The Endocrine System

Coordinate of the functions of the body occurs via different systems.

**Nervous system**:
- operates via electrical impulses and neurotransmitters
- excites or inhibits neurons, muscles and glands
- nerve impulses produce their effect quite rapidly, within millisecond
- the lingering effect of the N.S. stimulus is very short

**Endocrine System**:
- releases messenger molecules called hormones into the bloodstream
- bloodstream transports this to virtual all cells to see
- action of the messenger depends on the presence of specific receptors for these hormones
- Hormones act slower over a period of seconds to several hours
- Lingering effect of the Endocrine system is longer lasting
Coordination of Body Functions

Additional mechanisms are present

• Direct Communication
  – Exchange of ions and molecules between adjacent cells across gap junctions
  – Occurs between two cells of same type
  – Highly specialized and relatively rare

• Paracrine Communication
  – Uses chemical signals to transfer information from cell to cell within single tissue
  – Most common form of intercellular communication

### Table 10.1: Mechanisms of Intercellular Communication

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Transmission</th>
<th>Chemical Mediators</th>
<th>Distribution of Effects</th>
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</thead>
<tbody>
<tr>
<td>Direct communication</td>
<td>Through gap junctions</td>
<td>Ions, small solutes, lipid-soluble materials</td>
<td>Usually limited to adjacent cells of the same type that are interconnected by connexins</td>
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<tr>
<td>Paracrine communication</td>
<td>Through extracellular fluid</td>
<td>Paracrine factors</td>
<td>Primarily limited to a local area, where paracrine factor concentrations are relatively high. Target cells must have appropriate receptors</td>
</tr>
<tr>
<td>Endocrine communication</td>
<td>Through the bloodstream</td>
<td>Hormones</td>
<td>Target cells are primarily in other tissues and organs and must have appropriate receptors</td>
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<tr>
<td>Synaptic communication</td>
<td>Across synaptic clefts</td>
<td>Neurotransmitters</td>
<td>Limited to very specific area, target cells must have appropriate receptors</td>
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Endocrine System

• The Endocrine System Regulates long-term processes such as Growth …. Development ……Reproduction

• The Endocrine system includes all cells and tissues which produce and secrete hormones or agents that have an effect beyond their tissue of origin.

• Hormones are produced in the cells of Endocrine Glands. The product is released into the extracellular space where it diffuses into a rich network of capillaries and lymph vessels.

Endocrine System

• Typical organs of the endocrine system

Hypothalamus
- Production of ADH, oxytocin, and regulatory hormones

Pituitary Gland
- Anterior lobe: ACTH, TSH, GH, PRL, FSH, LH, and MSH
- Posterior lobe: Release of oxytocin and ADH

Pineal Gland
- Melatonin

Parathyroid Glands
- (located on the posterior surface of the thyroid gland)
- Parathyroid hormone (PTH)

Figure 18-1 Organs and Tissues of the Endocrine System
Hormones are **chemicals** that are secreted by endocrine cells into the extra-cellular fluids and regulate metabolic functions of other cells in the body.

- Hormones can be divided into three groups
  1. Amino acid derivatives
  2. Peptide hormones
  3. Lipid derivatives (steroids and eicosanoids)
Amino Acid Derivatives

Examples of Amino Acid derived hormones are the Catecholamines, (such as Dopamine, NorEpi and Epi) and Thyroid hormones. They are all derived from the amino acid Tyrosine.

Catecholamines

Amino Acid Derivatives

Another example of Amino Acid Derived Hormones, are those derived from the amino acid Tryptophan (Serotonin and Melatonin).
Amino Acid Derivatives

There was some science linking Turkey dinners with feeling sleepy. Tryptophan is the biochemical precursor to serotonin, which has a calming effect on the brain and body. And tryptophan is indeed found in turkey meat. It's also present in chocolate, some fruits, dairy, red meat, and eggs.

However, tryptophan is almost certainly not the cause of Turkey Day food coma. The levels of tryptophan that we ingest in a Thanksgiving-sized portion of turkey is not all that much more than is found in what we eat on any other day.

Peptide Hormones

Peptide hormones are chains of amino acids and can result in large protein hormones.

Many of them are synthesized on ribosomes in a pre-prohormones state and need to be activated before or after secretion.

Pre-prohormones are cleaved by special enzymes in the E.R. to ProHormones and further modified in the Golgi Apparatus into the actual hormone.

Hormones are then packaged and stored into secretory vesicles and released via exocytosis when the correct signal arrives.
Peptide Hormones

- Peptide Hormones include all hormones secreted by:
  - Hypothalamus, heart, thymus, digestive tract, pancreas, and posterior lobe of the pituitary gland, as well as several hormones produced in other organs
- Peptide Hormones come in different sizes; examples include
  - **Short chain polypeptides**
    - *Antidiuretic hormone (ADH)* and *oxytocin (OXT)* (each 9 amino acids long)
  - **Small proteins**
    - *Growth hormone (GH)*; 191 amino acids and *prolactin (PRL)*; 198 amino acids

Examples of Peptide Hormones

TRH has a tri-peptide structure ((pyro)Glu-His-Pro-NH₂)

Insulin (51 AA, 2 polypeptide chains)
Lipid Derived Hormones

- Lipid derived hormones fall into two main categories
  - **Steroid Hormones** are based on a slight modification of the cholesterol molecule.
  - **Eicosanoids** - derived from arachidonic acid, a 20-carbon fatty acid

Steroid Hormones

- Steroid Hormones are based on a slight modification of the cholesterol molecule.
- Most steroids are produced by the cortex of the adrenal glands and the gonads.
Eicosanoids are released by almost all cell membranes. They are produced from arachidonic acid, a derivative of membrane phospholipids via activation of a membrane bound phospholipase A2 enzyme.

Products of Arachidonic acid metabolism are
- Leukotrienes
- Prostaglandins
- Thromboxanes.

They all have a wide range of localized effects and have thus mostly paracrine functions.
Fate of a Hormone

Hormones are released into the blood stream where they will be transported and exert their effect depending on their chemistry!

- Most amino acid based and peptide hormones are water soluble (hydrophilic) ! They have no real problem getting around.
- Lipid derived hormones are not water soluble (hydrophobic) and require specific proteins in the blood stream to get around. Those are called the blood transport proteins

In the latter case, an equilibrium exists between bound hormone and free hormone. Keep in mind that **only the free hormone** is able to diffuse into a cell and exert its effect.

Free Hormone + Binding Protein $\rightarrow$ Hormone-Protein complex

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Fate of a Hormone

- Thyroid and Steroid Hormones are hydrophobic hormones
- When they enter bloodstream, > 99% become attached to special transport proteins to enhance their solubility
- Only the free (unbound) hormone will exert the effect on cells.
- Bloodstream contains thus substantial reserve of bound hormones and remain in circulation much longer because most are “bound”

In this example, the thyroid hormone T4 is a hydrophobic molecule. It circulates mostly bound to thyroid binding proteins in the blood stream. Only the free, non-protein-bound T4 is able to pass into the body's cells, where it can be converted into T3, the most active thyroid hormone.
In the blood stream, several fates await a hormone following its secretion.

**Free Hormones**
- Remain functional for less than 1 hour because
  1. Diffuse out of bloodstream and bind to receptors on target cells
  2. Are broken down and absorbed by cells of liver or kidneys
  3. Are broken down by enzymes in plasma or interstitial fluids
Hormone Action

- Hormones are messengers that will influence the activity of certain cells.
- They do so by binding to specific receptors.
- These receptors are proteins and are located either in the plasma membrane and/or within the cell
- For a target cell to respond, it must have these receptors that the hormone (aka messenger) can bind to.

Hormone Action

- Many examples of interaction of chemicals (e.g. neurotransmitters) with receptor and chemical interplay have been seen in A&P 1.

  - **ACh and Nicotinic Cholinergic receptors**
  - These receptors were proteins located in the plasma membrane of the post-synaptic cell (e.g. dendrites and soma)
  - Lack of receptor, blocking the receptor or lack of neurotransmitter all resulted in reduced or no electrical signals.
  - In many instances, the interaction of hormones and receptor is similar.
Hormones / Neurotransmitter

**Hormones**
- Rely on diffusion into bloodstream
- Concentrations thus become quite diluted
- Hormones are usually found in the order of ~ $10^{-8}$ M or lower
- Receptors therefore have high affinity for the hormones

**Neurotransmitters**
- Effect is faster, more concentrated within synapse
- Diffusion distance is very short
- Concentrations are ~ $10^{-4}$ M
- Affinity of receptor in synapse is relatively low

Hormone Action

- Another example was that of NorEpinephrine (neurotransmitter from Symp. N.S.)
- Those receptors were located in tissue activated by the S.N.S.

- If you recall, epinephrine (a hormone) also binds to these receptors and mediate similar effects.
Studies have shown that the interplay between hormones and receptor can result in different actions.

Both receptors in the diagram above bind epinephrine but ….

- Alpha receptors in peripheral blood vessels result in vasoconstriction
- Activation of Beta receptors in coronaries result in vaso-relaxation.

(What tissue type are the receptors activating?)

The event that occurs within a cell (tissue) is dependent on how the receptor is connected to other specific membrane proteins and not on the hormone.

The hormone is just a chemical messenger that switches on cellular event within the cell!

The Receptors are thus “molecular switches” that are linked to cellular response systems.

- **Hydrophobic hormones** typically change gene expression, leading to slow but sustained responses.
- **Hydrophilic hormones** typically activate rapid, short-lived responses that can be of drastic impact.
From our previous discussion about hormone chemistry, we can make a distinction between two general kinds of hormones.

• Those that are lipid soluble (hydrophobic): these will zip right into the cell without the need for a membrane bound receptor. The receptor for this messenger is located inside the cell.

• Those that are lipid insoluble (hydrophilic): these hormones need to bind to a plasma membrane receptor before they can exert and effect.

The binding of the hormone to the receptor results in an action by the receptor. This is referred to as receptor activation.

This combination between \{hormone -> receptor -> cellular events\} is called a signal transduction pathway.

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Hormone - Receptor Interplay

Signal Transduction via Intracellular Receptors

• Most lipid -soluble messengers are steroid hormones, thyroid hormones, steroid derivatives.

• They can diffuse into the cell (simple trans-membrane diffusion) according to their concentration gradient and don’t need specific transporters to enter.

• However they do need receptors to exert their effect. These Receptors are usually located within the nucleus or in the cytoplasm.

• Activation of the receptor by the hormone turns it into a transcription factor: it will alter rate of DNA transcription in nucleus and hence, change pattern of specific protein synthesis.
Binding to the carrier protein is highly reversible, and at the target cell the free hormones moves easily through the membrane systems and binds to its receptor, found mostly the nucleus (but some hormones have receptors in cytoplasm).

Lipid based hormones are hydrophobic and thus requires a carrier protein while in the plasma.

Signal Transduction via Intracellular Receptors

Binding to the receptor kicks off a chaperone molecule that keeps the receptor in an inactive state.

The “receptor-steroid” complex can now bind to a specific sequence of the DNA and start the process of translation.

The hormone-receptor complex thus acts as a transcription factor to alter gene expression.
**Signal Transduction via Intracellular Receptors**

- **Receptor**
- **Diffusion through membrane lipids**
- **CYTOPLASM**
- **Target cell response**
- **Alteration of cellular structure or activity**
- **Translation and protein synthesis**
- **Binding of hormone to cytoplasmic or nuclear receptors**
- **Transcription and mRNA production**
- **Gene activation**
- **Binding of hormone–receptor complex to DNA**
- **Transport across plasma membrane**
- **Increased ATP production**
- **Binding of receptors at mitochondria and nucleus**

**Signal Transduction via Cell Membrane Receptors**

- These are the pathways that become activated by hormones signals that **can not** diffuse through the plasma membrane.

- They need to interact first with a membrane receptor before the signal transduction pathway can be started.

- The hormone is called the **first messenger**, and the intracellular product produced by the action of the activated receptor is called the **second messenger**.

- **Only the second messenger will alter cellular events** (thus if something inhibits the production of the 2nd messenger, there will be no effect).
G-protein coupled receptors

- G-protein coupled receptors work in relay to pass on the action to the inside of the cell via activation of membrane bound enzyme.

Concept of 1st and 2nd Messengers

- The hormone is considered as the 1st messenger.
- A second messenger is a non-protein product, produced by the activation of a specific enzyme via the G-protein, and released inside the cell.
- Produced and Released into the cell, the 2nd messenger can now activate and influence other cellular events.
- These cellular events that become activated are cell specific
  - Release of calcium from SER in smooth muscle
  - Activation of lipases in adipose tissue
  - Opening of ion channels in cardiac tissue
  - ……..
G-protein coupled receptors work in relay to pass on the action to the inside of the cell.

Concept of 1st and 2nd Messengers

Two major kinds of G-protein coupled Receptors

Two important G-protein pathways can be distinguished. They are different by the fact that the G-protein activates a different target protein (enzyme).

**System 1**: Activation of an enzyme that uses ATP as a substrate and produces cyclic AMP as a product.

**System 2**: Activation of an enzyme that uses Phosphatidyl Inositol Phosphates (PIP’s) as a substrate.
System 1: The adenylate cyclase system

In this system the target enzyme is Adenylate Cyclase. This enzyme converts ATP into cyclic AMP (cAMP)

\[
ATP + H_2O \rightarrow c-AMP + PP_i
\]

Note: other receptors and G-proteins activate enzymes called Phosphodiesterases, that result in the break down cAMP to AMP. (what would their purpose be?)

Receptors, G-proteins and Adenylate Cyclase

cAMP is thus the intracellular second messenger. It will activate Protein Kinase A!

Active Protein Kinase A will phosphorylate specific proteins and activate ( or de-activate) these proteins.
Protein Kinases & Phosphorylation

A protein Kinase is an enzyme that adds a phosphate group to a protein. By doing so, it can activate ( "wake-up") a dormant protein (such as an enzyme).

A protein Phosphatase is an enzyme that removes the phosphate group from protein. By doing so, it reverses the previous action and puts the enzyme back to ‘sleep’!

Amplification Effect of cAMP

The activation of Adenylate Cyclase by a hormone has a fast amplification effect. This example shows how fast a little Glucagon can generate a whole lot of glucose!
**Terminating cAMP effects**

Because of the fast amplification effect of cAMP, it needs to be terminated in order to prevent it from going out of control.

This is done by:

- Activation of Phosphodiesterase enzymes (remember, PDE break down cAMP)
- Activation of Phosphatase enzyme that de-phosphorylate phosphorylated proteins.
- Activation of a inhibitory G protein that turns off the adenylate cyclase.

These enzymes are controlled via activation or inhibition by means via of different hormones-receptor interactions.

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**Activation and Inactivation of Adenylate Cyclase**

Whereas some Specific receptors (thus with specific hormones) are coupled to stimulatory G proteins (and thus activate), some receptors (binding other hormones) are coupled to inhibitory G proteins. These turn off the AC enzyme and/or activate PDE. This ends the previous activation of cellular events and is a way to “switch off” a turned on event.
G-protein coupled Receptors and Phosholipase C

Whereas the target enzyme in System 1 is Adenylate Cyclase, the target enzyme in System 2 is Phospholipase C!

System 1: Activation of an enzyme that makes cyclic AMP

System 2: Activation of an enzyme that makes Phosphatidyl Inositol Phosphates (PIP’s).

What reaction does Phospholipase C catalyze?

It acts on phospholipid membrane components called Phosphatidyl Inositol Bi Phosphates (PIP₂).

\[ \text{PIP}_2 \rightarrow \text{Diacylglycerol} + \text{Inositol TriPhosphate} \]

\[ \quad \text{(DAG)} \quad \text{(IP}_3 \text{)} \]

DAG and IP₃ are thus your second messengers!
G-protein coupled Receptors and Phospholipase C

What effects do DAG and IP₃ have?

**DAG**
- DAG activates a class of Protein Kinases called PK-C
- PK-C’s will phosphorylate and activate proteins
- Can for example phosphorylate Calcium channels and open them

**IP₃**
- Acts on the smooth ER
- Results is that calcium will be released into the cytoplasm
- Calcium in turn will bind to and activate calmodulin
- Activated calmodulin can now activate enzymes and other proteins

**Effects on Ca²⁺ Levels**
- Some G proteins use Ca²⁺ as a second messenger
- Opening of Ca²⁺ channels
- Release of stored Ca²⁺ from SER
- Ca²⁺ acts as second messenger
- Activates enzymes

Examples:
- Epinephrine and norepinephrine (α₁ receptors)
- Oxytocin
- Regulatory hormones of hypothalamus
- Several eicosanoids

**G-protein coupled Receptors and Phospholipase C**

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**G-protein coupled Receptors and Phospholipase C**
The interaction of a hormone with a receptor is like a hit and run mechanism.

- The more hormones present, the more hit and run effects
- If a receptor has a higher affinity, it causes a hormone to stay on the receptor longer and thus keep the triggering action going.
- The more receptors on a cell, the easier it is for a hormone to find a receptor

When a hormone dissociates (stops interacting) from a receptor it can jump on a new receptor and start the trigger again.

This lasts until the hormone (messenger) is destroyed or removed.

Because of their importance and their interaction with cell receptors, hormones are present in very small quantities and only released when needed or when induced by specific stimuli. via stringent feedback cycles.

Once the desired effect is obtained, the hormone concentration is reduced via
- inhibition or attenuation of production of the hormone through negative feedback
- breakdown via degrading enzymes or removal via diffusion
- when located in the blood stream, the hormone can be removed by the action of kidney and/or liver

Concentration of a molecule can be adjusted quickly only if the lifetime of the molecule is short. Lifetime of most hormones is very short!
Abundance of Receptor are regulated as well by physiological feedback systems.

**Up-regulation.**

When a cell is not being targeted by a lot of hormones due to a shortage of messengers (or when the presence of antagonists block the action of the receptors), the receptor numbers tend to increase.

**Down-regulation.**

When there is an abundance of a certain hormone (resulting in over-stimulation), the number of cellular receptors for that hormone tend to decrease over time.

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**Control of Hormone Release**

- Endocrine Activity is controlled by Endocrine Reflexes
- **Endocrine Reflexes are the** Functional counterparts of neural reflexes
  - In most cases, controlled by negative feedback mechanisms
    - Stimulus triggers production of hormone, the direct or indirect effects of the hormone reduce intensity of the stimulus (and reduces hormone production)
  - This keeps the hormone within a certain functional range and variations in concentration are kept within a narrow desirable range
Control of Hormone Release

- Hormones are synthesized and released in response to:
  - Humoral stimuli
  - Neural stimuli
  - Hormonal stimuli

Humoral Stimuli

- Humoral stimuli – secretion of hormones in direct response to changing blood levels of ions and nutrients
- Example: concentration of calcium ions in the blood
  - Declining blood Ca\(^{2+}\) concentration stimulates the parathyroid glands to secrete PTH (parathyroid hormone)
  - PTH causes Ca\(^{2+}\) concentrations to rise and the stimulus is removed
Neural Stimuli

- Neural stimuli – nerve fibers stimulate hormone release

- Example:
  - Preganglionic sympathetic nervous system (SNS) fibers stimulate the adrenal medulla to secrete catecholamines

Hormonal Stimuli

- Hormonal stimuli – release of hormones in response to hormones produced by other endocrine organs

- Example:
  - The hypothalamic hormones stimulate the anterior pituitary
  - In turn, pituitary hormones stimulate targets to secrete still more hormones
Nervous System Modulation

• The nervous system modifies the stimulation of endocrine glands and their negative feedback mechanisms

• For example, control of blood glucose levels
  • Normally the endocrine system maintains blood glucose
  • Under stress, the body needs more glucose
  • The hypothalamus and the sympathetic nervous system are activated to supply ample glucose

Hormone-Target Cell Interaction

There are three types of hormone interaction:

- Permissiveness – one hormone cannot exert its effects without another hormone being present
- Synergism – more than one hormone produces the same effects on a target cell
- Antagonism – one or more hormones opposes the action of another hormone
General Endocrine disorders

Many of the endocrine disorders are due to malfunctioning glands or malfunctioning feedback systems.

In simple endocrine reflexes, only one hormone is involved.

We will cover some complex feedback systems where more than one hormone is involved.

In the latter case, the definition of a trop(h)ic hormone becomes important: it is a hormone whose only function is to regulate the release of another hormone!

General Endocrine disorders

1. **Hypo-secretion**

- Gland secretes too little hormone
- If the gland itself is not functioning properly
  \[= \text{primary hypo-secretion}\]
- If the gland is normal but there is a problem with the tropic hormone that stimulates the gland
  \[= \text{secondary hypo-secretion}\]
- If the tropic-hormone releasing gland is normal but something is missing that results in secretion of the tropic hormone
  \[= \text{tertiary hypo-secretion}\]
General Endocrine disorders

2. **Hyper-secretion**

- Primary hyper-secretion
  gland is secreting too much hormone on its own

- Secondary hyper-secretion
  over-stimulation of a gland by the tropic hormone
  (thus too much tropic hormone is made/present)

Most hyper-secretions result from endocrine-cell tumors
3. **Hypo- and hyper-responsiveness**

In both conditions, nothing is actually wrong with the secretion of the hormones but the response is abnormal.

- Hypo-responsiveness can be due to
  - Deficient receptors or lack of receptors
  - Deficient membrane proteins that interact with an otherwise normal receptor (e.g. G-proteins or the target enzymes of the alpha subunits)
  - Lack or deficiency of enzymes that turn pro-hormones into active hormones

- Hyper-responsiveness is most often due to an abnormal up-regulation of receptors for the hormone.