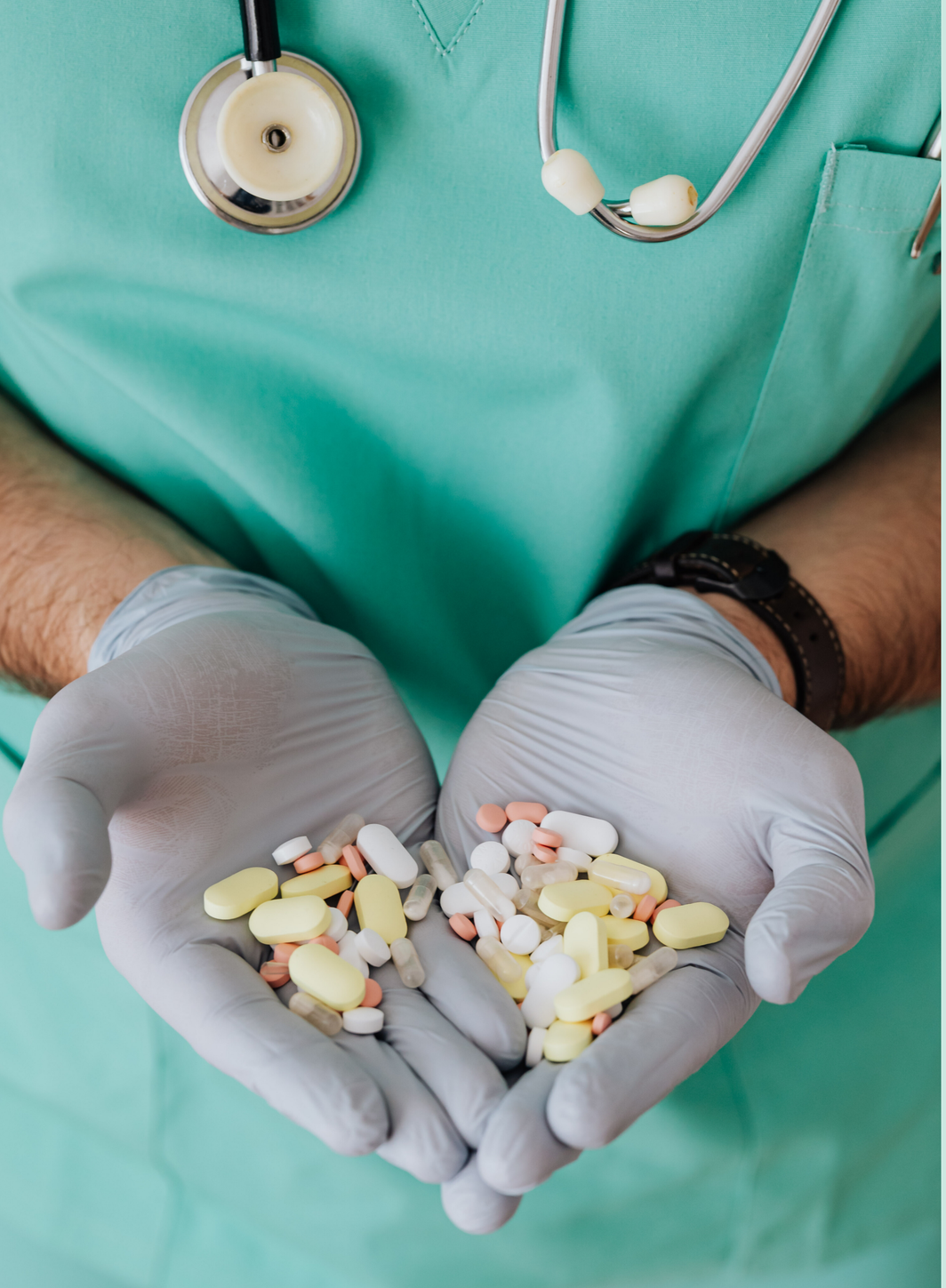


Sheet# 6

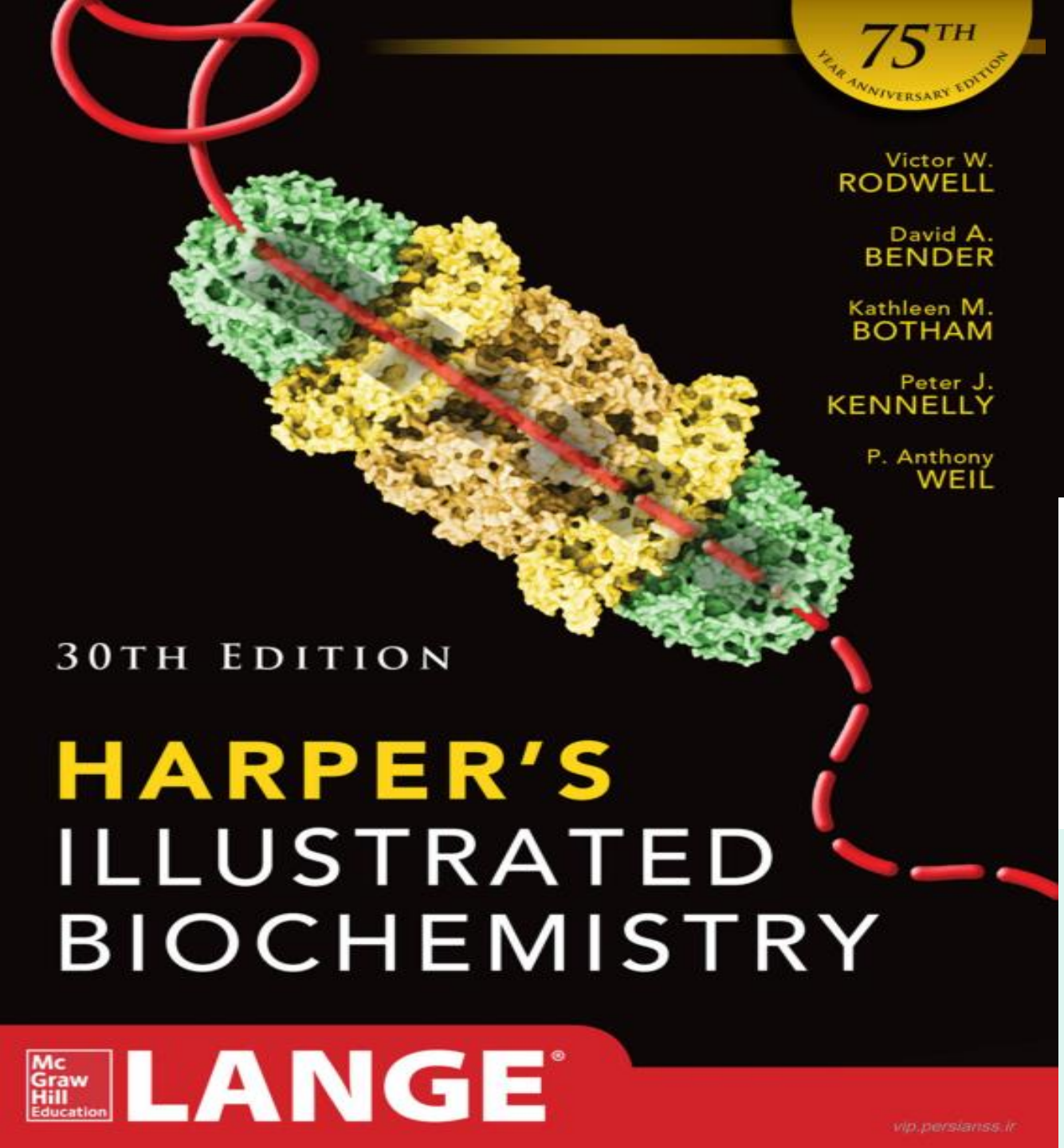
PASSION ACADEMIC TEAM YU - MEDICINE

Endocrine system

Lec. Title : Hormone Action & Signal Transduction (Part 2) + Regulation of Glucose Metabolism .

Written By : Abdallah AL-Qashi
Roqaya Mahmoud

IF YOU COME BY ANY MISTAKE , PLEASE KINDLY REPORT IT TO SHAGHAFBATCH@GMAIL.COM



Hormone Action & Signal Transduction

CHAPTER

42

The first slide in this script is slide no. 20 from the file (Hormone Action - Signal Transduction) & all slides from the file (Regulation of Glucose Metabolism) which all found in the batch site (https://shaghaf-batch.site123.me)

Some hormones act Through a protein Kinase Cascade

The discovery that the EGF receptor contains an intrinsic tyrosine kinase activity that is activated by the binding of the ligand EGF was an important breakthrough.

The insulin and IGF-I receptors also contain intrinsic ligand-activated tyrosine kinase activity.

Sheet #1

- EGF receptors one of the most exciting and landmark receptors that are related to molecular biology as well as cancer development .

- EGF receptors is a family of receptors like EGF 2 (CHER2) receptors that has vole in many cancers mainly breast cancer. If the patient has HER2 positive cancer, it is considered one of the aggressive cancers .

- EGF receptors normally are expressed on live surface of cells to respond to the triggers that are responsible for growth .

They can be up regulated by many causes like mutations or over expression , so they can be associated with certain pathological conditions like cancer.

Insulin Transmits Signals by Several Kinase Cascades

The insulin, epidermal growth factor **(EGF), and IGF-I receptors** have intrinsic protein tyrosine kinase activities located in their cytoplasmic domains.

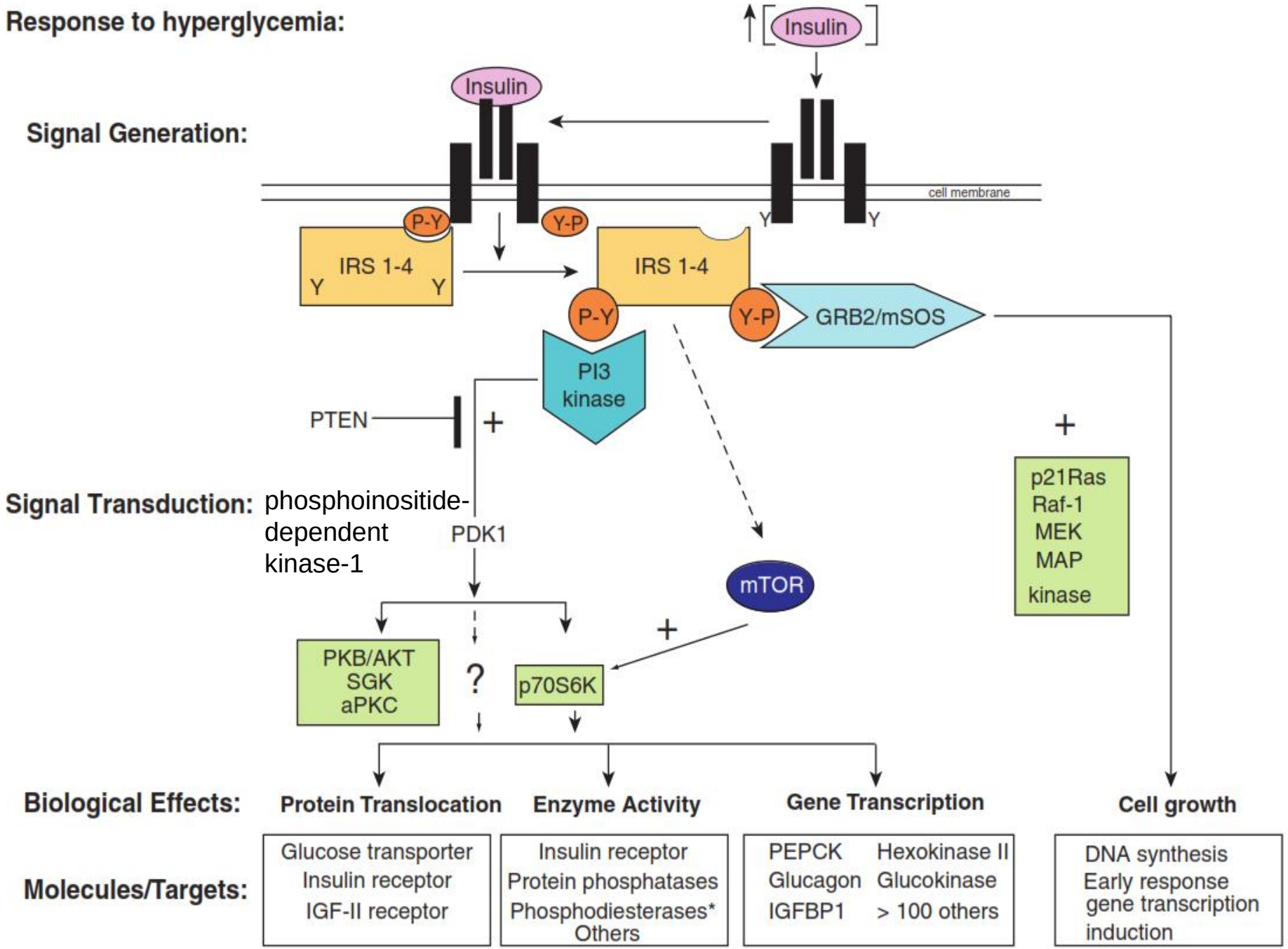


FIGURE 42–8 **Insulin signaling pathways.** The insulin signaling pathways provide an excellent example of

Sheet #2

- Briefly, Beta cells will release insulin under hyperglycemic conditions. So, the presence of this ligand (insulin) in the blood will cause certain signaling pathway in the target cells.

- Receptor of insulin consist of four subunits (tetrameric structure) & they are different subunits, so we called it heterotetrametric structure.

- After binding of insulin to its receptor, there will be self phosphorylation of cytoplasmic domain of insulin receptor.

- This phosphorylation will activate this domain (tyrosine). Then, this domain will phosphorylate IRS that has tyrosine residues to activate it.

- So, active IRS will have phosphorylated tyrosine residues.

- Then, active IRS will activate other pathways like P13 kinase .

- Activated P13 kinase will cause activation of PDk1 that also will activate different pathways, some of them are unknown, but eventually they will cause the biological effects that illustrated in the slides .

Sheet #3

Active IRS also will activate mTOR by unknown Pathway .

mTOR is a connecting molecule . In integration of most pathways , we will meet mTOR .

- mTOR is abbreviation of mammalian target of rapamycin, which means mammalians have proteins can be targeted by rapamycin (antimicrobial) .

- activated mTOR will activate transcription factor (p70S6k) and then it will cause the Biological effects like gene transcription .

- PTEN protein inhibits the Pl3 kinase activity (in normal conditions) . If Pl3 kinase gene is mutated, there will be a continuous growth of cell and it may lead to cancer .

- 10% - 20% of patients with breast cancer have mutation in this gene (P13 kinase gene) Also, if there is mutation in PTEN gene, there will be tumor development due to loss of inhibitor factor to P13 kinase. So, signals transduction is very important in cancer and tumor development , to help us in designing the treatment.

- Active IRS also will activate GRB2/mSOS that is responsible for cell growth.

- **You must know the general mechanisms. You don't have to know the details in slide (22 +23).**

FIGURE 42–8 Insulin signaling pathways. The insulin signaling pathways provide an excellent example of the "recognition → hormone release → signal generation → effects" paradigm outlined in Figure 42–1. Insulin is released into the bloodstream from pancreatic β-cells in response to hyperglycemia. Binding of insulin to a target cell-specific plasma membrane heterotetrameric insulin receptor (IR) results in a cascade of intracellular events. First, the intrinsic tyrosine kinase activity of the insulin receptor is activated, and marks the initial event. Receptor activation results in increased tyrosine phosphorylation (conversion of specific Y residues → Y-P) within the receptor. One or more of the insulin receptor substrate (IRS) molecules (IRS 1-4) then bind to the tyrosine-phosphorylated receptor and themselves are specifically tyrosine phosphorylated. IRS proteins interact with the activated IR via N-terminal PH (pleckstrin homology) and PTB (phosphotyrosine binding) domains. IR-docked IRS proteins are tyrosine phosphorylated and the resulting P-Y-residues form the docking sites for several additional signaling proteins (ie, PI-3 kinase, GRB2, and mTOR). GRB2 and PI3K bind to IRS P-Y residues via their SH (*Src* Homology) domains, Binding to IRS-Y-P residues leads to activation of the activity of many intracellular signaling molecules such as GTPases, protein kinases, and lipid kinases, all of which play key roles in certain metabolic actions of insulin. The two best-described pathways are shown. In detail, phosphorylation of an IRS molecule (probably IRS-2) results in docking and activation of the lipid kinase, PI-3 kinase; PI-3K generates novel inositol lipids that act as "second messenger" molecules. These, in turn, activate PDK1 and then a variety of downstream signaling molecules, including protein kinase B (PKB/AKT), SGK, and aPKC. An alternative pathway involves the activation of p70S6K and perhaps other as yet unidentified kinases. Next, phosphorylation of IRS (probably IRS-1) results in docking of GRB2/mSOS and activation of the small GTPase, p21Ras, which initiates a protein kinase cascade that activates Raf-1, MEK, and the p42/p44 MAP kinase isoforms. These protein kinases are important in the regulation of proliferation and differentiation of many cell types. The mTOR pathway provides an alternative way of activating p70S6K and appears to be involved in nutrient signaling as well as insulin action. Each of these cascades may influence different biological processes, as shown (protein translocation, protein/enzyme activity, gene transcription, cell growth). All of the phosphorylation events are reversible through the action of specific phosphatases. As an example, the lipid phosphatase PTEN dephosphorylates the product of the PI-3 kinase reaction, thereby antagonizing the pathway and terminating the signal. Representative effects of major actions of insulin are shown in each of the boxes. The asterisk after phosphodiesterase indicates that insulin indirectly affects the activity of many enzymes by activating phosphodiesterases and reducing intracellular cAMP levels. (aPKC, atypical protein kinase C; GRB2, growth factor receptor binding protein 2; IGFBP, insulin-like growth factor binding protein; IRS 1–4, insulin receptor substrate isoforms 1–4; MAP kinase, mitogen-activated protein kinase; MEK, MAP kinase kinase and ERK kinase; mSOS, mammalian son of sevenless; mTOR, mammalian target of rapamycin; p70S6K, p70 ribosomal protein S6 kinase; PDK1, phosphoinositide-dependent kinase; PI-3 kinase, phosphatidylinositol 3-kinase; PKB, protein kinase B; PTEN, phosphatase and tensin homolog deleted on chromosome 10; SGK, serum and glucocorticoid-regulated kinase.)

GH, PL, IP and CKine

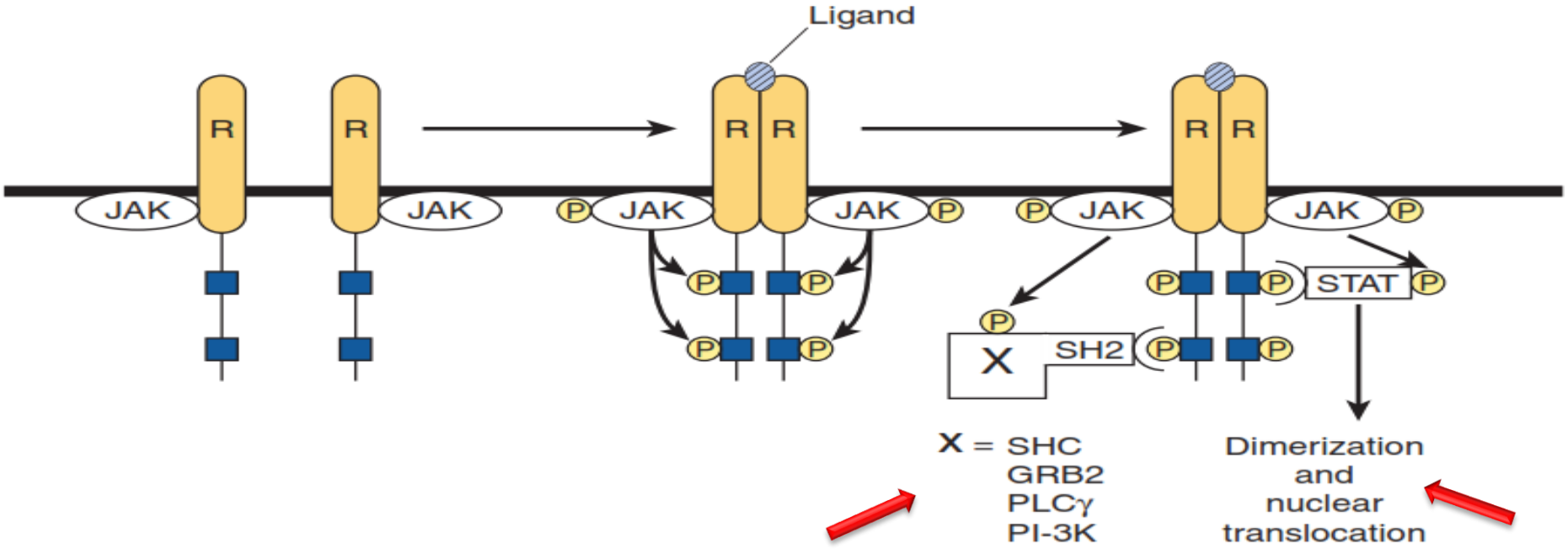


FIGURE 42–9 Initiation of signal transduction by receptors linked to Jak kinases. The receptors (R) that bind prolactin, growth hormone, interferons, and cytokines lack endogenous tyrosine kinase. Upon ligand binding, these receptors dimerize and an associated protein (Jak1, Jak2, or TYK) is phosphorylated. Jak-P, an active kinase, phosphorylates the receptor on tyrosine residues. The STAT proteins associate with the phosphorylated receptor and then are themselves phosphorylated by Jak-P. The phosphorylated STAT protein, STAT Ⓟ dimerizes, translocates to the nucleus, binds to specific DNA elements, and regulates transcription. The phosphotyrosine residues of the receptor also bind to several SH2 domain-containing proteins (X-SH2). This results in activation of the MAP kinase pathway (through SHC or GRB2), PLCγ, or PI-3 kinase.

Sheet #4

JAL/STAT pathway receptor is a monomeric receptor but after the binding of ligand, there will be dimerization of receptor and then there will be self phosphorylation for JAK protein . Then, JAK will phosphorylate cytoplasmic domain , STAT and SH2. Then, the phosphorylated cytoplasmic domain is responsible for recruitment of phosphorylated STAT and then there will be dimerization and nuclear translocation for STAT to perform certain signals on the genes .

HORMONES CAN INFLUENCE SPECIFIC BIOLOGIC EFFECTS BY MODULATING TRANSCRIPTION

How hormones affect transcription

(1) Actively transcribed genes are in regions of “open” chromatin (experimentally defined as relative susceptibility to the enzyme DNase I), which allows for the access of transcription factors to DNA.

(2) Genes have regulatory regions, and transcription factors bind to these to modulate the frequency of transcription initiation.

Sheet #5

(1) The regions of genes are divided into two kinds depending on its conformations :

1) euchromatin (open area) is loose, don't take stain , and has active genes.
2) heterochromatin (close area) is condensed DNA and has inactive genes.

- We can distinguish between the two types by DNase 1 enzymes (open area is digested by this enzyme) .

(2) The regulatory regions mostly are localized before the genes .

(3) The hormone receptor complex can be one of these transcription factors. The DNA sequence to which this binds is called a HRE.

(4) Alternatively, other hormone generated signals can modify the location, amount, or activity of transcription factors and thereby influence binding to the regulatory or response element.

(5) Members of a large superfamily of nuclear receptors act with—or in a manner analogous to—the hormone receptors.

(6) These nuclear receptors interact with another large group of coregulatory molecules to effect changes in the transcription of specific genes.

Several HREs Have Been Defined

They generally are found within a few hundred nucleotides upstream (5′) of the transcription initiation site, but they may be located within the coding region of the gene, in introns.

HRE → Region that regulate gene expression .

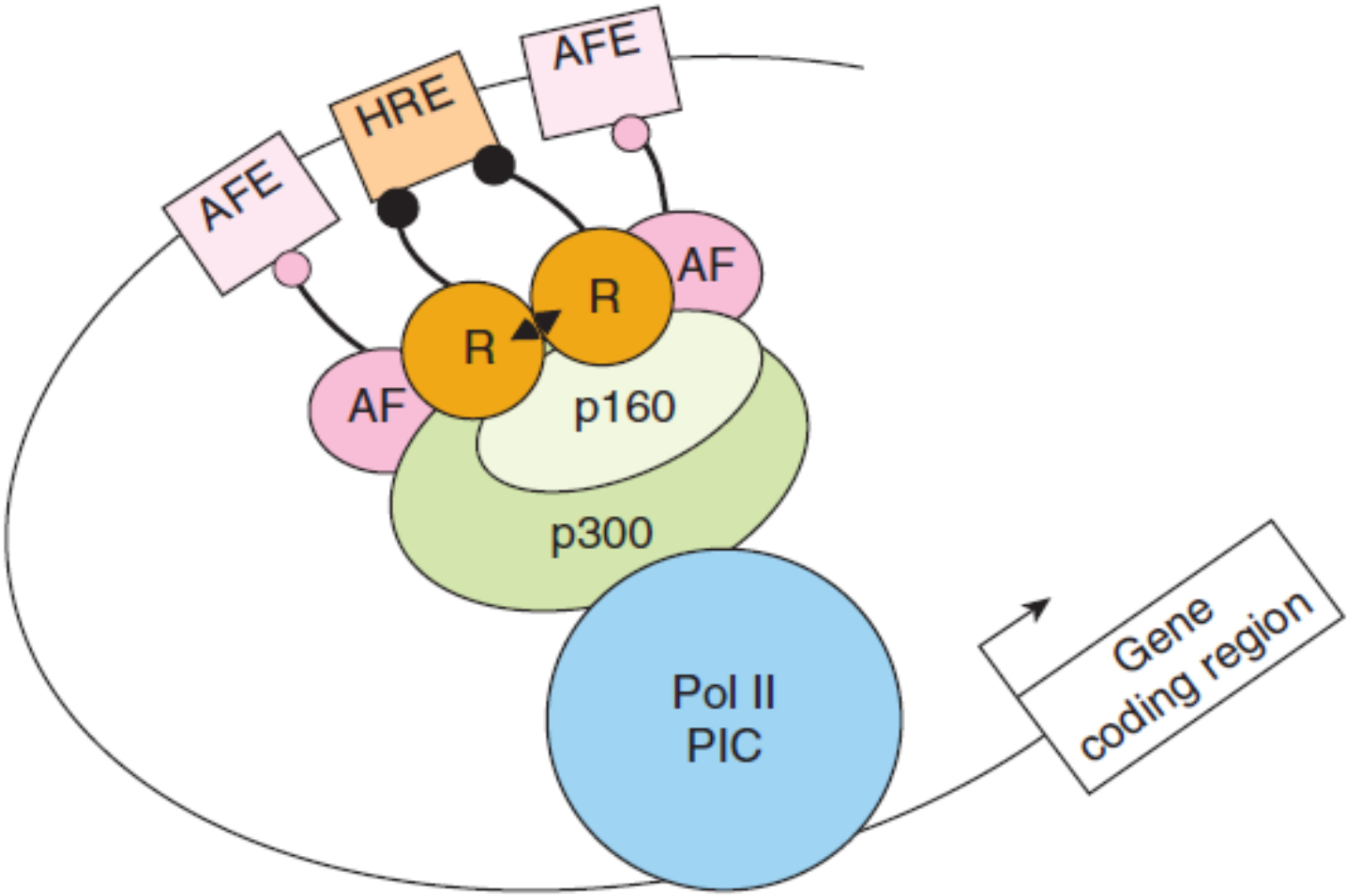


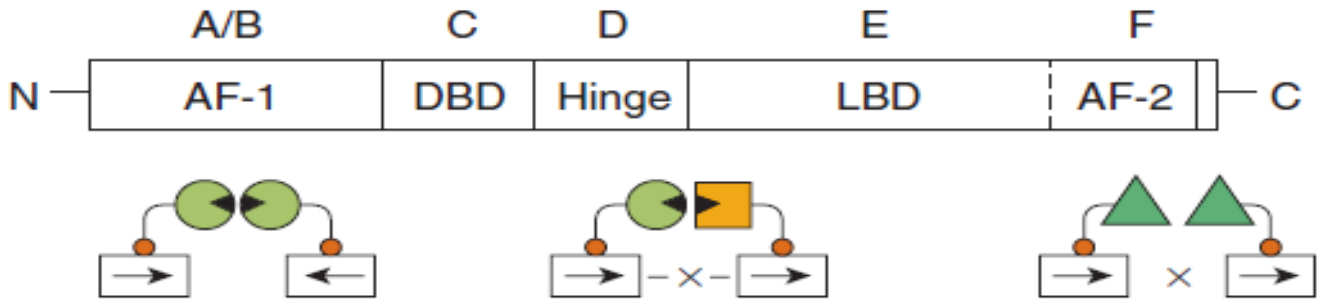
FIGURE 42–11 The hormone response transcription unit.

Sheet #5

- Pol II stands for DNA polymerase type II .
- Pol II is responsible for transcription with other helpers like regulatory proteins, coregulatory proteins .
- P300, P160 → are transcription factors.
- we need to have stable complex structure that will be complete only by certain sequences (AFE , HRE , AFE) that are responsible for binding of receptors , regulatory proteins...etc.
- So , if we loss this sequences , there will be no transcription or minimal transcription. Pay attention that this sequences are away from gene that they regulate it . Some of this sequences are called silencer because they make the gene silence .

There Is a Large Family of Nuclear Receptor Proteins

Diverse set of transcription factors, >50 members



	GR, MR, PR AR, ER	TR, RAR, VDR PPARα, β, γ FXR, CAR, LXR, PXR/SXR	COUP-TF, TR2, NUR77 HNF-4, TLX
Receptors:	Steroid class	RXR partnered	Orphans
Binding:	Homodimers	Heterodimers	Homodimers
Ligand:	Steroids	9-Cis RA + (x)	?
DNA element:	Inverted repeat	Direct repeats	Direct repeats

FIGURE 42–12 **The nuclear receptor superfamily.** Members of this family

Chapter 42

A Large Number of Nuclear Receptor Coregulators Also Participate in Regulating Transcription

The first of these to be described was the **CREB-binding protein, CBP.**

CREB stands for CAMP regulatory element binding protein .
CBP stands for CREB with binding protein .

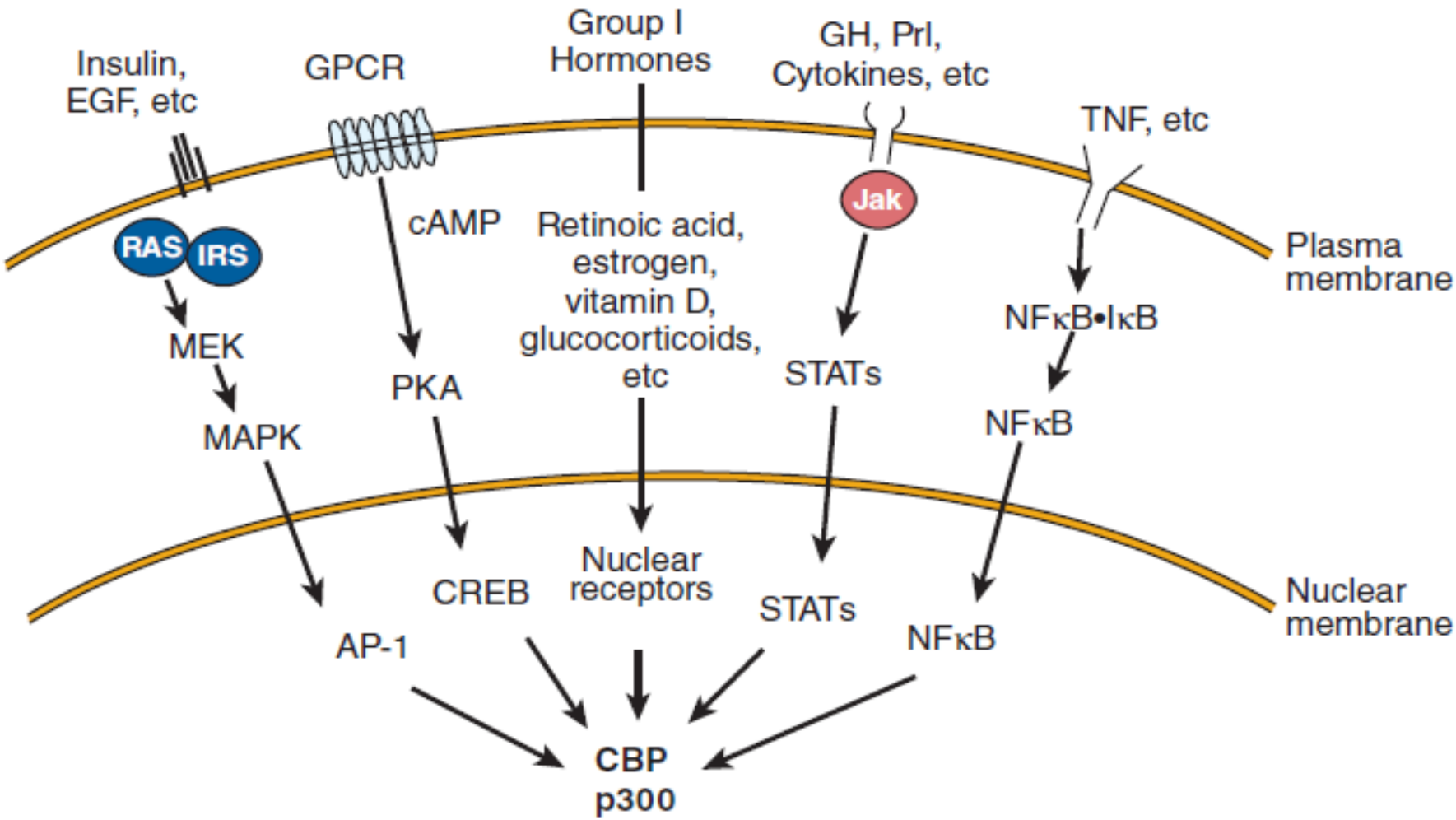


FIGURE 42–13 Several signal transduction pathways converge on CBP/p300. Many ligands that associate with membrane or nuclear receptors eventually converge on CBP/p300. Several different signal transduction pathways are employed. (EGF, epidermal growth factor; GH, growth hormone; Prl, prolactin; TNF, tumor necrosis factor; other abbreviations are expanded in the text.)

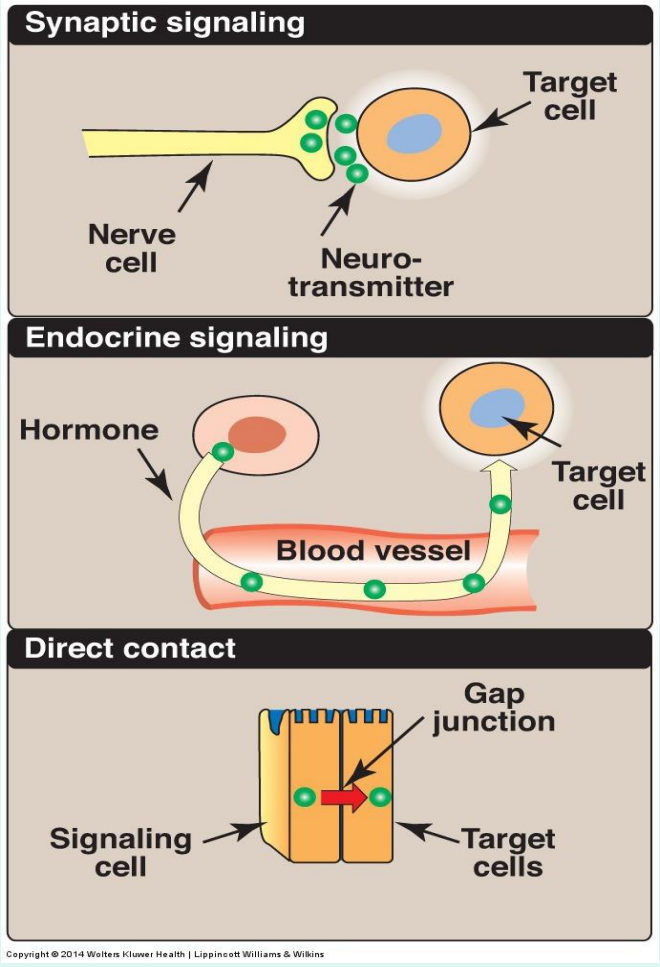
Example of hormonal control

REGULATION OF GLUCOSE METABOLISM

REGULATION OF METABOLISM

- Figure 8.5

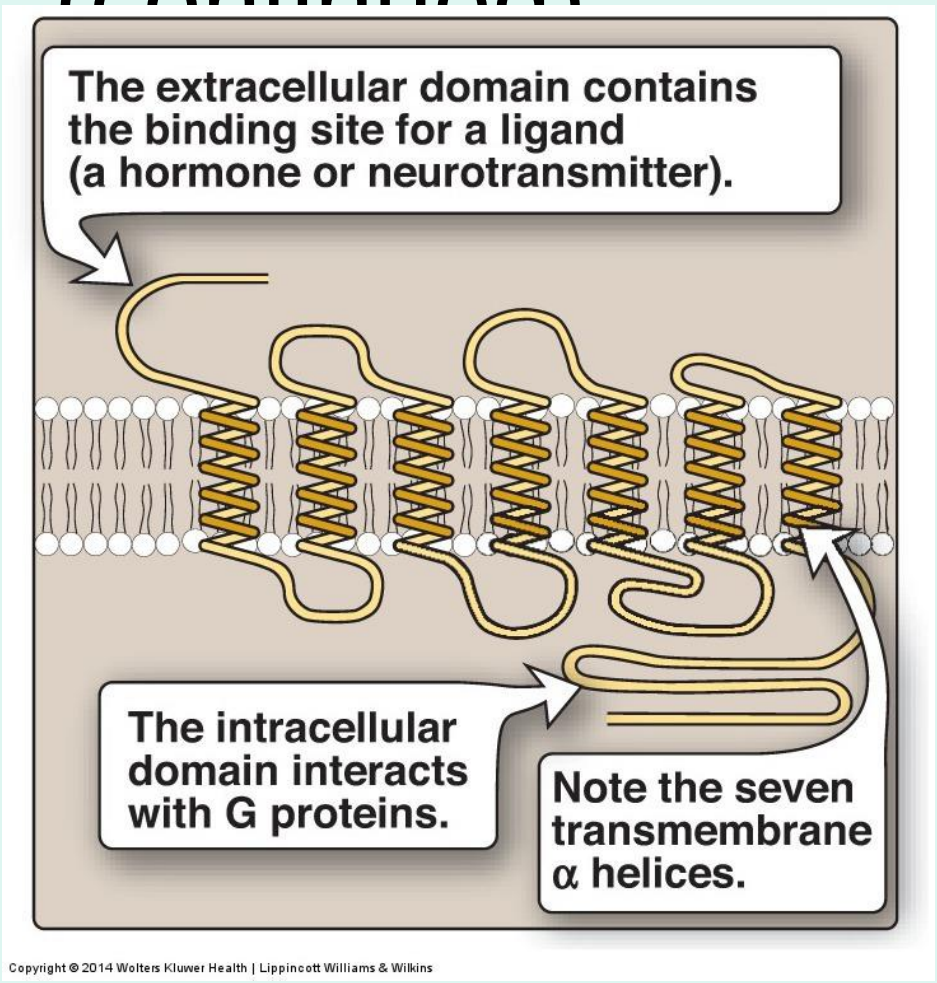
Some commonly used mechanisms for transmission of regulatory signals between cells.



REGULATION OF METABOLISM (continued)

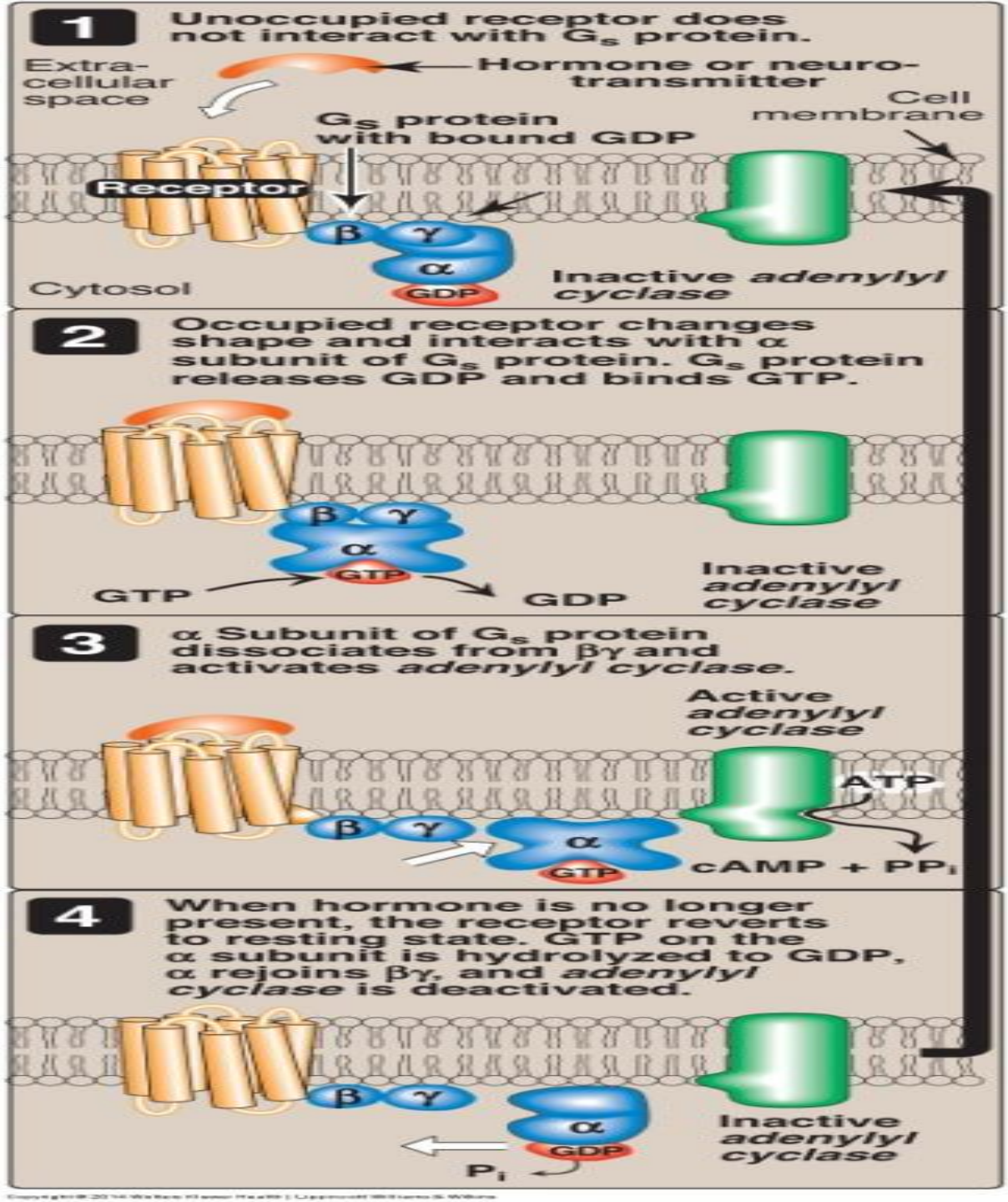
- Figure 8.6

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



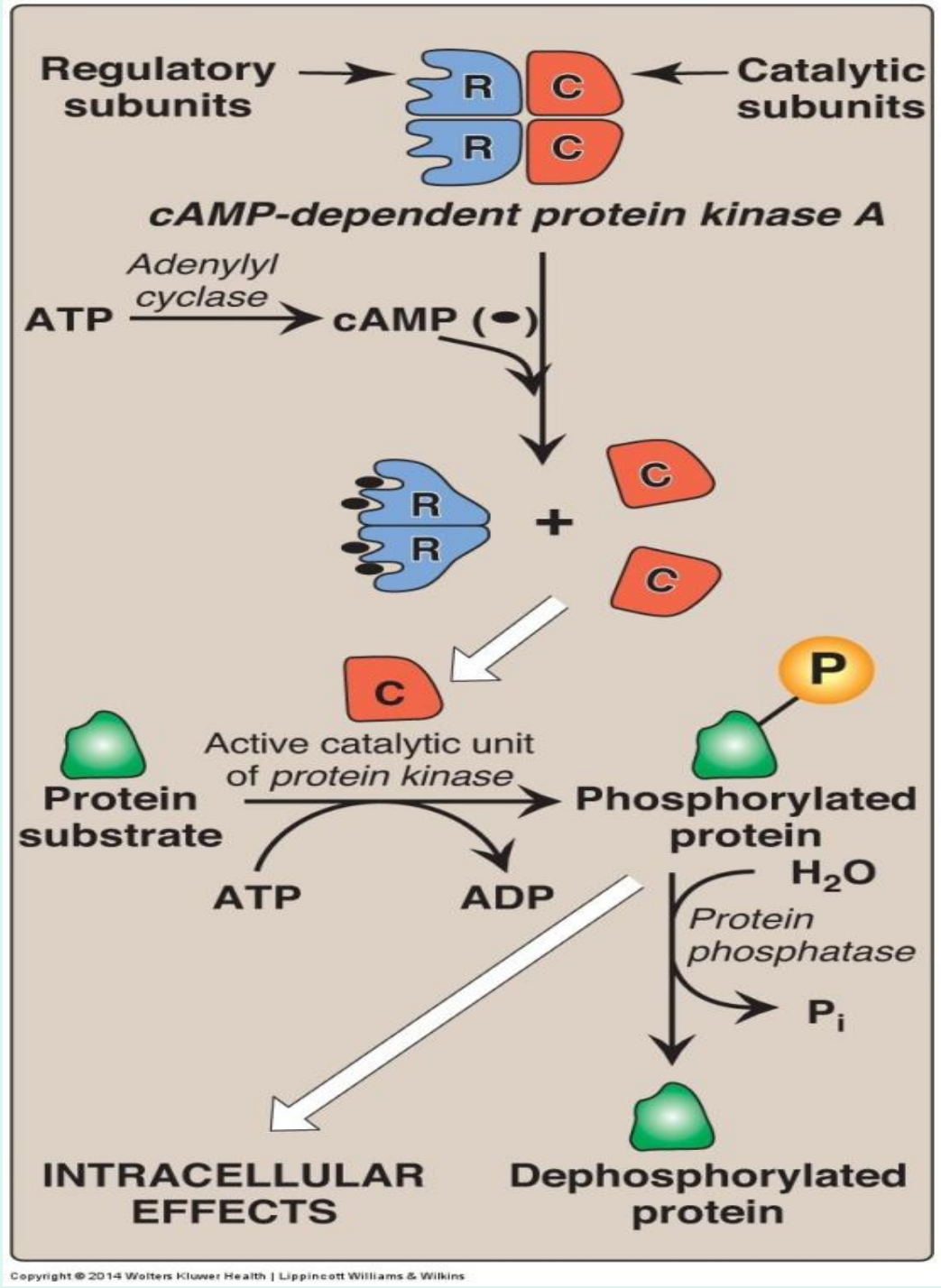
- Figure 8.7

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.



- Figure 8.8

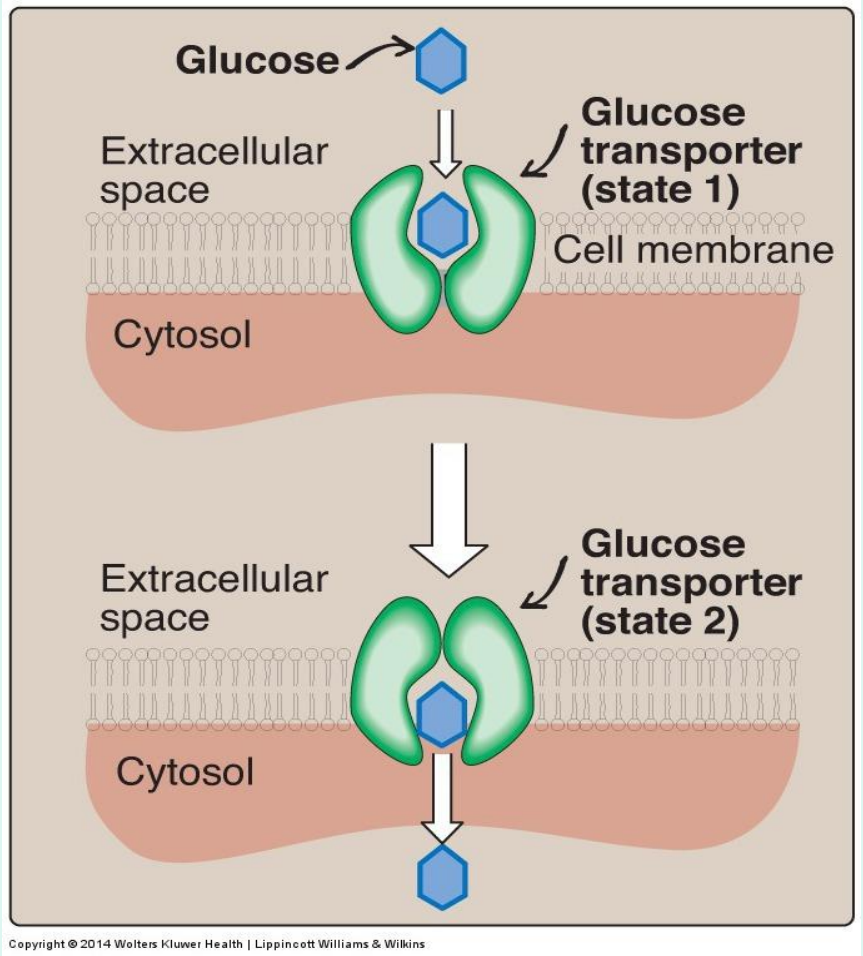
Actions of cyclic AMP (cAMP). P_i = inorganic phosphate.



TRANSPORT OF GLUCOSE INTO CELLS (continued)

- Figure 8.10

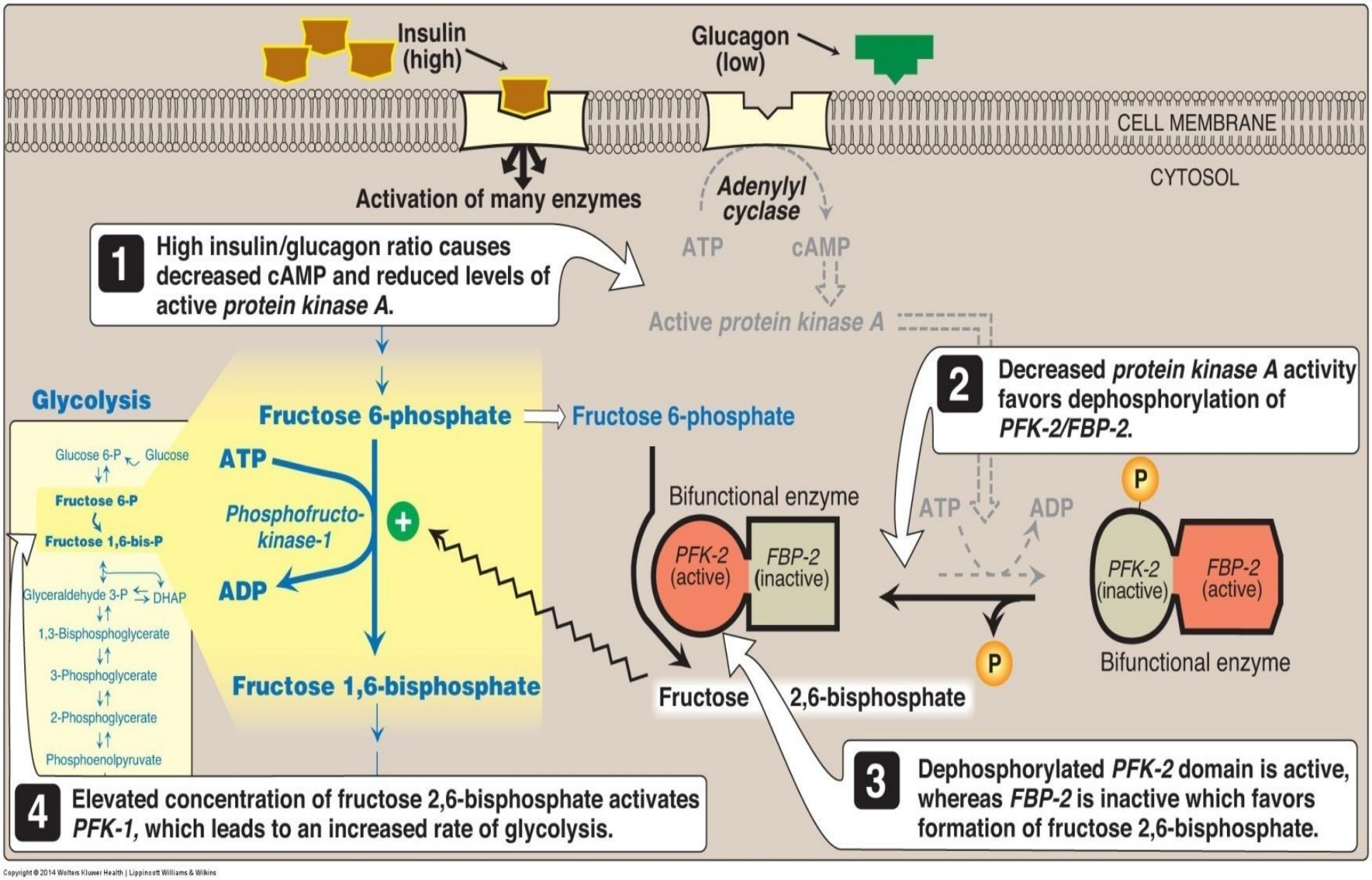
Schematic representation of the facilitated transport of glucose through a cell membrane. [Note: Glucose transporter proteins are monomeric and contain 12 transmembrane α helices.]



Sheet #6

Glucose transporters depend on passive diffusion, so, if glucose level is high inside the cell, glucose will reverse to the plasma . To solve this problem , the glucose will be phosphorylated to form glucose - 6 – phosphate .

- Glycolysis



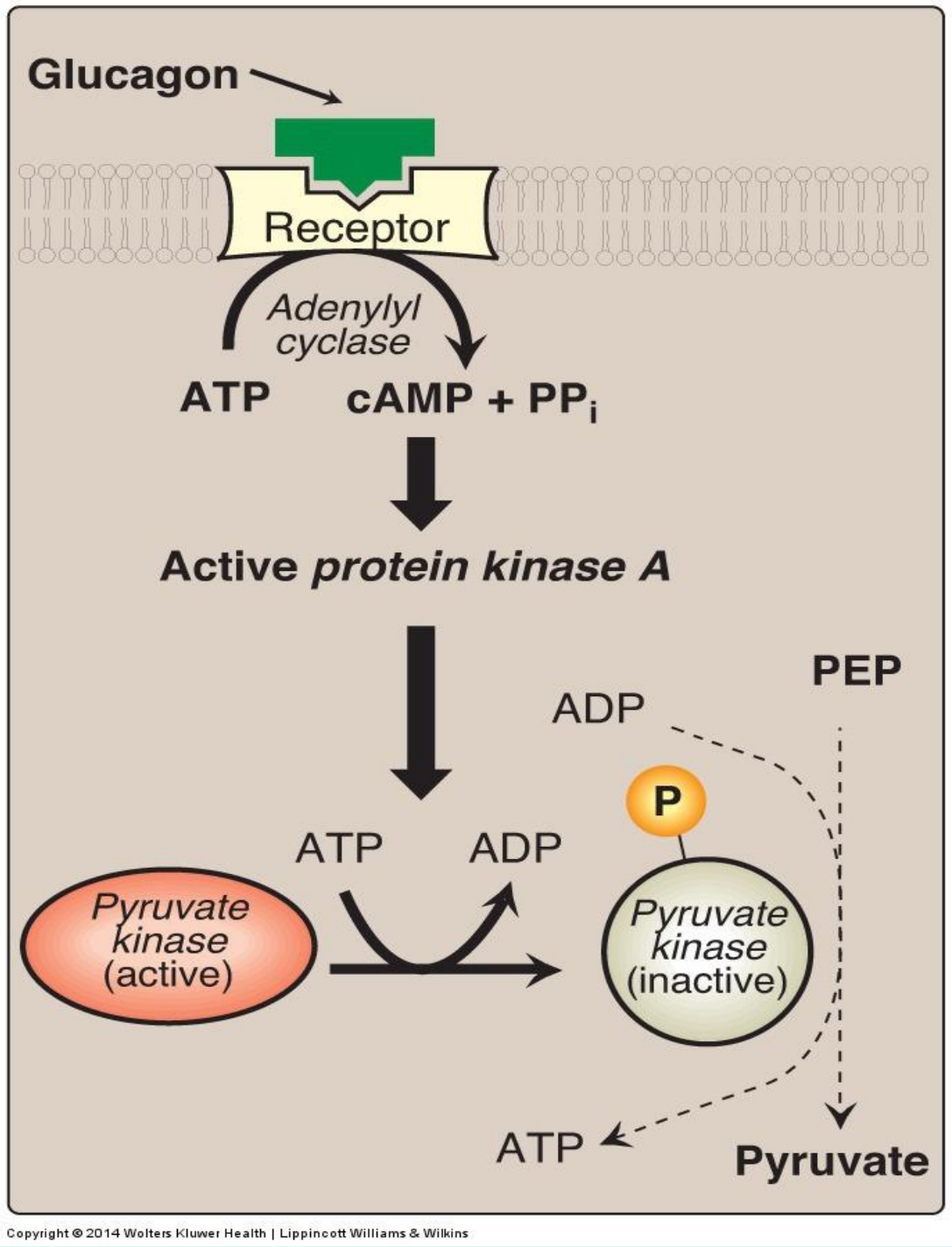
Sheet #7

Effect of elevated insulin concentration on the intracellular concentration of fructose 2,6-bisphosphate in liver. PFK-2 = phosphofructokinase-2; FBP-2 = fructose 2,6-bisphosphatase; cAMP = cyclic AMP; P = phosphate.

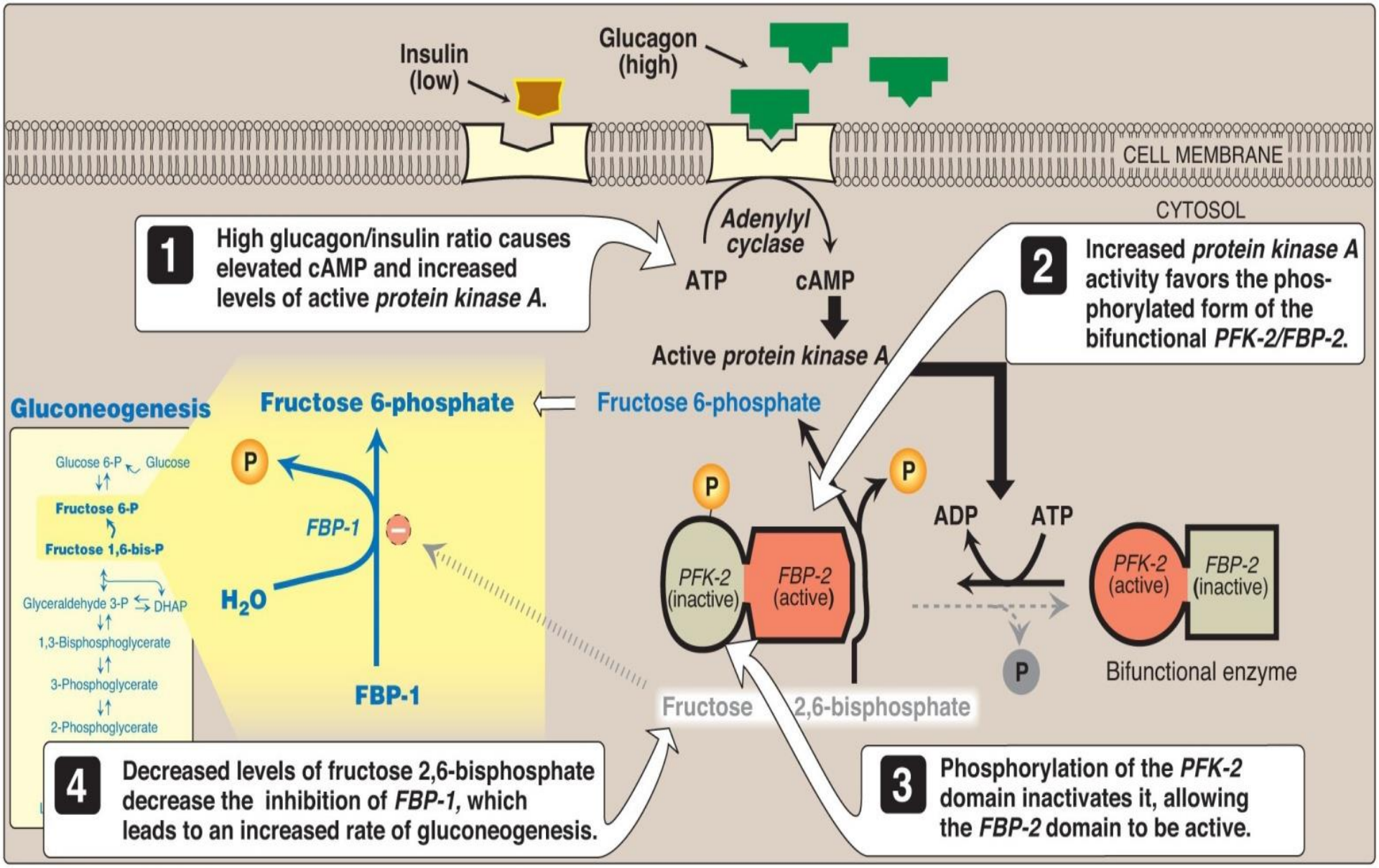
Active FBP-2 converts Fructose 2,6-bisphosphate to fructose 6 - phosphate .
Insulin stimulate glycolysis and glucagon inhibit it .

- Figure 8.19

Covalent modification of hepatic *pyruvate kinase* results in inactivation of the enzyme. cAMP = cyclic AMP; PEP = phosphoenolpyruvate; P = phosphate; PP_i = pyrophosphate.



- Gluconeogenesis

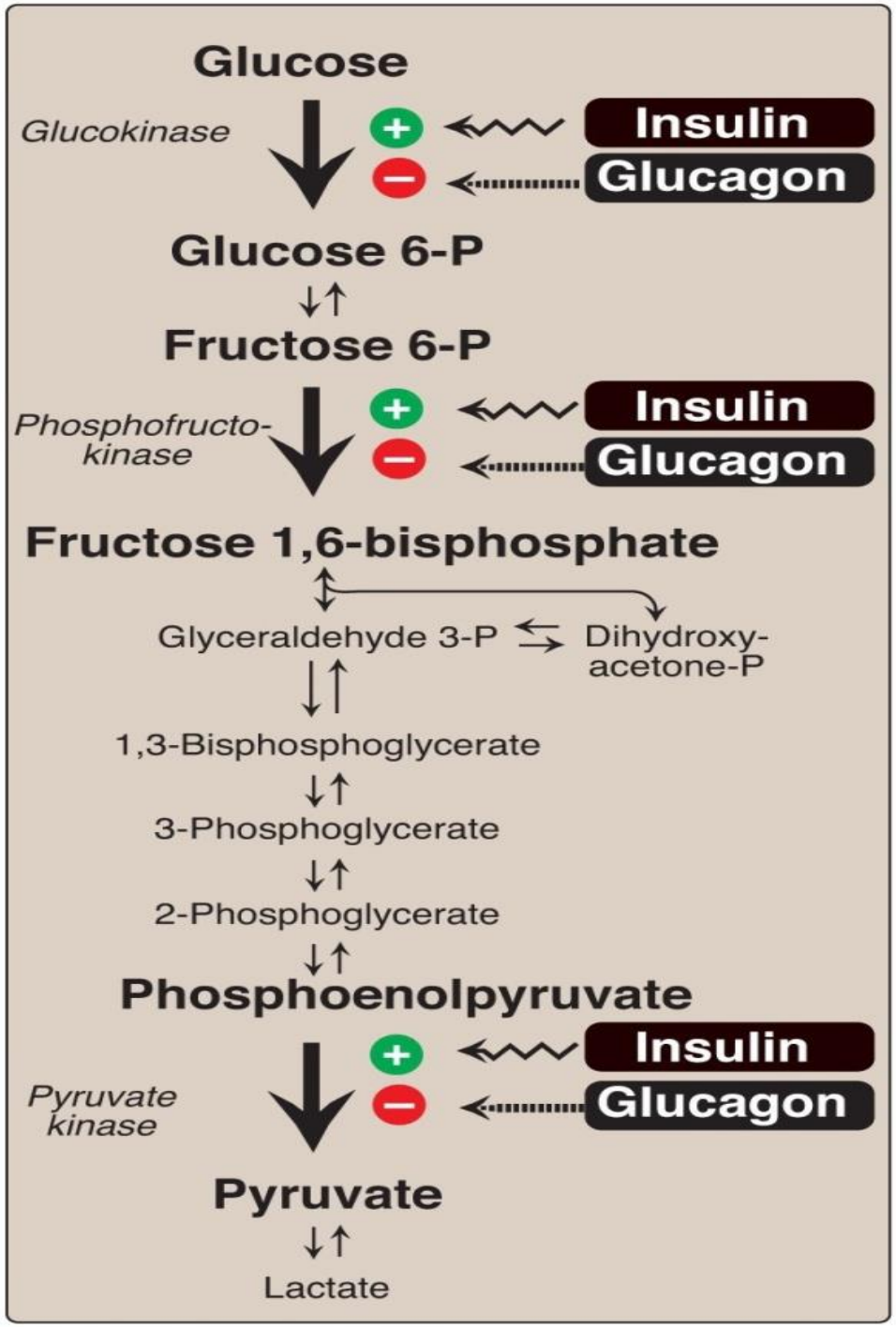


Sheet #8

Effect of elevated glucagon on the intracellular concentration of fructose 2,6-bisphosphate in the liver. cAMP = cyclic AMP; *PFK-2 = phosphofructokinase-2; FBP-2 = fructose 2,6-bisphosphatase; FBP-1 = fructose 1,6-bisphosphatase;* P = *phosphate.*

- Figure 8.23

Effect of insulin and glucagon on the synthesis of key enzymes of glycolysis in liver. P = phosphate.



Hormonal Assay

- Radioimmunoassay(RIA)
- Enzyme-Linked Immunosorbent Assay(ELISA)
- Fluorescence Polarization Immune Assay(FPIA)
- Chemiluminescence enzyme immunoassay(CLIA)