



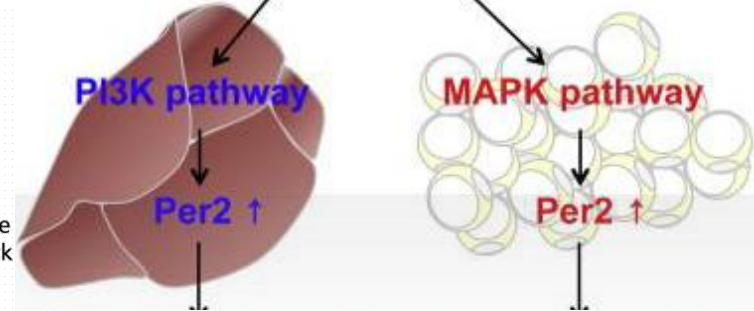
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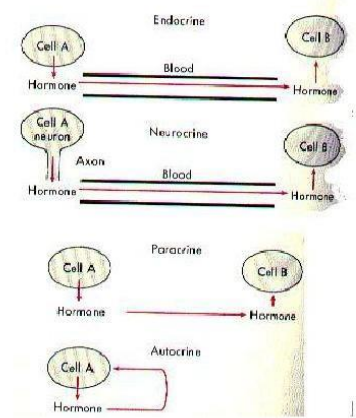
# Integration of Metabolism: hormones & Cellular Signaling

Feeding

Insulin



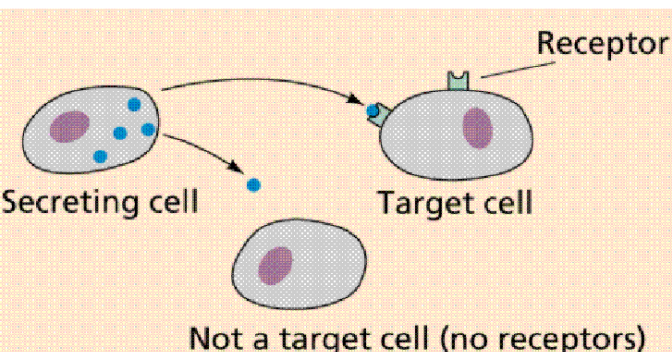
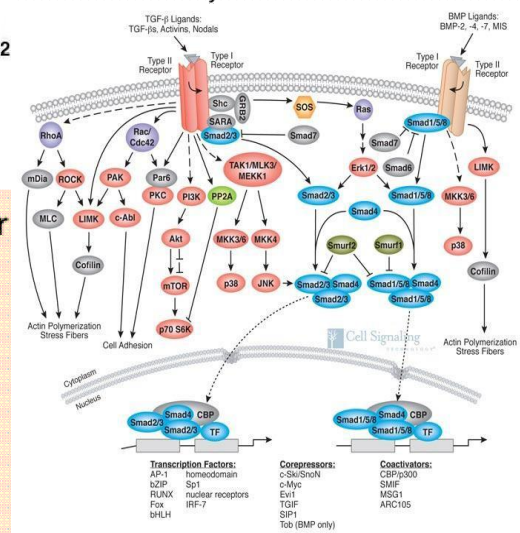
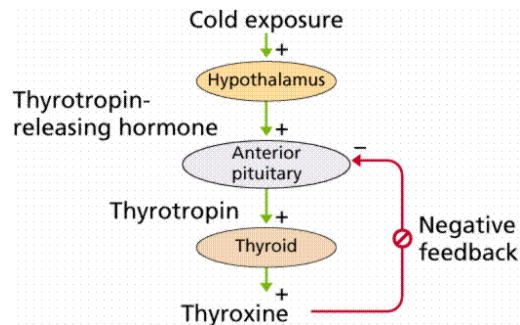
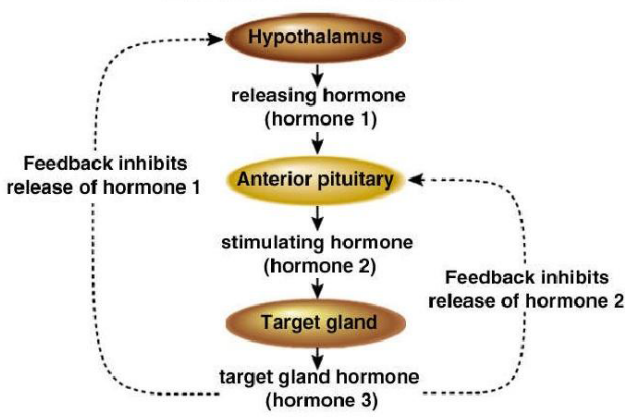
Types of cell-to-cell signaling



**Endocrine Hormones:** travel via bloodstream to target cells  
**Neurocrine hormones:** released from nerve terminals  
**Paracrine hormones:** act on adjacent cells  
**Autocrine hormones:** Released and act on the cell that secreted them.  
**Intracrine Hormones:** act within the cell that produces them.

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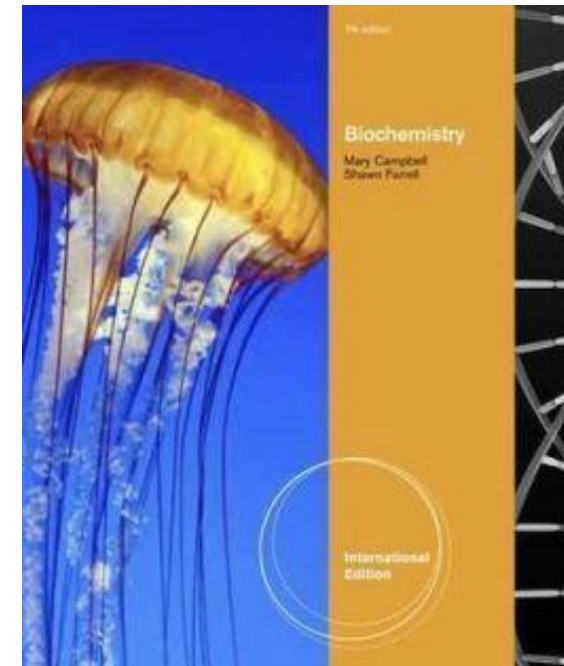
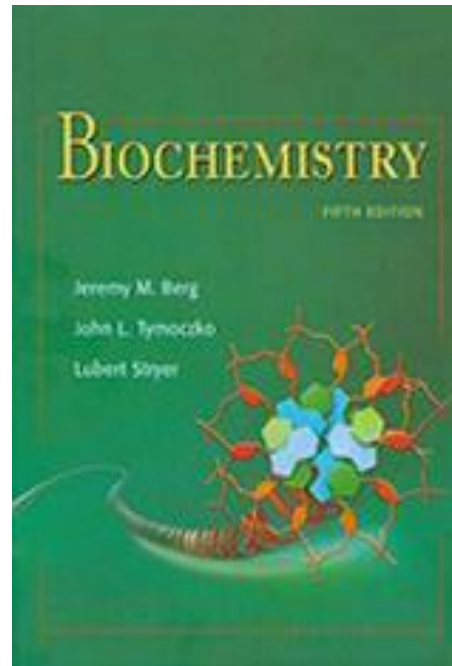
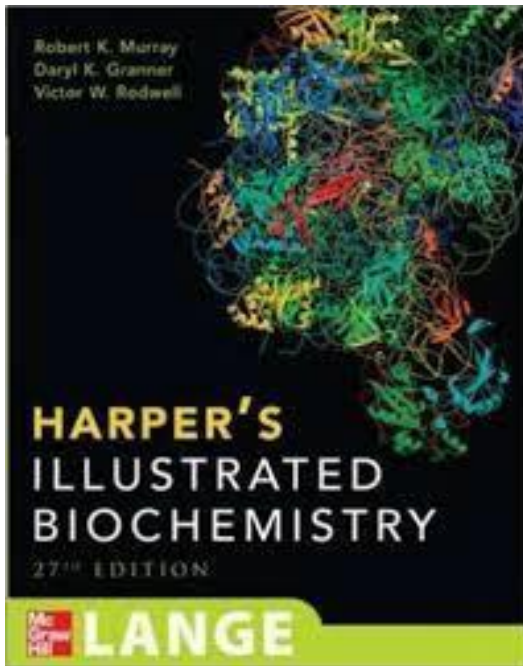
## Endocrine Glands





# Resources for the 3 lectures

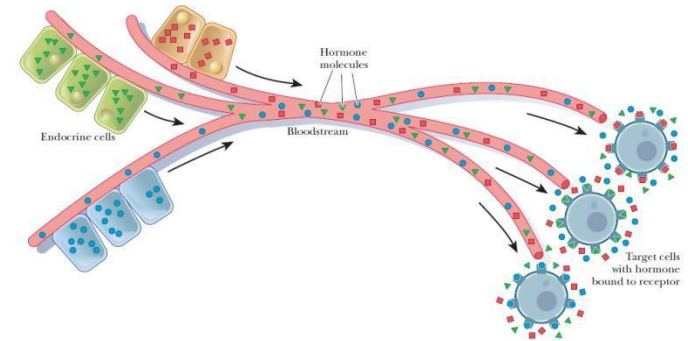
- Harper's Illustrated Biochemistry
- Stryer's Biochemistry
- Campbell's Biochemistry





# Hormones: The Remote Controllers

- **What are hormones?** Organic, blood, low amounts, source & target
- **Functions:**
  - They help maintain homeostasis
  - Mediate responses to external stimuli
  - Play roles in growth and development
- **Classes:**
  - Endocrine hormones
    - Distance; stability; & concentration
  - Paracrine hormones
  - Autocrine hormones

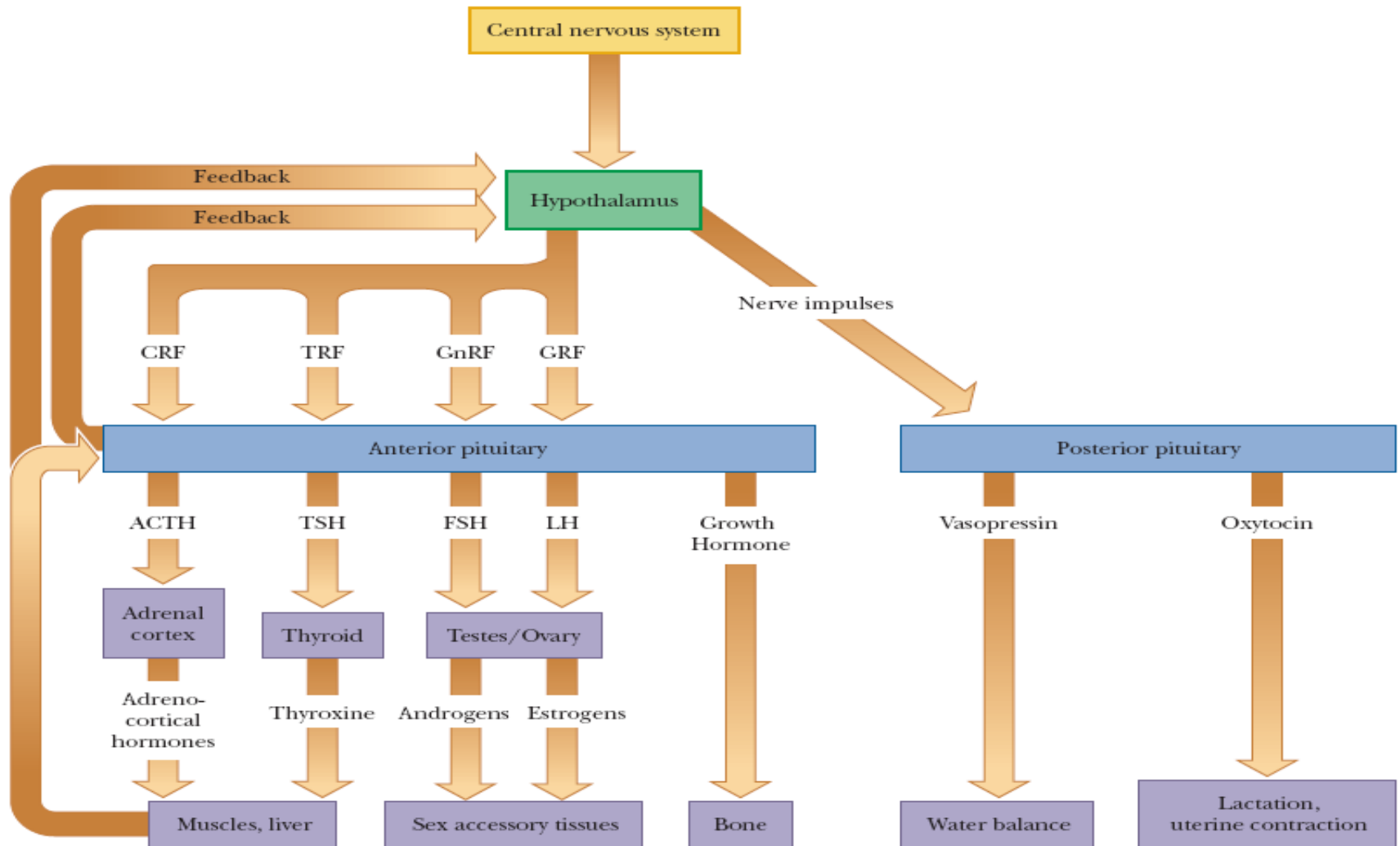


## Signaling by Secreted Molecules



# Nervous vs./& Endocrine

Two systems act individually and together in regulating the human physiology





# The Target Cell Concept

- The definition of a target has been expanded to include any cell in which the hormone (ligand) binds to its receptor, regardless of the action
- **200 types** of differentiated cells in humans
- Only a few produce hormones! (**<50 known hormones**)
- All of **75 trillion cells** in a human are targets to one or more
- One hormone → several cell types
- One cell type → several hormones
- One hormone → several effects



# The Target Cell Concept

- Several factors determine the response of a target cell to a hormone:

## Factors affect the concentration of the hormone at the target cell

- ✓ The rate of synthesis and secretion of the hormone
- ✓ The proximity of the target cell to the hormone source (dilution)
- ✓ The  $K_d$  of the hormone – receptor complex
- ✓ The rate of conversion of inactive form to the fully active form
- ✓ The rate of clearance from the plasma



# The Target Cell Concept

- Several factors determine the response of a target cell to a hormone:

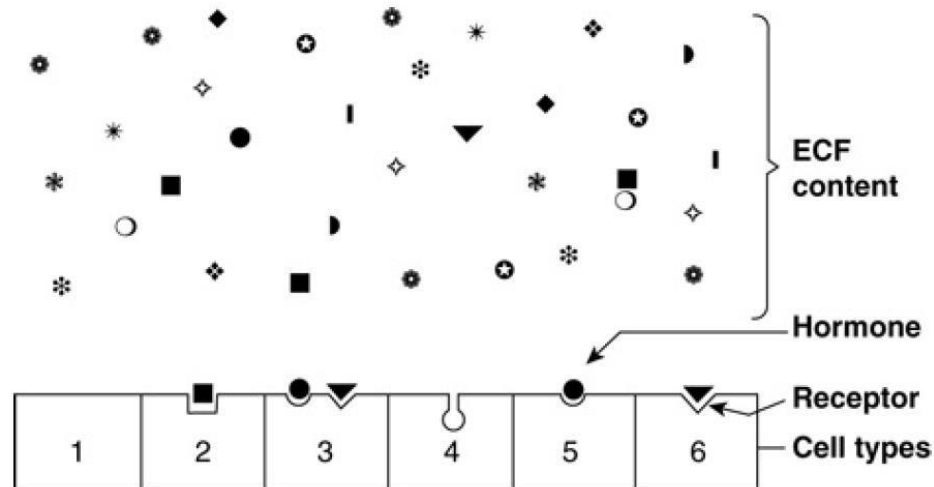
## Factors affecting the target cell response

- ✓ The number, relative activity, and state of occupancy of receptors
- ✓ The metabolism (activation / inactivation) of the hormone in the target cell
- ✓ The presence of factors within target cell necessary for the response
- ✓ Up- or down-regulation of the receptors upon interaction with ligand
  - ✓ Post-receptor desensitization of the cell



# Receptors Discriminate Precisely

- Major challenge:
  - Atto- to nano-molar range ( $10^{-15}$  to  $10^{-9}$  mol/L) vs. Structurally similar molecules (sterols, amino acids, peptides, and proteins): micro- to milli-molar ( $10^{-6}$  to  $10^{-3}$  mol/L) range

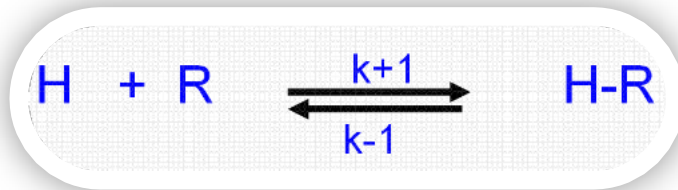




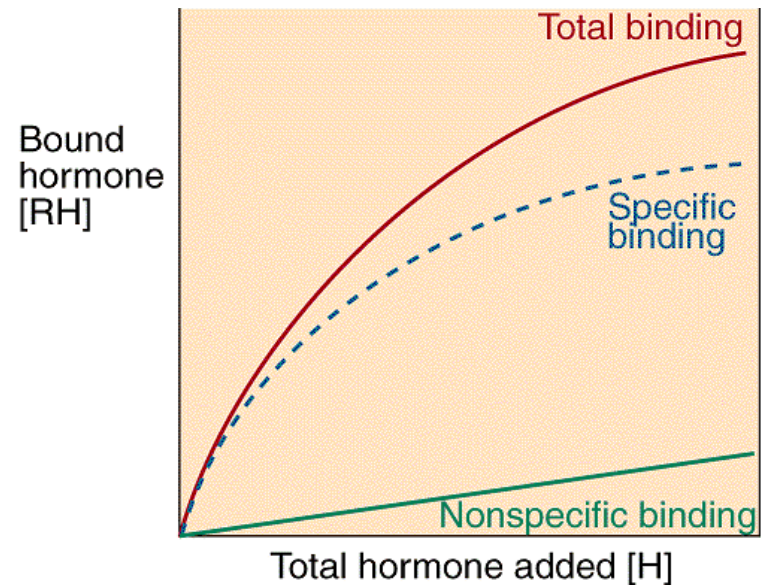


# Accordingly; Hormone-Receptor Interactions

- Should be specific: displaceable by agonist or antagonist
- Should be saturable
- Should occur within the concentration range provided



- Dissociation constant  $K_d$
- $K_d = \{[\text{H}] \times [\text{R}]\} / [\text{H-R}]$

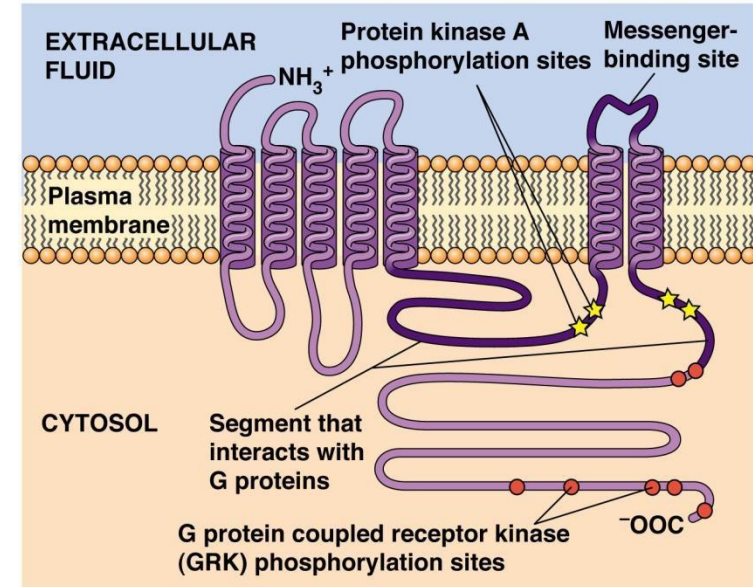


- 20 X dissociation constant is enough to saturate the receptor
- $K_d$  values for many hormone range from  $10^{-9}$  to  $10^{-11}$  M



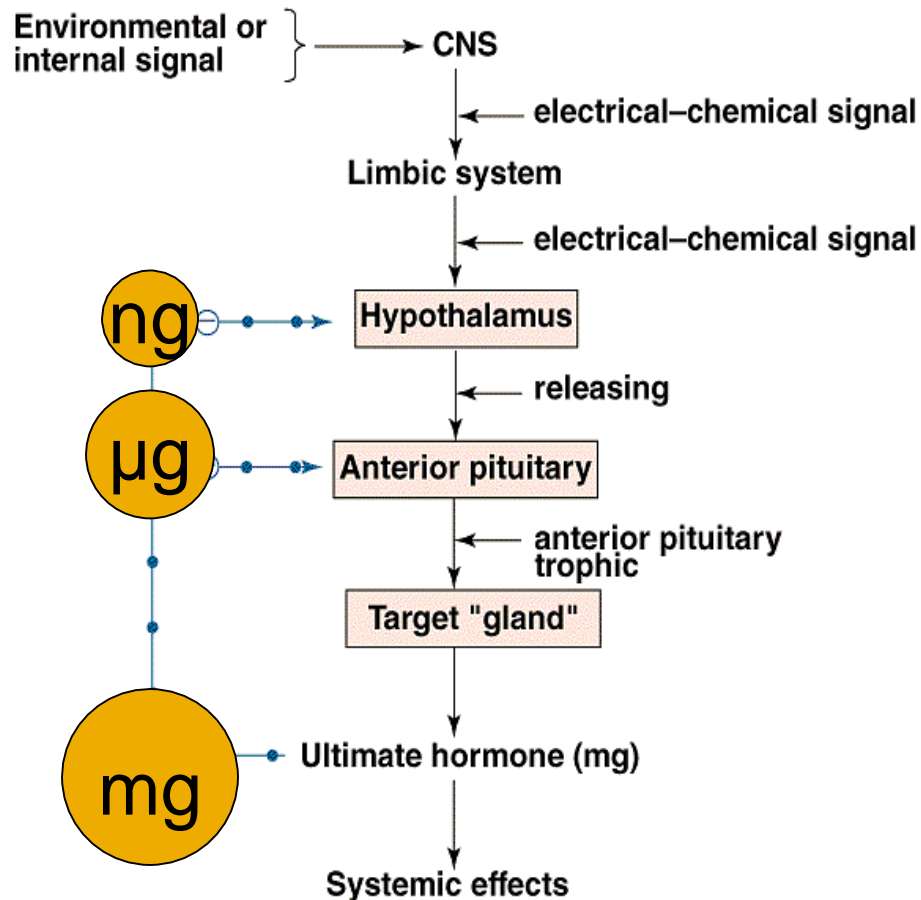
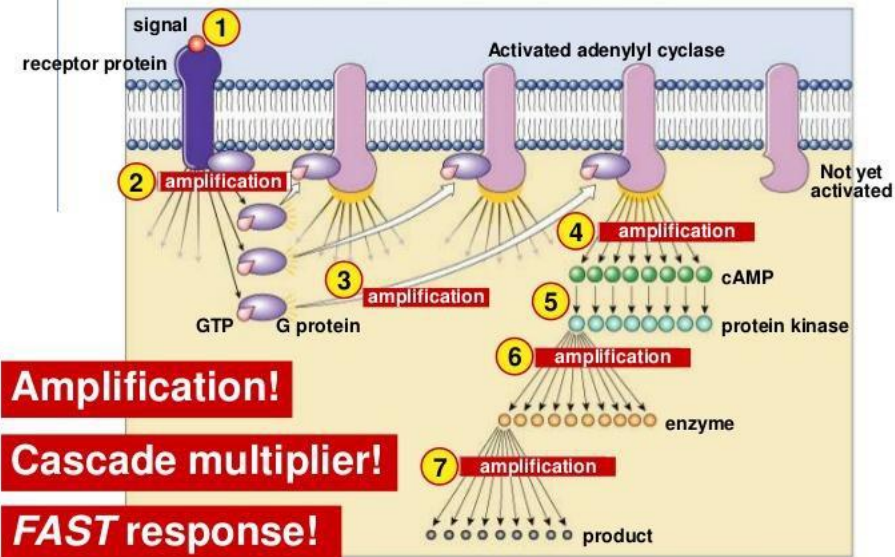
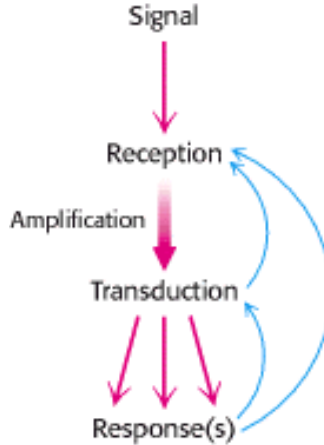
# Receptor Domains

- All receptors have at least two functional domains:
  - **Recognition domain**
  - **Coupling or signal transduction domain**
- Coupling occurs in two general ways:
  - Changing the activity of an enzyme (Polypeptide & catecholamines, plasma membrane)
  - Direct (steroids, retinoids, and thyroid hormones, intracellular)
- Steroid, thyroid, and retinoid hormone receptors:
  - Hormone binding site ; DNA binding site; co-regulator proteins binding site, cellular trafficking proteins binding site
- Receptor–effector coupling provides the first step in amplification





# Signal Amplification

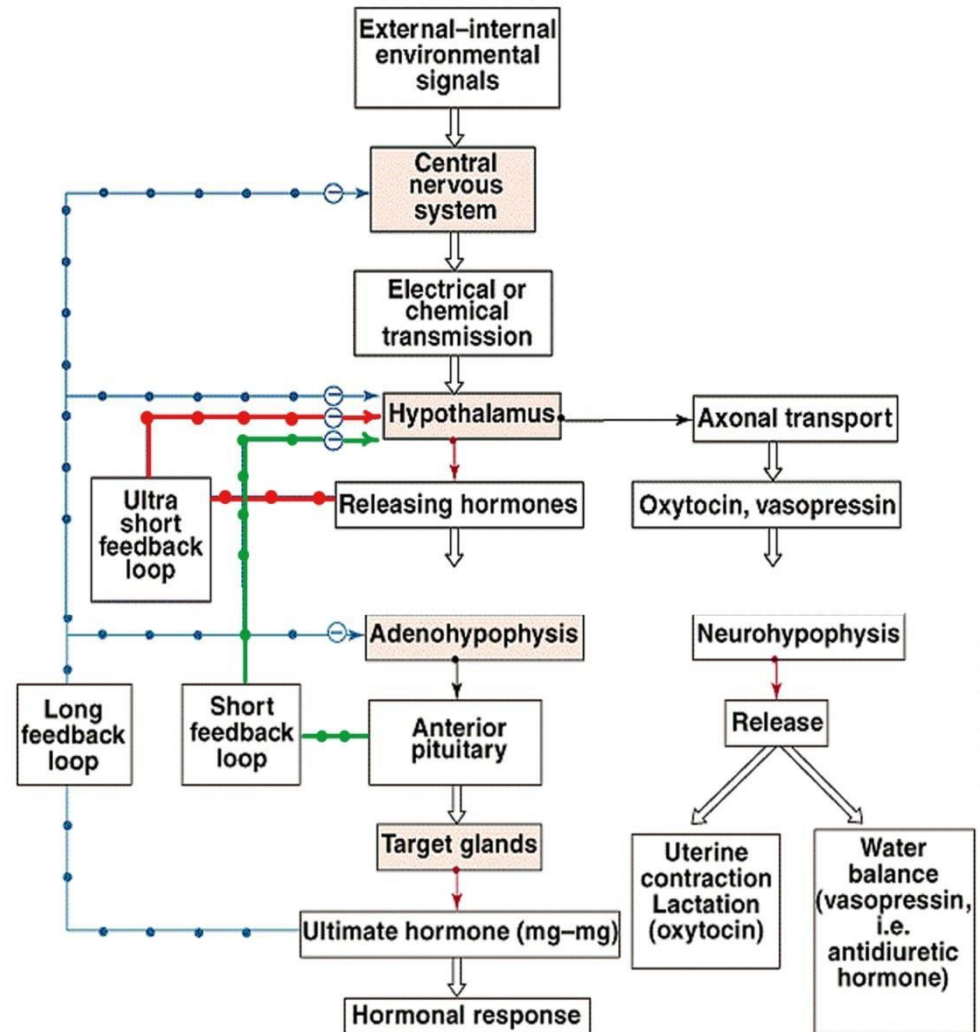
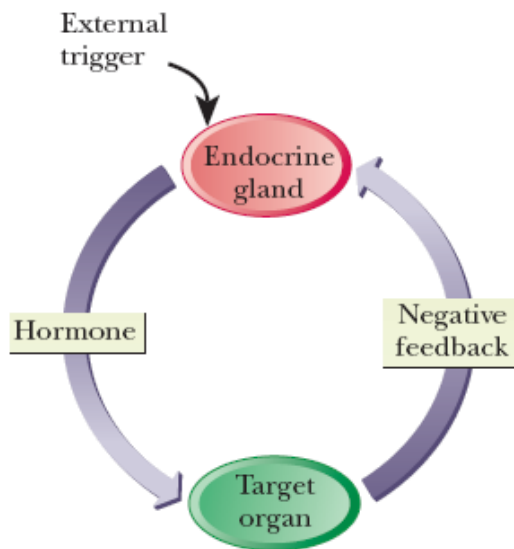


(a) Signaling pathway	(b) Number of molecules activated
<b>RECEPTION</b> Binding of epinephrine to G protein-linked receptor	1 molecule
<b>TRANSDUCTION</b> Inactive G protein → Active G protein	$10^2$ molecules
Inactive adenylyl cyclase → Active adenylyl cyclase	$10^2$ molecules
ATP → Cyclic AMP	$10^4$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



# How the release is controlled?

- Feedback inhibition
  - Ultrashort loop
  - Short loop
  - Long loop





# Classification of Hormones

## Chemical Structure

- Chemical composition; solubility; location of receptors; nature of the signal used to mediate hormonal action
- ✓ **Polypeptides:** Pituitary hormones; Hypothalamic releasing hormones; Insulin, Growth factors...
- ✓ **Amino acid derivatives:** Adrenalin, Thyroid hormones
- ✓ **Steroids**



# Classification of Hormones

## Mechanism of Action

- Hormones that bind to intracellular receptors
  - Steroids
  - Thyroid hormones
  - Calcitriol, retinoic acid

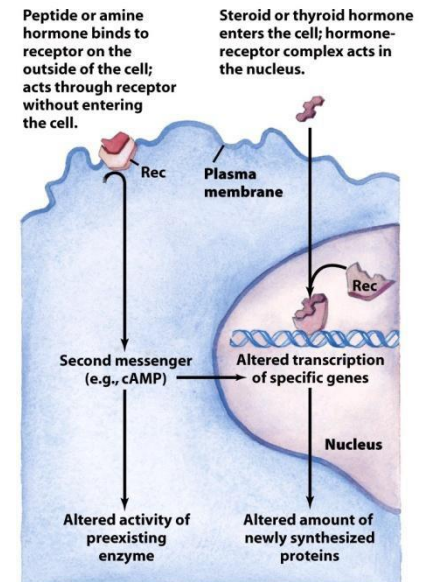
Long Half- life  
(hrs-days)

Transport  
proteins

**KOSH**  
EDUTECH PVT LTD



compilation of knowledge





# Classification of Hormones

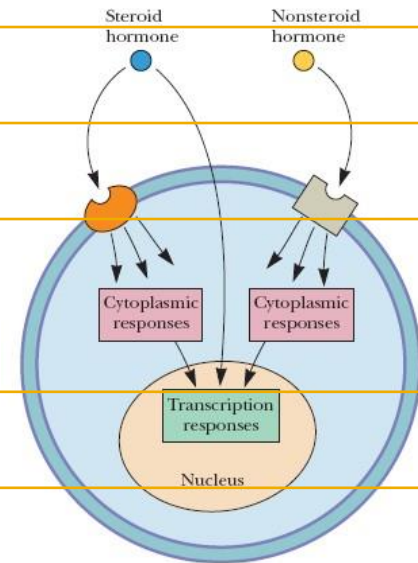
## Mechanism of Action

- Hormones that bind to cell surface receptors (According to second messenger):
  - cAMP ( $\beta$  adrenergic factor, glucagon, ACTH)
  - cGMP (atrial natriuretic factor, Nitric oxide)
  - Calcium or phosphatidyl inositol (oxytocin, TRH)
  - Kinase or phosphatase cascade (insulin, GH)



# General Features of Hormone Classes

	Group I	Group II
Types	Steroids, iodothyronines, calcitriol, retinoids	Polypeptides, proteins, glycoproteins, catecholamines
Action	Slow	Fast
Solubility	Lipophilic	Hydrophilic
Transport proteins	Yes	No
Plasma $t_{1/2}$	Long (hrs - days)	Short (minutes)
Receptor	Intracellular	Plasma membrane
Mediator	Receptor-hormone complex	cAMP, cGMP, $Ca^{2+}$ , kinase cascades, metabolites of phosphoinositols







# Hormones Classes

## Steroid hormones

- A. Sex hormones - are divided into 3 groups
  - 1. Male sex hormones or Androgens
  - 2. Female sex hormones or Estrogens
  - 3. Pregnancy hormones or Progestines
  
- B. Hormones of Adrenal Cortex
  - 1. Mineralocorticoids: aldosterone. ...
  - 2. Glucocorticoids: cortisol. ...
  - 3. Adrenal androgens: male sex hormones mainly dehydroepiandrosterone (DHEA) and testosterone



# Hormones Classes

## Non steroid hormones

### A. Peptide and protein hormones

- ✓ All hypothalamic, pituitary, digestive hormones
- ❖ All pituitary hormones are made from single polypeptide chains **EXCEPT**: TSH; FSH; LH (homodimers) – glycoproteins ( $\approx 25$  kDa)

### B. Amino acid derivatives

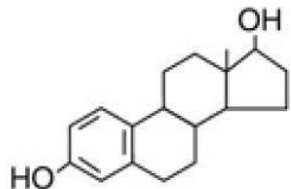
- ✓ Amines - derived from tyrosine or tryptophan TH, dopamine, epinephrine, melatonin



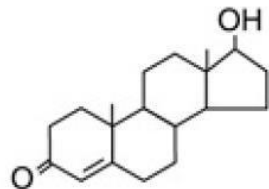
# Structure of Hormones

- Lipid – soluble hormones:

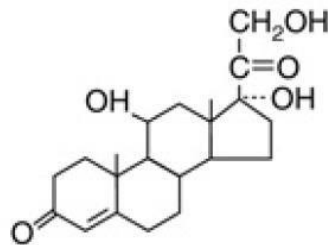
## A. Cholesterol derivatives



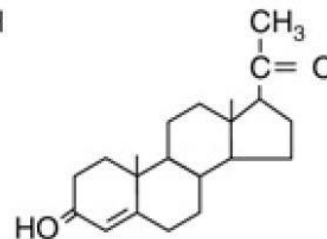
17β-Estradiol



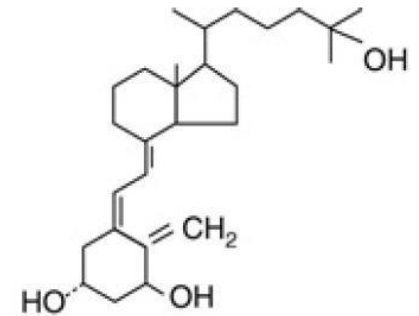
Testosterone



Cortisol



Progesterone



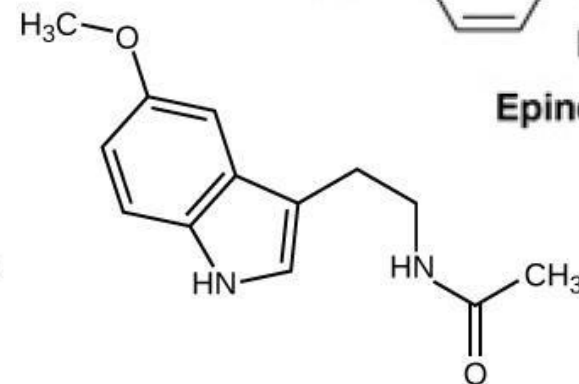
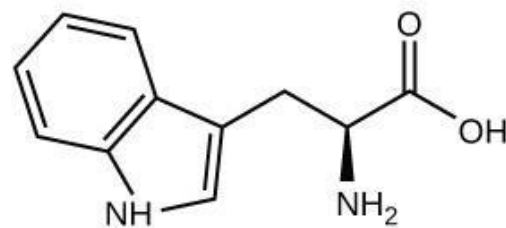
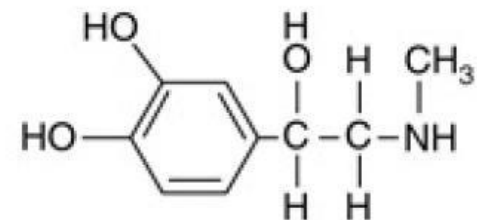
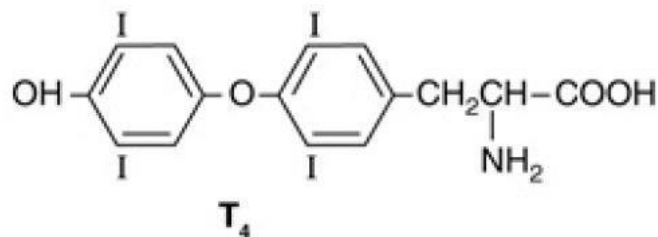
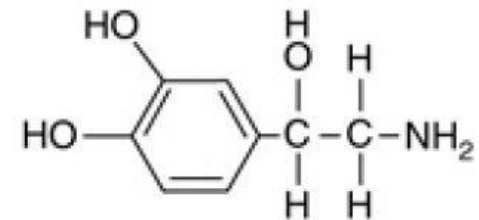
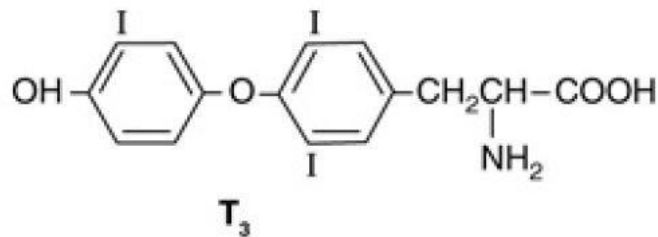
1,25(OH)<sub>2</sub>-D<sub>3</sub>



# Structure of Hormones

## ■ Amino Acid-Derived Hormones

### Tyrosine derivatives

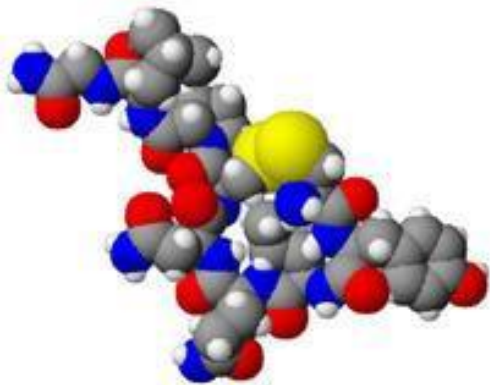




# Structure of Hormones

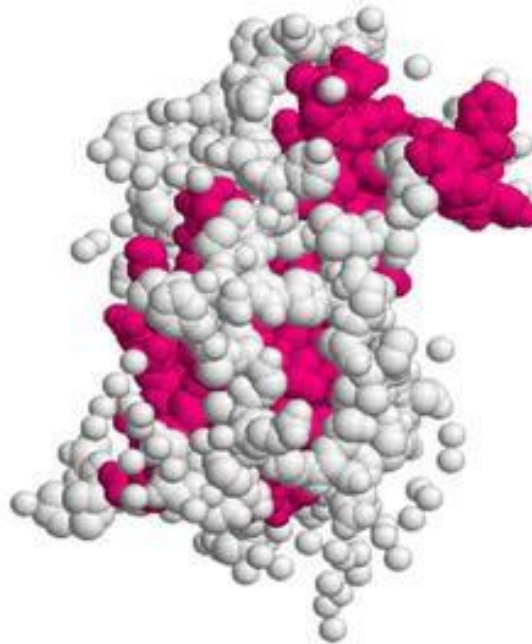
- Peptide & Protein Hormones

Oxytocin



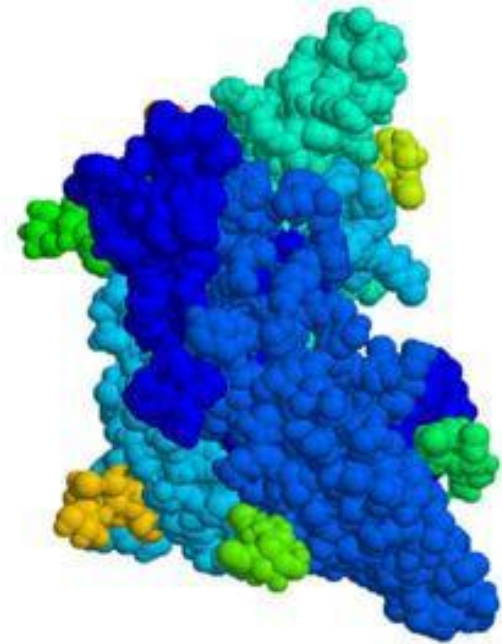
(a)

GH



(b)

FSH



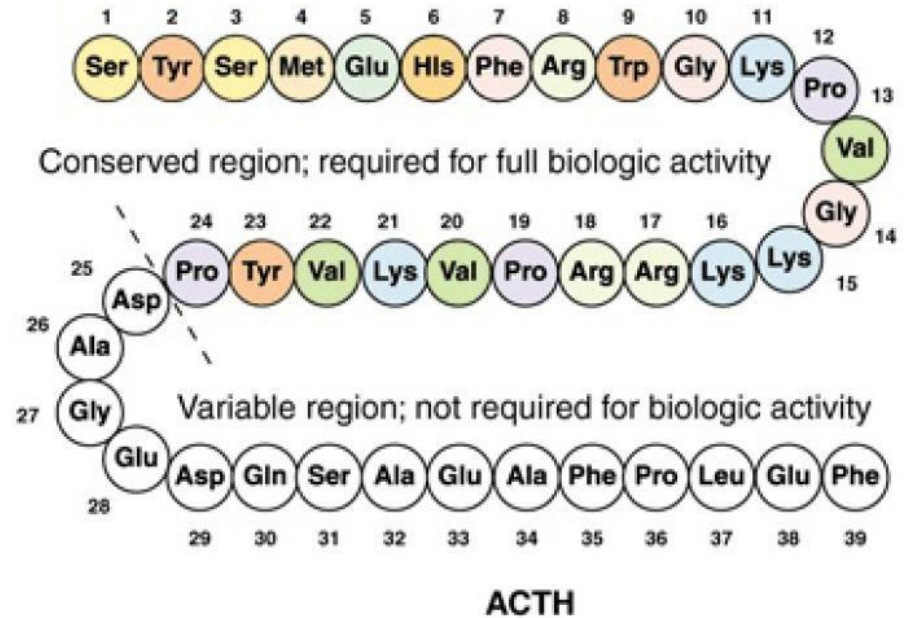
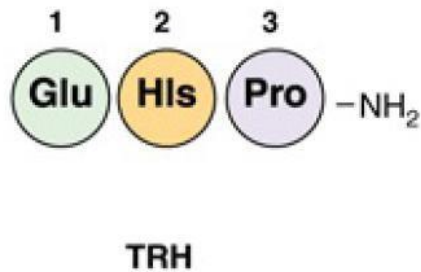
(c)



# Structure of Hormones

- Peptide & Protein Hormones

## C. Peptides of various sizes





# Structure of Hormones

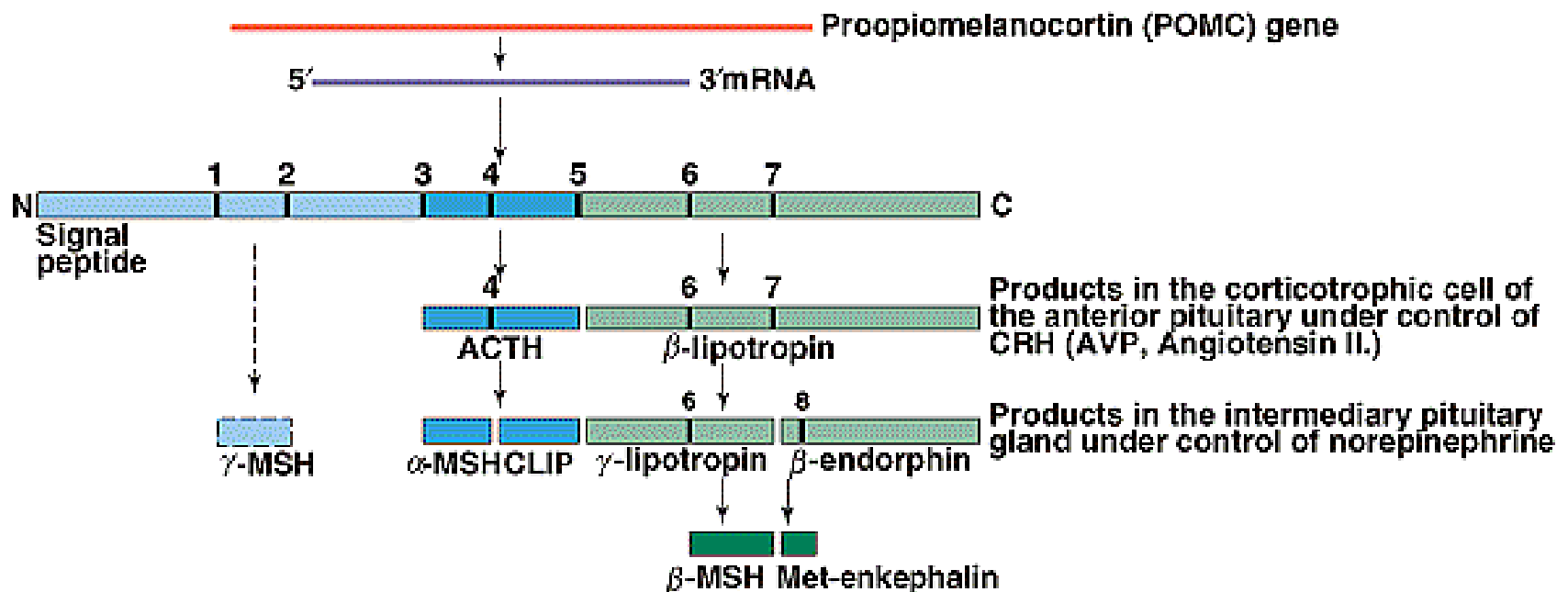
## Peptide & Protein Hormones

Hormone	Structure
GHRH	44
TRH	3
GnRH	10
CRH	41
ADH	9
Vasopressin	9
Angiotensin I	10
Angiotensin II	8
Insulin	51
Glucagon	29



# Synthesis of Peptide Hormones

- From precursor polypeptides
  - One gene may code more than one hormone (POMC)
  - The cleavage depends on specific enzymes

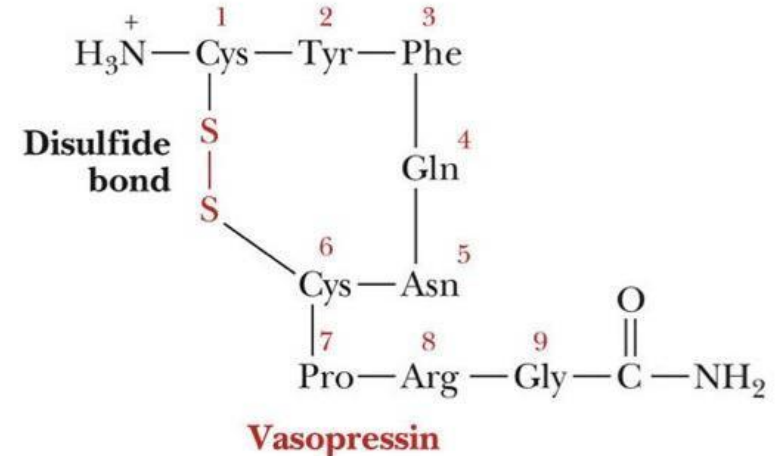
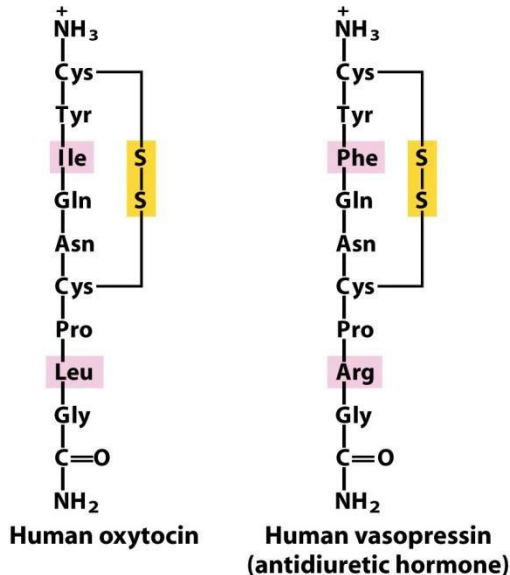
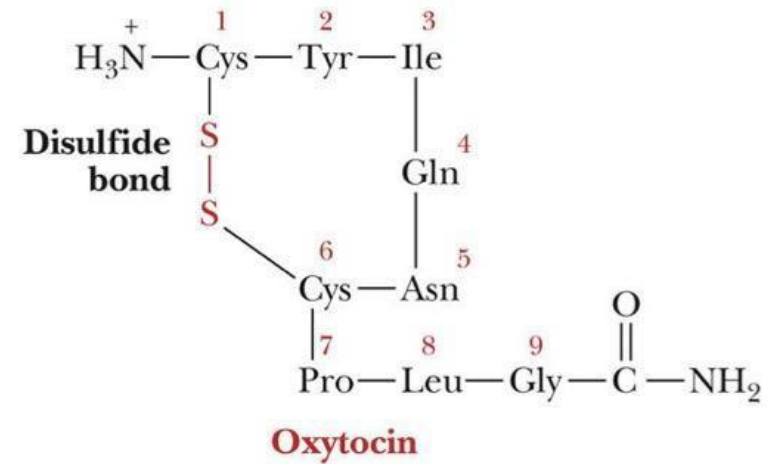






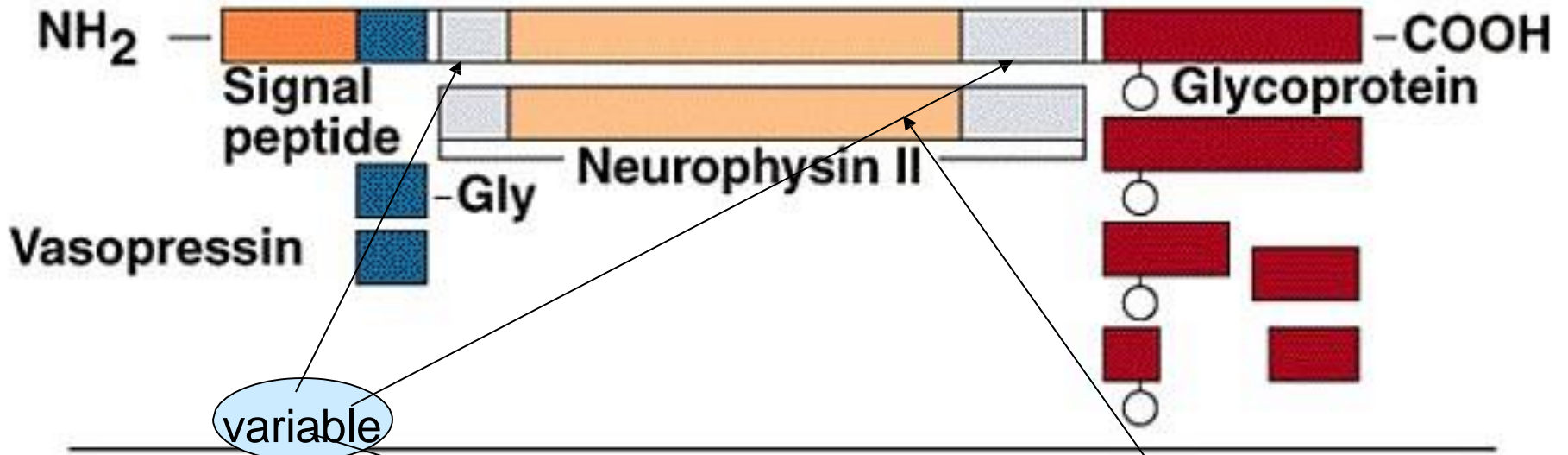
# Synthesis of Peptide Hormones

- From precursor genes
  - Vasopressin and oxytocin
  - Synthesis in separate cell bodies of hypothalamic neurons

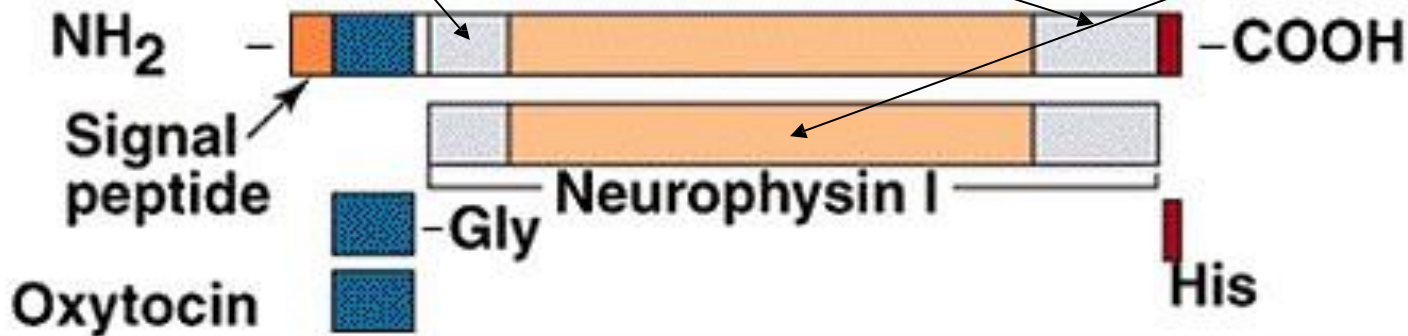




# Prepro-vasopressin



# Prepro-oxytocin

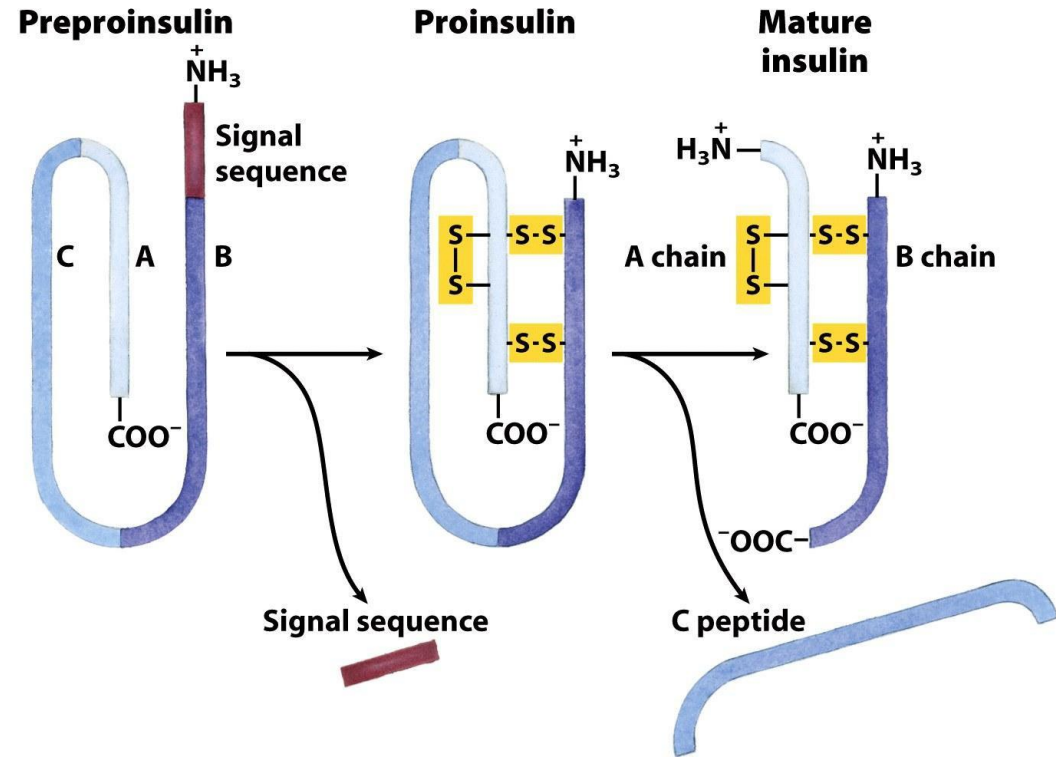
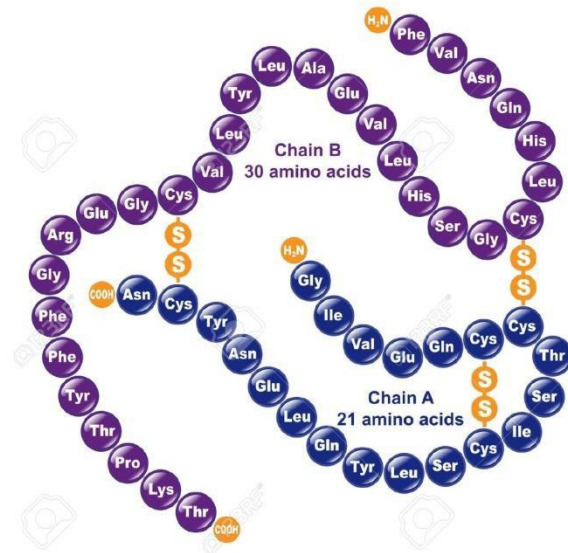




# Synthesis of Peptide Hormones

- Peptide & Protein Hormones
- From Pre-pro-hormones
- A larger precursor preproinsulin
  - 23 aa signal sequence
  - 3 disulfide bonds
- Proinsulin
  - Remove the C peptide
- Mature insulin
  - A and B chains

## Human Insulin





# Target cells interactive effects

- 1. Permissive effects** – one hormone enhances the effect of a later hormone
  - ✓ **Estrogen up-regulates progesterone receptors** in uterus
  - ✓ **Thyroid hormone increases the effect of epinephrine** on breakdown of triglycerides in adipocytes
- 2. Integrative effects** – hormones produce complementary effects on different tissues
  - ✓ **PTH and calcitriol increase ECF calcium**



# Target cells interactive effects

## 3. Synergistic effects:

- ✓ Both **FSH** and **estrogen** necessary for **normal oocyte development**
- ✓ **FSH** and **testosterone** together increase **spermatogenesis**

## 4. Antagonistic effects:

- ✓ **Insulin** and **glucagon**



Detection, and generation of cellular response

# Transduction of Hormonal 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 2<sup>nd</sup> 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!!!**)
  - Permits fine tuning but can pose problems
- Types of 2<sup>nd</sup> messengers:
  - **Small molecules: cAMP, cGMP, Ca<sup>+2</sup>**
  - **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?
  - Degradation of the second messenger
  - Dephosphorylation by hydrolysis

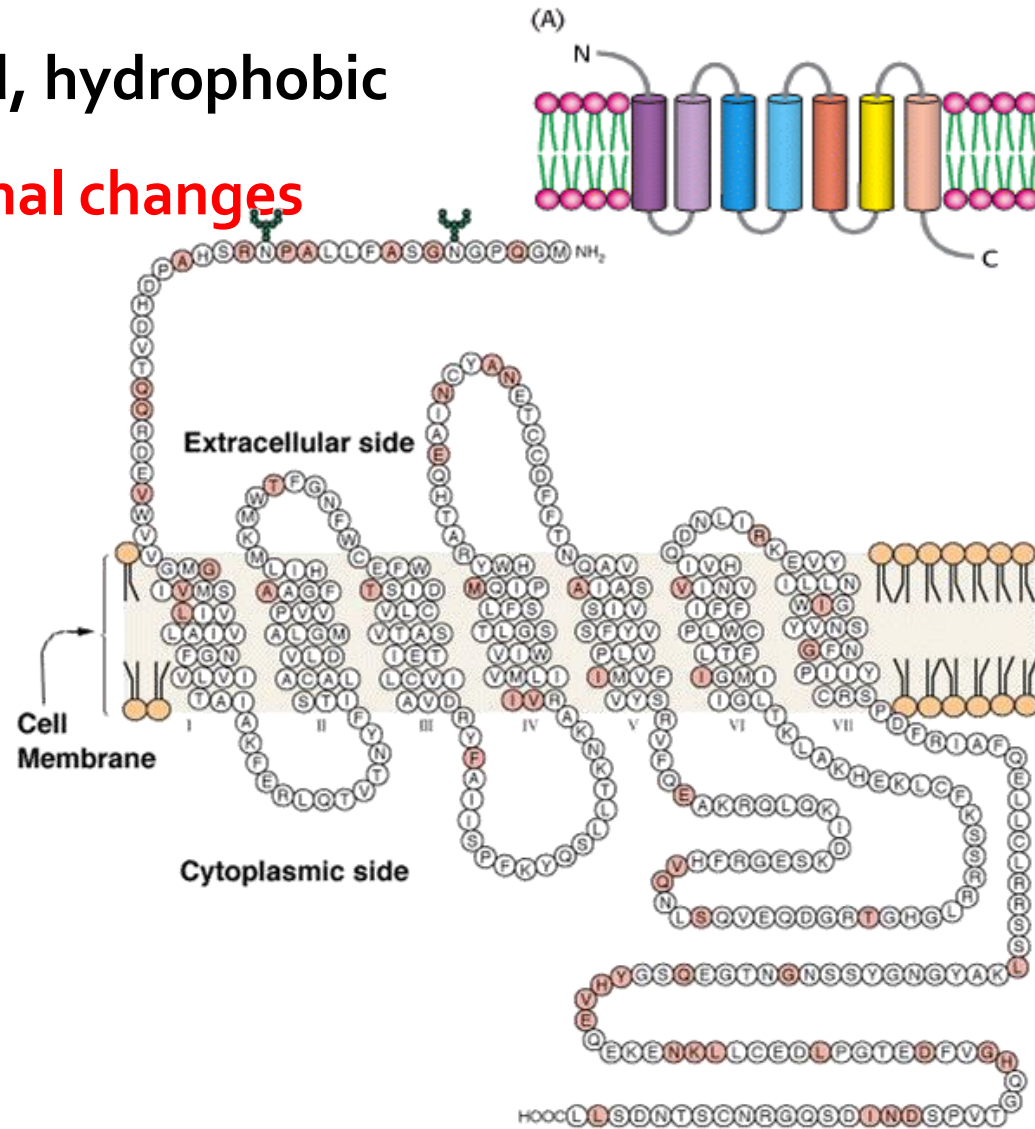
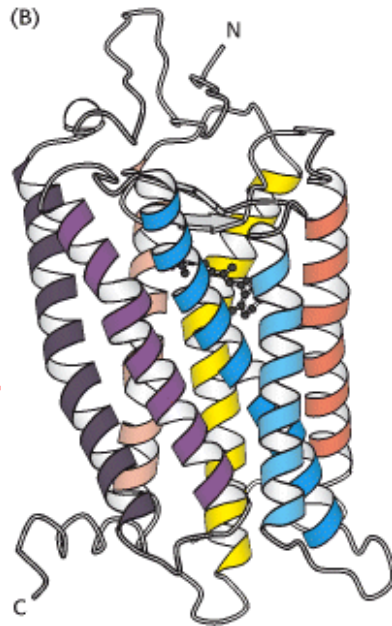


# Membrane Associated Receptors

## 7-Transmembrane Helix Receptors (7TM)

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

Rhodopsin receptor



- Many Ser & Thr residues



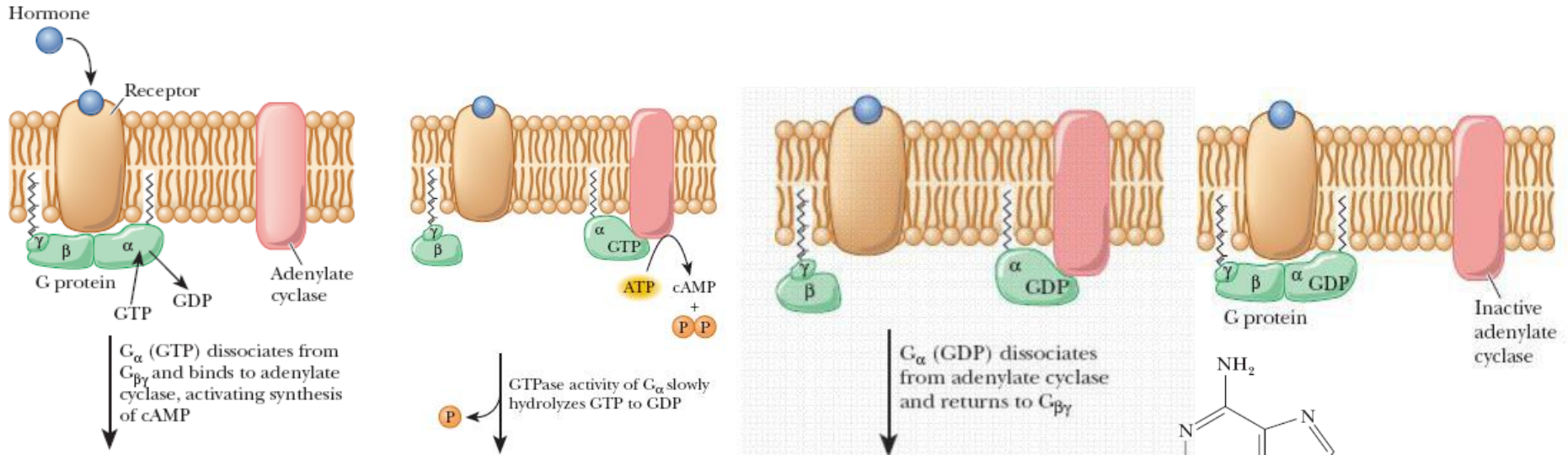
# Biological Functions Mediated by 7TM

- Examples:
- 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**



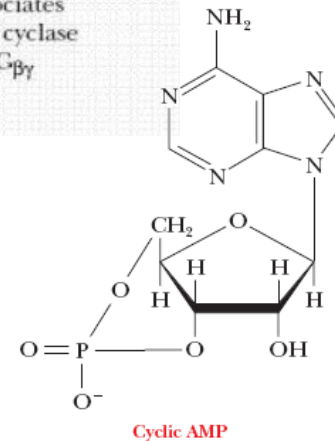
# G-proteins & cAMP



- cAMP: small & heat stable

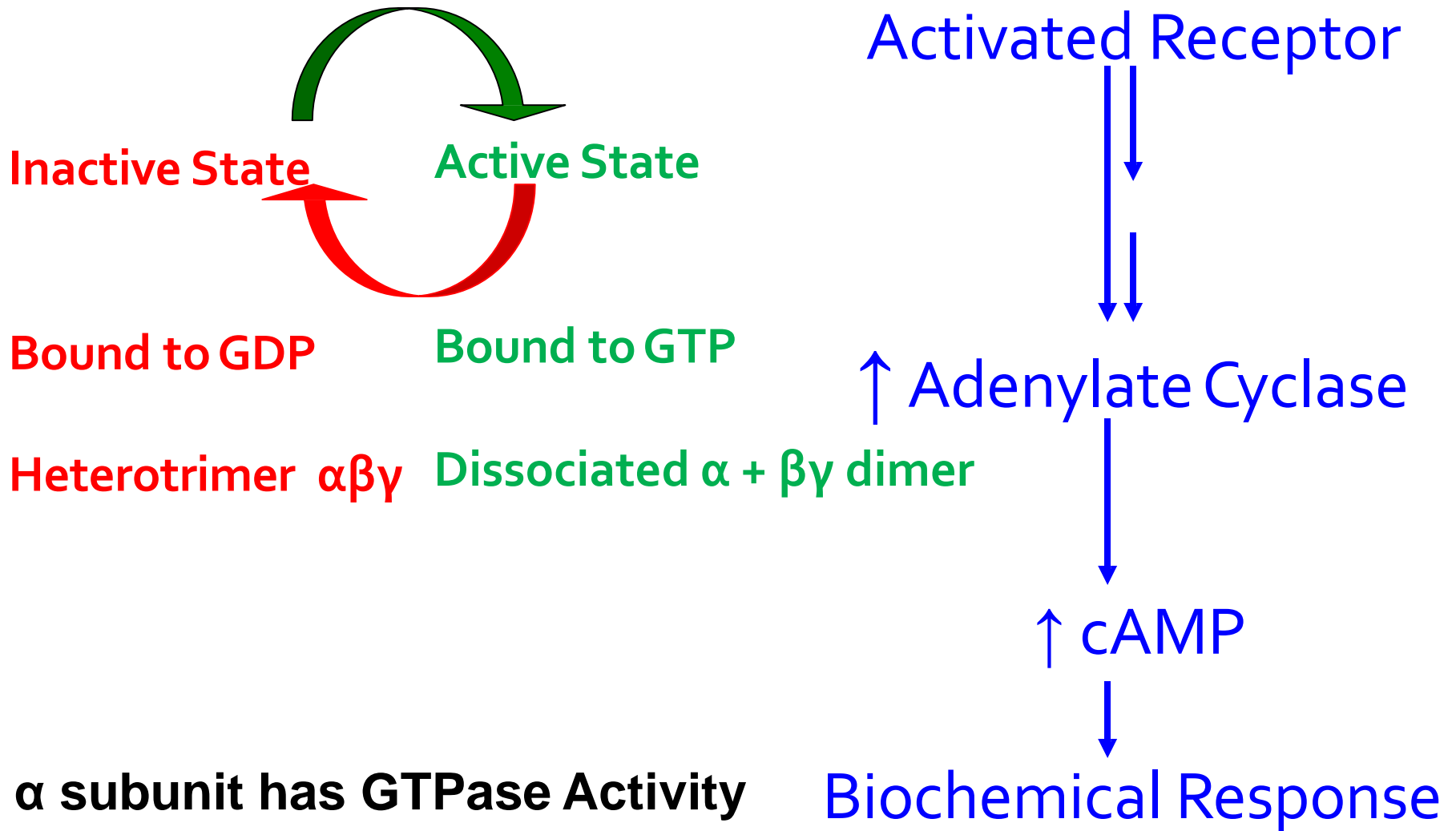
- Plasma membrane

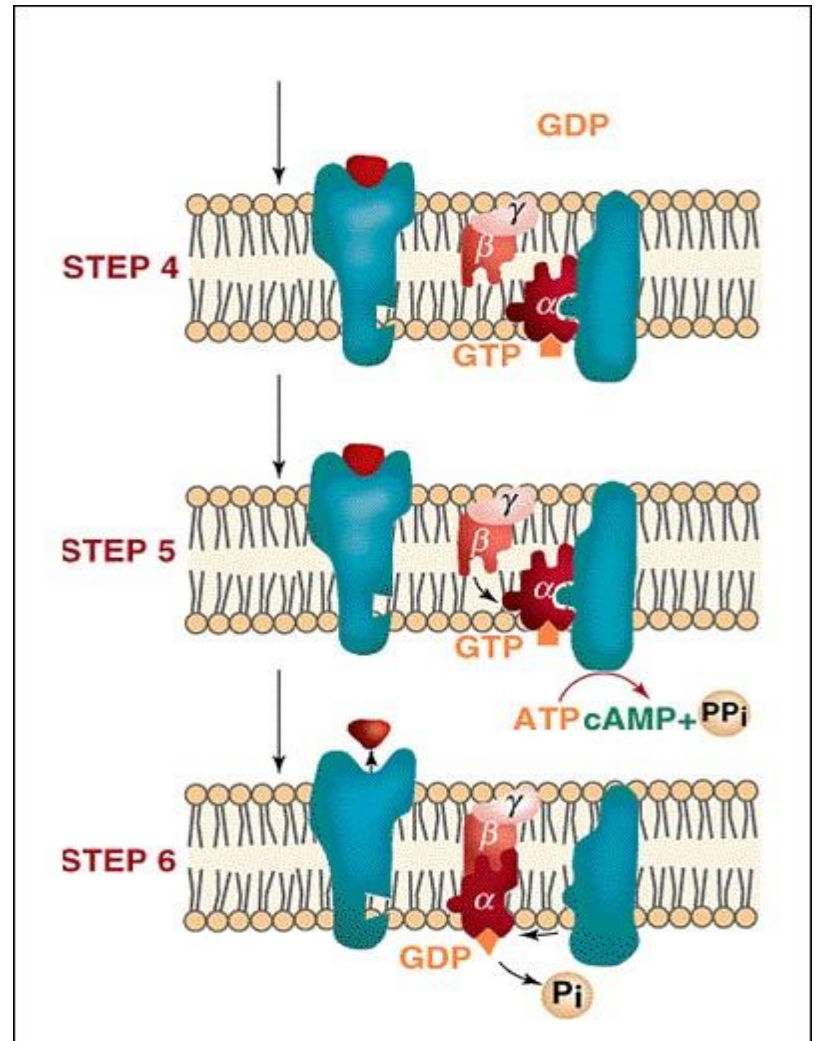
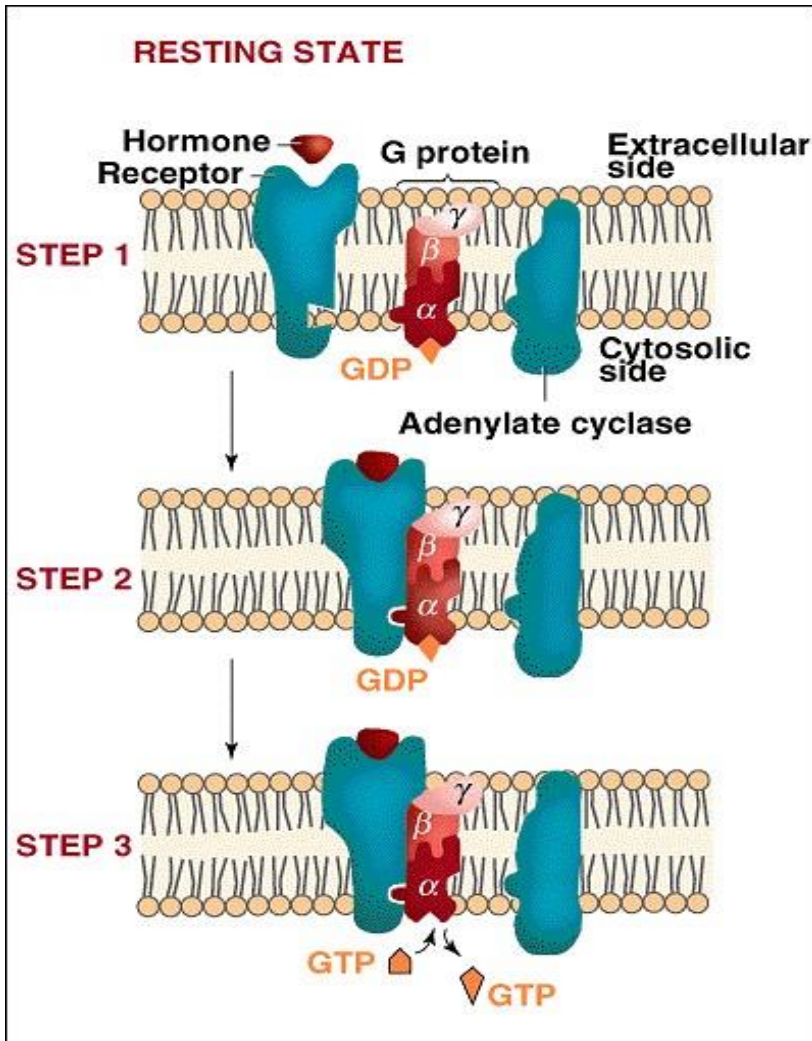
- Hormone → Specific receptor (β<sub>1</sub>- or β<sub>2</sub>-adrenergic receptor) → G protein → Adenylate cyclase → cAMP → protein kinase A → phosphorylation





# G Protein cycles between two forms

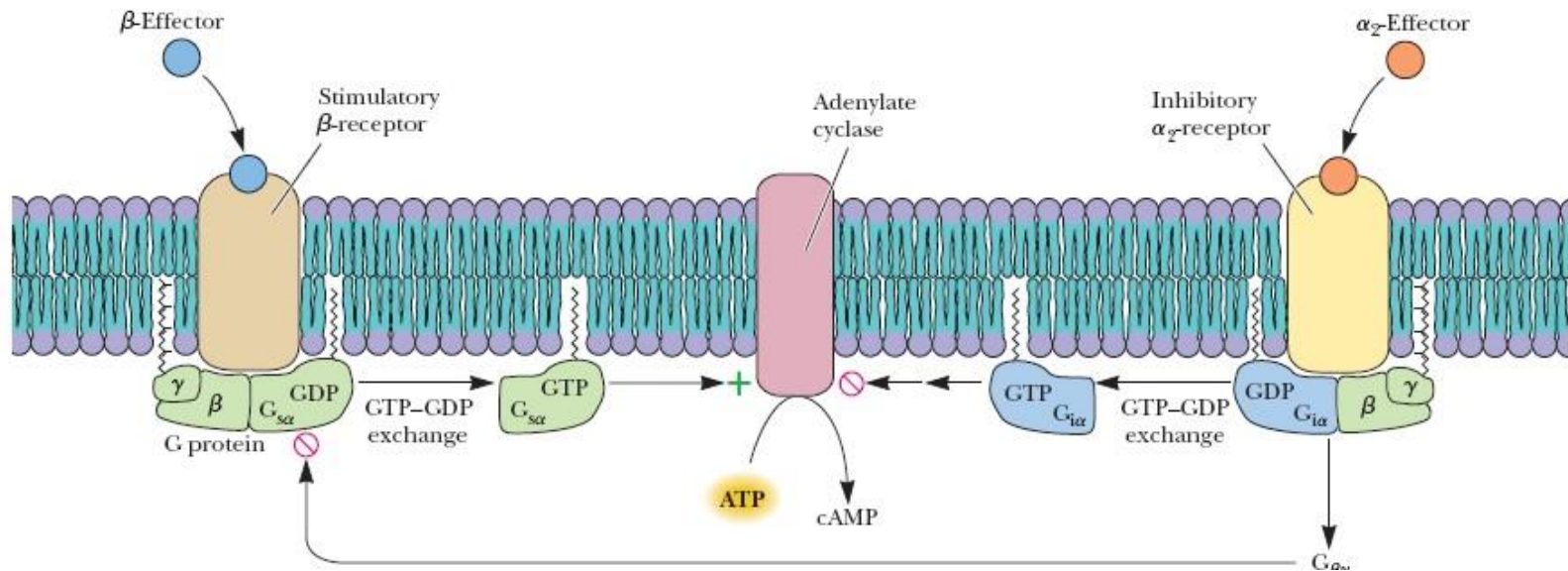




**$\alpha$  subunit has GTPase Activity**



# G protein: stimulatory or inhibitory?



## ■ Cyclic AMP & G Proteins:

- Hormone → receptor ( $\alpha_2$ -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 Proteins (cont.)

- $\alpha$  and  $\gamma$  Subunits have covalently attached fatty acid
- $\alpha$  and  $\beta\gamma$  can interact with other proteins
- All 7TM receptors appear to be coupled to G proteins

## GPCRs

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

Signal Transduction

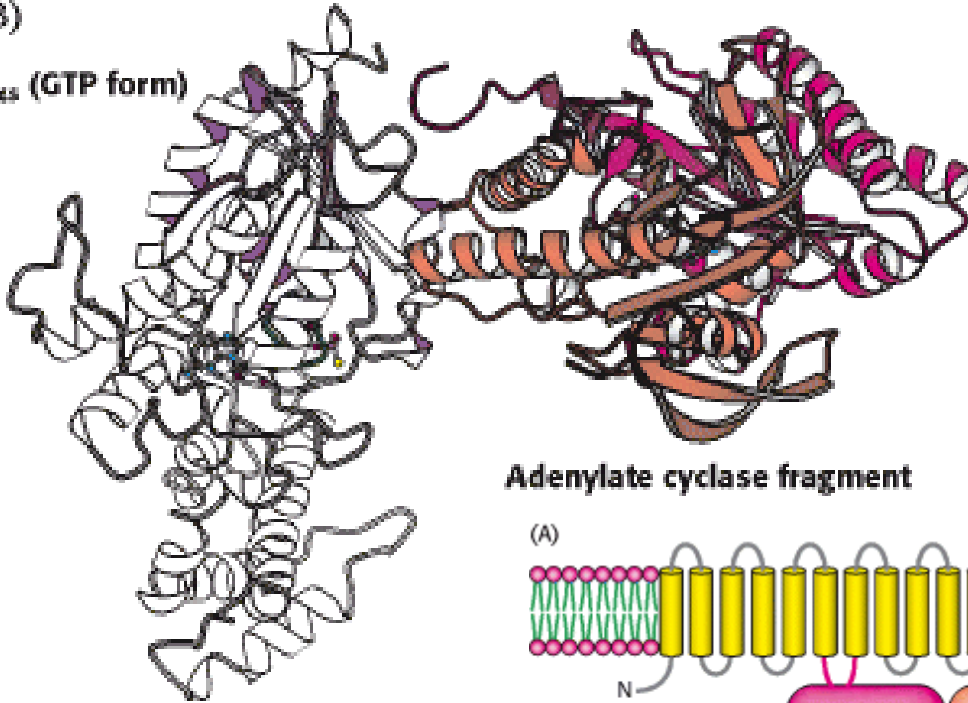
© Sinauer Associates, Inc.



# Adenylate Cyclase

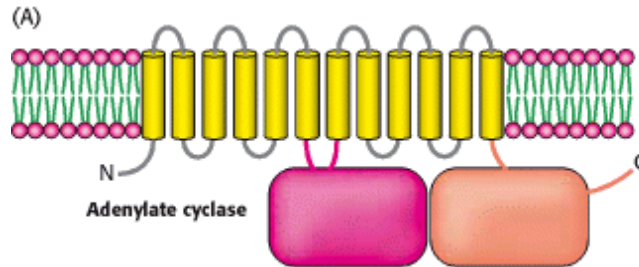
(B)

$G_{\alpha s}$  (GTP form)

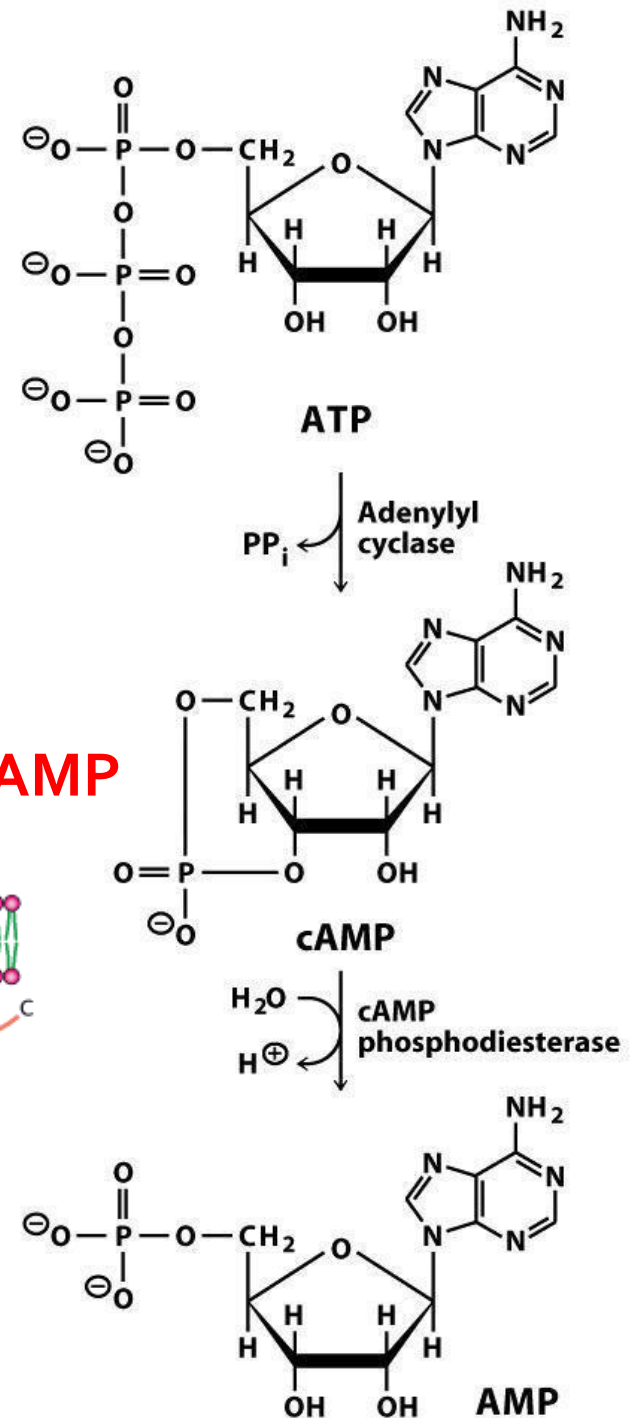


Adenylate cyclase fragment

3'5' **CAMP**



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



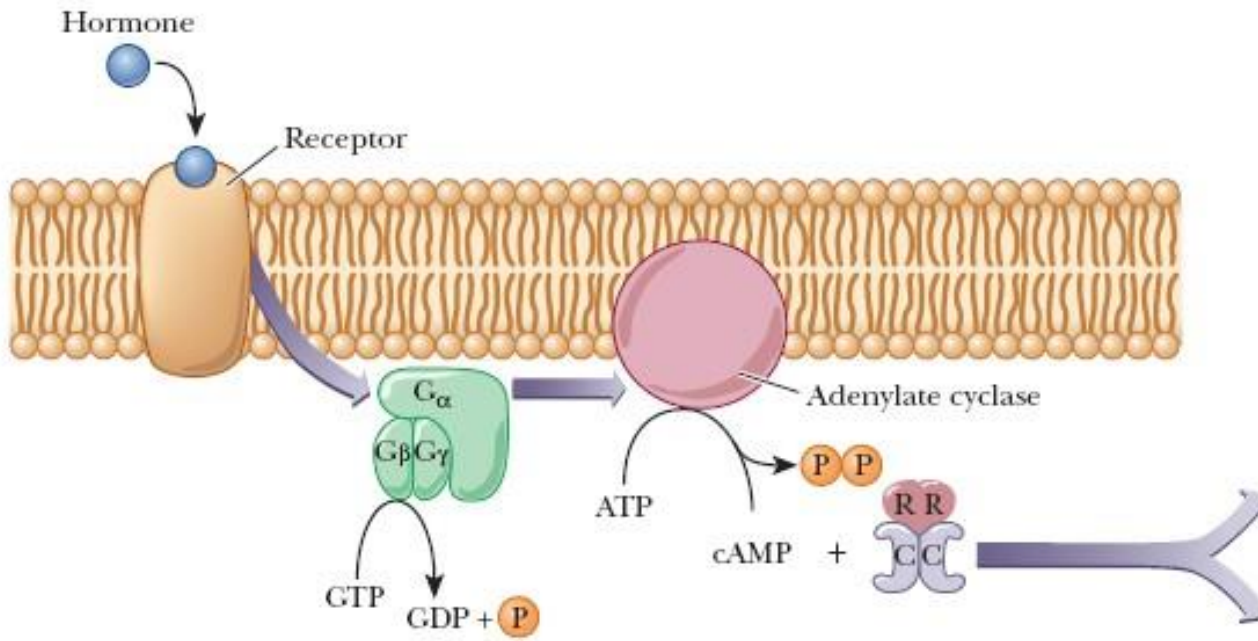


# cAMP can affect a wide range of cellular processes

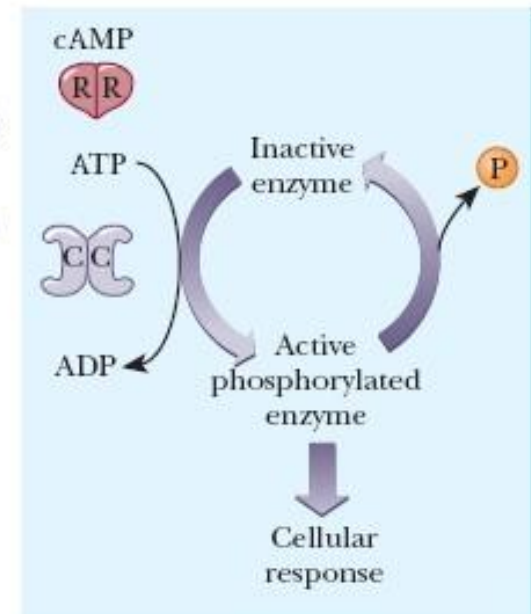
- ↑ degradation of storage fuels
- ↑ **secretion of acid by gastric mucosa**
- Dispersion of melanin pigment granules
- ↓ aggregation of blood platelets
- Opening of chloride channels



# Then what?



Usually:  
Ser or Thr



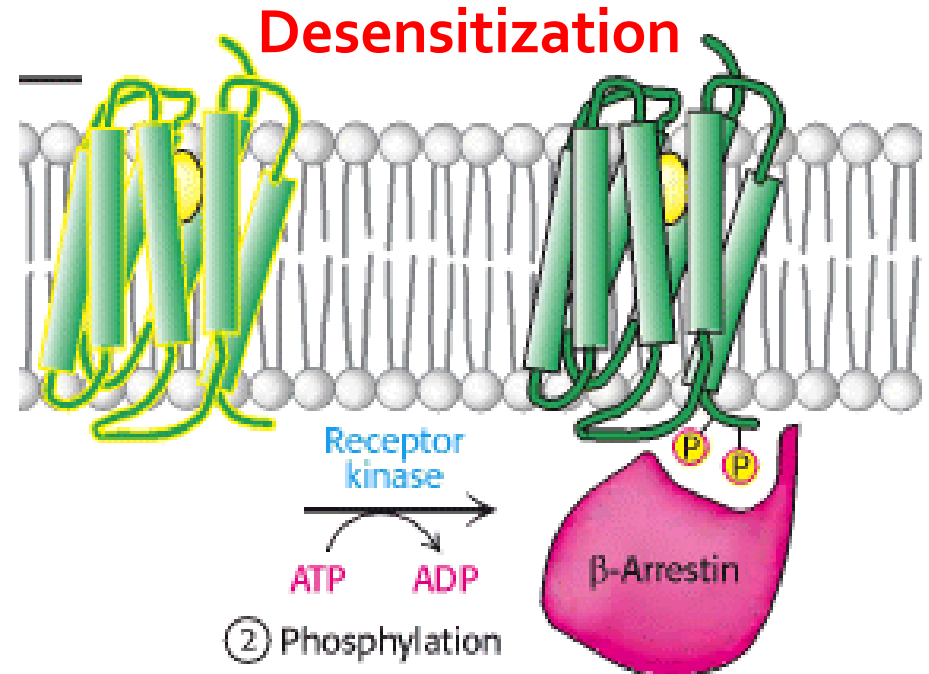
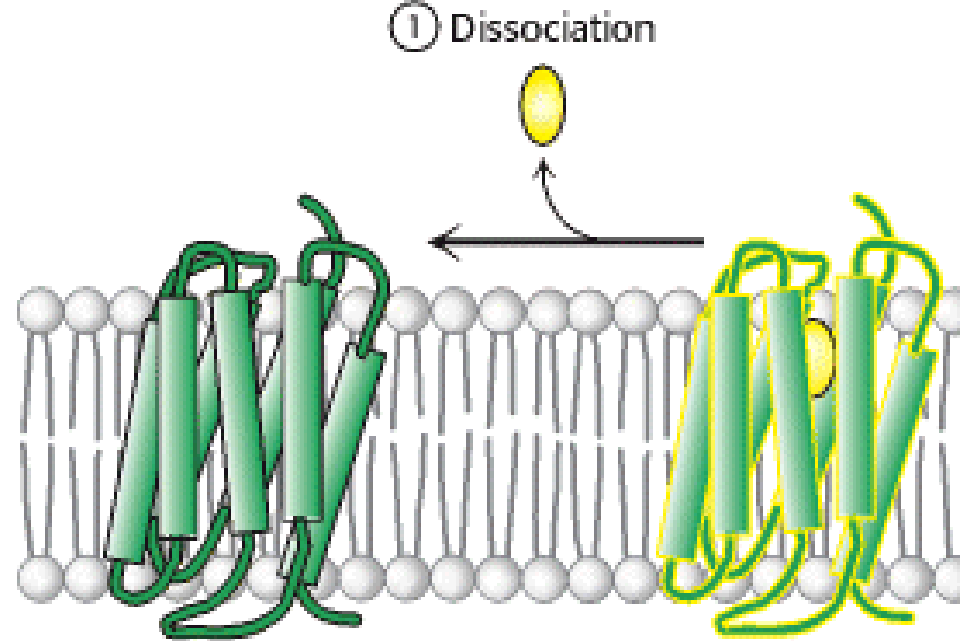
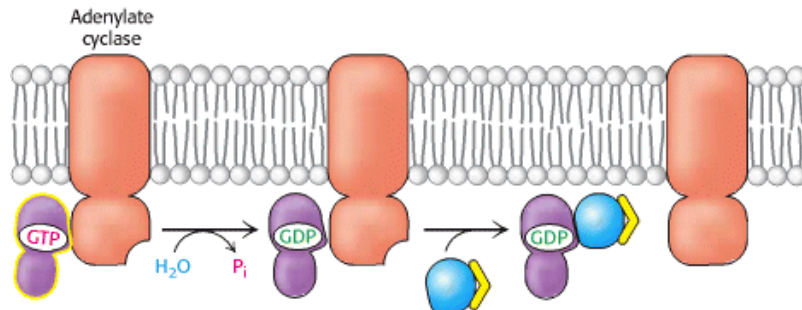
Signal Amplification

Glycogen  
Synthase!!



# Switching off the signal

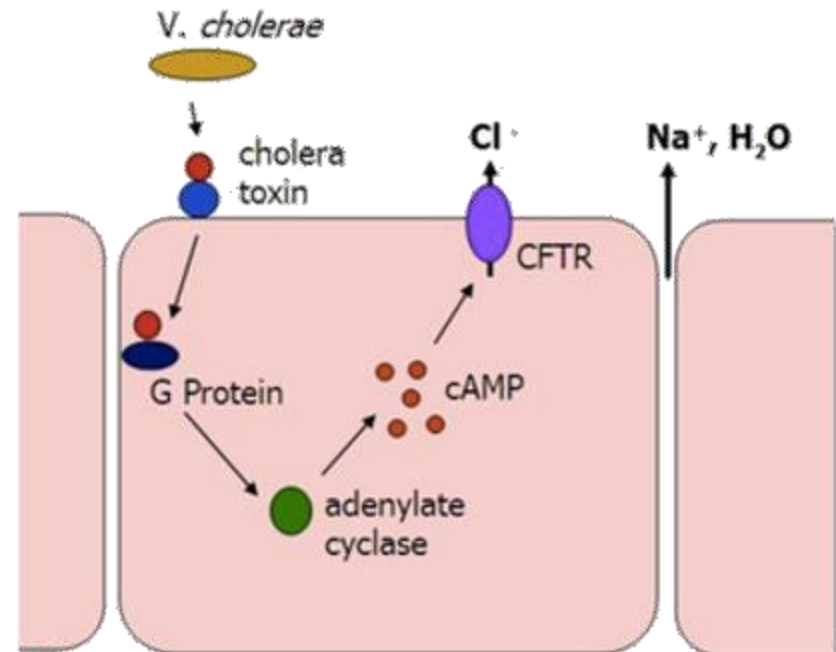
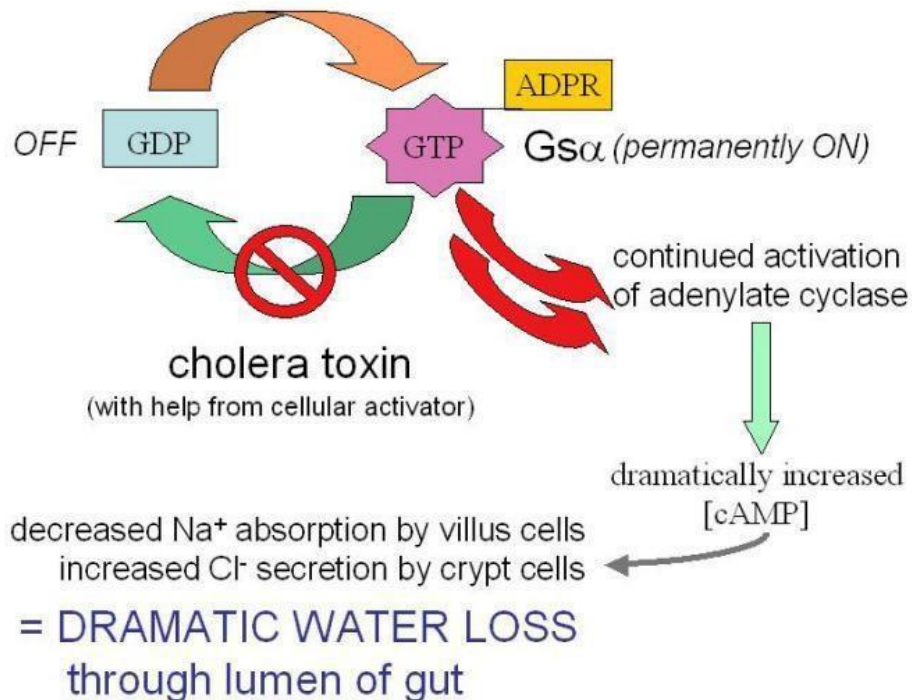
- **Dissociation** of the hormone
- **GTPase** activity of  $G\alpha$  subunit
- **Hydrolysis** of cAMP (phosphodiesterase)
- Phosphorylation of the hormone bound-receptor followed by binding to  **$\beta$ -Arrestin**





# Cholera

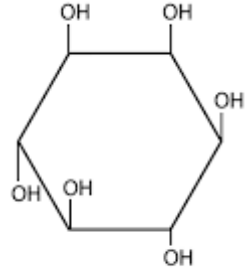
- Cholera toxin → unregulated activity of adenylate cyclase in epithelial cells → Excessive cAMP in epithelial cells stimulates active transport of  $\text{Na}^+$  → large flow of  $\text{Na}^+$  and water from the mucosa → diarrhea





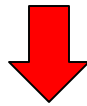
# The Phosphoinositide Cascade

- Used by many hormones (e.g. ADH)
- Binding of a hormone to 7TM receptor

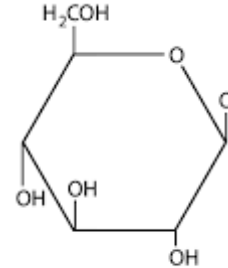


Inositol

Activation of G Protein



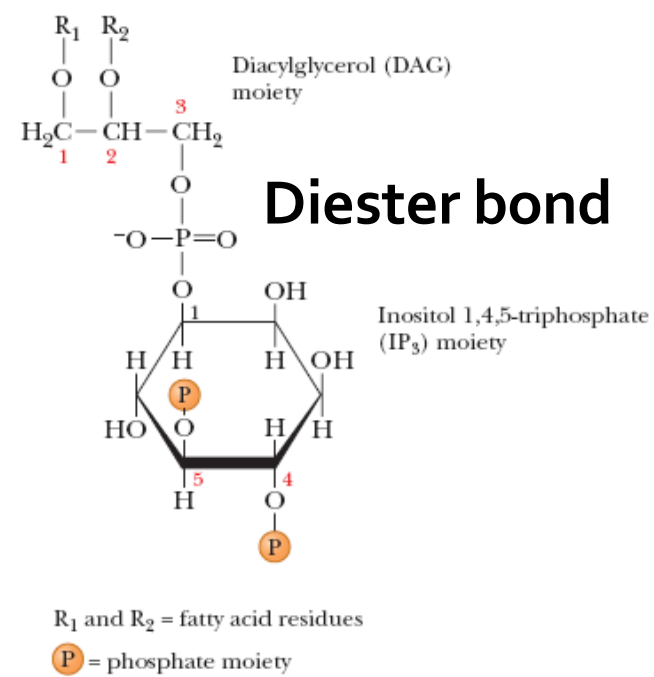
Activation of Phospholipase C  
(many isoforms) – PIP<sub>2</sub>



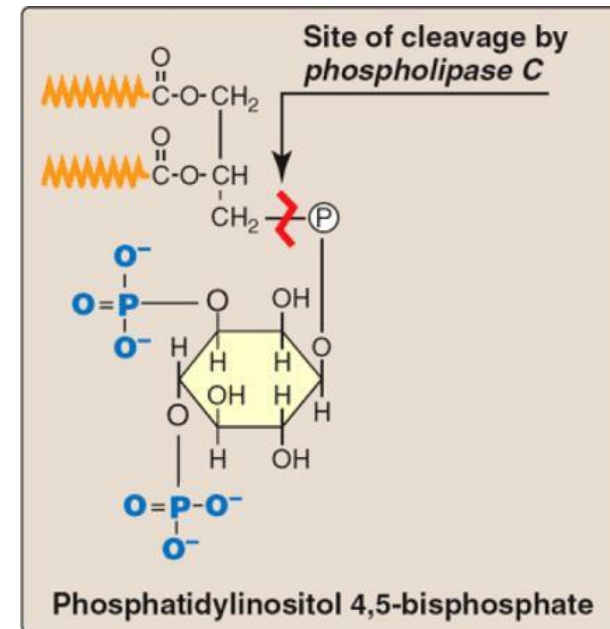
Glucose

©Nutrientsreview.com

- Two messengers are produced
  - Inositol 1,4,5-trisphosphate, hydrophilic, (Soluble)
    - IP<sub>3</sub> is the actual second messenger
  - Diacylglycerol, amphipathic (membrane)

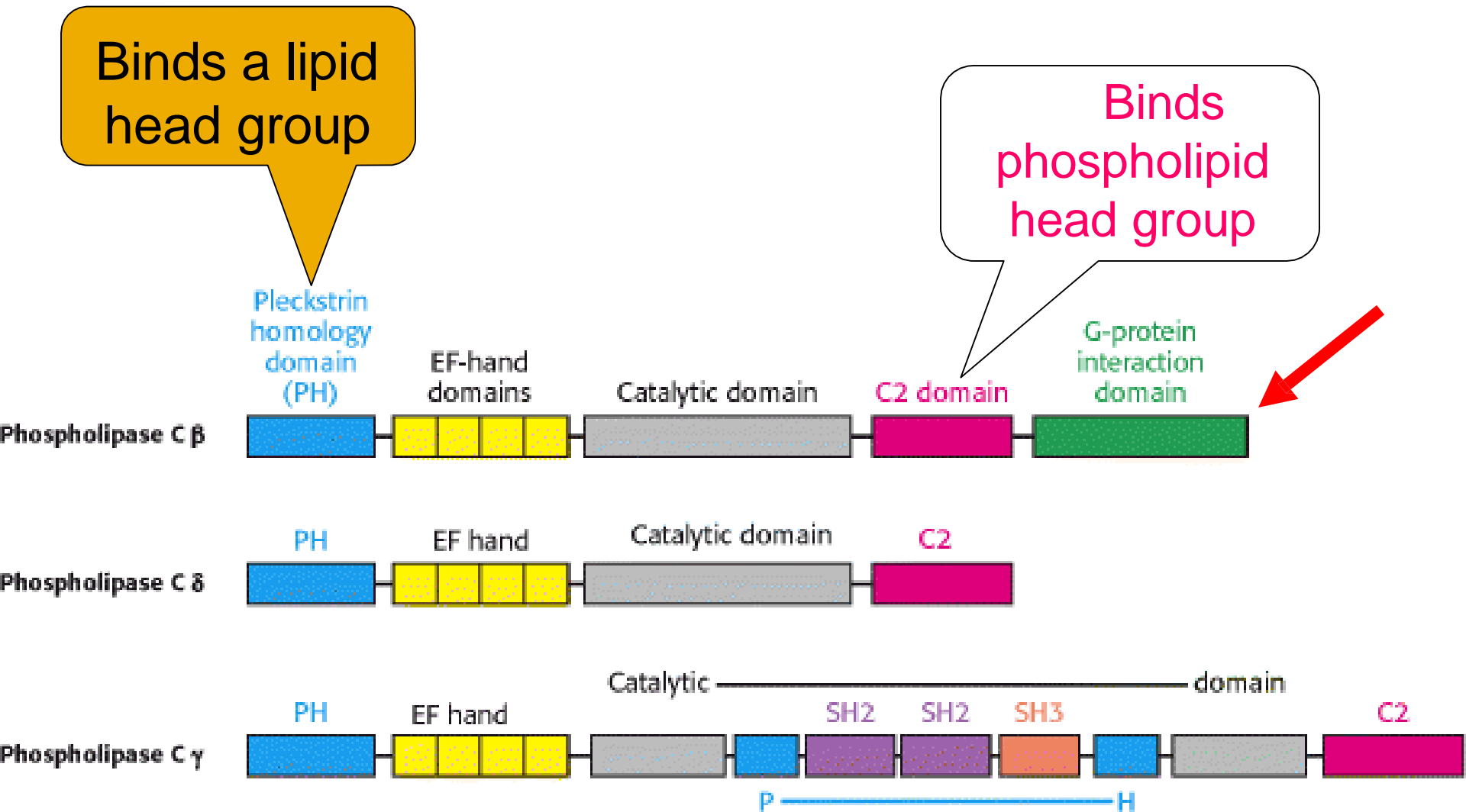


Phosphatidylinositol 4,5-bisphosphate (PIP<sub>2</sub>)





# The domain structures of three isoforms of Phospholipase C







# Binding of a G protein brings the enzyme into a catalytically active form

Membrane

G  
Protein

Pleckstrin  
homology  
domain  
(PH)

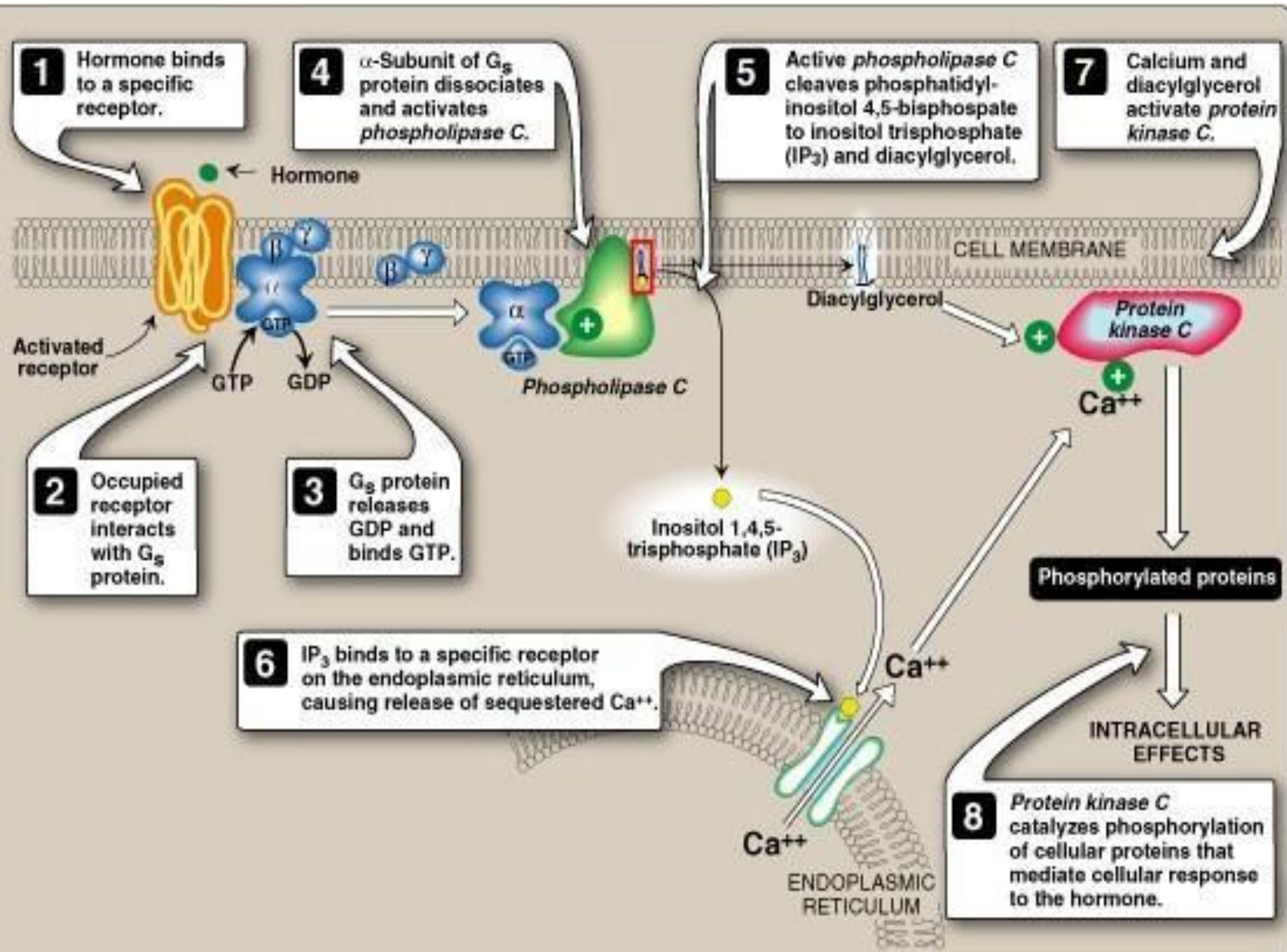
EF-hand  
domains

Catalytic domain

C2 domain

G-protein  
interaction  
domain







# Effects of Second Messengers

## Inositol trisphosphate (IP<sub>3</sub>)

- ✓ Opens Calcium Channels
- ✓ Binding to IP<sub>3</sub>-gated Channel
- ✓ Cooperative binding (sigmoidal)

## Diacylglycerol (DAG)

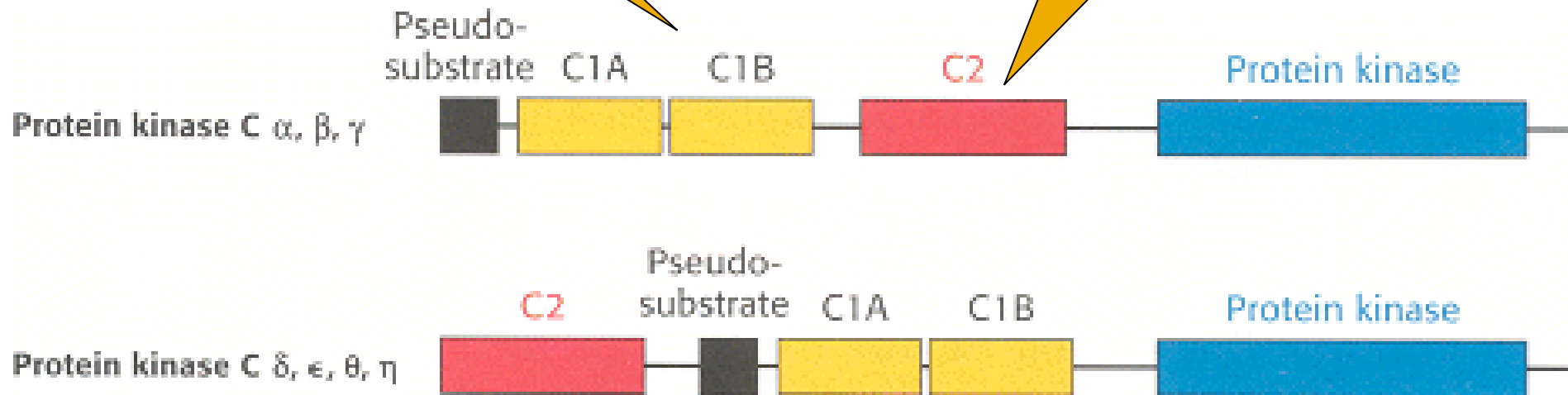
- ✓ Activates Protein Kinase C
- ✓ Ca<sup>2+</sup> is required
- ✓ Phosphorylation of many target proteins



# The domain structures of protein kinase C isoforms

Binds Diacylglycerol

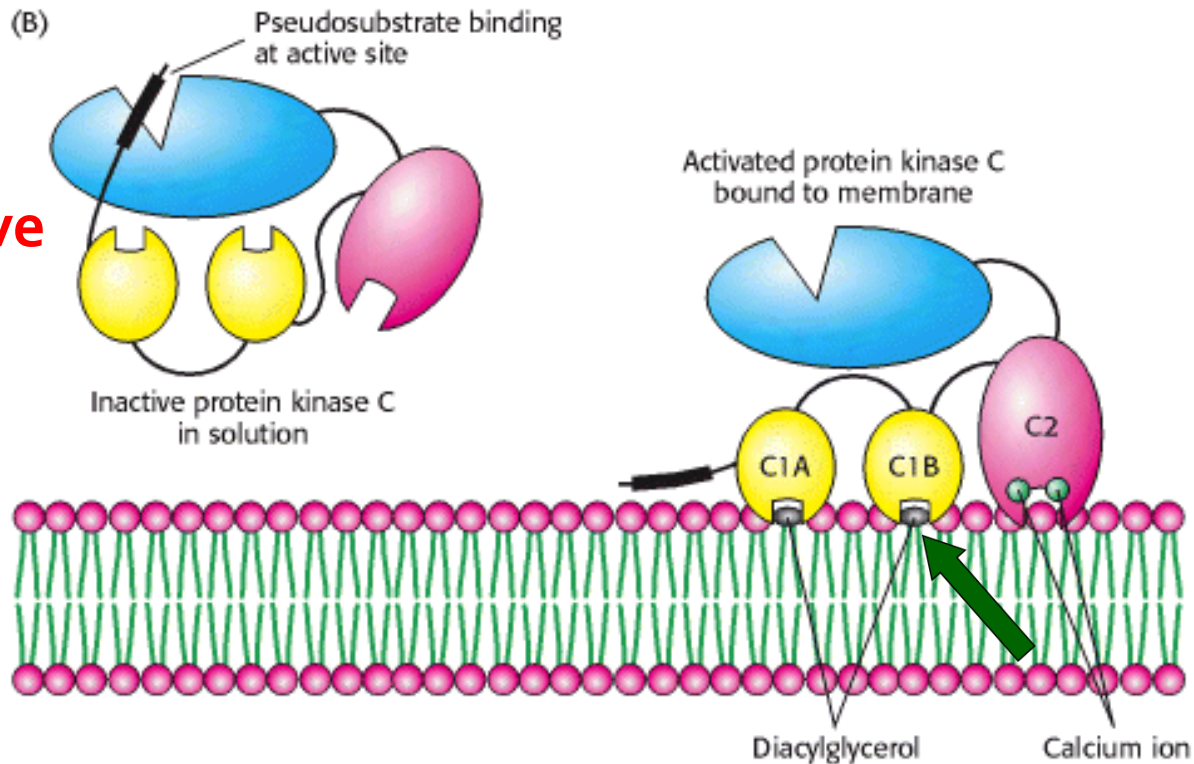
Interaction with phospholipids





# Pseudosubstrate Sequence

Competitive  
Inhibitor



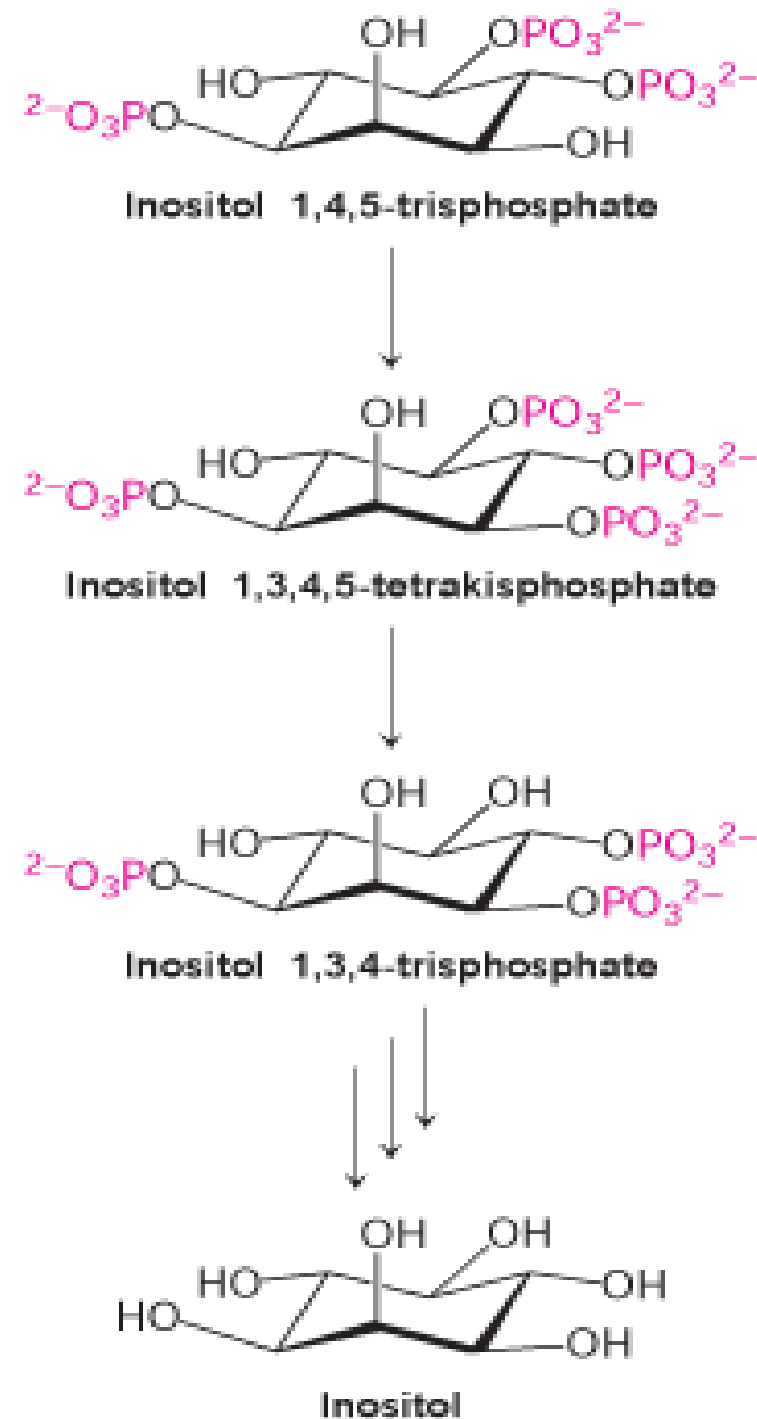
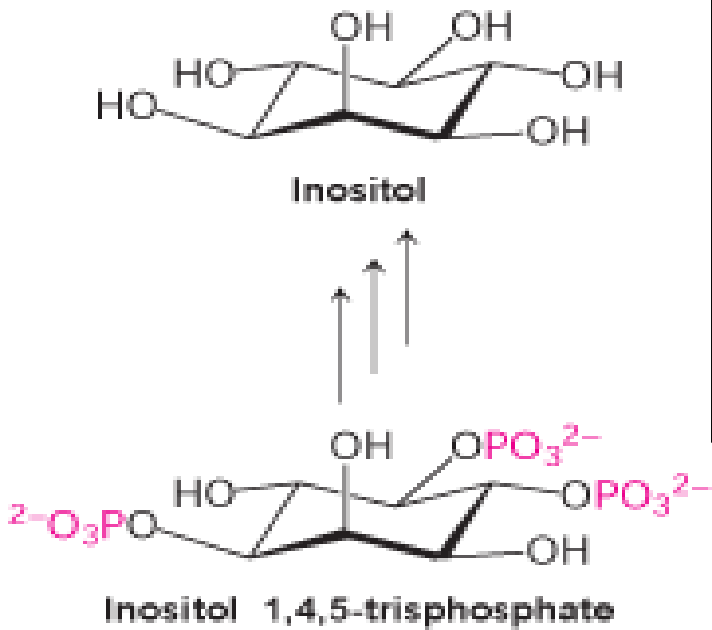
- Resembles the substrate sequence: A-R-K-G-A-L-R-Q-K
- Substrate Sequence: (S,T)
- Binds to the Enzyme's Active Site



# Termination of IP<sub>3</sub> Signal

IP<sub>3</sub> is a Short-Lived Messenger

Lithium ions,  
used to treat  
some  
psychological  
disorders  
Inhibits IP<sub>3</sub>  
recycling

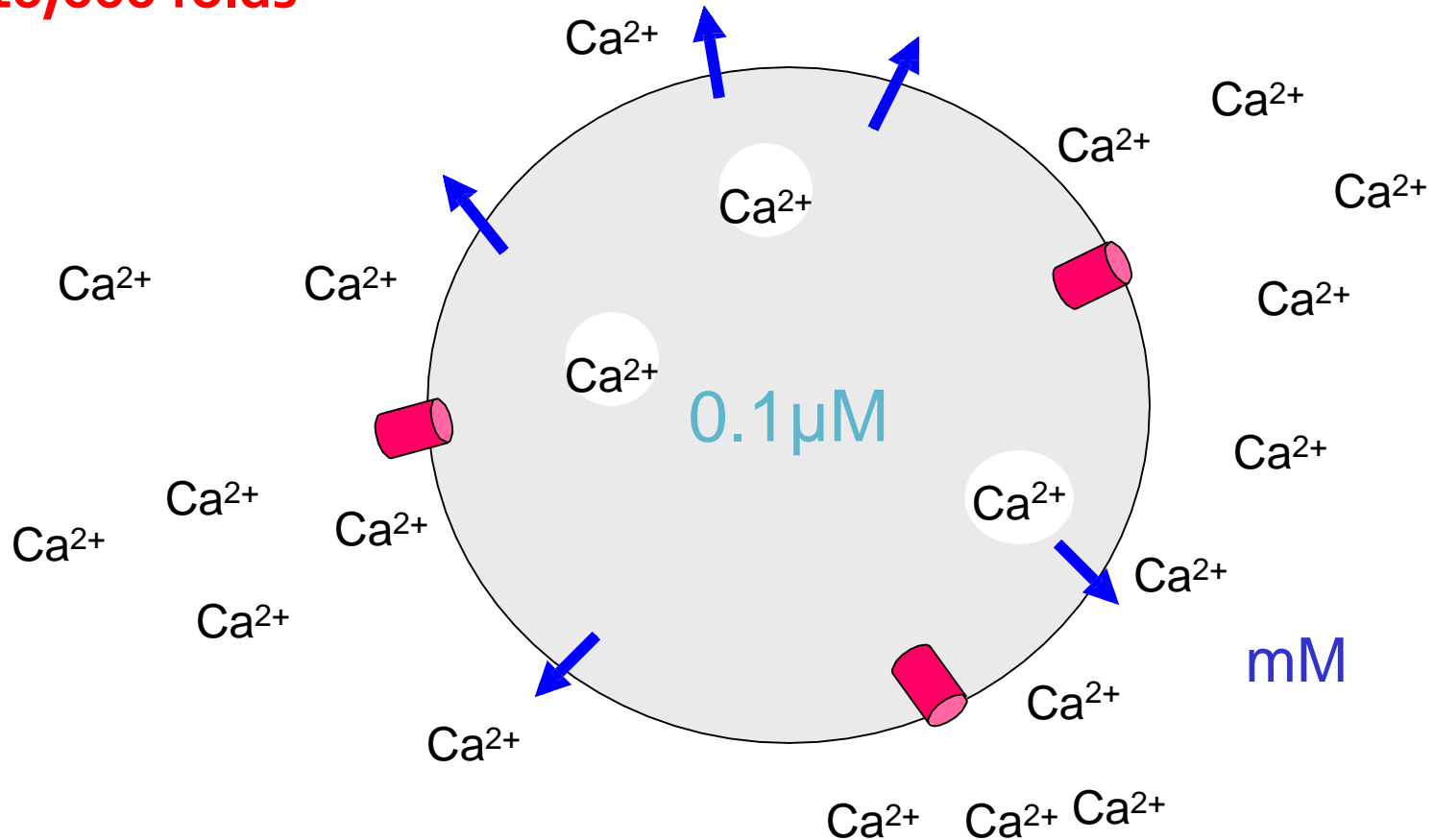




# Why $\text{Ca}^{2+}$ ?

A large difference in concentration

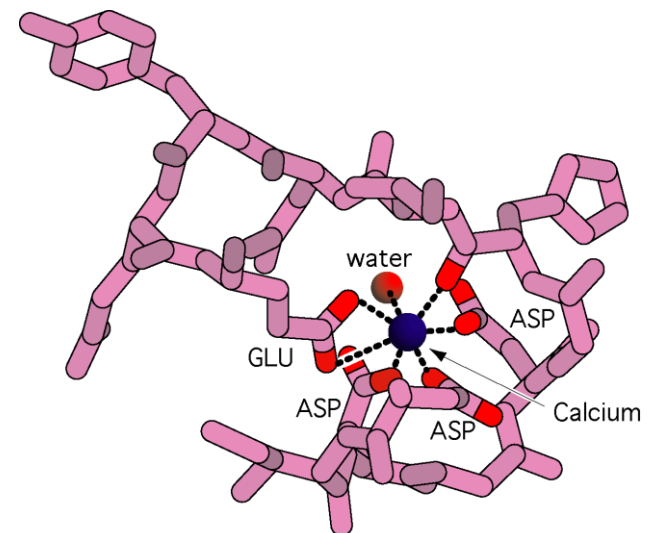
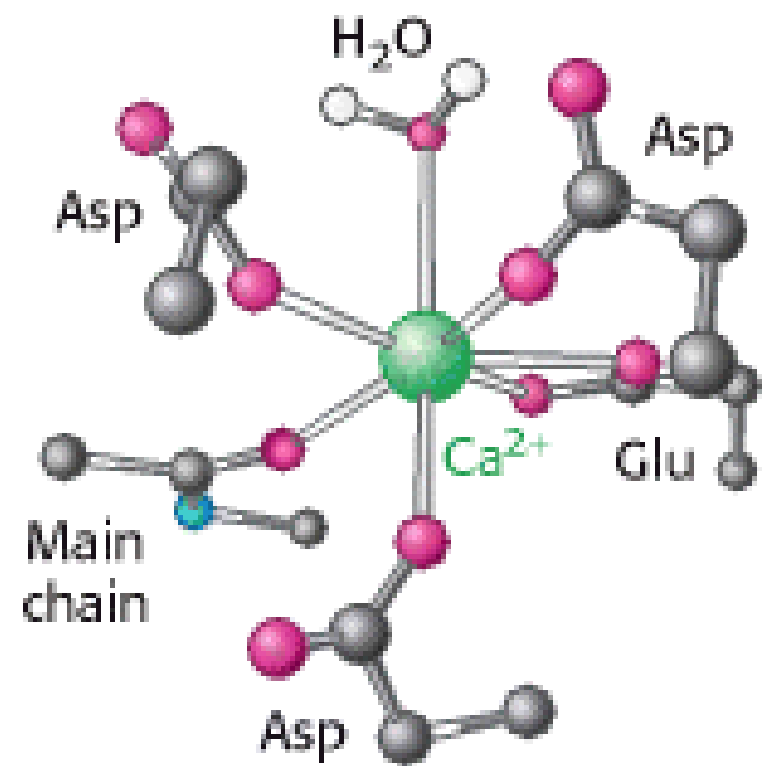
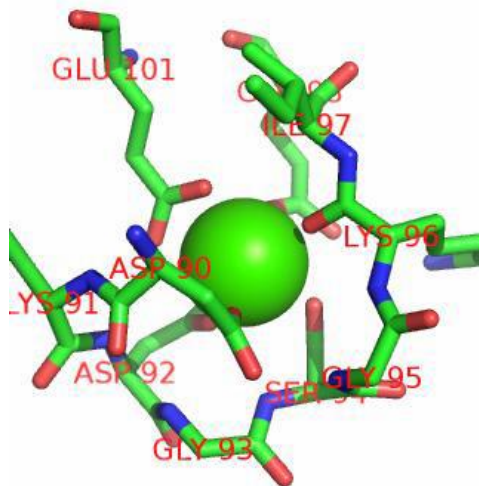
10,000 folds





# Why $\text{Ca}^{2+}$ ?

- Ability to bind protein tightly
- 6-8 bonds with oxygen
- Conformational changes







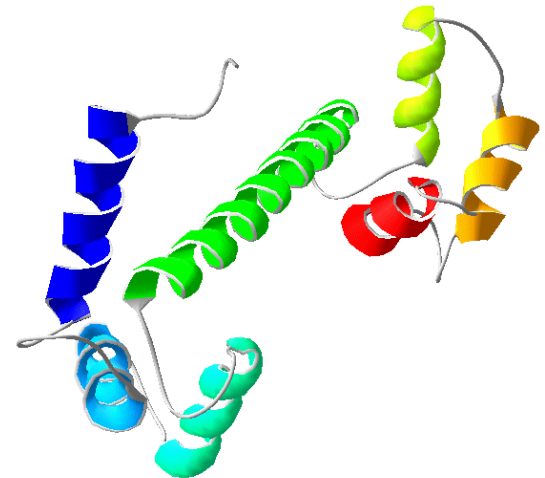
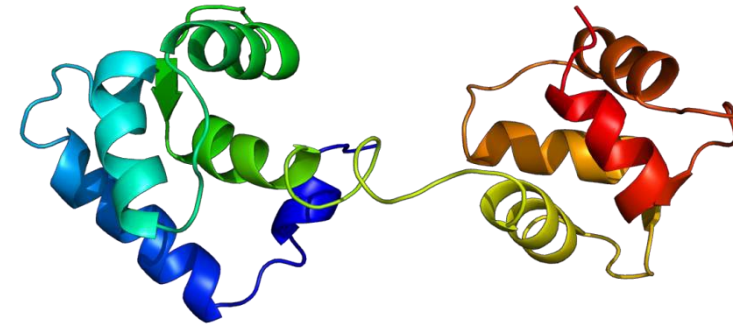
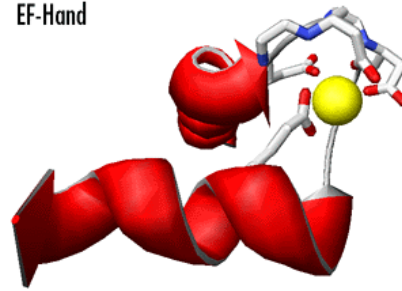
# Calcium Binding Proteins

- Mediate the effects of Calcium ( $\text{Ca}^{+2}$ )
- Many proteins  
Calmodulin, Troponin C, Parvalbumin

- Similar structures

- Rich in Asp and Glu
  - Gln, Asn, Ser
- Several  $\alpha$  helical segments
- Binding site is formed by
  - Helix Loop Helix
    - Super-secondary structure

EF-Hand

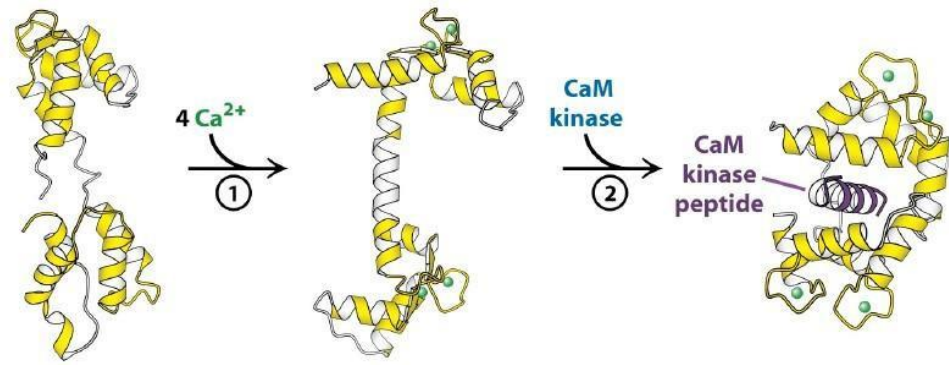




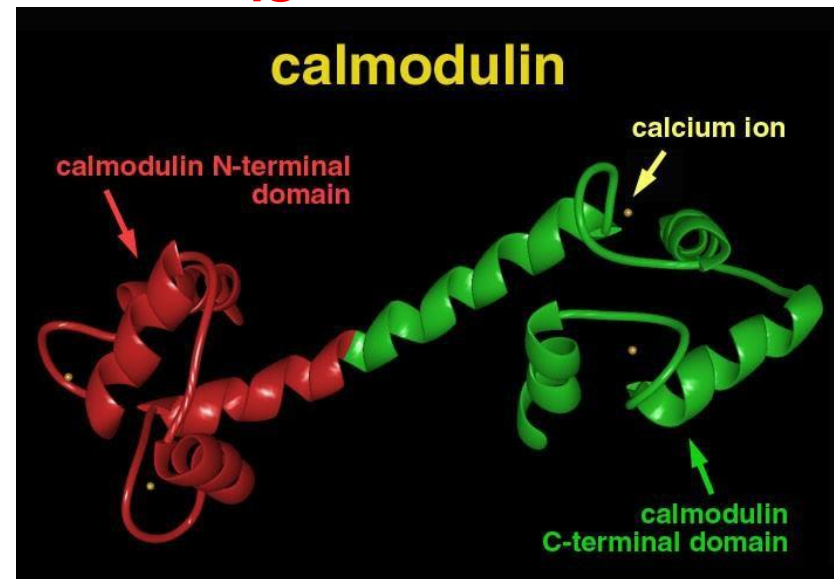
# Calmodulin ( $\approx 17$ kD)

## Calcium-modulated protein

- Found in almost all eukaryotes
- Consists of two globular regions
  - Connected by flexible region
  - Each contains 2 EF hands
  - Four  $\text{Ca}^{2+}$  binding sites
- Calcium-Calmodulin complex can bind to a large number of target proteins including:

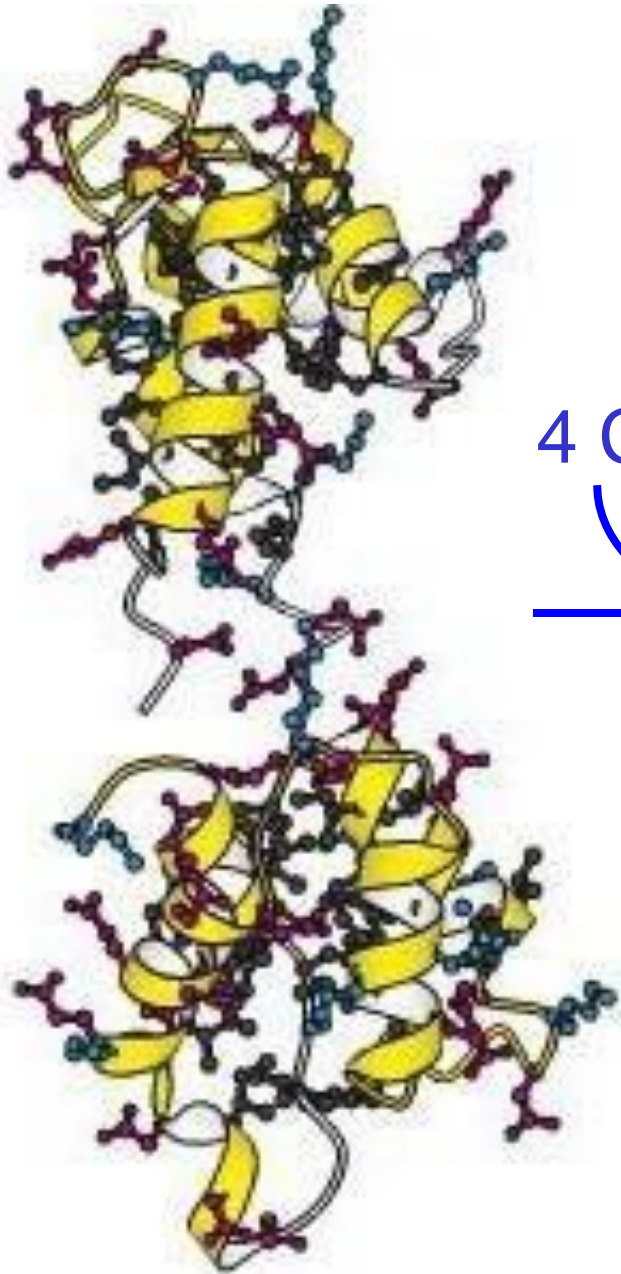


149 amino acids

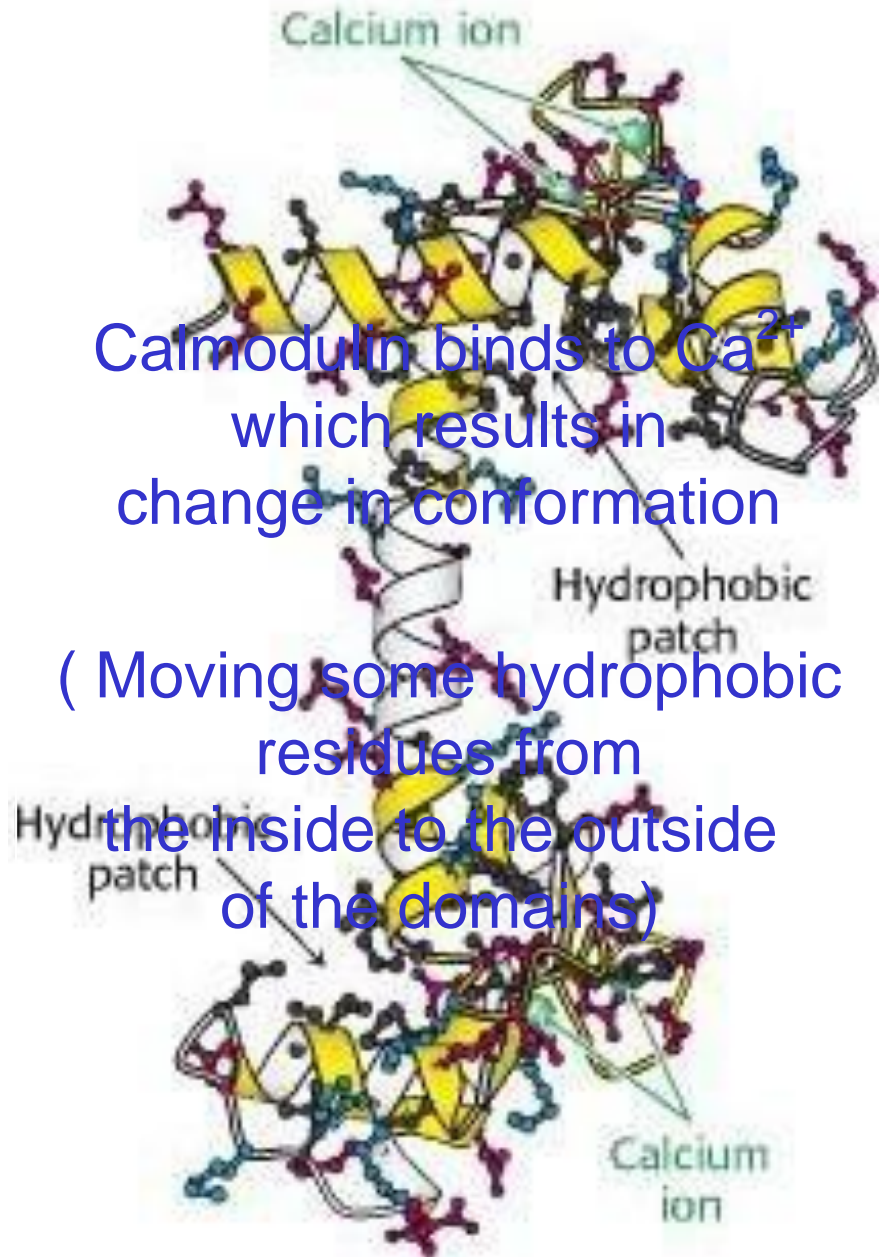
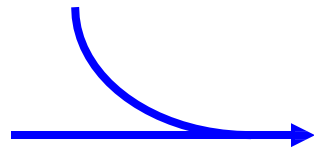


Calmodulin-dependant Protein Kinase

$\text{Ca}^{2+}$  ATP'ase Pump



4  $\text{Ca}^{2+}$



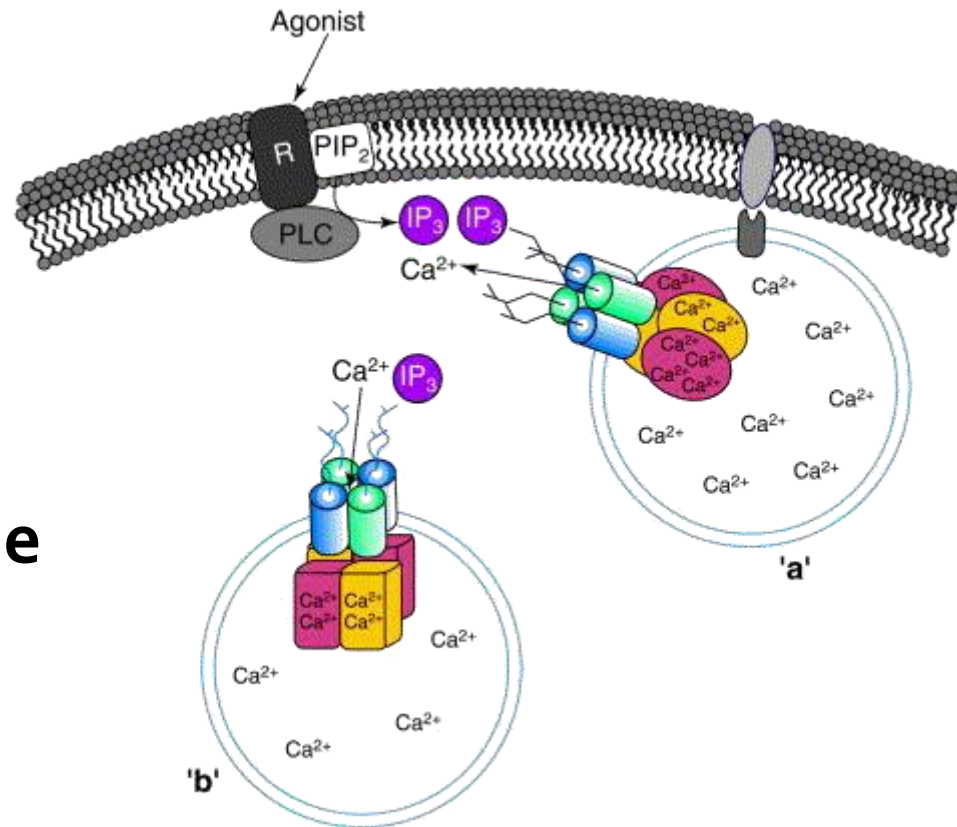
Calmodulin binds to  $\text{Ca}^{2+}$   
which results in  
change in conformation

( Moving some hydrophobic  
residues from  
the inside to the outside  
of the domains)



# Ca<sup>2+</sup> Transporter

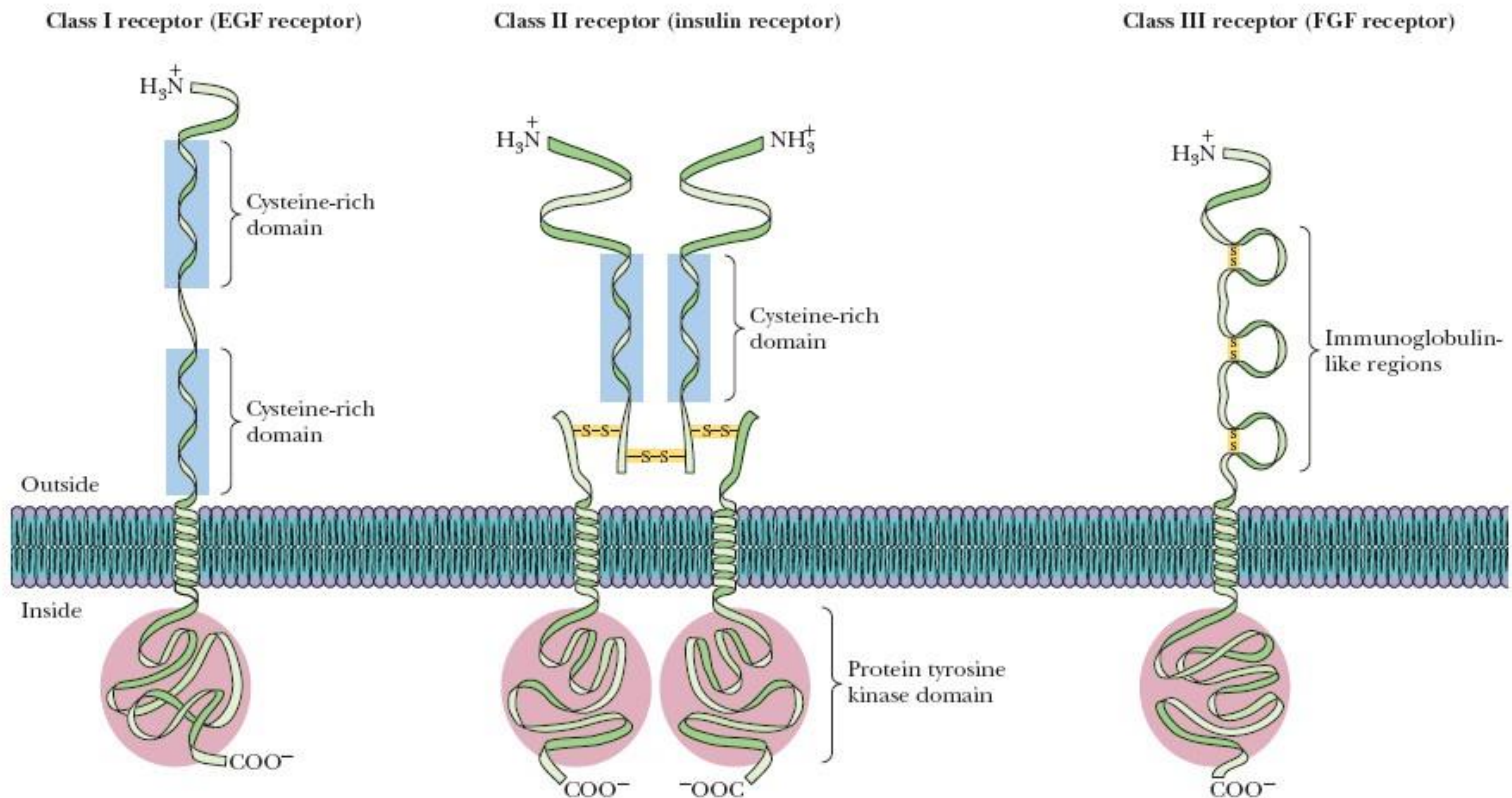
- In sarcoplasmic reticulum
  - 80% of the membrane proteins
  - 10 membrane spanning helices
  - Ca<sup>2+</sup> move against a large concentration gradient
  - 2 Ca<sup>2+</sup> / ATP (high)
    - Depletion of ATP leads to tetany, Rigor mortis





# Receptor Tyrosine Kinases Cascade

- Second Messengers
- Span the membrane, several subclasses (class II, Insulin R), hormone receptor & tyrosine kinase portion



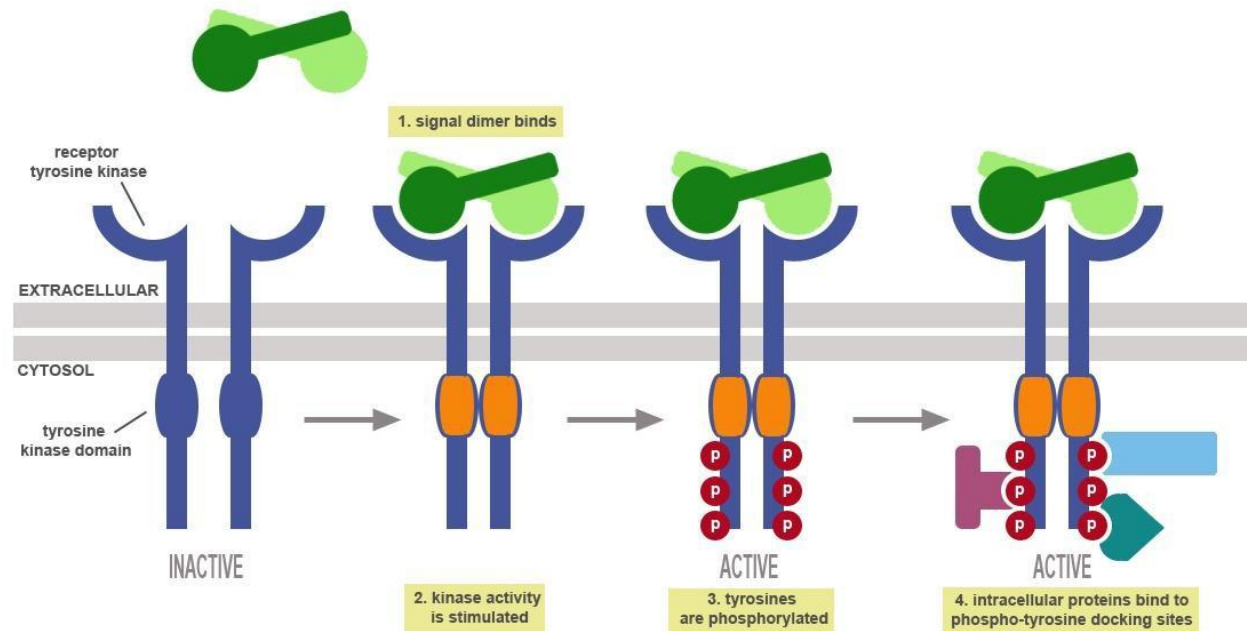


# Second Messengers

## Receptor Tyrosine Kinases

- When activated (**dimer**) → tyrosines on target proteins:
  - Alterations in membrane transport of ions & amino acids & the transcription of certain genes
  - **Dimerization is necessary but not sufficient for activation (kinase activity)**

- **Phospholipase C** is one of the targets
- Insulin-sensitive protein kinase: activates **protein phosphatase 1**





# Signal Transduction through Tyrosine Kinase

**Growth hormones:**

- ✓ Epidermal Growth Factor
- ✓ Platelet-derived growth Factor
- ✓ GH
- ✓ Insulin

Hormone Binding



Dimerization of the receptor



Auto phosphorylation of the receptor



Phosphorylation of the target proteins

# Growth Hormone dimerization

Binding of one molecule of growth hormone



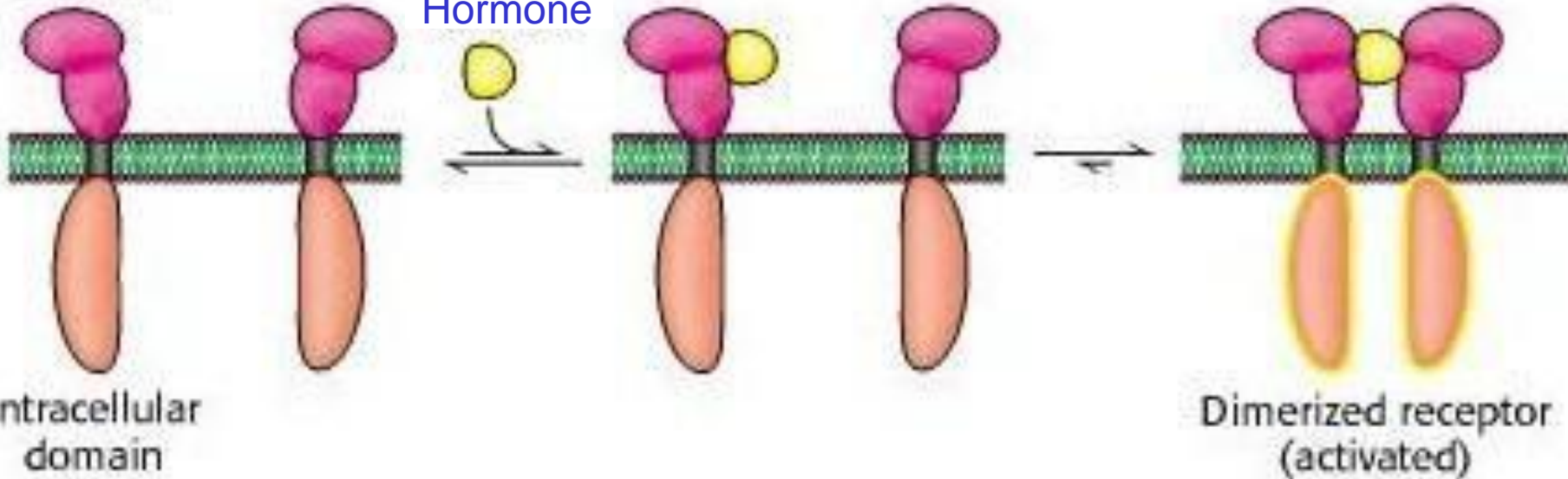
Dimerization of the receptor

(B)

Extracellular domain

Growth Hormone

Intracellular domain





# Janus

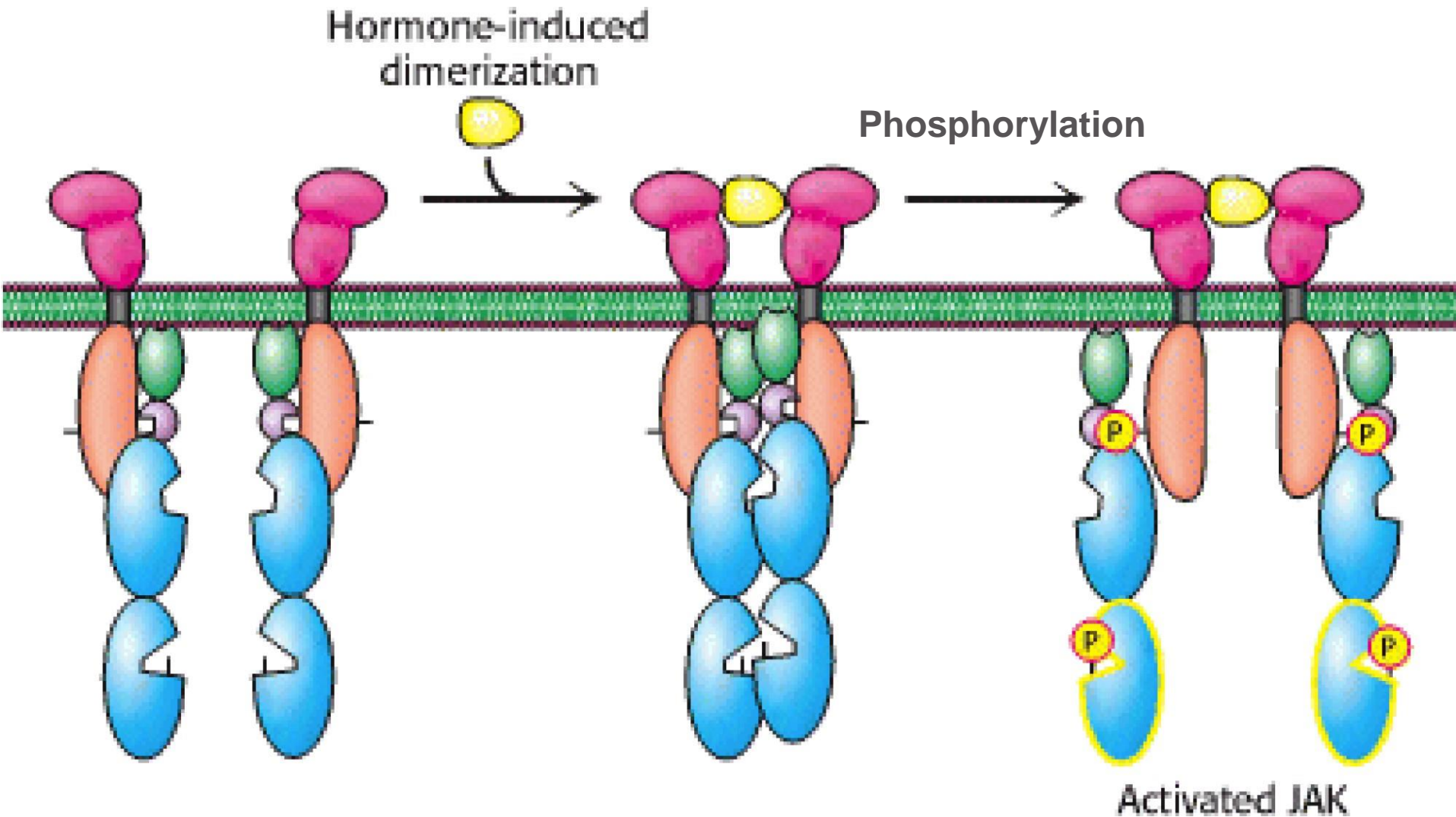
Each Intracellular Domain is associated with a protein kinase called Janus Kinase



Interaction with membrane

Binds peptides that contain Phosphotyrosine

Receptor dimerization brings two JAKs together  
Each Phosphorylates key residues on the other

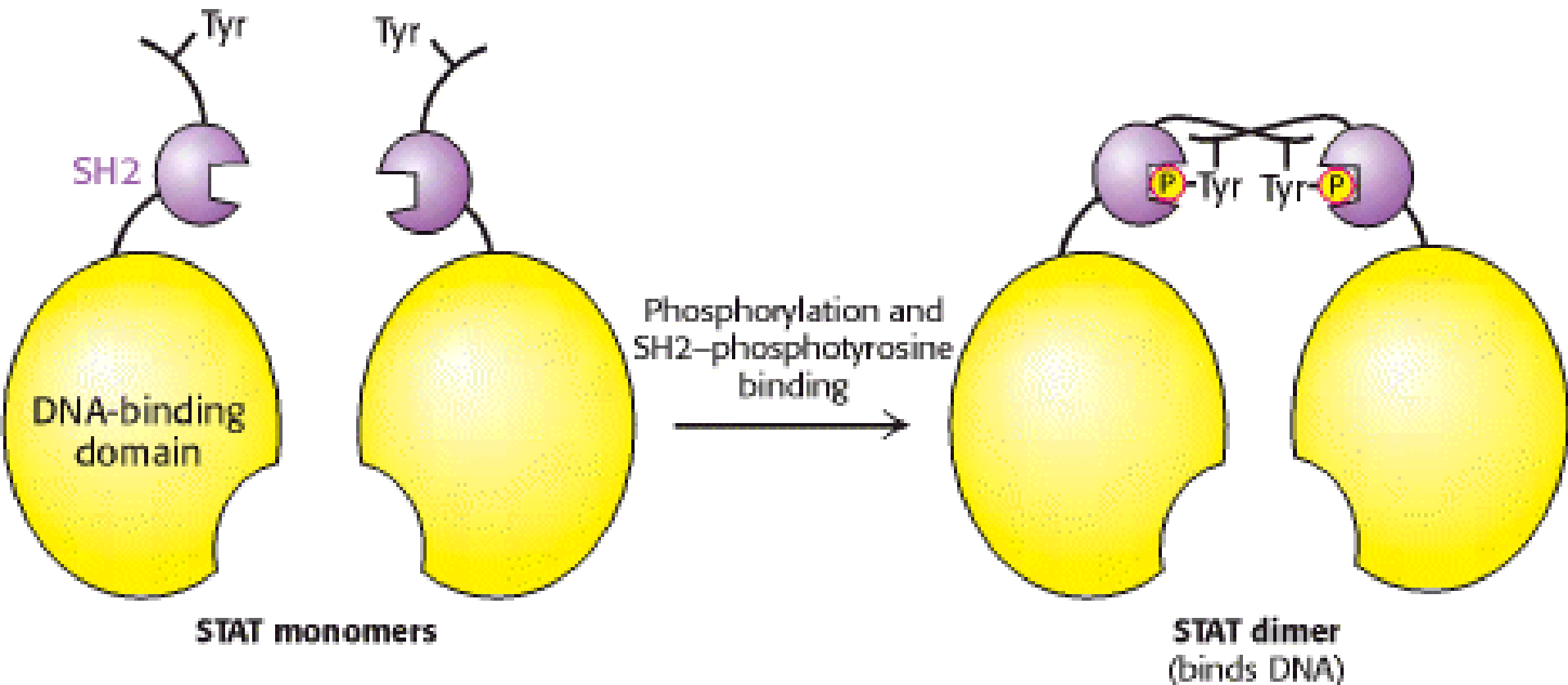


# Activated JAK 2 can Phosphorylate other substrates

- **STAT**
  - Signal Transducers & Activators of Transcription
- Regulator of transcription
- STAT Phosphorylation
  - ➔ **Dimerization**
    - ➔ Binding to specific DNA sites
- If JAK2 remains active it will produce **Cancer**

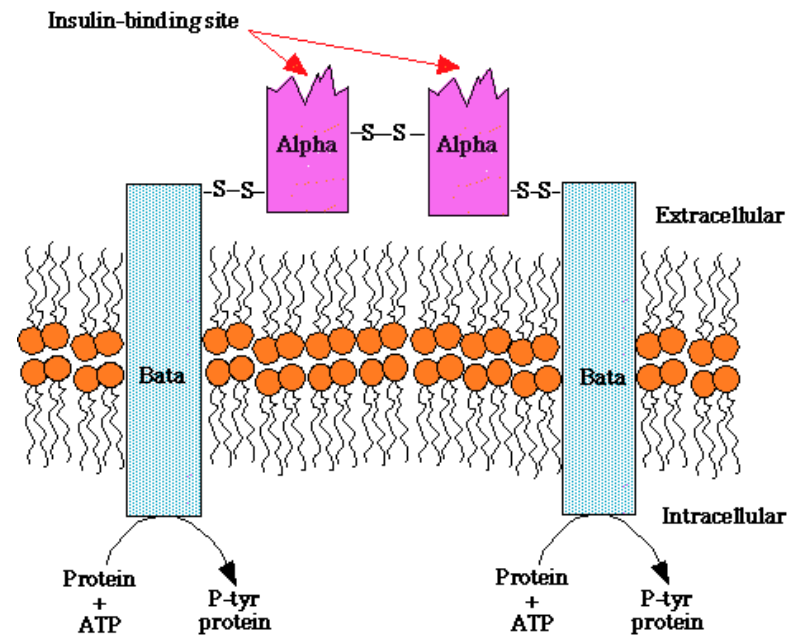
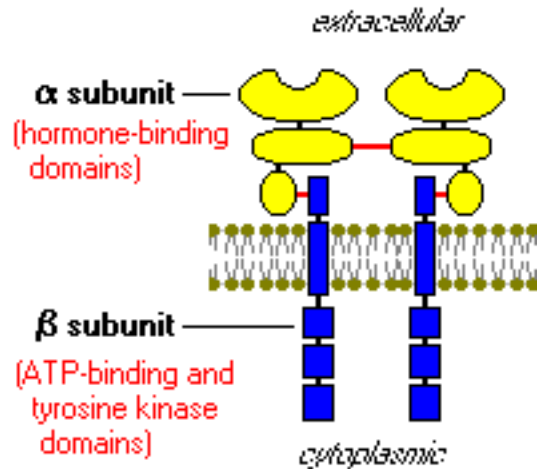
STAT is phosphorylated on a tyrosine residue near the carboxyl terminus

Phosphorylated tyr binds to SH2 domain of another STAT molecule



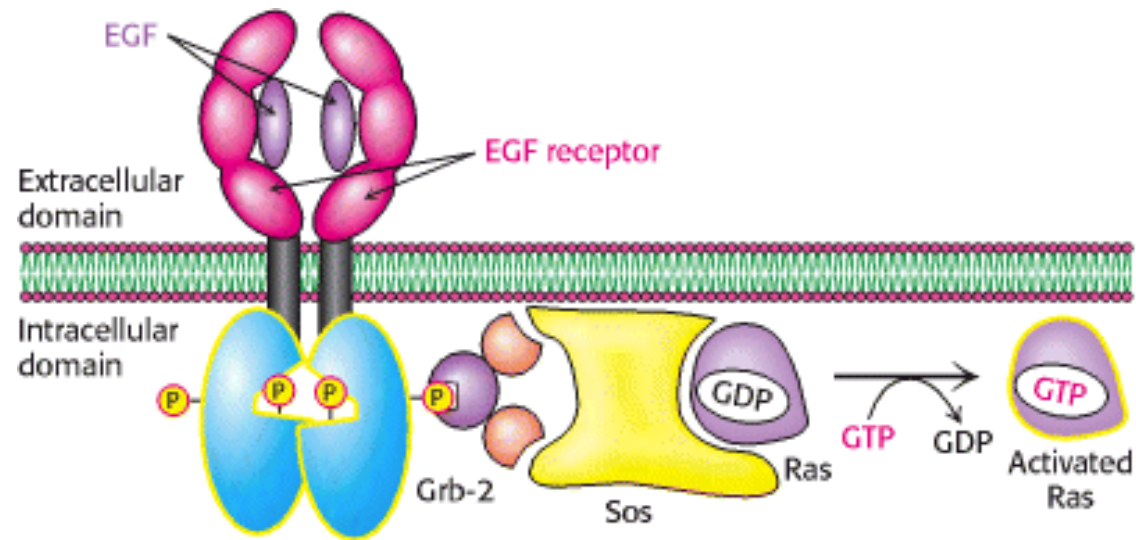
# Tyrosine Kinase & other Hormones

- Insulin Receptor
- Tetramer ( $2^{\alpha}$ ;  $2^{\beta}$ ), dimer ( $2^{\alpha\beta}$  pairs)
- Disulfide bridges
- Insulin Binding  $\rightarrow$  Activation of the Kinase



# Ras is a member of small G proteins family

- Monomeric
- 2 forms: GDP  $\leftrightarrow$  GTP
- Smaller (1 subunit)
- GTPase activity
- Many similarities in structure and mechanism with  $G_{\alpha}$
- Include several groups or subfamilies
- Major role in growth, differentiation, cellular transport, motility etc...



# Impaired $GTP_{ase}$ activity can lead to cancer in human

- Mammalian cells contain 3 different Ras proteins

Mutation →

Loss of ability to hydrolyze GTP → Ras

is locked in "ON" position →

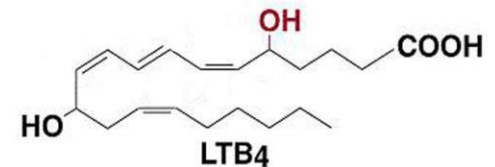
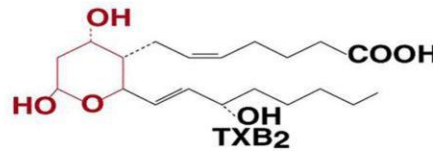
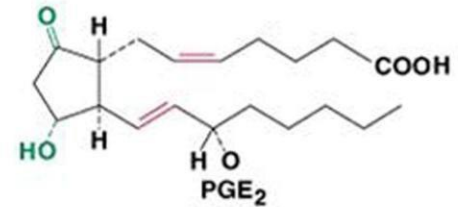
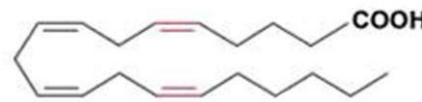
continuous growth stimulation

# Eicosanoids

- 20 carbon signaling molecules

- Several Classes:

- Prostaglandins
- Thromboxanes
- Leukotrienes



- Produced In Almost all Tissues
- Wide Range of Responses
- Local Hormones (autocrine & paracrine)
- Very Potent (very low conc.)
- Short Half Life
- Not Stored



# Some Functions of the Prostaglandins and Thromboxanes

- What 2 stands for?

- PGI<sub>2</sub>, PGE<sub>2</sub>, PGD<sub>2</sub>

- Increase
  - Vasodilation, cAMP
- Decrease
  - Platelet Aggregation
  - Lymphocyte Migration
  - Leucocyte Aggregation

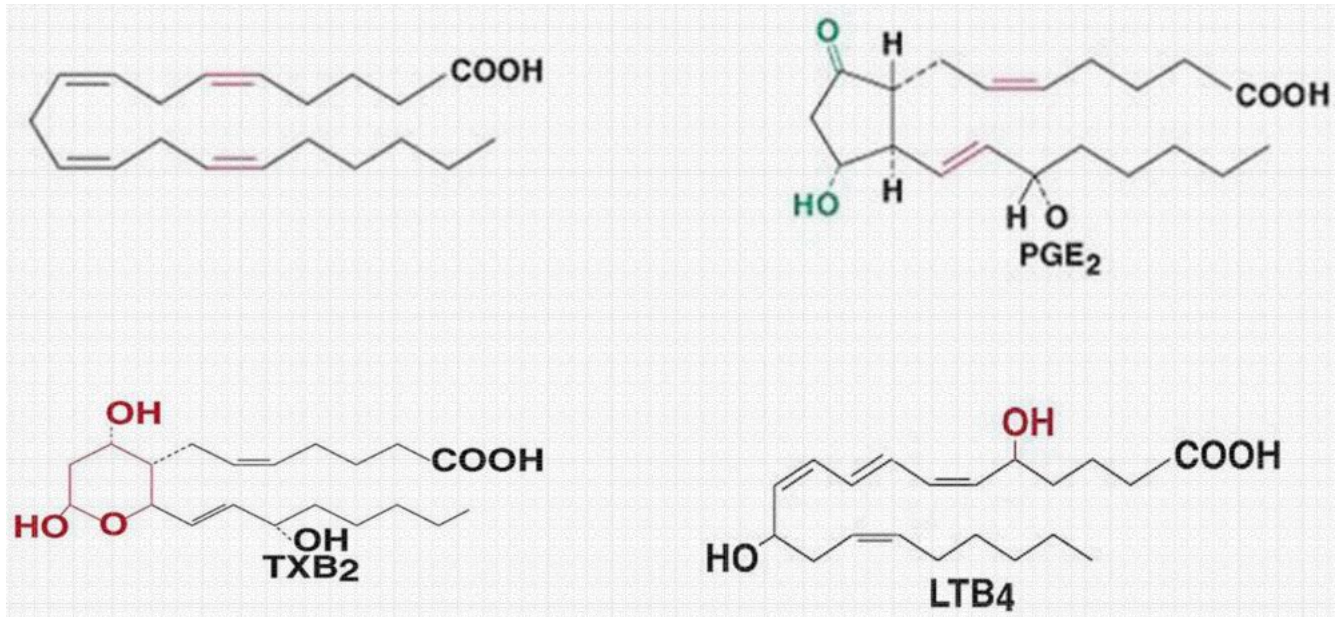
- PGF<sub>2</sub>α Increases

- Vasoconstriction
- Bronchoconstriction
- Smooth Muscle Contraction

- Thromboxanes Increases

- Vasoconstriction
- Platelet Aggregation
- Lymphocyte Proliferation
- Bronchoconstriction

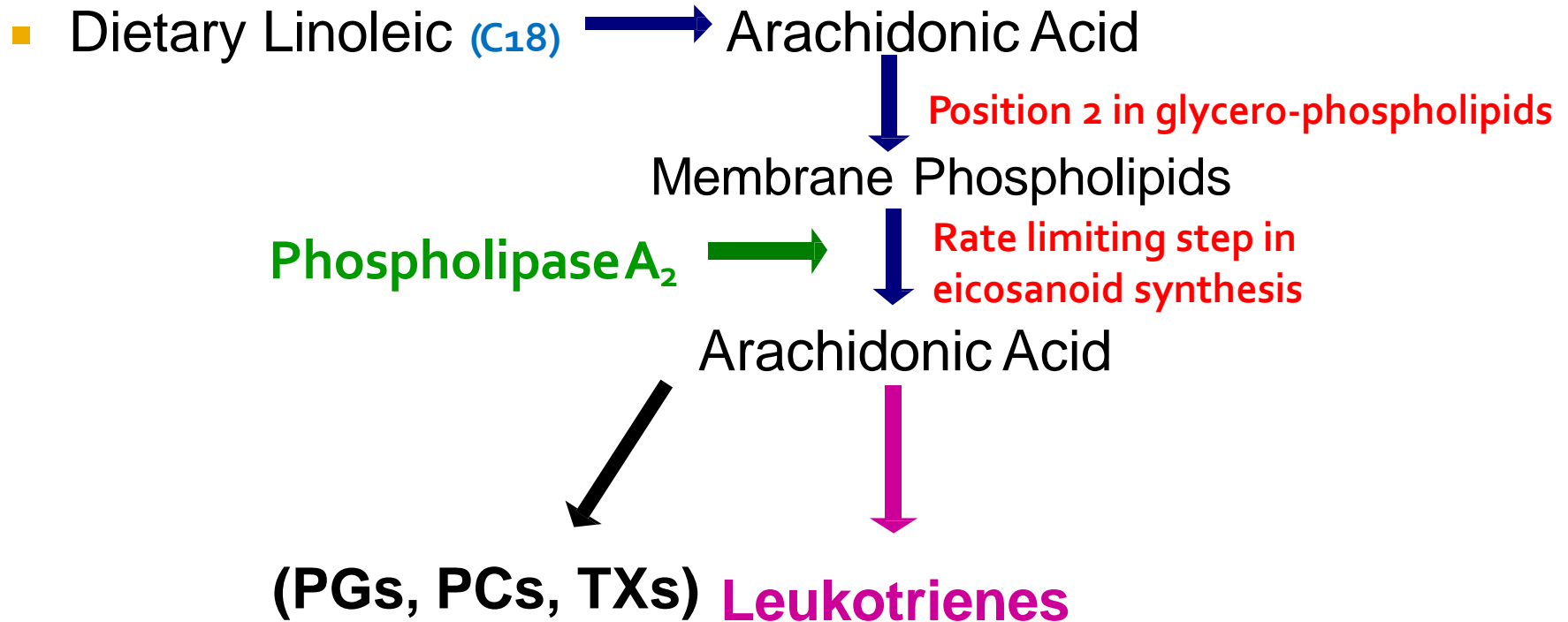
# Eicosanoids Structure



- Arachidonic acid (20, 4, no ring)
- Prostaglandins (20, 2, 5-ring)
- Thromboxanes (20, 2, 6-ring, oxygen)
- leukotrienes (20, 3 conjugated, no ring)

# Eicosanoids Synthesis

Elongation & further desaturation



# Synthesis and Degradation of Hormones

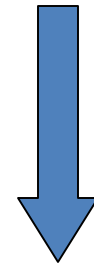
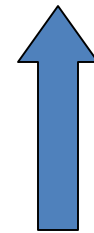
# Chemistry of Hormones

- **Steroids**
- Small molecules - NO
- Amino acid derivatives
  - Thyroid hormones

---

- Catecholamines
- Proteins and peptides
- FA derivatives - eicosanoids

Receptor inside the cell



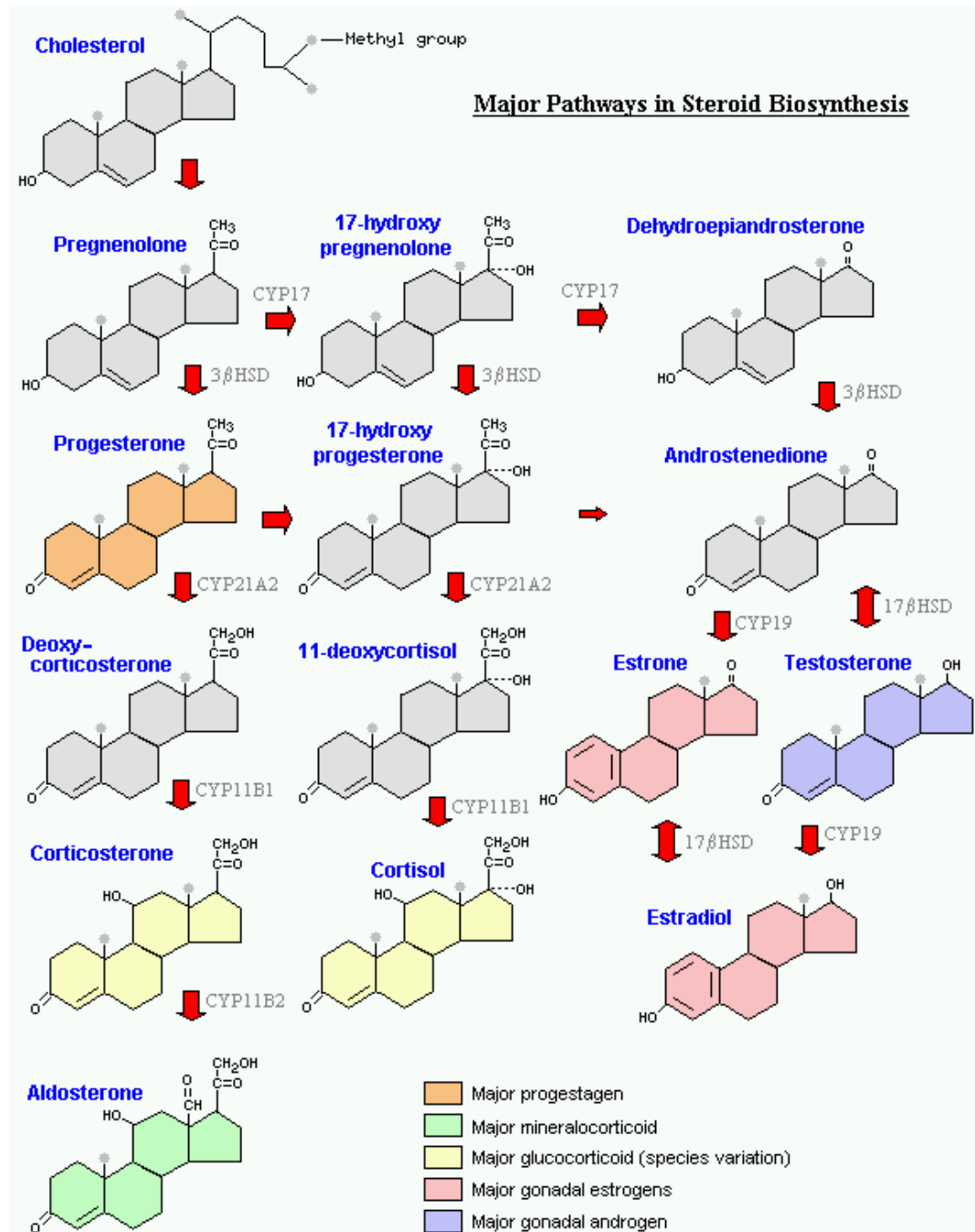
Surface receptor

# Steroid hormone synthesis

- C21:

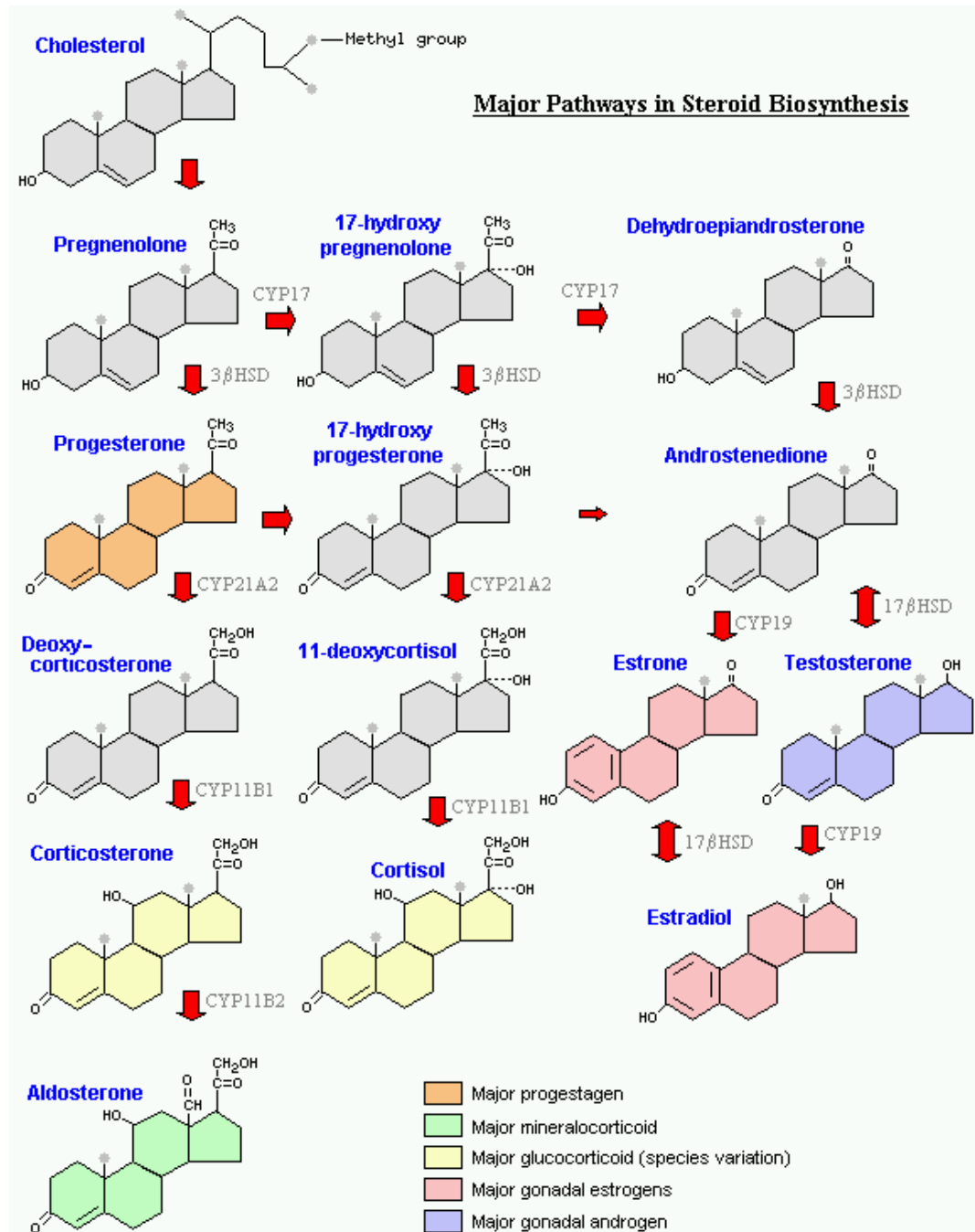
- Progesterone: directly from pregnenolone

- Cortisol & Aldosterone: from progesterone



# Steroid hormone synthesis

- C19
  - Testosterone
  - from progesterone or pregnenolone
  - 2c shortage
- C18 (estrogen):
  - Aromatase
  - Cleaves C18
  - Reduction



# Steroid hormone breakdown

- Steran core cannot be cleaved
- In the liver: hydroxylation and conjugation with glucuronides or sulphates
- Urinary excretion:
  - Of metabolites
  - Of unchanged hormones



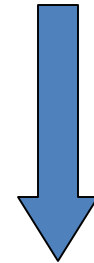
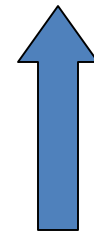
# Chemistry of Hormones

- Steroids
- **Small molecules - NO**
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  - Thyroid hormones

---

- Catecholamines
- Proteins and peptides
- FA derivatives - eicosanoids

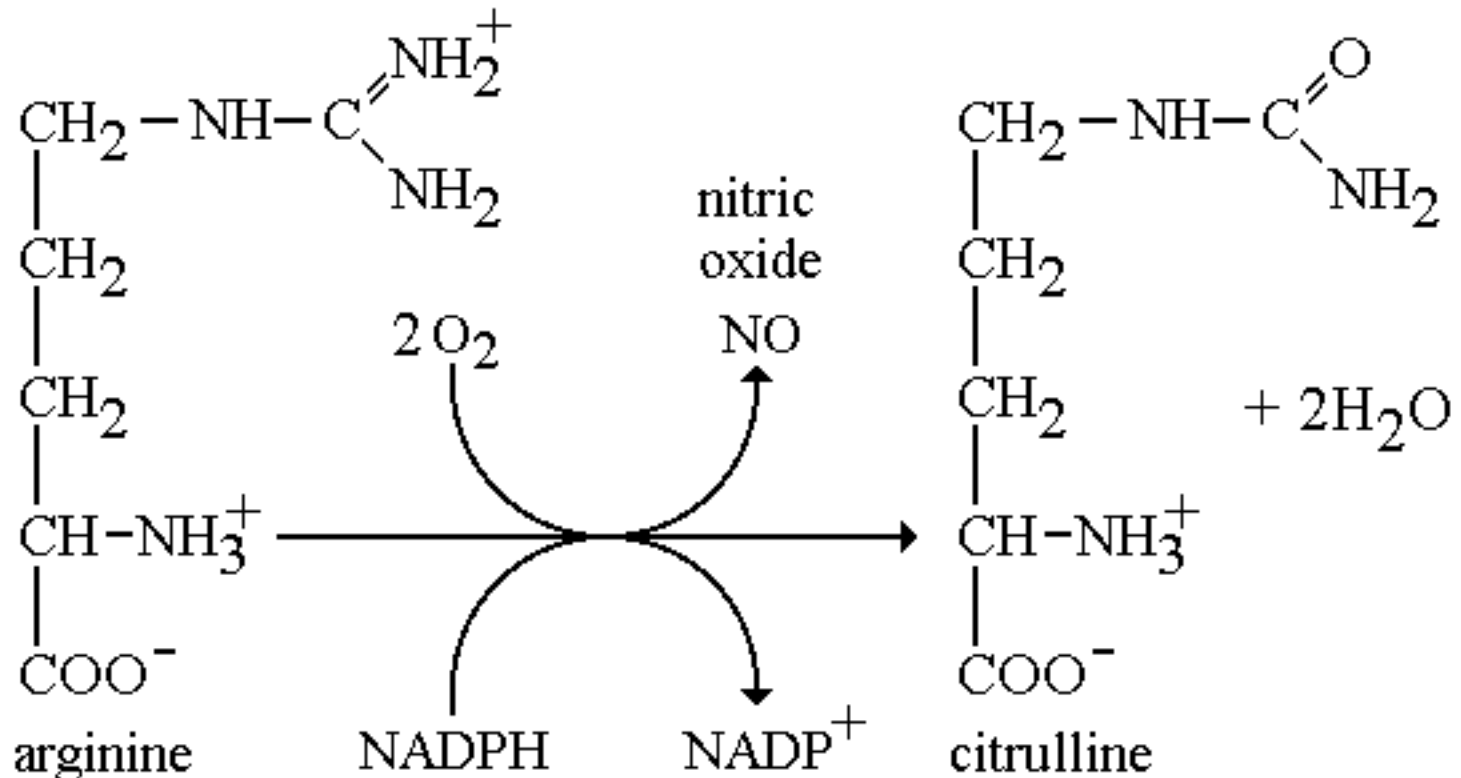
Receptor inside the cell



Surface receptor

# Nitric oxide (NO)

- NO: synthesized by NO-synthase



# Nitric oxide synthase isozymes

- NO-synthase (NOS)
  - In neurons (NOS-I): neurotransmission
  - In macrophages (NOS-II): kills bacteria
  - Endothelial (NOS-III): smooth muscle → cGMP → vasodilation
- Clinical correlation:
  - Nitrates in the treatment of angina
  - Refractory hypotension during septic shock

# Chemistry of Hormones

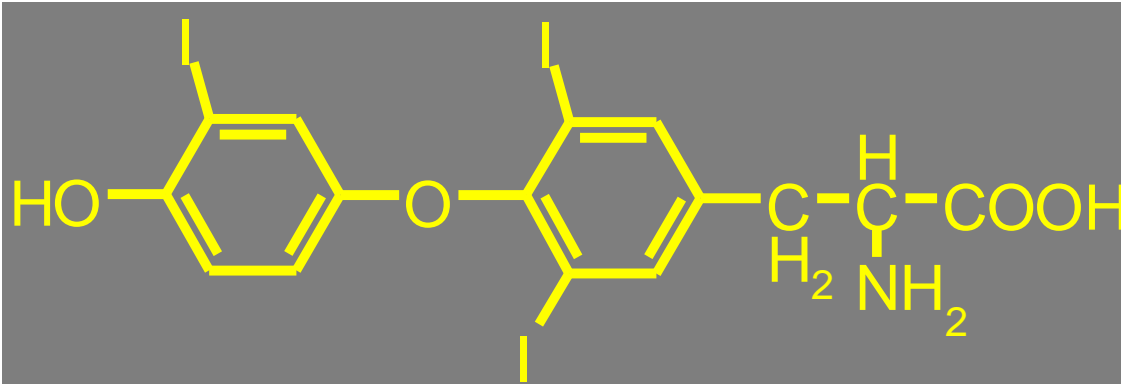
- Steroids
- Small molecules - NO
- **Amino acid derivatives**
  - Thyroid hormones
  - Catecholamines
- Proteins and peptides
- FA derivatives - eicosanoids

Receptor inside the cell

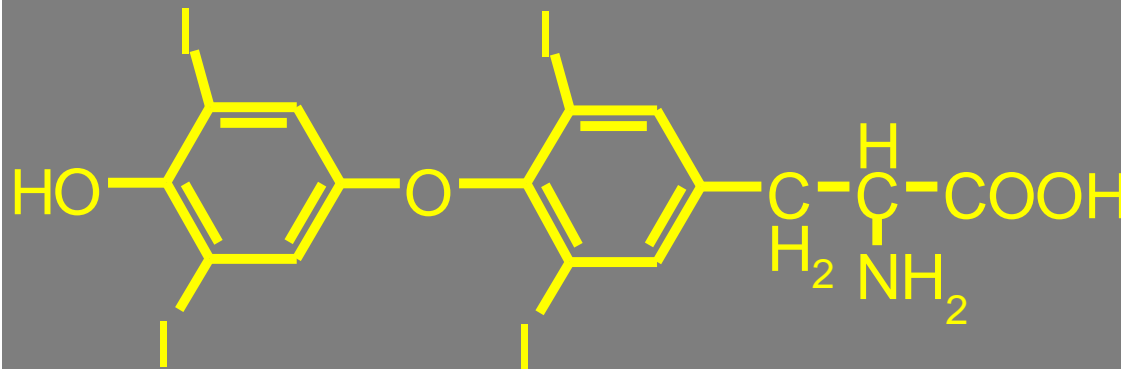


Surface receptor

# Thyroid hormones



**Triiodothyronine (T3)**

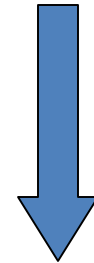
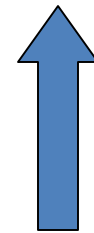


**Thyroxine (T4)**

# Chemistry of Hormones

- Steroids
  - Small molecules - NO
  - Amino acid derivatives
    - Thyroid hormones
- 
- **Catecholamines**
  - Proteins and peptides
  - FA derivatives - eicosanoids

Receptor inside the cell

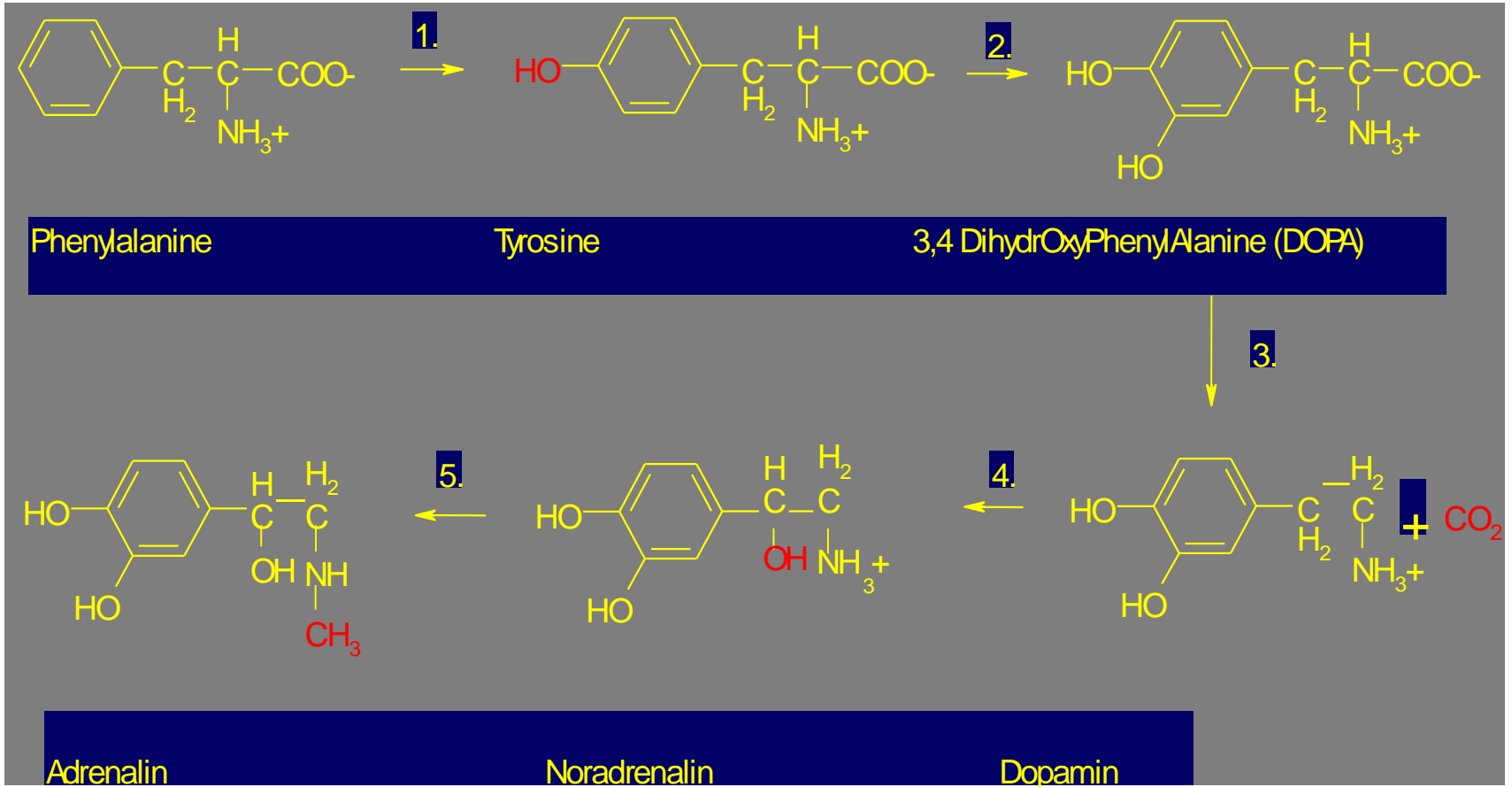


Surface receptor

# Catecholamine synthesis

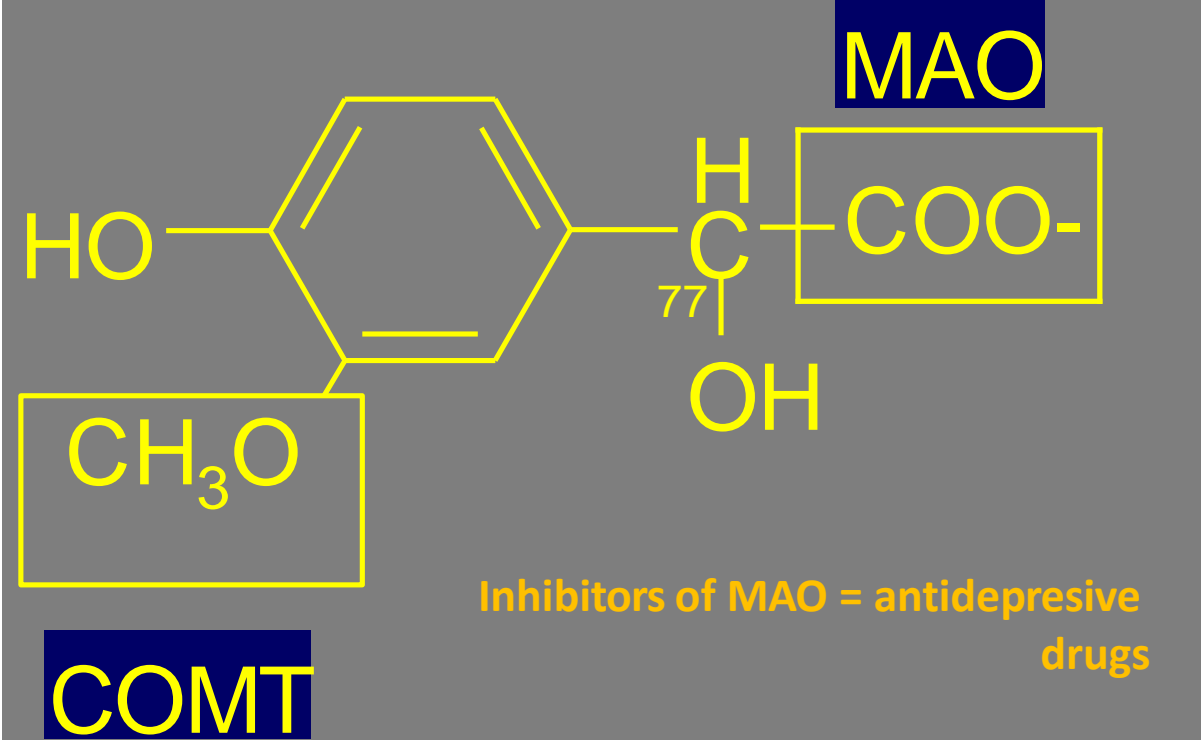
- Substrate = Phe or Tyr
- Synthesis located in: adrenal medulla, nerve tissue
- Products:
  - Dopamine, adrenaline (hormones)
  - Noradrenaline (neurotransmitter)

# Catecholamine synthesis





# Catecholamine breakdown



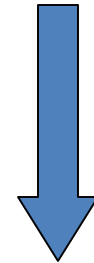
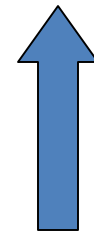
# Chemistry of Hormones

- Steroids
- Small molecules - NO
- Amino acid derivatives
  - Thyroid hormones

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- Catecholamines
- **Proteins and peptides**
- FA derivatives - eicosanoids

Receptor inside the cell



Surface receptor

# Protein and peptide hormones

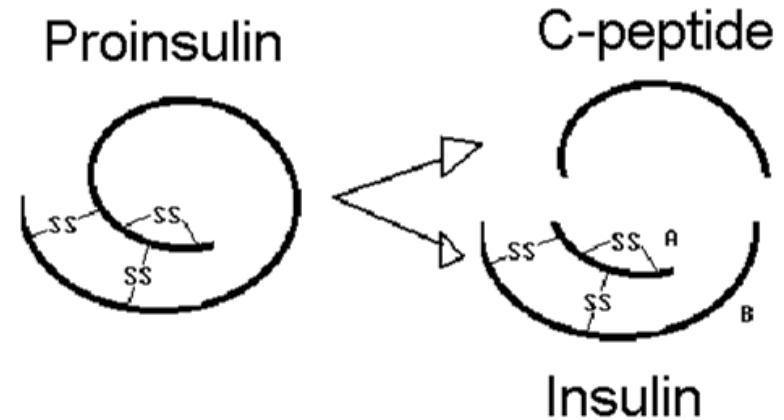
- CNS mediators: neuropeptides, opioids
- Hypothalamic releasing hormones and pituitary peptides
- Insulin and glucagone
- Growth factors: IGF, CSF, EPO

...and many others

# General steps of peptide synthesis

## “Precursor Polypeptides”

- Expression of “pre-pro” protein
- Transport to ER
- Splitting the signaling sequence



- Cleavage to definite peptide(s) and final modification in Golgi
  - Proinsulin to insulin
  - Proopiomelanocortine (POMC) to MSH and ACTH

# Degradation of peptide hormones

- Lysosomal after endocytosis of complex hormone-receptor
- Chemical modification (liver): rearrangement of S-S bridges, cleavage
- Renal excretion of small peptides