AL-RASHEED UNIVERSITY COLLEGE
DEPARTMENT OF MEDICAL LABORATORY TECHNIQUES

Introduction to Metabolism and Glycolysis

Lecture 6

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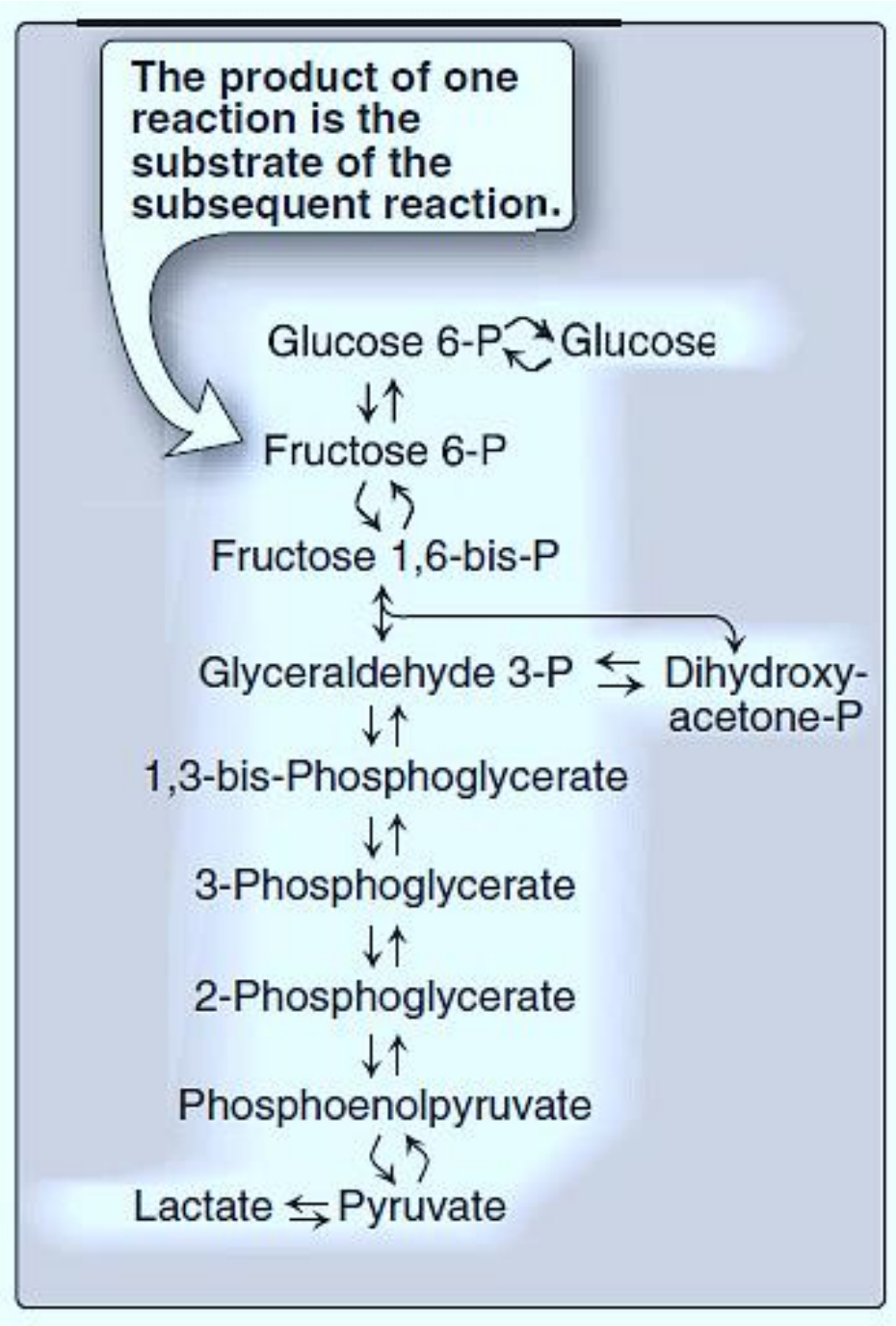


الوحدة الثانية - المحاضرة الثانية - الزمن: 90 دقيقة

أهداف المحاضرة الثانية:

يتوقع في نهاية المحاضرة أن يكون الطالب قادراً على:

By the end of the lecture, the student should be able to:

1. Explain the regulation of metabolism
2. Know some commonly used mechanisms for transmission of regulatory signals between cells.
3. Describe the intracellular communication, intercellular communication, second messenger systems and adenylyl cyclase.
4. Define protein kinases
5. Describe dephosphorylation of proteins
6. Explain the hydrolysis of cyclic adenosine monophosphate

موضوعات المحاضرة الثانية:

➢ REGULATION OF METABOLISM

- Intracellular communication
- Intercellular communication
- Second messenger systems
- Adenylyl cyclase
  - Guanosine triphosphate–dependent regulatory proteins:
  - Protein kinases
  - Dephosphorylation of proteins
  - Hydrolysis of cyclic adenosine monophosphate:

II. REGULATION OF METABOLISM

- The pathways of metabolism must be coordinated so that the production of energy or the synthesis of end products meets the needs of the cell.
- Furthermore, individual cells do not function in isolation but, rather, are part of a community of interacting tissues.
- Thus, a sophisticated communication system has evolved to coordinate the functions of the body.

- Regulatory signals that inform an individual cell of the metabolic state of the body as a whole include hormones, neurotransmitters, and the availability of nutrients.

- These, in turn, influence signals generated within the cell (Figure 2.5).

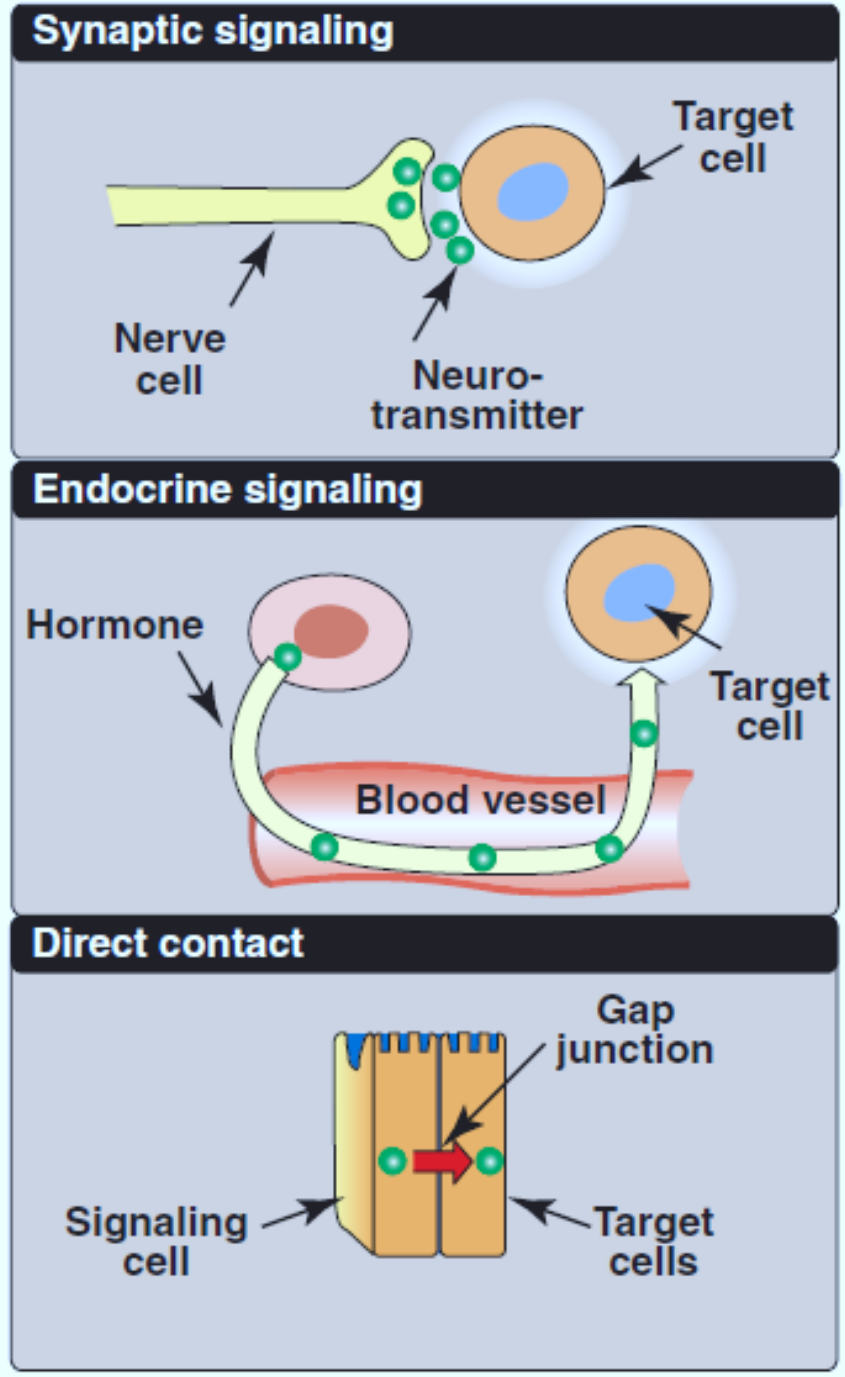


Figure 2.5 Some commonly used mechanisms for transmission of regulatory signals between cells .

A. Intracellular communication

- The rate of a metabolic pathway can respond to regulatory signals that arise from within the cell.
- For example, the rate of a pathway may be influenced by the availability of substrates, product inhibition, or alterations in the levels of allosteric activators or inhibitors.
- These intracellular signals typically elicit rapid responses, and are important for the moment-to-moment regulation of metabolism.

B. Intercellular communication

- The ability to respond to intercellular signals is essential for the development and survival of organisms.
- Signaling between cells provides for long-range integration of metabolism and usually results in a response, such as a change in gene expression, that is slower than is seen with intracellular signals.
- Communication between cells can be mediated, for example, by surface-to-surface contact and, in some tissues, by formation of gap junctions, allowing direct communication between the cytoplasms of adjacent cells.
- However, for energy metabolism, the most important route of communication is chemical signaling between cells by bloodborne hormones or by neurotransmitters.

C. Second messenger systems

- Hormones or neurotransmitters can be thought of as signals and their receptors as signal detectors.
- Each component serves as a link in the communication between extracellular events and chemical changes within the cell.
- Many receptors signal their recognition of a bound ligand by initiating a series of reactions that ultimately result in a specific intracellular response.

- “Second messenger” molecules, so named because they intervene between the original messenger (the neurotransmitter or hormone) and the ultimate effect on the cell, are part of the cascade of events that translates (transduces) hormone or neurotransmitter binding into a cellular response.

- Two of the most widely recognized second messenger systems are the calcium / phosphatidylinositol system and the *adenylyl cyclase* (*adenylate cyclase*) system, which is particularly important in regulating the pathways of intermediary metabolism.

D. Adenylyl cyclase

- The recognition of a chemical signal by some plasma (cell) membrane receptors, such as the β- and α_2-adrenergic receptors, triggers either an increase or a decrease in the activity of *adenylyl cyclase* (AC).
- This is a membrane-bound enzyme that converts ATP to 3',5'-adenosine monophosphate (commonly called cyclic AMP, or cAMP).
- The chemical signals are most often hormones or neurotransmitters, each of which binds to a unique type of membrane receptor.

- Therefore, tissues that respond to more than one chemical signal must have several different receptors, each of which can be linked to *AC*.

- These receptors, known as G protein–coupled receptors (GPCRs), are characterized by an extracellular ligand-binding domain, seven transmembrane α helices, and an intracellular domain that interacts with G proteins (Figure 2.6).

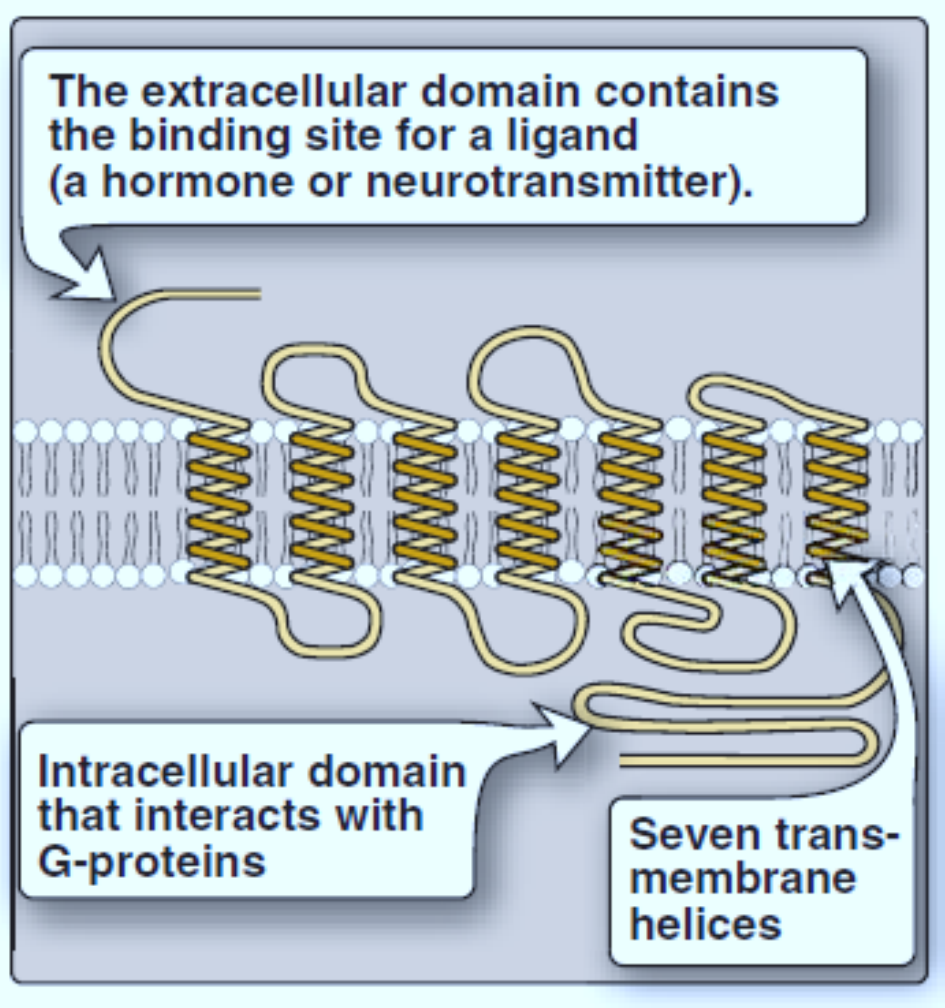


Figure 2.6 Structure of a typical G protein–coupled receptor of the plasma membrane.

1. Guanosine triphosphate–dependent regulatory proteins:

- The effect of the activated, occupied GPCR on second messenger formation is not direct but, rather, is mediated by specialized trimeric proteins (α, β, and γ subunits) of the cell membrane.
- These proteins, referred to as G proteins because the α subunit binds guanine nucleotides (GTP and GDP), form a link in the chain of communication between the receptor and AC.
- In the inactive form of a G protein, the α-subunit is bound to GDP (Figure 2.7).
- Binding of ligand causes a conformational change in the receptor, triggering replacement of this GDP with GTP.

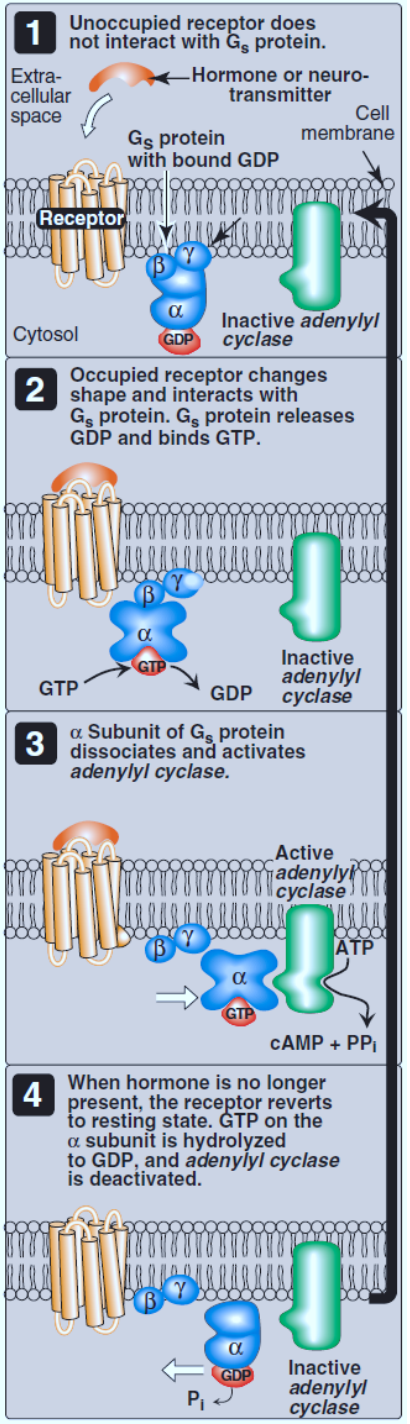
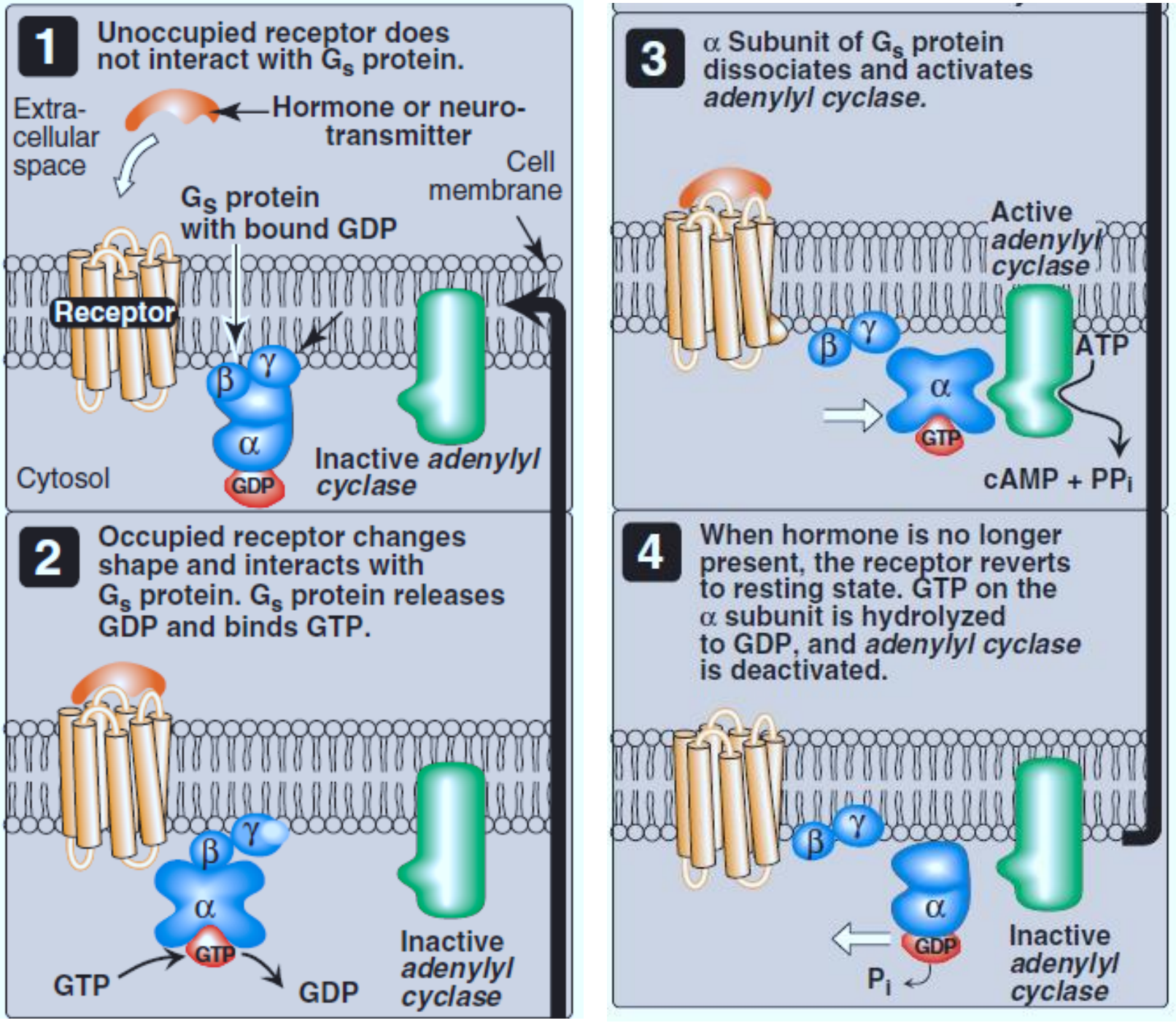


Figure 2.7 The recognition of chemical signals by certain membrane receptors triggers an increase (or, less often, a decrease) in the activity of *adenylyl cyclase*. GDP = guanosine diphosphate; GTP = guanosine triphosphate; cAMP = cyclic AMP.


1
Unoccupied receptor does not interact with G_s protein.
Extra-cellular space
Hormone or neuro-transmitter
Cell membrane
G_s protein with bound GDP
Receptor
β
γ
α
GDP
Cytosol
Inactive adenylyl cyclase
2
Occupied receptor changes shape and interacts with G_s protein. G_s protein releases GDP and binds GTP.
β
γ
α
GTP
GTP
GDP
Inactive adenylyl cyclase
3
α Subunit of G_s protein dissociates and activates adenylyl cyclase.
Active adenylyl cyclase
β
γ
α
GTP
ATP
cAMP + PP_i
4
When hormone is no longer present, the receptor reverts to resting state. GTP on the α subunit is hydrolyzed to GDP, and adenylyl cyclase is deactivated.
β
γ
α
GDP
P_i
Inactive adenylyl cyclase

- Many molecules of active Gα protein are formed by one activated receptor.
- [Note: The ability of a hormone or neurotransmitter to stimulate or inhibit AC depends on the type of Gα protein that is linked to the receptor. One type, designated G_s, stimulates AC, whereas another type, designated G_i, inhibits the enzyme (not shown in Figure 2.7).]
- The actions of the Gα–GTP complex are short-lived because Gα has an inherent *GTPase* activity, resulting in the rapid hydrolysis of GTP to GDP. This causes inactivation of the Gα, its dissociation from AC, and reassociation with the βγ dimer.
- Toxins from Vibrio cholerae (cholera) and Bordetella pertussis (whooping cough) cause inappropriate activation of *adenylyl cyclase* through covalent modification (ADP-ribosylation) of different G proteins. With cholera, the *GTPase* activity of Gαs is inhibited in intestinal cells. With whooping cough, $G\alpha_i$ is inactivated in respiratory-tract cells.

2. Protein kinases:

- The next key link in the cAMP second messenger system is the activation by cAMP of a family of enzymes called cAMP-dependent *protein kinases* such as *protein kinase A* (Figure 2.8).
- cAMP activates *protein kinase A* by binding to its two regulatory subunits, causing the release of two active, catalytic subunits.
- The active subunits catalyze the transfer of phosphate from ATP to specific serine or threonine residues of protein substrates.

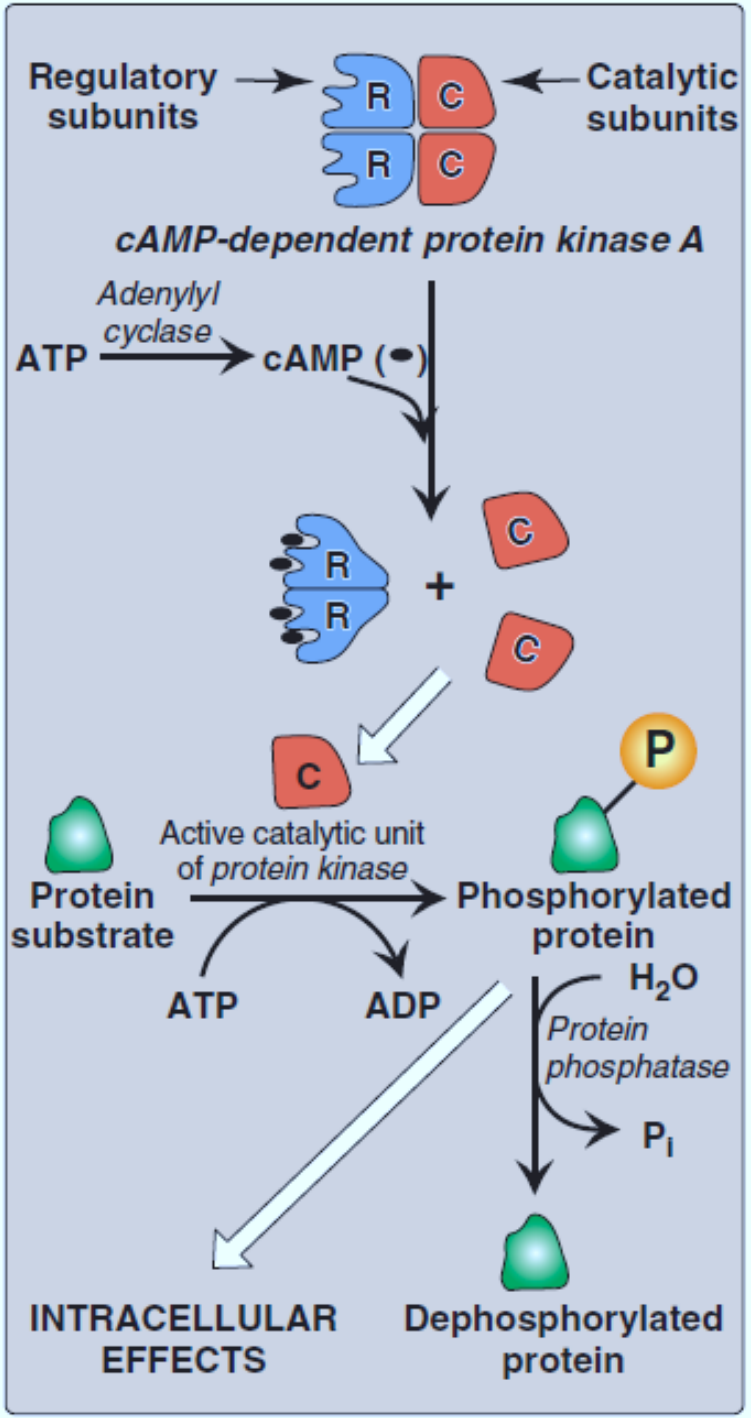


Figure 2.8 Actions of cyclic AMP (cAMP). P_i = inorganic phosphate.

- The phosphorylated proteins may act directly on the cell's ion channels or, if enzymes, may become activated or inhibited.
- *Protein kinase A* can also phosphorylate proteins that bind to DNA, causing changes in gene expression.
- [Note: Several types of *protein kinases* are not cAMP dependent, for example, *protein kinase C*.]

3. Dephosphorylation of proteins:

- The phosphate groups added to proteins by *protein kinases* are removed by *protein phosphatases*, enzymes that hydrolytically cleave phosphate esters (see Figure 2.8). This ensures that changes in protein activity induced by phosphorylation are not permanent.

4. Hydrolysis of cyclic adenosine monophosphate:

- cAMP is rapidly hydrolyzed to 5'-AMP by *cAMP phosphodiesterase*, one of a family of enzymes that cleave the cyclic 3',5'-phosphodiester bond.
- 5'-AMP is not an intracellular signaling molecule. Therefore, the effects of neurotransmitter- or hormone-mediated increases of cAMP are rapidly terminated if the extracellular signal is removed.
- [Note: *Phosphodiesterase* is inhibited by the methylxanthine derivative, caffeine.]

نشاط فردي (1/2/2)

List some commonly used mechanisms for transmission of regulatory signals between cells

1. ……
2. ……
3. ……

نشاط فردي (2/2/2)

Describe briefly each of the following:

1. Protein kinases
2. Dephosphorylation of proteins
3. Hydrolysis of cyclic adenosine monophosphate