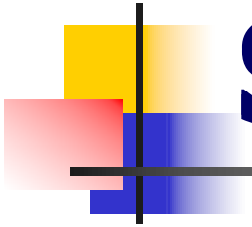


Section 2

Signal Transduction of Cell Membrane

Lei CHEN（陈蕾）
Email: chenleiqd@163.com

Signal Transduction of Cell Membrane

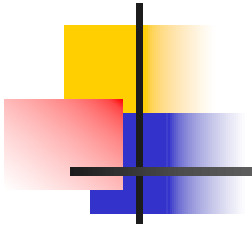
- **Hydrophobic** signal substances (steroid hormones, vitamin D, thyroid hormones)

  diffusion—intracellular receptor

- **Hydrophilic** signal substances:

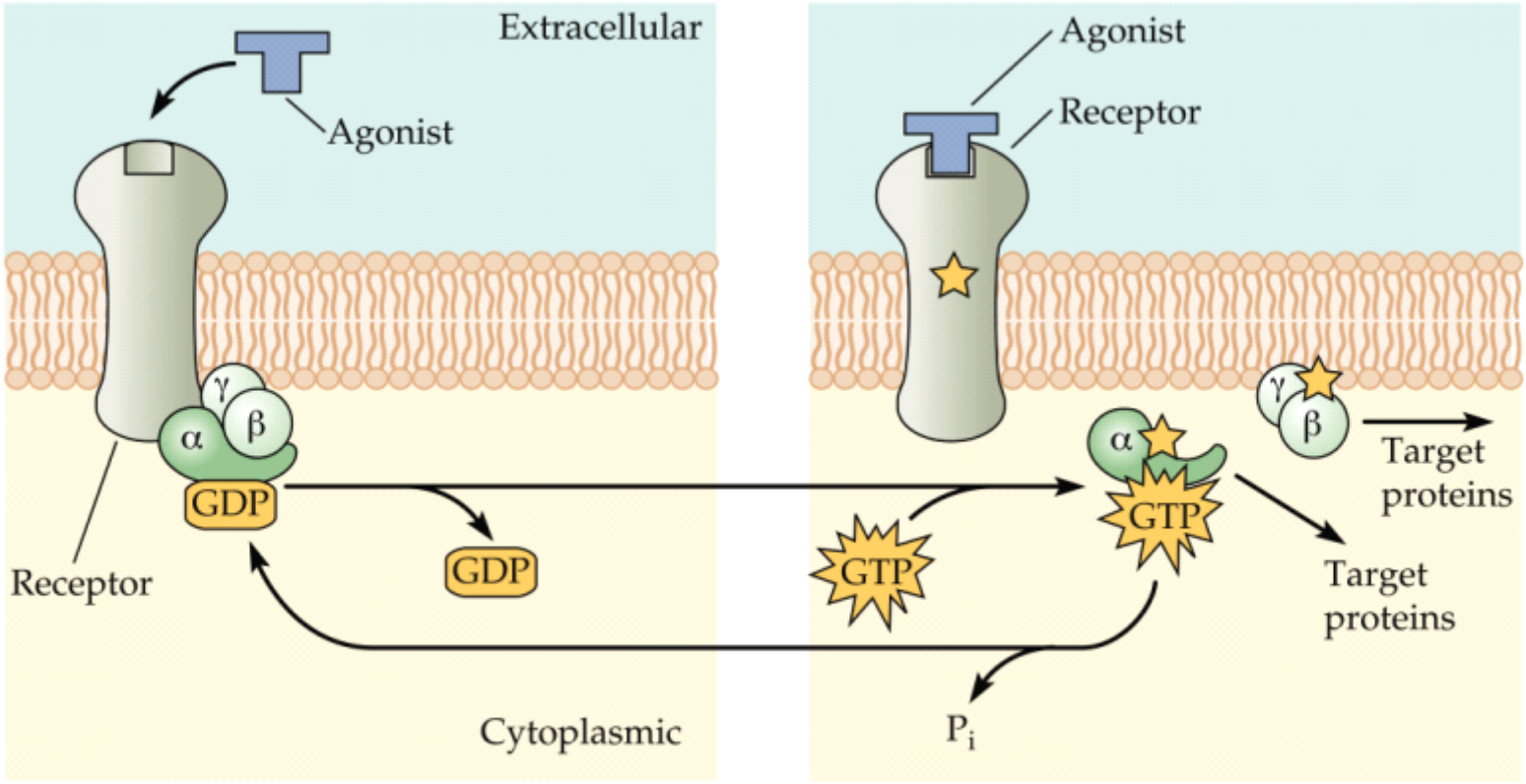
  membrane protein (receptor or ionic channel)--signal transduction

Signal Transduction of Cell Membrane

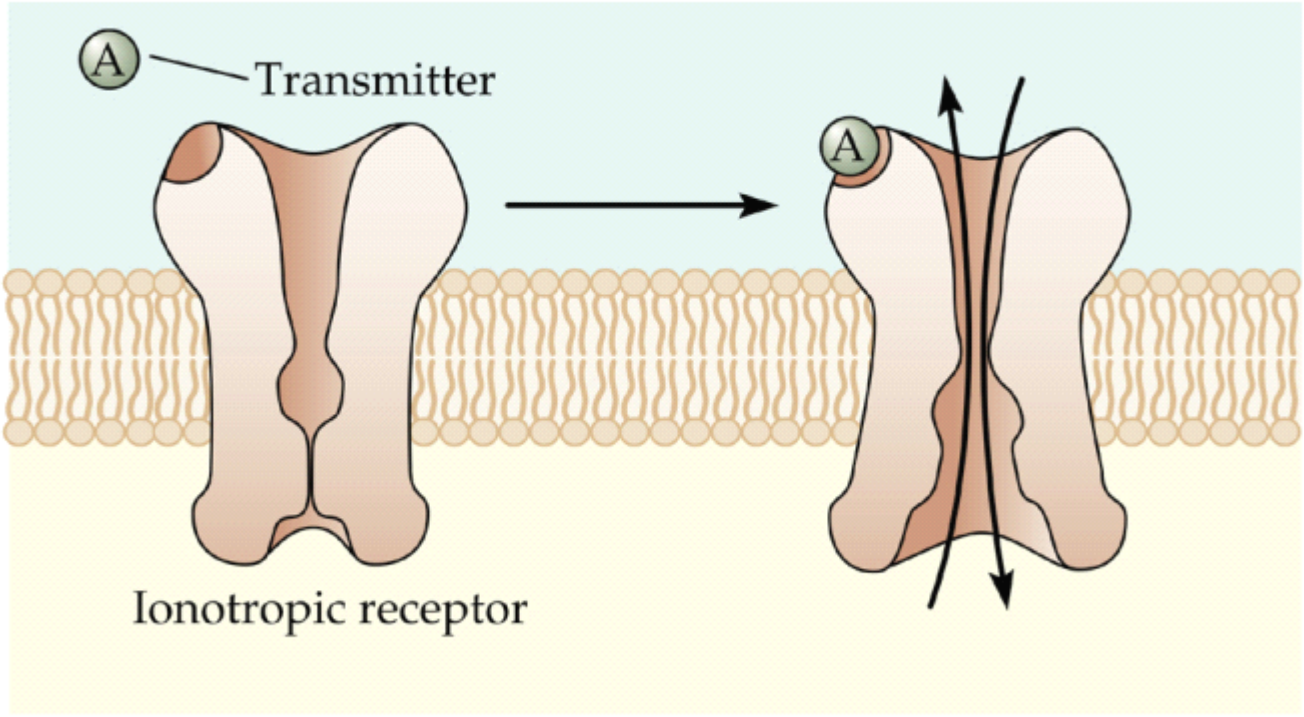


- Signal transduction mediated by G-protein coupled receptor
- Signal transduction mediated by ion channel coupled receptor
- Signal transduction mediated by enzyme-coupled receptor

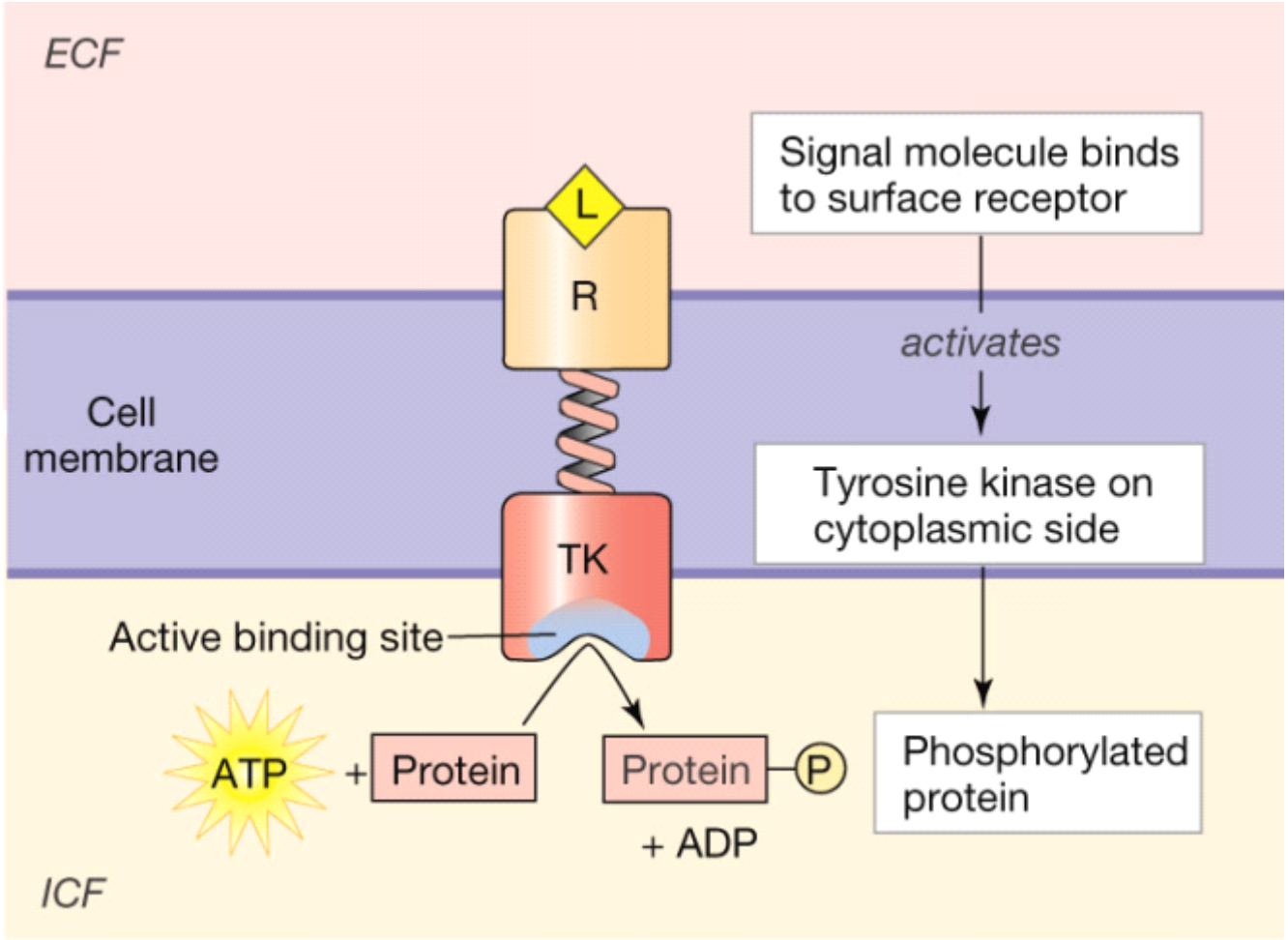
Signal transduction mediated by G-protein coupled receptor



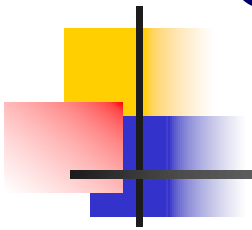
Signal transduction mediated by ion channel receptor



Signal transduction mediated by tyrosine kinase receptor



Cellular transmembrane signal transduction



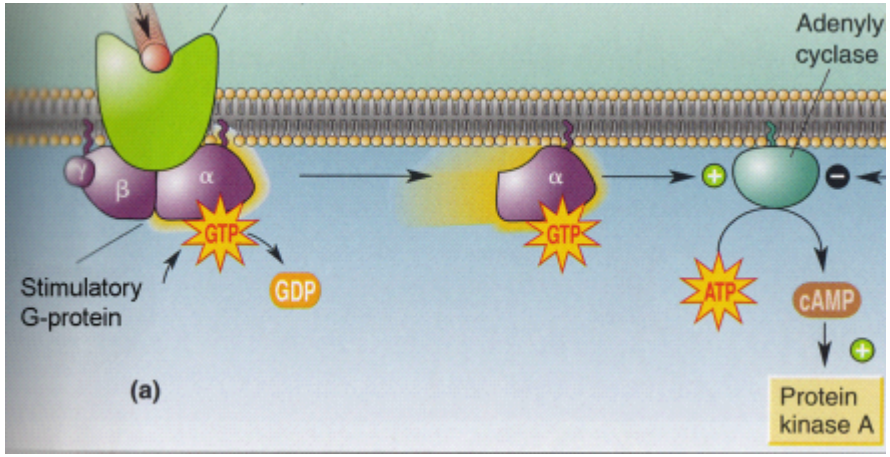
- Signal transduction mediated by G-protein coupled receptor
- Signal transduction mediated by ion channel coupled receptor
- Signal transduction mediated by enzyme-coupled receptor

Signal transduction mediated by G-protein coupled receptor

Signal molecules

- G protein coupled receptor
- G protein

Gilman and Rodbell (1994)



- G protein effector
- Second messenger

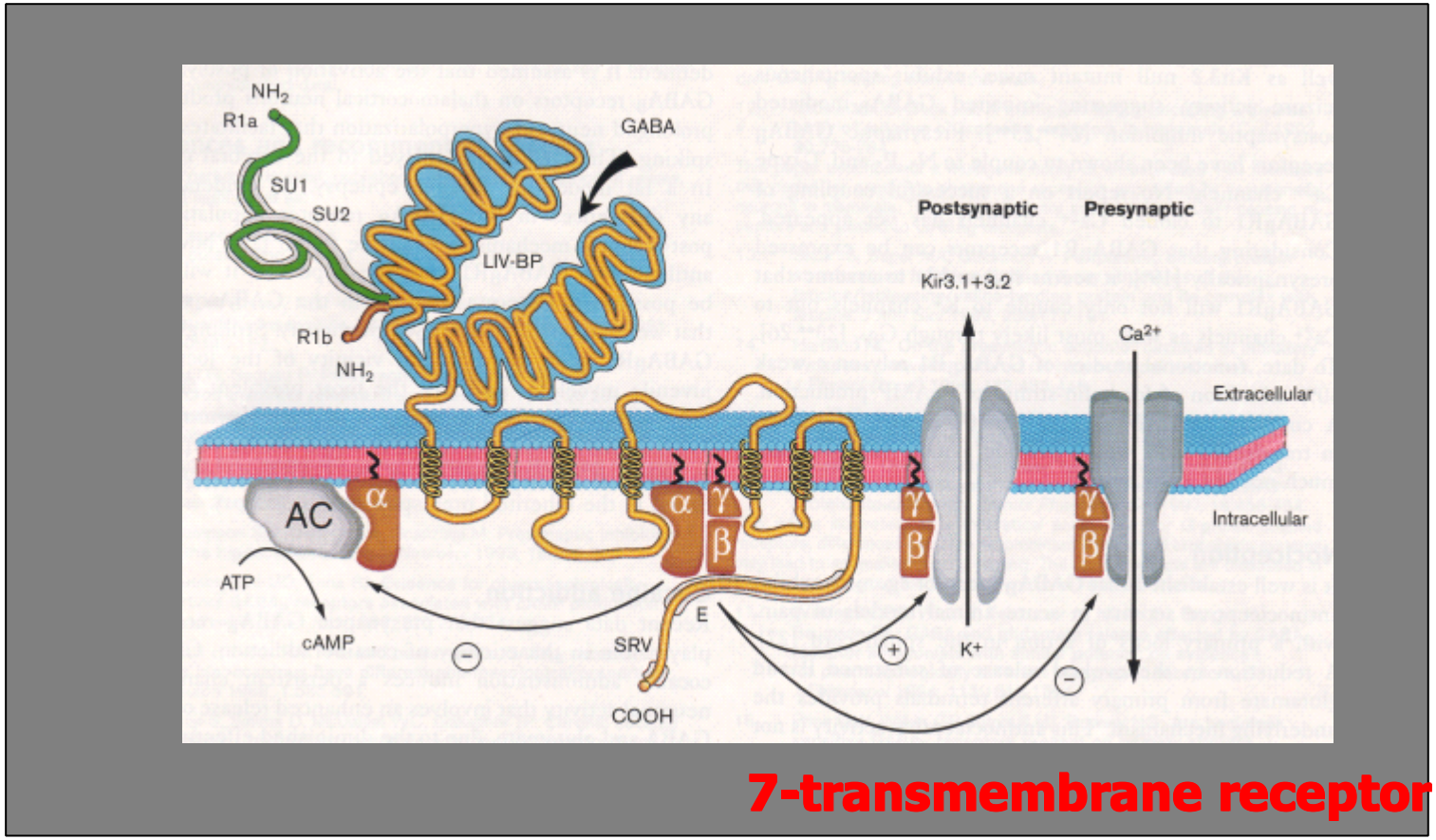
Sutherland (1971); Furchgott, Murad and Ignarro (1998)

- Protein kinase

Krebs (1992)

1. G protein coupled receptor (metabotropic receptor)

- $GABA_B$ receptor



1. G protein coupled receptor (metabotropic receptor)

- The basic structure is that the receptor consist of a peptide chain that traverses the membrane seven times, 7-transmembrane receptor.
- There is a ligand binding site on the extracellular part of the receptor, while the intracellular part of the receptor molecule is for G protein.
- The conformation of the receptor changes after the ligand binding, then the receptors combine with and activate G protein.

2. G protein

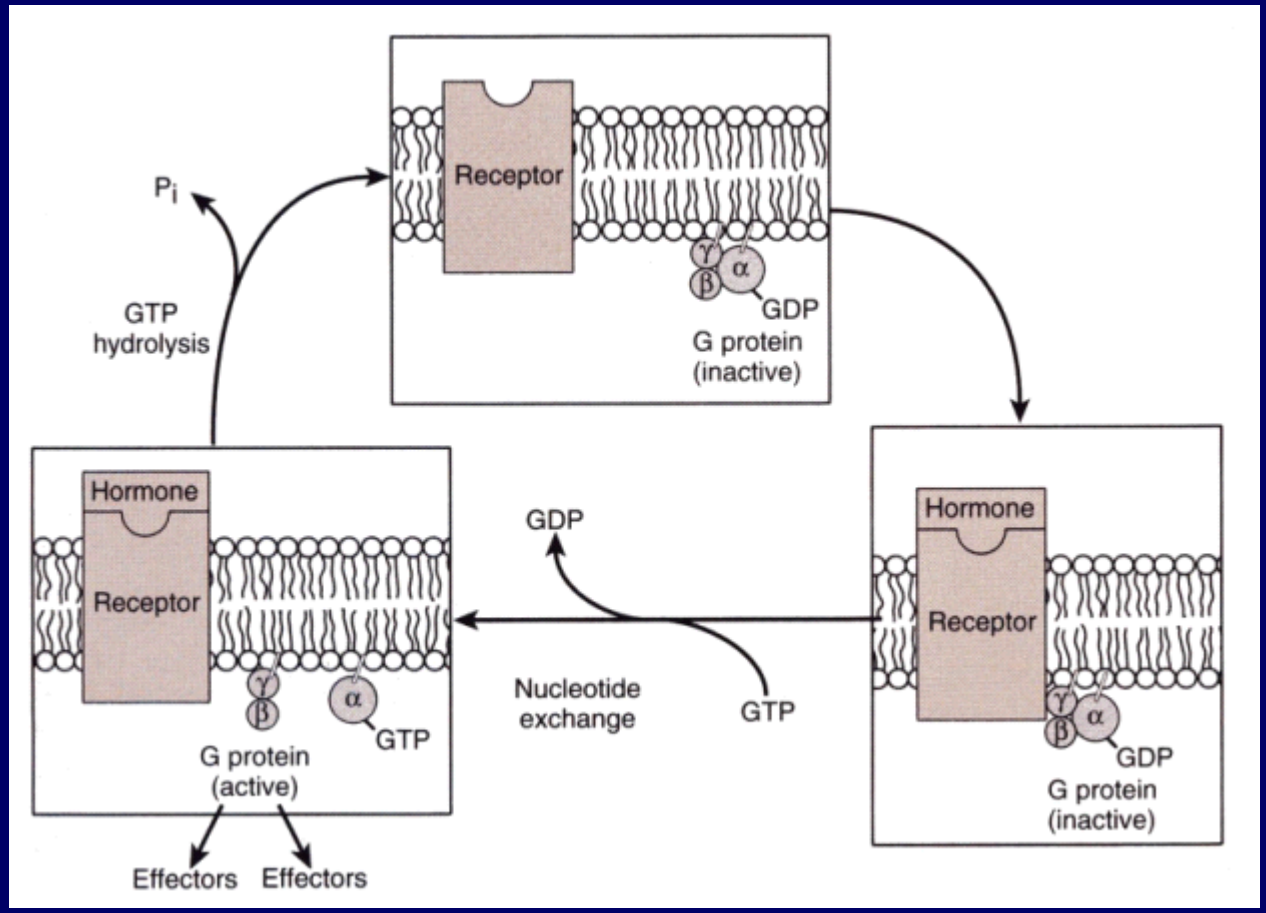
- **G Protein:** plasma-membrane regulatory protein that responds to an activated receptor and, in turn, interacts with membrane ion channels or enzymes.
- G_s, $G_{i/o}$, G_q, G_t, G_g, G_{12}

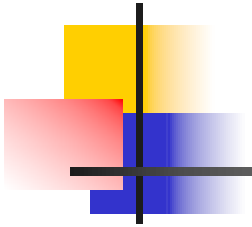
Major family of trimeric G protein

Family	Some member	Action mediated	Functions
I	G_s	α	Activate adenylyl cylclase, Ca^{2+} channels
II (Gi)	$G\alpha_i$	α	Inhibit adnylyl cyclase
		β γ	Activates K^+ channel
	$G\alpha_o$	β γ	Activates K^+ channel, inactivate Ca^{2+} channels
		α and β γ	Activates phospholipase C-β
	$G\alpha_t$	α	Activates cyclic GMP phosphodiesterase
III	G_q	α	Activates phospholipase C-β
IV	G12	α	Na^+ 、H^+ exchange, cell proliferation

2. G protein

- **Activation and inactivation of G protein**





2. G protein

1. The changes of conformation of the receptor cause the receptor to combine with the G protein.
2. This combination causes alpha subunit of the G protein to dissociate GDP and bind GTP.
3. When bound to GTP, alpha subunits dissociates from the remaining beta and gamma subunits.
4. Then two functional units produced, alpha-GTP and beta gamma.
5. Both these two functional units could further link up with G protein effectors.
6. Once the alpha subunits of G protein activates its effector protein, a GTPase activity cleaves the GTP into GDP plus Pi. This cleavage renders the alpha subunit inactive, allowing it to recombine with beta and gamma subunits.

3. G protein effector

- **Enzyme:** catalyze the generation of second messengers
  - **Adenylyl cyclase, AC**
  - **Phospholipase C, PLC**
  - **Phospholipase A_2, PLA_2**
  - **Guanylyl cyclase, GC**
  - **Phosphodiesterase, PDE**
- **Ion channels**

4. Second messenger

- **Second messenger:** intracellular substance that increases as a result of combination of extracellular chemical messenger (the "first" messenger) with plasma-membrane receptor; serves as relay from plasma membrane to intracellular biochemical machinery, where it alters some aspect of cell's function.

4. Second messenger

- Cyclic adenosine monophosphate, cAMP
- Inositol triphosphate, IP_3
- Diacylglycerol, DG
- Cyclic guanosine monophosphate, cGMP
- Ca^{2+}
- NO

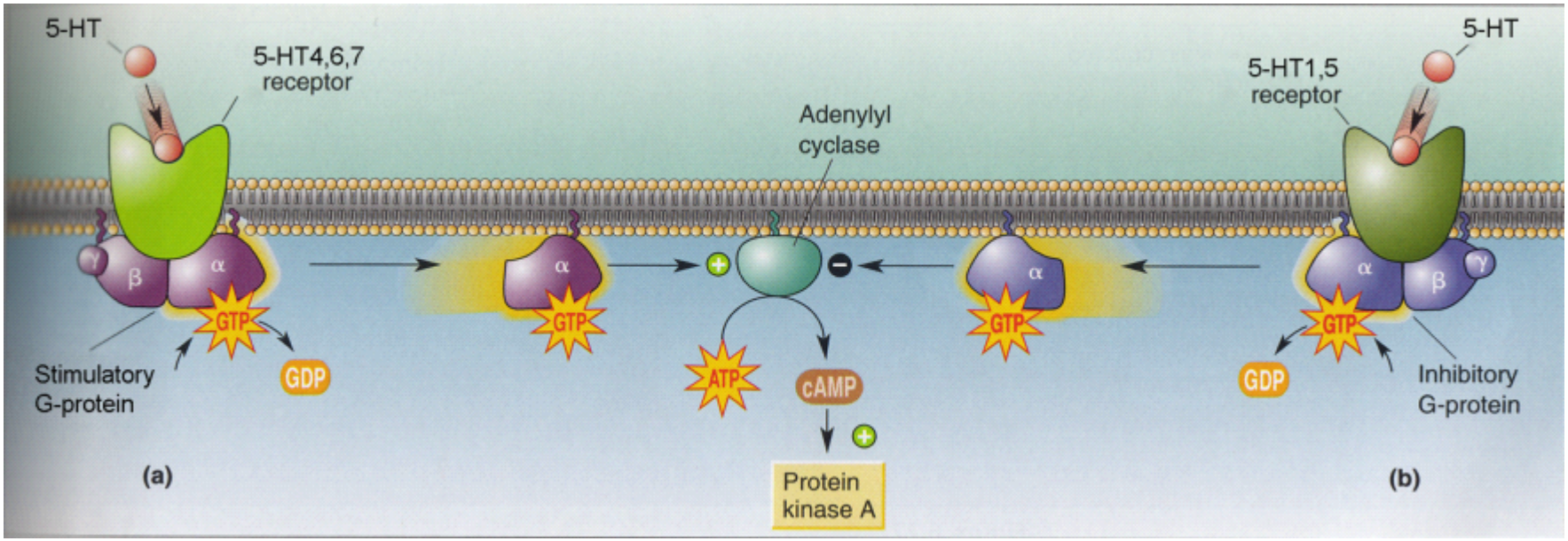
5. Protein kinase

- **Protein kinase** is the name for any enzyme that phosphorylates other proteins by transferring to them a phosphate group from ATP.
- Protein kinase A, PKA
- Protein kinase C, PKC

Pathways of G protein-mediated signal transduction

- Receptor-G protein-AC pathway
- Receptor-G protein-PLC pathway
  - IP3-Ca^{2+} pathway
  - DG-PKC pathway

Receptor-G protein-AC pathway

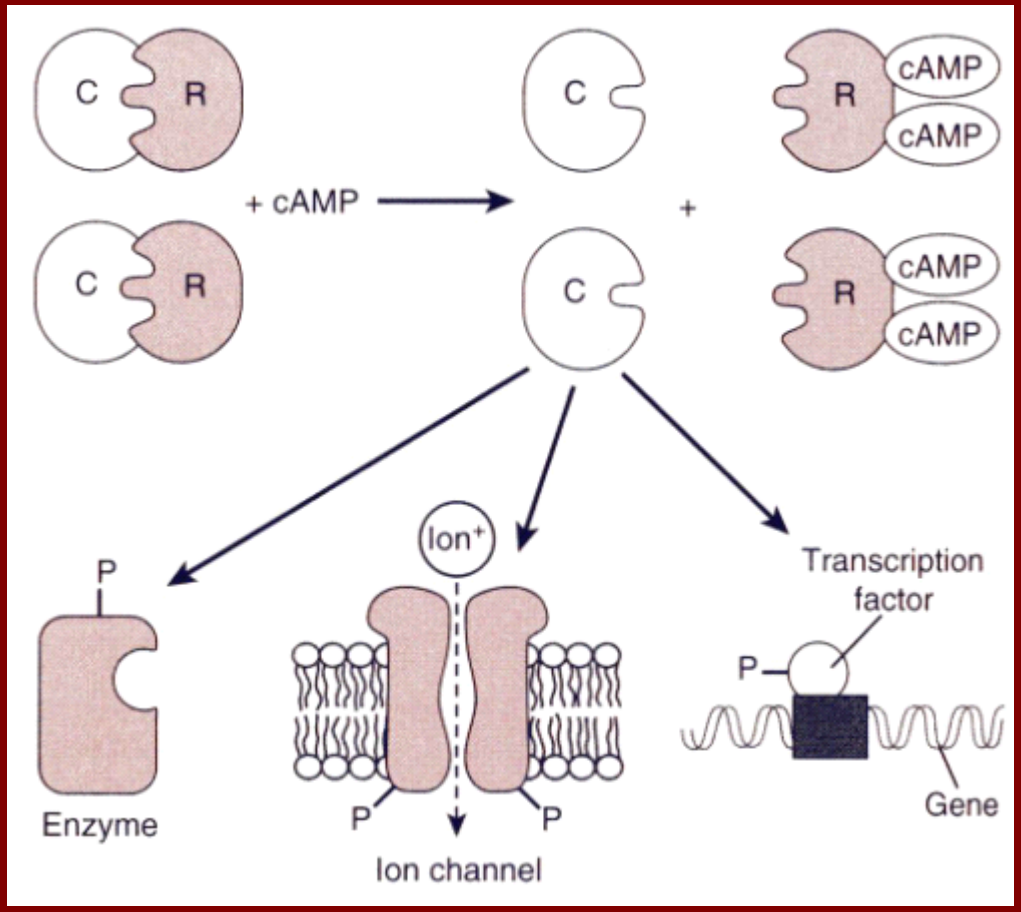


G_s protein

G_i protein

Receptor-G protein-AC pathway

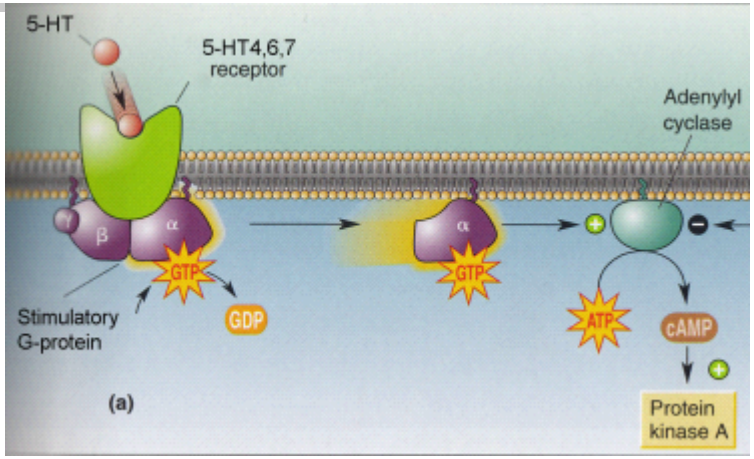
- **Activation of PKA**



- cAMP binds to the regulatory subunits, leading to their dissociation from the catalytic subunits.
- The free catalytic subunits are then enzymatically active and able to phosphorylate serine residues on their target proteins.

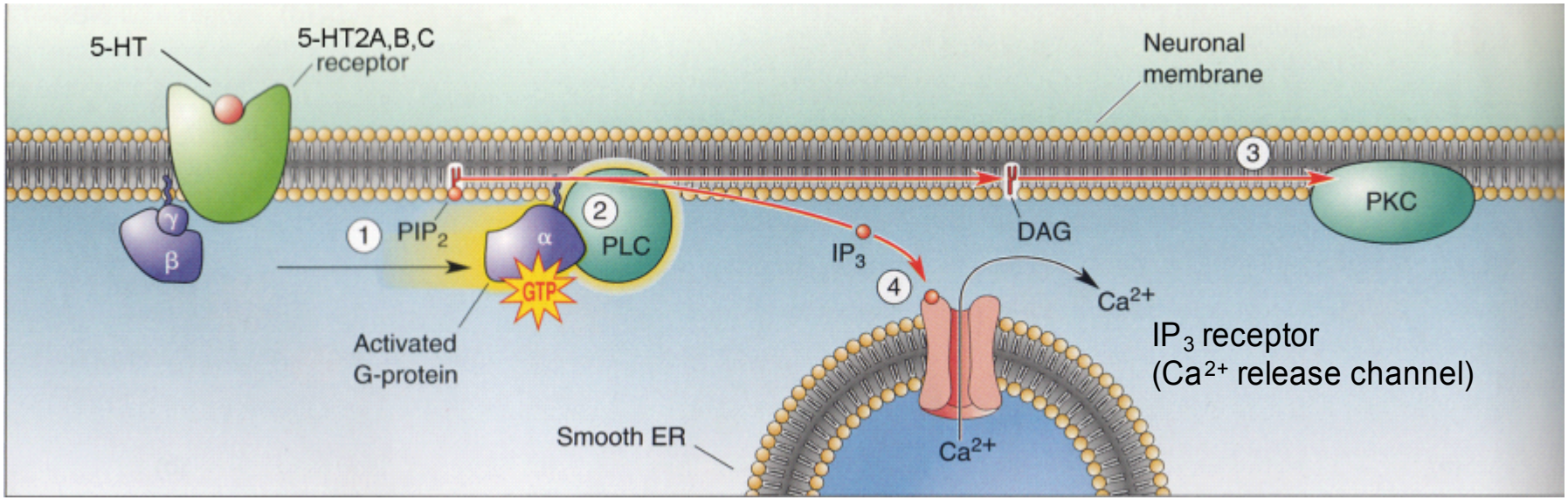
Amplification cascade

- 1 ligand-receptor activates 100 Gs
- 1 Gs activates 1 AC
- 1 AC produces 100 cAMP
- 1 cAMP activates 100 protein kinases



- **Therefore, the end result is that a single molecule of the first messenger could cause the generation of 1 million product molecules.**
- **This could explain how hormones and other messengers can be effective at extremely low extracellular concentration.**

Receptor-G protein-PLC pathway



PIP_2: phosphatidylinositol bisphosphate

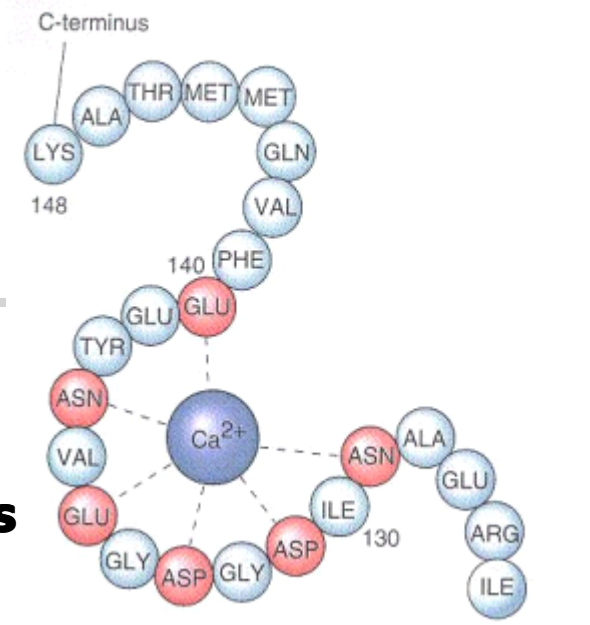
PLC catalyzes the breakdown of PIP2 to produce DG and IP3.

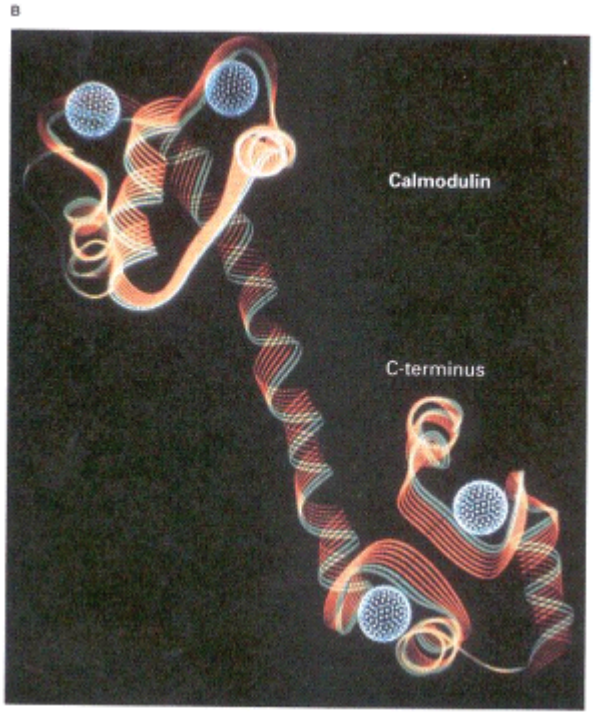
Calmodulin

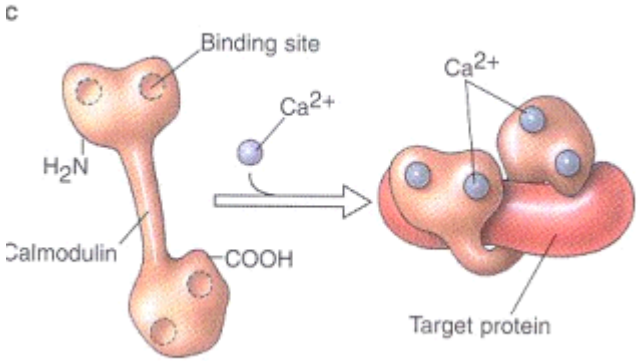
(A)Amino acid sequence of the Ca2+ binding site at the C-terminus. Each binding site contains aspartate, glutamate, and asparagine residuces

(B)Model of the calmodulin molecule with four bound Ca2+

(C)Diagram illustrating Ca2+ induced conformational change





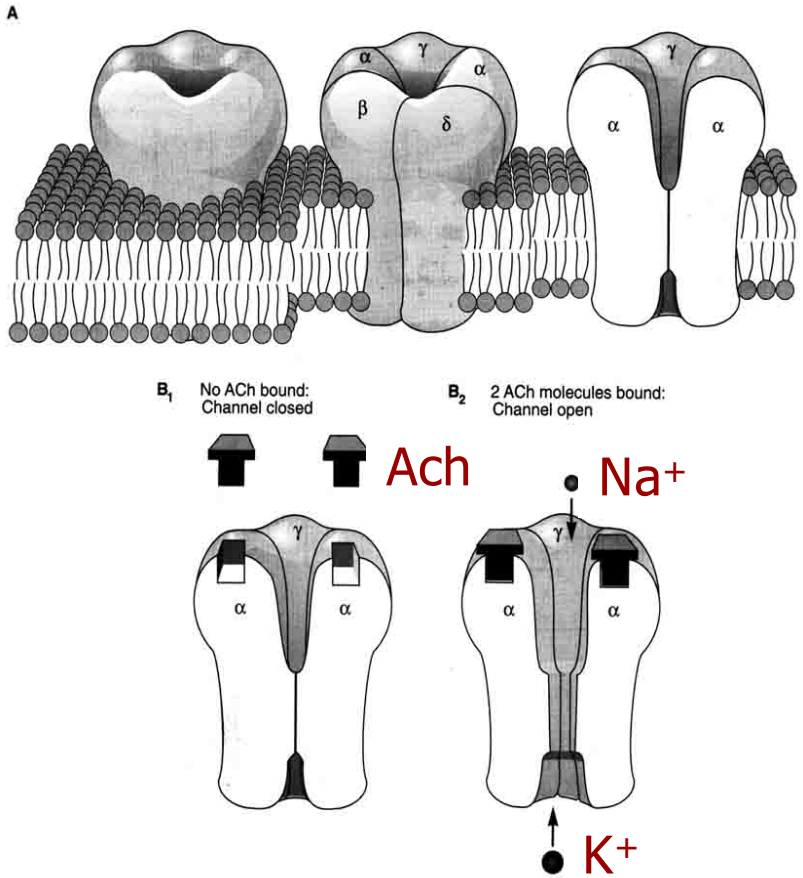


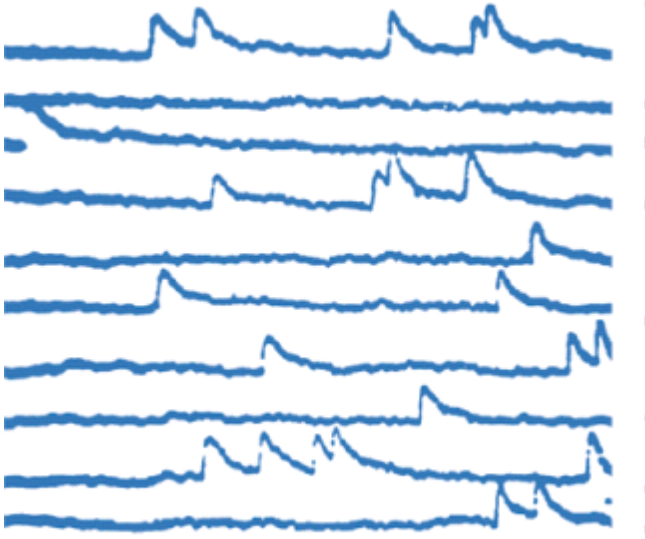
Cellular transmembrane signal transduction

- Signal transduction mediated by G-protein coupled receptor
- Signal transduction mediated by ion channel coupled receptor
- Signal transduction mediated by enzyme-coupled receptor

Signal transduction mediated by ionotropic receptor

- **Nicotinic Ach receptor**

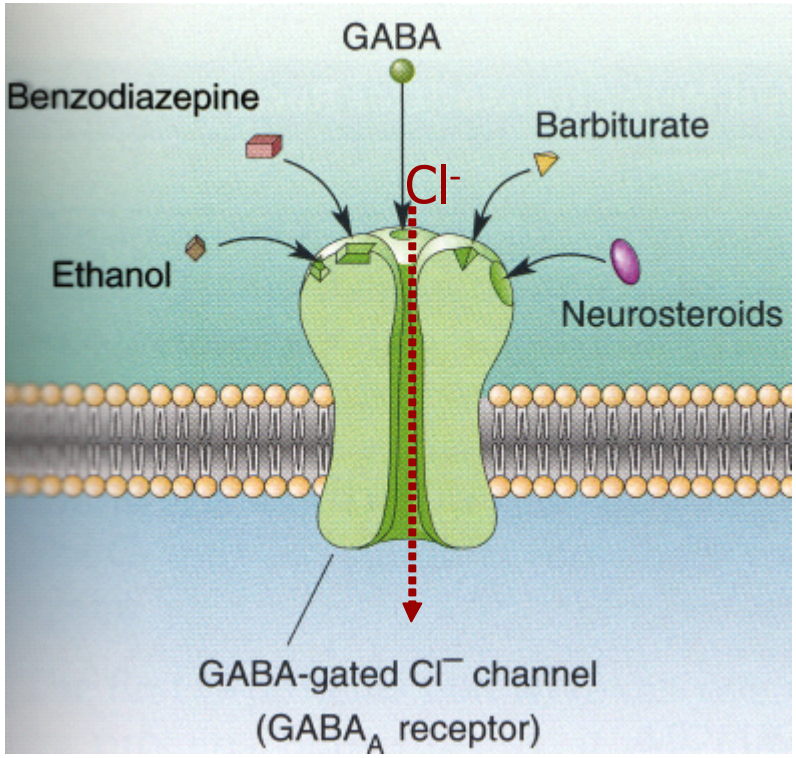


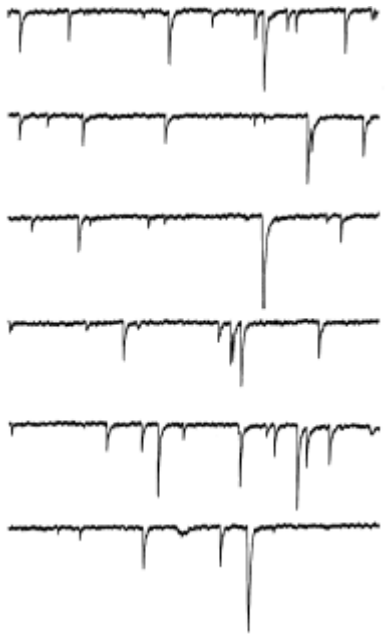


End plate potential

Signal transduction mediated by ionotropic receptor

- $GABA_A$ receptor

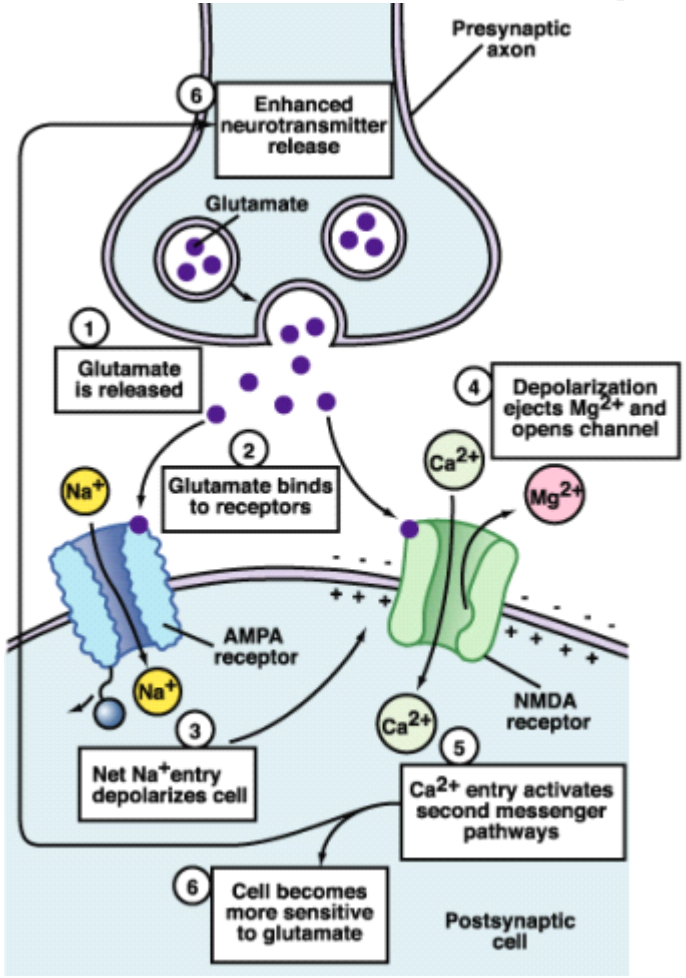


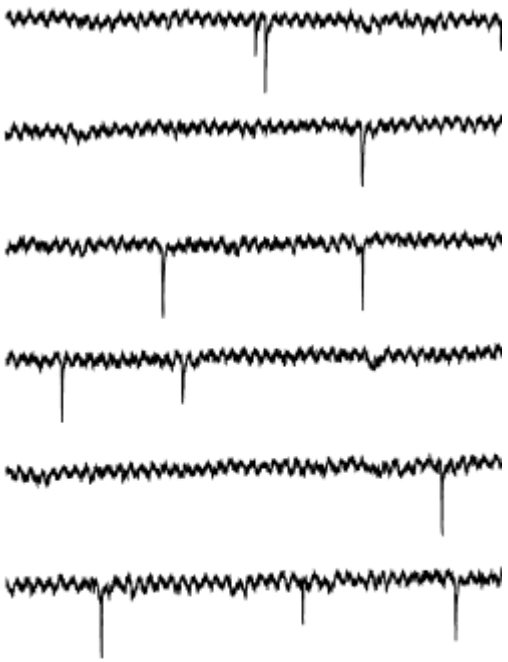


Inhibitory postsynaptic current

Signal transduction mediated by ionotropic receptor

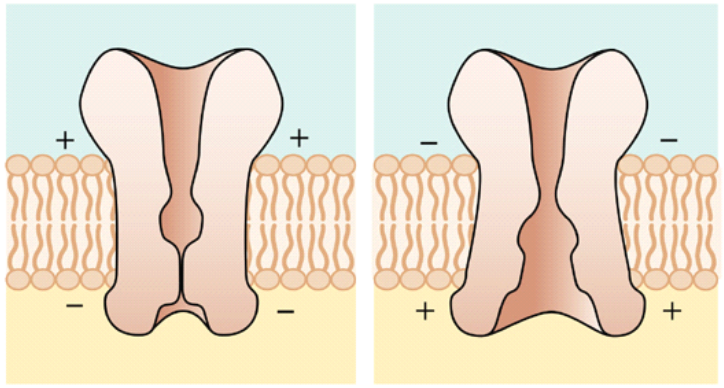
- Glutamate receptor



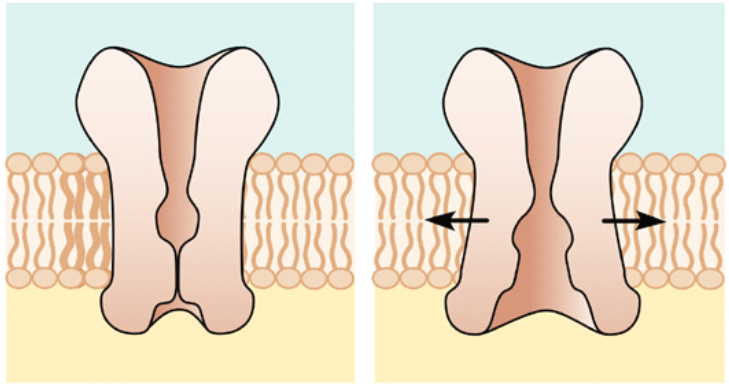


Excitatory postsynaptic current

Channels activated by physical changes in the cell membrane



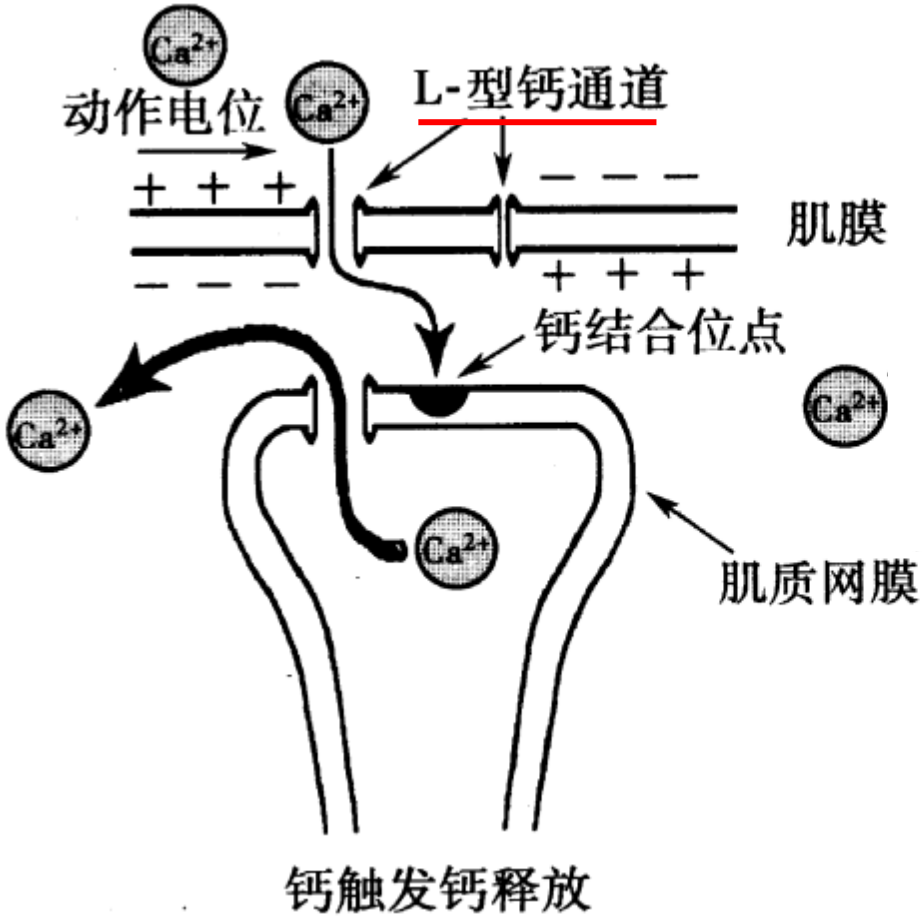
Voltage-activated



Stretch-activated

- **Voltage-gated channels** – open and close in response to changes in the membrane potential
- **Mechanically-gated channels** – open and close in response to physical deformation of channels

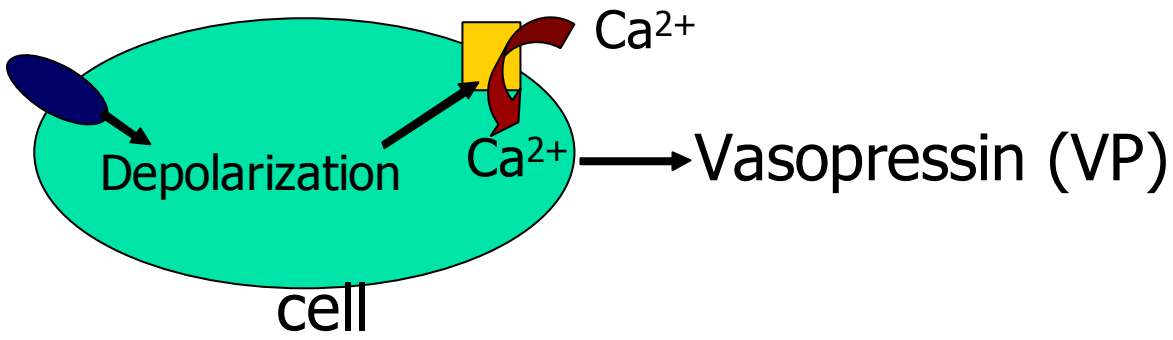
Voltage-gated ion channel

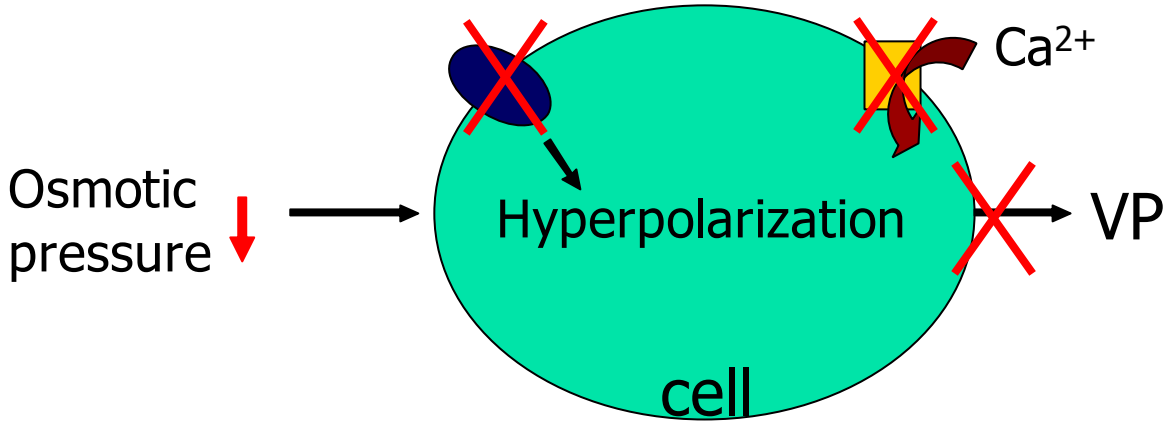


Cardiac muscle

Mechanically-gated ion channel

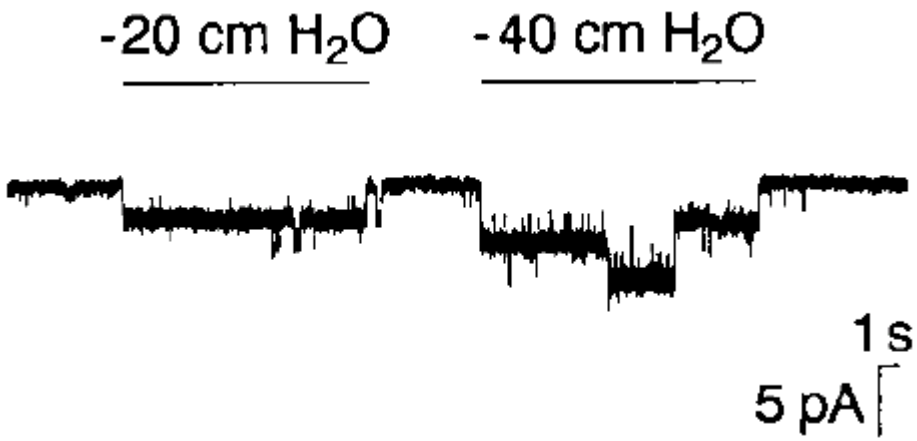
- Mechanically-gated cation channel



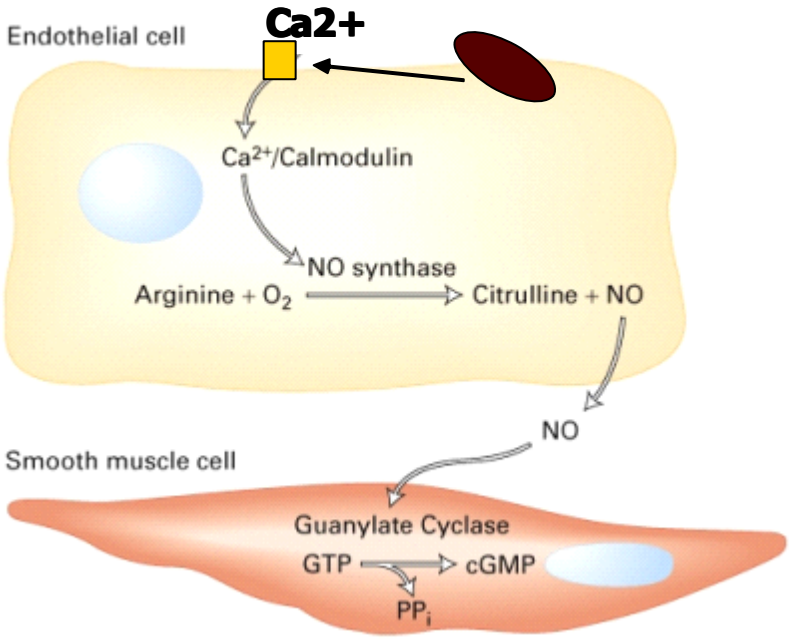


Hypothalamus

Single channel recording from a stretch activated ion channel



Stretch activated cation channel



Molecular Identification of a Eukaryotic, Stretch-Activated Nonselective Cation Channel Kanzaki et al. 1999

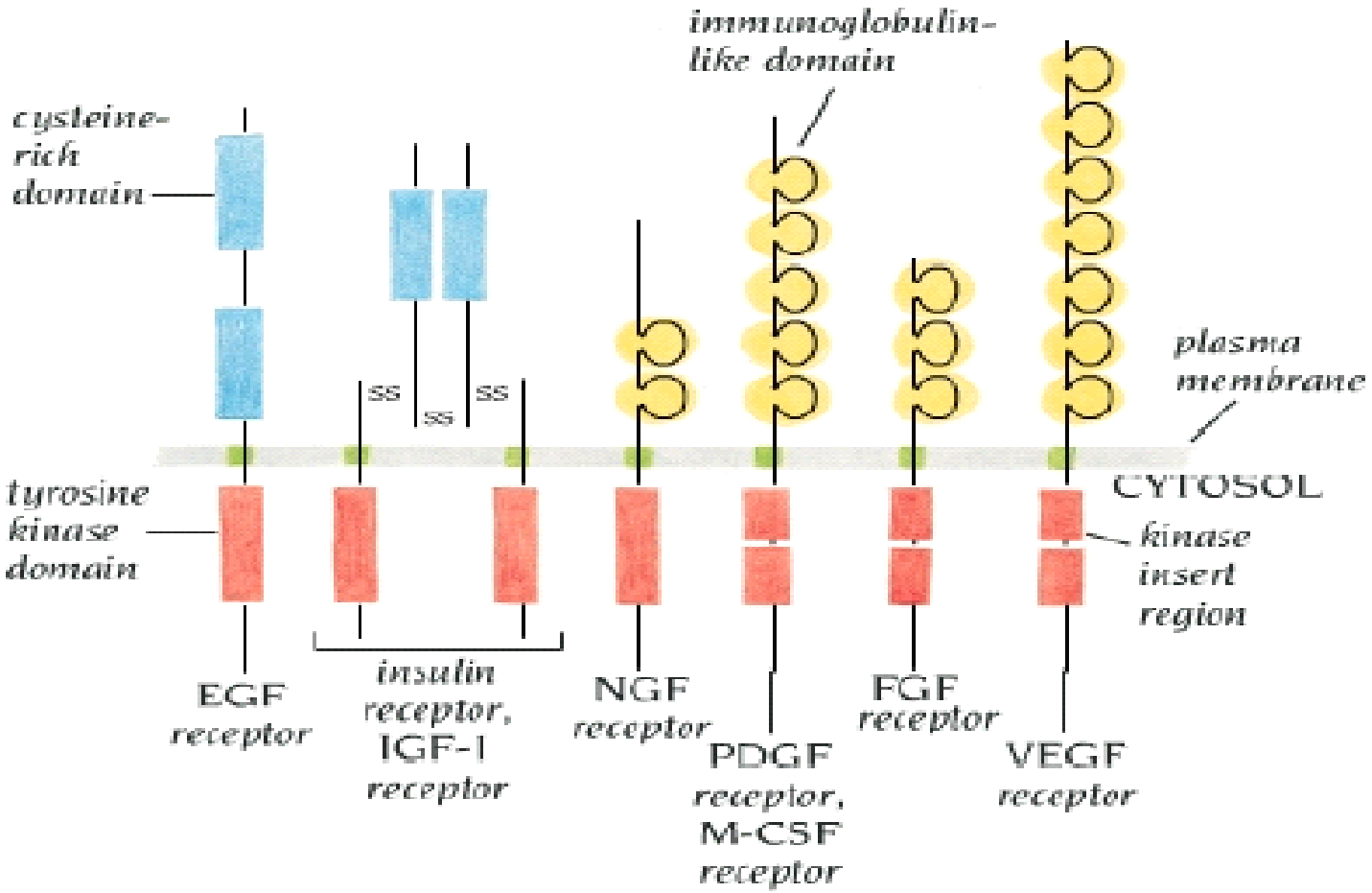
Cellular transmembrane signal transduction

- Signal transduction mediated by G-protein coupled receptor
- Signal transduction mediated by ion channel coupled receptor
- Signal transduction mediated by enzyme-coupled receptor

Signal transduction mediated by enzyme-coupled receptor

- The receptors have intrinsic enzyme activity
- Tyrosine kinase receptor, TKR
- Guanylyl cyclase receptor, GCR

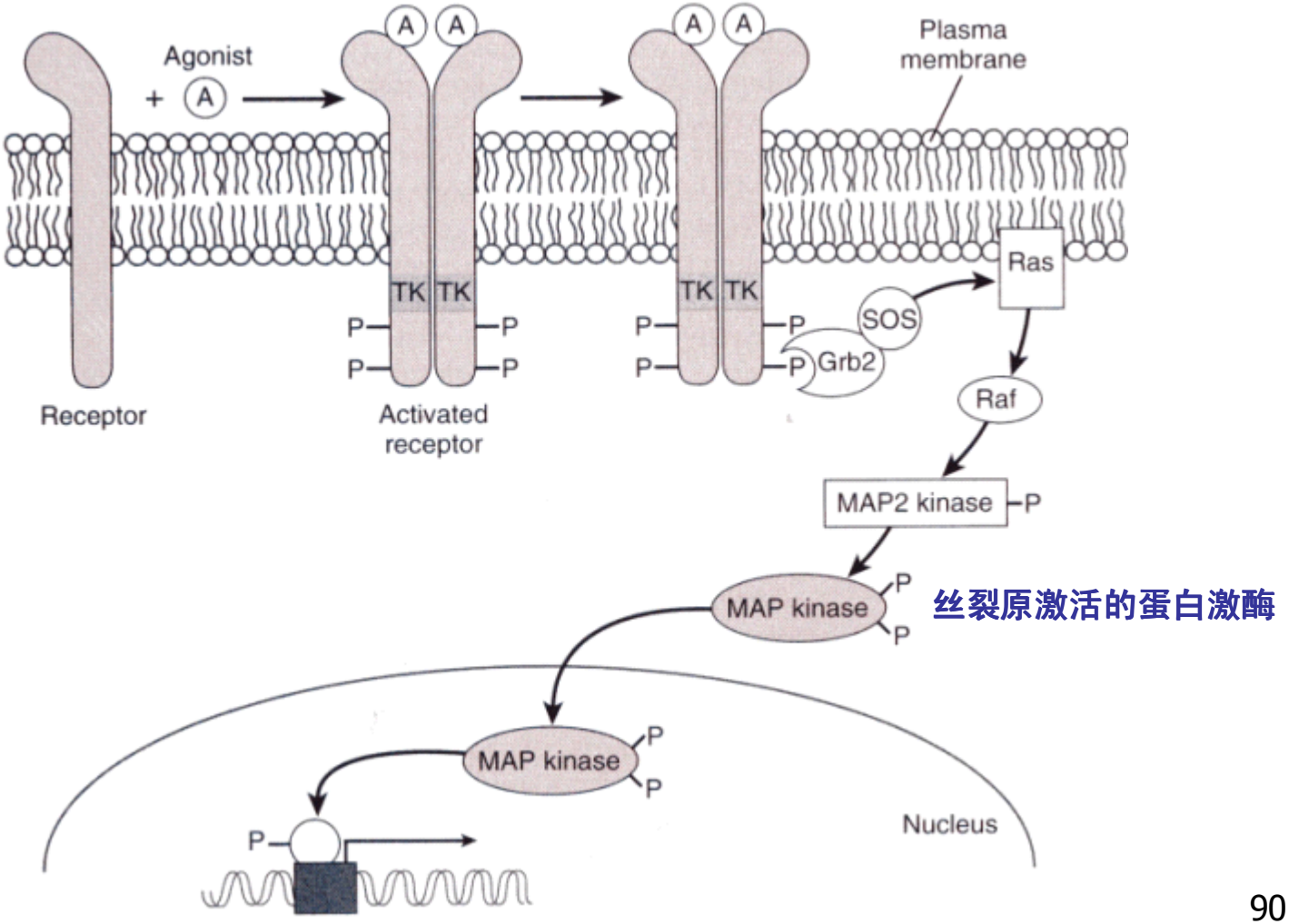
Tyrosine kinase receptor



Cytokine

EGF: epidermal growth factor
PDGF: platelet-derived growth factors
FGF: fibroblast growth factors
NGF: nerve growth factor
IGF-1: insulin growth factor
VEGF: vascular endothelial growth factor
HGF: hepatocyte growth factors

Tyrosine kinase receptor



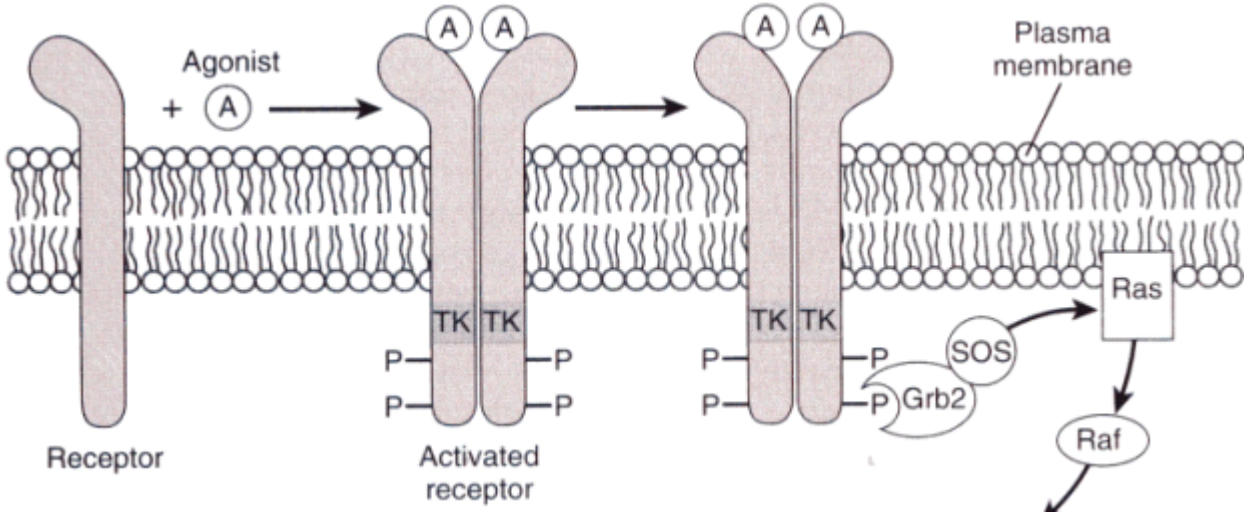
丝裂原激活的蛋白激酶

The sequence of events for tyrosine kinase receptor

- The binding of a specific messenger to the receptor changes the conformation of the receptor (dimer).
- So that the enzymatic portion located at the intracellular side of the receptor is activated.
- This results in the auto-phosphorylation of the receptor.
- The newly created phosphotyrosine on the cytoplasmic portion of the receptor then serves as “docking” site for cytoplasmic proteins.
- The bound docking proteins then bind other proteins, which leads to a cascade of signaling pathways within the cell.

Tyrosine kinase receptor

- **Auto-phosphorylation of the receptor**: **the receptor phosphorylates its own tyrosine groups.**

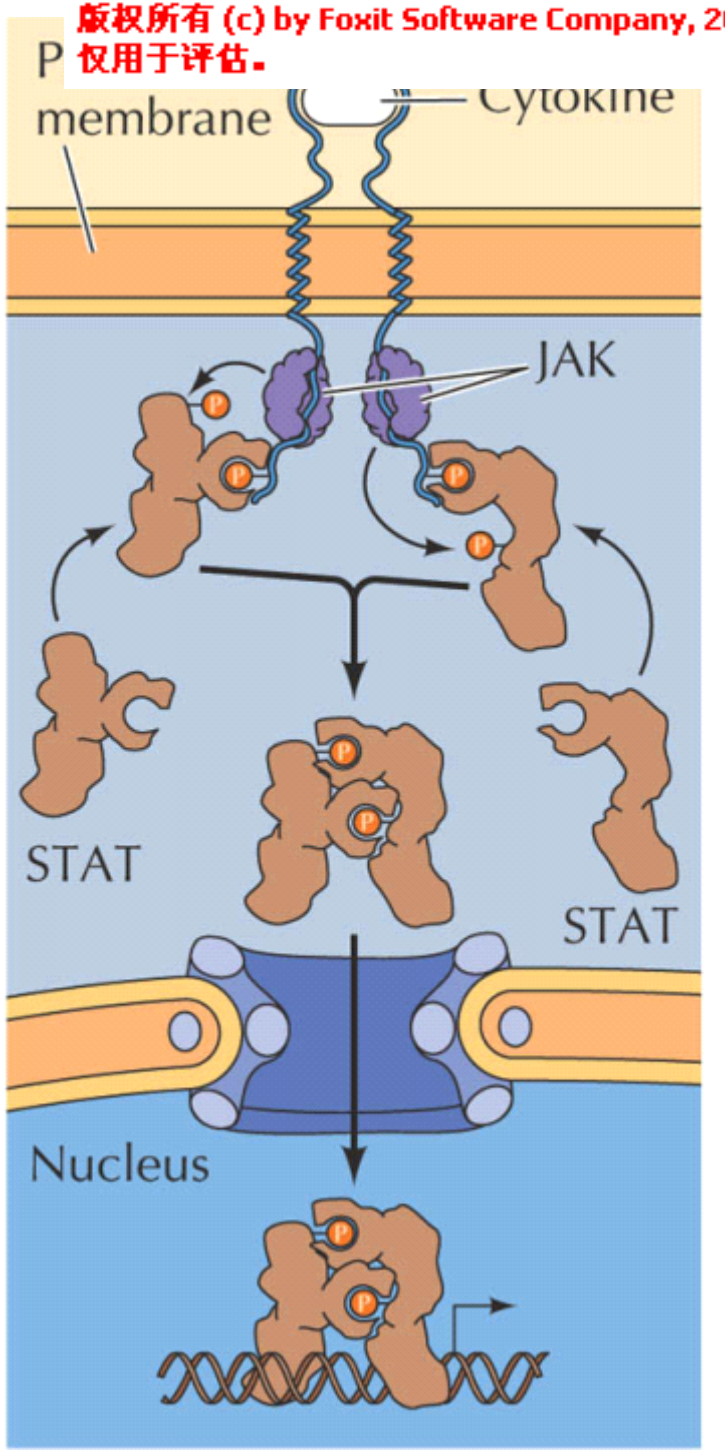


Receptor-associated tyrosine kinase

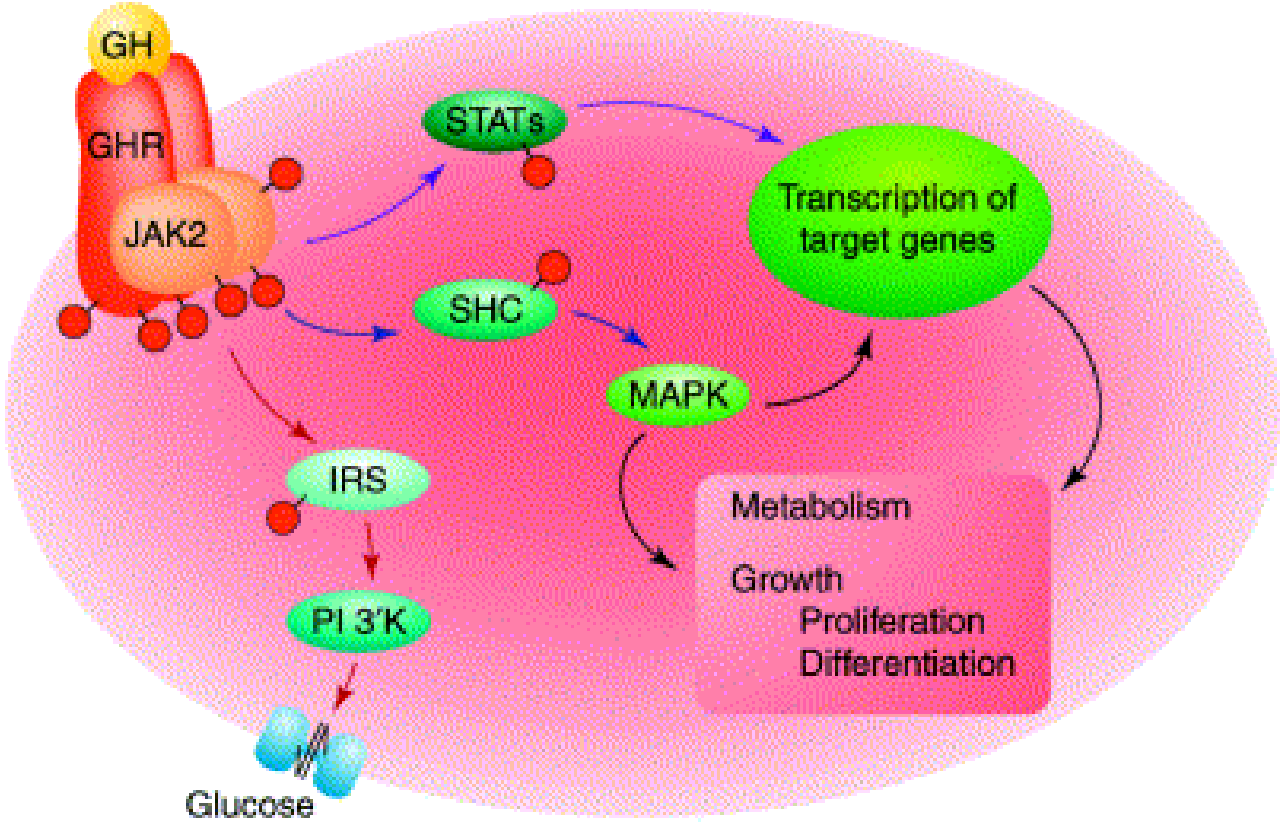
JAK: Janus kinase

STAT: signal transducers and activators of transcription

信号转导与转录激活因子



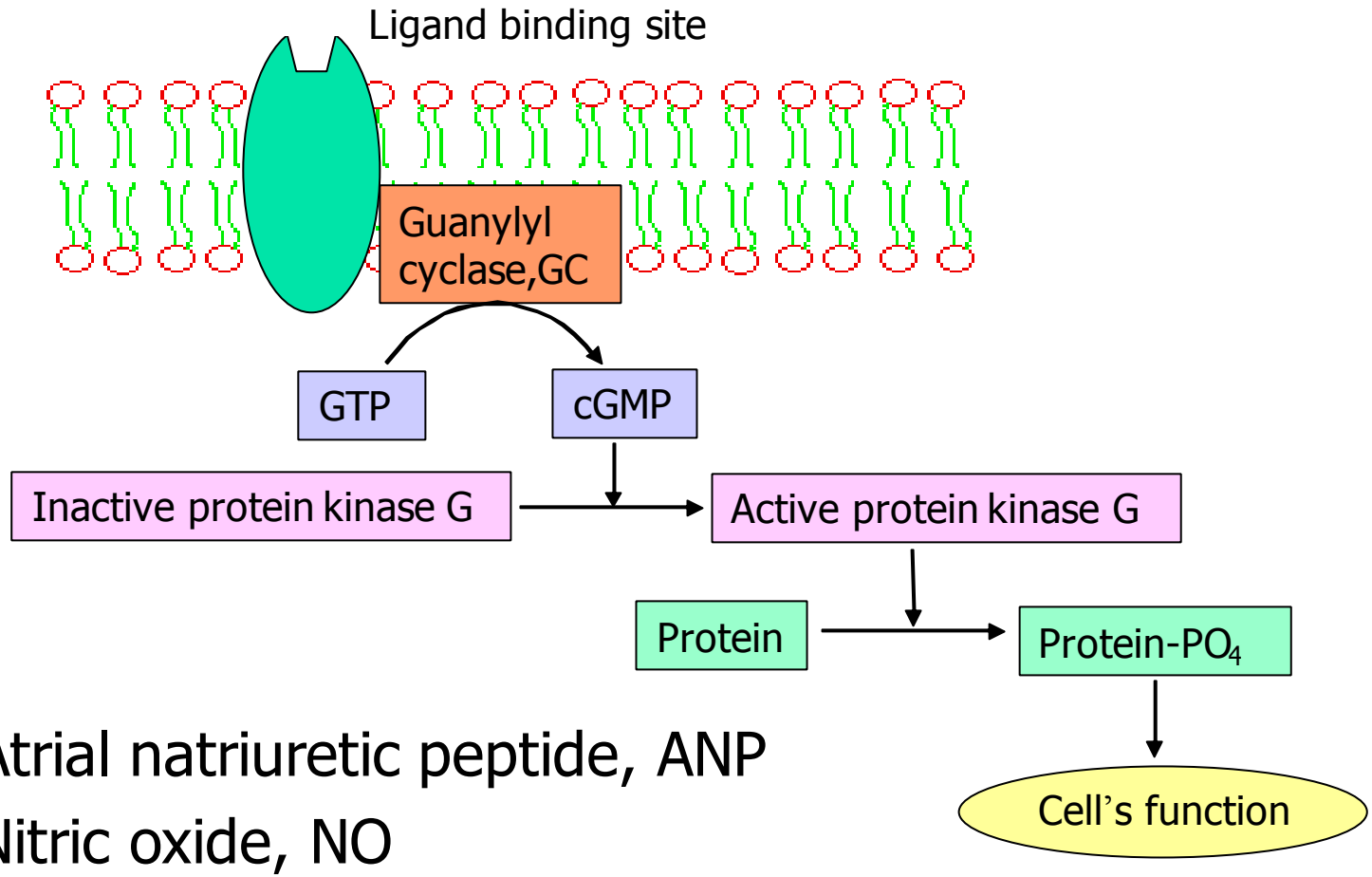
GH-GHR signal transduction



Function of tyrosine kinase receptor

- Most of the receptors with intrinsic tyrosine kinase activity bind first messengers that typically influence cell proliferation and differentiation.

Guanylyl cyclase receptor

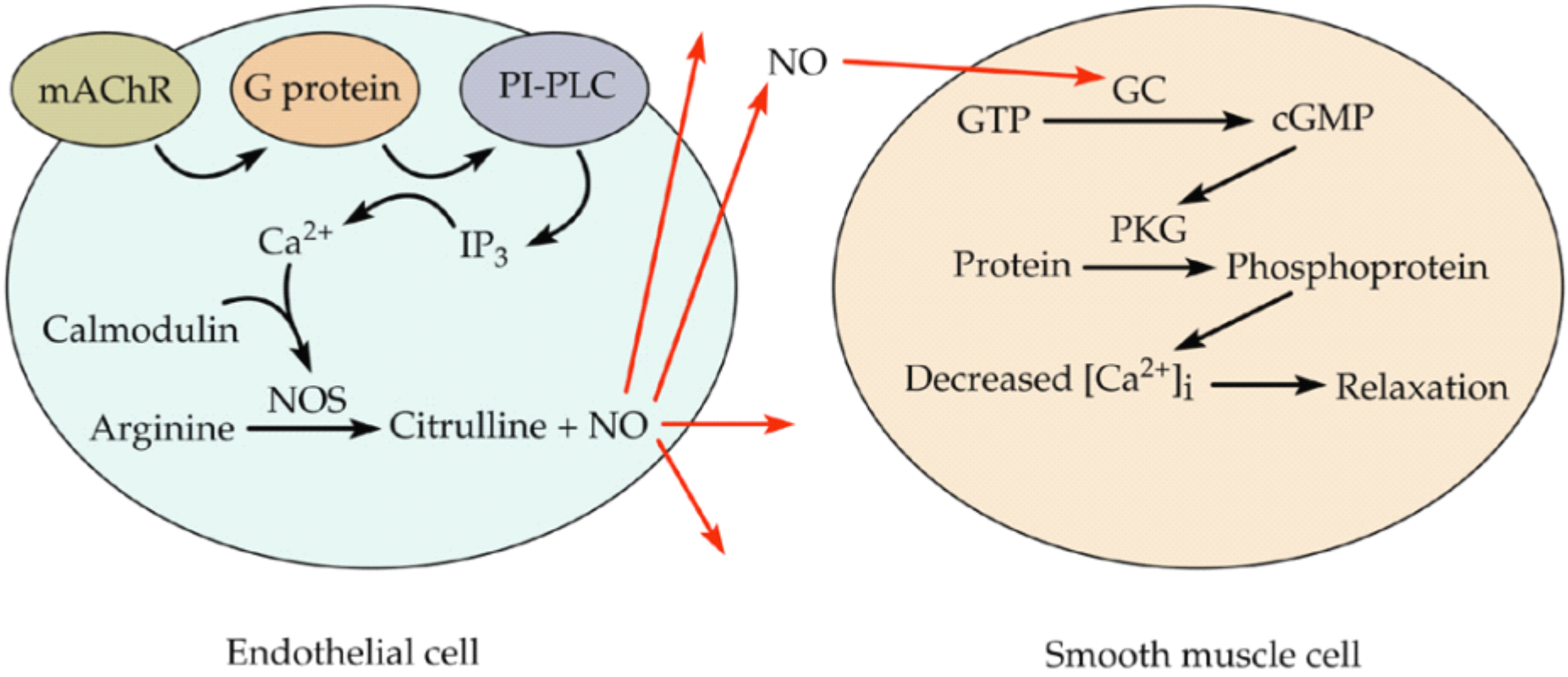


- Atrial natriuretic peptide, ANP
- Nitric oxide, NO

Atrial natriuretic peptide, ANP

- Synthesized and released by atrial muscle cells
- Stimulates kidney to excrete natrium and water
- Relaxes vascular smooth muscles

Receptor guanylyl cyclase



NOS: nitric oxide synthase

A overview of calcium regulation in cells

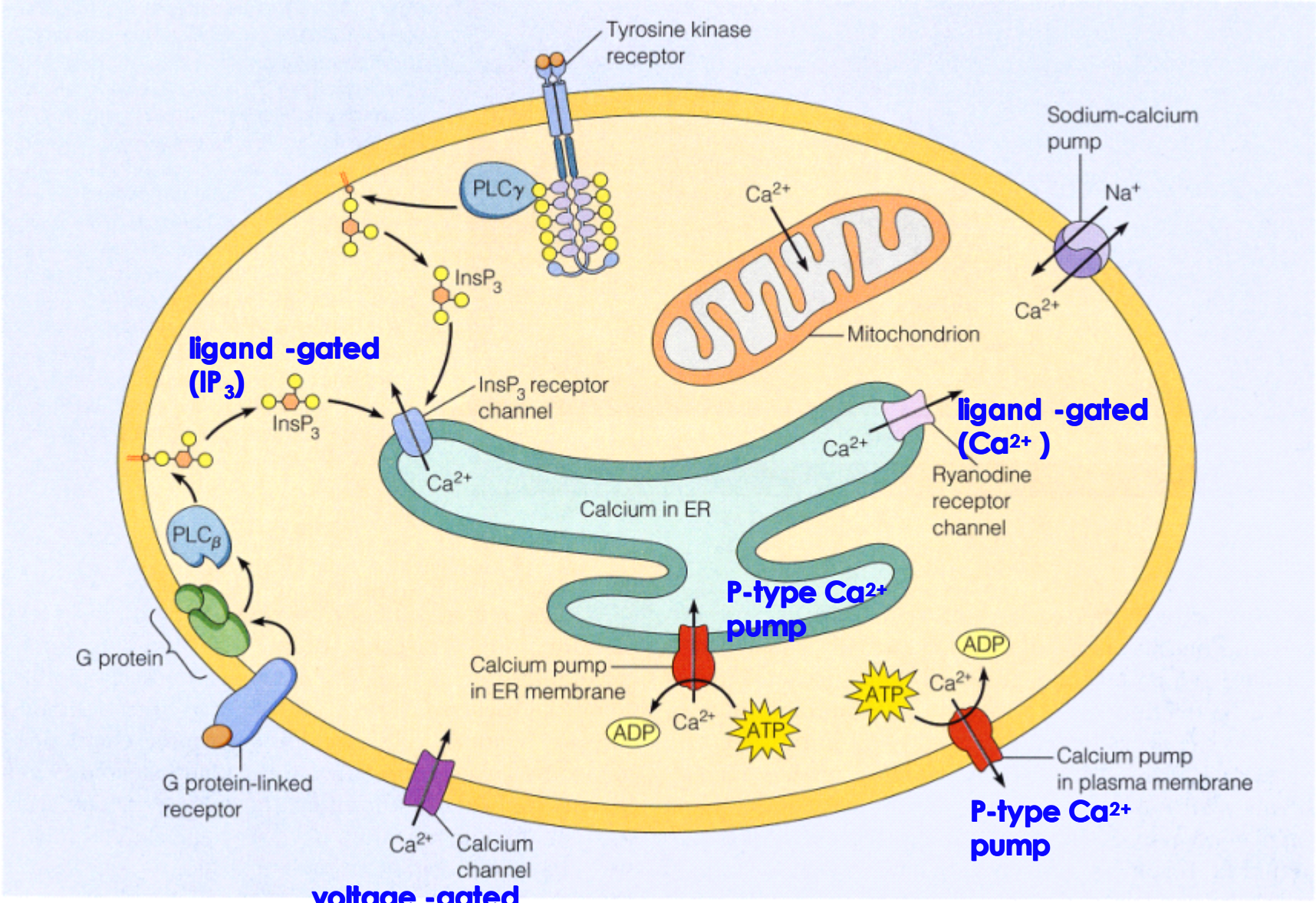
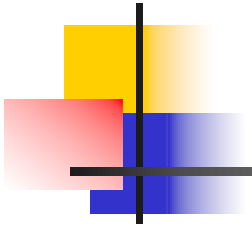


Figure 10-11 An Overview of Calcium Regulation in Cells.



Summary

Signal transduction mediated by

- G-protein coupled receptor
  - cAMP-PKA pathway
  - IP3-Ca^{2+} pathway
  - DG-PKC pathway
- Ion channel coupled receptor
- Enzyme coupled receptor

Questions

- **Define each term**:
  - Second messenger
  - Protein kinase
- **Answer the following question**
  - Describe the generation of IP3 and DAG and their intracellular signaling roles
  - Describe the activation and inactivation of G protein
  - Describe the sequence of events for receptor-G protein-AC pathway