In the beginning…

Endocrine System

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

**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**

*Glandular secretory cells (epithelial tissue)*
*Release substances into surrounding tissues (ductless)*

**Endocrine System (classic definition):**

- **Gland**
- **Hormone**
- **Blood**
- **Target Cell**

**Neuroendocrine:**

- **Neuron**
- **Hormone**
- **Blood**
- **Target Cell**

**Paracrine:**

- **Cell**
- **Hormone**
- **Interstitial Fluid**
- **Target Cell**

**Autocrine:**

- **Cell**
- **Hormone**
- **Target Cell**

We will focus on the classical endocrine system.
Overview of Endocrine System:

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

Gland → Hormone → Target Cell → Effect

General Classes of Hormones:

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

   ![Tryptophan](image1)
   ![Melatonin](image2)

   Triiodothyronine (T₃)

   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

![Peptide biosynthesis diagram](image)

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

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

![Steroid biosynthesis diagram](image)

- Biosynthesis occurs primarily in smooth ER...
- Steroids inactivated by liver; cleared through kidneys / intestines
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>

**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’)

- Hormones differ in mechanism of action:

  **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
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  - Utilized by large, charged hormones (e.g., peptides)
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  **A) Enzyme-linked receptors**
  - Binding of hormone directly activates enzyme (e.g., kinase)
  
  **B) G protein-linked receptors**
  - Primarily responsible for changing cell activity

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

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

Costanzo – Figure 9.6

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Costanzo – Figure 9.7

Endocrine System

Cell membrane

DNA-binding domain

NH₂

Cytosol

Demethylation and binding to SREs

Nucleus

SREs

Transcription

mRNA

Translation

New proteins

Physiologic actions

Maximal hormone

[Diagram showing the mechanism of gene transcription and translation]
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:

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

**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 systems.

Pituitary gland composed of both epithelial and neural tissue:

- Anterior pituitary (adenohypophysis)
  - Contains glandular cells
- Posterior pituitary (neurohypophysis)
  - Contains hypothalamic neurons
Hypothalamus / Pituitary Gland:

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)

Hypothalamus / Pituitary Gland:

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:

- 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:
  
  ![Diagram of hypothalamic-hypophysial portal system]

  1° capillary bed → Portal vessels → 2° capillary bed

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

Hypothalamus / Pituitary Gland:

- Regulatory hormones activate / inhibit cells in the anterior pituitary:
  
  A) **Acidophils:** (granules bind acid stains)
  1) **Somatotrophs** (growth hormone – GH; ~ 20%)
  2) **Lactotrophs** (prolactin – PRL; ~ 15%)
     - Cell # varies according to sex / age

  B) **Basophils:** (granules bind basic stains)
  1) **Corticotrophs** (adrenocorticotropic hormone – ACTH; ~ 15%)
  2) **Thyrotrophs** (thyroid-stimulating hormone TSH; ~ 5%)
  3) **Gonadotrophs** (follicle-stimulating hormone – FSH; luteinizing hormone – LH; ~ 15%)

- Chromophobes (immature / support cells; ~ 30%)
Anterior Pituitary Hormones:

Group I: Glycoproteins (TSH / FSH / LH)
- Consists of two subunits: \( \alpha \)-subunit (~ 92 – 93 a.a. residues) and \( \beta \) sub-unit (~ 110 – 145 a.a. residues); connected via disulfide bond
- Sub-units coded by different genes
- Biological activity dependent on variation in \( \beta \) sub-unit
- 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

\( \alpha \)MSH:
- Controls color change in many vertebrates; little activity in humans

Addison’s disease
Anterior Pituitary Hormones:
Group III: Single-chain peptide hormones (GH / PRL)

A. Growth Hormone:
- 191 a.a. residues; two internal disulfide bonds

Regulation of GH Secretion:
- Secreted in pulsatile pattern (2 hr. bursts)
- ↑ rate during puberty (growth spurt)
- Stimulatory Factors: Hypoglycemia, Starvation, Exercise / stress
- Inhibitory Factors: Hyperglycemia, Obesity, Senescence

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

**In adulthood:**

B. Prolactin:

- 198 a.a. residues; three internal disulfide bonds

Regulation of GH Secretion:

- Up regulated during pregnancy / lactation
- Primarily under inhibitory regulation

**Stimulatory Factors**
- Sleep

**Inhibitory Factors**
- Somatostatin

The Endocrine System
Anterior Pituitary Hormones:
Group III: **Single-chain peptide hormones (GH / PRL)**

B. **Prolactin:**

- Simulates growth / development of mammary tissue
  (puberty / pregnancy)
- Simulates production of milk proteins / free fatty acids / lactose
  (suckling stimulation)
- Decreased fertility during breast-feeding
- Work in conjunction with estrogen and progesterone

**Pathophysiology:**

**Hyperprolactinemia**

Symptoms: Galactorrhea / infertility

Cause: Multiple causes

Treatment: Bromocriptine (dopamine agonist)

Posterior Pituitary Hormones:

**Oxytocin / Antidiuretic Hormone:**

- Homologous 9 a.a. residues

**Pathways:**

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

- Bioactive hormone synthesized from prohormones

**OR**

Norris (Vertebrate Endocrinology, 3rd ed.) – Figure 6.2 / 6.3
Posterior Pituitary Hormones:

A. Oxytocin:
- Stimulatory Factors:
  - Infant cues (e.g., sound)
- Inhibitory Factors:
  - Opioids (endorphins)
- Breast (Suckling):
  - Simulates movement of milk down duct system to nipple (milk letdown reflex)
- Uterus (Dilation of cervix):
  - Triggers powerful rhythmic contractions of uterus (childbirth)

B. Antidiuretic Hormone:
- Stimulatory Factors:
  - ↑ plasma osmolarity
  - Hypovolemia
- Inhibitory Factors:
  - ↓ plasma osmolarity
  - Ethanol
- Kidneys:
  - Stimulates water reabsorption from kidney filtrate

Pitosin:
- Synthetic agonist
1) ADH binds with receptor; activates cAMP pathway

2) Protein kinase triggers water channels (Aquaporin – 2) to embed in apical plasma membrane

### Pathophysiology:

**Diabetes Insipidus**

- **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% Thyrroxine (T₄)
    - 4 iodine atoms
    - Tetraiodothyronine
  - 10% Triiodothyronine (T₃)
    - 3 iodine atoms
Thyroid Hormone – Synthesis:

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

- **Blood**
  - I⁻
  - Na⁺
  - K⁺

- Basal membrane
- Apical membrane

- ¹⁺ Active Transport
- ²⁺ Active Transport

**Goitrogens:**
Chemicals that block iodine uptake by the thyroid
- Perchlorate ion (ClO₄⁻)
- Thiocyanate (SCN⁻)

**Dietary goitrogens exist:**
Example:
- Sweet potatoes (cyanogenic glucosides)

**Step 2:** Synthesis of thyroglobin (TG):
- Glycoprotein (contains 4 – 8 tyrosine residues)
- Synthesized in rough ER; packaged in Golgi apparatus; stored as colloid
**Thyroid Hormone – Synthesis:**

Step 3: Iodination of tyrosine residues (thyroglobin):
- Inorganic iodide oxidized by thyroid peroxidase
- Requires hydrogen peroxide
- Triggers iodination of tyrosine residues

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

Step 5: Hydrolysis of thyroglobin (releases hormone)
- Colloid engulfed to form endosome (endocytosis)
  - Endosome + lysosome (hydrolytic enzymes) = endolysosome
- T₃ / T₄ released into blood (passive transport)

Thyroid Hormone – Transport:
- Majority of circulating thyroid hormones bound to carrier proteins:
  - Thyroxine-binding globulin (~ 75%)
    - Single polypeptide chain
  - Transthyretin (~ 20%)
    - 4 polypeptide chains (2 binding sites)
  - Albumin (~ 5%)
    - Single polypeptide chain

T₃ / T₄ somewhat hydrophobic (↓ solubility)
Thyroid Hormone – Activation:

- Conversion occurs at tissue level:
  - A) ~ 45% of T\textsubscript{4} converted to T\textsubscript{3} (5'-iodinase)
    - Biologically active; lost via kidney after sulfur conjugation
  - B) ~ 55% of T\textsubscript{4} converted to rT\textsubscript{3} (reverse T\textsubscript{3}; 5'-iodinase)
    - Biologically inactive; lost rapidly via kidney

- During starvation, 5'-iodinase inhibited, thus lowering O\textsubscript{2} consumption and metabolic rate (brain 5'-iodinase not affected…)

Thyroid Hormone – Regulation:

- TSH stimulates release of T\textsubscript{3}/T\textsubscript{4}:
  - ↑ iodide uptake
  - ↑ synthesis of thyroglobulin
  - ↑ endocytosis / hydrolysis of thyroglobulin

- Mechanism of action = G-protein / cAMP pathway

- Additional Stimulatory Factors: Thyroid-stimulating immunoglobulins
- Additional Inhibitory Factors: T\textsubscript{3} / T\textsubscript{4} (Wolff-Chaikoff effect)

- Additional Stimulatory Factors: I\textsubscript{excess}
- Additional Inhibitory Factors: T\textsubscript{3} / T\textsubscript{4} (Wolff-Chaikoff effect)
Thyroid Hormone – Action:

- **T<sub>3</sub>** binds to intracellular receptor (nuclear)

**Thyroid hormone (T<sub>3</sub>)**

- Increases basal metabolic rate (BMR)
  - ↑ Na<sup>+</sup>/K<sup>+</sup> ATPase activity
  - (↑ O<sub>2</sub> consumption)
  - (↑ heat production)
- Increases output
  - ↑ heart rate
  - ↑ stroke volume
  - (triggers synthesis of β-adrenergic receptors)
- Promotes CNS maturation
  - (Newborn Hypothyroid Test)
- Promotes energy substrates
  - • ↑ glucose absorption
  - • ↑ glucogenolysis
  - • ↑ gluconeogenesis
  - • ↑ lipolysis
  - • ↑ proteolysis
- Synthesis of key metabolic enzymes
- Increases cardiac output
  - • ↑ heart rate
  - • ↑ stroke volume
- Promotes growth
  - • ↑ bone formation
  - • ↑ bone maturation
  - (works in synergy with GH and somatomedins)
- "Fountain of Youth"
- Food restriction = ↓ thyroid hormones = longer life
Adrenal Gland Anatomy:

- 2 glands; located superiorly 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 mineralcorticoids

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

**Endocrine System**

**Blood**

- Cholesterol

- **Pregnenolone**

- **Progestrone**
  - 3β-hydroxysteroid dehydrogenase
  - 21β-hydroxylase

- **11 Deoxycorticosterone**
  - 11β-hydroxylase

- **Corticosterone**
  - Aldosterone synthase

- **Aldosterone**

- **17-hydroxypregnenolone**
  - 17α-hydroxylase
  - 3β-hydroxysteroid dehydrogenase

- **17-hydroxyprogesterone**
  - 21β-hydroxylase

- **17-hydroxyprogesterone**
  - 11β-hydroxylase

- **Cortisol**

- **Dehydroepiandrosterone**
  - 17,20-lyase
  - 3β-hydroxysteroid dehydrogenase

- **Androstenedione**
  - Lack of enzymes in various zones equates to different products
Adrenal Hormones – Regulation:

Cortisol / Adrenal androgens:
- Display diurnal pattern that is pulsatile
  - 10 pulses / day
  - Highest in morning

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
- Somatostatins

Aldosterone:
- Renin-angiotensin system (RAS) regulates release

Triggers:
1) Kidneys measure blood pressure
   - Juxtaglomerular cells (JG cells)
   - ↓ pressure = renin

2) Kidneys measure [Na+] in filtrate
   - Macula densa cells
   - ↓ [Na+] = renin release

\[ [K^+] \text{ in interstitial fluid directly stimulates aldosterone release} \]
Endocrine System

Adrenal Hormones – Action:

Cortisol

- Stimulation of gluconeogenesis
- Diabetogenic Activity (anti-insulin effects)

Suppression of inflammation / immune response
- ↑ lipocortin synthesis (inhibits prostaglandin production)
- ↓ proliferation of T lymphocytes
- ↓ release of histamine

Immunosuppressive drugs

Maintenance of vascular responsiveness
(triggers up-regulation of β1-adrenergic receptors)

Manipulation of sleep cycles
- ↓ REM sleep
- ↑ awake time

Recall: Largest bursts of cortisol just before waking

- Inhibition of bone formation
  - ↓ collagen synthesis
  - ↓ osteoblast production
  - ↓ intestinal Ca²⁺ absorption

Adrenocortical steroids bind to Intracellular receptor
Endocrine System

Adrenal Hormones – Action:

- **Aldosterone**
  - ↑ Na⁺ reabsorption
  - ↑ K⁺ secretion
  - ↑ H⁺ secretion
  - **Kidney**

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

- YES – but...

- **cortisol**
  - 11 β-hydroxysteroid dehydrogenase
  - found in [high] in renal tissue

- **cortizone**
  - low receptor affinity

Adrenocortical steroids bind to intracellular receptor

- **Androgens**
  - **♂** = limited function
  - **♀** = major androgen

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

Androgens = limited function
♀ = major androgen

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

11 β-hydroxysteroid dehydrogenase found in high in renal tissue

Pathophysiology:

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

- **Symptom(s):** Hypoglycemia, Weight loss / weakness, Hyperkalemia, Metabolic acidosis, Hypotension, Loss of sex drive, Decreased pubic / axillary hair
- **Cause(s):** Adrenal cortex destruction (autoimmune)
- **Treatment(s):** Hormone replacement therapy

**Cushing’s Disease**  
(Enhanced secretion of ACTH)

- **Symptom(s):** Hyperglycemia, Central obesity / round face, Buffalo hump, Muscle wasting, Osteoporosis, Hypertension, Virilization (women)
- **Cause(s):** Pituitary adenoma (tumor)
- **Treatment(s):** Tumor removal
Endocrine System

Adrenal Hormones:

Pathophysiology:

**Conn’s Disease**  
(Primary hyperaldosteronism)

**Symptom(s):**  
Increased ECF volume  
Hypertension  
Hypokalemia  
Metabolic alkalosis

**Cause(s):**  
Adrenal hyperplasia

**Treatment(s):**  
Aldosterone antagonists  
Tumor removal (surgery)

Pancreatic Hormones
Pancreas Anatomy:

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

Both exocrine and endocrine function:
Exocrine = Digestive enzymes
Endocrine = blood glucose regulation

Pancreatic islets composed of:
α-cells: Periphery of islets; produce glucagon
β-cells: Center of islets; produce insulin
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

First hormone to:
1) Be isolated from animal source for therapy
2) Have protein structure determined
3) Have mechanism of action determined

Connecting protein cleaved in Golgi apparatus

Connecting peptide (C peptide)

However:
Levels measured medically to determine endogenous rate of insulin production
No physiological function known for C peptide...
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:**

1. Insulin binds to α subunits; triggers conformational change
2. Tyrosine kinase autophosphorylates; phosphorylates intracellular enzymes / proteins
3. Insulin-receptor complex internalized; either degraded, stored, or recycled
Endocrine System

Pancreatic Hormones:
A. **Insulin**:

**Actions on Target Tissues:**

- Insulin also enhances uptake of potassium by cells
- Decrease blood glucose concentrations
- Increase fat deposition; decrease lipolysis
- Increase protein synthesis; decrease blood [a.a.]

Liver cell
- Glucose
  - glucokinase
  - Glucose-6-phosphate
  - glycogen synthetase
  - Glycogen

Fat cell
- Lipids
- Lipogenesis
- Fatty acids
- Glucose

Muscle cell
- Amino acids
- Glucose

† # of GLUT 4 transporter proteins

Pathophysicsology:

**Diabetes mellitus**

**A. Insulin:**

**Symptom(s):**
- Increased blood concentrations of glucose, amino acids, and fatty acids
- Metabolic ketoacidosis ('fruity breath')
- Increased urine output and thirst
- Hyperkalemia

**Cause of symptom:**
- Decreased glucose and amino acid uptake by cells; increased lipolysis of fats
- Increased conversion of fatty acids to ketoacids
- Increased glucose load in kidney filtrate
- Increase in K+ exiting cells

**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

Biguanide drugs
Pancreatic Hormones:

A. **Insulin**:

**Pathophysiology:**

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**Obesity linked with Type II diabetes:**

- Over-eating (adulthood)
- Normal # fat cells; increased size
- Reduced # of insulin receptors
- Cellular desensitization to insulin
- ↑ insulin

Word of warning:

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**Diabetes mellitus**

’a sweet pass through’

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**Pancreatic Hormones:**

B. **Glucagon**:

- Single chain polypeptide
  (29 a.a. residues)

**Regulation:**

- Decreased blood glucose levels stimulate secretion

**Actions on Target Tissues:**

- Increase blood glucose concentrations
  - Stimulates glycogenolysis
  - Stimulates gluconeogenesis
  (targets liver cells)

- Increase blood fatty acid concentrations
  - Stimulates lipolysis

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

**‘Hormone of Starvation’**

Promotes mobilization and utilization of stored nutrients
**Endocrine System**

**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

\[ \downarrow \text{blood [glucose]} \]

\[ \text{SST} \]

\[ \uparrow \text{blood [glucose]} \]

\[ \text{D} - \text{cells} \]

\[ \beta - \text{cells} \]

\[ (+) \]

\[ (-) \]

\[ (+) \]

\[ (-) \]

\[ (+) \]

\[ (-) \]

**‘Hormone of Moderation’**

Regulates the responses of insulin and glucagon to ingestion of food
Forms of Ca\(^{2+}\) in Blood:

- **Total Ca\(^{2+}\)**:
  - **Protein-bound** (albumin): 40%
  - **Ultrafilterable**: 60%
  - **Complexed to anions**: 10%
  - **Ionized Ca\(^{2+}\)**: 50%

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

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

Key element in numerous physiological functions

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

Individual in Ca\textsuperscript{2+} balance:

\[350 = 150 + 200\]

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

Calcium Regulation Hormones:

A. Parathyroid hormone:
   - Produced by parathyroid glands
   - Single chain polypeptide (84 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
Calcium Regulation Hormones:

A. Parathyroid hormone:

**Regulation:**
- Influenced directly by plasma $[\text{Ca}^{2+}]$.

Activation of $\text{Ca}^{2+}$ sensing receptors triggers G protein / $\text{IP}_3$ & DAG; shuts down PTH secretion.
- $\text{Mg}^{2+}$ triggers similar events.

**Actions on Target Tissues:**
- Increases bone resorption.
- Increases $\text{Ca}^{2+}$ reabsorption at kidney.
- $\&$ Decreases PO$_4^{3-}$ reabsorption at kidney (phosphaturia).
- Enhances $\text{Ca}^{2+}$ 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

Humoral Hypercalcemia of Malignancy:
Tumors secrete PTH-related peptide; homologous with PTH

Calcium Regulation Hormones:
A. Parathyroid hormone:

Hyperparathyroidism
Symptoms:
- Hypercalcemia
  - ↑ bone resorption
  - ↑ kidney Ca\(^{2+}\) reabsorption
  - ↑ intestinal Ca\(^{2+}\) absorption
- Hypophosphatemia
  - ↓ kidney PO\(_4\)\(^{3-}\) reabsorption

Cause:
- Parathyroid adenoma (primary)
- Renal failure (secondary)

Treatment:
- Surgery (primary hyperparathyroidism)

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

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

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

B. Calcitonin:
- Single chain peptide

(32 a.a. residues)

Intra-chain disulfide ring

Regulation:
- Increased plasma [Ca^{2+}] stimulates secretion
- Utilize calcium sensing receptors

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

Mechanism of action = G-protein / cAMP pathway

Actions on Target Tissues:

Calcitonin

↓ Decreases bone resorption

Calcitonin

↓ Osteoclast activity / recruitment

↓ resorption of bone

Calcium Regulation Hormones:

C. Vitamin D:

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

Diet

7 - Dehydrocholesterol

Photolysis

Cholecalciferol (Vitamin D₃)

Diet
Calcium Regulation Hormones: Irradiated food = adequate amount of vitamin (developed countries)

C. Vitamin D:

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

  ![Diagram of Vitamin D synthesis and regulation]

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

- Additional modifications necessary for activation of Vitamin D

  ![Diagram showing steps of Vitamin D activation]

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

  - Regulation:
    - ↓ [Ca^{2+}]
    - ↑ PTH
    - ↓ [phosphate]
**Calcium Regulation Hormones:**

**C. Vitamin D:**

(steroid hormone)

**Actions on Target Tissues:**

**Vitamin D**

- Increases Ca\(^{2+}\) & PO\(_{4}^{3-}\) absorption at small intestine
  - Induces synthesis of calbindin D-28 K
  - Cytosolic transport protein (4 Ca\(^{2+}\) / protein)

- Increases Ca\(^{2+}\) & PO\(_{4}^{3-}\) absorption at kidneys
  - Unique from PTH which decreases PO\(_{4}^{3-}\) reabsorption

- Increases bone resorption
  - Works with PTH to stimulate osteoclast activity

Mechanism of action = Internal Receptor System

**Endocrine System**

**Responsible for increase in plasma [Ca\(^{2+}\)] & [PO\(_{4}^{3-}\)]**

(associated with laying down new bone)

**Calcium Regulation Hormones:**

**C. Vitamin D:**

(steroid hormone)

**Pathophysiology:**

**Vitamin D deficiency**

**Rickets:**

(children) & (adults)

- 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