

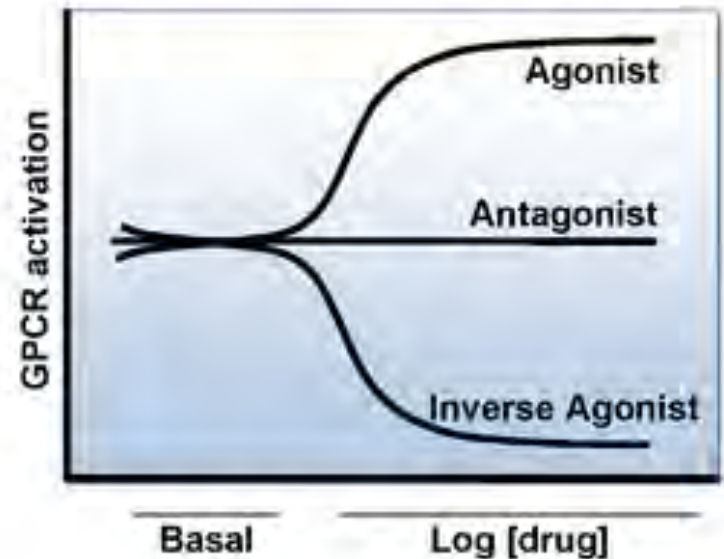
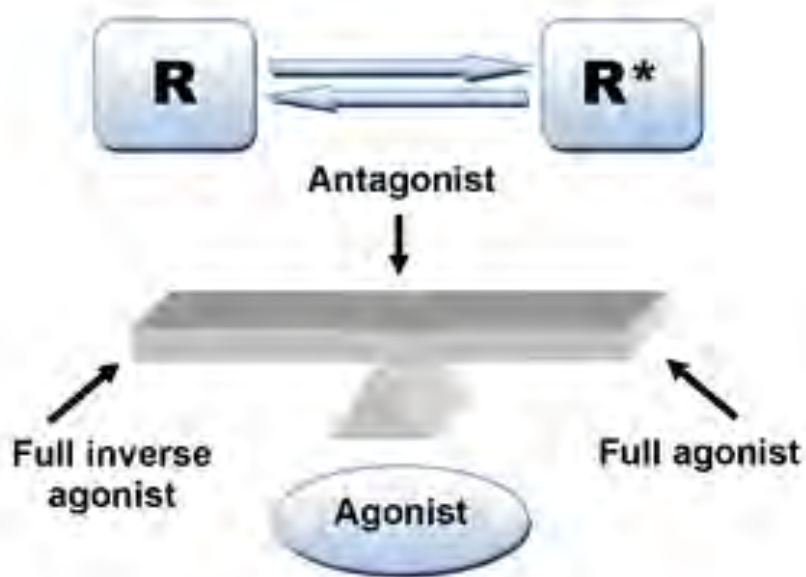
# Signal transduction

1. Nuclear receptors
2. G protein-coupled receptors
3. Receptor Tyrosine kinases (RTK)
4. Receptors with associated kinases

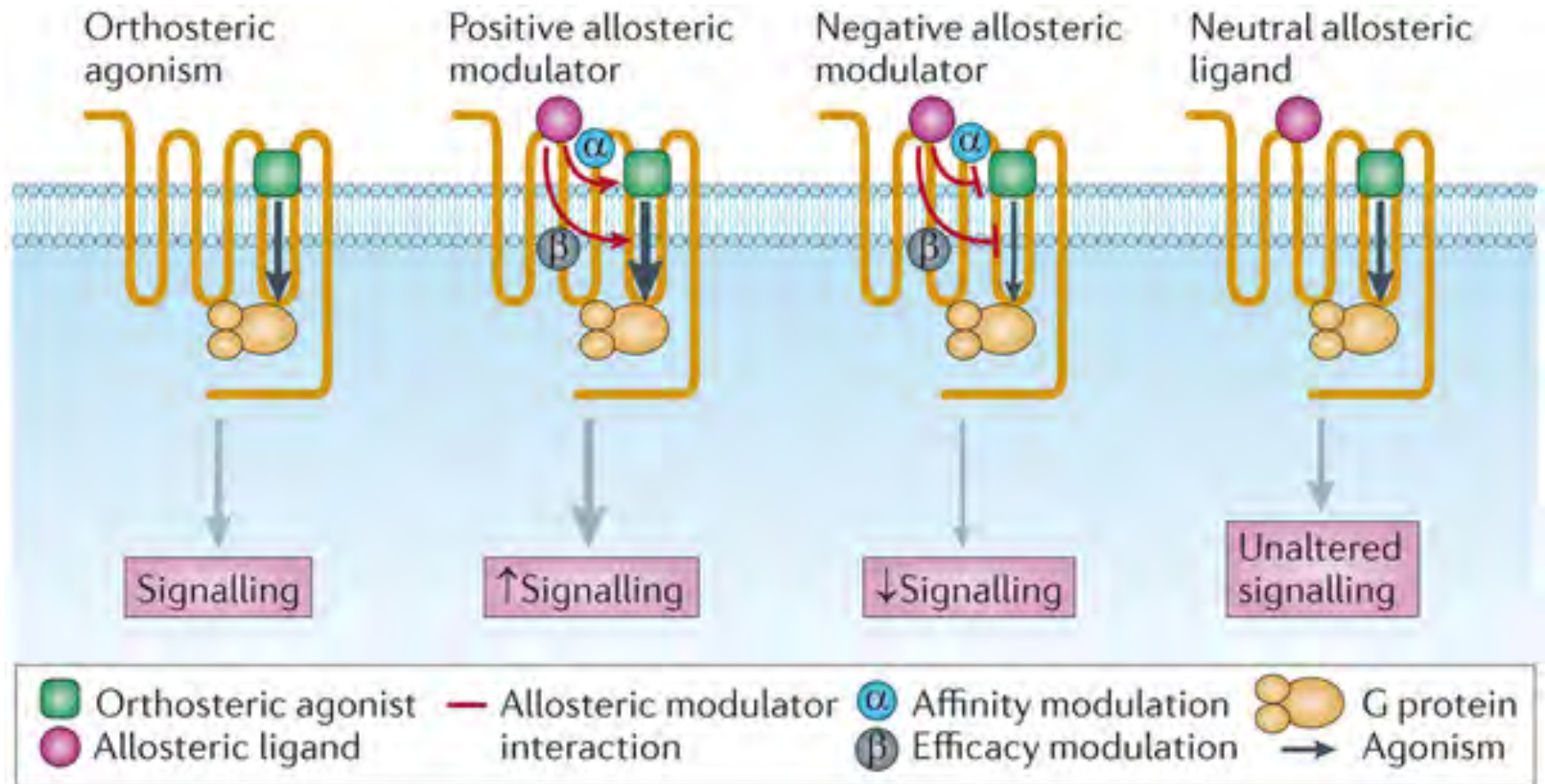
# Receptor definition (biochemical)

Biomolecule or Biomolecule complex,

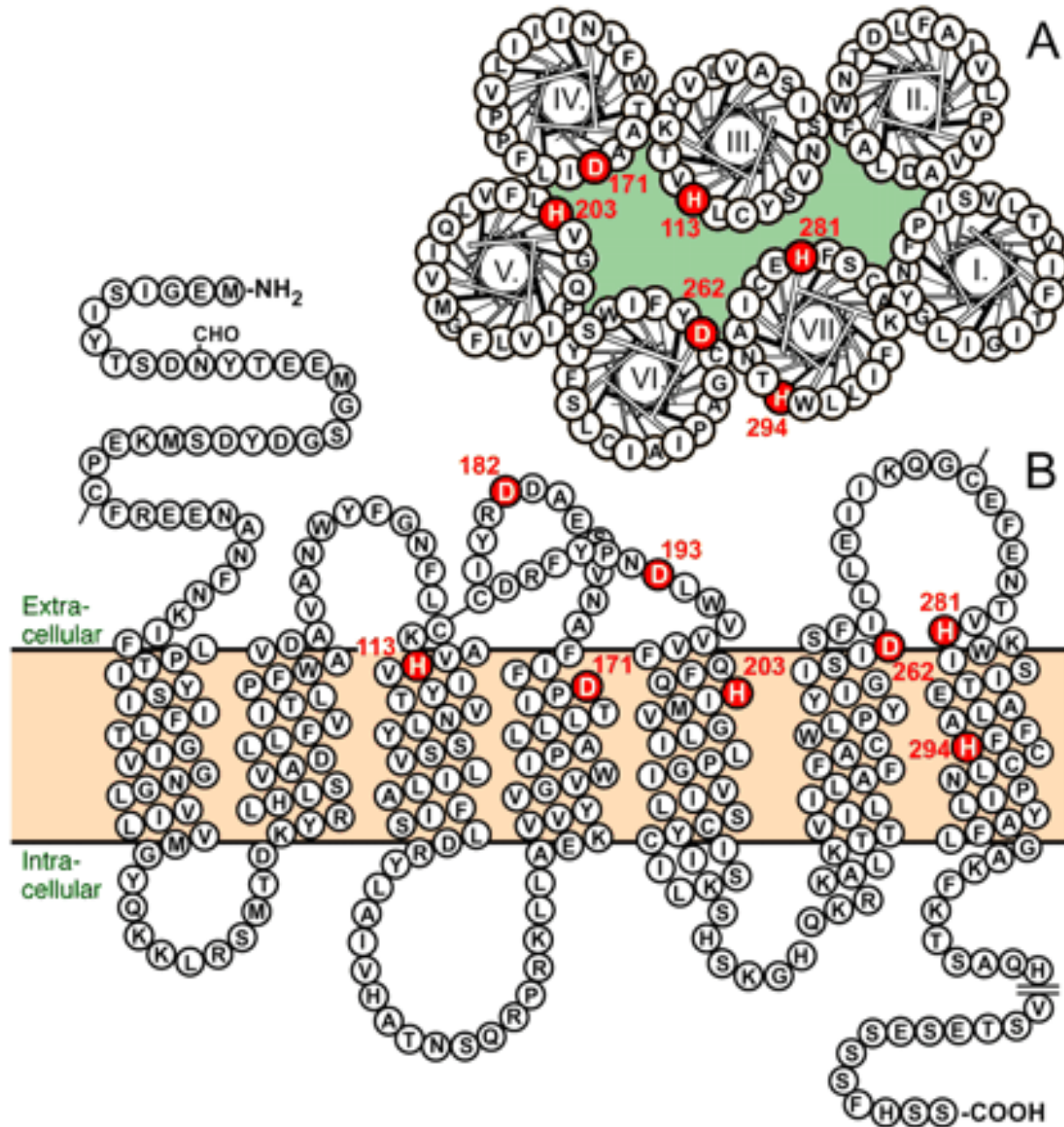
- Signal molecule binds,
- Structural changes
- Activation of one or more signal transduction cascades



# Receptor ligands (biochemical)



# G protein-coupled receptors



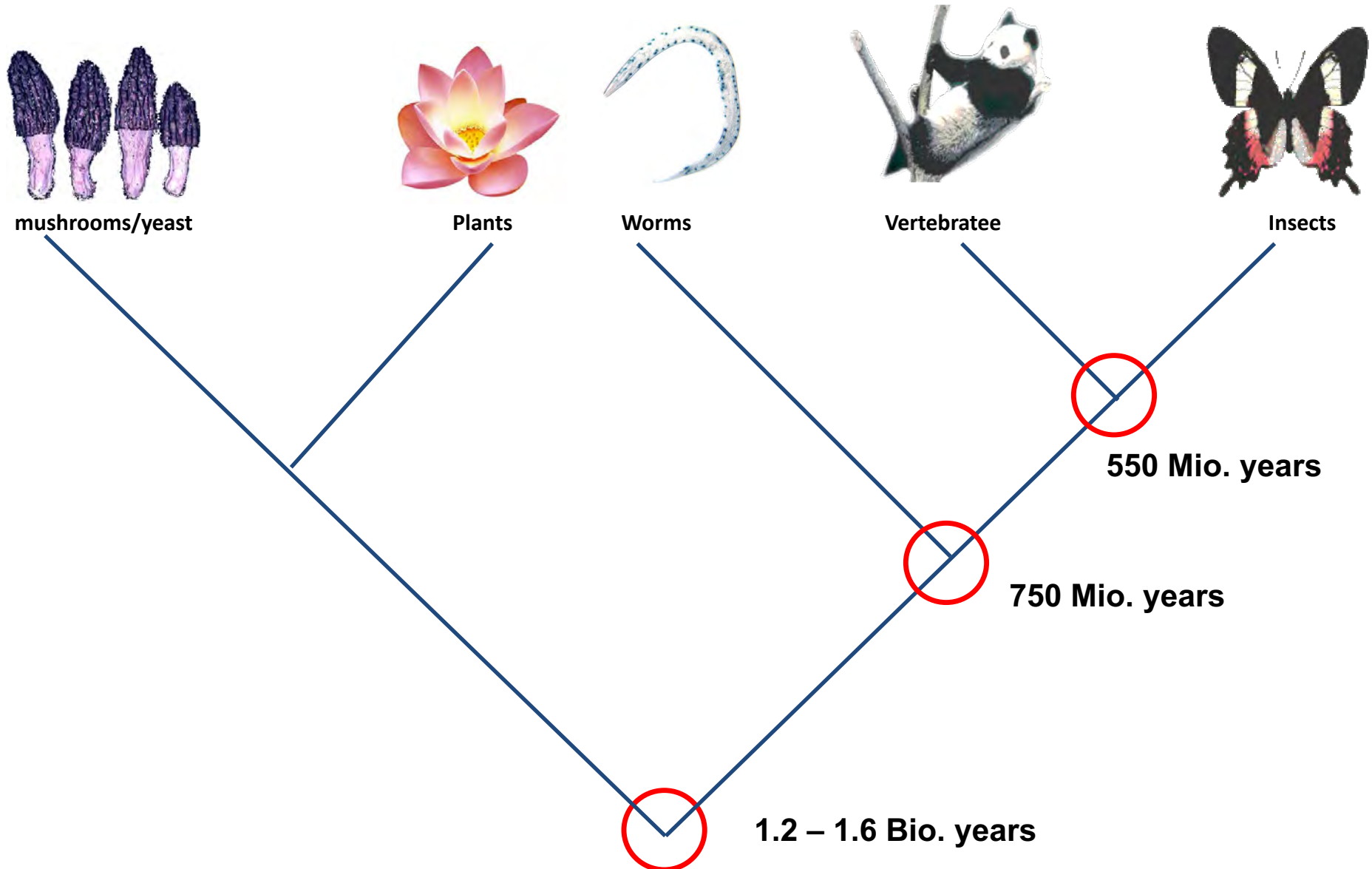


# G protein-coupled receptors



Nobel price of chemistry 2012  
Lefkowitz/Kobilka

# Phylogeny of GPCR



# GPCR-Classification

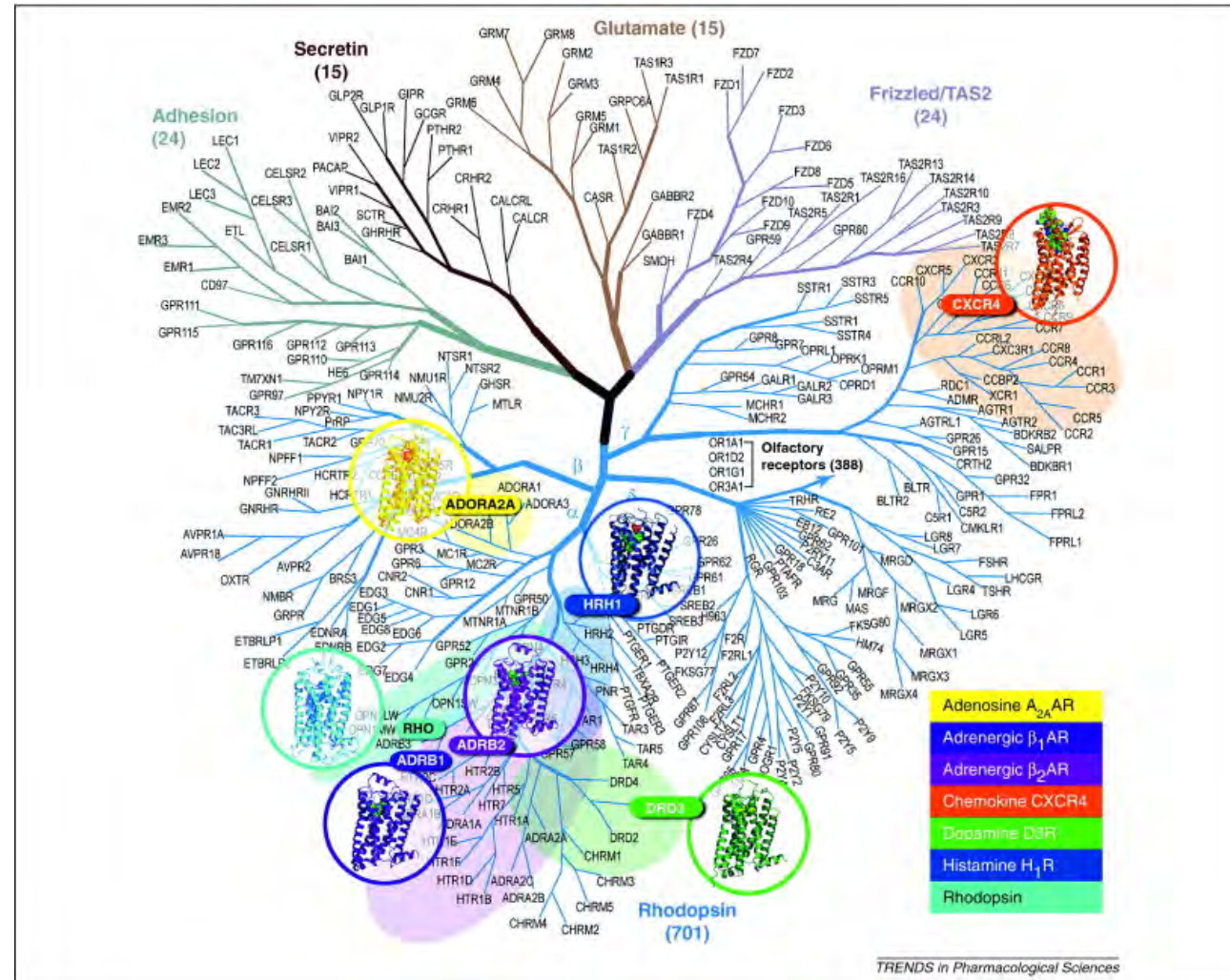
**G**lutamate (Family C)

**R**hodopsin (Family A)

**A**dhesion (Family B)

**F**rizzled/Taste2

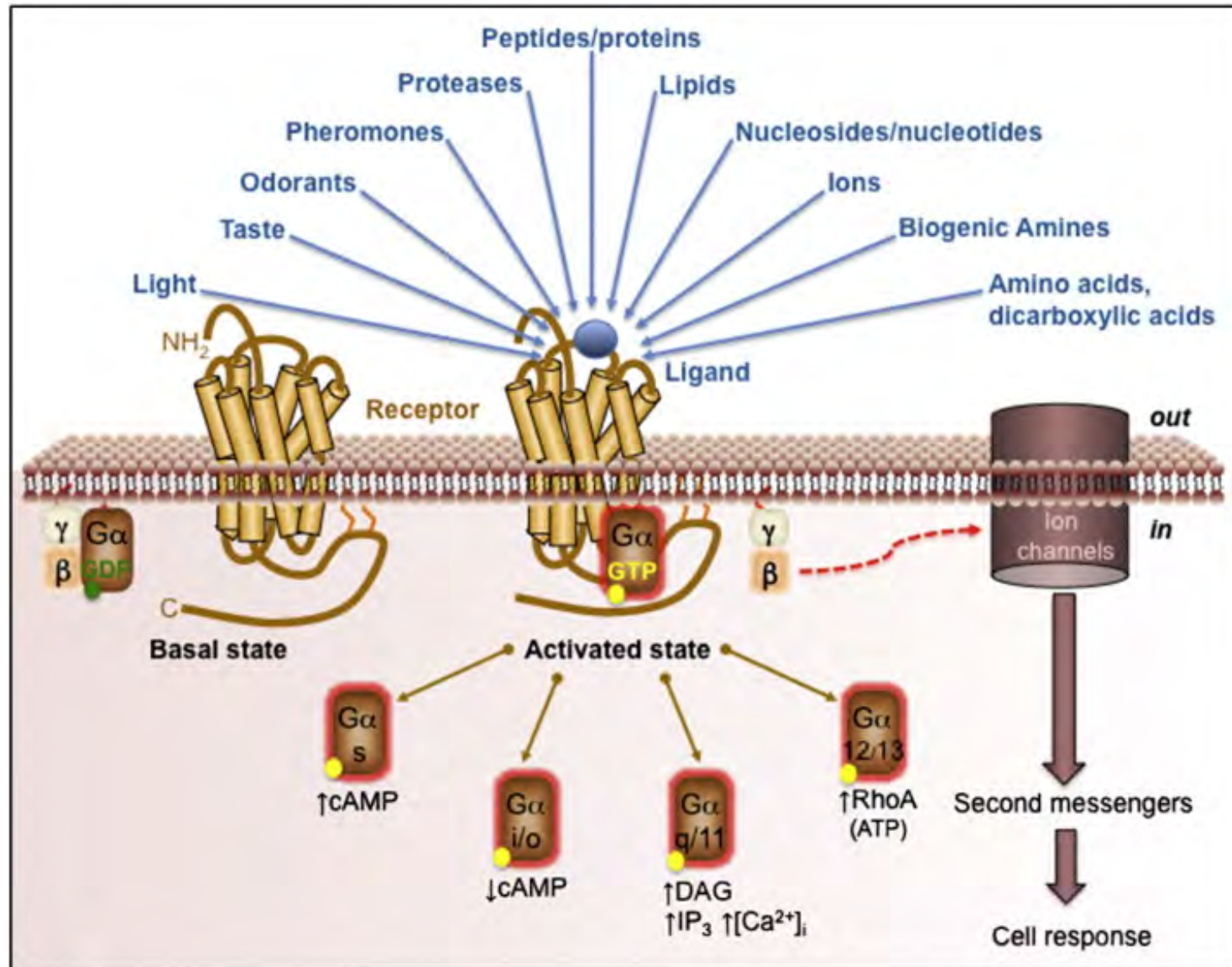
**S**ecretin (Family B)



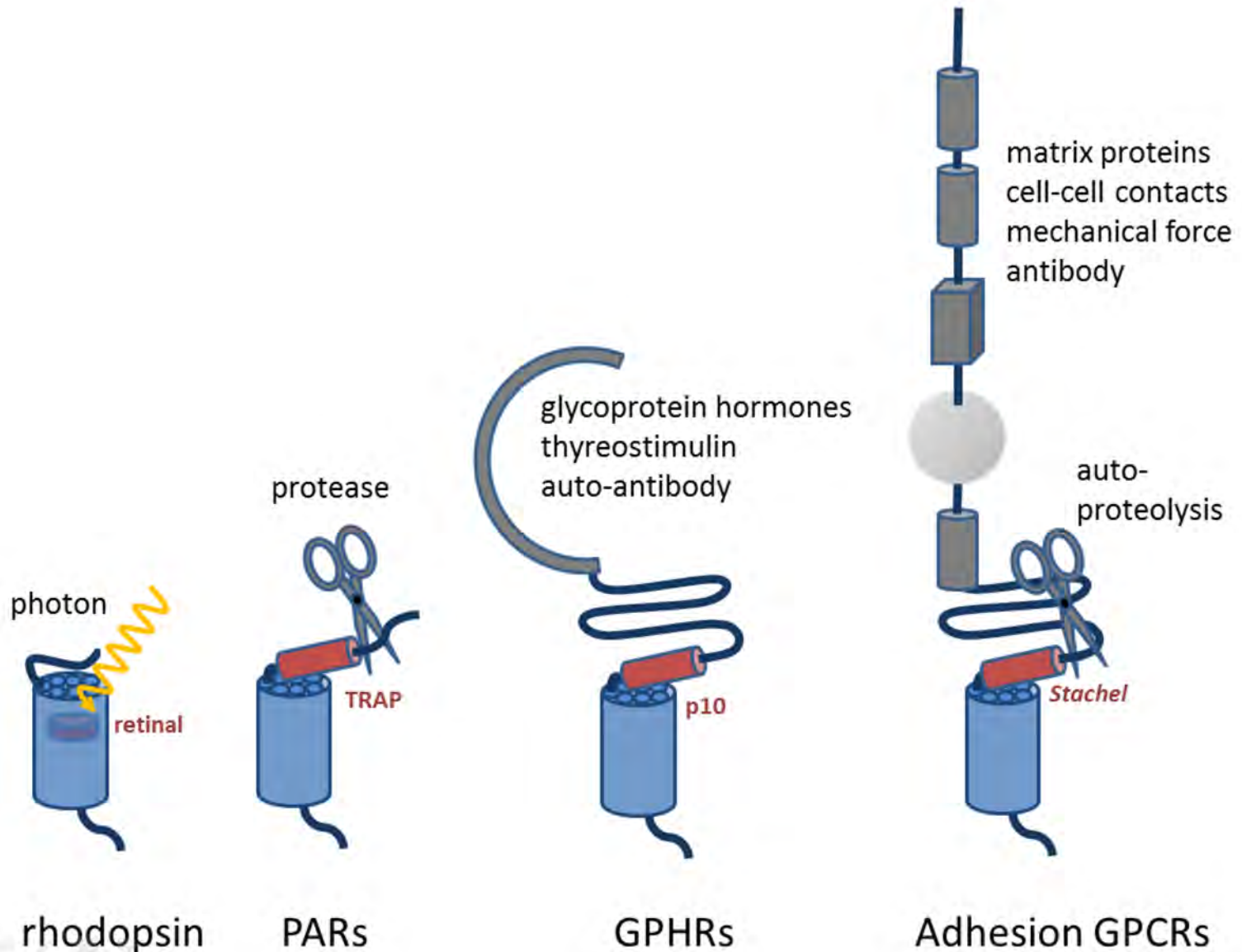


# GPCR Gene Repertoire

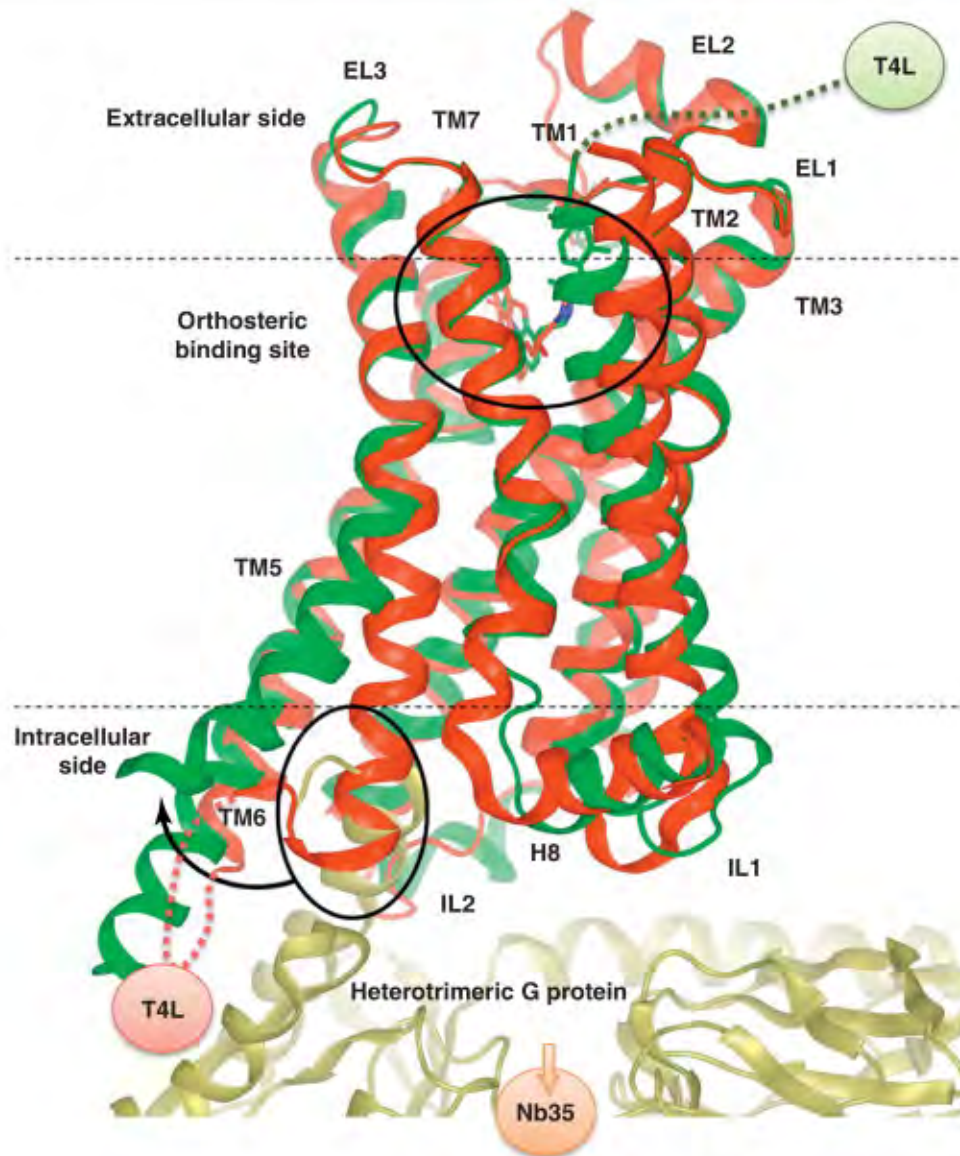
|                                 | Agonist | Orphan | $\psi$ |
|---------------------------------|---------|--------|--------|
| Family A (Rhodopsin)            | ~200    | ~80    | 30     |
| Adhesion/Family B (Secretin-R.) | 25      | 35     | 1      |
| Family C (Glutamate R.)         | 12      | 7      | -      |
| Frizzled                        | 11      | -      | -      |
| ~385 intact Odorant             |         | ~570   |        |



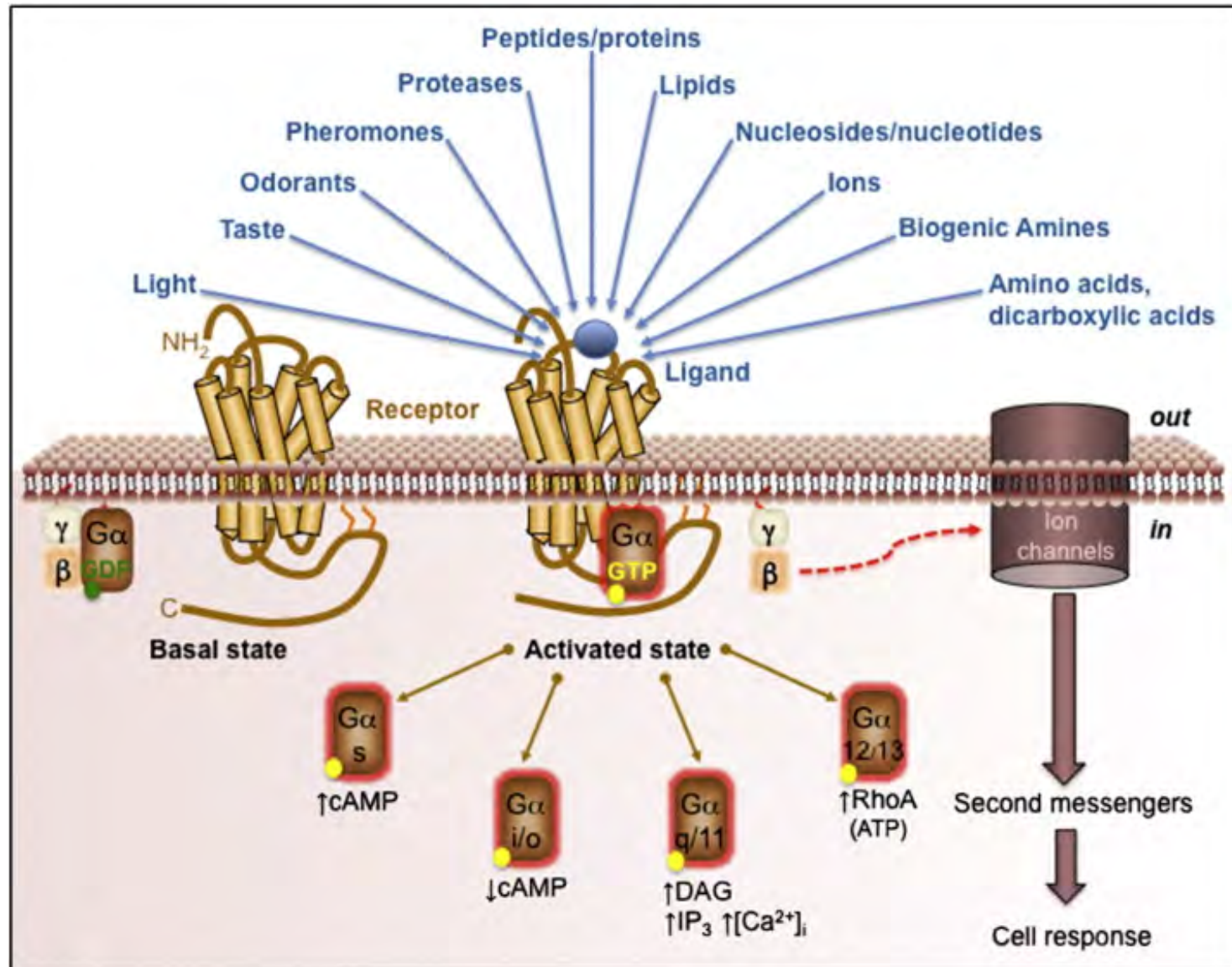
# Ligand binding at GPCR – internal Agonists



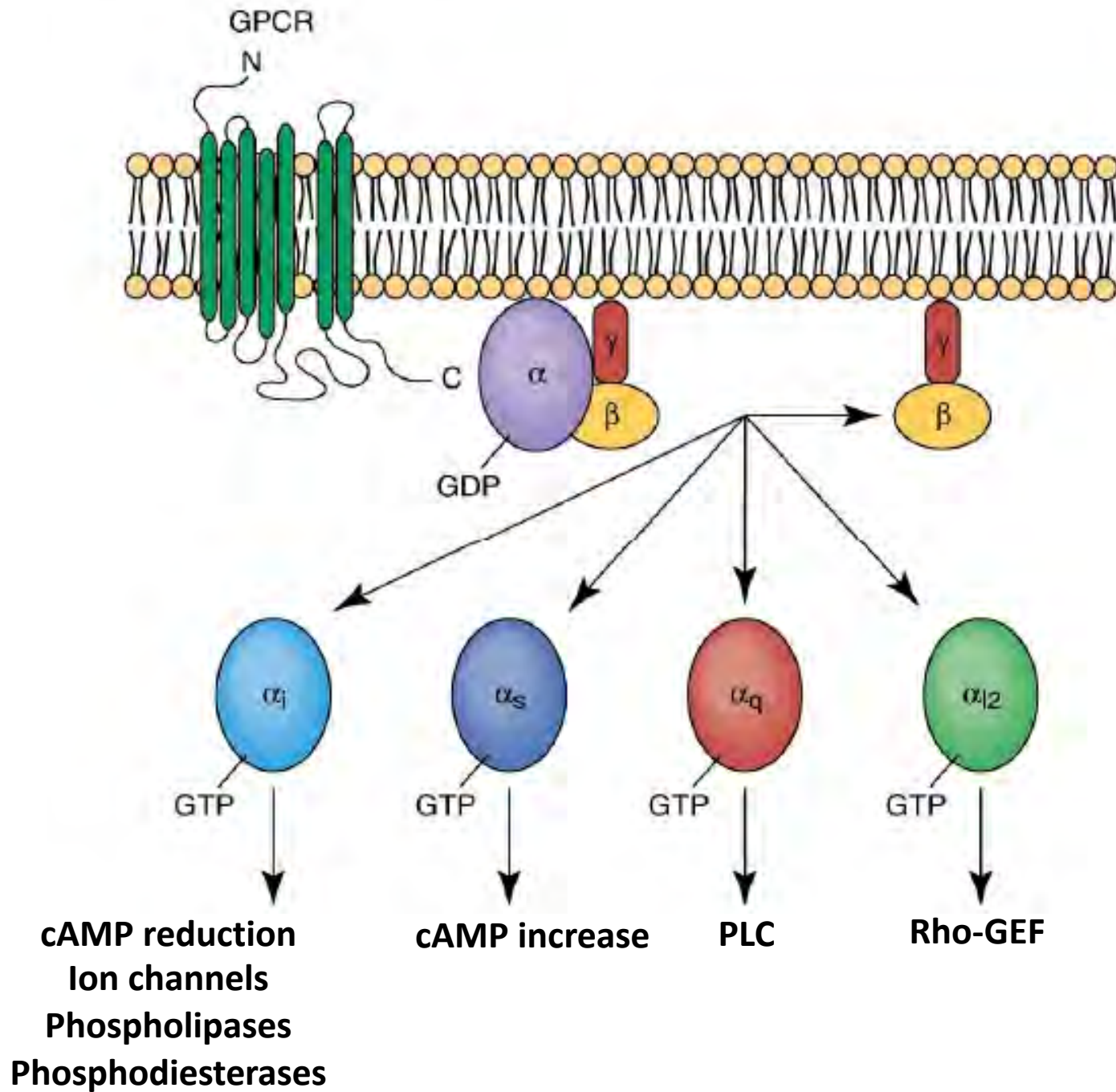
# Structural Changes after Ligand binding









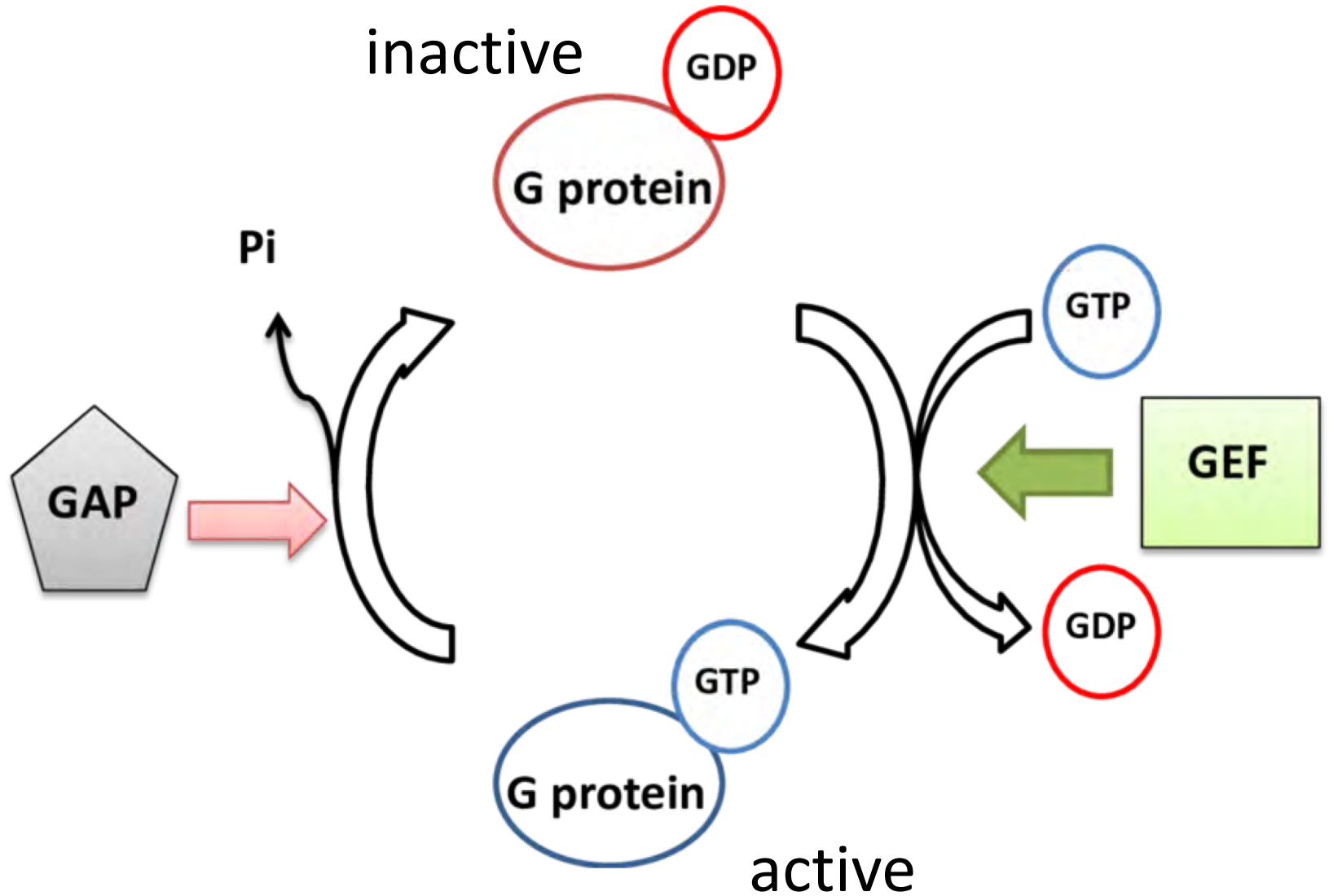


# $\beta/\gamma$ -Subunits of heterotrimeric G Proteins

- Important for Interaction of the G protein with the GPCR
- Inhibition of the spontaneous dissoziation of the  $\alpha$ -subunit-bound GDP
- Activation or inhibition of adenylyl cyclase isoforms
- Regulation of ion channels
- Regulation of signal switch-off by G protein-coupled receptor kinases (GRKs)



# G-protein cycle



# G-protein cycle



Nobel Prize in Physiology or Medicine, 1994



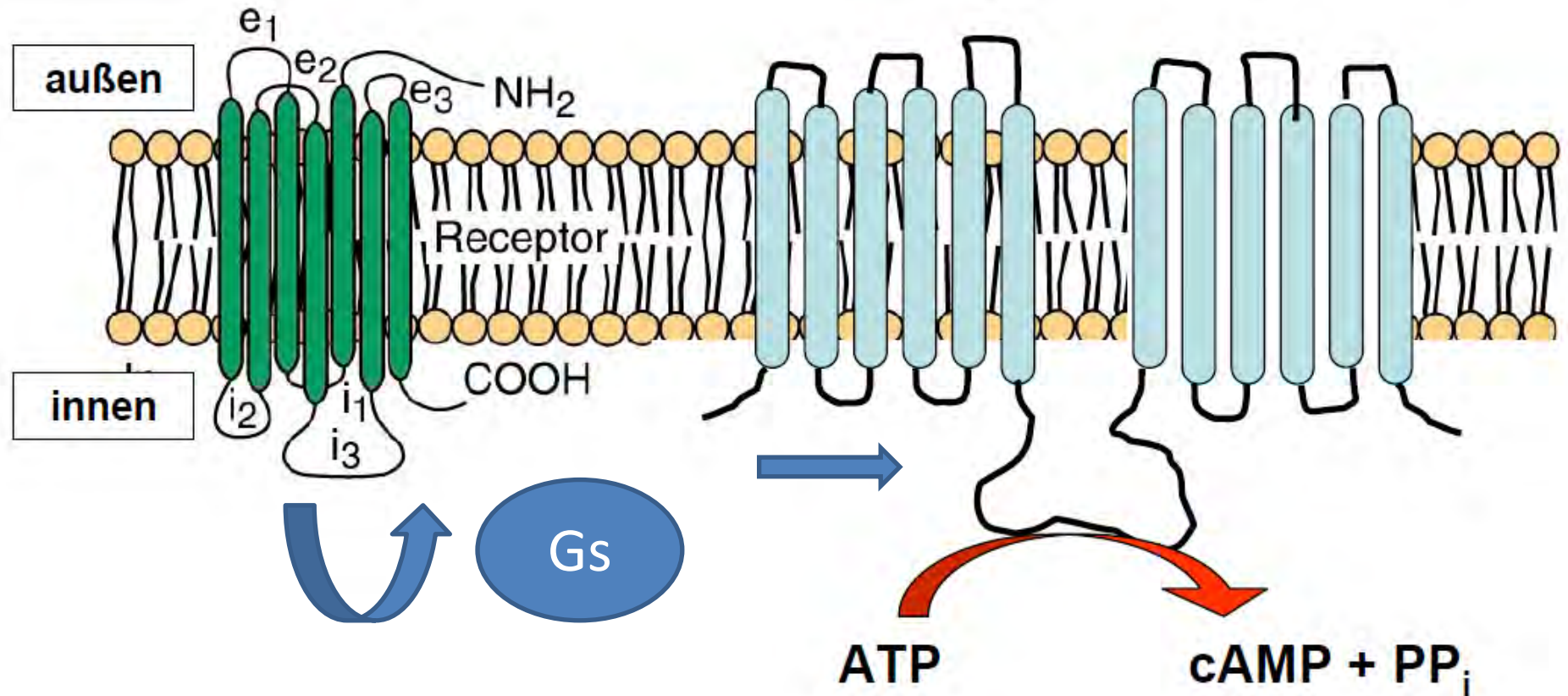
ALFRED G. GILMAN



MARTIN RODBELL

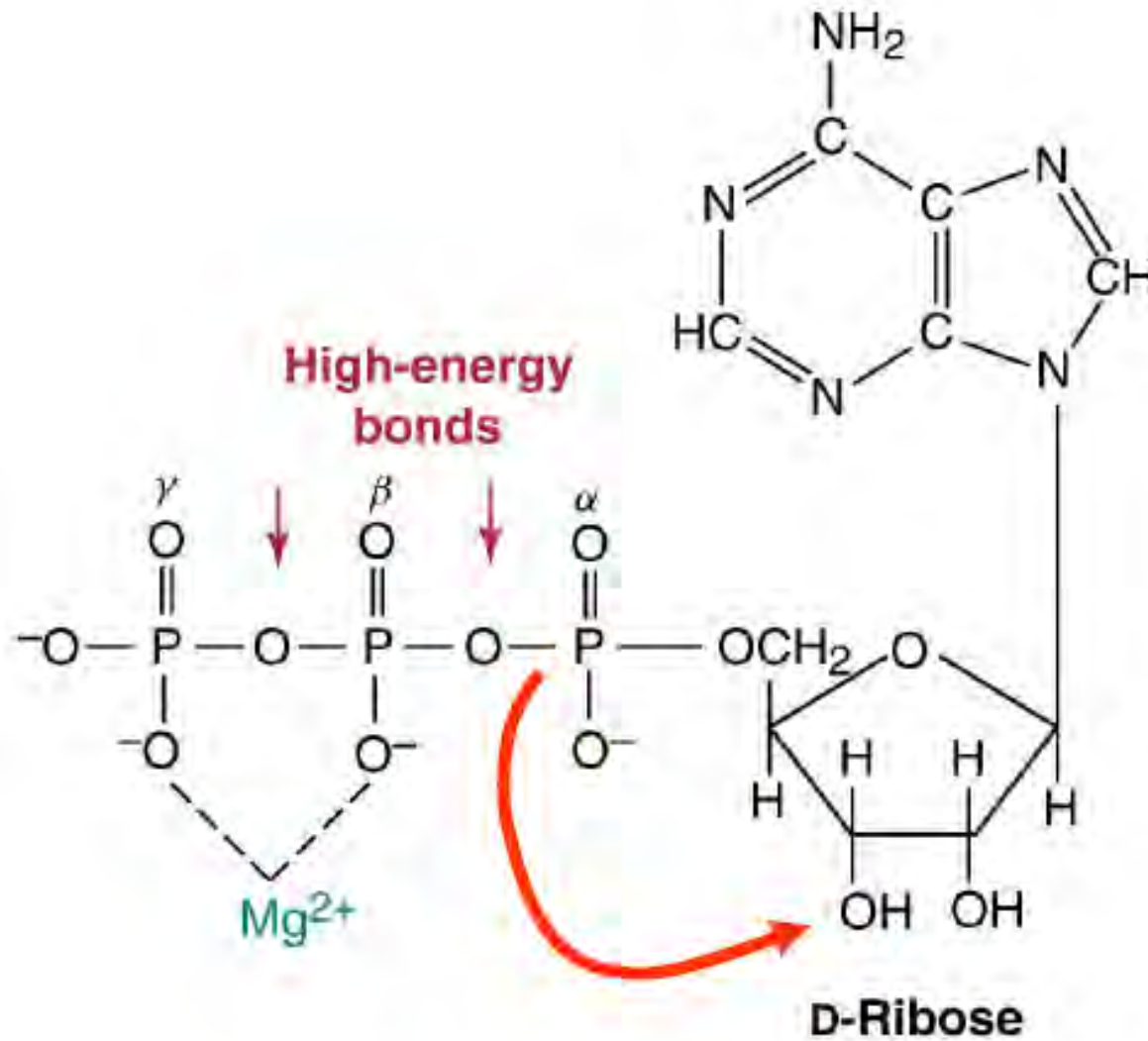
*"for their discovery of G-proteins and the role of these proteins in signal transduction in cells"*

# Adenylyl cyclase Activation



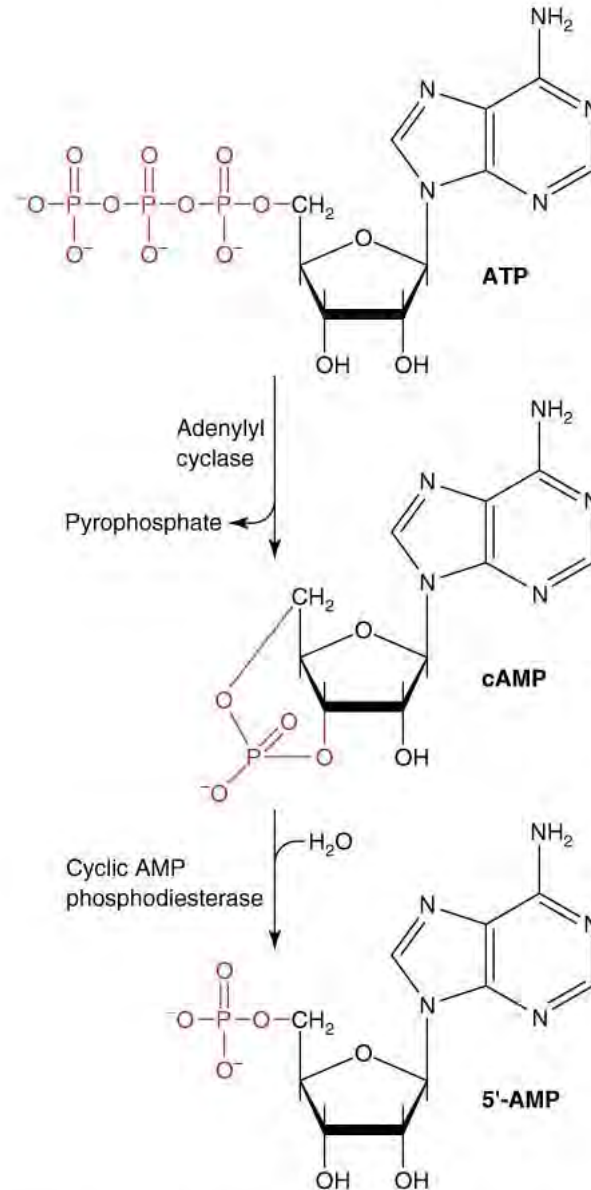


# Adenylyl cyclase activation



**Adenosine 5'-triphosphate**

# Adenylyl cyclase Activation



# cAMP – Protein kinase A – Activation

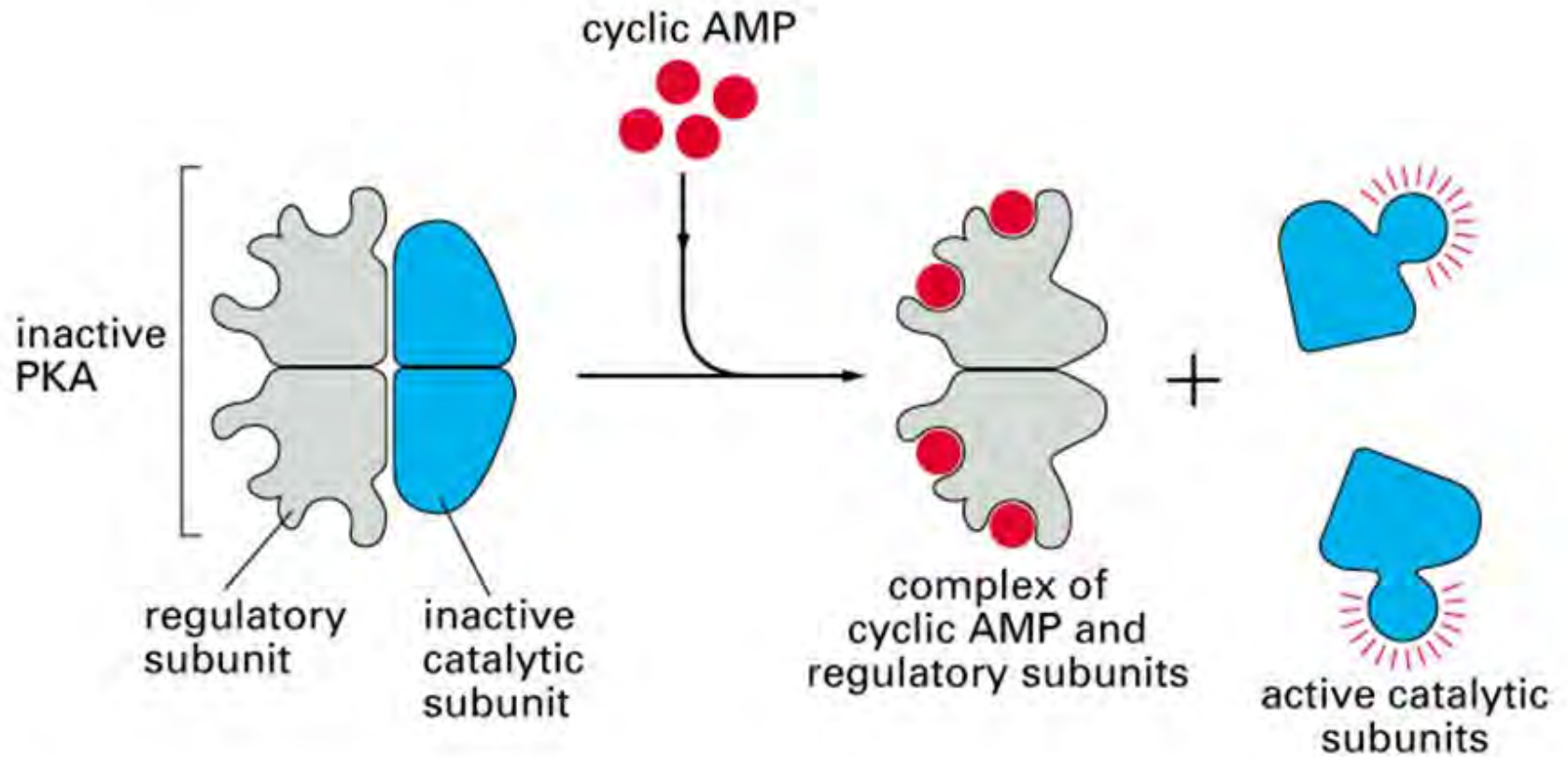
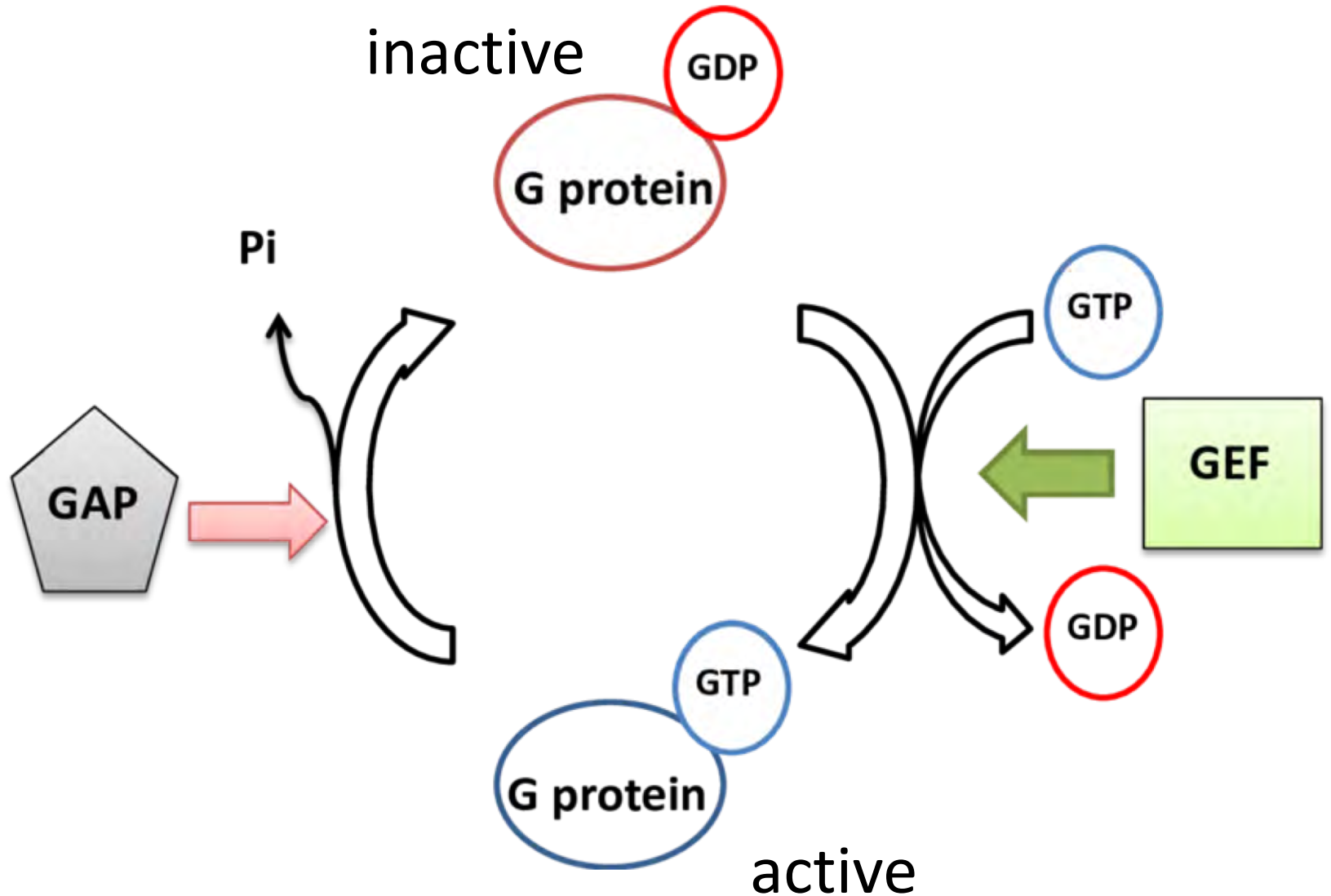


Figure 15–32. Molecular Biology of the Cell, 4th Edition.

# PKA - Function

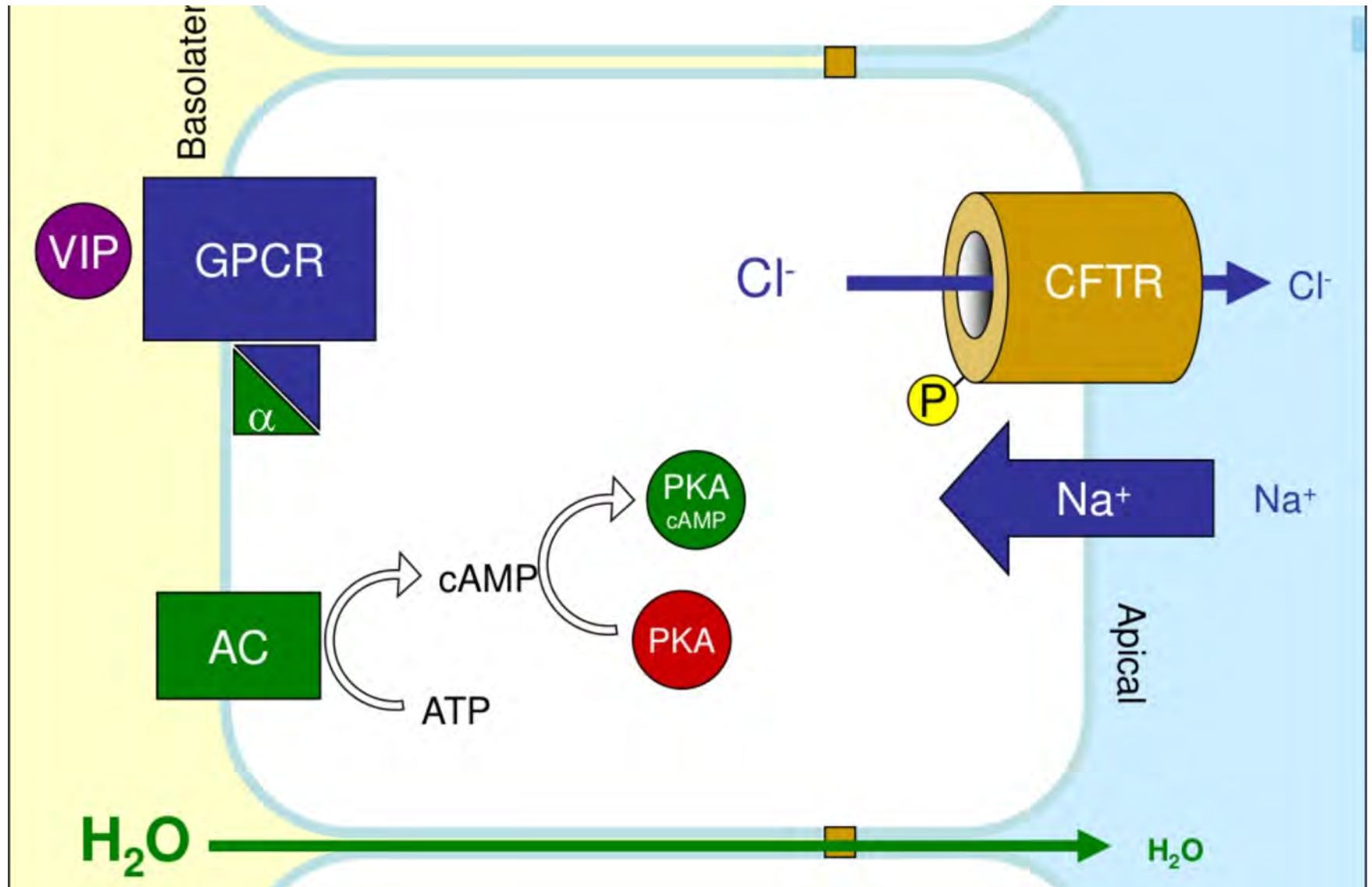
- phosphorylates serine residues
- activates glycogen degradation
  - activates phosphorylase kinase
- inhibits glycogen synthesis
  - inactivates glycogen synthase
  - inactivates phosphoprotein phosphatase 1
- increases Gluconeogenesis
  - activates protein biosynthesis
  - of G6Pase, PEPCK, Pyr-Carboxylase, etc.
- inhibits Glycolysis
  - converts Fructose-6-P-2-Kinase to Fructose-2,6-BP-Phosphatase

# G-protein cycle and Cholera toxin

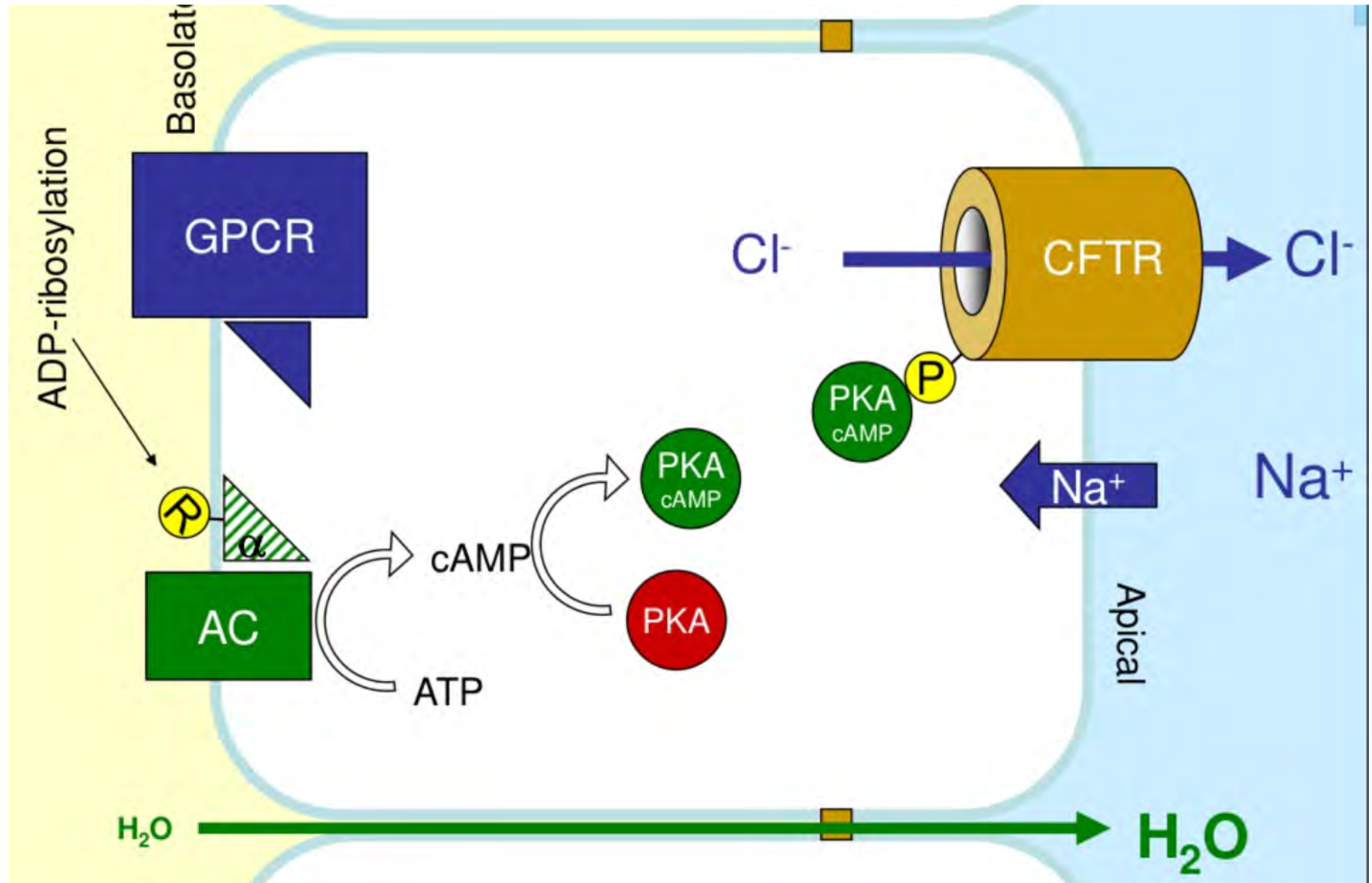




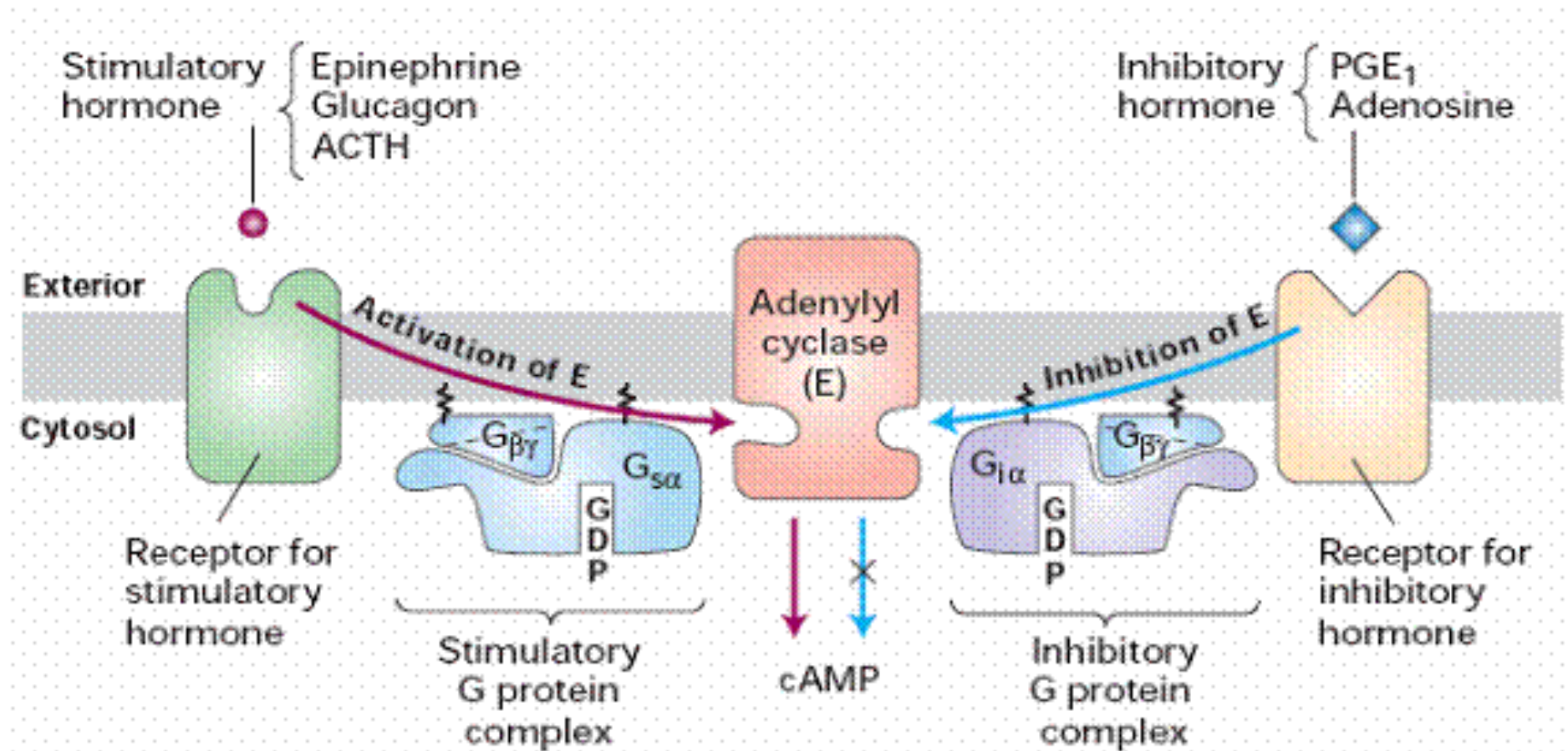
# G-protein cycle and Cholera toxin



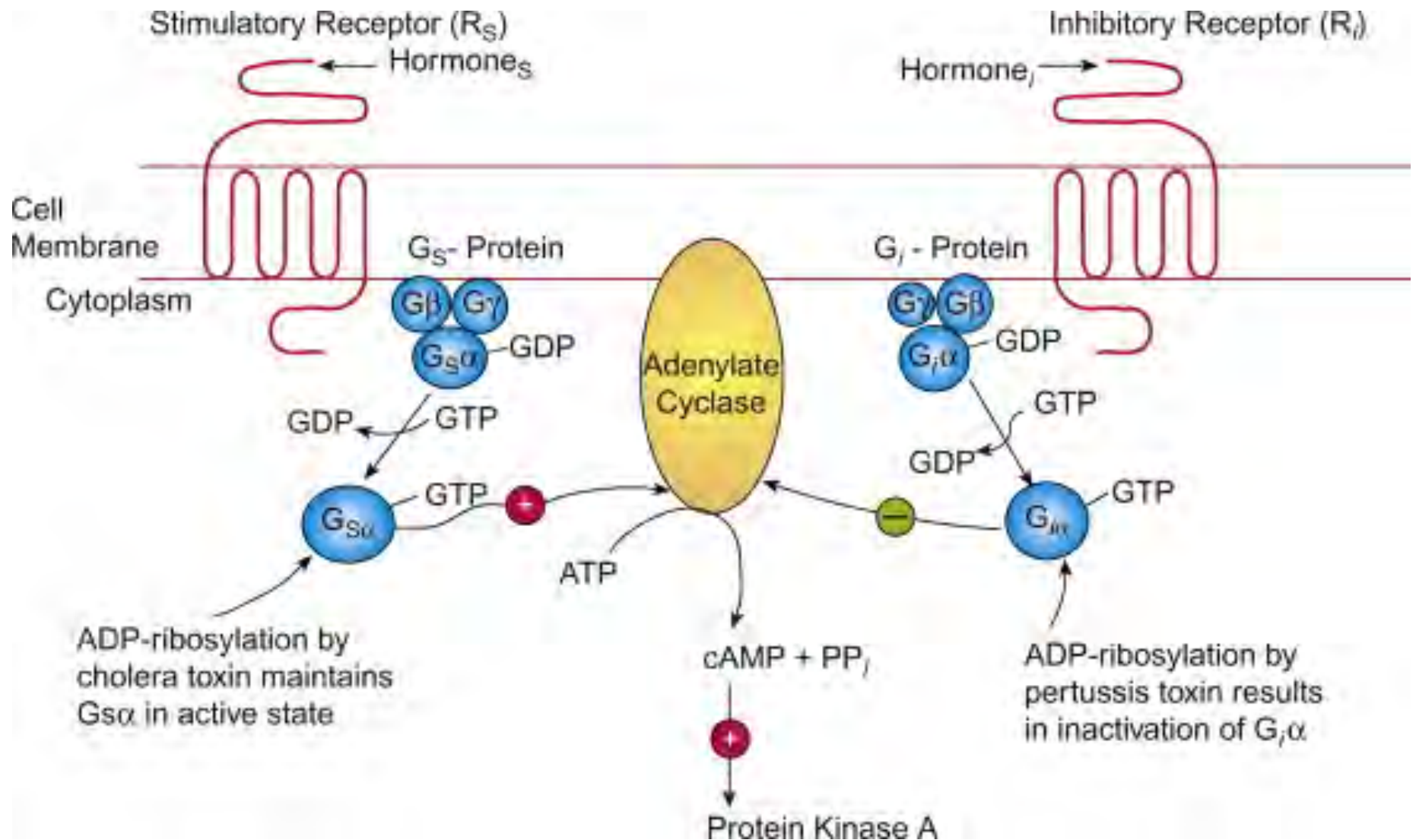
# G-protein cycle and Cholera toxin



# Interplay of Signal cascades

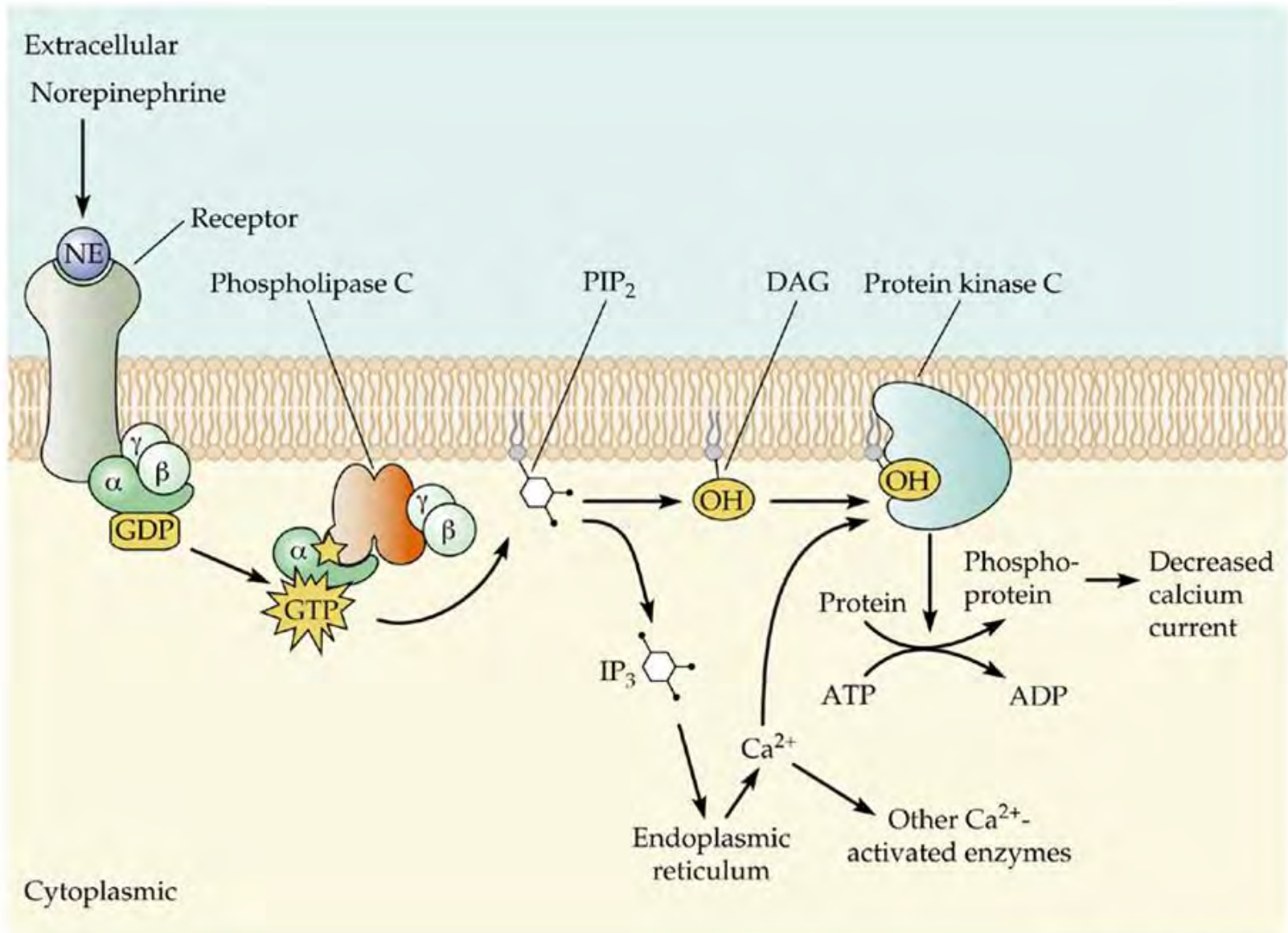


# Toxins acting on G-protein Signaling



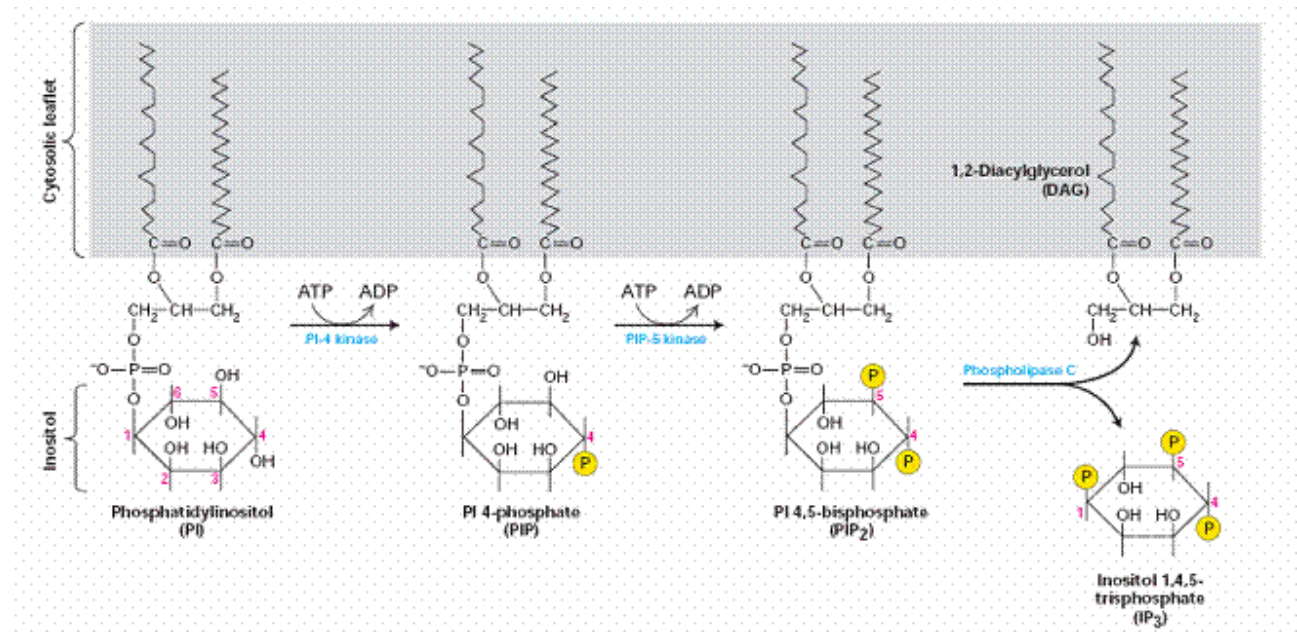
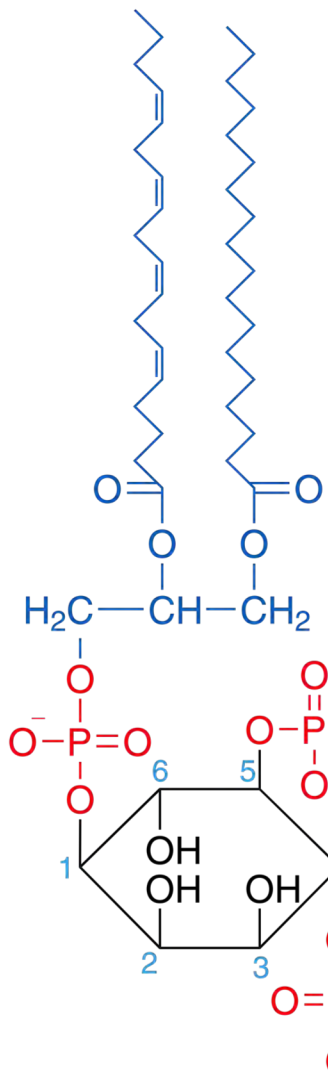


# Gq-Protein Signaling

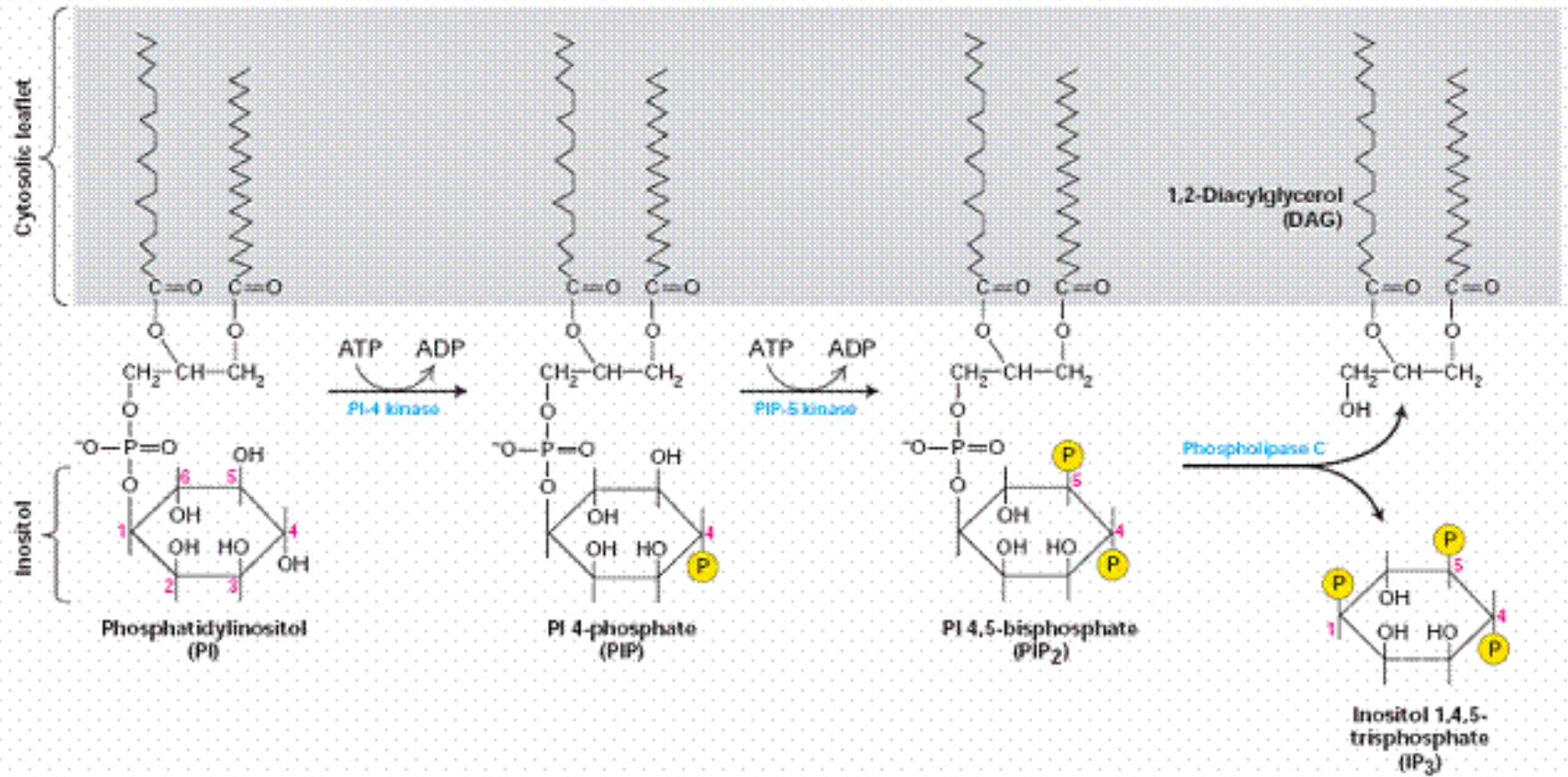




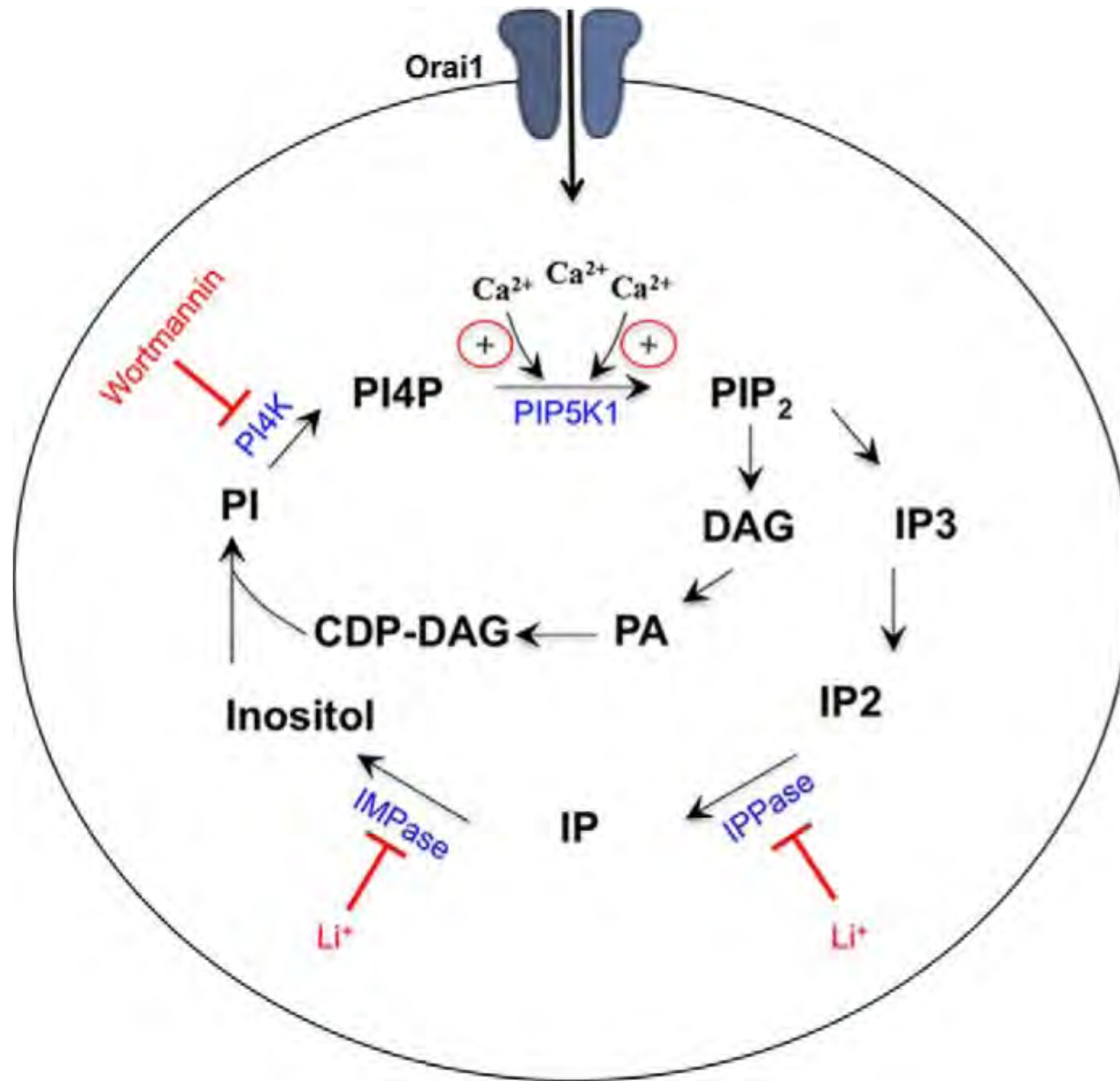
# Gq-Protein Signaling



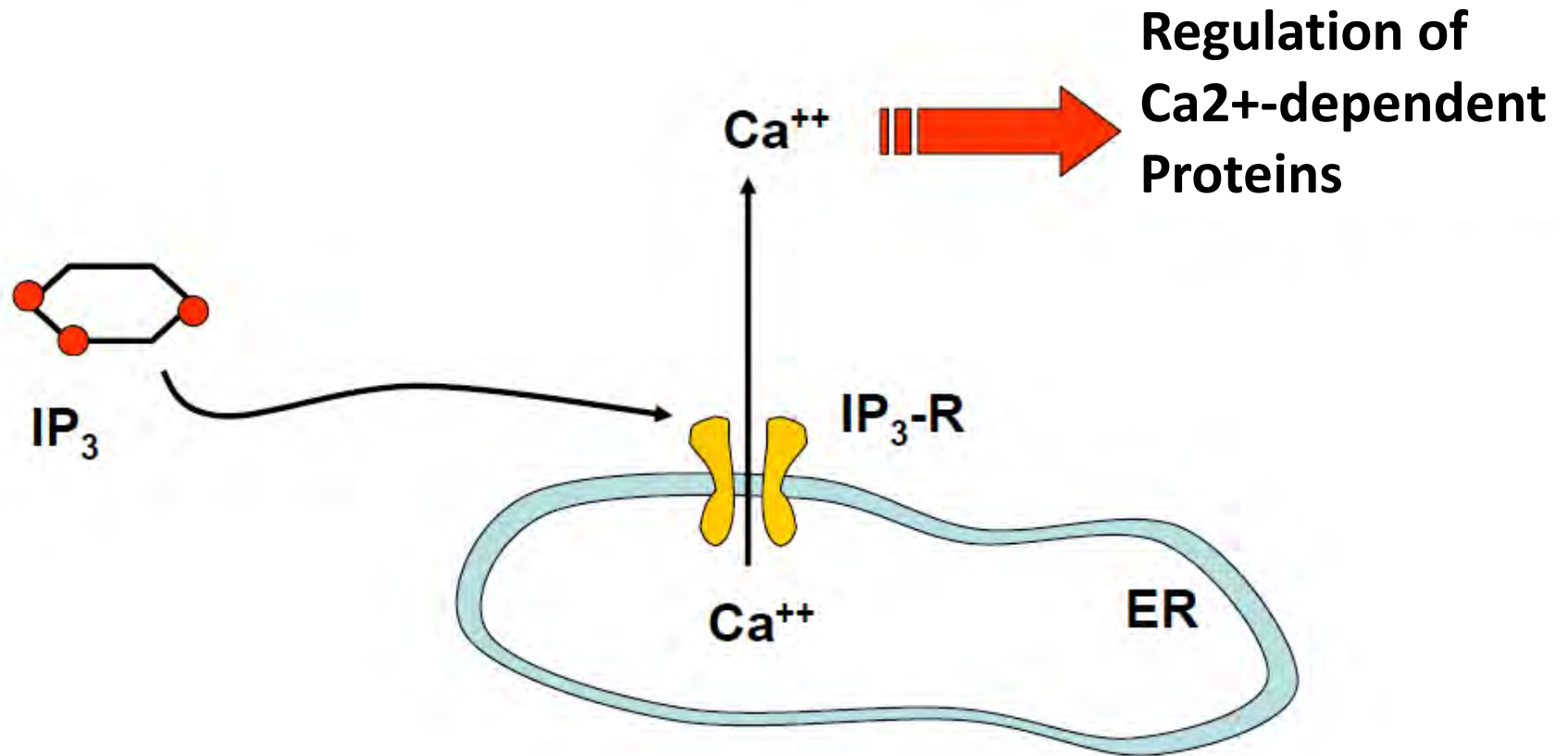
# Gq-Protein Signaling



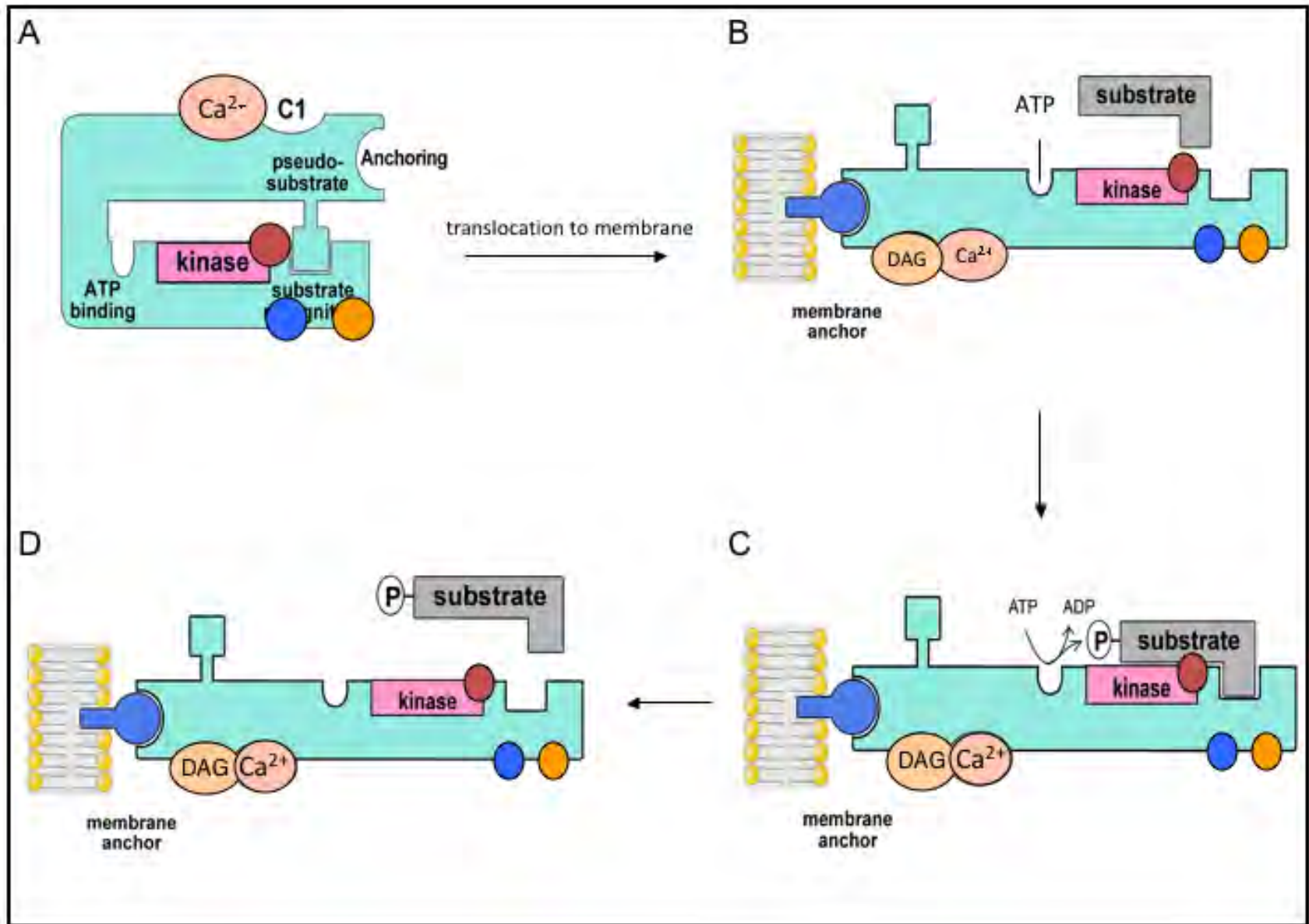
# Gq-Protein Signaling



# Gq-Protein Signaling



# Activation of PKC





# Activation of PKC

- **DAG:** Membrane binding + Activation

- **Ca<sup>++</sup>:** Activation

**(only *conventional* PKCs ( $\alpha$ ,  $\beta$ ,  $\gamma$ );**

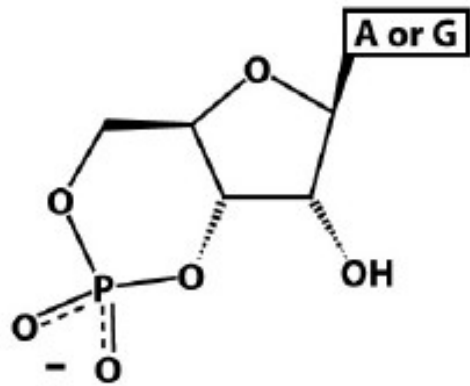
***new* PKCs (only DAG)**

***atypic* PKCs (Serine phosphorylation)**

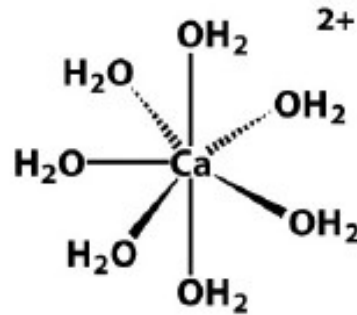
***conventional:***

- 
- **Phosphorylates Serine-/Threonine residues**
  - **Regulation of growth and differentiation**
  - **Rearrangement of the Actin cytoskeleton**
  - **cancerogenesis**

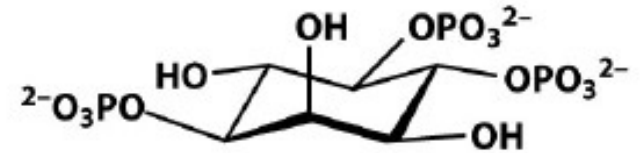
# „Second“ messenger



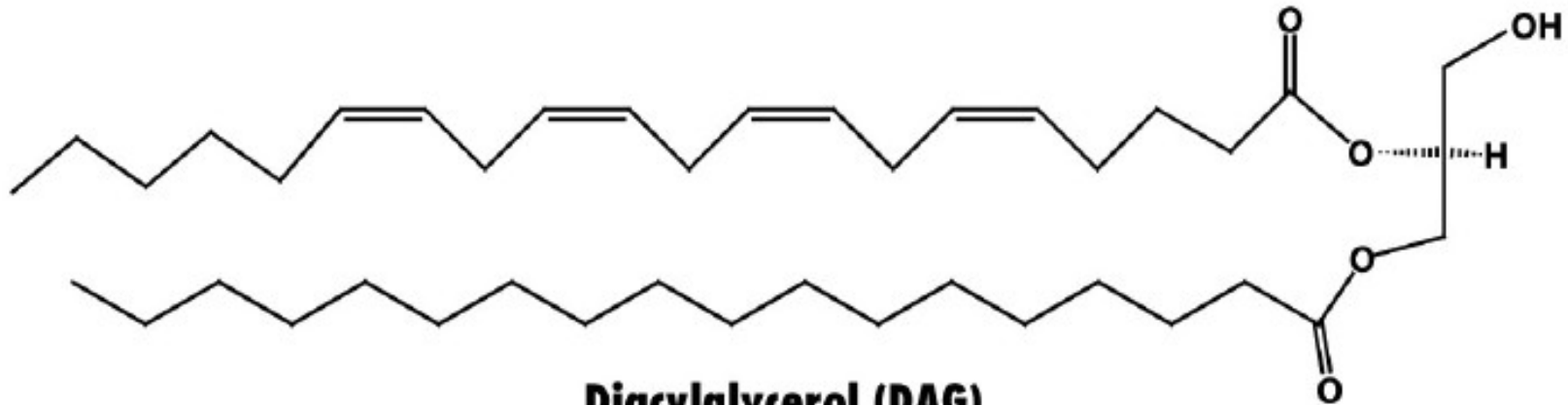
**cAMP, cGMP**



**Calcium ion**

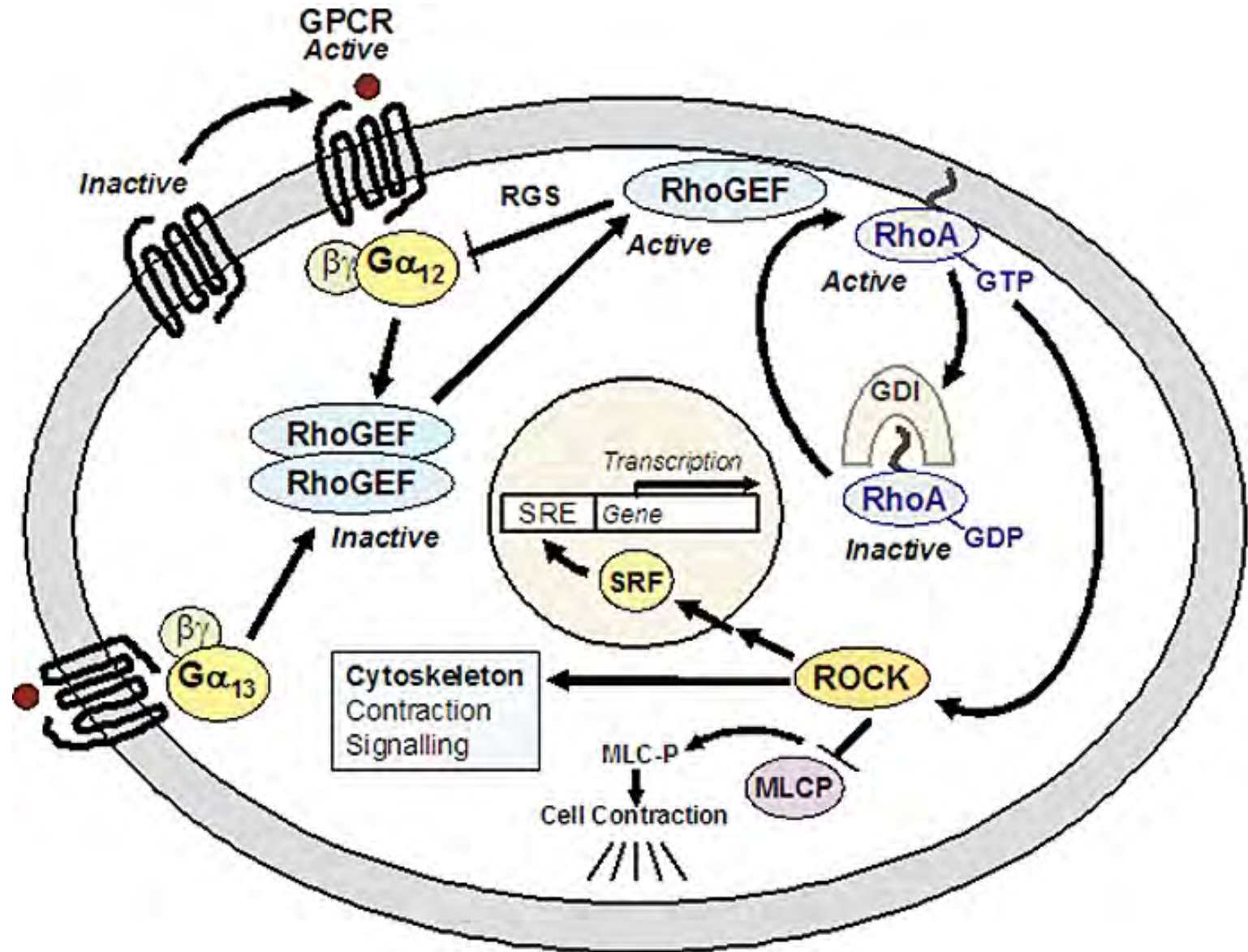


**Inositol 1,4,5-trisphosphate ( $\text{IP}_3$ )**

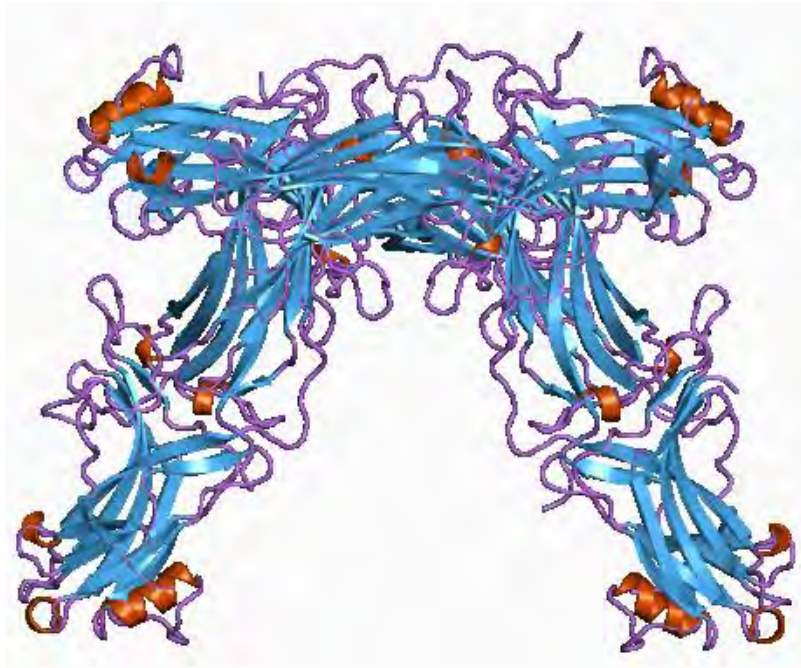


**Diacylglycerol (DAG)**

# G12/13 Protein - Rho-GEF Signaling pathway



# G Protein-independent GPCR Signal transduction

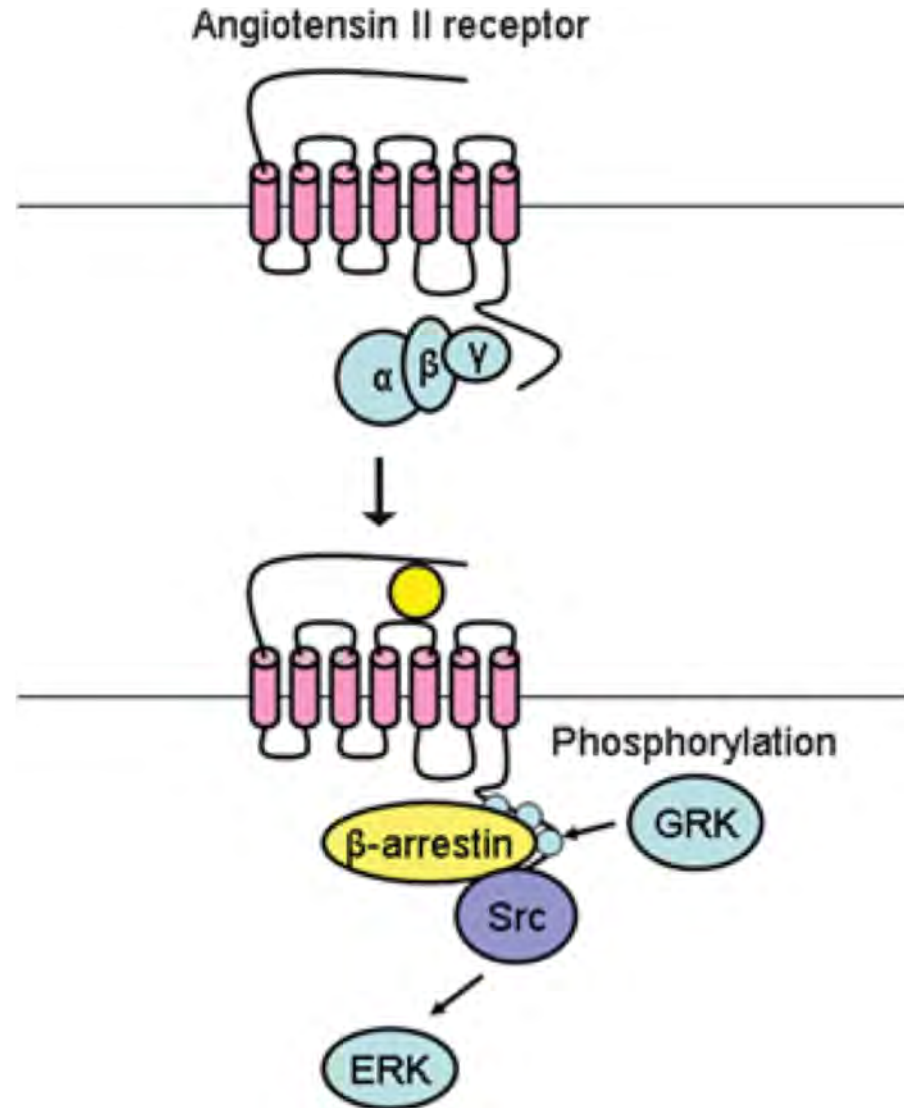


Arrestin-1 = Retina





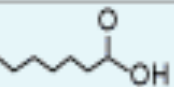






Arrestin-2 = classical GPCR

Arrestin-3 = classical GPCR

Arrestin-4 = Retina

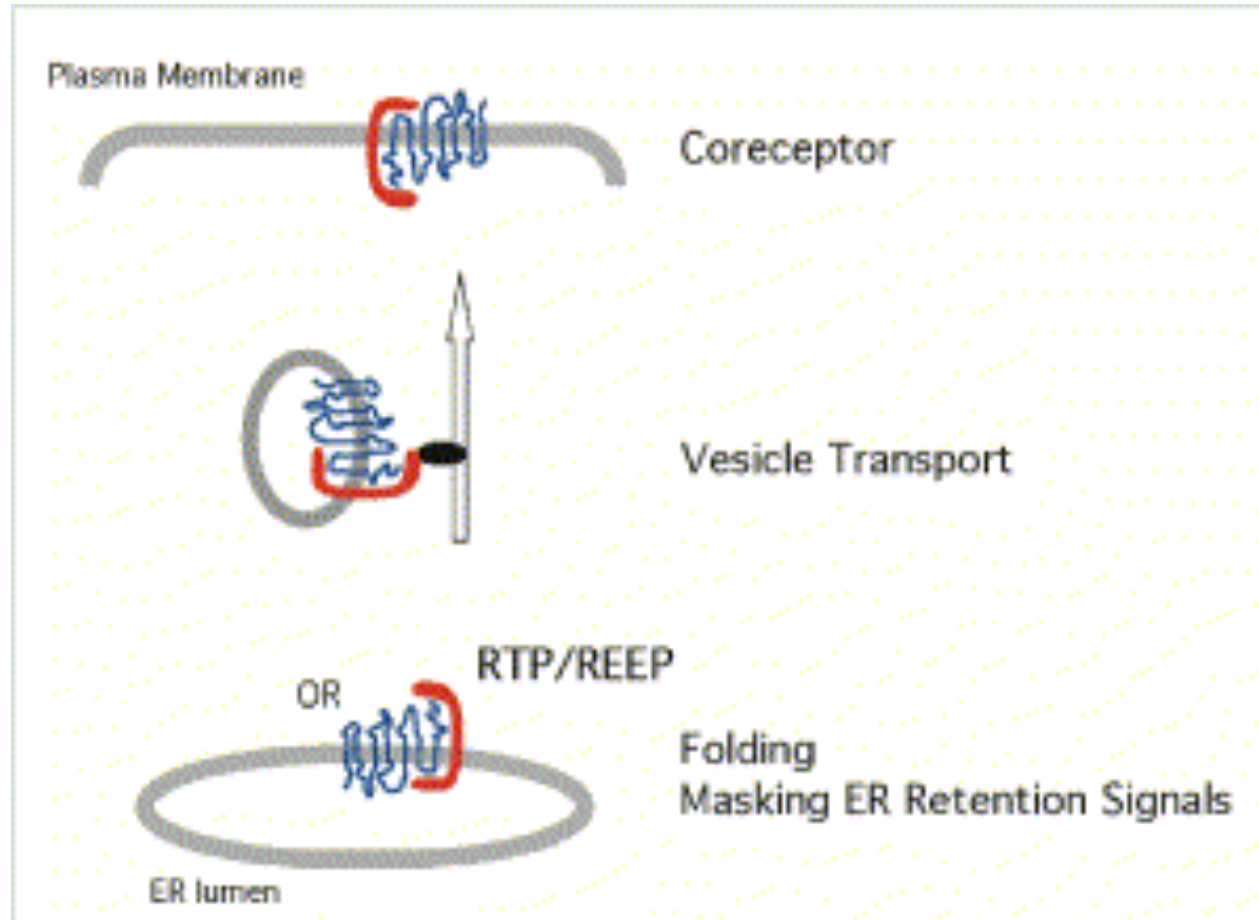


# Ligand specificity of odorant receptors

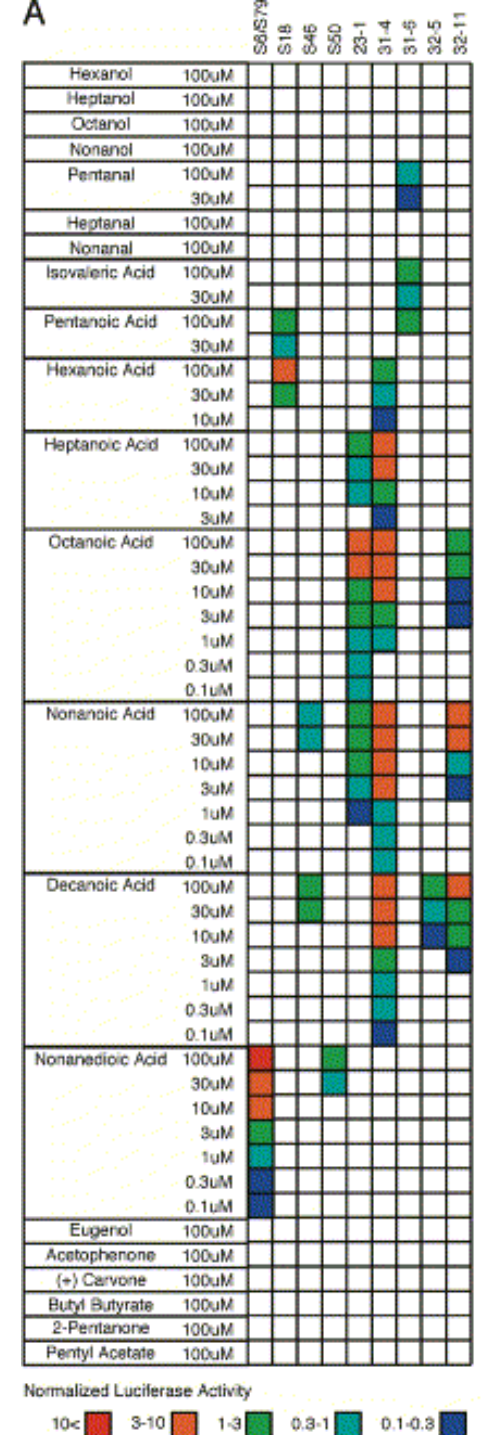
| Odorant receptors                                                                            |   |                                                                                   |   |                                                                                     |                                                                                     |                                                                                   |                                                                                     |                                                                                      |   |                                                                                       |                                                                                      |                                                                                       |    |                                                                                       | Description              |
|----------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|---|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|---|---------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|----|---------------------------------------------------------------------------------------|--------------------------|
|                                                                                              | 1                                                                                   | 2                                                                                 | 3 | 4                                                                                   | 5                                                                                   | 6                                                                                 | 7                                                                                   | 8                                                                                    | 9 | 10                                                                                    | 11                                                                                   | 12                                                                                    | 13 | 14                                                                                    |                          |
| <b>Odorants</b>                                                                              |                                                                                     |                                                                                   |   |                                                                                     |                                                                                     |                                                                                   |                                                                                     |                                                                                      |   |                                                                                       |                                                                                      |                                                                                       |    |                                                                                       |                          |
| <b>A</b>    |                                                                                     |                                                                                   |   |                                                                                     |    |                                                                                   |                                                                                     |                                                                                      |   |                                                                                       |                                                                                      |                                                                                       |    |                                                                                       | rancid, sour, goat-like  |
| <b>B</b>    |                                                                                     |  |   |                                                                                     |                                                                                     |  |                                                                                     |                                                                                      |   |                                                                                       |                                                                                      |                                                                                       |    |                                                                                       | sweet, herbal, woody     |
| <b>C</b>    |    |                                                                                   |   |    |    |                                                                                   |    |                                                                                      |   |    |   |                                                                                       |    |                                                                                       | rancid, sour, sweaty     |
| <b>D</b>    |                                                                                     |  |   |                                                                                     |    |  |                                                                                     |                                                                                      |   |                                                                                       |                                                                                      |                                                                                       |    |                                                                                       | violet, sweet, woody     |
| <b>E</b>   |   |                                                                                   |   |   |   |                                                                                   |   |   |   |   |  |   |    |                                                                                       | rancid, sour, repulsive  |
| <b>F</b>  |                                                                                     |                                                                                   |   |  |  |                                                                                   |  |                                                                                      |   |  |                                                                                      |                                                                                       |    |                                                                                       | sweet, orange, rose      |
| <b>G</b>  |  |                                                                                   |   |  |  |                                                                                   |  |  |   |  |                                                                                      |  |    |  | waxy, cheese, nut-like   |
| <b>H</b>  |                                                                                     |                                                                                   |   |  |  |                                                                                   |  |                                                                                      |   |  |                                                                                      |  |    |                                                                                       | fresh, rose, oily floral |

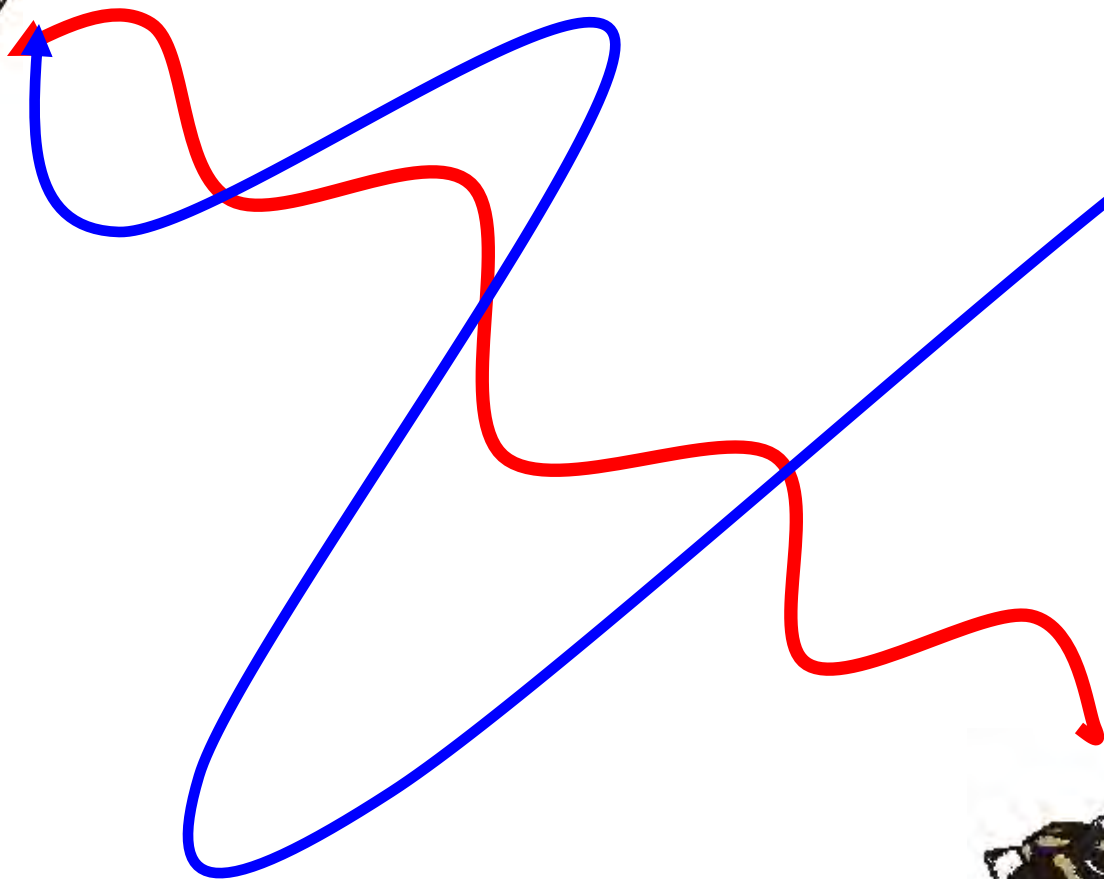


# Accessory Proteins of odorant receptors

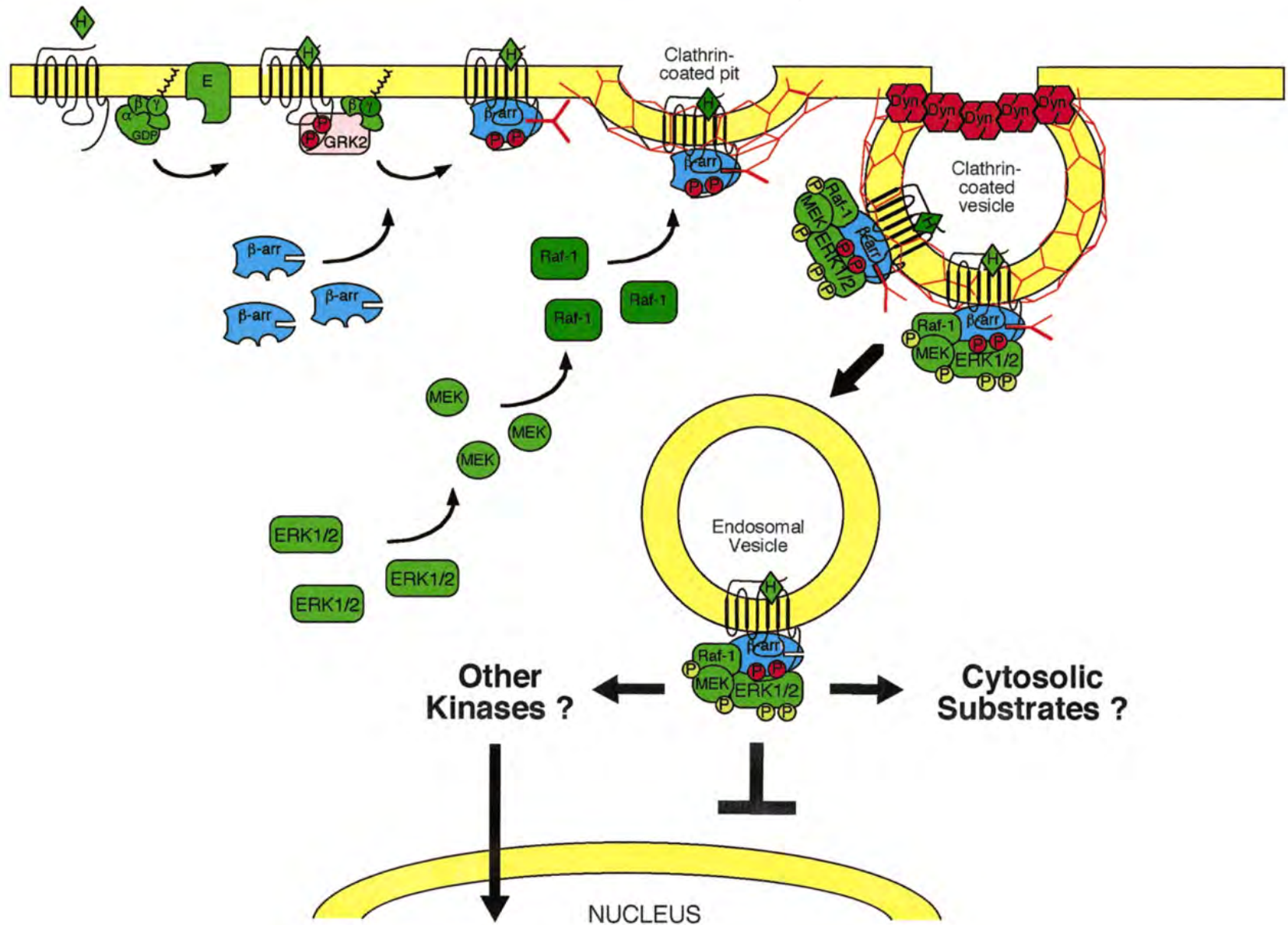


Saito et al., Cell. 2004 Nov 24;119(5):679-91.



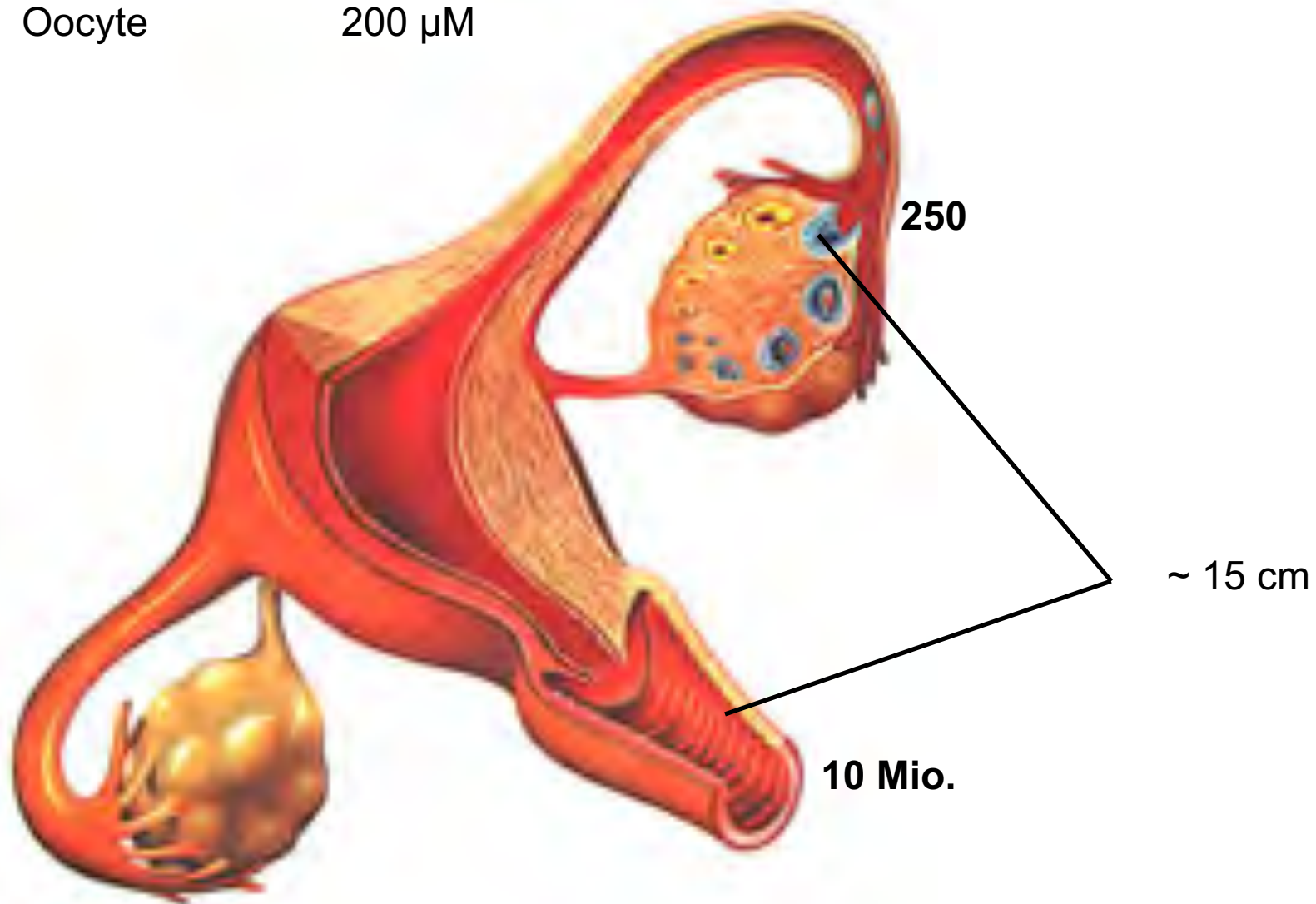


# GPCR – Signal Inactivation



Sperm 60  $\mu\text{m}$

Oocyte 200  $\mu\text{m}$

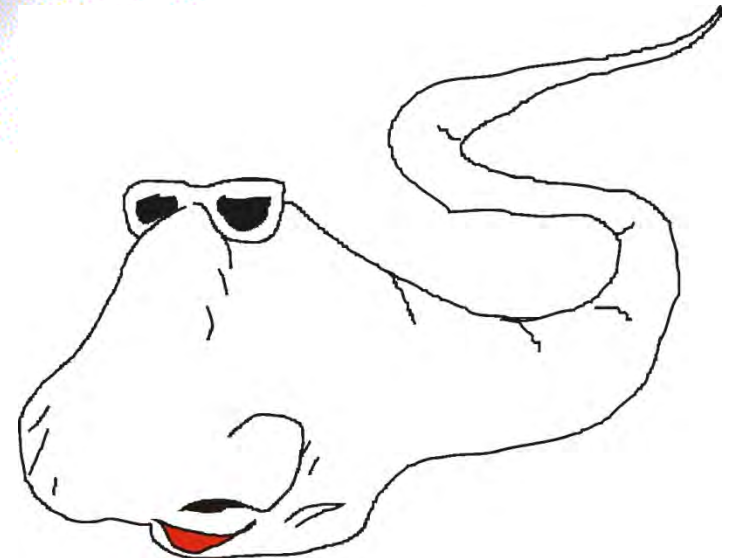
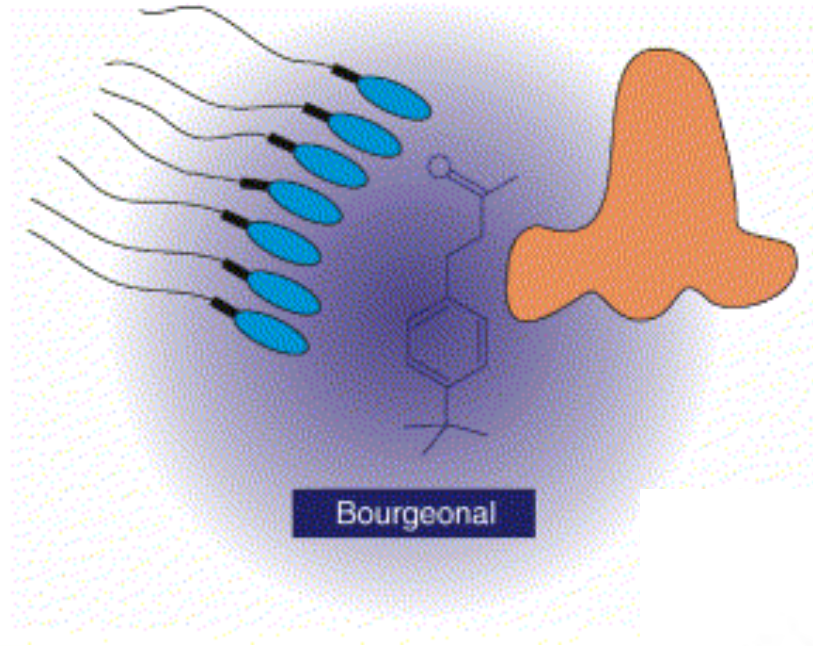






# Bourgeonal – Sperm Chemotaxis

## Odorant receptor



lily of the valley