Medicine and Surgery

A.Y. 2025/2026 - Programme Code: 6734

84284-Signaling pathways in health and disease I.C.

Module A – 84285 **Cell signaling** 4 CFU

Lecture A.02
Cell surface receptors and nuclear receptors

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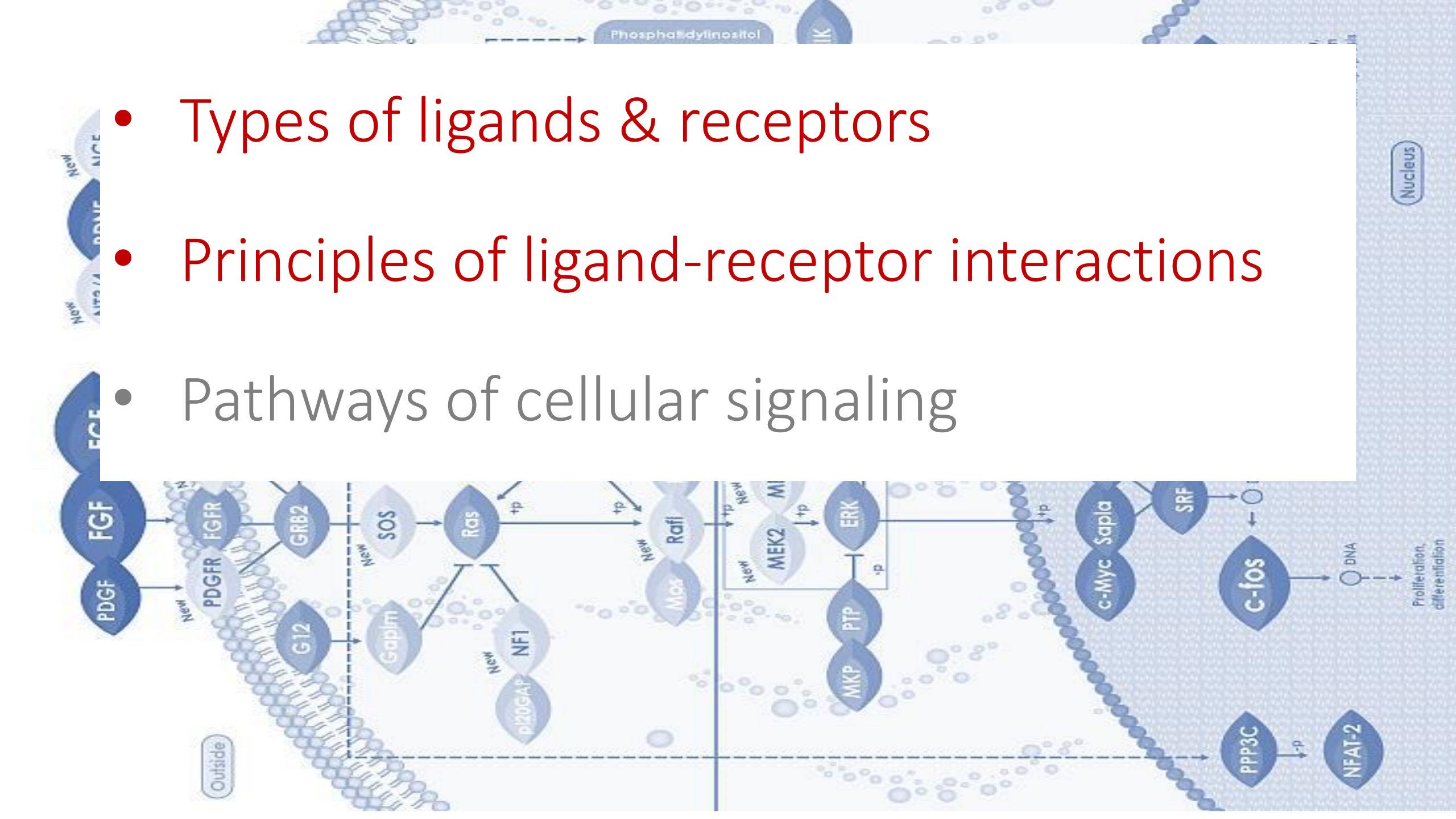


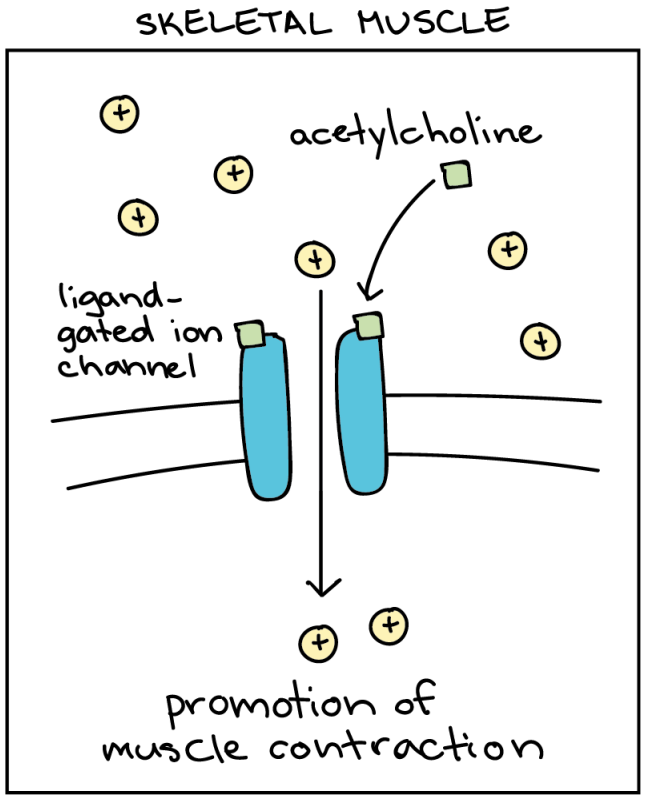
- Types of ligands & receptors
- Principles of ligand-receptor interactions
- Pathways of cellular signaling

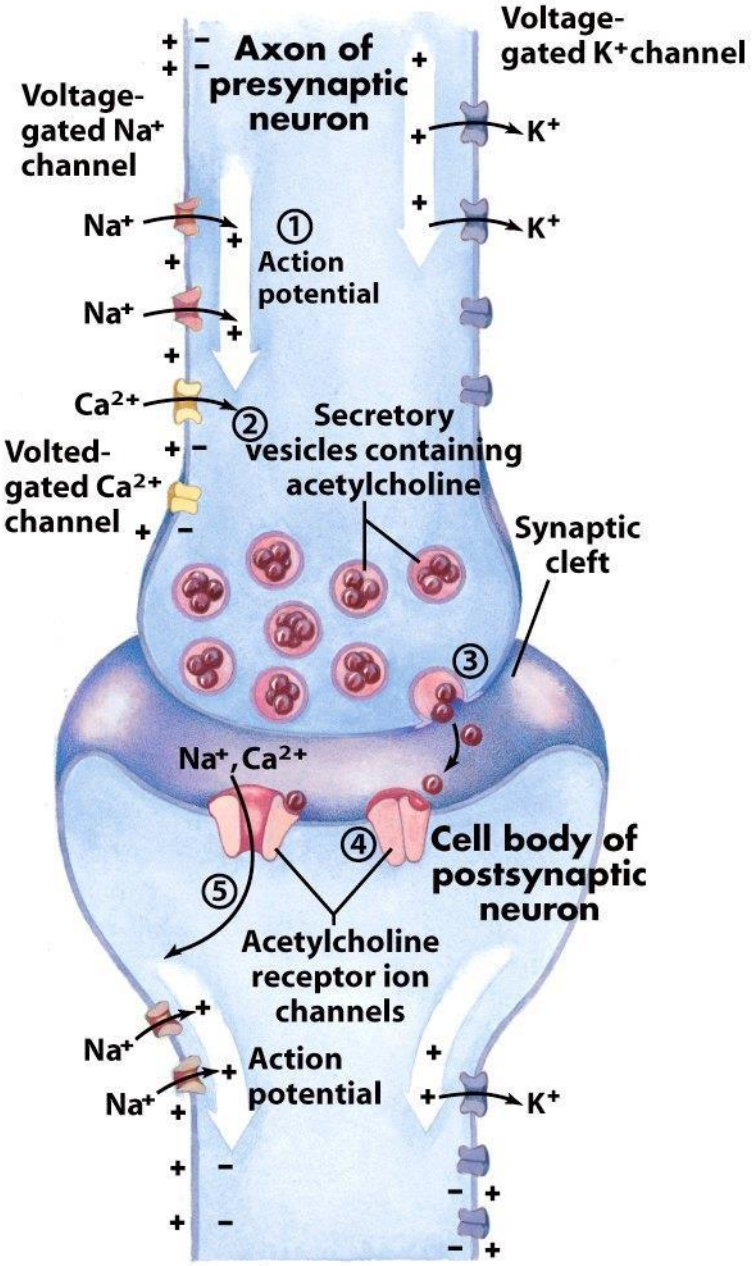
… molecular details of representative signal transduction systems, as classified according to the type of receptor

RECEPTORS

- MEMBRANE-
  - Ionotropic receptors (ion channels)
  - Metabotropic receptors (G proteins)
  - Catalytic receptors (enzymes)

- INTRACELLULAR-





Acetylcholine: a key excitatory neurotransmitter in neuromuscular junctions and in some synapses

4- Acetylcholine binds to nicotinic receptors (gated cationic channels) in the post-synaptic membrane of the next neuron in the circuit (or a myocyte) and triggers cell depolarization by causing such ligand-gated ion channel to open (1 ms).

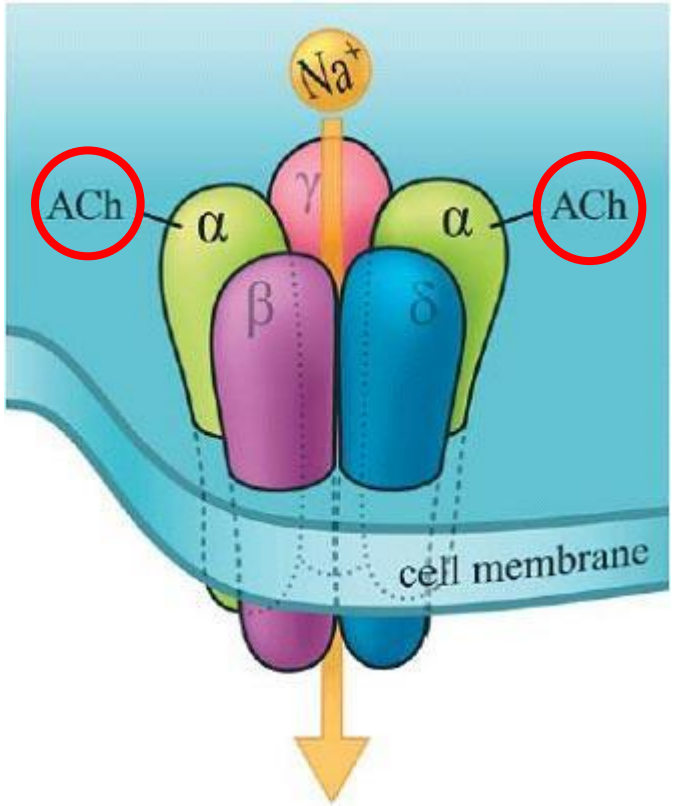
5- Extracellular Na^+ and Ca^{++} enter through this channel and serve as «intracellular second messengers» by depolarizing the post-synaptic cell (changing V_m) and affecting other membrane proteins that are sensitive to V_m.

Nicotinic acetylcholine receptor (ionotropic)

A post-synaptic ligand-gated cationic channel that converts chemical signals into electric modifications

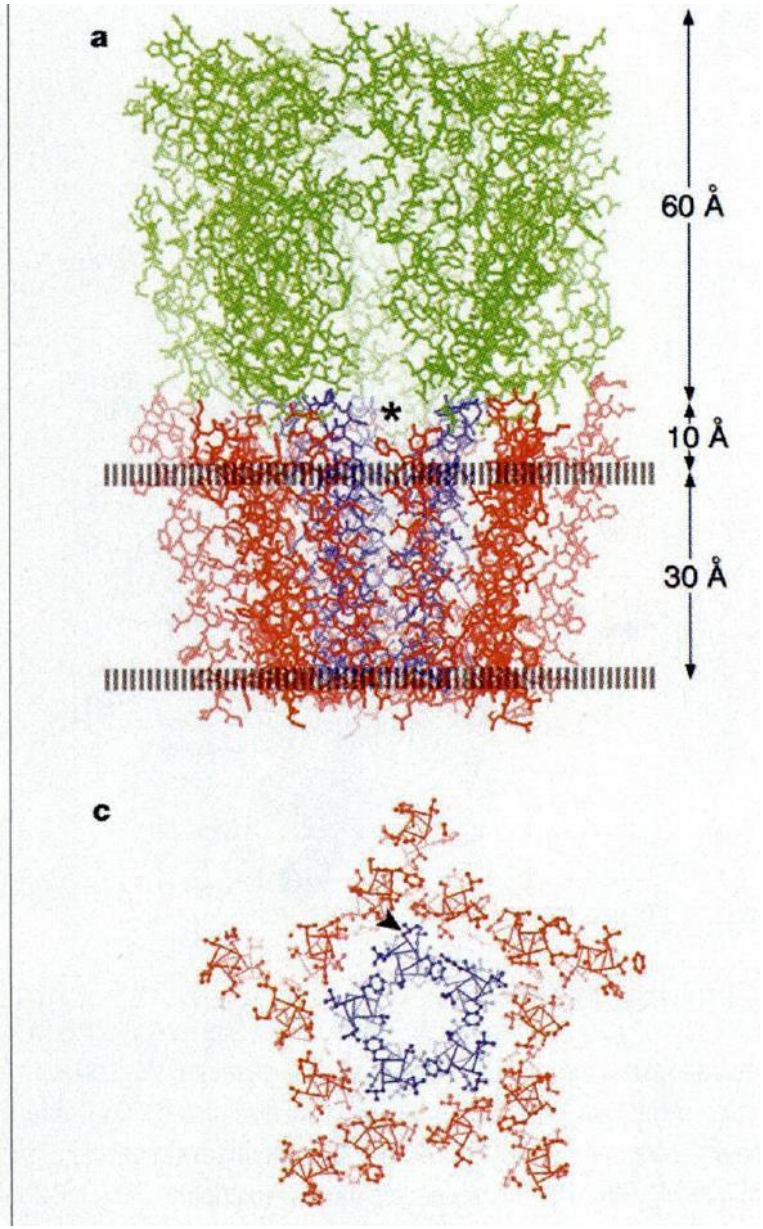
- neuromuscular junctions
- sympathetic and parasympathetic ganglia
- adrenal medulla
- central nervous system

- pentameric structure ($\alpha_2\beta\gamma\delta$ subunits)
- four transmembrane α-helices (M1-4) in each subunit



Miyazawa A, Fujiyoshi Y, Unwin N.
Structure and gating mechanism of the acetylcholine receptor pore.
Nature. 2003, 423: 949-955.

Nicotinic acetylcholine receptor (ionotropic)



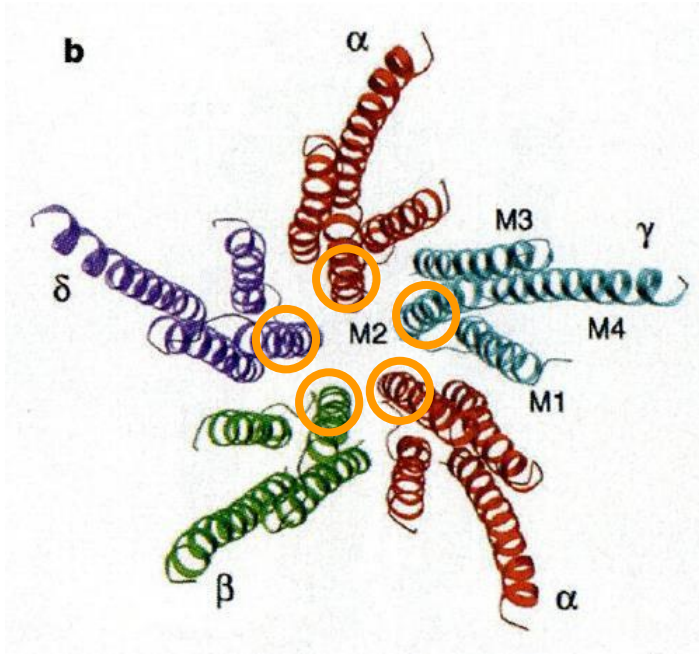


Figure 3 Pentameric structure of the pore. **a**, View normal to the receptor axis showing the α-helical pore structure (blue, pore-facing; red, lipid-facing helices) in relation to the membrane surfaces (broken lines) and the β-sheet structure (green) comprising the ligand-binding domain[8] (ball-and-stick representation); the asterisk denotes open space at a subunit interface. **b**, Stereo view of the pore, as seen from the synaptic cleft, with subunits shown in different colours (α, red; β, green; γ, cyan; δ, blue)[8]. **c**, Cross-sectional slab through the pentamer at the middle of the membrane, showing partitioning of the structure into pore- and lipid-facing parts, with intervening spaces (ball-and-stick representation); the arrowhead identifies α-Leu 257 (see text).

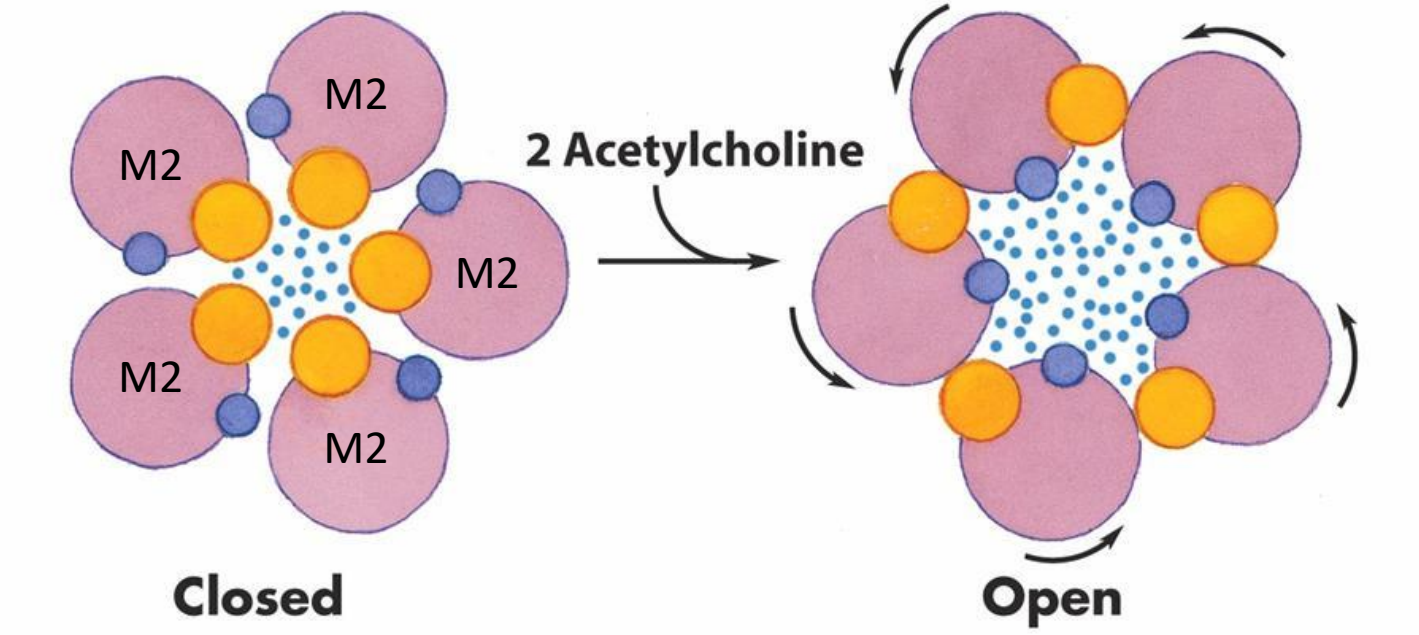
?

Nicotinic acetylcholine receptor (ionotropic)

In the middle of the membrane, the ring consisting of the side chains of five Leu residues on the M2 helices closes the channel

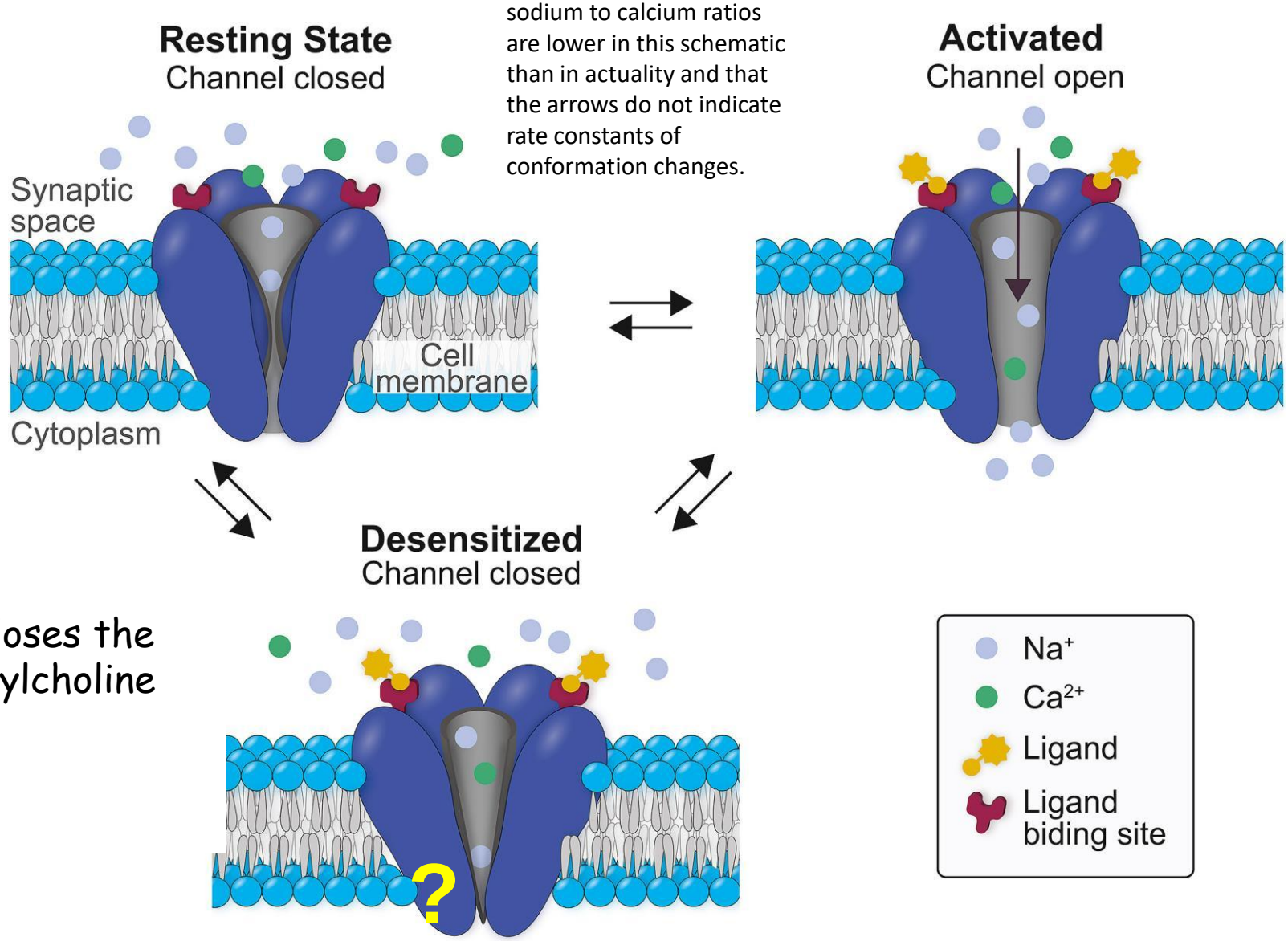
The allosteric modification induced by the binding of 2 Ach to the α–subunits generates a rotation of the M2 helices

The rotation moves the residues of Leu away from the center of the channel and exposes polar residues, thus opening the passage to the cations



Nicotinic acetylcholine receptor (ionotropic)

Representation of the main functional states of the nAChR. In the resting state, the ACh binding sites are not occupied, and the water-filled pore is closed and non-conducting to cations. In the open, activated state, the ion channel is open, providing a water-filled pore through the membrane that is permeable to small cations.



The acetylcholine signal is transient: an intrinsic timer of the receptor (?) closes the channel even in the presence of acetylcholine (Desensitization)

Like most ligand-gated ion channels, the ACh binding sites are (usually) occupied, but the pore is closed and non-conducting in the desensitized state.

https://doi.org/10.1016/j.neuropharm.2020.108256

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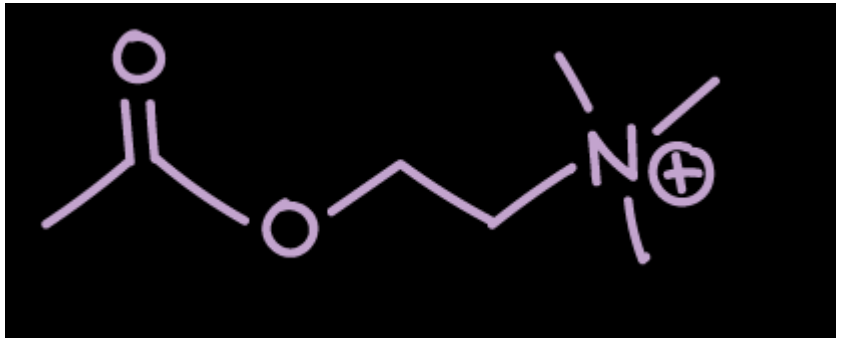
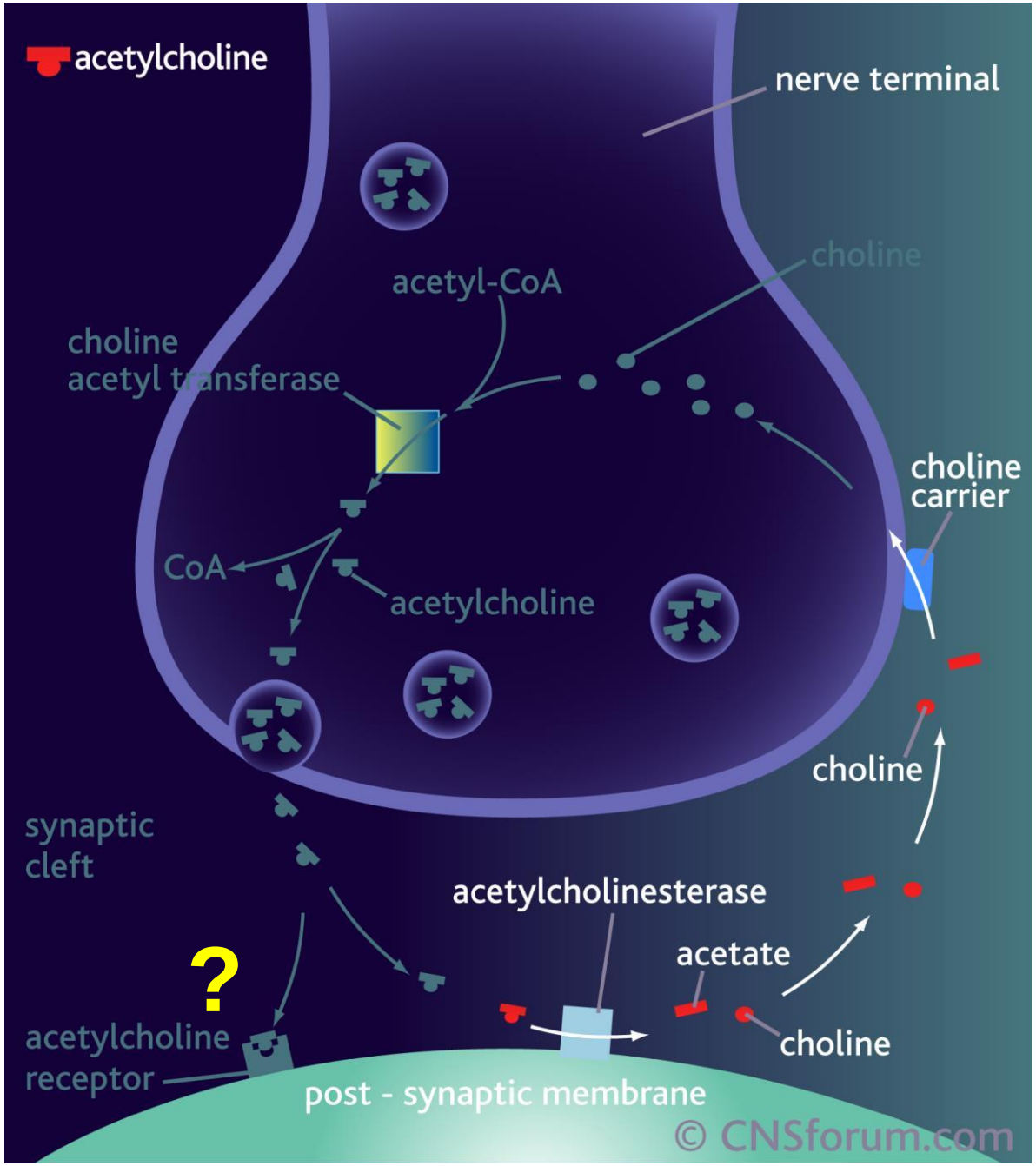


Acetylcholinesterase is the enzyme that catalyzes the hydrolysis of the neurotransmitter acetylcholine into choline and acetic acid, a reaction necessary to allow a cholinergic neuron to return to its resting state after activation



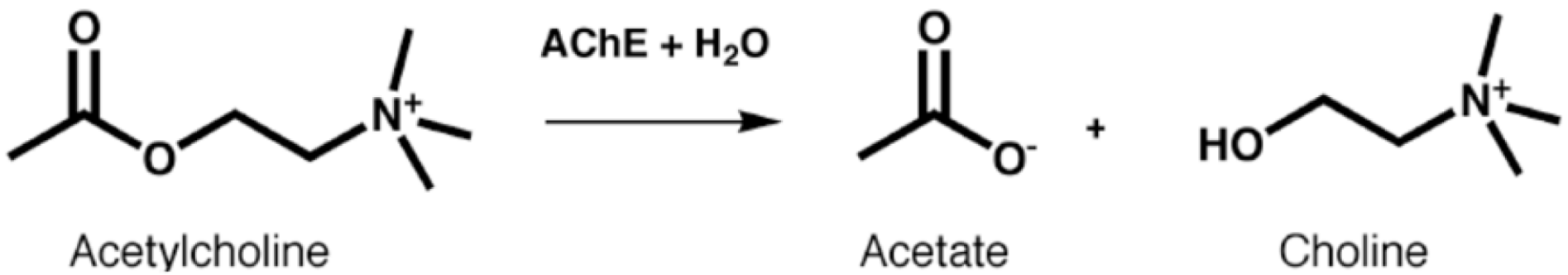


Figure 1.
Enzymatic hydrolysis of ACh by AChE.

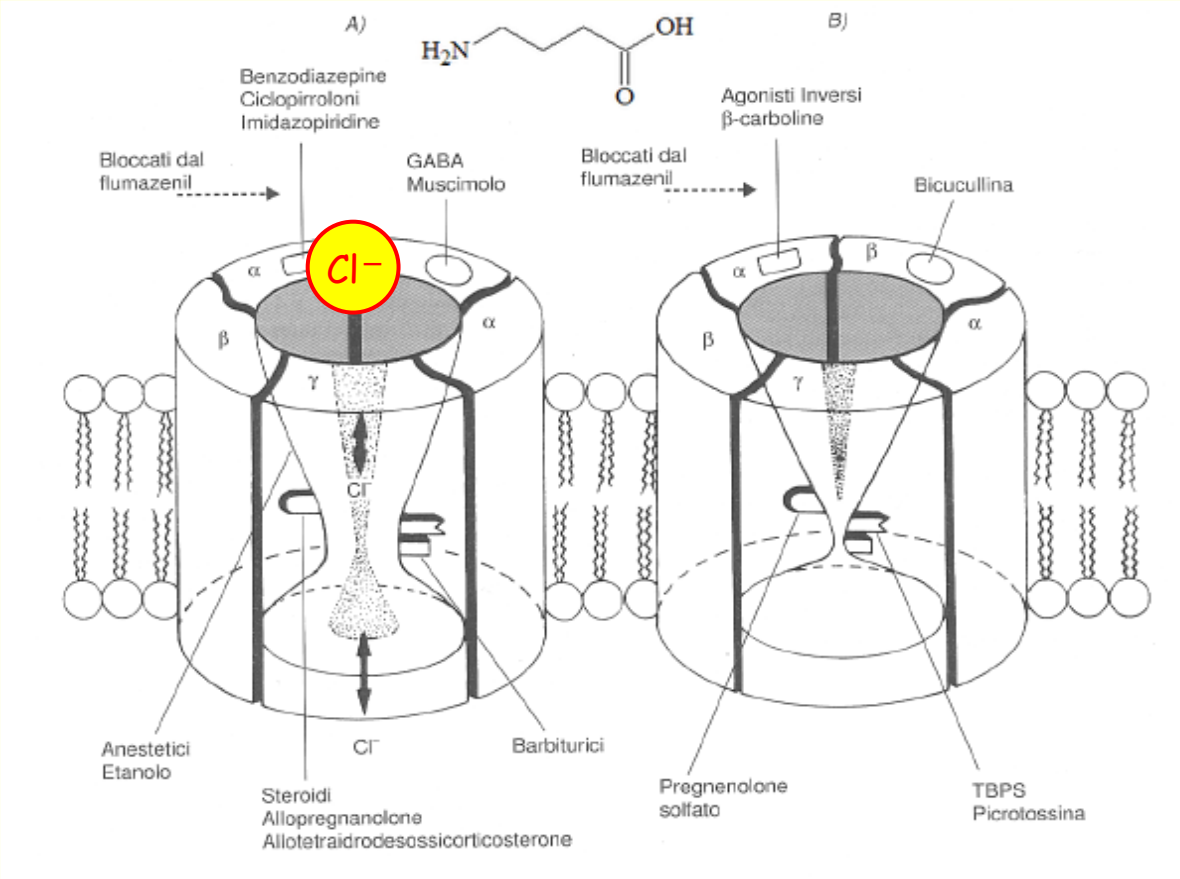
Dvir H, Silman I, Harel M, Rosenberry TL, Sussman JL. (2010) Chem Biol Interact. 187:10-22.

IONOTROPIC RECEPTORS

- Acetylcholine
- GABA γ-aminobutyric acid
- Glutamate
- Serotonin
- Glycine

It is worth noting that all of the ionotropic receptors listed are named after their ligand name!

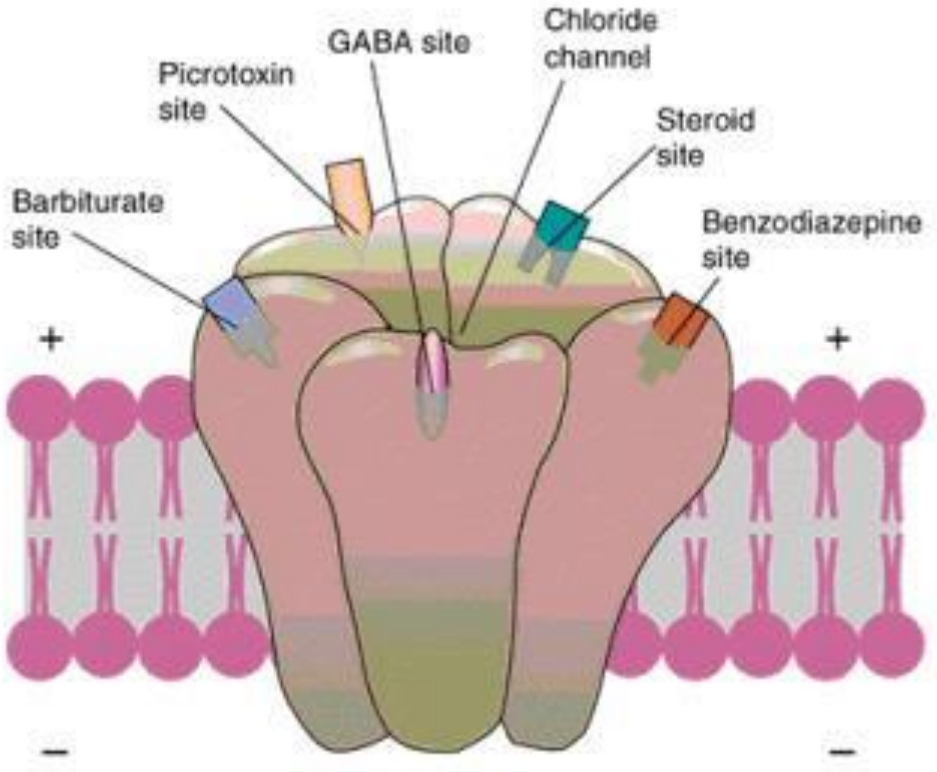
Recettore canale per il GABA



- Il recettore $GABA_A$ è un canale ionico permeabile al cloro
- La stimolazione produce una iperpolarizzazione che riduce la eccitabilità cellulare
- L'attività recettoriale è regolata da fosforilazioni da parte di PKA e PKC

Ligands (neurotransmitters) that stimulate ion channels can depolarize or hyperpolarize the target cell membrane depending on the type of ion that passes through the pore

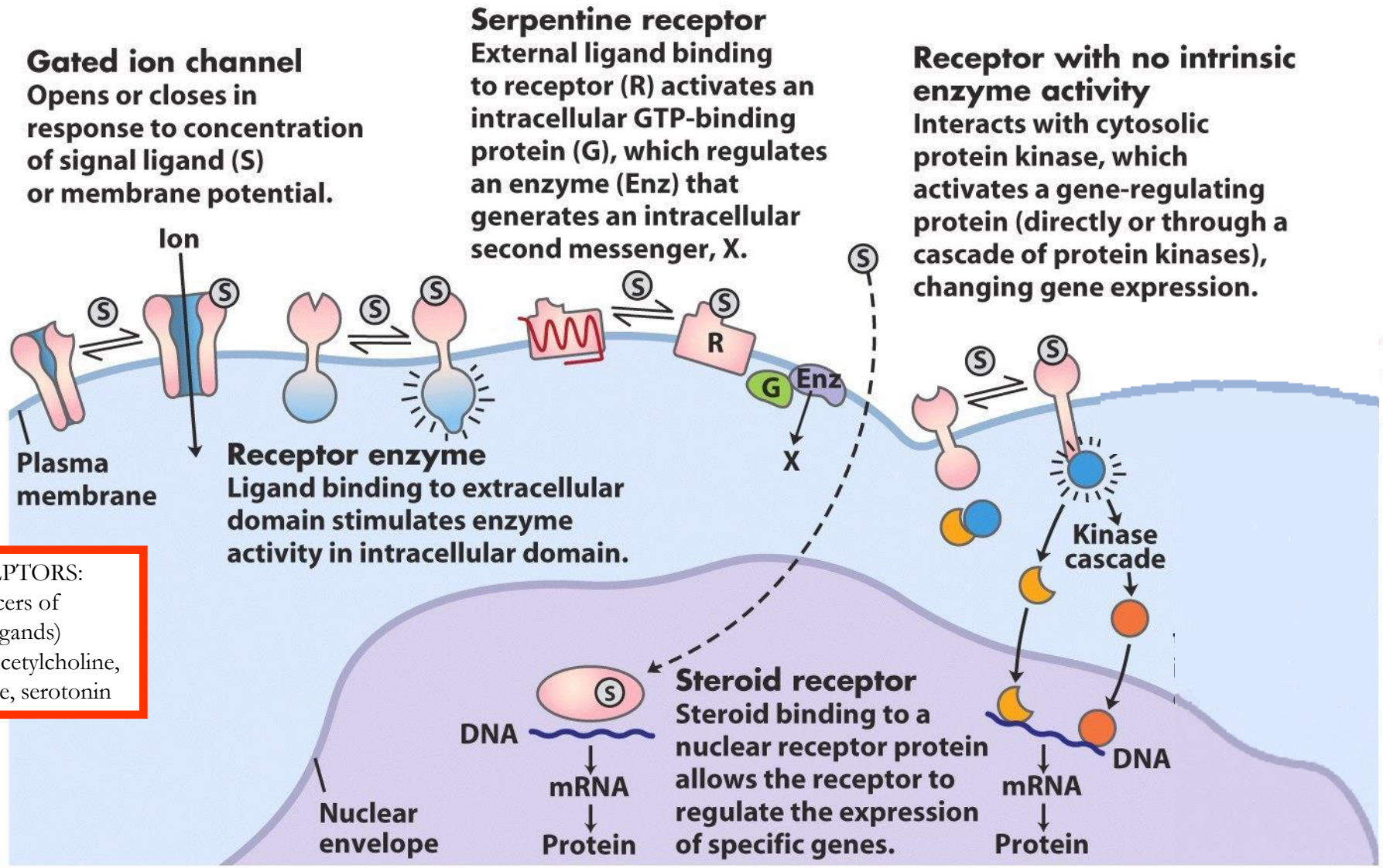
► Schematic Illustration of a $GABA_A$ Receptor, with Its Binding Sites



Several different pharmacological substances can modulate the effect of GABA by binding to GABA receptors at different sites from the GABA itself. (benzodiazepines, barbiturates, alcohol, picrotoxin and certain steroids)

increase the effectiveness of GABA (anxiolytic)

reduce the effectiveness of GABA (anxiogenic)



IONOTROPIC RECEPTORS:
the simplest transducers of extracellular signal (ligands)
e.g. nicotinic receptor of Acetylcholine, $GABA_A$, glycine, glutamate, serotonin