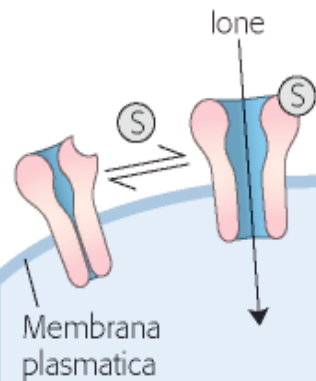


RECETTORI COINVOLTI NELLA TRASDUZIONE DEL SEGNALE

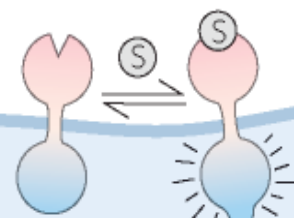
Canale ionico controllato

Si apre o si chiude in risposta alla concentrazione di un segnale ligando (S) o di un potenziale di membrana



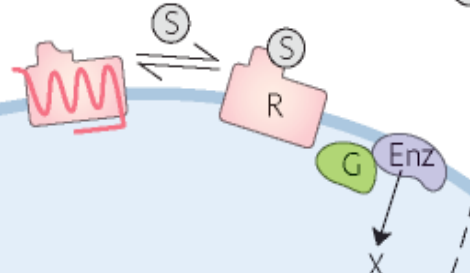
Recettore enzimatico

Il ligando che si lega al dominio extracellulare stimola un'attività enzimatica nel dominio intracellulare



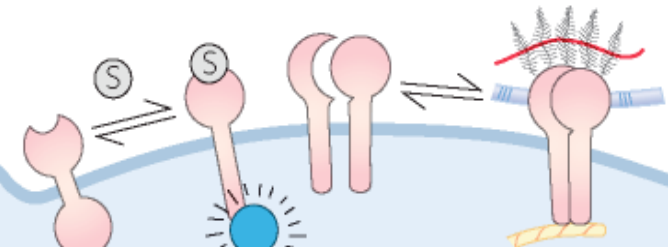
Recettore a serpentina

Un ligando esterno che si lega al recettore (R) attiva una proteina legante il GTP (G) intracellulare che regola un enzima (Enz) che genera un secondo messaggero intracellulare, X



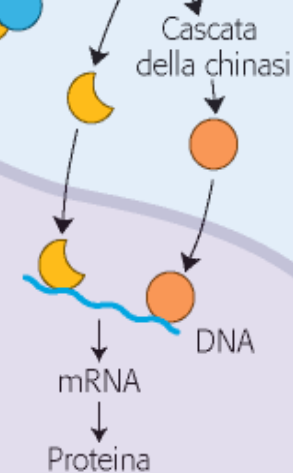
Recettore senza attività enzimatica intrinseca

Interagisce con la proteina chinasi citosolica che attiva una proteina regolatrice di geni (direttamente o attraverso una cascata di proteine chinasi), modificando l'espressione genica



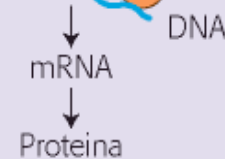
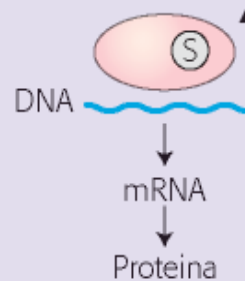
Recettore di adesione

Il ligando che si lega al dominio extracellulare, cambia la conformazione, alterando così la sua interazione col citoscheletro



Recettore degli steroidi

Lo steroide, legandosi ad un recettore proteico nucleare, permette al recettore di regolare l'espressione di specifici geni



SISTEMA RECETTORIALE BETA ADRENERGICO

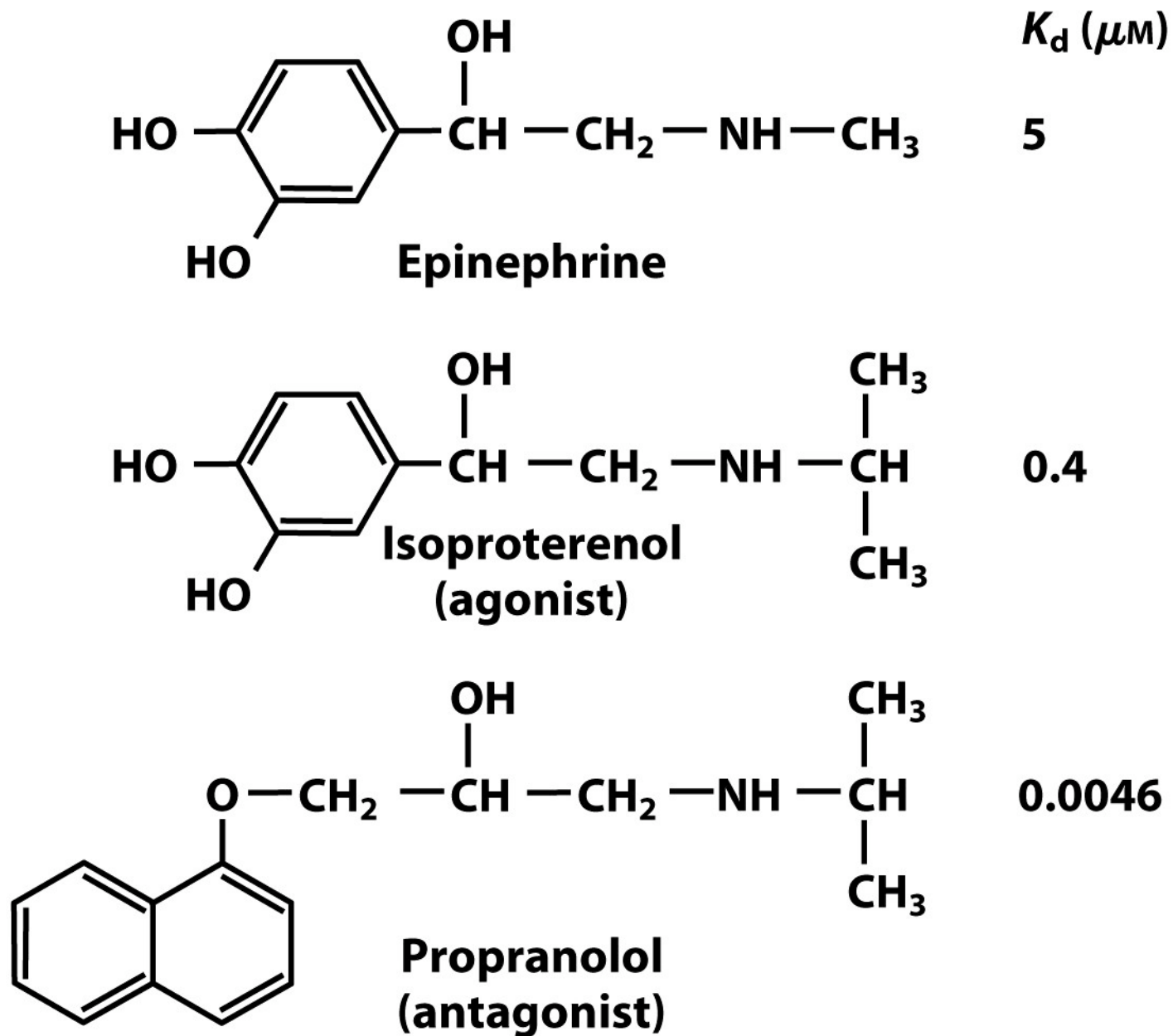


Figure 12-3

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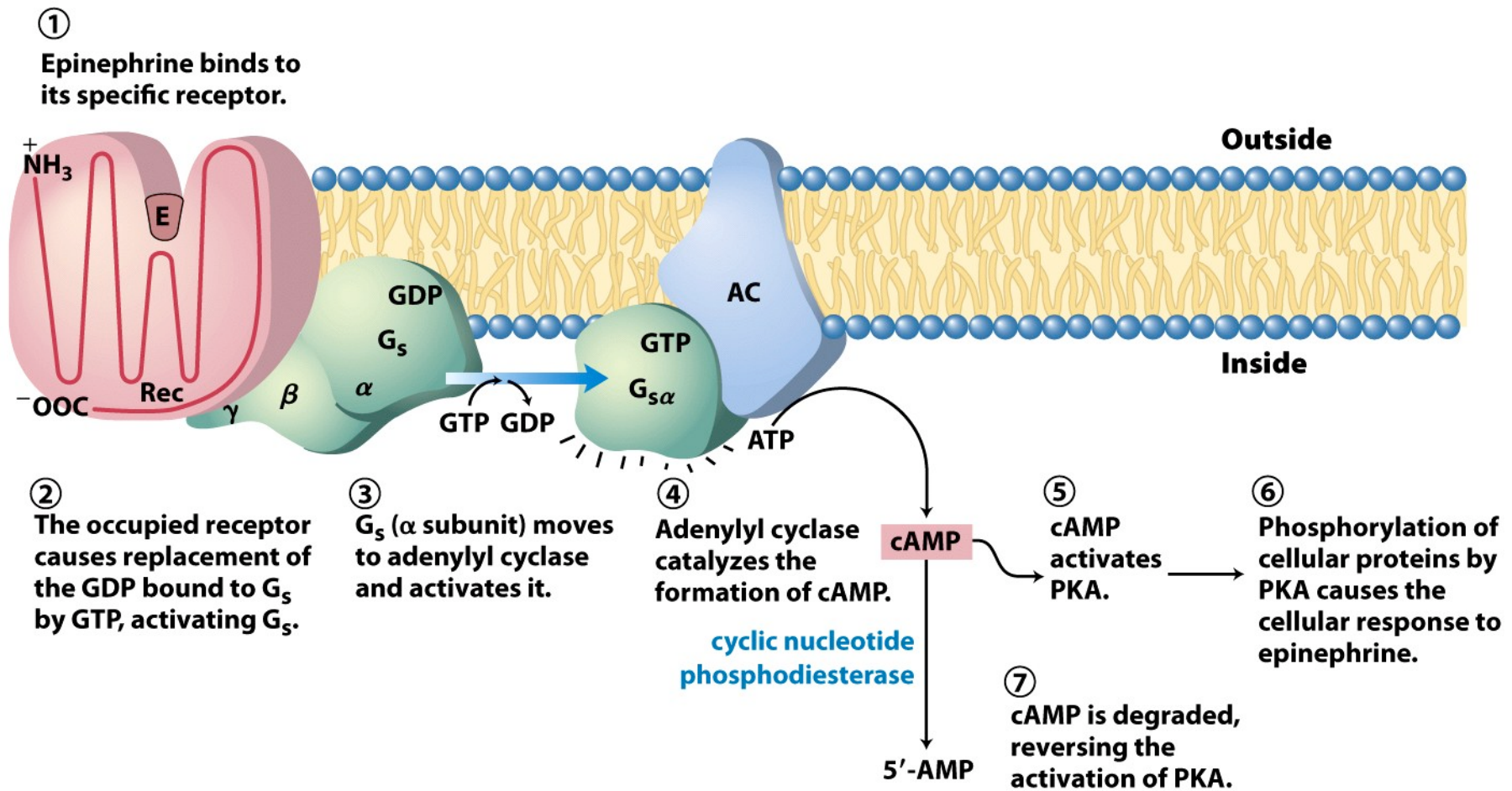


Figure 12-4a
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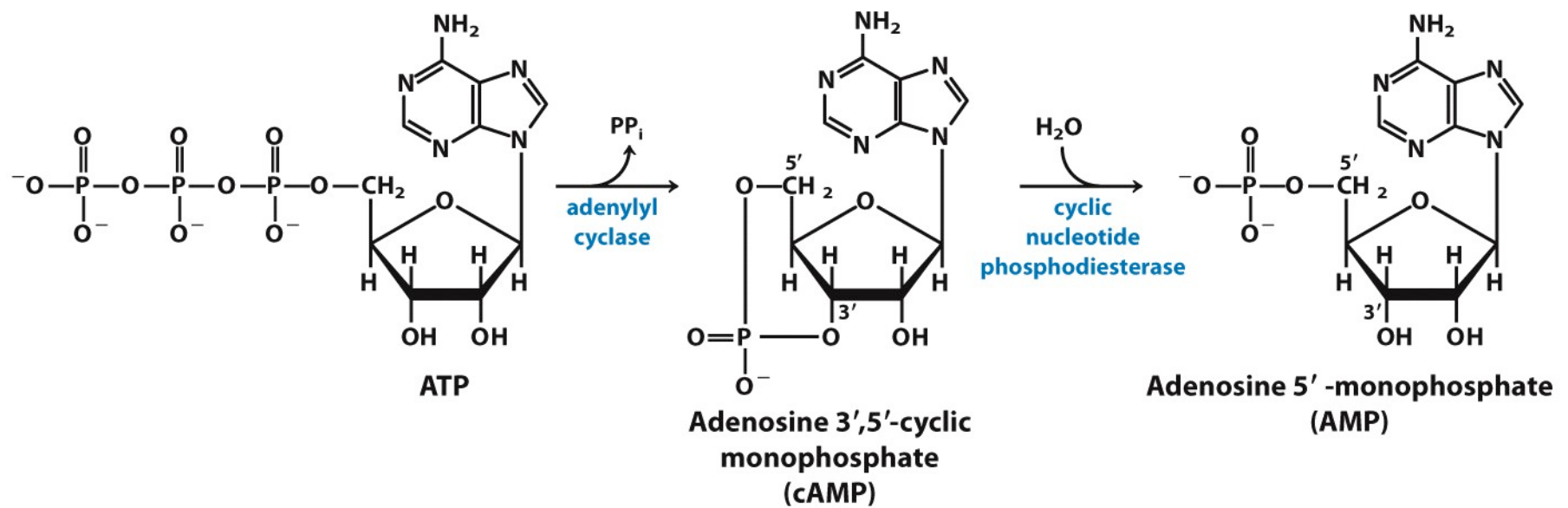


Figure 12-4b

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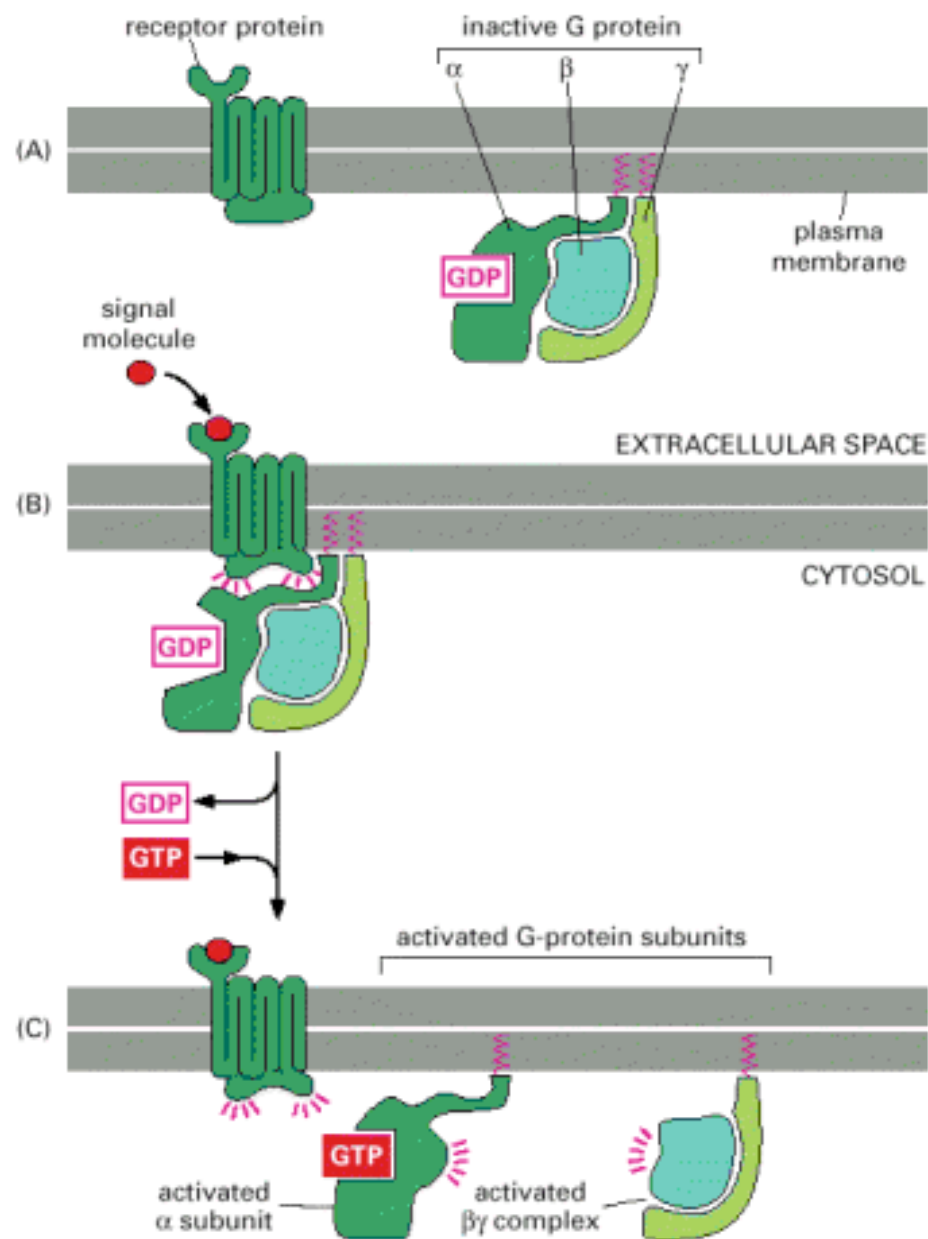
Recettori Accoppiati a Proteine G (GPCR)

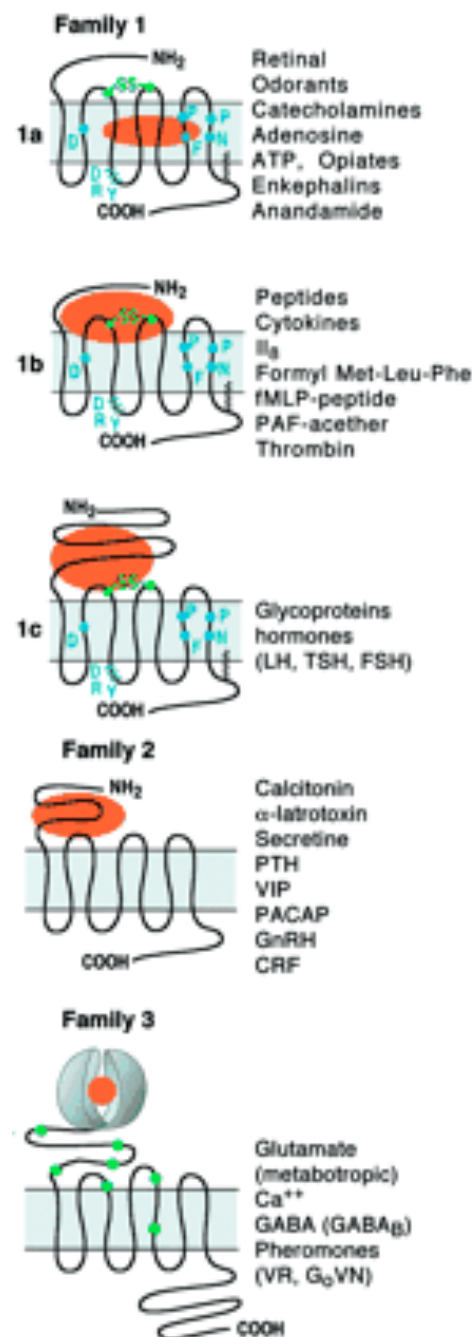
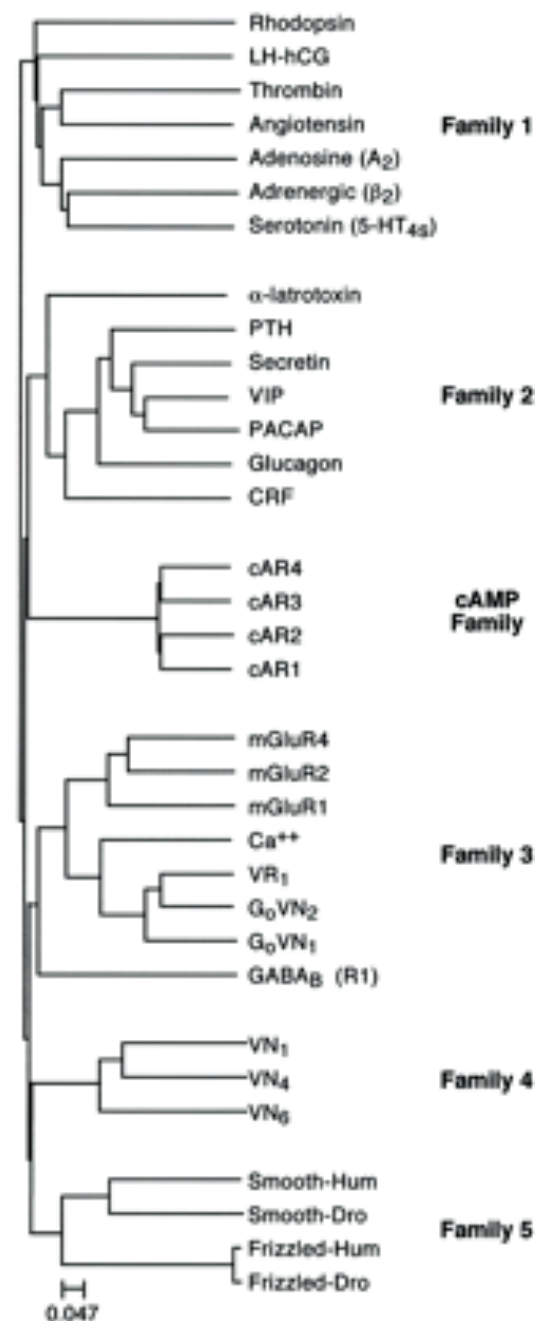
ADRENALINA
 DOPAMINA
 SEROTONINA
 ANGIOTENSINA
 ORMONI GLICOPROTEICI (FSH,LH, TSH)
 SOMATOSTATINA
 VASOPRESSINA
 CALCITONINA
 GLUCAGONE
 TROMBINA
 FOTONI (rodopsina)
 Etc...

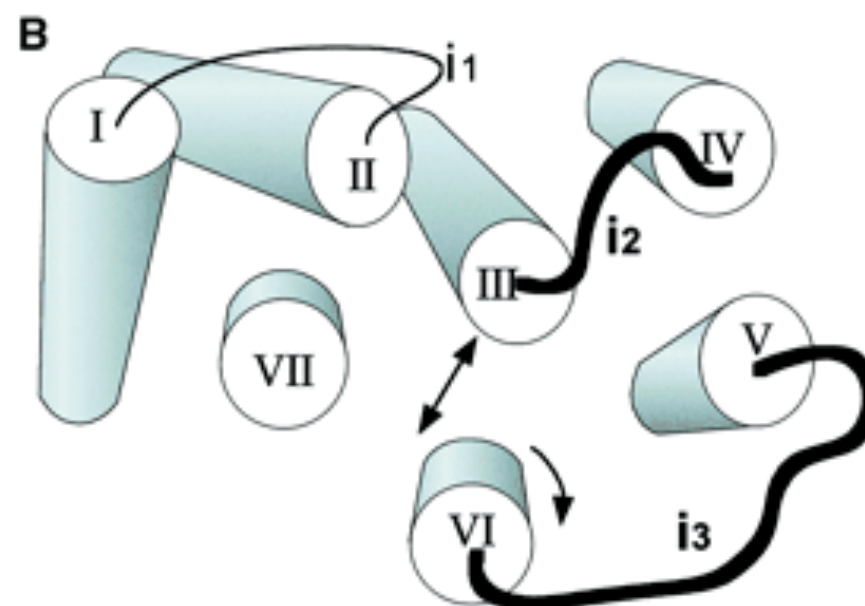
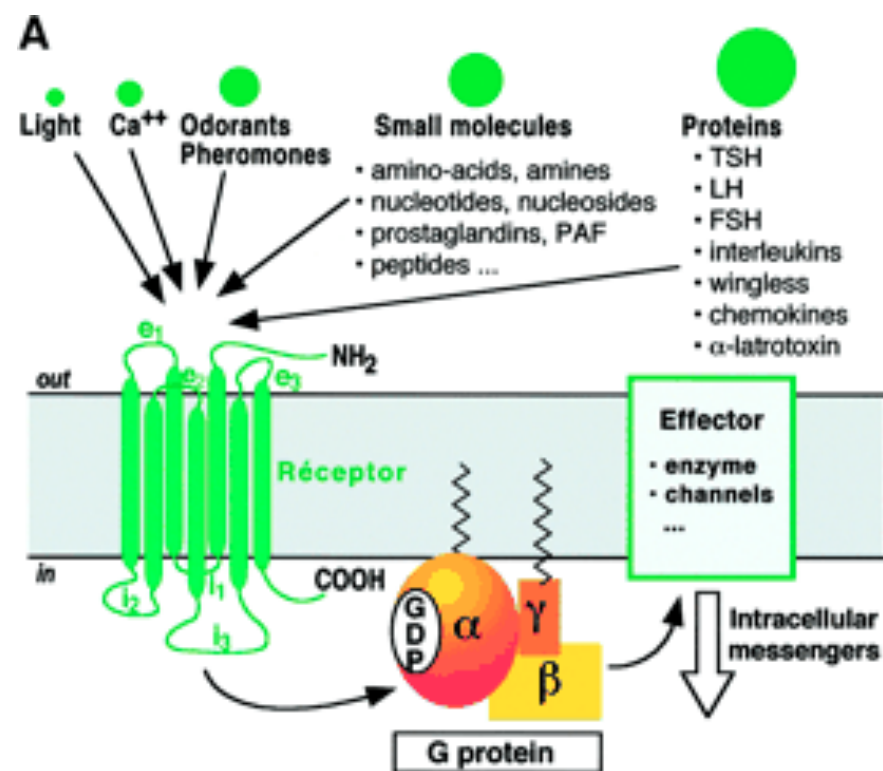


NEUROTRASMISSIONE
 AZIONE ORMONALE
 SECREZIONE ORMONALE
 CHEMIOTASSI ESOCITOSI
 CONTROLLO PRESSIONE ARTERIOSA
 EMBRIOGENESI
 CRESCITA E DIFFERENZIAMENTO CELLULARE
 OLFATTO GUSTO
 VISTA
 INFEZIONE VIRALE





A**B**



MUTAZIONI RECETTORIALI SONO ALLA BASE DI ALCUNE PATOLOGIE

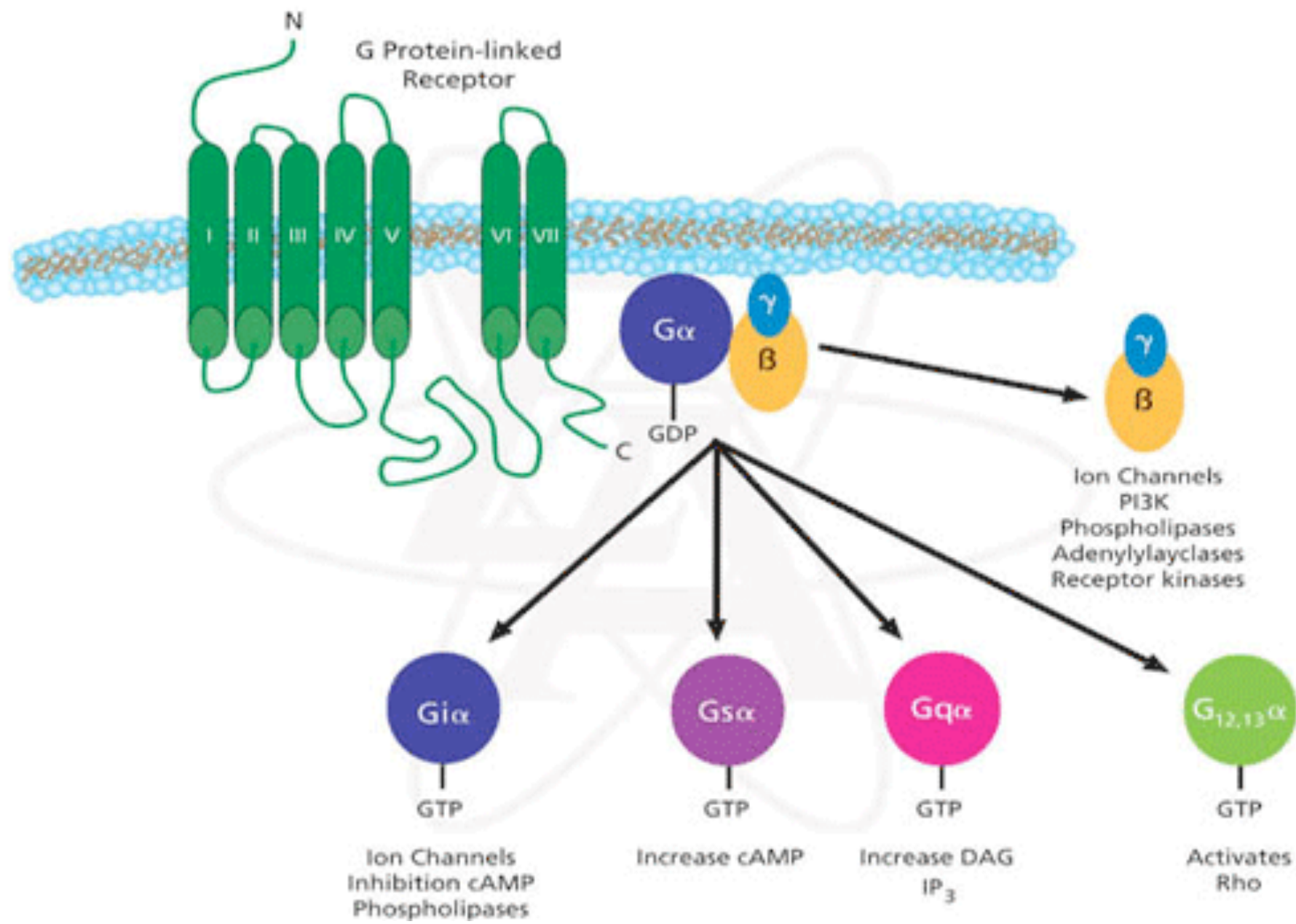
Mutazioni del 3 loop citoplasmatico  Recettore costitutivamente attivo

Es: nel recettore per il TSH  Adenomi tiroidei

Nel recettore per LH  Pubertà precoce familiare

Mutazioni in altri siti  Recettore inattivo

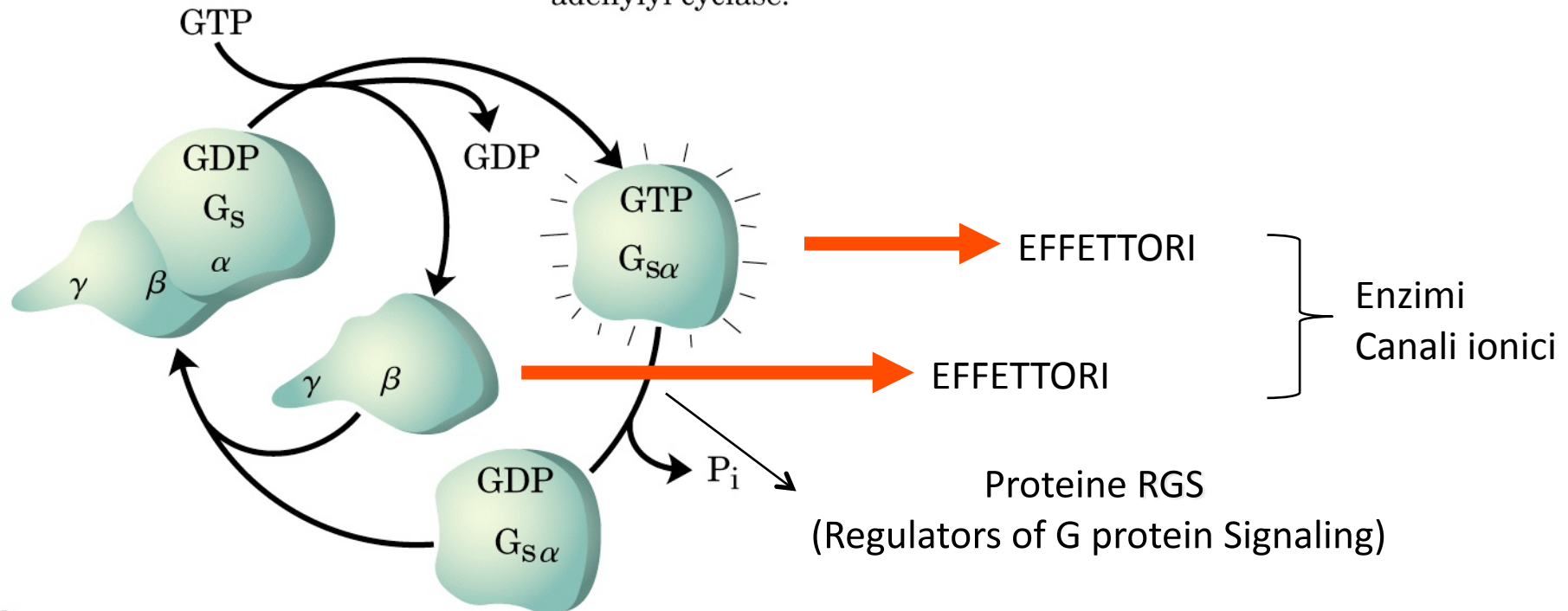
Es: recettore per la vasopressina  Diabete insipido congenito



LE PROTEINE G ETEROTRIMERICHE

- ① G_s with GDP bound is turned off; it cannot activate adenylyl cyclase.
- ② Contact of G_s with hormone-receptor complex causes displacement of bound GDP by GTP.
- ③ G_s with GTP bound dissociates into α and $\beta\gamma$ subunits. $G_{s\alpha}$ -GTP is turned on; it can activate adenylyl cyclase.

Ciclo di attivazione-deattivazione



- ④ GTP bound to $G_{s\alpha}$ is hydrolyzed by the protein's intrinsic GTPase; $G_{s\alpha}$ thereby turns itself off. The inactive α subunit reassociates with the β , γ subunits.

	SOME FAMILY MEMBERS	ACTION MEDIATED BY	FUNCTIONS
I	G_s	α	activates adenylyl cyclase; activates Ca ²⁺ channels
	G_{olf}	α	activates adenylyl cyclase in olfactory sensory neurons
II	G_i	α	inhibits adenylyl cyclase
		$\beta\gamma$	activates K ⁺ channels
	G_o	$\beta\gamma$	activates K ⁺ channels; inactivates Ca ²⁺ channels
		α and $\beta\gamma$	activates phospholipase C- β
	G_t (transducin)	α	activates cyclic GMP phosphodiesterase in vertebrate rod photoreceptors
III	G_q	α	activates phospholipase C- β

* Families are determined by amino acid sequence relatedness of the α subunits. Only selected examples are shown. About 20 α subunits and at least 4 β subunits and 7 γ subunits have been described in mammals.

Gα-subunits (20 geni in 4 classi; diverse varianti di splicing)

Gα_{i/o} class

Gα _{i1}	<i>Gnai1</i>	Widely distributed
Gα _{i2}	<i>Gnai2</i>	Ubiquitous
Gα _{i3}	<i>Gnai3</i>	Widely distributed
Gα _o	<i>Gnao</i>	Neuronal, neuroendocrine
Gα _z	<i>Gnaz</i>	Neuronal, platelets
Gα _{gust}	<i>Gnag</i>	Taste cells, brush cells
Gα _{t1}	<i>Gnat1</i>	Retinal rods, taste cells
Gα _{t2}	<i>Gnat2</i>	Retinal cones, stem cells

Gα_{q/11} class

Gα _q	<i>Gnaq</i>	Ubiquitous
Gα ₁₁	<i>Gna11</i>	Ubiquitous
Gα ₁₄	<i>Gna14</i>	Kidney, lung, spleen
Gα _{15/16}	<i>Gna15</i>	Haematopoietic cells

Gα_s class

Gα _s	<i>Gnas</i>	Ubiquitous
Gα _{sXL}	<i>Gnasxl</i>	Neuroendocrine
Gα _{olf}	<i>Gnal</i>	Olfactory epithelium, brain

Gα_{12/13} class

Gα ₁₂	<i>Gna12</i>	Ubiquitous
Gα ₁₃	<i>Gna13</i>	Ubiquitous

Gβ-subunits**(5 geni; varianti di splicing)**

Gβ	<i>Gnb1</i>	Widely, retinal rods
Gβ ₂	<i>Gnb2</i>	Widely distributed
Gβ ₃	<i>Gnb3</i>	Widely, retinal cones
Gβ ₄	<i>Gnb4</i>	Widely distributed
Gβ ₅	<i>Gnb5</i>	Primarily brain

Gγ-subunits**(12 geni; diverse varianti di splicing)**

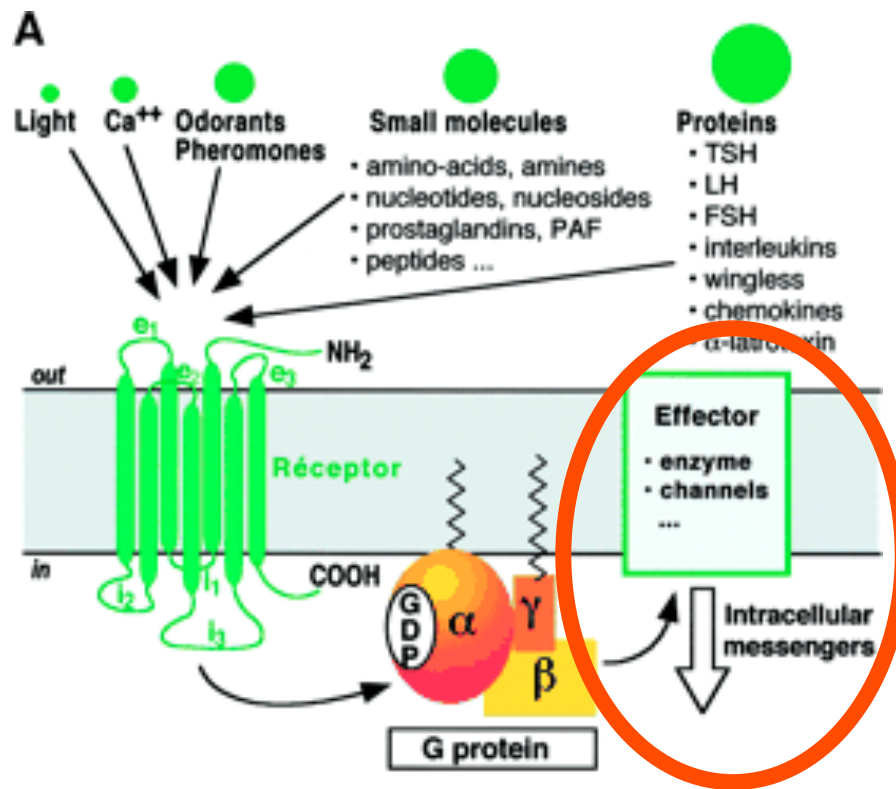
Gγ ₁ , Gγ _{rod}	<i>Gngt1</i>	Retinal rods, brain
Gγ ₁₄ , Gγ _{cone}	<i>Gngt2</i>	Retinal cones, brain
Gγ ₂ , Gγ ₆	<i>Gng2</i>	Widely distributed
Gγ ₃	<i>Gng3</i>	Brain, blood
Gγ ₄	<i>Gng4</i>	Brain, other tissues
Gγ ₅	<i>Gng5</i>	Widely distributed
Gγ ₇	<i>Gng7</i>	Widely distributed
Gγ ₈ , Gγ ₉	<i>Gng8</i>	Widely distributed
Gγ ₁₀	<i>Gng10</i>	Widely distributed
Gγ ₁₁	<i>Gng11</i>	Widely distributed

Gγ ₁₂	<i>Gng12</i>	Widely distributed
Gγ ₁₃	<i>Gng13</i>	Taste buds

IMPORTANZA DELLE SUBUNITA' $\beta\gamma$:

- ✓ Impedisce la dissociazione del GDP dalla subunita' alpha
- ✓ Importante per l'interazione con il recettore (che è solo in grado di legare l'eterotrimerico)
- ✓ Controllano il processo di desensitizzazione
- ✓ Attivano canali K^+ ed inibiscono quelli del Ca^{2+}
- ✓ Attivano fosfolipasi C e MAPK

I SISTEMI EFFETTORI



**EFFETTORI DI
PROTEINE G**



SECONDI MESSAGERI

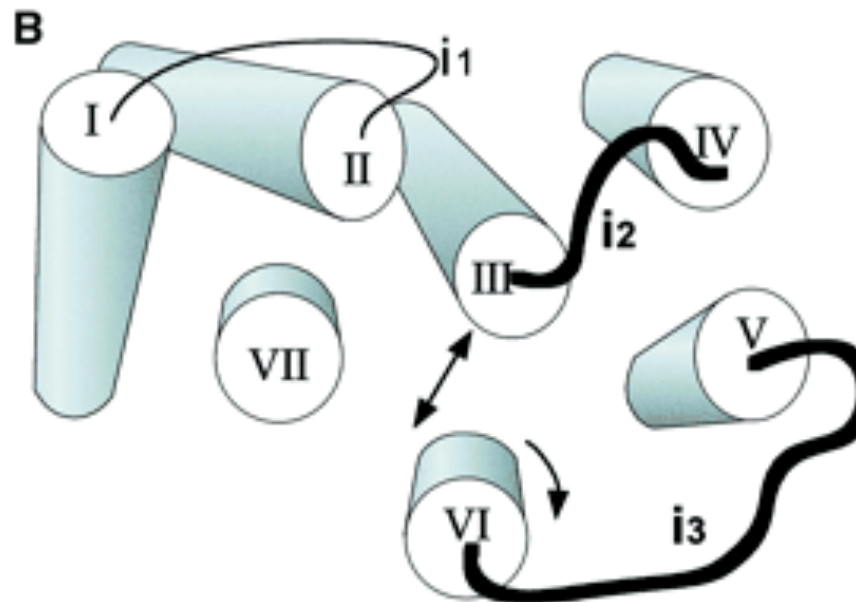


TABLE 4. *G protein effectors*

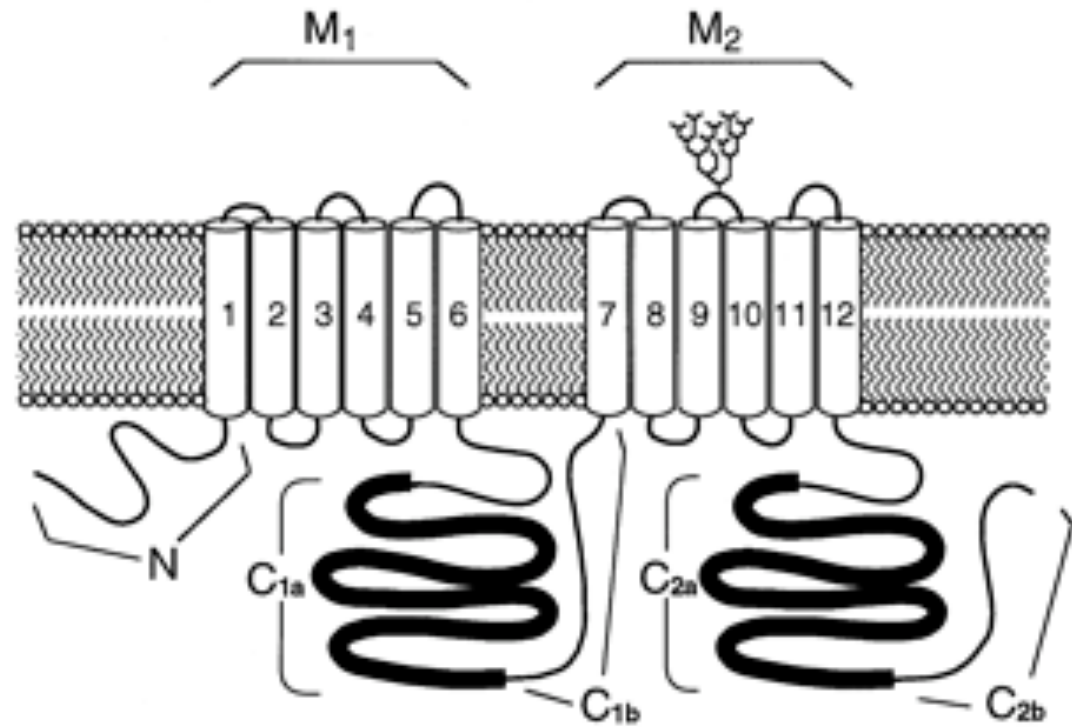
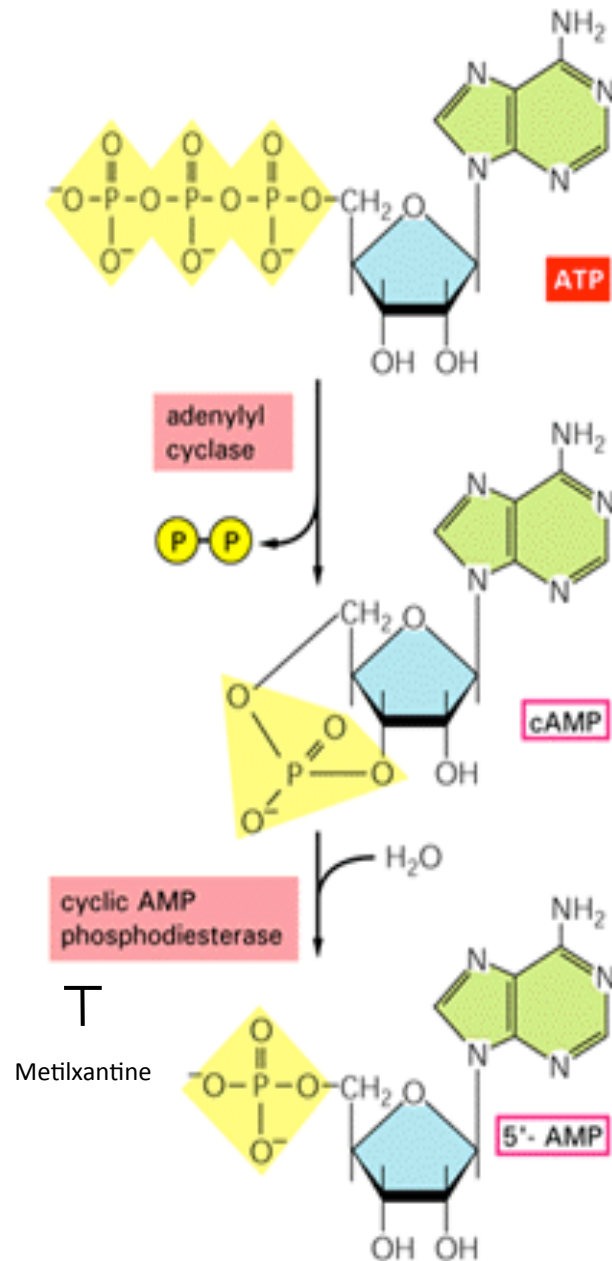
Class	Isotypes	G Protein Selectivity	Reference No.
<i>Second messenger-generating and metabolizing enzymes</i>			
Adenylyl cyclase	I	$\alpha_s + \beta\gamma - \alpha_o - \alpha_z$	19, 95, 133, 159, 258, 313, 545-549, 551, 552, 554, 596-598, 604
	II	$\alpha_s + \beta\gamma +$	
	III	$\alpha_s +$	
	IV	$\alpha_s + \beta\gamma +$	
	V	$\alpha_s + \alpha_z$	
	VI	$\alpha_s +$	
	VII	$\alpha_s +$	
	VIII	$\alpha_s +$	
	IX	$\alpha_s +$	
cGMP phosphodiesterase		$\alpha_i -$	214
Phospholipase C	β_1	$\alpha_q \alpha_{11}, \alpha_{15}, \alpha_{16} + \beta\gamma +$	78, 229, 311, 328, 329, 393, 427, 429, 430, 512, 513, 555, 618
	β_2	$\alpha_q \alpha_{11}, \alpha_{15}, \alpha_{16} + \beta\gamma +$	
	β_3	$\alpha_q \alpha_{11}, \alpha_{15}, \alpha_{16} + \beta\gamma +$	
	β_4	$\alpha_q \alpha_{11}, \alpha_{15}, \alpha_{16} + \beta\gamma +$	
Phosphoinositide 3-kinase	p120 γ /p101	$\beta\gamma + \alpha_{o1} +$	526
Phospholipase A ₂		$\beta\gamma +$	262
<i>Ion-selective channels</i>			
K ⁺ channels	IKACH	$\alpha_i + \beta\gamma +$	106, 629
	IKATP	$\alpha_i +$	106
Ca ²⁺ channels	Neuronal N type	$\alpha_{11} - \alpha_{12} - \beta_1 - \beta_3 -$	63, 104, 248, 497, 625
	Cardiac L type	$\alpha_s +$	
Na ⁺ channels	Cardiac	$\alpha_s +$	492
	Epithelial cell	$\alpha_{12} -$	341
Cl ⁻ channels	Cardiac	$\alpha_s +$	156
	Epithelial cell	$\alpha_{10} -$	156

→ Cellule pace-maker del cuore

Secondi messaggeri: Calcio, cAMP, IP_3 , DAG

- Generare una o più risposte legandosi, all'interno della cellula, a substrati specifici e modularne l'attività.
- Essere degradata e/o rimossa dal citoplasma, in modo tale che la variazione di concentrazione sia transitoria e dipendente dallo stimolo che l'ha generata.

L'ADENILATO CICLASI (I-IX)



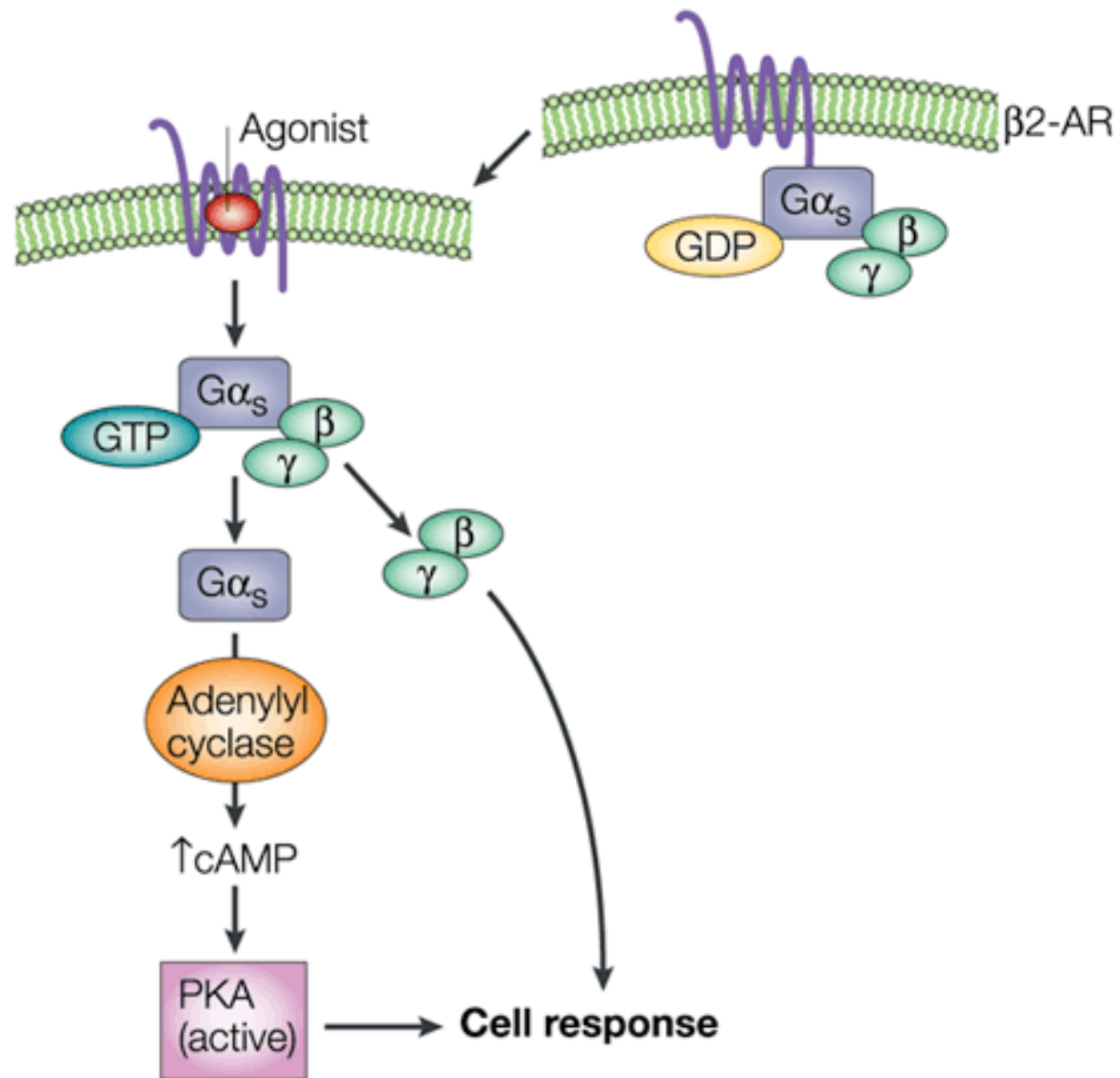


TABLE 12–3**Some Signals That Use cAMP as Second Messenger**

Corticotropin (ACTH)
Corticotropin-releasing hormone (CRH)
Dopamine [D₁, D₂]
Epinephrine (β-adrenergic)
Follicle-stimulating hormone (FSH)
Glucagon
Histamine [H₂]
Luteinizing hormone (LH)
Melanocyte-stimulating hormone (MSH)
Odorants (many)
Parathyroid hormone
Prostaglandins E₁, E₂ (PGE₁, PGE₂)
Serotonin [5-HT-1a, 5-HT-2]
Somatostatin
Tastants (sweet, bitter)
Thyroid-stimulating hormone (TSH)

Note: Receptor subtypes in square brackets. Subtypes may have different transduction mechanisms. For example, serotonin is detected in some tissues by receptor subtypes 5-HT-1a and 5-HT-1b, which act through adenylyl cyclase and cAMP, and in other tissues by receptor subtype 5-HT-1c, acting through the phospholipase C-IP₃ mechanism (see Table 12–4).

Table 12-3

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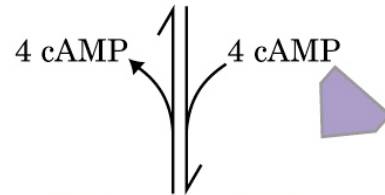
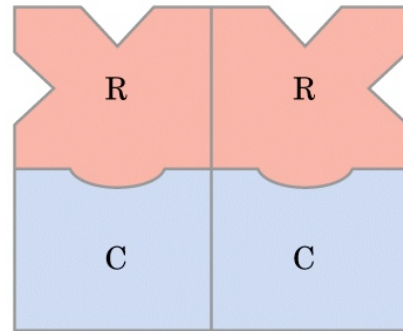
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PKA

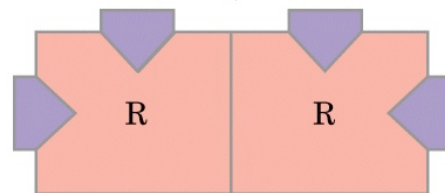
Inactive PKA

Regulatory subunits:
empty cAMP sites

Catalytic subunits:
substrate-binding
sites blocked by
autoinhibitory
domains of R subunits

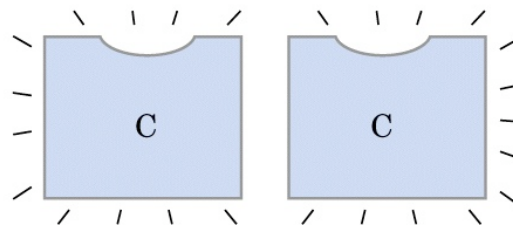


Regulatory subunits:
autoinhibitory
domains buried

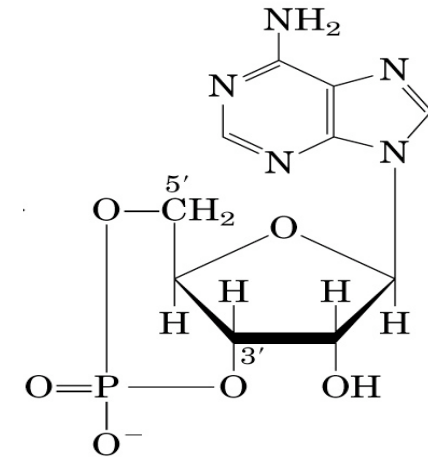


Active PKA

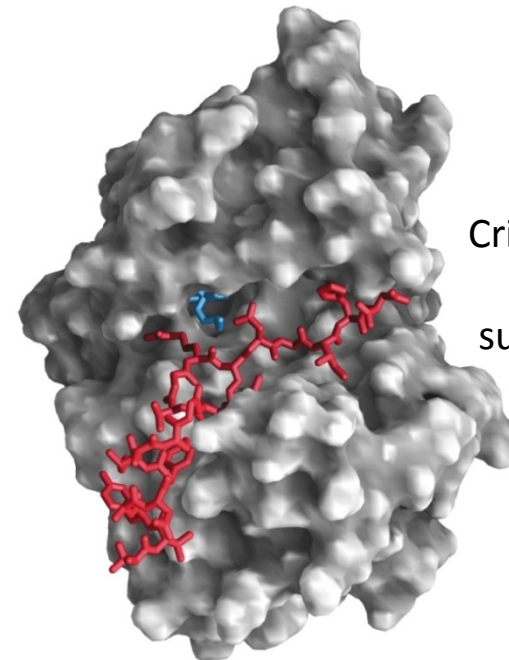
Catalytic subunits:
open substrate-
binding sites



(a)



Adenosine 3',5'-cyclic
monophosphate
(cAMP)



(b)

Cristallografia ai raggi X
del sito che lega il
substrato in una sub C

TABLE 12–2**Some Enzymes and Other Proteins Regulated by cAMP-Dependent Phosphorylation (by PKA)**

Enzyme/protein	Sequence phosphorylated*	Pathway/process regulated
Glycogen synthase	RASCTSSS	Glycogen synthesis
Phosphorylase <i>b</i> kinase α subunit β subunit	VEFRRLSI RTKRSGSV }	Glycogen breakdown
Pyruvate kinase (rat liver)	GVLRRASVAZL	Glycolysis
Pyruvate dehydrogenase complex (type L)	GYLRRASV	Pyruvate to acetyl-CoA
Hormone-sensitive lipase	PMRRSV	Triacylglycerol mobilization and fatty acid oxidation
Phosphofructokinase-2/fructose 2,6-bisphosphatase	LQRRRGSSIPQ	Glycolysis/gluconeogenesis
Tyrosine hydroxylase	FIGRRQSL	Synthesis of L-dopa, dopamine, norepinephrine, and epinephrine
Histone H1	AKRKASGPPVS	DNA condensation
Histone H2B	KKAKASRKESYSVYVYK	DNA condensation
Cardiac phospholamban (cardiac pump regulator)	AIRRAST	Intracellular [Ca ²⁺]
Protein phosphatase-1 inhibitor-1	IRRRRPTP	Protein dephosphorylation
PKA consensus sequence [†]	xR[RK]x[ST]B	Many

*The phosphorylated S or T residue is shown in red. All residues are given as their one-letter abbreviations (see Table 3–1).

[†]x is any amino acid; B is any hydrophobic amino acid. See Box 3–3 for conventions used in displaying consensus sequences.

Table 12-2

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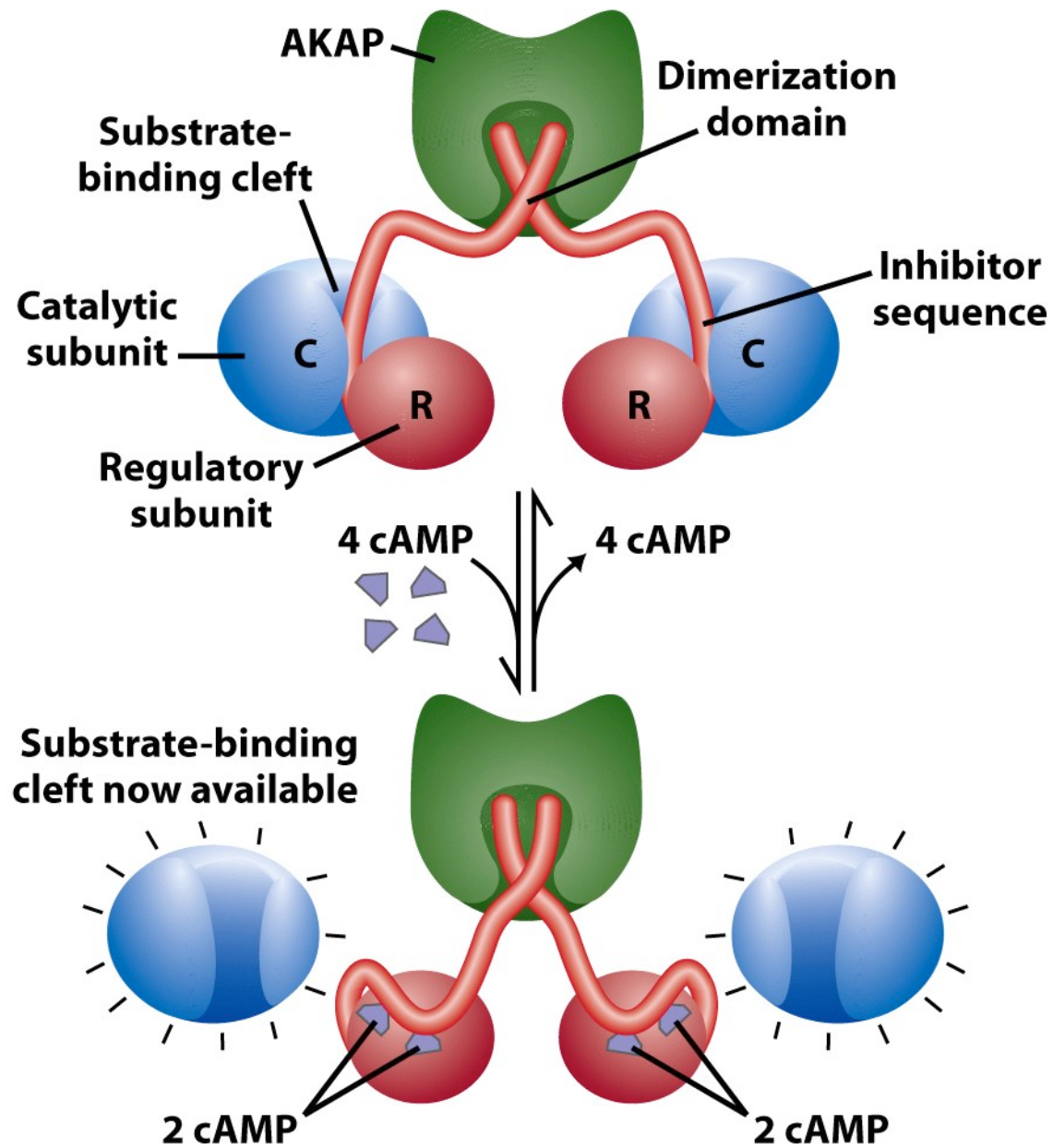


Figure 12-6a
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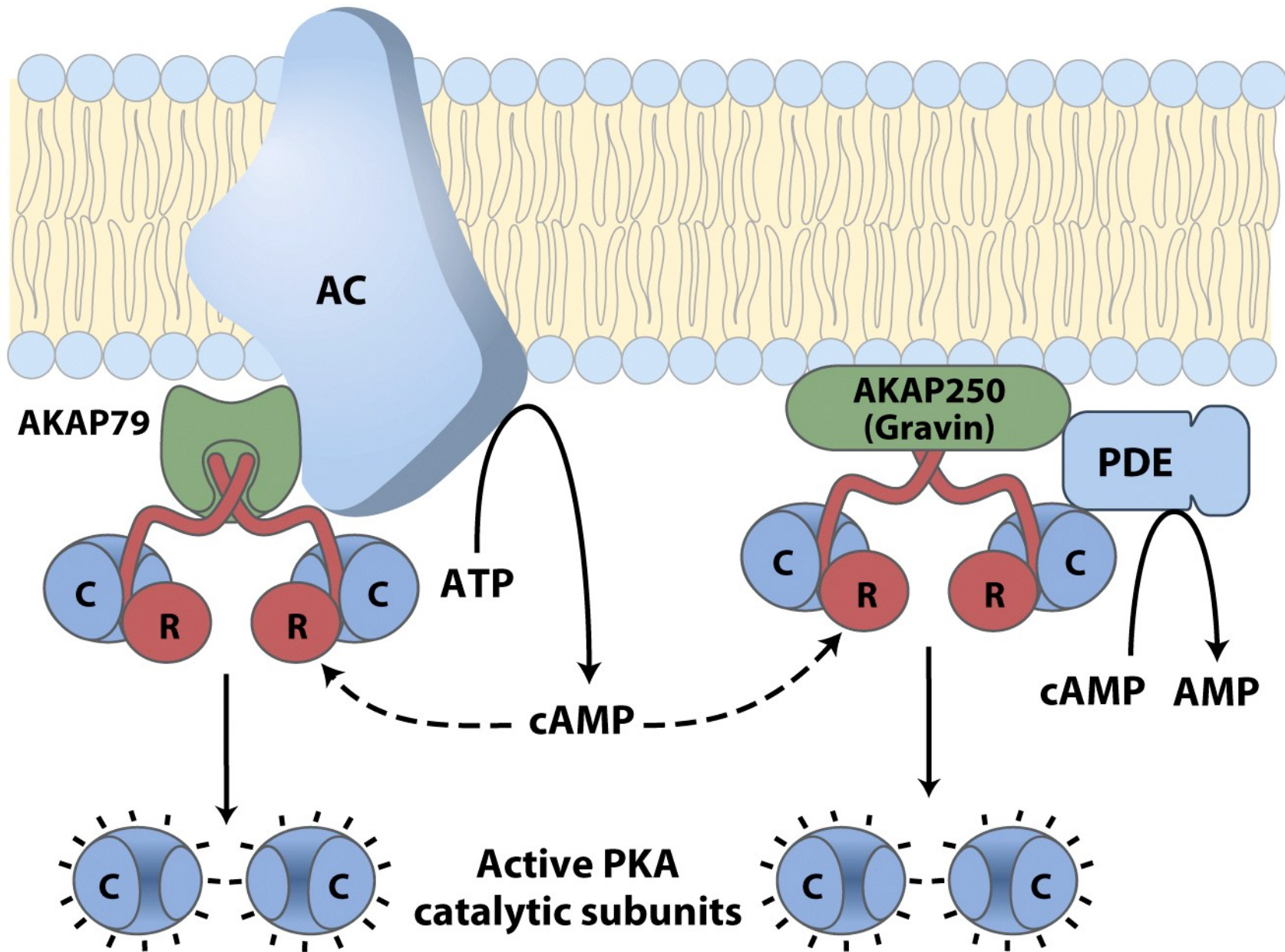
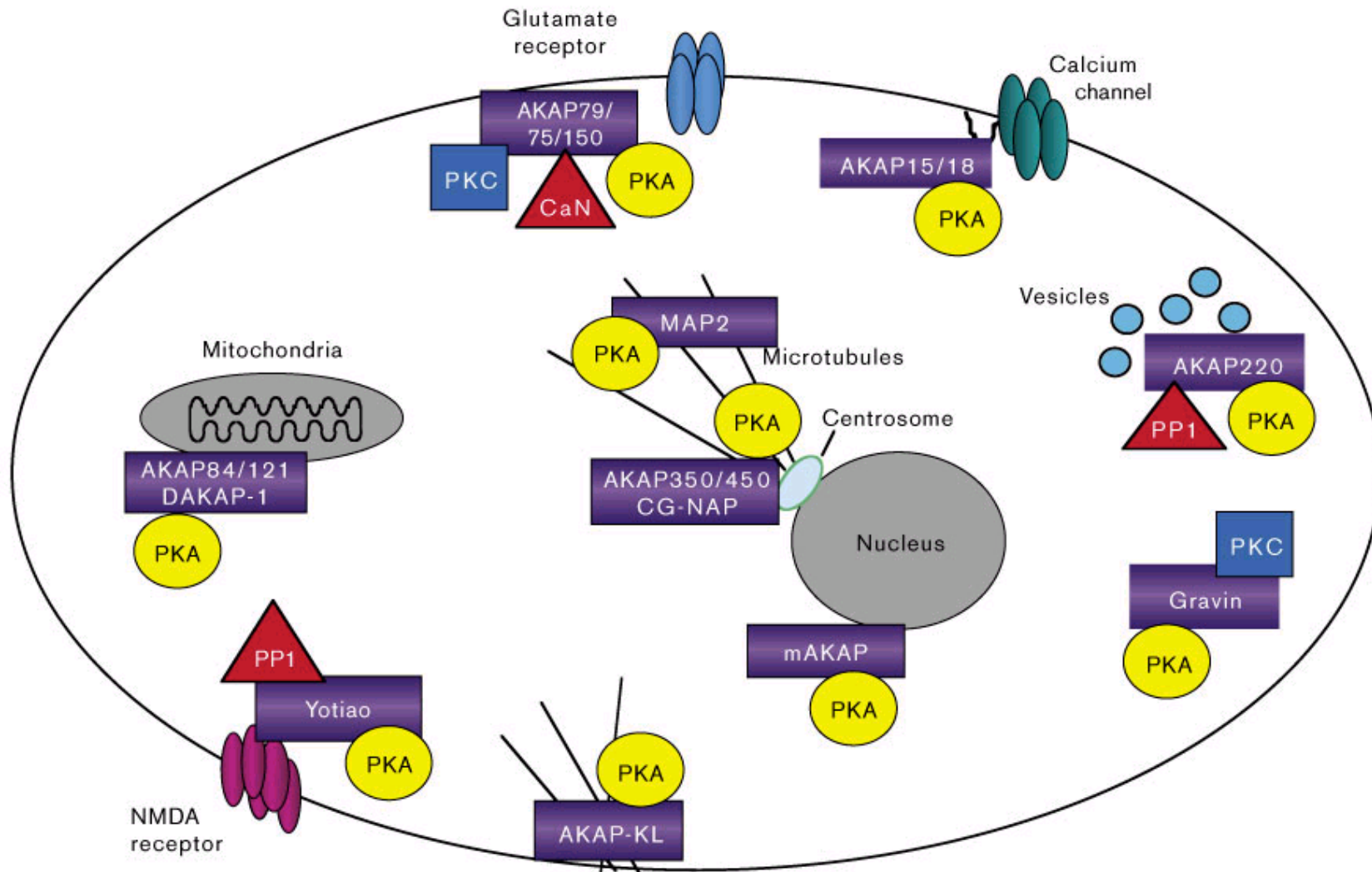
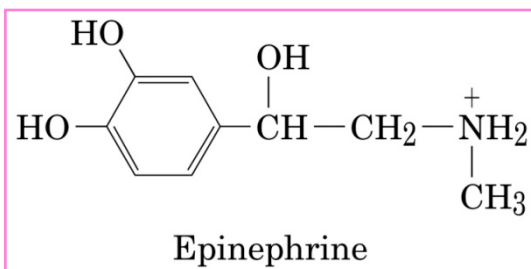


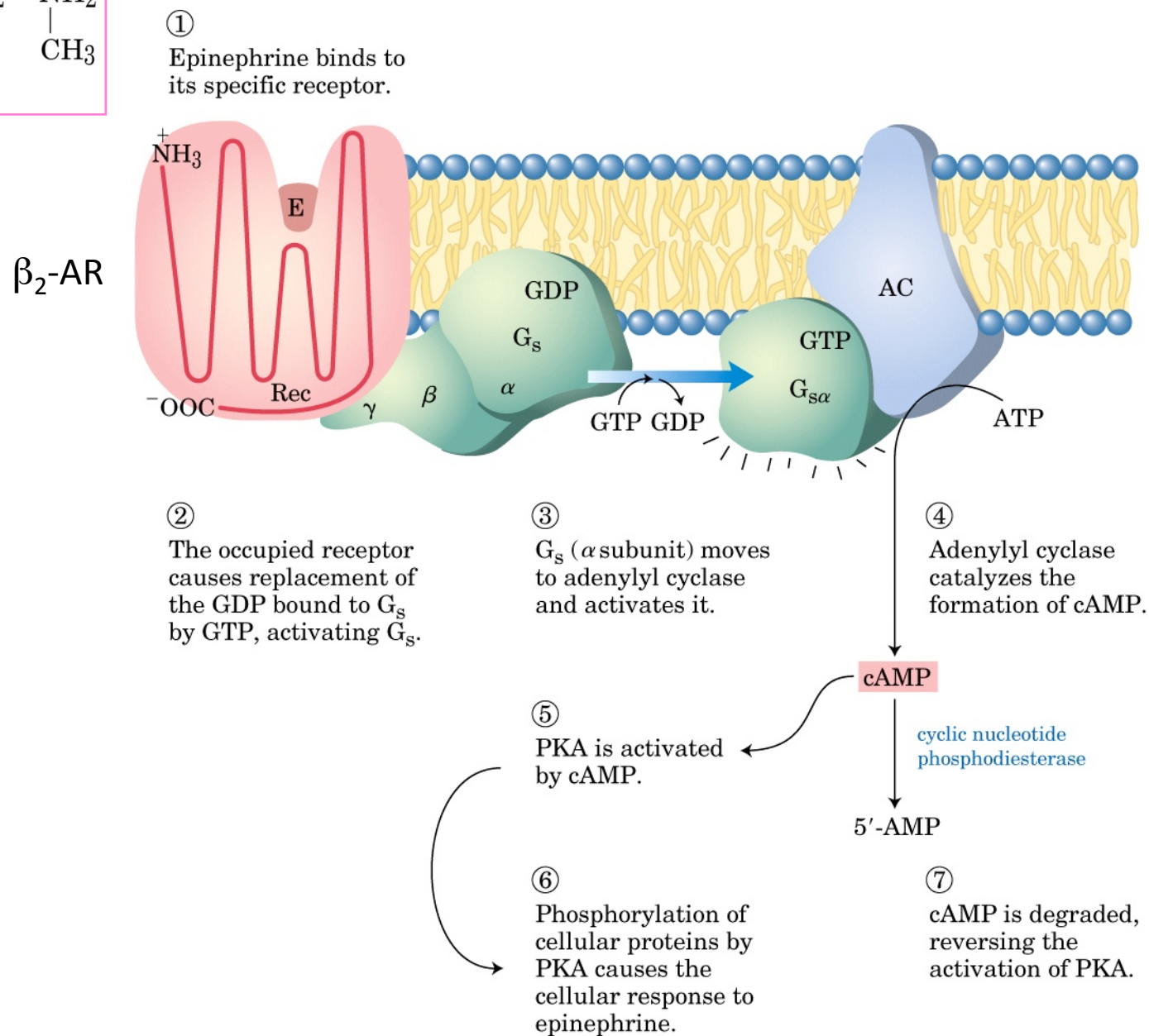
Figure 12-9
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La PKA è compartimentalizzata in prossimità del substrato mediante interazione fra le subunità regolatorie e “proteine impalcatura” (AKAP)

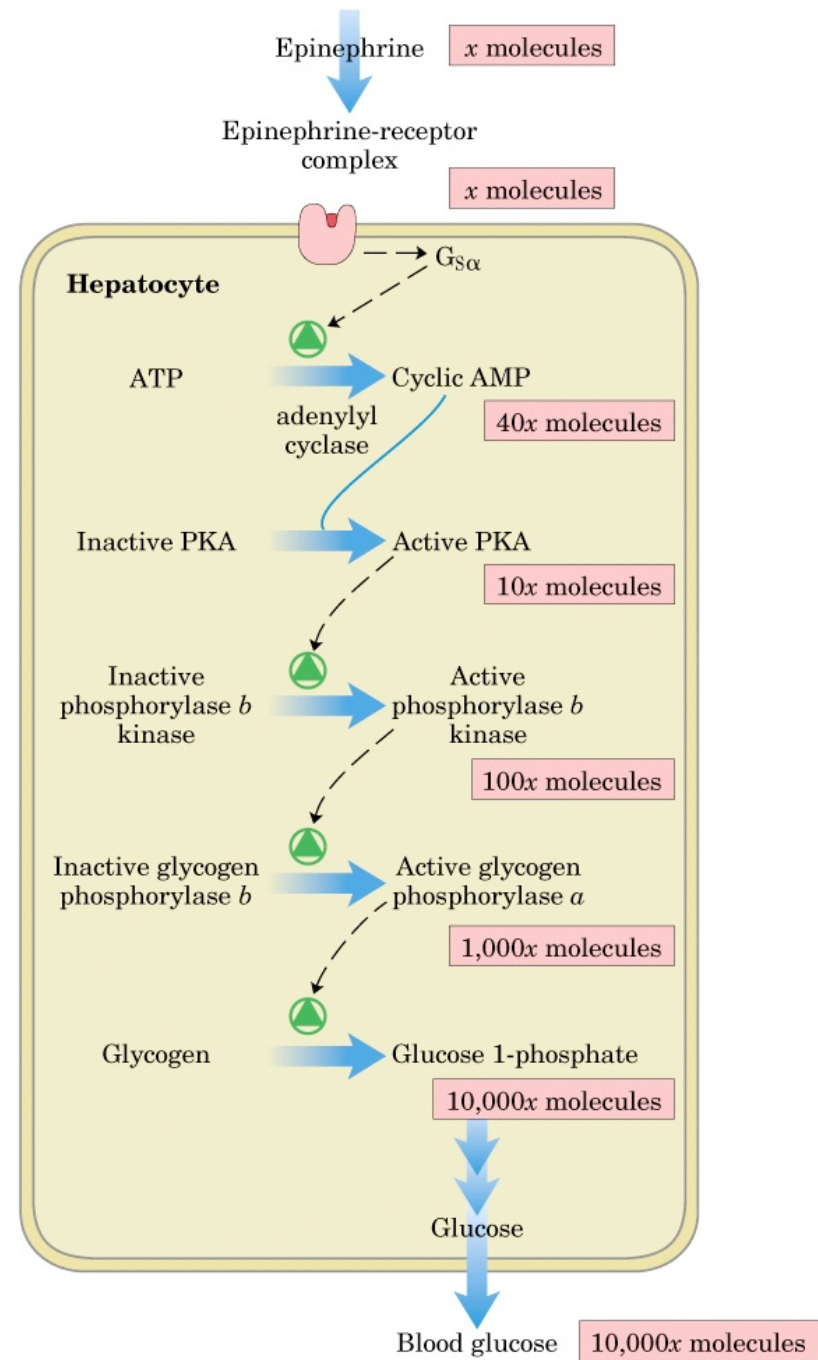




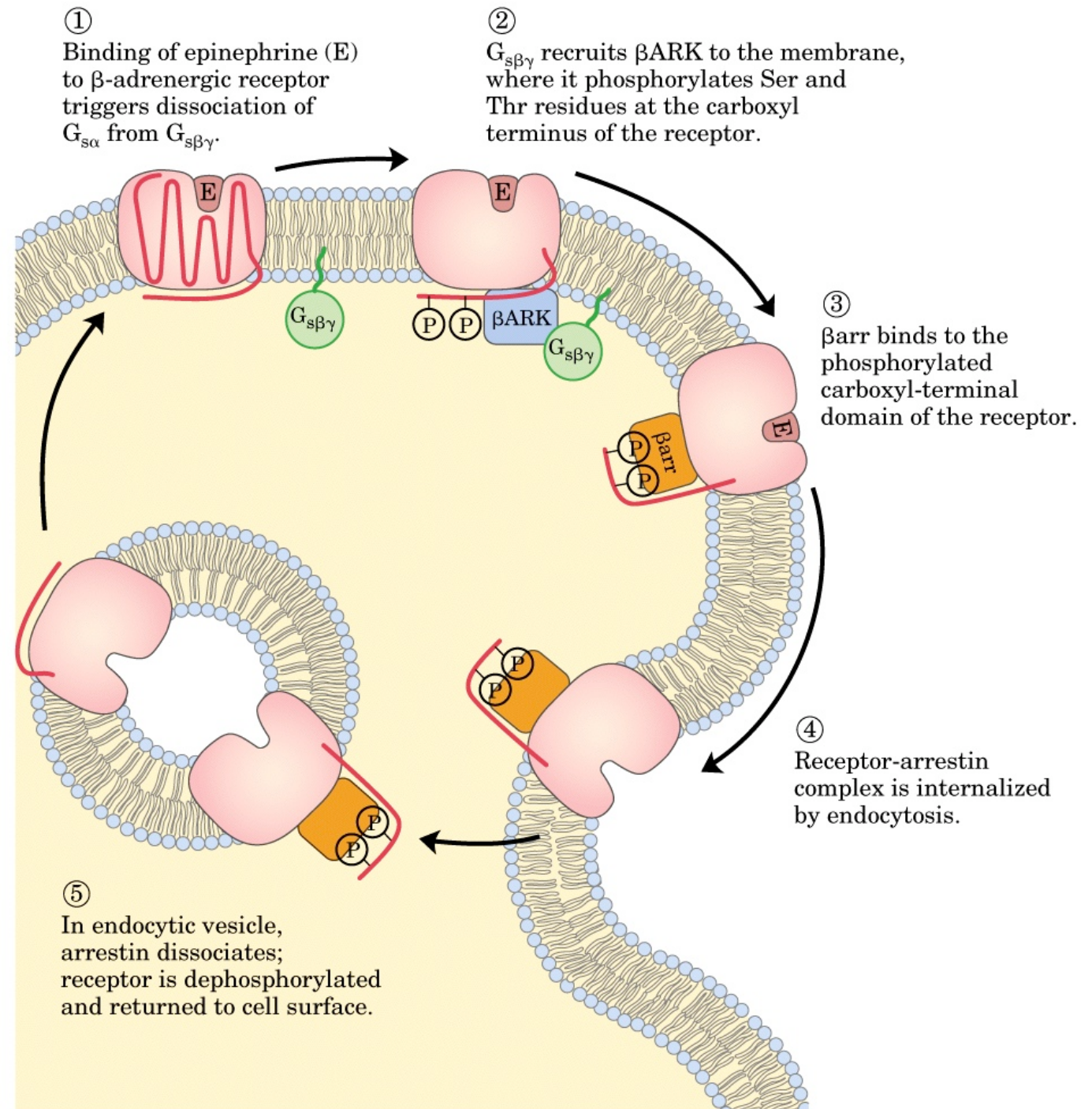
RECETTORE β ADRENERGICO



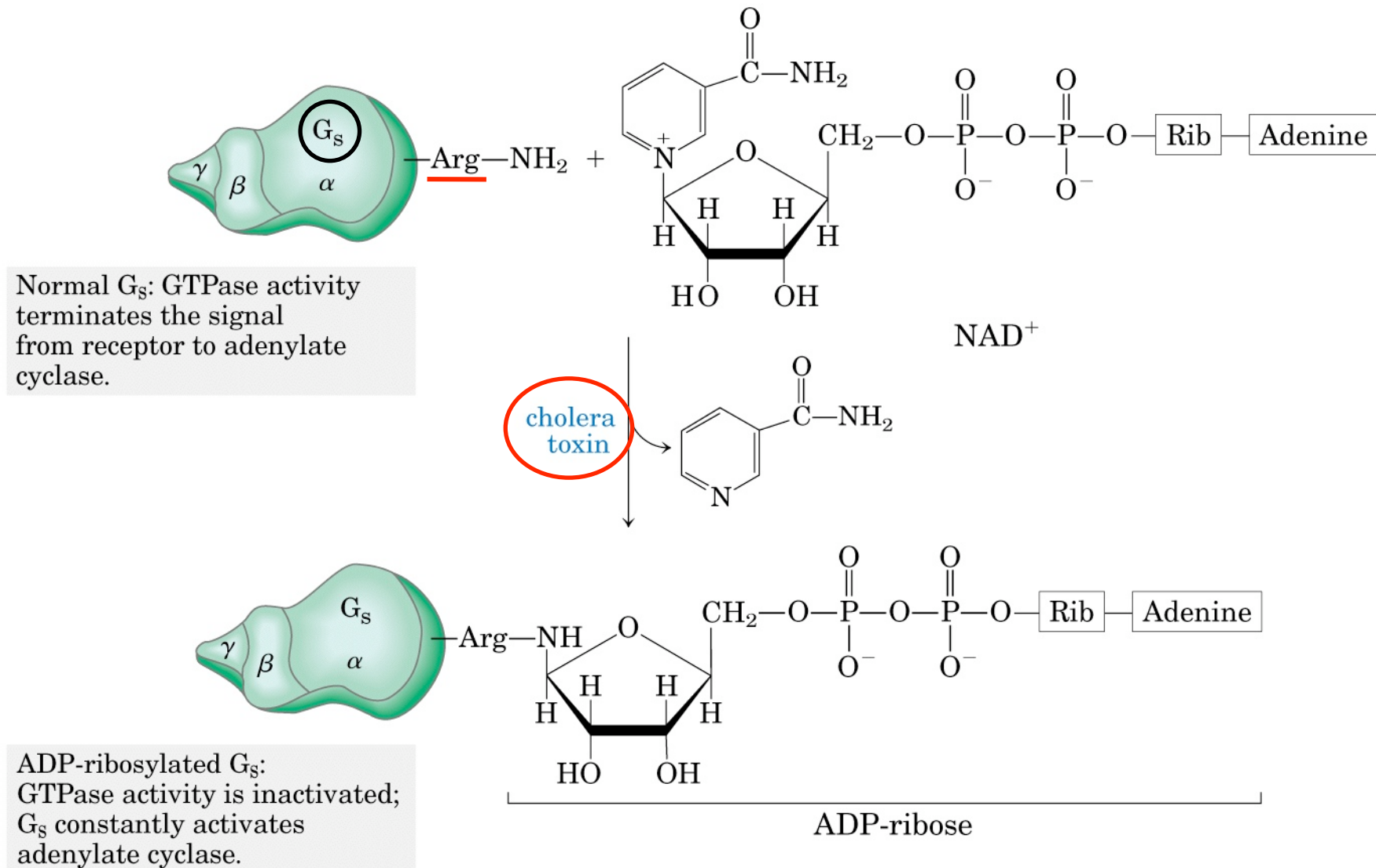
Cascata dell'adrenalina negli epatociti



Desensibilizzazione del recettore β adrenergico



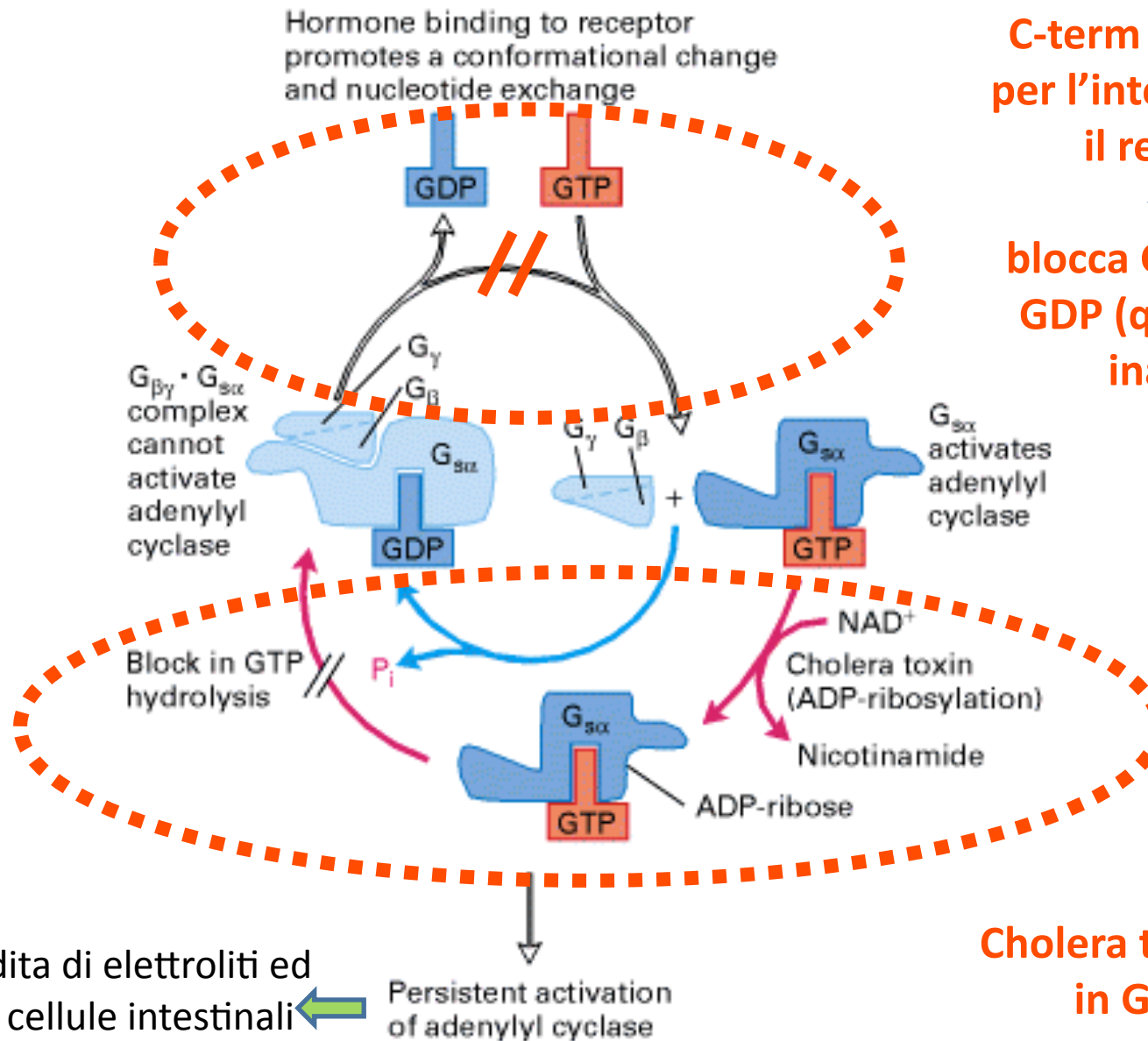
ATTIVITA' ADP-RIBOSIL-TRANSFERASICA (COLERA E PERTOSSE)



Pertussis tx ADP-
ribosila una cisteina
C-term importante
per l'interazione con
il recettore

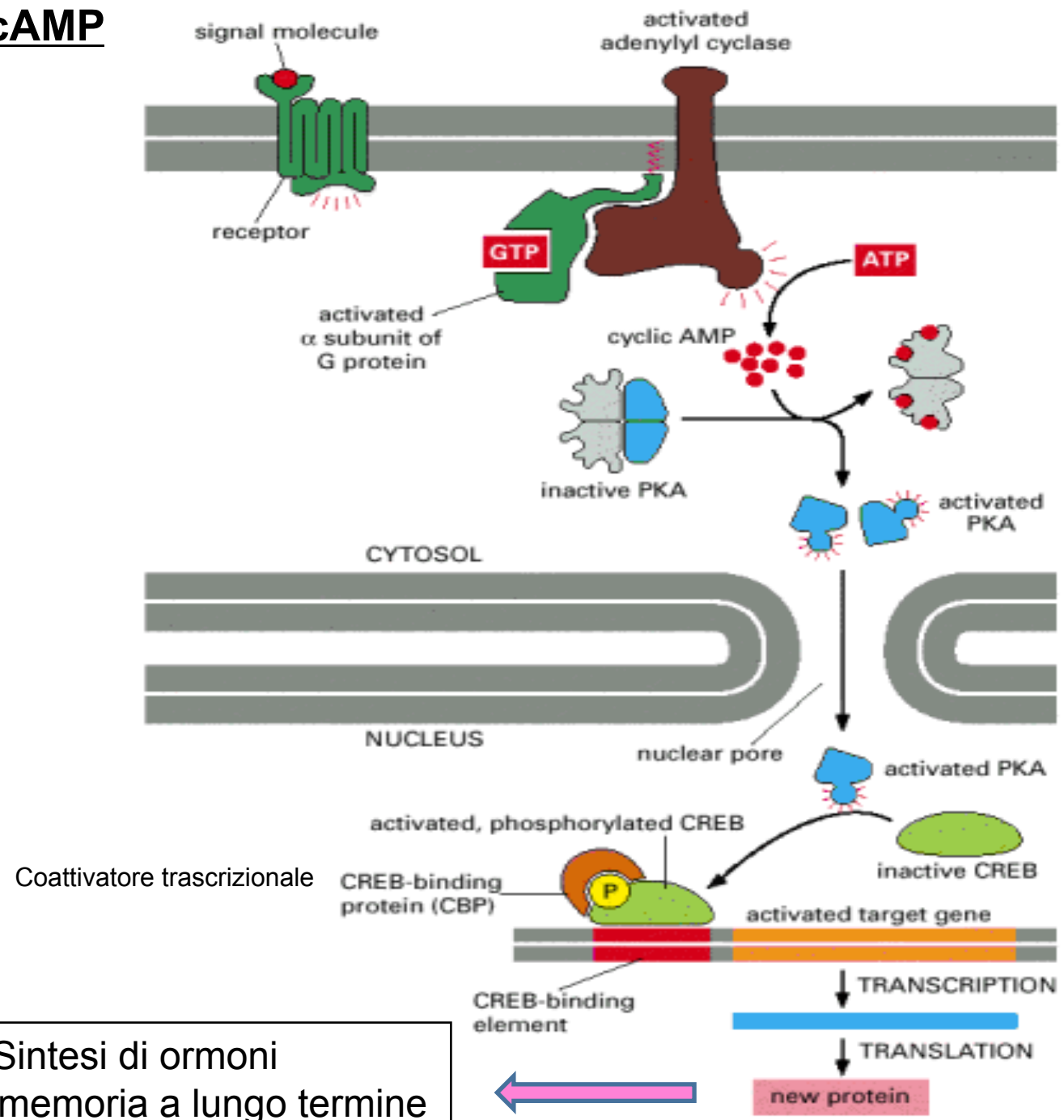


blocca $G_{\alpha i}$ legata a
GDP (quindi stato
inattivo)



Cholera tx blocca $G_{\alpha s}$
in GTP state

Risposte lente all'cAMP



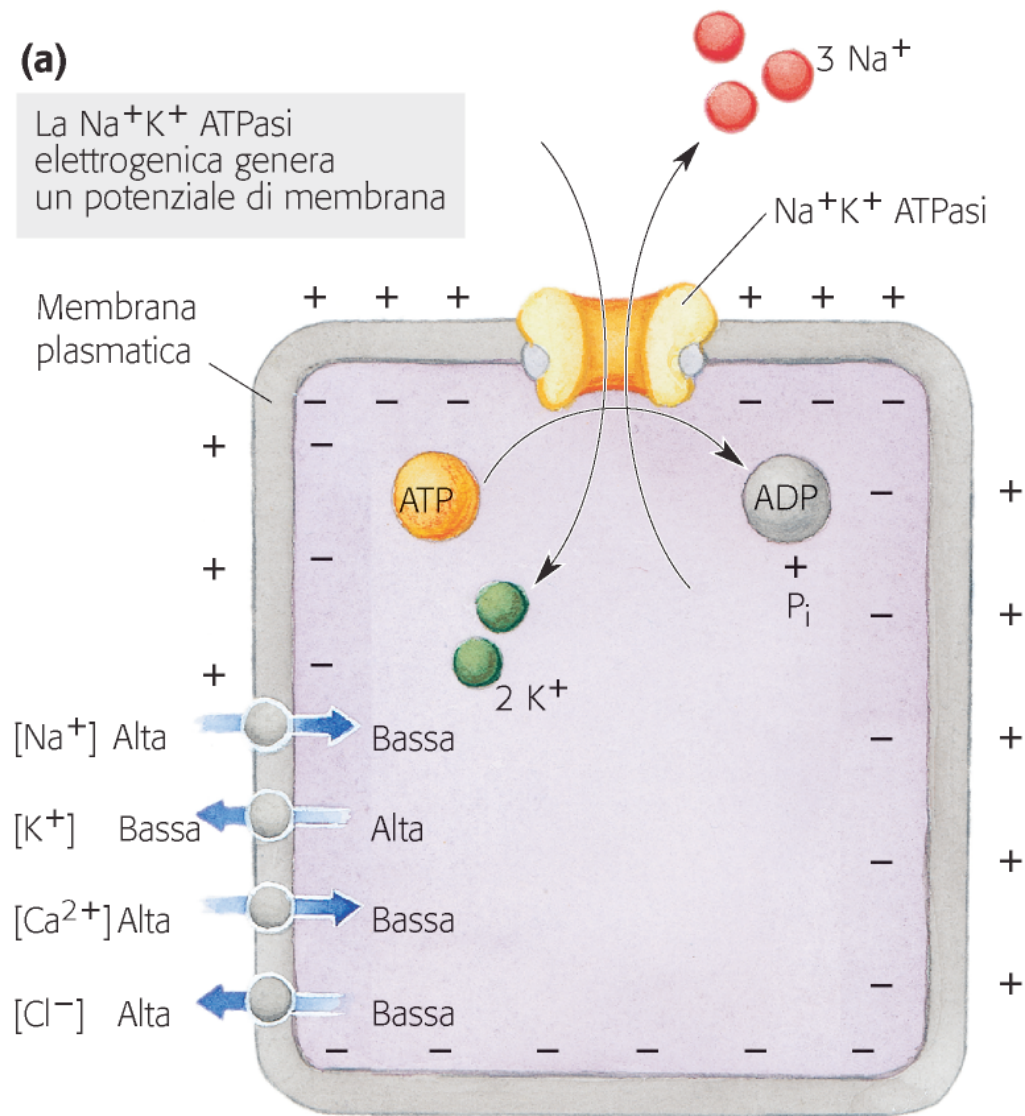
CANALI IONICI

CANALI CONTROLLATI DA LIGANDI: il legame di piccole molecole genera una transizione molecolare allosterica nella proteina che apre o chiude il canale.

CANALI CONTROLLATI DAL VOLTAGGIO: un dominio proteico carico si sposta in risposta a una variazione del potenziale transmembrana, causando l'apertura o la chiusura del canale.

(a)

La Na^+K^+ ATPasi elettrogenica genera un potenziale di membrana



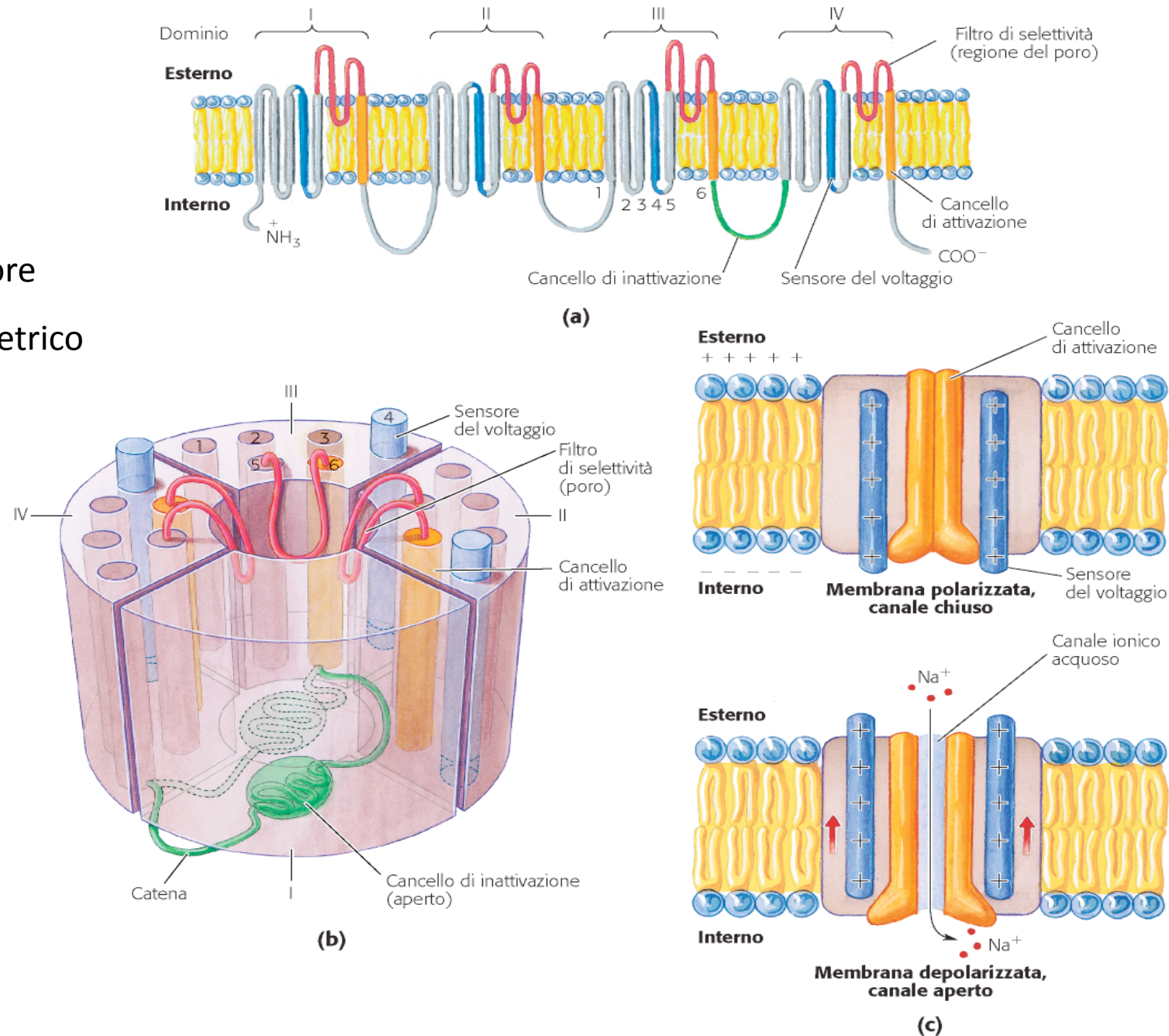
(b)

Gli ioni tendono a muoversi attraverso una membrana polarizzata in favore del gradiente elettrochimico

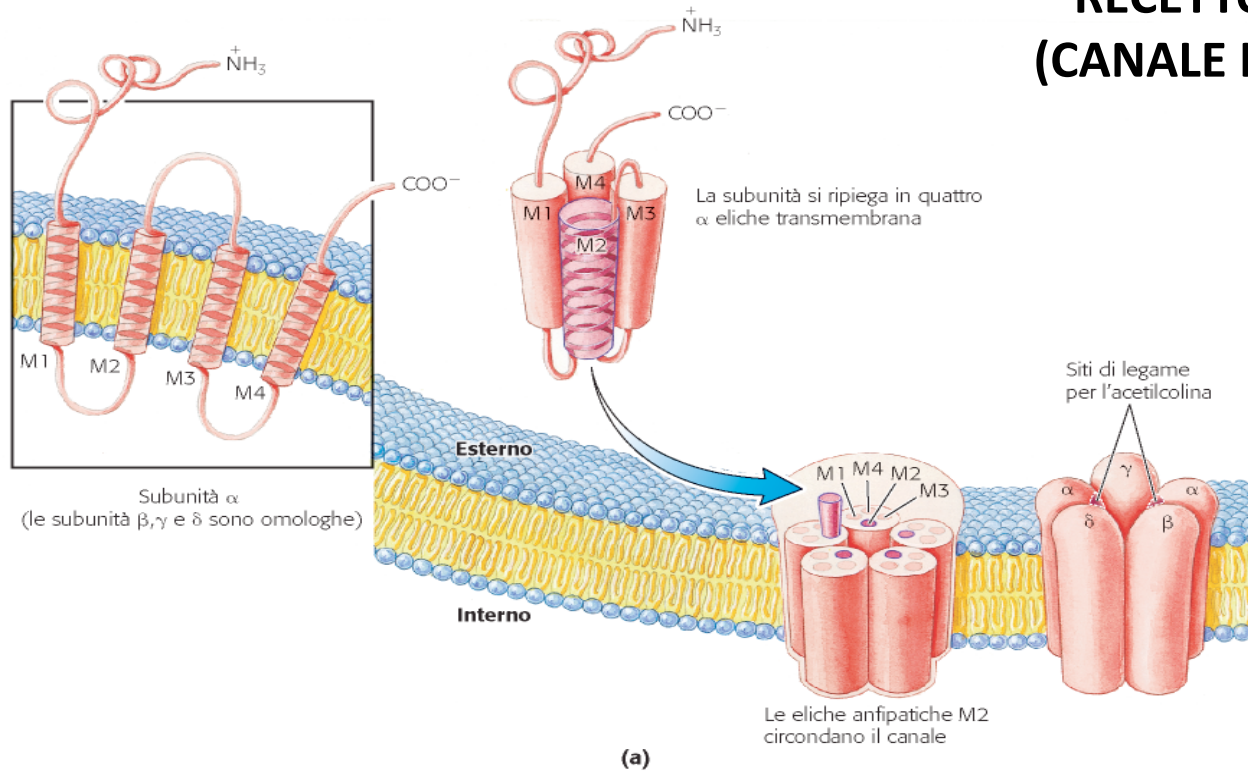
Il potenziale di membrana di una data cellula, in un dato momento, dipende dal tipo e dal numero di canali ionici chiusi o aperti in quell'istante

CANALE NEURONALE PER IL Na⁺ (canale controllato da voltaggio)

- Neuroni
- Miociti del cuore
- Muscolo scheletrico



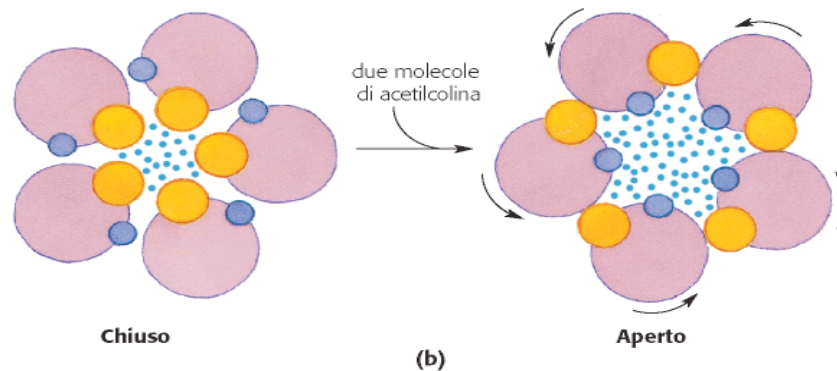
RECETTORE DELL'ACETILCOLINA (CANALE IONICO CONTROLLATO DA LIGANDO)



Le grosse catene dei residui di Leu delle eliche M2 ostruiscono il canale

Il legame di due molecole di acetilcolina causa una rotazione delle eliche M2

Le eliche M2 sono ora più piccole, i residui polari sono allineati al canale



$\downarrow$ $\text{Na}^+, \text{Ca}^{2+}, \text{K}^+$



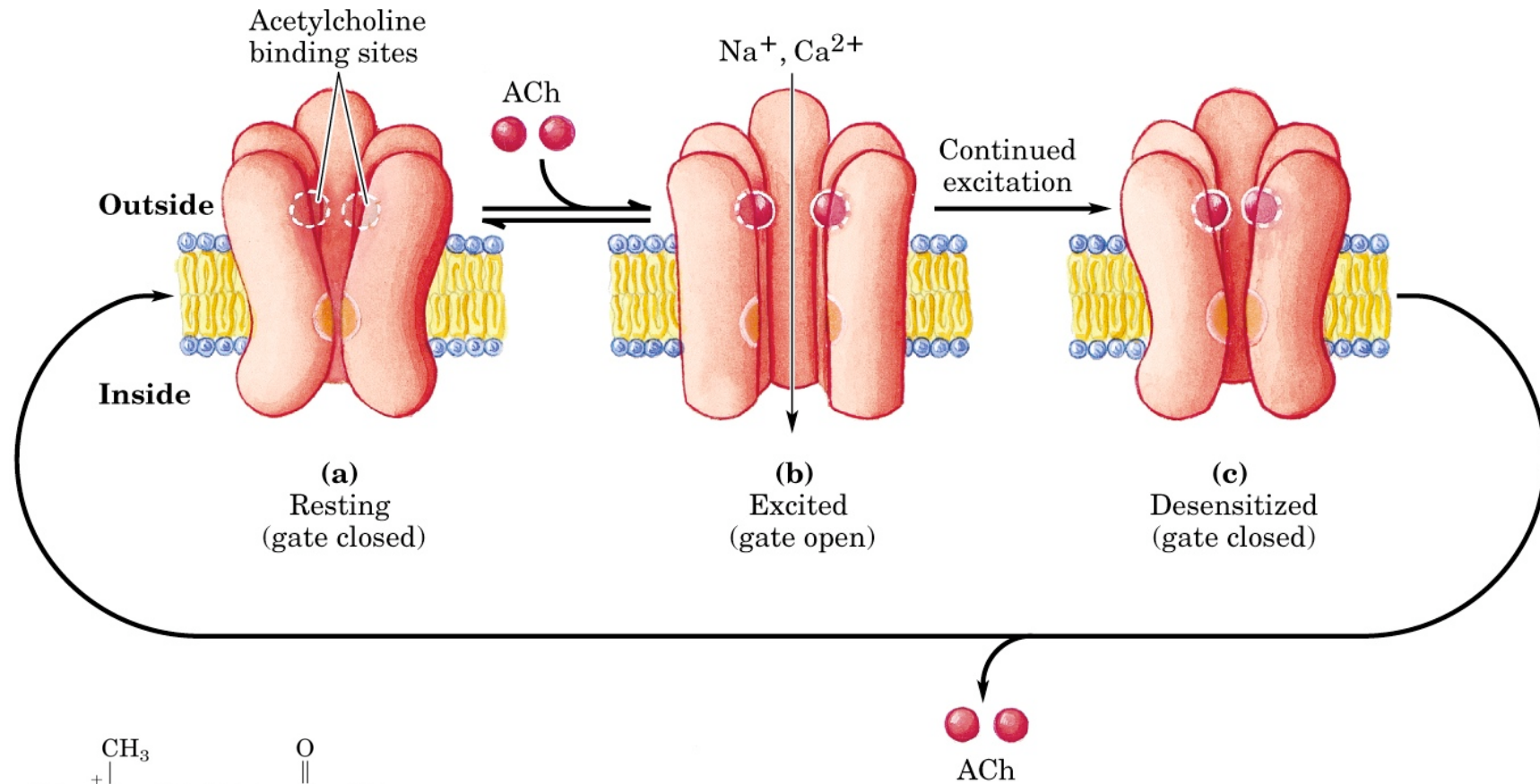
Depolarizzazione



Contrazione
(fibre muscolari)

Potenziale d'azione
(neurone postsinaptico)

I TRE STATI DEL RECETTORE DELL'ACETILCOLINA



CANALI IONICI E TRASMISSIONE NEURONALE

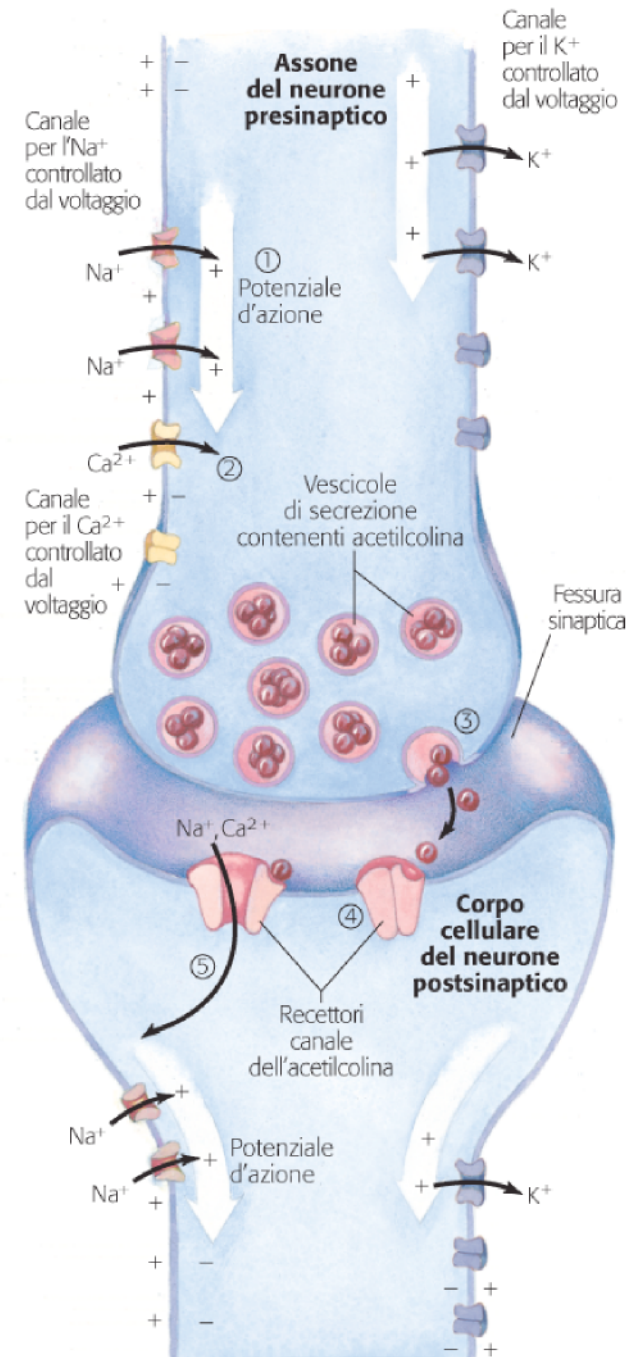


TABELLA 11.8 Alcune malattie causate da difetti nei canali ionici

Canale ionico	Gene difettoso	Malattia
Na ⁺ (controllato dal voltaggio, muscolo-scheletrici)	<i>SCN4A</i>	Paralisi iperpotassiemica periodica (o paramiotonia congenita)
Na ⁺ (controllato dal voltaggio, neuronale)	<i>SCN1A</i>	Epilessia generalizzata con attacchi febbrili
Na ⁺ (controllato dal voltaggio, muscolo cardiaco)	<i>SCN5A</i>	Lunga QT sindrome 3
Ca ²⁺ (neuronale)	<i>CACNA1A</i>	Emicrania emiplegica familiare
Ca ²⁺ (controllato dal voltaggio, retina)	<i>CACNA1F</i>	Cecità notturna stazionaria congenita
Ca ²⁺ (policistina-1)	<i>PKD1</i>	Malattia renale policistica
K ⁺ (neuronale)	<i>KCNQ4</i>	Sordità dominante
K ⁺ (controllato dal voltaggio, neuronale)	<i>KCNQ2</i>	Convulsioni benigne neonatali familiari
Catione non specifico (cGMPdipendenti, retina)	<i>CNCG1</i>	Retinite pigmentosa
Recettore dell'acetilcolina (muscolo scheletrico)	<i>CHRNA1</i>	Sindrome miastenica congenita
Cl ⁻	<i>CFTR</i>	Fibrosi cistica