Cell Signaling
and
Regulation of Metabolism

Objectives

By the end of this lecture, students are expected to:

- Differentiate different steps in signaling pathways
- Describe the second messenger systems
- Recognize the function of signaling pathways for
  - Signal transmission
  - Amplification
- Discuss the role of signaling pathways in regulation and integration of metabolism

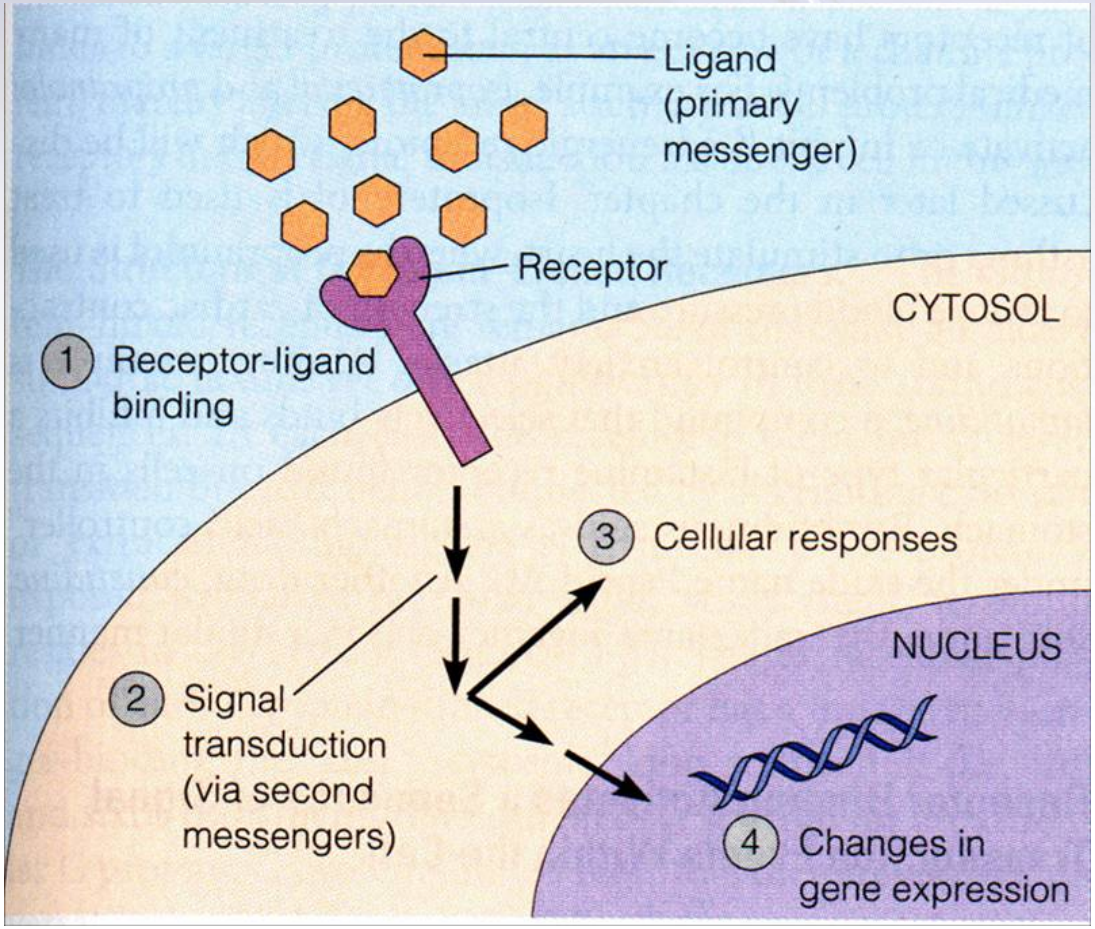
No cell lives in isolation

- Cells communicate with each other
- Cells send and receive information (signals)
- Information is relayed within cell to produce a response

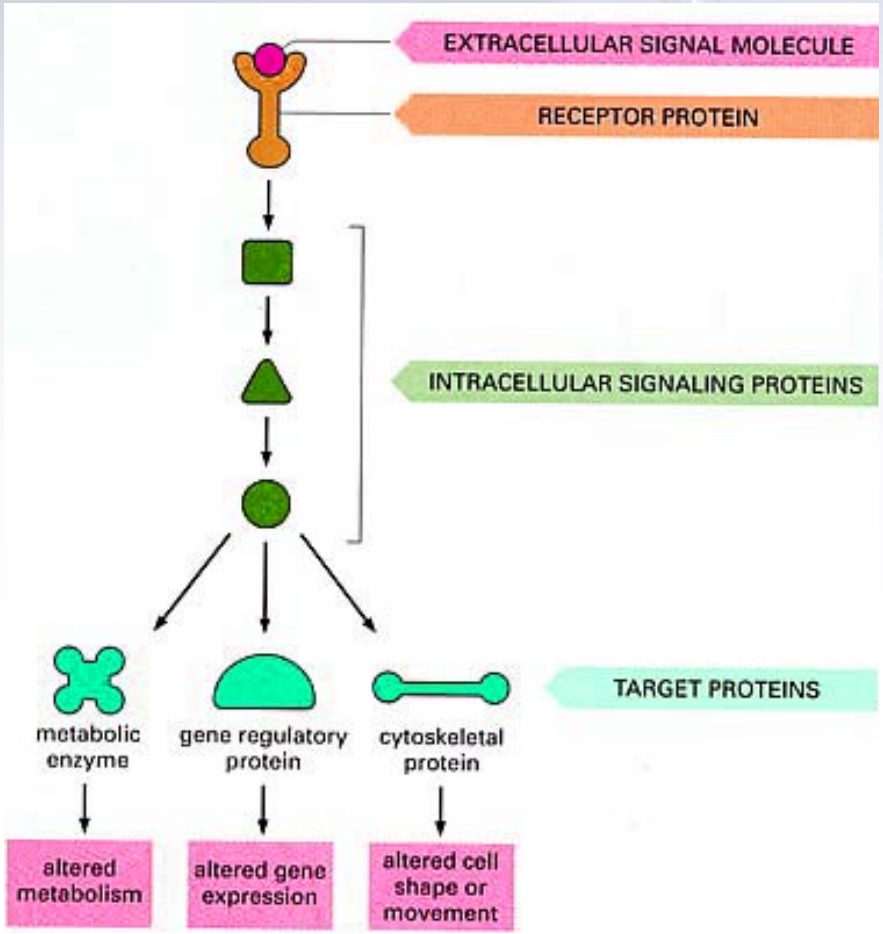
Signaling Process

- Recognition of signal
  - Receptors
- Transduction
  - Change of external signal into intracellular message with amplification and formation of second messenger
- Effect
  - Modification of cell metabolism and function

General Signaling Pathway



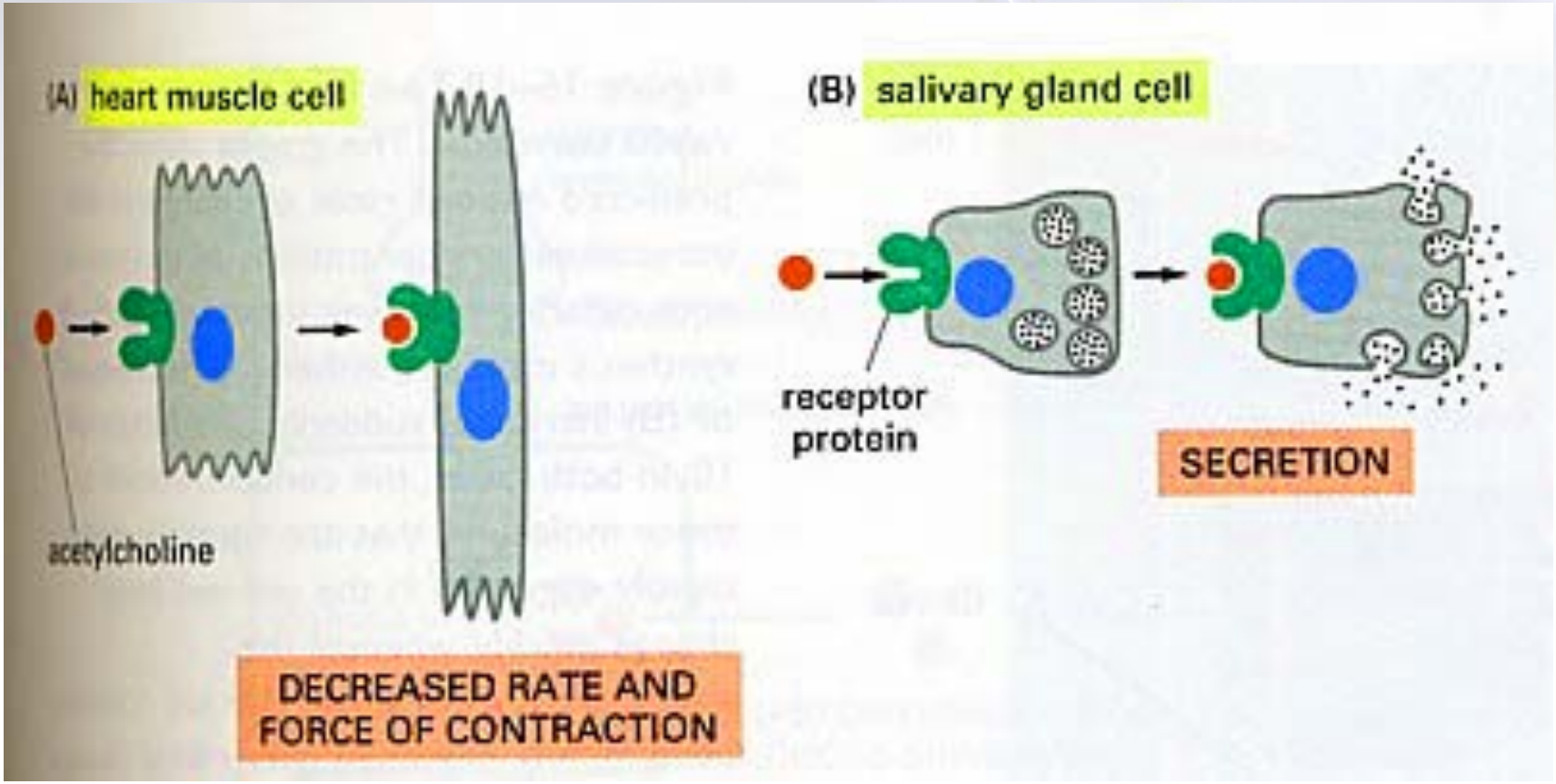
Signaling Cascades



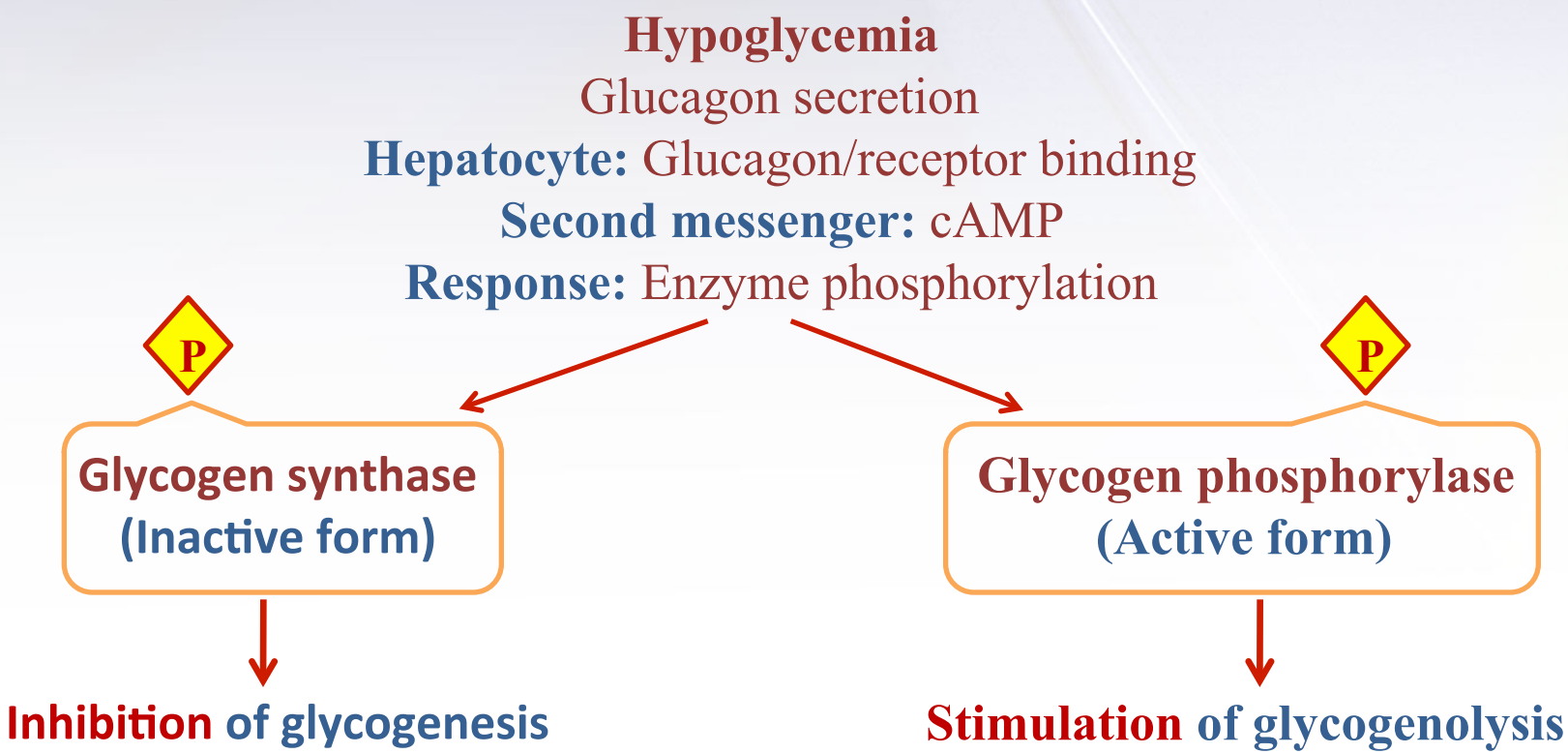
Recognition

- Performed by receptors
- Ligand will produce response only in cells that have receptors for this particular ligand
- Each cell has a specific set of receptors

Different Responses to the Same Signaling Molecule. (A) Different Cells



Different Responses to the Same Signaling Molecule. (B) One Cell but, Different Pathways



GTP-Dependant Regulatory Proteins (G-Proteins)

G-Proteins: Trimeric membrane proteins (αβγ) G-stimulatory (G_s) and G-inhibitory (G_i) binds to GTP/GDP

Forms of G-Proteins

Inactive form	Active form
Trimeric –bound GDP (αβγ/GDP)	α-bound GTP (α/GTP)

The α-subunit has intrinsic GTPase activity, resulting in hydrolysis of GTP into GDP and inactivation of G-proteins

Signaling Pathways for Regulation of Metabolism

Two important second messenger systems:

- Adenylyl cyclase system
- Calcium/phosphatidylinositol system

Adenylyl Cyclase System

Adenylyl cyclase: Membrane-bound enzyme, Converts ATP to cAMP

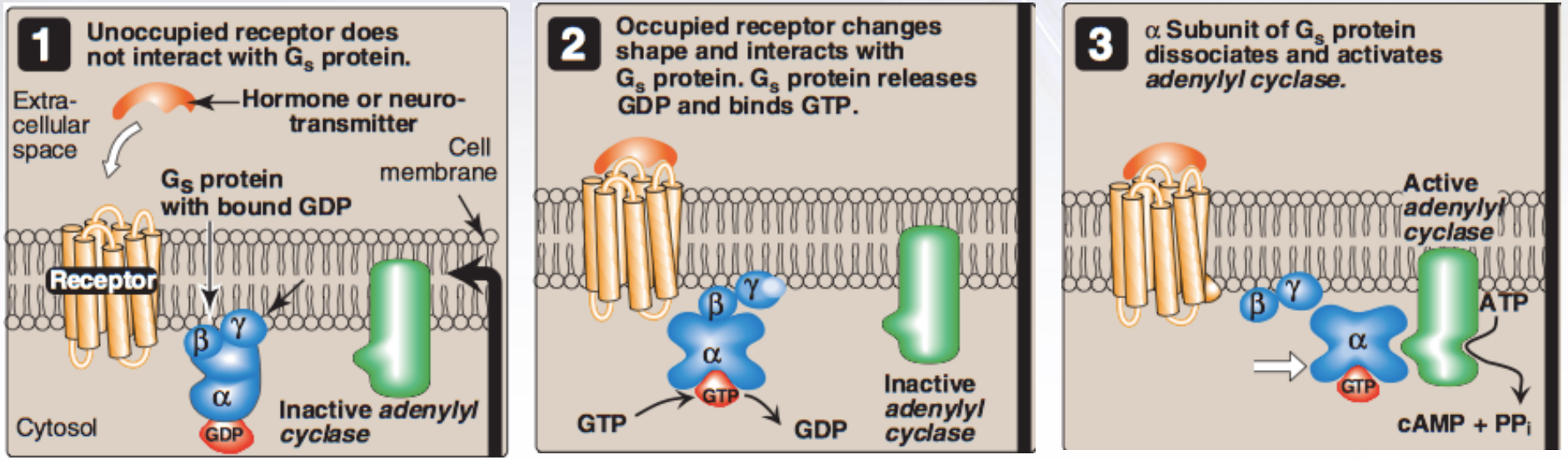
Activation/Inhibition:

Signal: Hormones or neurotransmitters (e.g., Glucagon and epinephrine) or Toxins (e.g., Cholera and pertussis toxins)

Receptor: G-protein coupled receptor

Response: Activation/inhibition of protein kinase A (cAMP-dependent protein kinase)

Signal Transduction: Adenylyl Cyclase System

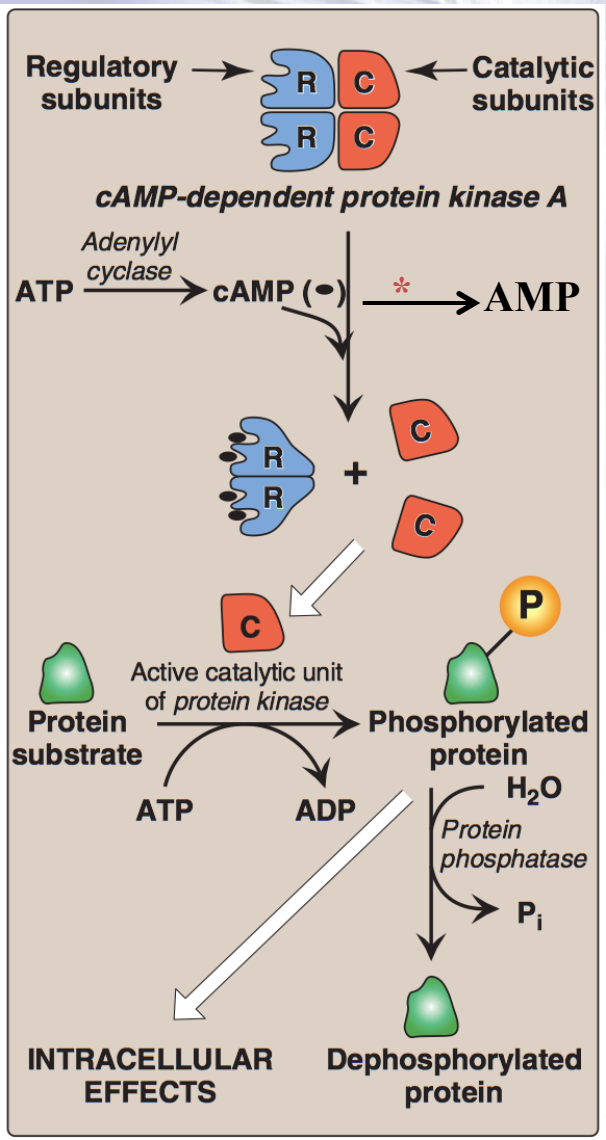


Resting state: No Signal

Ligand/Receptor Binding Activation of G_s-protein

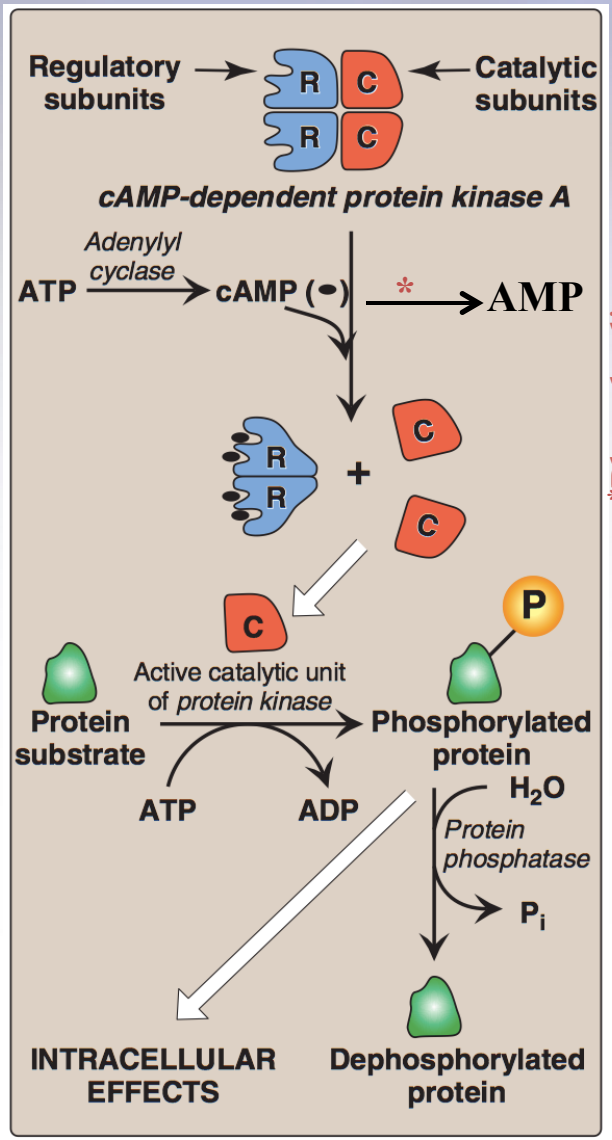
Activation of adenylyl cyclase

Actions of cAMP



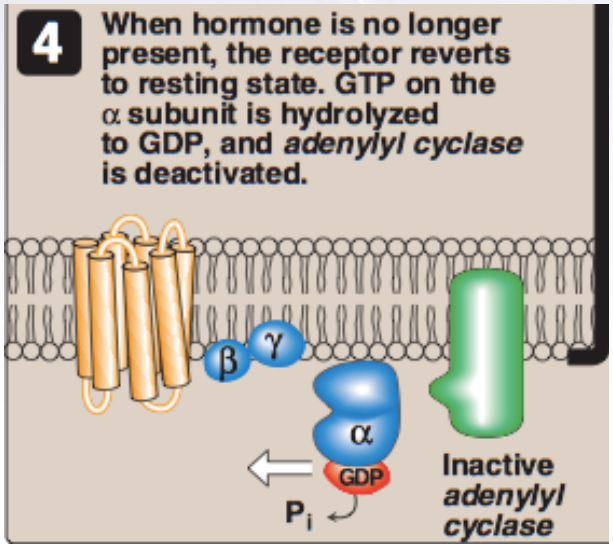
*Phosphodiesterase

Signal Termination

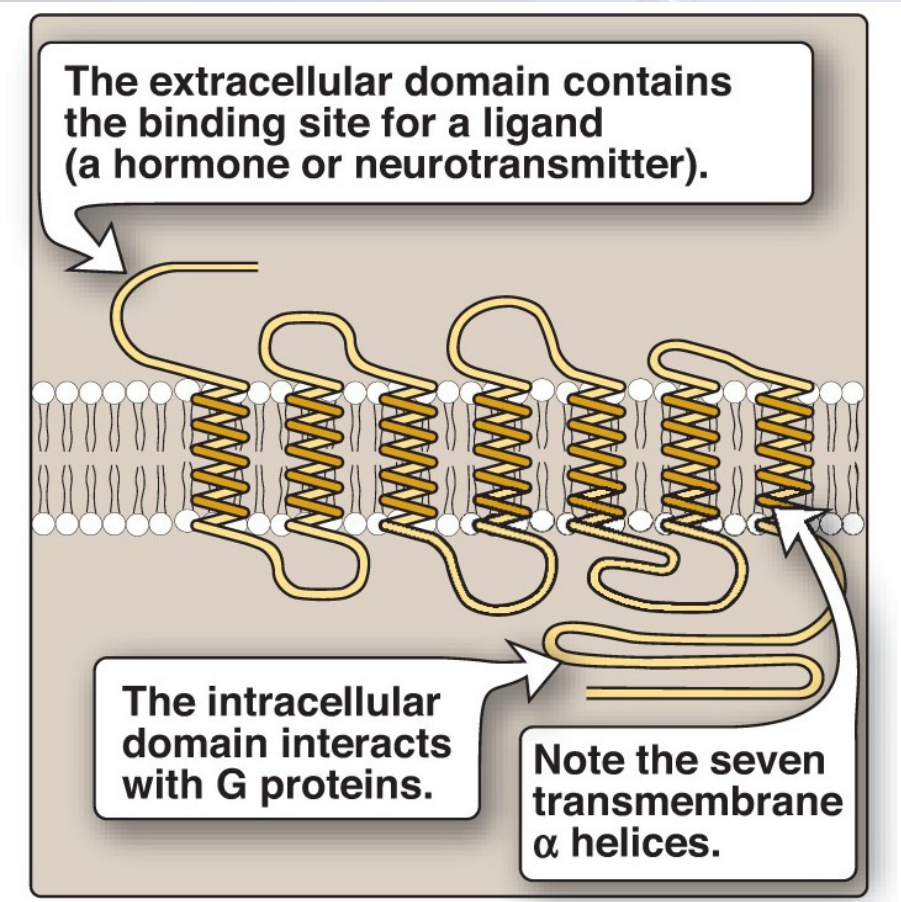


*Phosphodiesterase

- Protein phosphatase
- Phosphodiesterase → ↓cAMP → Inactive protein kinase



G-Protein Coupled Membrane Receptor



Regulation of Glycogen Metabolism by Glucagon: Effects on Glycogen Synthase and Phosphorylase

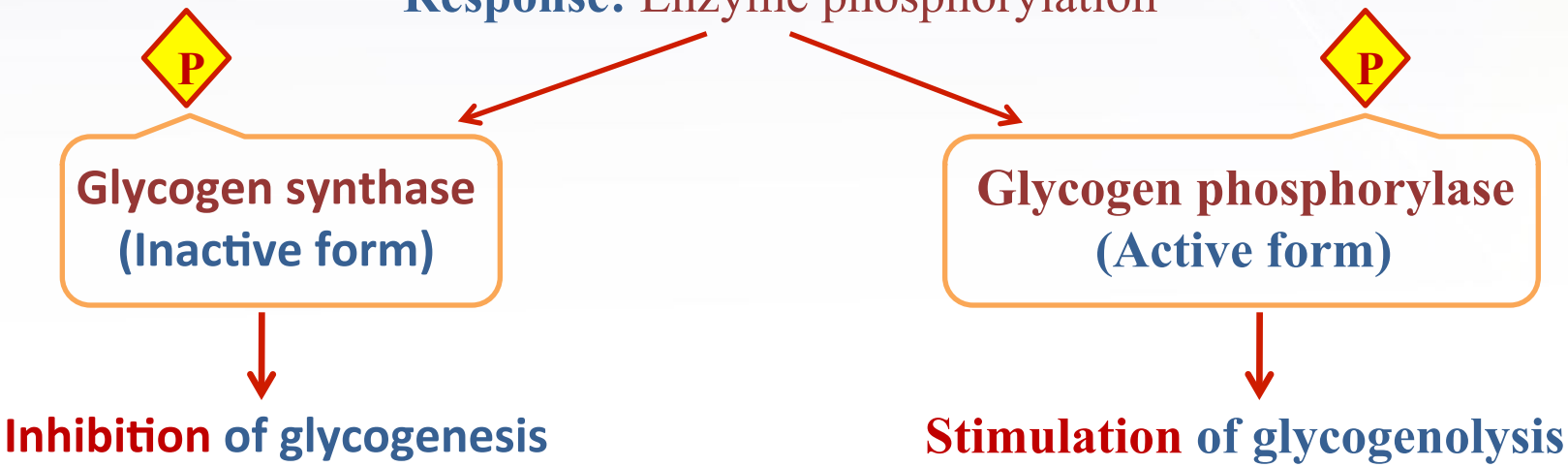
Hypoglycemia

Glucagon secretion

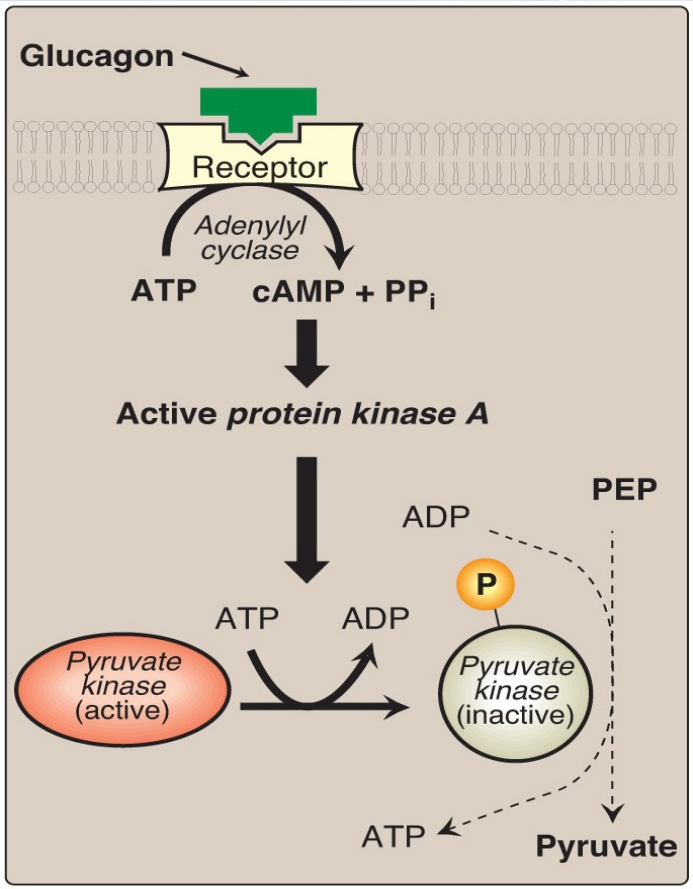
Hepatocyte: Glucagon/receptor binding

Second messenger: cAMP

Response: Enzyme phosphorylation



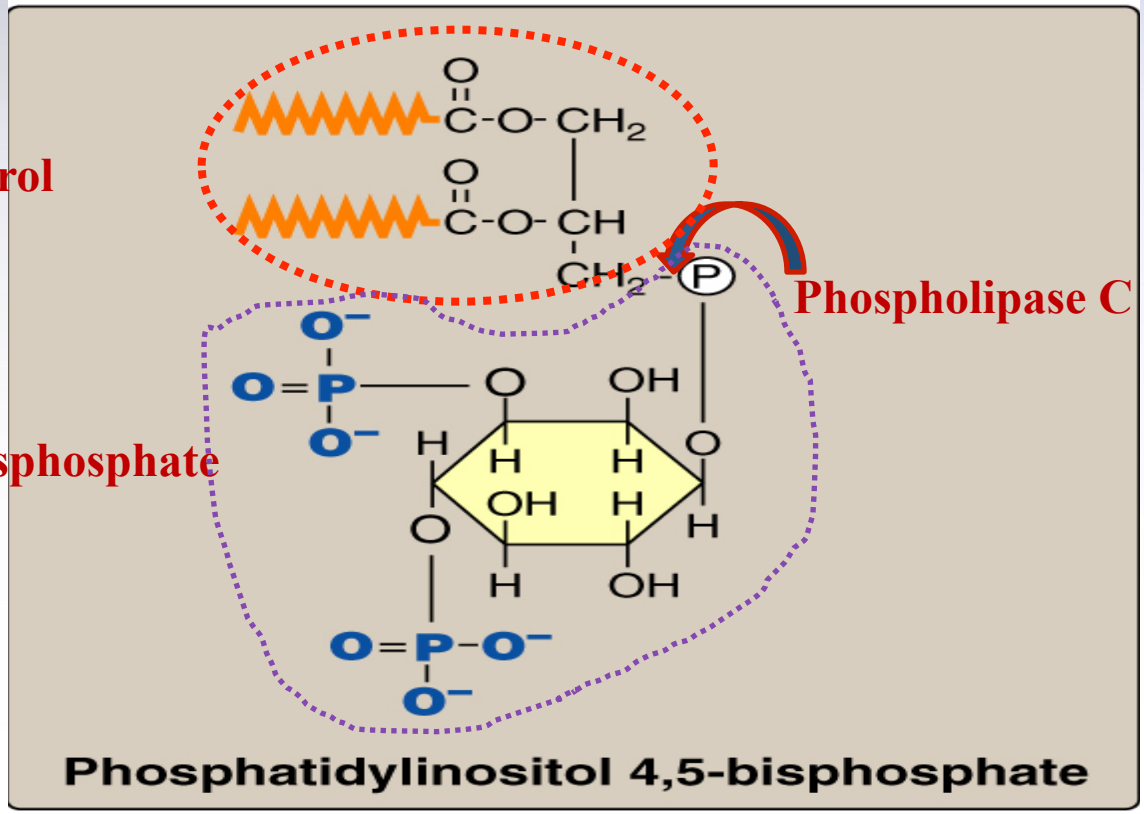
Pyruvate Kinase Regulation: Covalent Modification



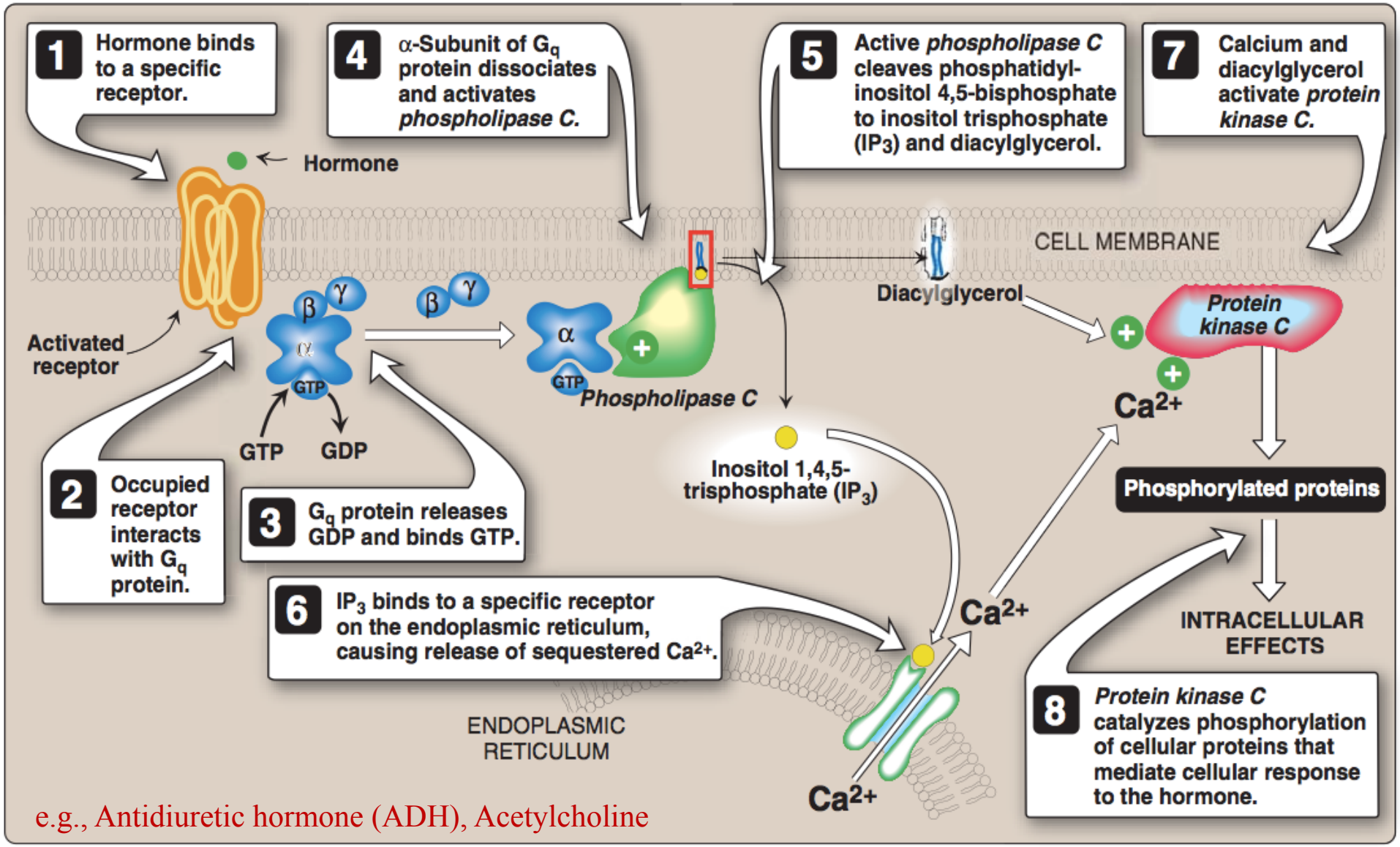
Calcium/Phosphatidylinositol System

Diacylglycerol (DAG)

Inositol Trisphosphate (IP_3)

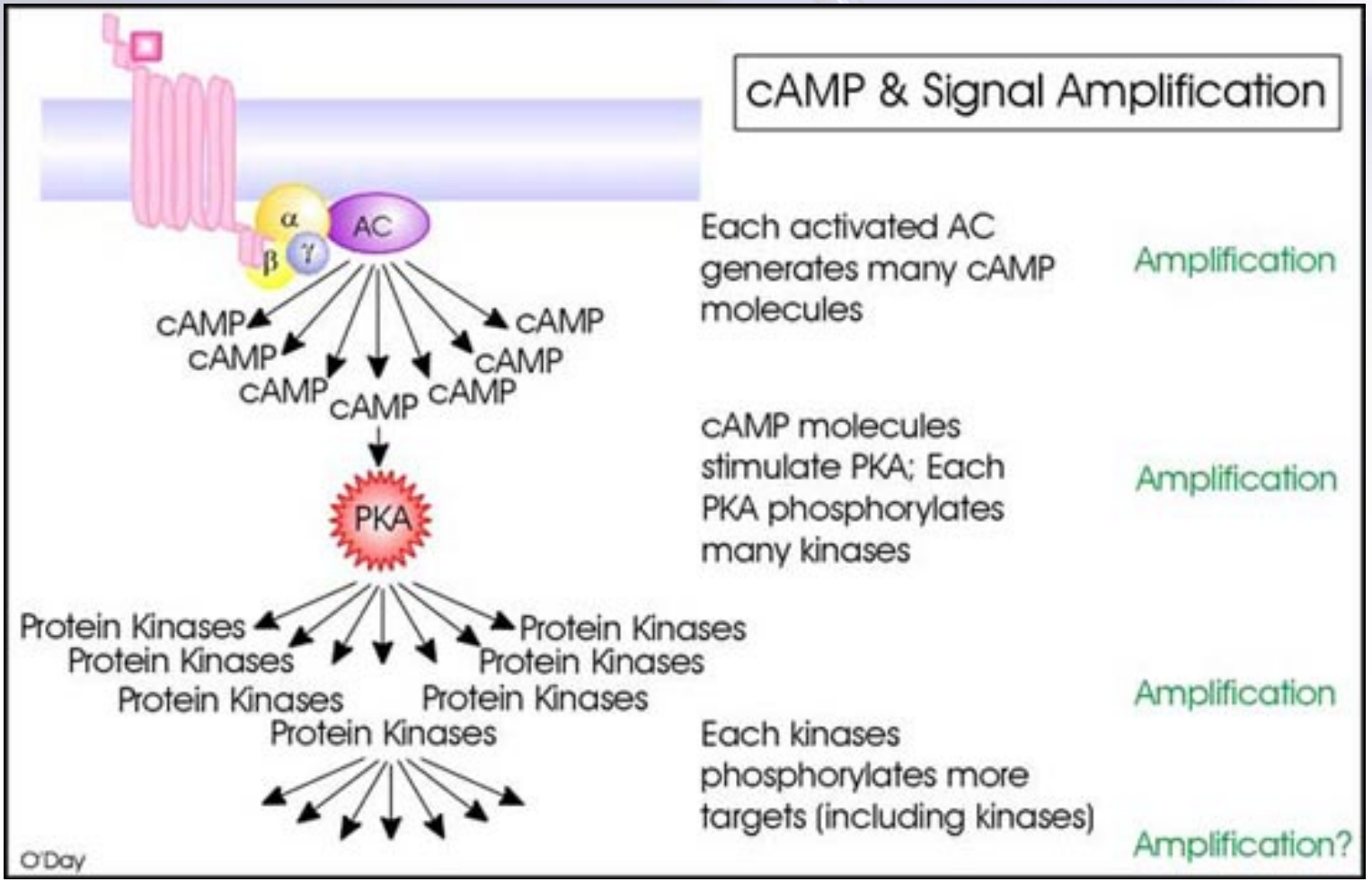


Intracellular Signaling by Inositol trisphosphate



e.g., Antidiuretic hormone (ADH), Acetylcholine

Signal Amplification



Take home messages

Cell signaling allows

- Signal transmission and amplification
- Regulation of metabolism
- Intercellular communications & coordination of complex biologic functions

Reference

Lippincott's Illustrated reviews: Biochemistry 6th edition, Unit 2, Chapter 8, Pages 91-107; and Chapter 17, Pages 204-205.