Mammalian Physiology

Endocrinology

PHYSIOLOGY, Chapter 39 & 43
Berne, Levy, Koeppen, Stanton
Objectives

• Describe the classes of hormones & their functions
• Identify the mechanism of action of different hormones
• Describe the regulation of secretion
• Discuss sensitivity and responsiveness
• Describe technique for measuring hormone concentration
• Discuss the hypothalamus – pituitary axis
• Discuss the actions of growth hormone
Endocrine System: Overview

- Endocrine system – the body’s second great controlling system which influences metabolic activities of cells by means of hormones

- Hormones
  - Regulate the metabolic function of other cells
  - Have lag times ranging from seconds to hours
  - Tend to have prolonged effects
  - Are classified as amino acid-based (amines), peptides, or steroids
Function of Endocrine System

- Control of digestive tract & its accessories
- Control of energy production
  - Storage, mobilization, interconversion & utilization of metabolic fuels
  - Insulin, glucagon, epinephrine, growth hormone, cortisol, thyroxine
- Control of composition and volume of extracellular fluid (ECF)
  - ADH, ACTH, aldosterone, cortisol, renin, parathyroid hormone
- Adaptation to hostile environment
  - Acclimatization to cold; resistance to infection, noxious agents, stress
  - Pituitary, adrenal, and thyroid hormones
- Growth and development
  - Practically all
- Reproduction
  - Survival of species, not individual member
  - Estrogen, progesterone, lutenizing hormone, follicle stimulation hormone, testosterone
Hormonal Signaling

- **Autocrine** – chemicals that exert their effects on the same cells that secrete them
- **Paracrine** – locally acting chemicals that affect cells other than those that secrete them
- **Neurocrine** – hormones released by a neuron into the blood to a distant target cell
- **Endocrine** – hormones - chemicals which are released from a gland into the blood and affect cells at distant sites
Classes of Hormones

- **Amines**
  - Derived from tyrosine
  - Catecholamines (2\textsuperscript{nd} OH\textsuperscript{−} in ortho position)
  - Thyroid hormone (iodination of benzene ring)
Classes of Hormones

- Proteins & Peptides
  - Specific DNA coding for protein synthesis
  - Insulin, growth hormone, glucagon
Classes of Hormones

Steroids

Derived from cholesterol – modifications of side chains, hydroxylation, or ring aromatization confer uniqueness

Cortisol, estrogen, progesterone, testosterone, aldosterone
Hormone Action

• Hormones alter target cell activity by one of two mechanisms
  – Second messengers involving:
    • Regulatory G proteins
    • Phosphatidylinositol phosphate - calcium
  – Direct gene activation involving steroid hormones
  – Altered membrane permeability
• The precise response depends on the type of the target cell
• Hormones produce one or more of the following cellular changes in target cells
  – Alter plasma membrane permeability
  – Stimulate protein synthesis
  – Activate or deactivate enzyme systems
  – Induce secretory activity
  – Stimulate mitosis
Hormone Receptors

• Function is regulated by specific cell receptors on target cells
• Receptors located
  – On membrane – catecholamines, protein hormones
  – In cytoplasm – steroid hormones
  – In nucleus – thyroid hormone
• Mechanism of action
  – 2nd messenger
  – Transcription/translation
  – Altered membrane permeability
Target Cell Activation

• Target cell activation depends on three factors
  – Blood levels of the hormone
  – Relative number of receptors on the target cell
  – The affinity of those receptors for the hormone
• Up-regulation – target cells form more receptors in response to the hormone
• Down-regulation – target cells lose receptors in response to the hormone
• 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
Sensitivity and Responsiveness

Sensitivity: amount of hormone that elicits ½ the maximal response – reflects affinity of receptor for hormone
Responsiveness: effect obtained with saturating concentrations of hormone – reflects number of membrane receptors
Sensitivity

Decrease in sensitivity due to:

1. Decrease in affinity of receptors
2. Increase or decrease in concentration of modulating cofactors
3. Increase rate of degradation
4. Increase in concentration of antagonistic hormones
Responsiveness

Decrease in responsiveness due to:

1. Decreased number of functional target cells
2. Decreased total number of receptors per cell
3. Decreased concentration of enzyme being activated by hormone
4. Decreased concentration of essential precursor
5. Increased concentration on non-competitive inhibitor
Receptor Binding

Binding of hormone to receptor is reversible \([H] + [R] \leftrightarrow [HR]\)

\[
K_{assoc} = \frac{[HR]}{[H] \cdot [R]} \quad \text{and} \quad \frac{[HR]}{[H]} = K \cdot [R]
\]

\(K_{assoc} = \text{affinity constant}\)
\(R = \text{number of receptors}\)

Binding of hormone to receptor follows saturation kinetics
Scatchard plot describes binding kinetics
Radioimmunoassay

Sample is incubated with radiolabeled tracer hormone (I\(^{125}\)) and fixed amount of antibody specific for that hormone.

Hormone and tracer compete for binding sites on antibody.

Since binding sites on antibody are fixed or limited, progressive increases in amount of non-labeled hormone will decrease amount of tracer bound.

At end of incubation, bound tracer molecules are separated from unbound – ratio of bound to free is proportional to concentration of unlabeled hormone.
Radioimmunoassay

A SATURATION PLOT

If increasing amounts of radiolabeled hormone are incubated with a fixed amount of an antibody to that hormone, the quantity of the hormone that binds to the antibody saturates.

[Total labeled hormone]

[Total unlabeled hormone]

C DISPLACEMENT CURVE

Increasing the amount of unlabeled hormone gradually decreases the amount of labeled antibody.

Displacement of a labeled hormone by an unlabeled hormone

Equilibrium exists between the labeled hormone, the antibody, and the hormone-antibody complex.

With the addition of a small amount of the unlabeled hormone, some of which binds to the antibody, fewer antibodies are labeled.

Further addition of unlabeled hormone leads to further displacement of the labeled hormone from the antibody. The number of labeled antibodies is thus less than that in 2.
Scatchard Plot

Plot of \([\text{HR}] \text{ vs } [\text{HR}]\) where slope is \(K_{\text{assoc}}\) and \(\frac{[\text{HR}]}{[\text{H}]\text{ X intercept is } R_o}\)

Scatchard plot is usually exponential – identifying two classes of receptors – high affinity and low affinity
Low affinity receptors may represent a reserve or may illustrate negative cooperativity

Negative cooperativity – affinity of unoccupied receptors is decreased when adjacent receptors are bound – moderates hormone action & protects against sudden hormone increase

Receptors also have capacity for down regulation – chronic ↑ in hormone concentration causes a ↓ in receptor number
Hormone Concentrations in the Blood

- Hormones circulate in the blood in two forms – free or bound
  - Steroids and thyroid hormone are attached to plasma proteins
  - All others are unencumbered
- Concentrations of circulating hormone reflect:
  - Rate of release
  - Speed of inactivation and removal from the body
- Hormones are removed from the blood by:
  - Degrading enzymes
  - The kidneys
  - Liver enzyme systems
- Blood levels of hormones:
  - Are controlled by negative feedback systems
  - Vary only within a narrow desirable range
Hormone Release

Hormone release is by exocytosis for those hormones stored in secretory granules – peptide and catecholamine hormones

Hormones not stored in granules – thyroid and steroid hormones – transfer through the plasma membrane

a. Increase in intracellular Ca++
b. Translocation of secretory granules to cell membrane
c. Secretory granules fuse with cell membrane
d. Common membrane is lysed and hormone is released into interstitial space
Regulation of Secretion

Hormones are not secreted at a uniform rate – secretion is a function of:
- diurnal variations
- cyclical release
- dietary conditions
- external stimuli

Secretion is under feedback control – negative feedback predominantly
Regulation of Secretion

• Feedback regulation requires
  – Detector of imbalance in homeostasis
  – Means of signaling secretion
  – Secretory cells
  – Target organ – capable of responding to signal
  – Mechanism for shutting off secretion

• In simplest case, detection, signaling, and shut-off all reside in same cell ie pancreatic beta-cells

• In complex case, CNS, and other glands interact – hypothalamus-pituitary axis
Simple Negative Feedback

- Effectors are controlled such that their activities oppose any deviation in the controlled variable.
- Maintains function within normal range.

Example: Glucose homeostasis

Set Point: 90 mg/100 ml blood
Feedback Loops

Long-loop feedback – peripheral gland hormones or substrates arising from hormone effects on tissues exert feedback control on both anterior pituitary and hypothalamus

Short-loop feedback – pituitary tropic hormones exert feedback control on hypothalamus

Ultra short-loop feedback – hypothalamus releasing hormones exert feedback control on the hypothalamus
Hormone Release: 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
Hormone Release: Neural Stimuli

• Neural stimuli – nerve fibers stimulate hormone release
  – Preganglionic sympathetic nervous system (SNS) fibers stimulate the adrenal medulla to secrete catecholamines (epinephrine and nor-epinephrine)
Hormone Release: Hormonal Stimuli

- Hormonal stimuli – release of hormones in response to hormones produced by other endocrine organs
  - 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
• The nervous system can override normal endocrine controls
  – 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
      – Decrease insulin secretion
      – Increase hepatic glucose output
Hypothalamus – Pituitary Axis

- Pituitary gland – two-lobed organ that secretes eight major hormones
- Neurohypophysis – posterior lobe (neural tissue) and the infundibulum
  - Receives, stores, and releases hormones from the hypothalamus
- Adenohypophysis – anterior lobe, made up of glandular tissue
  - Synthesizes and secretes a number of hormones
Pituitary Hormones

- **Anterior Pituitary**
  - Growth hormone (GH)
  - Adrenal corticotropic hormone (ACTH)
  - Thyroid stimulating hormone (TSH)
  - Follicle stimulating hormone (FSH)
  - Lutenizing hormone (LH)
  - Prolactin (PRL)

- **Posterior Pituitary**
  - Oxytocin
  - Anti-diuretic hormone (vasopressin)

Anterior pituitary hormones are synthesized, stored, and secreted by hormone-specific cell types in anterior pituitary

Posterior pituitary hormones are synthesized in hypothalamus, but stored and secreted in posterior pituitary
Pituitary - Posterior Lobe

- The posterior lobe is a downgrowth of hypothalamic neural tissue
- Has a neural connection with the hypothalamus (hypothalamic-hypophyseal tract)
- Nuclei of the hypothalamus synthesize oxytocin and antidiuretic hormone (ADH)
- These hormones are transported to the posterior pituitary
Pituitary - Anterior Lobe

- The anterior lobe of the pituitary is an outpocketing of the oral mucosa
- There is no direct neural contact with the hypothalamus
- There is a vascular connection, the hypophyseal portal system, consisting of:
  - The primary capillary plexus
  - The hypophyseal portal veins
  - The secondary capillary plexus
Hypothalamus-Pituitary Axis
Activity of the Adenohypophysis

- The hypothalamus sends a chemical stimulus to the anterior pituitary
  - Releasing hormones stimulate the synthesis and release of hormones
  - Inhibiting hormones shut off the synthesis and release of hormones
- The tropic hormones that are released are:
  - Thyroid-stimulating hormone (TSH)
  - Adrenocorticotropic hormone (ACTH)
  - Follicle-stimulating hormone (FSH)
  - Luteinizing hormone (LH)
Anterior Pituitary

- Hormones of anterior pituitary act independently of each other
- Each has its own stimulus for release
- Anterior pituitary is six glands in one
Growth Hormone (GH)

• Produced by somatotropic cells of the anterior lobe that:
  – Stimulate most cells, but target bone and skeletal muscle
  – Promote protein synthesis and encourage the use of fats for fuel
  – Inhibits glucose uptake
• Most effects are mediated indirectly by somatomedins – produced in liver from HGH
• Antagonistic hypothalamic hormones regulate GH
  – Growth hormone–releasing hormone (GHRH) stimulates GH release
  – Growth hormone–inhibiting hormone (GHIH) (somatostatin) inhibits GH release
Thyroid Stimulating Hormone (Thyrotropin)

- Tropic hormone that stimulates the normal development and secretory activity of the thyroid gland
- Triggered by hypothalamic peptide thyrotropin-releasing hormone (TRH)
- Rising blood levels of thyroid hormones act on the pituitary and hypothalamus to block the release of TSH
Adrenocorticotropic Hormone (ACTH, Corticotropin)

- Stimulates the adrenal cortex to release corticosteroids
- Triggered by hypothalamic corticotropin-releasing hormone (CRH) in a daily rhythm
- Internal and external factors such as fever, hypoglycemia, and stressors can trigger the release of CRH
Gonadotropins

- Gonadotropins – follicle-stimulating hormone (FSH) and luteinizing hormone (LH)
  - Regulate the function of the ovaries and testes
  - FSH stimulates gamete (egg or sperm) production
  - LH stimulates androgen secretion
  - Absent from the blood in prepubertal boys and girls
  - Triggered by the hypothalamic gonadotropin-releasing hormone (GnRH) during and after puberty
Functions of Gonadotropins

- In females
  - LH works with FSH to cause maturation of the ovarian follicle
  - LH works alone to trigger ovulation (expulsion of the egg from the follicle)
  - LH promotes synthesis and release of estrogens and progesterone
- In males
  - LH stimulates interstitial cells of the testes to produce testosterone
  - LH is also referred to as interstitial cell-stimulating hormone (ICSH)
Prolactin (PRL)

• In females, stimulates milk production by the breasts
• Triggered by the hypothalamic prolactin-releasing hormone (PRH)
• Inhibited by prolactin-inhibiting hormone (PIH)
• Blood levels rise toward the end of pregnancy
• Suckling stimulates PRH release and encourages continued milk production
Posterior Pituitary and Hypothalamic Hormones

- The posterior pituitary is composed of axons of hypothalamic neurons, storing antidiuretic hormone (ADH) and oxytocin.
- ADH and oxytocin are synthesized in the hypothalamus.
- ADH influences water balance.
- Oxytocin stimulates smooth muscle contraction in breasts and uterus (lactation and parturition).
  - Positive feedback
- Both use PIP-calcium second-messenger mechanism.
Growth Hormone

HGH is a protein hormone that stimulates post-natal somatic growth & development and also has effects on metabolism of proteins, fats, & carbohydrates. HGH is species specific – only primate GH will stimulate growth in humans. Effects on long bone growth occur prior to epiphyseal closure. Evidence for growth hormone presence from hypophysectomized rats.

HGH is a major determinant of growth, but in and of itself cannot bring growth back completely to normal.
Synthesis & Release of Growth Hormone

Growth hormone release stimulated by GHRH from the hypothalamus and inhibited by somatostatin released from the hypothalamus.

Effects are mediated by binding to $G_s$ and $G_i$ protein-receptors by GHRH and somatostatin respectively and subsequent increase or decrease in cAMP.
Growth Hormone Actions

• Effects on bone growth manifested on chondrogenesis & calcification – cartilage formation and normal closure of epiphyseal plates of long bones

• Effects on soft tissue mass – enlargement of organs in proportion to bone growth – kidney, connective tissue, skin

• Metabolic effects
  – Protein anabolic – promotes protein storage, positive nitrogen balance, increased amino acid uptake and protein synthesis
  – Carbohydrates – increased glucose production by liver, antagonizes insulin action in muscle & adipose tissue
  – Lipid – decrease body fatness with GH administration – ↓ synthesis of ffa & TG from glucose and ↑ mobilization of ffa from fat depots
Metabolic Action of Growth Hormone

The effects of HGH on linear growth, organ size, and lean body mass are mediated by somatomedin produced in the liver from HGH.

Key:
- Increases, stimulates
- Reduces, inhibits
- Initial stimulus
- Physiological response
- Result
# Growth Hormone Secretion

## Regulation of HGH secretion

<table>
<thead>
<tr>
<th>Stimulation</th>
<th>Inhibition</th>
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<tbody>
<tr>
<td>Glucose decrease</td>
<td>Glucose increase</td>
</tr>
<tr>
<td>Free fatty acid decrease</td>
<td>Free fatty acid increase</td>
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<tr>
<td>Amino acid increase (arginine)</td>
<td>Cortisol</td>
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<tr>
<td>Fasting</td>
<td>Obesity</td>
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<tr>
<td>Prolonged caloric deprivation</td>
<td>Pregnancy</td>
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<td>Stage 4 sleep</td>
<td>Somatostatin</td>
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<tr>
<td>Exercise</td>
<td>HGH</td>
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<td>Stress</td>
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<td>Estrogens</td>
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<td>Dopamine</td>
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<td>Serotonin</td>
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<td>α-Adrenergic agonists</td>
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<tr>
<td>γ-Aminobutyric acid</td>
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<tr>
<td>Enkephalins</td>
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![Diagram of Growth Hormone Secretion](image)
Growth Hormone Secretion

Secretion is episodic and pulsatile – peak during the first few hours of sleep.
GH is highest in pubertal youths.
GH effects are moderated by IGF$_1$ (somatomedin).
Secretion is also increased following a meal high in protein, with prolonged fasting, and after exercise.
Growth Hormone Actions

Growth Hormone is diabetogenic

GH → glucose release → hyperglycemia → stimulates insulin secretion by β cells of pancreas to increase glucose uptake, but GH inhibits insulin, so hyperglycemia persists → increased insulin secretion → β cells hypertrophy and eventually degenerate → diabetes manifests

Plasma Glucose (mg/dl)

Insulin injection

½ hr 1 hr

Normal

HPX

Hypophysectomy leads to insulin hypersensitivity
Insulin and IGF₁ Receptors

Insulin and IGF₁ receptors are heterodimers with tyrosine kinase domains on β subunit and autophosphorylation sites.

Similarity in receptors explains diabetogenic effect of growth hormone – IGF₁ will displace insulin from the insulin receptor, but will not activate glucose transport process – insulin will not displace IGF₁ from the IGF₁ receptor.
Insulin and IGF$_1$

% bound $^{125}$I-insulin

IGF$_1$ displacement of $^{125}$I-insulin

Insulin displacement of $^{125}$I-insulin

% bound $^{125}$I-IGF$_1$

Insulin displacement of $^{125}$I-IGF$_1$

IGF$_1$ displacement of $^{125}$I-IGF$_1$
GH Hypersecretion Effects

• Before epiphyses close
  – Pituitary giantism (ht>8 ft)
  – Males more than females
  – Symetrically overgrown
  – Marked CHO deficits
  – Diabetic
  – Usually die by early 20’s
  – Arthritis due to overgrowth of cartilage

• After epiphyses close
  – Acromegly
  – Growth only possible where responsive cartilage persists
    • Elongation of jaw bone
    • Deformities of bones of face, hands, feet
    • Thick, coarse skin
    • Overgrowth of underlying tissue
    • Hypertrophy of muscles & non-endocrine organs
  – Diabetic

Acromegalic patient
GH Hyposcretion Effects

- **Pituitary dwarfism**
  - Overall lack of anterior pituitary hormones
  - Dwarfism accompanied by hypothyroidism, adrenal insufficiency, & sexual immaturity
  - Corrected by administration of thyroid hormone, cortisol, and growth hormone together – growth hormone alone is insufficient to restore growth

- **Isolated genetic deficiency in HGH**
  - Sexual, ateliotic dwarfism
  - Show sexual maturity, capable of reproduction, no abnormalities other than short stature
  - Short stature due to unresponsiveness to GH

No known disease results from GH deficiency in adults