Chapter 19
Functional Organization of the Endocrine system

I. Introduction.
   A. Endocrine: \textit{(endo within crino to separate)} \textbf{gland} - Ductless gland that secretes a hormone internally generally into the blood.
   B. The \textbf{endocrine system}:
      1. functions closely with the nervous system
      2. regulates and integrates body processes and
      3. maintains homeostasis.
      4. The endocrine system uses hormones as messengers to send a signal to other cells and tissues.
   C. Hormones \textit{(GK. to set in motion)} are \textit{classically defined} as chemical intercellular messenger molecules
      1. Produced in small amounts, hormones are released into the interstitial fluid, diffuse into the blood and are transported to other cells or tissues where they initiate a regulatory change in function in a target tissue.
   D. The \textbf{target tissue} is the tissue being regulated by the hormone.
      1. Must have the receptors / cofactors and enzymes which allow the cell be regulated by the specific hormone.

II. Location of classic and nonclassic endocrine glands within the body (Table 19.1)

<table>
<thead>
<tr>
<th>Classical Endocrine Glands and Their Hormones</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pituitary</td>
</tr>
<tr>
<td>Anterior lobe</td>
</tr>
<tr>
<td>Hormones: Growth (GH), Thyroid stimulating (TSH), follicle stimulating (FSH), Luteinizing (LH), Prolactin</td>
</tr>
<tr>
<td>Intermediate lobe</td>
</tr>
<tr>
<td>melanocyte stimulating hormone (MSH)</td>
</tr>
<tr>
<td>Posterior lobe</td>
</tr>
<tr>
<td>Oxytocin, antidiuretic hormone (ADH)</td>
</tr>
<tr>
<td>Hypothalamus</td>
</tr>
<tr>
<td>releasing factors for Pituitary</td>
</tr>
<tr>
<td>Pineal body</td>
</tr>
<tr>
<td>melatonin</td>
</tr>
<tr>
<td>Thyroid</td>
</tr>
<tr>
<td>Thyroxine, triiodothyroxine, calcitonin</td>
</tr>
<tr>
<td>Parathyroid</td>
</tr>
<tr>
<td>parathyroid hormone.</td>
</tr>
<tr>
<td>Adrenal glands</td>
</tr>
<tr>
<td>Cortex</td>
</tr>
<tr>
<td>aldosterone, glucocorticoids, gonadocorticoids</td>
</tr>
<tr>
<td>Medulla</td>
</tr>
<tr>
<td>epinephrine, norepinephrine</td>
</tr>
<tr>
<td>Gonads</td>
</tr>
<tr>
<td>Ovaries</td>
</tr>
<tr>
<td>estrogen, progesterone</td>
</tr>
<tr>
<td>Testes</td>
</tr>
<tr>
<td>Testosterone</td>
</tr>
<tr>
<td>Pancreas (Islets)</td>
</tr>
<tr>
<td>Glucagon, insulin</td>
</tr>
<tr>
<td>Thymus</td>
</tr>
<tr>
<td>Thymosin- white cell production</td>
</tr>
</tbody>
</table>

Nonclassic endocrine organs:
   1. Adipose tissue - leptin; \textbf{heart} - antinatriuretic hormone; \textbf{Skin} - vitamin D; \textbf{Liver} - somatomedins (stimulate cell division in cartilage)
III. Comparison and contrast of the Nervous System and Endocrine System
   A. The endocrine system is a control system like the nervous system.
   B. The scope of its control reaches to virtually every organ system in the body.

<table>
<thead>
<tr>
<th></th>
<th>Nervous System</th>
<th>Endocrine System</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mode of action</td>
<td>Sends chemical signals via action potentials in axons.</td>
<td>Sends chemical signals via the bloodstream</td>
</tr>
<tr>
<td>Sight of action</td>
<td>highly specific</td>
<td>very general (whole body)</td>
</tr>
<tr>
<td>Response time</td>
<td>rapid (milliseconds)</td>
<td>slow (minutes)</td>
</tr>
<tr>
<td>Duration</td>
<td>Short (msec to min.)</td>
<td>Long (minutes to days)</td>
</tr>
<tr>
<td>Modulation</td>
<td>Frequency modulated (all or none action potential - strong signals have higher frequency)</td>
<td>amplitude modulated (changes in hormone concentration)</td>
</tr>
</tbody>
</table>

IV. Interactions of the endocrine system and nervous system.
   A. The endocrine system and nervous system are intimately related to each other.
      1. Neurons secrete hormones directly into the blood stream.
      2. Neurons directly innervate (control) endocrine glands.
      3. Hormones regulate neuronal cells directly.

V. Classification of Intercellular Chemical signals.
   A. Intercellular chemical signals allow one cell to communicate with another.
      1. These signals coordinate and regulate the activities of most cells.

VI. Classification of Chemical Signals

<table>
<thead>
<tr>
<th>Intercellular Chemical Signal</th>
<th>Description</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autocrine</td>
<td>Secreted by cells in a local area and influences the activity of the same cell type</td>
<td>Prostaglandins (local vasodilation with tissue damage)</td>
</tr>
<tr>
<td>Paracrine</td>
<td>Secreted into tissue space and effects localized tissue on other tissue type.</td>
<td>Histamine, prostaglandins.</td>
</tr>
<tr>
<td>Hormone</td>
<td>Secreted into the blood by specialized cells and travels to distant target tissue to influence cells.</td>
<td>Thyroxine, Insulin</td>
</tr>
<tr>
<td>Neurotransmitter, neurohormone</td>
<td>Produced by neurons but functions like hormones.</td>
<td>Oxytocin, ADH</td>
</tr>
<tr>
<td>Neurotransmitter</td>
<td>Produced by neurons and secreted into the extracellular space by nerve terminals, travels short distance to influence postsynaptic cell.</td>
<td>Acetylcholine, epinephrine, opioids.</td>
</tr>
<tr>
<td>Pheromone</td>
<td>Secreted into the environment, modifies physiology and behavior of other individuals.</td>
<td>Sex pheromones</td>
</tr>
</tbody>
</table>
VII. **Structural Categories of Hormones.** *(Table 17.2)*
   A. **Amines** *(Amino acid derivatives)*
   B. **Proteins**
   C. **Glycoproteins** *(proteins and carbohydrates)*
   D. **Polypeptides**
   E. **Steroids**

VIII. **Mechanisms of control of hormone secretion rate.**
   A. Nonhormonal control of hormone secretion
   B. Nervous system control of hormone secretion
   C. Hormonal regulation of hormone secretion
   D. Positive and Negative Feedback

IX. **Transport and distribution of hormones in the body**
   A. Hormones travel in the body either as free hormones or in combination with a binding protein.
      1. Only the free hormone can diffuse through capillary walls into the interstitial space.
   B. Changes in hormone available to the target cell are due to:
      1. Changes in free hormone concentration
      2. Changes in the concentration of plasma binding protein

X. **Procedure for hormone function in physiological regulation**
   1. Target cells must have specific receptor proteins
   2. Activation of the receptor must cause a specific sequence of changes in the target cell.
   3. There must be a mechanism to quickly turn off the action of the regulator.
      a. Without an off switch physiological control would be impossible.

XI. **The off mechanism (metabolism and excretion of hormones):**
   A. The concentration and time a given hormone is in the blood stream determines the activity to the hormone.
      1. The concentration of a hormone in the blood is determined by:
         a. rate of secretion of the hormone
         b. rate of removal of the hormone from the blood
         1. Precise regulation of hormone levels occurs when the hormone is active for only short periods.
   B. **Half life** of hormone:
      1. Half life is the time it takes for half of a given concentration of the hormone to be destroyed or eliminated from the body.
2. **Factors that Decrease in half life**
   a. Primarily controlled by the rate of elimination of hormone from blood stream
   b. 4 means of removal
      (1) Excretion
      (2) Metabolism
      (3) Active transport
      (4) Conjugation

3. **Factors that Prolong half life**
   a. Binding to plasma proteins -
   b. Carbohydrate components

XII. **Effects of Hormone concentrations on Tissue Response**
A. The effects of hormones are very dependent on concentration.
B. Normal responses are produced only within physiological range.
   1. Hormones in abnormally high (pharmacological) concentrations may produce results much different compared to physiological concentrations.
      a. High concentrations of hormones may allow hormone to bind to and active other related receptors
      b. Some hormones can be converted into other biological products by the target tissue.
         (1) testosterone into dihydrotestosterone (DHT) or estrogen
         (2) administration of high doses one hormone can lead to significant quantities of another active hormone.
   C. **Up-regulation or priming**
   
D. **Down regulation or desensitization**

XIII. **Mechanisms of Hormone Action**
A. Hormones of the same chemical class have similar hormone actions within the cell.
   1. Similarities involve:
      a. Receptor location (internal vs external)
         (1) Depends on the chemical nature of the hormone.
            (a) Steroids and thyroxines are lipids and pass through the cell membrane.
               i) Receptors for these hormones are located inside the cell.
            (b) Water soluble proteins can not pass through the cell membrane so their receptors must be located on the cell surface.
               i) These require the activation of a second messenger system.
      b. Events within the cell after the hormone combines with the receptor.
XIV. Characteristics of hormone receptor interactions

1. Specificity
2. High affinity
3. Low capacity

B. Hormones that bind to Nuclear receptors

1. Lipophilic steroids and thyroid hormones travel through the blood attached to binding globulins called carrier proteins.
2. Hormone dissociated from the carrier protein in the blood and passes through the cell wall.
3. Hormone binds to a receptor in the cytoplasm or nucleus (nuclear hormone receptor).
4. These receptors function as transcription factors.
   a. Nuclear hormone receptors have two regions
      (1) ligand binding domain
      (2) DNA binding domain
   b. Activated receptors (bound to a hormone) binds to a specific region of DNA called a hormone response element.
5. Binding to the DNA causes transcription of mRNA that is used to produce specific proteins

6. Mechanism of STEROID action
   a. Steroids bind to a receptor in cell cytoplasm or nucleus.
      (1) The Receptor has two domains:
          (a) Steroid binding domain
          (b) DNA binding domain
   b. Receptor-hormone complex forms a dimer (homodimer) within the nucleus
   c. Dimer binds to the a specific DNA binding sequence called the hormone response element
      (1) - two half sites 6 nucleotides long form a palindrome.
   d. Activated hormone response element causes activation/ transcription of the gene.
7. **Mechanism of Thyroid Hormone Action** (VDG Fig. 19.6 and 19.7)
   a. T4 travels in blood bound to thyroxine-binding globulin (TBG)
   b. T3 can travel freely in blood (very small percent)
   c. T4 that enters target cell is converted to T3 by a receptor protein
   d. T3 enters the nucleus where it binds to another receptor that has a ligand binding domain.
   e. Dimerization occurs (heterodimer)
      1. The receptor combines with a Vitamin A Derivative 9-cis retinoic Acid
   f. Heterodimer binds to a hormone response element of DNA
   g. Transcription of a gene is activated.

C. **Hormones that use second messengers systems**
   1. Catecholamines (Epi, NE), glycoproteins, polypeptides can not enter the cell
   2. Must work through a surface receptor
   3. Activate one of three second messenger systems classified by the enzyme/signal transduction mechanism they active.
      a. Adenylate cyclase-Cyclic AMP Second messenger systems
      b. Pholholipase C-Ca++ Second messenger systems
      c. Tyrosine Kinase.
   4. **Adenylate cyclase-Cyclic AMP Second messenger systems** (See VDG fig. 19.8)
      a. Hormone bind to the receptor
      b. Activation of Receptor protein- connected to G-protein
      c. Dissociation of Alpha subunit of the G-Protein from the beta and gamma subunits.
      d. Alpha subunit activates adenylate cyclase
      e. Activated Adenylate cyclase catalyzes the conversion of ATP to cAMP in the cytoplasm.
      f. cAMP activates protein kinase enzymes that were already present in the cytoplasm in an inactive state.
      g. Activated protein kinase transfers phosphate groups to other enzymes in the cytoplasm
      h. Altered enzyme activity mediate the target cell’s response to the hormone.
      i. Off Mechanism: Phosphodiesterase hydrolyzes cAMP into inactive fragments.
(1) Hormone effect therefore depends on the constant stimulation of the receptor to produce more hormone. (No hormone- no effect)

(2) Theophylline -phosphodiesterase inhibitors (maintain high levels of cAMP within the cell)
   (a) for bronchiol dilation in astematics
   (b) (enhances Epinephrine’s effects on smooth muscle causing dilation of the bronchiole)
   (c) caffeine is also a phosphodiesterase inhibitor.

5. **Phospholipase C -Ca++ Second messenger systems (See VDG fig. 19.10)**
   a. There are low amounts of Ca++ in the cytoplasm due to active transport either out of the cell or into the endoplasmic reticulum (Storage of Ca++)
   b. Various stimuli can evoke Ca++ release into the cytoplasm.
   c. Effects of Ca++ release:
      (1) Ca++ influx in through voltage gated Ca++ channels in actives release of neurotransmitters
      (2) Activates muscle contraction
      (3) Ca++ serves as a second messenger for hormones
   d. Activation of G-protein coupled receptors activates a membrane protein Phospholipase C
   e. PLC catalyzes the conversion of a particular phospholipid in the membrane into Inositol triphosphate (IP3) and Diacylglycerol (DAG)
   f. IP3 enters the cytoplasm and binds to receptors on the ER causing Ca++ release from the ER.
   g. Ca+ poors out of the ER into the cytoplasm
   h. Ca++ activates calmodulin
   i. Calmodulin activates protein kinase which phosphorylates other enzymes
   j. Altered enzymes activity mediate the target cell’s response to the hormone.
   k. EG. Alpha-adrenergic effects of epinephrine (complement to beta through cAMP).

6. **Tyrosine Kinase Second messenger System (See VDG fig. 19.11)**
   a. Insulin uses a special second messenger system along with many other growth factors within the cell. (Platelet derived growth factor/epidermal growth factor)
   b. Receptor for insulin is in the plasma membrane and acts as a kind of enzyme (Tyrosine Kinase)
   c. Kinase is an enzyme that adds phosphate groups to proteins
      (1) Tyrosine kinase adds phosphates to the amino acid tyrosine within the peptide
   d. Insulin receptor consists of 2 subunits
      (1) Dimerize when bound to insulin
      (2) 2 sites
         (a) insulin binding site (external)
         (b) enzymatic site (internal)
   e. Binding of insulin and dimerization cause activation of the receptor
   f. The each subunit of the dimer phosphorylates the other dimer (autophosphorylation)
g. Activated tyrosine kinase then activates other cytoplasmic proteins.
h. Activated cytoplasmic proteins act as signaling molecules in the cell.
i. Signaling molecules may activate phosphorylation cascades or may activate phospholipase C-calmodulin-Ca++ release.
j. Produces very complex effects.
7. Hormone may act at the same target cells and produce antagonistic effects
   a. Insulin (synthesis of fat) and glucagon (breakdown of fat).