General Mechanisms of Hormone Actions

Endocrine Block

OBJECTIVES

By the end of this lecture, students should be able to:

- **Acquire the knowledge for general consequence of hormone-receptor interaction**
- **Understand different mechanisms of action of hormones**
- **Recognize the biomedical importance due to disturbance in the normal mechanisms of hormonal action**

Lecture Outlines

- **Background**
- **Factors determining the response of a target cell to a hormone**
- **Hormone-receptor interaction**
- **General features of hormone classes**
- **Classification of hormones by mechanism of action**
- **Biomedical importance**

Background

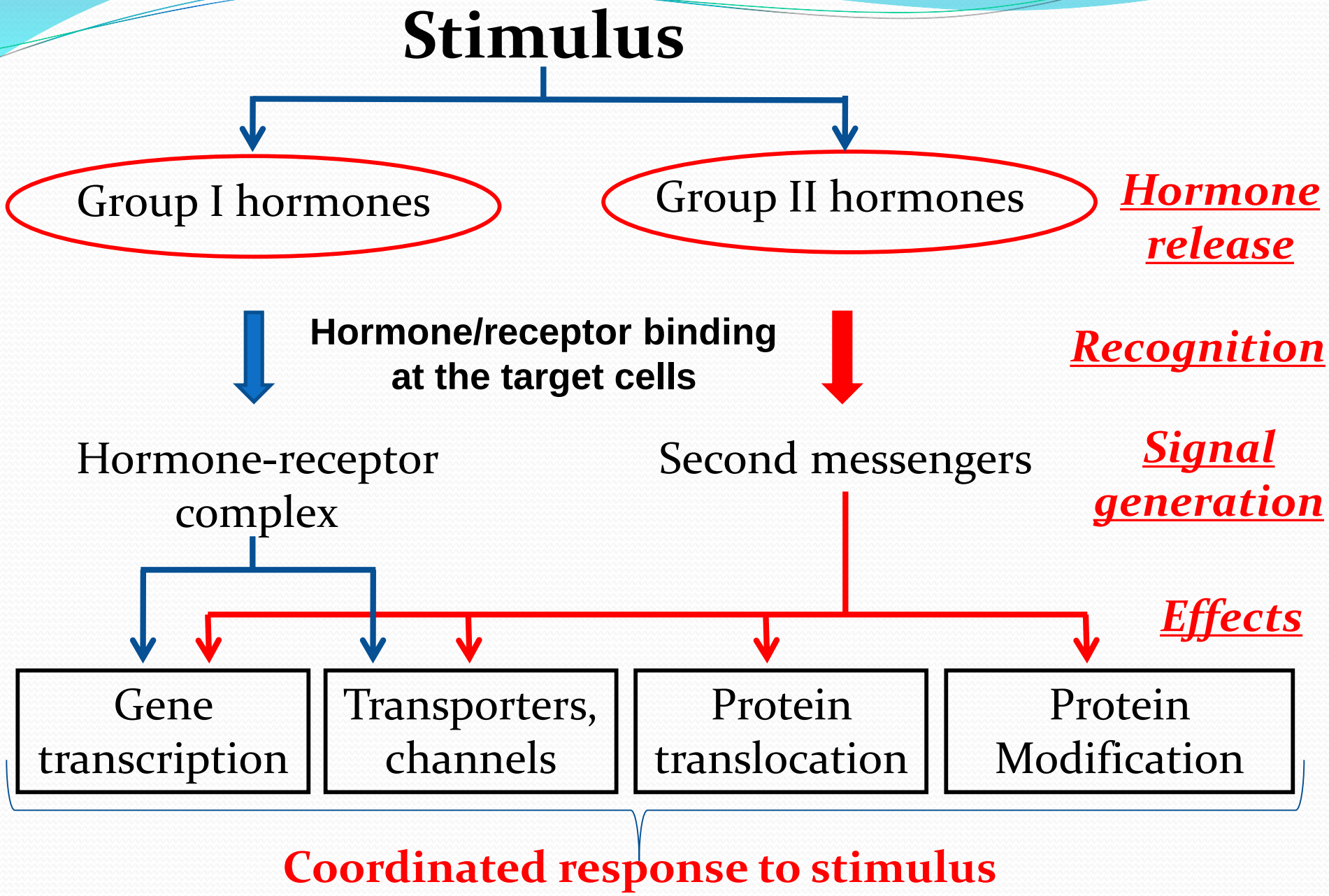
- **Multicellular organisms depend in their survival on their adaptation to a constantly changing environment**
- **Intercellular communication is necessary for this adaptation to take place**
- **Human body synthesizes many hormones that can act specifically on different cells of the body**

Background

- **More than one hormone can affect a given cell type**
- **Hormones can exert many different effects in one cell or in different cells**
- **A target is any cell in which the hormone (ligand) binds to its receptor**

Factors determining the response of a target cell to a hormone

- The rate of synthesis & secretion of the hormones
- The conversion of inactive forms of the hormone into the fully active form
- The rate of hormone clearance from plasma (half-life & excretion)
- The number, relative activity, and state of occupancy of the specific receptors
- Post-receptor factors


Stimulus
Group I hormones
Group II hormones
Hormone release
Hormone/receptor binding at the target cells
Recognition
Hormone-receptor complex
Second messengers
Signal generation
Effects
Gene transcription
Transporters, channels
Protein translocation
Protein Modification
Coordinated response to stimulus

General Features of Hormone Classes

	Group I	Group II
Types	Steroids Thyroid Hs (T_3 & T_4) Calcitriol, retinoids	Polypeptides Glycoproteins Catecholamines
Solubility	Lipophilic	Hydrophilic
Transport proteins	Yes	No
Plasma half-life	Long (hours – days)	Short (minutes)
Receptor	Intracellular	Plasma membrane
Mediator	Receptor-hormone complex	cAMP, cGMP, Ca^{2+}, metabolites of complex phosphoinositols, tyrosine kinase cascades

Classification of Hormones by Mechanism of Action

I. Hormones that bind to intracellular receptors (Steroid-Thyroid superfamily):

Steroid hormones
Thyroid Hormones (T_3 & T_4)
Calcitriol (active form of vitamin D, 1,25$[OH]_2$-D_3)
Retinoic acid

Mechanism of Action of Steroid-Thyroid Hormones

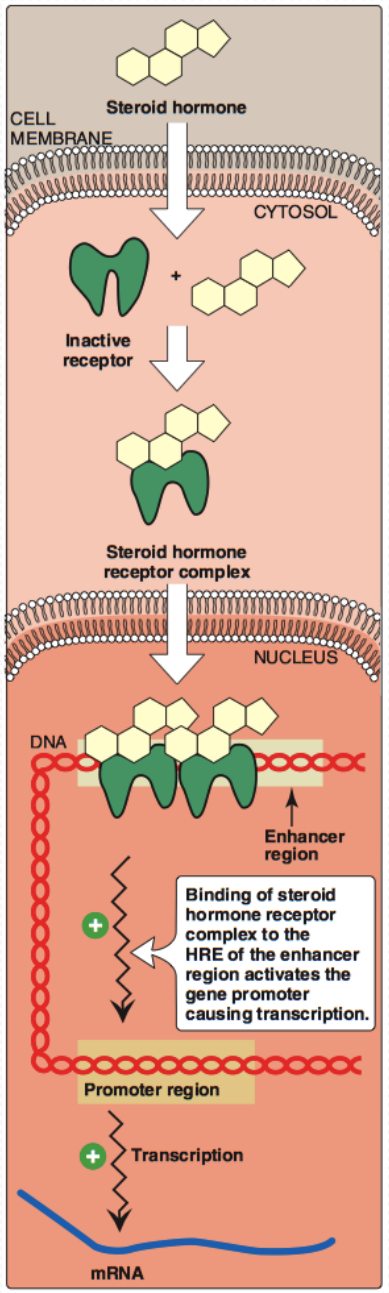
Steroid Hormones:

- Glucocorticoids
- Mineralocorticoids
- Sex hormones:
- Male sex hormones: Androgens
- Female sex hormones:Estrogens & Progestins

Thyroid Hormones (T_3 & T_4)

Calcitriol ($1,25[OH]_2$-D_3)

Retinoic acid



Classification of Hormones by Mechanism of Action

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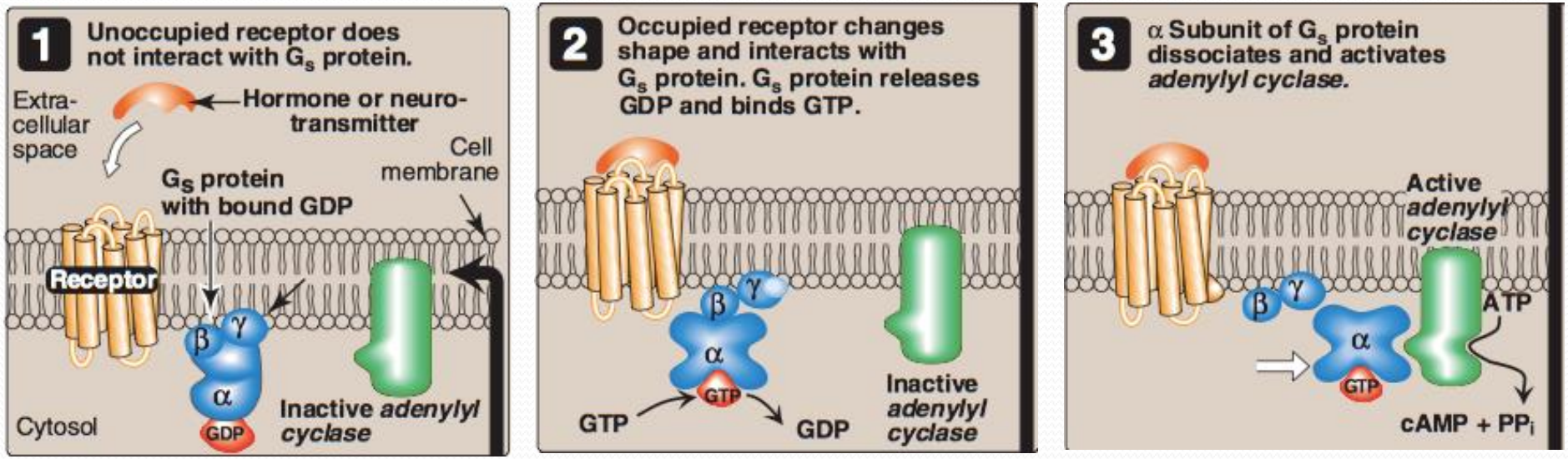
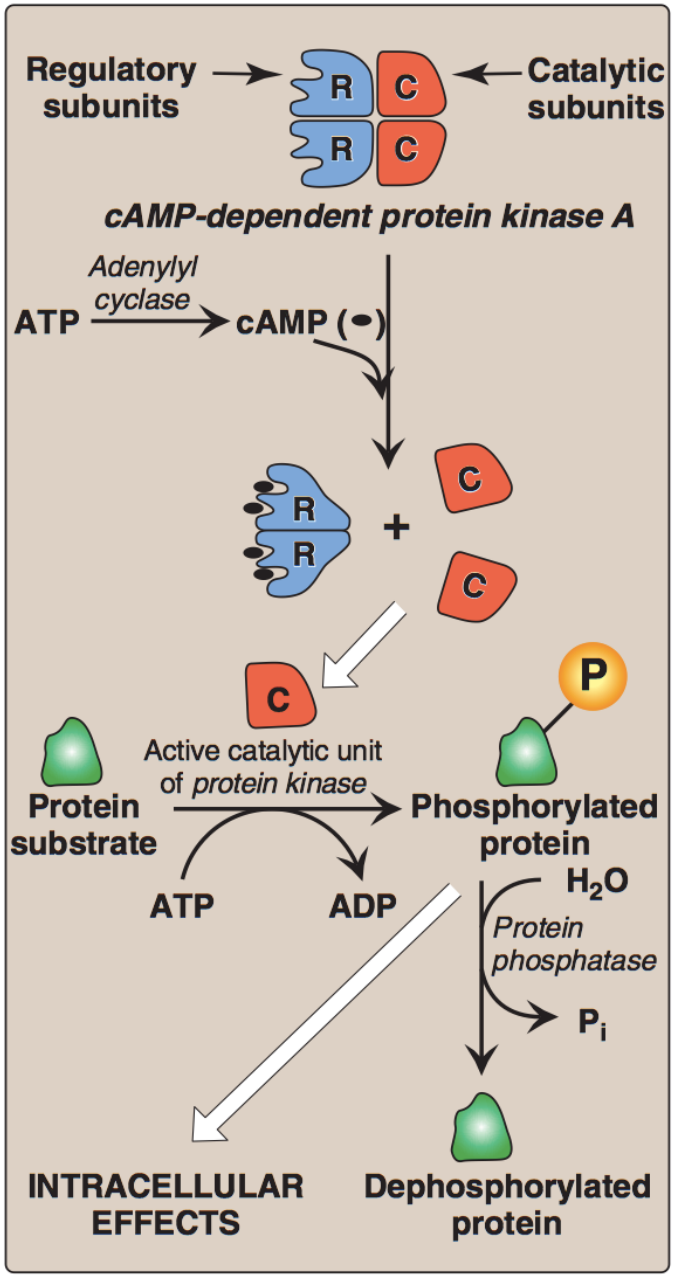
II. Hormones that bind to cell surface receptors
A. The second messenger is cAMP

- Catecholamines (α_2- Adrenergic)
- Catecholamines (β- Adrenergic)
- Ant. Pituitary: ACTH, FSH, LH & TSH
- ADH (Renal V2-receptor)
- Calcitonin & PTH
- Glucagon

Cascade for formation of cAMP by cell-surface hormones

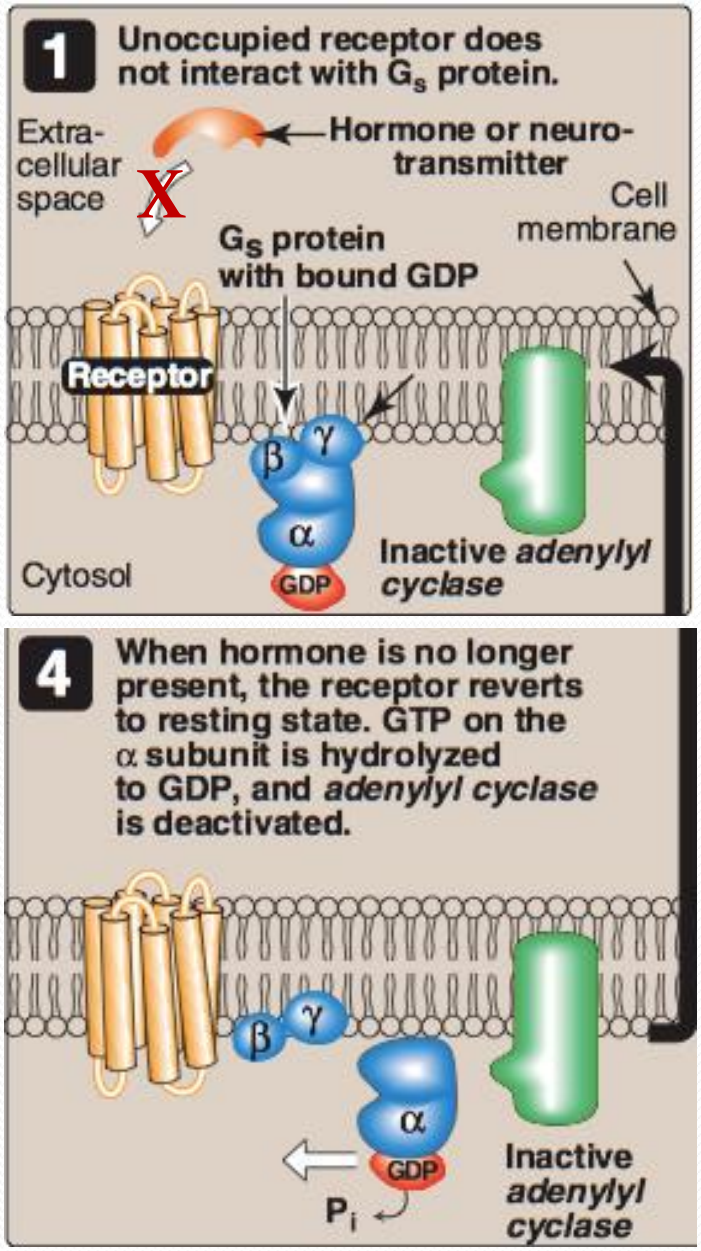


Actions of cAMP



Abortion of Hormonal Stimulus

1. Release of hormone from its receptor (unbound receptor)
2. Dephosphorylation of protein substrate by phosphatase
3. Degradation of cAMP into AMP by phosphodiesteras
4. Inactivation of protein kinase A by a decrease of cAMP
5. Hydrolysis of GTP into GDP
6. Binding of α-subunit to βγ-subunits
7. Inactivation of adenylyl cyclase



Classification of Hormones by Mechanism of Action

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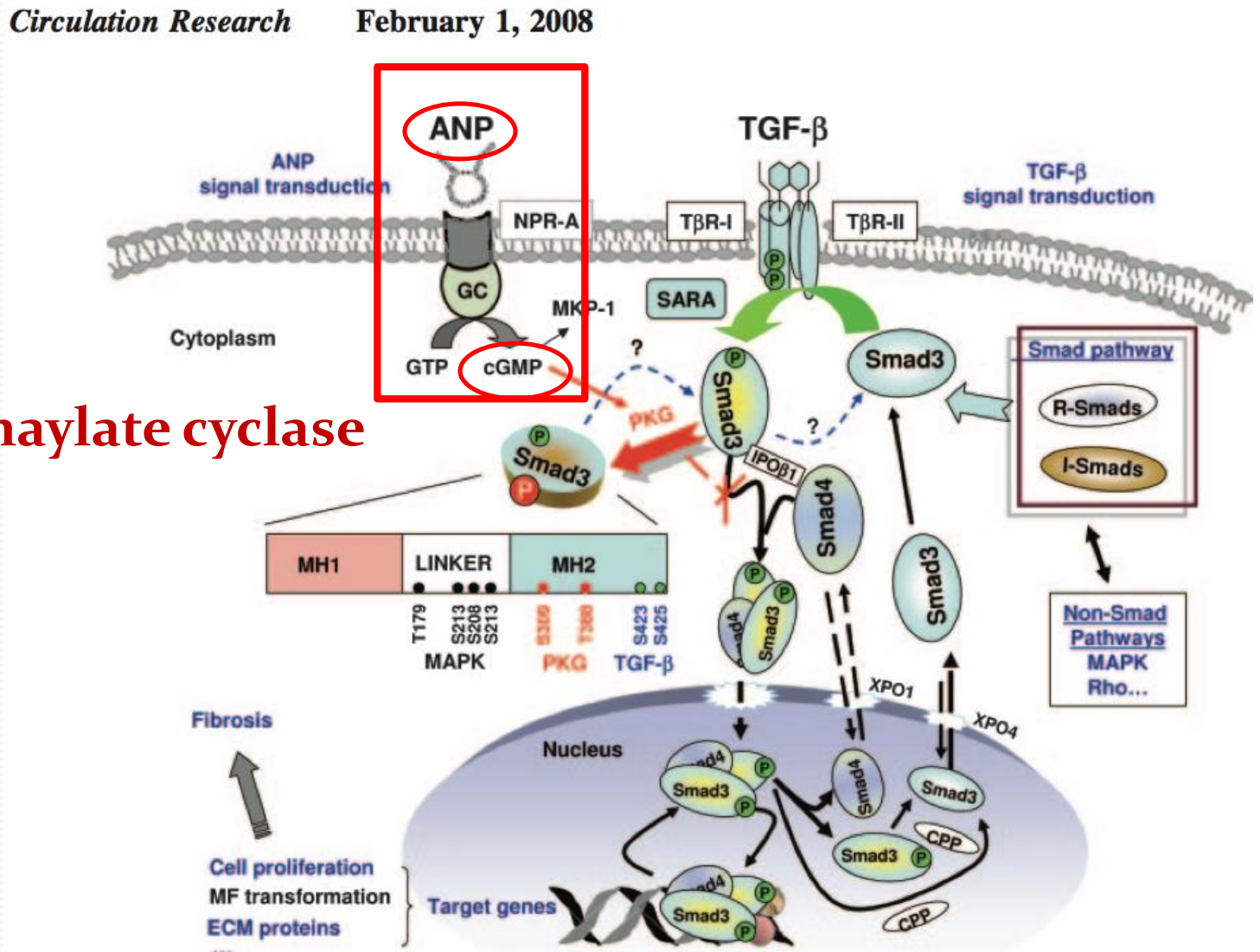
II. Hormones that bind to cell surface receptors
B. The second messenger is cGMP

Atrial natriuretic peptide (ANP)

Nitric oxide

Atrial Natriuretic Peptide (ANP)



GC: Gunaylate cyclase

Classification of Hormones by Mechanism of Action

continued…

II. Hormones that bind to cell surface receptors

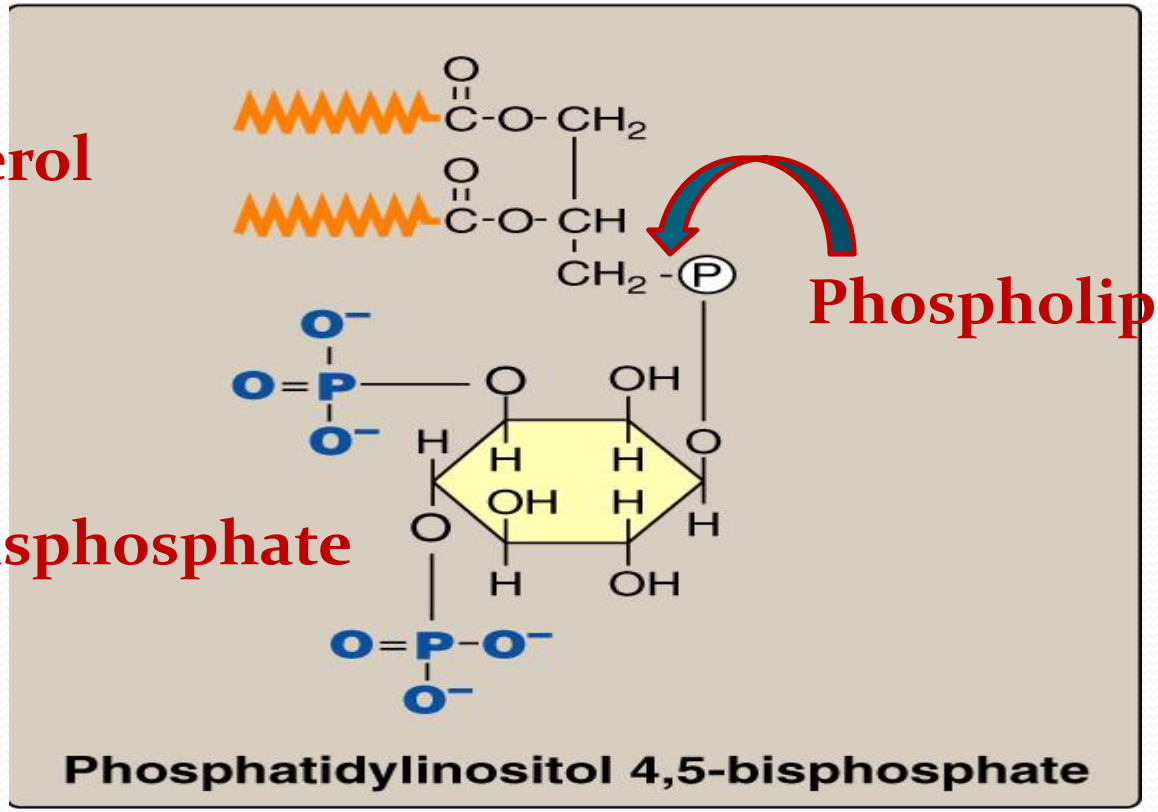
C. The second messenger is calcium or phosphatidylinositol (or both)

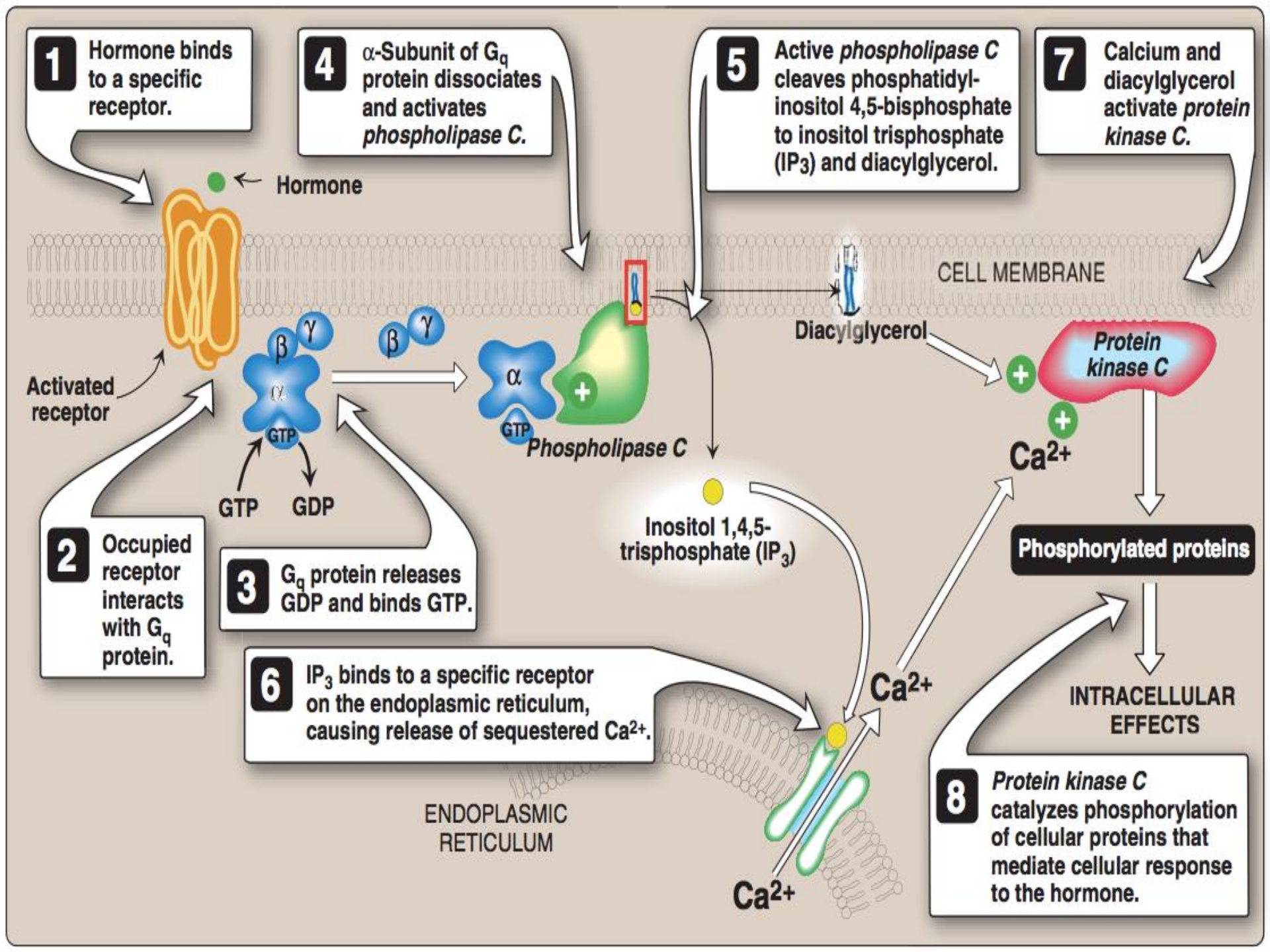
- Acetylcholine (muscarinic)
- Catecholamines (α_1- Adrenergic)
- Angiotensin II
- ADH (vasopressin): Extra-renal V1-receptor

Calcium/Phosphatidylinositol System

Diacylglycerol (DAG)

Inositol Trisphosphate (IP_3)




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

Classification of Hormones by Mechanism of Action

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II. Hormones that bind to cell surface receptors

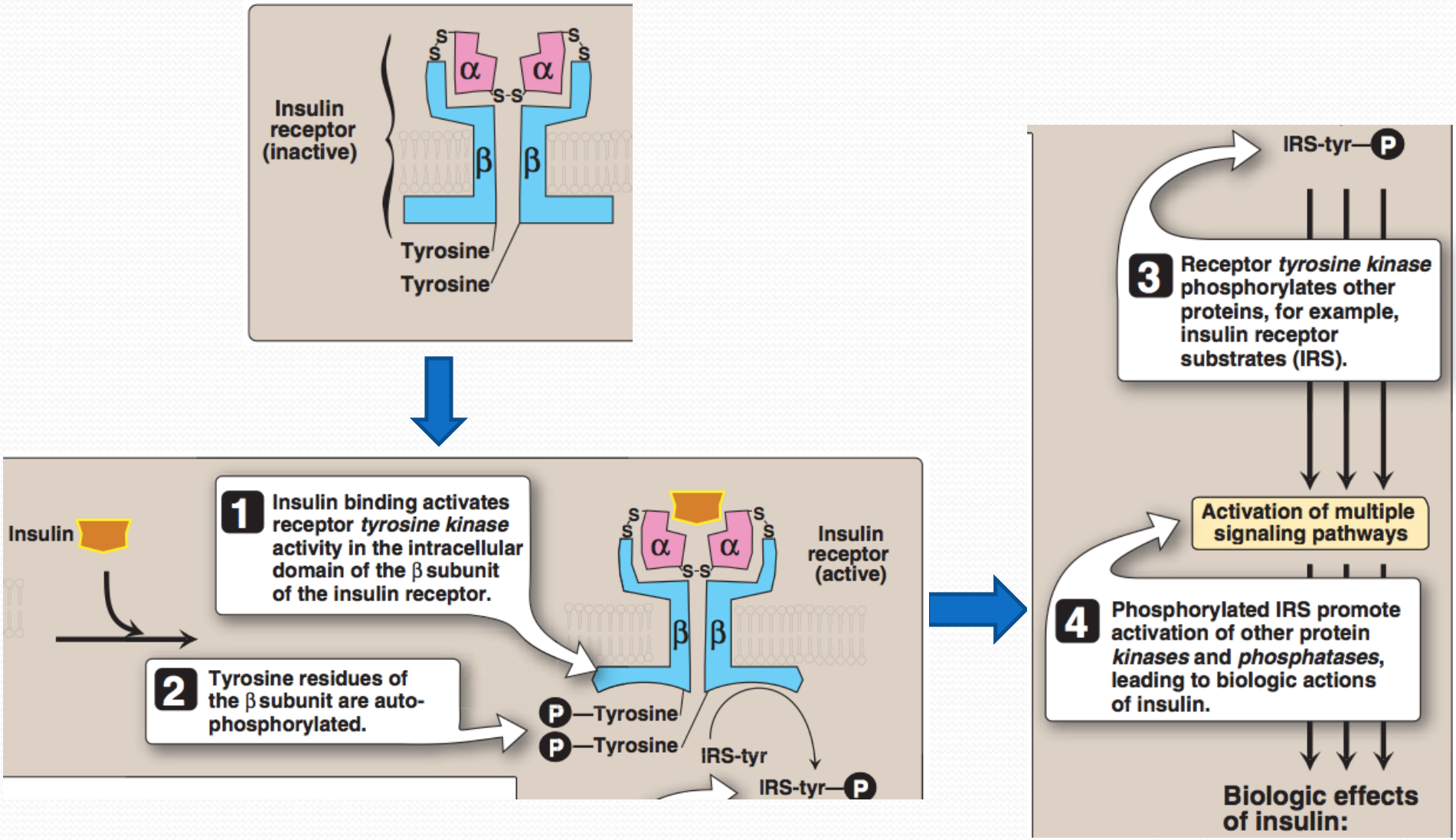
D. The second messenger is a tyrosine kinase cascade

GH & Prolactin

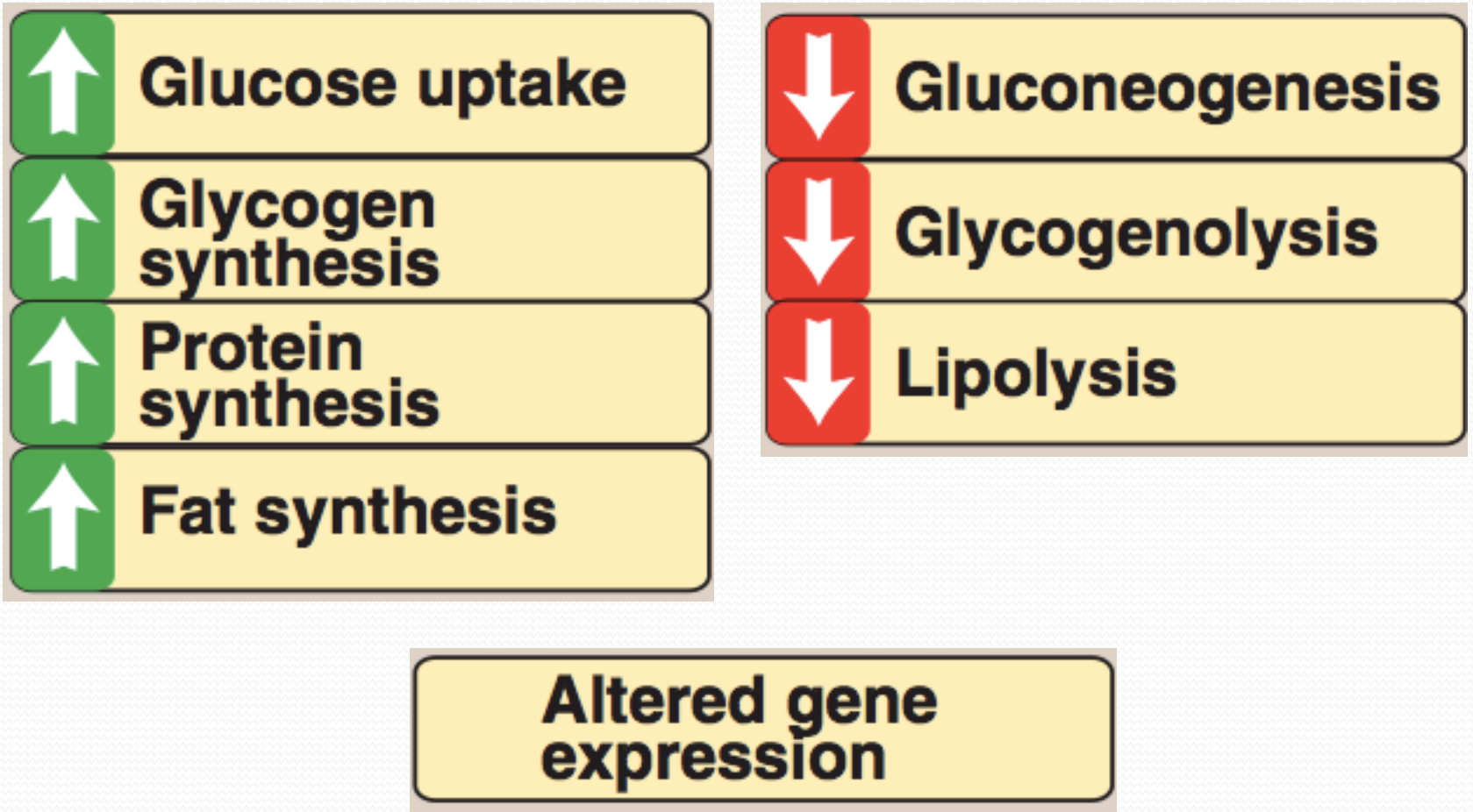
Insulin

Erythropoietin

Mechanism of Insulin action



Biologic Effects of Insulin



Biomedical Importance

- **Excessive** (e.g., hyperthyroidism, Cushing), **deficient** (e.g., hypothyroidism, Addison), or **inappropriate secretion** (e.g., syndrome of inappropriate secretion of ADH "SIADH") of hormones are major causes of diseases

- Pharmacological treatment of these diseases depends on replacement of deficient hormone (*hypo-*) or use of drugs that interfere with the mechanism of action of the hormones (*hyper- or inappropriate*)

Take home message

- **Hormones are involved in responses to a stimulus, using a variety of signaling mechanisms to facilitate cellular adaptive responses.**
- **Group I hormones are lipophilic, while group II are hydrophilic. Other differences exist between both groups.**
- **Hormones can be classified according to their mechanism of action *(specific examples of each category were discussed)***
- **Biomedically, studying hormones' actions in details helps to:**
  - **understand consequences of abnormal hormone release-related diseases (excessive, deficient or inappropriate)**
  - **design therapeutic approach for such diseases.**

References

- Lippincott's Illustrated Reviews Biochemistry: 6th edition, Chapters 8, 17 and 23.

- Buxton, Iain LO, and Dayue Duan. "Cyclic GMP/Protein Kinase G Phosphorylation of Smad3 Blocks Transforming Growth Factor-β–Induced Nuclear Smad Translocation." (2008): 151-153.

THANK YOU