In the beginning...

- **Multi-celled organism**
- **Cells specialized for specific functions**

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**

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:**

- **Gland** ➔ **Hormone** ➔ **Target Cell** ➔ **Effect**

**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

- **Hypothalamus**
- **Pituitary gland**
- **Thyroid gland**
- **Parathyroid gland**
- **Thymus gland**
- **Adrenal gland**
- **Pancreas**
- **Ovary**
- **Testis**

- **Blood**
- **Neuron**
- **Paracrine**
- **Autocrine**

**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:**

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

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

**Target Cells:** Cells specialized to respond to hormones

- Specific receptors present (200 – 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

Internal Receptor Systems
- Utilized by hydrophobic hormones (e.g., steroids)
- Receptors located in cytoplasm / nucleus
  - A/B: Initiate DNA binding (e.g., transcription factors)
  - C: Activates DNA by conformational change
  - D: Hinge region (goes through conformational change)
  - E: Hormone-binding region
### Overview of Endocrine System:

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

- Hormone levels maintained via feedback mechanisms:
  - **Negative Feedback**: Some feature of hormone action, directly or indirectly, inhibits further secretion of the hormone
  - Long loop:
    - Hypothalamus → Pituitary gland → Endocrine gland → Hormone → Target tissue
  - Short loop:
    - Ultrashort loop → Short loop
  - **Positive Feedback**: Some feature of hormone action, directly or indirectly, enhances further secretion of the hormone

### Feedback regulation of synthesis:

<table>
<thead>
<tr>
<th>Property</th>
<th>Amines</th>
<th>Peptides</th>
<th>Steroids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Storage of hormone</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Mechanism of secretion</td>
<td>Exocytosis</td>
<td>Exocytosis</td>
<td>Diffusion</td>
</tr>
<tr>
<td>Plasma protein binding</td>
<td>Rarely</td>
<td>Rarely</td>
<td>Yes</td>
</tr>
<tr>
<td>Lifetime in blood</td>
<td>Seconds</td>
<td>Minutes</td>
<td>Hours</td>
</tr>
<tr>
<td>Time course of action</td>
<td>Seconds</td>
<td>Minutes – Hours</td>
<td>Hours – Days</td>
</tr>
</tbody>
</table>

### Receptors:

| Plasma membrane | Plasma membrane | Cytosolic / Nuclear |

### Hypothalamus / Pituitary Gland:

The hypothalamus and pituitary gland function in a coordinated fashion to orchestrate multiple endocrine system.

#### 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
  - 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 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:
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    - Inhibiting hormones (inhibitory effect)
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:

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

Anterior Pituitary Hormones:

Group I: Glycoproteins (TSH / FSH / LH)
- Consists of two subunits: α-subunit (~ 92 – 93 a.a. residues) and β sub unit (~ 110 – 145 a.a. residues; connected via disulfide bond

- Sub-units coded by different genes
- Biological activity dependent on variation in β 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

Group II: Pro-opiomelanocortin derivatives (ACTH)
- Post translational modification of POMC (prohormone); results in production of multiple hormones
- Hormone production dependent on enzymes present

- UP regulates adrenal cortex activity
- Produces anabolic effects in CNS
- Melanocyte-stimulating hormone (αMSH)
- Stimulates lipolysis in adipose tissue
- Controls color change in many vertebrates; little activity in humans

Addison’s disease

Group III: Single-chain peptide hormones (GH / PRL)
- 191 a.a. residues; two internal disulfide bonds
- Secreted in pulsatile pattern (2 hr. bursts)
- ↑ rate during puberty (growth spur)

Stimulatory Factors
Hypoglycemia
Starvation
Exercise / stress

Inhibitory Factors
Hyperglycemia
Obesity
Senescence

Regulation of GH Secretion:

GHRH: Growth hormone releasing hormone
SRIF: Somatostatin; Somatostatin releasing inhibiting hormone

Somatomedins (IGF)
- Stimulates lipolysis in adipose tissue
- Controls color change in many vertebrates; little activity in humans

Protein synthesis
Bone growth

Glucose
FFA
Glycogen

Synergisms with thyroid hormones / sex steroids

Growth Hormone:
- Growth Hormone
  - Indirect actions
  - Direct actions

Somatomedins
- Carbohydrate metabolism
- Insulin-like growth factors (IGF; mammals)
- Somatomedins
- Fat cells
- Chondrocytes
- Muscles

Insulin
Liver
Lipoprotein synthesis
Fat cells
Anterior Pituitary Hormones:
Group III: Single-chain peptide hormones (GH / PRL)

A. Growth Hormone:
During early development:
- Gigantism (+GH)
- Pituitary dwarfism (-GH)
In adulthood:
- Acromegaly (+GH)

Pathophysiology:
- Gigantism
  - Cause: Pituitary tumor
  - Treatment: Somatostatin analogs
- Pituitary dwarfism
  - Cause: Multiple causes
  - Treatment: Exogenous GH
- Acromegaly
  - Cause: Pituitary tumor
  - Treatment: Somatostatin analogs

Cause:
- Multiple causes
Treatment:
- Exogenous GH

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

Stimulatory Factors
- Sleep

Inhibitory Factors
- Somatostatin

B. Prolactin:
- 198 a.a. residues; three internal disulfide bonds
- Simulates growth / development of mammary tissue
- Simulates production of milk proteins / free fatty acids / lactose (puberty / pregnancy) / suckling stimulation
- Decreased fertility during breastfeeding

Pathophysiology:
- Hyperprolactinemia
  - Symptoms: Galactorrhea / infertility
  - Cause: Multiple causes
  - Treatment: Bromocriptine (dopamine agonist)

Hyperprolactinemia

Posterior Pituitary Hormones:

A. Oxytocin:
- Stimulatory Factors
  - Infant cues (e.g., sound)
- Inhibitory Factors
  - Opioids (endorphins)

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

Inhibitory Factors
- Oxytocin (inhibitor)

Pathophysiology:
- Pitosin: Synthetic agonist

Pathophysiology:
- Stimulates contraction of uterus (delivery)

B. Antidiuretic Hormone:
- Stimulatory Factors
  - Plasma osmolality
  - Hypovolemia
- Inhibitory Factors
  - Ethanol (blocks ADH release from pituitary)

Stimulatory Factors
- Plasma osmolality

Inhibitory Factors
- Ethanol

Pathophysiology:
- Antidiuretic Hormone
  - Stimulates water reabsorption from kidney filtrate
**Posterior Pituitary Hormones:**

**B. Antidiuretic Hormone:**

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**
  - **Causes:**
    - No ADH produced (e.g., bad gene)
    - Unresponsive kidney (e.g., bad AQP2)
  - **Treatment:** ADH analogue (e.g., Desmopressin)

**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:
  - **Thyroxine (T4):** 4 iodine atoms
  - **Triiodothyronine (T3):** 3 iodine atoms
**Endocrine System**

**Thyroid Hormone**

**– Synthesis:**

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

- Na$^+$ $\rightarrow$ I$^-$ $\rightarrow$ I$^-$ $\rightarrow$ Blood

**Goitrogens:**
- Chemicals that block iodine uptake by the thyroid
  - Percholate ion (ClO$_4^-$)
  - Thiocyanate (SCN$^-$)

**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

**Step 4**: Coupling of iodinated tyrosines

- Two iodinated tyrosines coupled together
- DIT $+$ MIT = triiodothyronine ($T_3$); DIT $+$ DIT = tetraiodothyronine ($T_4$)
- Much more $T_4$ than $T_3$ synthesized (10x)

**Step 5**: Hydrolysis of thyroglobin (release hormone):

- Colloid engulfed to form endosome (endolysosome)
- Endosome + lysosome (lysosomal enzymes) = ondysosomes
- $T_3$ / $T_4$ released into blood (passive transport)

**Thyroid Hormone**

**– Transport:**

- Majority of circulating thyroid hormones bound to carrier proteins:
  - Thyroxine-binding globulin (~ 75%)
  - Transferrin (~ 20%)
  - Albumin (~ 5%)
- Carrier proteins synthesized by liver
- Protect hormones from clearance
- Provide reservoir ($T_4$ half-life = 7 days)
- Higher affinity for $T_3$
Thyroid Hormone – Activation:

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

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

- During starvation, 5'-iodinase inhibited, thus lowering O2 consumption and metabolic rate (even if thyroid not affected)

Thyroid Hormone – Action:

- **T3 binds to intracellular receptor (nuclear)**
  - Increases basal metabolic rate (BMR)
    - ↑ Na+/K+ ATPase activity
    - ↑ O2 consumption
    - ↑ heat production
  - Increases cardiac output
    - ↑ heart rate
    - ↑ stroke volume
  - Converts to T3 (triggers synthesis of key metabolic enzymes)
    - ↑ glucose absorption
    - ↑ glucogenolysis
    - ↑ lipolysis
    - ↑ proteolysis
  - Promotes CNS maturation (Newborn Hypothyroid Test)
    - ↑ bone formation
    - ↑ bone maturation
    - Stimulation of growth (in synergy with GH and somatomedins)

- "Fountain of Youth" Food restriction → ↓ thyroid hormones → longer life

Thyroid Hormone – Regulation:

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

- Mechanism of action = G-protein / cAMP pathway

- Down regulates TSH receptors

- Additional Stimulatory Factors
  - Additional Inhibitory Factors
  - Thyroid-stimulating immunoglobulins
  - (Wolff-Chaikoff effect)

Thyroid Hormone:

- **Hypothyroidism** (insufficient thyroid hormones)
  - Symptom(s): ↓ basal metabolic rate
  - Weight gain / lerosis
  - Heart production (↑ cold sensitivity)
  - Myxedema
  - Growth / mental retardation (perinatal)
  - Results: Thyroiditis
  - Cause(s): Immunologic / inflammatory failure
  - Treatment(s): Hormone replacement therapy

- **Hyperthyroidism** (excess thyroid hormones)
  - Symptom(s): ↑ basal metabolic rate
  - Weight loss / excitability
  - ↑ heart production (grasping / cardiac output)
  - Increased cardiac output
  - Increased glucose utilization
  - Goiter
  - Cause(s): Autoimmune disease
  - Treatment(s): Drug administration (e.g., propylthiouracil)

Adrenal Gland Anatomy:

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

Adrenal Gland Pathophysiology:

- First characterized endocrine disorder (~1850)

- Chondriome
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

Stimulatory Factors

- ACTH secretion drives pattern:
  - Cholesterol uptake by mitochondria
  - Cholesterol action

- Highest in morning

- 10 pulses / day

Glucose synthesis
- Glucose synthesis
- Protein synthesis

- Aldosterone
- Cortisol

- Glucose (hyperglycemia)

- Inflammation / immune response
  - Suppression of inflammation / immune response (inhibits prostaglandin production)
  - Inhibition of bone formation

Maintenance of vascular responsiveness
- Stimulation of vascular responsiveness (triggers up-regulation of \( \beta \)-adrenergic receptors)
- Inhibition of bone formation
  - \( \beta \)-collagen synthesis
  - \( \beta \)-osteoblast activity
  - \( \beta \)-intestinal Ca\(^{2+}\) absorption

Inhibitory Factors

- Somatostatins
- Opioids

- GLUONEOGENESIS
- Lipolysis
- Fatty acids

- Mineralocorticoids

- Androgens

- Cortisol
- Glucocorticoids

- Aldosterone

- Lipid synthesis
- Lipogenesis

- Mineralcorticoids
- Progesterone
- Deoxycorticosterone
- Androstenedione
- Dehydroepiandrosterone
- Pregnenolone
- Androgens

- Aldosterone
- Deoxycorticosterone
- Androstenedione
- Dehydroepiandrosterone
- Pregnenolone

Immunosuppressive drugs

- Gluconeogenesis
- Lipolysis
- Fatty acids

- Aldosterone
- Deoxycorticosterone
- Androstenedione
- Dehydroepiandrosterone
- Pregnenolone

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- Gluconeogenesis
- Lipolysis
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- Pregnenolone

- Aldosterone
- Deoxycorticosterone
- Androstenedione
- Dehydroepiandrosterone
- Pregnenolone
Adrenal Hormones - Action:

Aldosterone

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

Intracellular receptor

• ↑ Na+ reabsorption
• ↑ K+ secretion
• ↑ H+ secretion

Kidney

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

YES – but...

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

Androgens

= limited function
= major androgen

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

Adrenal Hormones:

Pancreatic Hormones:

Endocrine System

Conn’s Disease
(Primary hyperaldosteronism)

Symptom(s):
Increased ECF volume
Hypertension
Hyperkalemia
Metabolic acidosis

Cause(s):
Adrenal hyperplasia

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

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

Connecting protein (C peptide)

No physiological function known for C peptide...

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Costanza...
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
3) ATP closes ATP-sensitive K⁺ channels
   • Depolarizes membrane
4) Depolarization opens voltage-gated Ca²⁺ channels
5) Increased intracellular Ca²⁺ levels triggers insulin secretion

**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.]

**Pathophysiology:**

Type I:
(Insulin-dependent; juvenile onset)
- Decreased blood glucose: targets liver cells
- Fatty acids used as substrate for gluconeogenesis
Type II:
(non-insulin-dependent; adult onset)
- Hyperkalemia
- Increased urine output and thirst

**Treatment:**
Insulin replacement therapy

**Diabetes mellitus**
('fruity' breath)

**Symptom(s):**
- Increased blood concentrations of glucose, amino acids, and fatty acids
- Metabolic ketoacidosis (keto skin)
- Increased ketones in urine
- Hyperkalemia

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

**Mechanism of Action:**
Tyrrosine kinase autophosphorylates insulin receptor complex; internalized, either degraded, stored, or recycled

**Hormone of Starvation**

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

**Regulation:**
Decreased blood glucose levels stimulate secretion

**Actions on Target Tissues:**
Glucagon
- Increase blood glucose concentrations
  • Stimulates gluconeogenesis
  • Stimulates lipolysis

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

**Hormone of Abundance**

- Stimulation of stored nutrients

**Pathophysiology:**

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

**Regulation:**
- Decreased blood glucose levels stimulate secretion

**Actions on Target Tissues:**
Glucagon
- Increase blood glucose concentrations
  • Stimulates gluconeogenesis
  • Stimulates lipolysis

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

**Hormone of Starvation**

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

**Regulation:**
Decreased blood glucose levels stimulate secretion

**Actions on Target Tissues:**
Glucagon
- Increase blood glucose concentrations
  • Stimulates gluconeogenesis
  • Stimulates lipolysis

**Mechanism of action:**
G-protein / cAMP pathway
Pancreatic Hormones:

C. Somatostatin:
- Single chain polypeptide
- Regulation: Increased blood levels of all nutrient forms stimulate secretion
- Additional Stimulatory Factors: Glucagon, Insulin
- Additional Inhibitory Factors: Glucagon, Insulin

Actions on Target Tissues:
- Decrease insulin secretion
- "Hormone of Moderation"
- Regulates the responses of insulin and glucagon to ingestion of food
- \[\text{Blood [glucose]} \]
- \(\alpha\)-cells (+) \(\beta\)-cells (--) 
- \(\gamma\)-cells (++)

Calcium Regulation

Forms of Ca\(^{2+}\) in Blood:
- \(\text{Total Ca}^{2+}\)
- Protein-bound Ca\(^{2+}\)
- Ultralabile Ca\(^{2+}\)
- Complexed to anions
- Ionized Ca\(^{2+}\)

Hypocalcemia:
- Decrease in plasma [Ca\(^{2+}\)]
- Hyperreflexia
- Spontaneous twitching
- Muscle cramps
- Tingling / numbness
- Chvostek sign
- Hyporeflexia

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

Overall Ca\(^{2+}\) Homeostasis:
- Individual in Ca\(^{2+}\) balance:
- 350 = 150 + 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 (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 [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\(^{2+}\) absorption at kidney
- Decreases PO\(_4\)\(^{3-}\) reabsorption at kidney (phosphaturia)
- Enhances Ca\(^{2+}\) resorption by lowering solubility constant (\([\text{Ca}^{2+}] \times [\text{PO}_4^{3-}]\)) at bone
- Increases Ca\(^{2+}\) absorption at small intestine (indirect action; activates vitamin D production)

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

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B. Calcitonin:

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

**Actions on Target Tissues:**
- Decreases bone resorption
- Decreases PO\(_4\)\(^{3-}\) reabsorption at kidney

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

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C. Vitamin D:

**Pathophysiology:**

**Hyperparathyroidism**
- Symptoms:
  - Hypercalcemia
  - Increased kidney Ca\(^{2+}\) reabsorption
  - Increased intestinal Ca\(^{2+}\) absorption
  - Hypophosphatemia
- Cause:
  - Parathyroid adenoma (primary)
  - Renal failure (secondary)
- Treatment:
  - Surgery (primary hyperparathyroidism)

**Hypoparathyroidism**
- Symptoms:
  - Hypocalcemia
  - Decreased kidney Ca\(^{2+}\) reabsorption
  - Decreased intestinal Ca\(^{2+}\) absorption
  - Hyperphosphatemia
- Cause:
  - Thyroid surgery (cancers, etc.)
  - Autoimmune / congenital
- Treatment:
  - Ca\(^{2+}\) / Vitamin D supplements

**Humoral Hypercalcemia of Malignancy:**
- Tumors secrete PTH-related peptide; homologous with PTH
  - Hypophosphatemia
  - Decreased kidney PO\(_4\)\(^{3-}\) reabsorption

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

**Calcium Regulation Hormones:**

- Produced by parafollicular cells (C cells) of thyroid gland

**Vitamin:**
- An organic compound that must be obtained from the diet.
Calcium Regulation Hormones:

C. Vitamin D:
- Derived in skin of humans by action of ultraviolet light:
  - Vitamin D deficiency can result from lack of irradiation to skin

**Actions on Target Tissues:**
- Vitamin D increases Ca\(^{2+}\) & PO\(_4\)\(^{3-}\) absorption at small intestine
  - \(\text{Induces synthesis of calbindin D-28 K}\)
- Vitamin D increases Ca\(^{2+}\) & PO\(_4\)\(^{3-}\) absorption at kidneys
  - \(\text{Unique to PTH which decreases PO}_4\)\(^{3-}\) reabsorption
- Vitamin D increases bone resorption
  - \(\text{Works with PTH to stimulate osteoclast activity}\)
  - \(\text{Mineralized old bone is resorbed to provide Ca}^{2+}\) & PO\(_4\)\(^{3-}\) for new bone

**Mechanism of action = Internal Receptor System**

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

**Vitamin D Resistance:**
- Kidney unable to produce active hormone
  - Absence of \(\alpha\)-hydroxylase
  - Chronic renal failure

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

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