Chapter 6 – Cellular Signaling and Membrane Receptors

Objectives

Given the synopsis in this chapter, competence in each objective will be demonstrated by responding to multiple choice, matching, put-in-order, or fill-in questions, at the level of 85% or greater proficiency for each student.

A. To explain the similarities and differences between synaptic, endocrine, and paracrine signaling.
B. To explain the derivation, characteristics, and general function of chemical messengers, including the amino acids, amines, peptides, steroids, and eicosanoids.
C. To explain the organization of transmembrane receptor proteins, including channel linked receptors, tyrosine kinase linked receptors, and G-protein coupled receptors
A. To explain how water-soluble chemical messengers, through binding to channel linked receptors, tyrosine kinase linked receptors, and G-protein coupled receptors, cause responses.
A. To explain, using cortisol as an example, how lipid-soluble chemical messengers, through binding to intracellular receptors, cause responses.

Overview

Cellular signaling is a communication process to control and coordinate the behavior of cells. The communication is reciprocal, as most cells both receive and send signals. Most cellular signaling uses chemical messengers, although some signaling uses mechanical or other physical stimuli.

Cellular signaling is often categorized according to whether the chemical messenger exerts it effects locally, or has to travel long distances. ***Synaptic signaling*** is an example of local cellular signaling based on neurotransmitters secreted from neurons. ***Endocrine signaling*** is an example of long distance signaling based on hormone is secreted from endocrine glands. ***Paracrine signaling*** is an example of local cellular signaling based on cytokines secreted from cells of the immune.

Chemical messengers fall into several classes of molecules; amino acids, amines, peptides, steroids, and eicosanoids. As a generalization, amino acids, most amines, peptides and most eicosanoids bind to transmembrane proteins. Thyroid amines and most steroid hormones bind to intracellular receptors (which are transcription factors).

Cells have specialized proteins that serve as receptors to recognize and bind to specific chemical messengers. Most water-soluble messengers and most lipid soluble eicosanoids bind to transmembrane receptor proteins on the outside of the cell. The receptor proteins initiate different forms of internal signaling and fall into three major groups. ***Channel linked receptors*** open ion channels, ***Enzyme linked receptors*** control specific enzymes, and ***G-protein coupled* receptors** interact with G-proteins to produce second messengers that initiate and coordinate intracellular signaling.

Lipid-soluble messengers, such as thyroid amines and steroids, often bind to intra-cellular receptor proteins (transcription factors) to control the expression of specific genes.

Categories of Cellular Signaling

Although the mechanisms of chemical signaling have much in common, they are often grouped into the following categories.

- **Synaptic signaling** – utilizes chemical messengers secreted from the pre-synaptic membranes of neurons to bind with receptors on the post-synaptic membranes of other neurons or muscle cells.
  - Chemical messengers secreted at synapses are usually called ***neurotransmitters***.
- **Endocrine signaling** – utilizes chemical messengers, released or secreted by various endocrine cells and neurons, that travel through the blood to bind with receptors of distant cells.
  - Chemical messengers released / secreted into blood are usually called ***hormones***.
- **Paracrine signaling** – utilizes chemical messengers released or secreted by cells which diffuse short distances to bind with receptors of neighboring cells.
  - Chemical messengers of the immune system that bind with receptors of nearby cells are often called ***cytokines***.

Classes of Chemical Messengers

Chemical messengers fall into a small number of chemical classes: amino acids, amines, peptides, steroids, and eicosanoids

Amino acids

The most notable amino acid chemical messengers are Glutamate, Aspartate, Glycine, and Gamma Amino Butyric Acid.

- These amino acids are water-soluble neurotransmitters.
- Bind to channel linked receptors or G-protein coupled receptors (GPCRs)
- Synthesized in neurons and stored in vesicles.

Amines

The amines include thyroid hormones, catecholamines, indolamines, and histamine and of which are derived from amino acids.

- Thyroid amines
    - Thyroxin and Triiodothyronin are lipid-soluble hormones
    - Bind to intracellular receptors (transcription factors)
    - Synthesized from tyrosine on demand and released.
- Catecholamines
    - The catecholamines, which include Dopamine, Norepinephrine, and Epinephrine, are water-soluble neurotransmitters or hormones.
    - Bind to G-protein coupled receptors (GPCRs)
    - Synthesized from tyrosine in neurons and stored in vesicles.
- Indolamines
    - The indolamines include serotonin and are water-soluble neurotransmitters and paracrines
    - Bind to G-protein coupled receptors (GPCRs)
    - Synthesized from tryptophan in neurons and platelets and stored in vesicles.
- Histamine
    - Histamine is water-soluble paracrine.
    - Bind to G-protein coupled receptors (GPCRs)
    - Synthesized from histidine and stored in vesicles.

Peptides

The peptides make up a huge category of chemical messengers that include the hypothalamic regulatory hormones, the pituitary hormones, the pancreatic hormones, the gastrointestinal hormones, the cytokines, and many, many others.

- Peptides are water-soluble hormones, neurotransmitters, or paracrines (cytokines)
- Most bind to G-protein coupled receptors (GPCRs)
- Insulin, Growth hormone, and Prolactin bind to tyrosine kinase receptors (RTK)
- Synthesized from pre-polypeptide, pro-peptide, and stored in vesicles.

Steroids

Steroids include Aldosterone, Hydrocortisone (Cortisol), Testosterone, Estradiol, and Progesterone.

- Steroids are lipid-soluble hormones.
- Bind to intracellular receptors (transcription factors)
- Synthesized from cholesterol on demand and released

Eicosanoids

Eicosanoids are composed of two fatty acids connected by a carbon. The most common are prostaglandins, prostacyclin, thromboxane, leukotriene, and endocannabinoids.

- Eicosanoids are lipid-soluble paracrines
- Bind to G-protein coupled receptors (GPCRs)
- Synthesized from Arachidonic acid on demand and released.

Transmembrane Receptor Proteins

Transmembrane receptor proteins are proteins imbedded in cell membranes with the receptors commonly on the exterior of the plasma membrane. Water-soluble chemical messengers bind to these receptors, which include channel linked receptors, tyrosine kinase linked receptors, and G-protein coupled receptors are shown in a schematic (cartoon) form in Figure 6.1.

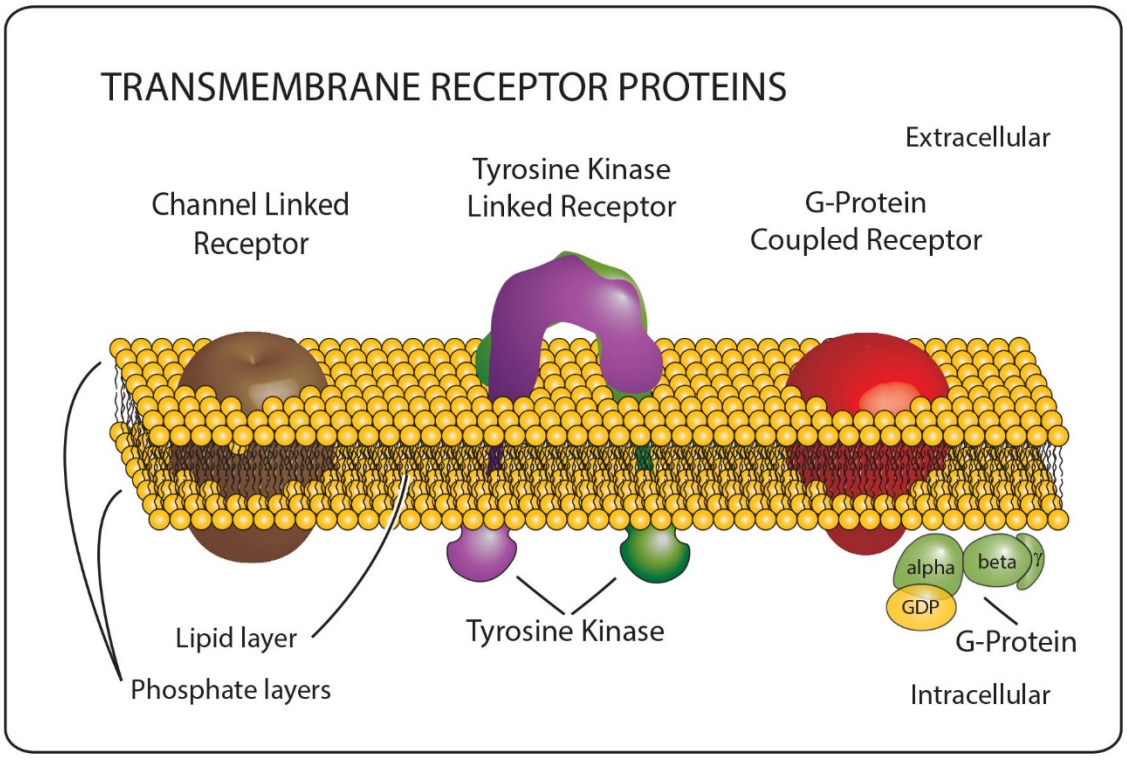


Figure 6.1 © 2019 David G. Ward, PhD

Channel linked Receptors

Channel linked receptors are transmembrane proteins that function as both receptor and ion channel. Commonly, the receptor faces the exterior of the cell and the channel passes through the plasma membrane. In some instances, the receptor faces the interior of the cell and the channel may pass through the plasma membrane or through the membrane of an intracellular organelle (such as the smooth endoplasmic reticulum).

Channels that respond to a chemical messenger are often called ligand gated channels. The binding of an appropriate water-soluble chemical messenger usually causes the channel to open and allows the diffusion of certain ions (such as sodium, chloride, or calcium) through the channel.

Tyrosine Kinase linked Receptors (RTK)

The tyrosine kinase linked receptors are specific examples of enzyme linked receptors, where the transmembrane proteins operates as both receptor and enzyme. The receptor faces the exterior of the cell and the enzyme (tyrosine kinase) faces the cytoplasm.

The binding of an appropriate water-soluble chemical messenger activates the enzyme, that in turn catalyzes a cascade of intracellular responses.

G-protein coupled Receptors (GPCRs)

The G-protein coupled are transmembrane proteins that function as a receptor and as a coupling to intracellular G-proteins (G-α, G-β/γ). The receptor faces the exterior of the cell and the coupling end faces the cytoplasm.

The binding of an appropriate water-soluble or lipid-soluble chemical messenger causes G-α to release GDP and bind GTP, causing the G-α unit and the G-β/γ unit to separate from the receptor.

- G-α regulates metabolic responses and/or ion channels by stimulating (or inhibiting) enzymes (especially adenylyl cyclase or guanylyl cyclase, and phospholipase C), that in turn produce additional messengers that control a cascade of intracellular responses.
- G-β/γ regulate the opening (or closing) of ion channels, as well as other intracellular responses.

Examples of Channel linked Receptors (Ligand gated channels)

Upon the binding of a chemical messenger to the channel, the channel opens and allows the diffusion of ions through the channel. Figure 6.2 shows two examples involving amino acid neurotransmitters. In the first example, glutamate binds to a sodium channel linked AMPA receptor, which opens the channel allowing positively charged sodium ions to diffuse into the cell. In the second example, glycine binds to a chloride channel linked glycine receptor, which opens the channel allowing negatively charged chloride ions to diffuse into the cell. A primary effect of changes in concentration is to change the membrane potential, as we will consider further in chapter 7.

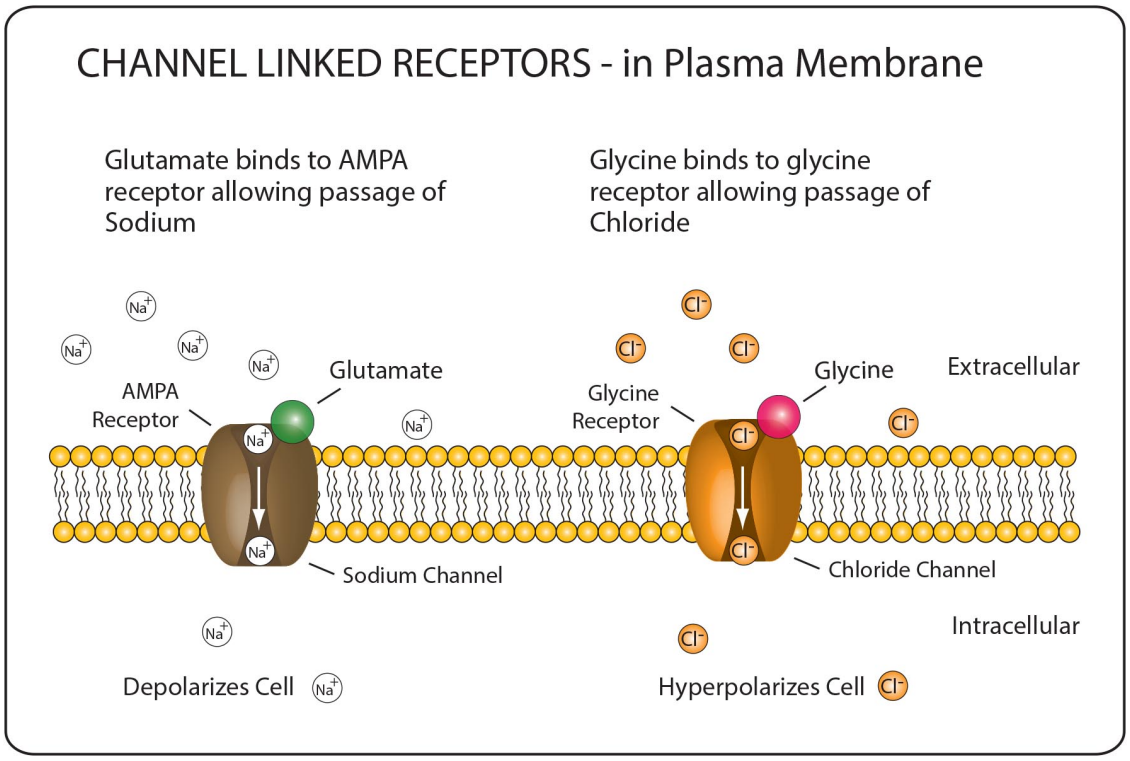
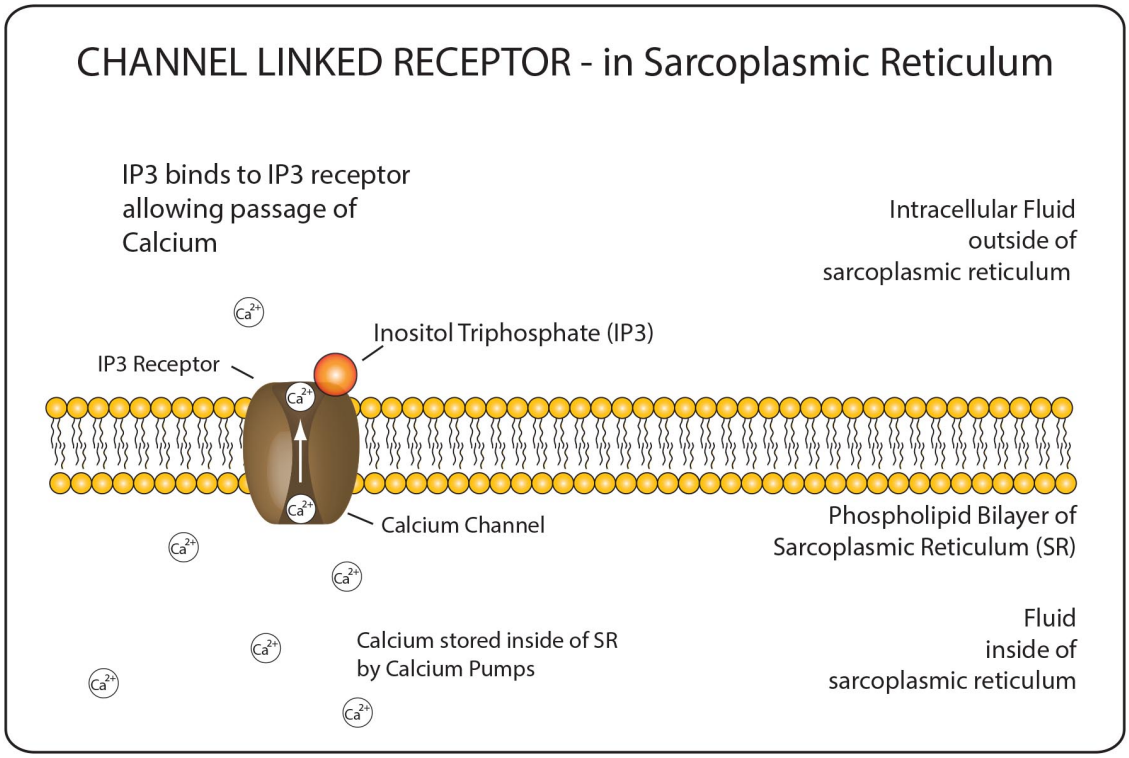


Figure 6.2 © 2019 David G. Ward, PhD

Figure 6.3 shows another example, this time involving inositol triphosphate (IP_3). IP_3 is an intracellular chemical messenger that binds to a calcium channel linked IP_3 receptor in the sarcoplasmic reticulum (SR, smooth ER) of muscle cells. When these channels open, calcium ions diffuse into the intracellular fluid (cytosol) surrounding the SR. Increased calcium in the cytosol can cause depolarization, muscle contraction, the secretion of water-soluble neurotransmitters and hormones; and can change the activity of intracellular proteins by way of calcium-calmodulin (not shown). A common protein affected by calcium-calmodulin is the myosin protein in smooth muscle (considered further in chapter 11).



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Example of Tyrosine kinase linked Receptors (RTK)

Upon the binding of a chemical messenger to the tyrosine kinase linked receptor, the tyrosine kinase, which is on the intracellular side, auto-phosphorylates. The tyrosine kinase also phosphorylates tyrosine in intracellular proteins. An example involving the binding of the hormone insulin to a tyrosine kinase linked receptor (RTK) is shown in Figure 6.4. The following sequence of events occurs.

1. Insulin binds to a tyrosine kinase linked receptor and activates the tyrosine kinase.
2. The tyrosine kinase phosphorylates a large number of IRSs (Insulin Receptor Substrates).
3. The IRSs mostly activate the PI3K-PDK-1-Akt pathway, that in turn orchestrates critical insulin responses, including: transfer of glucose transporters to the plasma membrane, increased conversion of glucose to glycogen, increased protein synthesis, and increased cell growth.
4. Tyrosine kinase also phosphorylates Shc (Src homology and collagen proteins).
5. Shc activates the Ras-Grb2-SOS-Ras-MAPK pathway that in turn stimulates cellular proliferation and gene expression.

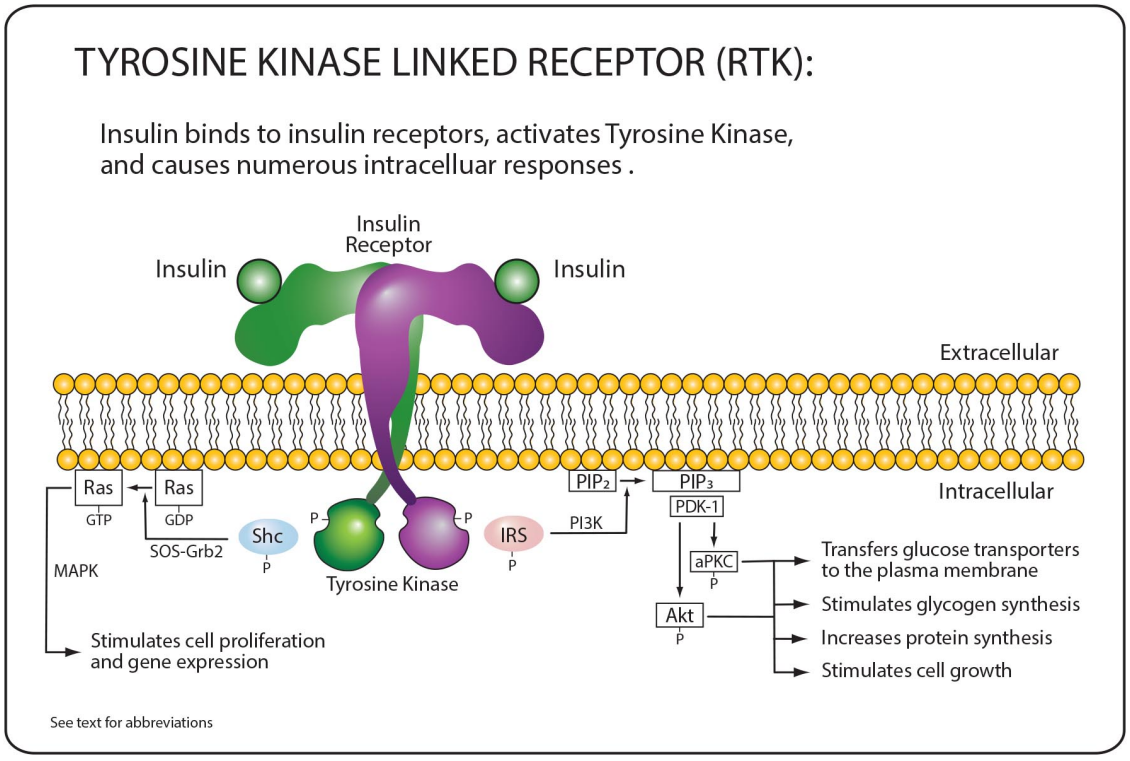


Figure 6.4 © 2019 David G. Ward, PhD

Abbreviations: *IRS*, Insulin Receptor Substrate; *PI3K*, Phosphoinositide 3-Kinase; *PIP2*, Phosphatidylinositol (4,5)-biphosphate; *PIP3*, Phosphatidylinositol (3,4,5)-triphosphate; *PDK-1*, 3-Phosphoinositide-Dependent protein Kinase-1; *Akt*, Protein Kinase B; *aPKC*, alpha Protein Kinase C; *Shc* , Src (Sarcoma) homology and collagen proteins; *Grb2*, Growth factor receptor-bound protein-2; *Sos*, Son of sevenless; *Ras*, Rat sarcoma small G-protein; *MAPK*, Mitogen-Activated Protein Kinase.

Examples of G-Protein coupled Receptors (GPCRs)

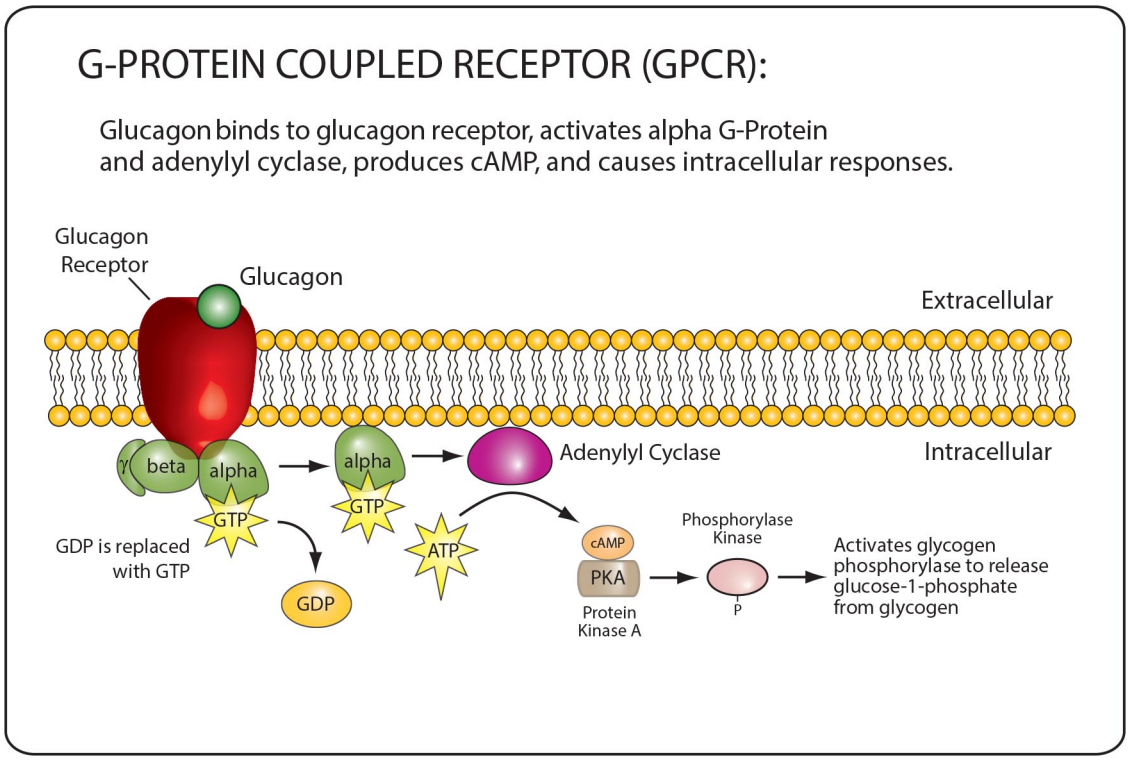
Binding of a chemical messenger to the receptor causes the G-protein α to release GDP and bind GTP, causing the G-α unit and the G-β/γ unit to separate from the receptor.

- G-protein α regulates metabolic responses and/or ion channels by stimulating (or inhibiting) enzymes; such as adenylyl cyclase, or phospholipase C.
  - Adenylyl cyclase catalyzes ATP to cAMP, an intracellular messenger.
  - Phospholipase C catalyzes phosphatidyl inositol (4,5)-biphosphate (PIP2) to inositol triphosphate (IP3) and diacyl glycerol (DAG), both intracellular messengers.
- G-protein β/γ regulate the opening (or in some cases closing) of ion channels, and other intracellular actions.

G-protein α - Adenylyl Cyclase

An example of glucagon binding to a G-protein coupled glucagon receptor, causing the production of cAMP, is shown in Figure 6.5. The following sequence of events occurs.

1. Glucagon binds to a G-protein coupled glucagon or epinephrine binds to a Beta receptor.
2. G protein α subunit activates adenylyl cyclase
3. Adenylyl cyclase catalyzes ATP to cAMP
4. cAMP activates protein kinase-A
5. Protein kinase-A phosphorylates various enzymes that orchestrate responses. For example, protein kinase-A phosphorylates phosphorylase kinase, that in turn phosphorylates glycogen phosphorylase, that in turn releases glucose-1-phosphate from glycogen.



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G-protein α – Phospholipase C

An example of acetylcholine binding to a G-protein coupled muscarinic-3 (M-3) receptor, causing the activation of phospholipase C, is shown in Figure 6.6. The following sequence of events occurs.

1. Acetylcholine binds to a G-protein coupled M-3 receptor.
2. G protein α subunit activates phospholipase C (PLC)
3. Phospholipase C (PLC) catalyzes phosphatidylinositol (4,5)-biphosphate (PIP_2) to inositol triphosphate (IP_3) and to diacylglycerol (DAG)
    a. IP_3 opens Ca^{++} ion channels in the sarcoplasmic reticulum (smooth ER)
        i. Ca^{++} ions stimulate smooth muscle contraction or depolarization
    b. DAG activates Protein Kinase C (PKC)
        ii. Protein Kinase C (PKC) phosphorylates K^+ ion channels causing them to close, and thus increasing depolarization

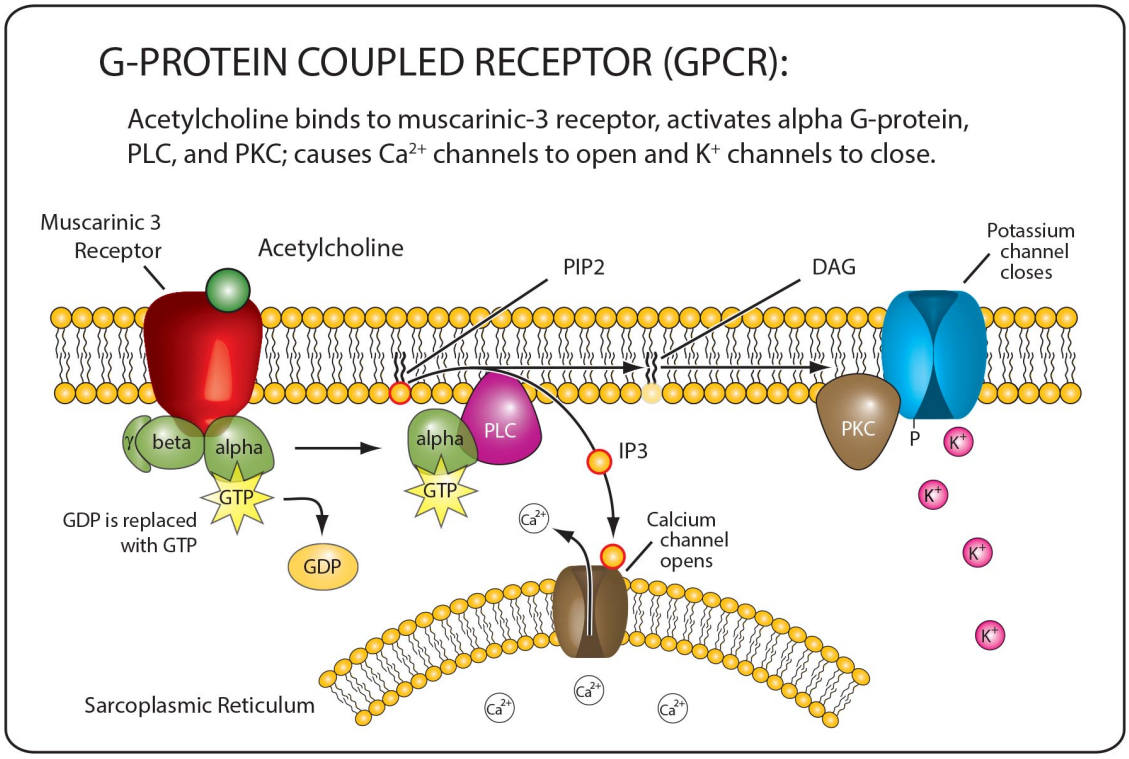

Figure 6.6 © 2019 David G. Ward, PhD

G-protein β/γ

An example of acetylcholine binding to a G-protein coupled Muscarinic-2 receptor, causing the release of the G-protein β subunit, is shown in Figure 6.7. The following sequence of events occurs.

1. Acetylcholine binds to a G-protein coupled Muscarinic-2 receptor
2. G-protein β and γ binds to a potassium channel
3. The potassium channel opens, allowing potassium ions to leave the cell

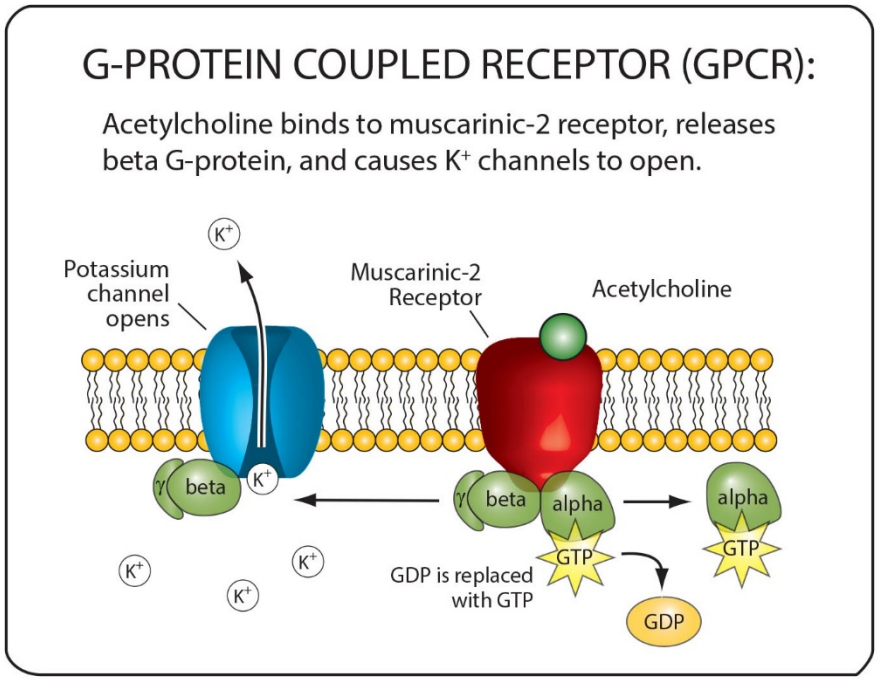

Figure 6.7 © 2019 David G. Ward, PhD

Intracellular Receptor Proteins

Intracellular receptor proteins are located in the cytosol of cells. Certain lipid-soluble chemical messengers pass through the phospholipid bilayer and bind to intracellular receptor proteins to form transcription factors, that in turn bind to response element receptors of specific genes. For this reason, the intracellular receptor are often called response element binding (REB) proteins. An example of a metabolic response initiated by the hormone cortisol is shown in Figure 6.8. The following sequence of events occurs.

1. Cortisol passes through the phospholipid bilayer and binds to a Glucocorticoid Response Element Binding protein (GREB) in the cytosol.
2. The conformation of the GREB protein is altered, exposing a nuclear localization signal which allows the hormone receptor complex to pass through a nuclear pore.
3. The cortisol-GREB complex binds to the Glucocorticoid Response Element in the promoter region of the PEPCK gene and activates transcription of the gene.

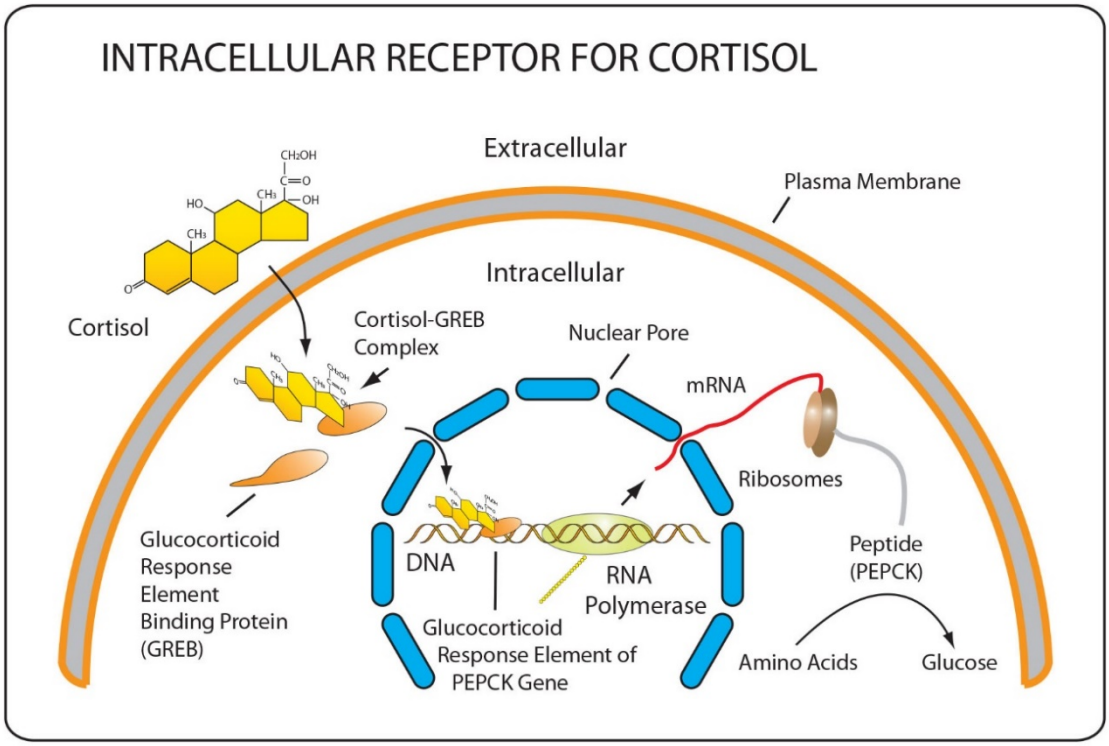

Figure 6.8 © 2014 David G. Ward, PhD

PEPCK (phosphoenolpyruvate carboxykinase) is thought to be a key enzyme in gluconeogenesis that allows for the production of glucose from amino acids. In response to low blood glucose, together with other physical stresses, cortisol shifts metabolism toward conserving glucose and using fat and protein as a source of energy. Increases in gluconeogenesis is consistent with this pattern.

It is well documented that lipid-soluble steroids, such as cortisol, and lipid-soluble thyroid hormones, such as triiodothyronine, bind to intracellular receptor proteins. However, it is also well documented that lipid-soluble eicosanoids bind to G-protein coupled receptors. Therefore, it appears that only certain lipid-soluble chemical messengers depend on intracellular receptor proteins.

Quiz Yourself

1-5. Matching

A)	amines	are synthesized as short chains of amino acids	1) _____
B)	steroids	are synthesized from single amino acids	2) _____
C)	peptides	are synthesized from cholesterol	3) _____
D)	amino acids	include glycine and glutamate	4) _____
E)	none of the above	include epinephrine	5) _____

6-10. Matching

A)	are water-soluble	steroids	6) _____
B)	are lipid-soluble	thyroxin	7) _____
		peptides	8) _____
		amino acids	9) _____
		most non-thyroid amines	10) _____

11-15. Matching (chemical messengers)

A)	Bind to intracellular receptors (Transcription factors)	Steroid messengers	11) _____
B)	Bind to G-protein coupled receptors (GPCRs)	Amino acid messengers	12) _____
C)	Bind to tyrosine kinase linked receptors	Eicosanoid messengers	13) _____
D)	Bind to channel linked receptors	*Most* peptide messengers	14) _____
E)	B and D	Non-thyroid amine messengers	15) _____

16-20. Matching (REB = response element binding)

A)	G-protein coupled receptors (GPCRs)	Utilize adenylyl cyclase	16) _____
B)	Channel linked receptors	Utilize phospholipase C	17) _____
C)	Enzyme linked receptors	Include ligand-gated channels	18) _____
D)	Intracellular receptors	Include the tyrosine kinase linked receptors	19) _____
		Often are REB proteins that form transcription factors	20) _____

Fill in

21. Chemical messengers bind to _____-cellular or _____-cellular receptors.

22. Water-soluble chemical messengers bind to _____ gated channels, _____ linked receptors, or _____ coupled receptors.

23. RTKs phosphorylate _____ and _____, causing activation, respectively, of Akt and MAPK

24. GPCRs control enzymes such as adenylyl cyclase to produce _____.

25. In addition to affecting cyclase, GPCRs can increase the activity of _____, causing production of _____ and _____.

Study Questions

1. Describe the major classes of chemical messenger.
2. Compare and contrast the organization of channel linked receptors, tyrosine kinase linked receptors, and G-protein coupled receptors.
3. Explain how water-soluble chemical messengers, using glucagon as an example, cause cellular responses.
4. Explain how lipid-soluble chemical messengers, using cortisol as an example, lead to intracellular mediated responses.