Detection, and generation of cellular response

Transduction of hormone signal

Signal Transduction

- **Transduction: conversion of one form of a signal to another so as cells can produce many kinds of responses in different ways**

- **Amplification is a MUST**

- **Signal (polar, large) should bind receptors:**
  - **Intrinsic**
  - **Transmembrane**
  - **Intra- & extracellular domains**

- **Is that enough? The need for 2nd messenger**
  - **Few in number**
  - **Restricted movement**

Second messengers

- **Ability to diffuse to other cellular compartments**
- **Amplification of the signal**
  - **Enzyme activation**
  - **Membrane channels**
- **Some second messengers are common in multiple signaling pathways (≈ 30 hormones uses cAMP!!!)**
- **Types of 2^{nd} messengers:**
  - **Small molecules: cAMP, cGMP, Ca^{+2}**
  - **Phosphorylation through kinases**

Signal Termination

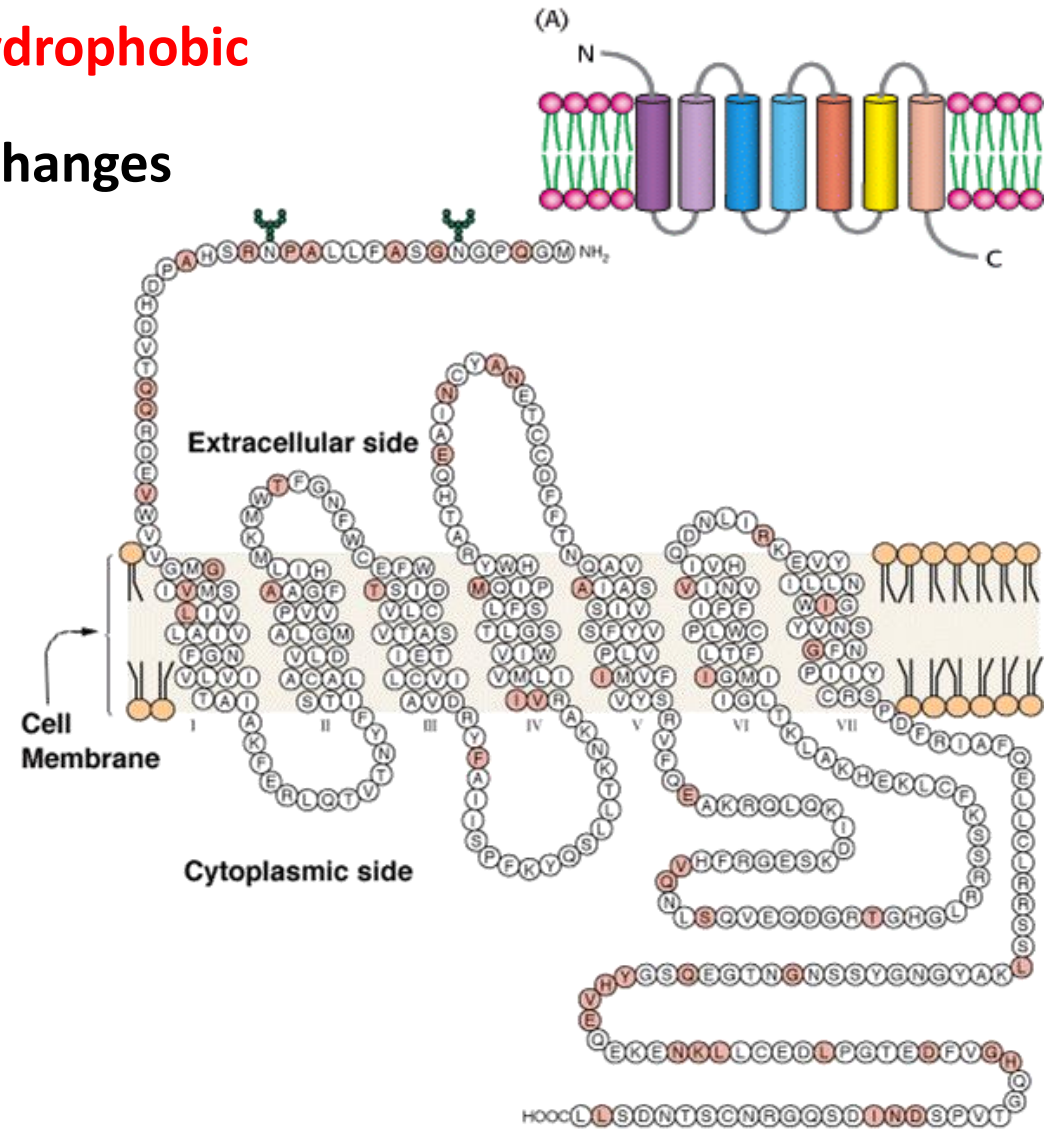
- **Is it important?**
  - **Keeps cells responsive to new signals**
  - **Failure of termination may cause problem e.g GH & cancer**

- **How it is achieved?**
  - **Reversible (non-covalent) → concentration drop**
  - **Degradation of the second messenger**
  - **Dephosphorylation by hydrolysis**

Membrane Associated Receptors
7-Transmembrane Helix Receptors (7TM)

- **7 α-helices: H-bonding, rigid, hydrophobic**
- **Signal induces conformational changes**
- **Is it enough?**

Rhodopsin receptor



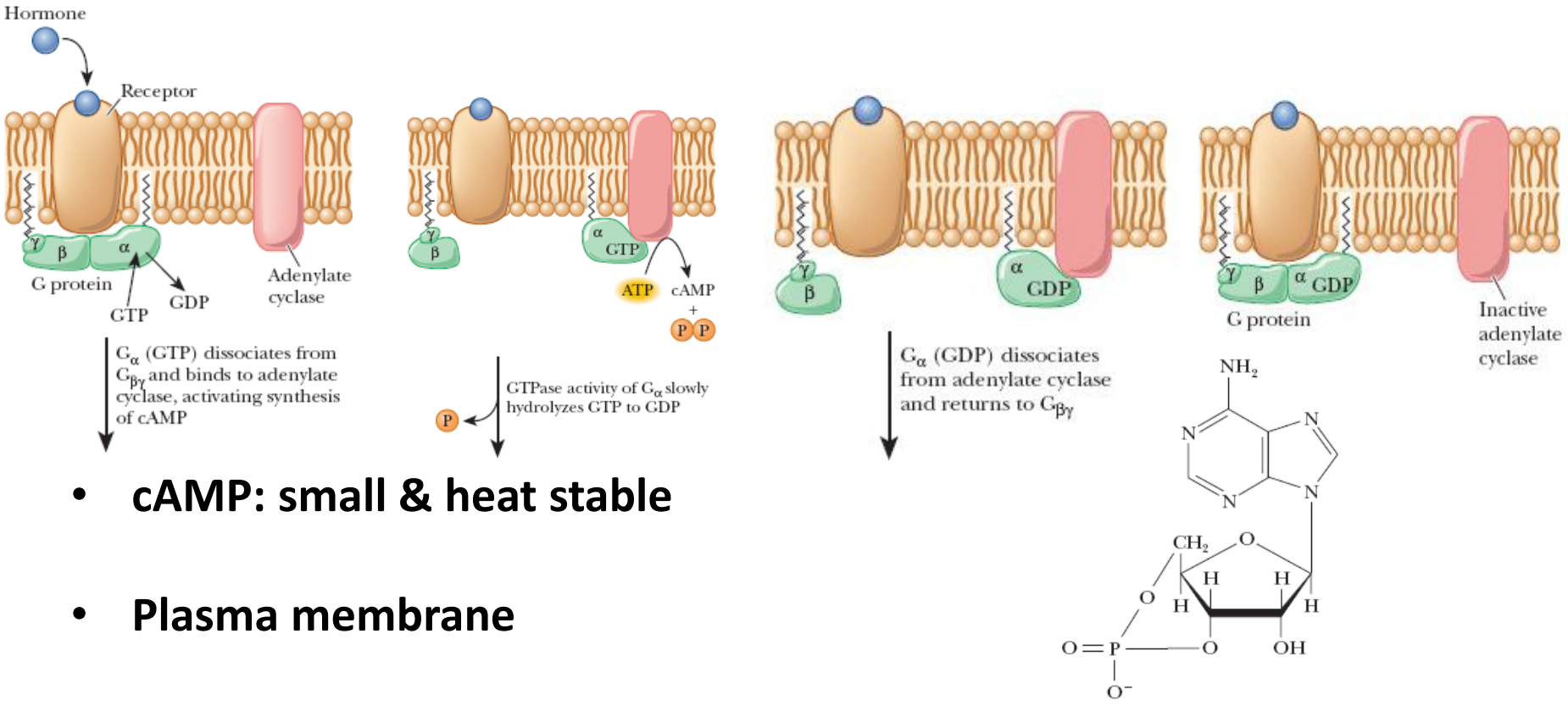
- **Many Ser & Thr residues**

Biological Functions Mediated by 7TM

- Smell, Taste, Vision
- Neurotransmission
- Hormone Secretion
- Chemotaxis
- Exocytosis
- Cell Growth, Development
- Viral Infection

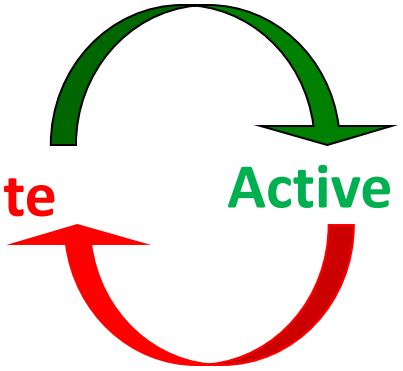
All these receptors share the same basic structure; however, they differ in their specificity and effects

G-proteins & cAMP



- **cAMP: small & heat stable**
- **Plasma membrane**
- **Hormone → Specific receptor (β1- or β2-adrenergic receptor) → G protein → Adenylate cyclase → cAMP → protein kinase A → phosphorylation**

G Protein cycles between two forms



Inactive State — **Active State**

Bound to GDP — **Bound to GTP**

Heterotrimer αβγ — **Dissociated α + βγ dimer**

α subunit has GTPase Activity

Activated Receptor

↓

↑ Adenylate Cyclase

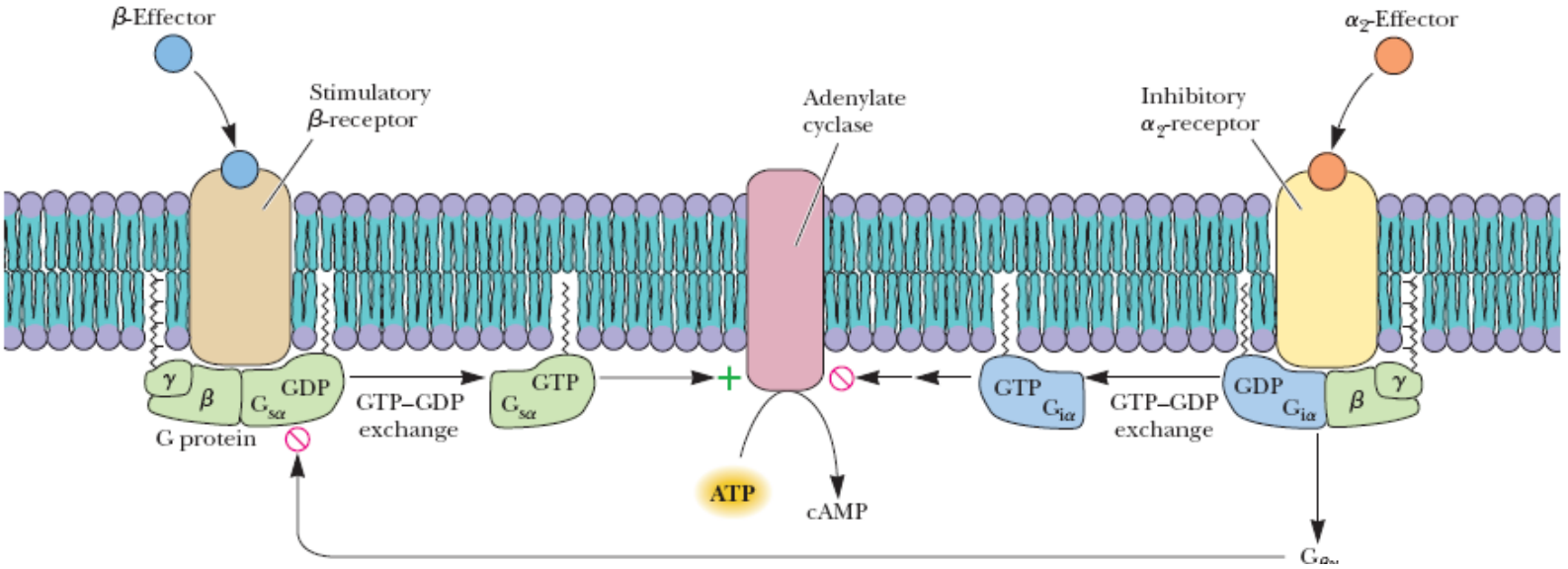
↓

↑ cAMP

↓

Biochemical Response

G protein: stimulatory or inhibitory?



- **Cyclic AMP & G Proteins:**
  - Hormone → receptor (α2-receptor) → G protein → inhibits adenylate cyclase

G Proteins

- G proteins:
  - More than 100 known G protein–coupled receptors and more than 20 known G proteins
  - Can be activated by combinations of hormones
    - Epinephrine & glucagon act via a stimulatory G protein in liver cells
  - Other than cAMP:
    - Stimulating phospholipase C
    - Opening or closing membrane ion channels

G_α subunit transduce many activities

G_s	↑ Adenylate Cyclase
G_{olf}	↑ Adenylate Cyclase
Transducin	↑ cGMP Phosphodiesterase
G_i	↓ Adenylate Cyclase
G_o	Ca^{2+} Channels
Gq	↑ Phospholipase C

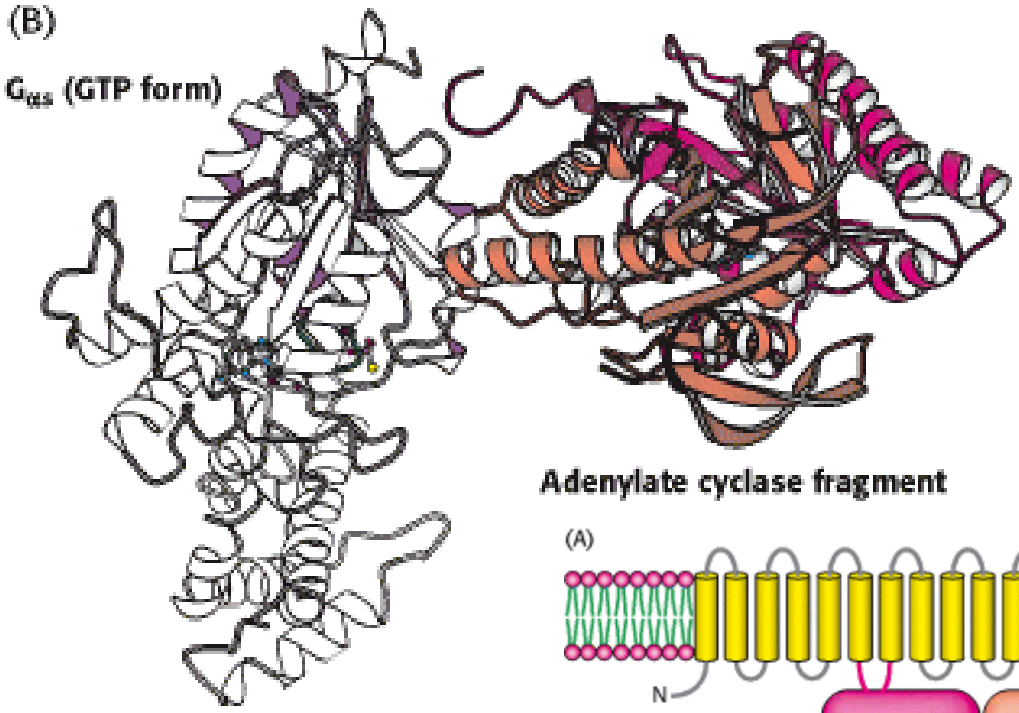
G Proteins (cont.)

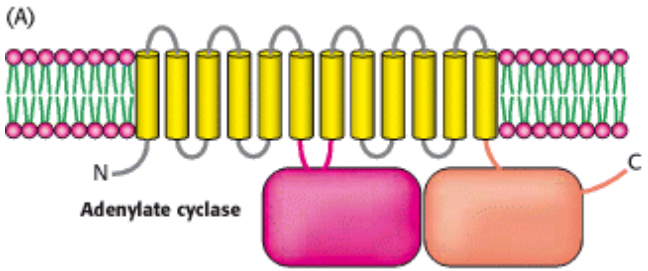
- α and γ Subunits have covalently attached fatty acid
- α and βγ can interact with other proteins
- All 7TM receptors appear to be coupled to G proteins

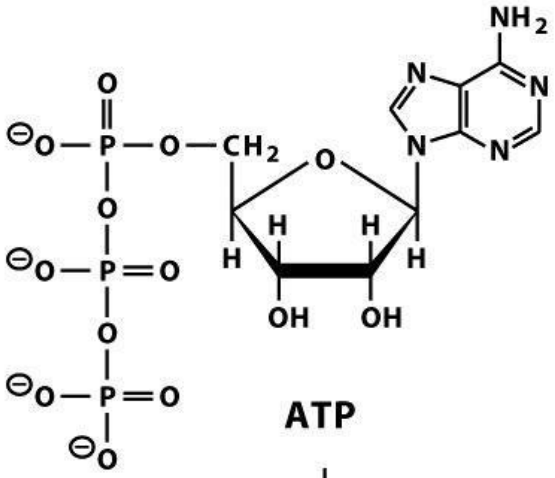
GPCRs

- Amplification: receptor → 100's of G protein → 100's of adenylate cyclase → 100's X 1000's molecules/sec of cAMP

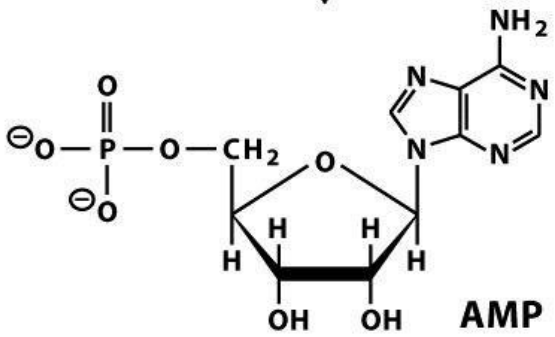
Adenylate Cyclase







3'5' CAMP

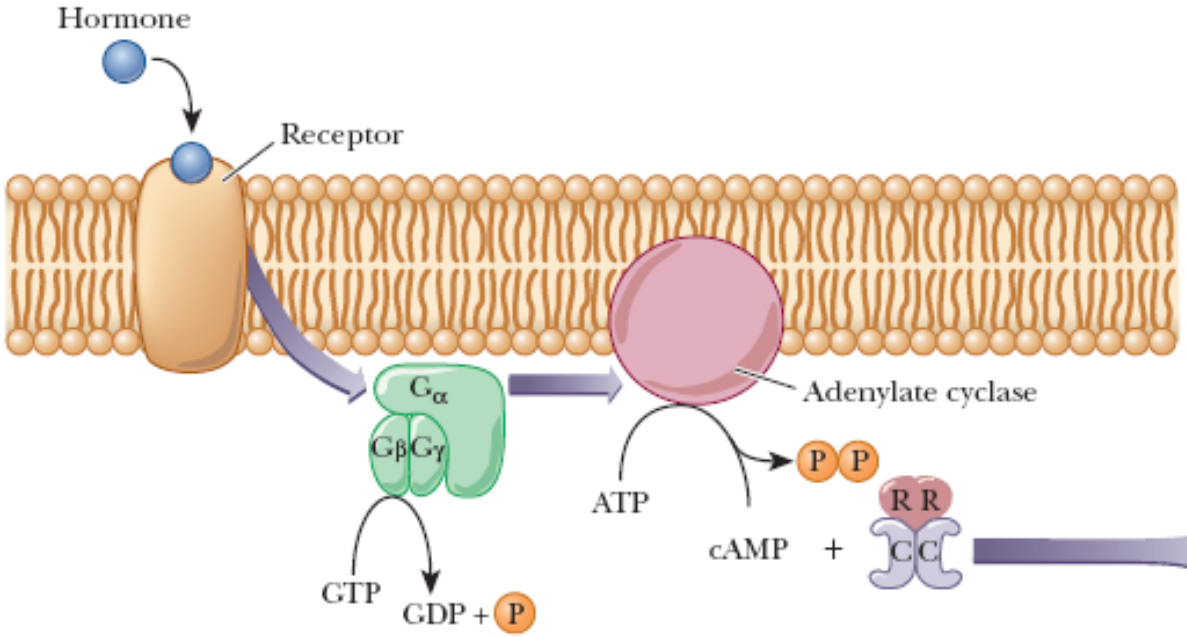


- **Membrane protein**
- **12 helices**
- **Two large intracellular domains**
- **Activated by G protein**

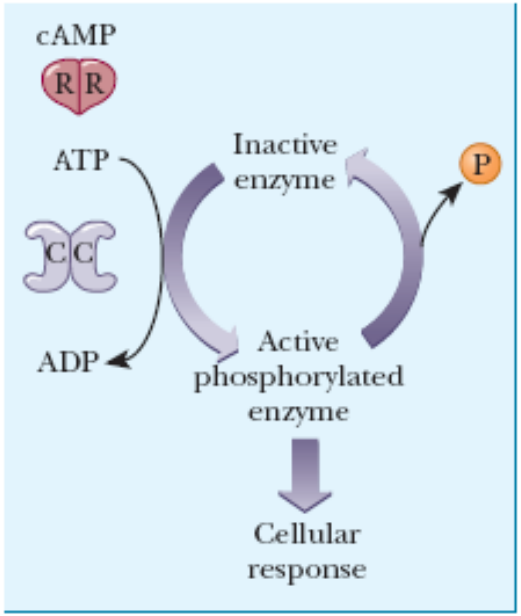
cAMP can affect a wide range of cellular processes

- ↑ degradation of storage fuels
- ↑ secretion of acid by gastric mucosa
- Dispersion of melanin pigment granules
- ↓ aggregation of blood plateletes
- Opening of chloride channels
- Gastric Ulcer: caffiene worsen their case (↑ cAMP)
  - Blocks adenosine receptors & inhibits phosphodiesterase

Then what?



Usually:
Ser or Thr



Glycogen Synthase!!

Switching off the signal

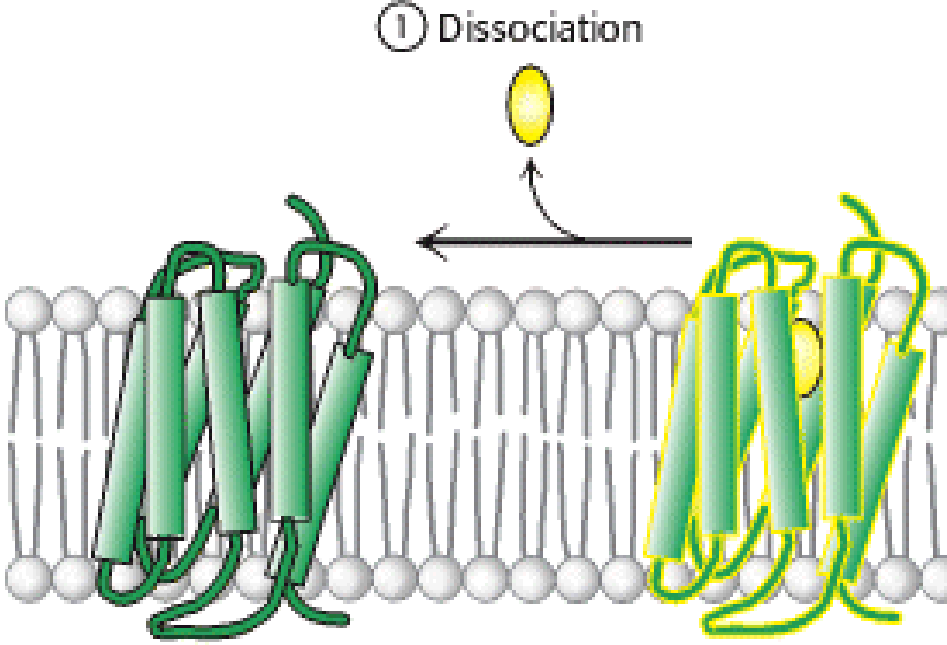
Dissociation of the hormone

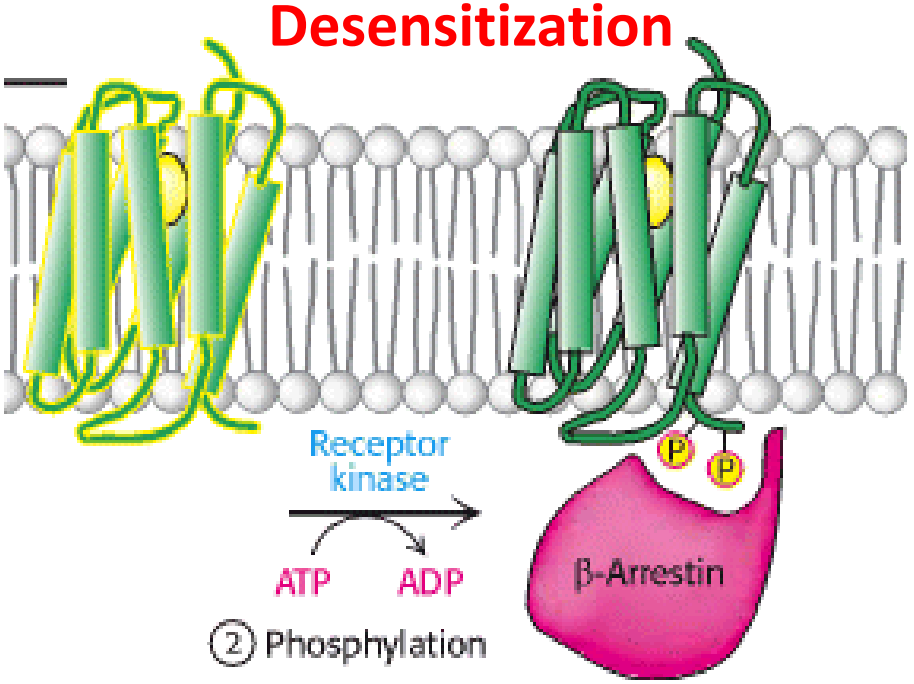
Concentration –

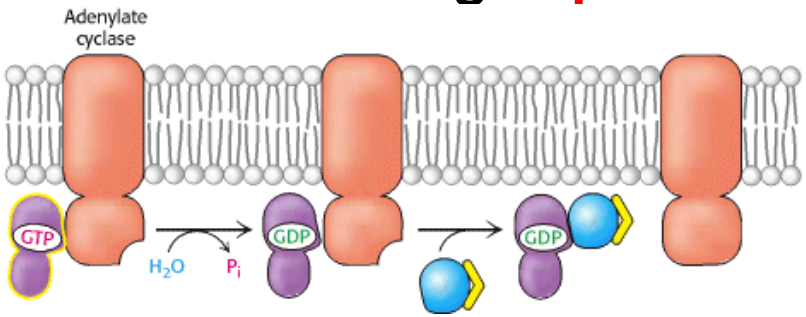
GTPase activity of Gα subunit

Hydrolysis of cAMP (phosphodiesterase)

Phosphorylation of the hormone bound-receptor followed by binding to β-Arrestin







Cholera

- **Cholera toxin → unregulated activity of adenylate cyclase in epithelial cells → Excessive cAMP in epithelial cells stimulates active transport of Na^+ → large flow of Na^+ and water from the mucosa → diarrhea**