CHAPTER 12
Signal Transduction

Key topics:

– General features of signal transduction
– Structure and function of G-protein coupled receptors
– Structure and function of enzyme-linked receptors
– Structure and function of gated ion channels
– Physiological processes using signal transduction
Biological Role of Signal Transduction

• Cells receive signals from the environment beyond the plasma membrane
  – Antigens
  – Hormones
  – Neurotransmitters
  – Light
  – Touch
  – Pheromones

• These signals cause changes in the cell’s composition and function
  – Differentiation and antibody production
  – Growth in size or strength
  – Sexual vs. asexual cell division
Receptors

- Receptor: A membrane-bound or soluble protein or protein complex, which exerts a physiological effect (intrinsic effect) after binding its natural ligand.
  - G-protein coupled receptors
    - Epinephrine receptor
  - Enzyme-linked receptors
    - Insulin receptor
  - Ligand-gated ion channels
    - Nicotinic acetylcholine receptor
  - Other membrane receptors
    - Integrin receptors
  - Nuclear receptors
    - Steroid receptors
Five Features of Signal-Transducing Systems

(a) Specificity
Signal molecule fits binding site on its complementary receptor; other signals do not fit.

(b) Amplification
When enzymes activate enzymes, the number of affected molecules increases geometrically in an enzyme cascade.

(c) Modularity
Proteins with multivalent affinities form diverse signaling complexes from interchangeable parts. Phosphorylation provides reversible points of interaction.

(d) Desensitization/Adaptation
Receptor activation triggers a feedback circuit that shuts off the receptor or removes it from the cell surface.

(e) Integration
When two signals have opposite effects on a metabolic characteristic such as the concentration of a second messenger $X$, or the membrane potential $V_m$, the regulatory outcome results from the integrated input from both receptors.

Figure 12-1
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Receptors Bind Specific Ligands

Typical ligands are:

- **Small ions**
  - ferric ion: bacterial ferric receptor
- **Organic molecules**
  - Adrenalin: epinephrine receptor
- **Polysaccharides**
  - Heparin: fibroblast growth factor
- **Peptides**
  - Insulin: insulin receptor
- **Proteins**
  - Vascular endothelial growth factor: VEGF receptor
Receptors Bind Specific Ligands

Specificity
Signal molecule fits binding site on its complementary receptor; other signals do not fit.

Figure 12-1a
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Receptor Binding Studies: Filter Assay

• Rationale:
  – Equilibrium binding of labeled ligand with the receptor
  – \( R + L \rightleftharpoons RL \)
  – The bound complex becomes radioactive
  – Free receptor remains non-radioactive
  – Free ligand can pass through the filter
  – Complex cannot pass because the protein binds to the filter

• Steps:
  – Isolate membranes
  – Add ligand to membranes
  – Pass through a filter
  – Wash off unbound ligand
  – Measure bound radioactivity, which is proportional to [COMPLEX]
Receptor Binding Studies: Nonspecific Binding

Problem:
Hydrophobic ligands are nonspecifically soaked into the membrane.

Solution:
• Measure total binding
• Measure nonspecific binding (NSB) in the absence of receptors
• Subtract NSB from Total to get specific binding
• Analyze specific binding data
Receptor Binding Studies: Data

![Graph showing bound hormone, [RL] vs. total hormone added, [L] + [RL] with curves for total binding, specific binding, and nonspecific binding.](image)

Box 12-1 figure 1a
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Receptor Binding Studies: Data Analysis

- Determine
  - Binding constant
  - Number of receptors
  - Number of sites
  - Cooperativity

\[
\frac{[\text{Bound ligand}]}{[\text{Free ligand}]} = \frac{B_{\text{max}}}{K_d} - \frac{1}{K_d} \cdot [\text{Bound ligand}]
\]
Receptor Binding Studies: Data Analysis

\[ \text{Slope} = - \frac{1}{K_d} \]

\[ B_{\text{max}} \]
Signaling Through the Membrane

1. G protein-coupled receptor
   External ligand (L) binding to receptor (R) activates an intracellular GTP-binding protein (G), which regulates an enzyme (Enz) that generates an intracellular second messenger (X).

2a. Receptor tyrosine kinase
   Ligand binding activates tyrosine kinase activity by autophosphorylation.


3. Receptor guanylyl cyclase
   Ligand binding to extracellular domain stimulates formation of second-messenger cyclic GMP.

4. Gated ion channel
   Opens or closes in response to concentration of signal ligand or membrane potential.

5. Adhesion receptor (integrin)
   Binds molecules in extracellular matrix, changes conformation, thus altering its interaction with cytoskeleton.

6. Nuclear receptor
   Hormone binding allows the receptor to regulate the expression of specific genes.

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G-Protein Coupled Signaling

• G-Protein Coupled Receptors (GPCRs) are $\alpha$-helical integral membrane proteins
• G-proteins are heterotrimeric ($\alpha\beta\gamma$) membrane-associated proteins that bind GTP
• G-proteins mediate signal transduction from GPCRs to other target proteins
Prototypical G-protein: Ras

Box 12-2 figure 2
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GPCRs: The Receptors

(a) β2-adrenergic receptor
(b) Morphine analog in ligand-binding site
(c) Histamine H1 receptor
(d) Doxepin in ligand-binding site

Figure 12-13
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Epinephrine: The Fight or Flight Hormone

- Hormone made in adrenal glands (pair of organs on top of kidneys)
- Mediates stress response: mobilization of energy
- Binding to receptors in muscle or liver cells induces breakdown of glycogen
- Binding to receptors in adipose cells induces lipid hydrolysis
- Binding to receptors in heart cells increases heart rate
Epinephrine and Analogs

\[
\text{Epinephrine} \quad K_d (\mu M) = 5
\]

\[
\text{Isoproterenol (agonist)} \quad K_d (\mu M) = 0.4
\]

\[
\text{Propranolol (antagonist)} \quad K_d (\mu M) = 0.0046
\]

Figure 12-3
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Sensing the Epinephrine Signal via a G-Protein Coupled Receptor

1. Epinephrine binds to its specific receptor.
2. Hormone-receptor or complex causes the GDP bound to $G_{\alpha}$ to be replaced by GTP, activating $G_{\alpha}$.
3. Activated $G_{\alpha}$ moves to adenyl cyclase, and activates it. Many $G_{\alpha}$ subunits may be activated by one occupied receptor.
4. Adenyl cyclase catalyzes the formation of cAMP.
5. cAMP activates PKA.
6. Phosphorylation of cellular proteins by PKA causes the cellular response to epinephrine.
7. cAMP is degraded, reversing the activation of PKA.

Figure 12-4a
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Synthesis of cAMP

- cAMP is a secondary messenger
  - Allosterically activates cAMP-dependent protein kinase A (PKA)
  - PKA activation leads to activation of enzymes that produce glucose from glycogen

Figure 12-4b
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Signal Amplification in Epinephrine Cascade

- Activation of few GPCRs leads to the activation of few adenylyl cyclase enzymes
- Every active adenylyl cyclase enzyme makes several cAMP molecules, thus activating several PKA enzymes
- These activate thousands of glycogen-degrading enzymes in the liver tissue
- At the end, tens of thousands of glucose molecules are released to the bloodstream
Signal Amplification

Figure 12-7
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Self-Inactivation in G-protein Signaling

- Epinephrine is meant to be a short-acting signal
- The organism must stop glucose synthesis if there is no more need to fight or flee
- Down-regulation of cAMP occurs by the hydrolysis of GTP in the $\alpha$ subunit of the G-protein
Self-Inactivation in G-protein Signaling

1. G_s with GDP bound is turned off; it cannot activate adenylyl cyclase.
2. Contact of G_s with hormone-receptor complex causes displacement of bound GDP by GTP.
3. G_s with GTP bound dissociates into α and βγ subunits. G_sα-GTP is turned on; it can activate adenylyl cyclase.
4. GTP bound to G_sα is hydrolyzed by the protein’s intrinsic GTPase; G_sα thereby turns itself off. The inactive α subunit reassociates with the βγ subunit.

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Desensitization of $\beta$-Adrenergic Receptors

1. Binding of epinephrine (E) to $\beta$-adrenergic receptor triggers dissociation of $G_{s\beta\gamma}$ from $G_{sc}$ (not shown).

2. $G_{s\beta\gamma}$ recruits $\beta$ARK to the membrane, where it phosphorylates Ser residues at the carboxyl terminus of the receptor.

3. $\beta$- Arrestin ($\beta$arr) binds to the phosphorylated carboxyl-terminal domain of the receptor.

4. Receptor-arrestin complex enters the cell by endocytosis.

5. In endocytic vesicle, arrestin dissociates; receptor is dephosphorylated and returned to cell surface.

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cAMP is a common secondary messenger

• A large number of GPCRs mediate their effects via cAMP
  – Both activating and inhibiting cAMP synthesis
• The human genome encodes about 1000 GPCRs
  – With ligands such as hormones, growth factors, and neurotransmitters
• There are also hundreds of different GPCRs that can be responsible for similar processes
  – Such as taste or smell
• Ligands for many GPCRs have yet to be identified
<table>
<thead>
<tr>
<th>Enzyme/protein</th>
<th>Sequence phosphorylated*</th>
<th>Pathway/process regulated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glycogen synthase</td>
<td>RASCTSSS</td>
<td>Glycogen synthesis</td>
</tr>
<tr>
<td>Phosphorylase b kinase</td>
<td>VEFRLS1 RTKRSGSV</td>
<td>Glycogen breakdown</td>
</tr>
<tr>
<td>α subunit</td>
<td></td>
<td></td>
</tr>
<tr>
<td>β subunit</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pyruvate kinase (rat liver)</td>
<td>GVLRRASVAZL</td>
<td>Glycolysis</td>
</tr>
<tr>
<td>Pyruvate dehydrogenase complex (type L)</td>
<td>GYLRRASV</td>
<td>Pyruvate to acetyl-CoA</td>
</tr>
<tr>
<td>Hormone-sensitive lipase</td>
<td>PMRRSV</td>
<td>Triacylglycerol mobilization and fatty acid oxidation</td>
</tr>
<tr>
<td>Phosphofructokinase-2/fructose 2,6-bisphosphatase</td>
<td>LQRRRGSSIPQ</td>
<td>Glycolysis/gluconeogenesis</td>
</tr>
<tr>
<td>Tyrosine hydroxylase</td>
<td>FIGRRQSL</td>
<td>Synthesis of L-dopa, dopamine, norepinephrine, and epinephrine</td>
</tr>
<tr>
<td>Histone H1</td>
<td>AKRKA$GPPVS</td>
<td>DNA condensation</td>
</tr>
<tr>
<td>Histone H2B</td>
<td>KKAKA$RKEYSVYVYK</td>
<td>DNA condensation</td>
</tr>
<tr>
<td>Cardiac phospholamban (cardiac pump regulator)</td>
<td>AIRRRA$T</td>
<td>Intracellular [Ca$^{2+}$]</td>
</tr>
<tr>
<td>Protein phosphatase-1 inhibitor-1</td>
<td>IRRRRP$TP</td>
<td>Protein dephosphorylation</td>
</tr>
<tr>
<td>PKA consensus sequence$^\dagger$</td>
<td>xR[RK]x[SST]B</td>
<td>Many</td>
</tr>
</tbody>
</table>

*The phosphorylated S or T residue is shown in red. All residues are given as their one-letter abbreviations (see Table 3–1).

$^\dagger$x is any amino acid; B is any hydrophobic amino acid. See Box 3–2 for conventions used in displaying consensus sequences.

Table 12-2
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**TABLE 12-3**  Some Signals That Use cAMP as Second Messenger

<table>
<thead>
<tr>
<th>Signal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corticotropin (ACTH)</td>
</tr>
<tr>
<td>Corticotropin-releasing hormone (CRH)</td>
</tr>
<tr>
<td>Dopamine [$D_1$, $D_2$]</td>
</tr>
<tr>
<td>Epinephrine ($\beta$-adrenergic)</td>
</tr>
<tr>
<td>Follicle-stimulating hormone (FSH)</td>
</tr>
<tr>
<td>Glucagon</td>
</tr>
<tr>
<td>Histamine [$H_2$]</td>
</tr>
<tr>
<td>Luteinizing hormone (LH)</td>
</tr>
<tr>
<td>Melanocyte-stimulating hormone (MSH)</td>
</tr>
<tr>
<td>Odorants (many)</td>
</tr>
<tr>
<td>Parathyroid hormone</td>
</tr>
<tr>
<td>Prostaglandins $E_1$, $E_2$ ($PGE_1$, $PGE_2$)</td>
</tr>
<tr>
<td>Serotonin [5-HT-1a, 5-HT-2]</td>
</tr>
<tr>
<td>Somatostatin</td>
</tr>
<tr>
<td>Tastants (sweet, bitter)</td>
</tr>
<tr>
<td>Thyroid-stimulating hormone (TSH)</td>
</tr>
</tbody>
</table>

*Note: Receptor subtypes in square brackets. Subtypes may have different transduction mechanisms. For example, serotonin is detected in some tissues by receptor subtypes 5-HT-1a and 5-HT-1b, which act through adenylyl cyclase and cAMP, and in other tissues by receptor subtype 5-HT-1c, acting through the phospholipase C–IP$_3$ mechanism (see Table 12-4).*

Table 12-3
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cAMP is able to mediate multiple signals due to localization of protein kinase A

- PKA is localized to particular structures by anchoring protein
- Different anchors are expressed in different cell types to determine the downstream affect of cAMP
Some bacterial toxins are enzymes that inactivate G-proteins

- Adenylate cyclase is now always (constitutively) active and produces too much cAMP from ATP
- Cholera toxin and pertussis toxin function this way
GPCRs can use other secondary messenger molecules

- i.e., Inositol-1,4,5-triphosphate (IP$_3$) and/or Calcium
Calcium modulates the function of many enzymes through calmodulin.

**TABLE 12–5** Some Proteins Regulated by Ca\(^{2+}\) and Calmodulin

<table>
<thead>
<tr>
<th>Protein</th>
<th>Regulated by Ca(^{2+}) and Calmodulin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenylyl cyclase (brain)</td>
<td>(brain)</td>
</tr>
<tr>
<td>Ca(^{2+})/calmodulin-dependent protein kinases (CaM kinases I to IV)</td>
<td>(CaM kinases I to IV)</td>
</tr>
<tr>
<td>Ca(^{2+})-dependent Na(^+) channel (Paramecium)</td>
<td>(Paramecium)</td>
</tr>
<tr>
<td>Ca(^{2+})-release channel of sarcoplasmic reticulum</td>
<td></td>
</tr>
<tr>
<td>Calcineurin (phosphoprotein phosphatase 2B)</td>
<td></td>
</tr>
<tr>
<td>cAMP phosphodiesterase</td>
<td></td>
</tr>
<tr>
<td>cAMP-gated olfactory channel</td>
<td></td>
</tr>
<tr>
<td>cGMP-gated Na(^+), Ca(^{2+}) channels (rod and cone cells)</td>
<td></td>
</tr>
<tr>
<td>Glutamate decarboxylase</td>
<td></td>
</tr>
<tr>
<td>Myosin light-chain kinases</td>
<td></td>
</tr>
<tr>
<td>NAD(^+) kinase</td>
<td></td>
</tr>
<tr>
<td>Nitric oxide synthase</td>
<td></td>
</tr>
<tr>
<td>Phosphatidylinositol 3-kinase</td>
<td></td>
</tr>
<tr>
<td>Plasma membrane Ca(^{2+}) ATPase (Ca(^{2+}) pump)</td>
<td></td>
</tr>
<tr>
<td>RNA helicase (p68)</td>
<td></td>
</tr>
</tbody>
</table>

*Figure 12-11*  
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Enzyme-linked Membrane Receptors

• Many membrane receptors consists of:
  – extracellular ligand-binding domain, and of
  – intracellular catalytic domain

• The most common catalytic domains have the tyrosine kinase activity
  – Adds a phosphate group to itself; auto-phosphorylation leads to a conformational change allowing binding and catalytic phosphorylation of specific target proteins
  – Adds a phosphate group to a tyrosine in specific target proteins

• Some catalytic domains have guanylyl cyclase activity
  – Convert GTP to cGMP, a secondary messenger
Receptor Tyrosine Kinases

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Insulin: The Hormone for Glucose Uptake and Metabolism

- Insulin is a peptide hormone that is produced by the \( \beta \)-cells of islets of Langerhans in the pancreas.
- Insulin is produced and released from the pancreas in response to nutrients such as glucose.
- Insulin reaches target cells, such as liver, muscle, or fat tissue cells via bloodstream.
- Binding of insulin to the insulin receptor initiates a cascade of events that leads to increased glucose uptake and metabolism.
- Inability to make or sense insulin \( \rightarrow \) diabetes.
Glucose Import in Myocytes

1. Glucose transporters “stored” within cell in membrane vesicles.

2. When insulin interacts with its receptor, vesicles move to surface and fuse with the plasma membrane, increasing the number of glucose transporters in the plasma membrane.

3. When insulin level drops, glucose transporters are removed from the plasma membrane by endocytosis, forming small vesicles.

4. The smaller vesicles fuse with larger endosome.

5. Patches of the endosome enriched with glucose transporters bud off to become small vesicles, ready to return to the surface when insulin levels rise again.
Insulin Signaling Cascade: Ligand Binding

- Insulin binding to the extracellular domains of the receptor activates the catalytic domain inside the cell.

- Catalytic domain in one receptor phosphorylates Tyr residues in another receptor.

- Receptor auto-phosphorylation allows binding and phosphorylation of protein IRS-1.
Insulin Signaling Cascade

- Indirect interaction of phosphorylated IRS with protein Ras initiates a series of protein phosphorylations.

- ERK, one of the phosphorylated protein kinases, enters the nucleus.

- A transcription factor Elk1 becomes phosphorylated and stimulates the expression of specific genes:
  - glucose transporter (GLUT4)
Insulin Signaling Cascade

1. Insulin receptor binds insulin and undergoes autophosphorylation on its carboxyl-terminal Tyr residues.

2. Insulin receptor phosphorylates IRS-1 on its Tyr residues.

3. SH2 domain of Grb2 binds to P–Tyr of IRS-1. Sos binds to Grb2, then to Ras, causing GDP release and GTP binding to Ras.


5. Raf-1 phosphorylates MEK on two Ser residues, activating it. MEK phosphorylates ERK on a Thr and a Tyr residue, activating it.

6. ERK moves into the nucleus and phosphorylates nuclear transcription factors such as Elk1, activating them.

7. Phosphorylated Elk1 joins SRF to stimulate the transcription and translation of a set of genes needed for cell division.

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Another Tyrosine Kinase

The JAK-STAT signaling system

- JAK: a protein kinase
- STATs: signal transducers and activators of transcription
Crosstalk between a Tyrosine Kinase Receptor and a GPCR
Receptor Guanylyl Cyclases

- Catalytic domain converts GTP to cGMP
- Works through activation of protein kinase G
SH2-domains bind proteins with phosphotyrosine residue
Modular Structure of Signaling Proteins

Figure 12-23
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Regulation of signaling by a scaffold protein
Gated Ion Channels

• Regulate transport of ions across cell membranes

• Responds to:
  – Changes in the membrane potential
  – Ligand binding to specific receptor sites

• Many important roles in the nervous system
  – Voltage-gated sodium channels
  – Nicotinic acetylcholine receptor
  – Ionotropic glutamate receptor
  – Gamma aminobutyric acid receptor A
Membranes are electrically polarized

• The inside of the cell is typically negatively charged compared to the outside: $V_m$ –50 to –70 mV

• The membrane potential is largely due to electrogenic Na$^+$/K$^+$ ATPase
  – 3 Na$^+$ out
  – 2 K$^+$ in

• Flow of ionic species across the membrane depends on its concentration gradient and overall electrical potential
Membranes are electrically polarized

The electrogenic Na\(^+\)K\(^+\) ATPase establishes the membrane potential.

Membrane potential = −50 to −70 mV

Plasma membrane

3 Na\(^+\) → Na\(^+\)K\(^+\) ATPase

2 K\(^+\) ← ATP

ADP + P\(_i\) → ATP

(a)

(b)

Ions tend to move down their electrochemical gradient across the polarized membrane.

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Voltage-Gated and Ligand-Gated Ion Channels in Nerve Signaling

- Nerve signals within nerves propagate as electrical impulses
- Propagation of the impulse involves opening of voltage gated Na⁺-channels
- Opening of voltage-gated Ca²⁺ channels at the end of the axon triggers the release of neurotransmitter acetylcholine
- Acetylcholine opens the ligand-gated ion channel on the receiving cell
Voltage-Gated Sodium Channel

- Extracellular funnel
- Selectivity filter
- Central cavity
- Activation gate
Voltage-Gated Sodium Channel

Figure 12-27c
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The Acetylcholine Receptor

• Nicotinic acetylcholine receptor:
  – Ion channel for influx of Na\(^+\), Ca\(^{2+}\)
  – Gate opened by acetylcholine
The Acetylcholine Receptor

Bulky, hydrophobic Leu side chains of M2 helices close the channel.

Binding of two acetylcholine molecules causes twisting of the M2 helices.

M2 helices now have smaller, polar residues lining the channel.

Acetylcholine

\[
\begin{align*}
\text{H}_3\text{C} & \quad \text{C} \\
\text{O} & \quad \text{CH}_2 \quad \text{CH}_2 \\
\text{CH}_3 & \quad \text{N} \quad \text{CH}_3
\end{align*}
\]
Integrins mediate cell adhesion

• Extracellular domain interacts with Arg-Gly-Asp–containing proteins:
  – Collagen, fibrinogen, fibronectin, and others

• This triggers cytoskeleton rearrangement and gene expression

• Newly expressed genes bind to intracellular domain triggering extracellular response
Integrins mediate cell adhesion

1. Collagen in extracellular matrix triggers outside-in signal

2. Responses: setting of cell polarity, survival and proliferation, changes in cytoskeleton and gene expression

3. Talin in cytoskeleton triggers inside-out signal

4. Responses: cell adhesion and migration, assembly of extracellular matrix

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Direct Regulation of Transcription by Hormones

1. Hormone, carried to the target tissue on serum binding proteins, di uses across the plasma membrane and binds to its specific receptor protein in the nucleus.

2. Hormone binding changes the conformation of the receptor; it forms homo- or heterodimers with other hormone-receptor complexes and binds to specific regulatory regions called hormone response elements (HREs) in the DNA adjacent to specific genes.

3. Receptor attracts coactivator or corepressor protein(s) and, with them, regulates transcription of the adjacent gene(s), increasing or decreasing the rate of mRNA formation.

4. Altered levels of the hormone-regulated gene product produce the cellular response to the hormone.

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Bacterial chemotaxis is controlled by enzyme-coupled receptors

Figure 12-31
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<table>
<thead>
<tr>
<th>Signaling component</th>
<th>Mammals</th>
<th>Plants</th>
<th>Bacteria</th>
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<tbody>
<tr>
<td>Ion channels</td>
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<tr>
<td>Electrogenic ion pumps</td>
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<td>Two-component His kinases</td>
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<td>Adenylyl cyclase</td>
<td>+</td>
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<td>Guanylyl cyclase</td>
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<td>Receptor protein kinases (Ser/Thr)</td>
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<td>Ca(^{2+}) as second messenger</td>
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<td>Ca(^{2+}) channels</td>
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<td>Calmodulin, CaM-binding protein</td>
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<td>MAPK cascade</td>
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<td>Cyclic nucleotide-gated channels</td>
<td>+</td>
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<td>IP(_3)-gated Ca(^{2+}) channels</td>
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<td>Phosphatidylinositol kinases</td>
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<td>GPCRs</td>
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<td>Trimeric G proteins</td>
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<td>PI-specific phospholipase C</td>
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<td>Tyrosine kinase receptors</td>
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<td>SH2 domains</td>
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<tr>
<td>Nuclear steroid receptors</td>
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<td>Protein kinase A</td>
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<td>Protein kinase G</td>
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Plants and animals use structurally similar signaling molecules.
Plants and animals use similar signal transduction pathways.
Sensory perception is mediated by GPCRs

Figure 12-43
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Generation of a nerve impulse in response to light

1. Light absorption converts 11-cis-retinal to all-trans-retinal, activating rhodopsin (Rh).
2. Activated rhodopsin catalyzes replacement of GDP by GTP on transducin (T), which then dissociates into Tγ and Tβγ.
3. Tγ-GTP activates cGMP phosphodiesterase (PDE) by binding and removing its inhibitory subunit (I).
4. Active PDE reduces [cGMP] to below the level needed to keep cation channels open.
5. Cation channels close, preventing influx of Na⁺ and Ca²⁺; membrane is hyperpolarized. This signal passes to the brain.
6. Continued efflux of Ca²⁺ through the Na⁺-Ca²⁺ exchanger reduces cytosolic [Ca²⁺].
7. Reduction of [Ca²⁺] activates guanylyl cyclase (GC) and inhibits PDE; [cGMP] rises toward “dark” level, reopening cation channels and returning V_m to prestimulus level.
8. Slowly, arrestin dissociates, rhodopsin is dephosphorylated, and all-trans-retinal is replaced with 11-cis-retinal. Rhodopsin is ready for another phototransduction cycle.
9. Rhodopsin kinase (RK) phosphorylates “bleached” rhodopsin; low [Ca²⁺] and recoverin (Recov) stimulate this reaction. Arrestin (Arr) binds phosphorylated carboxyl terminus, inactivating rhodopsin.

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Generation of a nerve impulse in response to smell

1. Odorant (O) arrives at the mucous layer and binds directly to an olfactory receptor (OR) or to a binding protein (BP) that carries it to the OR.

2. Activated OR catalyzes GDP-GTP exchange on a G protein (G\textsubscript{olf}), causing its dissociation into \( \alpha \) and \( \beta\gamma \).

3. \( G\alpha \)-GTP activates adenylyl cyclase, which catalyzes cAMP synthesis, raising [cAMP].

4. cAMP-gated cation channels open. \( Ca^{2+} \) enters, raising internal [\( Ca^{2+} \)].

5. \( Ca^{2+} \)-gated chloride channels open. Efflux of Cl\(^-\) depolarizes the cell, triggering an electrical signal to the brain.

6. \( Ca^{2+} \) reduces the affinity of the cation channel for cAMP, lowering the sensitivity of the system to odorant.

7. \( G_{olf} \alpha \) hydrolyzes GTP to GDP, shutting itself off. Cyclic AMP PDE hydrolyzes cAMP. Receptor kinase phosphorylates OR, inactivating it. Odorant is removed by metabolism.
Generation of a nerve impulse in response to taste

1. Sweet-tasting molecule (S) binds to sweet-taste receptor (SR), activating the G protein gustducin ($G_{gust}$).

2. Gustducin $\alpha$ subunit activates adenylyl cyclase (AC) of the apical membrane, raising [cAMP].

3. PKA, activated by cAMP, phosphorylates a $K^+$ channel in the basolateral membrane, causing it to close. The reduced efflux of $K^+$ depolarizes the cell sending an electrical signal to the brain.
Cell cycle is regulated intracellularly by cyclin-dependent protein kinases.
CDKs are regulated by phosphorylation and proteolysis

1. No cyclin present; CDK is inactive.
2. Cyclin synthesis leads to its accumulation.
3. Cyclin-CDK complex forms, but phosphorylation on Tyr15 blocks ATP-binding site; still inactive.
4. Phosphorylation of Thr160 in T loop and removal of Tyr15 phosphoryl group activates cyclin-CDK manyfold.
5. CDK phosphorylates phosphatase, which activates more CDK.
6. CDK phosphorylates DBRP, activating it.
7. DBRP triggers addition of ubiquitin molecules to cyclin by ubiquitin ligase.
8. Cyclin is degraded by proteasome, leaving CDK inactive.
Growth factors trigger transcriptional regulation of CDKs
Constitutive activation of CDKs can lead to cancer

Figure 12-51
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Protein kinase inhibitors may be a treatment for cancer
Damage to macromolecules can trigger programmed cell death (apoptosis)
Chapter 12: Summary

In this chapter, we learned:

- Cell signaling is triggered by receptors that sense the extracellular environment
  - Binding tightly to specific messenger molecules
- GPCRs bind GTP and activate interacting proteins
- Receptor tyrosine kinases activate protein kinases with auto-phosphorylation
- Receptor guanylyl cyclases generate the secondary messenger cGMP
- Voltage-gated ion channels generate and propagate nerve impulses
- Vision, smell, and taste are sensed by GPCRs
- Disregulation of intracellular signaling cascades can lead to cancer