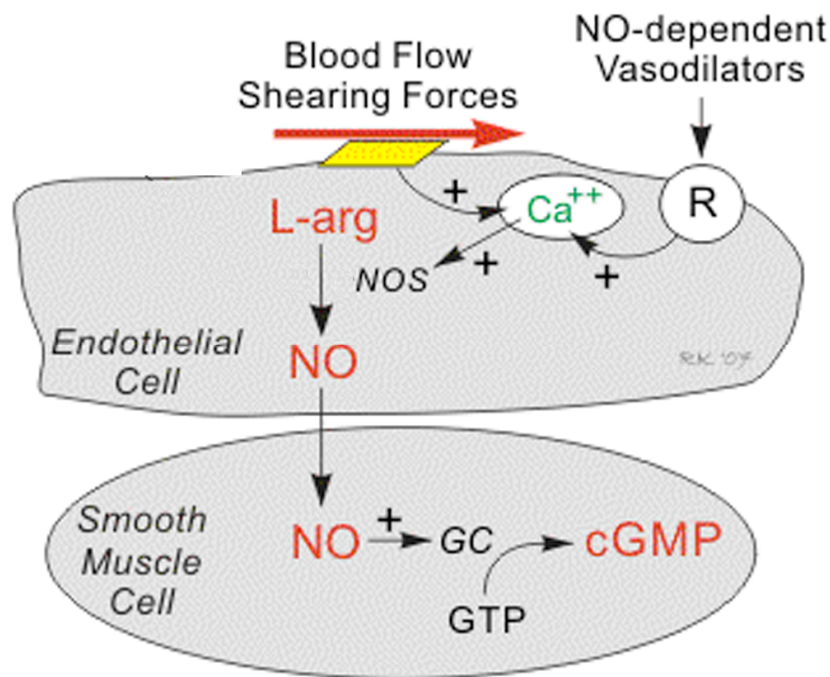


EFFETTO MIORILASSANTE DEL cGMP NEL MUSCOLO LISCIO



Nei vasi sanguigni (in particolare nelle arteriole) l'aumento di flusso sanguigno determina un incremento dell'attrito a livello dell'endotelio vascolare che innesca l'apertura di canali del Ca²⁺.

Canali del Ca²⁺ possono aprirsi anche in seguito all'azione di vasodilatatori presenti nel mezzo extracellulare.

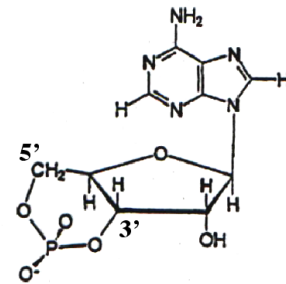
Nelle cellule endoteliali, l'aumento dei livelli intracellulari di Ca²⁺ stimola l'attività NOS (nitric oxide synthase).

NO diffonde dall'endotelio all'interno delle cellule muscolari lisce, attivando un pool di guanilato ciclasti solubili che innalzano i livelli cGMP.

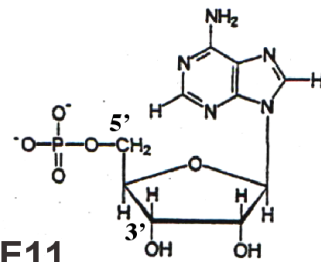
Nelle cellule muscolari lisce il cGMP attiva la PKG I che fosforila:

- Canali del K⁺ posti sulla membrana plasmatica (Maxi K⁺ channels), attivandoli e producendo iperpolarizzazione.
- Recettori per l'IP₃ nel reticolo endoplasmatico, inibendoli.
- Protein fosfatasi della catena leggera della miosina, attivandola.

Fosfodiesterasi dei nucleotidi ciclici



3', 5'-cyclic AMP



5'-AMP

Tipi e specificità

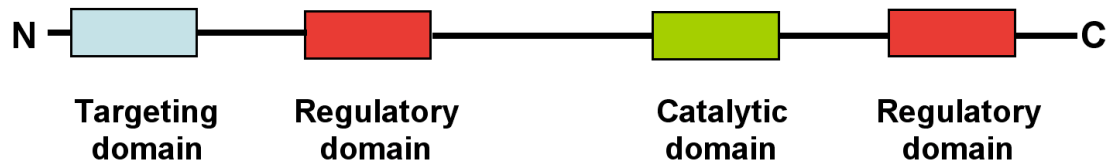
Undici famiglie di fosfodiesterasi (PDE) identificate.

Specifiche per il **cAMP** : PDE4, PDE7, PDE8

Specifiche per il **cGMP** : PDE5, PDE6, PDE9

Con **doppia specificità**: PDE1, PDE2, PDE3, PDE10, PDE11

Struttura generale



PDE1

Calmodulin binding
(inhibitory)

Present in **PDE1**
only

PDE2

cGMP binding (stimulatory)

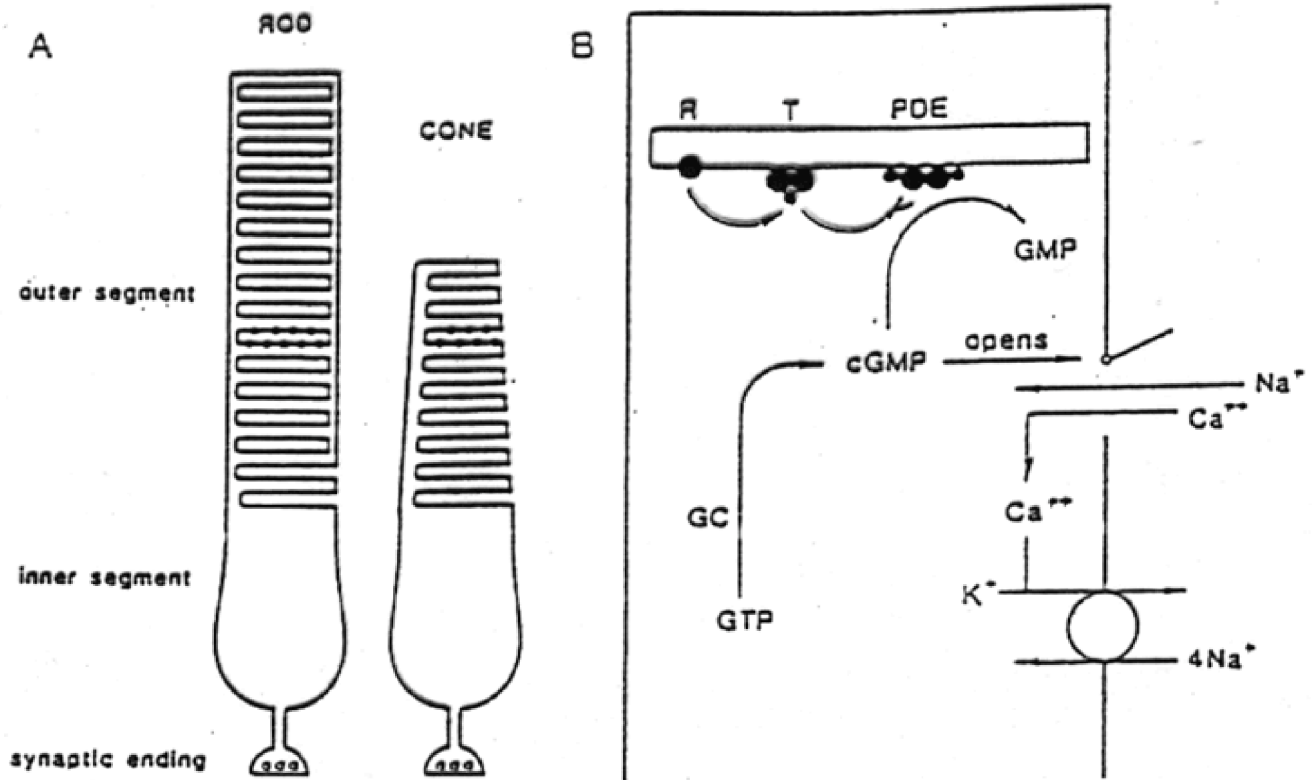
PDE1-5

Phosphorylation sites for
various kinases (e.g. PKA and
insulin-regulated kinases)

PDE6

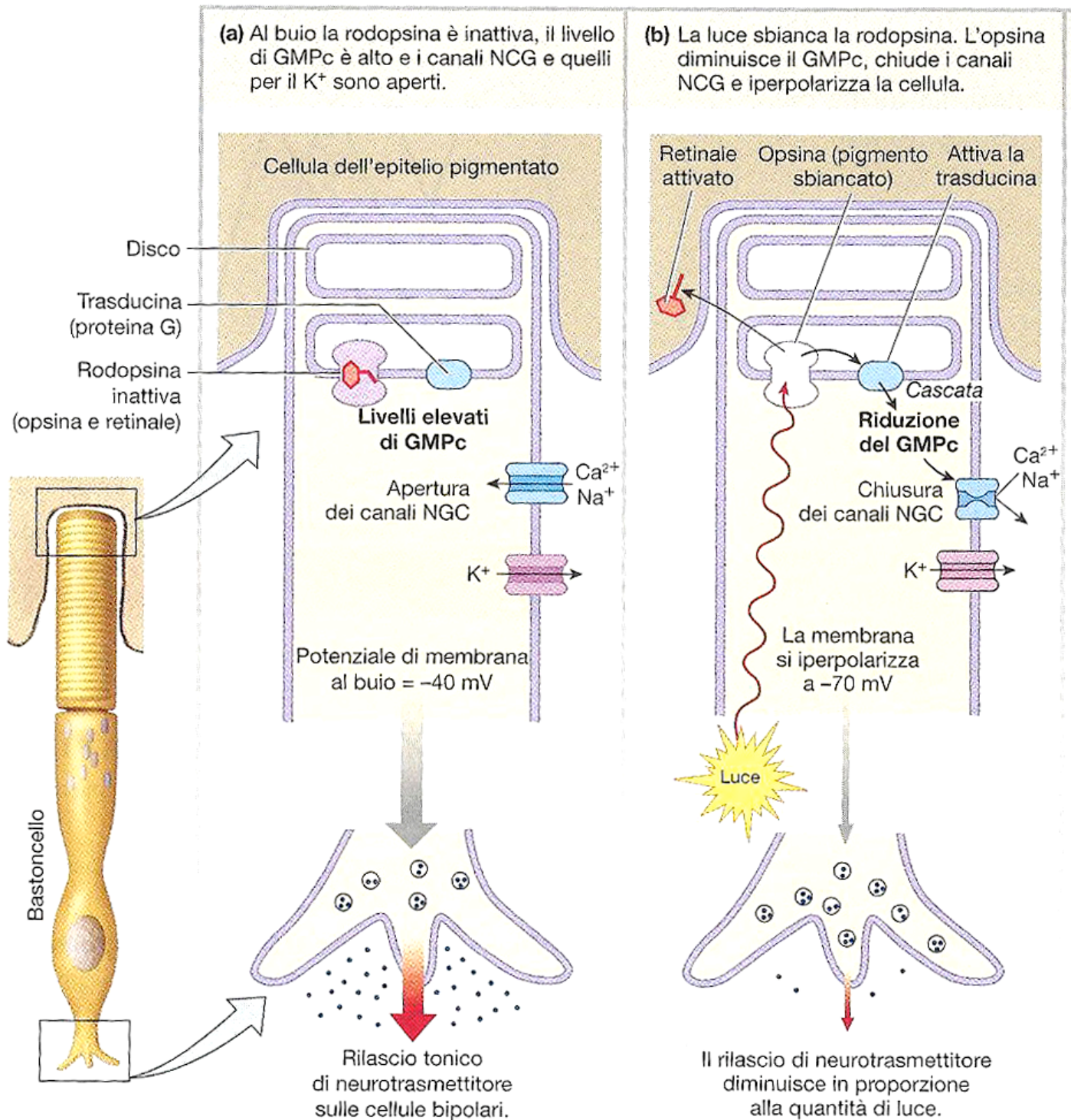
Transducin-binding domain

Photoreceptor cells and the cGMP cascade of vision

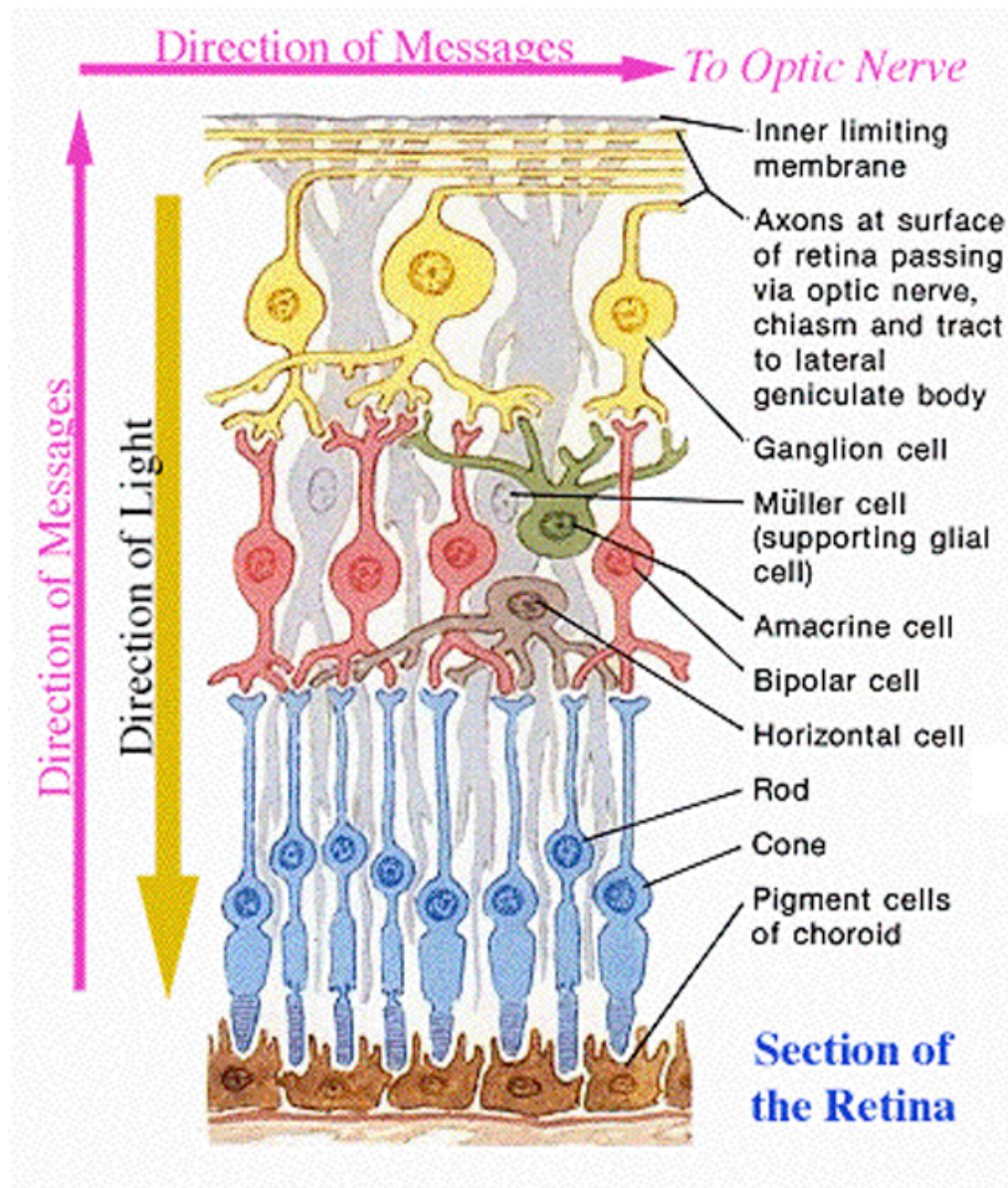


(A) Structure of a rod and cone. Phototransduction occurs in the outer segment, which contains the visual pigment (filled circles). The synaptic terminal contacts second-order horizontal and bipolar cells (not shown). (B) cGMP cascade. The cationic channel in the surface membrane (trap door at the right) is held open in darkness by the binding of cGMP, which is synthesized from the precursor GTP by guanylate cyclase (GC). In darkness Ca^{2+} and Na^+ enter the cell through the open channel, partially depolarizing the membrane. Photoexcitation of rhodopsin (R) causes it to catalytically activate the GTP-binding protein transducin (T), which in turn activates cGMP phosphodiesterase (PDE). Activated PDE hydrolyzes cGMP to 5'-GMP (GMP), allowing the channel to close and hyperpolarize the membrane. Na^+ is extruded by a pump in the inner segment (not shown), while Ca^{2+} is extruded by an exchanger which is driven by entry of Na^+ and efflux of K^+ . Continued operation of the exchanger at the onset of light produces a fall in the intracellular concentration of Ca^{2+} .

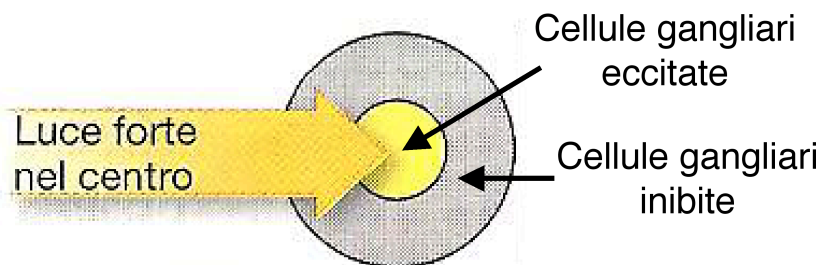
Idrolisi del cGMP nei fotorecettori ed attivazione del meccanismo della visione (II)



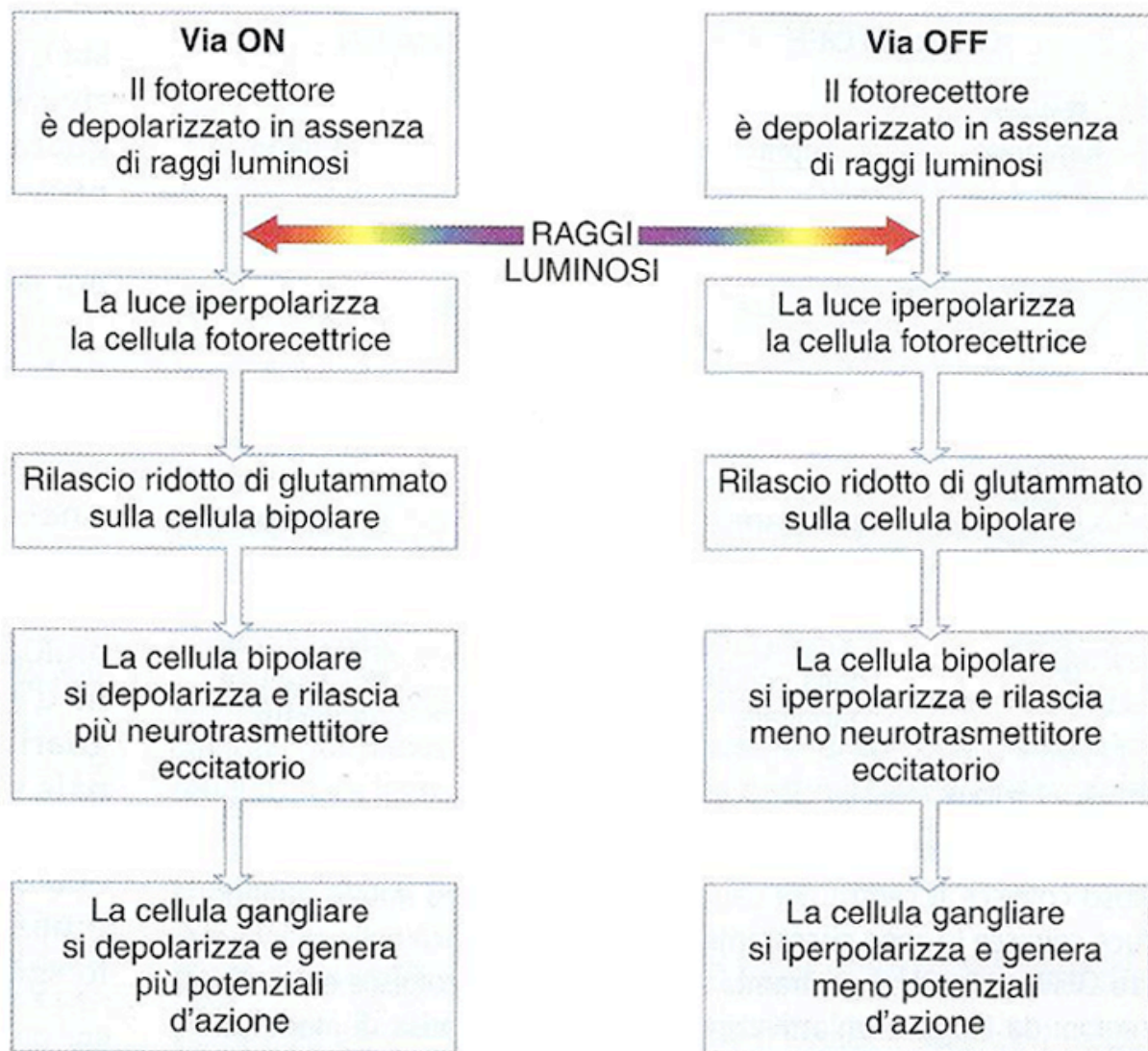
Organizzazione cellulare della retina e campi recettoriali



Campo recettoriale



Vie di segnalazione ON ed OFF

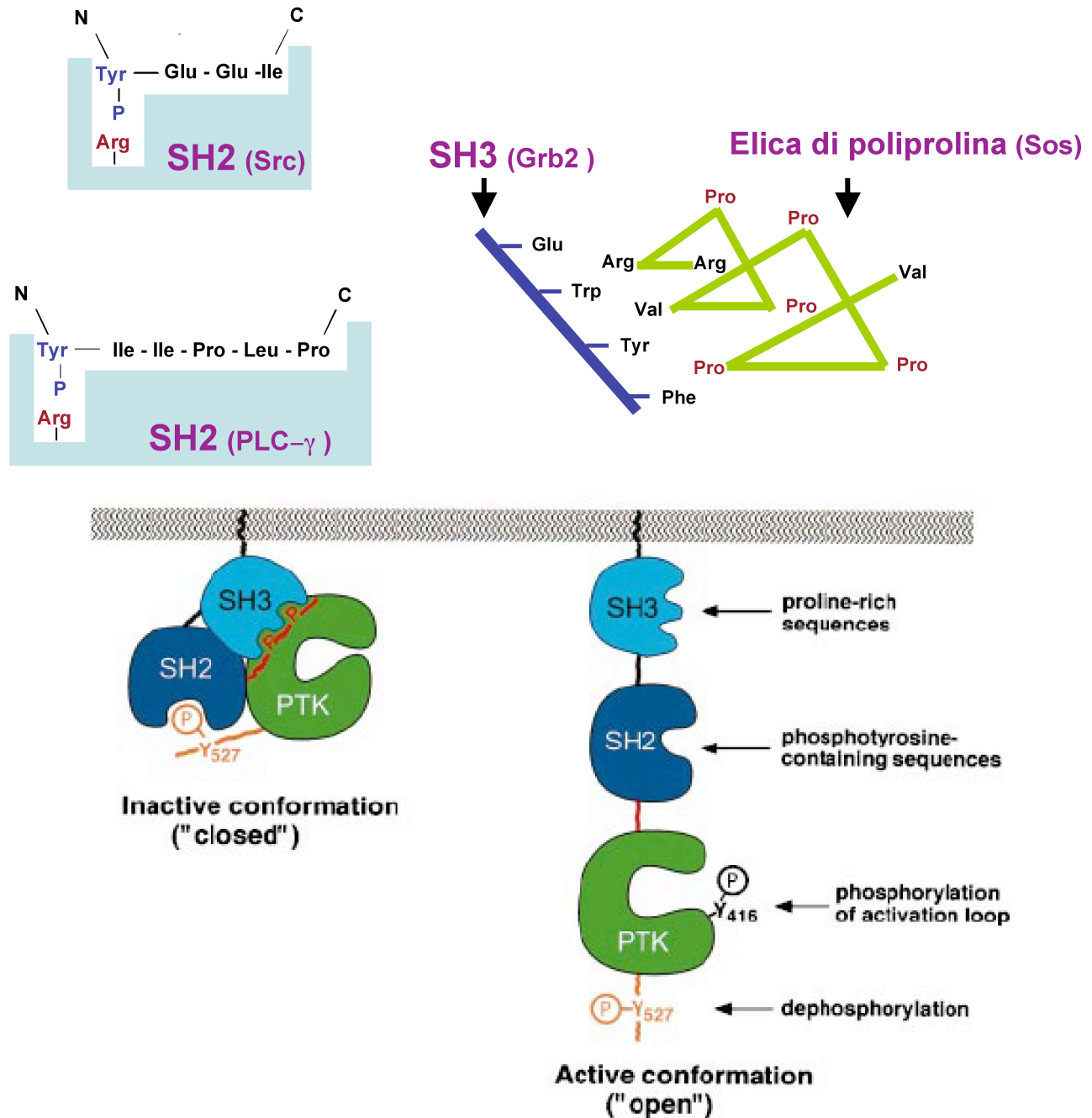


Nelle cellule bipolari ON il glutammato blocca un canale cationico mediante un recettore metabotropo (mGluR6) accoppiato ad una $G\alpha_o$.
In assenza di rilascio di glutammato dal fotorecettore il canale cationico si apre e la cellula bipolare si depolarizza.

Nelle cellule bipolari OFF il glutammato attiva recettori ionotropi AMPA e kainato.
In assenza di rilascio di glutammato dal fotorecettore la cellula bipolare si iperpolarizza.

Recettori ionotropi AMPA e kainato sono anche presenti nelle cellule gangliari.

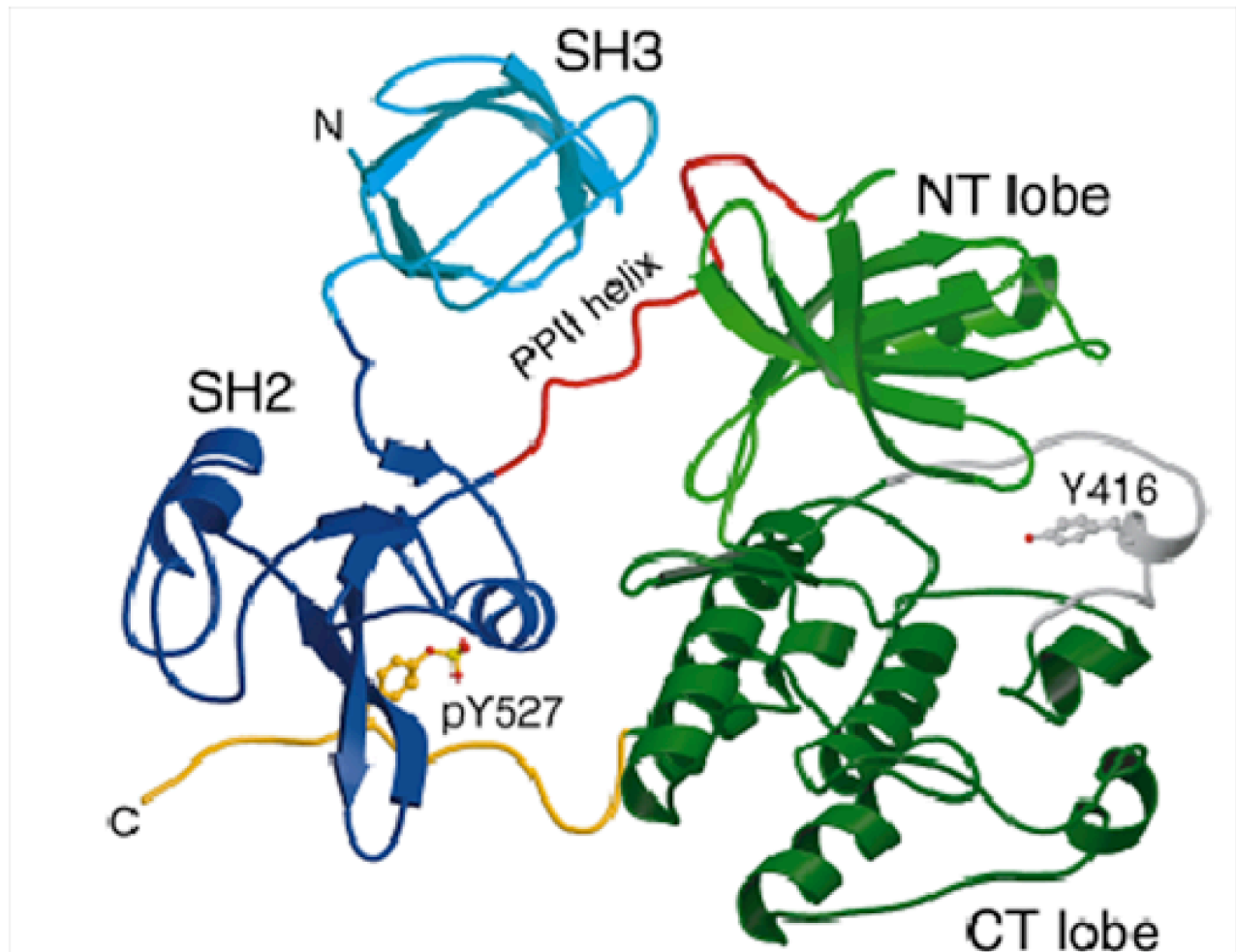
Domini SH2 ed SH3 e meccanismo di attivazione di Src



Autoregulation and activation of Src.

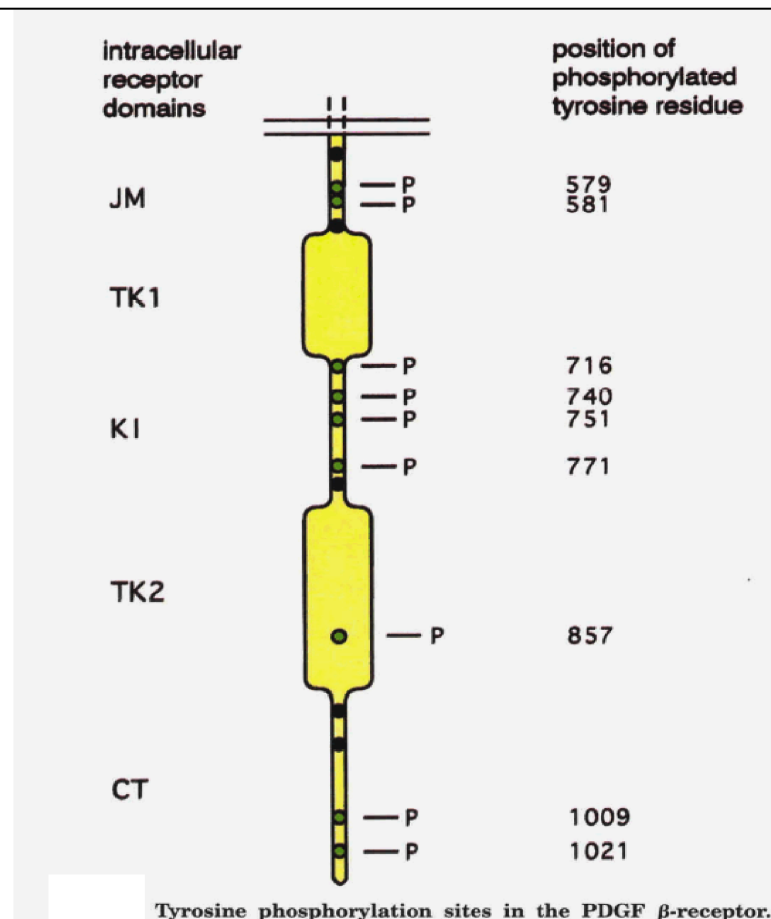
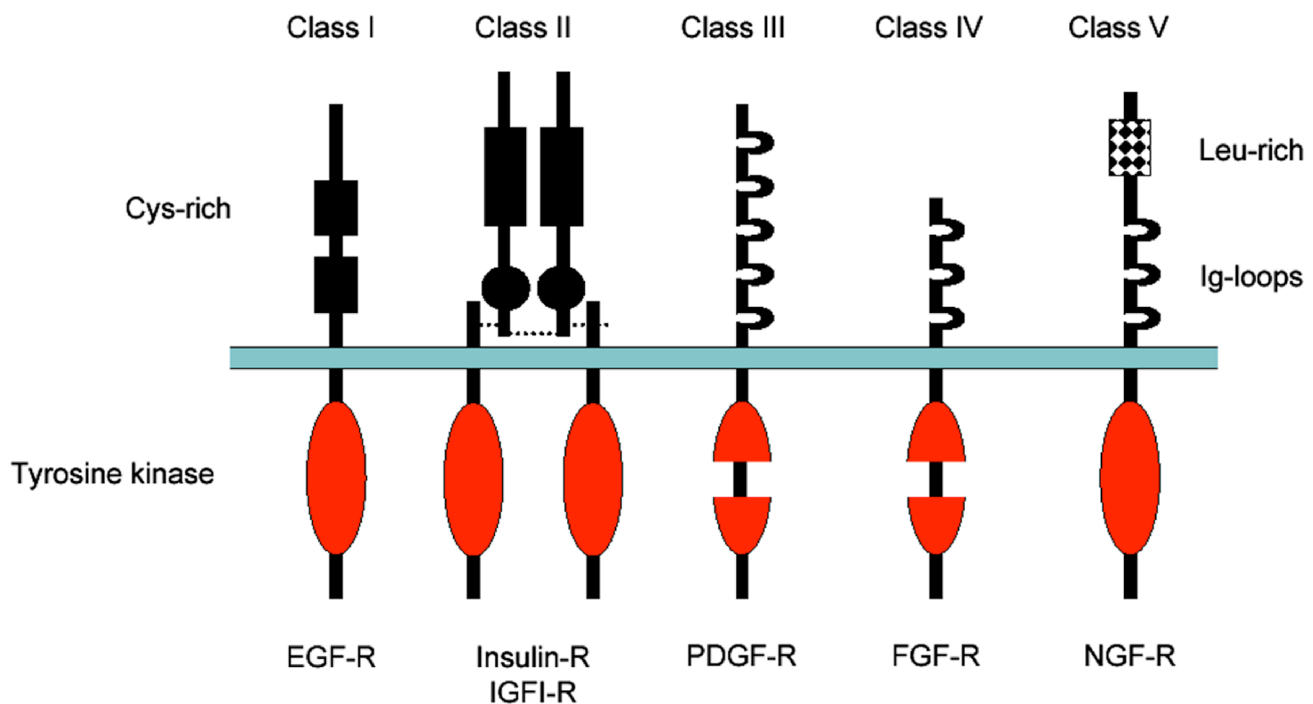
The kinase domain of Src is held in an inactive state through two distinct intramolecular interactions: the binding of the SH2 domain to pTyr527 and the binding of the SH3 domain to the SH2-kinase linker, which contains a short polyproline type II helix. As a result of extracellular stimuli, the kinase activity of Src can be enhanced by binding of the SH3 domain to proline-rich sequences, binding of the SH2 domain to phosphotyrosine containing sequences, or dephosphorylation of pTyr527. Full activation of Src requires autophosphorylation of Tyr416 in the A-loop.

Modello della forma inattiva di Src

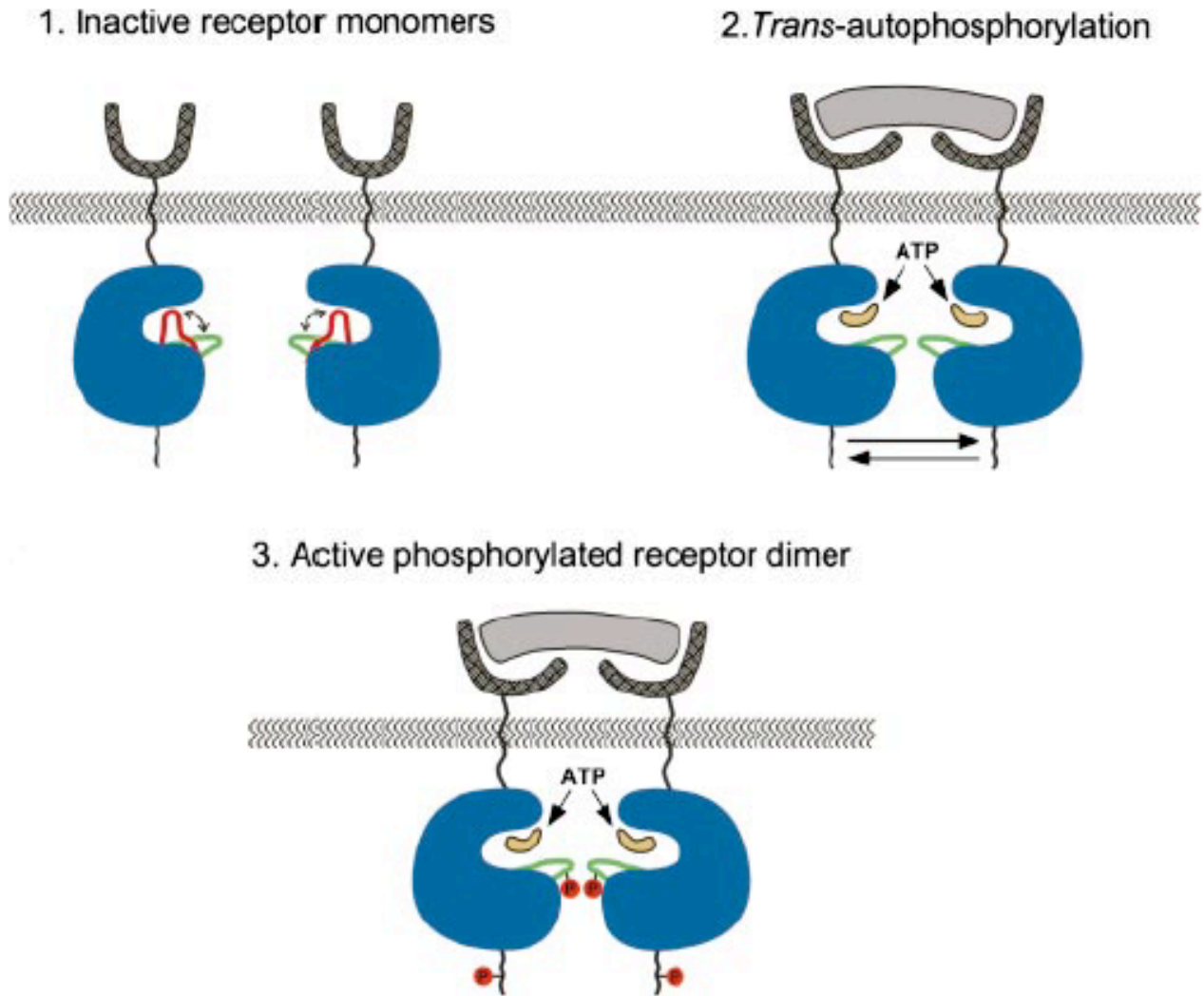


Ribbon diagram of downregulated Src. The amino- and carboxy-terminal kinase lobes are shown in *light* and *dark green*, respectively. The activation loop in the kinase domain, containing Tyr-416 (*ball and stick*), is shown in *gray*. The SH2 and SH3 domains are shown in *dark blue* and *cyan*, respectively. The SH2-kinase linker, which contains a short stretch of polyproline type II helix (PPII helix), is shown in *red*. The carboxy-terminal tail, which contains pTyr-527 (*ball and stick*), is shown in *orange*. The amino and carboxy termini are denoted by N and C.

Struttura dei recettori per i fattori di crescita (TKRs, tyrosin-kinase receptors)



Meccanismo di attivazione dei recettori per i fattori di crescita



Model for stimulation of tyrosine kinase activity by receptor dimerization.

The A-loop of RTKs is relatively mobile and probably adopts numerous conformations. A majority of these conformations (*red*) will interfere with protein substrate binding and perhaps ATP binding. A subset of conformations (*green*) are compatible with substrate (protein and ATP) binding. In the absence of ligand, the probability of a *trans*-autophosphorylation event occurring between randomly colliding receptors is low. Binding of ligand to the extracellular domain substantially increases local receptor (substrate/enzyme) concentration, providing sufficient opportunity for *trans*-autophosphorylation to occur. Autophosphorylation of the A-loop tyrosine(s) shifts the A-loop equilibrium toward the active conformation, which accommodates substrate binding and facilitates the proper positioning of residues involved in MgATP binding. Autophosphorylation occurs on additional tyrosines, which serve as binding sites for downstream signaling proteins.