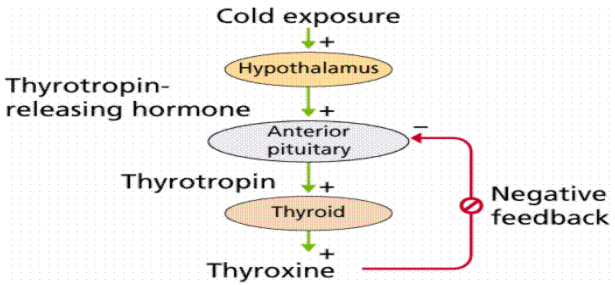

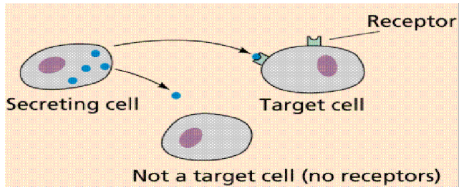

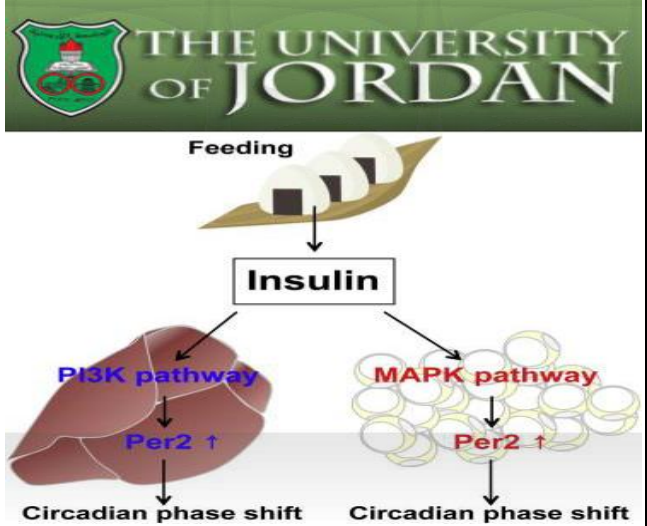

ENDOCRINE BIOCHEMISTRY

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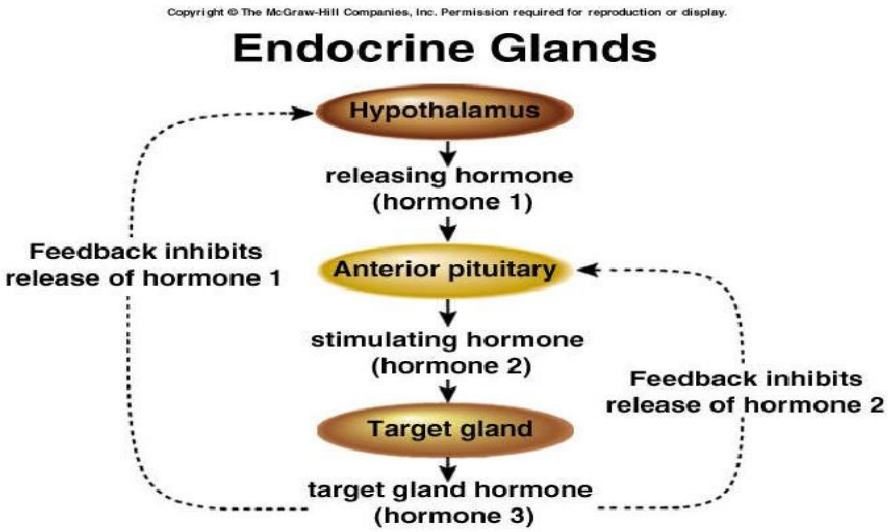
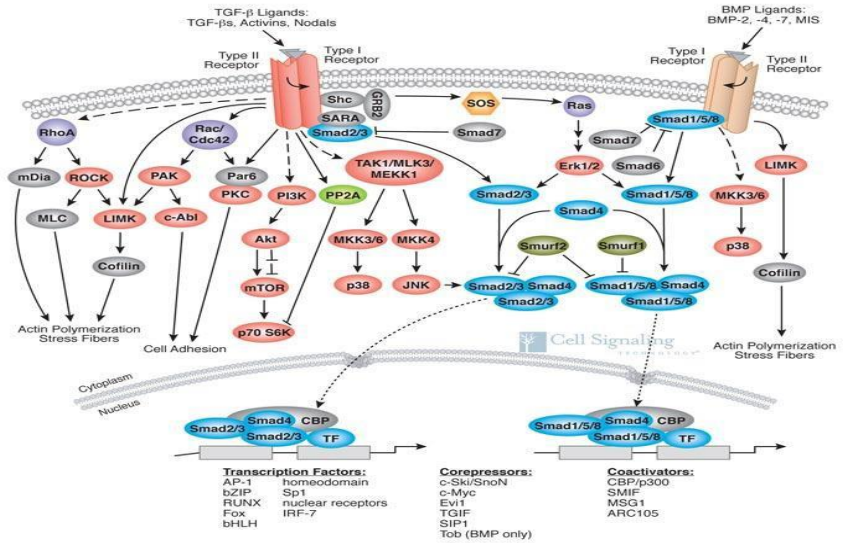
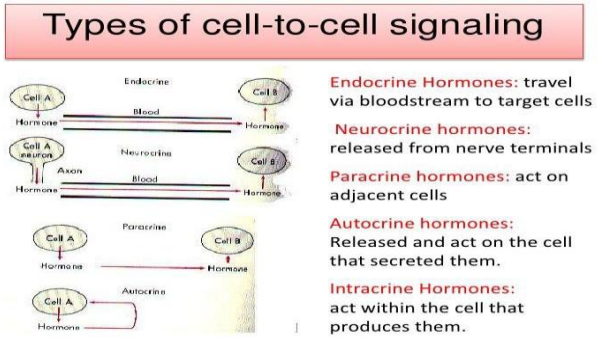
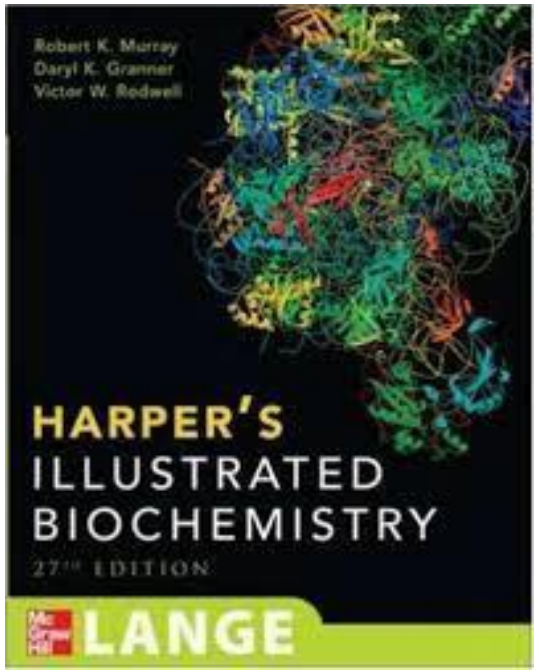


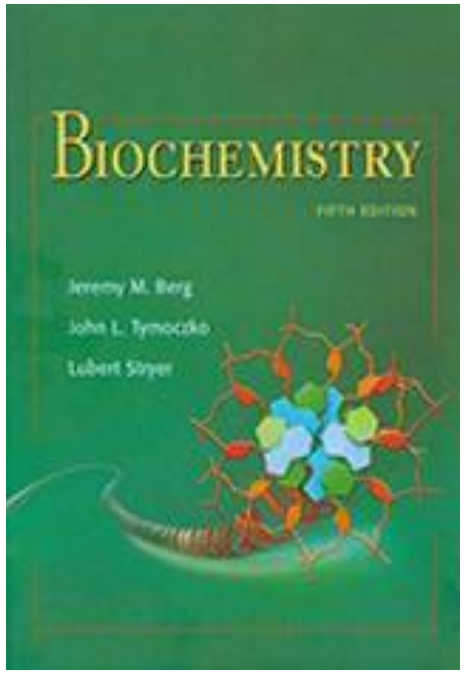


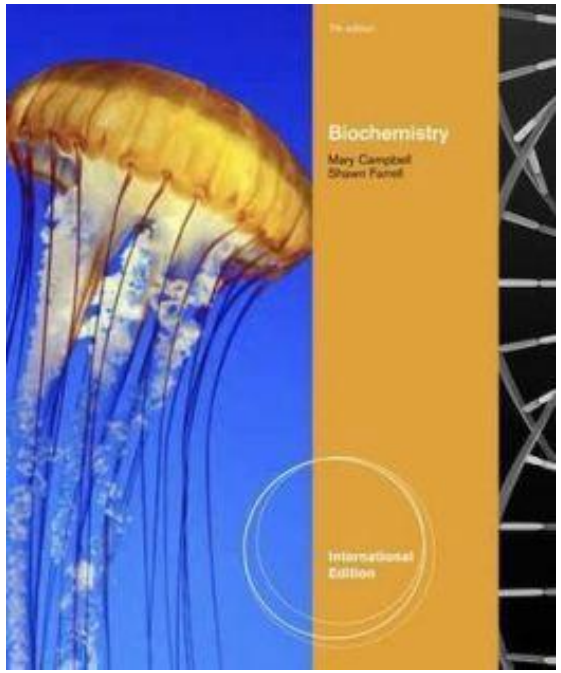


RESOURCES

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





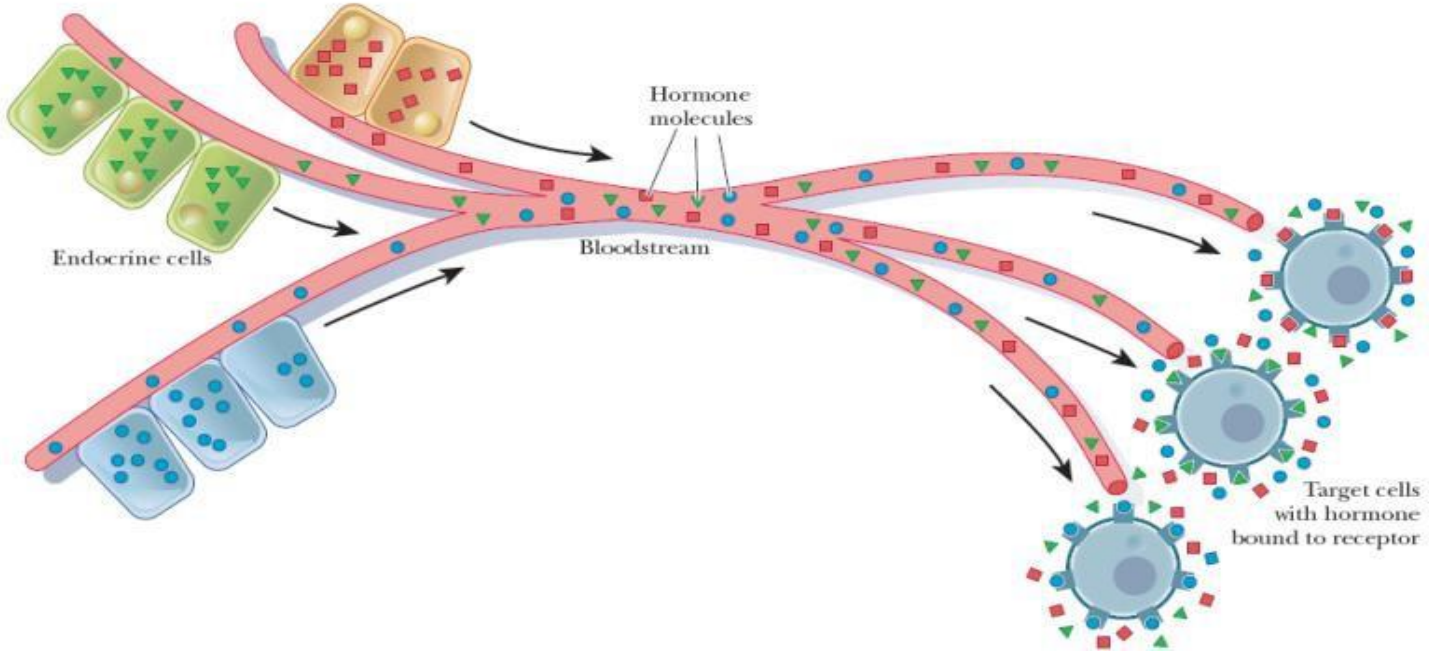


WHAT SHOULD WE COVER?

- ❑ Definitions
- ❑ The major challenge
- ❑ The target cell concept
- ❑ Regulation
- ❑ Classification
- ❑ Target cell interactive effects
- ❑ Synthesis and degradation of hormones
- ❑ Signal transduction, cascades, and receptors
- ❑ Eicosanoids (handout)

1. DEFINITIONS

- **What are hormones?**
  - Exocrine vs. endocrine
  - Organic, blood, low amounts, source & target
  - Remote Controllers
  - Hormao (Greek): excite or arouse



DO ALL FIT THE DEFINITION?!

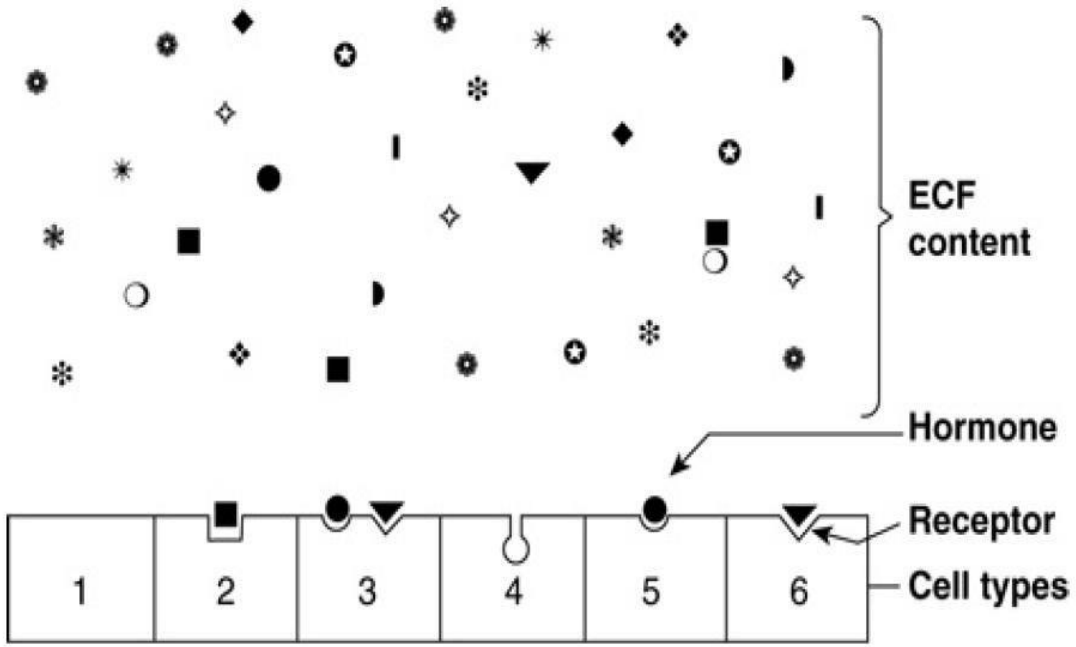
- ❑ Endocrine
- ❑ Paracrine
- ❑ Autocrine
- ❑ Neuroendocrine
- ❑ Intracrine
- ❑ Juxtracrine
- ❑ Phermonal

2. MAJOR CHALLENGE

- **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

2. MAJOR CHALLENGE (CONCENTRATION)

- 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

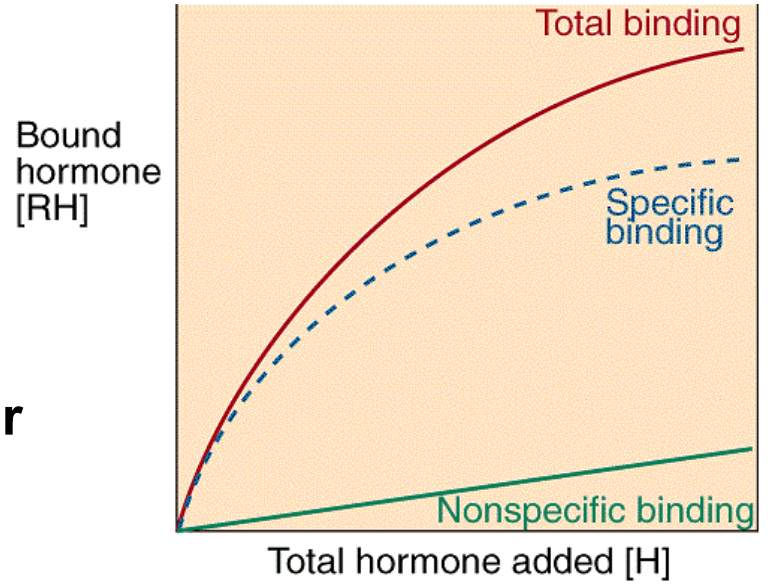


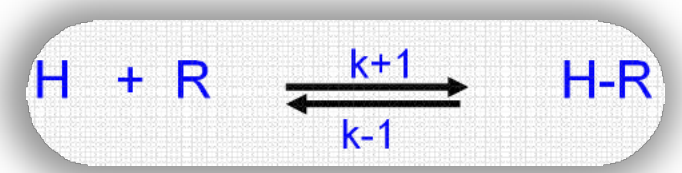
2. MAJOR CHALLENGE (DESENSITIZATION)

- Response fades up upon continuous release!

H-R INTERACTION

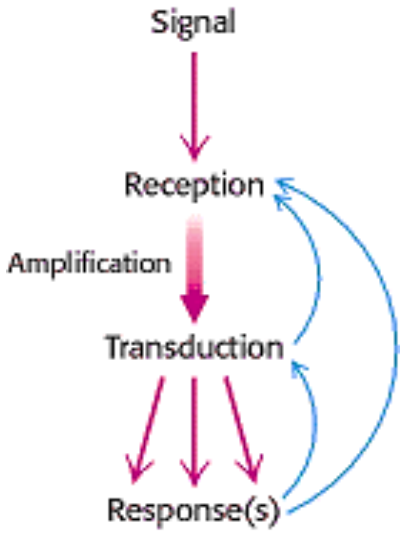
- Should be specific: displaceable by agonist or antagonist
- Should be saturable
- Should occur within the concentration range provided
- Dissociation constant Kd
- Kd = {[H] X [R]} / [H-R]
- 20 X dissociation constant is enough to saturate the receptor
- Kd values for many hormone range from 10^{-9} to 10^{-11} M

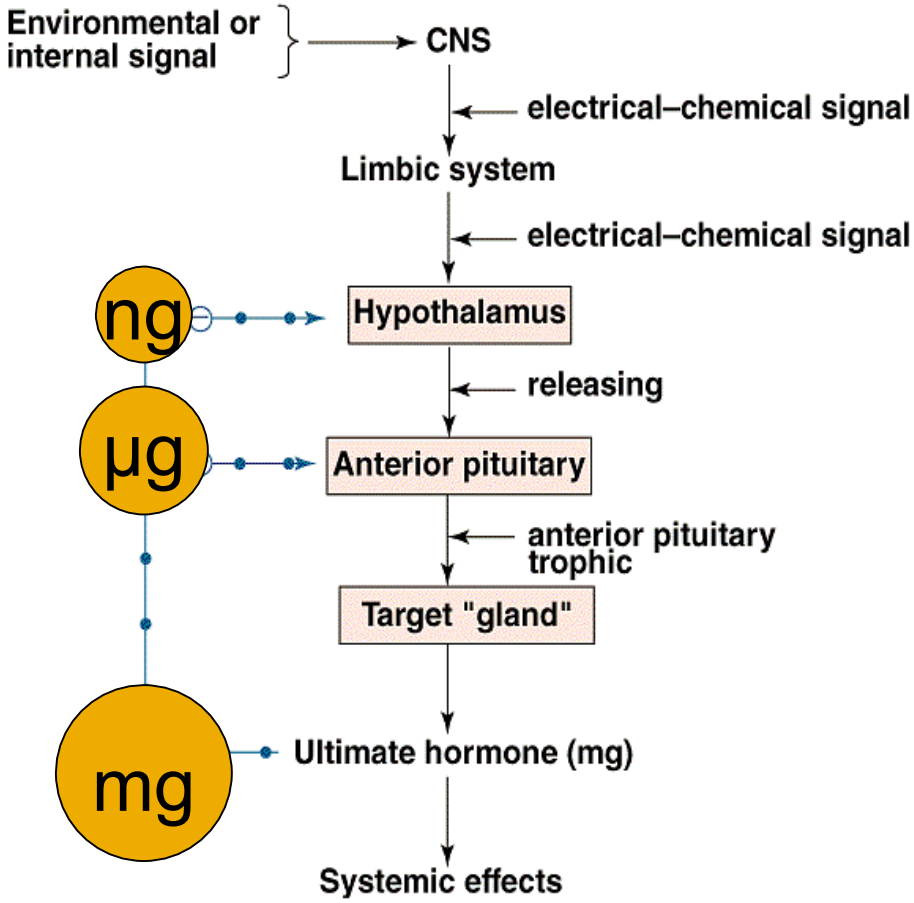


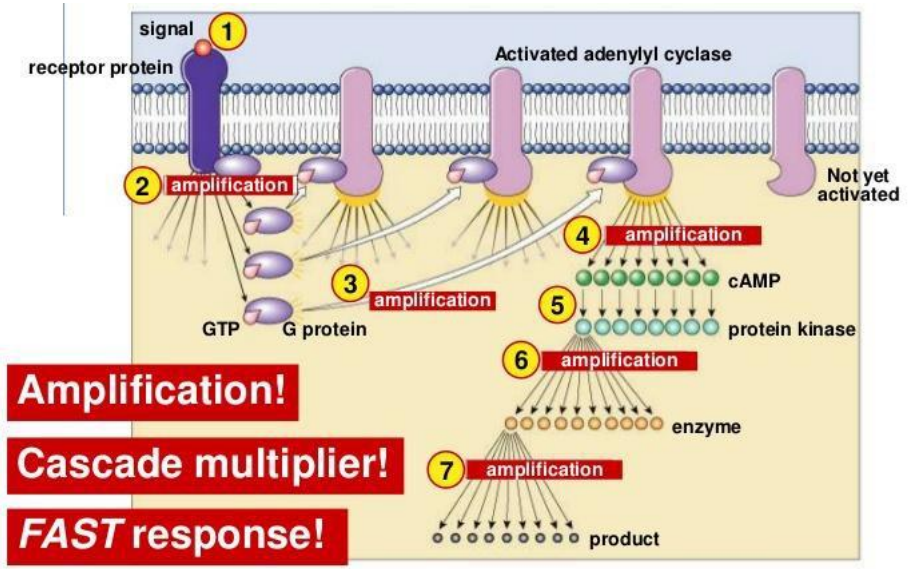


ANOTHER SOLUTION!

- **Signal amplification**



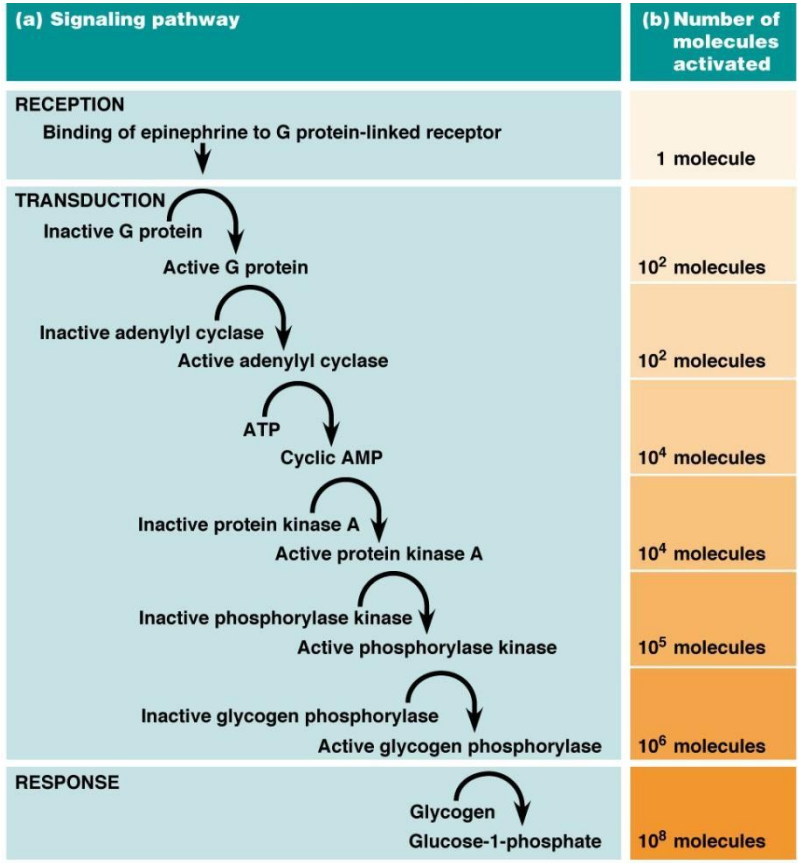




Amplification!

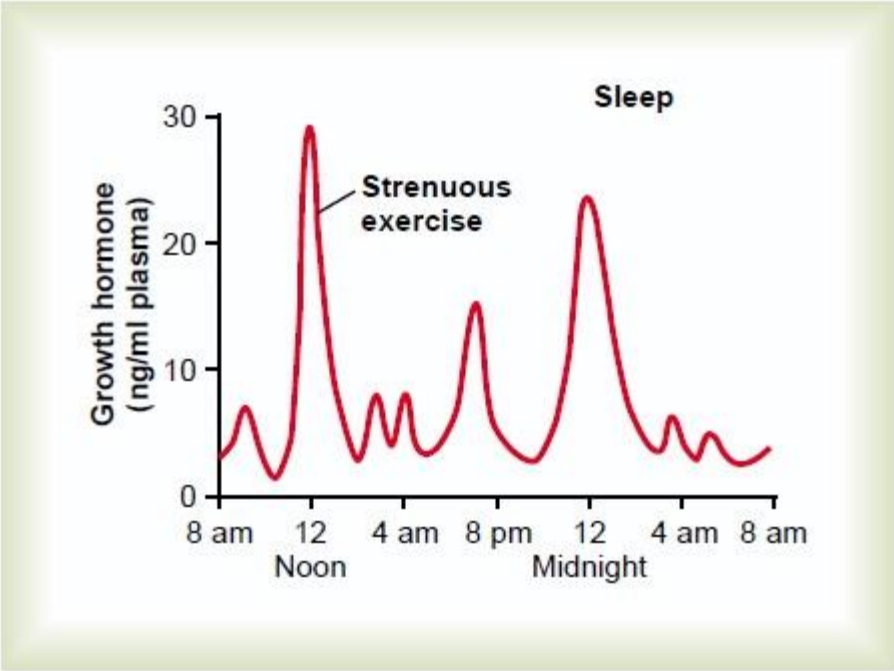
Cascade multiplier!

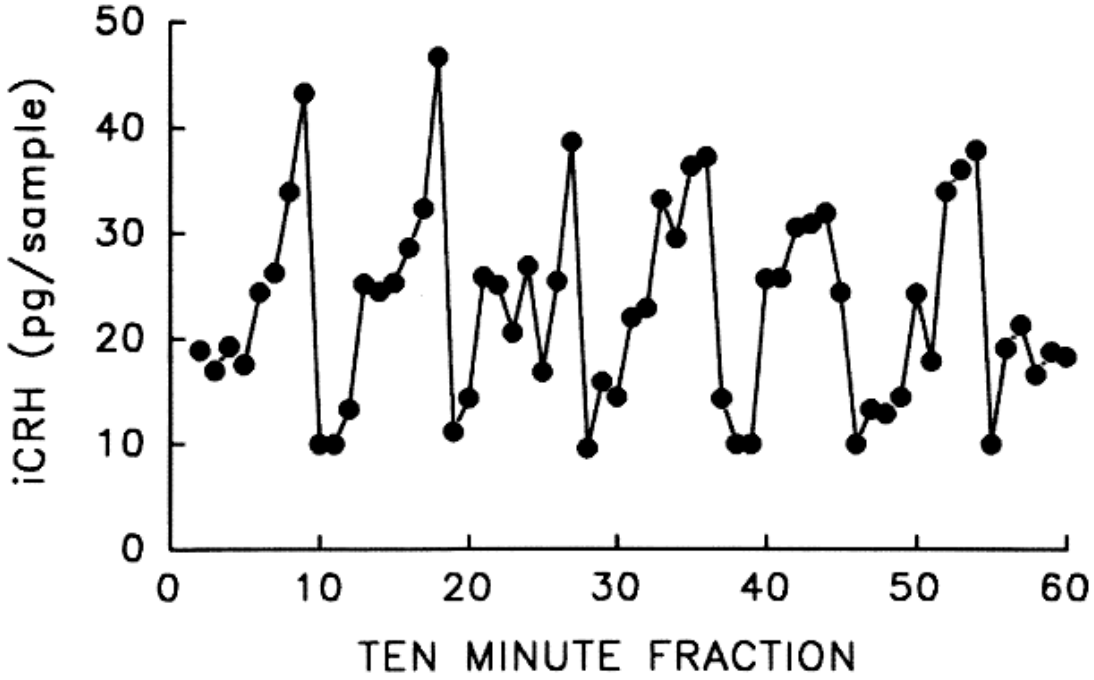
***FAST* response!**



PULSATILE MANNER

- Coordinated with concentration and rate of clearance from plasma





3. THE TARGET CELL CONCEPT

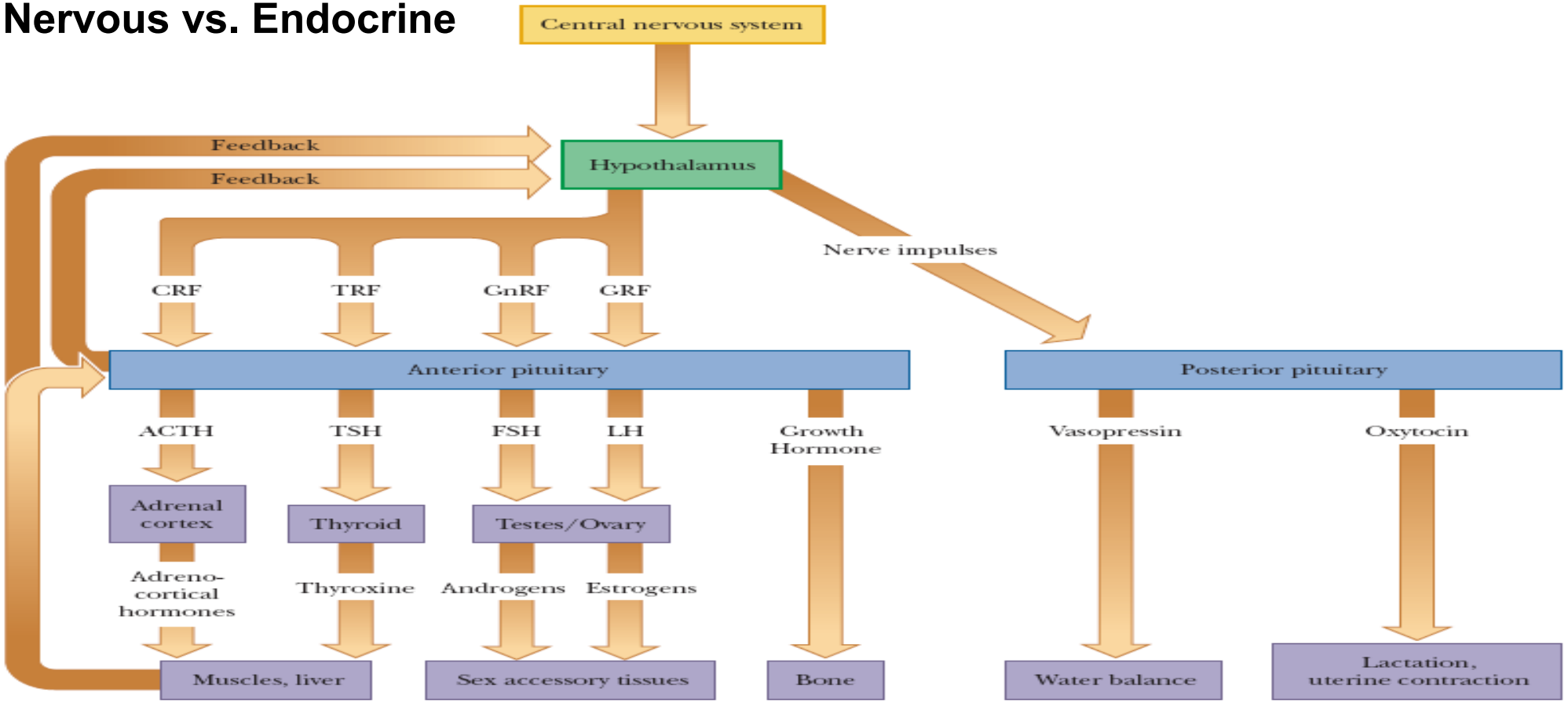
Factors affect the concentration of the hormone at the target cell
✓ The rate of synthesis and secretion of the hormone
✓ The proximity of the target cell to the hormone source (dilution)
✓ The $\mathbf{K_d}$ of the hormone – receptor complex
✓ The rate of conversion of inactive form to the fully active form
✓ The rate of clearance from the plasma

3. THE TARGET CELL CONCEPT

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

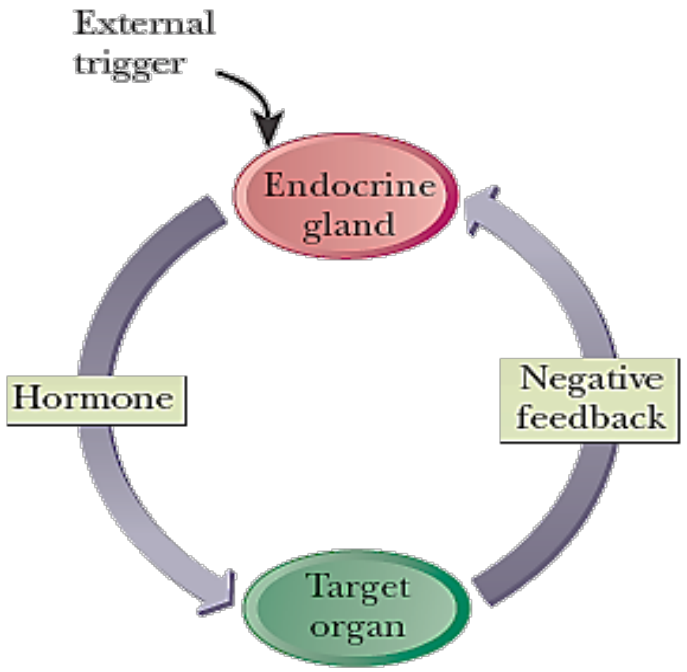
4. MAJOR REGULATION OF THE BODY'S HOMEOSTASIS

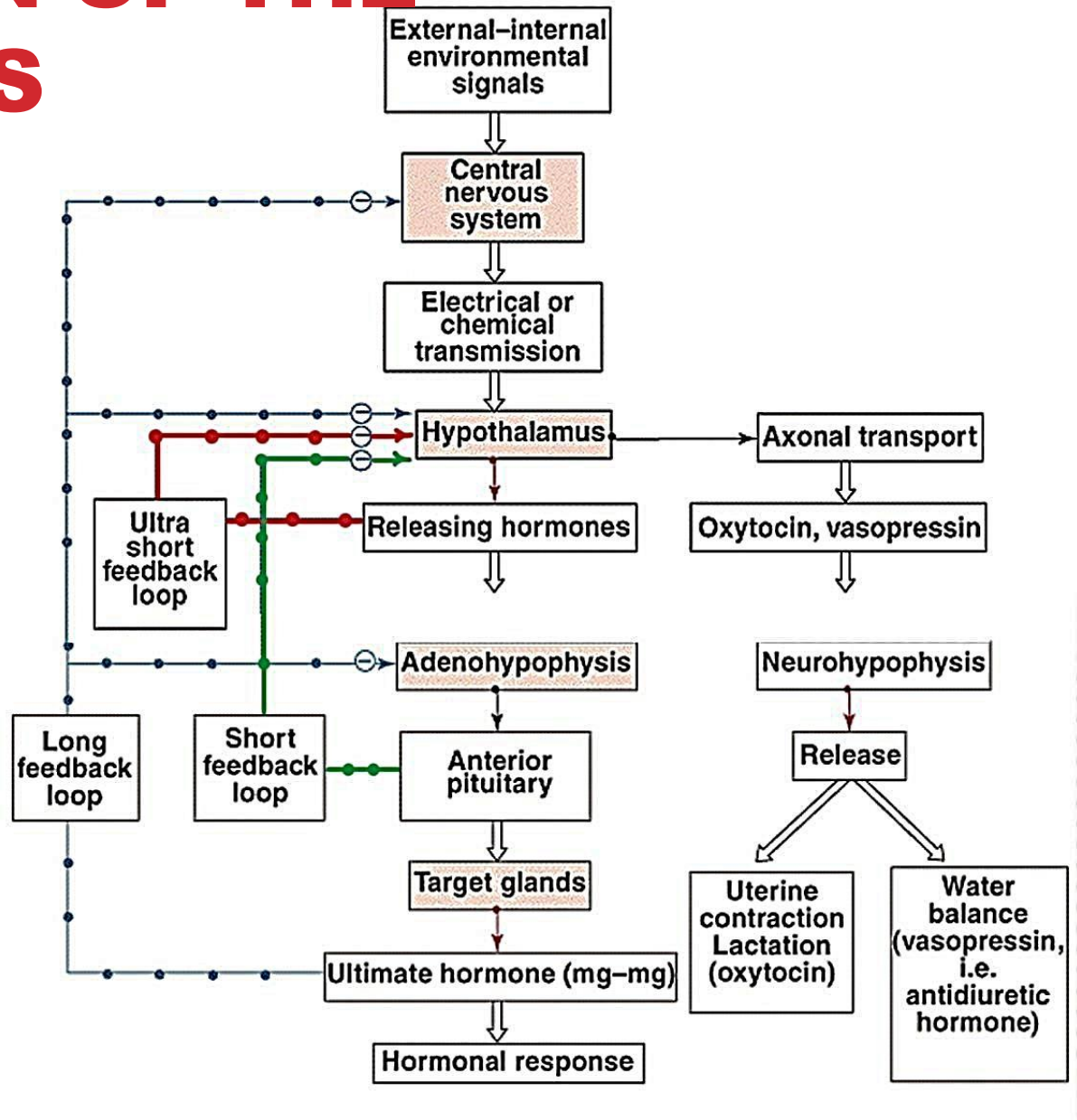
- Nervous vs. Endocrine



4. MAIN REGULATION OF THE ENDOCRINE SIGNALS

- ❑ Ultrashort loop
- ❑ Short loop
- ❑ Long loop



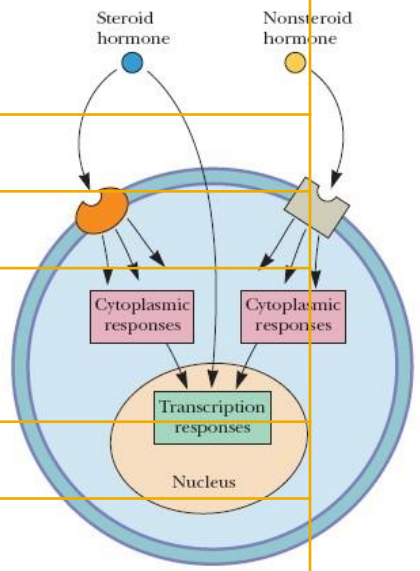


5. CLASSIFICATION

- Solubility → transport
- Chemistry
- Processing and modification
- Synthesis
- Mechanism of action

5.1 SOLUBILITY

	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



5.2 CHEMISTRY

- **Peptides, polypeptides, and proteins:**
  - Pituitary hormones; Hypothalamic releasing hormones; Insulin, Growth factors…

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

5.2 CHEMISTRY

- **Amino acid derivatives:**
  - Adrenalin, Thyroid hormones
- **Steroids**
  - Sex hormones, Hormones of Adrenal Cortex
- **Eicosanoids**
  - Prostaglandins, Leukotrienes, and Thromboxanes
- **Gasses**
  - NO

5.3 PROCESSING AND MODIFICATION

- **Secreted in final active form**
  - Aldosterone, hydrocortisone, estradiol, catecholamines
- **Modified directly in target tissues**
  - Insulin, POMC
- **Modified indirectly in non-target tissues**
  - T4 to T3 (liver)
  - D3 to active D (liver and kidneys)

5.4 SYNTHESIS

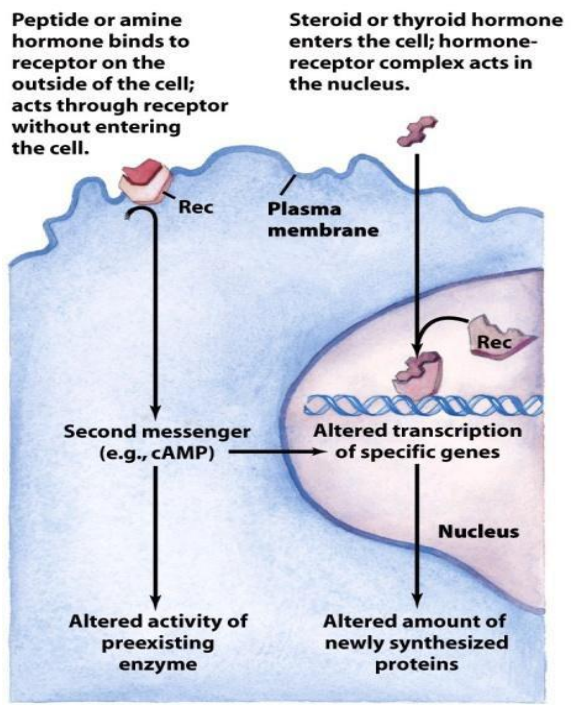
- **Peptide and proteins**
  - Alternative splicing
  - Post-translational modification
  - Preprohormones
- **Steroids**
- **Amines**
- **Eicosanoids**

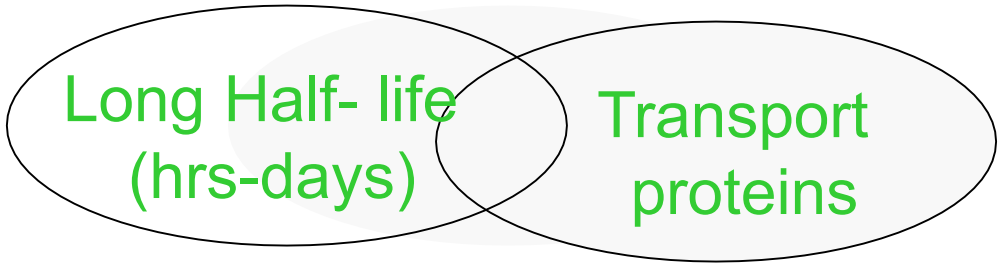
5.5 MECHANISM OF ACTION

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

5.5 MECHANISM OF ACTION

- **Hormones that bind to intracellular receptors**
  - Cytoplasmic vs. nuclear
    - HSP vs. corepressors (dimerization)
  - Steroids
  - Thyroid hormones
  - Calcitriol, retinoic acid





FREE VS. BOUND!

6. TARGET CELL INTERACTIVE EFFECTS

- **Permissive effects – one hormone enhances the effect of a later hormone**
  - Upregulation of receptors or enzyme synthesis
  - Estrogen up-regulates progesterone receptors in uterus
  - Thyroid hormone increases the effect of epinephrine on breakdown of triglycerides in adipocytes

- **Integrative effects – hormones produce complementary effects on different tissues**
  - PTH and calcitriol increase ECF calcium

6. TARGET CELL INTERACTIVE EFFECTS

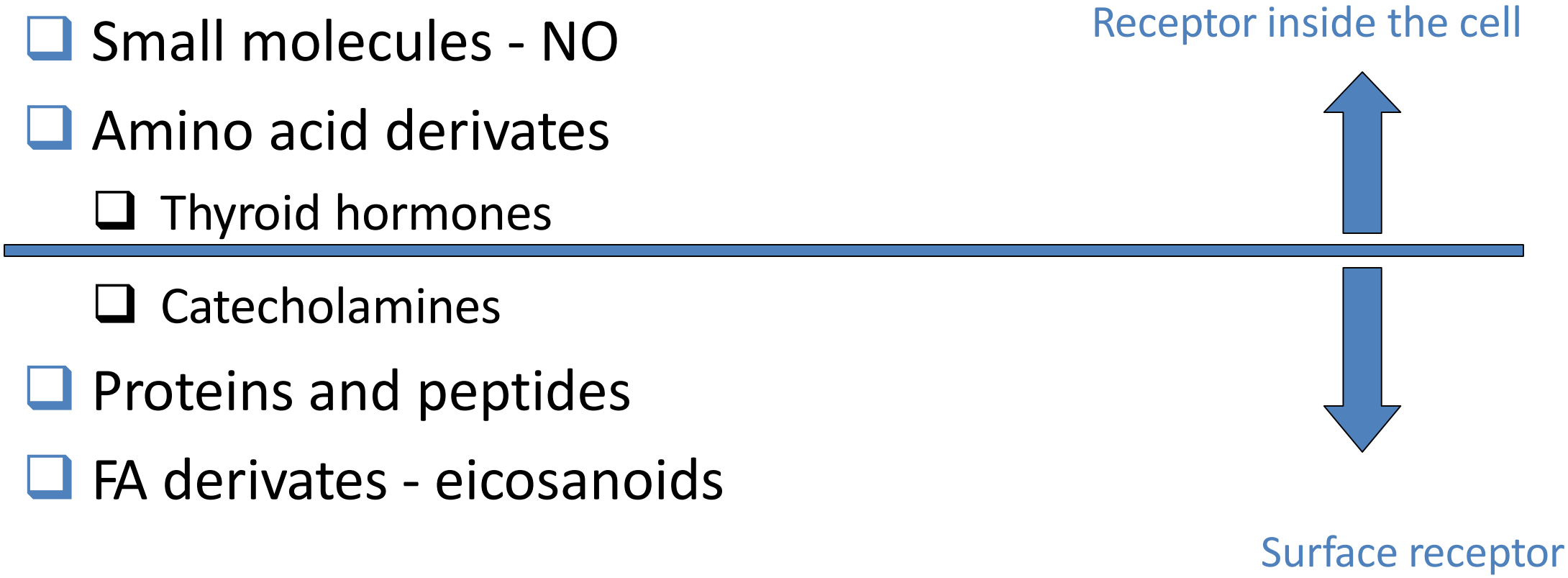
- **Synergistic effects**
  - Both FSH and estrogen necessary for normal oocyte development
  - FSH and testosterone together increase spermatogenesis

- **Antagonistic effects:**
  - Insulin and glucagon

7. SYNTHESIS AND DEGRADATION OF HORMONES ACCORDING TO THEIR CHEMISTRY

CHEMISTRY OF HORMONES

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



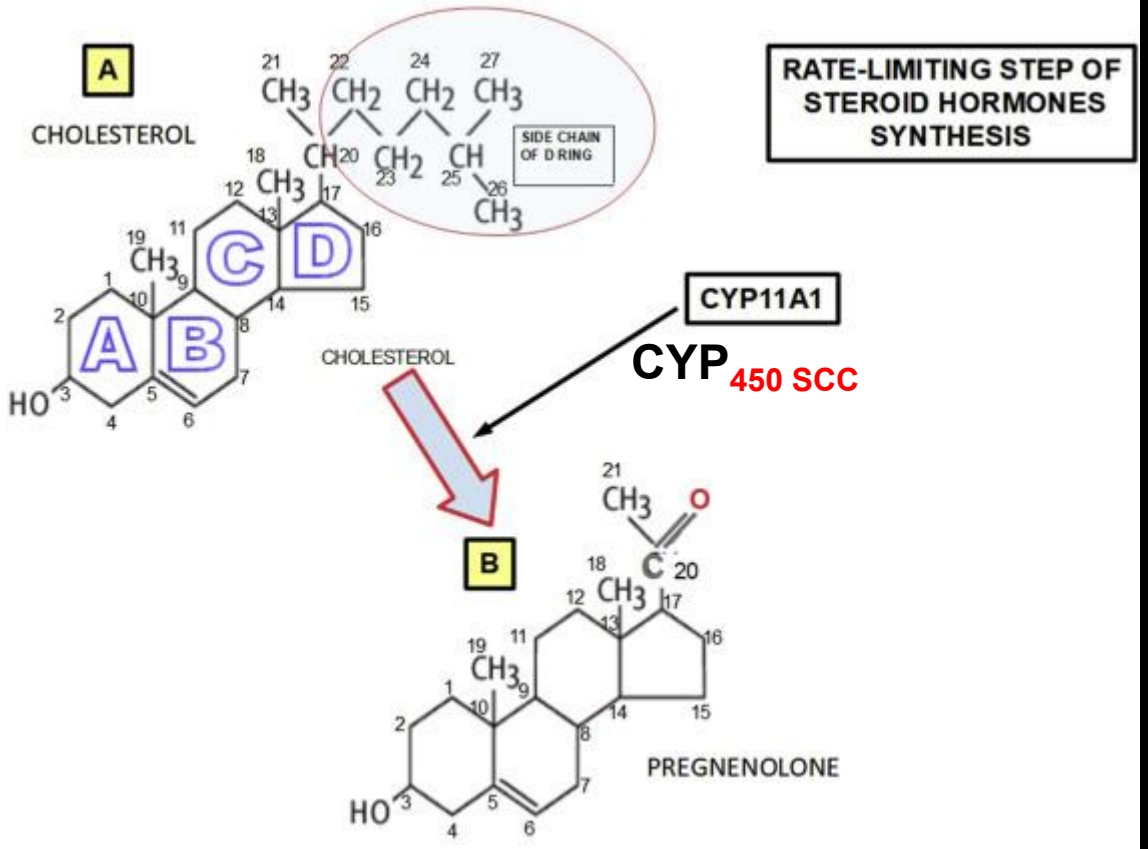
7.1 STEROIDS

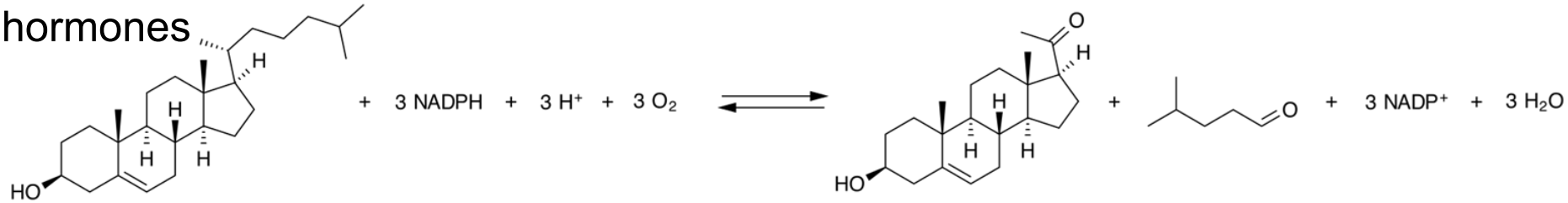
- Mitochondria and SER of respective tissues
- Specific enzymes involved ($CYP_{450\ SCC}$)

- **Steran core cannot be cleaved**

- **In the liver: hydroxylation and conjugation with glucuronides or sulphates**

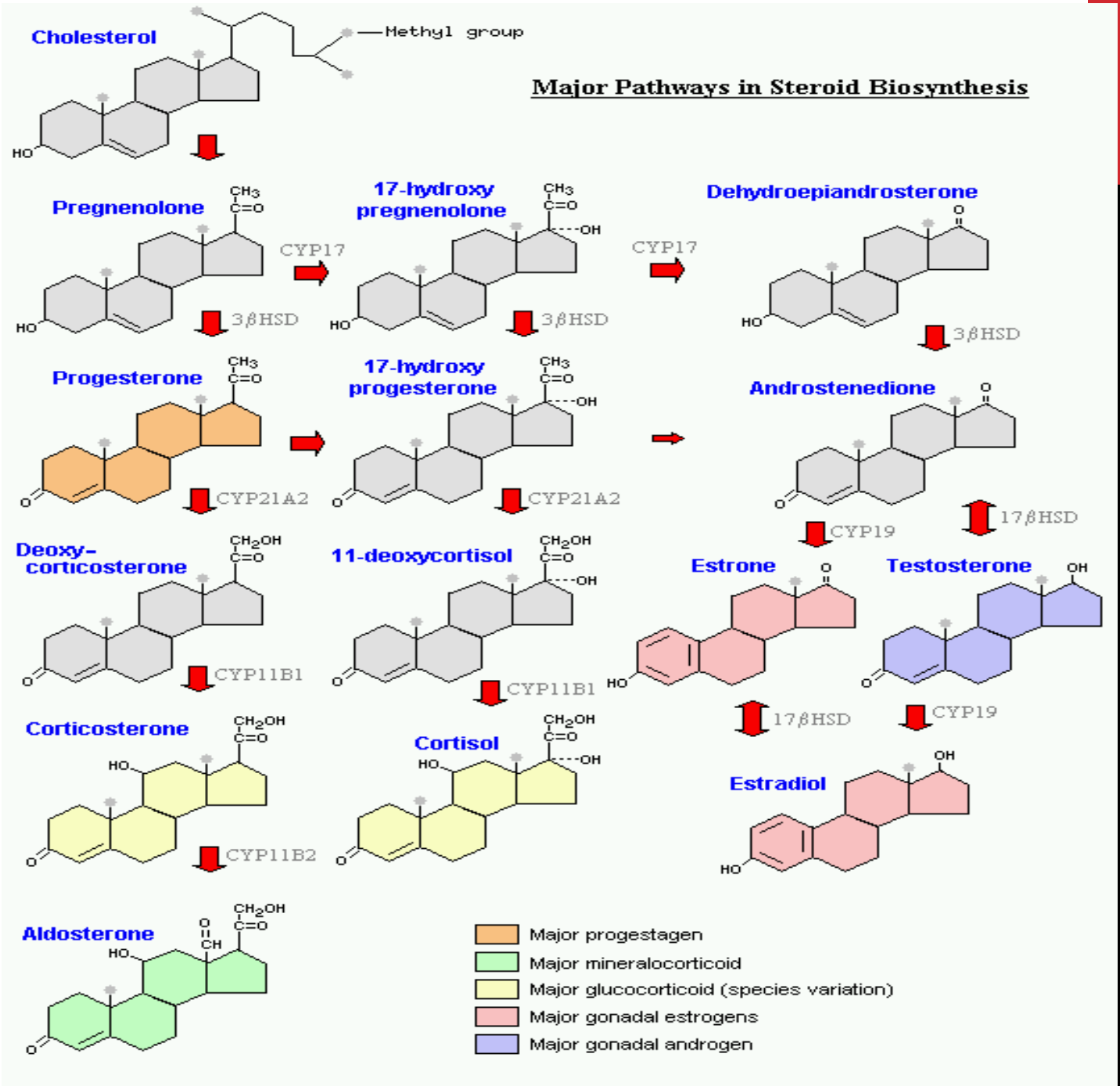
- **Urinary excretion:**
  - Of metabolites
  - Of unchanged hormones





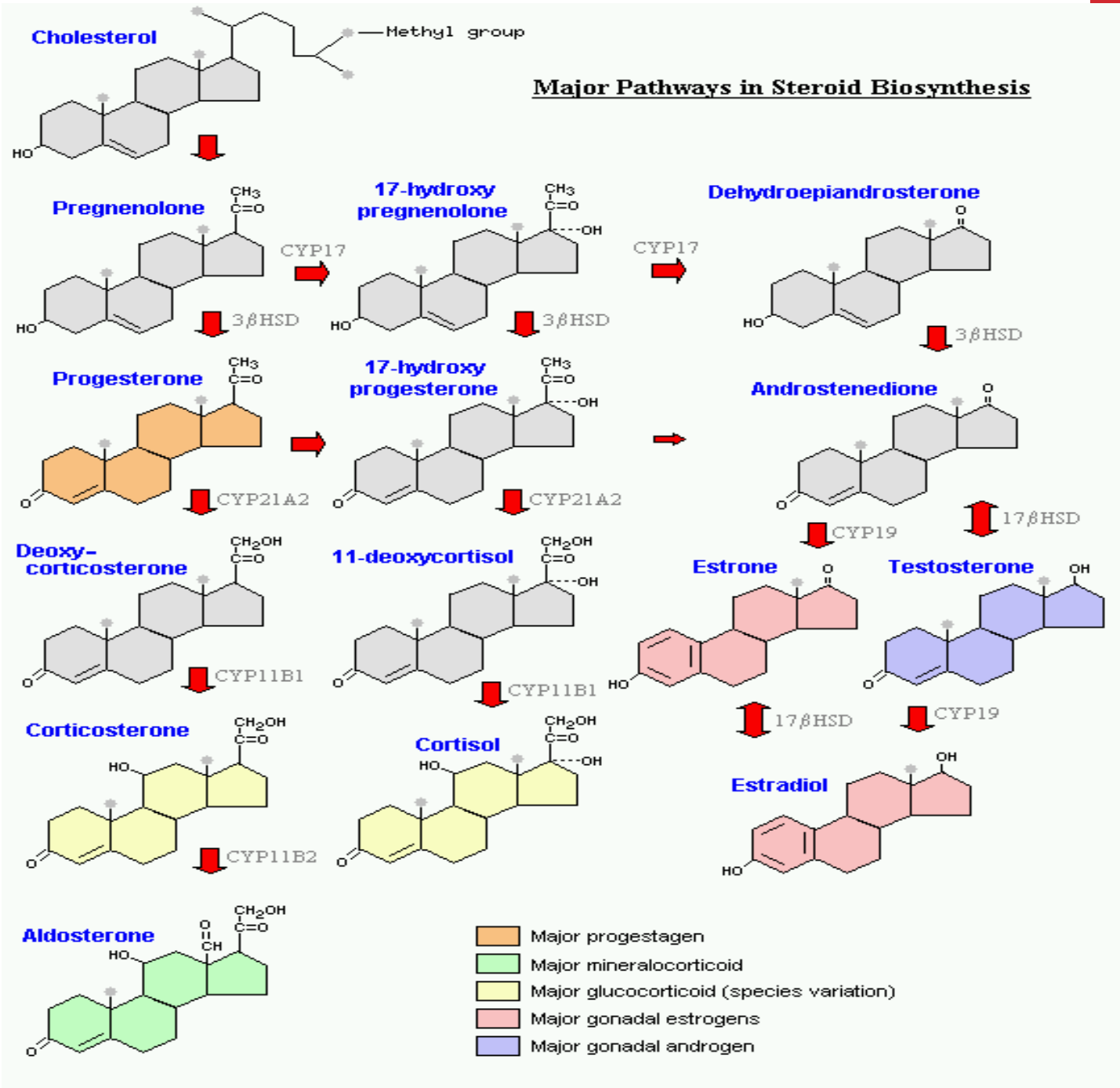
7.1 STEROIDS

- C21:
  - Progesterone: directly from pregnenolone
  - Cortisol & Aldosterone:
    - from progesterone



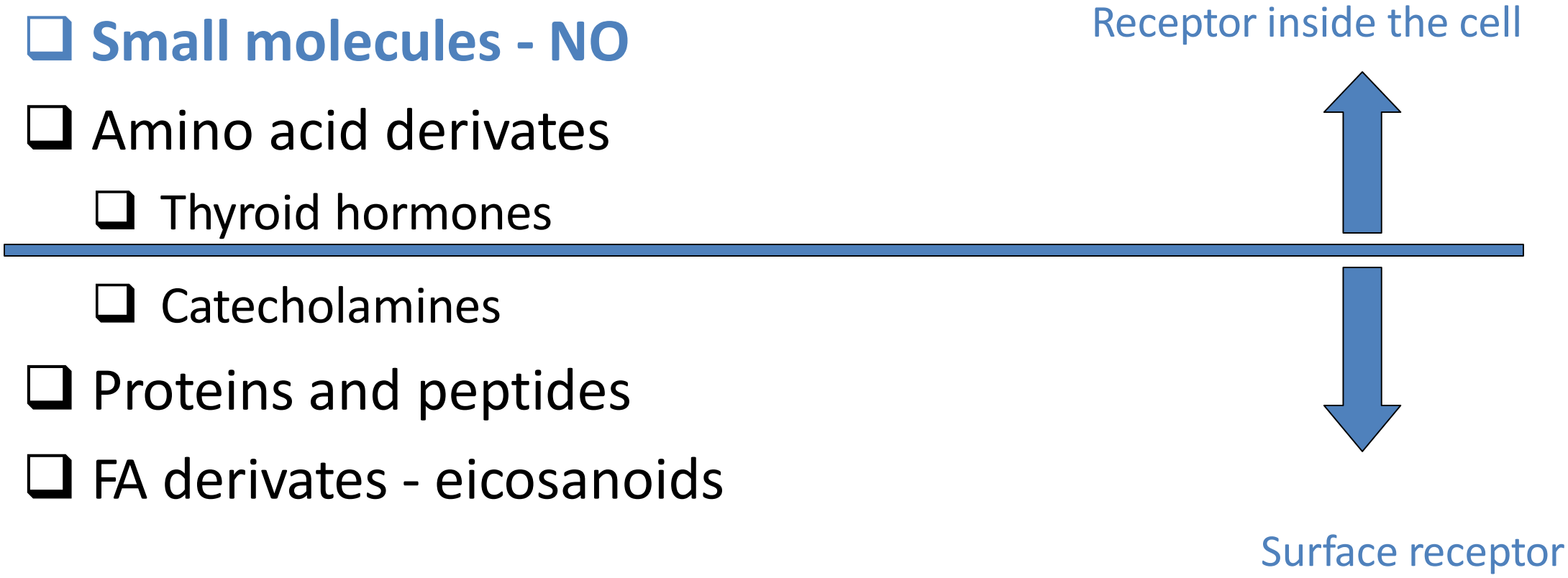
7.1 STEROIDS

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



CHEMISTRY OF HORMONES

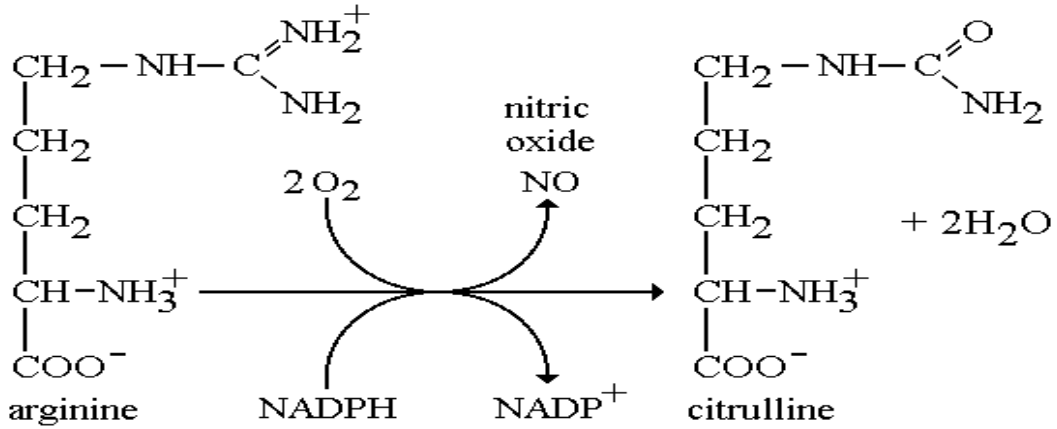
- Steroids
- **Small molecules - NO**
- Amino acid derivates
  - Thyroid hormones
  - Catecholamines
- Proteins and peptides
- FA derivates - eicosanoids



7.2 SMALL MOLECULES - NO

- **NO-synthase (NOS) isozymes**
  - 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
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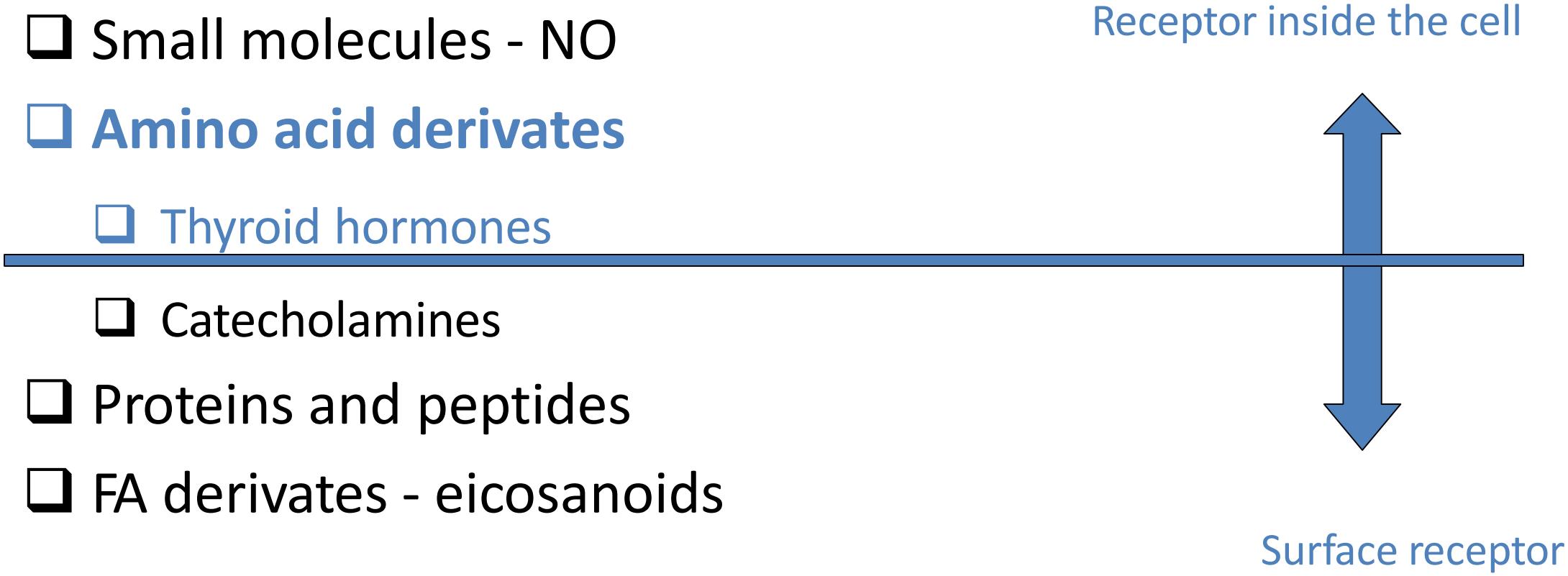
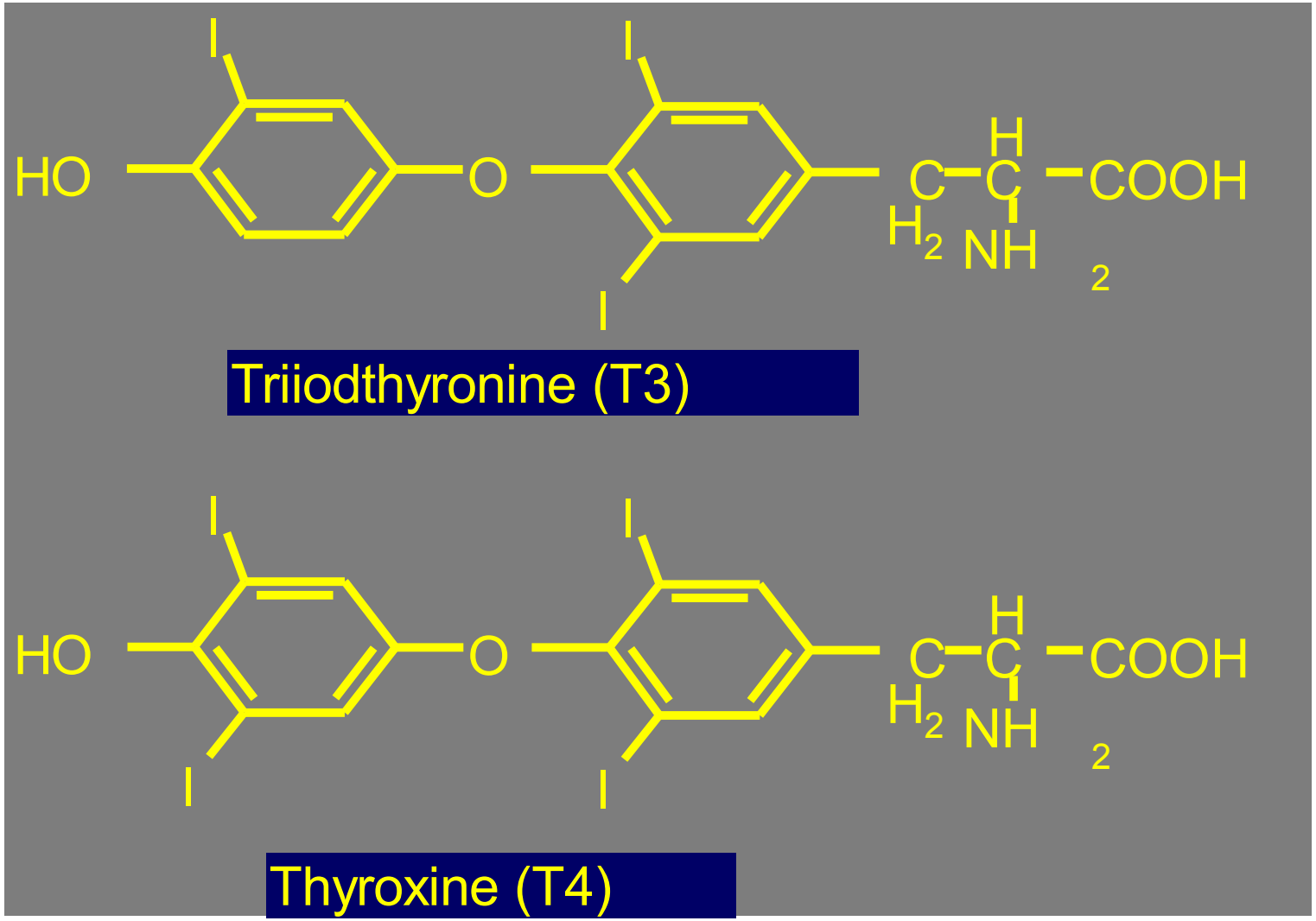
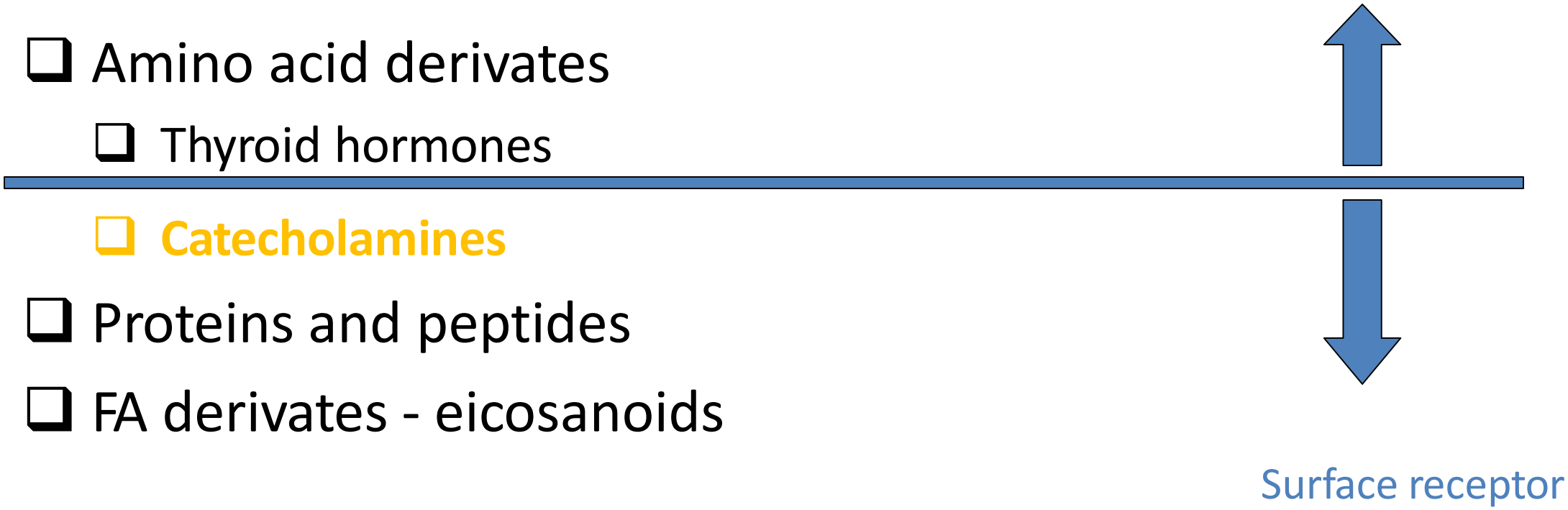


7.3 THYROID HORMONES



CHEMISTRY OF HORMONES

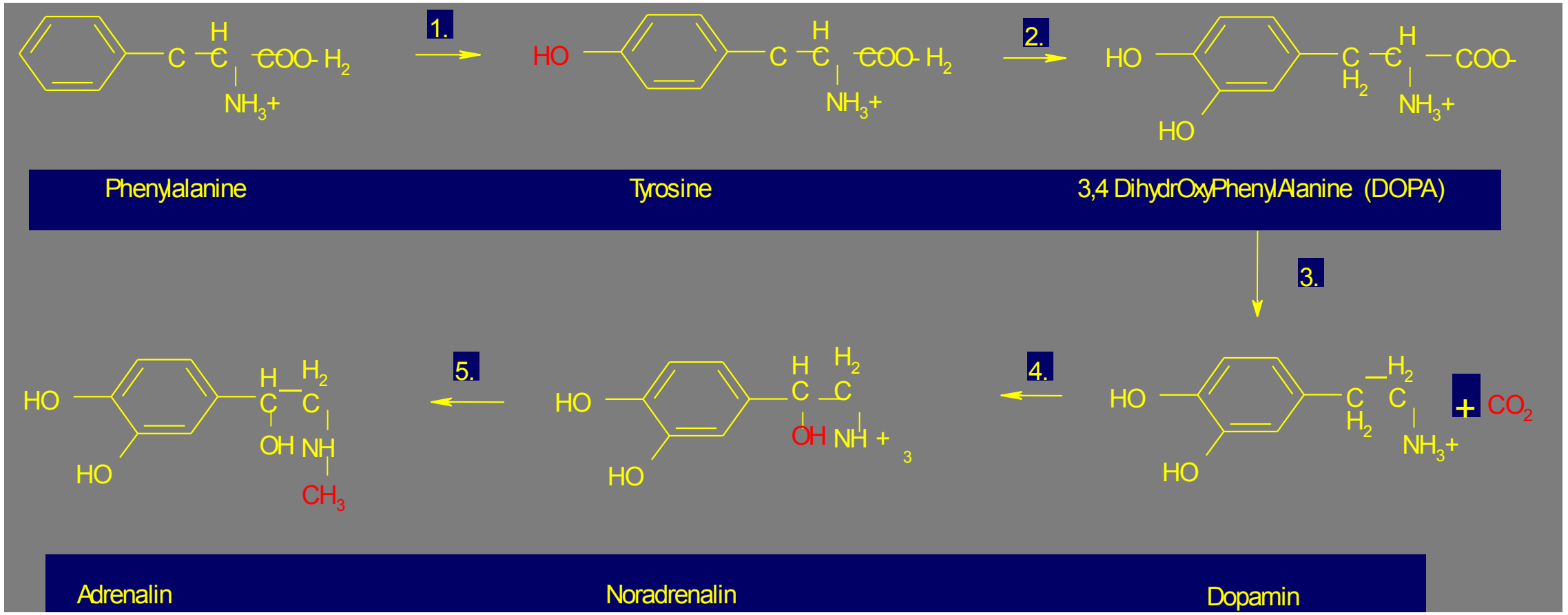
- Steroids
- Small molecules - NO
- Amino acid derivates
  - Thyroid hormones
  - **Catecholamines**
- Proteins and peptides
- FA derivates - eicosanoids



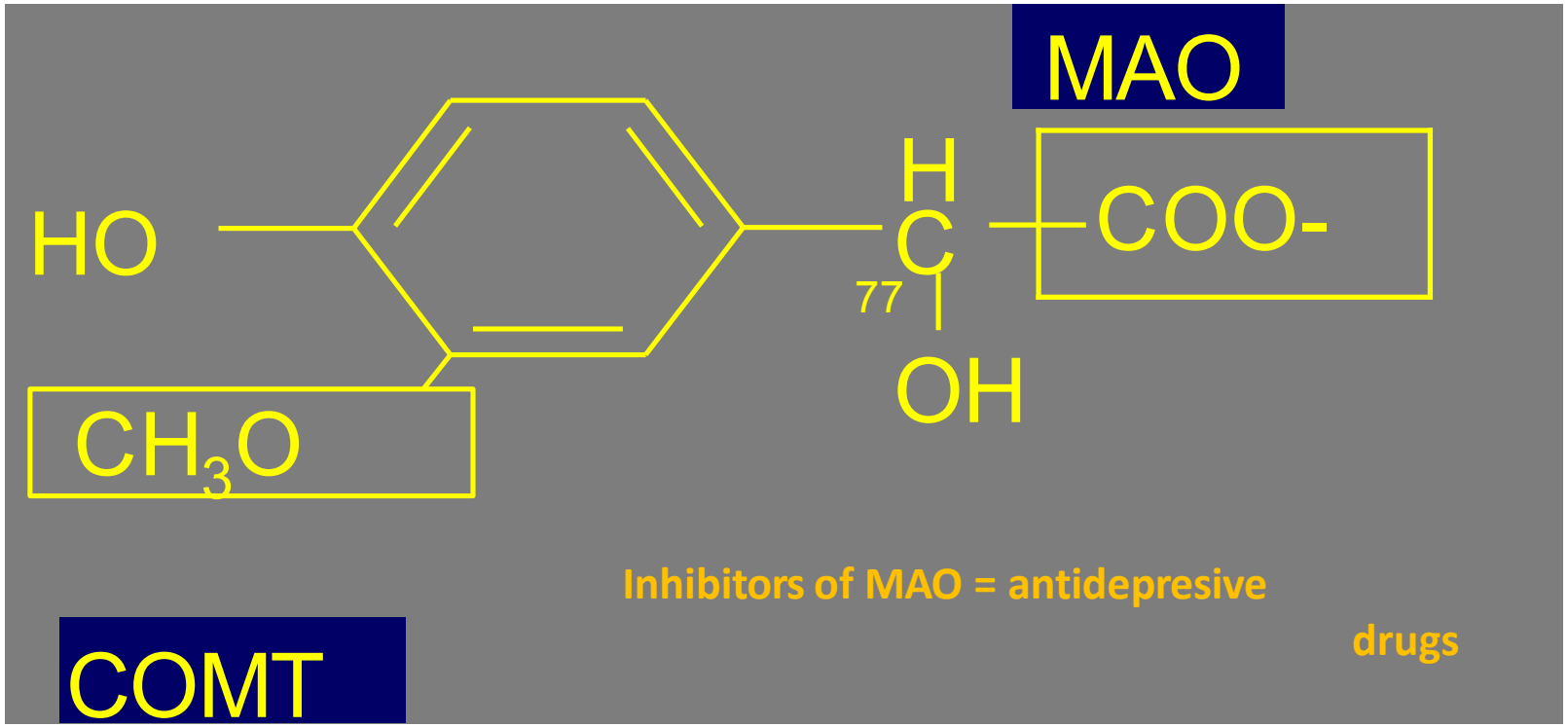
7.4 CATECHOLAMINE

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

7.4 CATECHOLAMINE

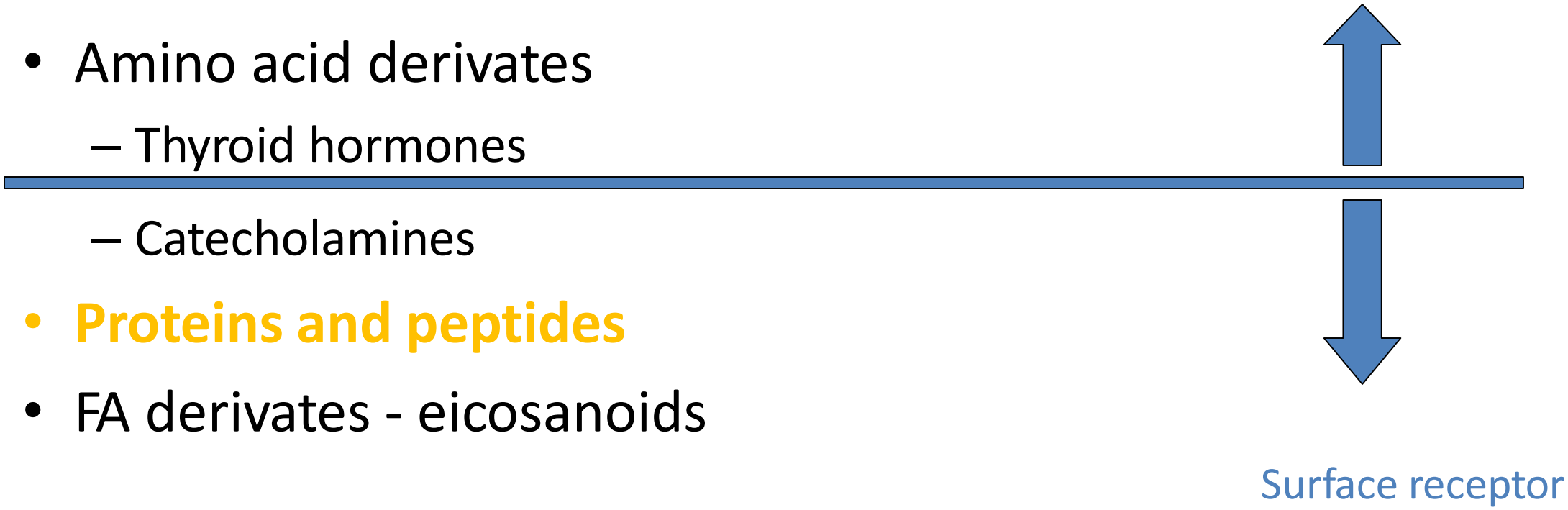


7.4 CATECHOLAMINE



CHEMISTRY OF HORMONES

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

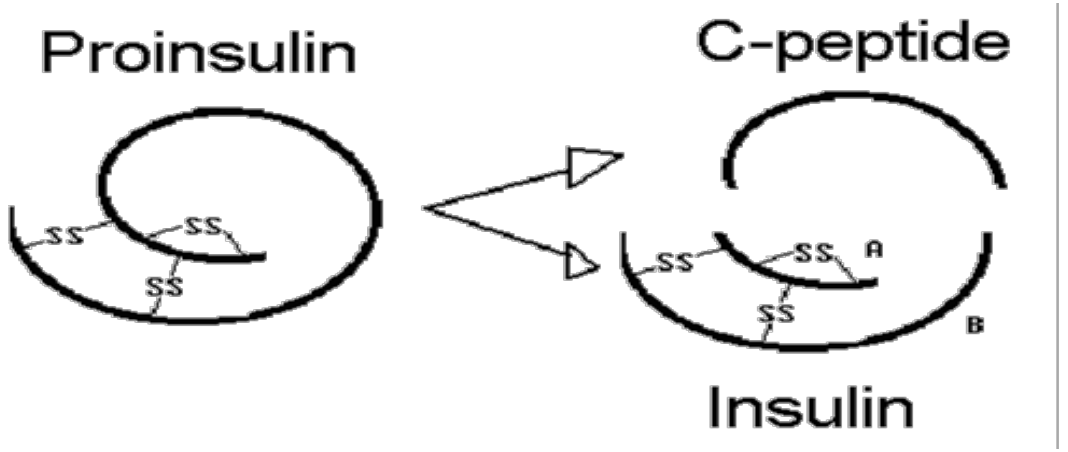


7.5 PROTEIN AND PEPTIDE HORMONES

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

7.5 GENERAL STEPS OF PEPTIDE SYNTHESIS "PRECURSOR POLYPEPTIDES"

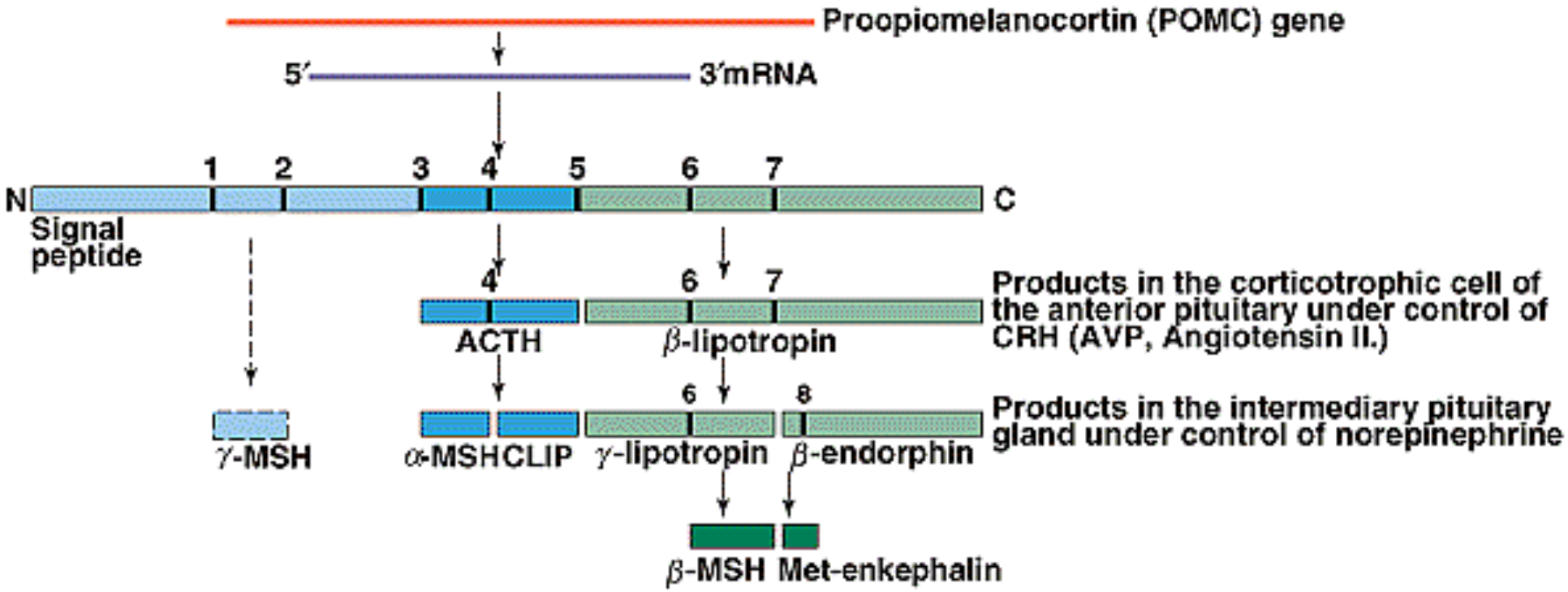
- Expression of "pre-pro" protein
- Transport to ER
- Splitting the signaling sequence



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

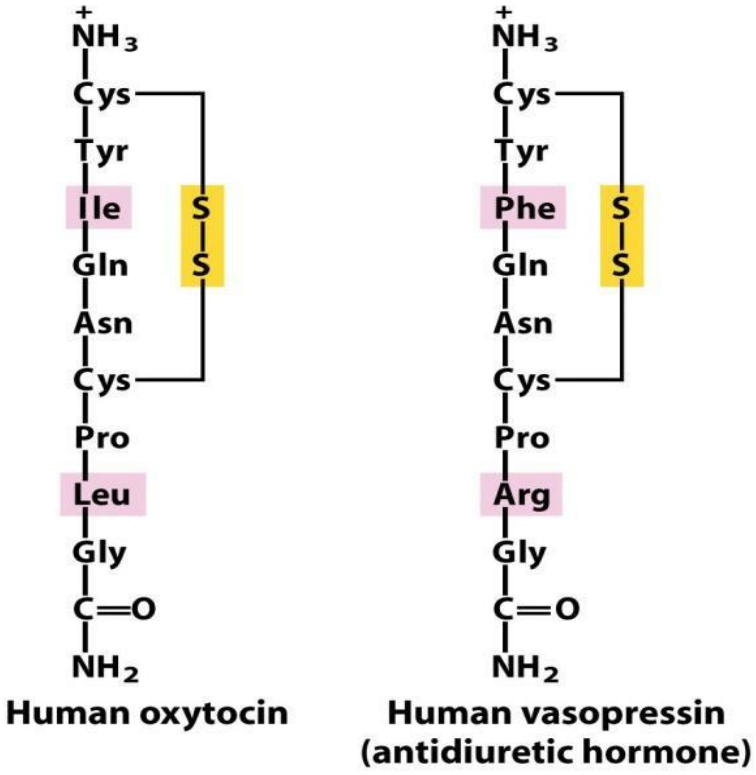
7.5 PEPTIDE AND PROTEINS

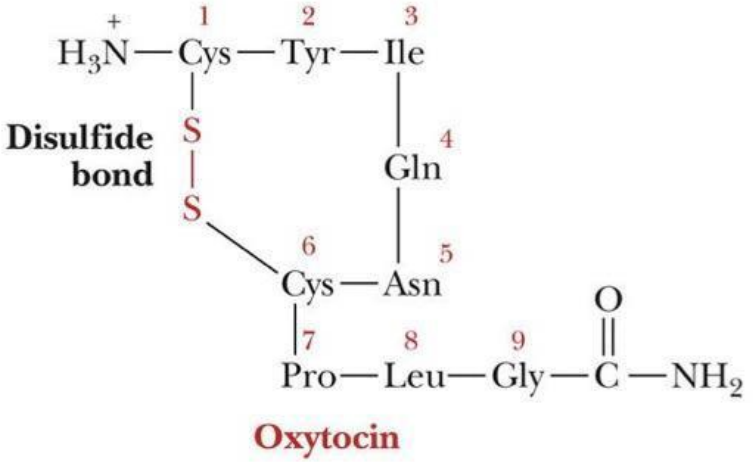
- **From precursor polypeptides**
  - One gene may code more than one hormone (POMC)
  - The cleavage depends on specific enzymes

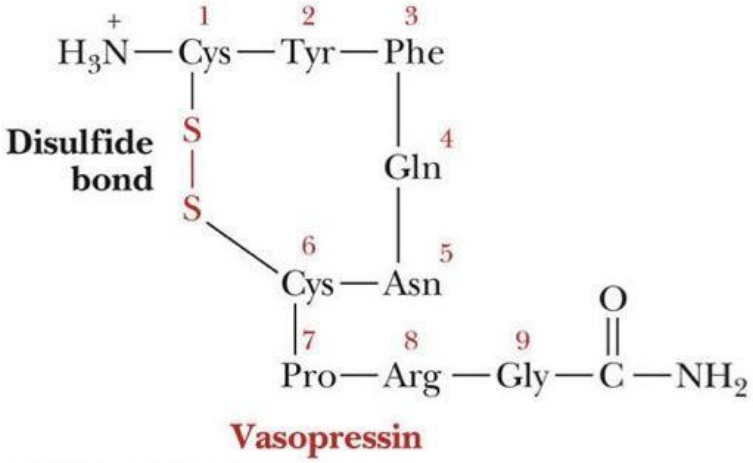


7.5 PEPTIDE AND PROTEINS

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

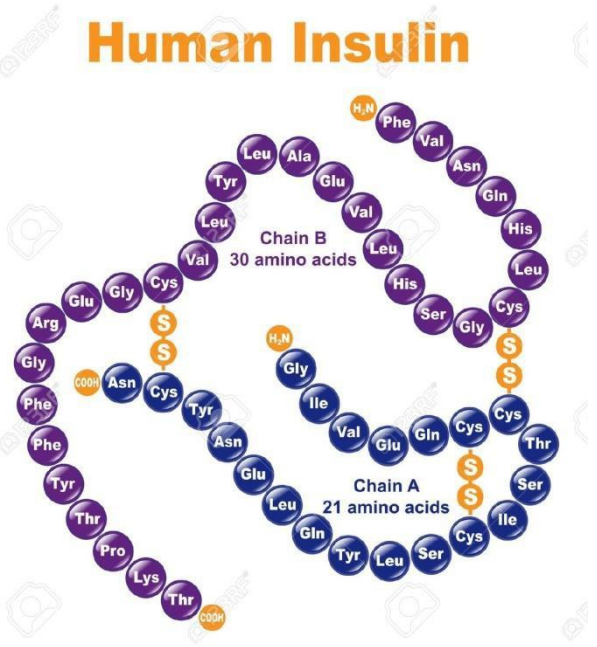


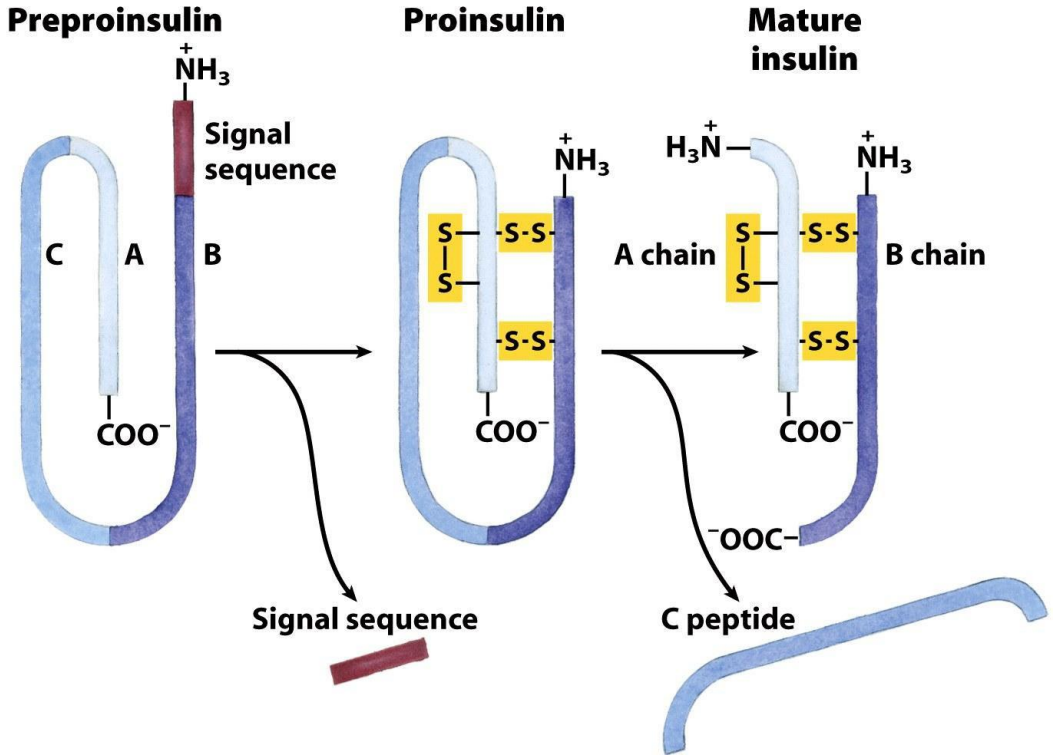




7.5 PEPTIDE AND PROTEINS

- **From Pre-pro-hormones**
  - A larger precursor pre-pro-insulin
    - 23 aa signal sequence
    - 3 disulfide bonds
  - Proinsulin
    - Remove the C peptide
  - Mature insulin
    - A and B chains





7.5 DEGRADATION

- **Lysosomal**
  - After endocytosis of hormone-receptor complex
- **Chemical modification (liver)**
  - Rearrangement of S-S bridges, cleavage
- **Renal excretion of small peptides**

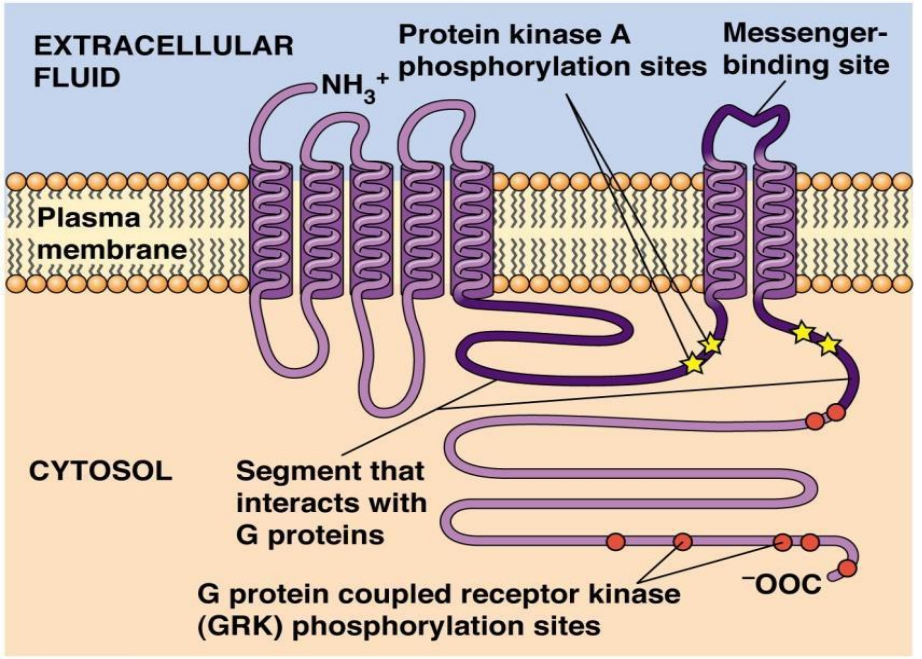
8. SIGNAL TRANSDUCTION, CASCADES, AND RECEPTORS

8.1 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 not peripheral!
  - Transmembrane
  - Intra- & extracellular domains

8.1 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**

8.1 THE NEED FOR 2ND MESSENGER

- **Is that enough?**
  - Few in number
  - Restricted movement

8.1 2ND 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 2nd messengers:**
  - Small molecules: cAMP, cGMP, Ca^{+2}
  - Phosphorylation through kinases

8.1 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

8.2 TYPES OF MEMBRANE ASSOCIATED RECEPTORS

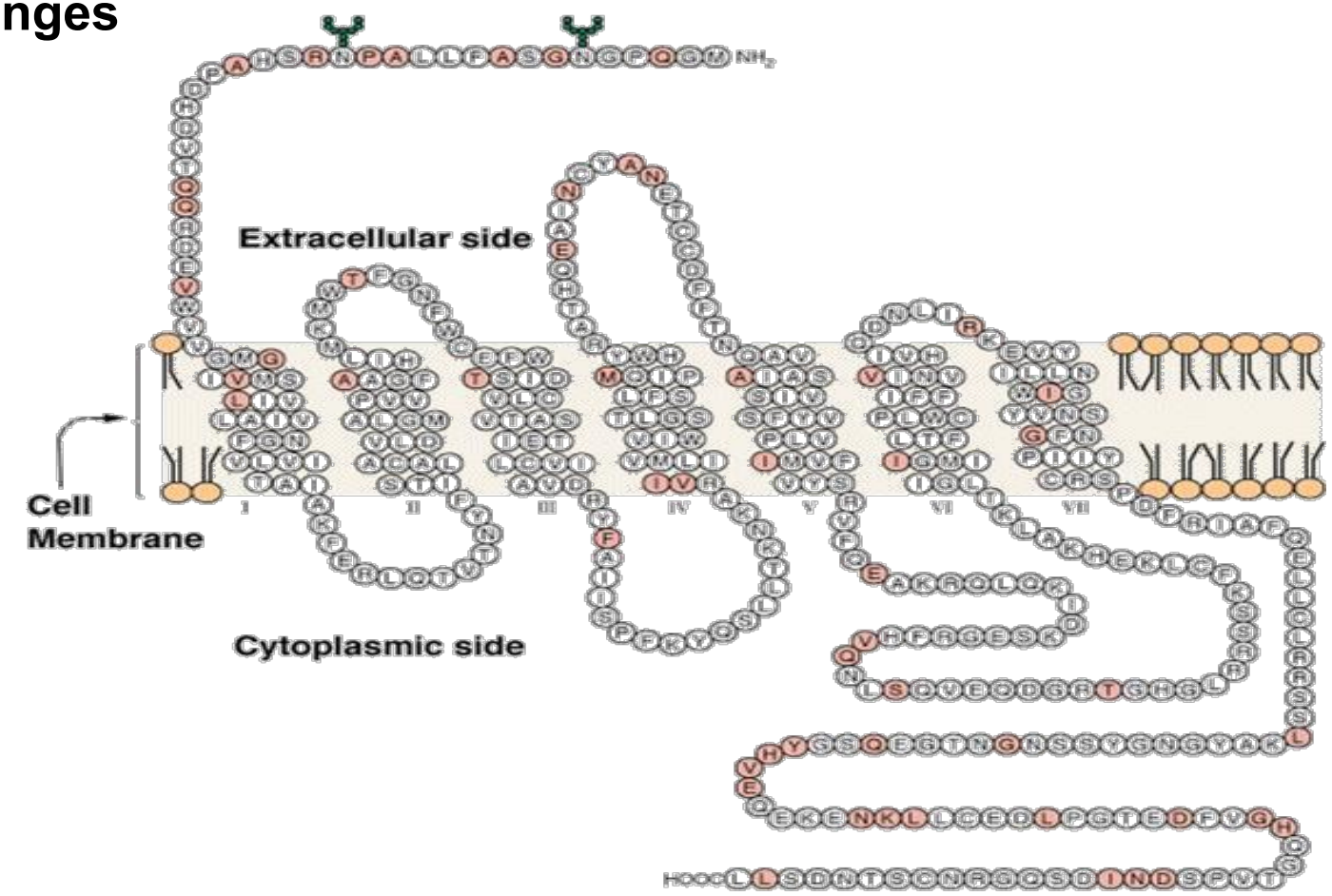
- **7-transmembrane helix receptor**
  - G-protein coupled (cAMP, Phospholipase C, Ion channels)

- **Tyrosine kinase receptor**

8.2 7-TRANSMEMBRANE HELIX RECEPTOR

- 7 α-helices: H-bonding, rigid, hydrophobic
- Signal induces conformational changes
- Is it enough?
- Many Ser & Thr residues

Rhodopsin receptor

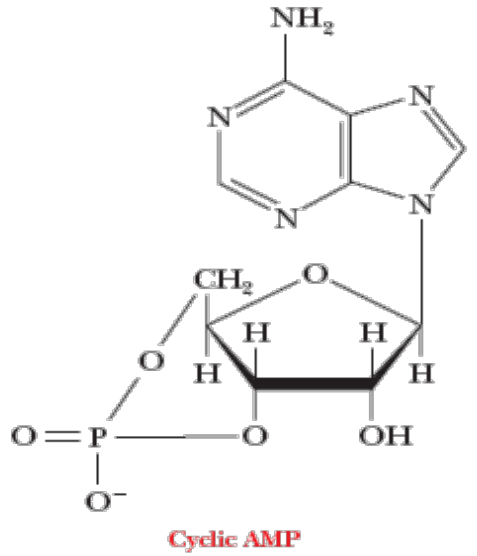


8.2 BIOLOGICAL FUNCTIONS MEDIATED

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

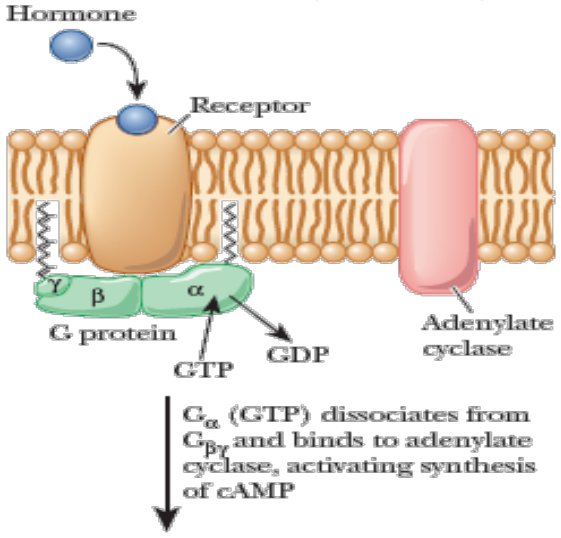
- All these receptors share the same basic structure; however, they differ in their specificity and effects

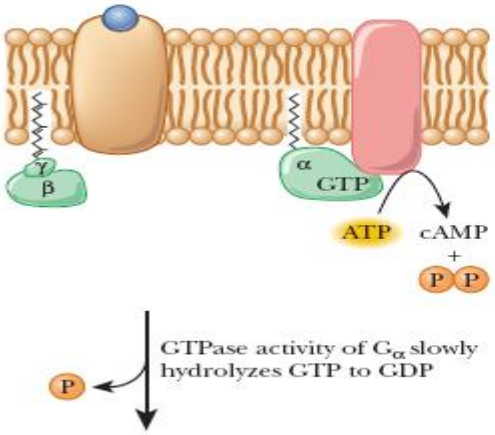
8.2. A. G-PROTEIN COUPLED

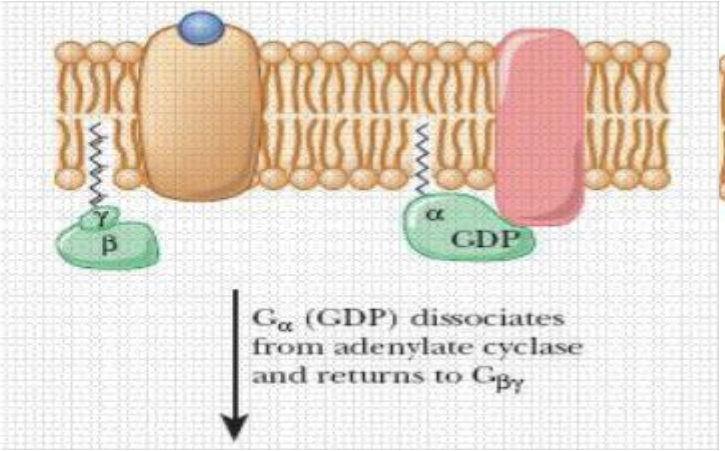


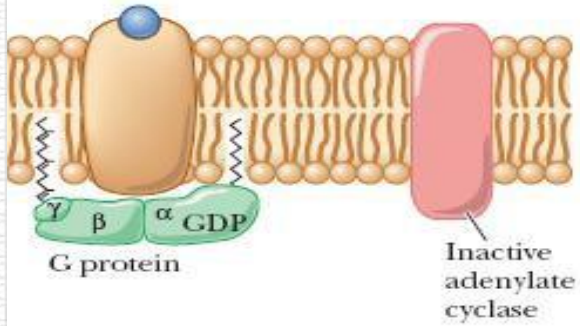
Cyclic AMP

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



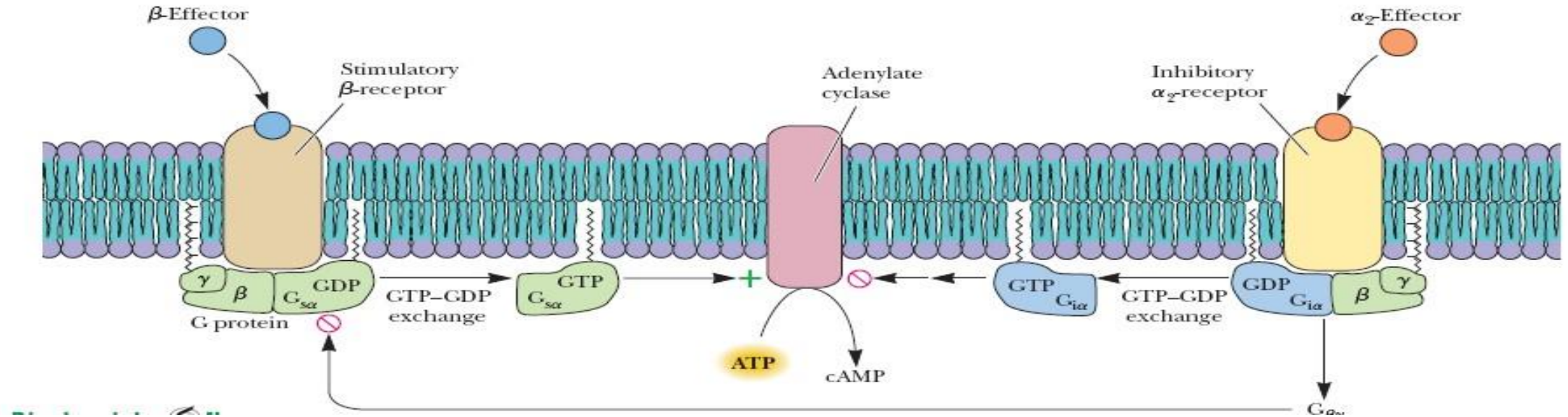






8.2. A. G-PROTEIN COUPLED

- Stimulatory or inhibitory?
- Hormone → receptor (α2-receptor) → G protein → inhibits adenylate cyclase



8.2. B. 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

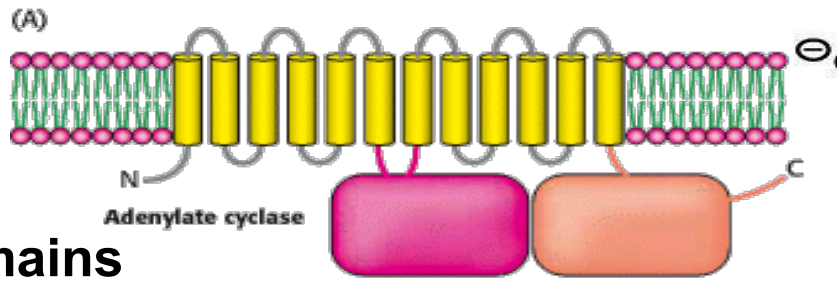
G-PROTEINS

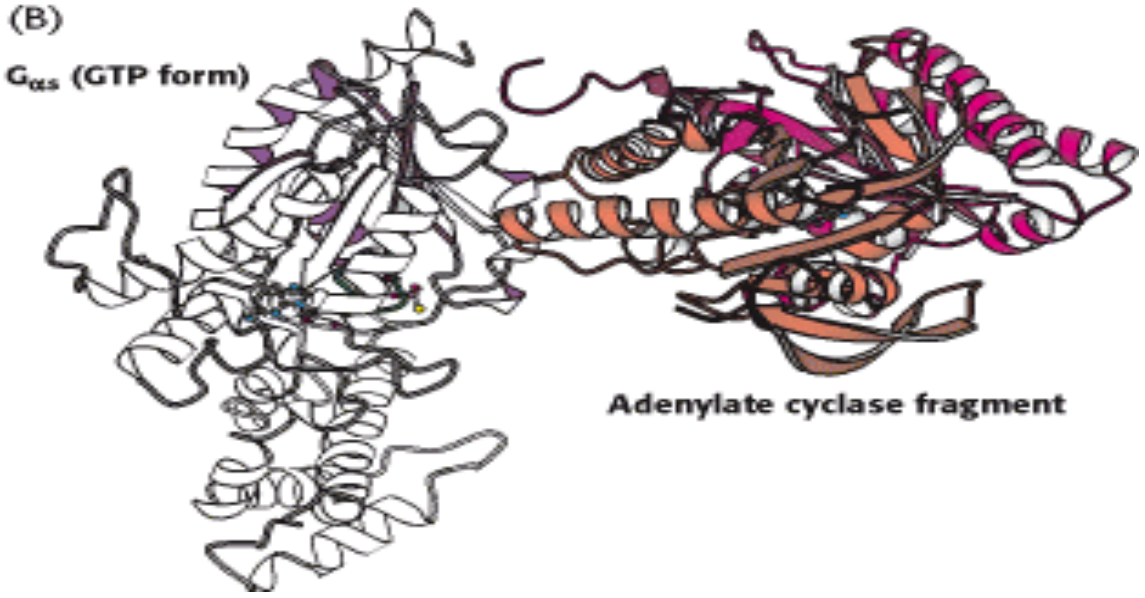
G_{α} class	Initiating signal	Downstream signal
$G_{\alpha s}$	β-Adrenergic: amines, glucagon, parathyroid hormone, many others	Stimulates adenylate cyclase
$G_{\alpha i}$	Acetylcholine, α-adrenergic: amines, many neurotransmitters	Inhibits adenylate cyclase
$G_{\alpha q}$	Acetylcholine, α-adrenergic: amines, many neurotransmitters	Increases IP_3 and intracellular calcium
$G_{\alpha t}$	Photons	Stimulates cGMP phosphodiesterase
$G_{\alpha 13}$	Thrombin, other agonists	Stimulates Na^+ and H^+ exchange

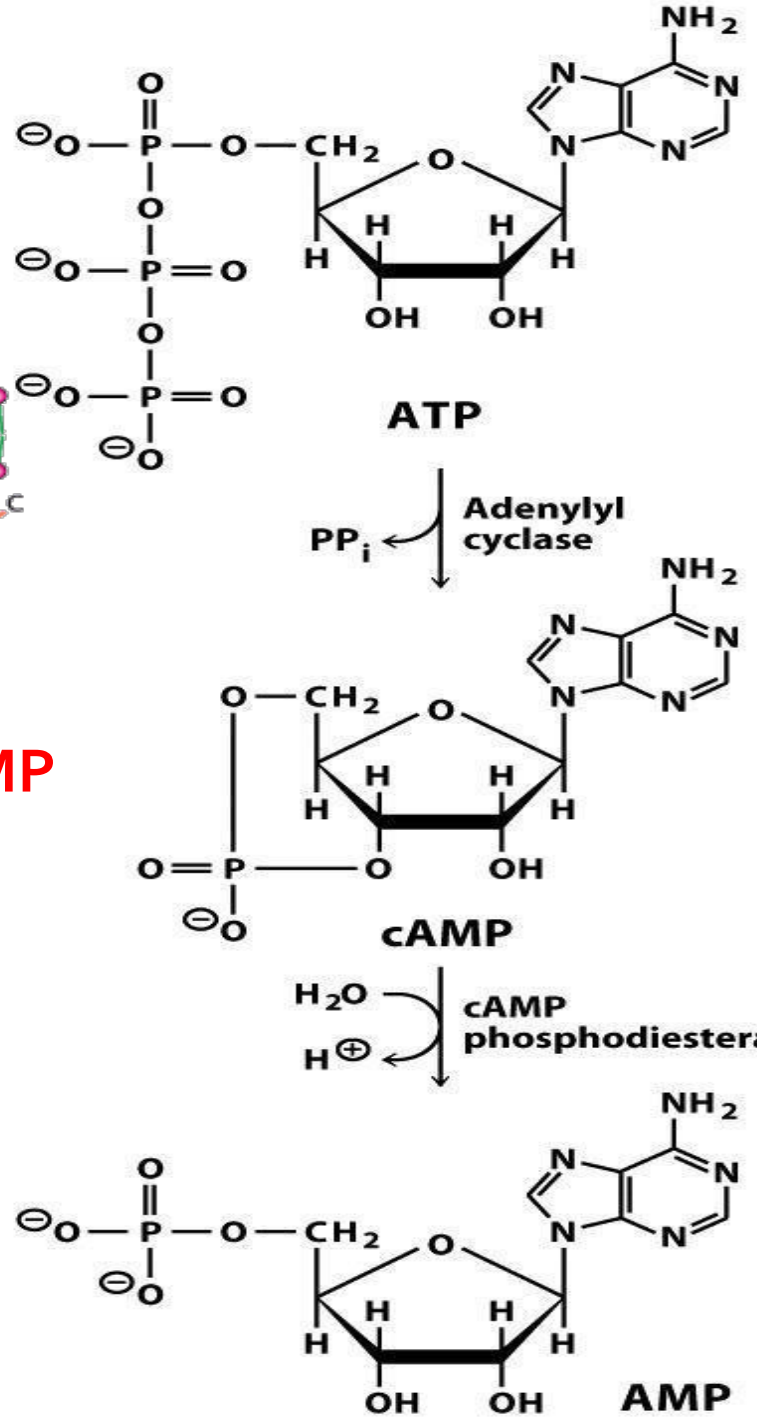
8.2. B. G-PROTEINS

8.2.C. ADENYLATE CYCLASE

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





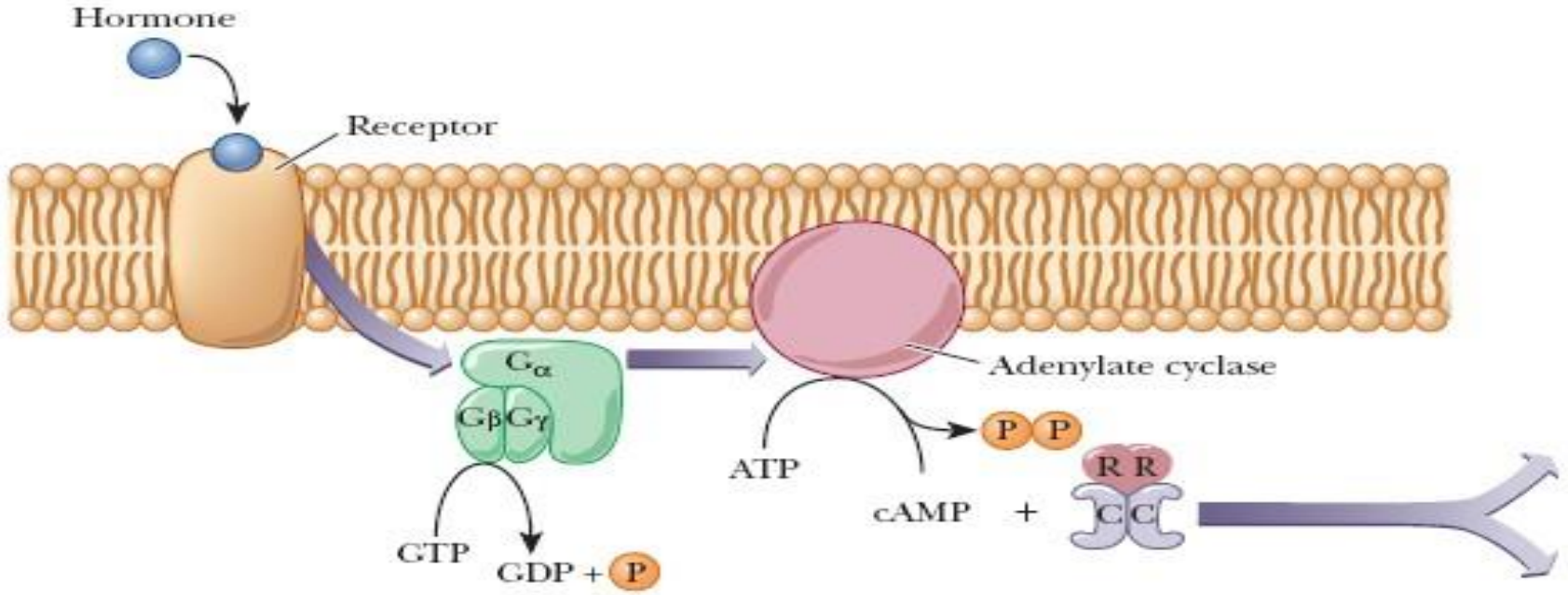


3'5' CAMP

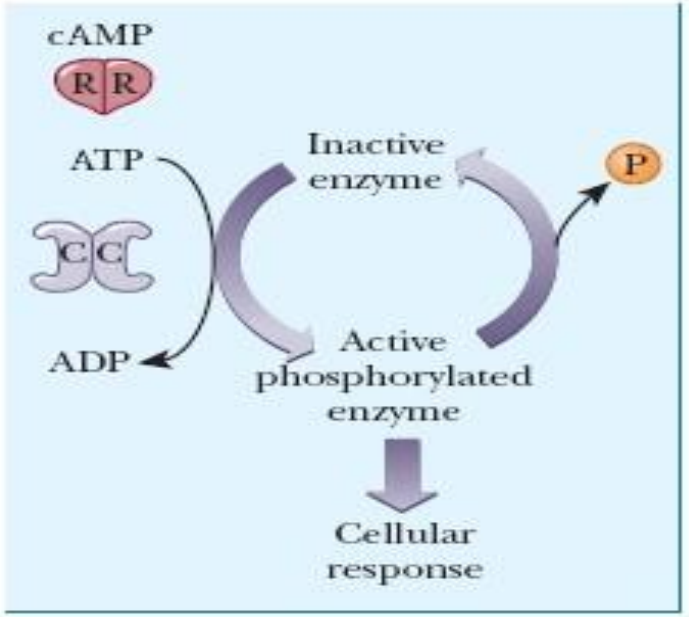
8.2.C. CAMP CAN AFFECT WIDE RANGE OF PROCESSES

- ↑ degradation of storage fuels
- ↑ secretion of acid by gastric mucosa (caffeine: phosphodiesterase & adenosine)
- Dispersion of melanin pigment granules
- ↓ aggregation of blood plateletes
- Opening of chloride channels

8.2.C. THEN WHAT? AMPLIFICATION



Usually: Ser or Thr

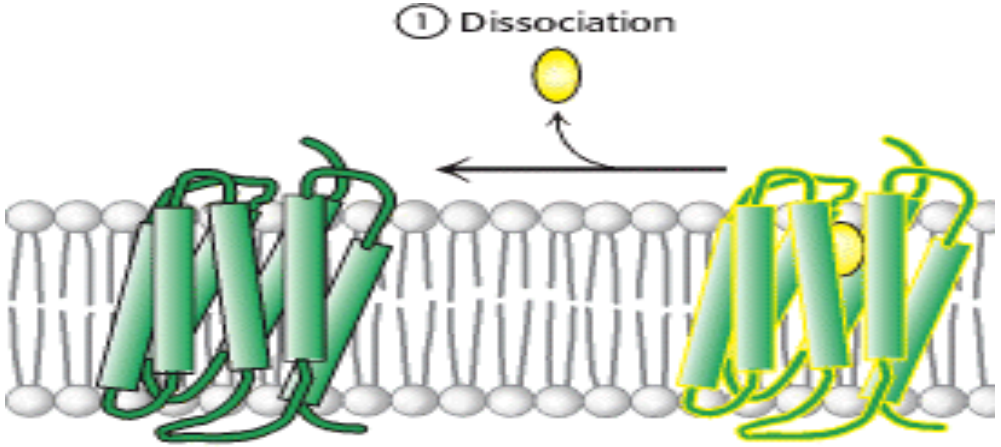


Signal Amplification

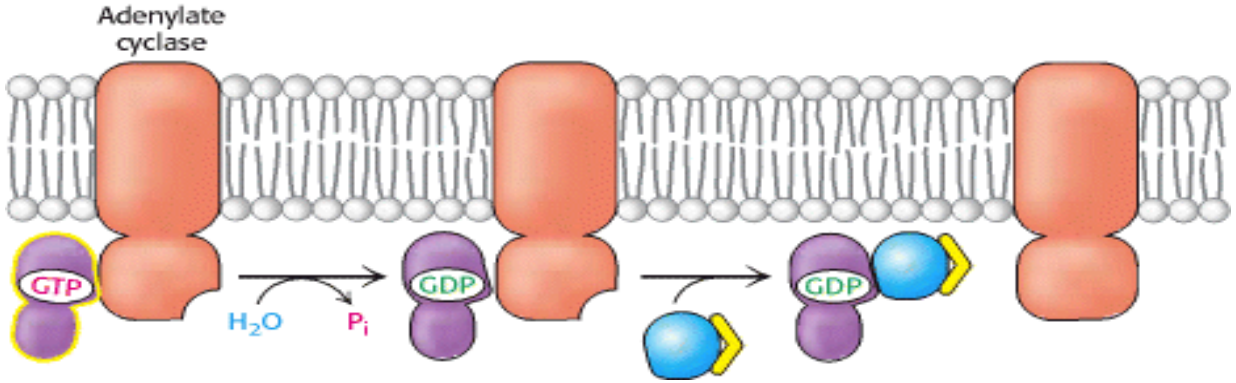
Glycogen Synthase!!

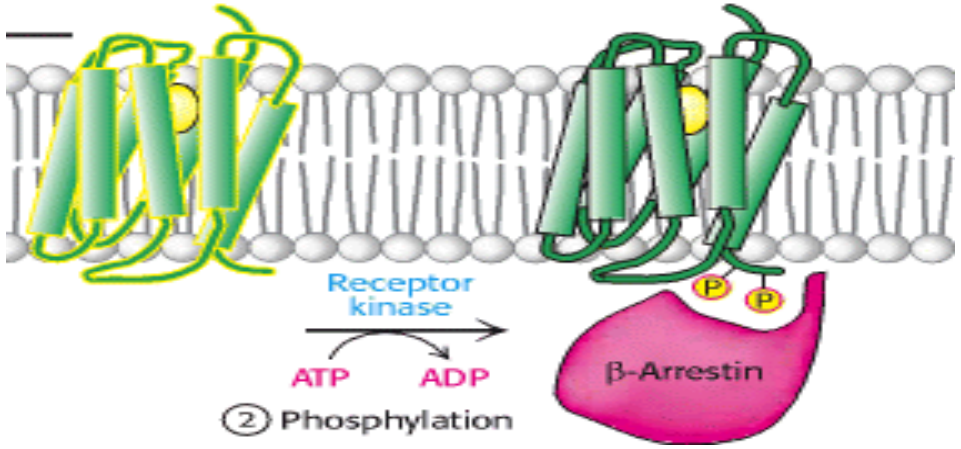
8.2.C. THEN WHAT? SWITCHING OFF

- Dissociation of the hormone
- GTPase activity of Gα subunit
- Hydrolysis of cAMP (phosphodiesterase)
- Phosphorylation of the hormone bound-receptor followed by binding to β-Arrestin



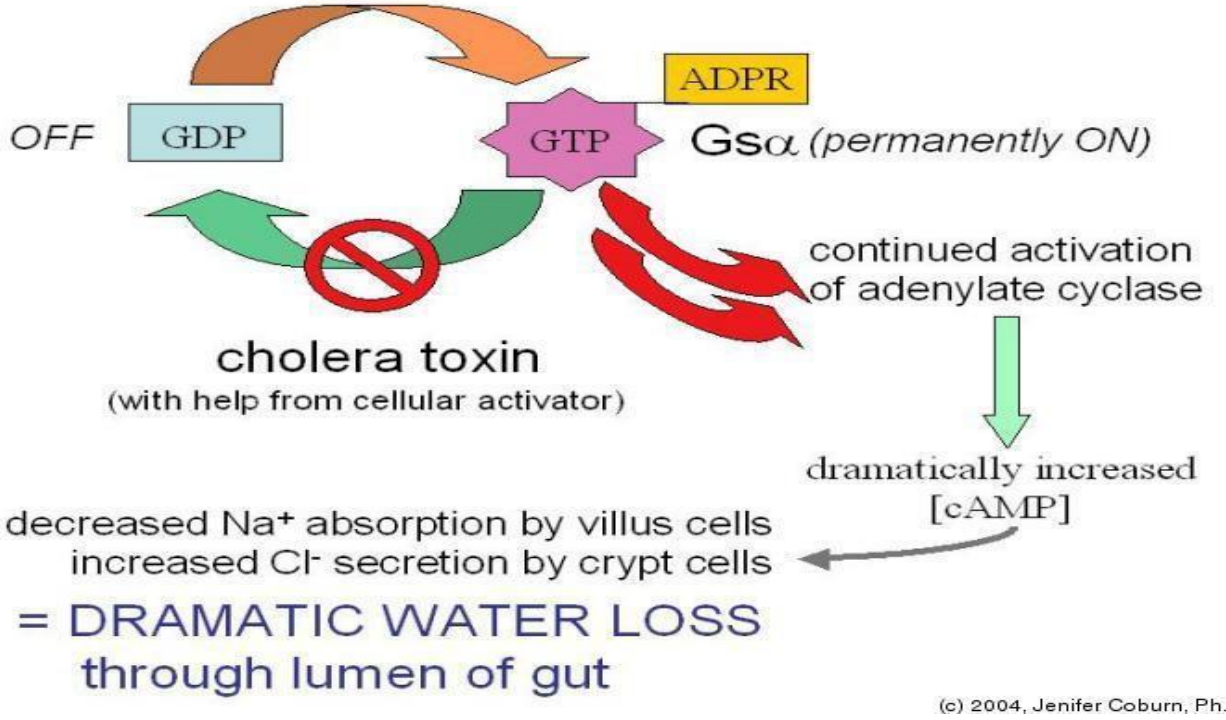
Desensitization

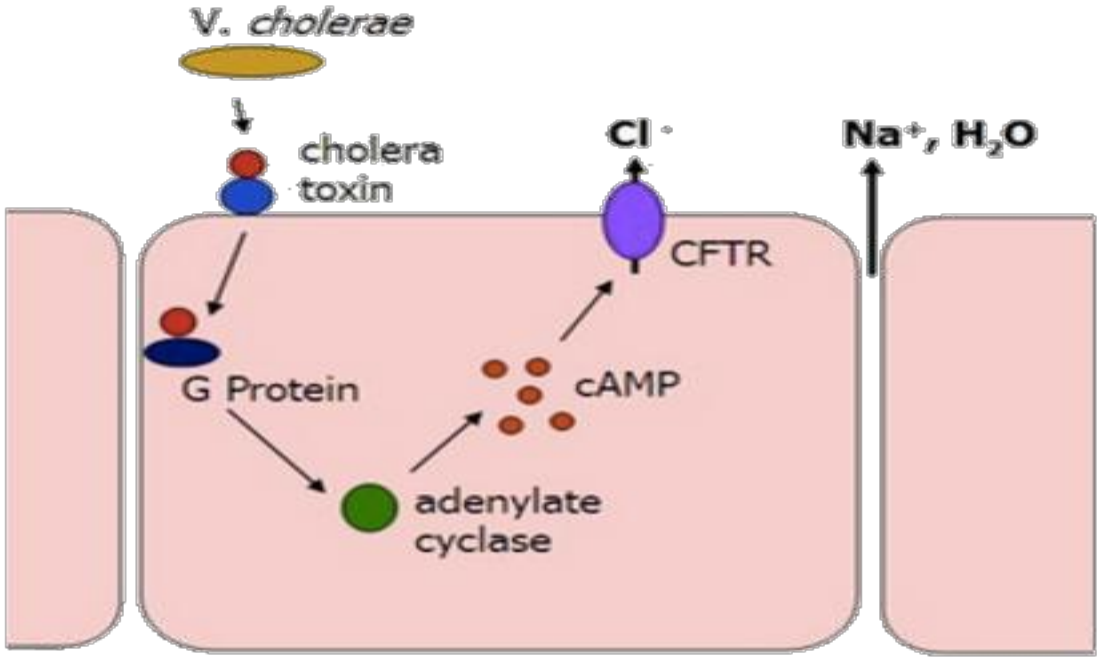




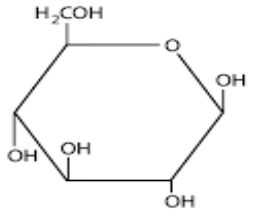
8.2.C. CHOLERA

- 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

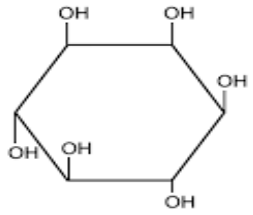




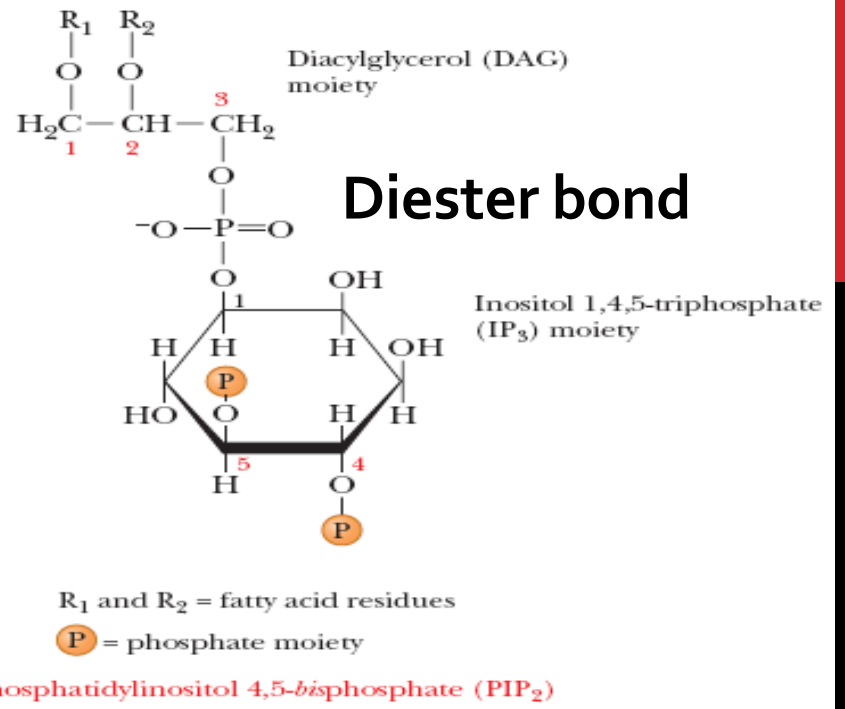
8.3 THE PHOSPHOINOSITIDE CASCADE



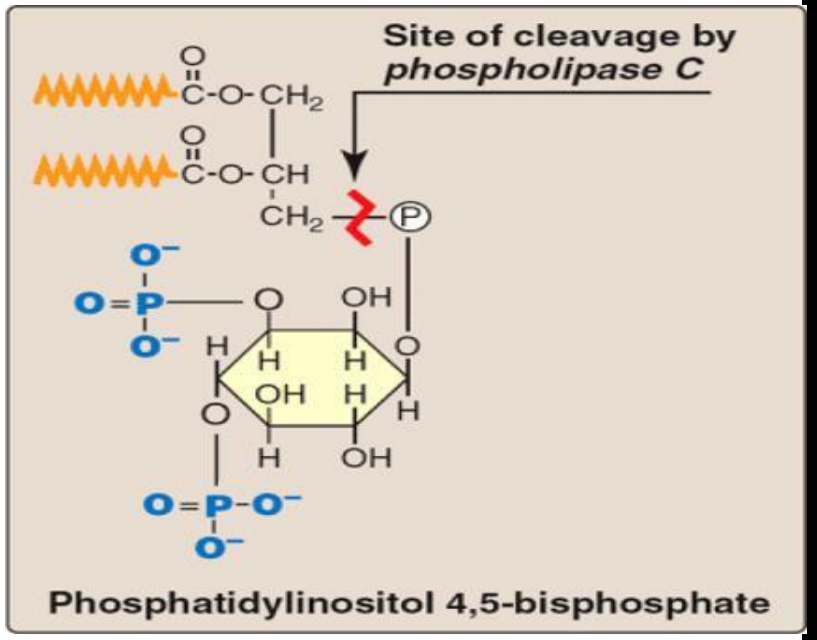
Glucose



Inositol



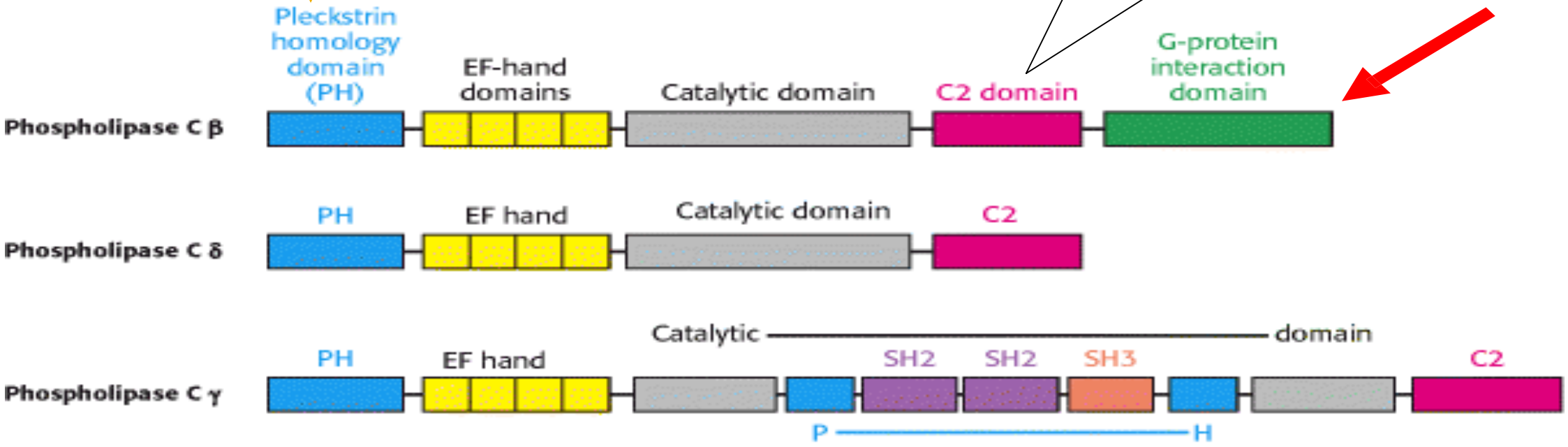
- Used by many hormones (e.g. ADH)
- Binding of a hormone to 7TM receptor
- Activation of G Protein
- Activation of Phospholipase C (many isoforms) – PIP2
- Two messengers are produced
- Inositol 1,4,5-trisphosphate, hydrophilic, (**Soluble**)
  - IP3 is the actual second messenger
- Diacyclglycerol, amphipathic (**membrane**)



THE DOMAIN STRUCTURE ISOFORMS OF PHOSPHOLIPASE C

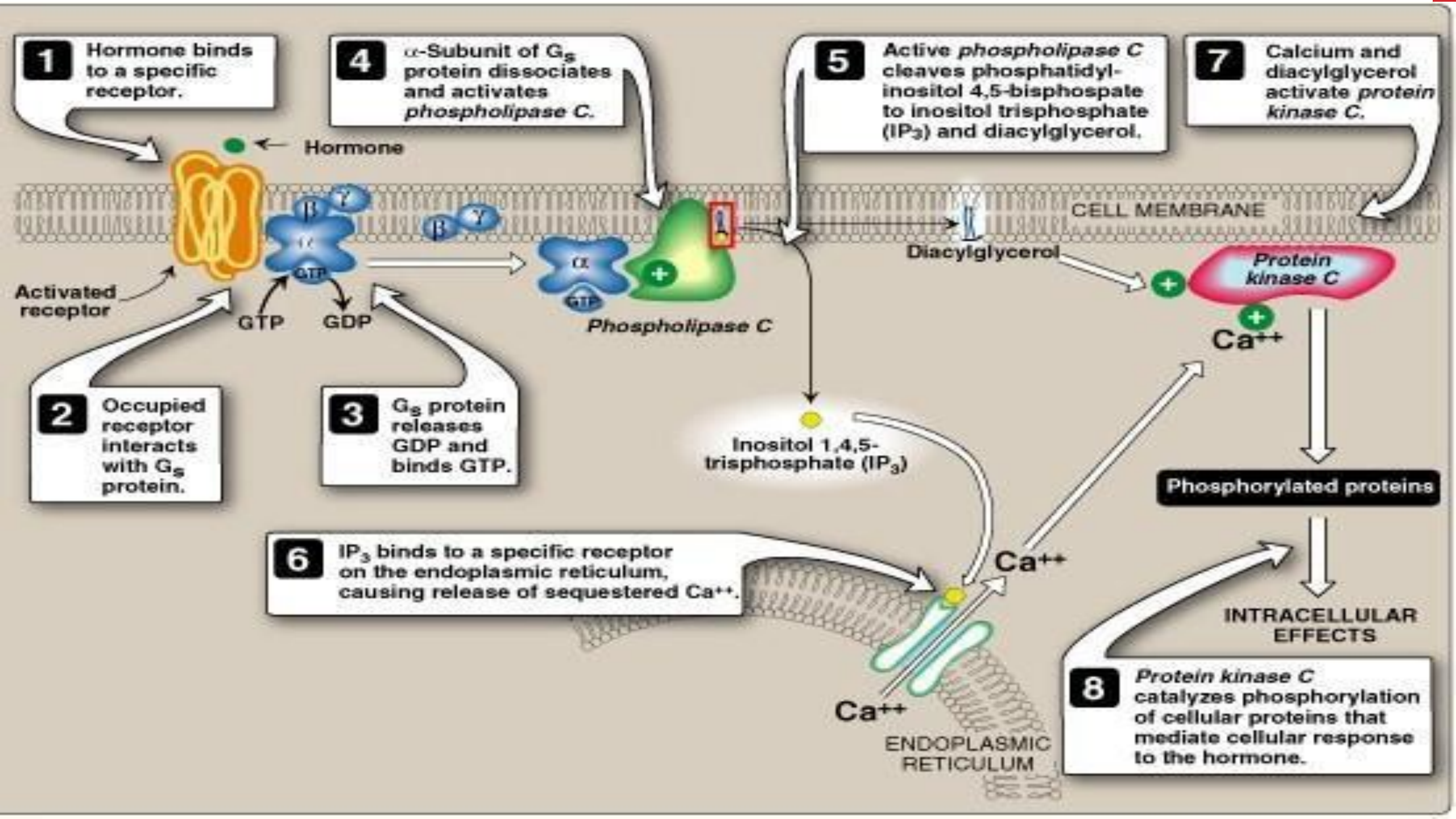
Binds a lipid head group

Binds phospholipid head group



BINDING OF A G PROTEIN BRINGS THE ENZYME INTO A CATALYTICALLY ACTIVE FORM

Membrane


1 Hormone binds to a specific receptor.
Hormone
Activated receptor
2 Occupied receptor interacts with G_s protein.
GTP
GDP
3 G_s protein releases GDP and binds GTP.
4 α-Subunit of G_s protein dissociates and activates *phospholipase C*.
Phospholipase C
5 Active *phospholipase C* cleaves phosphatidyl-inositol 4,5-bisphospate to inositol trisphosphate (IP_3) and diacylglycerol.
CELL MEMBRANE
Diacylglycerol
7 Calcium and diacylglycerol activate *protein kinase C*.
Protein kinase C
Ca^{++}
Inositol 1,4,5-trisphosphate (IP_3)
Phosphorylated proteins
6 IP_3 binds to a specific receptor on the endoplasmic reticulum, causing release of sequestered Ca^{++}.
Ca^{++}
Ca^{++}
ENDOPLASMIC RETICULUM
INTRACELLULAR EFFECTS
8 *Protein kinase C* catalyzes phosphorylation of cellular proteins that mediate cellular response to the hormone.

EFFECTS OF SECOND MESSENGERS

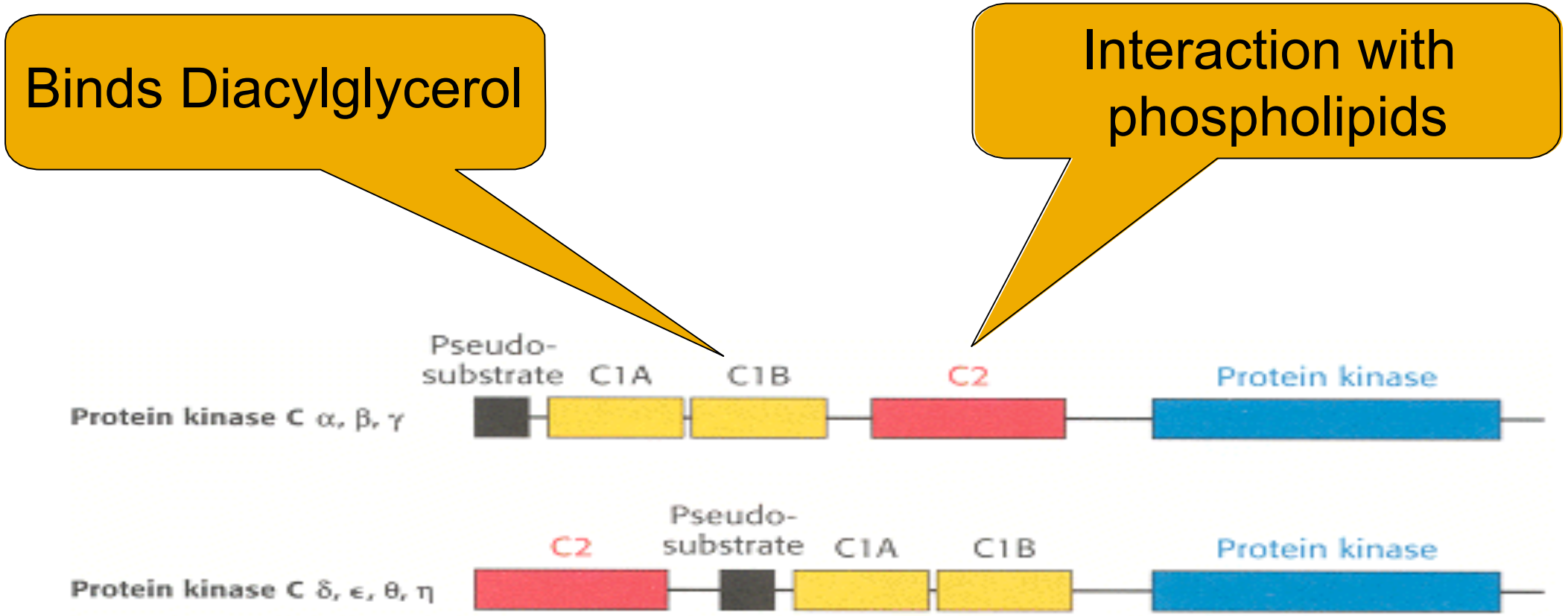
INOSITOL TRISPHOSPHATE (IP3)

- ❑ Opens Calcium Channels
- ❑ Binding to IP3-gated Channel
- ❑ Cooperative binding (sigmoidal)

DIACYLGLYCEROL (DAG)

- ❑ Activates Protein Kinase C
- ❑ Ca^{+2} is required
- ❑ Phosphorylation of many target proteins

THE DOMAIN STRUCTURES OF PROTEIN KINASE C ISOFORMS



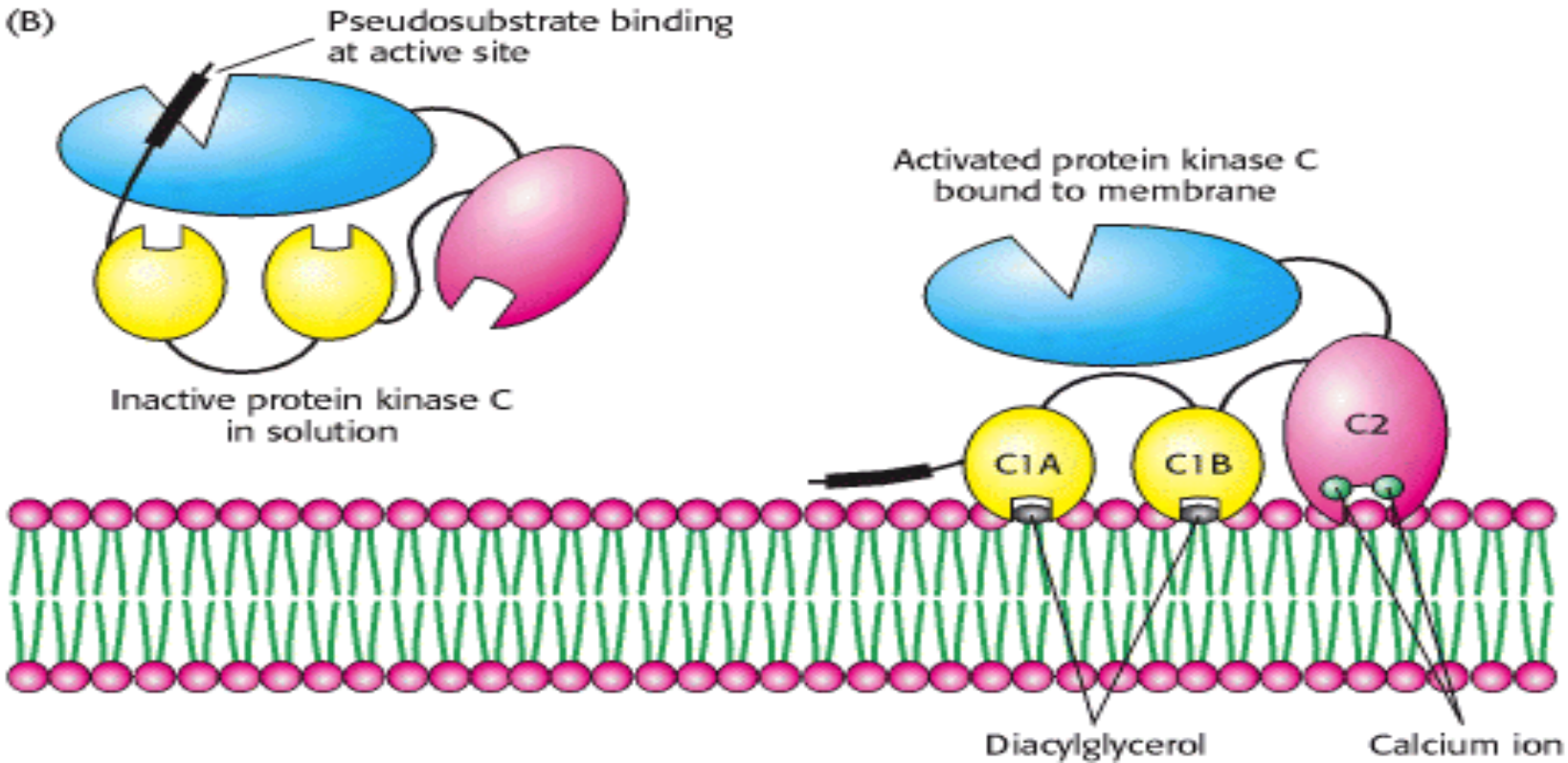
PSEUDO-SUBSTRATE SEQUENCE

Resembles the substrate sequence: A-R-K-G-A-L-R-Q-K

Substrate Sequence: (S,T)

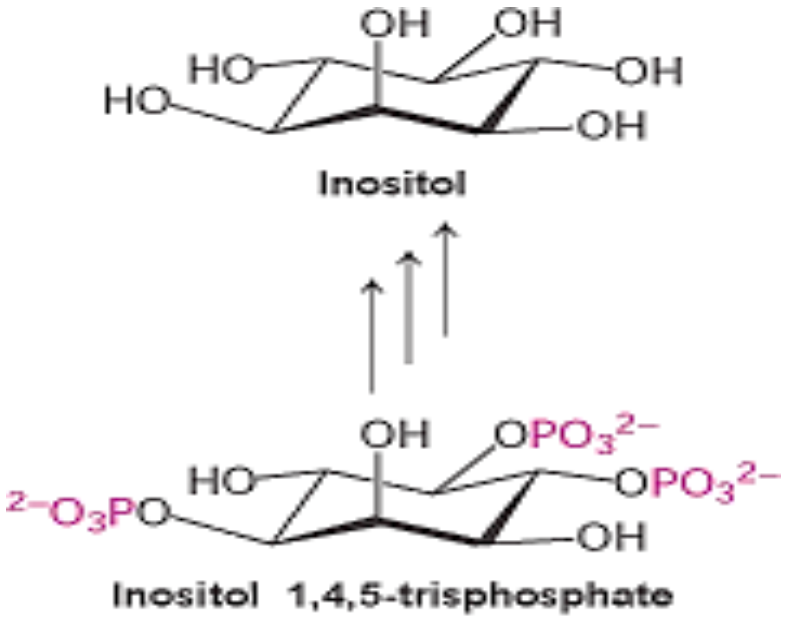
Binds to the Enzyme's Active Site

Competitive Inhibitor

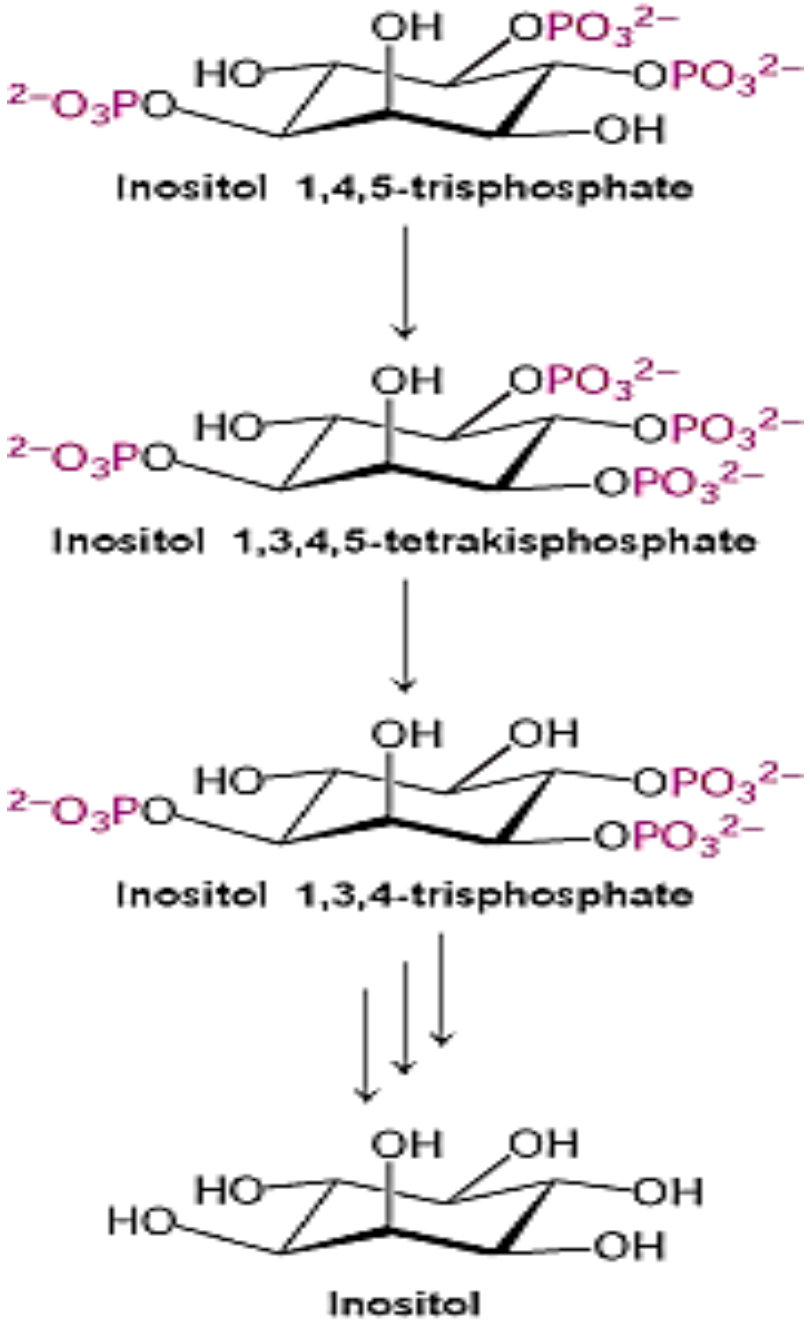


TERMINATION OF IP3 SIGNAL

- IP_3 is a Short-Lived Messenger

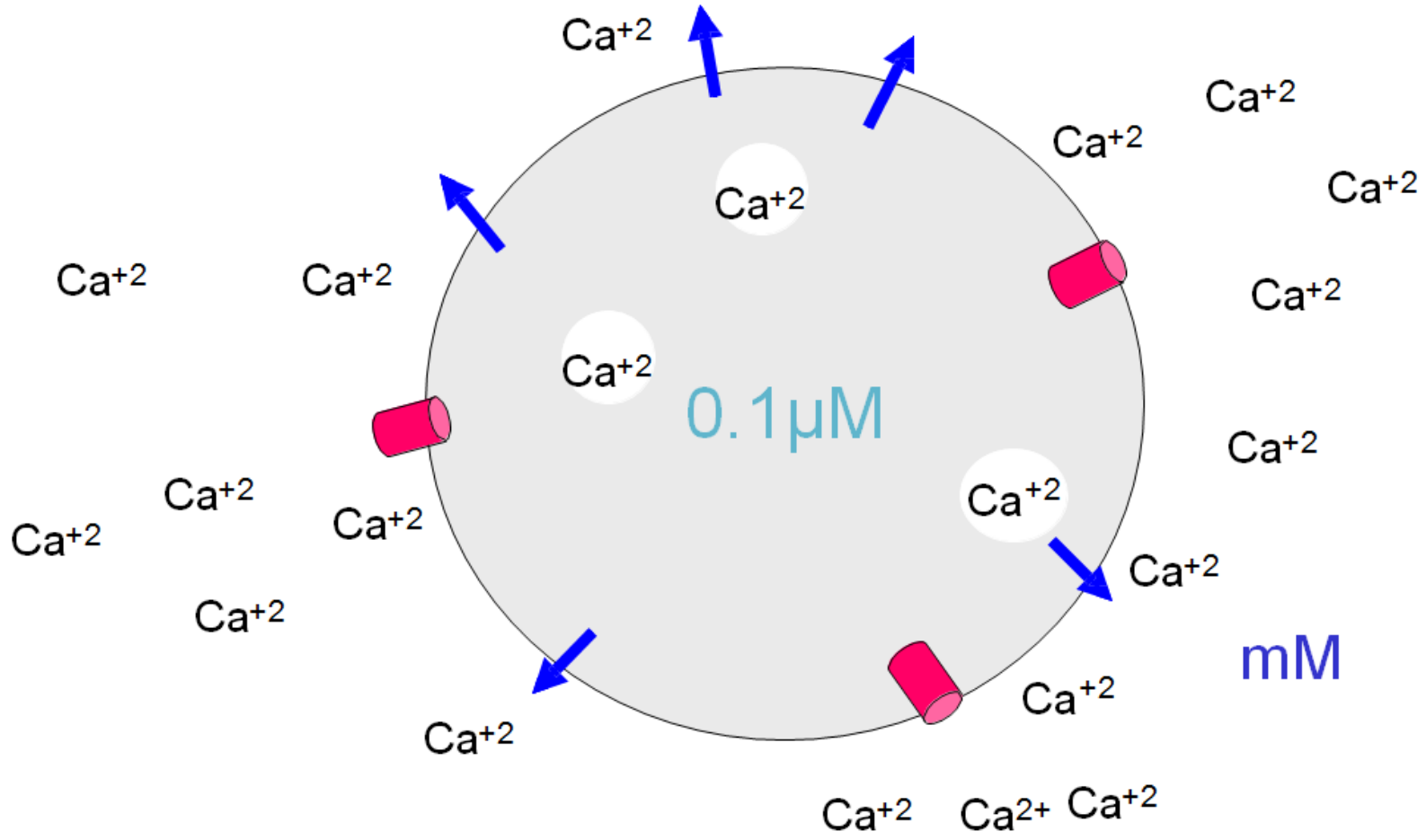


Lithium ions, used to treat some psychological disorders Inhibits IP_3 recycling



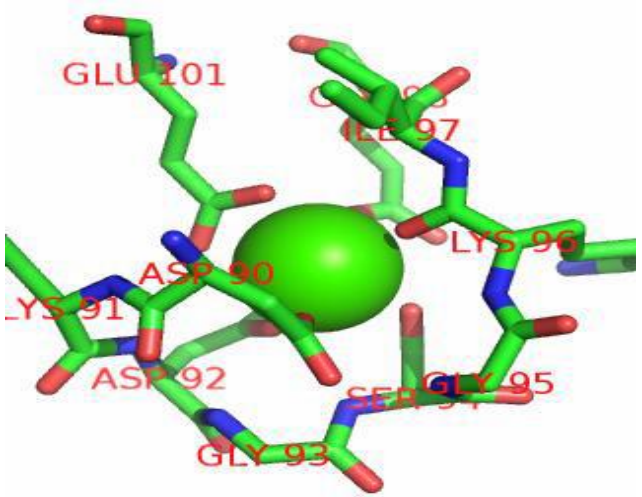
WHY CALCIUM

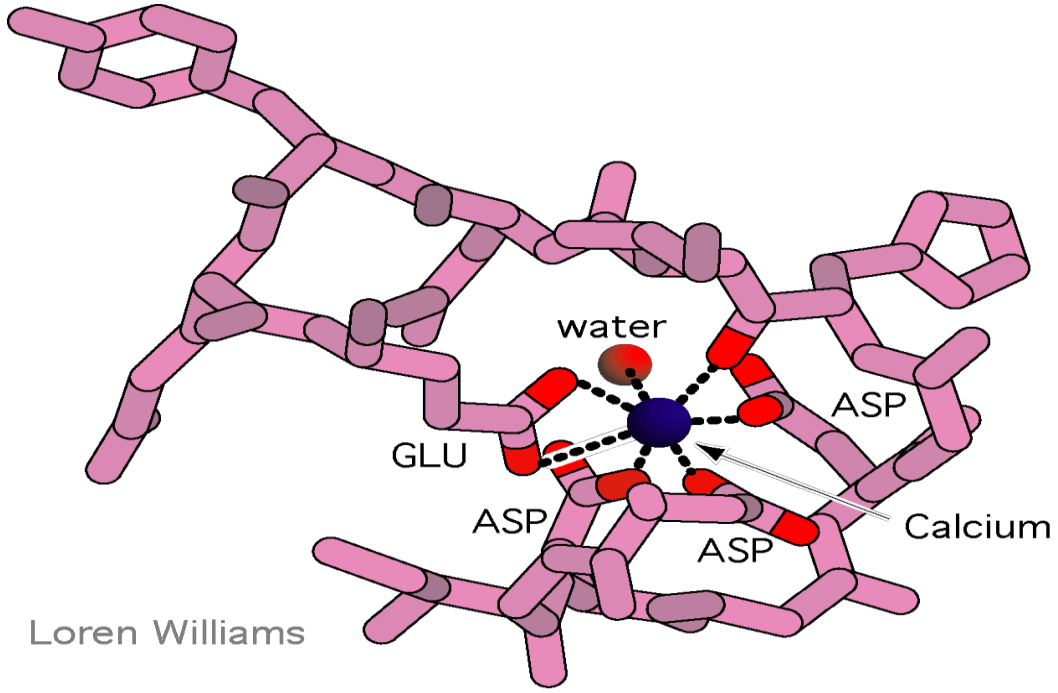
- A large difference in concentration

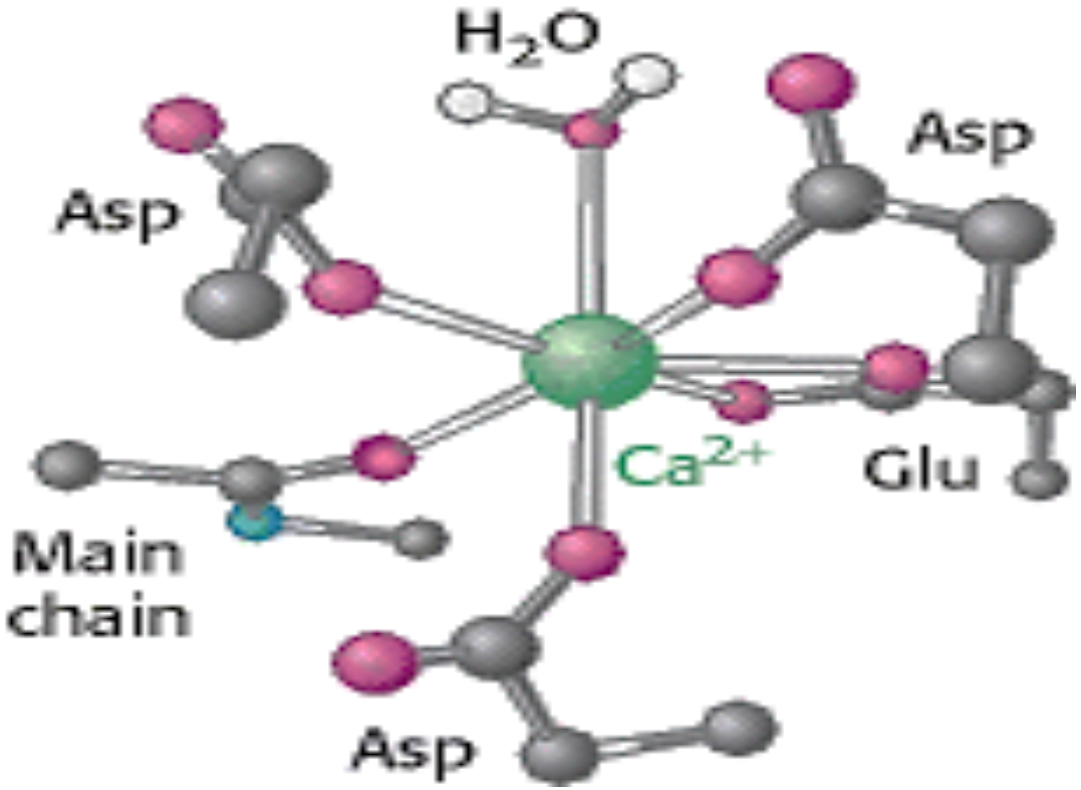


WHY CALCIUM

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

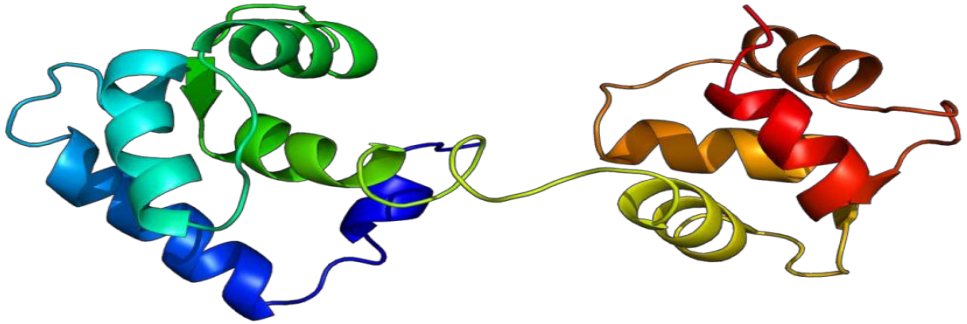




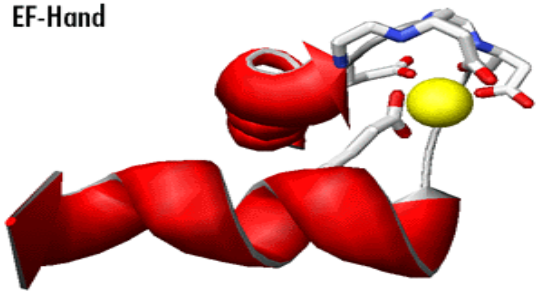


CALCIUM BINDING PROTEINS

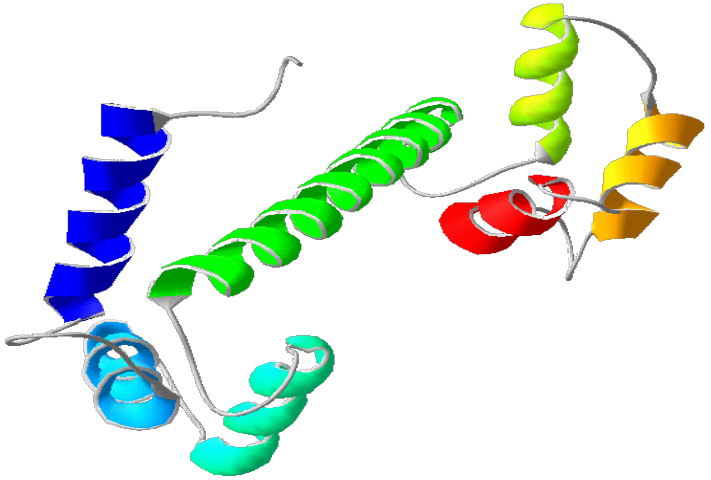
- **Mediate the effects of Calcium (Ca^{+2})**
- **Many proteins**
- **Calmodulin, Troponin C, Parvalbumin**



EF-Hand

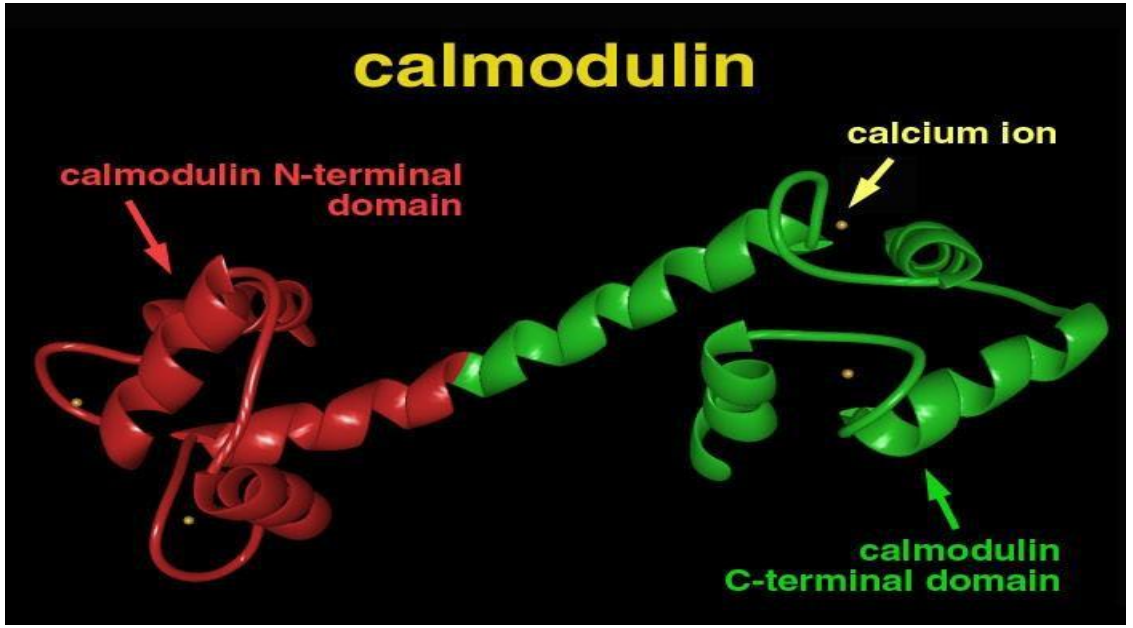


- **Similar structures**
  - Rich in Asp and Glu
    - Gln, Asn, Ser
  - Several α helical segments
  - Binding site is formed by
    - Helix Loop Helix
    - Super-secondary structure

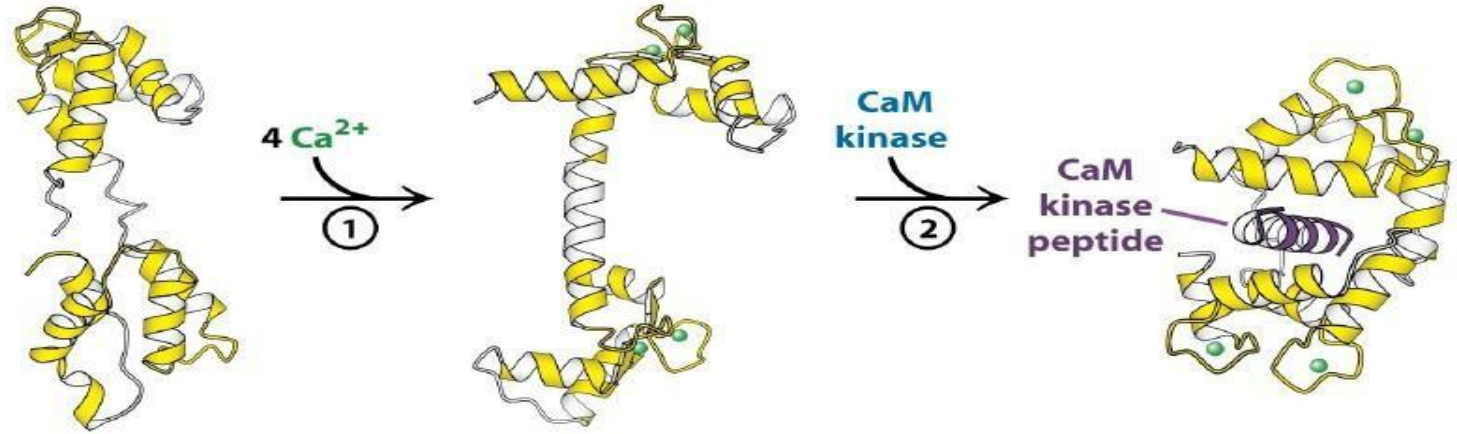


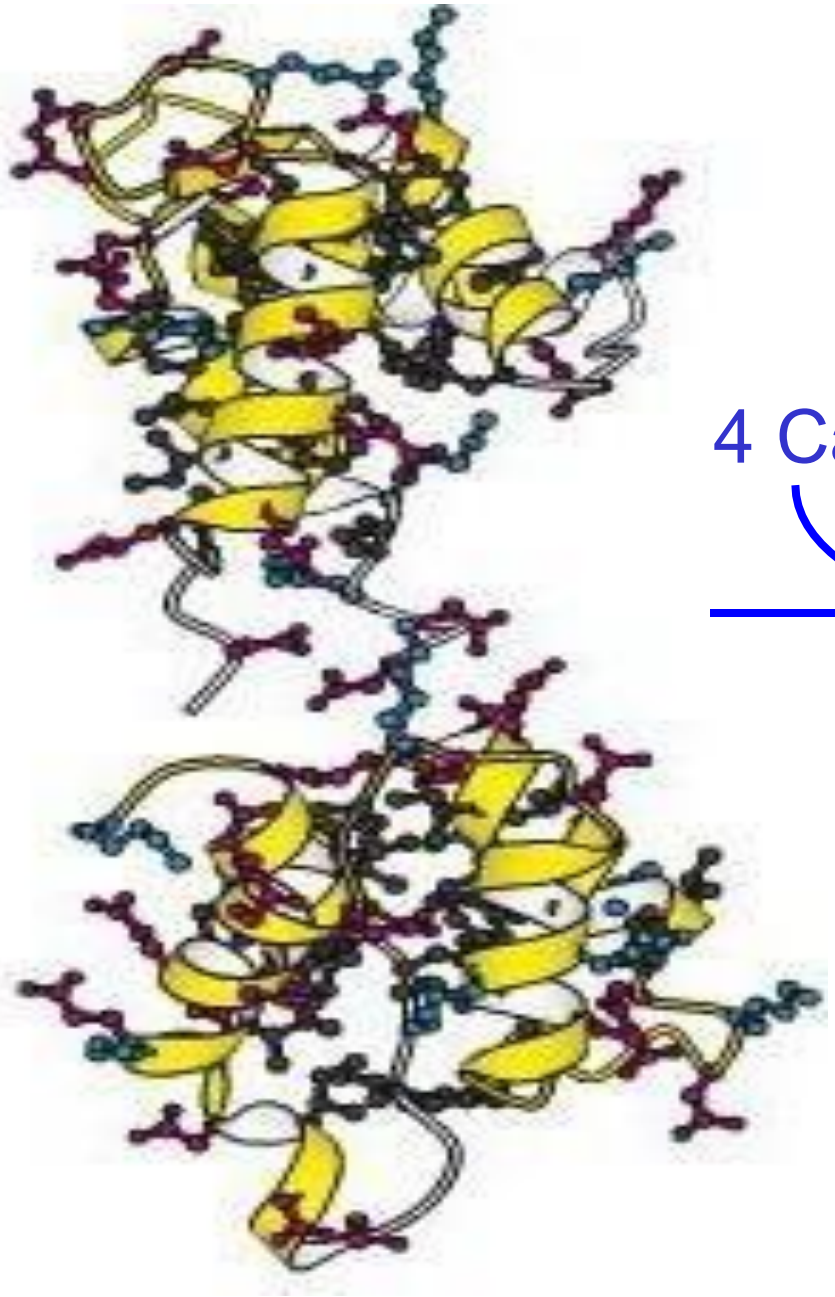
CALMODULIN ≈ 17 KD

149 amino acids

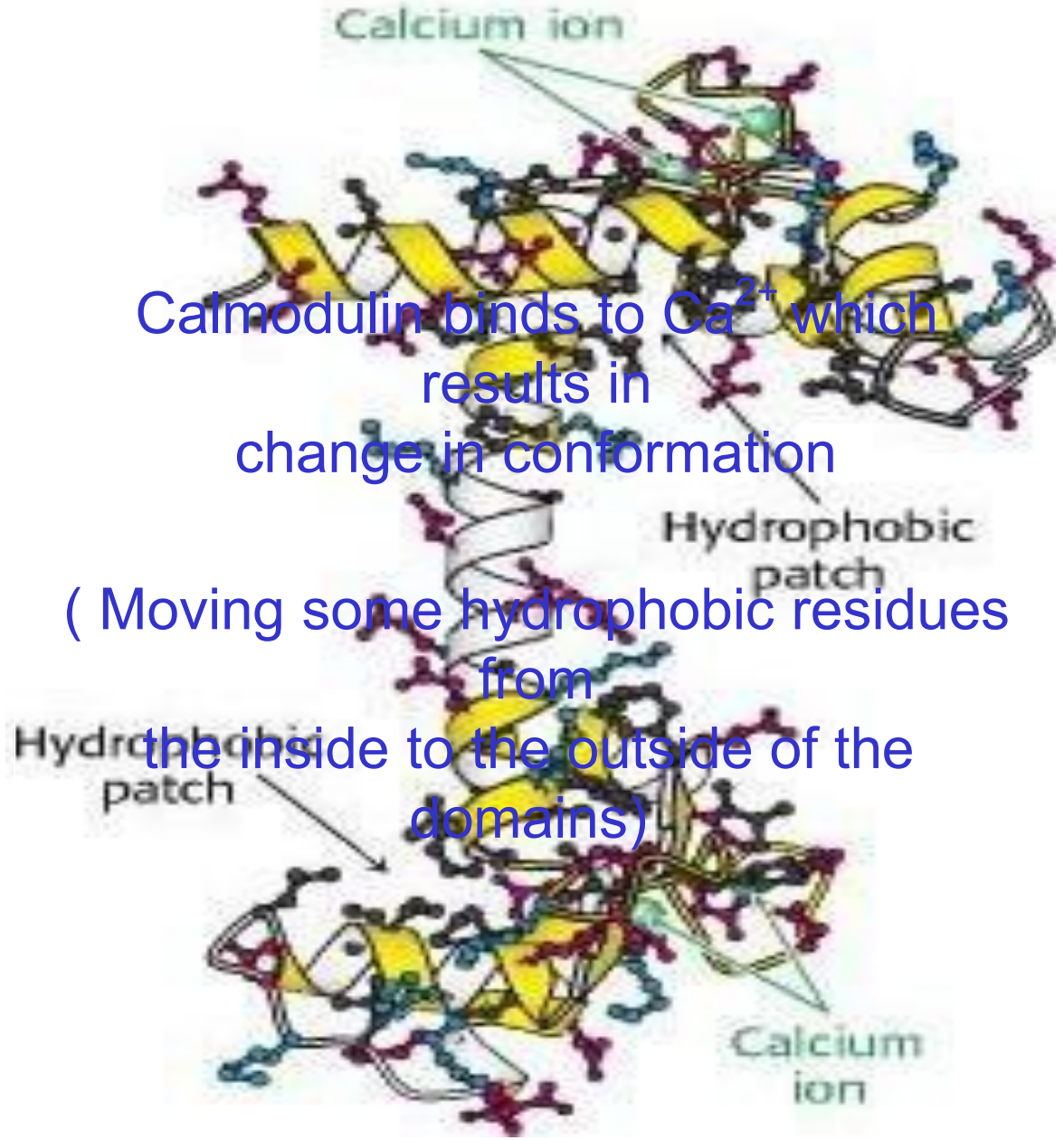


- Found in almost all eukaryotes
- Consists of two globular regions
- Connected by flexible region
- Each contains 2 EF hands
- Four Ca^{+2} binding sites
- Calcium-Calmodulin complex can bind to a large number of target proteins including: **Calmodulin-dependant Protein Kinase** **Ca^{2+} ATP'ase Pump**





4 Ca^{2+}

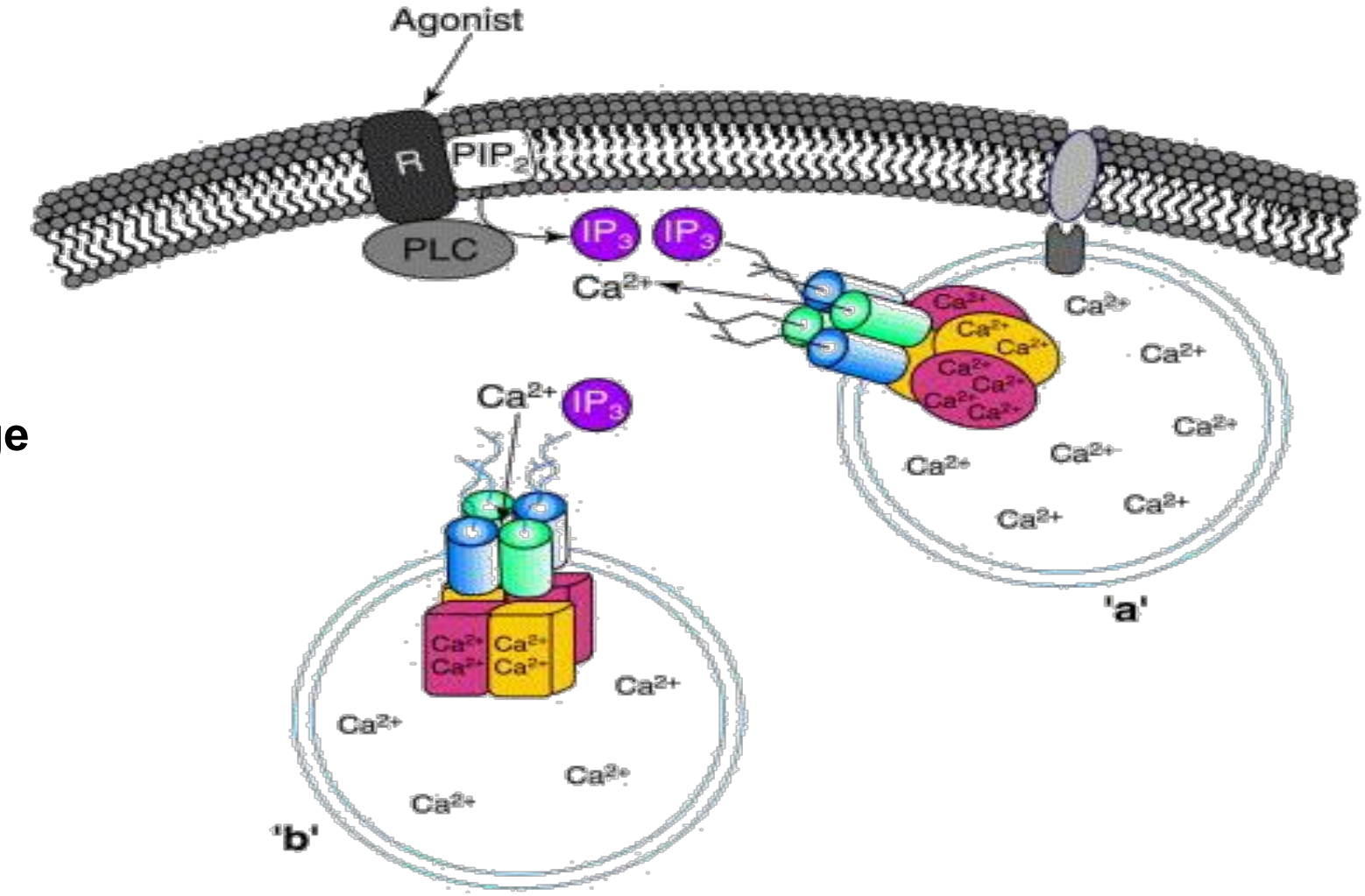


Calmodulin binds to Ca^{2+} which results in
change in conformation

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

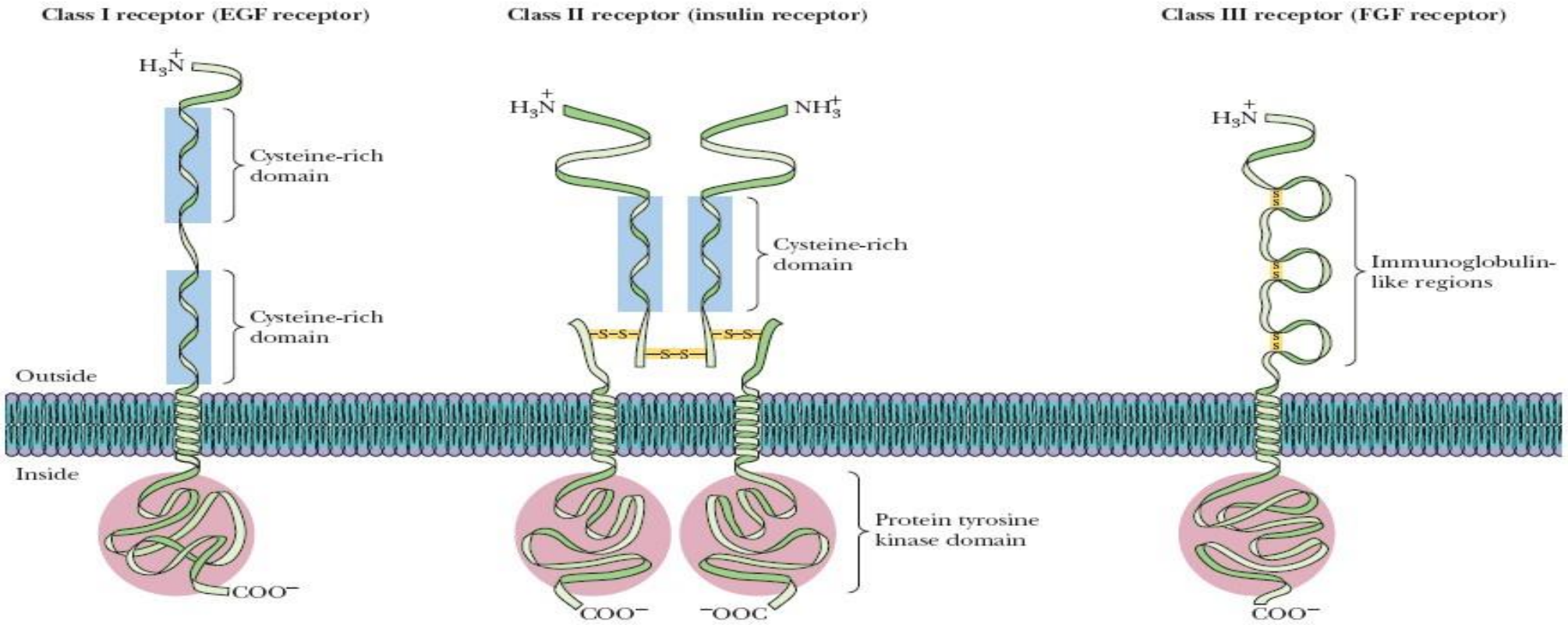
CALCIUM TRANSPORTER

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

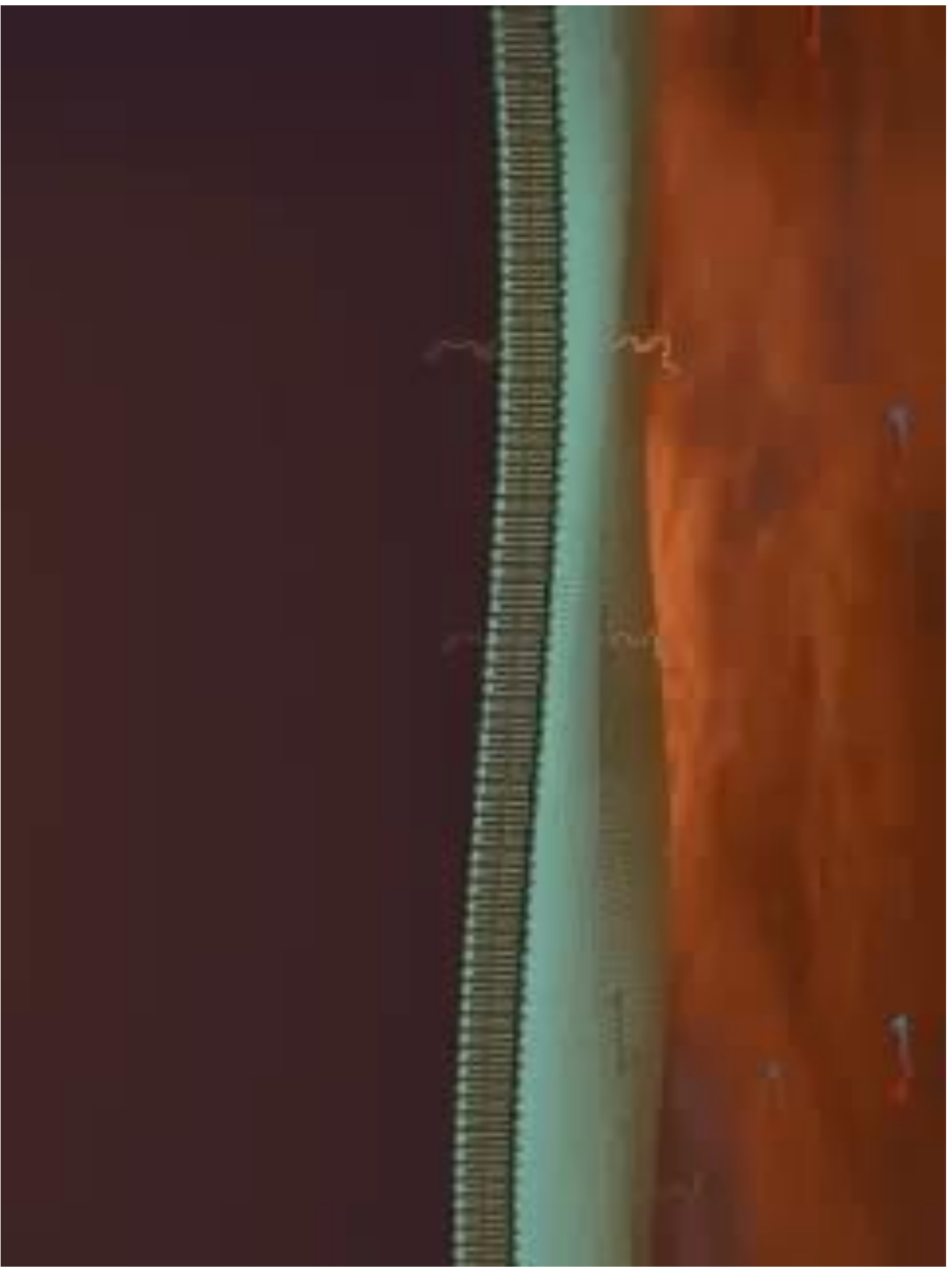


8.4 RECEPTOR TYROSINE KINASES CASCADE

- Second Messengers
- Span the membrane, several subclasses

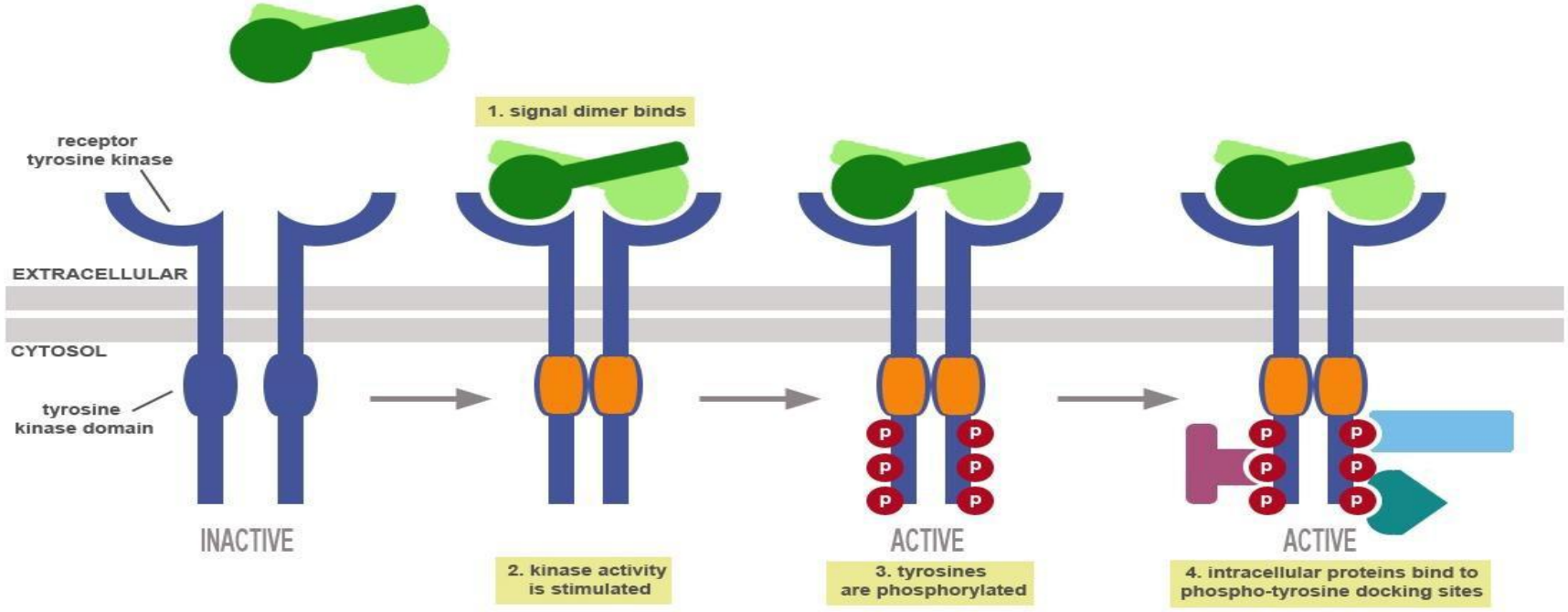


RECEPTOR TYROSINE KINASES



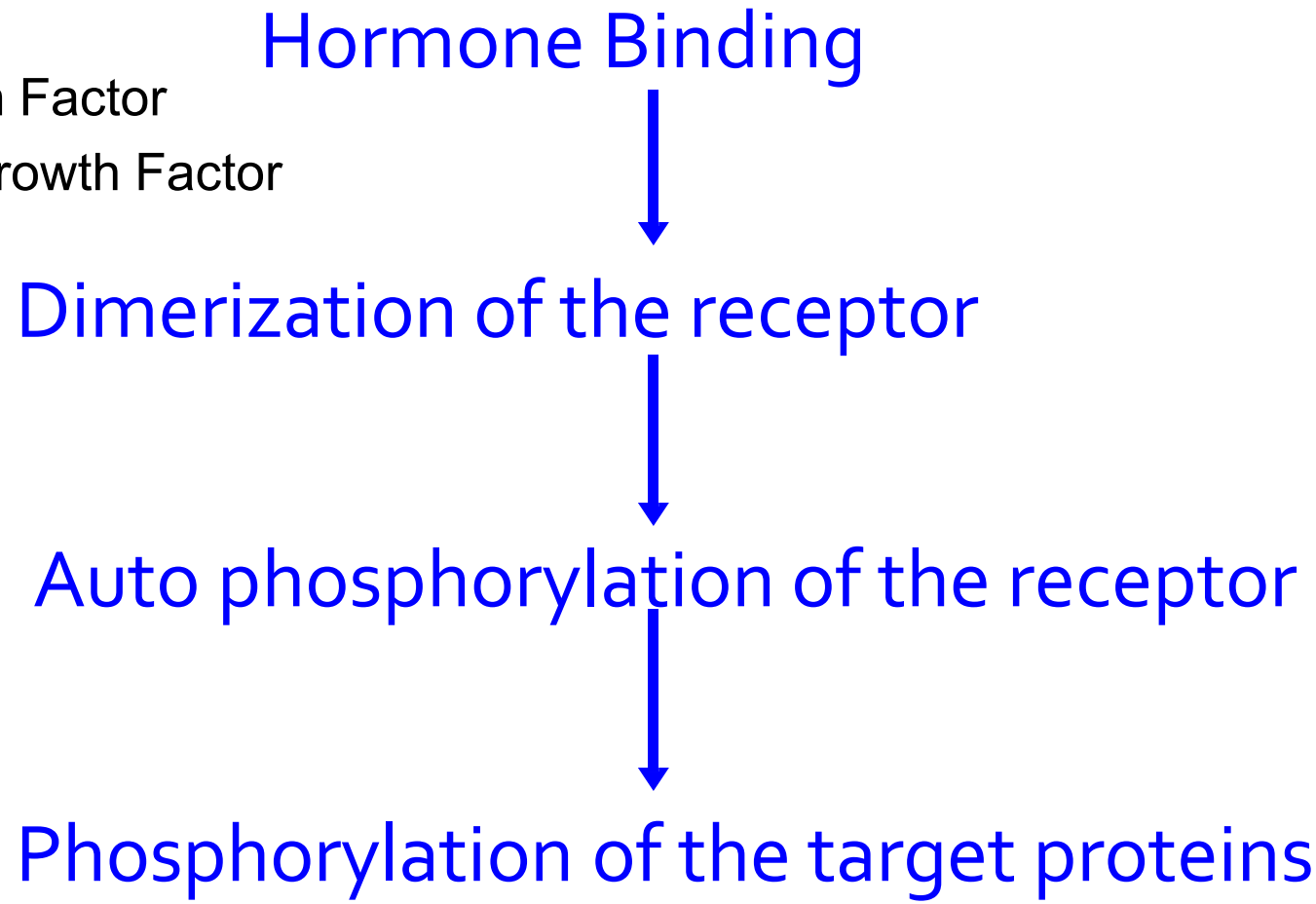
RECEPTOR TYROSINE KINASES CASCADE

- **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



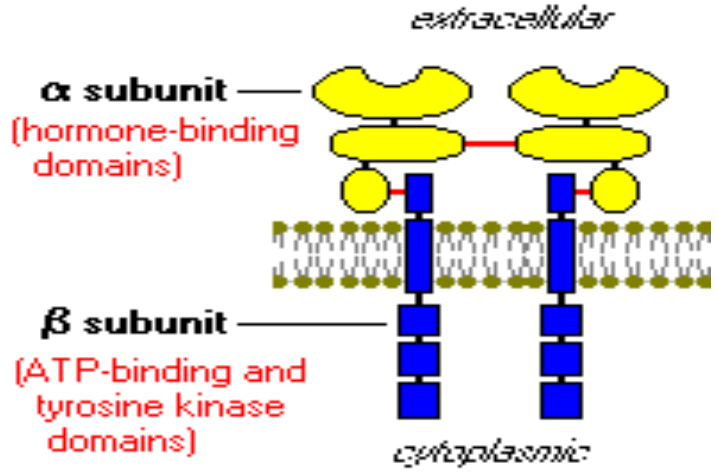
SIGNAL TRANSDUCTION THROUGH TYROSINE KINASES

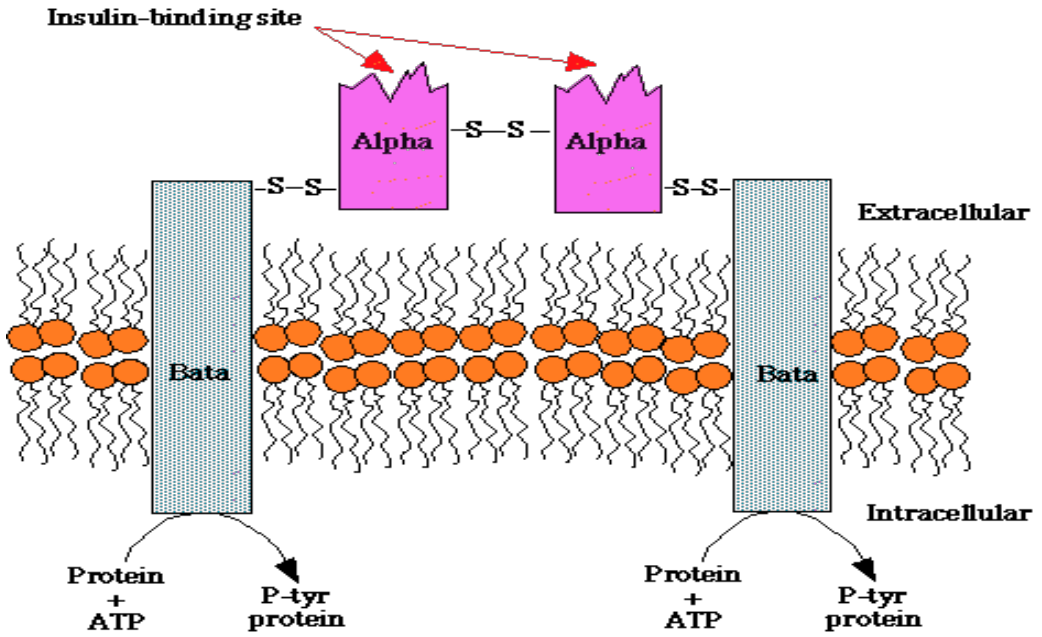
- **Growth hormones:**
  - Epidermal Growth Factor
  - Platelet-derived growth Factor
  - GH
  - Insulin



INSULIN RECEPTOR

- Tetramer (2α; 2β), dimer (2αβ pairs)
- Disulfide bridges
- Insulin Binding → Activation of the Kinase

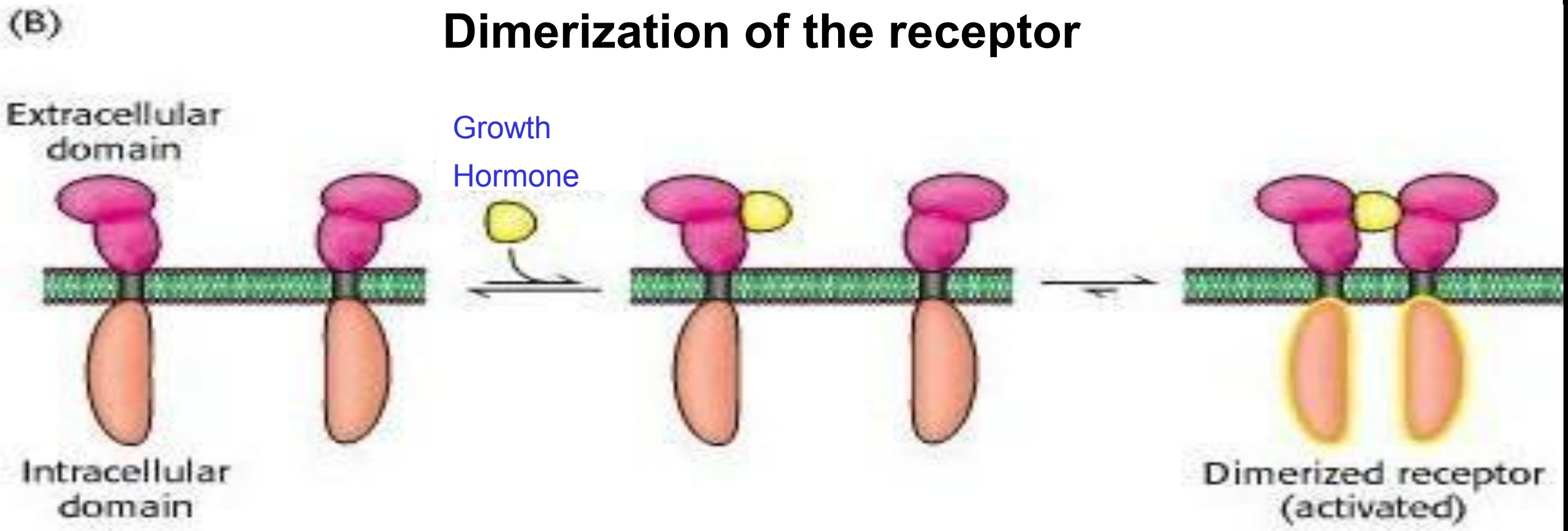




GROWTH HORMONE DIMERIZATION

Binding of one molecule of growth hormone

Dimerization of the receptor



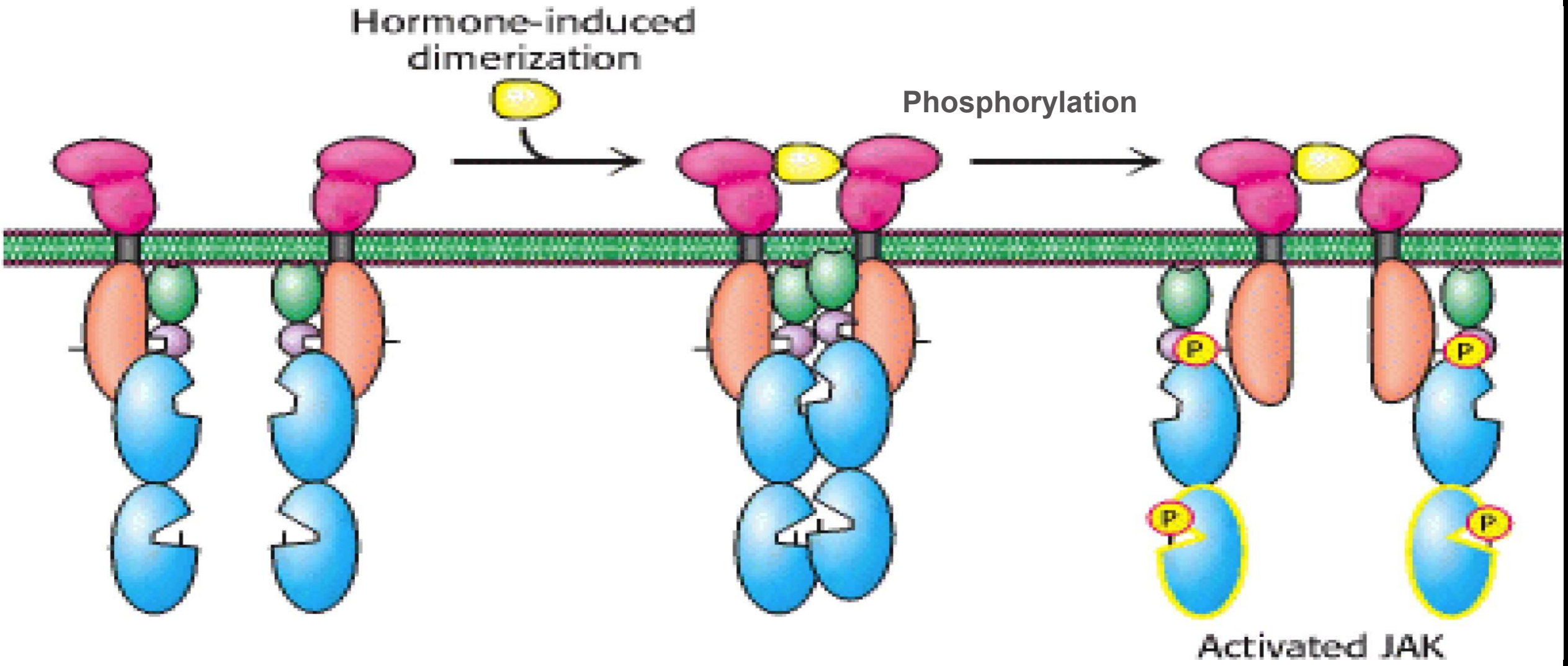
Janus

Each Intracellular Domain is associated with a protein kinase called Janus Kinase 2

Interaction with membrane

Binds peptides that contain Phosphotyrosine

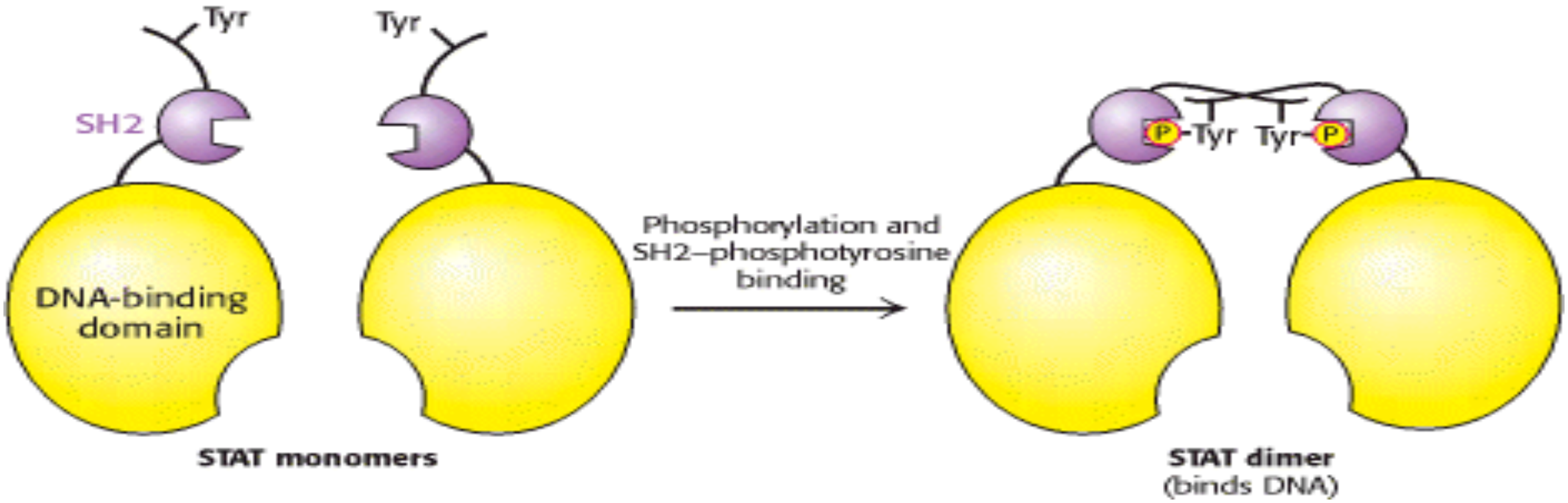
RECEPTOR DIMERIZATION BRINGS TWO JAKS TOGETHER EACH PHOSPHORYLATES KEY RESIDUES ON THE OTHER



ACTIVATED JAK2 CAN PHOSPHORYLATE OTHER SUBSTRATES

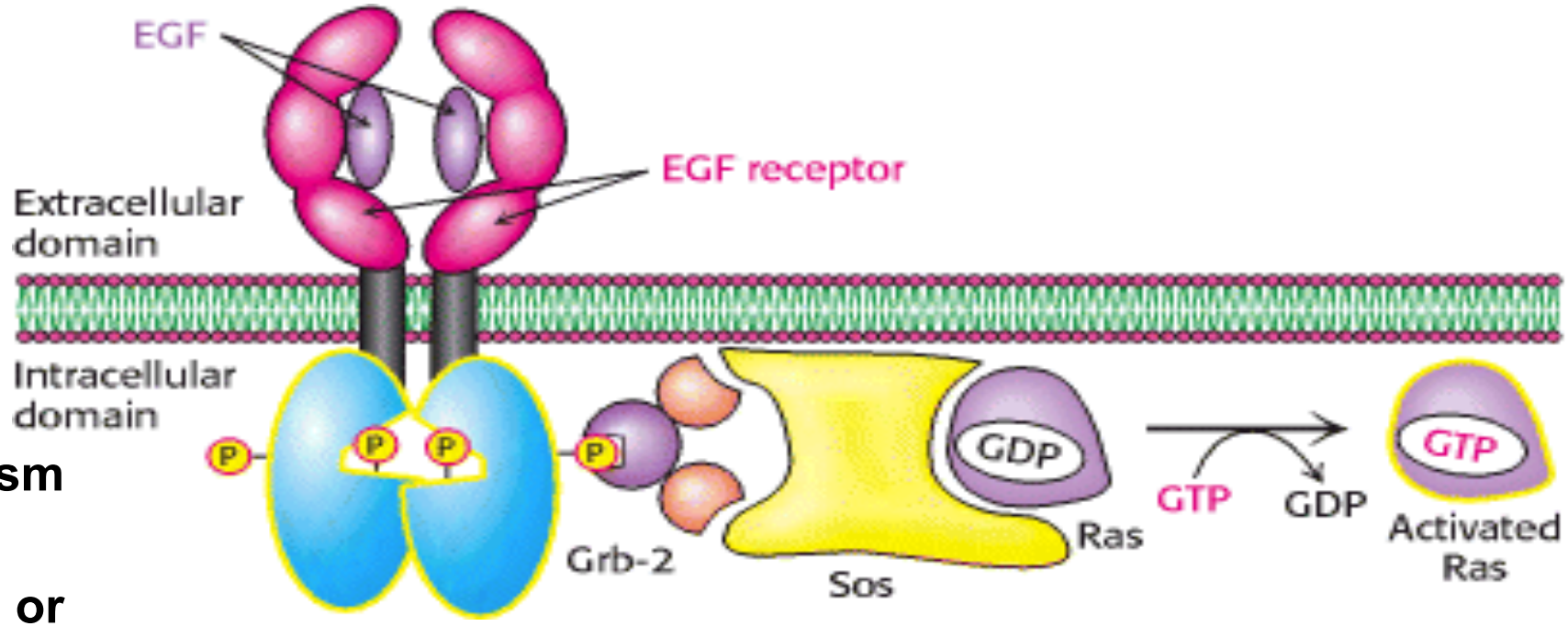
- **STAT**
  - Signal Transducers & Activators of Transcription
- **Regulator of transcription**
- **STAT Phosphorylation**
- **Dimerization**
- **Binding to specific DNA sites**
- **If JAK2 remains active it will produce Cancer**

- STAT is phosphorylated on a tyrosine residue near the carboxyl terminus
- Phosphorylated tyr binds to SH2 domain of another STAT molecule



RAS IS A MEMBER OF SMALL G PROTEINS FAMILY

- Monomeric
- 2 forms: GDP ↔ GTP
- Smaller (1 subunit)
- GTPase activity
- Many similarities in structure and mechanism with Gα
- 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 Ras proteins

- Mutation →
  - Loss of ability to hydrolyze GTP
    - → Ras is locked in “ON” position
      - →continuous stimulation of growth