Endocrine System

In the beginning...

Single-celled organism

Cell responsible for all physiological processes

Multi-celled organism

Cells specialized for specific functions

Evolutionary processes

How do cells communicate?

1) Nervous system (electrical / chemical signaling)
   • Rapid / conscious or sub-conscious / internal or external communication
2) Endocrine system (chemical signaling)
   • Slow / sustained / sub-conscious / internal or external communication

Endocrine System

Hormone:

Any substance produced and secreted by one cell that regulates another cell

See Tables 9.1 / 9.2 (Costanzo – pgs. 380 – 381)

Overview of Endocrine System:

Endocrine System: Hormones and the various cells that secrete / receive them

Gland → Hormone → Target Cell → Effect

Marie & Hoehn – Figure 16.1

- Glandular secretory cells (epithelial tissue)
- Release substances into surrounding tissues (ductless)
Endocrine System

Overview of Endocrine System:

Endocrine System: Hormones and the various cells that secrete / receive them

<table>
<thead>
<tr>
<th>Gland</th>
<th>Hormone</th>
<th>Target Cell</th>
<th>Effect</th>
</tr>
</thead>
</table>

Endocrine (classic definition):

<table>
<thead>
<tr>
<th>Gland</th>
<th>Hormone</th>
<th>Blood</th>
<th>Target Cell</th>
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</table>

Neuroendocrine:

<table>
<thead>
<tr>
<th>Neuron</th>
<th>Hormone</th>
<th>Blood</th>
<th>Target Cell</th>
</tr>
</thead>
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Paracrine:

<table>
<thead>
<tr>
<th>Cell</th>
<th>Hormone</th>
<th>Interstitial Fluid</th>
<th>Target Cell</th>
</tr>
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</table>

Autocrine

<table>
<thead>
<tr>
<th>Cell</th>
<th>Hormone</th>
<th>Target Cell</th>
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</thead>
</table>

We will focus on the classical endocrine system

General Classes of Hormones:

1) Amines:
   - Derived from individual amino acids
   - May incorporate inorganic ions

   Majority of amines inactivated in liver or at site of action
Overview of Endocrine System:

Endocrine System: Hormones and the various cells that secrete / receive them

Gland → Hormone → Target Cell → Effect

General Classes of Hormones:

2) Peptides:
- Most common type of hormone
- Composed of amino acids (3 – 200+ a.a.)
- Synthesis follows Central Dogma

Peptides inactivated by blood, liver, and kidney proteases

Preprohormone
- Signal peptide cleaved
- Prohormone (e.g., insulin)
- May be glycosylated or phosphorylated
- Basal secretion (continuous)
- Stimulus-coupled secretion (episodic)

Peptides inactivated by blood, liver, and kidney proteases

Endocrine System: Hormones and the various cells that secrete / receive them

General Classes of Hormones:

3) Steroids:
- Derived from cholesterol
- Complex biosynthetic pathways
- Very little stored (lipid soluble)

Steroids inactivated by liver; cleared through kidneys / intestines

Endocrine System: Hormones and the various cells that secrete / receive them

Target Cells: Cells specialized to respond to hormones

Specific receptors present (2000 – 10,000)

Cell activity primarily regulated by # of active receptors present

**** Up Regulation / Down Regulation ****
- Depends on affinity of receptors, but does not define why change has occurred (e.g., activation / inactivation)
- Cell changes may be: 1) prolonged and irreversible (e.g., puberty)
- 2) transient and reversible (e.g., fight-or-flight)
Overview of Endocrine System:

**Endocrine System:** Hormones and the various cells that secrete / receive them

- **Gland** → **Hormone** → **Target Cell** → **Effect**

**Hormones differ in mechanism of action:**

1. **2nd Messenger Systems**
   - Utilized by large, charged hormones (e.g., peptides)
   - Receptors located on cell surface

   A) **Enzyme-linked receptors**
      - Binding of hormone directly activates enzyme (e.g., kinase)

   B) **G protein-linked receptors**

2. **Internal Receptor Systems**
   - Utilized by hydrophobic hormones (e.g., steroids)
   - Receptors located in cytoplasm / nucleus

   **Domains**
   - **A**: Initiates DNA binding (e.g., transcription factors)
   - **B**: Activates DNA binding (e.g., zinc fingers – highly conserved)
   - **C**: Hinge region (goes through conformational change)
   - **D**: Hormone-binding region
   - **E**: Hormone-binding region

**Costanzo – Figure 9.6**

**Costanzo – Figure 9.7**
Overview of Endocrine System:

**Endocrine System:** Hormones and the various cells that secrete / receive them

- Gland → Hormone → Target Cell → Effect

- Hormone levels maintained via feedback mechanisms:

  - Long loop
  - Short loop
  - Ultra-short loop

A) **Negative Feedback:** Some feature of hormone action, directly or indirectly, inhibits further secretion of the hormone

B) **Positive Feedback:** Some feature of hormone action, directly or indirectly, enhances further secretion of the hormone

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**Property** | **Amines** | **Peptides** | **Steroids**
--- | --- | --- | ---
Feedback regulation of synthesis | Yes | Yes | Yes
Storage of hormone | Several days | One day | Very little
Mechanism of secretion | Exocytosis | Exocytosis | Diffusion
Plasma protein binding | Rarely | Rarely | Yes
Lifetime in blood | Seconds | Minutes | Hours
Time course of action | Seconds | Minutes – Hours | Hours – Days
Receptors | Plasma membrane | Plasma membrane | Cytosolic / Nuclear
The hypothalamus and pituitary gland function in a coordinated fashion to orchestrate multiple endocrine system.

**Hypothalamus / Pituitary Gland:**

- **Endocrine System**

The hypothalamus and pituitary gland composed of both epithelial and neural tissue:

- **Anterior pituitary (adenohypophysis)**
  - Contains glandular cells
- **Posterior pituitary (neurohypophysis)**
  - Contains hypothalamic neurons

The hypothalamus is in direct control of the pituitary by both neural and hormonal mechanisms.

**The connection between the hypothalamus and posterior pituitary is neural:**

- Neural cell bodies located in hypothalamus
  - Supraoptic nucleus (SON)
  - Paraventricular nucleus (PVN)
- Posterior pituitary collection of axons
  - Release neurohormones into neighboring capillary bed (oxytocin – OT; antidiuretic hormone – ADH)

**The connection between the hypothalamus and anterior pituitary is neural and endocrine:**

- Neural cell bodies located in hypothalamus with axonal endings at median eminence (ME):
  - Supraoptic nucleus (SON)
  - Paraventricular nucleus (PVN)
  - Arcuate nucleus (ARC)
  - Preoptic area (POA)
  - Suprachiasmatic nucleus (SCN)
- Hypothalamic neurons release regulatory hormones at ME:
  - Releasing hormones (stimulatory effect)
  - Inhibiting hormones (inhibitory effect)
The hypothalamus is in direct control of the pituitary by both neural and hormonal mechanisms.

The connection between the hypothalamus and anterior pituitary is neural and endocrine:

- Regulatory hormones travel to anterior pituitary via hypothalamic-hypophysial portal system:
  - 1st capillary bed
  - Portal vessels
  - 2nd capillary bed

Important Implications:
1) Regulatory hormones delivered to pituitary rapidly and in high concentration
2) High levels of regulatory hormones do not appear in systemic circulation

The connection between the hypothalamus and anterior pituitary is neural and endocrine:

- Regulatory hormones activate / inhibit cells in the anterior pituitary:
  - **Acidophils** (granules bind acid stains)
    - Somatotrophs (growth hormone – GH; ~ 20%)
    - Lactotrophs (prolactin – PRL; ~ 15%)
    - Cell # varies according to sex / age
  - **Basophils** (granules bind basic stains)
    - Corticotrophs (adrenocorticotrophic hormone – ACTH; ~ 15%)
    - Thyrotrophs (thyroid-stimulating hormone – TSH; ~ 5%)
    - Gonadotrophs (follicle-stimulating hormone – FSH; luteinizing hormone – LH; ~ 15%)
  - Chromophobes (immature / support cells; ~ 30 %)

These hormones target endocrine glands (TSH = thyroid gland; LH / FSH = gonads), up regulating activity of glands

Group I: Glycoproteins (TSH / FSH / LH)
- Consists of two subunits: α-subunit (~ 92 – 93 a.a. residues) and β-subunit (~ 110 – 145 a.a. residues); connected via disulfide bond
- Sub-units coded by different genes
- Biological activity dependent on variation in β-subunit
- Large carbohydrate component (~ 15 – 30% MW of molecule)
- Assists in folding protein / prevention of proteolytic breakdown

Human chorionic gonadotropin (HCG) structurally related to glycoprotein family
Anterior Pituitary Hormones:

Group II: Pro-opiomelanocortin derivatives (ACTH)
- Post-translational modification of POMC (prohormone); results in production of multiple hormones
- Hormone production dependent on enzymes present
  - ACTH: Controls color change in many vertebrates; little activity in humans
  - αMSH: Produces analgesic effects in CNS
  - Stimulates lipolysis in adipose tissue
  - Up regulates adrenal cortex activity

Anterior Pituitary Hormones:

Group III: Single-chain peptide hormones (GH / PRL)

A. Growth Hormone:
- 191 a.a. residues; two internal disulfide bonds
- Secreted in pulsatile pattern (2 hr. bursts)
- ↑ rate during puberty (growth spurt)
- Regulation of GH Secretion:
  - Stimulatory Factors: Hypoglycemia, Starvation, Exercise / stress
  - Inhibitory Factors: Hyperglycemia, Obesity, Senescence
  - Growth Hormone Release Inhibiting Hormone (SRIF)
  - Growth Hormone Releasing Hormone (GHRH)
  - Somatomedins (IGF)
  - Hypothalamus

Synergisms with thyroid hormones / sex steroids
Anterior Pituitary Hormones:
Group III: Single-chain peptide hormones (GH / PRL)

A. Growth Hormone: Pathophysiology:

During early development:
- Gigantism (↑GH)
  - Cause: Pituitary tumor
  - Treatment: Somatostatin analogs
- Pituitary dwarfism (↓GH)
  - Cause: Multiple causes
  - Treatment: Exogenous GH

In adulthood:
- Acromegaly (↑GH)
  - Cause: Pituitary tumor
  - Treatment: Somatostatin analogs

B. Prolactin:
- 198 a.a. residues; three internal disulfide bonds
- Simulates growth / development of mammary tissue
  - In puberty / pregnancy
- Simulates production of milk proteins, free fatty acids, lactose
  - (suckling stimulation)
- Work in conjunction with estrogen and progesterone

Regulation of GH Secretion:
- Upregulated during pregnancy / lactation
- Primarily under inhibitory regulation

Stimulatory Factors
- Sleep

Inhibitory Factors
- Somatostatin

Pathophysiology:
- Hyperprolactinemia
- Symptoms: Galactorrhea / infertility
- Cause: Multiple causes
- Treatment: Bromocriptine (dopamine agonist)
Posterior Pituitary Hormones: Oxytocin / Antidiuretic Hormone:

- Homologous 9 a.a. residues

Oxytocin / Antidiuretic Hormone:

• Bioactive hormone synthesized from prohormones

Oxytocin (OT) / Antidiuretic Hormone (ADH)

- Synthesized from prohormones

Oxytocin (OT) / Antidiuretic Hormone (ADH)

- Genes on same chromosome but on different DNA strands

Oxytocin (OT) / Antidiuretic Hormone (ADH)

- Neurophysins assist in transporting OT / ADH down axon (hormone binding proteins)

Oxytocin (OT) / Antidiuretic Hormone (ADH)

- Stimulatory Factors:
  - Infant cues (e.g., sound)

Oxytocin (OT) / Antidiuretic Hormone (ADH)

- Inhibitory Factors:
  - Opiods (endophins)

Oxytocin (OT) / Antidiuretic Hormone (ADH)

- Antidiuretic Hormone:
  - Stimulates water reabsorption from kidney filtrate

Oxytocin (OT) / Antidiuretic Hormone (ADH)

- Stimulatory Factors:
  - Plasma osmolality
  - Hypovolemia

Oxytocin (OT) / Antidiuretic Hormone (ADH)

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Oxytocin (OT) / Antidiuretic Hormone (ADH)

- Stimulatory Factors:
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Oxytocin (OT) / Antidiuretic Hormone (ADH)

- Inhibitory Factors:
  - Opiods (endophins)
1) ADH binds with receptor; activates cAMP pathway
2) Protein kinase triggers water channels (Aquaporin – 2) to embed in apical plasma membrane

Posterior Pituitary Hormones:
B. Antidiuretic Hormone:

ADH is also called vasopressin (AVP)

Kidneys
- Stimulates water reabsorption from kidney filtrate

Blood Vessels
- Triggers contraction of vascular smooth muscle

Stimulatory Factors
- ↑ plasma osmolarity
- Hypovolemia
- Blood pressure drop

Inhibitory Factors
- ↓ plasma osmolarity
- Ethanol

Antidiuretic Hormone

Pathophysiology:
Diabetes Insipidus
- A tasteless passer through

Symptoms:
- Large volumes of urine
- Concentrated body fluids

Cause:
- No ADH produced (e.g., bad gene)
- Unresponsive kidney (e.g., bad AQP2)

Treatment:
- ADH analogue (e.g., Desmopressin)

Thyroid gland
Thyroid Gland Anatomy:
- Bi-lobed gland located in throat region
- Derived from endoderm of embryonic alimentary canal (Thyroglossal stalk)
- Parathyroid gland embedded in tissue

Follicle: Cluster of follicular cells (thyrocytes – simple cuboidal) surrounding lumen (as large as 1 cm)

Colloid: Thyroid hormone storage material (located in lumen)
- Can store 1 week worth of thyroid hormones
- Production of hormones not tightly regulated

Thyroid Hormone:
- Biogenic amine; derived from tyrosine
  - Requires iodine
- Two forms:
  - 90% Thyroxine (T₄)
    - 4 iodine atoms
    - Tetraiodothyronine
  - 10% Triiodothyronine (T₃)
    - 3 iodine atoms

Goiter

Iodized salt...
Endocrine System

Thyroid Hormone – Synthesis:

**Step 1: Accumulation of inorganic iodide (follicular cells):**

<table>
<thead>
<tr>
<th>Blood</th>
<th>Blood</th>
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</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Image" /></td>
<td><img src="image2.png" alt="Image" /></td>
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</table>

**Goitrogens:**

Chemicals that block iodine uptake by the thyroid:
- Perchlorate ion (IO₃⁻)
- Thiocyanate (SCN⁻)

Example: Sweet potatoes (cyanogenic glucosides)

Dietary goitrogens exist:

**Step 2: Synthesis of thyroglobin (TG):**

- Glycoprotein (contains 4 – 8 tyrosine residues)
- Synthesized in rough ER; packaged in Golgi apparatus; stored as colloid

**Step 3: Iodination of tyrosine residues (thyroglobin):**

- Inorganic iodide oxidized by thyroid peroxidase
  - Requires hydrogen peroxide
  - Triggers iodination of tyrosine residues
Endocrine System

**Thyroid Hormone – Synthesis:**

**Step 4:** Coupling of iodinated tyrosines
- Two iodinated tyrosines coupled together
- $\text{DIT} + \text{MIT} = \text{triiodothyronine}$; $\text{DIT} + \text{DIT} = \text{tetraiodothyronine}$
- Much more $T_4$ than $T_3$ synthesized (10x)

$\text{DIT} + \text{MIT} = \text{triiodothyronine}$; $\text{DIT} + \text{DIT} = \text{tetraiodothyronine}$

Only a fraction of tyrosine coupled (~10%)**

**Endocrine System**

**Thyroid Hormone – Synthesis:**

**Step 5:** Hydrolysis of thyroglobulin (releases hormone)
- Colloid engulfed to form endosome (endocytosis)
- Endosome + lysosome (hydrolytic enzymes) = endolysosome
- $T_3$ / $T_4$ released into blood (passive transport)**

**Endocrine System**

**Thyroid Hormone – Transport:**
- Majority of circulating thyroid hormones bound to carrier proteins:
  - **Thyroxine-binding globulin (~75%)**
    - Single polypeptide chain
  - **Transothymin (~20%)**
    - 4 polypeptide chains (2 binding sites)
  - **Albumin (~5%)**
    - Single polypeptide chain
- Carrier proteins synthesized by liver
  - Protect hormones from clearance
  - Provide reservoir ($T_4$ half-life = 7 days)
  - Higher affinity for $T_4$ {quote}somewhat hydrophobic {quote}
Endocrine System

Thyroid Hormone – Activation:

- **T₃** is the more active form of thyroid hormone at the tissues.

  **Remember:** 10x more T₄ than T₃ in circulation

  - Conversion occurs at tissue level:
    - A) ~45% of T₄ converted to T₃ (5' - iodosidase)
      - Biologically active; lost via kidney after sulfur conjugation
    - B) ~55% of T₄ converted to rT₃ (reverse T₃; 5' - iodosidase)
      - Biologically inactive; lost rapidly via kidney

  - During starvation, 5' - iodosidase inhibited, thus lowering O₂ consumption and metabolic rate (brain 5' - iodosidase not affected...)

  - Biologically active; lost via kidney after sulfur conjugation
  - Biologically inactive; lost rapidly via kidney

**Additional Inhibitory Factors**

- Thyroid-stimulating immunoglobulins

**Thyrotropin-stimulating hormone (TSH)**

- TSH stimulates release of T₃ / T₄:
  - ↑ iodide uptake
  - ↑ synthesis of thyroglobulin
  - ↑ endocytosis / hydrolysis of thyroglobulin

- Mechanism of action = G-protein / cAMP pathway

**Additional Stimulatory Factors**

- Thyroid-stimulating immunoglobulins

**Thyroid hormone (T₃)**

- Increases basal metabolic rate (BMR)
  - ↑ Na⁺/K⁺-ATPase activity
  - ↑ O₂ consumption
  - ↑ heat production

- Increases cardiac output
  - ↑ heart rate
  - ↑ stroke volume
  - Triggers synthesis of β-adrenergic receptors

- Promotes CNS maturation
  - (Newborn Hypothyroid Test)

- Increases energy substrates
  - ↑ glucose absorption
  - ↑ gluconeogenesis
  - ↑ proteolysis

- Synthesis of key metabolic enzymes

**Promotes growth**

- ↑ bone formation
- ↑ bone maturation

**“Fountain of Youth”**

Food restriction = ↓ thyroid hormones = longer life
Endocrine System

Thyroid Hormone:

Hypothyroidism (insufficient thyroid hormones)

Symptom(s):
- ↓ basal metabolic rate
- Weight gain / lethargy
- ↓ heat production (cold sensitivity)
- Decreased cardiac output
- Myxedema

Growth / mental retardation (perinatal)

Cause(s):
- Thyroid (autoimmune)
- Hypothalamic / pituitary failure
- I deficiency
- Congenital (e.g., genetic)

Treatment(s):
- Hormone replacement therapy

Hypothyroidism

Symptom(s):
- ↑ basal metabolic rate
- Weight loss / excitability
- ↑ heat production (prolific sweating)
- Increased cardiac output
- Exophthalmos

Cause(s):
- Graves' disease
- Thyroid neoplasm (e.g., tumor)
- Hypothalamic / pituitary failure

Treatment(s):
- Drug administration (e.g., propylthiouracil)
- Thyroidectomy
- Radioactive ablation (131I)

Cretinism

Thyroiditis (autoimmune)

First characterized endocrine disorder (~ 1850)

Cretinism

Adrenal Gland Anatomy:

- 2 glands; located superiority to each kidney
- Two disparate regions:
  - Adrenal medulla
    - Inner zone (20% of tissue)
    - Neuroectodermal origin (neural crest)
    - Release catecholamines (epinephrine / norepinephrine)
  - Adrenal cortex
    - Outer zone (80% of tissue)
    - Derived from mesoderm (mesenchyme)
    - Release steroid hormones

Adrenal glands, when corrected for weight, receive the highest blood flow of any organ in the human body.
Adrenal Hormones:

A) Zona glomerulosa
- Outermost layer; organized into whorls
- Synthesizes mineralocorticoids

B) Zona fasciculata
- Middle layer; organized into cords
- Synthesizes glucocorticoids

C) Zona reticularis
- Innermost layer; many reticular fibers
- Synthesizes androgens

Adrenal Hormones – Synthesis:

Step 1: Uptake of cholesterol (plasma)
- Enters via LDL complexes (LDL = low-density lipoproteins)

Step 2: Synthesis of pregnenolone
- Occurs in mitochondria

Step 3: Synthesis of various hormones
- Lack of enzymes in various zones equates to different products

Adrenal Hormones – Regulation:

- Display diurnal pattern that is pulsatile
- ACTH secretion drives pattern:
  - ↑ cholesterol uptake by mitochondria
  - ↑ cholesterol desmolase activity

Mechanism of action = G-protein / cAMP pathway

Additional Stimulatory Factors
- Sleep-wake transition
- Stress
- ADH

Additional Inhibitory Factors
- Opioids
- Somatostatin
**Adrenal Hormones**

**Aldosterone:**
- Regulation:
  - Renin-angiotensin system (RAS) regulates release
  - Triggers:
    1. Kidneys measure blood pressure
      - Juxtaglomerular cells (JG cells)
      - Pressure (down) = renin
    2. Kidneys measure [Na⁺] in filtrate
      - Macula densa cells
      - [Na⁺] = renin release

**Endocrine System**

**Cortisol**

**Adrenocortical steroids:**
- Stimulation of gluconeogenesis
- Suppression of inflammatory response
- Maintenance of vascular responsiveness
- Manipulation of sleep cycles
- Inhibition of bone formation
- Diabetogenic activity (anti-insulin effects)
- Immunosuppressive drugs
Adrenal Hormones – Action:

**Aldosterone**

- ↑ Na+ reabsorption
- ↑ K+ secretion
- ↑ H+ secretion

Interestingly, aldosterone receptors in the kidney also have high affinity for cortisol – Potential problem?

YES – but...

<table>
<thead>
<tr>
<th>Cortisol</th>
<th>Cortizone</th>
</tr>
</thead>
<tbody>
<tr>
<td>high receptor affinity</td>
<td>low receptor affinity</td>
</tr>
</tbody>
</table>

In renal tissue

Androstenedione = limited function

Androgens = major androgen

- development of pubic / axillary hair
- libido (sex drive)

Endocrine System

**Adrenocortical steroids bind to intracellular receptor**

Endocrine System

**Addison’s Disease** (Primary adrenocortical insufficiency)

- Symptom(s): Hypoglycemia, weight loss, weakness, hyperpigmentation, decreased pubic / axillary hair

- Cause(s): Adrenal cortex destruction (autoimmune)

- Treatment(s): Hormone replacement therapy

Cushing’s Syndrome (Excess glucocorticoids: adrenal hyperplasia)

- Symptom(s): Hyperglycemia, central obesity, round face, buffalo hump, muscle wasting, osteoporosis, hypertension, virilization (men)

- Cause(s): Phallic adenoma (tumor)

- Treatment(s): Tumor removal

Conn’s Disease (Primary hyperaldosteronism)

- Symptom(s): Increased ECF volume, hypertension, hypokalemia, metabolic alkalosis

- Cause(s): Adrenal hyperplasia

- Treatment(s): Aldosterone antagonists (surgery)
Pancreatic Hormones

Pancreas Anatomy:
- $\alpha$-cells: Periphery of islets; produce glucagon
- $\beta$-cells: Center of islets; produce insulin
- Embryonic origin: Pancreatic duct (endoderm)

Exocrine = Digestive enzymes
Endocrine = Blood glucose regulation

Pancreatic islets composed of:
- D-cells: Scattered; produce somatostatin (SST)

Pancreatic Hormones:
A. Insulin:
- Polypeptide; 2 chains ($A = 21$ a.a.; $B = 30$ a.a.) connected via two disulfide bonds
- Synthesized from single chain (pro-insulin)
- Gene = Chromosome 11
- Connecting peptide (C peptide)
- Connecting protein cleaved in Golgi apparatus
- Gene = Chromosome 11
- Connecting protein cleaved in Golgi apparatus
- However: Levels measured medically to determine endogenous rate of insulin production
- No physiological function known for C peptide...

Embryonic origin: Pancreatic duct (endoderm)
Endocrine cells clustered in pancreatic islets (islets of Langerhans)

Marieb & Hoehn (Human Anatomy and Physiology, 8th ed.) – Figure 16.13
Costanzo (Physiology, 4th ed.) – Figure 9.26
Costanzo (Physiology, 4th ed.) – Figure 9.27
### Additional Inhibitory Factors

Increased fasting

### Pancreatic Hormones: A. Insulin:

#### Regulation:

Glucose levels in blood most important regulator of insulin secretion:

1. Glucose transported into β cells
2. Glucose metabolized to produce ATP (substrate level phosphorylation)
3. ATP closes ATP-sensitive K⁺ channels
   - Depolarizes membrane
4. Depolarization opens voltage-gated Ca²⁺ channels
5. Increased intracellular Ca²⁺ levels triggers insulin secretion

#### Mechanism of Action:

- **Step 1:** Insulin binds to α subunits; triggers conformational change
  - Tyrosine kinase autophosphorylates; phosphorylates intracellular enzymes / proteins

- **Step 2:** Insulin-receptor complex internalized; either degraded, stored, or recycled

- **Step 3:** Tyrosine kinase subphosphorylates; phosphorylates intracellular enzymes / proteins

#### Actions on Target Tissues:

- **Hormone of Abundance**
  - Ensures that excess nutrients are stored for future use
  - Decrease blood glucose concentrations
  - Increase fat deposition; decrease lipolysis
  - Increase protein synthesis; decrease blood [a.a.]
  - Insulin also enhances uptake of potassium by cells
Pancreatic Hormones:

A. Insulin:

Pathophysiology:

- **Diabetes mellitus**
  - "a sweet passer through"

<table>
<thead>
<tr>
<th>Symptom(s)</th>
<th>Cause of symptom</th>
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<tbody>
<tr>
<td>Increased blood concentrations of glucose, amino acids, and fatty acids</td>
<td>Decreased glucose and amino acid uptake by cells; increased lipolysis of fats</td>
</tr>
<tr>
<td>Metabolic ketoacidosis (fruity breath)</td>
<td>Increased conversion of fatty acids to ketoacids</td>
</tr>
<tr>
<td>Increased urine output and thirst</td>
<td>Increased glucose load in kidney filtrate</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>Increase in K⁺ exiting cells</td>
</tr>
</tbody>
</table>

**Type I** (insulin-dependent; juvenile-onset):

- **Cause:** Decrease in # of β-cells (autoimmune)
- **Treatment:** Insulin replacement therapy

**Type II** (non-insulin-dependent; adult-onset):

- **Cause:** Down-regulation of insulin receptors (target cells)
- **Treatment:** Caloric restriction / weight reduction

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Endocrine System

Pancreatic Hormones:

B. Glucagon:

**Actions on Target Tissues:**

- **Glucagon**
  - Increase blood glucose concentrations
  - Stimulates glucogenolysis (targets liver cells)
  - Stimulates lipolysis
  - Fatty acids used as substrates for gluconeogenesis

**Mechanism of action:** G-protein / cAMP pathway
Pancreatic Hormones:
C. Somatostatin:
• Single chain polypeptide
(14 a.a. residues)
Regulation:
• Increased blood levels of all nutrient forms stimulate secretion
Additional Stimulatory Factors
Glucagon
Additional Inhibitory Factors
Insulin

Actions on Target Tissues:
Somatostatin
Decrease insulin secretion
Decrease glucagon secretion

Calcium Regulation
Forms of Ca\(^{2+}\) in Blood:

- **Total Ca\(^{2+}\)**
  - Albumin-bound (40%)
  - Protein-bound (60%)
- **Ionized Ca\(^{2+}\)**
  - Compressed to anions (10%)
  - Ultrafiltrable (50%)

Key element in numerous physiological functions

Only form of Ca\(^{2+}\) that is biologically active

Hypocalcemia:
- Decrease in plasma [Ca\(^{2+}\)]
- Hyper-reflexia
- Spontaneous twitching
- Muscle cramps
- Tingling / numbness
- Chvostek sign
- Lower threshold potential

Hypercalcemia:
- Increase in plasma [Ca\(^{2+}\)]
- Constipation
- Polyuria / polydipsia
- Hyporeflexia
- Lethargy / coma

Overall Ca\(^{2+}\) Homeostasis:

Individual in Ca\(^{2+}\) balance:

\[350 = 150 \times 200\]

Three hormones tightly regulate Ca\(^{2+}\) levels:
1. Parathyroid hormone (PTH)
2. Calcitonin
3. Vitamin D

Calcium Regulation Hormones:

**A. Parathyroid hormone:**
- Produced by parathyroid glands
- Single chain polypeptide (94 a.a. residues)
- ProPTH modified to active hormone in Golgi apparatus (6 a.a. removed)
- Biologic activity resides entirely in the N-terminal 34 amino acids

Small glands (~ 4) embedded on dorsal surface of thyroid gland

- Chief Cells = PTH
- Oxyphil = ?
**Calcium Regulation Hormones:**

**A. Parathyroid hormone:**

**Regulation:**
- Influenced directly by plasma \([\text{Ca}^{2+}]\)
- Activation of Ca\(^{2+}\) sensing receptors triggers G protein / IP\(_3\) & DAG; shuts down PTH secretion
- Mg\(^{2+}\) triggers similar events

**Actions on Target Tissues:**
- Increases bone resorption
- Increases Ca\(^{2+}\) reabsorption at kidney
- Increases Ca\(^{2+}\) absorption at small intestine
- Decreases PO\(_4^{3-}\) reabsorption at kidney (phosphaturia)
- Increases Ca\(^{2+}\) resorption by lowering solubility constant \([\text{Ca}^{2+}] \times [\text{PO}_4^{3-}]\) at bone

Mechanism of action = G protein / cAMP pathway

**Overall Ca\(^{2+}\) Homeostasis:**

Three hormones tightly regulate Ca\(^{2+}\) levels:
1. Parathyroid hormone (PTH)
2. Calcitonin
3. Vitamin D
Endocrine System

**Calcium Regulation Hormones:**

**A. Parathyroid hormone:**

**Hyperparathyroidism**

- **Symptoms:**
  - Hypercalcemia
  - ↑ bone resorption
  - ↑ intestinal Ca\(^{2+}\) absorption
  - ↑ kidney Ca\(^{2+}\) reabsorption

- **Causes:**
  - Parathyroid adenoma (primary)
  - Renal failure (secondary)

- **Treatment:**
  - Surgery (primary hyperparathyroidism)

**Hypoparathyroidism**

- **Symptoms:**
  - Hypocalcemia
  - ↓ bone resorption
  - ↓ intestinal Ca\(^{2+}\) absorption
  - ↓ kidney Ca\(^{2+}\) reabsorption
  - ↓ kidney PO\(_4\)\(^{3-}\) reabsorption
  - Hyperphosphatemia

- **Causes:**
  - Thyroid surgery (cancers, etc.)
  - Autoimmune / congenital

- **Treatment:**
  - Ca\(^{2+}\)/ Vitamin D supplements

**Pathophysiology:**

**Humoral Hypercalcemia of Malignancy:**

Tumors secrete PTH-related peptide; homologous with PTH

**Calcium Regulation Hormones:**

**B. Calcitonin:**

- **Produced by parafollicular cells (C cells) of thyroid gland**
- **Single chain peptide**
- **(32 a.a. residues)**
- **Intra-chain disulfide ring**
- **Decreases bone resorption**
- **Utilize calcium sensing receptors**

**Mechanism of action** = G protein / cAMP pathway

Overall, physiological role uncertain; changes in levels do not trigger derangement Ca\(^{2+}\) metabolism

**Calcium Regulation Hormones:**

**C. Vitamin D:**

- **Produced by photolysis of cholesterol**
- **Diet**
- **7 - Dehydrocholesterol**
- **Cholecalciferol (Vitamin D\(_3\))**

**Vitamin:**

An organic compound that must be obtained from the diet.
C. **Vitamin D:**

- Derived in skin of humans by action of ultraviolet light:

  ![Diagram of Calcium Regulation](image)

  - Sunlight 
  - 7-Dihydrocholesterol (from liver)
  - Tachysterole 
  - Previtamin D3 
  - Vitamin D3 (Epi-dermis)
  - Vitamins (Reserve substrates) 
  - Cholecalciferol (Vitamin D3) 
  - Systemic Circulation 
  - Within Blood 
  - Cholecalciferol (Transcalciferin) 
  - Ring-Binding Protein 
  - Ring-Binding Protein 
  - Ring-Binding Protein

  Vitamin D deficiency can result from lack of irradiation to skin.

  Irradiated food = adequate amount of vitamin (developed countries)

- Additional modifications necessary for activation of Vitamin D:

  ![Diagram of Vitamin D Activation](image)

  - Liver
  - 25-OH-cholecalciferol
  - 1α-hydroxylase
  - Kidney
  - 1,25-(OH)2-cholecalciferol
  - Active form

  - Regulation of Vitamin D synthesis occurs at the level of the kidney

  ![Diagram of Regulation](image)

- **Mechanism of action = Internal Receptor System**

- **C. **Vitamin D:**

  - Induces synthesis of calbindin D-28K
  - Cytosolic transport protein (Ca2+; phosphate)
  - Increases Ca2+ & PO43- absorption at small intestine
  - Increases Ca2+ & PO43- absorption at kidneys
  - Increases bone resorption

    - Works with PTH to stimulate osteoclast activity

    - ???

    - Mineralized old bone is resorbed to provide Ca2+ and PO43- for new bone

  - Responsible for increase in plasma Ca2+ & PO43-

    - (associated with laying down new bone)

  - Actions on Target Tissues:

    - Vitamin D
Endocrine System

Calciun Regulation Hormones:

C. Vitamin D:

Pathophysiology:

Vitamin D deficiency: 

Rickets:
- Symptoms: Growth failure / skeletal deformities
- Cause: Inadequate sunlight / diet
- Treatment: Vitamin D supplements

Osteomalacia:
- Symptoms: Softening of weight-bearing bones
- Cause: Inadequate sunlight / diet
- Treatment: Vitamin D supplements

Vitamin D Resistance:
- Kidney unable to produce active hormone
  - Absence of 1α-hydroxylase
  - Chronic renal failure

(Children) (Adults)