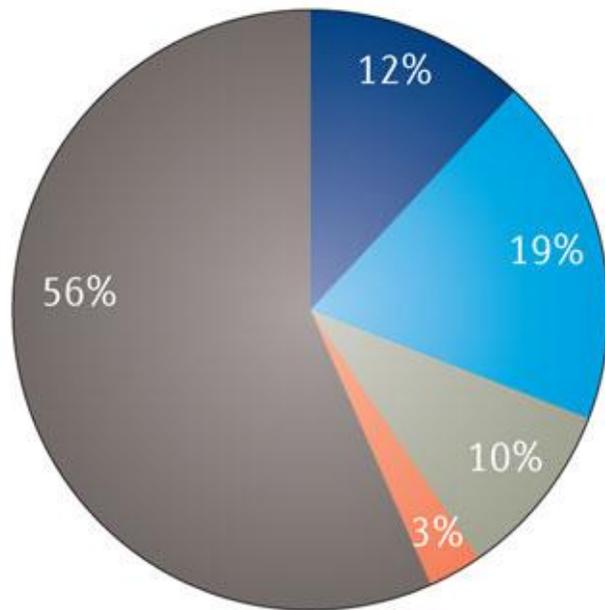
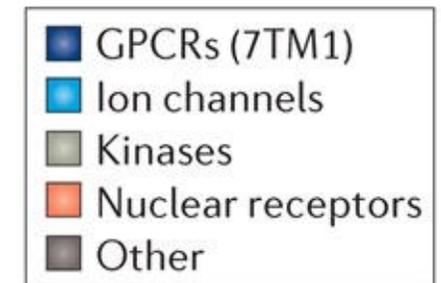
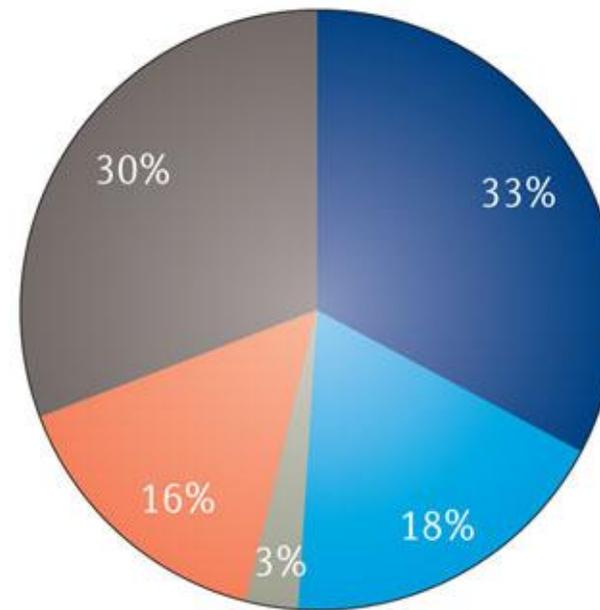


# TARGETS DEI FARMACI ATTUALMENTE IN USO

**a** Proportion of human protein drug targets in major families



Proportion of small-molecule drugs that target major families

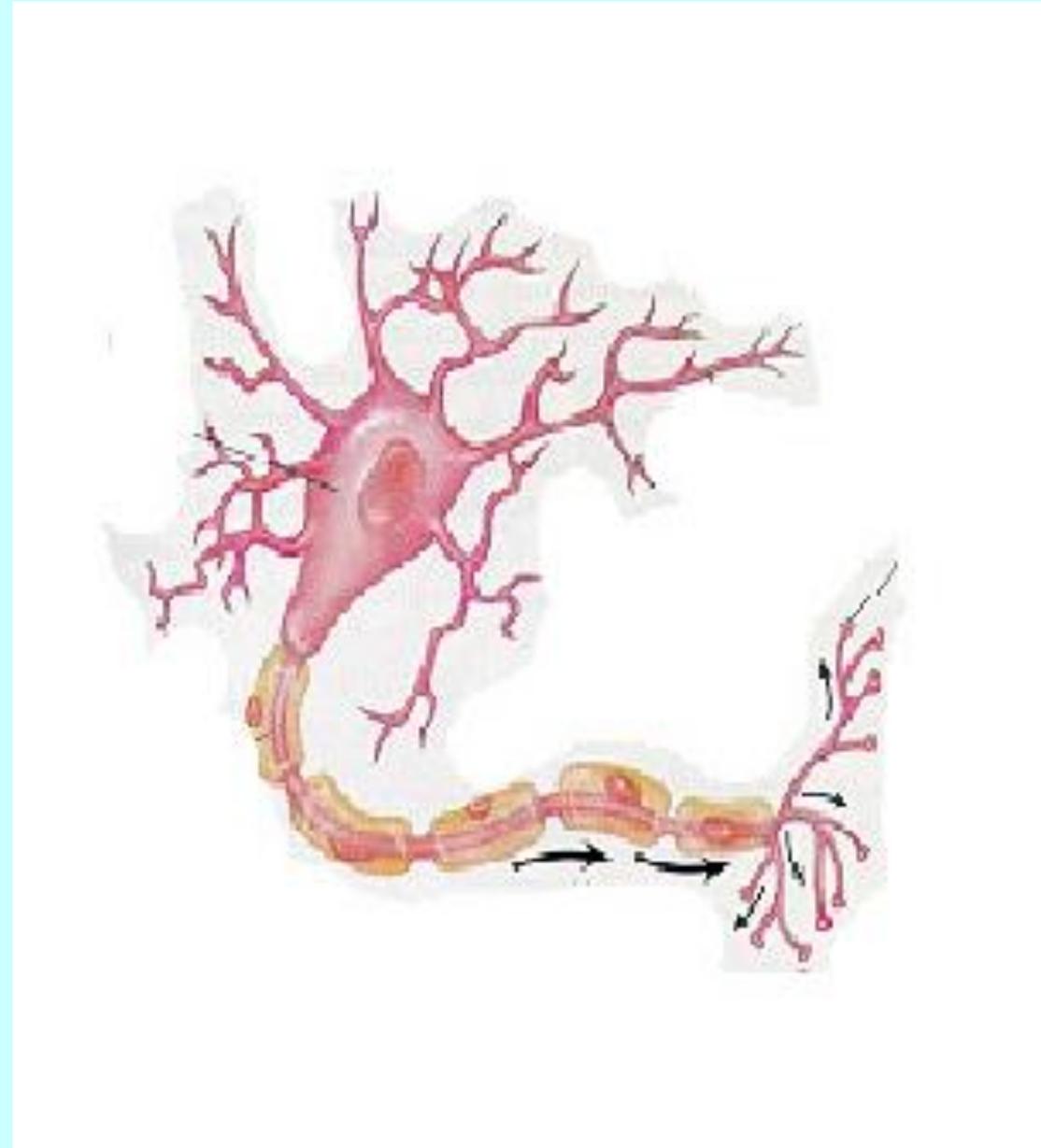


Distribuzione dei targets di farmaci per famiglia genica (sinistra) e distribuzione per la frazione di farmaci che hanno come target queste famiglie (destra); è evidente il dominio storico di quattro famiglie.

Santos, R., Ursu, O., Gaulton, A. et al. A comprehensive map of molecular drug targets. *Nat Rev Drug Discov* **16**, 19–34 (2017).  
<https://doi.org/10.1038/nrd.2016.230>

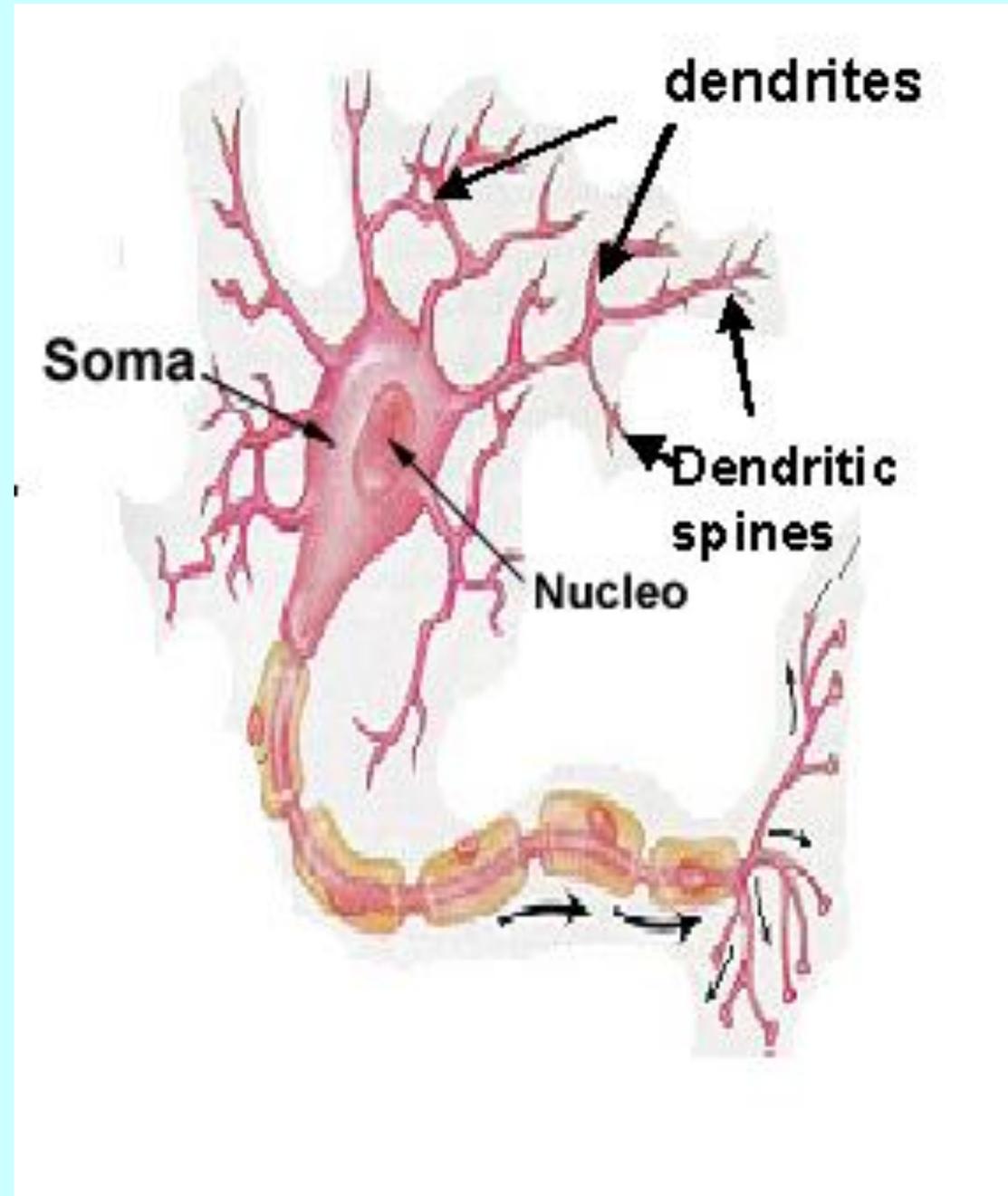
# NEURONI

- Il corpo umano contiene circa 100 miliardi di neuroni.
- Sono cellule specializzate nel trasmettere e ricevere informazioni.
- Possono variare forma e dimensione ma hanno tutti la stessa struttura di base.



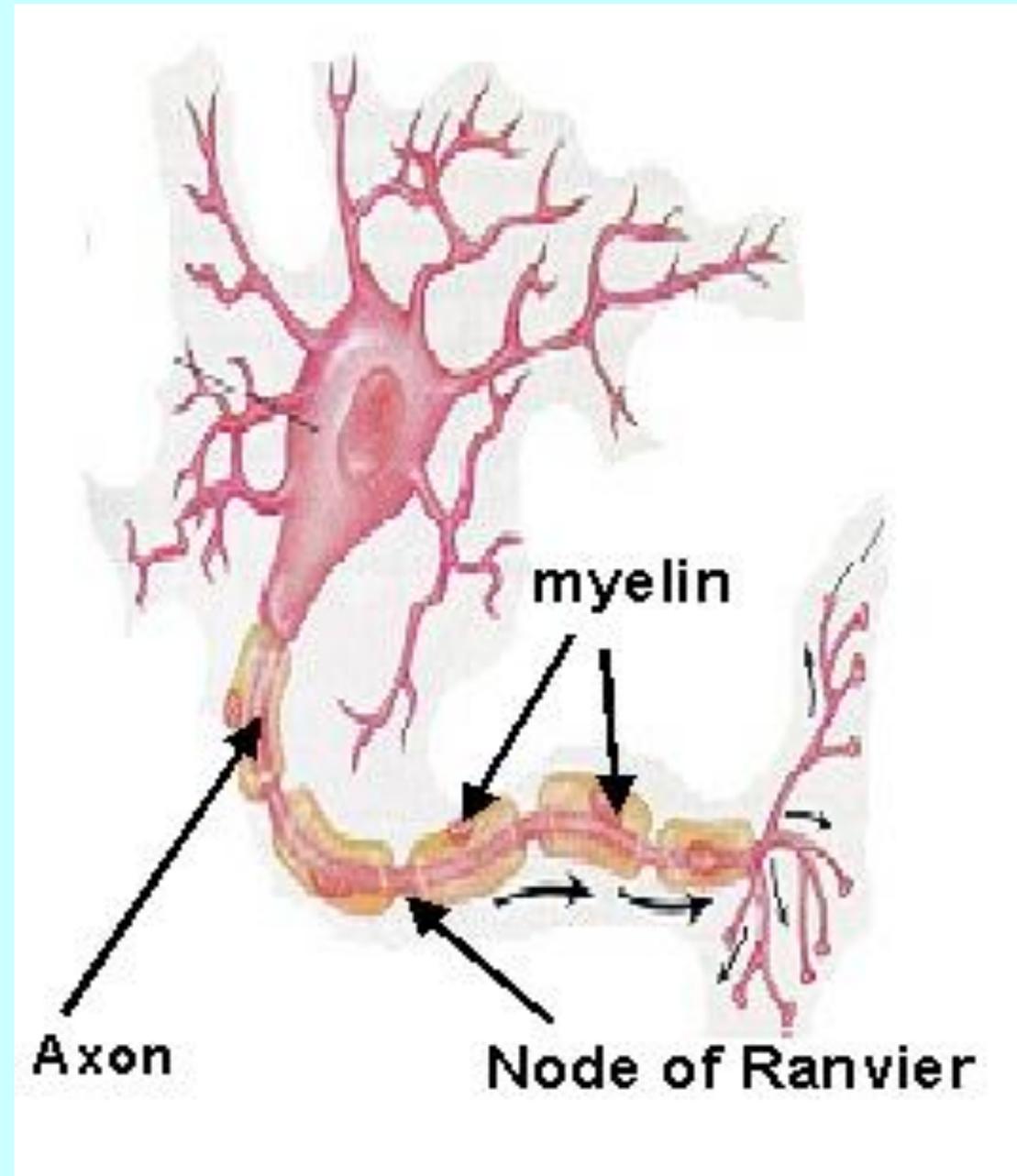
# STRUTTURA DEI NEURONI

- Corpo della cellula (**Soma**).
- I **Dendriti** sono i ricevitori di informazioni della cellula.
- Ricevono informazioni chimiche attraverso le loro estremità, le **Sinapsi** che sono ricoperte da recettori.



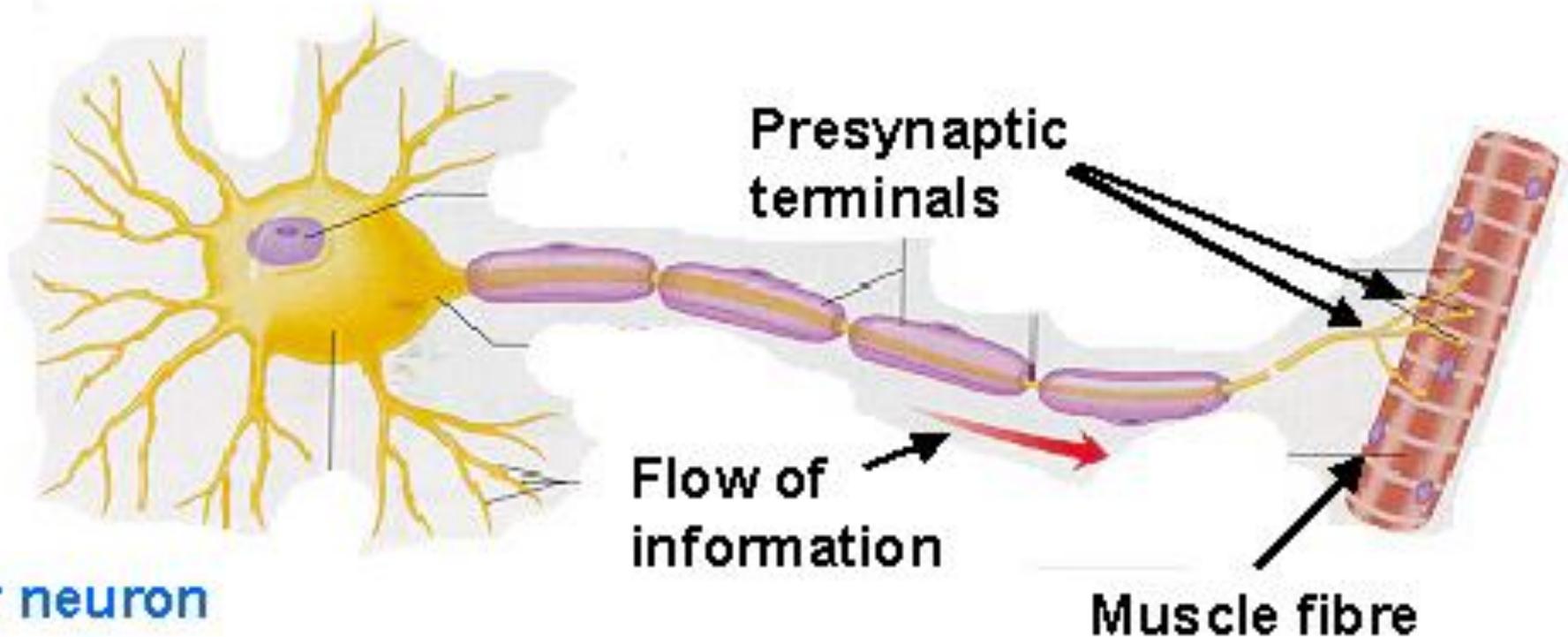
# ASSONI

- L'impulso neuronale (**Potenziale d'Azione**) fluisce lungo l'assone.
- In molti vertebrati gli assoni sono ricoperti di una sostanza isolante (**Mielina**).
- I segmenti sono separati da regioni non mielinate chiamate **Nodi di Ranvier**.



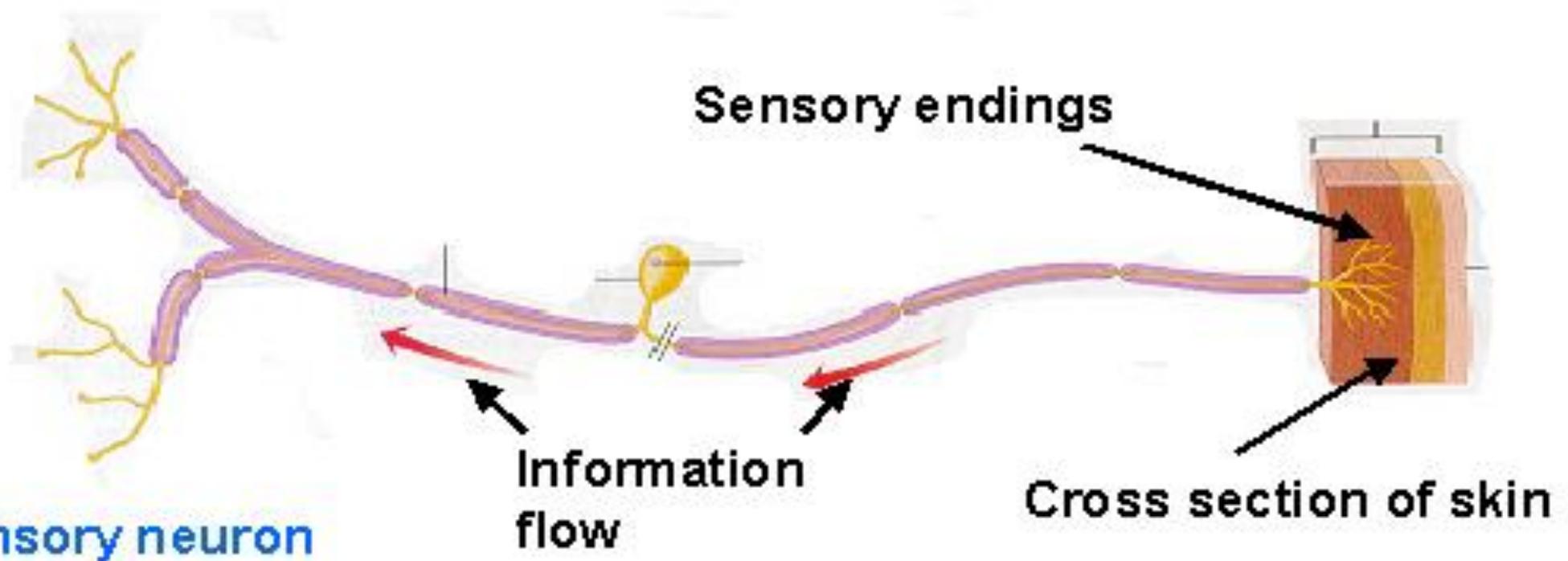
# IL FLUSSO DI INFORMAZIONI

- Il **Potenziale d'Azione** fluisce dal Soma al terminale presinaptico.
- L'assone che porta l'informazione verso la periferia si chiama **Assone Efferente**.



# IL FLUSSO DI INFORMAZIONI

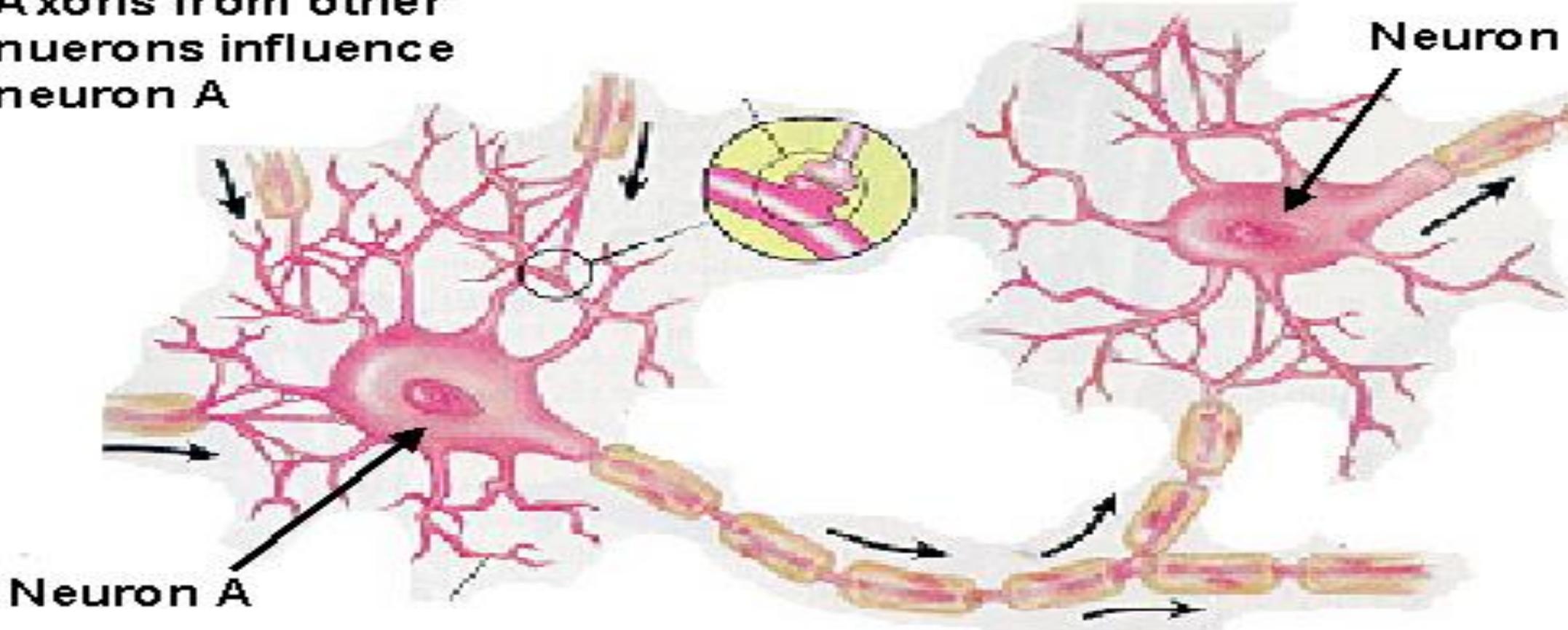
- L'assone che riceve l'informazione dalla periferia si chiama **Assone Afferente**.



# TERMINALI PRESINAPTICI

- Alla fine degli assoni ci sono i **Terminali Presinaptici**.
- Quando il potenziale d'azione raggiunge il terminale viene secreto un neurotrasmettitore che attraversa la sinapse per raggiungere i recettori di un altro neurone.

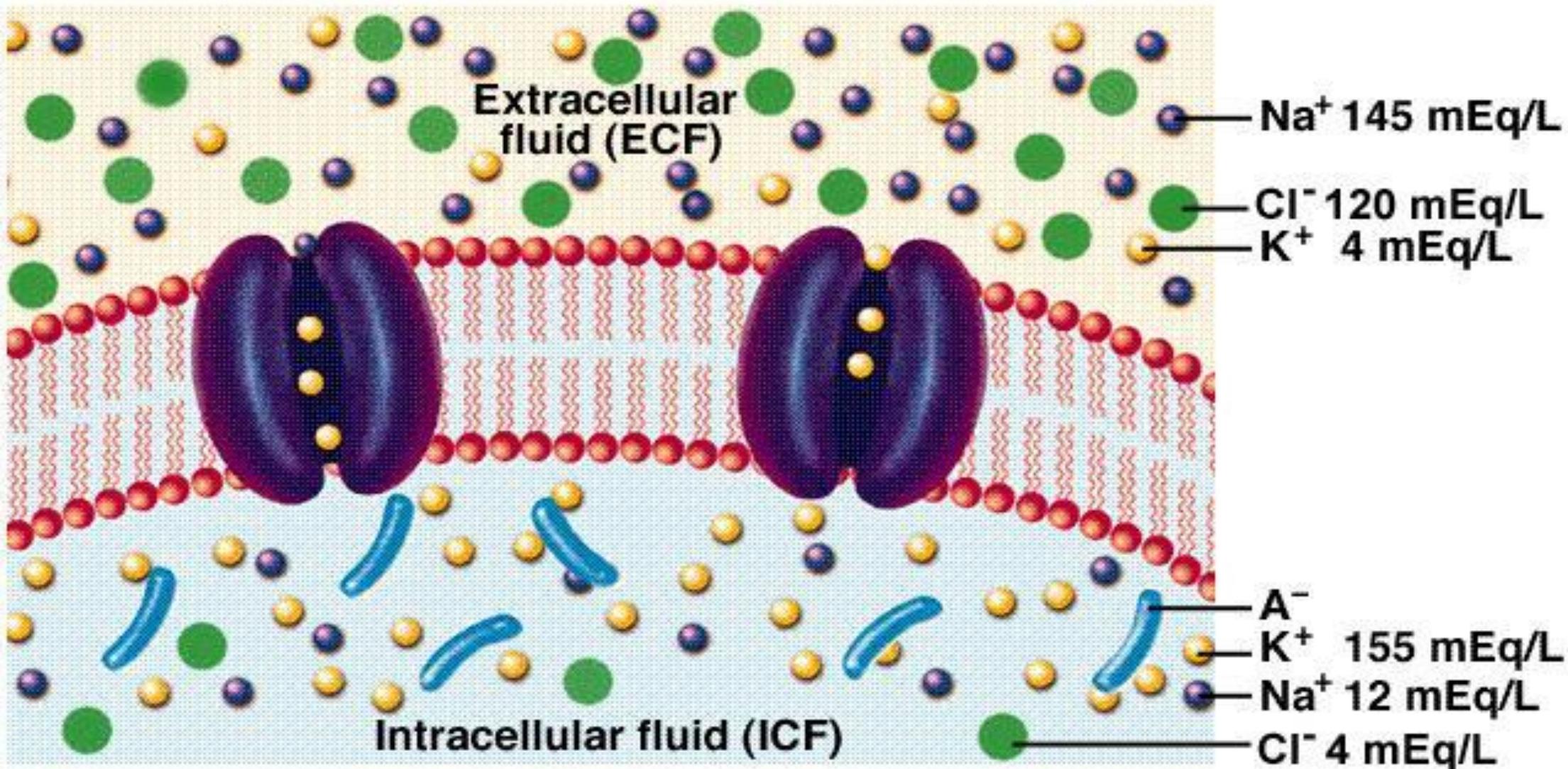
**Axons from other neurons influence neuron A**



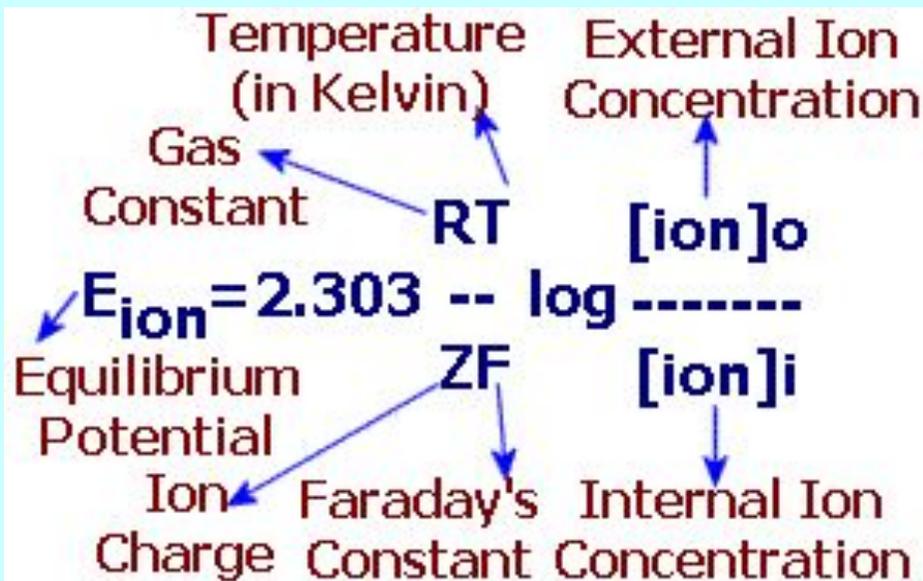
**Message flows down axon of neuron A to influence neuron B**

# POTENZIALE DI MEMBRANA

## Resting Membrane Potential



# POTENZIALE DI MEMBRANA



La permeabilità è una misura della facilità di passaggio degli ioni attraverso la membrana ( $cm^2/s$ )

Quindi l'equazione di Nerst risulta essere:

$$E = \frac{RT}{F} \ln \frac{P_K K_o + P_{Na} Na_o + P_{Cl} Cl_i}{P_K K_i + P_{Na} Na_i + P_{Cl} Cl_o} \quad E = 59 \log_{10} \frac{P_K K_o + P_{Na} Na_o + P_{Cl} Cl_i}{P_K K_i + P_{Na} Na_i + P_{Cl} Cl_o}$$

# POTENZIALE DI MEMBRANA

L'interno delle cellule è normalmente carico negativamente rispetto all'esterno.

Infatti:

**Il citoplasma è ricco di  $K^+$  e povero di  $Na^+$ , all'esterno la situazione è invertita.**

$[K^+]_i = 140 \text{ mM}$ ,  $[K^+]_o = 4 \text{ mM}$ ,  $[Na^+]_i = 12 \text{ mM}$ ,  $[Na^+]_o = 140 \text{ mM}$ .

$[Cl^-]_i = 4 \text{ mM}$  e  $[Cl^-]_o = 120 \text{ mM}$

La permeabilità della membrana agli ioni è variabile, normalmente è maggiore per il  $K^+$

$P_K = 10^{-7}$ ,  $P_{Na} = 10^{-8}$ ,  $P_{Cl} = 10^{-8}$

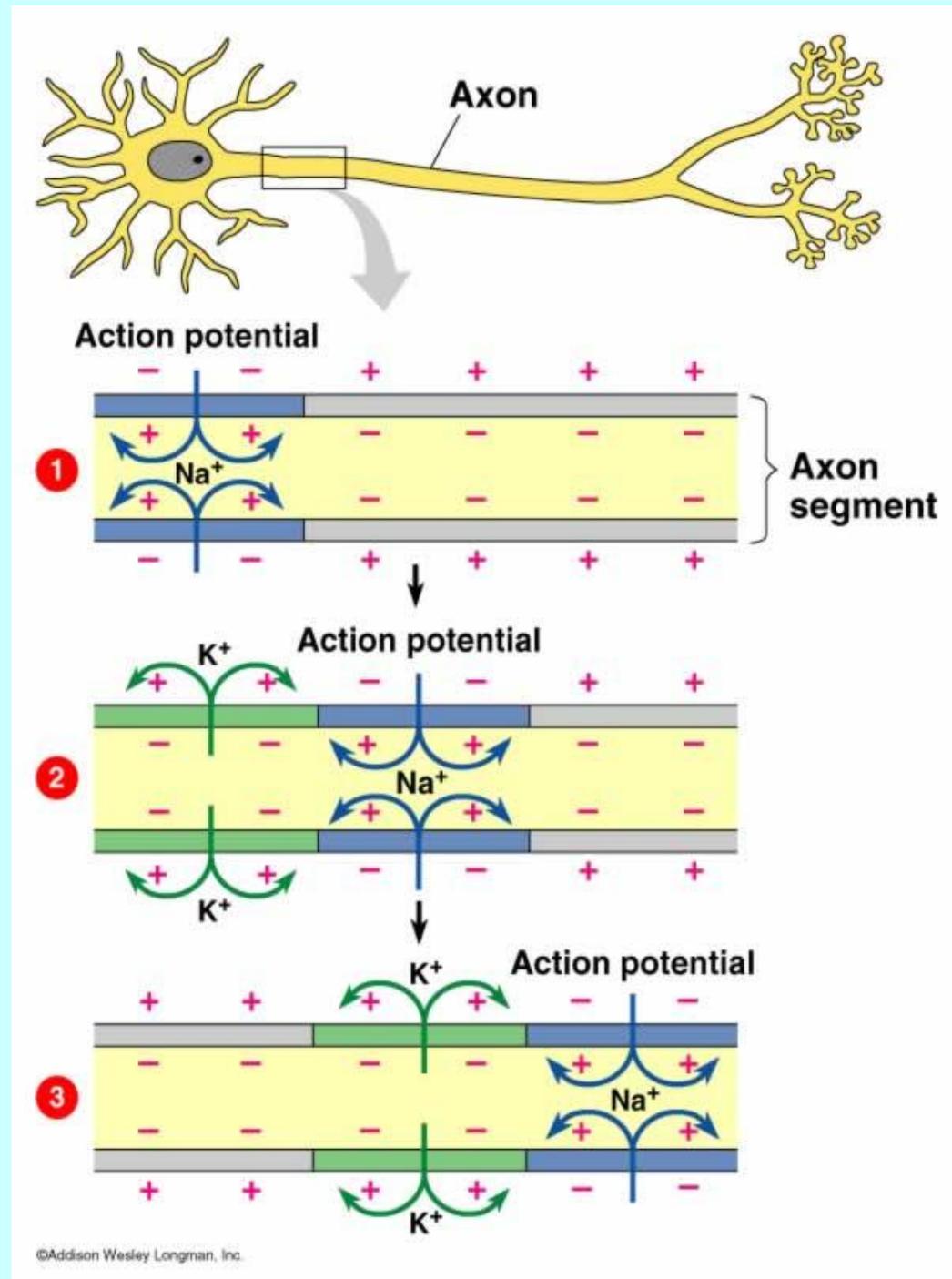
Gli anioni del citoplasma sono perlopiù organici e non diffondono attraverso la membrana e c'è un processo di trasporto attivo per mantenere allo stato di equilibrio gli ioni  $K^+$  e  $Na^+$  (ATPase).

$$E = 59 \log_{10} \frac{(10^{-7})(0.004) + (10^{-8})(0.12) + (10^{-8})(0.004)}{(10^{-7})(0.14) + (10^{-8})(0.012) + (10^{-8})(0.12)} = -52.9 \text{ mV}$$

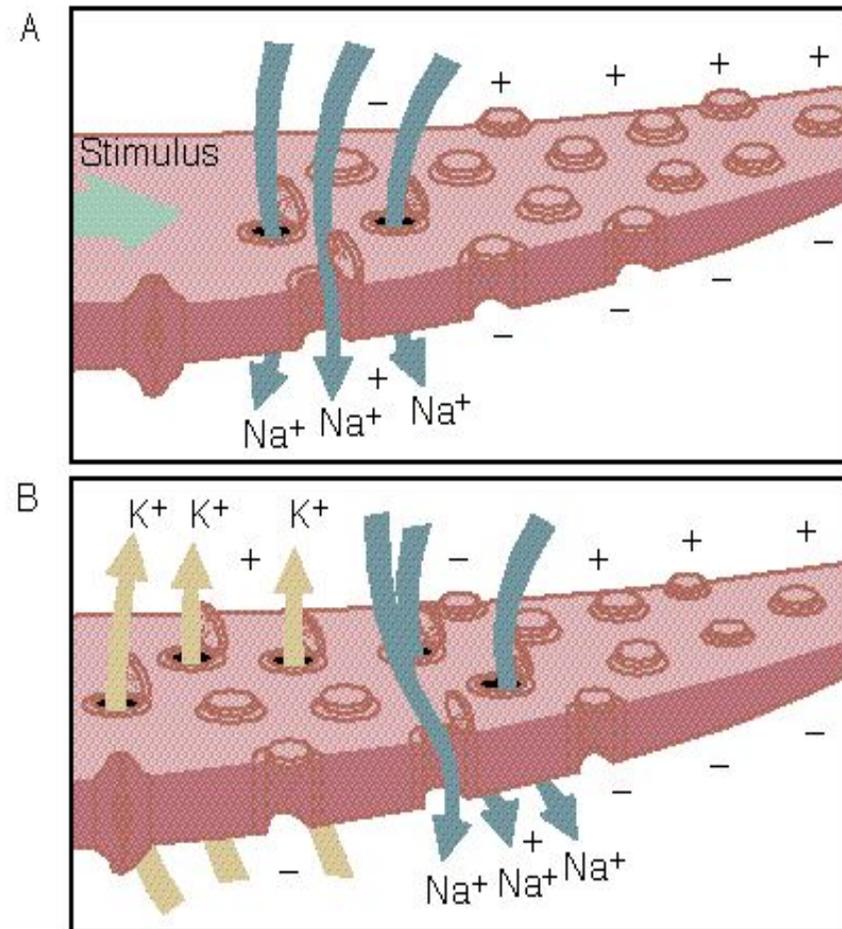
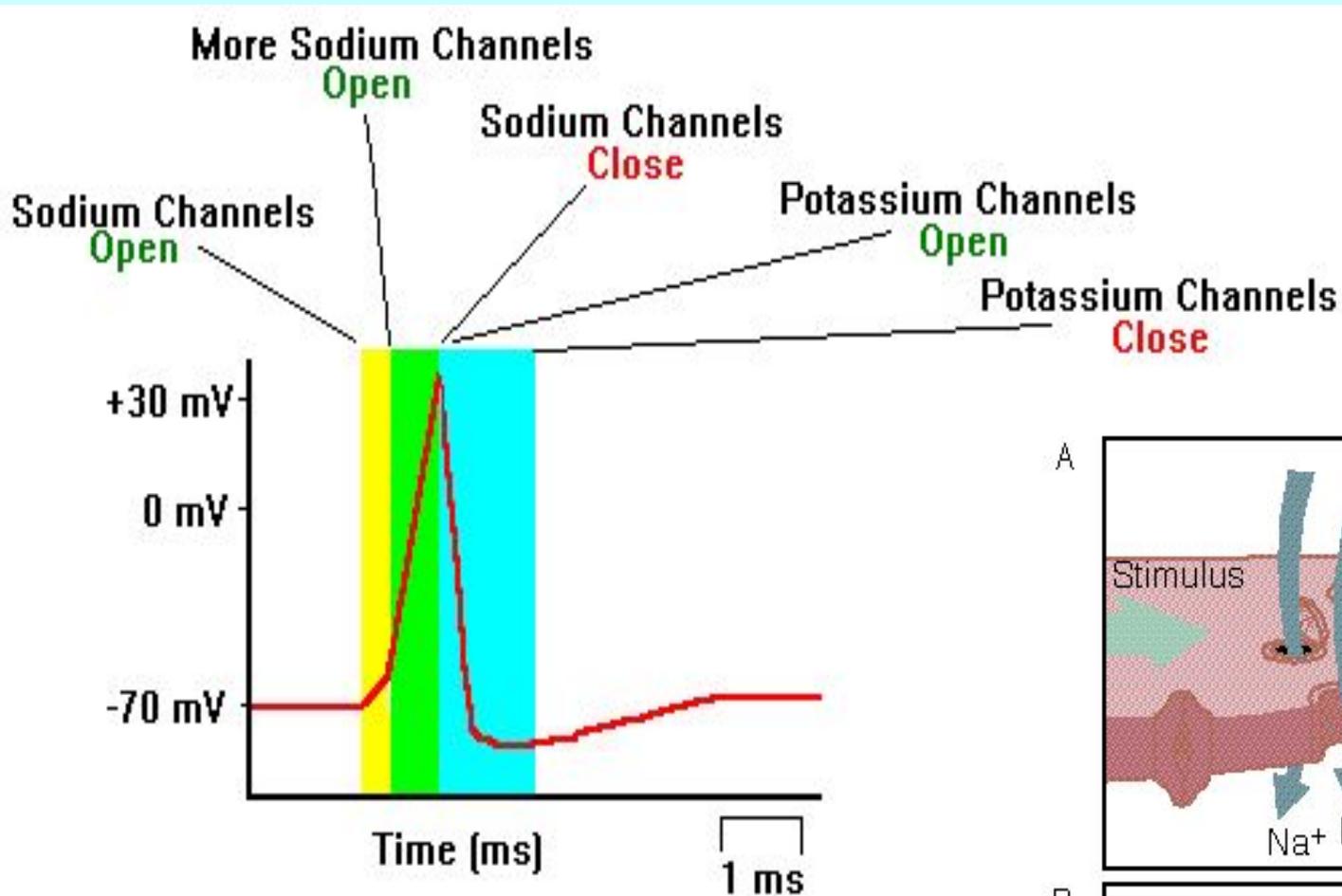
Il potenziale nelle varie cellule può andare dai  $-20$  ai  $-100 \text{ mV}$  in funzione delle variazioni di permeabilità.

# POTENZIALE D'AZIONE

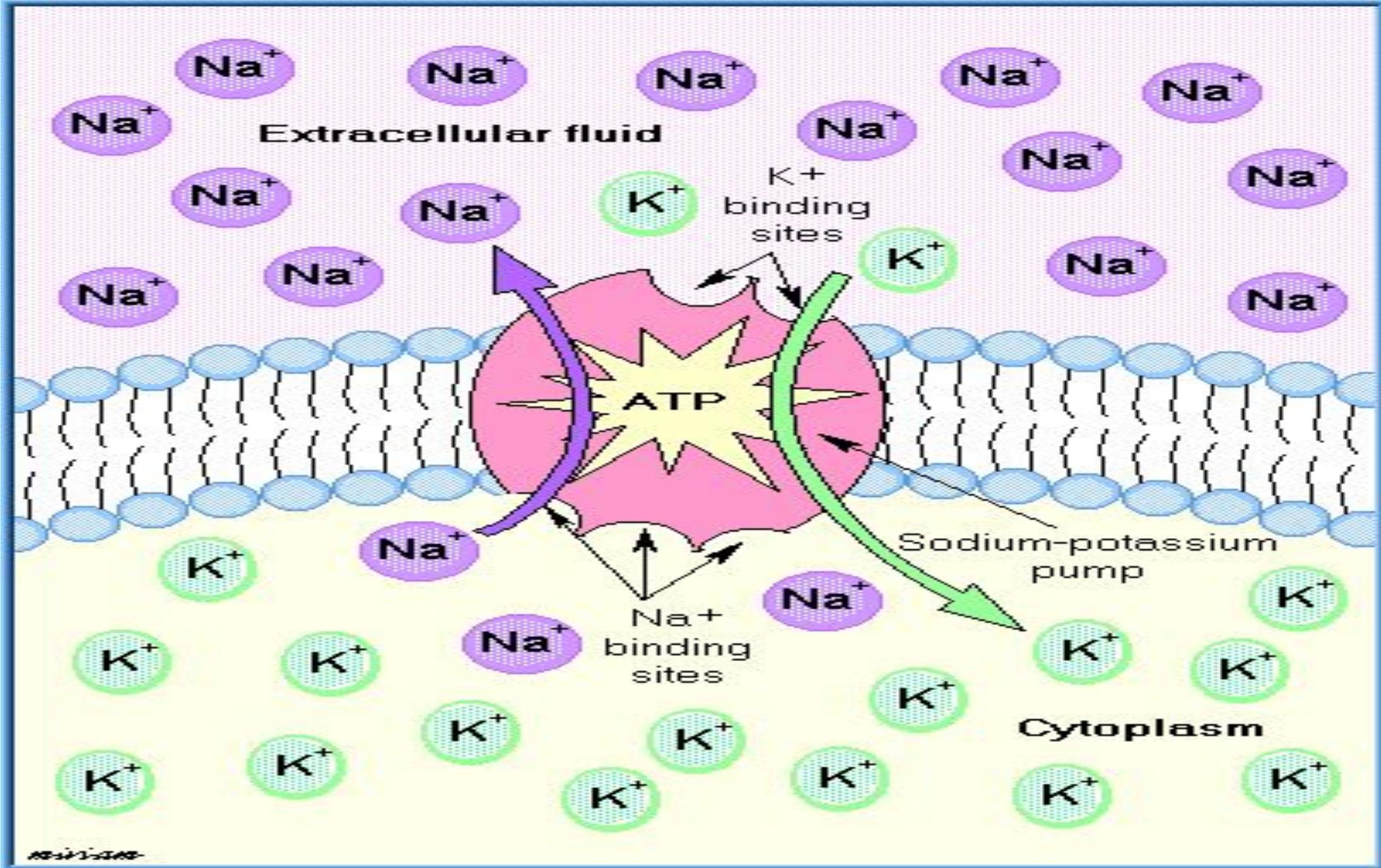
- Una carica positiva applicata all'interno dell'assone lo depolarizza.
- Si produce un potenziale d'azione che inverte la polarità della membrana (da -60 mV si passa a circa 40 mV)
- Il potenziale di membrana viene rapidamente ripristinato passando prima da una leggera iperpolarizzazione.
- Il processo dura circa 2 msec.



# POTENZIALE D'AZIONE

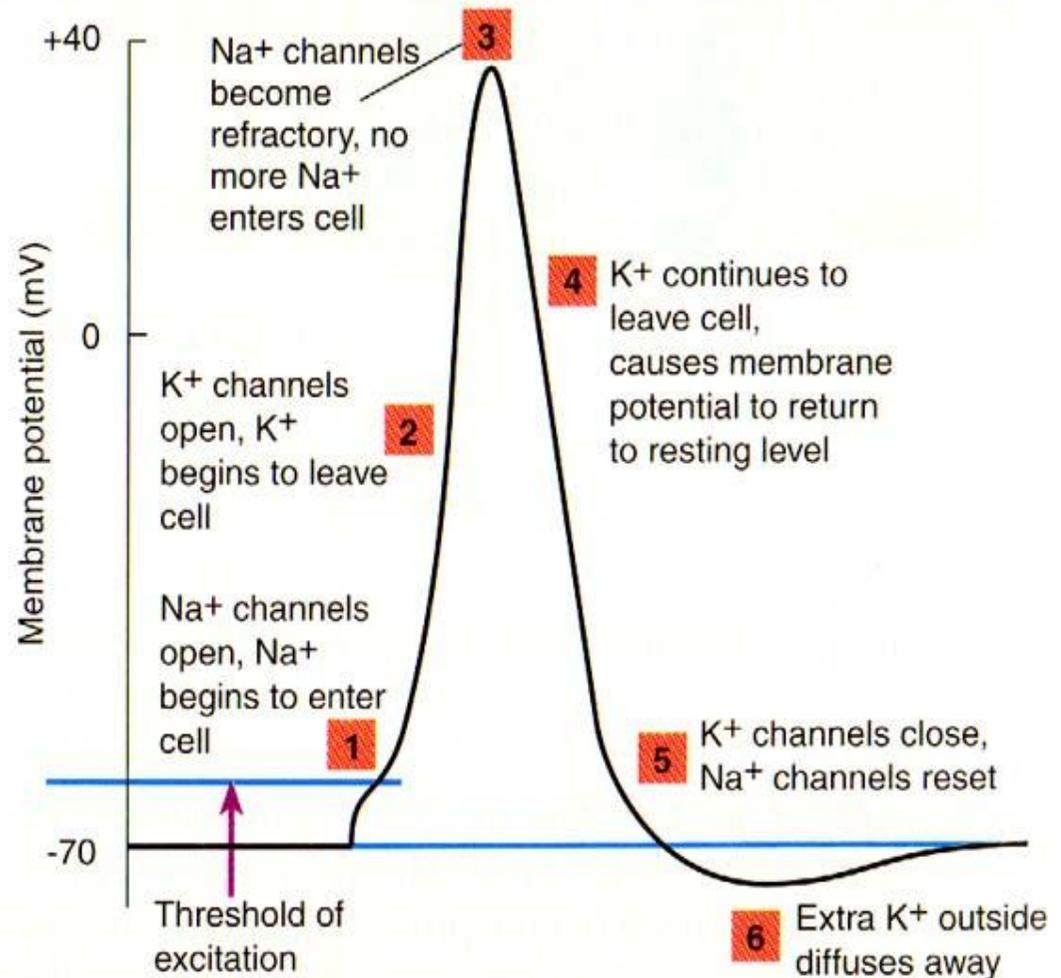
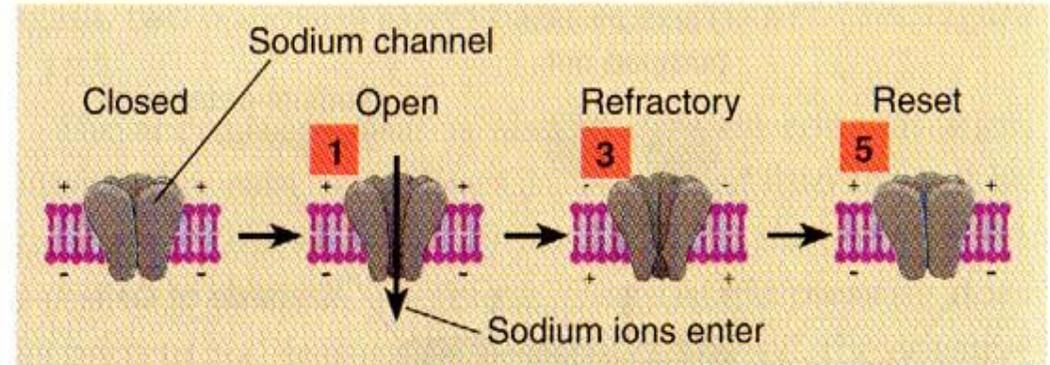


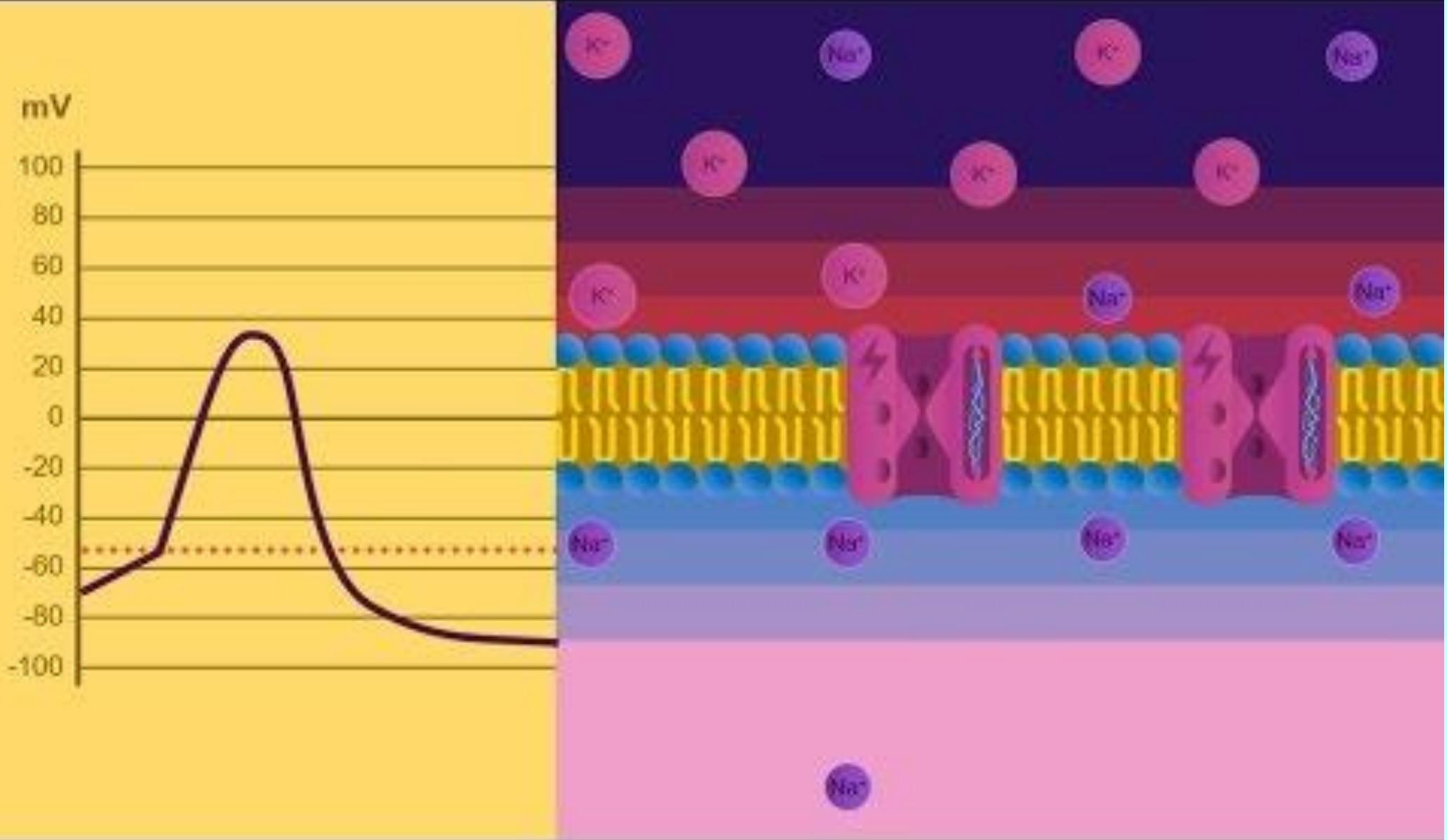
# POTENZIALE D'AZIONE



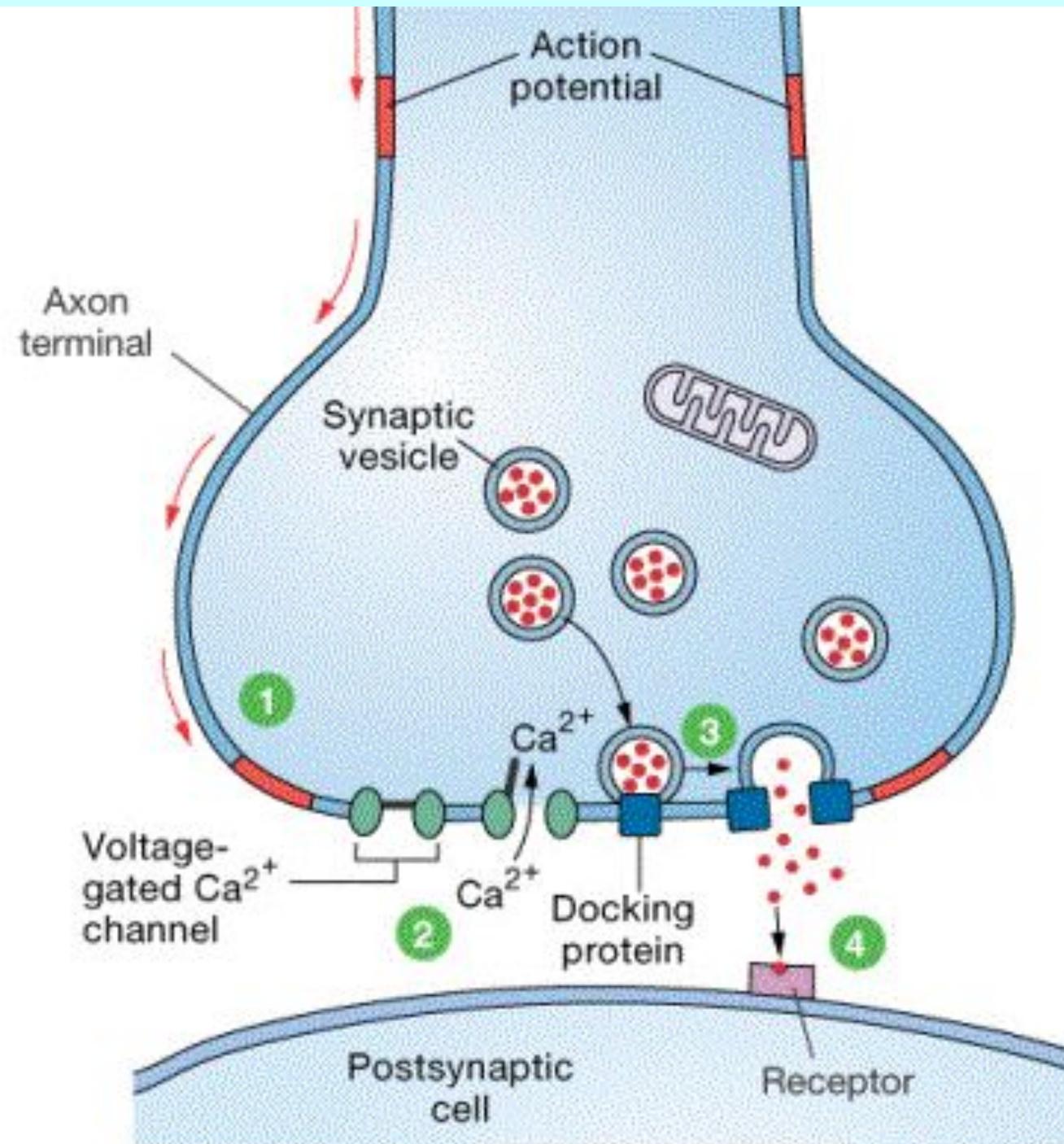
# POTENZIALE D'AZIONE

- Dopo il potenziale d'azione i canali del sodio rimangono chiusi per circa 1 msec (periodo refrattario assoluto).
- I canali del sodio quindi si riaprono ma i canali del potassio rimangono aperti per ulteriori 2-4 msec in modo che non si possa generare un altro potenziale d'azione (periodo refrattario relativo).





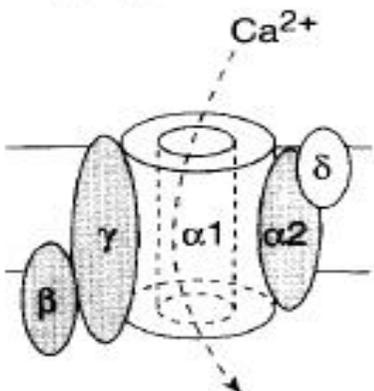
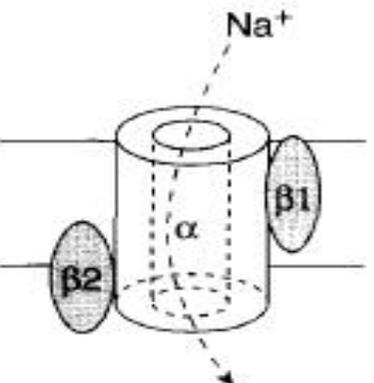
# POTENZIALE D'AZIONE



- 1 An action potential depolarizes the axon terminal.
- 2 The depolarization opens voltage-gated  $\text{Ca}^{2+}$  channels and  $\text{Ca}^{2+}$  enters the cell.
- 3 Calcium entry triggers exocytosis of synaptic vesicle contents.
- 4 Neurotransmitter diffuses across the synaptic cleft and binds with receptors on the postsynaptic cell.

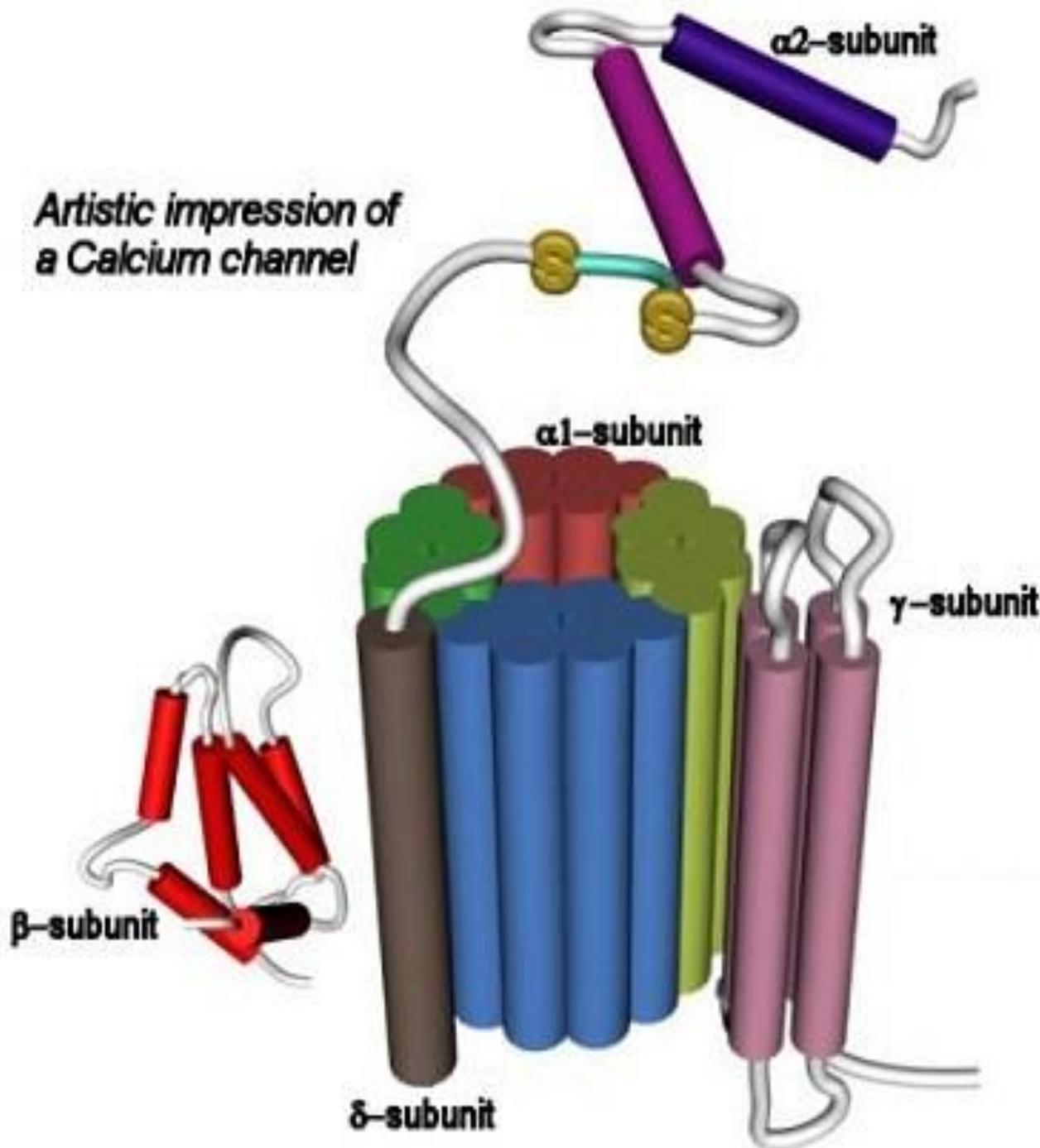
# CANALI IONICI VOLTAGE-GATED

Table 1. Voltage-gated ion-channel families

Subunit structure	Nomenclature and tissue distribution	Molecular identity	Disease targets
<p><b>Ca<sup>2+</sup> channel</b></p> <p>Subunits: α1, β, γ, α2-δ</p> 	<p>P/Q-type (neuronal)</p> <p>N-type (neuronal)</p> <p>L-type (cardiac)</p> <p>L-type (neuronal)</p> <p>R-type (neuronal)</p> <p>T-type (neuronal)</p> <p>L-type (skeletal)</p> <p>T-type (cardiac)</p>	<p><b>Of α1 subunit</b></p> <p>α1A</p> <p>α1B</p> <p>α1C</p> <p>α1D</p> <p>α1E?</p> <p>α1G</p> <p>α1S</p> <p>?</p>	<p><b>For Ca<sup>2+</sup>-channel blockers</b></p> <p>Angina, arrhythmia, hypertension, atherosclerosis, pain, neuroprotection, migraine, stroke, Alzheimer's, cognitive enhancement and dementia</p>
<p><b>Na<sup>+</sup> channel</b></p> <p>Subunits: α, β1, β2</p> 	<p>Brain I</p> <p>Brain II</p> <p>Brain III</p> <p>Brain VI</p> <p>Peripheral neuronal 1</p> <p>Sensory neurone-specific</p> <p>Glial</p> <p>Skeletal muscle 1</p> <p>Heart/skeletal muscle 2</p>	<p><b>Of α subunit</b></p> <p>BI</p> <p>BII, BIIA</p> <p>BIII</p> <p>BVI</p> <p>PN1</p> <p>SNS (PN3)</p> <p>NaG</p> <p>SKM1</p> <p>SKM2</p>	<p><b>For Na<sup>+</sup>-channel blockers/modulators</b></p> <p>Epilepsy, pain, anaesthesia, neuroprotection, arrhythmia and migraine</p>

# CANALI DEL CALCIO (voltage-gated)

*Artistic impression of a Calcium channel*



Sono composti da subunità simili a quelle dei canali del sodio e del potassio. Ne sono state identificate quattro:  $\alpha_1$ ,  $\alpha_2$ - $\delta$ ,  $\beta$ , e  $\gamma$ .

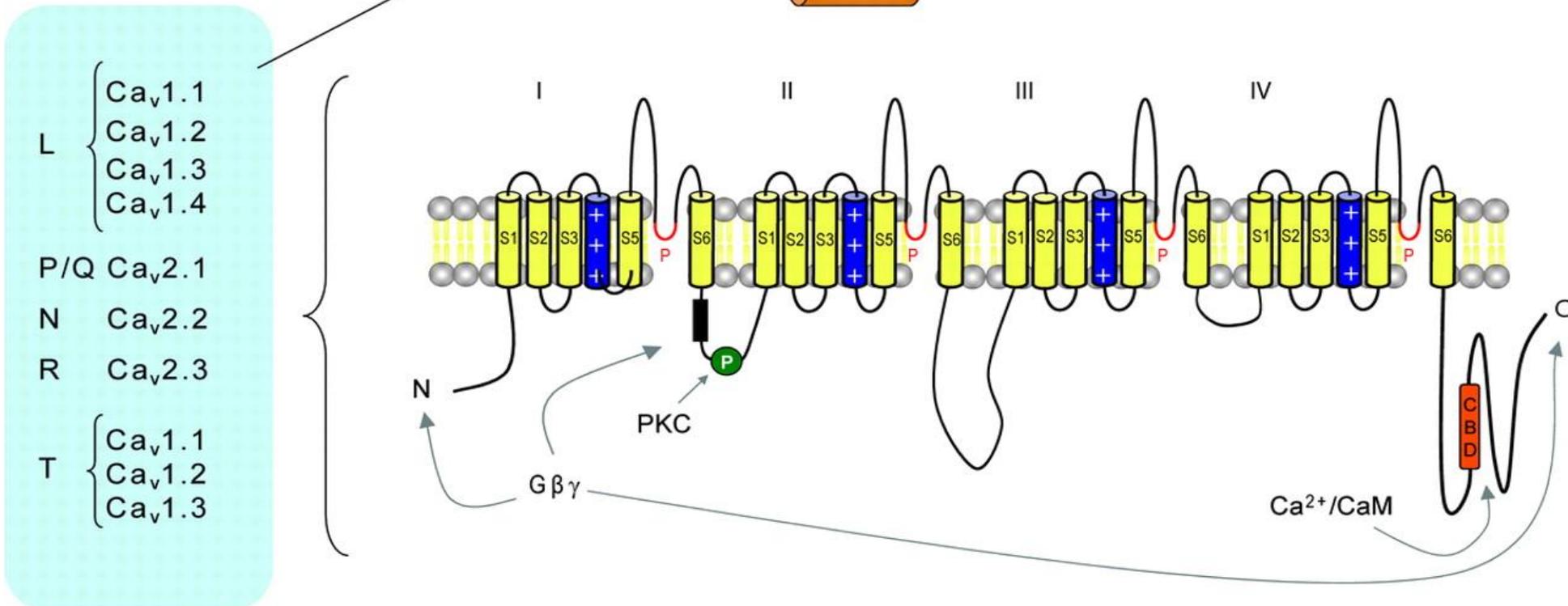
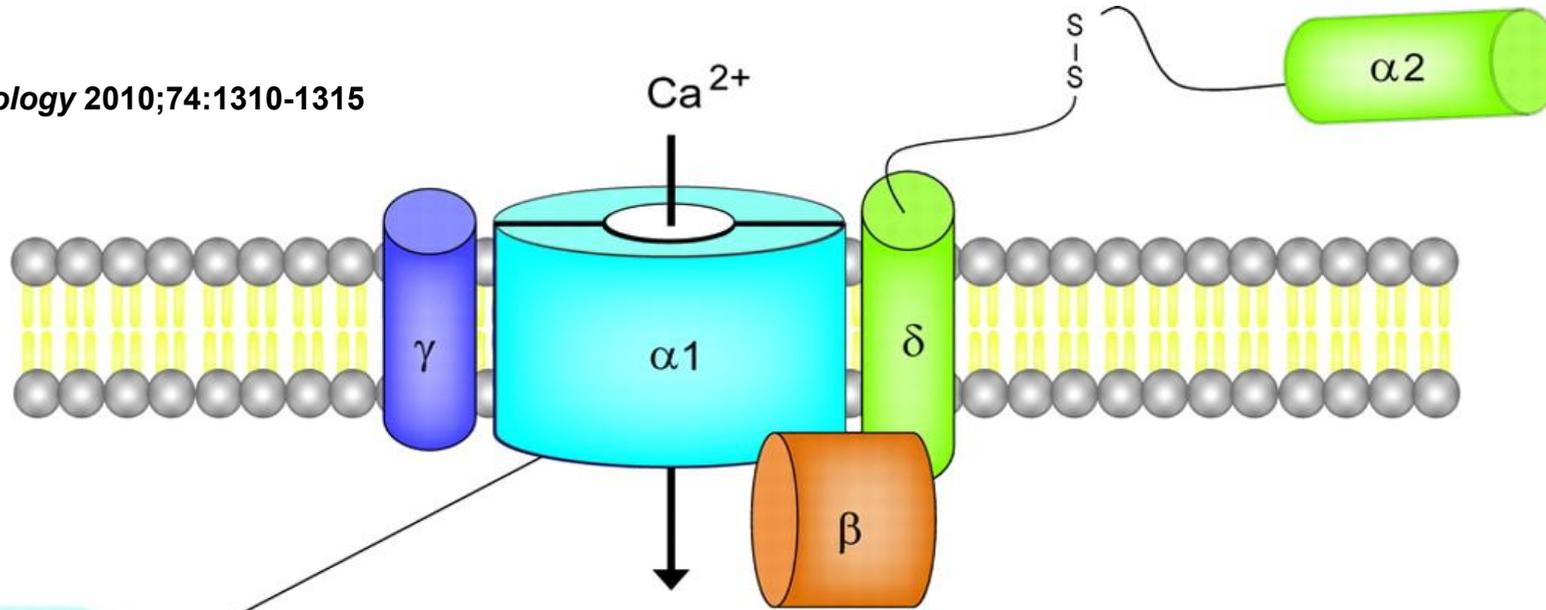
Le subunità  $\alpha$  contengono il canale con il filtro per lo ione e influenzano l'apertura. In questa subunità ci sono quattro domini omologhi che contengono sei eliche transmembrana. La quarta elica transmembrana di ogni dominio forma un sensore del voltaggio come per la subunità  $\beta$  del canale del sodio.

La subunità  $\beta$  è situata intracellularmente. La subunità  $\gamma$  è una glicoproteina con quattro segmenti transmembrana, ha un duplice ruolo: limitare l'afflusso di  $\text{Ca}^{2+}$  stabilizzando lo stato inattivato del canale e ridurre il rilascio sarcoplasmico di  $\text{Ca}^{2+}$  indotto dalla depolarizzazione.

La subunità  $\alpha_2$  è una proteina extracellulare altamente glicosilata che è attaccata alla subunità  $\delta$  transmembrana con un legame disolfuro. La subunità  $\alpha_2$  fornisce supporto strutturale mentre la  $\delta$  modula l'attivazione voltaggio-dipendente.

# CANALI DEL CALCIO

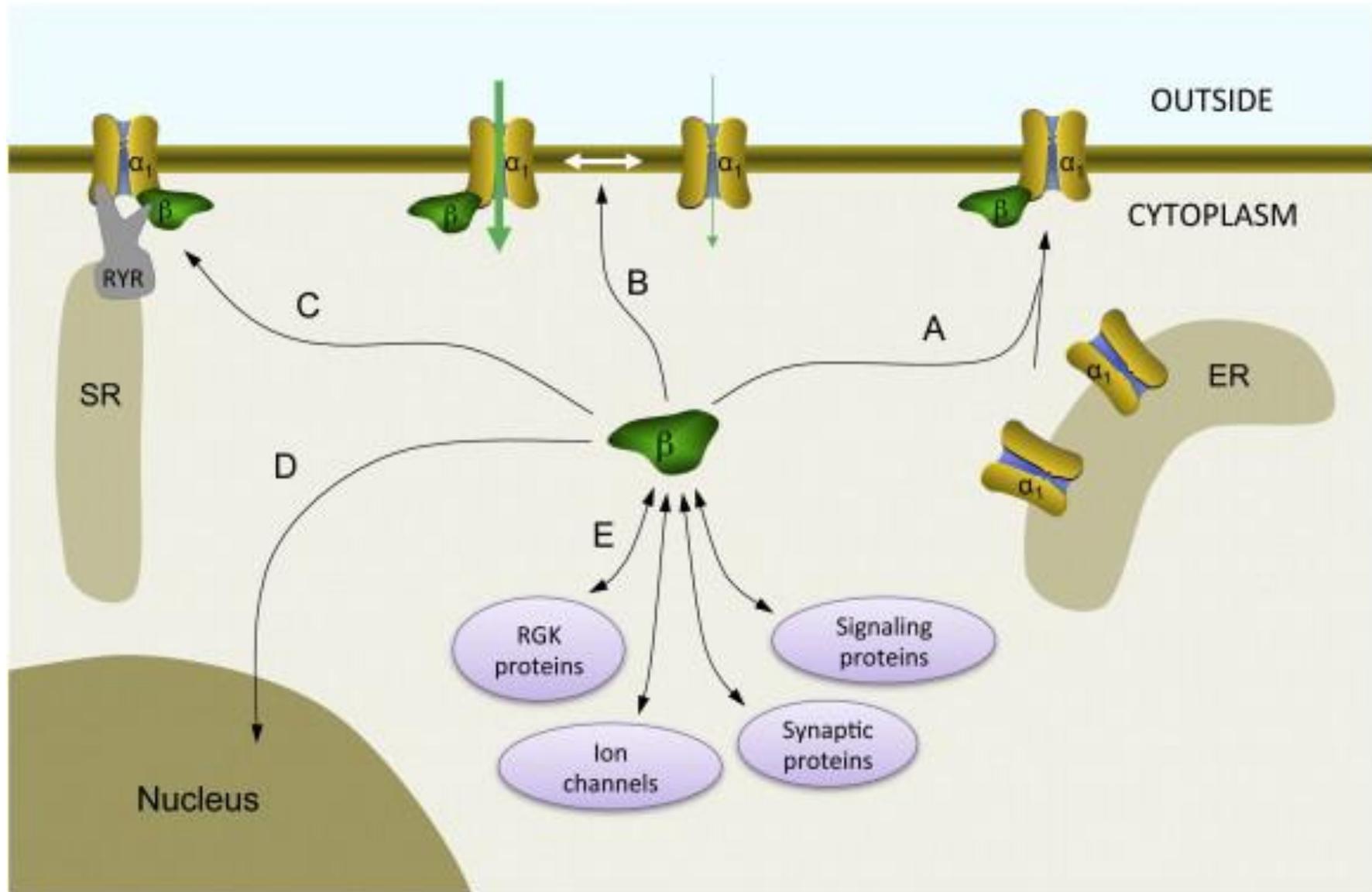
Benarroch E E *Neurology* 2010;74:1310-1315



**Struttura del canale del calcio voltage-gated (Cav) Tutti i canali Cav contengono una subunità formante il poro ( $\alpha 1$ ) che determina le principali proprietà biofisiche e farmacologiche.**

# CANALI DEL CALCIO

<https://doi.org/10.1016/j.bbamem.2012.08.028>



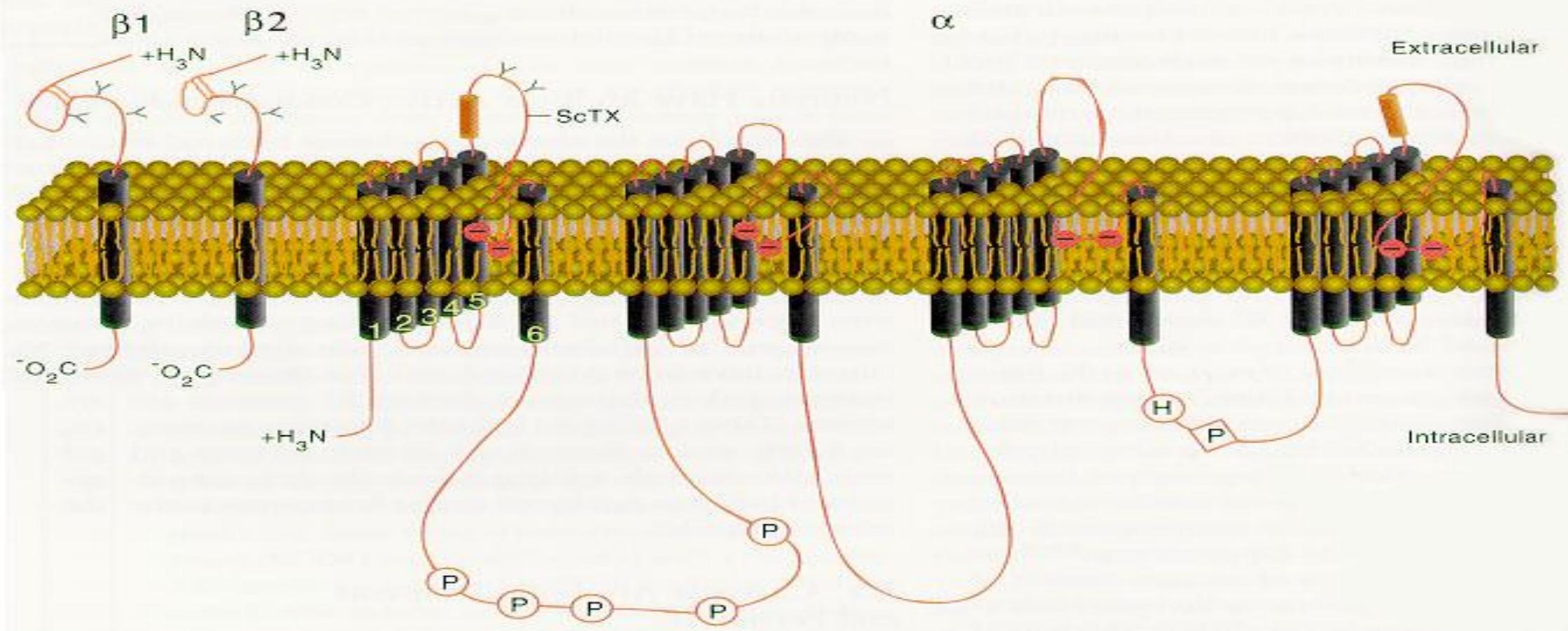
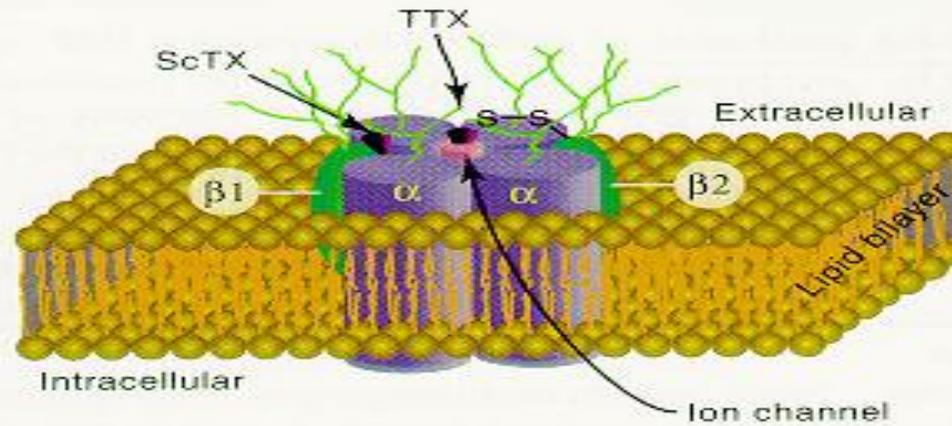
## Principali funzioni di Cavβ.

(A) Cavβ migliora la localizzazione di Cavα1 sulla membrana plasmatica prevenendo la degradazione di Cavα1 ed esponendo i segnali di esportazione di ER su Cavα1.

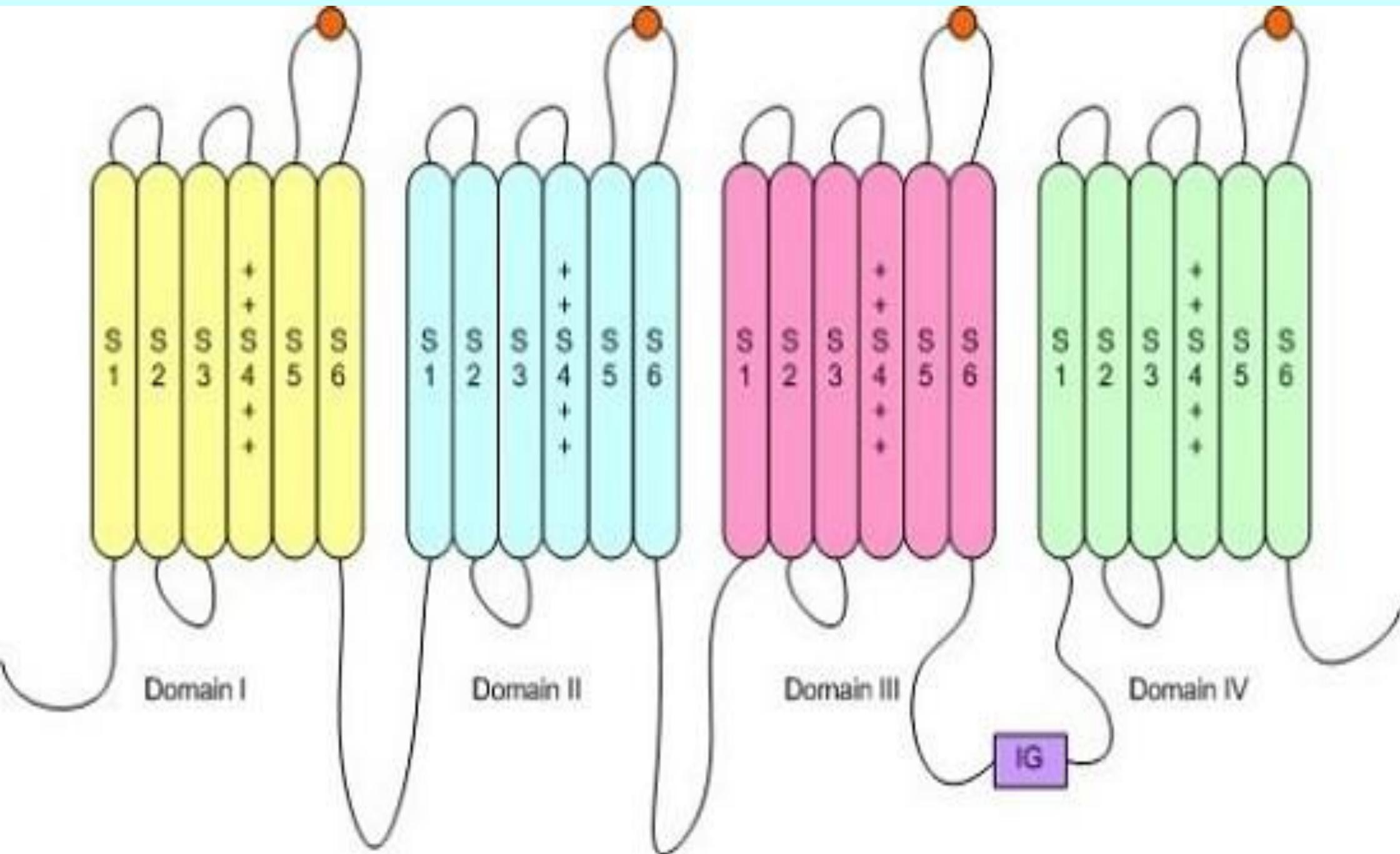
(B) Cavβ promuove il gating VGCC, determinando un miglioramento complessivo della corrente.

(C) Cavβ interagisce con il recettore della rianodina (RYR) nel reticolo sarcoplasmatico (SR) delle

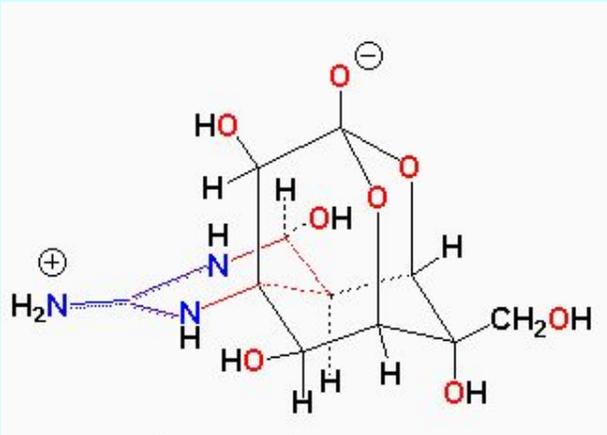
# CANALI DEL SODIO



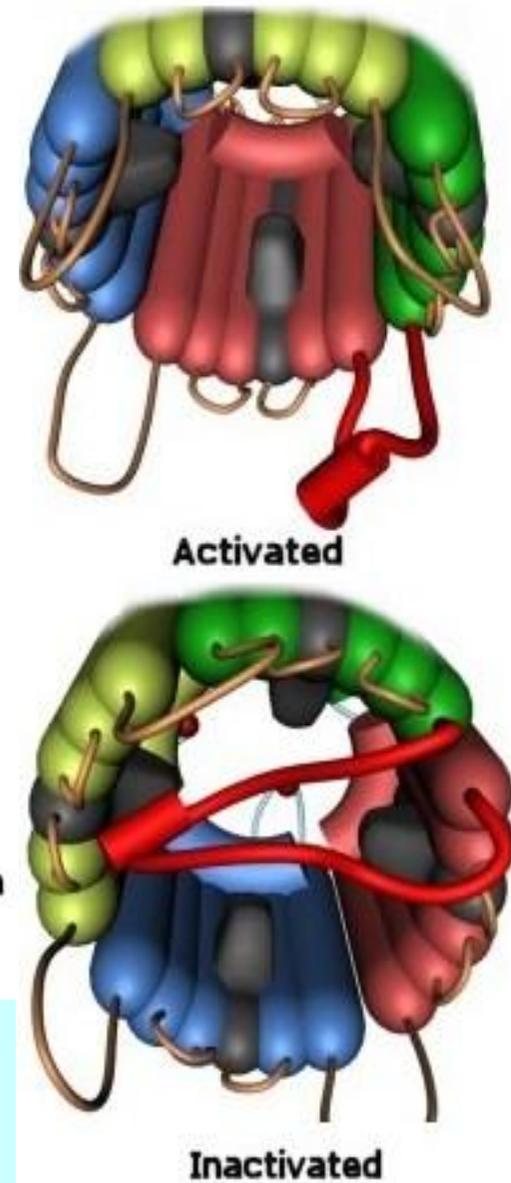
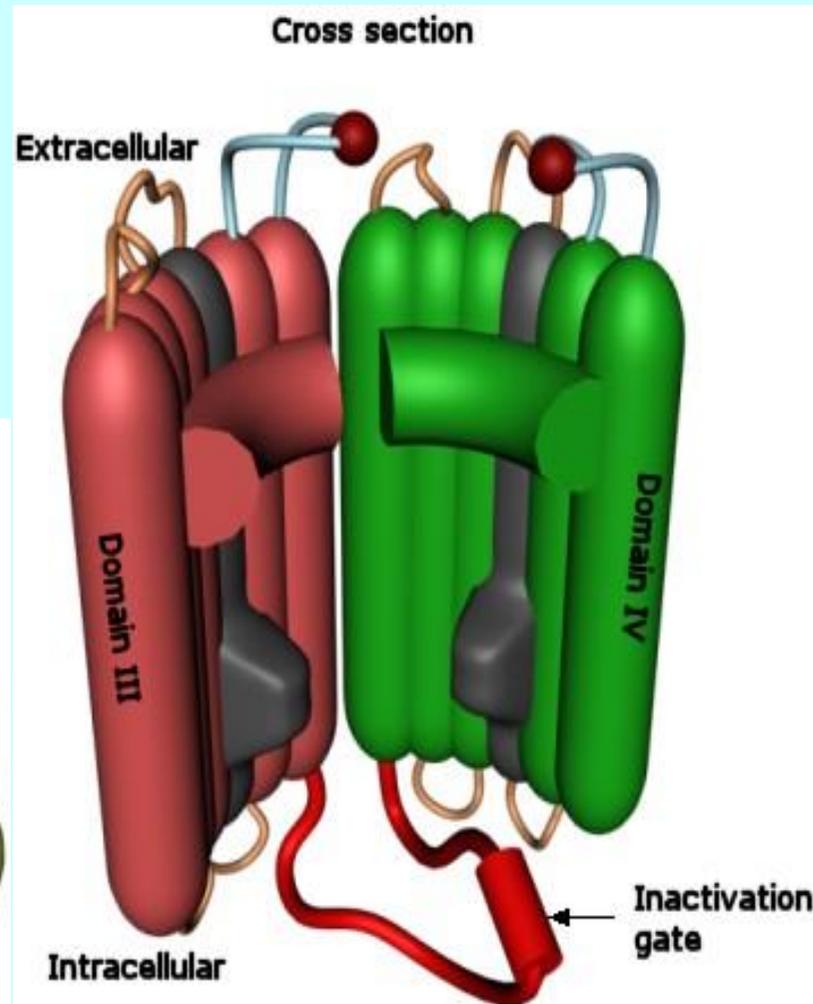
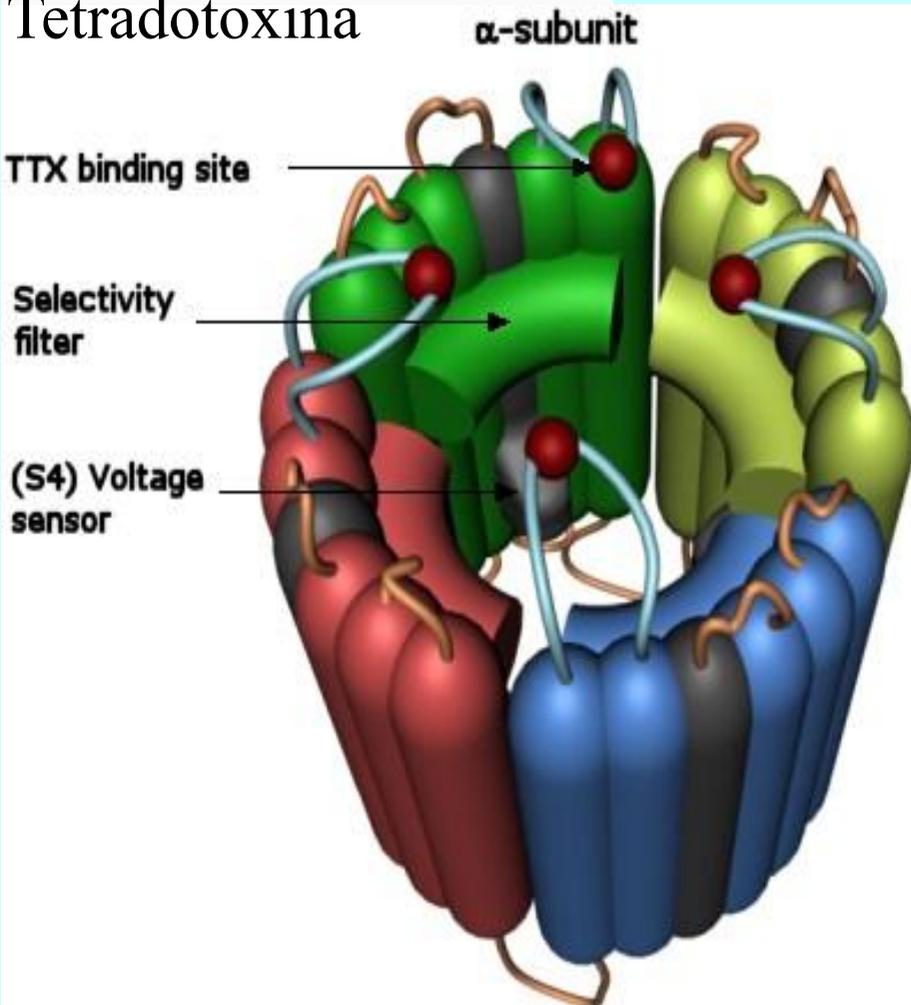
# CANALI DEL SODIO



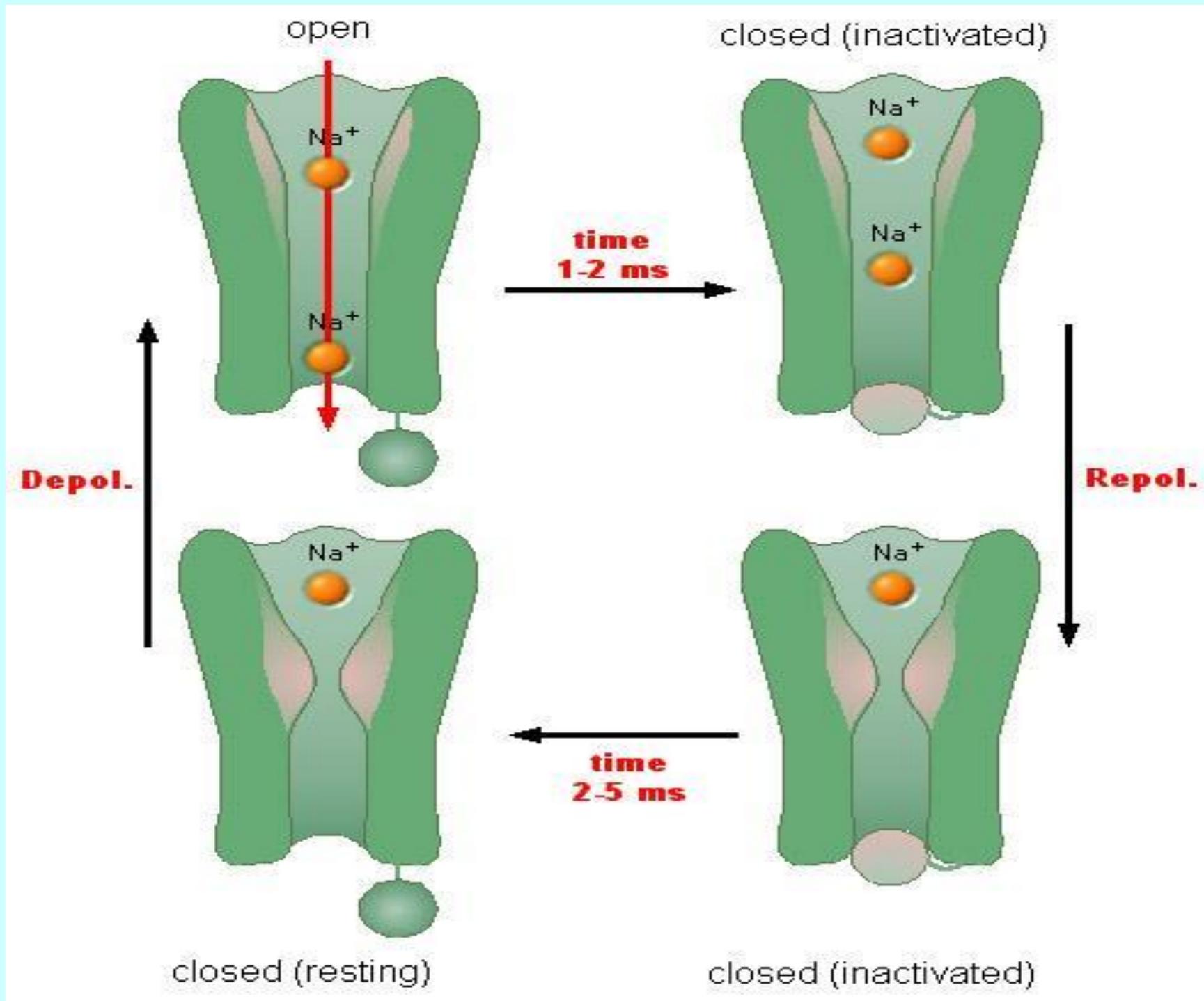
# CANALI DEL SODIO



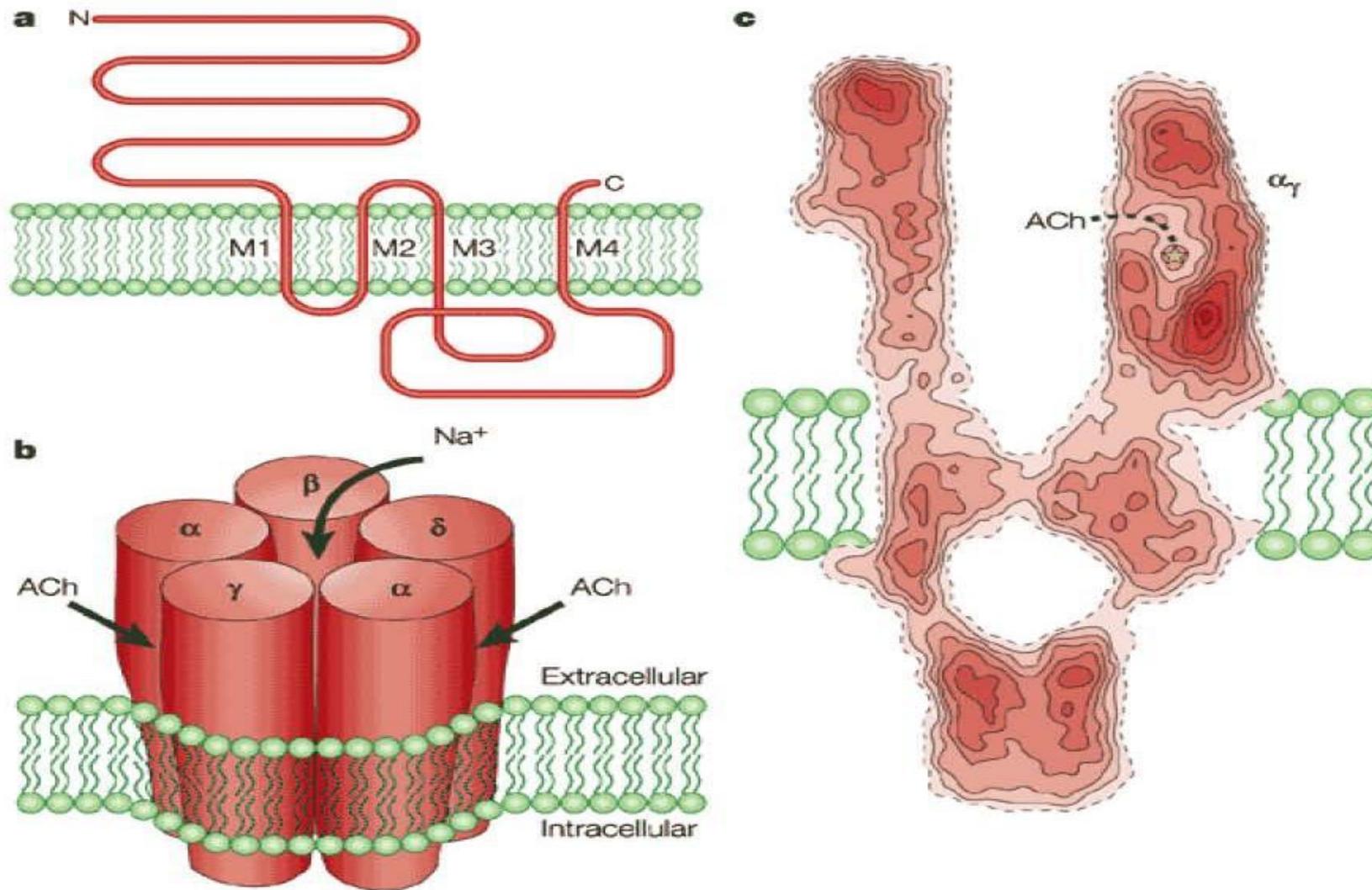
Tetrodotossina



# CANALI DEL SODIO



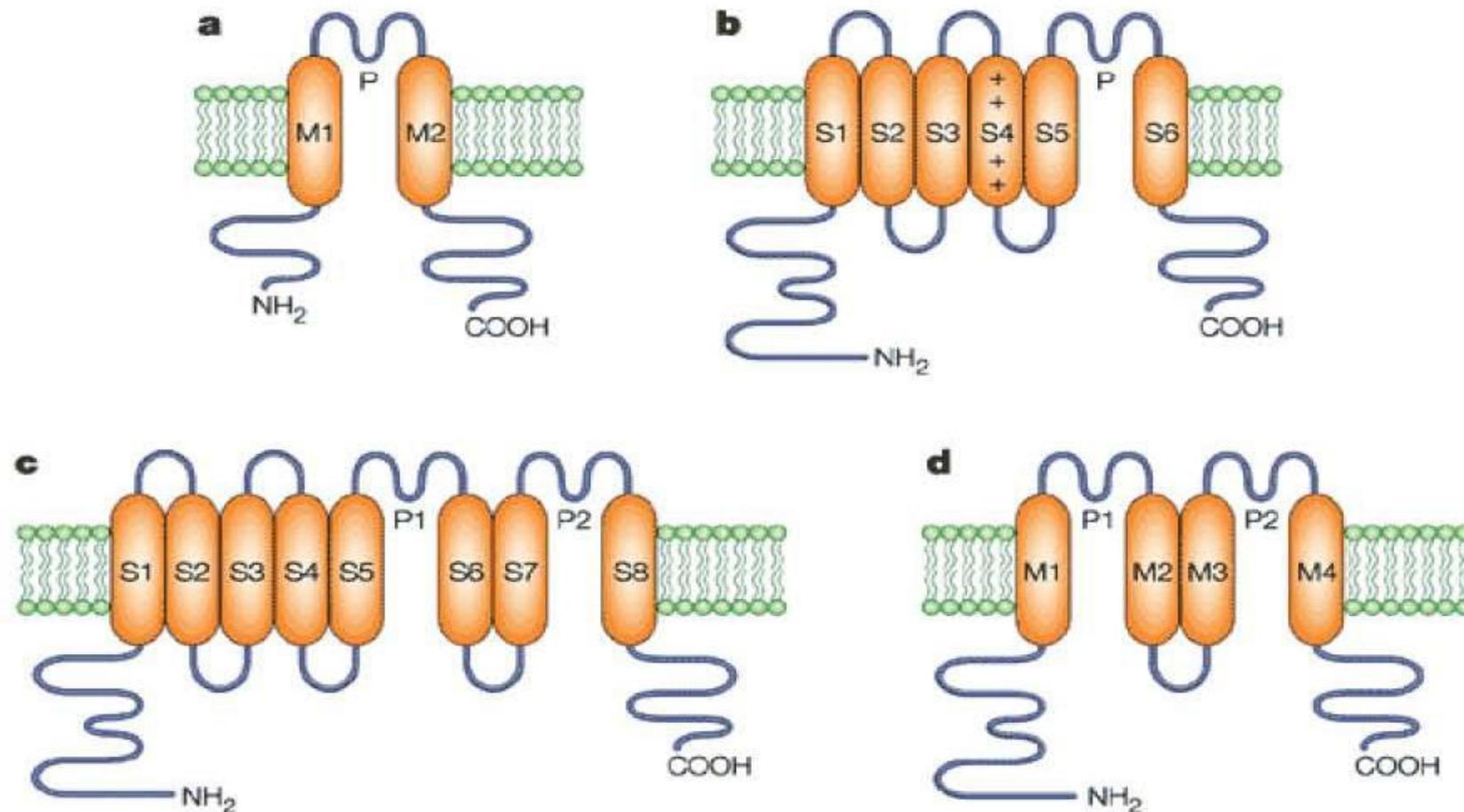
# CANALI DEL SODIO (Nicotinici)



Nature Reviews | Neuroscience

Figure 1 | **Structure of the nicotinic acetylcholine receptors.** **a** | The threading pattern of receptor subunits through the membrane. **b** | A schematic representation of the quaternary structure, showing the arrangement of the subunits in the muscle-type receptor, the location of the two acetylcholine (ACh)-binding sites (between an  $\alpha$ - and a  $\gamma$ -subunit, and an  $\alpha$ - and a  $\delta$ -subunit), and the axial cation-conducting channel. **c** | A cross-section through the 4.6-Å structure of the receptor determined by electron microscopy of tubular crystals of *Torpedo* membrane embedded in ice. Dashed line indicates proposed path to binding site. Part c reproduced with permission from Ref. 22 © 1999 Academic Press.

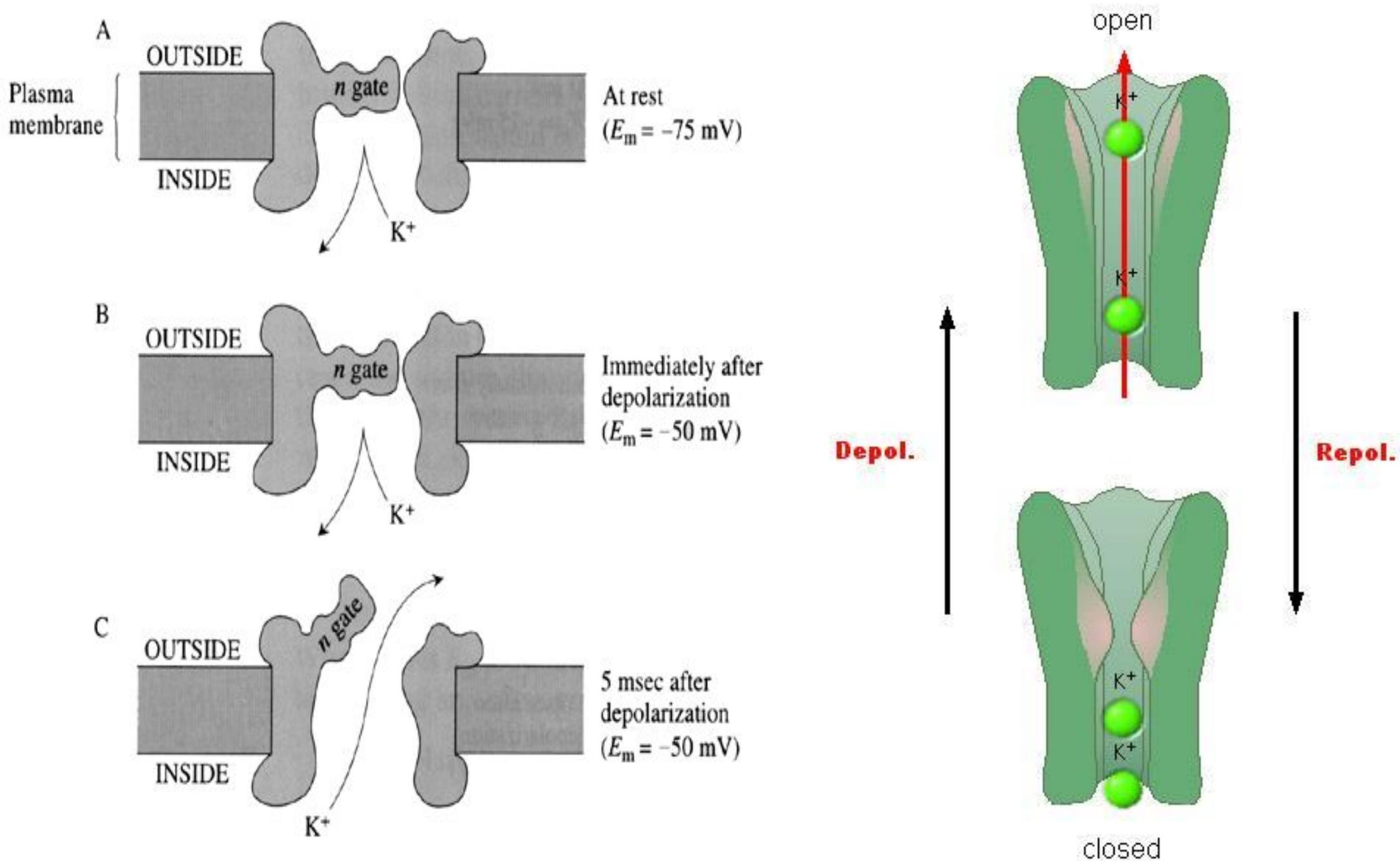
# CANALI DEL POTASSIO



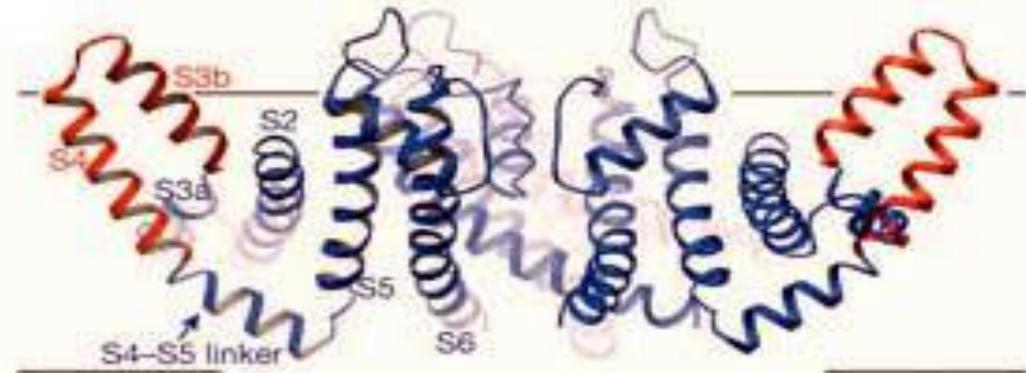
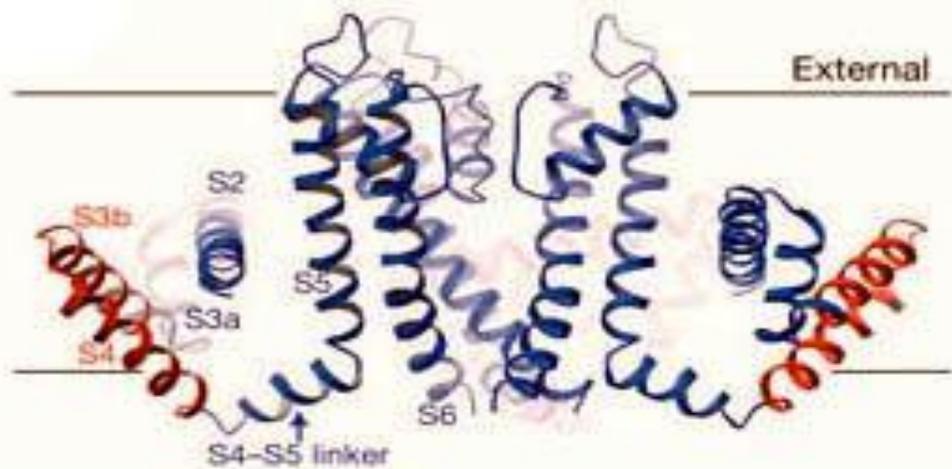
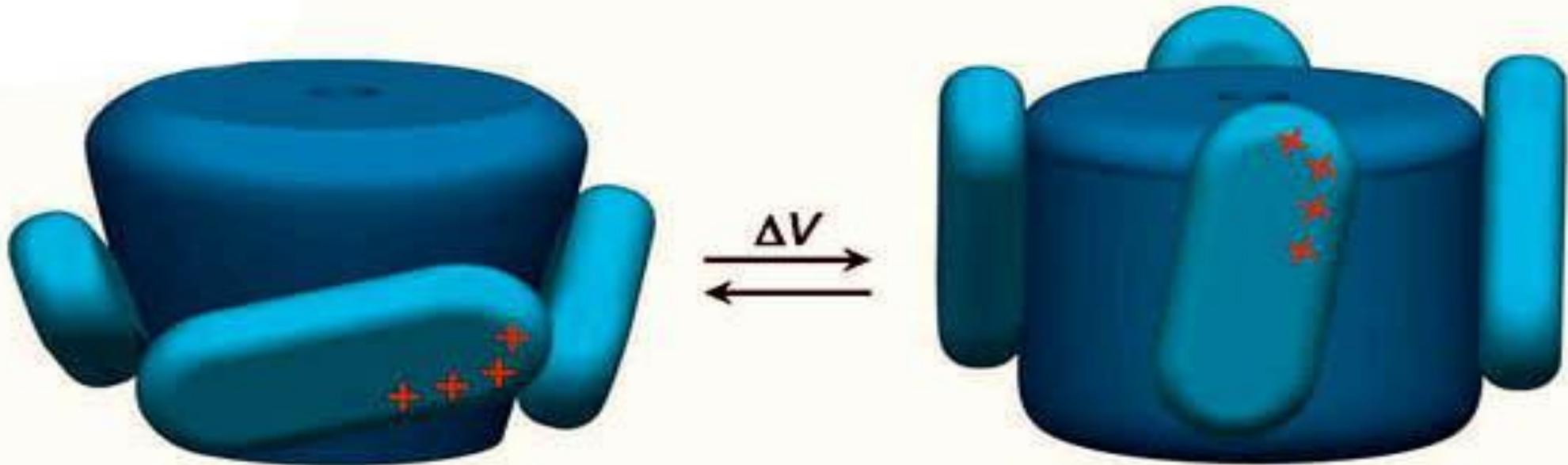
Nature Reviews | Neuroscience

Figure 1 | **The four main classes of potassium channel.** **a** | 2TM/P channels (which consist of two transmembrane (TM) helices with a P loop between them), exemplified by inwardly rectifying K<sup>+</sup> channels and by bacterial K<sup>+</sup> channels such as KcsA. **b** | 6TM/P channels, which are the predominant class among ligand-gated and voltage-gated K<sup>+</sup> channels. **c** | 8TM/2P channels, which are hybrids of 6TM/P and 2TM/P, and were first found in yeast. **d** | 4TM/2P channels, which consist of two repeats of 2TM/P channels. 8TM/2P and 4TM/2P probably assemble as dimers to form a channel. 4TM/2P channels are far more common than was originally thought. These so-called 'leakage' channels are targets of numerous anaesthetics<sup>39</sup>. S4 is marked with plus signs to indicate its role in voltage sensing in the voltage-gated K<sup>+</sup> channels.

# CANALI DEL POTASSIO

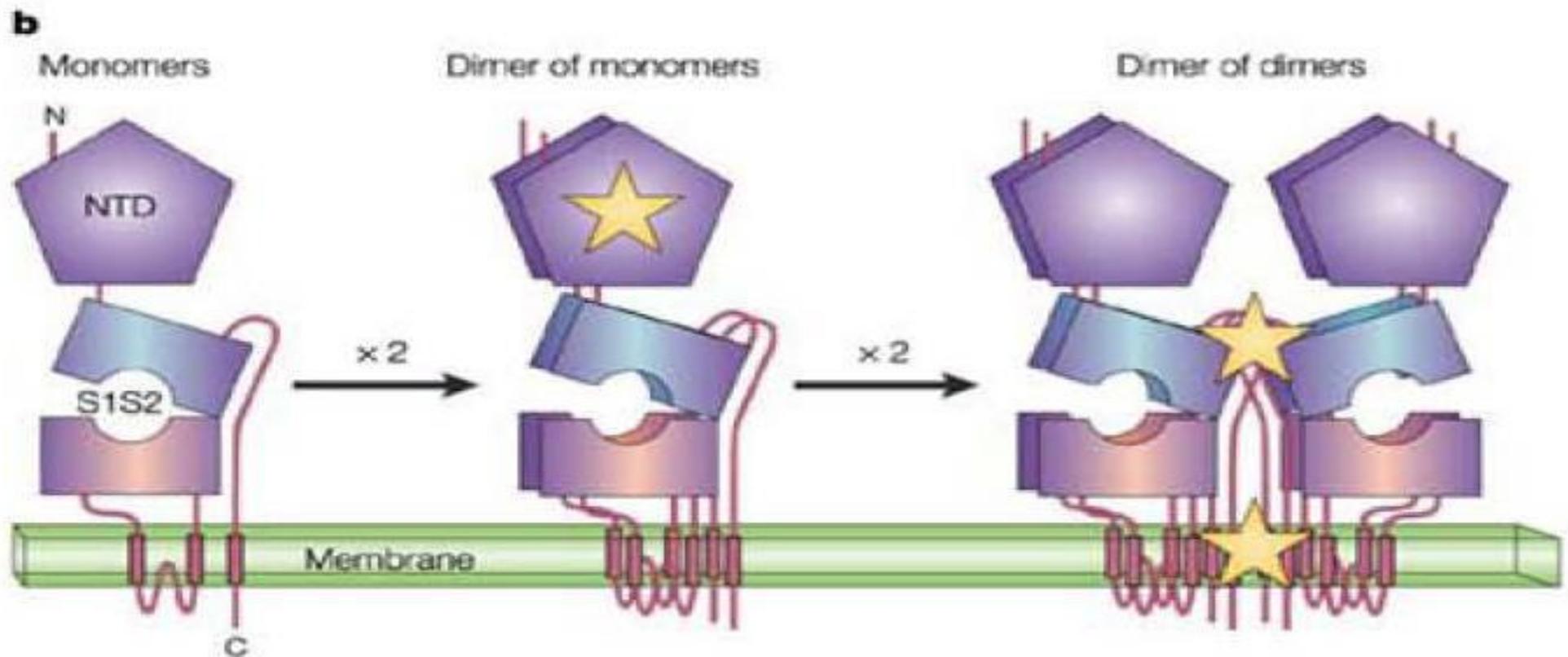
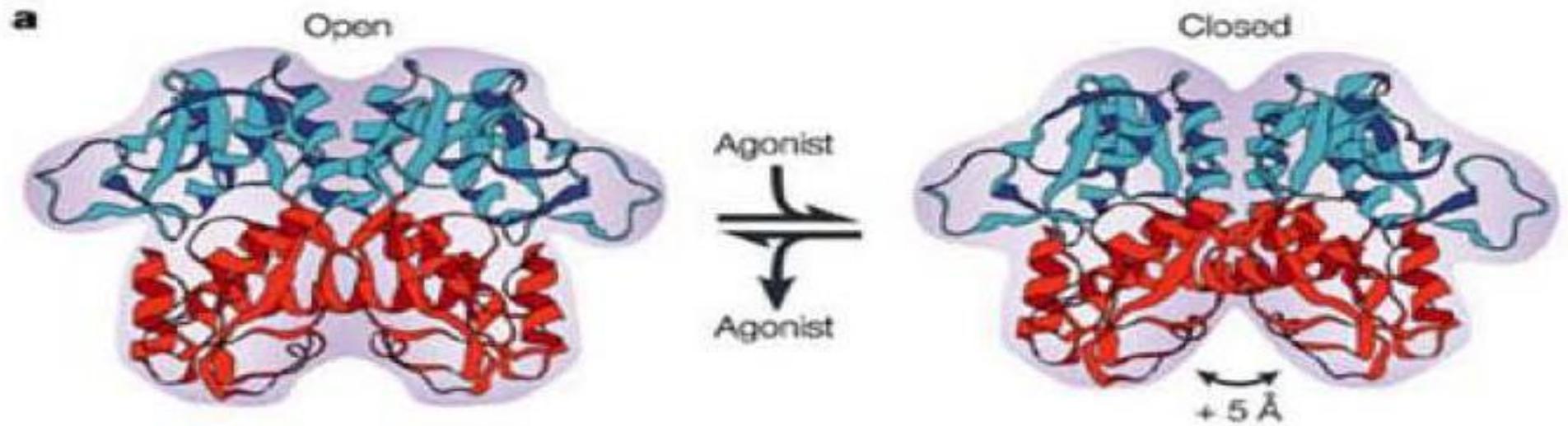


# CANALI DEL POTASSIO





# CANALI DEL CALCIO (iGlu)



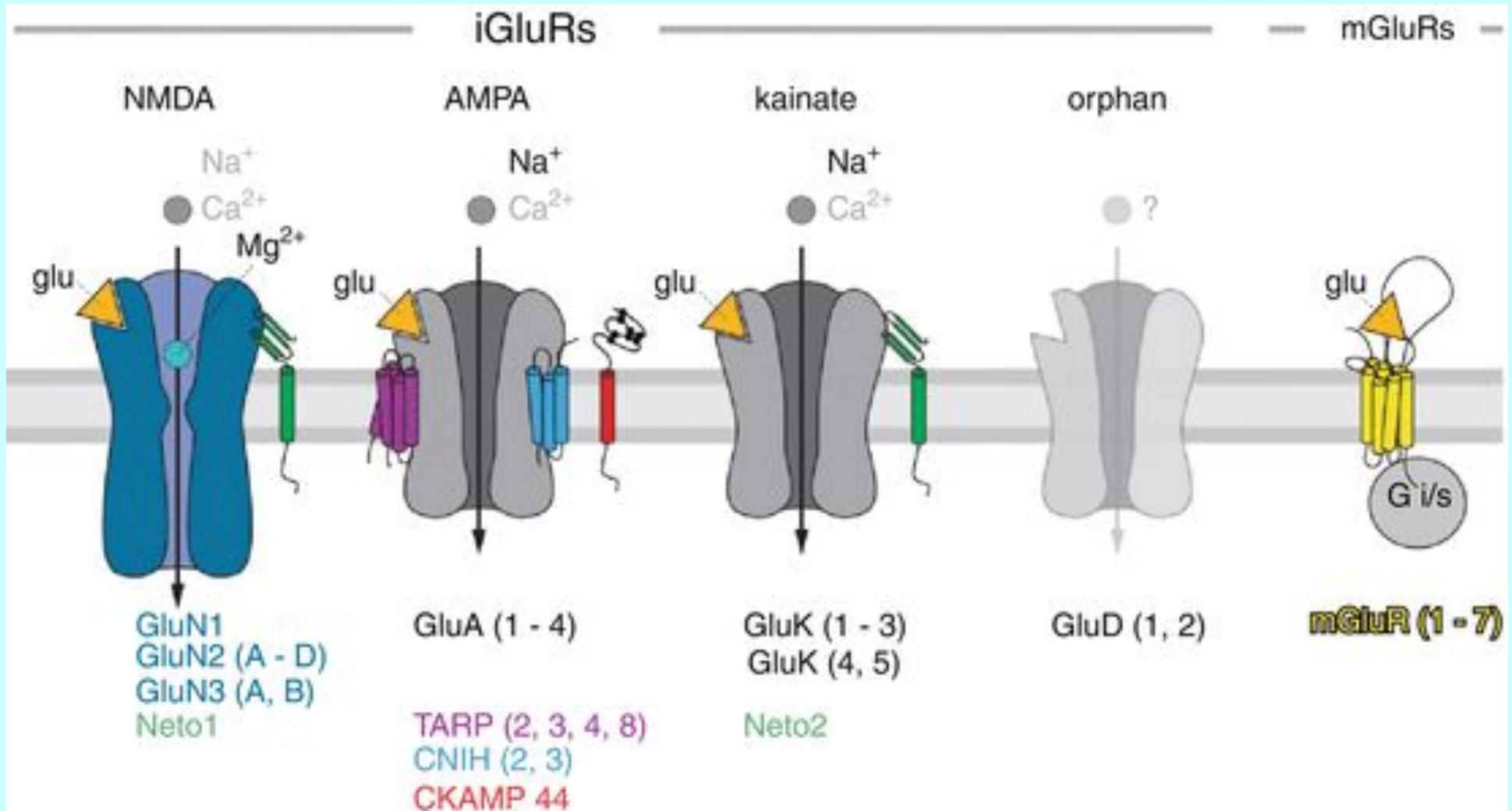
# LIGAND-GATED ION CHANNELS (LICS, LGIC) - IONOTROPIC RECEPTORS

## IONOTROPIC TRANSMEMBRANE RECEPTOR FOR GLUTAMATE (IGLUR)

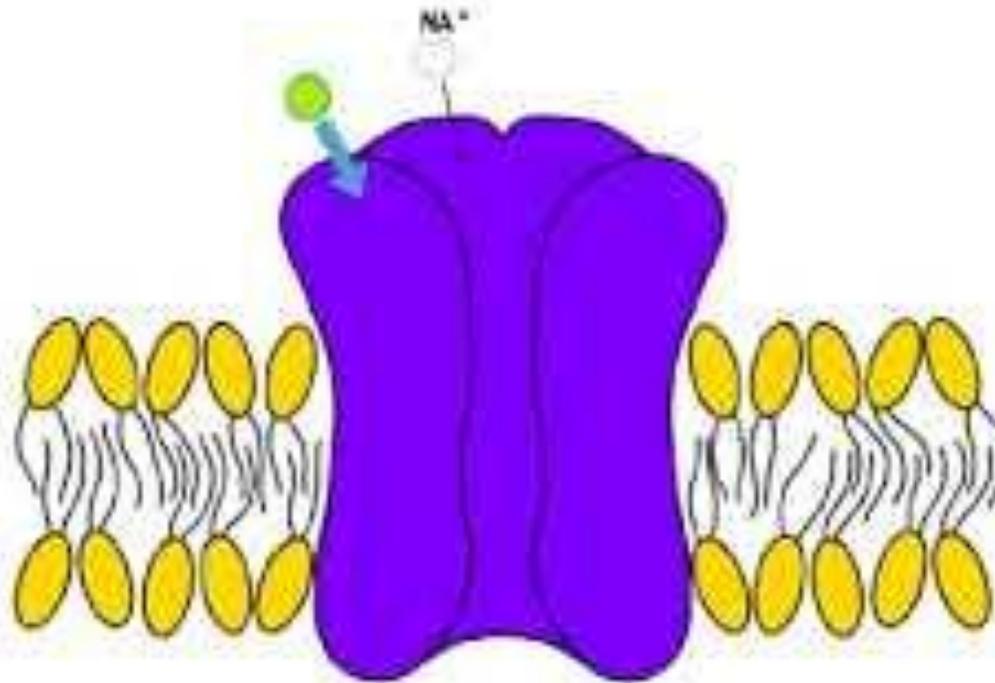
N-methyl-D-aspartate receptor - **NMDA** receptor

$\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor - **AMPA** receptor

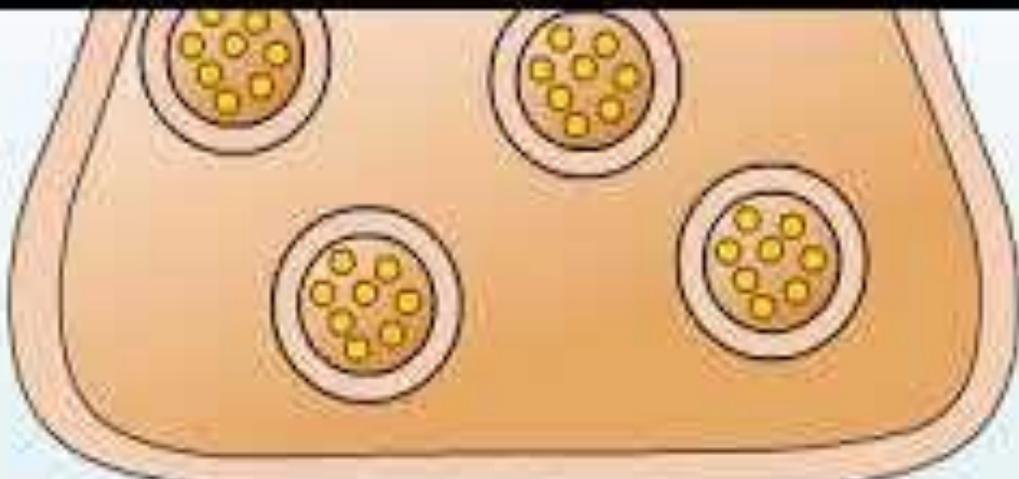
Kainate receptors



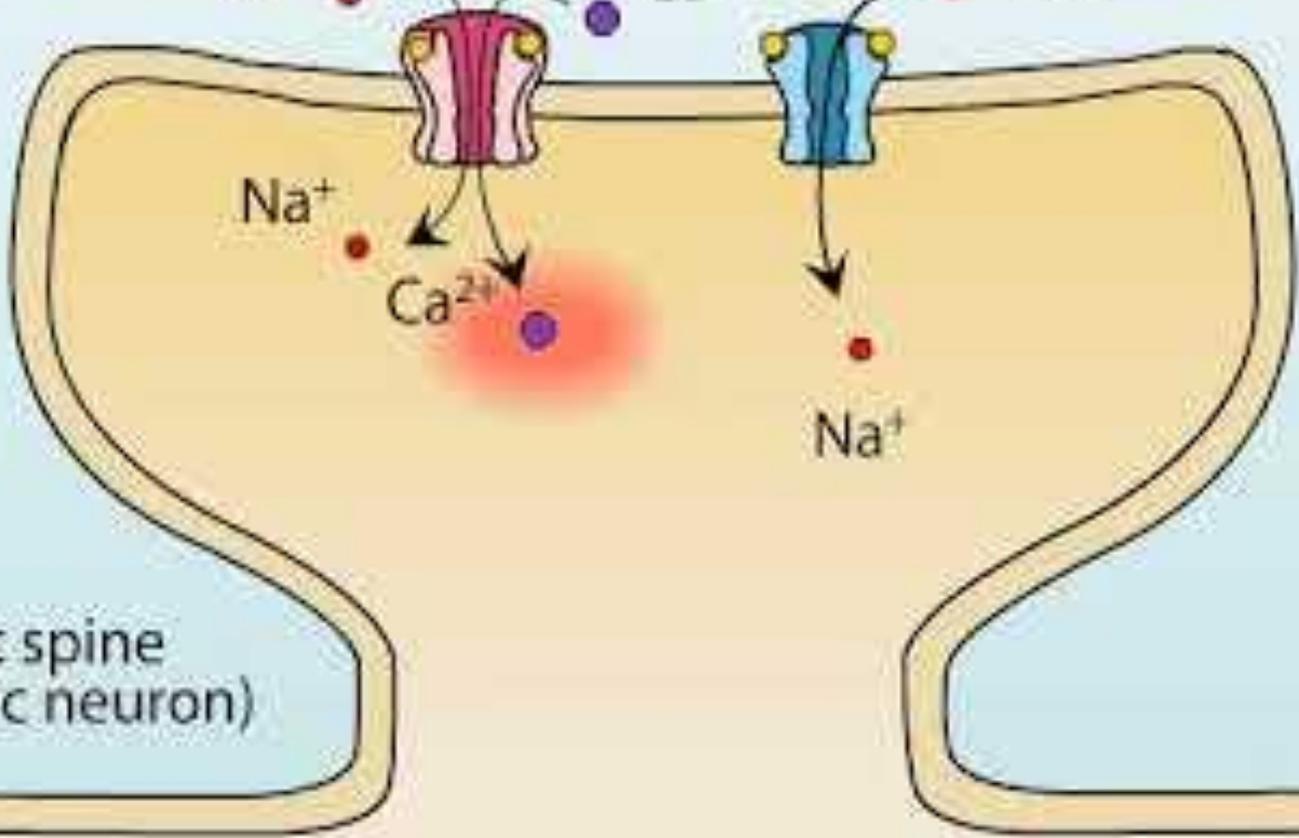
# NMDA, AMPA, KAINATE RECEPTORS - IONOTROPIC



Axon terminal



$\text{Na}^+$   $\text{Ca}^{2+}$   $\text{Na}^+$



Dendritic spine  
(postsynaptic neuron)

# CANALI DEL CALCIO

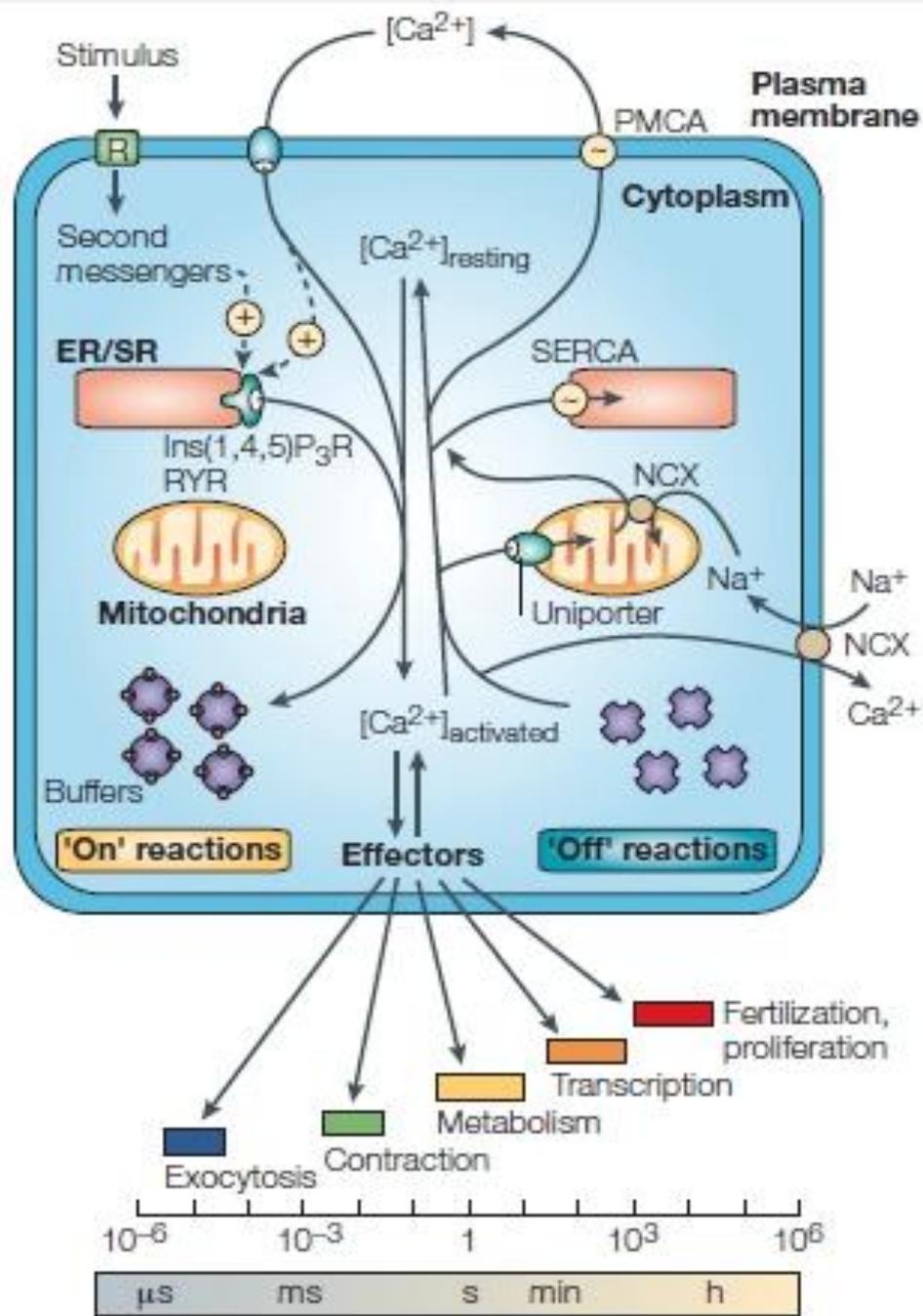
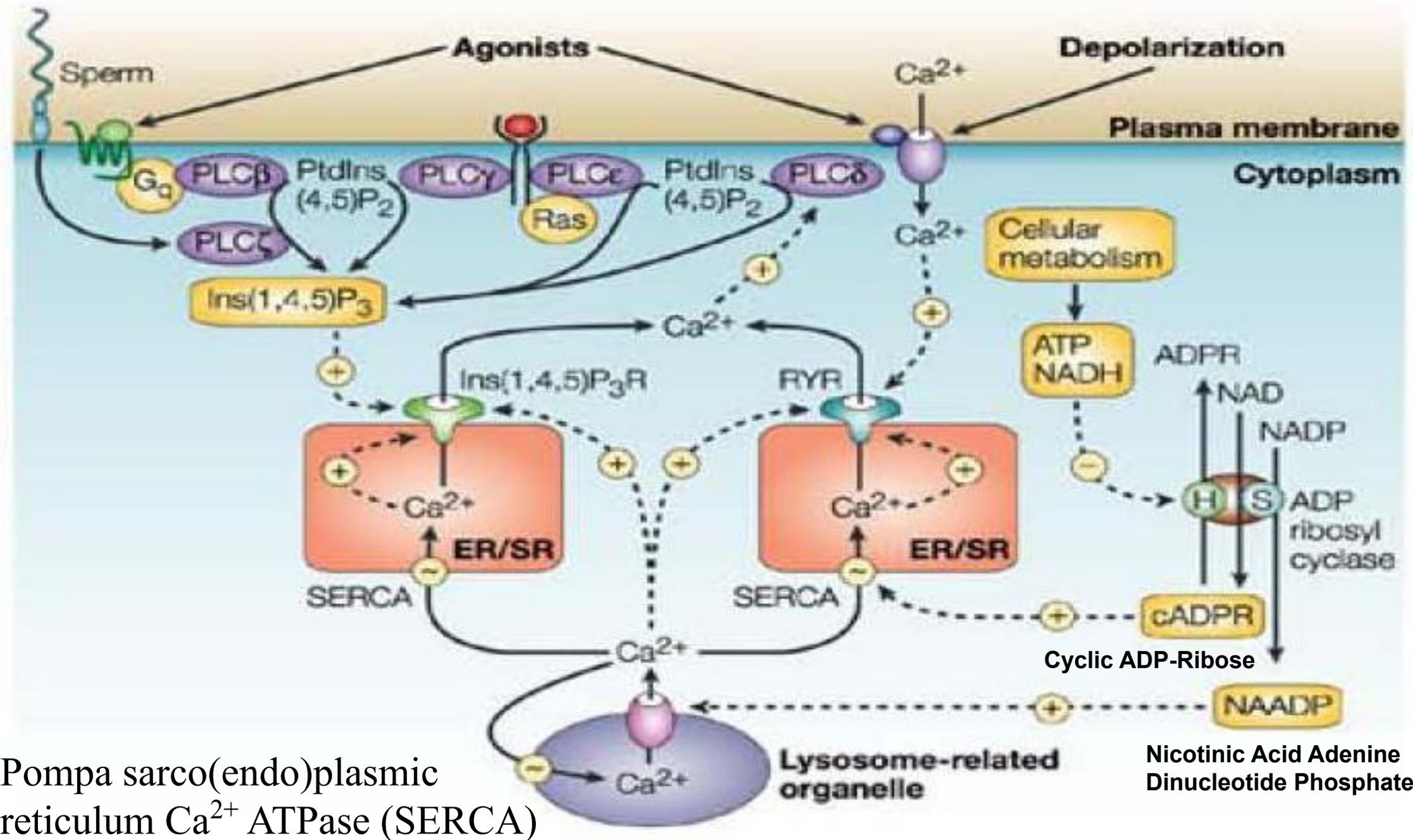


Figure 1 | **Calcium-signalling dynamics and homeostasis.**

During the 'on' reactions, stimuli induce both the entry of external  $Ca^{2+}$  and the formation of second messengers that release internal  $Ca^{2+}$  that is stored within the endoplasmic/sarcoplasmic reticulum (ER/SR). Most of this  $Ca^{2+}$  (shown as red circles) is bound to buffers, whereas a small proportion binds to the effectors that activate various cellular processes that operate over a wide temporal spectrum. During the 'off' reactions,  $Ca^{2+}$  leaves the effectors and buffers and is removed from the cell by various exchangers and pumps. The  $Na^+/Ca^{2+}$  exchanger (NCX) and the plasma-membrane  $Ca^{2+}$ -ATPase (PMCA) extrude  $Ca^{2+}$  to the outside, whereas the sarco(endoplasmic reticulum  $Ca^{2+}$ -ATPase (SERCA) pumps  $Ca^{2+}$  back into the ER. Mitochondria also have an active function during the recovery process in that they sequester  $Ca^{2+}$  rapidly through a uniporter, and this is then released more slowly back into the cytosol to be dealt with by the SERCA and the PMCA. Cell survival is dependent on  $Ca^{2+}$  homeostasis, whereby the  $Ca^{2+}$  fluxes during the off reactions exactly match those during the on reactions.  $[Ca^{2+}]$ ,  $Ca^{2+}$  concentration; Ins(1,4,5) $P_3$ R, inositol-1,4,5-trisphosphate receptor; RYR, ryanodine receptor.

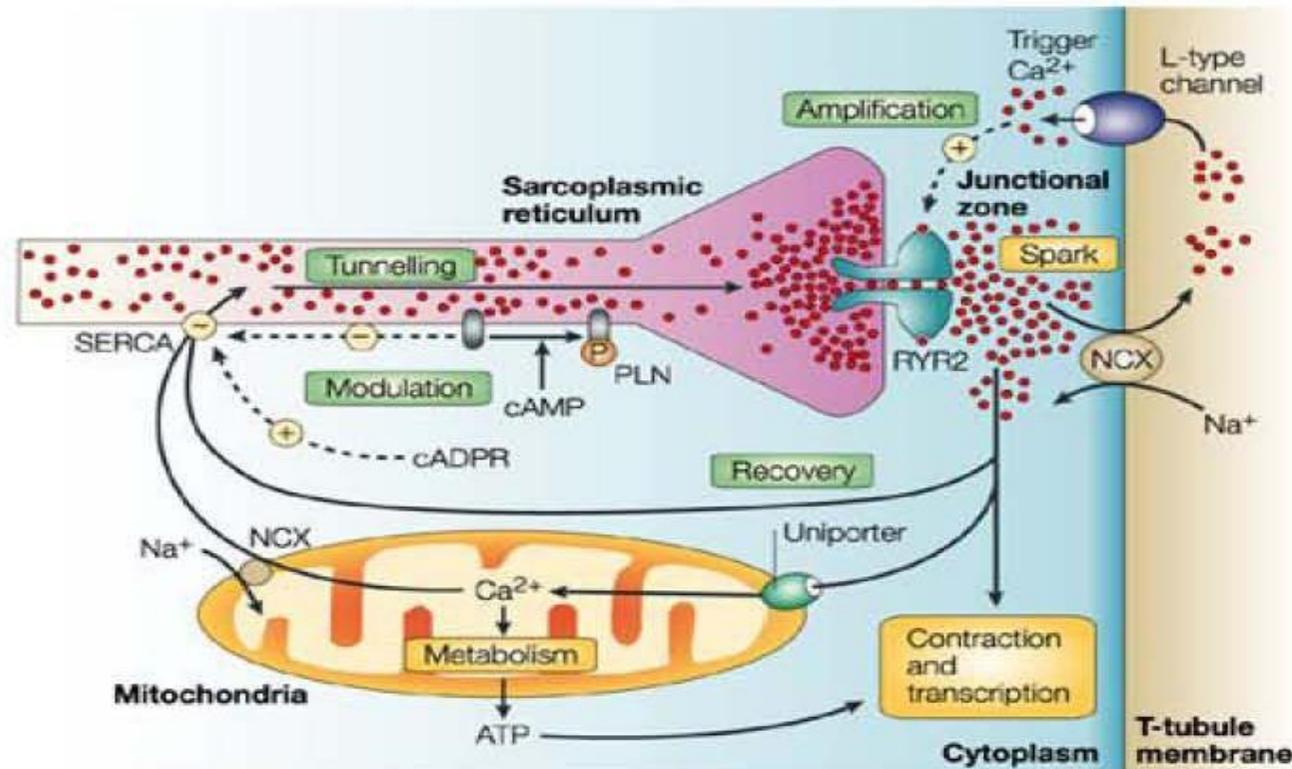
# CANALI DEL CALCIO



Pompa sarco(endo)plasmic reticulum  $Ca^{2+}$  ATPase (SERCA)

Nicotinic Acid Adenine Dinucleotide Phosphate

# CANALI DEL CALCIO



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**Figure 3 | Cardiac calcium-signalling module.** This self-contained module generates the localized Ca<sup>2+</sup> 'sparks' that are responsible for activating contraction and perhaps also gene transcription (Ca<sup>2+</sup> is shown as red circles). Signalling begins with an amplification step in the junctional zone, where the L-type channel on the T-tubule membrane responds to depolarization by introducing a small pulse of trigger Ca<sup>2+</sup>, which then diffuses across the narrow gap of the junctional zone to activate ryanodine receptor 2 (RYR2) (Box 2, part a) to generate a spark. Ca<sup>2+</sup> from this spark diffuses out to activate contraction. Recovery occurs as Ca<sup>2+</sup> is pumped out of the cell by the Na<sup>+</sup>/Ca<sup>2+</sup> exchanger (NCX) or is returned to the sarcoplasmic reticulum (SR) by sarco(endo)plasmic Ca<sup>2+</sup>-ATPase (SERCA) pumps on the non-junctional region of the SR. A proportion of this Ca<sup>2+</sup> travels through the mitochondria, during which time it stimulates the metabolism to provide the ATP that is necessary to maintain contraction and transcription. The Ca<sup>2+</sup> that is returned to the SR 'tunnels' back to the junctional zone to be used again for subsequent heart beats. This circulation of Ca<sup>2+</sup> is modulated by second messengers such as cyclic AMP (cAMP), which removes the inhibitory action of phospholamban (PLN), or by cyclic ADP ribose (cADPR) that activates the pump to increase the amount of releasable Ca<sup>2+</sup> in the SR.