Hormones, Receptors, and Signal Transduction
Learning Objectives

1. Learn the general structure and properties of hormones.

2. Know the differences between Hormones, Neurotransmitters & enzymes

3. Understand the general properties of signaling molecules (ligands), cell-surface receptors, & intracellular signal transduction components.

4. Know the G protein cycle of reactions involved in GPCR signaling.
General characteristics of hormones

- Hormones are molecules synthesized by **specific** tissue. Classically these tissue were called **glands**.
- Hormones are secreted **directly** into the blood which **carries** them to their sites of action.
- Hormones are present at **very low** levels in the circulatory system.
- Hormones specifically affect or alter the activities of the responsive tissue (**target tissue**).
- Hormones act specifically via **receptors** located on, or in, **target** tissue.
What are the differences between Nerves and Hormones?
<table>
<thead>
<tr>
<th>Nevous System</th>
<th>Endocrine System</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nerve impulses mainly carry the signal within nerves</td>
<td>Hormones act as a chemical signal within the Endocrine S.</td>
</tr>
<tr>
<td>Nerve signals transmit along the nerves, and are</td>
<td>Hs. are transmitted through the blood stream and are controlled by</td>
</tr>
<tr>
<td>controlled by the CNS</td>
<td>endocrine glands</td>
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<tr>
<td>Nerve signals have rapid transmission</td>
<td>Hormones have slow speed of effect</td>
</tr>
<tr>
<td>Nerve signals generally short-lived</td>
<td>the hormonal effect is long-lasting</td>
</tr>
<tr>
<td>very few types of chemical coordinators called</td>
<td>many different types of hormones (chemical coordinators), where each</td>
</tr>
<tr>
<td>neurotransmitters</td>
<td>one affecting different, specific t.</td>
</tr>
</tbody>
</table>
What is the difference between Enzyme and Hormone?
<table>
<thead>
<tr>
<th>Enzymes</th>
<th>Hormones</th>
</tr>
</thead>
<tbody>
<tr>
<td>All enzymes are proteins</td>
<td>Not all the hormones are proteins</td>
</tr>
<tr>
<td>Enzymes are secreted and act on the <strong>same place</strong></td>
<td>Secretion and activation of Hs. take place in <strong>different locations</strong>.</td>
</tr>
<tr>
<td>Enzymes control all biochemical reactions of the cell.</td>
<td>Some of the biochemical reactions of the systems are controlled by hormones.</td>
</tr>
<tr>
<td>Enzymes take <strong>part in met.</strong></td>
<td>Hs. <strong>regulate</strong> metabolic activities.</td>
</tr>
<tr>
<td>Enzymes are <strong>substrate specific.</strong></td>
<td>hormones are <strong>specific to the target</strong> cell, tissue, or system</td>
</tr>
<tr>
<td>Enzymes are <strong>not changed</strong> after a reaction and could be used again.</td>
<td>Hormones are <strong>degenerated</strong> after the reaction.</td>
</tr>
</tbody>
</table>
Communication between cells requires:

**ligand**: the signaling molecule

**receptor protein**: the molecule to which the receptor binds - may be on the plasma membrane or within the cell
There are four basic mechanisms for cellular communication:

1. direct contact
2. paracrine signaling
3. endocrine signaling
4. synaptic signaling
Intercellular Communication

**Direct contact** – molecules on the surface of one cell are recognized by receptors on the adjacent cell.
Intercellular Communication

Paracrine signaling – signal released from a cell has an effect on neighboring cells

local ex. nitric oxide, histamines, prostaglandins
Intercellular Communication

**Endocrine signaling** – hormones released from a cell affect other cells throughout the body.

- Hormone secretion into blood by endocrine gland
- Blood vessel
- Distant target cells

Long distance ex. Estrogen, Thyroxine, GH, Epinephrine ....
Intercellular Communication

Synaptic signaling – nerve cells release the signal (neurotransmitter) which binds to receptors on nearby cells
Possible pathways of transmission of hormonal signal. Each hormone can work through one or more receptors; each hormone-receptor complex can work through one or more mediator proteins (either G proteins or other signaling mechanism), and each mediating protein or enzyme activated by hormone-receptor complexes can affect one or more effectors functions.
The four primary arenas of hormone action

- Reproduction
- Growth & Development
- Maintenance of internal environment
- Energy production, utilization & storage
How are hormones classified?
4 classes of hormones based on chemical structure

- **Peptides or Protein hormones**: They are synthesized as peptides or large polypeptides precursors that undergo processing before secretion. Examples: • Thyrotropin Releasing Hormone (TRH), made up of three amino acid residues (glu-His-Pro) • Insulin, made up of 51 amino acid residues; • GH (191 aa), PRL (198 aa) & Pituitary Gonadotrophins, made up of large Glycoproteins with subunits (alpha & beta).
ACTH, calcitonin, glucagon, vasopressin, oxytocin, hormones of hypothalamus (releasing factors).

• **Amino acid derivatives**: Examples: Adrenaline, Catecholamines, Thyroid Hormones;

• **Fatty acid derivatives**: Examples: Eicosanoids (Prostaglandins);

• **Steroid hormones**: These are derivatives of Cholesterol; Example:
  Estradiol, Progesterone, Testosterone, Cortisol, Aldosterone;
How are hormones classified according to solubility in aqueous medium in cells?
Hydrophilic Hormones (Lipophobic Hormones)

- Hormones that are soluble in aqueous medium;
- They cannot cross the cell membrane,
- Thus, they bind to receptor molecules on the outer surface of target cells, initiating reactions within the cell that ultimately modifies the functions of the cells;
- Examples: Insulin, Glucagon, Epinephrine, GH, PRL....
Lipophilic Hormones (Hydrophobic Hormones)

• Hormones that are not soluble in aqueous medium, but soluble in lipid;
• They can easily cross the cell membrane,
• Thus, they can enter target cells and bind to intracellular receptors to carry out their action;
• Examples: Thyroid hormones, Steroid hormones;
How do hormones exit in blood plasma?

• Hormones are normally present in blood plasma at very low concentrations;
• In blood, hormone binds to Specific Plasma Carrier Protein, forming a complex, which is then transported in the plasma to distant target cells;
• Plasma carrier proteins exist for all classes of endocrine hormones.
What are the functions of carrier proteins for hormones?
• Carrier proteins for:

• **Peptide Hormones** prevent destruction of peptide hormones by Protease enzymes in plasma;

• **Steroid Hormones** and **Thyroid Hormones** significantly increase the solubility of these very hydrophobic compounds in plasma (alpha-globulins or albumins)

• **Small, Hydrophilic Amino Acids** – derived hormones prevent their filtration by the kidneys, thus greatly prolonging their circulating half-life;
Some properties of Hydrophilic hormones receptors

- They are large, integral or transmembrane proteins with specificity and high affinity for a given hormone;
- Binding between hormone and receptor is reversible;
- Action of hormone depends on plasma level of hormone;
- Hydrophilic hormones initiate a response without entering target cells;
• Hydrophilic hormones cause a more rapid response and have a shorter duration of action than lipophilic hormones;

• Action of hydrophilic hormone can last seconds to hours;

• G – proteins are associated with hormone receptors on the cytosolic side of the cell membrane;

• G – protein is a protein that binds either GTP or GDP;
The mechanism of action of Lipophilic hormones with receptors in target cells

• Lipophilic hormone crosses cell membranes to bind with Intracellular Receptor, forming Hormone-Receptor Complex;

• Hormone-Receptor Complex then bind to Specific Sequence of Nucleotide Bases in DNA called Hormone Response Element (HRE);

• Binding of Hormone-Receptor Complex to HRE results in synthesis of Messenger-RNA required for biosynthesis of specific protein;
• Lipophilic hormones are slower to act and have longer duration of action than Hydrophilic hormones;
• Duration of action may range from hours to days;

What are some of the factors controlling hormone secretions?
H. secretion is influenced by variety of factors:

• Stimulatory and Inhibitory agents, such as: Hypothalamic Peptides or Neurotransmitters;

• Other hormones: Gonadotrophin Releasing Hormone (GnRH), are released in a pulsatile fashion;

• Some hormones exhibit Circadian Rhythm: Adreno-Cortico-Trophic Hormone (ACTH), Cortisol; Prolactin, TSH, GH and PTH have peak secretion at different times during the day or night;
• Stress can increase hormone synthesis and release (e.g., ACTH, GH and Prolactin).
• Hormones synthesized by target cells may regulate release by Negative Feed Back control.
• Changes in metabolic products caused by hormone action may exert feedback control;
• Other hormones or drugs may modulate normal endocrine responses.
Hormone Receptors

Nuclear receptors
estrogens

Cytoplasmic receptors
Most steroid and thyroid hormones

Cell surface membrane receptors
Polypeptide hormones and catecholamines
Inactivation of hormones

After biochemical effect hormones are released and metabolized. Hormones are inactivated mainly in liver. Inactive metabolites are excreted mainly with urine.

Half-life time:
- From several min to 20 min - for the majority of hormones
- Till 1 h - for steroid hormones
- Till 1 week - for thyroid hormones
THE FINAL EFFECTS OF HORMONE ACTIONS

1. **Change the permeability of cell membrane**, accelerate the penetration of substrates, enzymes, coenzymes into the cell and out of cell.

2. **Acting on the allosteric centers affect the activity of enzymes** (Hormones penetrating membranes).

3. **Affect the activity of enzymes through the messengers (cAMP)**. (Hormones that can not penetrate the membrane).

4. **Act on the genetic apparatus** of the cell (nucleus, DNA) and promote the synthesis of enzymes (Steroid and thyroid hormones).
Structure and function of receptors

• Globular proteins acting as a cell’s ‘letter boxes’

• Located mostly in the cell membrane

• Receive messages from chemical messengers coming from other cells

• Transmit a message into the cell leading to a cellular effect

• Different receptors specific for different chemical messengers

• Each cell has a range of receptors in the cell membrane making it responsive to different chemical messengers
**Mechanism**

- Receptors contain a binding site (hollow or cleft in the receptor surface) that is recognised by the chemical messenger.
- Binding of the messenger involves intermolecular bonds.
- Binding results in an induced fit of the receptor protein.
- Change in receptor shape results in a ‘domino’ effect.
- Domino effect is known as **Signal Transduction**, leading to a chemical signal being received inside the cell.
- Chemical messenger does not enter the cell. It departs the receptor unchanged and is not permanently bound.
Overall process of receptor/messenger interaction

- Binding interactions must be:
  - strong enough to hold the messenger sufficiently long for signal transduction to take place
  - weak enough to allow the messenger to depart
- Implies a fine balance
- Drug design - designing molecules with stronger binding interactions results in drugs that block the binding site - antagonists
Messenger binding

Bonding forces

- Ionic
- H-bonding
- van der Waals

Example:

Binding site

Receptor
How does the Binding Site Change Shape?

**Substrate binding**

- **Bonding forces**
- **Induced fit** - Binding site alters shape to maximise intermolecular bonding

Intermolecular bonds not optimum length for maximum binding strength

Intermolecular bond lengths optimised