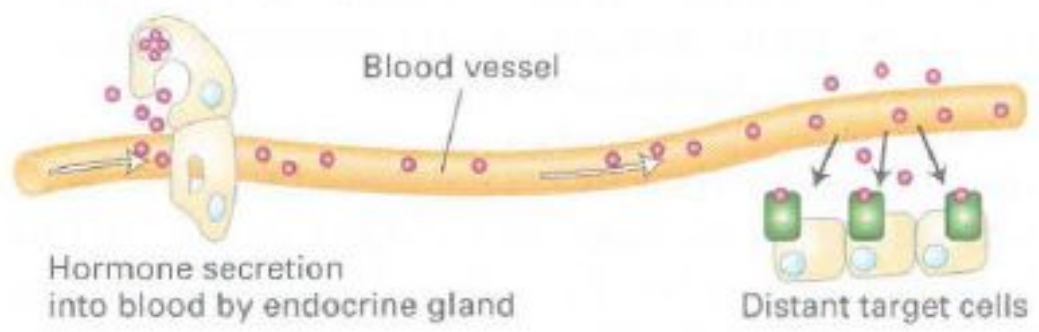
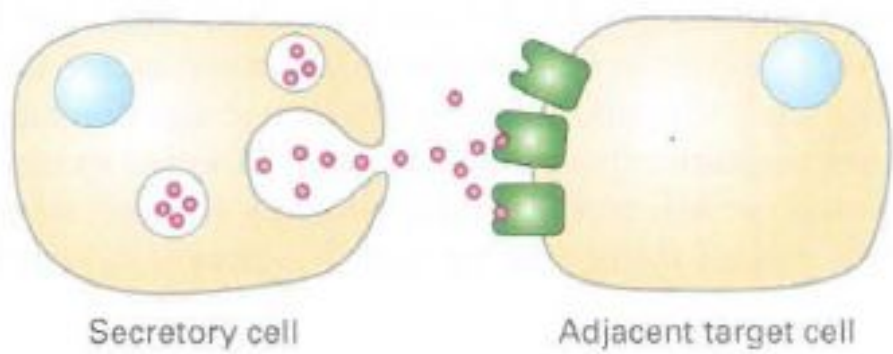


Сигналінг

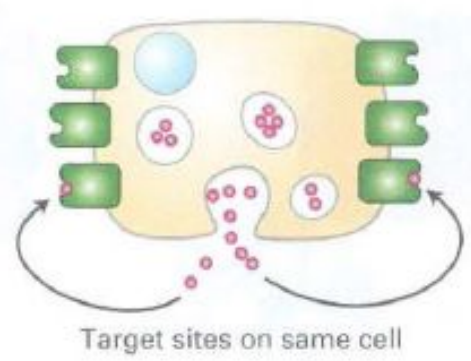
(a) Endocrine signaling



(b) Paracrine signaling



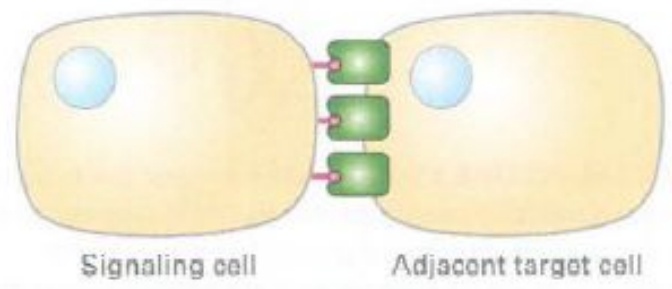
(c) Autocrine signaling

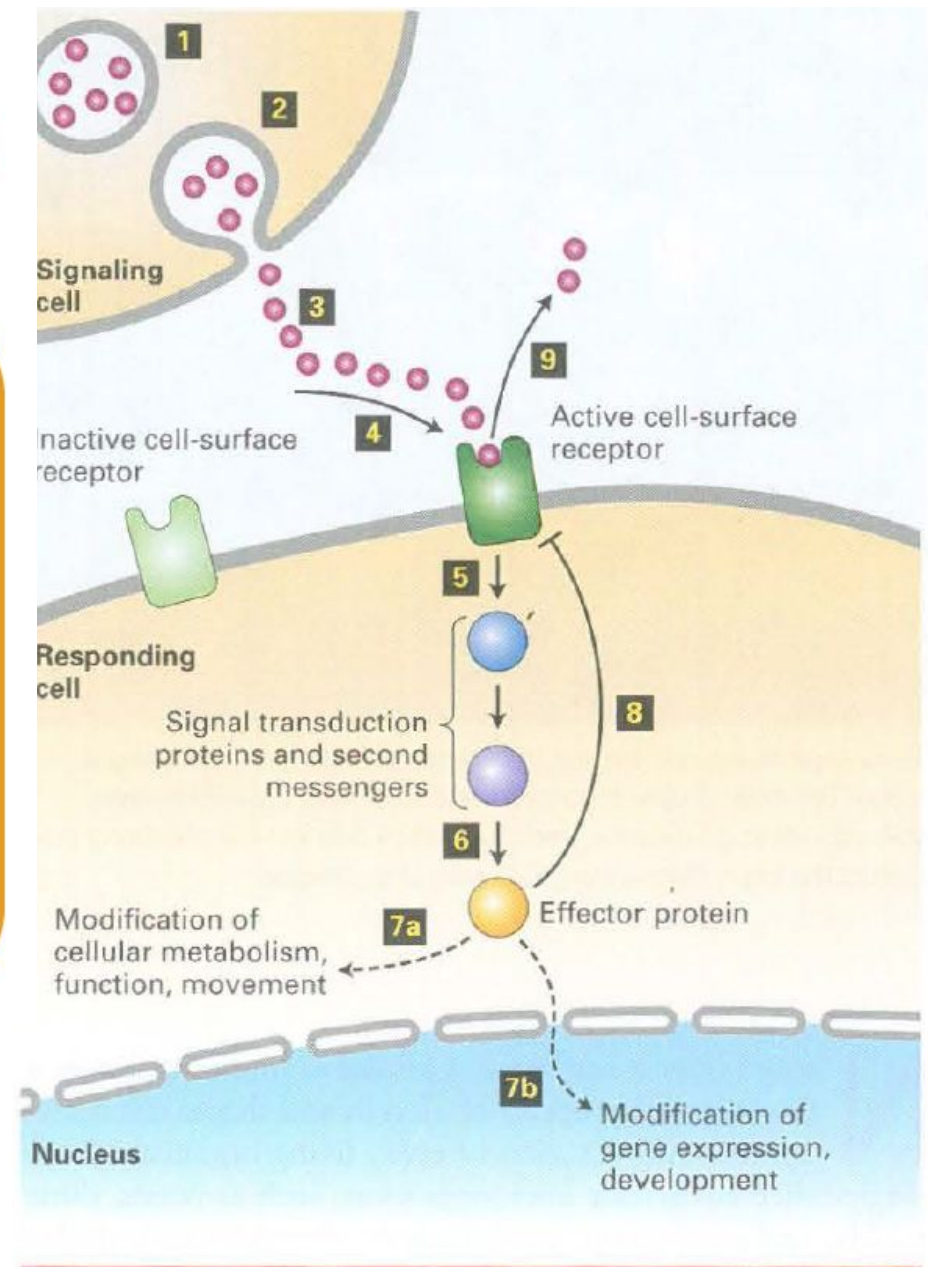
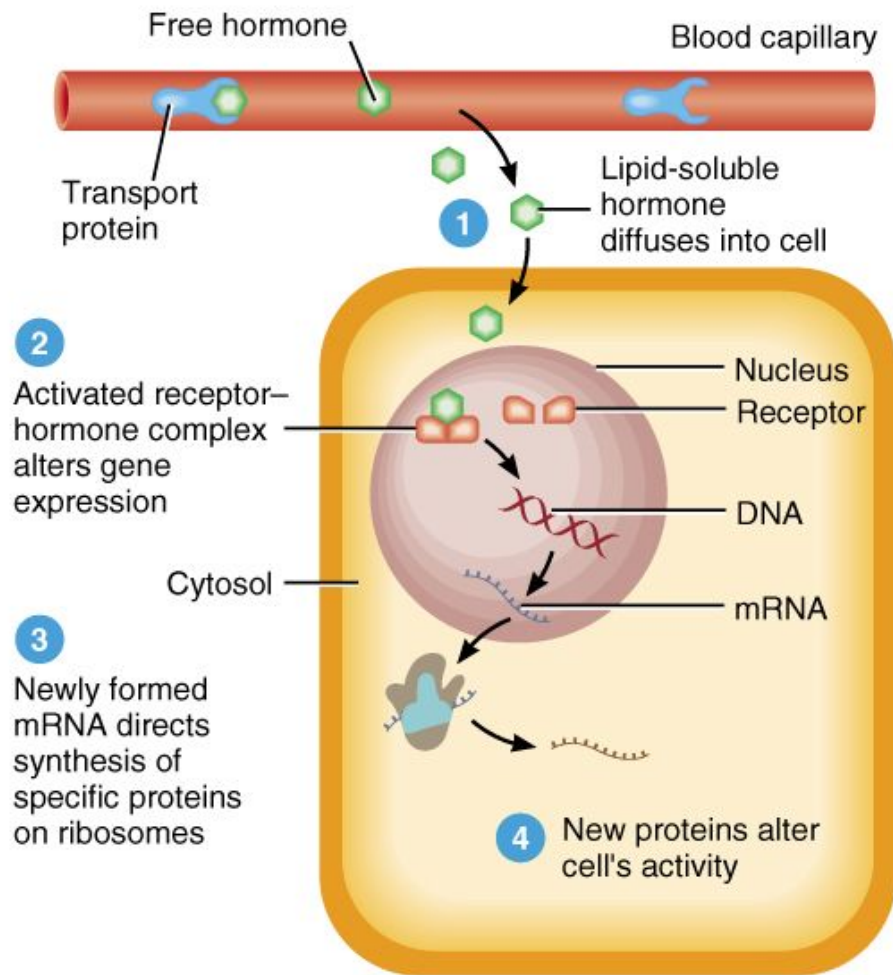


Key:

- Extracellular signal
- Receptor
- Membrane-attached signal

(d) Signaling by plasma-membrane-attached proteins





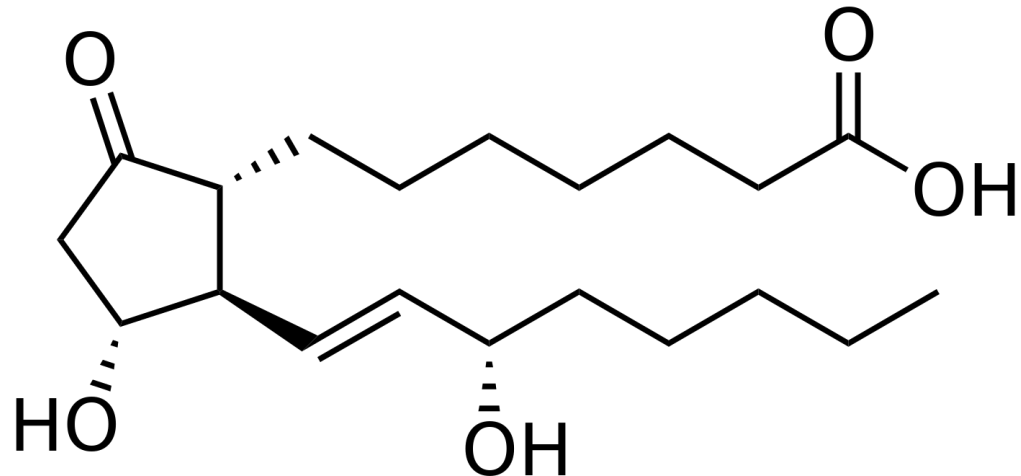
Ліпофільні


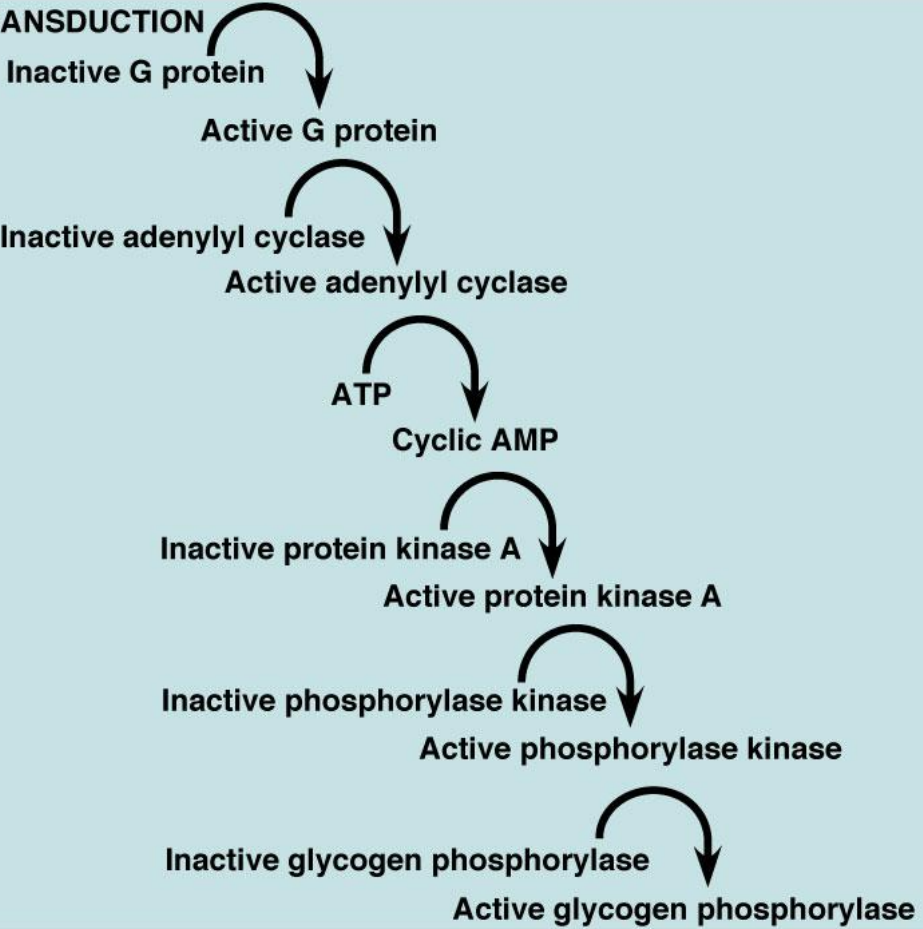

Гідрофільні+простагланди

# простагландины

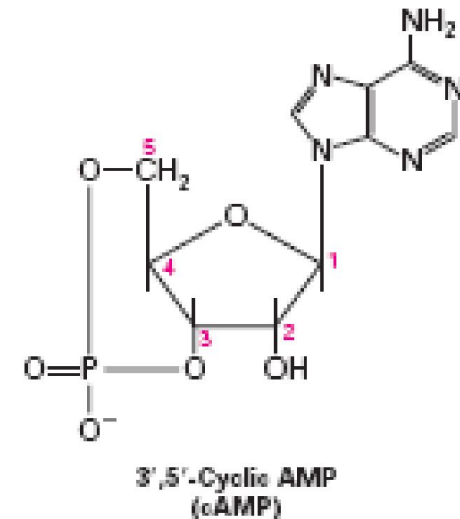
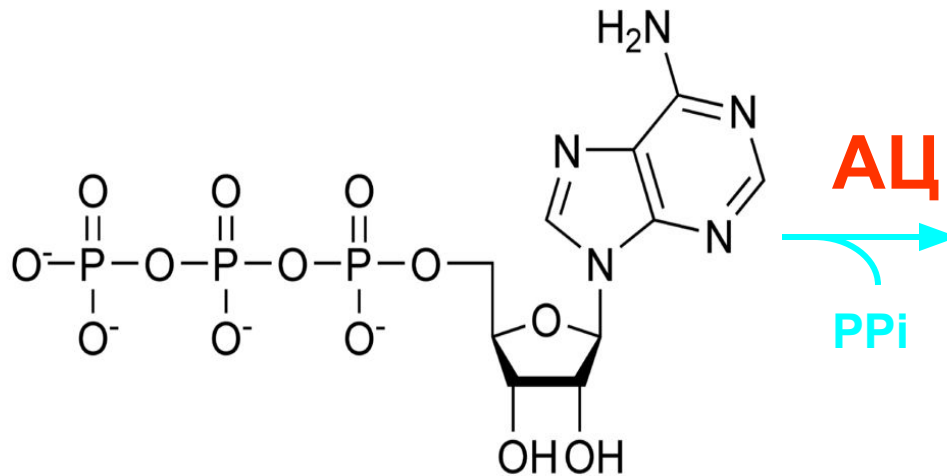
- Влияние на терморегуляторный центр гипоталамуса приводящее к жару
- Регуляция воспаления
- Сенсибилизация спинальных нейронов к боли
- Вазоконстрикция/вазодилатация

Ингибиторы  
циклоксигеназы-  
жаропонижающие,  
противовоспалительные  
и слабые обезболивающие  
(аспирин, ибупрофен)



(a) Signaling pathway	(b) Number of molecules activated
<b>RECEPTION</b> Binding of epinephrine to G protein-linked receptor 	1 molecule
<b>TRANSDUCTION</b>  <p>Inactive G protein → Active G protein</p> <p>Inactive adenylyl cyclase → Active adenylyl cyclase</p> <p>ATP → Cyclic AMP</p> <p>Inactive protein kinase A → Active protein kinase A</p> <p>Inactive phosphorylase kinase → Active phosphorylase kinase</p> <p>Inactive glycogen phosphorylase → Active glycogen phosphorylase</p>	10 <sup>2</sup> molecules
	10 <sup>2</sup> molecules
	10 <sup>4</sup> molecules
	10 <sup>4</sup> molecules
	10 <sup>5</sup> molecules
	10 <sup>6</sup> molecules
<b>RESPONSE</b>  <p>Glycogen → Glucose-1-phosphate</p>	10 <sup>8</sup> molecules

# Вторинний месенджер - цАМФ

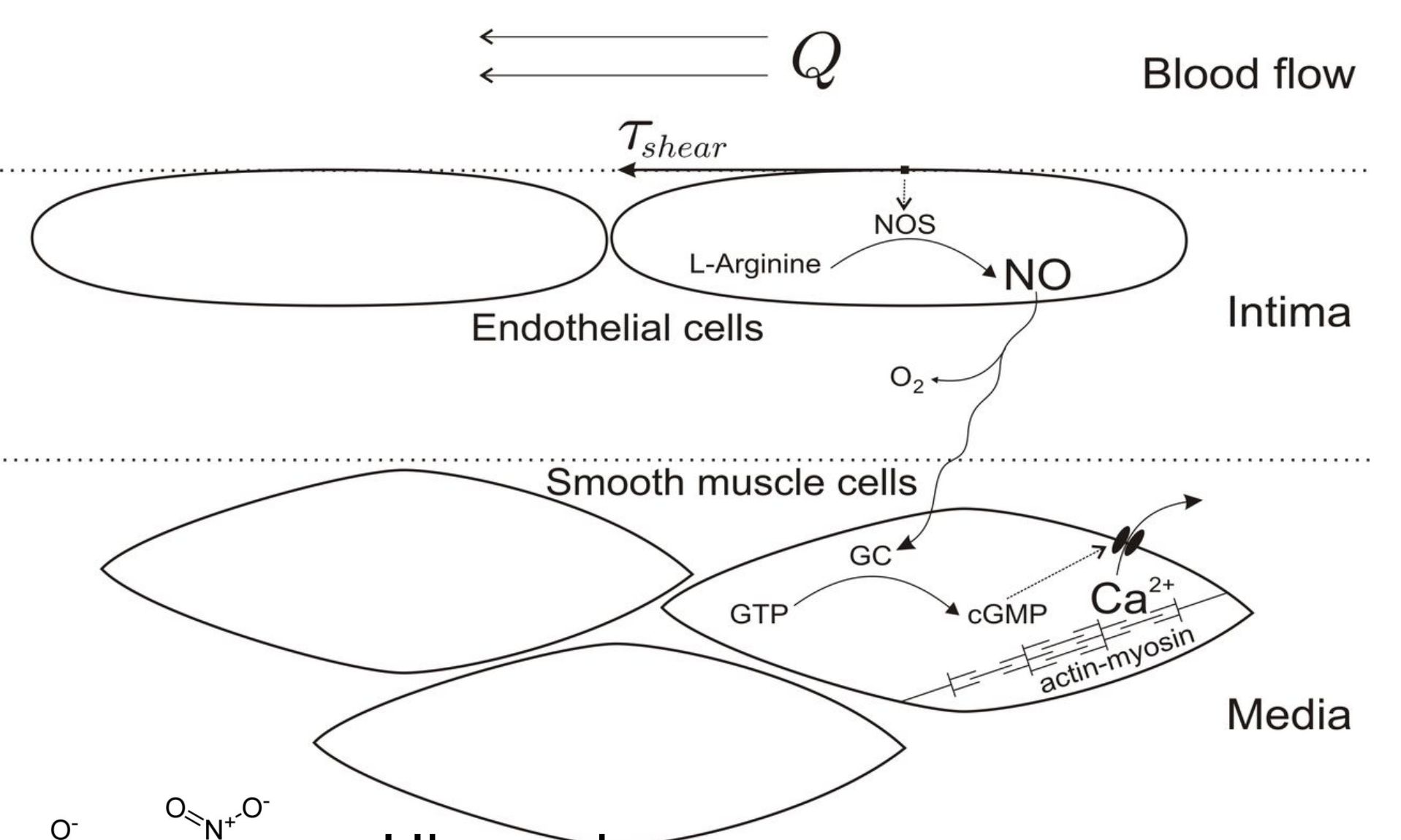


Activates protein kinase A (PKA)

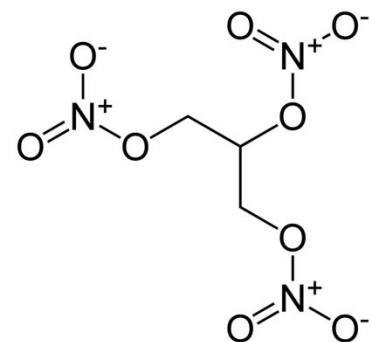
• АТФ

цАМФ

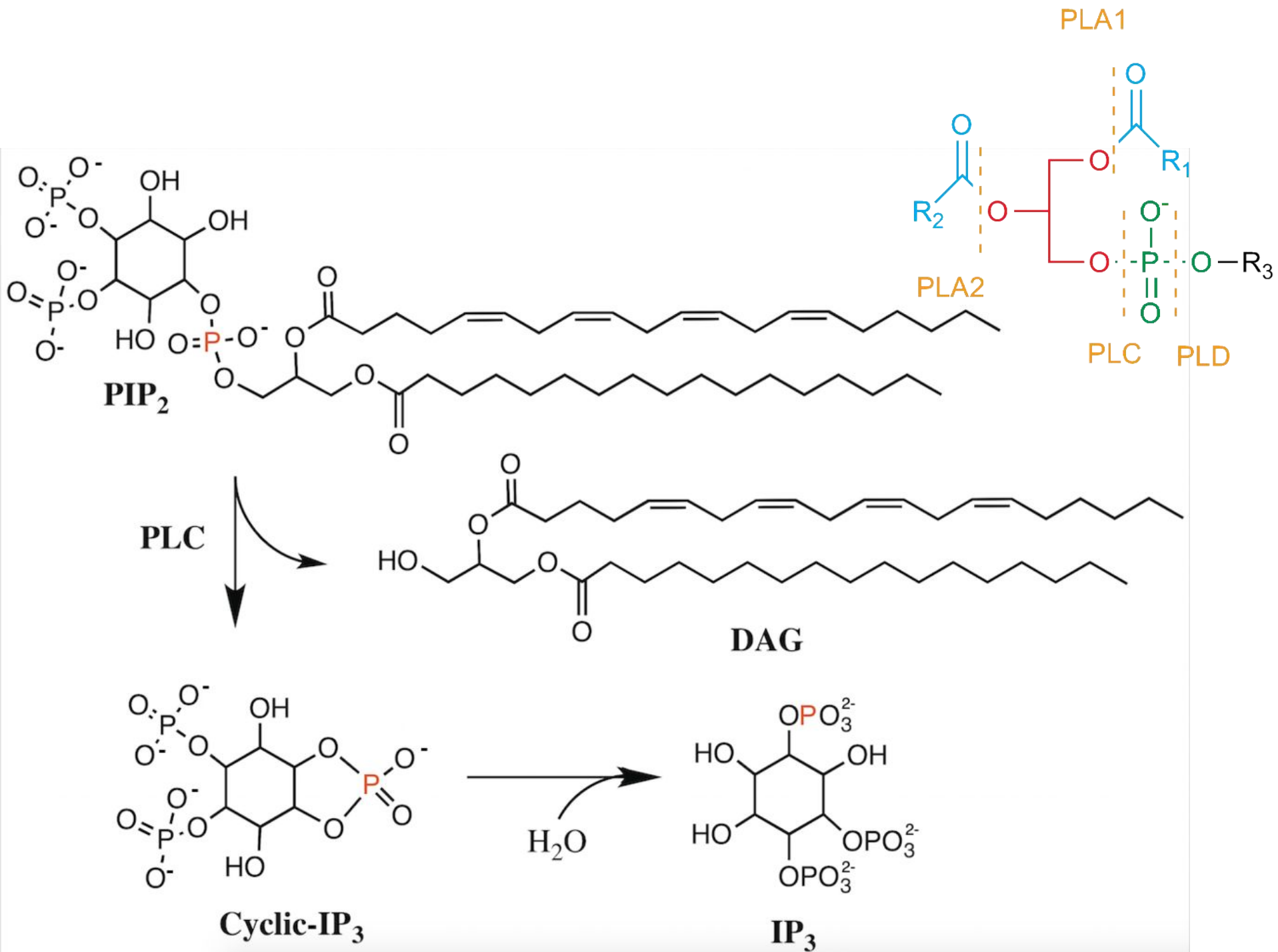
- Інгібітори фосфодієстерази:
- Силделафіл(віагра)-інгібітор фосфодієстерази типу 5
- Дротаверин(Ношпа)



- Нітрогліцерин використовується як лікарський засіб при стенокардії бо здатен розпадатися з утворенням N



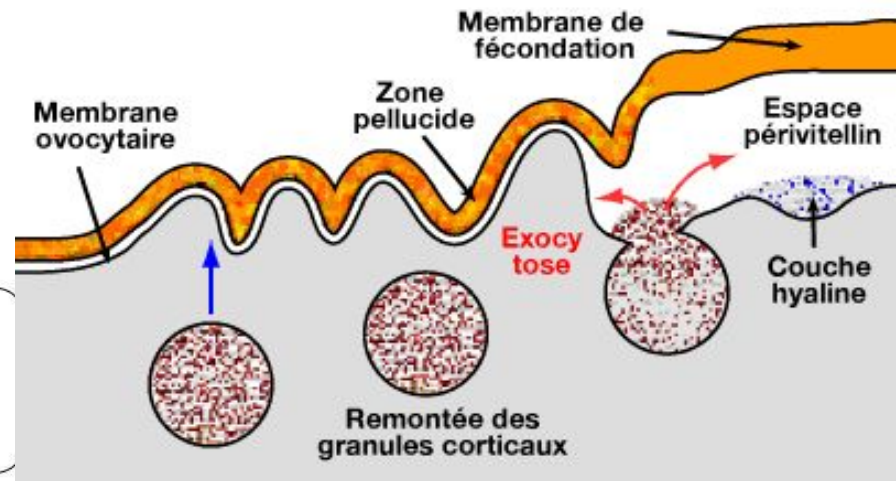
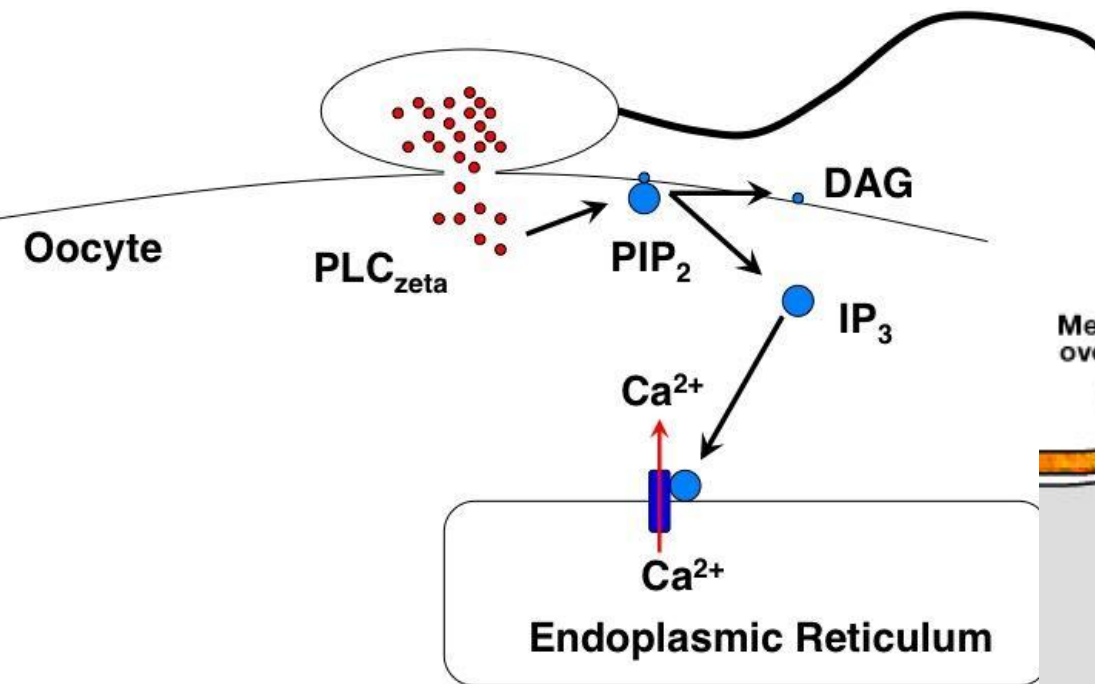
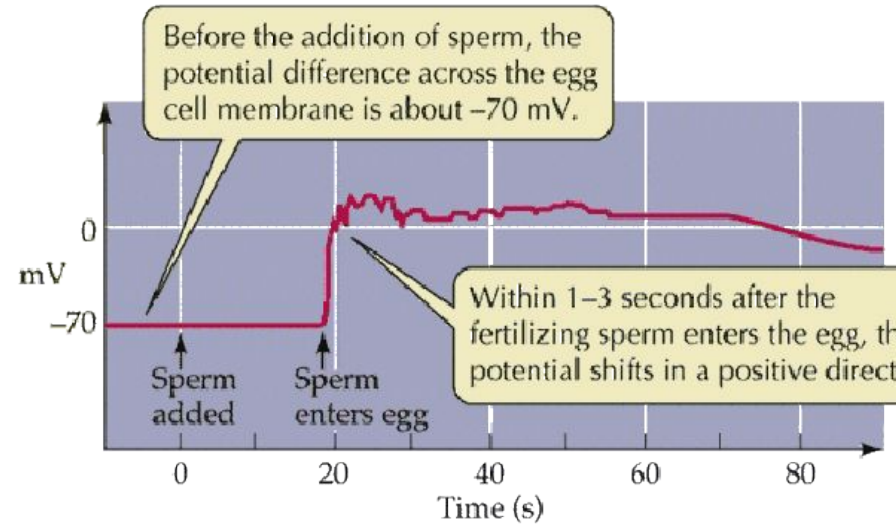






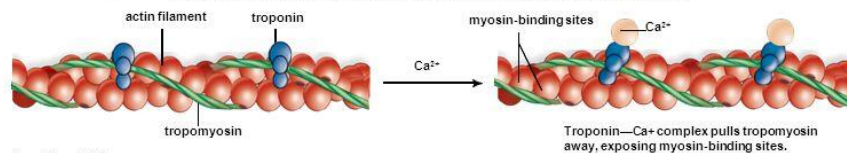
# Ca<sup>2+</sup>

- Екзоцитоз
- нейромедіатори
- Повільна блокада поліспермії
- Активація яйцеклітини
- Синаптична пластичність
- М'язове скорочення



# Ca<sup>2+</sup>

- Екзоцитоз
- нейромедіатори
- Повільна блокада поліспермії
- Активація яйцеклітини
- Синаптична пластичність
- М'язове скорочення



Function of Ca<sup>2+</sup>

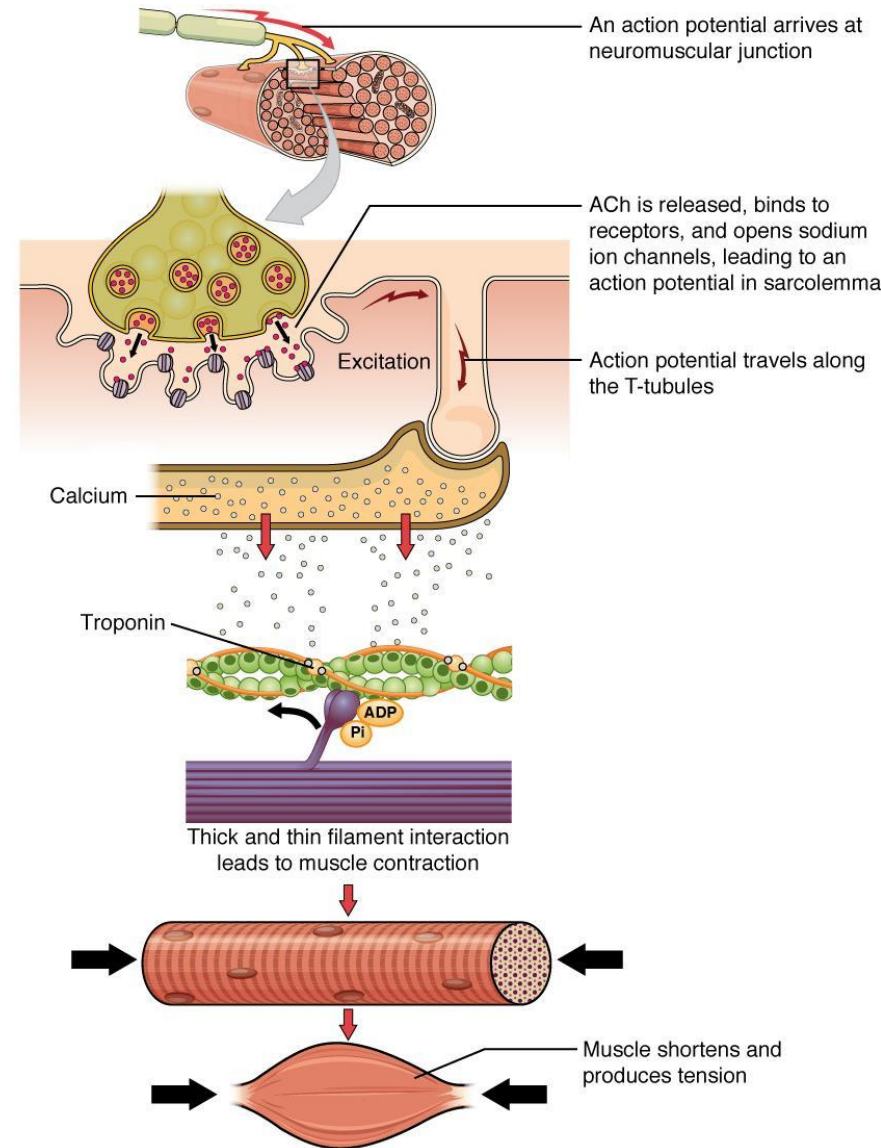
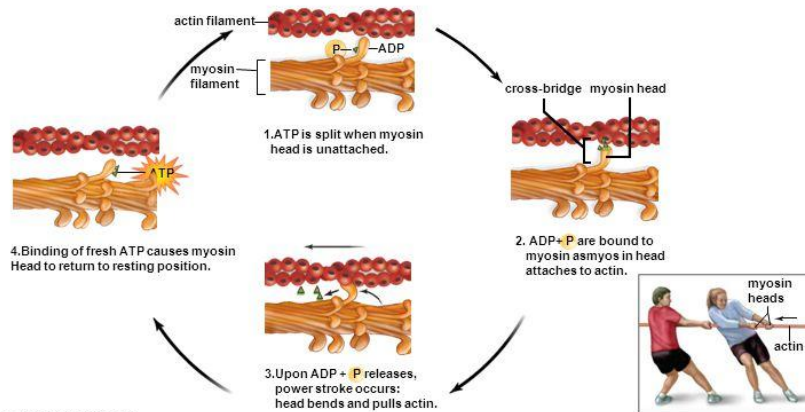
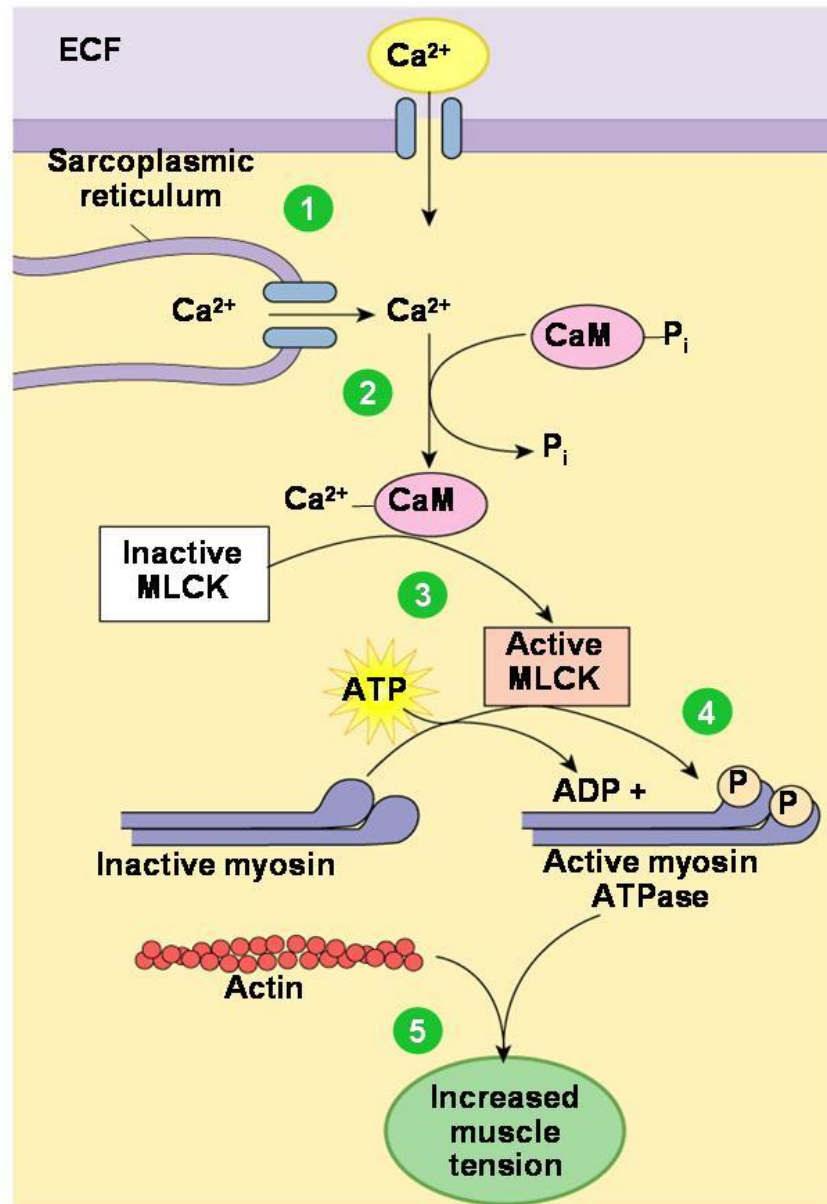


Figure 12.8 The role of calcium ions and ATP during muscular contraction.

# Ca<sup>2+</sup>

- Екзоцитоз
- нейромедіатори
- Повільна блокада поліспермії
- Активація яйцеклітини
- Синаптична пластичність
- М'язове скорочення



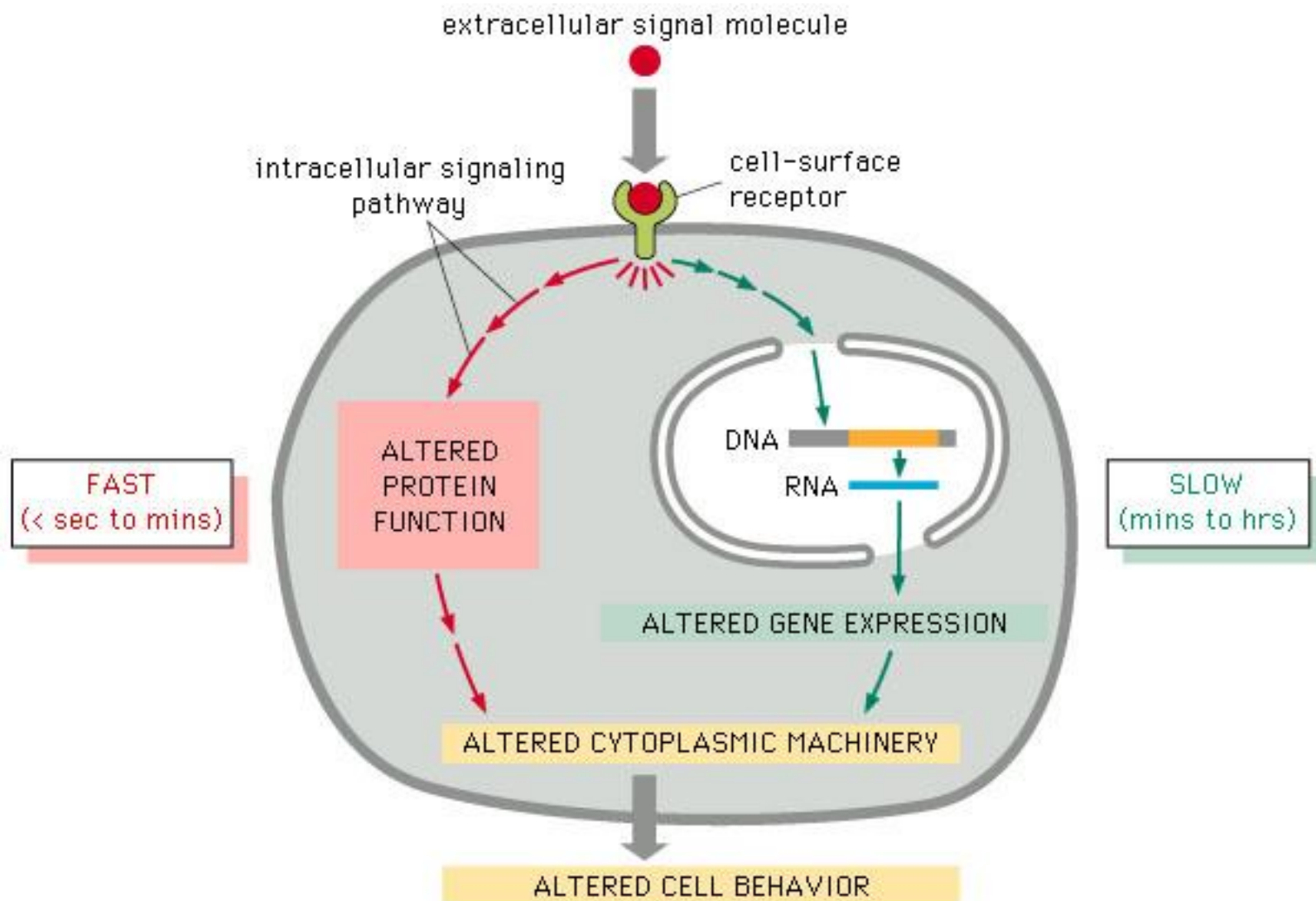
**1** Intracellular Ca<sup>2+</sup> concentrations increase when Ca<sup>2+</sup> enters cell and is released from sarcoplasmic reticulum.

**2** Ca<sup>2+</sup> binds to calmodulin (CaM).

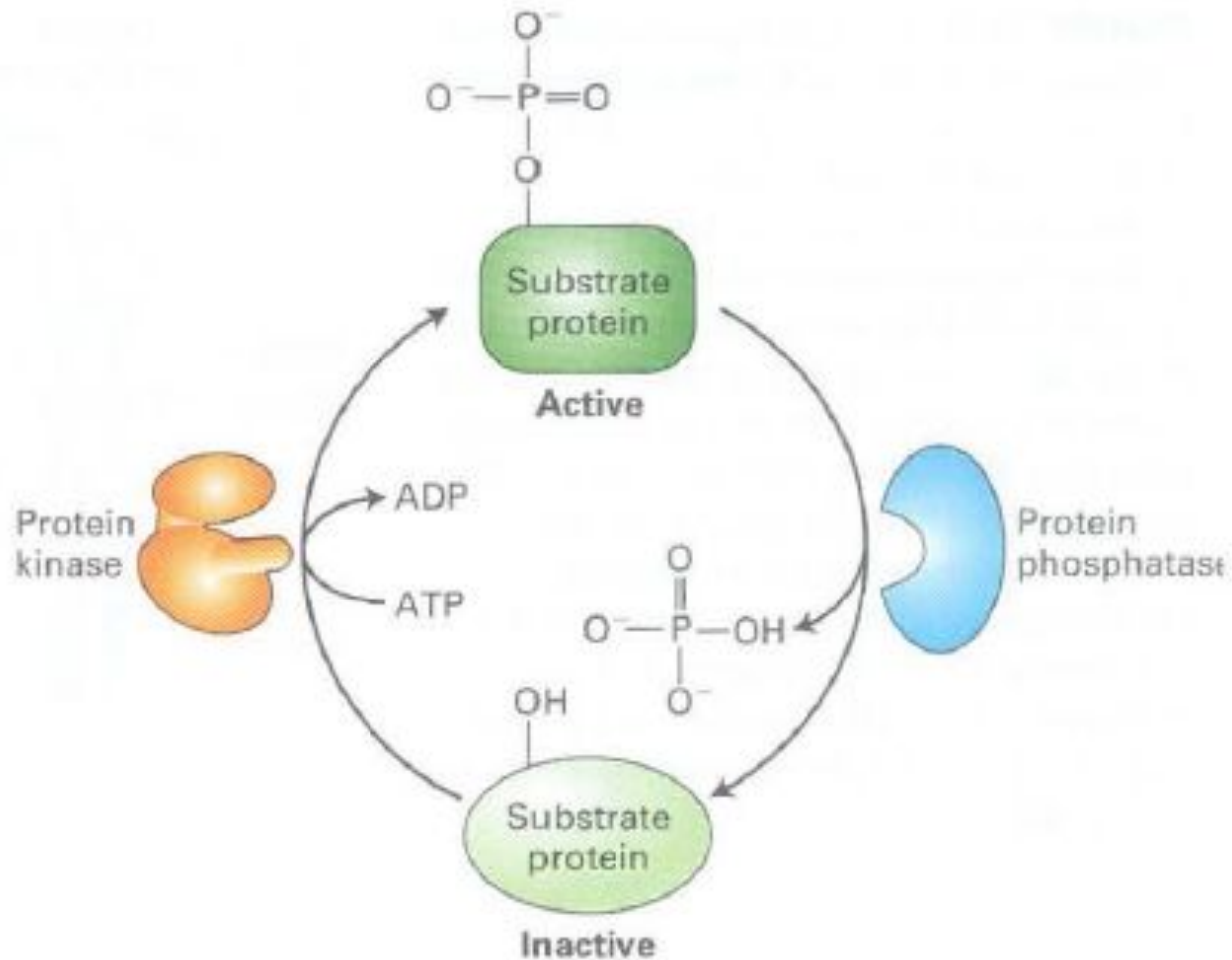
**3** Ca<sup>2+</sup>-calmodulin activates myosin light chain kinase (MLCK).

**4** MLCK phosphorylates light chains in myosin heads and increases myosin ATPase activity.

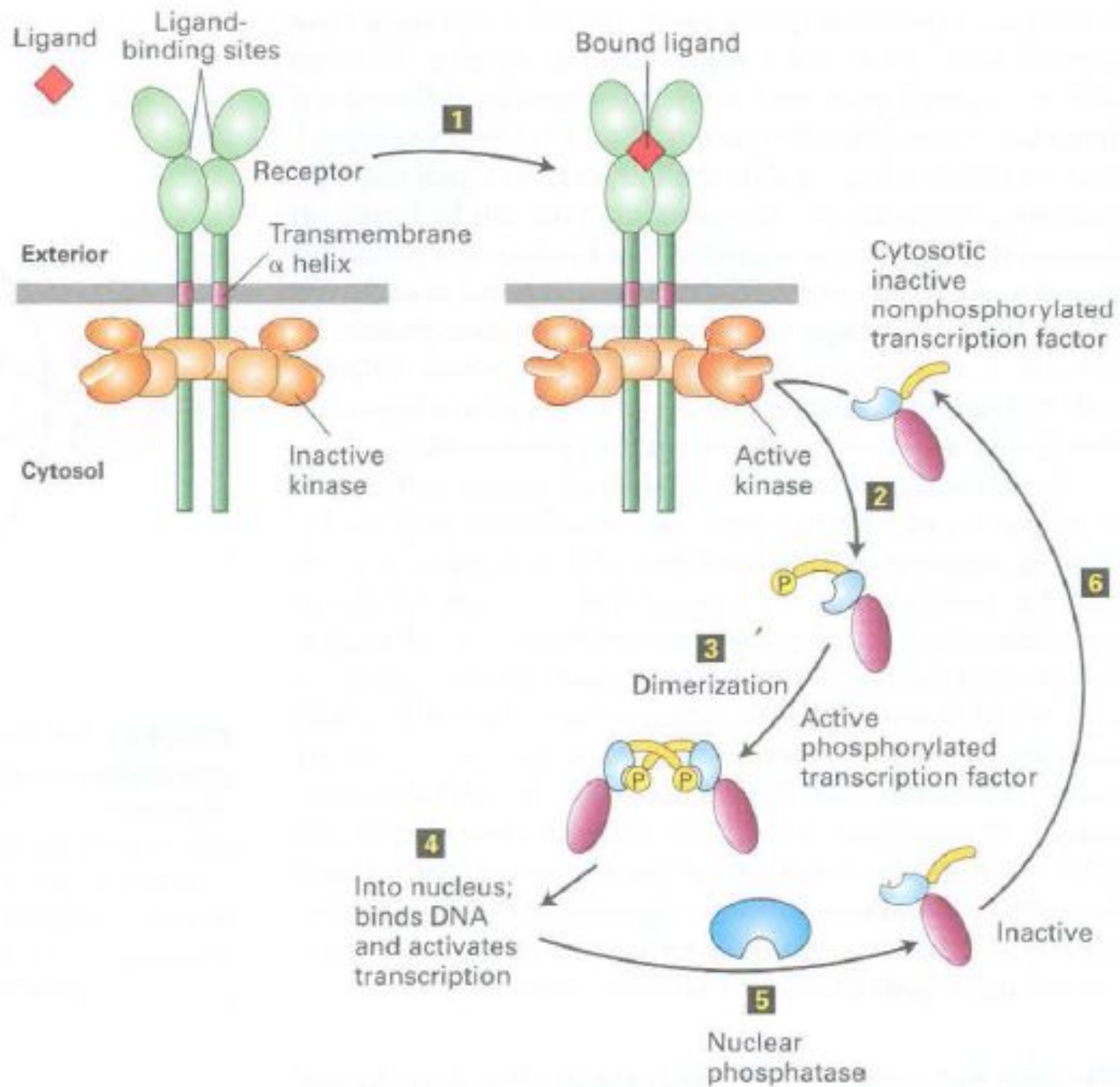
**5** Active myosin crossbridges slide along actin and create muscle tension.



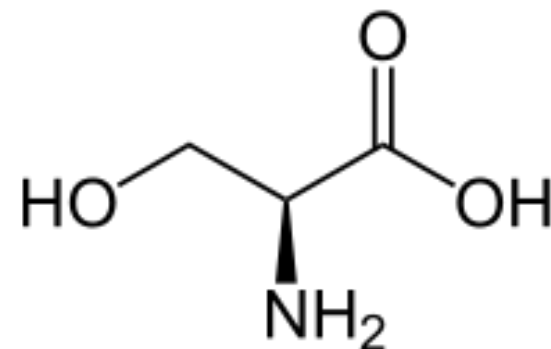
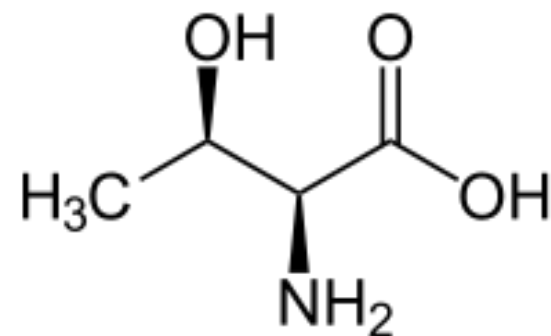
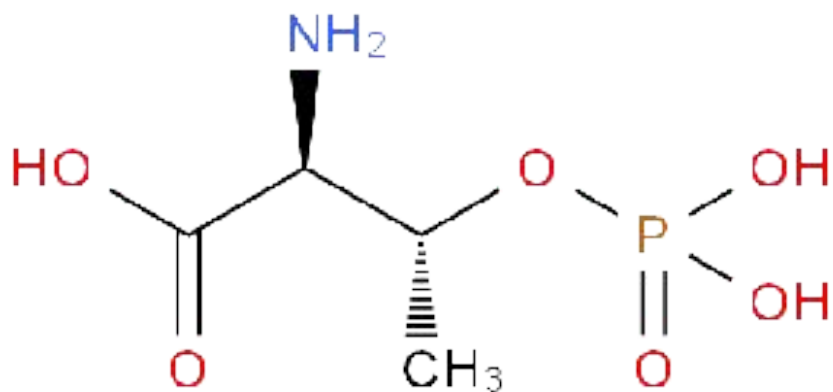
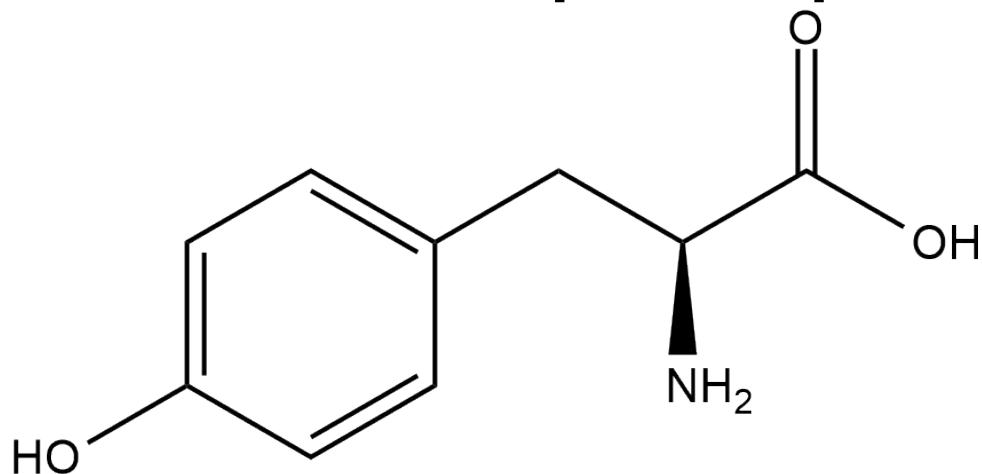
# протеїнкінази та фосфатази



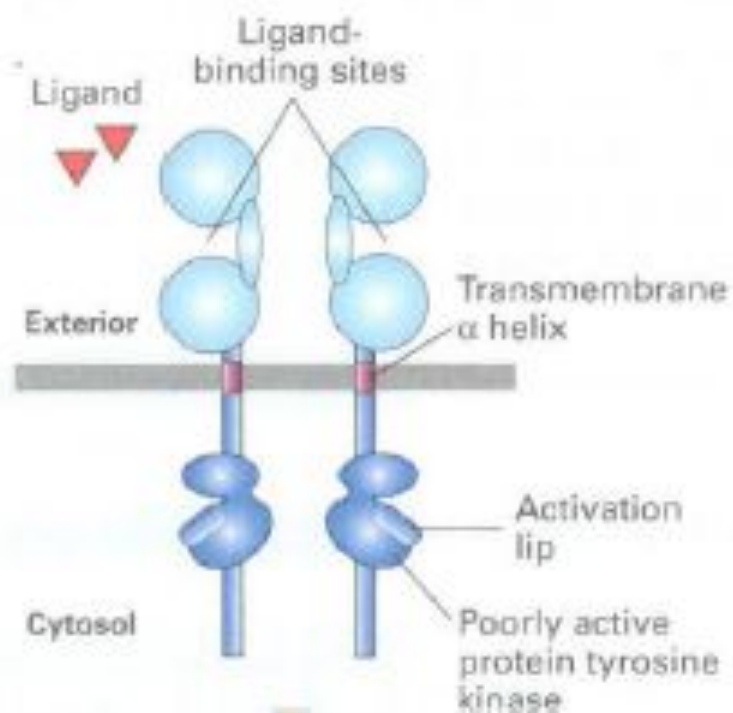




# Киназы бывают тирозиновые и серин-треониновые

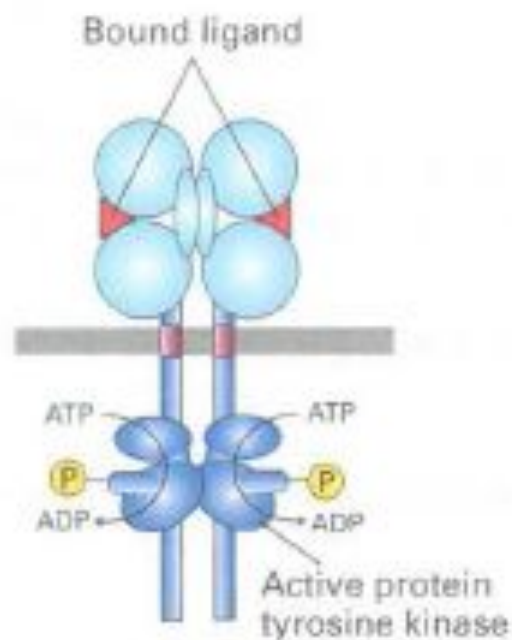






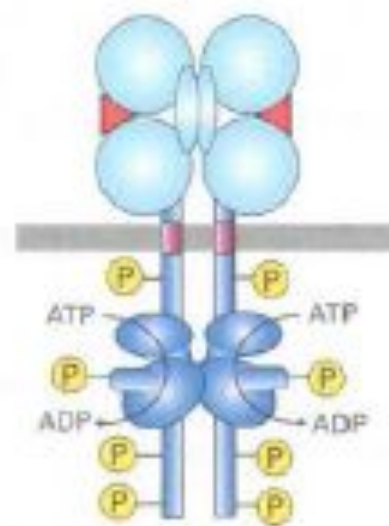
**1**

Receptor tyrosine kinases (RTKs) without bound ligand



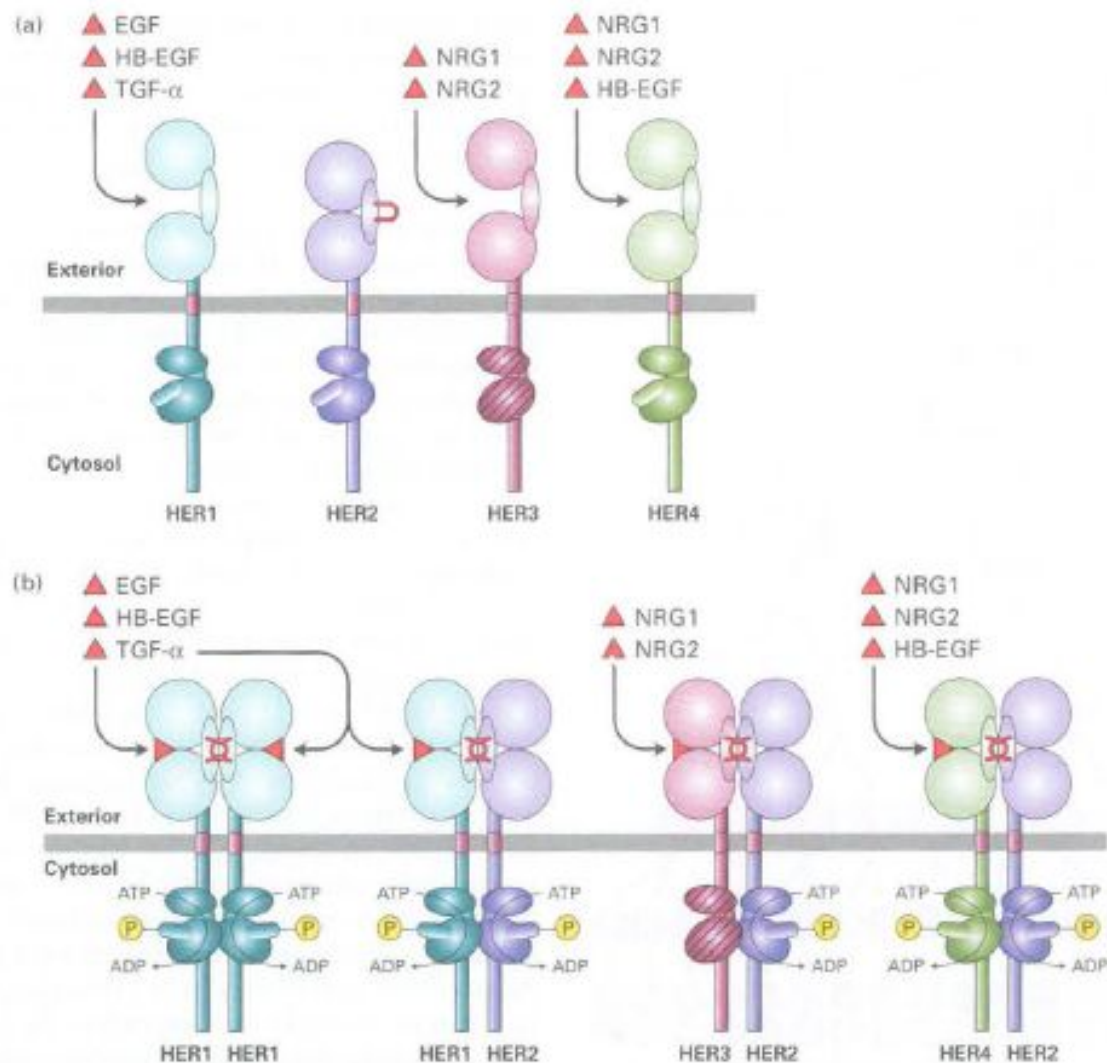
**2**

Dimerization and phosphorylation of activation lip tyrosines



**3**

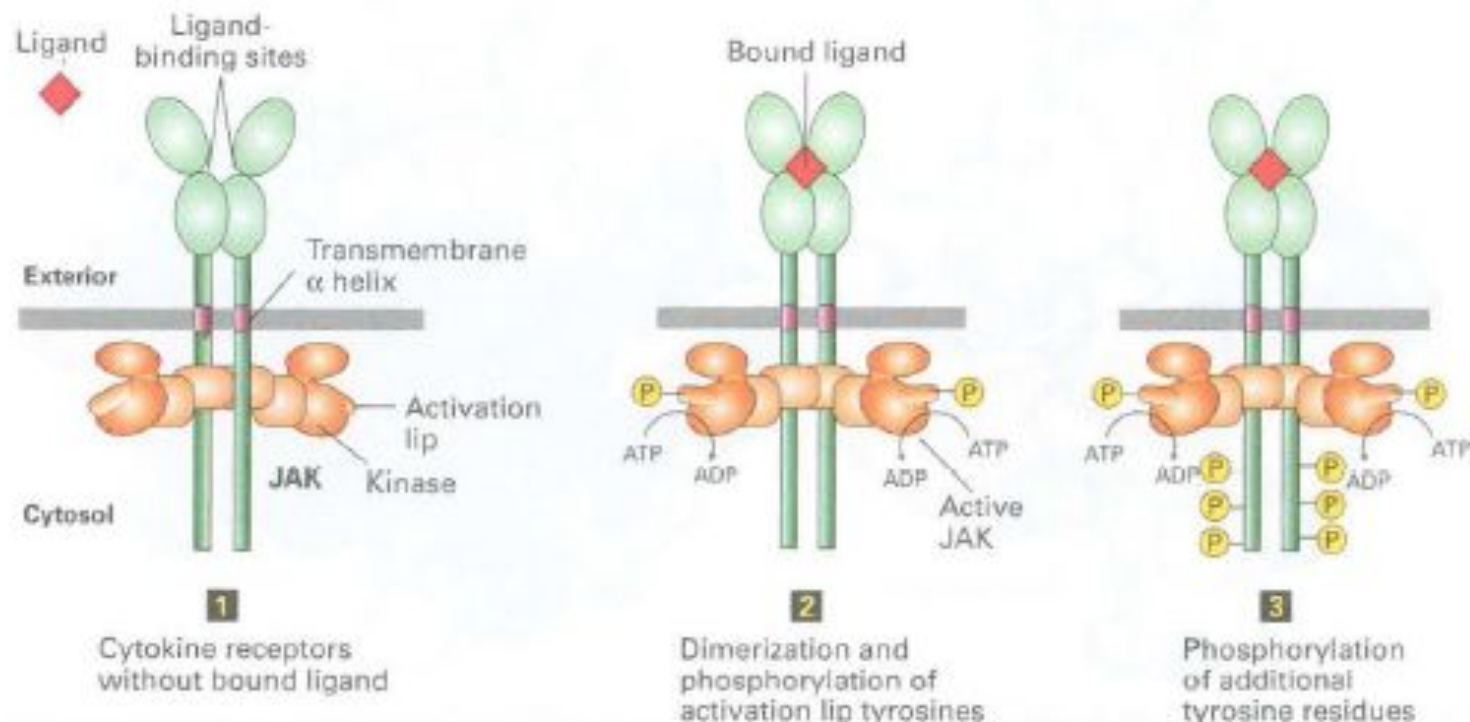
Phosphorylation of additional tyrosine residues



**FIGURE 16-7 The HER family of receptors and their ligands.**

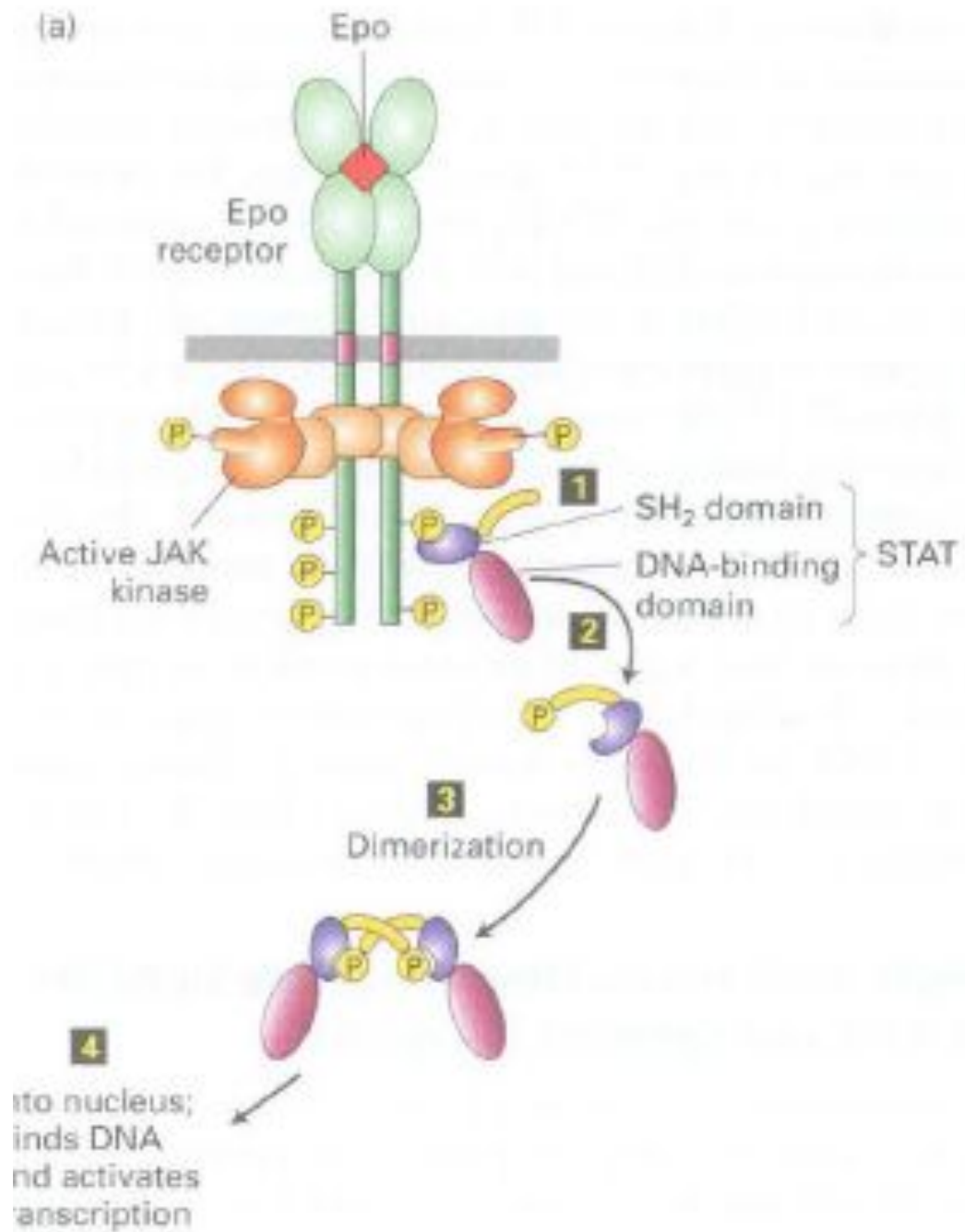
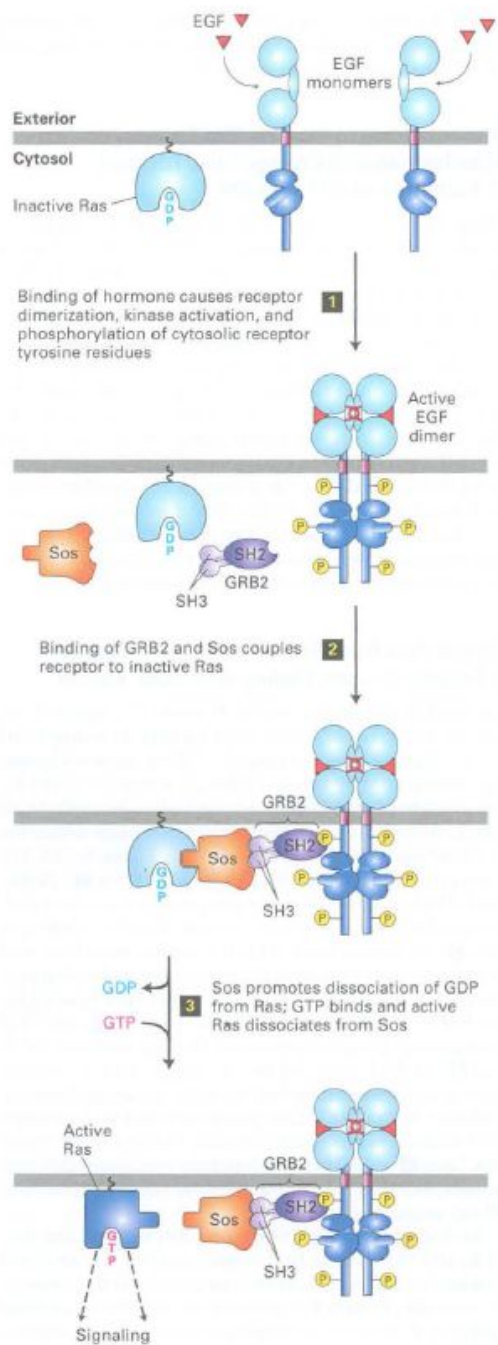
Humans express four receptor tyrosine kinases—denoted HER1, 2, 3, and 4—that bind epidermal growth factor (EGF) and other EGF family members. (a) As shown, the HER proteins differentially bind EGF, heparin-binding EGF (HB-EGF), tumor-derived growth factor  $\alpha$  (TGF- $\alpha$ ), and neuregulins 1 and 2 (NRG1 and NRG2). Note that HER2, which does not directly bind a ligand, exists in the plasma surface membrane in a preactivated state indicated by a red hook.

(b) Ligand-bound HER1 can form activated homodimers bound together by loop segments (red hooks), as detailed in Figure 16-4. HER2 forms heterodimers with ligand-bound HER1, HER3, and HER4 and facilitates signaling by all EGF family members. HER3 has a very poorly active kinase domain and can signal only when complexed with HER2. [After N. E. Hynes and H. A. Lane, 2005, *Nature Rev. Cancer* 5:341 (erratum in *Nature Rev. Cancer* 5:580), and A. B. Singh and R. C. Harris, 2005, *Cell Signal* 17(Oct.):1183.]

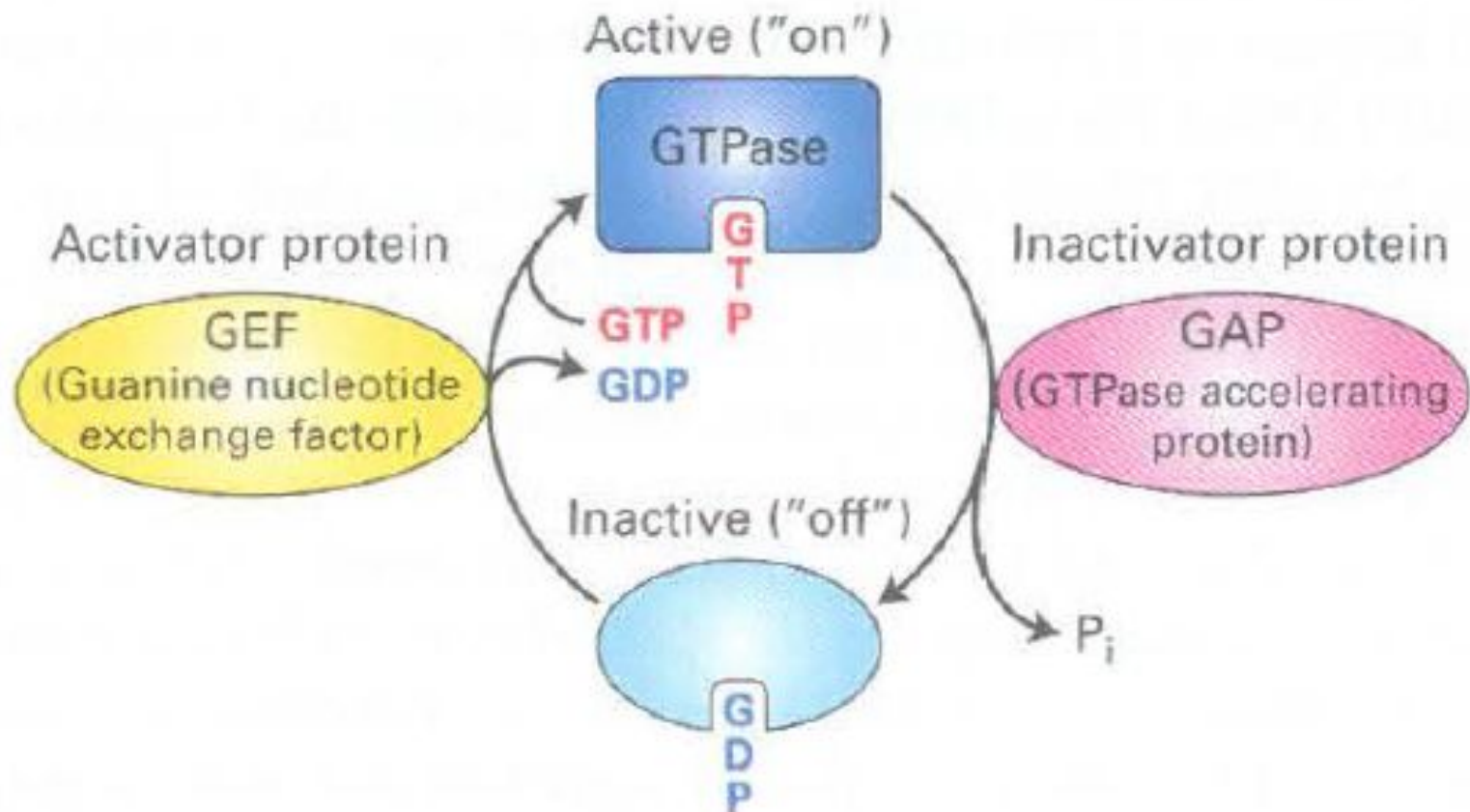


**FIGURE 16-10 General structure and activation of cytokine receptors.** The cytosolic domain of cytokine receptors binds tightly and irreversibly to a JAK protein tyrosine kinase. In the absence of ligand (**1**), the receptors form a homodimer but the JAK kinases are poorly active. Ligand binding causes a conformational change that

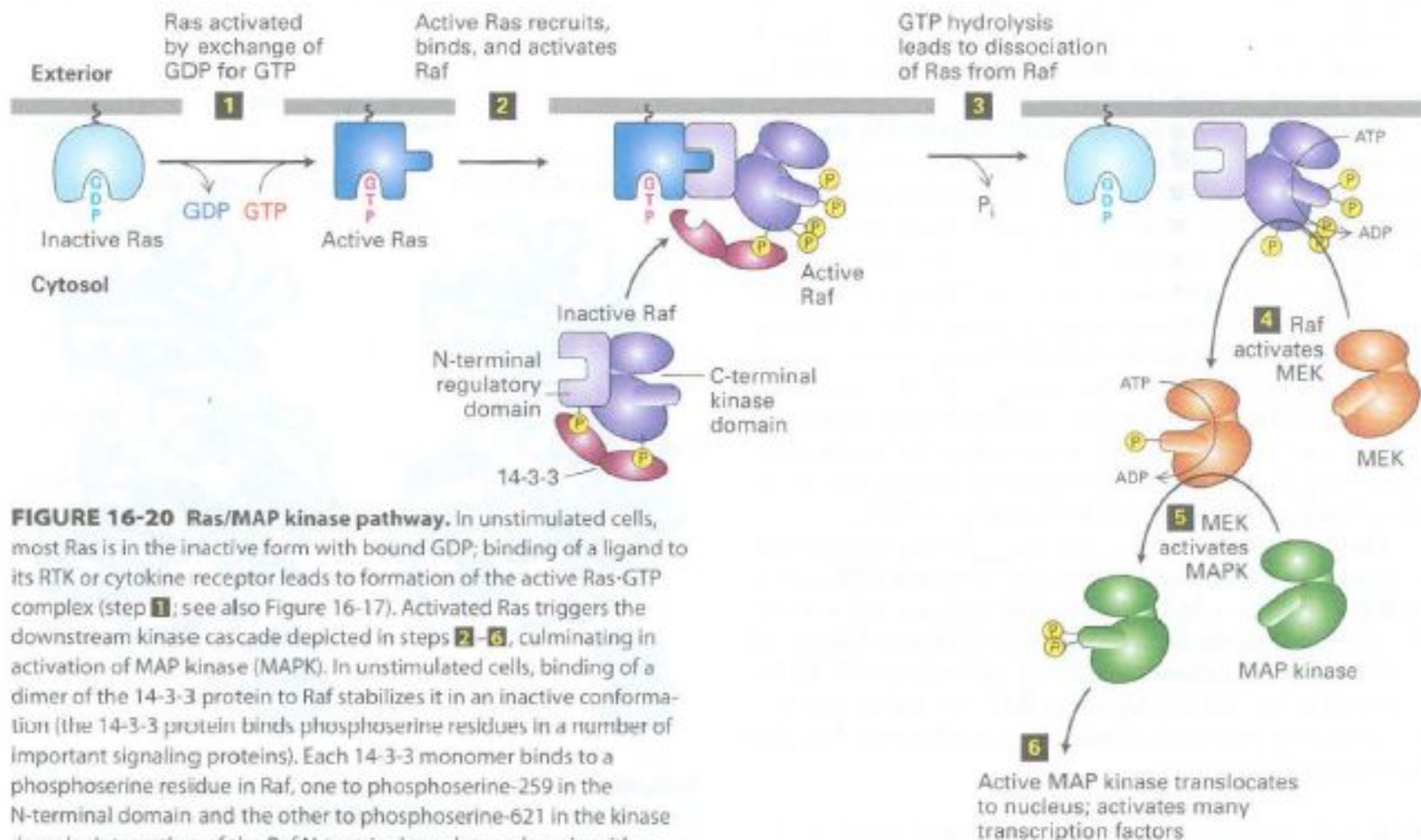
brings together the associated JAK kinase domains, which then phosphorylate each other on a tyrosine residue in the activation lip (**2**). Downstream signaling (**3**) then proceeds in a manner similar to that from receptor tyrosine kinases.



# G-protein



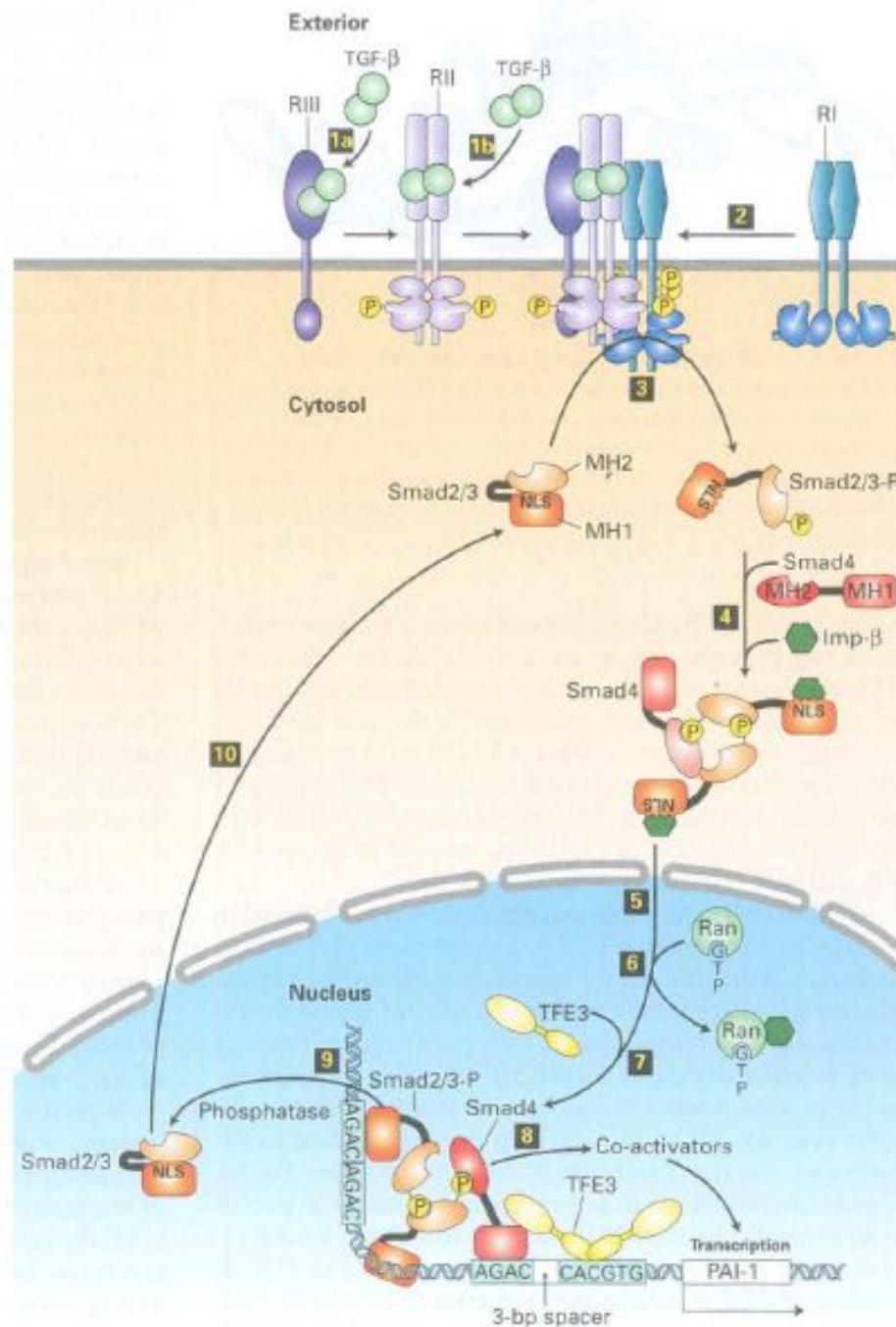




**FIGURE 16-20 Ras/MAP kinase pathway.** In unstimulated cells, most Ras is in the inactive form with bound GDP; binding of a ligand to its RTK or cytokine receptor leads to formation of the active Ras-GTP complex (step 1; see also Figure 16-17). Activated Ras triggers the downstream kinase cascade depicted in steps 2–6, culminating in activation of MAP kinase (MAPK). In unstimulated cells, binding of a dimer of the 14-3-3 protein to Raf stabilizes it in an inactive conformation (the 14-3-3 protein binds phosphoserine residues in a number of important signaling proteins). Each 14-3-3 monomer binds to a phosphoserine residue in Raf, one to phosphoserine-259 in the N-terminal domain and the other to phosphoserine-621 in the kinase domain. Interaction of the Raf N-terminal regulatory domain with Ras-GTP results in dephosphorylation of one of the serines that bind Raf to 14-3-3, phosphorylation of other residues, and activation of Raf kinase activity. After inactive Ras-GDP dissociates from Raf, it presumably can be reactivated by signals from activated receptors, thereby recruiting additional Raf molecules to the membrane. [See E. Kerkhoff and U. Rapp, 2001, *Adv. Enzyme Regul.* **41**:261; J. Avruch et al., 2001, *Recent Prog. Hormone Res.* **56**:127; and M. Yip-Schneider et al., 2000, *Biochem. J.* **351**:151.]

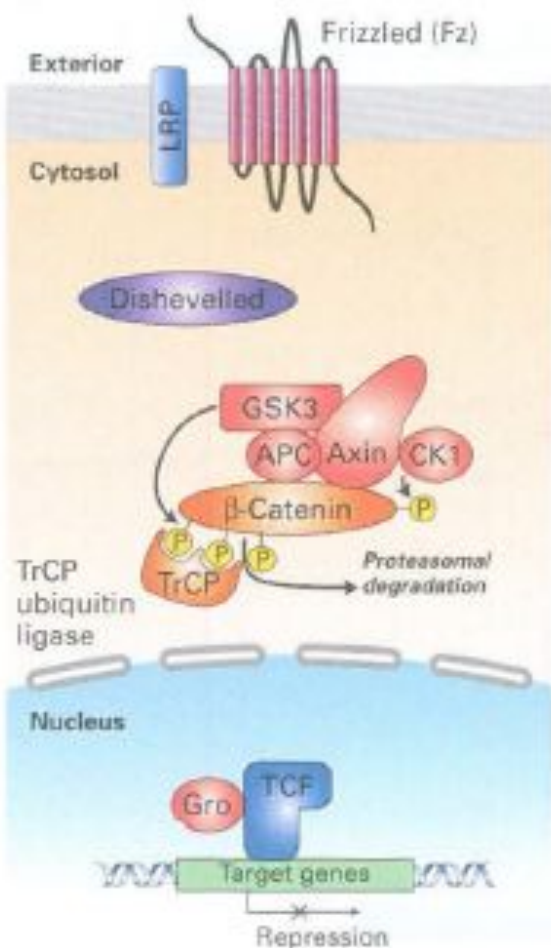
**FIGURE 16-28 TGF- $\beta$ /Smad signaling pathway.**

**Step 1a:** In some cells, TGF- $\beta$  binds to the type III TGF- $\beta$  receptor (RIII), which increases the concentration of TGF- $\beta$  near the cell surface and also presents TGF- $\beta$  to the type II receptor (RII). **Step 1b:** In other cells, TGF- $\beta$  binds directly to RII, a constitutively phosphorylated and active kinase. **Step 2:** Ligand-bound RII recruits and phosphorylates the juxtamembrane segment of the type I receptor (RI), which does not directly bind TGF- $\beta$ . This releases the inhibition of RI kinase activity that otherwise is imposed by the segment of RI between the membrane and its kinase domain. **Step 3:** Activated RI then phosphorylates Smad2 or Smad3 (shown here as Smad 2/3), causing a conformational change that unmasks its nuclear-localization signal (NLS). **Step 4:** Two phosphorylated molecules of Smad 2/3 bind to a co-Smad (Smad4) molecule, which is not phosphorylated, and with an importin, forming a large cytosolic complex. **Steps 5 and 6:** After the entire complex translocates into the nucleus, Ran-GTP causes dissociation of the importin as discussed in Chapter 13. **Step 7:** A nuclear transcription factor (e.g., TFE3) then associates with the Smad2/3/Smad4 complex, forming an activation complex that cooperatively binds in a precise geometry to regulatory sequences of a target gene. **Step 8:** This complex then recruits transcriptional co-activators and induces gene transcription (see Chapter 7). Smad 2/3 is dephosphorylated by a nuclear phosphatase (step 9) and recycles through a nuclear pore to the cytosol (step 10), where it can be reactivated by another TGF- $\beta$  receptor complex. Shown at the bottom is the activation complex for the gene encoding plasminogen activator inhibitor (PAI-1), and similar transcription complexes activate expression of genes encoding other extracellular matrix proteins such as fibronectin. [See A. Moustakas and C.-H. Heldin, 2009, *Development* **136**:3699, and D. Clarke and X. Liu, 2008, *Trends Cell Biol.* **18**:430.]

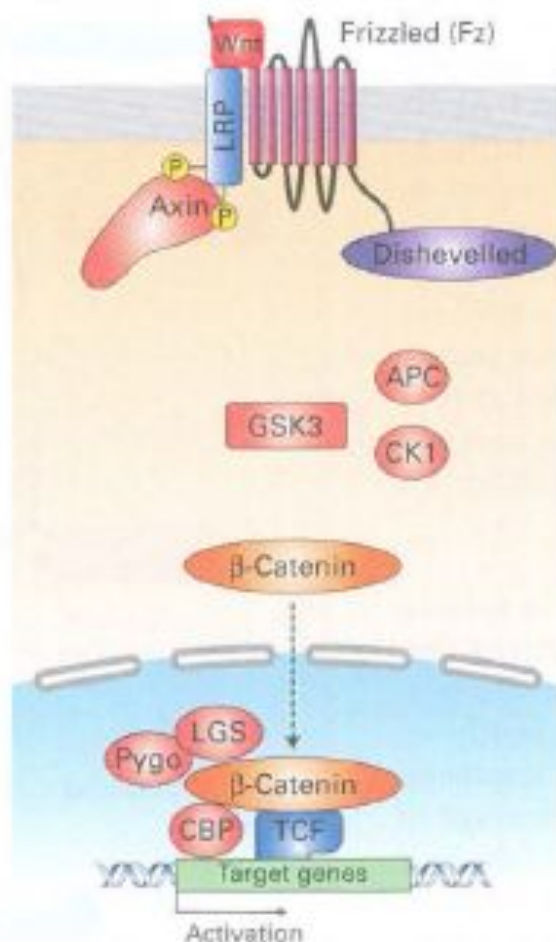




(a) -Wnt

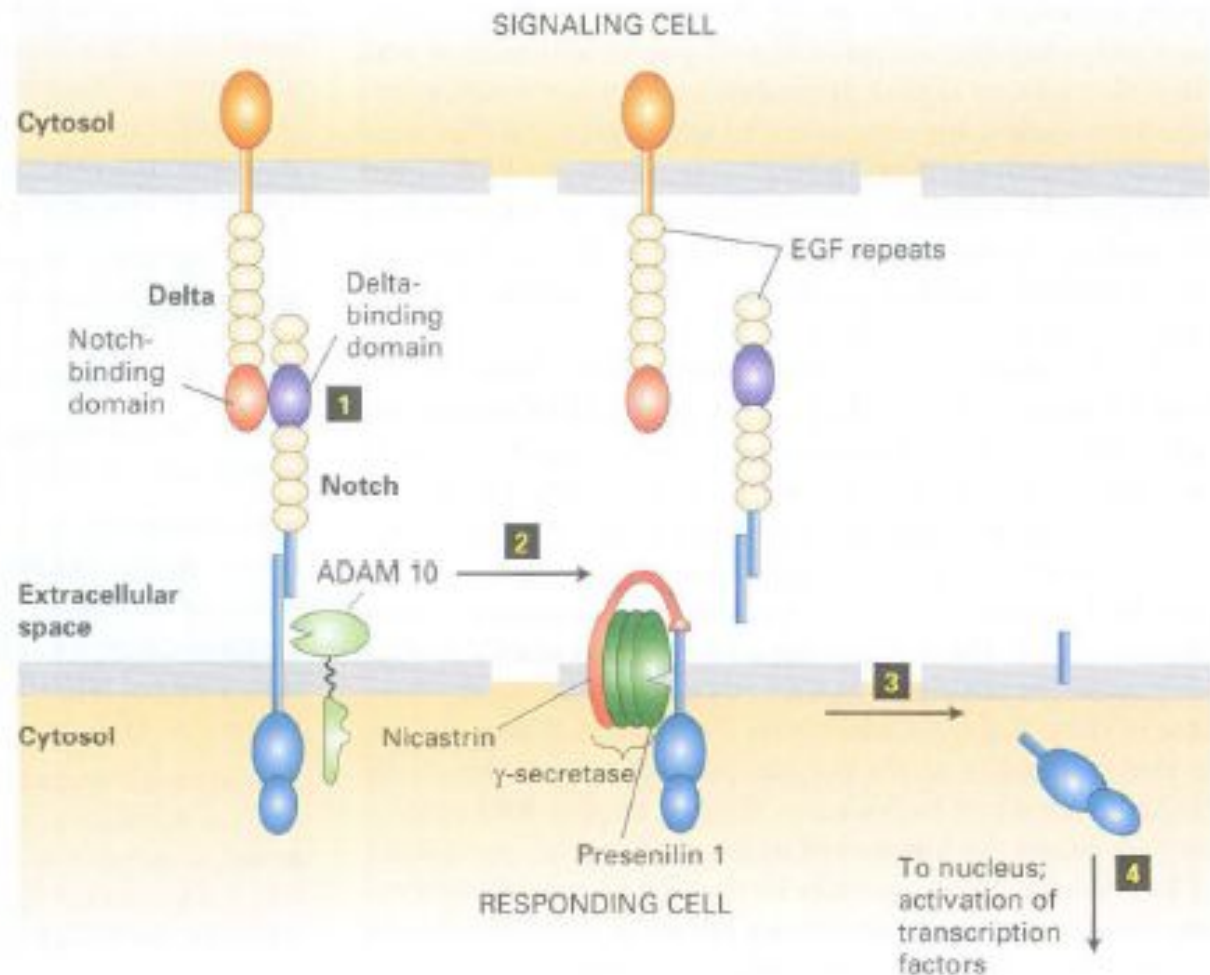


(b) +Wnt

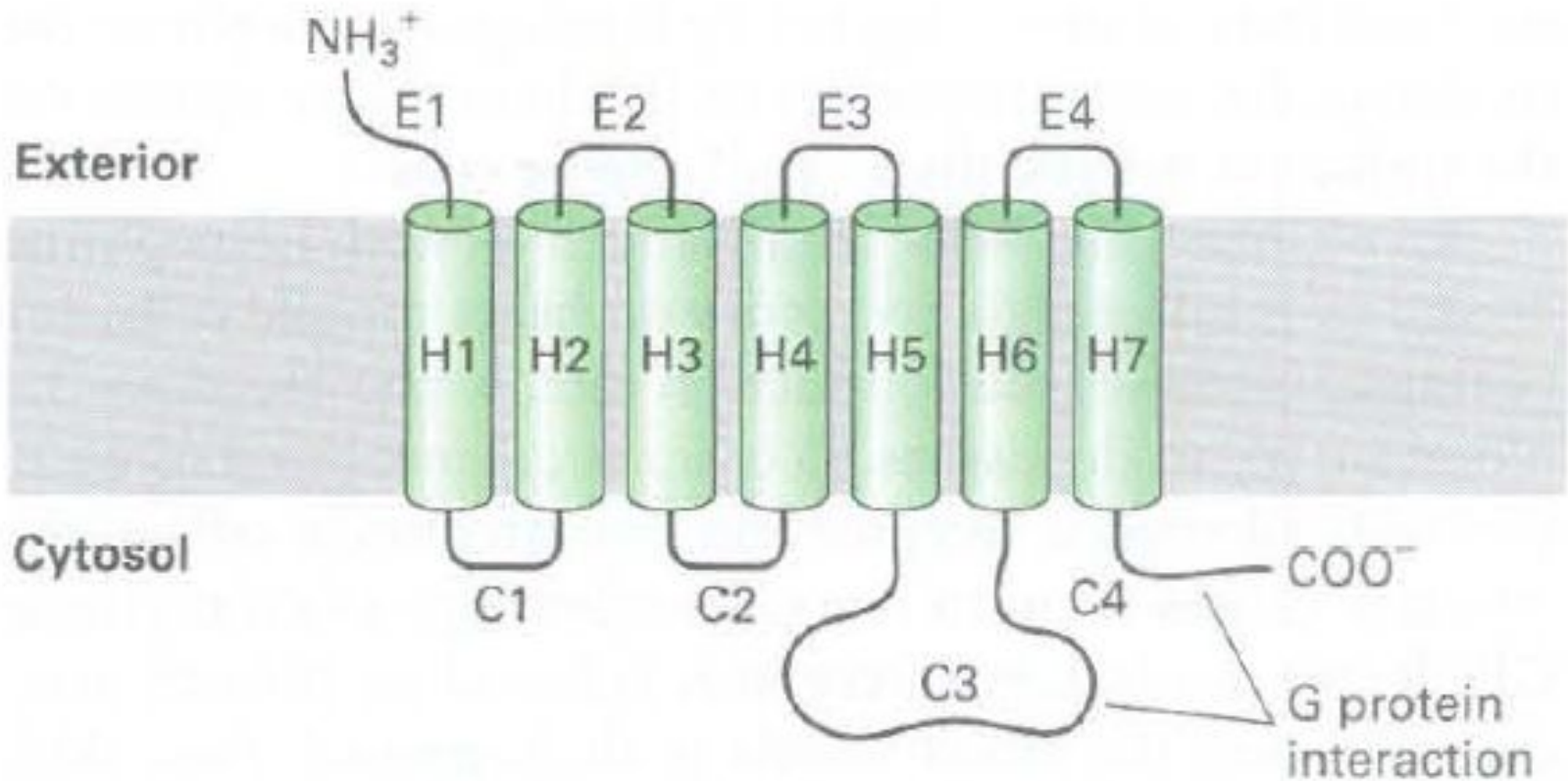


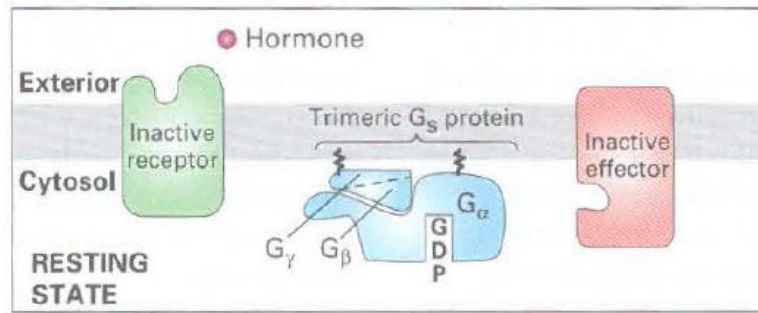
**FIGURE 16-30 Wnt signaling pathway.** (a) In the absence of Wnt, the transcription factor TCF is bound to promoters or enhancers of target genes, but its association with transcriptional repressors such as Groucho (Gro) inhibits gene activation.  $\beta$ -catenin is found in a complex with Axin (a scaffold protein), APC, and the kinases CK1 and GSK3, which sequentially phosphorylate  $\beta$ -catenin. Axin-mediated formation of this complex facilitates phosphorylation of  $\beta$ -catenin by GSK3 by an estimated factor of 20,000. The E3 TrCP ubiquitin ligase then binds to two of these phosphorylated  $\beta$ -catenin residues, leading to  $\beta$ -catenin ubiquitination and degradation in proteasomes. (b) Binding of Wnt to its receptor Frizzled (Fz) and to the LRP co-receptor triggers phosphorylation of LRP by GSK3 and another kinase, allowing subsequent binding of Axin. This disrupts the Axin-APC-CK1-GSK3- $\beta$ -catenin complex, preventing phosphorylation of  $\beta$ -catenin by CK1 and GSK3 and leading to accumulation of  $\beta$ -catenin in the cell. After translocation to the nucleus,  $\beta$ -catenin binds to TCF to displace the Gro repressor and recruits Pygo, LGS, and other proteins to activate gene expression. (After R. van Amerongen and R. Nusse, 2009, *Development* **136**:3205; F. Staal and J. Sen, 2008, *Eur. J. Immunol.* **38**:1788, and E. Verheyen and C. Gottardi, 2010, *Dev. Dyn.* **239**:34. See also the Wnt Homepage, [www.stanford.edu/group/nusselab/cgi-bin/wnt/](http://www.stanford.edu/group/nusselab/cgi-bin/wnt/).)

**FIGURE 16-35 Notch/Delta signaling pathway.** In the absence of Delta, the extracellular subunit of Notch on a responding cell is noncovalently associated with its transmembrane-cytosolic subunit. When Notch binds to its ligand Delta on an adjacent signaling cell (step **1**), Notch is first cleaved by the matrix metalloprotease ADAM 10, which is bound to the membrane, releasing the extracellular Notch segment (step **2**). Next the nicastrin subunit of the four protein  $\gamma$ -secretase complex binds to the stump generated by ADAM 10, and the presumed protease, presenilin 1, catalyzes an intramembrane cleavage that releases the cytosolic segment of Notch (step **3**). Following translocation to the nucleus, this Notch segment interacts with several transcription factors to affect expression of genes that in turn influence the determination of cell fate during development (step **4**). [See M. S. Brown et al., 2000, *Cell* **100**:391, and D. Seals and S. Courtneidge, 2003, *Genes Dev.* **17**:7.]

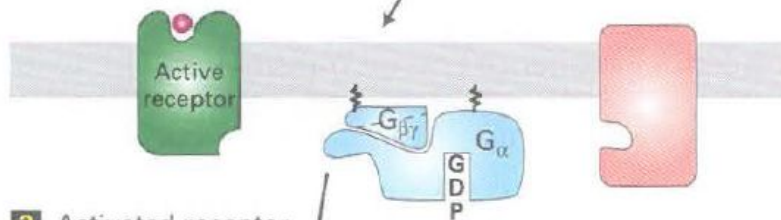


# GPCR(G-protein coupled receptors)

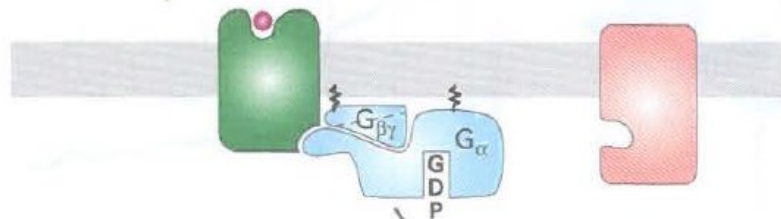




- 1** Binding of hormone induces a conformational change in receptor



- 2** Activated receptor binds to  $G_\alpha$  subunit



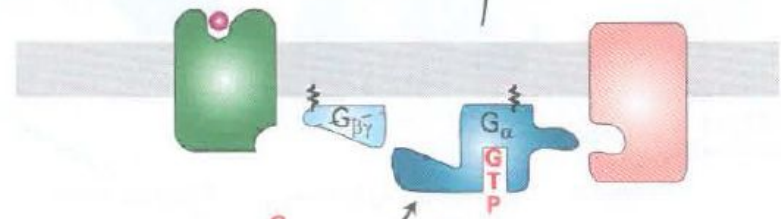
- 3** Activated receptor causes conformational change in  $G_\alpha$ , triggering dissociation of GDP



- 6** Hydrolysis of GTP to GDP causes  $G_\alpha$  to dissociate from effector and reassociate with  $G_{\beta\gamma}$



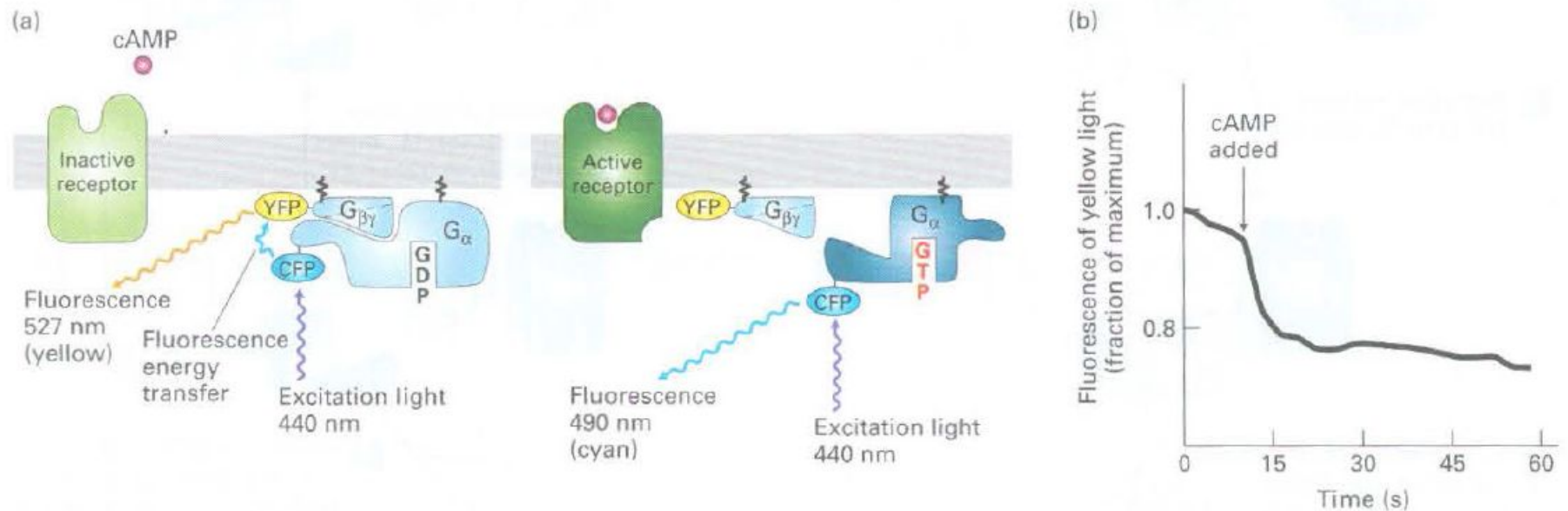
- 5** Hormone dissociates from receptor;  $G_\alpha$  binds to effector, activating it



- 4** Binding of GTP to  $G_\alpha$  triggers dissociation of  $G_\alpha$  both from the receptor and from  $G_{\beta\gamma}$







**EXPERIMENTAL FIGURE 15-18 Activation of G proteins occurs within seconds of ligand binding in amoeba cells.** In the amoeba *Dictyostelium discoideum* cell, cAMP acts as an extracellular signaling molecule and binds to a G protein-coupled receptor; it is not a second messenger. Amoeba cells were transfected with genes encoding two fusion proteins: a  $G_{\alpha}$  fused to cyan fluorescent protein (CFP), a mutant form of green fluorescent protein (GFP), and a  $G_{\beta}$  fused to another GFP variant, yellow fluorescent protein (YFP). CFP normally fluoresces 490-nm light; YFP, 527-nm light. (a) When CFP and YFP are nearby, as in the resting  $G_{\alpha}$ - $G_{\beta\gamma}$  complex, fluorescence energy transfer can occur between CFP and YFP (left). As a result, irradiation of resting cells with 440-nm light (which directly excites CFP but not YFP) causes

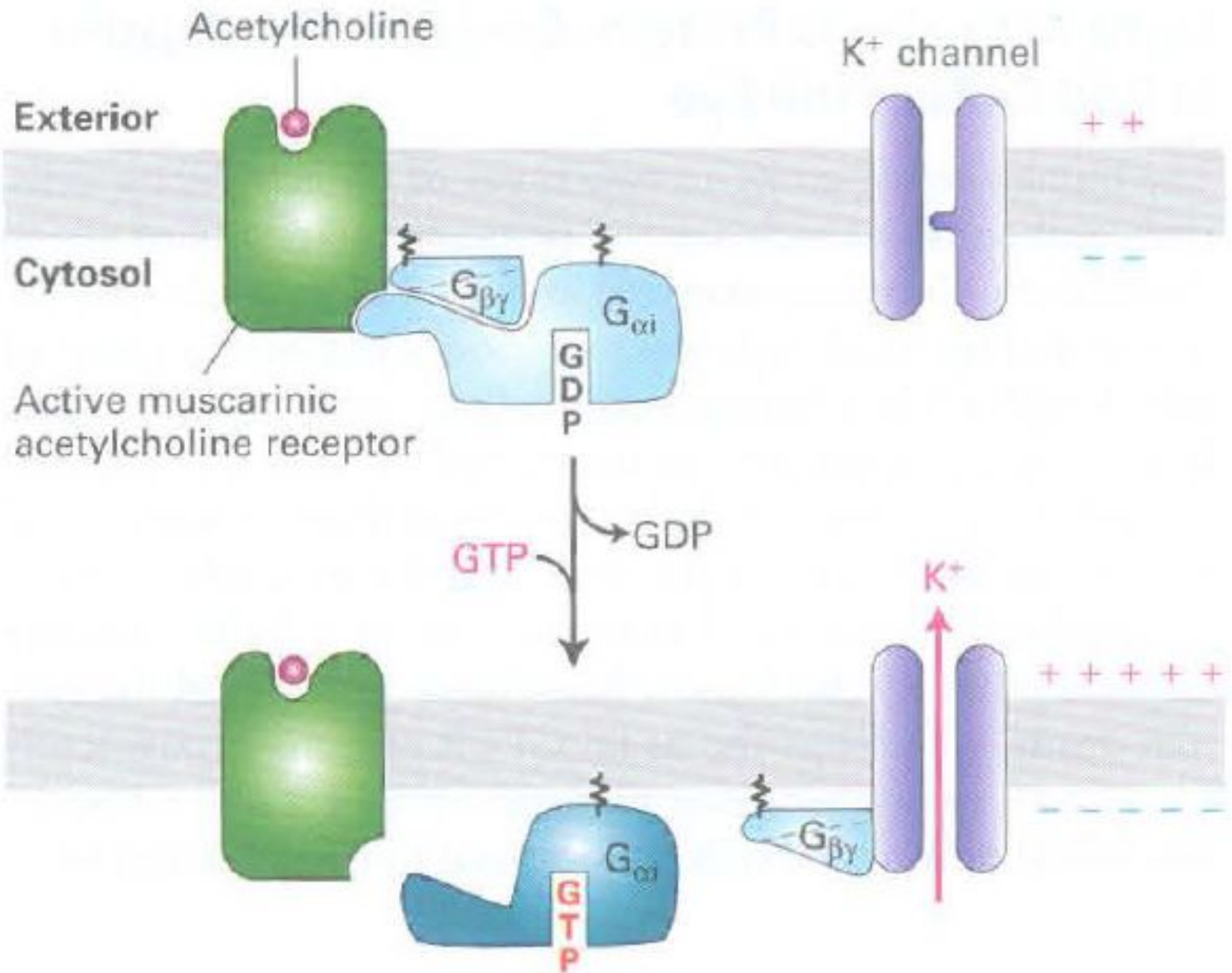
emission of 527-nm (yellow) light, characteristic of YFP. However, if ligand binding leads to dissociation of the  $G_{\alpha}$  and  $G_{\beta\gamma}$  subunits, then fluorescence energy transfer cannot occur. In this case, irradiation of cells at 440 nm causes emission of 490-nm light (cyan) characteristic of CFP (right). (b) Plot of the emission of yellow light (527 nm) from a single transfected amoeba cell before and after addition of extracellular cyclic AMP (arrow), the ligand for the G protein-coupled receptor in these cells. The drop in yellow fluorescence, which results from the dissociation of the  $G_{\alpha}$ -CFP fusion protein from the  $G_{\beta}$ -YFP fusion protein, occurs within seconds of cAMP addition. [Adapted from C. Janetopoulos et al., 2001, *Science* **291**:2408.]

**TABLE 15-1** Major Classes of Mammalian Trimeric G Proteins and Their Effectors<sup>\*</sup>

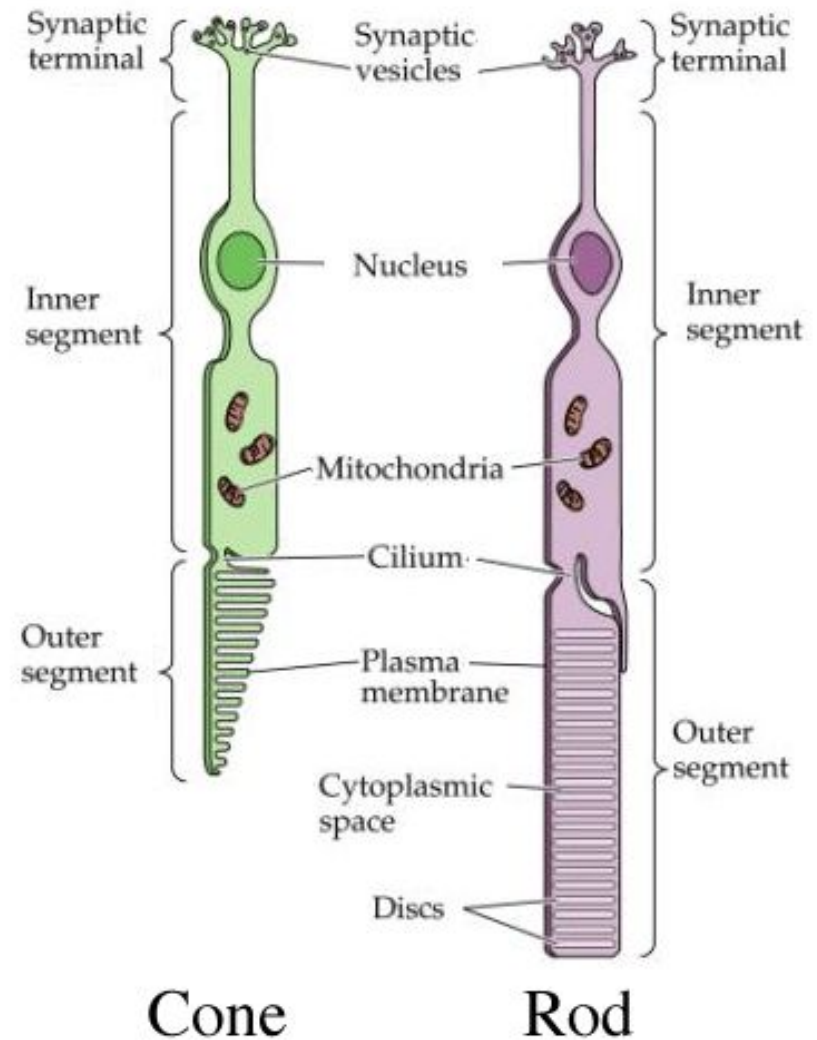
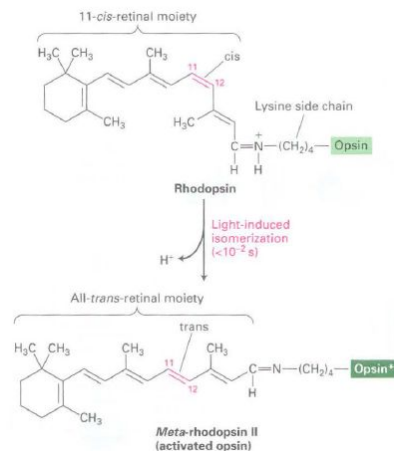
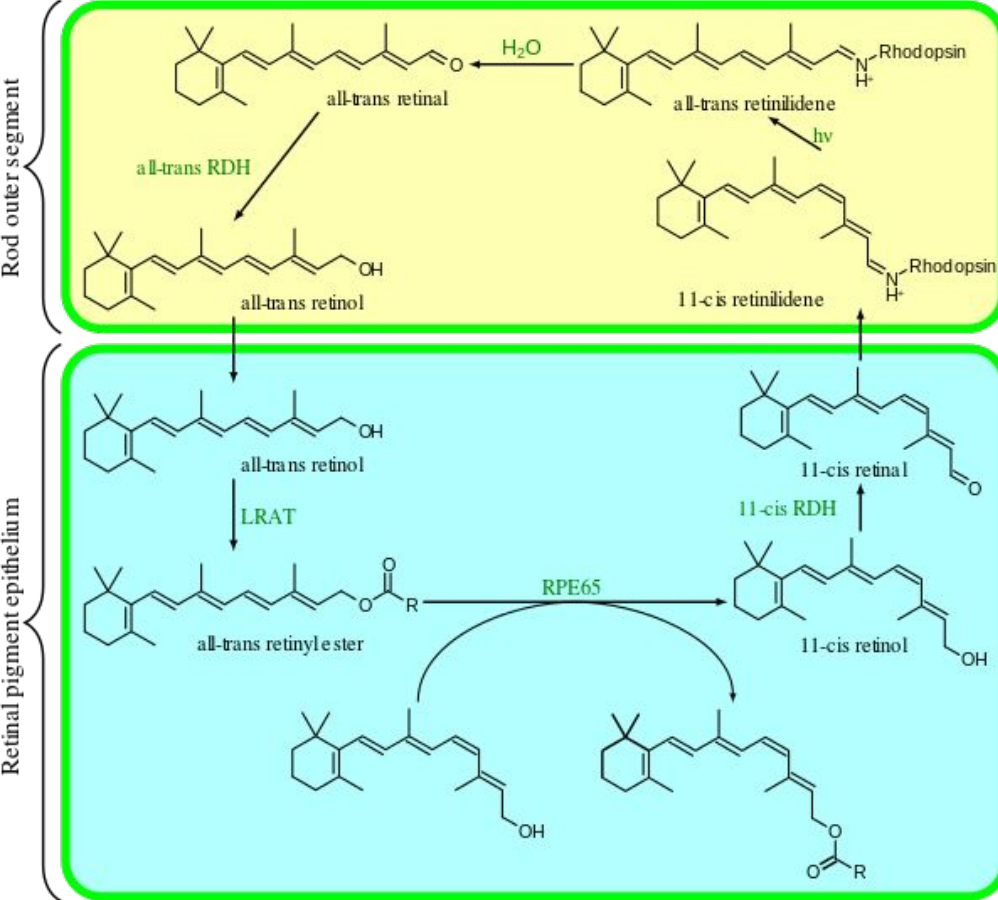
G <sub>α</sub> Class	Associated Effector	2nd Messenger	Receptor Examples
G <sub>αs</sub>	Adenylyl cyclase	cAMP (increased)	β-Adrenergic (epinephrine) receptor; receptors for glucagon, serotonin, vasopressin
G <sub>αi</sub>	Adenylyl cyclase K <sup>+</sup> channel (G <sub>βγ</sub> activates effector)	cAMP (decreased) Change in membrane potential	α <sub>2</sub> -Adrenergic receptor Muscarinic acetylcholine receptor
G <sub>αolf</sub>	Adenylyl cyclase	cAMP (increased)	Odorant receptors in nose
G <sub>αq</sub>	Phospholipase C	IP <sub>3</sub> , DAG (increased)	α <sub>1</sub> -Adrenergic receptor
G <sub>αo</sub>	Phospholipase C	IP <sub>3</sub> , DAG (increased)	Acetylcholine receptor in endothelial cells
G <sub>αt</sub>	cGMP phosphodiesterase	cGMP (decreased)	Rhodopsin (light receptor) in rod cells

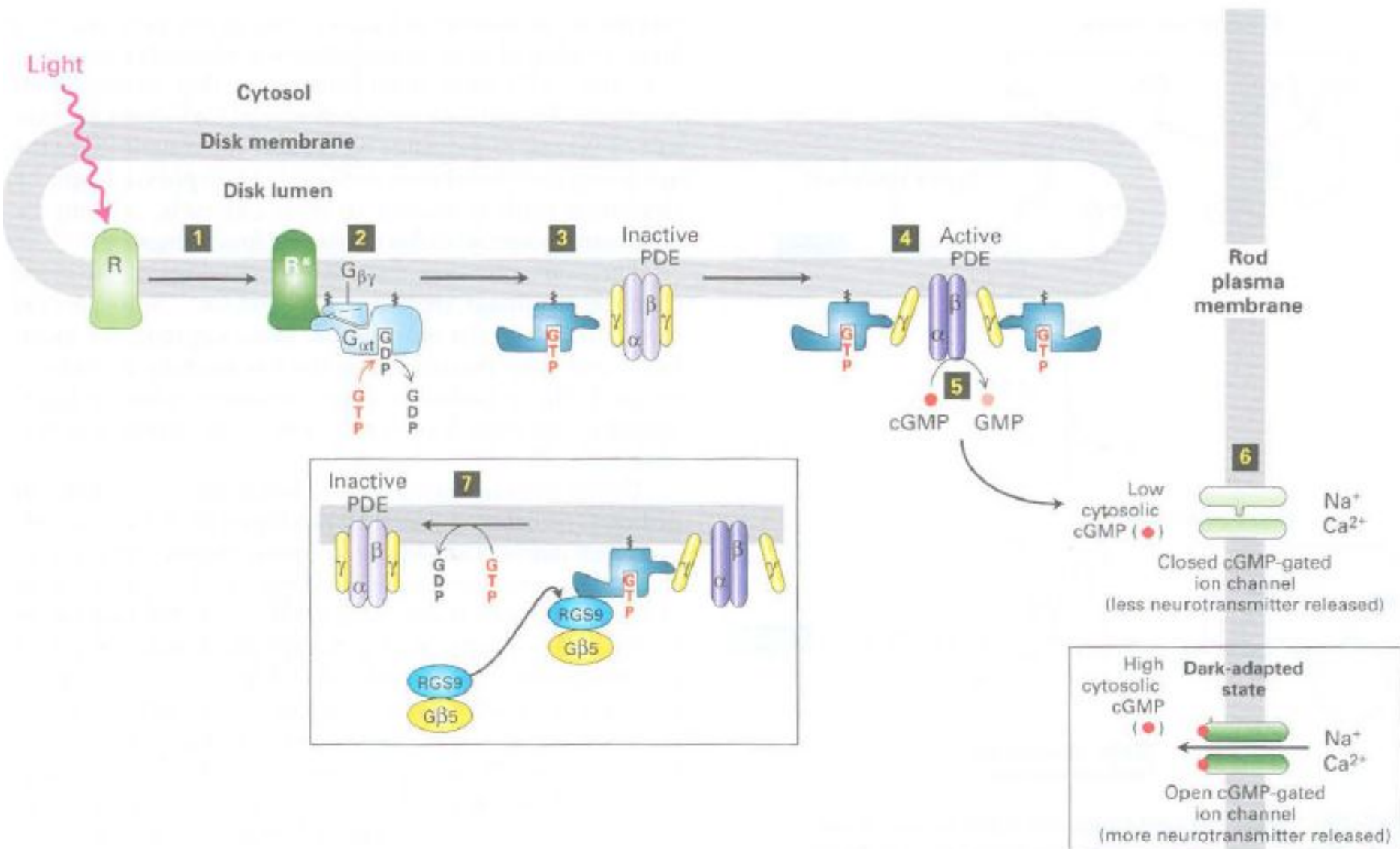
<sup>\*</sup>A given G<sub>α</sub> subclass may be associated with more than one effector protein. To date, only one major G<sub>αs</sub> has been identified, but multiple G<sub>αq</sub> and G<sub>αi</sub> proteins have been described. Effector proteins commonly are regulated by G<sub>α</sub> but in some cases by G<sub>βγ</sub> or the combined action of G<sub>α</sub> and G<sub>βγ</sub>. IP<sub>3</sub> = inositol 1,4,5-trisphosphate; DAG = 1,2-diacylglycerol.

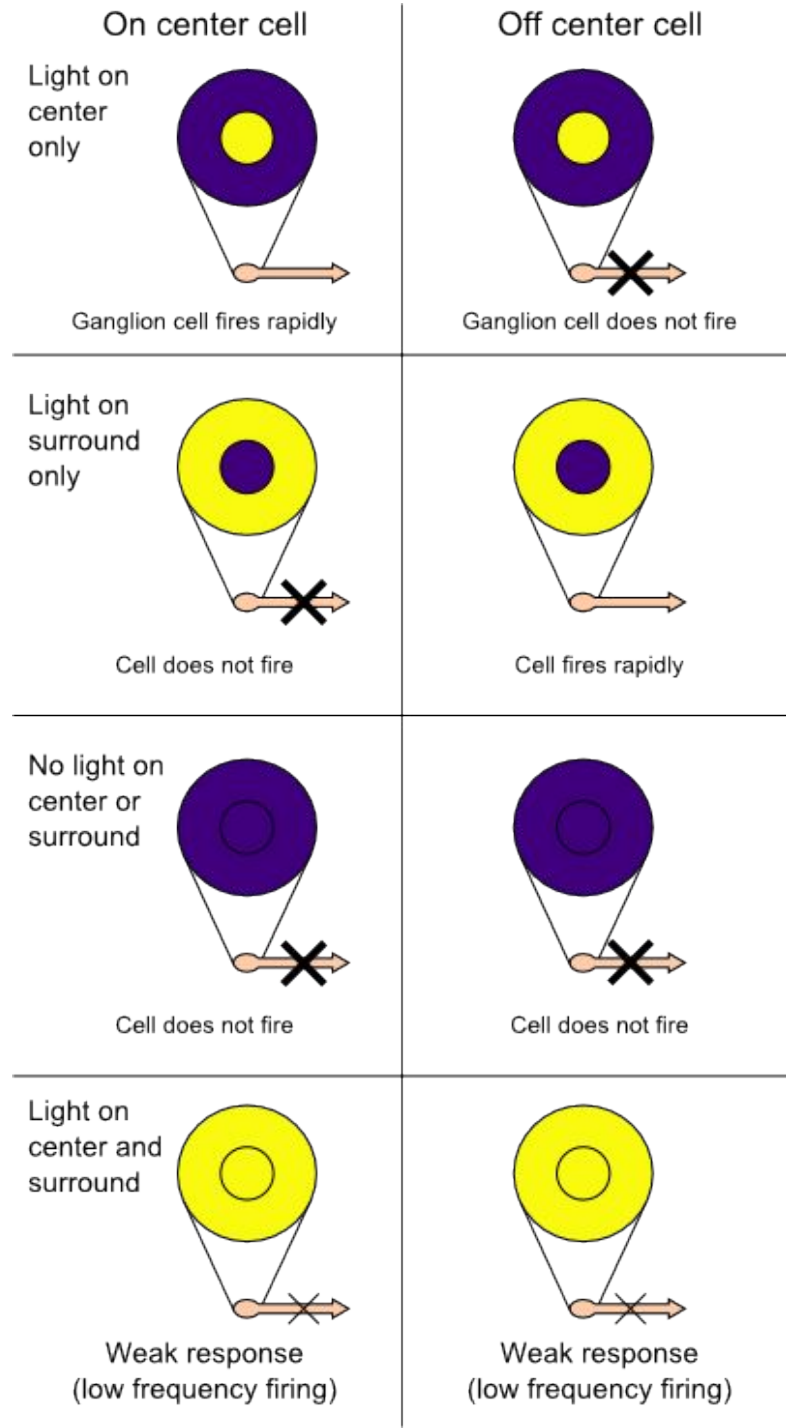
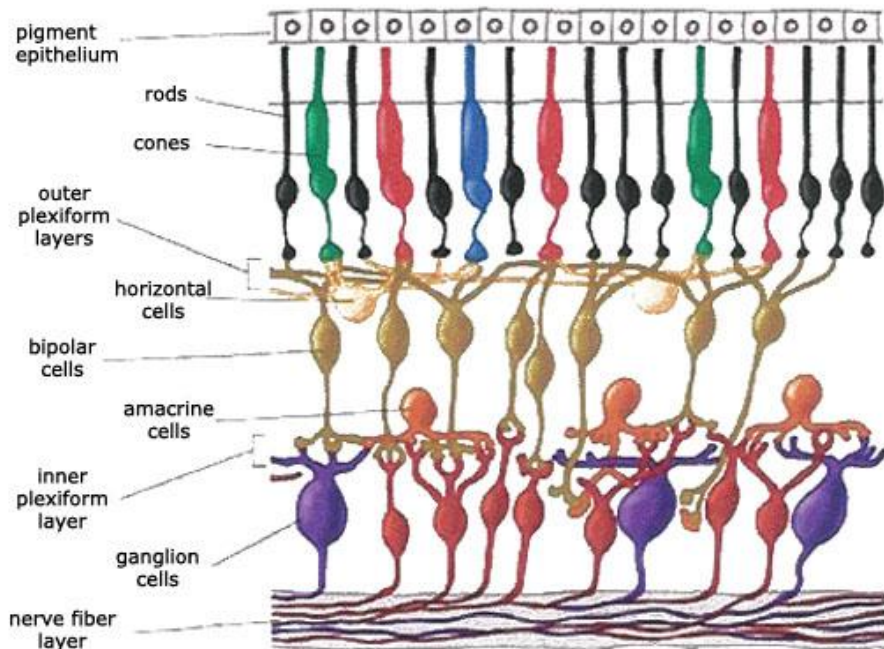
SOURCES: See L. Birnbaumer, 1992, *Cell* 71:1069; Z. Farfel et al., 1999, *New Eng. J. Med.* 340:1012; and K. Pierce et al., 2002, *Nature Rev. Mol. Cell Biol.* 3:639.





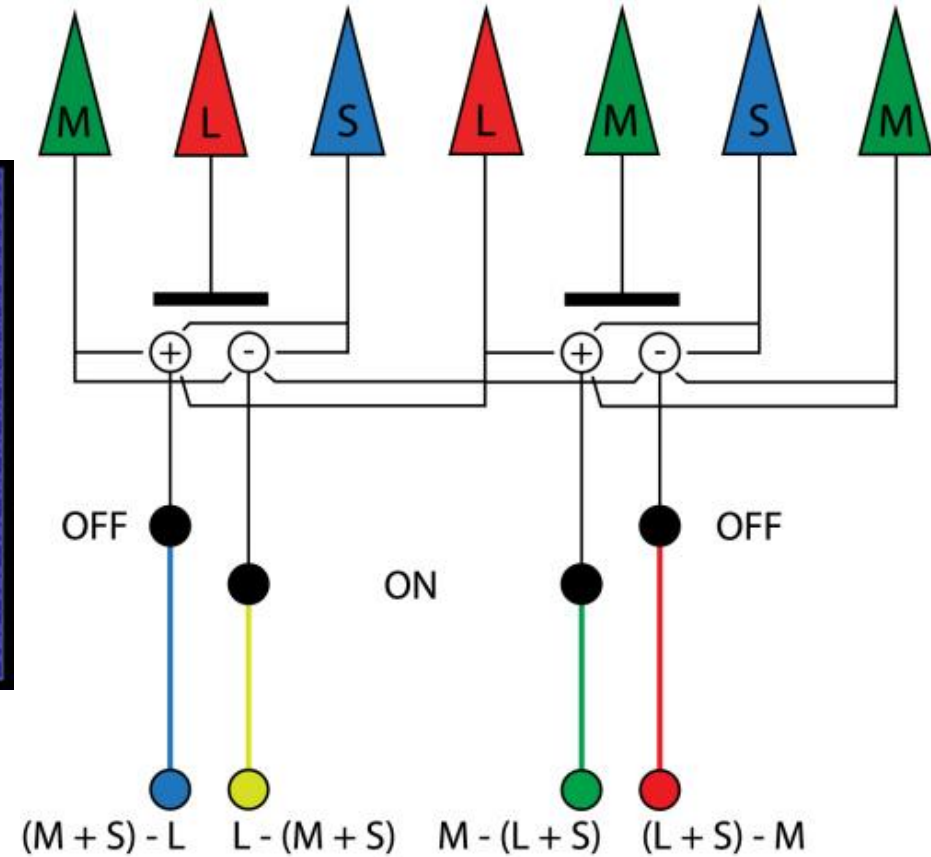
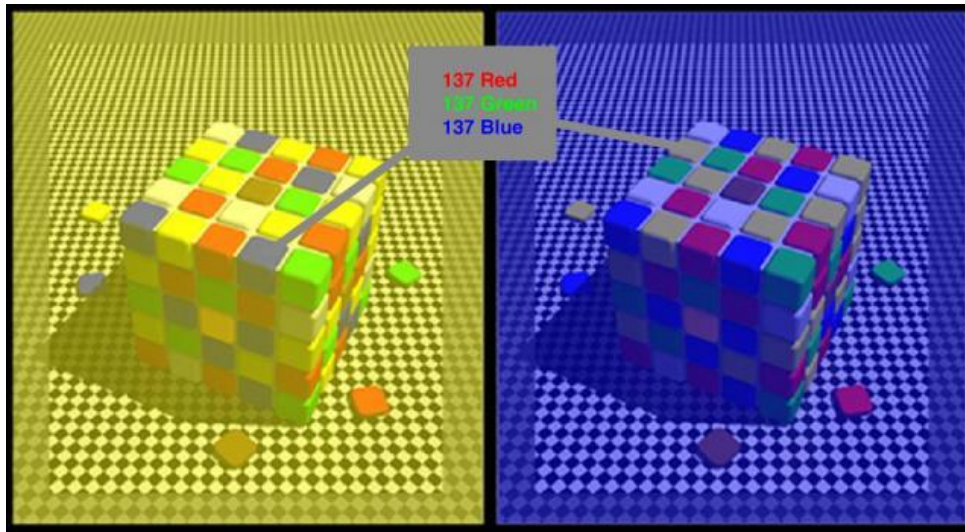




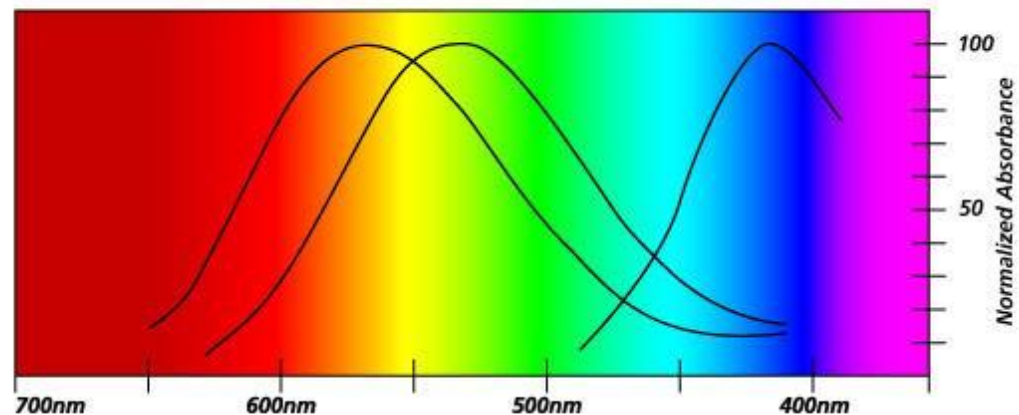


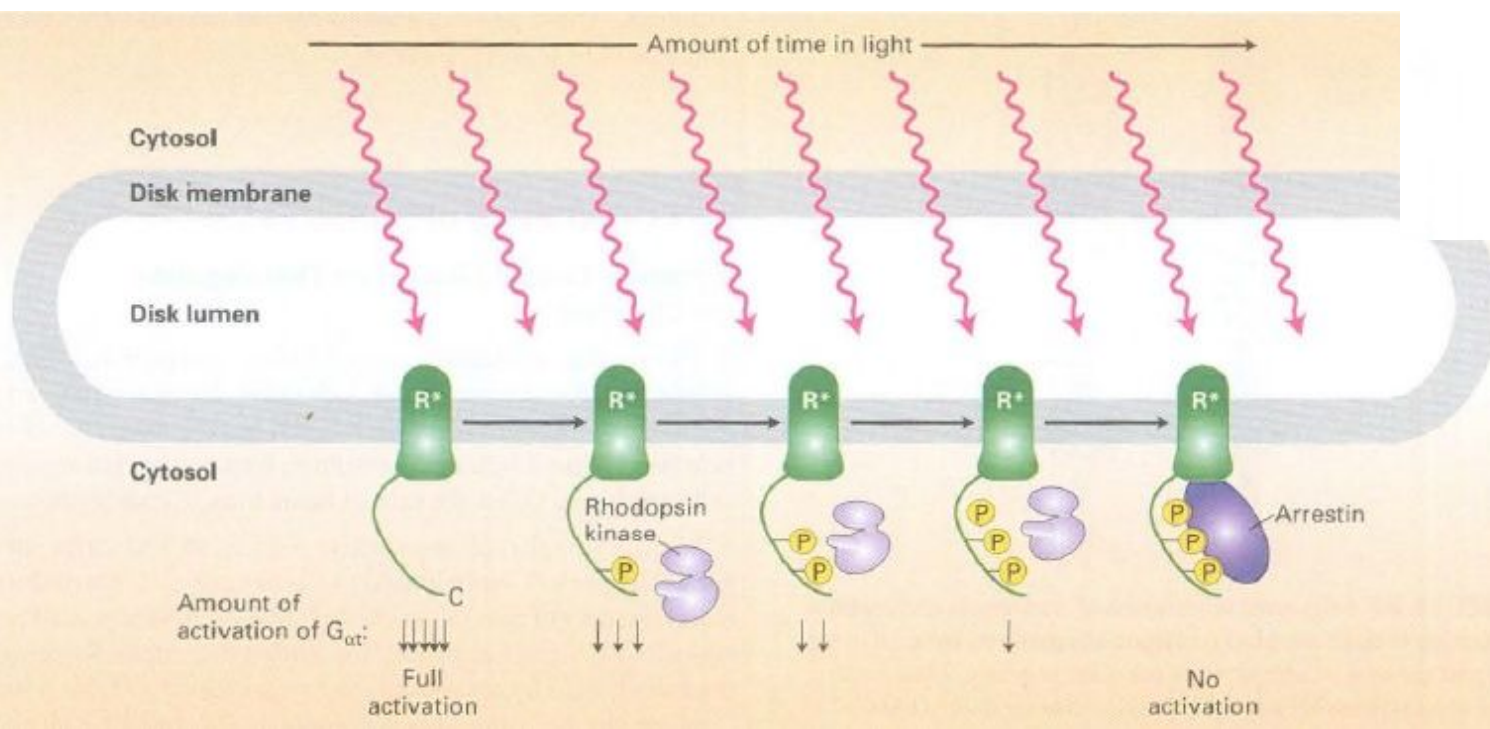
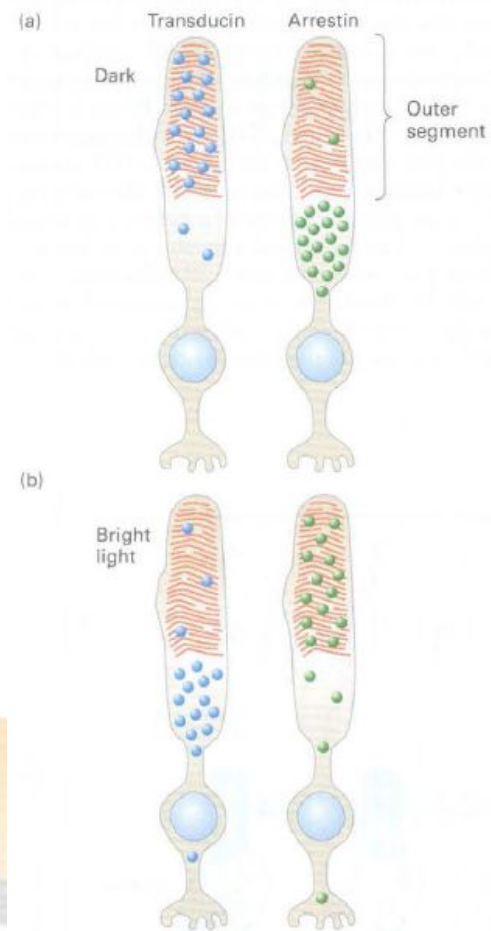


# opponent process



The Absorption of Light by the Three Different Cones

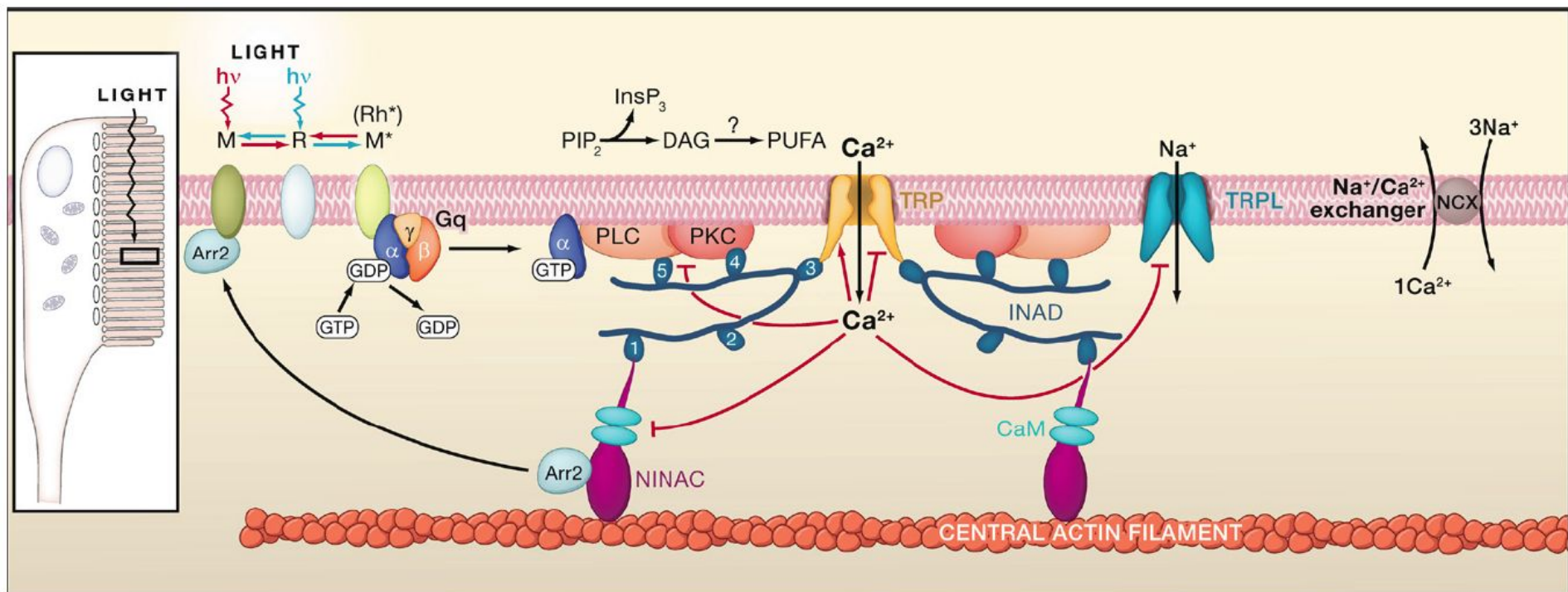








# безхребетні

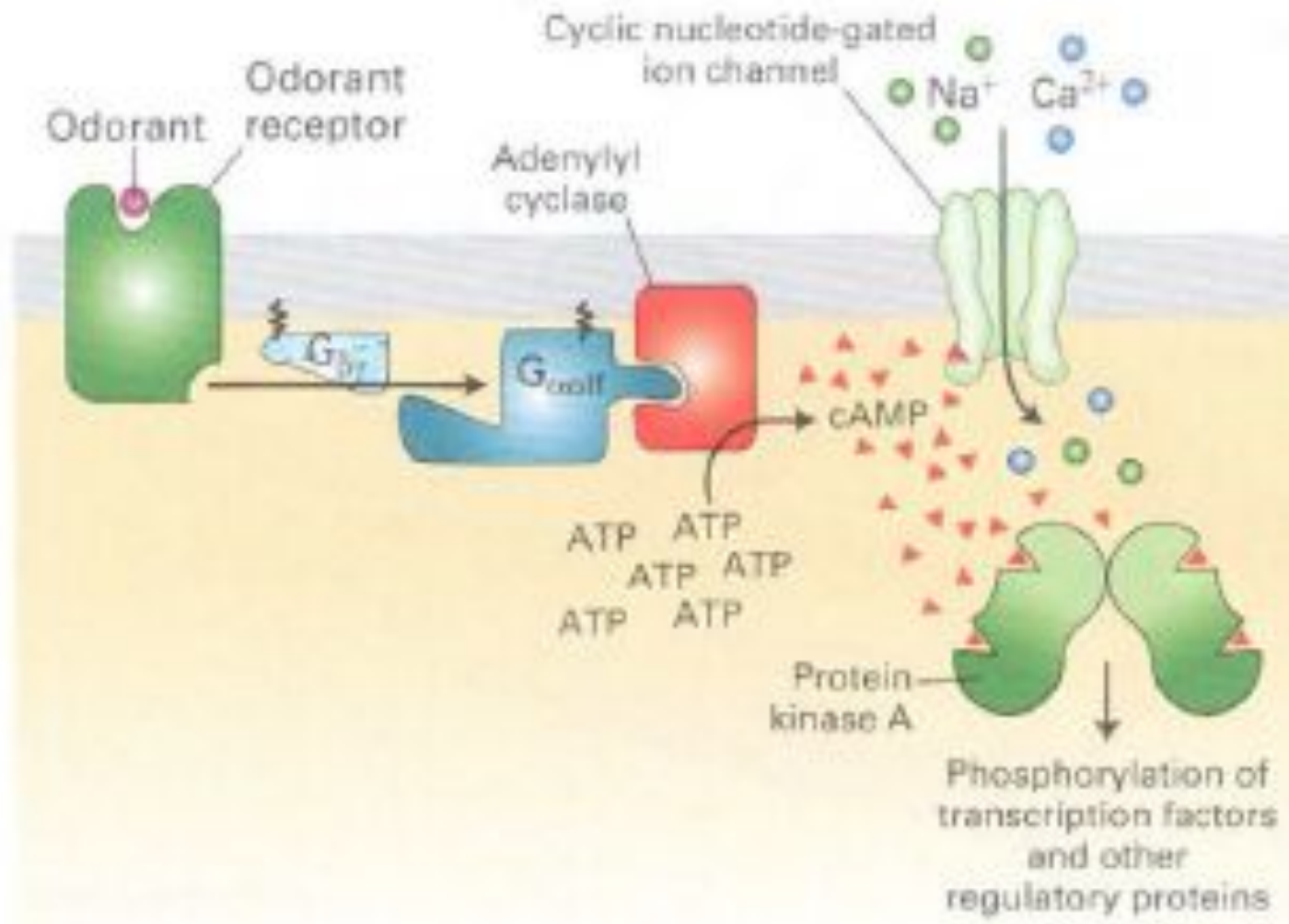


**Figure 4. Phototransduction in *Drosophila* Rhabdomeric Photoreceptors**

Absorption of a photon by rhodopsin (R) converts it to the thermostable, active metarhodopsin state ( $M^*$  or  $Rh^*$ ), which activates heterotrimeric  $G_q$  by GTP-GDP exchange essentially the same as in vertebrate rods. Active  $G_{aq}$  binds to and activates phospholipase C (PLC), which hydrolyzes phosphatidylinositol 4,5-bisphosphate ( $PIP_2$ ) to inositol 1,4,5-trisphosphate ( $InsP_3$ ) and diacylglycerol (DAG), with the latter potentially producing polyunsaturated fatty acids (PUFAs) via a DAG lipase. Two classes of light-sensitive channels (TRP and TRPL, with the first being primarily  $Ca^{2+}$  permeable) are activated by a still-unknown membrane-delimited effect of PLC activity.  $Ca^{2+}$  influx feeds back positively and negatively at multiple sites (indicated by red lines ending in arrowheads and small bars, respectively), including PKC (required for inactivation of PLC), NINAC/arrestin (Arr2), and the TRP/TRPL channels.  $Ca^{2+}$  is extruded by a  $Na^+/Ca^{2+}$  exchanger. TRP, PKC, and PLC are assembled into a signaling complex by the scaffolding protein INAD, possibly linked to the F-actin core via NINAC, a CaM-binding class III myosin. INAD has 5 PDZ domains, associated preferentially with different targets. The precise composition of the native complex is uncertain. Inset: schematic diagram of the rhabdomeric *Drosophila* photoreceptor, with microvilli forming a light-guiding rhabdomere. Submicrovillar cisternae at 10–100 nm beneath the base of the microvilli may release  $Ca^{2+}$  via  $InsP_3$  receptors in many rhabdomeric photoreceptors. However,  $InsP_3$  appears to play no role in photoactivation in *Drosophila*.



# H<sub>2</sub>OX



# Гіркий солодкий та умамі смак і НЮХ

