

Ciclo di attivazione-inattivazione delle proteine G da parte dei recettori eptaelica



Receptor-mediated G protein activation. The interaction of an endogenous ligand with its cell surface receptor (R) facilitates the coupling of the activated receptor (R*) with intracellular heterotrimeric G proteins. The R*-G protein coupling promotes the exchange of GDP for GTP on the G α -subunit. G α -GTP then dissociates from G $\beta\gamma$ and R*. Both subunits are free to modulate the activity of a wide variety of intracellular effectors. Termination of the signal occurs when the γ -phosphate of GTP is removed by the intrinsic GTPase activity of the G α -subunit, leaving GDP in the nucleotide binding pocket on G α . G α -GDP then reassociates with G $\beta\gamma$ and the cycle is complete. RGS proteins accelerate the intrinsic GTPase activity of G α -subunits, thereby reducing the duration of signaling events.

Activated receptor: Guanine-nucleotide Exchange Factor (**GEF**)

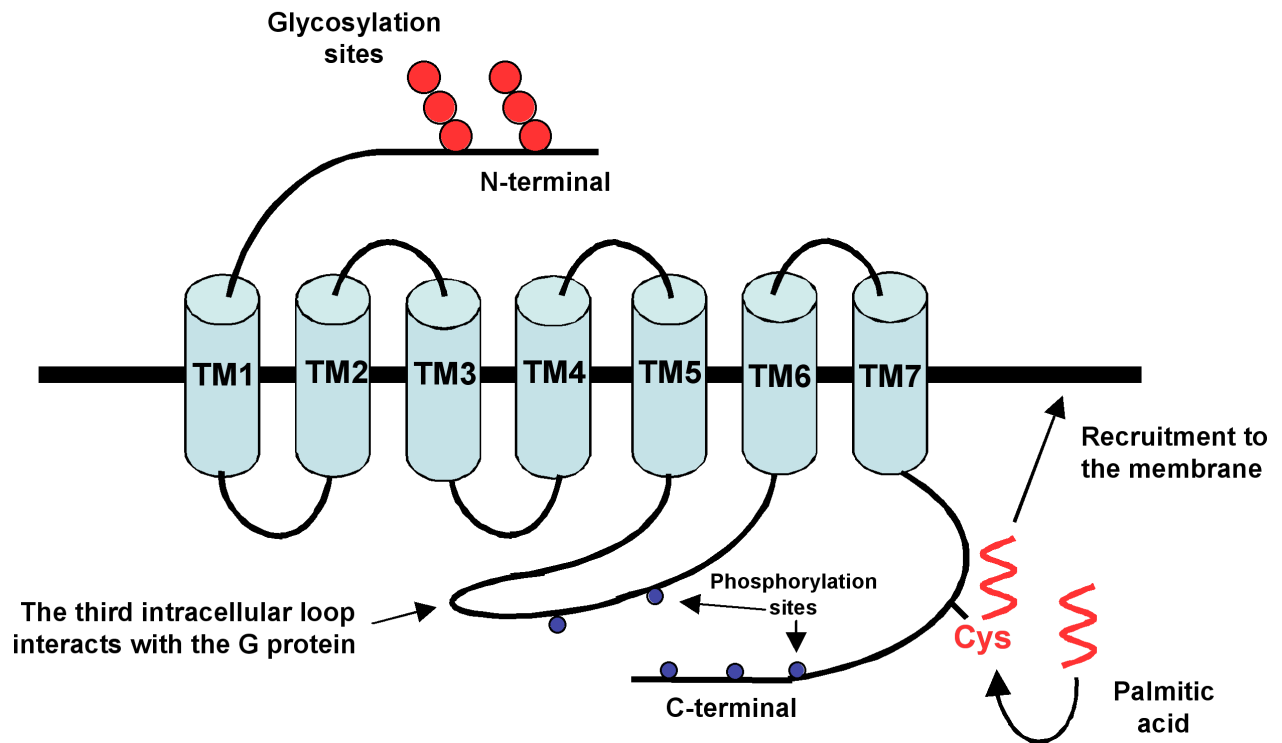
$\beta\gamma$ Subunit: Guanine-nucleotide Dissociation Inhibitor (**GDI**)

RGS (Regulators of G protein Signalling) : GTPase Activating Protein (**GAP**)

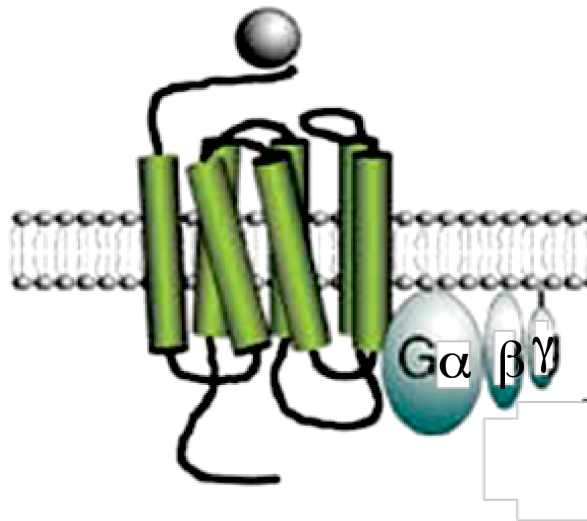
Relazione tra recettori eptaelica, proteine G ed effettori

Ligando	Recettore	Proteina G	Effettore
Catecolamine	Adrenergico α_1 Adrenergico α_2 Adrenergico α_1 Adrenergico α_2	G_q $G_{i/o}$ G_s G_s	Fosfolipasi C $\uparrow$ Adenilato ciclasi $\downarrow$ Adenilato ciclasi $\uparrow$ Canali del Ca^{2+} $\uparrow$ Adenilato ciclasi $\uparrow$
Acetilcolina	Muscarinici M_1, M_3, M_5 Muscarinici M_2, M_4	G_q $G_{i/o}$	Fosfolipasi C $\uparrow$ Adenilato ciclasi $\downarrow$ Canali del K^+ $\uparrow$
GABA	GABA _B	$G_{i/o}$	Adenilato ciclasi $\downarrow$
Glucagone		G_s	Adenilato ciclasi $\uparrow$
TSH		G_s G_q	Adenilato ciclasi $\uparrow$ Fosfolipasi C $\uparrow$
Vasopressina	V1 V2	G_q G_s	Fosfolipasi C $\uparrow$ Adenilato ciclasi $\uparrow$
Trombina		G_q $G_{i/o}$	Fosfolipasi C $\uparrow$ Adenilato ciclasi $\downarrow$
PGE2	EP1 EP2 EP3	G_q G_s $G_{i/o}$	Fosfolipasi C $\uparrow$ Adenilato ciclasi $\uparrow$ Adenilato ciclasi $\downarrow$
Retinale	Opsine	G_t	cGMP fosfodiesterasi $\uparrow$
LPA	LPA-1, -2, -3	$G_{i/o}$ G_q G_{12}, G_{13}	Adenilato ciclasi $\downarrow$ Fosfolipasi C $\uparrow$ Rho $\uparrow$

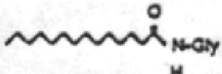
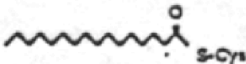
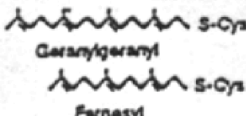
Visione planare della struttura dei recettori eptaelica



Visione tridimensionale dei recettori eptaelica e loro interazione con le proteine G



Major classes of lipidated proteins. The structure of the lipid and the attachment residue are shown, except for the complex GPI moiety. The subunit to which the lipid is attached is indicated in parentheses after the trimeric G protein.

Lipid	Structure	Representative proteins modified	Position of modification
N-Myristoyl		Trimeric G proteins (α) NRTKs	NH ₂ -terminus
S-Palmitoyl (S-acyl)		Trimeric G proteins (α) GPCRs Ras	Internal, no defined consensus
S-Prenyl		Trimeric G proteins (γ) Small G proteins Retinal GRK	COOH-terminus
GPI	Complex structure containing ethanolamine, sugars, and phosphatidylinositol	Many cell-surface proteins	COOH-terminus

Modalità di attivazione dei diversi tipi di recettori eptaelica

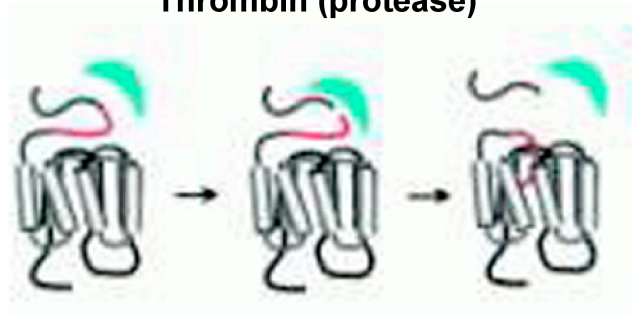
**Amines,
nucleotides,
eicosanoids,
lipids**



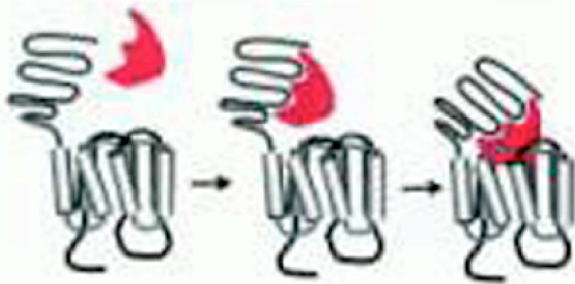
Peptide hormones



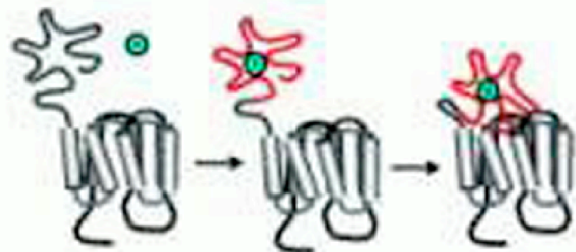
Thrombin (protease)



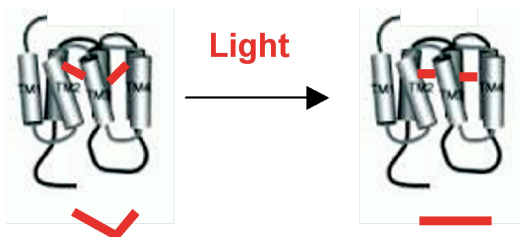
Glycoprotein hormones
(e.g. LH, FSH,TSH)



Neurotransmitters
(e.g. glutamate, GABA)

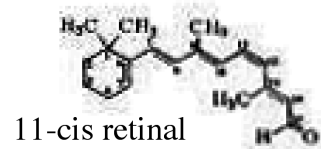


Light Receptor (opsin)

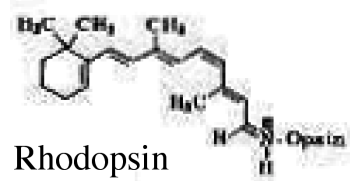


11-cis retinal

All-trans retinal

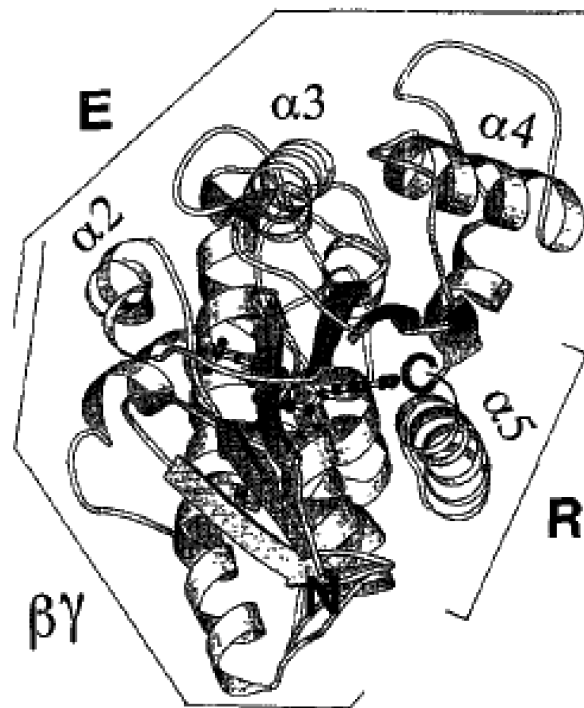
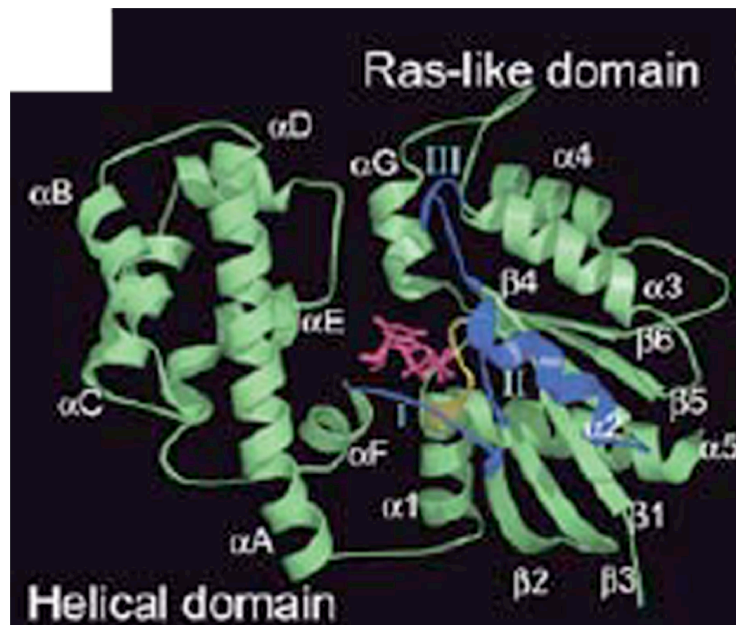


11-cis retinal



Rhodopsin

Struttura della subunità α



Structure of the α Subunit of Transducin

The first 25 residues at the N-terminus (N) and the last 6 residues at the C-terminus (C) are not shown. The faces of the molecule that interact with receptors (R), effectors (E), and $\beta\gamma$ subunits and the α helices are indicated.

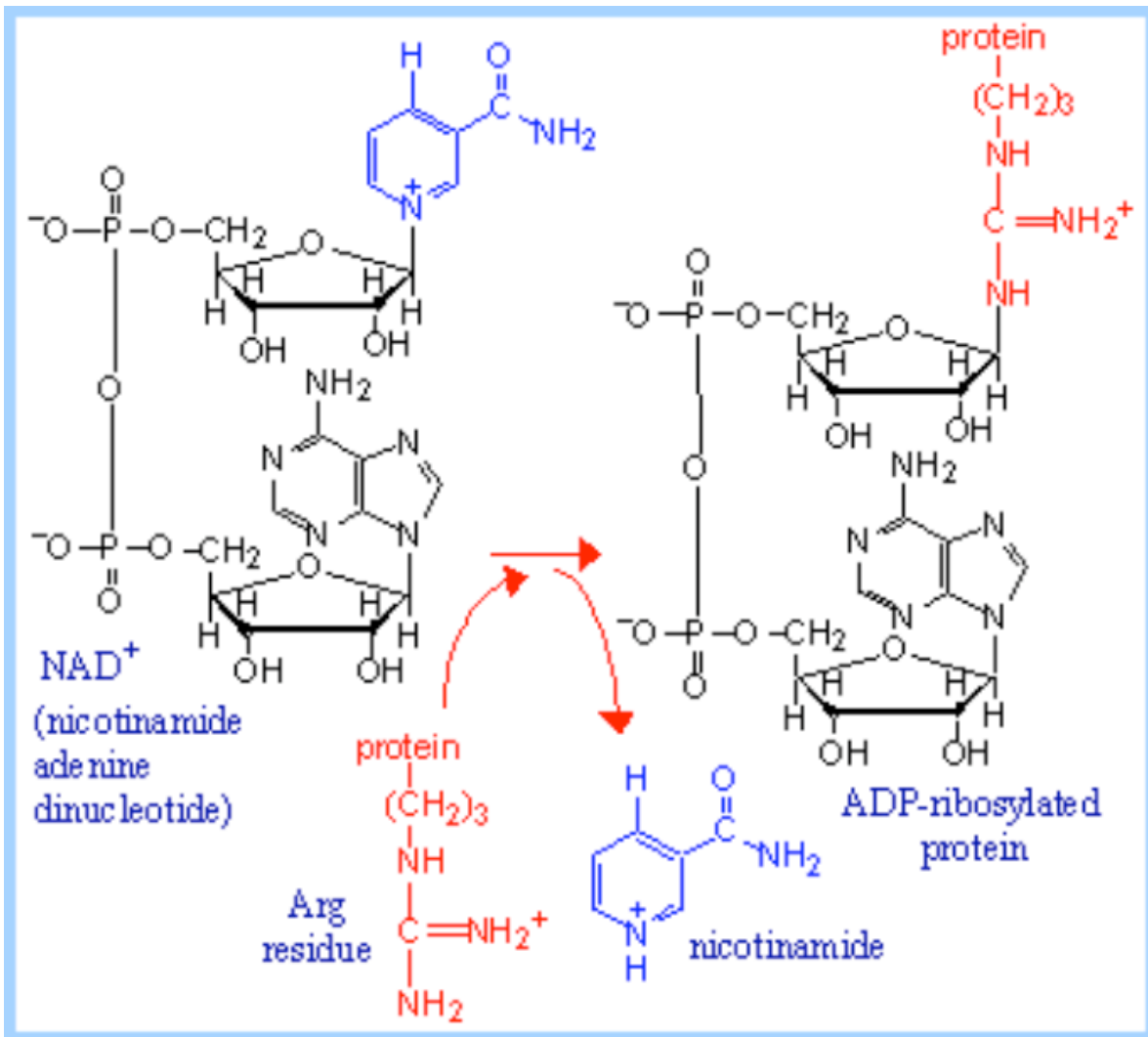
SUBUNITA' ALFA

Nel genoma umano, 16 geni codificano per 23 proteine $G\alpha$, suddivise in base all'omologia di sequenza in $G\alpha_s$, $G\alpha_{i/o}$, $G\alpha_q$ and $G\alpha_{12/13}$. Le subunità $G\alpha$ hanno un peso molecolare di 39 - 45 kDa e sono modificate post-traduzionalmente per esterificazione con acido miristico all' N-terminale (irreversibilmente) e/o con acido palmitico a livello di una cisteina prossima all' N-terminale (reversibilmente). La palmitoilazione è sufficiente per lo stabile inserimento delle proteine in membrana, mentre la sola miristoilazione determina la localizzazione di una frazione sostanziale delle proteine nel citosol.

Le subunità $G\alpha_s$ sono sensibili alla tossina colerica, che ne inibisce l'attività GTPasica.

Le subunità $G\alpha_{i/o}$ sono sensibili alla tossina della pertosse, che ne inibisce l'accoppiamento con il recettore.

Subunit' alfa e tossine batteriche



Cholera toxin catalyzes covalent modification of **G_s**. ADP-ribose is transferred from **NAD⁺** to an arginine residue at the GTPase active site of **G_s**. ADP-ribosylation **prevents GTP hydrolysis** by **G_s**. The **stimulatory** G-protein is **permanently activated**.

Pertussis toxin (whooping cough disease) catalyzes ADP-ribosylation at a cysteine residue of **G_i**, making the inhibitory **G_i incapable of exchanging GDP for GTP**. The **inhibitory** pathway is **blocked**.

Struttura del dimero $\beta\gamma$

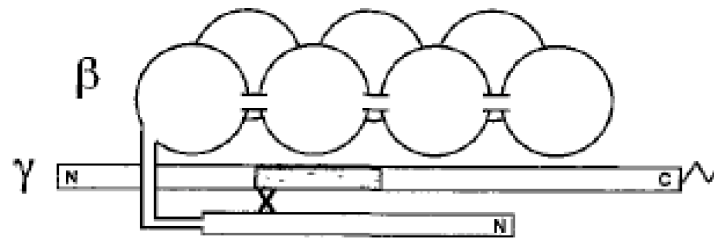
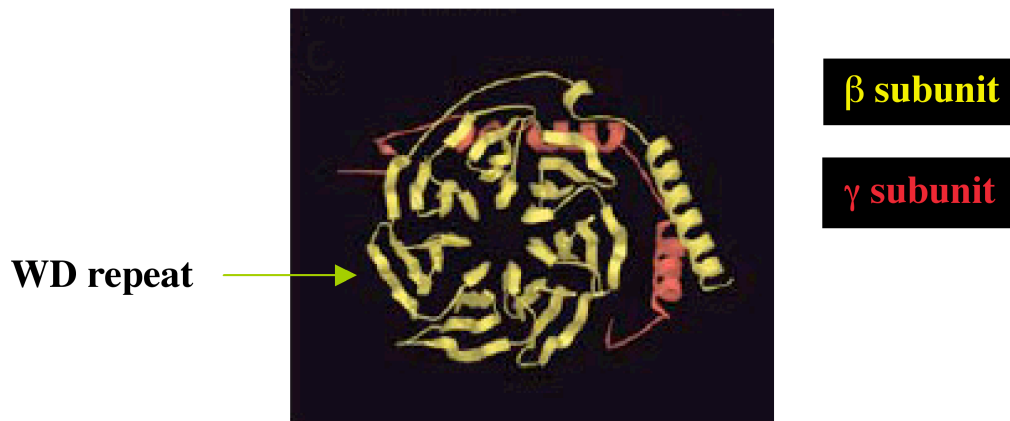


Figure 4. Model of the $\beta\gamma$ Subunit

The cores of the WD repeats are represented by circles connected by the variable regions. Each core is predicted to be a structure made up of a β strand–turn– β strand–turn– β strand. The putative α -helical region in the N-terminus of β is shown as a rectangle. The area of γ that determines the specificity of interaction with β_1 or β_2 is stippled (Spring and Neer, 1994). The X represents the site of the cross-link introduced by Bubis and Khorana (1990). The C-terminal prenyl group is indicated by a zigzag line.



The WD repeat, diagrammed below, consists of a conserved *core* of 23-41 residues usually bounded by Gly-His and Trp-Asp. The conserved cores are separated by variable regions that are rather short in the β subunits (7-11 aminoacids) and probably form loops.

X 6-94 [GH---- X 23-41 --WD]

Variable
length loop

Constant
length core

SUBUNITA' BETA E GAMMA

Nel genoma umano sono presenti 5 geni $G\beta$ e 12 geni $G\gamma$ che codificano per altrettante proteine. Tutte le subunità $G\gamma$ sono modificate post-traduzionalmente; al C-terminale delle subunità $G\gamma 1$, $G\gamma 8$ e $G\gamma 11$ viene introdotto un gruppo farnesilico e al C-terminale delle restanti uno geranil-geranilico. I suddetti gruppi lipidici consentono lo stabile inserimento delle proteine in membrana. La maggior parte delle possibili combinazioni $G\beta / G\gamma$ dà luogo a dimeri funzionali. C'è tuttavia qualche eccezione: per esempio, $G\beta 2$ non può appaiarsi con $G\gamma 1$.