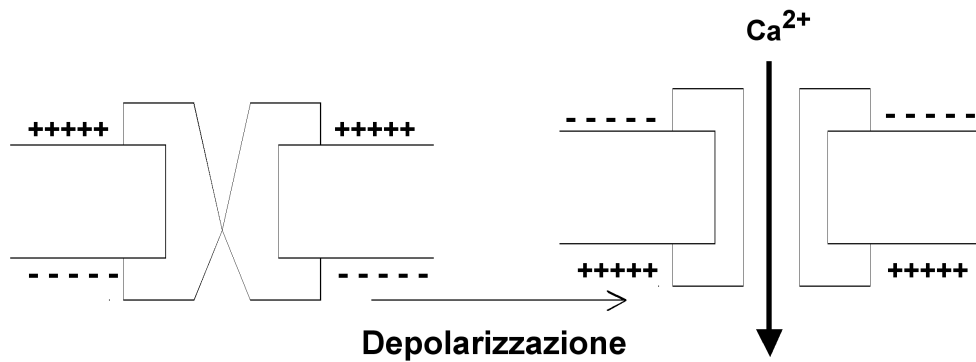
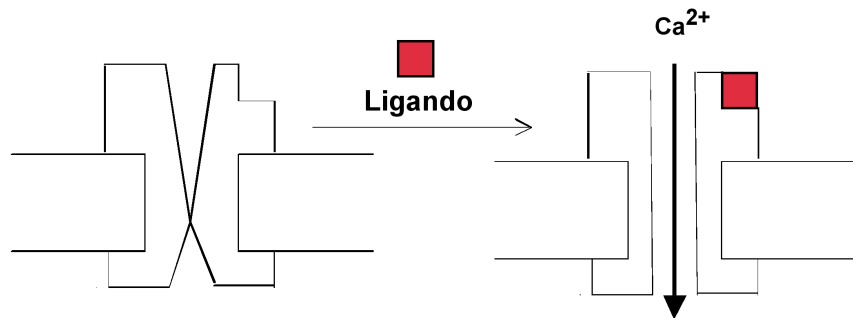


Canali del calcio presenti sulla membrana plasmatica

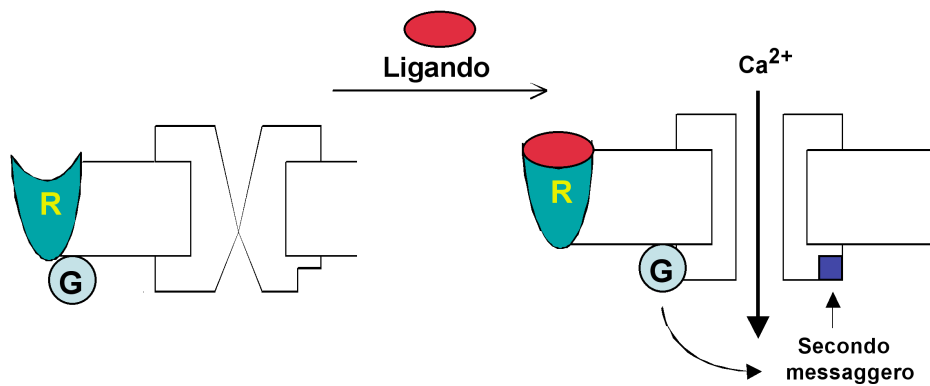
VOCC (Voltage-Operated Calcium Channel)



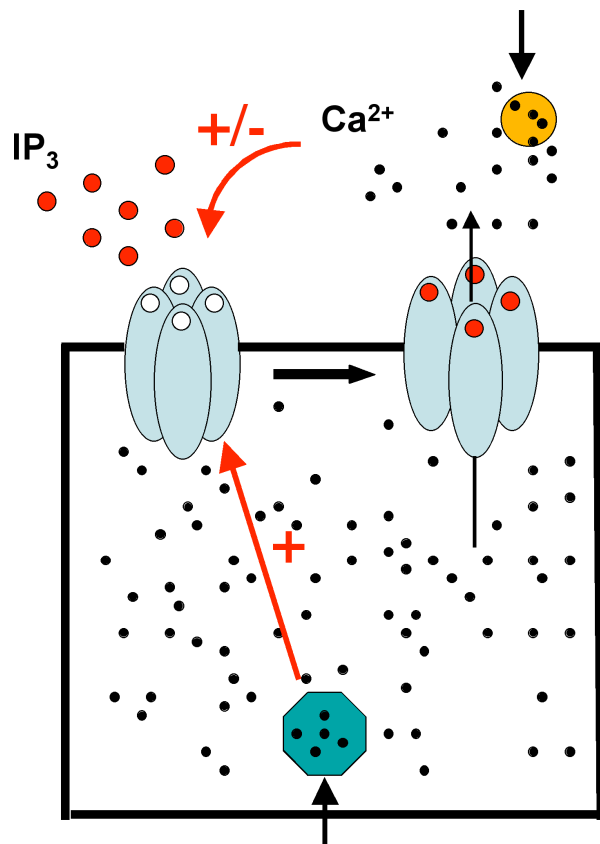
ROCC (Receptor-Operated Calcium Channel)



SMOOC (Second Messenger-Operated Calcium Channel)

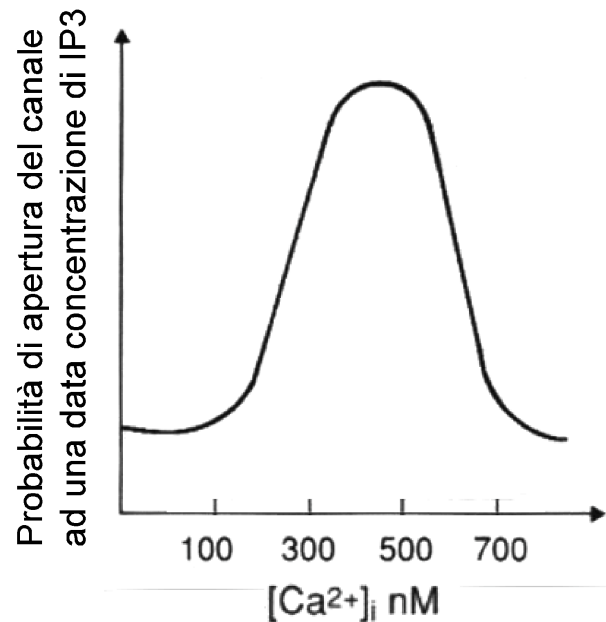


Cytosolic buffers
(calbindin, calretinin, parvalbumin)



ER buffers and chaperones
(calnexin, calreticulin, calsequestrin)

IP₃ receptor



The InsP₃ receptor is a homotetramer of about 310 kDa subunits surrounding a cationic pore. Each subunit binds one InsP₃ molecule, in a positively charged Arg/Lys-rich N-terminal region. Multiple isoforms are encoded by three genes, all of which share significant similarity to each other and partial homology with the three RyR (Ryanodin Receptor) genes. The cytoplasmic N-terminal region also has two ATP-binding sites and at least one Ca²⁺-binding site.

Modulation:

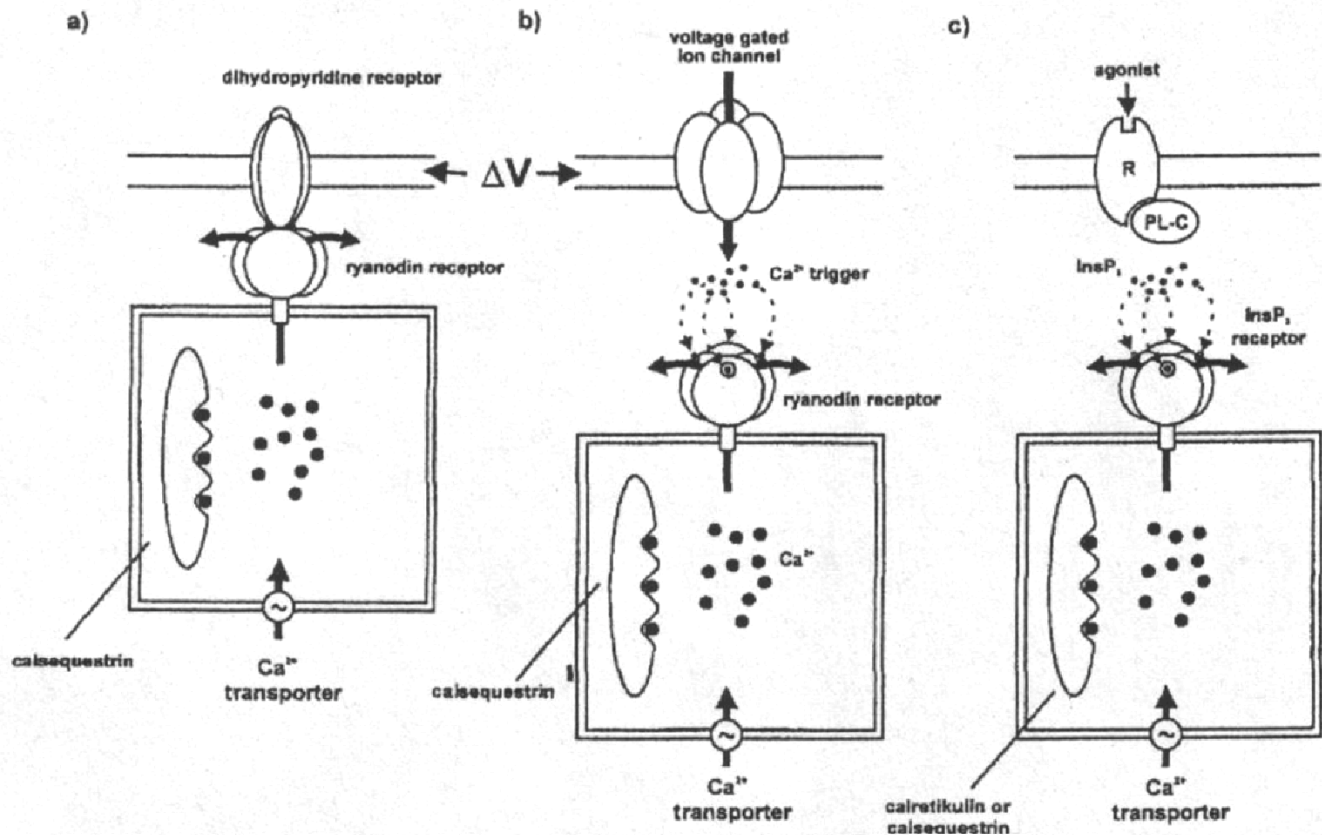
1) Ca²⁺ maximally enhances InsP₃-induced Ca²⁺ flux at concentrations around 500 nM; at low and high Ca²⁺ levels, the receptor is relatively insensitive to InsP₃.

2) Sensitivity to InsP₃ may also be conferred by interaction with ER luminal Ca²⁺-binding proteins (calreticulin and calnexin).

3) ATP stimulates InsP₃ receptor function, independently of phosphorylation or energy dependent processes. Maximal effect occurs at about 100 μM ATP.

4) The InsP₃ receptor can also be modulated through phosphorylation by Ca²⁺/CaM-dependent kinase II (CaMKII), cGMP-dependent protein kinase (PKG), protein kinase C (PKC) and cAMP-dependent protein kinase (PKA).

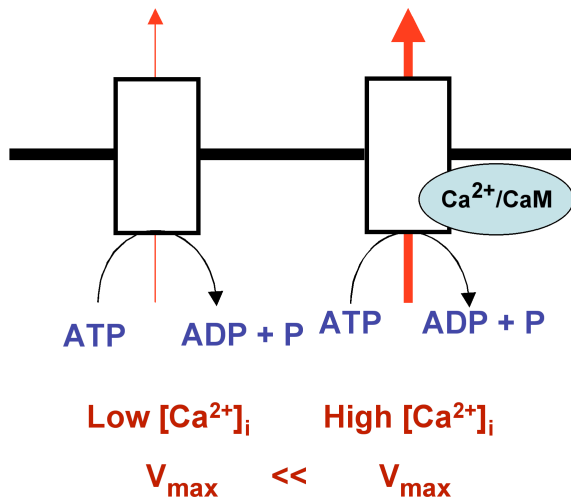
Ryanodine receptors



Tetrameric Ca^{2+} channels and control of Ca^{2+} release. a) A change in the membrane potential (ΔV) induces a conformational change in the dihydropyridine receptor of skeletal muscle; this is transmitted as a signal to the structurally coupled ryanodine receptor. Opening of the Ca^{2+} channel takes place and efflux of Ca^{2+} from the sarcoplasmic reticulum into the cytosol occurs. b) In cardiac muscle, the release of Ca^{2+} takes place by a Ca^{2+} -induced mechanism. A potential change ΔV induces opening of voltage-gated Ca^{2+} channels. Ca^{2+} passes through, which serves as the trigger for release of Ca^{2+} from Ca^{2+} storage organelles by binding to ryanodine receptors on the surface of the storage organelles. c) Membrane-associated signaling pathways are activated by ligands and lead, via activated receptor and phospholipase C (PL-C) to formation of InsP_3 and to release of Ca^{2+} from storage organelles.

Omeostasi del Ca^{2+} intracellulare

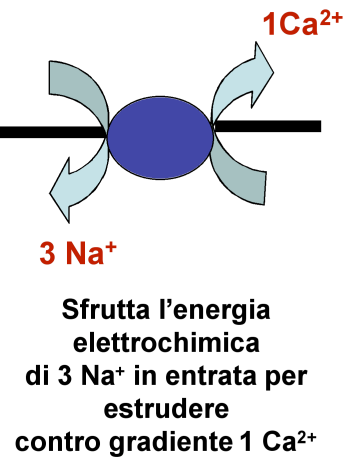
Plasmamembrane Ca^{2+} - ATPase (**PMCA**)



1 Ca^{2+} estruso per molecola di ATP idrolizzata

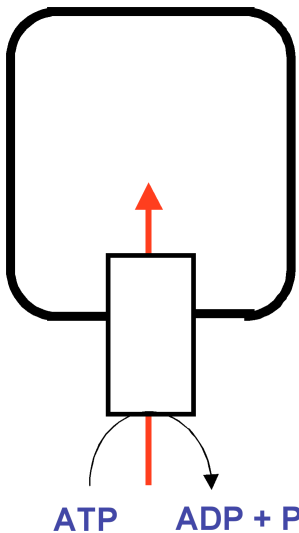
$$K_m (\text{Ca}^{2+}) = 150\text{-}200\text{nM}$$

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



Elevata capacità di trasporto ma bassa affinità per il Ca^{2+}
 $K_m > 1 \mu\text{M}$

Smooth endoplasmic reticulum Ca^{2+} - ATPase (**SERCA**)

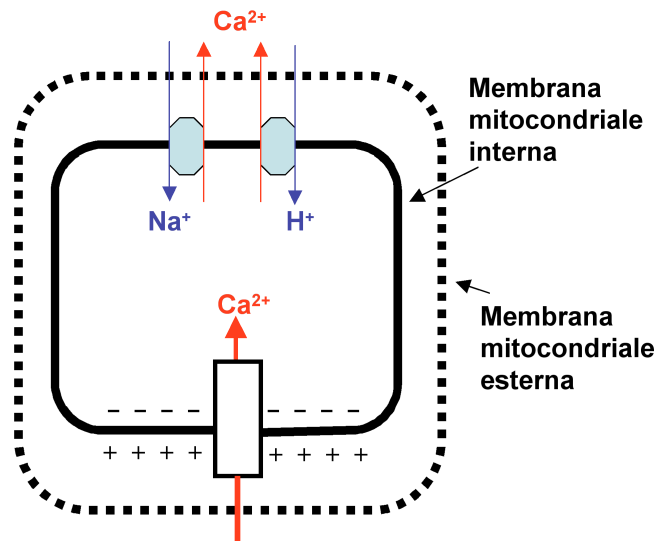


2 Ca^{2+} traslocati dal citosol al lume del reticolo endoplasmatico per molecola di ATP idrolizzata

$$K_m (\text{Ca}^{2+}) = 100\text{-}200\text{nM}$$

Non lega Ca^{2+} /CaM

Scambiatori $\text{Na}^+/\text{Ca}^{2+}$ e $\text{H}^+/\text{Ca}^{2+}$ mitocondriali



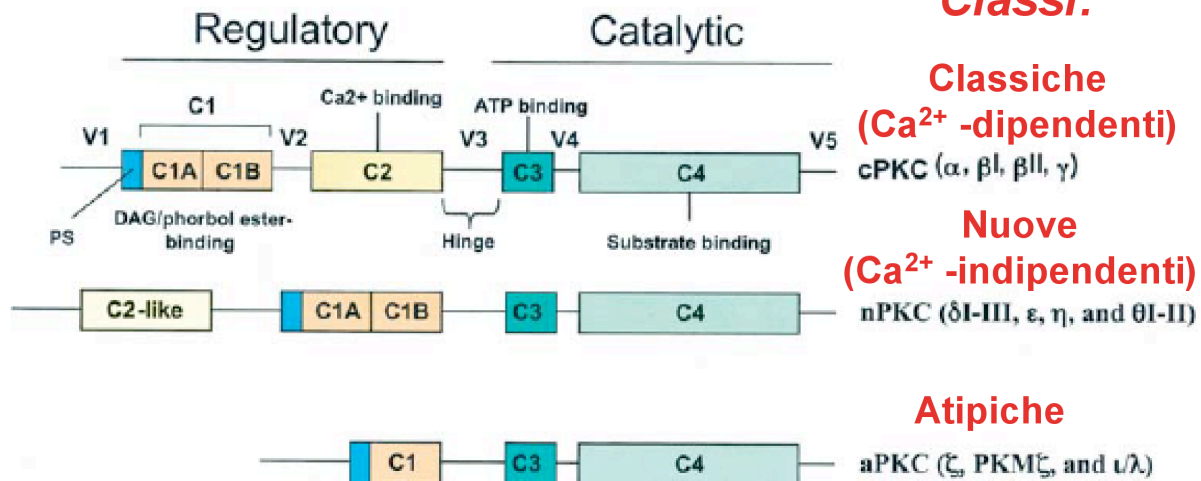
Trasportatore di Ca^{2+} mitocondriale

Trasporta il Ca^{2+} dal citosol all'interno del mitocondrio sfruttando il gradiente di potenziale elettrico a cavallo della membrana mitocondriale interna.

$$K_m (\text{Ca}^{2+}) > 5 \mu\text{M}$$

PROTEIN CHINASI C (PKC)

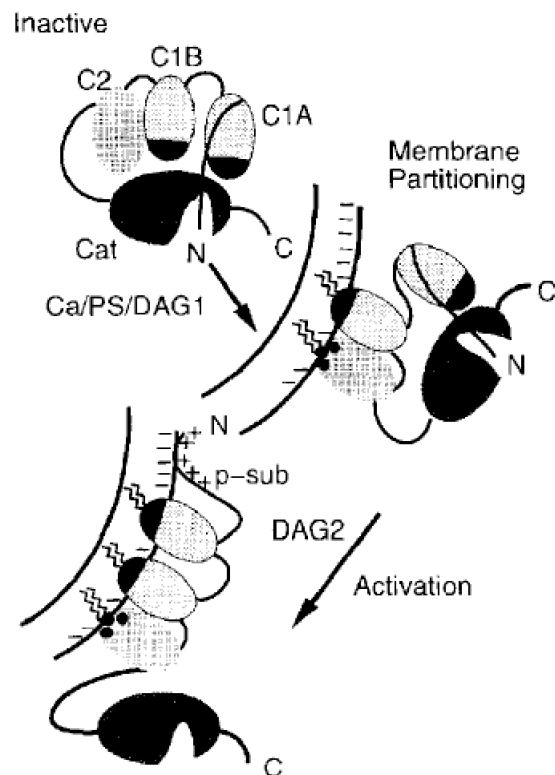
Struttura



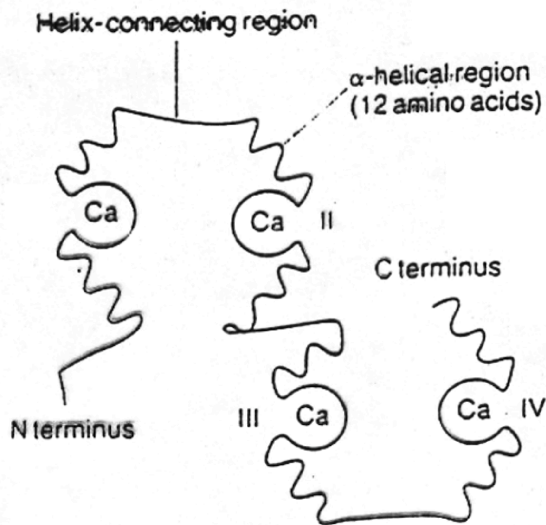
Ipotetico meccanismo di attivazione delle protein chinasi C classiche

Small black circles represent Ca²⁺ ions;
 zigzag lines represent lipids that are stereospecifically bound;
 '+' and '-' signs represent the potential for nonstereospecific electrostatic interactions.

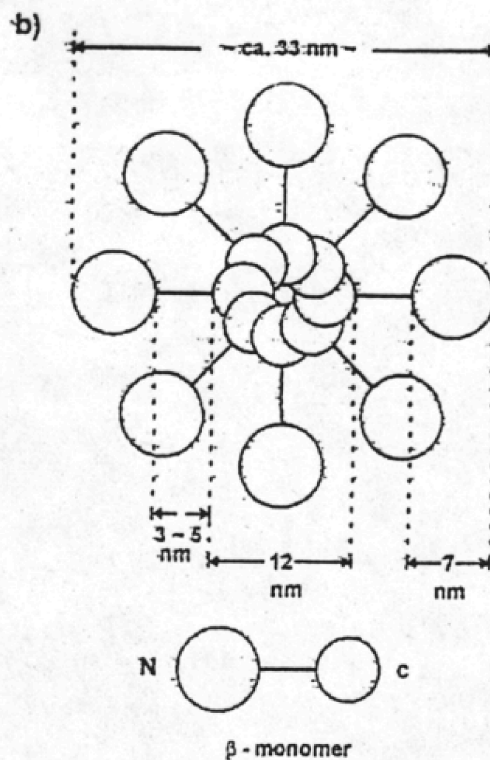
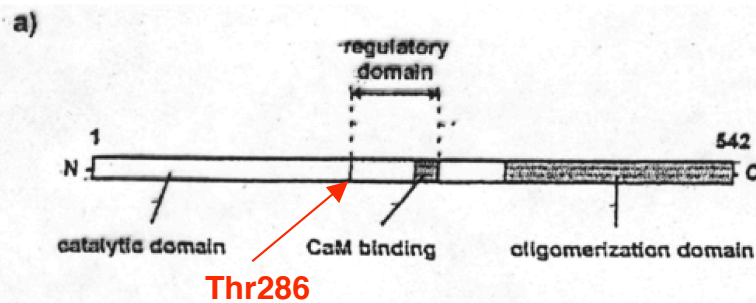
The hypothetical roles of the C1A domain in (a) and the C2 domain in (b) are inferred from structural considerations and are untested functionally.
 DAG1, first diacylglycerol;
 DAG2, second diacylglycerol;
 PS, phosphatidylserine;
 p-sub, pseudosubstrate.



Protein chinasi Ca^{2+} /calmodulina-dipendente di tipo II (CaM kinase II)



The four helix-loop-helix motifs which bind Ca^{2+} in the calmodulin polypeptide chain.



Primary structure and oligomeric structure of CaM kinase II of type β. a) Linear representation of the functional domain of CaM kinase IIβ. b) The oligomeric structure shown is proposed for an octamer of type β, based on electron-microscopic investigations (Kanascki et al., 1991). The N-terminal catalytic domain is represented as a larger circle, the C-terminal oligomerization domain by a smaller circle. CaM: calmodulin.

Regolazione della CaM kinase II

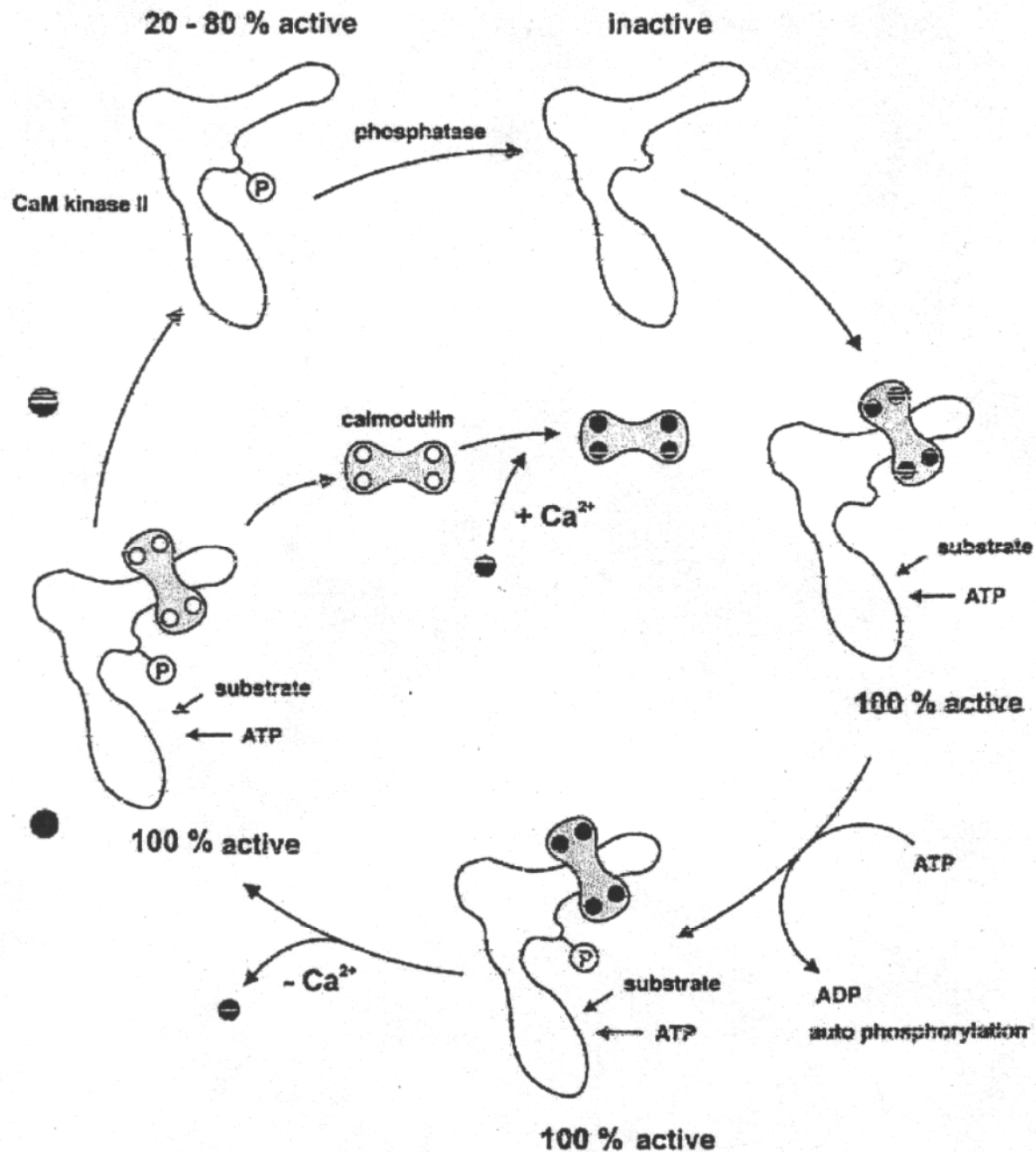
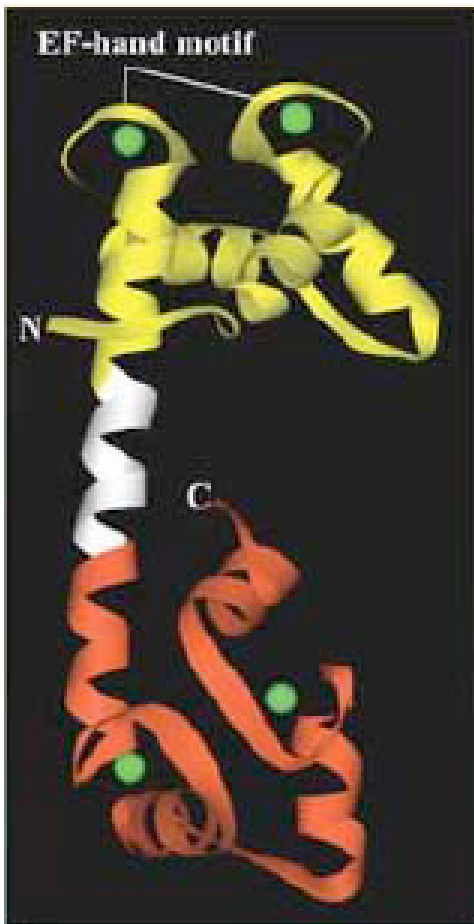
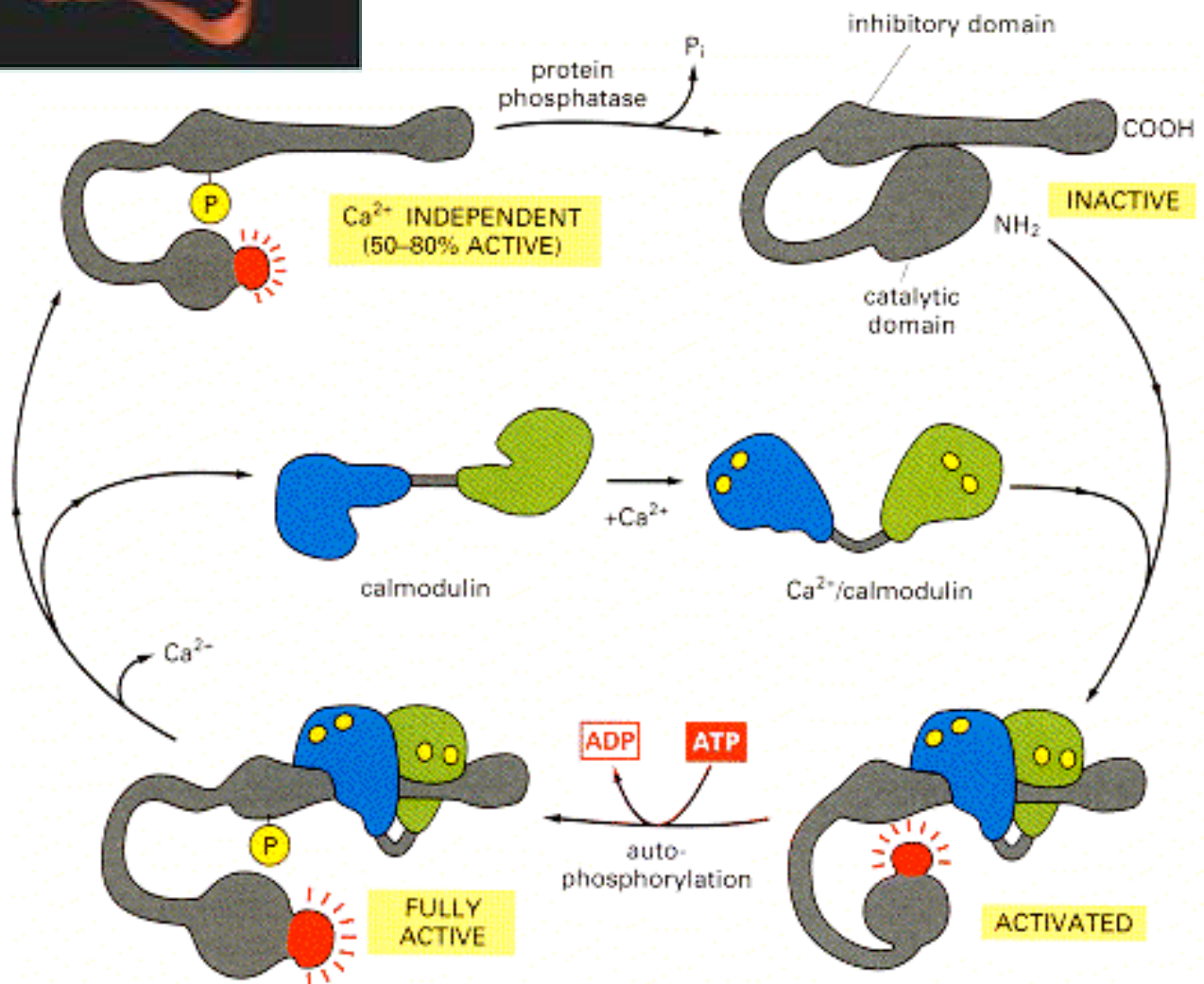
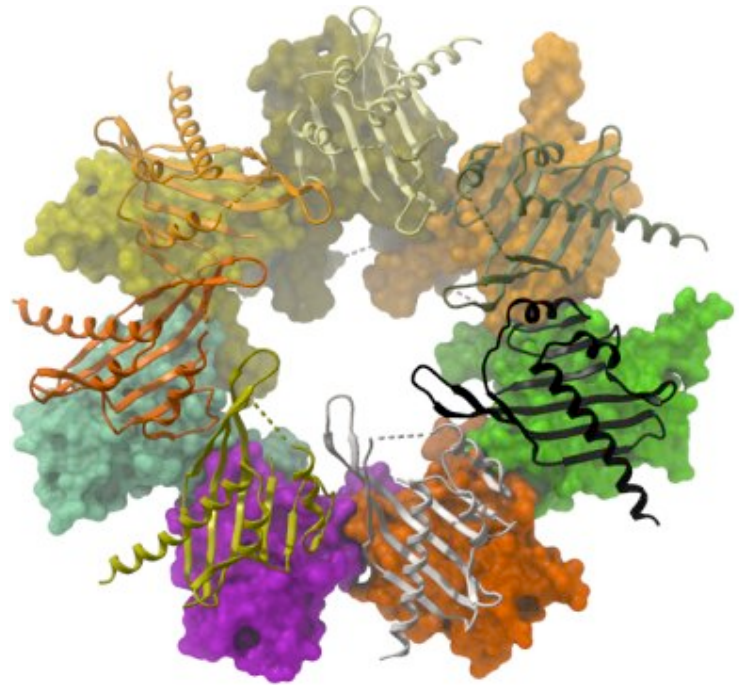


Fig. 7.14. Regulation of CaM kinase II. Scheme of regulation of CaM kinase II by Ca^{2+} /calmodulin and by autophosphorylation. CaM kinase II is inactive in the unphosphorylated form and in the absence of Ca^{2+} /calmodulin. Binding of Ca^{2+} /calmodulin activates the kinase for phosphorylation of protein substrates. In the process, autophosphorylation takes place at a conserved Thr residue that stabilizes the active state of the enzyme. In this state, significant residual activity is still present after dissociation of Ca^{2+} /calmodulin and the enzyme remains in an active state for a longer time after the Ca^{2+} signal has died away. The active state is only terminated when the activating phosphate residue is cleaved off by a protein phosphatase.



CamKII: subunità ed oligomero



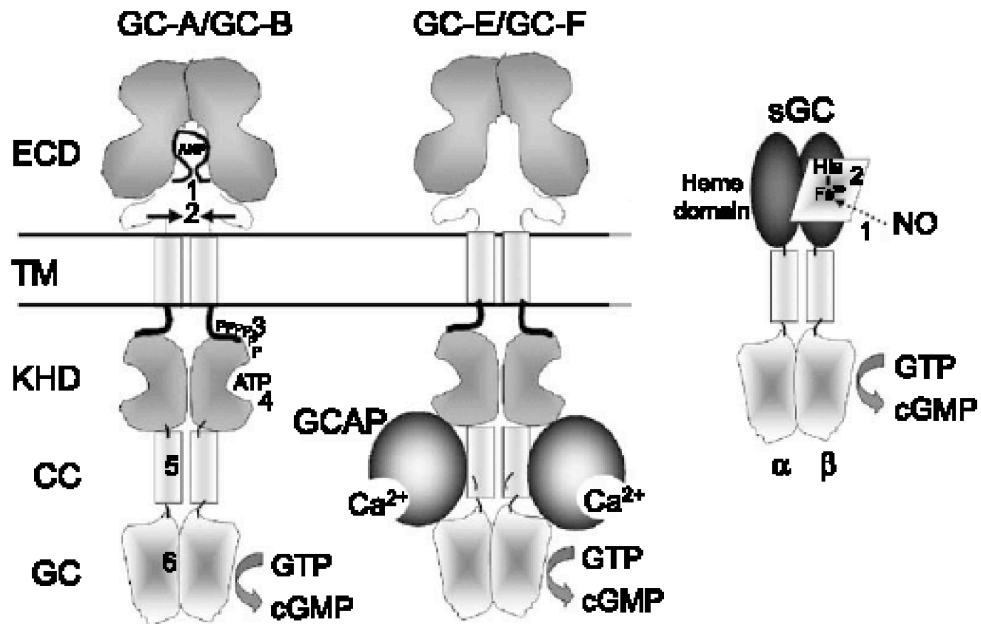
Guanilato ciclasti

GC di membrana/ Ligando

GC-A / ANP, BNP
 GC-B / CNP (C-type NP)
 GC-C / Enterotossina (STa)
 GC-D ?
 GC-E / GCAP
 GC-F/ GCAF
 GC-G ?

GC solubili

Eterodimeri costituiti da una subunità α ed una β . Ciascuna subunità comprende due isoforme (α_1 ed α_2 e β_1 e β_2).

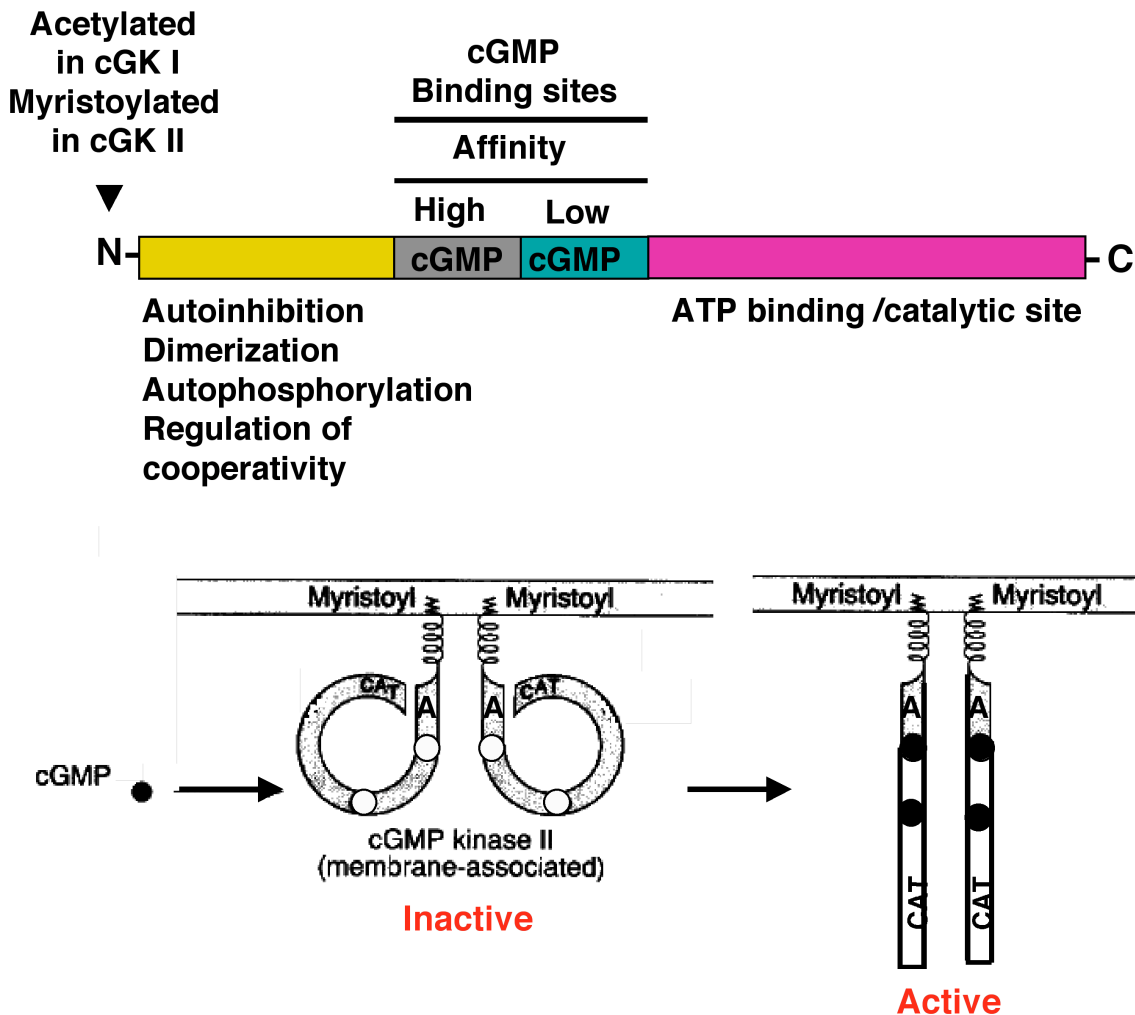


Domain structure of mammalian guanylyl cyclases (GC)

The membrane bound GC architecture is as follows: extracellular domain (ECD), transmembrane helix (TM), kinase homology domain (KHD), coiled-coil region (CC), and GC domain. For clarity, the guanylyl cyclase activating protein (GCAP) is shown with only one of its three calcium-binding sites. The sites of the postulated conformational changes during GC receptor activation for both the natriuretic peptide receptor and soluble GC are numbered. For GC-A/GC-B, these conformational changes include hormone binding (1), juxtapositioning of the extracellular domain (ECD) C termini (2), phosphorylation (3), ATP binding (4), coiled-coil adjustments (5), and conformational changes in the GC domain (6). The precise order of these conformational changes is not known. Furthermore, the activation mechanism likely involves multiple conformational changes at some of these sites to account for outside-in and inside-out signaling as part of the receptor's ability to alter its hormone affinity state upon activation.

The heterodimeric soluble guanylyl cyclase (sGC) contains a heme moiety within the N-terminal domain of the β_1 subunit. This latter domain contains the two known steps in the activation process of sGC: NO binding (1), and breakage of the Fe^{2+} -His105 bond (2).

Cyclic-GMP-dependent protein kinases (cGK)



Mammals have two cGK genes, *prkg1* and *prkg2*, that encode cGKI and cGKII. The N-terminus (90–100 residues) of cGKI is encoded by two alternatively spliced exons that produce the isoforms cGKI α and cGKI β . The enzymes are composed of three functional domains: an N-terminal domain, a regulatory domain, and a catalytic domain. The regulatory domain contains two tandem cGMP-binding sites that interact allosterically and bind cGMP with high and low affinity. Binding of cGMP to both sites releases the inhibition of the catalytic center by the N-terminal autoinhibitory/pseudosubstrate site and allows the phosphorylation of serine/threonine residues in target proteins and in the N-terminal autophosphorylation site. Activation of heterophosphorylation may be preceded by autophosphorylation. Autophosphorylation increases the spontaneous activity of cGKI and cGKII and is initiated by the binding of low cGMP concentrations to the high affinity site of cGKI. In addition to controlling activation and inhibition of the catalytic center, the N terminus has two other functions: dimerization, cGKs are homodimers that are held together by a leucine zipper present in the N terminus, and targeting, the enzymes are targeted to different subcellular localizations by their N termini.