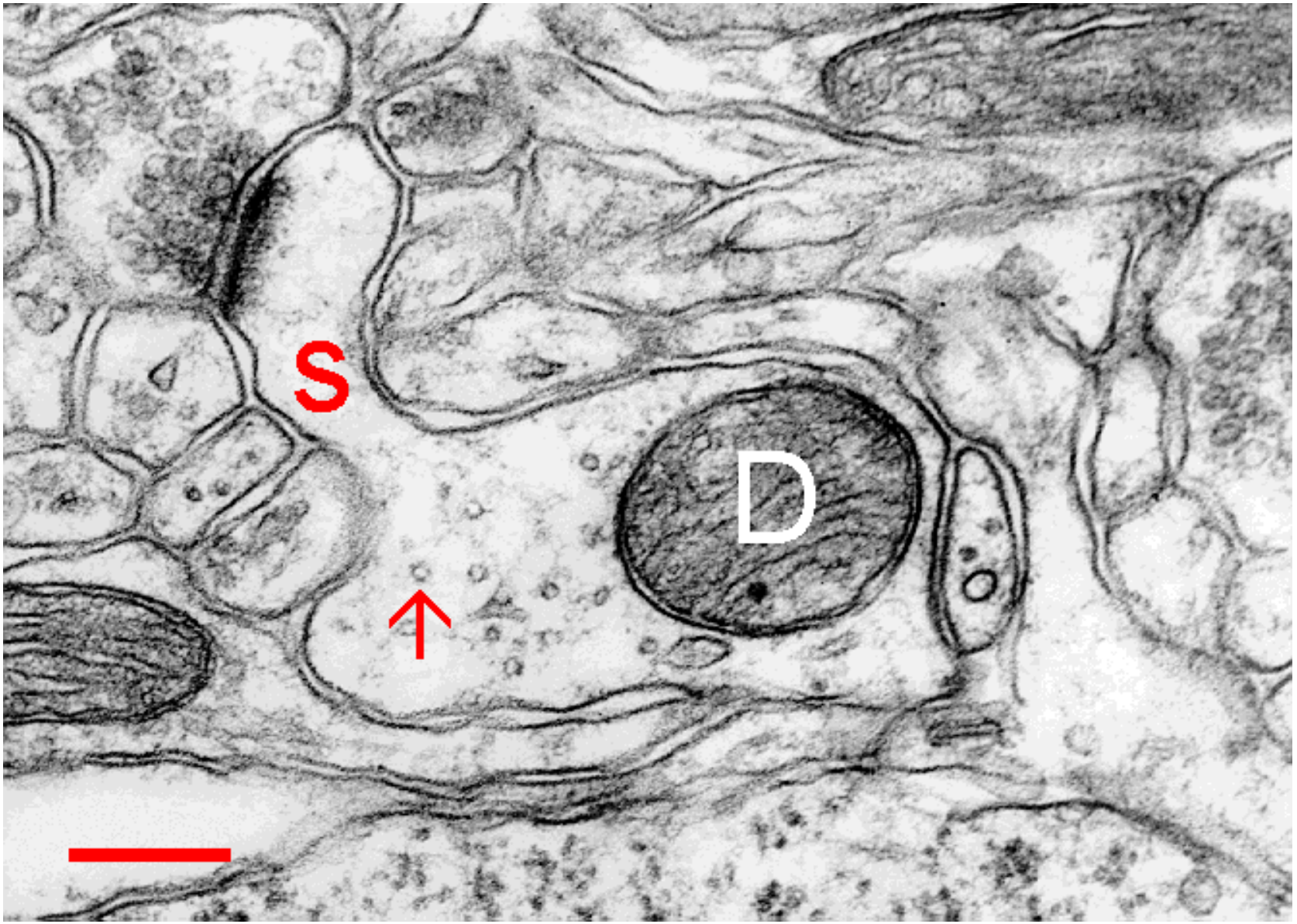



**Fig. 1.6.4.** *Axo-spinous synapse*. The short spine of a thin type (S) originates from the dendritic stem (D). Note obliquely sectioned thin parallel filaments in the postsynaptic density (so far unknown and undescribed structure). Microtubule marked by arrow. Scale = 200 nm. (Mouse, neocortex.)

# Synaptic transmission is:

- *one way direction (unidirectional)*
- *fast (120 m/s)*
- *short-term ( 0,3 do1 ms)*
- *specific*
- *accurate*

# Double transmission of the signal

- 1. electrical signal becomes chemical
- 2. chemical signal transmits to:
  - a) electrical (ionotropic-directly, metabotropic-indirectly)
  - b) chemical (metabotropic receptors modulates activity of the ionic channels))

# Chemical synaptic transmission

- Involves five crucial steps:

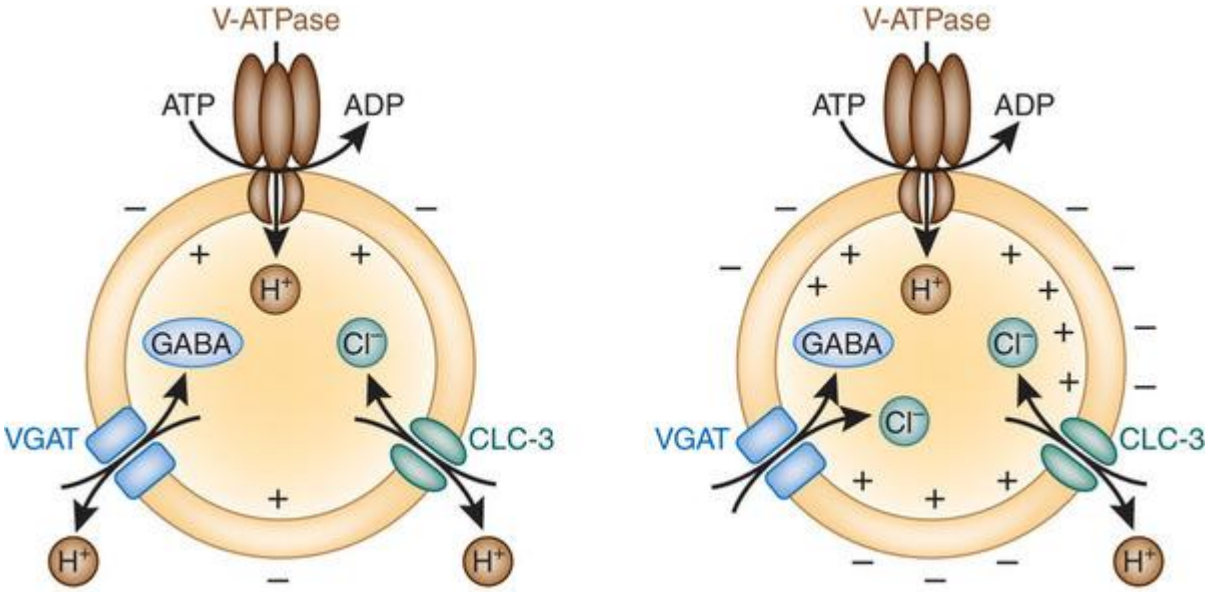
1. Neurotransmitter synthesis
2. Storage
3. Release
4. Receptor binding
5. Inactivation

# 1. Biosynthesis of the neurotransmitter in the presynaptic neuron

- Enzymes, cofactors and precursors are present in presynaptic element
- It is important site for the clinically useful drugs

## 2. Storage of the neurotransmitter in the presynaptic nerve terminal

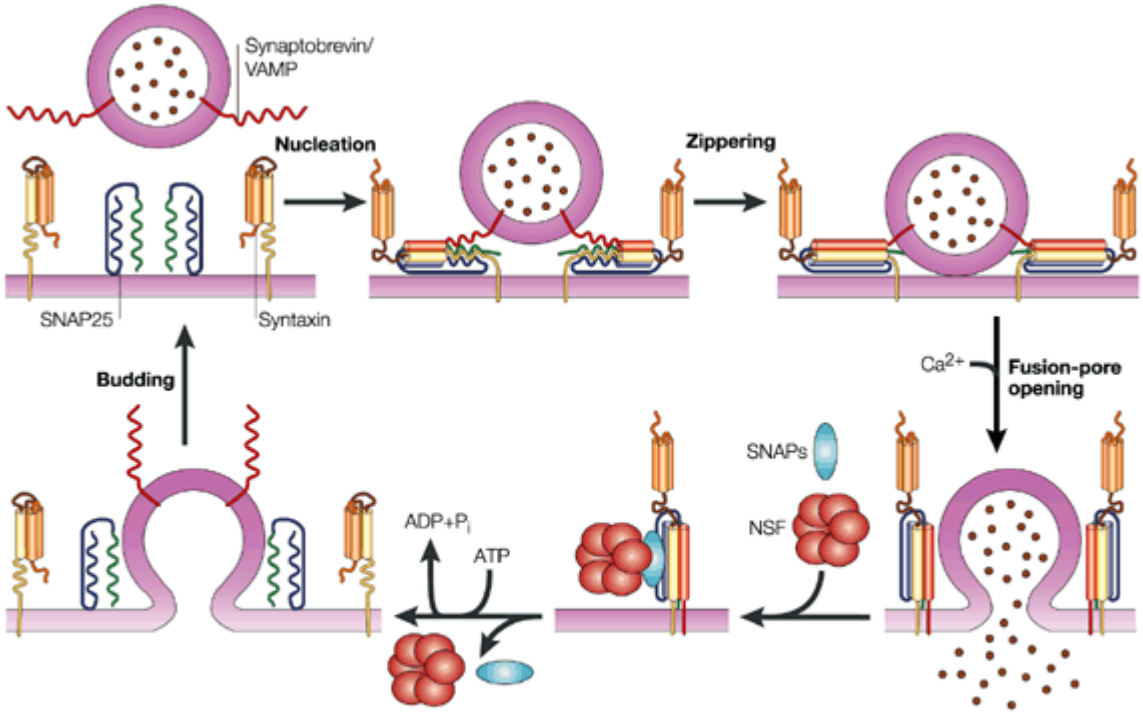
- When transmitters are stored in synaptic vesicles they are protected from the enzymes
- Classical neurotransmitters (acetylcoline, biogenic amines, and aminoacids such as GABA, glutamate) are stored in **small (≈50 nm in diameter) vesicles**
- Neuropeptide transmitters are stored in **large dense-core vesicles (≈100 nm in diameter)**



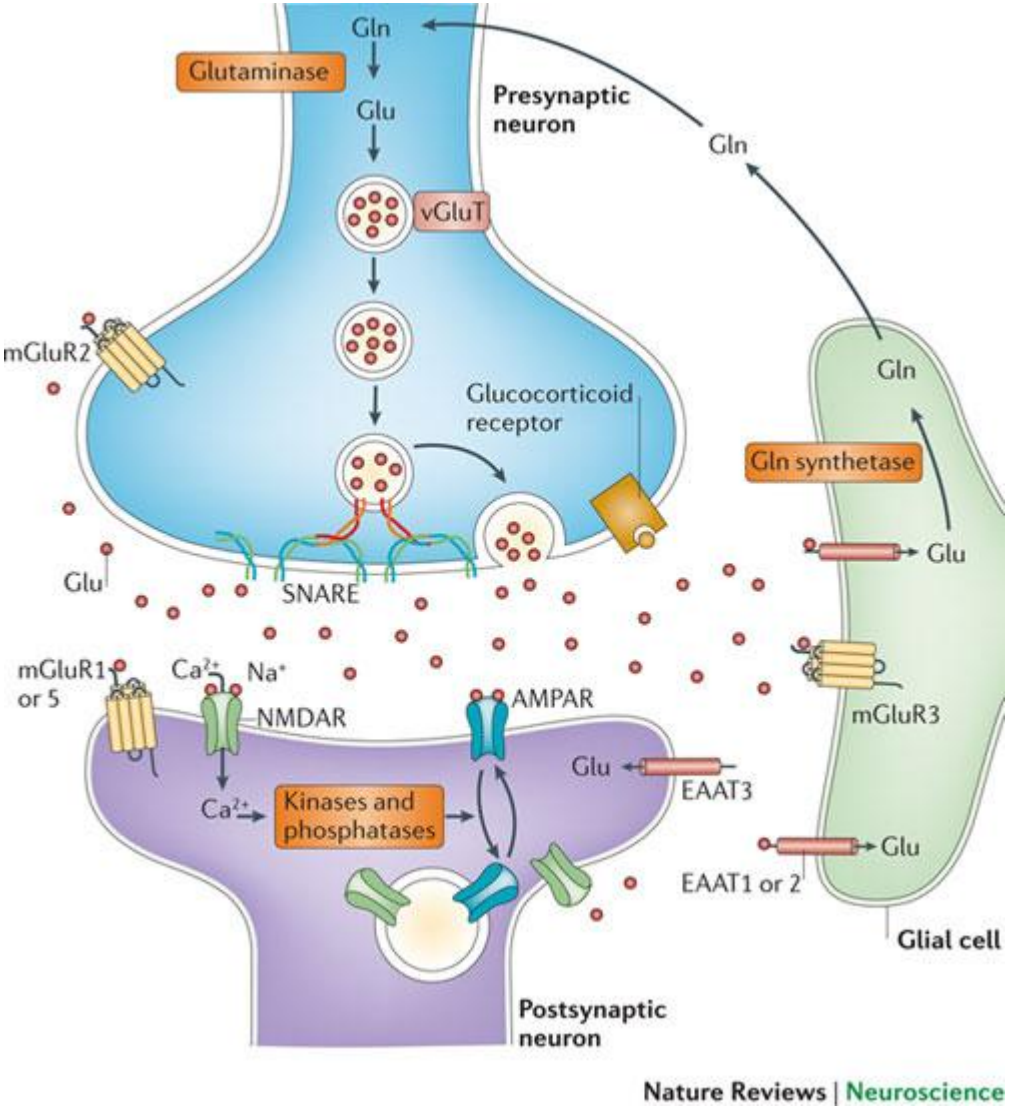

Ahnert-Hilger G, Jahn R. CLC-3 spices up GABAergic synaptic vesicles. Nautre Neuroscience 2011:14;405-7, doi:10.1038/nn.2786

# 3. Release

- ***Calcium triggers*** release of transmitters
- Plasma membrane docking
- Membrane fusion (exocytosis)
- Endocytosis and recycling




Nature Reviews | Neuroscience

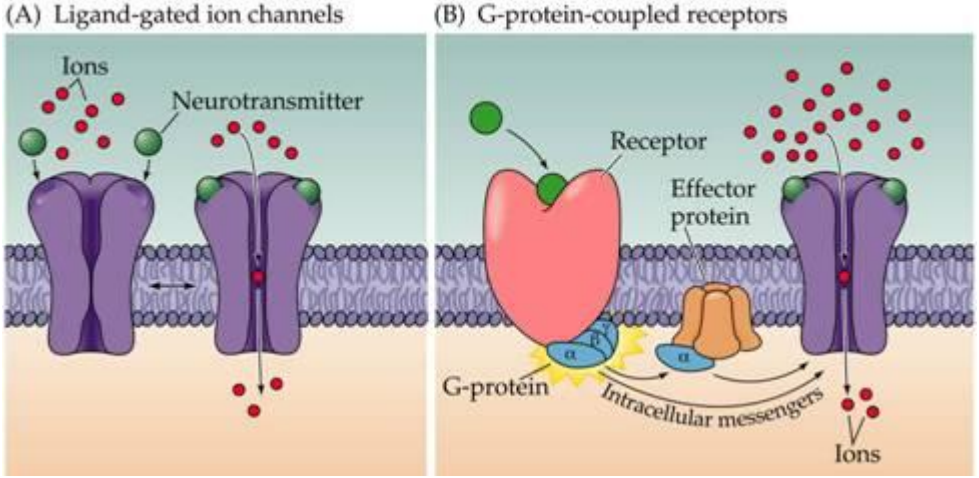



**From the following article:**
The stressed synapse: the impact of stress and glucocorticoids on glutamate transmission Maurizio Popoli, Zhen Yan, Bruce S. McEwen & Gerard Sanacora. Nature Reviews Neuroscience 13, 22-37 (January 2012)

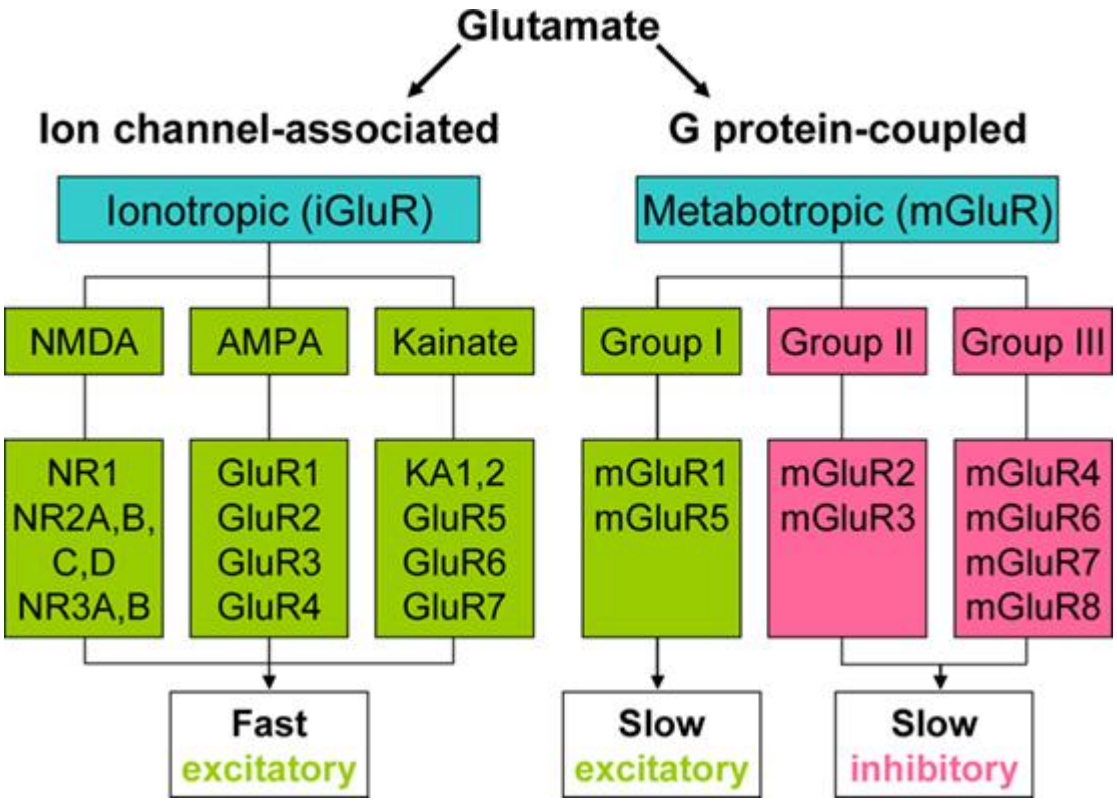
# 4. Receptor binding

- Released transmitter interacts with receptors located on the target (postynaptic) cell.
- Receptors are:

a) Ionotropic (proteins that form ionic chanels)
b) Metabotropic (proteins that alter intracellular process)
c) Autoreceptors (respond to transmitter release from the neuron and modulate transmitter release or synthesis)




B. Two major classes of **receptors**. 1. Ligand-Gated Ion Channels (**Ionotropic**) rci.rutgers.edu

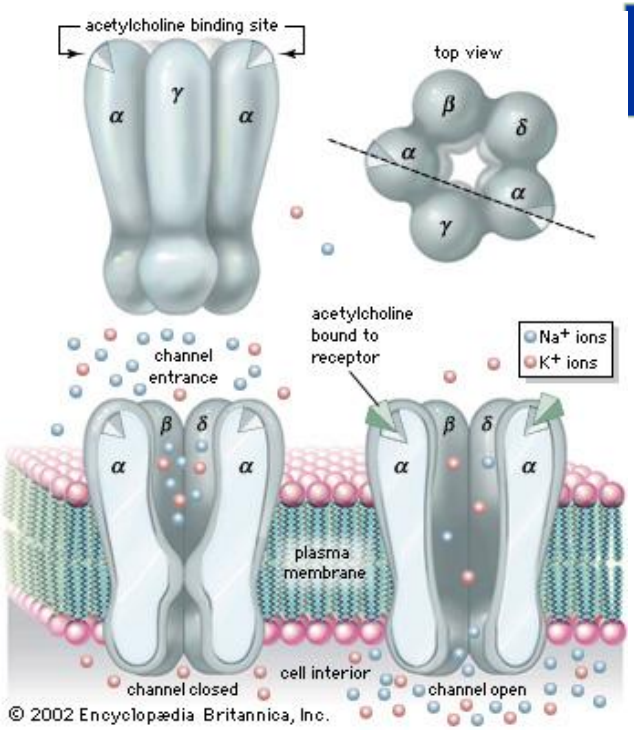

Glutamate
Ion channel-associated
G protein-coupled
Ionotropic (iGluR)
Metabotropic (mGluR)
NMDA
AMPA
Kainate
Group I
Group II
Group III
NR1
NR2A,B,
C,D
NR3A,B
GluR1
GluR2
GluR3
GluR4
KA1,2
GluR5
GluR6
GluR7
mGluR1
mGluR5
mGluR2
mGluR3
mGluR4
mGluR6
mGluR7
mGluR8
Fast
excitatory
Slow
excitatory
Slow
inhibitory

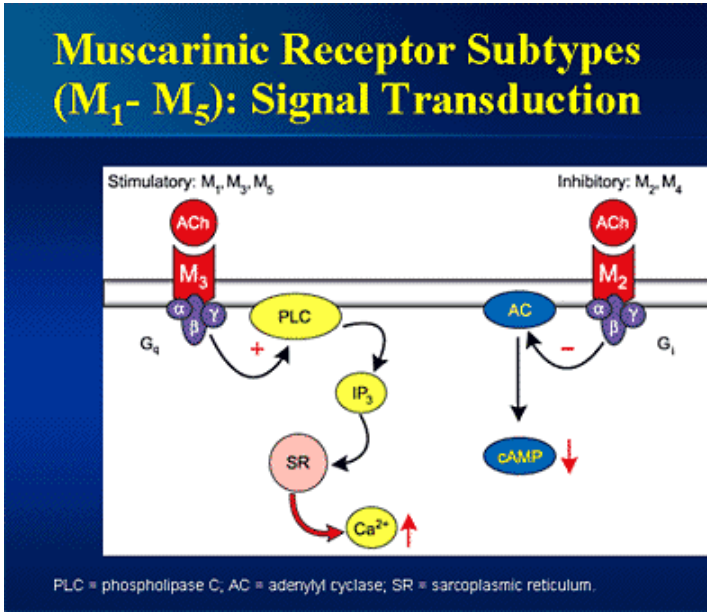
Acetylcholine (ACh)

ACh receptors

Nicotinic receptors

Muscarinic receptors




Acetylcholine receptors

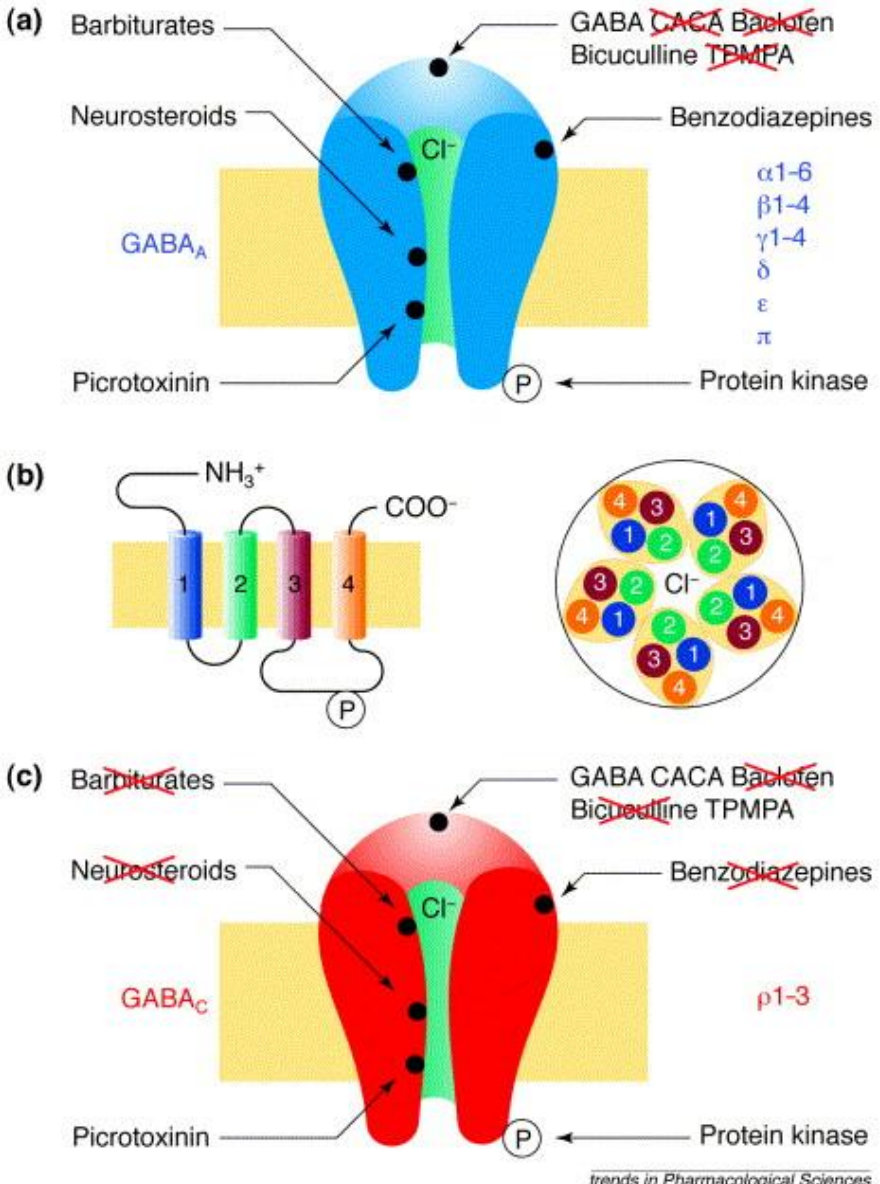
CNS (muscarinic and nicotinic)

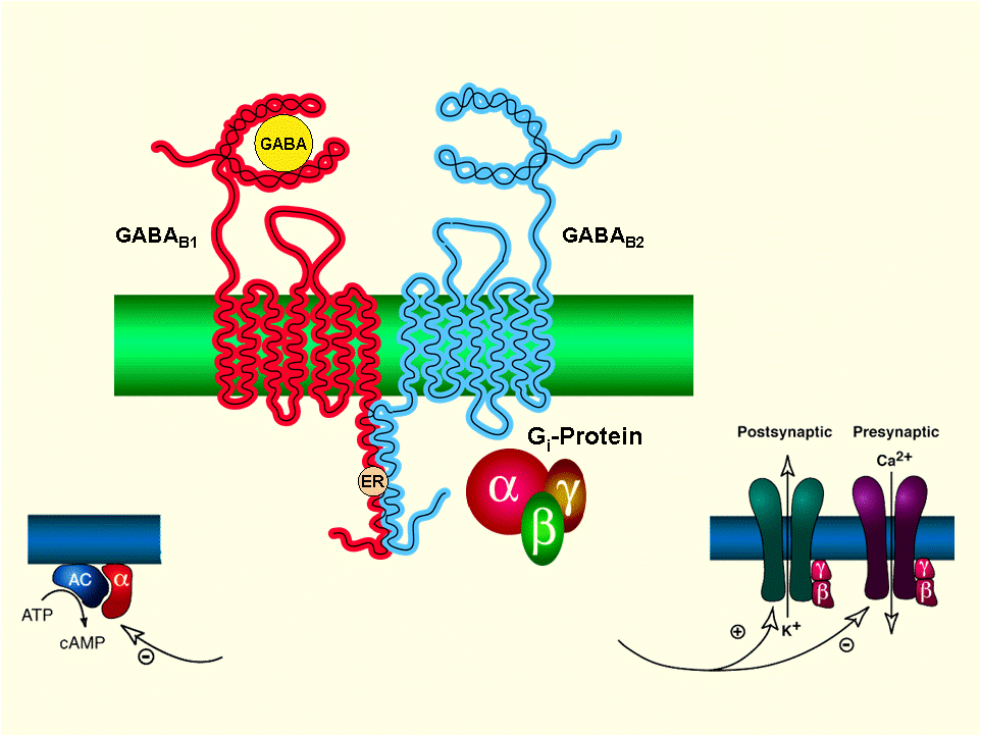
Autonomic (muscarinic and nicotinic)

Neuromuscular (nicotinic)

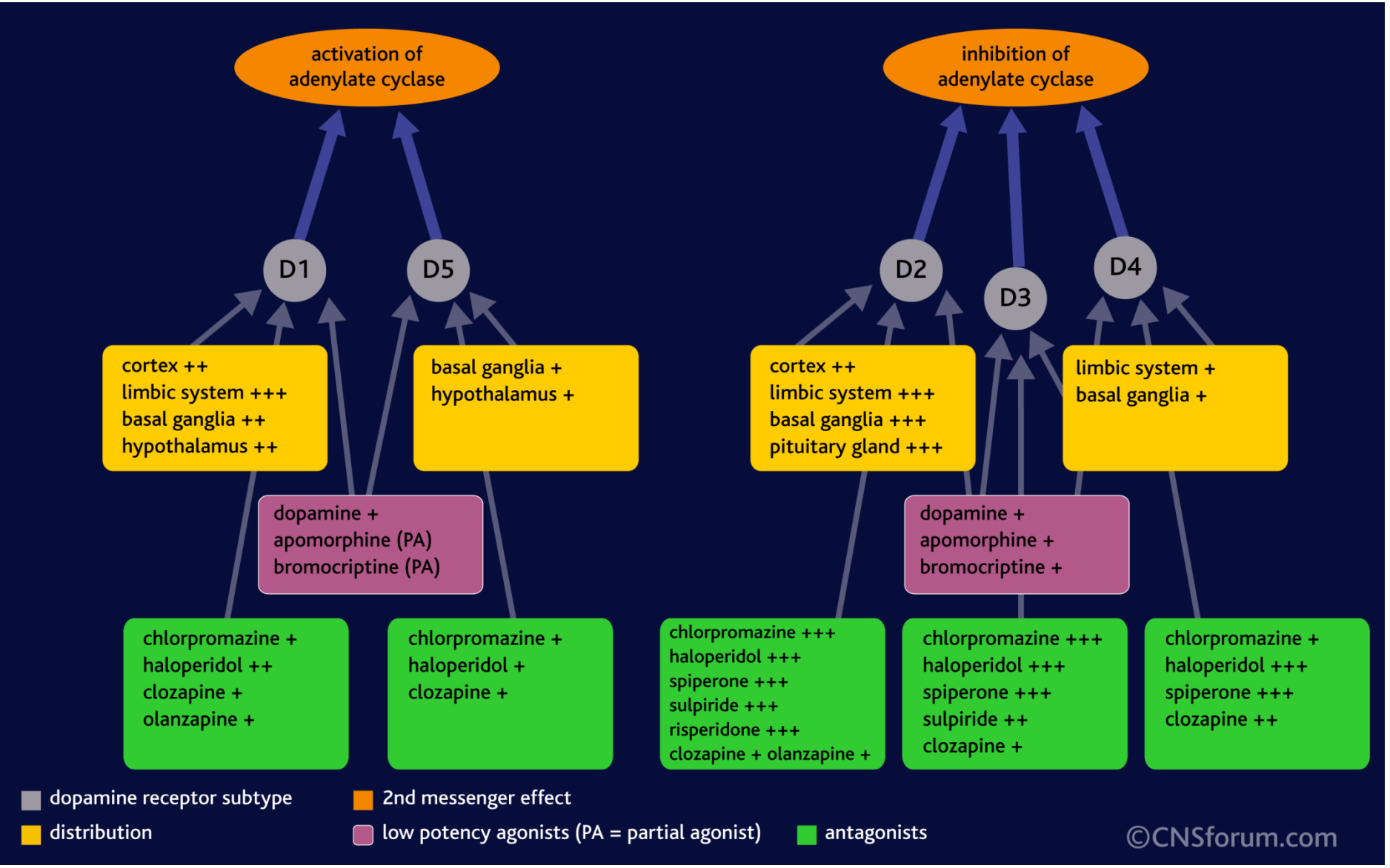
PharmacologyCorner.com

# GABA receptors

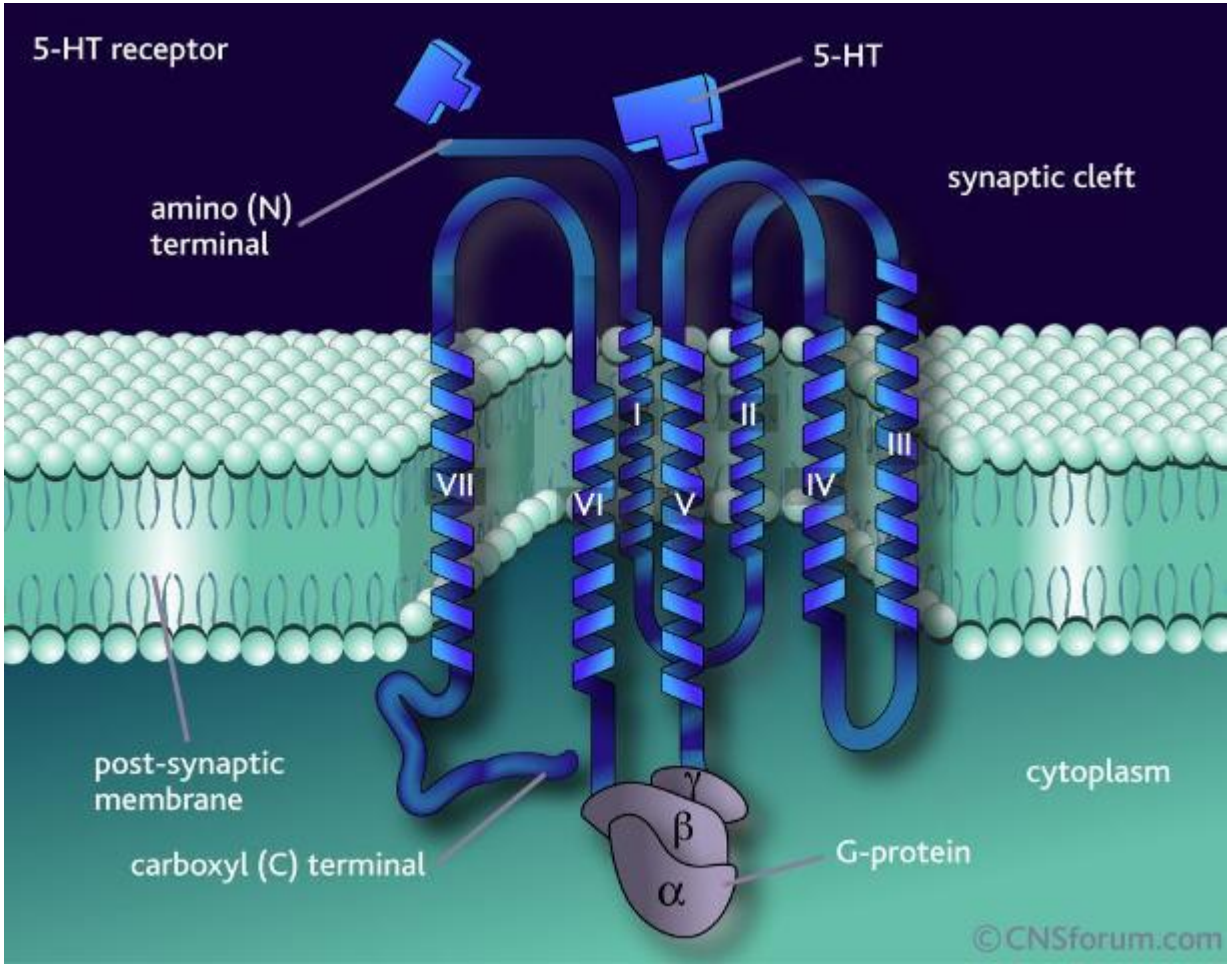


# Dopamine receptors



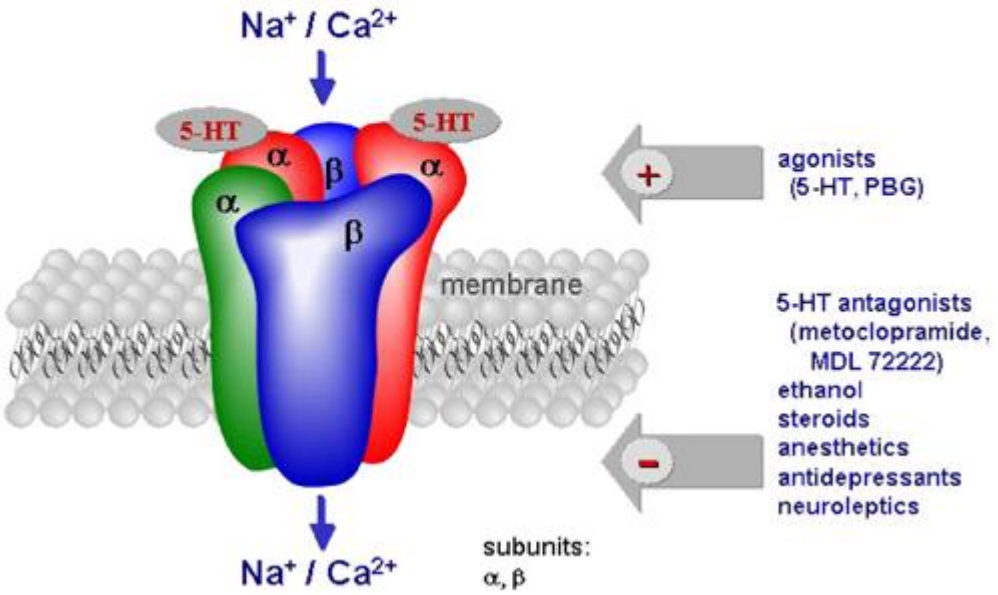
# Serotonin receptors



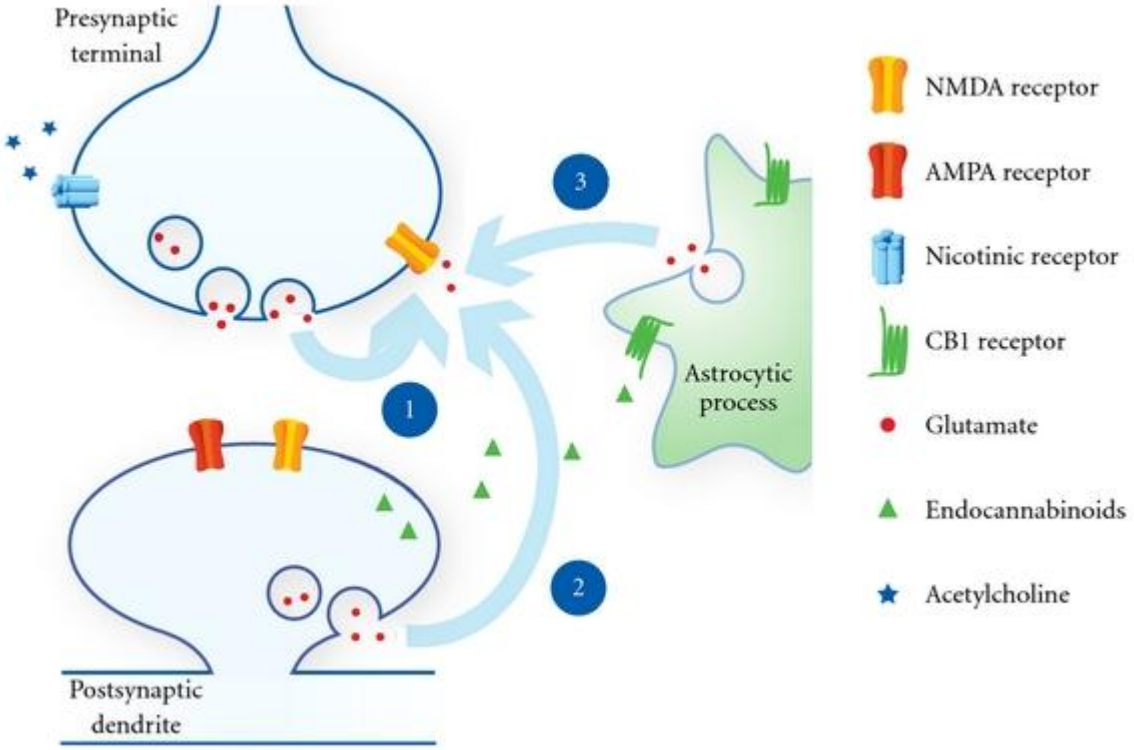
….except 5HT3 receptors

They are IONOTROPIC !!!!

**Pharmacology of the 5-HT$_3$ receptor**



# Were can we find autoreceptors?



What happens when the transmitter binds to a specific site at postsynaptic membrane ionotropic receptors?

- **POSTSYNAPTIC POTENTIAL (PSP)?**

What determines properties of PSP?

- **PROPERTIES OF PSP (EITHER EXCITATORY-EPSP OR INHIBITORY-IPSP) ARE DETERMINED BY THE NATURE OF GATING AND ION-PENETRATION PROPERTIES OF SINGLE CHANNELS**

# Postsynaptic potentials

- EPSP – depolarizes cell membrane
  - *Increase the probability of cell firing*

- IPSP – hyperpolarizes cell membrane
  - *Decrease the probability of cell firing*

## EPSP

- $Na^+$ i $K^+$ travels through the same ionic channel
- Ionotropic receptor – ligand gated channel
- Specific drugs and natural toxins prevents occurrence of EPSP

## Action potential

- $Na^+$ and $K^+$ travels through selective sodium and potassium channels
- Voltage gated channels
- Selective toxins blocks occurrence of AP such as tetrodotoxin (TTX)

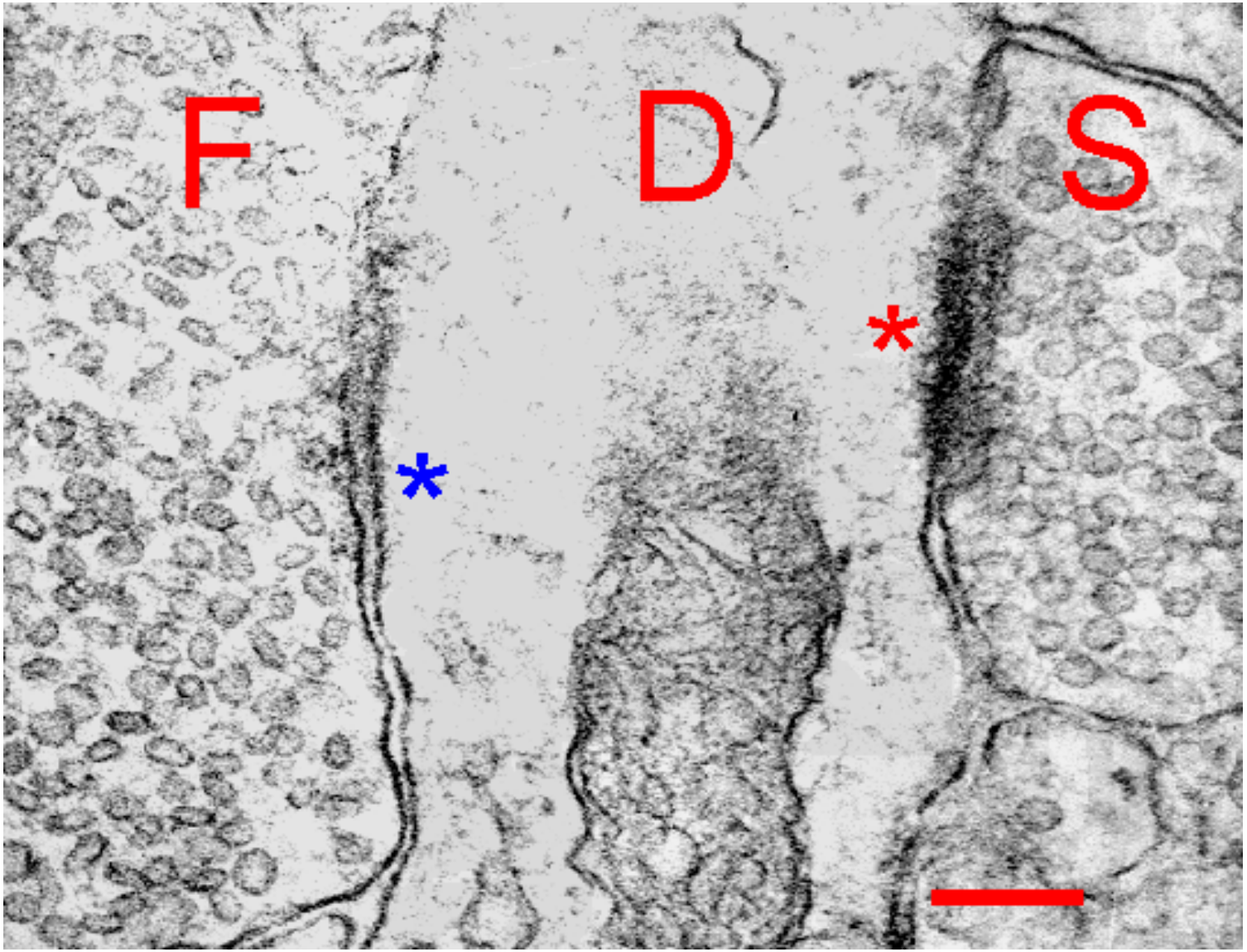
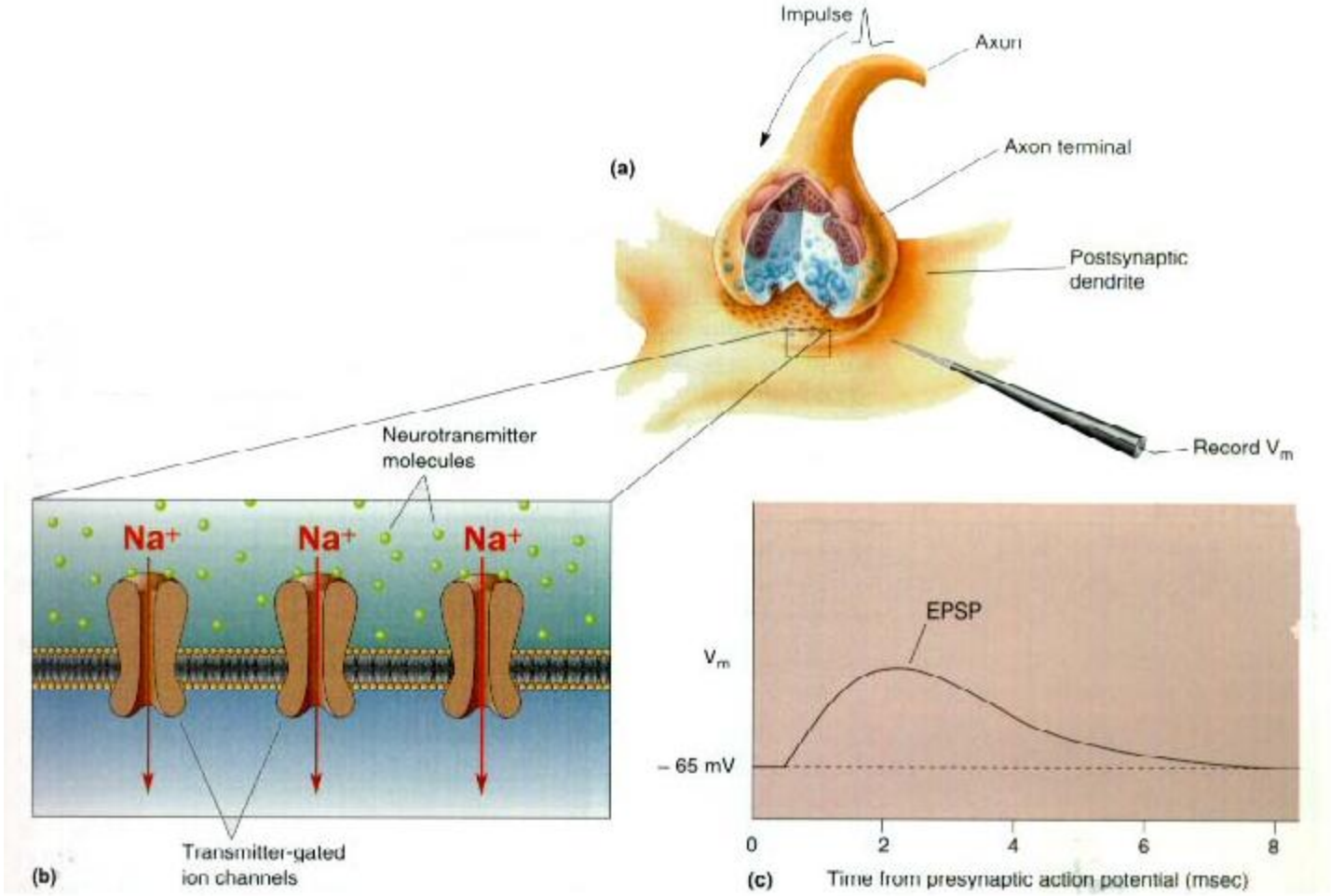
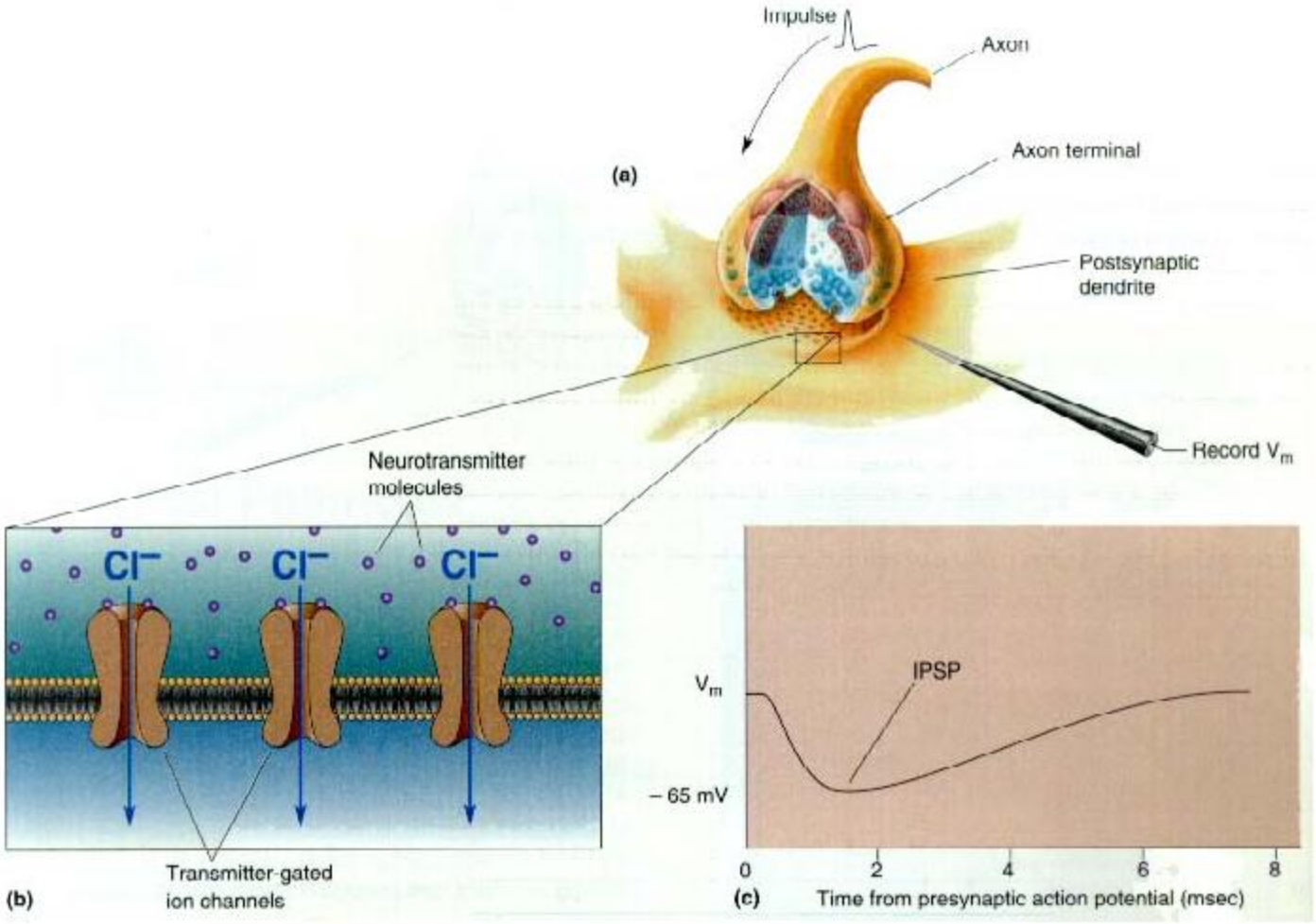



**Fig. 1.6.7.** Two *axo-dendritic synapses* on a dendritic stem (D). The *asymmetrical* (*Gray I*) type with spherical synaptic vesicles in the presynaptic bouton and prominent postsynaptic density (S, red asterisk) on the right, the *symmetrical* (*Gray II*) type with pleiomorphic or flat vesicles in the presynaptic bouton and only slight postsynaptic density (F, blue asterix on the left. Scale = 200 nm. (Rat, lateral geniculate nucleus.)

# Excitatory postsynaptic potential



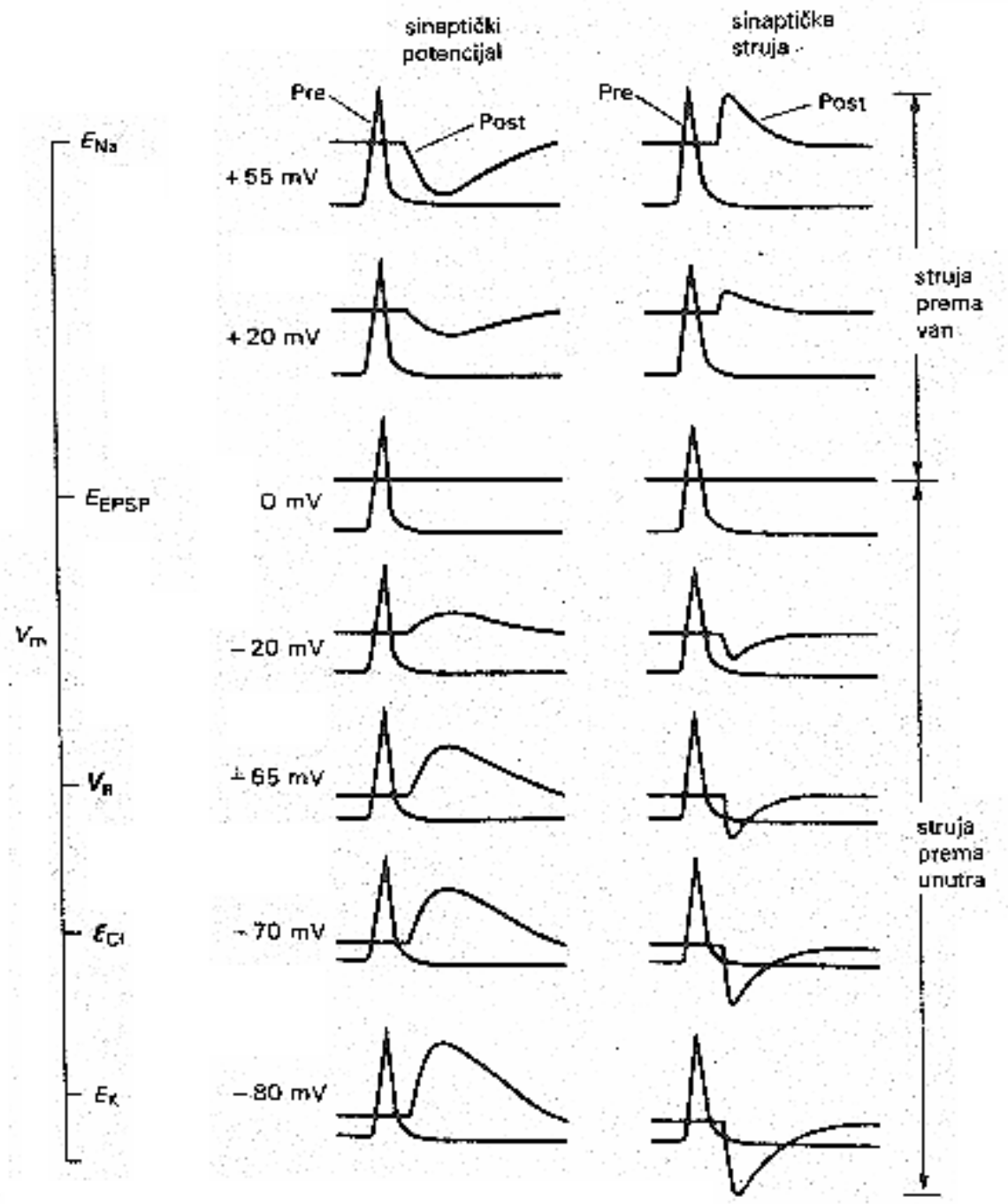
# Inhibitory postsynaptic potential



- PATCH CLAMP METHOD– current flowing through single isolated channel can be measured directly, provides insight into both the ionic mechanisms and molecular properties of PSP mediated by ionotropic receptors
- VOLTAGE CLAMP METHOD- keep the membrane potential fixed during the flow of synaptic current

# REVERSAL POTENTIAL

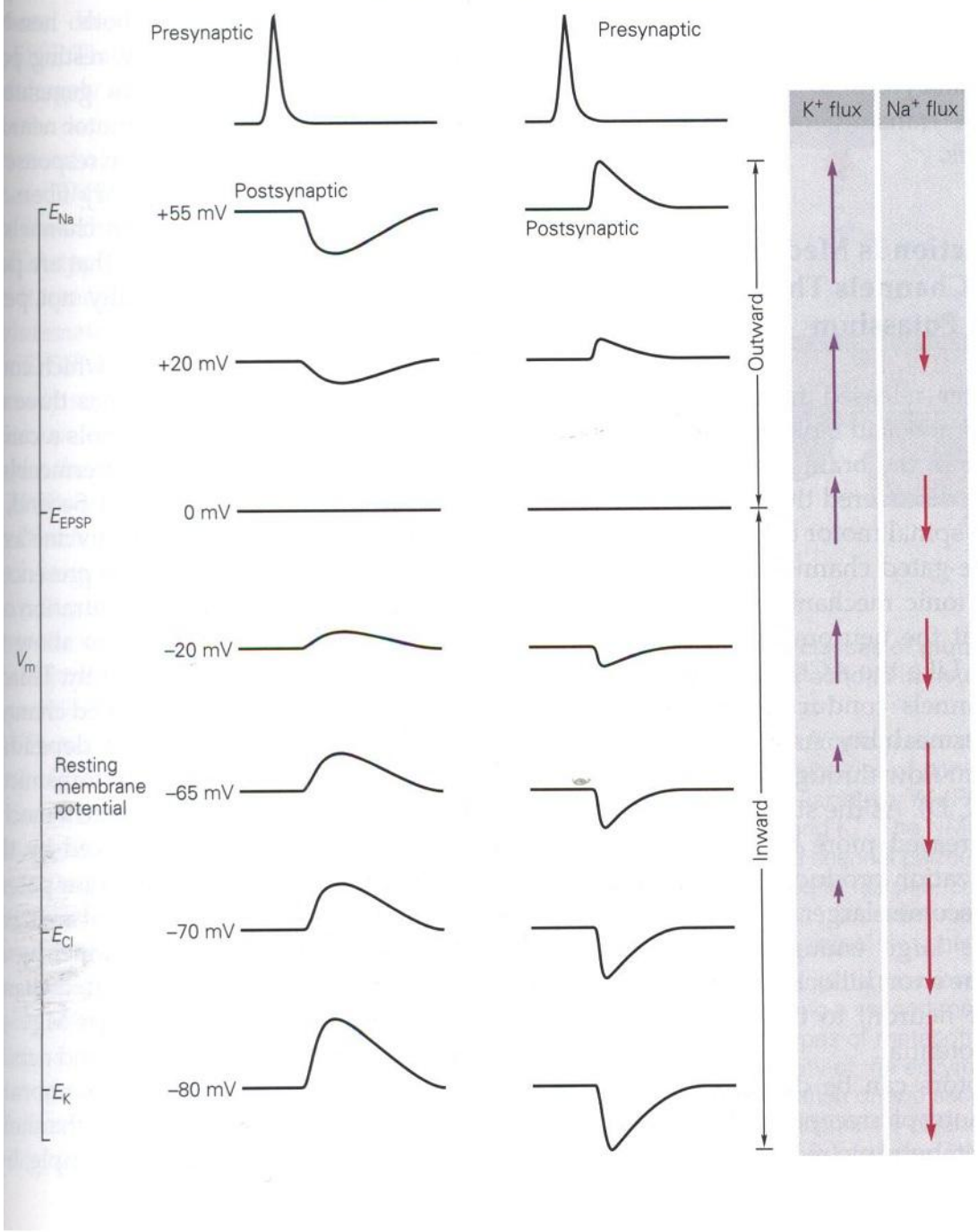
- REVERSAL POTENTIAL– is the potential at which given neurotransmitter causes ***no net current flow*** of ions through that neurotransmitter ion channel



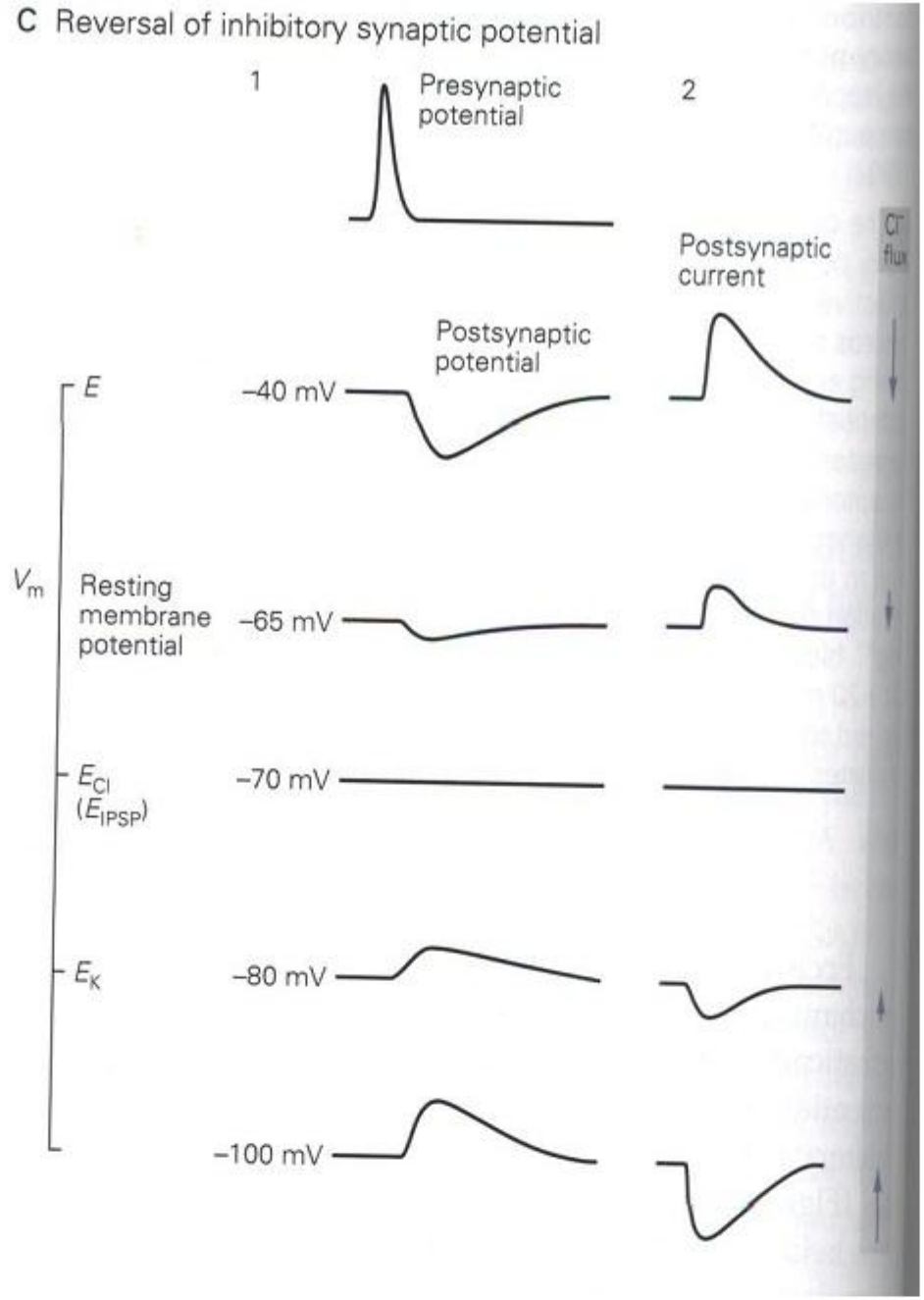

# EPSP

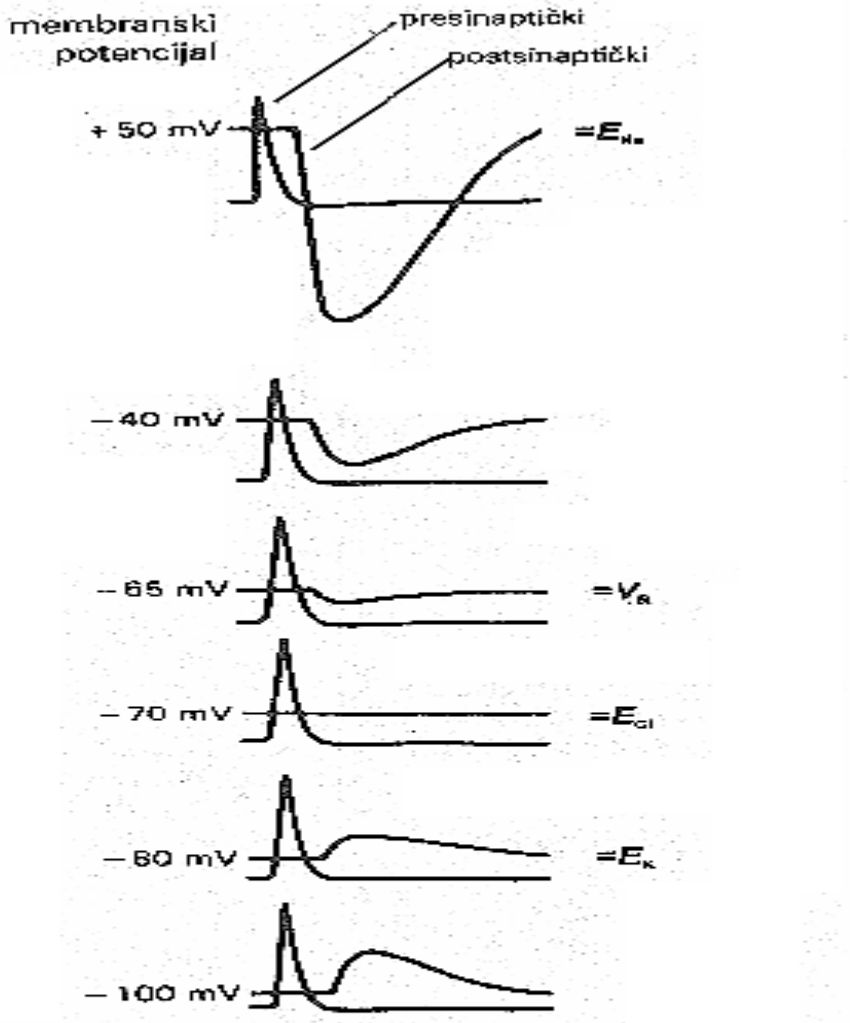
-ACh
-increases g(Na) i g(K)
- Na current in cell
- K current out
-depolarisation

Vm= -65 mV
ENa= +55 mV
EK= - 75 mV
EEPSP= 0mV


Presynaptic
Postsynaptic
+55 mV
+20 mV
0 mV
–20 mV
–65 mV
–70 mV
–80 mV
$E_{Na}$
$E_{EPSP}$
$E_{Cl}$
$E_K$
$V_m$
Resting membrane potential
Outward
Inward
$K^+$ flux
$Na^+$ flux

C Reversal of inhibitory synaptic potential






**Slika 10–6.** Potencijal obrata za IPSP jednak je ravnotežnom potencijalu $Cl^-$ ($E_{Cl}$). Pri $V_R$ (–65 mV), presinaptički akcijski potencijal uzrokuje hiperpolarizirajući IPSP, čija amplituda se poveća kad membranu depolariziramo. Međutim, kad je $V_m$ hiperpolariziran na –70 mV, IPSP nestane. Taj potencijal obrata, $E_{IPSP}$, jednak je $E_{Cl}$. S daljnjom hiperpolarizacijom, IPSP se pretvara u depolarizirajući postsinaptički potencijal (pri –80 i –100 mV) jer je sad $V_m$ hiperpolariziran u odnosu na $E_{Cl}$. No, čak i to depolarizirajuće djelovanje ima inhibicijski učinak, jer $V_m$ ostaje "prikovan" uz vrijednost –70 mV ili veću, što je bitno udaljeno od praga (–55 mV). Prema Kandel i sur. (1991), uz dopuštenje.

# IPSP

-GABA, glicin

-g($Cl^-$) increases (ionotropic)

-g($K^+$) increases (metabotropic)

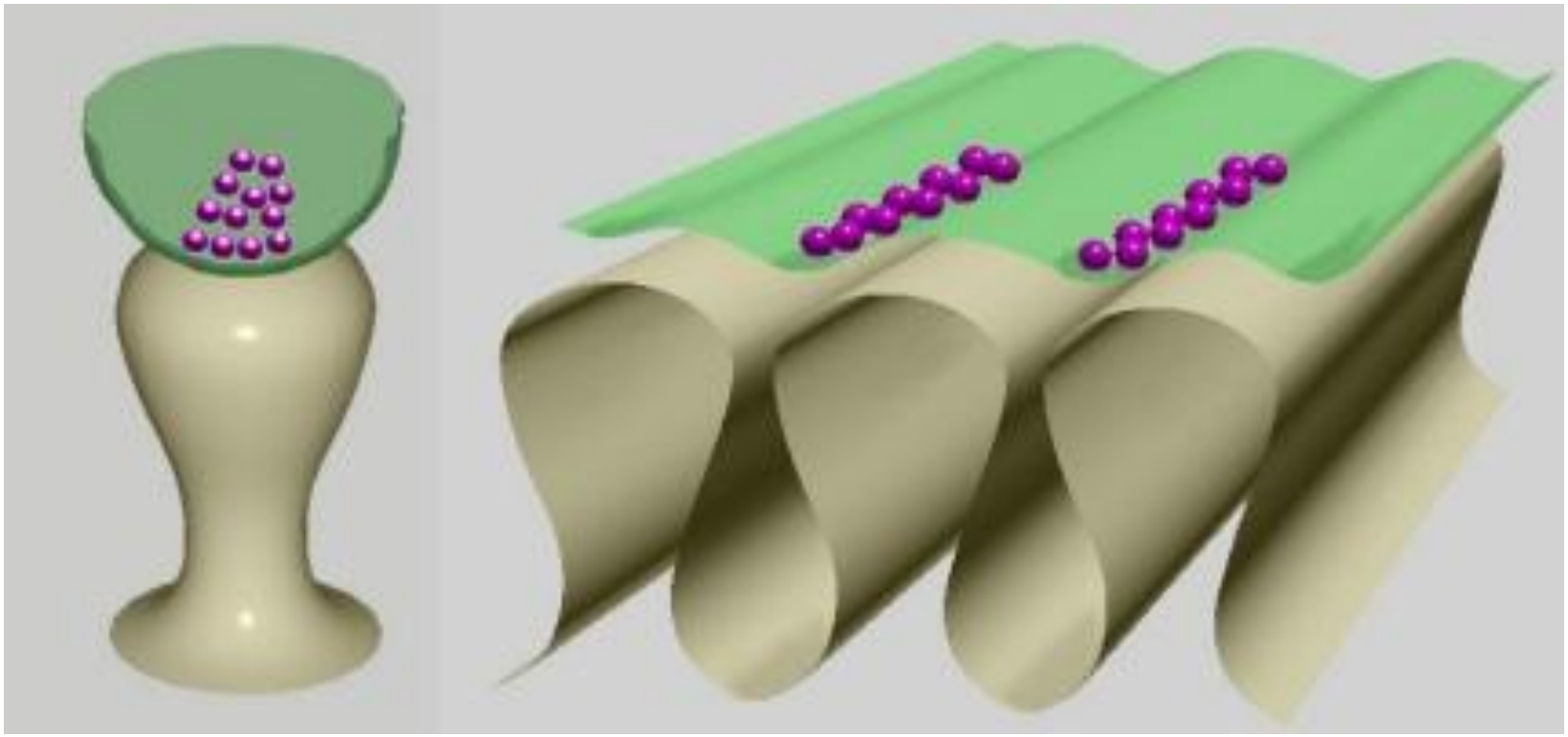
-hyperpolarization

-Vm= -65 mV

-ECl= -70 mV

-EK= -80 mV

# V. Central vs neuromuscular synapse



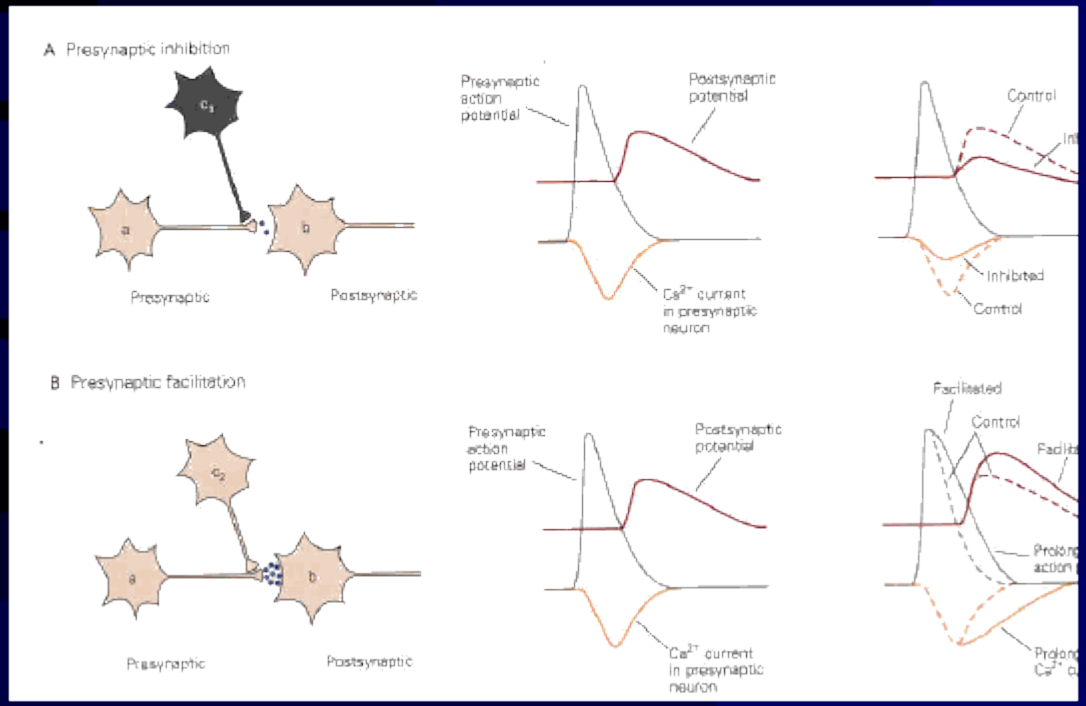
- **Fig. 2:** Basic shape of dendritic spine (*left*) compared to that of the neuromuscular junction (*right*). The dendritic spine attaches to the dendrite with a narrow neck and receives a synapse on a bulb-like head. This lollipop shape is similar to the shape of the interfolds sectioned transversely. Opened axon terminal in green, synaptic vesicles in purple.

# Central synapse *vs* Neuromuscular synapse

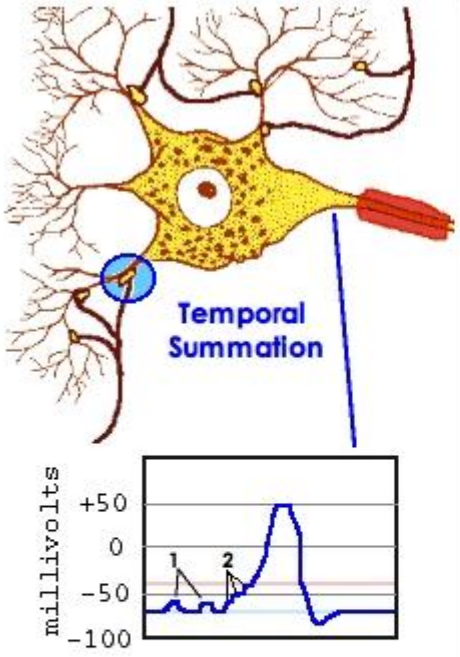
- cleft 15-20 nm
- EPSP < 1 mV
- 3-10 AP = 1 synaptic vesicles
- Several presynaptic AP = 1 postysnaptic AP
- Higher concentration of neurotransmitters – less binding affinity
- Excitatory and inhibitory
- Different neurotransmitters
- Numerous synapses on the same neuron

- cleft 60-100 nm
- EPSP has enchanced amplitude
- 1 AP = 200 synaptic vesicles
- 1 presynaptic AP = 1 postsynaptic AP
- higher binding affinity (40% for Ach)
- Only excitatory synapses
- Only one neurotransmitter (Ach)

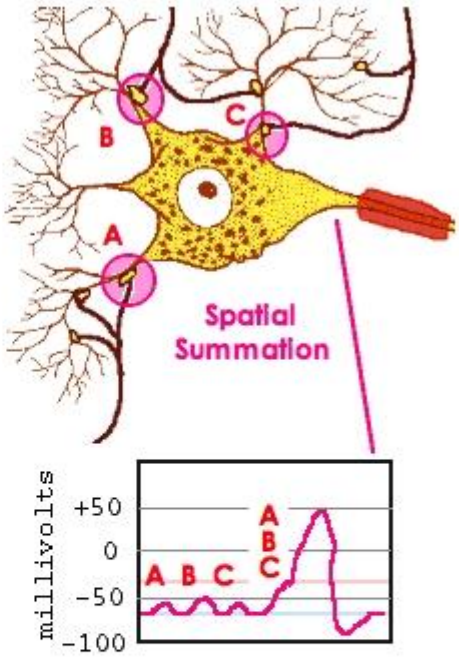
# Presynaptic inhibition and facilitation



# VII. Temporal and spatial summation

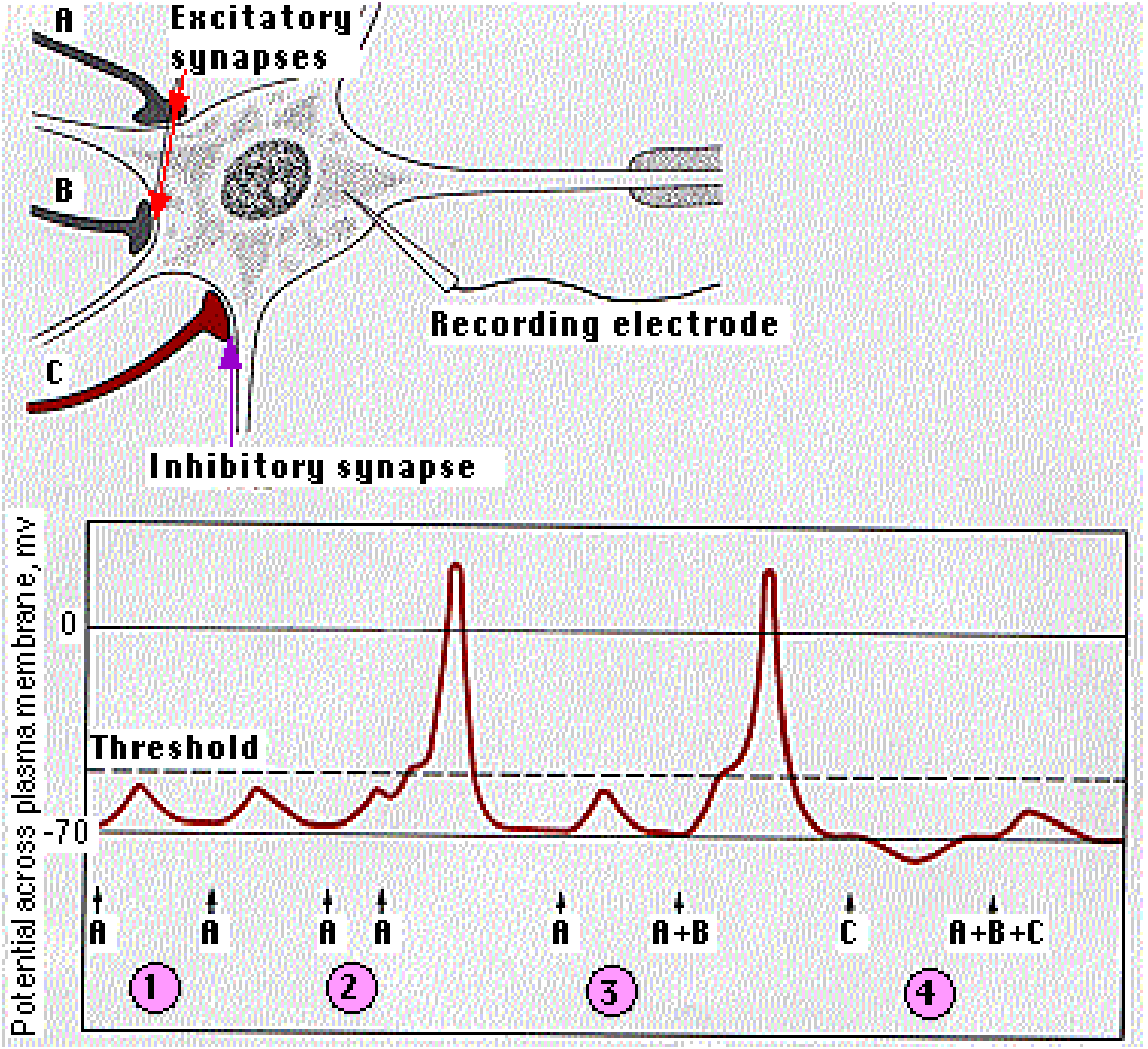



1. Two firings with a pause in between cause no action potential.
2. Three firings in rapid succession cause the neuron to reach the threshold of excitation.



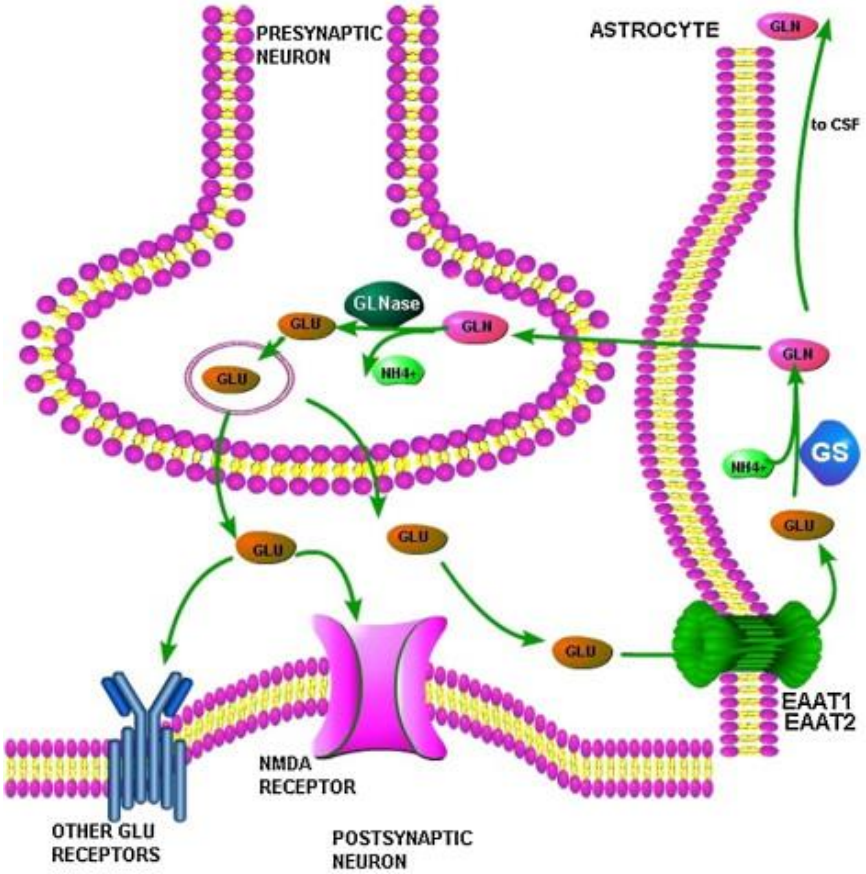

A, B, C Each of these firings alone causes a partial depolarization but not enough for an action potential.

But, if A,B,C fire simultaneously their combined effects will cause an action potential


A
Excitatory synapses
B
C
Recording electrode
Inhibitory synapse
Potential across plasma membrane, mv
0
-70
Threshold
A
A
A
A
A
A+B
C
A+B+C
1
2
3
4

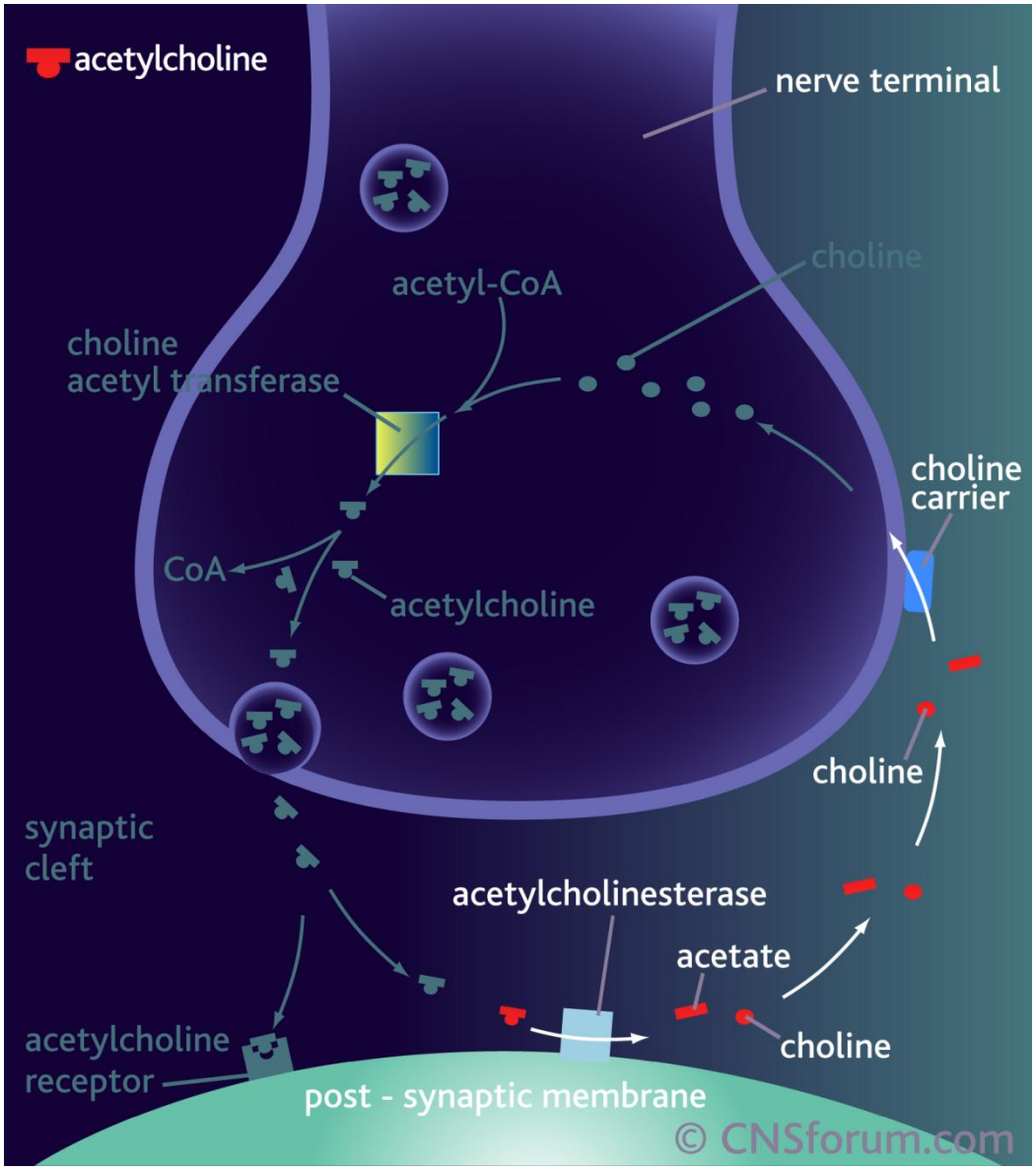
# Inactivation of transmitters from the synaptic cleft

- Difusion
- Enzyme degradation(acetylcholinesterase hydrolyzes Ach)
- Reuptake mechanism (noradrenalin, dopamin, serotonin, glutamate, GABA, glycin)

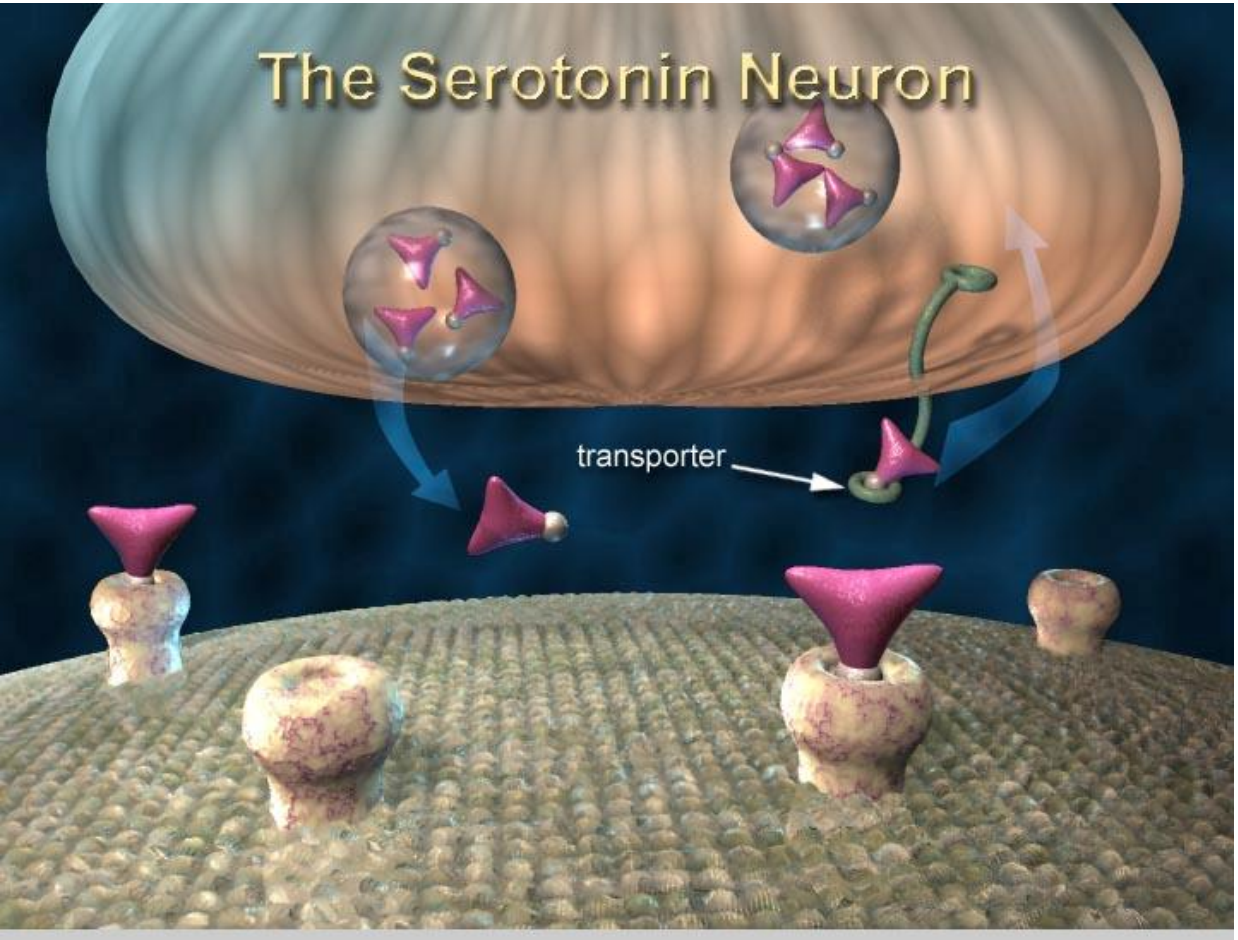



# 1. difusion

- Fig. 1. The glutamate–glutamine cycle in the brain. Glutamate released into the synaptic cleft acts on postsynaptic receptors (NMDA and other types of glutamate receptors). Then glutamate is rapidly removed from the synaptic cleft by glutamate transporters (e.g. EAAT1 and EAAT2) that are mainly located on surrounding astrocytes. Within the astrocytes, glutamate and ammonia are combined to form glutamine by glutamine synthetase (GS), an astrocyte-specific enzyme. To replenish the neurotransmitter pool of glutamate, glutamine is released from astroyctes and taken up by glutamatergic neurons. Once glutamine is taken up into the neuron, phosphate-activated glutamatetaminase (GLUTAMINEase) splits it into glutamate and ammonia. Glutamate is then incorporated in synaptic vesicles that will release it to the synaptic cleft, starting a new cycle.
- Courtesy of: Rodrigo and Felipo, Front. Biosci. 12, 883–890, Jan. 2007).




# 2. Enzymatic inactivation




Source: < http://www.drugabuse.gov/pubs/teaching/Teaching4/Teaching.html > Used with permission.

# 3. Reuptake mechanism

# Diseases of the synapses

- ***Myasthenia Gravis*** (affects nerve-muscle synapse)
- ***Lambert-Eaton Syndrome*** (loss of voltage gated calcium channels in the presyaptic terminals
- ***Botulism***
- ***Tetanus***