KEY CONCEPTS: GENERAL PRINCIPLES

- Hormones are categorized based on their chemical structure: amines, proteins, and steroids.
- The hormone RECEPTOR is the functional signaling mediator in the cell.
- Hormone receptor location and type are based on the chemical structure of the ligand (membrane v. intracellular).
- Bioavailability of hormones depends on multiple factors and most are regulated by feedback loops.

COMPONENTS OF THE ENDOCRINE SYSTEM

Classical Endocrine Glands:
Classical endocrine glands are ductless. Secrete hormones directly into the bloodstream or extracellular space. The entire organ is dedicated primarily to endocrine function.
GENERAL PRINCIPLES
Factors affecting hormone bioavailability
- Age
- Sex/Gender
- Obesity
- Circadian cycle
- Plasma binding proteins
- Receptor levels at target tissue
- Hormone half-life
- Pulsatility
- Feedback

HORMONE TRANSPORT
Hormone Binding Proteins
- Bind to hormones in blood to facilitate transport
- Generally increases the half-life of the hormone
- Mostly for steroid hormones (lipophilic)
  - Also: IGF-I, GH, T4/T3

Highly specific:
- Sex hormone binding globulin (SHBG) – binds estrogens and testosterone
- Corticosteroid binding globulin (CBG) – binds cortisol/corticosterone
- Thyroxine binding globulin (TBG) and transthyretin (TTR) – binds thyroid hormone

Non-specific:
- Albumin – binds most lipophilic compounds in blood
KEY CONCEPTS: HYPOTHALAMUS/PITUITARY

- The hypothalamus is the master regulator of most endocrine organs. Discrete nuclei secrete specific hormones that are released into circulation – either via the median eminence/hypophysial portal system to the anterior pituitary or directly from the posterior pituitary.

- The anterior pituitary has 5 major cell types that each make a different hormone. These cells are directly stimulated by their corresponding hypothalamic hormone (“hypothalamic releasing factors”).

- These 2 components make up the “HP” part of all 3-tiered endocrine regulatory axes: HPG, HPT, HPA, HPL.
Hypothalamus/Pituitary

Anterior Pituitary – 5 cell types
- Somatotrope – GH
- Gonadotrope – LH/FSH
- Corticotrope - ACTH
- Thyrotrope - TSH
- Lactotrope - Prolactin

DOPAMINE

Hormone action: inhibits prolactin release from the anterior pituitary.

Prolactin stimulates dopamine >>> inhibits prolactin

AVP/ADH

PVN and SON Integration of various inputs

Chemoreceptor trigger zone (CTZ)

Increased tone of parasympathetic and sympathetic nervous systems
GH stimulates IGF-I in liver – insulin dependent

IGF-I inhibits GH

IGF-I mimics insulin in muscle, but not liver and adipose due to lack of receptors

**Key Concepts: Adrenal**
- The adrenal gland consists of two main parts: the cortex (where steroid hormones are made) and the medulla (where catecholamines are made).
- The cortex is divided into 3 functional zones: zona glomerulosa (aldosterone), zona fasciculata (cortisol) and zona reticularis (androgens).
- The HPA axis regulates the synthesis and release of cortisol. H = CRH; P = ACTH
- ACTH stimulates multiple steps in the steroid biosynthesis pathway and also stimulates the enzyme required to make aldosterone.
- The Renn-Angiotensin system is the primary regulator of aldosterone.
**FUNCTIONALLY TWO GLANDS**

- Cortex derives from mesoderm
- Medulla derives from neural crest: modified "sympathetic postganglionic neurons"
- Sympathetic innervation synapses on medullary cells.

**Embryology**

- Cortex
  - zona glomerulosa (mineralocorticoids)
  - zona fasciculata (glucocorticoids: cortisol)
  - zona reticularis (weak androgens: DHEAS)

**HPA AXIS**

- H = hypothalamus (CRH/CRF)
- P = pituitary (ACTH)
- A = adrenal (multiple hormones)
MC2R = ACTH RECEPTOR in ADRENAL

CORTISOL = PLEIOTROPIC HORMONE
Functional Anatomy

- Zona glomerulosa

Primary Product: Aldosterone
(mineralocorticoid)

ALDOSTERONE REGULATION (NOT HPA)

Renin-Angiotensin system

- Angiotensin II directly stimulates glomerulosa cells to synthesize and secrete aldosterone.
- Aldosterone increases renal sodium absorption; potassium excretion.

No Aldosterone
No Cortisol

Hypotension
Hyperkalemia
Masculinization
High plasma renin
High ACTH

Note: different gene!

High 11DOC
No cortisol

Hypertension
Hypokalemia
Masculinization
High ACTH
RECAP OF IMPORTANT ENZYMES

<table>
<thead>
<tr>
<th>ENZYME</th>
<th>SYNONYM</th>
<th>GENE</th>
<th>Zone</th>
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<tbody>
<tr>
<td>Cholesterol side chain cleavage</td>
<td>Desmolase; P450scc</td>
<td>CYP11A1</td>
<td>all</td>
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<tr>
<td>21α-hydroxylase</td>
<td>P450c21</td>
<td></td>
<td>fasciculate and glomerulosa</td>
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<td>fasciculate and glomerulosa</td>
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<tr>
<td>Aldosterone synthase</td>
<td>P450aldo</td>
<td>CYP11B2</td>
<td>glomerulosa</td>
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<tr>
<td>11β-HSD1 and 2</td>
<td>not P450 family</td>
<td>kidney (type 2)</td>
<td></td>
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</tbody>
</table>

Catecholamines: dopamine, norepinephrine, epinephrine (aka – adreneline)
Tyrosine hydroxylase is rate limiting step.
Pathway stops at dopamine in the dopaminergic neurons in brain.
Peripheral nerves convert dopamine to norepinephrine
Cortisol stimulates conversion of norepinephrine to epinephrine – only in adrenal medulla.

KEY CONCEPTS: THYROID
- The thyroid gland is made up of follicles = a layer of epithelial cells surrounding a central lumen.
- Thyroid hormones are made and stored in the lumen of the follicle.
- T4 is the primary thyroid hormone made, but it is largely inactive. T3 is the active form of thyroid hormone.
- Thyroid hormones are bound very tightly in plasma – very little ‘free’ hormone. Conversion from T4→T3→T2 takes place intracellularly at target sites.
- Thyroid hormone production is regulated by the HPT axis: Hi TRH; P = TSH
- The primary function of thyroid hormones in adults is to maintain basal metabolic rate.
**THYROID GLAND – FUNCTIONAL ANATOMY**

**Cellular components:**

- **Follicle:** epithelial cells surrounding lumen
  - lumen filled with colloid – 30% of thyroid mass, thyroglobulin (TG) is major component

- **Parafollicular cells ("C" cells):**
  - produce calcitonin
  - other proteins that maintain follicle

- **Other cells:**
  - Epithelial cells, fibroblasts, lymphocytes, adipocytes

**THYROID FOLLICLE IS FUNCTIONALLY POLARIZED**

- **Basolateral surface** exposed to blood
  - Iodine uptake “trap”
  - Thyroid hormone release

- **Apical surface** exposed to lumen (colloid)
  - Thyroid hormone synthesis
  - Iodination of TG

**THYROID GLAND**

- $\text{MIT} = \text{mono iodothyronine}$
- $\text{DIT} = \text{diiodothyronine}$
- $\text{MIT} + \text{DIT} = \text{T3}$
- $\text{DIT} + \text{DIT} = \text{T4}$
Thyroid Hormone – Peripheral Conversion

**Type I**
- Outer and inner ring deiodinase
- Liver, kidney, thyroid, skeletal muscle
- Primary source of T3 in circulation

**Type II**
- Outer ring deiodinase
- Brain, pituitary, placenta, cardiac muscle

**Type III**
- Inner ring deiodinase
- Brain, placenta, skin

**Key Facts**
- More T4 produced and stored in thyroid
- 80% of T4 is peripherally deiodinated to T3
- T4 has low receptor affinity
- Reverse T3 has no biological activity
- Type II deiodinase is the thyroid hormone “sensor” in the pituitary

THYROID HORMONE – RECEPTOR (THR)

Nuclear receptor family
- same as steroid hormones
- forms heterodimers with retinoic acid receptor (RXR)

Expressed in nearly every cell type
- High affinity, low capacity for T3
- Low affinity for T4 – very little biological activity at physiological concentrations
- D2 converts T4 to T3 intracellularly

THYROID GLAND

**Physiology of T3**

- Increases Basal Metabolic Rate
  - Stimulates hepatic gluconeogenesis
  - Stimulates proteolysis
  - Stimulates lipolysis
  - Overall increased energy/oxygen consumption, increased thermogenesis

- Increases Brain Maturation

- Increases β-adrenergic receptors; heart, skeletal muscle, adipose tissue
THYROID GLAND
Regulated by HPT axis – classic negative feedback
- Hypothalamus - TRH
- Pituitary – TSH
  • Note: high levels of TRH also stimulate prolactin

KEY CONCEPTS: PANCREAS
- The endocrine pancreas consists of 2 predominant cell types: beta cells (insulin) and alpha cells (glucagon).
- Insulin is regulated by blood glucose levels. High blood glucose causes insulin release. Insulin then promotes glucose uptake into skeletal muscle and fat cells.
- Insulin receptors are membrane receptor tyrosine kinases. These receptors activate multiple intracellular signaling pathways to promote mitogenic and anabolic actions.
- Insulin inhibits release of glucagon. When blood glucose drops, this inhibition is relieved and glucagon is released.
- Glucagon increases blood glucose levels by promoting the metabolism of stored carbohydrates and fats.
- There are other hormones that counter the effects of insulin, but under normal physiological conditions these are minor in comparison to glucagon.

PANCREAS - ANATOMY
Exocrine pancreas. Majority of cells. Acinar cells secrete digestive enzymes. "pancreatic juice" into the pancreatic duct.

PANCREAS

Insulin Synthesis – beta cells only

- Cleavage of C-peptide critical. Exposes end of insulin chain that interacts with the receptor.
- Insulin and C-peptide released together
- C-peptide half-life = 35 min.
- Good indicator of pancreatic function.

Glucagon Synthesis – alpha cells only

- Incretins: GLP1, GLP2 made in intestine only
- Released in response to low glucose
- Opposite effects of insulin

INSULIN RELEASE

1. Glucose enters beta cell
2. Glucose is phosphorylated by glucokinase (traps) inside the cell.
3. Metabolism of glucose generates ATP.
4. ATP closes the K⁺ channel.
5. Increased intracellular K⁺ depolarizes membrane.
6. Depolarization opens voltage-gated Ca²⁺ channels.
7. Ca²⁺ stimulates exocytosis of insulin containing vesicles.

GLUT-2 = LOW affinity for glucose. Only when glucose is high will it transport.

INSULIN RECEPTORS: RECEPTOR TYROSINE KINASES

- Autophosphorylation of receptor recruits IRSs (insulin receptor substrates).
- IRSs activate intracellular signaling cascades

- Utilization of glucose to ATP & anabolic pathways
- Storage of FFAs as TG
- Anabolic action on liver (e.g., PHL, DHA, tyrosine)
- Protein synthesis (e.g., PHB, DHA, tyrosine)
- Cell proliferation/neoplasia
**PANCREAS**

**Insulin Action - anabolic**

**Primary Targets:**

- Liver – fuel storage (glycogen, lipogenesis, proteins); inhibits gluconeogenesis
- Adipose Tissue – glucose uptake, stimulates triglycerides
- Muscle – glucose uptake – glycogen, proteins

When insulin is present:

- AA from protein stimulate GH which stimulates IGF-I (liver).
- IGF-I stimulates glucose uptake in muscle, proliferation of visceral organ tissues; inhibits proteolysis.
- GH opposes insulin lipogenesis.

**KEY CONCEPTS: PARATHYROID**

- The parathyroid glands are 4 paired glands located on the surface of the thyroid gland.
- The primary cell type is the Chief Cell – makes parathyroid hormone (PTH).
- PTH release is stimulated when Ca^{2+} levels decrease.
- PTH stimulates Ca^{2+} and inhibits P, reabsorption in the kidney. PTH stimulates Ca^{2+} release from the bone. PTH stimulates 1α-hydroxylase to convert Vitamin D precursor to its active form.
- Vitamin D is a secosteroid hormone derived from cholesterol conversion in skin.
- Vitamin D increases Ca^{2+} and P, reabsorption from intestine, mobilizes Ca^{2+} from bone, and inhibits PTH.
- Vitamin D is important for bone mineralization (hardness).
**PARATHYROID**

**Calcium regulation**

**PTH**:  
- Chief cells  
- Primary targets:  
  - Kidney – increases Ca reabsorption; inhibits phosphate absorption  
  - Bone – releases Ca from bone

**Vitamin D**  
- 1,25-(OH)\(_2\)D\(_3\), dihydroxycholecalciferol = active form  
- Primary targets:  
  - Chief cells – inhibits PTH (directly and indirectly)  
  - Bone – mobilizes Ca from bone  
  - Gut – increases Ca absorption, stimulates phosphate reabsorption

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**PTH - REGULATION**

Plasma calcium concentration primary regulator

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**PTH Target - Bone**  
- 99% body Ca\(^{2+}\) content is in bone

- PTH: Increases M-CSF and RANK-L in osteoblasts  
  **stimulates osteoclasts**

- Vit. D: Stimulates both osteoblasts and osteoclasts
Osteoprotegerin (OPG) antagonist of RANK ligand. Estrogens stimulate and Cortisol inhibits OPG

**CALCIUM HOMEOSTASIS – Integrated Response**

**HYPOCALCEMIA**

**HYPOPHOSPHATEMIA**

**VITAMIN D DEFICIENT**

<table>
<thead>
<tr>
<th>Regulator</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTH</td>
<td>Increase bone resorption and plasma Ca++</td>
</tr>
<tr>
<td>Vitamin D</td>
<td>Increase bone resorption, plasma Ca++, intestinal Ca++ uptake</td>
</tr>
<tr>
<td>Calcitonin</td>
<td>Decrease bone resorption and plasma Ca++</td>
</tr>
<tr>
<td>Sex steroids (estrogen)</td>
<td>Increase 1α-hydroxylase activity, net decrease bone loss</td>
</tr>
<tr>
<td>GH and IGF-I</td>
<td>Stimulates bone synthesis and growth</td>
</tr>
<tr>
<td>Thyroid hormone</td>
<td>Increases bone turnover</td>
</tr>
<tr>
<td>Prolactin</td>
<td>Increases renal Ca++ absorption and 1α-hydroxylase activity</td>
</tr>
<tr>
<td>Glucocorticoids</td>
<td>Increase bone resorption, decrease bone synthesis</td>
</tr>
</tbody>
</table>