

# PSL300 endocrine notes

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## 1 Homeostasis

Homeostasis is not necessarily equilibrium.

Steps for feedback control:

1. stimulus (something happens)
2. sensor/receptor (the body detects it somehow)
3. afferent pathway (signal passes from sensor to control box via wire)
4. integrating centre (decides what to do)
5. efferent pathway (signal of what you need to do)
6. target/effectector thing does what needs to be done
7. response (desired outcome)

can oscillate around set point, negative feedback only turns on outside of normal range.

### 1.1 Negative feedback loop

1. Stimulus
2. Response
3. stimulus to get back to from homeostasis
4. stabilized

#### Example 1: regulation of cortisol secretion

cortisol stimulated to be released. hypothalamus release CRH, stimulate anterior pituitary, stimulate AACTH, stimulate adrenal cortex, release cortisol into target tissue. cortisol suppresses release of both CRH and ACTH hormone.

### 1.2 Positive feedback loop

1. Stimulus
2. Response
3. stimulus to get away from homeostasis (reinforcing)
4. Turned off by *outside* factor

#### Example 2: Childbirth

For example childbirth. stretch, releases oxytocin, stretches, releases more and more until baby is released, NOT homeostatic.

## 1.3 Intercellular communication

### 1.3.1 Local control

#### Definition 1: Gap Junctions

Small channels connecting the cytoplasm of adjacent cells, formed by the alignment of hexameric protein assemblies (connexons). They allow passive diffusion of ions and small molecules down concentration or electrical gradients.

#### Example 3: Cardiac Myocytes

Heart muscle cells use gap junctions to propagate action potentials rapidly, enabling synchronized contraction.

#### Definition 2: Contact-Dependent (Juxtacrine) Signalling

Direct signaling via membrane-bound ligand on one cell binding a receptor on a neighbouring cell, with no release of a soluble factor.

#### Example 4: Notch–Delta Interaction

In developmental processes, Delta ligand on a “sending” cell binds Notch receptor on an adjacent “receiving” cell, influencing cell fate decisions.

#### Definition 3: Autocrine Signaling

A cell secretes signaling molecules that diffuse in the immediate extracellular space and bind receptors on the same cell, reinforcing self-stimulation.

#### Example 5: T-Cell Activation

Activated T-cells secrete interleukin-2 (IL-2) and respond to it themselves, promoting proliferation.

#### Definition 4: Endocrine (Hormonal) Signaling

Long-distance communication where hormones are released into the bloodstream and act on distant target cells bearing the appropriate receptor.

#### Example 6: Insulin Regulation

Pancreatic  $\beta$ -cells secrete insulin into the blood; insulin binds receptors on liver, muscle, and fat to lower blood glucose.

#### Definition 5: Synaptic (Neuronal) Signaling

A neuron releases neurotransmitter into a synaptic cleft (20–40 nm wide); the ligand binds postsynaptic receptors for rapid, point-to-point communication.

#### Example 7: Neuromuscular Junction

Motor neuron releases acetylcholine onto muscle fiber receptors, triggering contraction.

#### Definition 6: Paracrine Signaling

A cell secretes factors that affect nearby cells (typically within 100  $\mu\text{m}$ ) before being degraded or taken up.

#### Example 8: Wound Healing

Platelets release platelet-derived growth factor (PDGF) to recruit fibroblasts for tissue repair.

### 1.3.2 Comparison table

Mode	Range	Speed	Ligand Type	Example
Gap Junction	0 distance	<1 ms	Ions, small metabolites	Cardiac conduction
Juxtacrine	Cell-cell	Seconds	Membrane proteins	Notch-Delta
Autocrine	$\leq 10 \mu\text{m}$	Seconds-minutes	Growth factors, cytokines	T-cell IL-2 loop
Paracrine	$\leq 100 \mu\text{m}$	Seconds-minutes	GF, NO, PG	Wound repair (PDGF)
Endocrine	Body-wide	Seconds-hours	Hormones	Insulin/glucagon
Synaptic	Nanometers	<1 ms	Neurotransmitters	Neuromuscular junction

## 1.4 Neurohormones

Neurotransmitters are chemicals secreted by neurons that diffuse across small gap to cell; Neurohormones are chemicals released by neurons

## 1.5 Endocrine system

Endocrine glands or cells release hormone through blood stream, only the cells of right receptors provide a response.

## 1.6 simple and complex reflexes

simple reflexes are mediated by either nervous or endocrine system, Complex mediated by both systems. Local control just has stimulus and response.

1. neural reflex terminates on single target cell or very local area
  2. electrical through nerve, then chemical cell to cell
  3. very fast and short, if need long, mediated by neuromodulators
  4. identical in strength
- 
1. endocrine, most cells exposed to hormone
  2. chemical cells in blood
  3. distribution of signal and onset of action much slower than in neural, last longer
  4. intensity correlated with amount of hormone secreted

## 2 hormones

One hormone can act on multiple tissues, alter activity of target cells. should have negative feedback to maintain homeostasis. initial identification by AA berthold: Process: remove gland that you think secretes hormone, replace gland, purify extract to determine effect of hormone.

### 2.1 Hormone types

1. Hydrophilic hormones: water soluble, can dissolve in plasma. not lipid soluble, cannot cross plasma membranes (lipid bilayer). Examples: peptides, proteins, catecholamines. **secreted by exocytosis**) made in advance, stored in vesicles
2. hydrophobic (lipophilic, do not dissolve in plasma. steroid, thyroid, etc. almost all 99% are bound to a carrier protein to travel through blood stream (some are free). secreted by diffusion, so only made on demand because it can't really be stored.

### 3 main types:

1. class 1 peptide/protein (3 or more amino acids) chains of amino acids. e.g. insulin
2. steroids (ALL derived from cholesterol (incl. estrogen)). only type that hydrophobic
3. amines derived from single amines

## 2.2 peptide/protein hormones

most hormones are of this type, they're made in advance. synthesized like secreted proteins. short half life in plasma. first protein created to encode hormone has signal sequences. created in ER via ribosome. preprohormone has other stuff incl hormone, then cleaved off into prohormone then pinched off, processed in Golgi complex, then cleaved off. eventually released by exocytosis. original peptide can go through a lot of cleavages.

single preprohormone can contain multiple copies of same hormone, or different types of hormones. a preprohormone can have other peptide fragments too.

### Example 9: insulin

Insulin is made alongside c peptide, so you can measure secreted insulin levels by measuring c peptide levels.

## 2.3 Steroid hormones

Only synthesized from cholesterol. not stored in vesicles, made on demand. bound to carriers in blood. long half life, diffuse into target cells, or endocytosis of carrier proteins. can either bind to cell or membrane

## 2.4 Amine hormones

### Example 10: melatonin

synthesized from tryptophan, it can behave like both peptide or steroid secreted at night. govern biological clock. also an anti oxidant

Tyrosine catecholamines are like peptides, numerous enzymes involved in creating catecholamine, dopamine into adrenaline. synthesized in adrenal medulla. (in cytosol). stored in vesicles. released via exocytosis. water soluble. bind to membrane receptors. synthesized from adrenal medulla (middle). thyroid like steroids.

## 2.5 Control of hormone release

### Definition 7: Stimuli for Hormone Secretion

The initial trigger for hormone release may be:

- A metabolite (e.g., glucose stimulates insulin release).
- Another hormone (tropic control).
- A neurotransmitter acting on an endocrine cell.

### Definition 8: Signal Transduction Mechanisms

Endocrine cells convert an external stimulus into hormone secretion via:

- Changes in membrane potential.
- Increases in cytosolic  $\text{Ca}^{2+}$ .
- Modulation of enzymatic activity.
- Enhanced transport of hormone precursors into the cell.
- Altered transcription of genes encoding hormones or processing enzymes.
- Promotion of endocrine cell survival and growth.

### Example 11: Glucose-Stimulated Insulin Release

1. Glucose enters the  $\beta$ -cell via GLUT2 transporters.
2. ATP/ADP ratio rises, closing ATP-sensitive  $K^+$  channels.
3. Membrane depolarization opens voltage-gated  $Ca^{2+}$  channels.
4.  $Ca^{2+}$  influx triggers exocytosis of insulin-containing granules.

### Definition 9: Hypothalamic–Pituitary Axis

A hierarchical endocrine control system:

- The hypothalamus secretes releasing/inhibiting hormones into the portal circulation.
- These act on the anterior pituitary to regulate tropic hormone release.
- Tropic hormones travel to peripheral endocrine glands, stimulating hormone output.
- A negative feedback loop typically inhibits upstream release.

### Example 12: Anterior vs Posterior Pituitary

- **Anterior pituitary** synthesizes and secretes its own hormones (e.g., ACTH, GH).
- **Posterior pituitary** stores and releases neurohormones (oxytocin, vasopressin) made in the hypothalamus and is **not** a true endocrine gland.

## 2.6 Hormone Interactions

### Definition 10: Synergistic Effects

Two or more hormones act together to produce a combined effect greater than the sum of their separate effects.

### Example 13: FSH and Testosterone

FSH and testosterone together promote spermatogenesis more effectively than either hormone alone.

### Definition 11: Permissive Effects

One hormone enhances the responsiveness of a target tissue to a second hormone that arrives later.

### Example 14: Thyroid Hormone and Epinephrine

Thyroid hormone upregulates  $\beta$ -adrenergic receptors in adipose tissue, increasing the lipolytic response to epinephrine.

### Definition 12: Antagonistic Effects

One hormone opposes the action of another, either by competing for receptors or by inducing opposite physiological effects.

### Example 15: Insulin vs Glucagon

Insulin lowers blood glucose by promoting uptake and storage, whereas glucagon raises blood glucose by stimulating glycogenolysis and gluconeogenesis.

## 3 Receptors and signalling

hormones bind to receptor, changes conformation and activity of receptor, leads to synthesis or modification of proteins.

1. large protein

2. families
3. can be multiple receptors for one ligand variable number in target cell, 500-100,000
4. activated and inhibited
5. in cell membrane, cytoplasm, and nucleus
6. high affinity, saturable
7. specific and reversible

## 4 Intracellular (Cytosolic & Nuclear) Hormone Receptors

Lipid-soluble hormones—including steroid hormones (cortisol, estrogen, testosterone), thyroid hormones ( $T_3/T_4$ ), vitamin D derivatives, and retinoids—diffuse across the plasma membrane to interact with receptors located inside the cell. These receptors fall into two major classes:

### 4.1 Cytosolic Receptors (Type I Nuclear Receptors)

**Location & Chaperones** In the absence of hormone, receptors reside in the cytosol bound to heat-shock proteins (e.g., HSP90).

**Ligand Binding** Hormone binding causes dissociation of the chaperones and receptor dimerization.

**Nuclear Translocation** The hormone–receptor complex translocates to the nucleus.

**DNA Interaction** In the nucleus, the dimer binds Hormone Response Elements (HREs) in target gene promoters.

**Transcriptional Modulation** Recruitment of coactivators or corepressors alters transcription of downstream genes.

### 4.2 Constitutive Nuclear Receptors (Type II Nuclear Receptors)

**Prebound to DNA** Receptors (e.g., thyroid hormone receptor, retinoic acid receptor) are already bound to HREs in the nucleus, often associated with corepressors.

**Ligand-Induced Switch** Hormone binding releases corepressors and recruits coactivators.

**Chromatin Remodeling** Histone acetylation and other modifications open chromatin.

**Gene Regulation** Transcription of target genes is up- or down-regulated.

### 4.3 Mechanisms & Effects

#### 4.3.1 Genomic (Classical) Pathway

- **Onset:** Slow (hours to days).
- **Action:** Direct alteration of gene transcription, leading to changes in mRNA and protein synthesis.
- **Physiological Example:** Upregulation of gluconeogenic enzymes by glucocorticoids.

#### 4.3.2 Non-Genomic (Rapid) Actions

- **Onset:** Rapid (seconds to minutes).
- **Mechanisms:**
  - Interaction of receptors with membrane-associated signaling complexes.
  - Activation of kinase cascades (e.g., MAPK, PI3K) or second messengers (cAMP,  $\text{Ca}^{2+}$ ).
  - Modulation of ion channels and cytoskeletal elements.
- **Functional Impact:** Allows cross-talk with other signalling pathways and immediate cellular responses.

## 5 Examples of Intracellular Receptor Signalling

### 5.1 Glucocorticoid Receptor (GR)

- **Ligand:** Cortisol
- **Genomic Effects:**
  - Induces anti-inflammatory genes (e.g., Annexin-1).
  - Represses pro-inflammatory transcription factors (e.g., NF- $\kappa$ B).
- **Non-Genomic Effects:**
  - Membrane-associated GR can inhibit platelet aggregation.

### 5.2 Thyroid Hormone Receptor (TR)

- **Ligands:** T<sub>3</sub>, T<sub>4</sub>
- **Constitutive Binding:** Prebound to DNA with corepressors.
- **Upon T<sub>3</sub> Binding:** Release of corepressors, recruitment of histone acetyltransferases, increased transcription of metabolic genes.

### 5.3 Vitamin D Receptor (VDR)

- **Ligand:** 1,25-Dihydroxyvitamin D<sub>3</sub>
- **Target Genes:**
  - *Calbindin* in intestinal epithelium (calcium absorption)
  - Genes regulating immune cell differentiation

## 6 G proteins

G proteins are heterotrimeric molecular switches composed of an  $\alpha$ -subunit (binds GDP/GTP), a  $\beta$ -subunit, and a  $\gamma$ -subunit. They couple G-protein-coupled receptors (GPCRs) to a variety of downstream effector enzymes and ion channels.

### 6.1 Activation Cycle

1. **Resting state:**  $\alpha$ -subunit bound to GDP associates with  $\beta\gamma$  to form an inactive trimer.
2. **Receptor activation:** Ligand binding induces a conformational change in the GPCR, which acts as a guanine nucleotide exchange factor (GEF).
3. **GDP/GTP exchange:** GDP is released from  $\alpha$ , GTP binds, and  $\alpha$  undergoes a conformational shift.
4. **Dissociation:**  $\alpha$ -GTP dissociates from the  $\beta\gamma$  dimer.
5. **Effector modulation:**  $\alpha$ -GTP and/or  $\beta\gamma$  interact with downstream targets.
6. **Termination:** Intrinsic GTPase activity of  $\alpha$  hydrolyzes GTP to GDP (often accelerated by RGS proteins), allowing reassociation with  $\beta\gamma$ .

### 6.2 $G_q$ Pathway

- **Alpha subunit:**  $\alpha_q$  (stimulatory).
- **Effector:** Phospholipase C- $\beta$  (PLC $\beta$ ).
- **Reaction:**



- **Second messengers:**

- **IP<sub>3</sub>:** Binds IP<sub>3</sub> receptors on the endoplasmic reticulum, causing Ca<sup>2+</sup> release.

- **DAG:** Remains in the plasma membrane and, together with elevated  $\text{Ca}^{2+}$ , activates Protein Kinase C (PKC).
- **Outcome:** PKC phosphorylates downstream targets; raised cytosolic  $\text{Ca}^{2+}$  regulates enzymes, channels and gene expression.

### 6.3 $G_i$ Pathway

- **Alpha subunit:**  $\alpha_i$  (inhibitory).
- **Effector:** Adenylyl cyclase (AC).
- **Action:**  $\alpha_i$ -GTP binds AC and *inhibits* conversion of ATP to cyclic AMP (cAMP).
- **Secondary effects:**
  - Lower cAMP → reduced Protein Kinase A (PKA) activity.
  - $\beta\gamma$  subunits can open GIRK ( $\text{K}^+$ ) channels, inhibit voltage-gated  $\text{Ca}^{2+}$  channels, or engage PI3K.
- **Outcome:** Decreased phosphorylation of PKA targets; modulation of ion flux and cell excitability.

### 6.4 $G_s$ Pathway

- **Alpha subunit:**  $\alpha_s$  (stimulatory).
- **Effector:** Adenylyl cyclase (AC).
- **Action:**  $\alpha_s$ -GTP *stimulates* AC, converting ATP into cAMP.
- **Second messenger cascade:**

$$\text{ATP} \xrightarrow{\text{AC}} \text{cAMP} \xrightarrow{\text{PKA}} \text{PKA-P targets}$$
- **PKA targets:**
  - Metabolic enzymes (e.g. glycogen phosphorylase kinase, hormone-sensitive lipase).
  - Transcription factors (e.g. CREB).
  - Ion channels (e.g. L-type  $\text{Ca}^{2+}$  channels in cardiac myocytes).
- **Examples:**
  - $\beta$ -adrenergic receptors in heart and adipose tissue.
  - Glucagon receptor in hepatocytes.

## 7 Calcium

critical for intracellular signalling, hormone secretion, blood clotting, neural excitability, build/maintain bone. most in extracellular matrix (bone) 0.1% ECF, 0.9 percent cells. can go in and out of ECF first (into intestine and also in/out of kidney). bone is mostly crystals: hydroxyapatite.

1. osteoblasts (form cells)
2. osteoclasts break bone (much bigger than osteoblasts). attach to bone matrix like suction cup, ruffled. they secrete HCl, eats away at bone. also secrete proteases (enzyme) that desolves bone. ionized Calcium then enters blood stream. **carbon dioxide + water, catalyzed by CA (carbonic anhydrase) creates H ion and bicarbonate.** free proton combines with chloride from bloodstream to create HCl.
3. osteocytes (osteoplasts surrounded by bone matrix, just maintain bone).

Bone dynamic (over 100 days). 3 weeks of osteoclasts break, then 3 months of osteoblasts replacing. osteoblasts promote osteoclast formation. osteoblasts has RANKL (rank ligand), and osteoclast precursor has receptor activator of nuclear factor kappa B (RANK). connects to rankL. but osteoprotegerin (OPG) is kinda like a condom, prevents RANKL from bonding with rank. after differentiating and fusion, get 3 nuclei osteoclast.

### Example 16: Denosumab Mimics OPG

Osteoprotegerin (OPG) is a soluble “decoy” receptor that binds RANKL, preventing it from activating RANK on osteoclast precursors and thus inhibiting bone resorption.

Denosumab is a fully human monoclonal antibody against RANKL. By binding RANKL with high affinity, denosumab acts just like OPG:

- It sequesters RANKL in the bone microenvironment.
- It prevents RANK–RANKL interaction on osteoclasts and their precursors.
- It thereby decreases osteoclast formation, function, and survival.

*In effect, denosumab serves as a pharmacologic OPG surrogate, reducing bone turnover and increasing bone mass.*

## 7.1 Hormones Controlling Plasma Calcium Homeostasis

The following hormones tightly regulate ionic calcium ( $[Ca^{2+}]$ ) levels in the blood by coordinated actions on bone, kidney, and intestine.

### 1. Parathyroid Hormone (PTH)

- *Source:* Chief cells of the parathyroid glands.
- *Stimulus for release:* Low plasma  $[Ca^{2+}]$ .
- *Receptor:* PTH1R, a  $G_s$  (and to a lesser extent  $G_q$ )-coupled receptor.
- *Actions:*
  - **Bone:** Binds osteoblasts to  $\uparrow$ RANKL and  $\downarrow$ OPG, promoting osteoclast differentiation and bone resorption  $\rightarrow$  release of  $Ca^{2+}$  and phosphate.
  - **Kidney:**
    - \*  $\uparrow$ Proximal tubular  $Ca^{2+}$  reabsorption.
    - \*  $\downarrow$ Proximal tubular phosphate reabsorption (“phosphate diuresis”).
    - \*  $\uparrow$  $1\alpha$ -hydroxylase activity  $\rightarrow$   $\uparrow$ calcitriol synthesis.
  - **Intestine (indirect):** Via  $\uparrow$ calcitriol, enhances dietary  $Ca^{2+}$  absorption.

### 2. Calcitriol (1,25-Dihydroxyvitamin D<sub>3</sub>)

- *Source:*
  - (a) Skin: UV-B-mediated conversion of 7-dehydrocholesterol  $\rightarrow$  cholecalciferol (vitamin D<sub>3</sub>).
  - (b) Liver: 25-hydroxylation  $\rightarrow$  25-hydroxyvitamin D<sub>3</sub>.
  - (c) Kidney: PTH-stimulated  $1\alpha$ -hydroxylation  $\rightarrow$  active calcitriol.
- *Receptor:* Vitamin D receptor (VDR), a nuclear transcription factor.
- *Actions:*
  - **Intestine:**  $\uparrow$ Expression of TRPV6, calbindin, and PMCA pumps  $\rightarrow$   $\uparrow$  $Ca^{2+}$  and phosphate absorption.
  - **Kidney:**  $\uparrow$ Distal tubular  $Ca^{2+}$  reabsorption.
  - **Bone:** At high levels, synergizes with PTH to promote osteoclastogenesis; at basal levels supports mineralization.

### 3. Calcitonin

- *Source:* Parafollicular (C) cells of the thyroid gland.
- *Stimulus for release:* High plasma  $[Ca^{2+}]$ .
- *Receptor:*  $G_s$ -coupled calcitonin receptor on osteoclasts and renal tubular cells.
- *Actions:*
  - **Bone:** Inhibits osteoclast activity and reduces bone resorption.
  - **Kidney:** Decreases renal  $Ca^{2+}$  and phosphate reabsorption.

These hormones act in concert to adjust calcium flux between the intestine, kidneys, and bone, thereby maintaining plasma  $[Ca^{2+}]$  within a narrow physiological range.

## 7.2 Effect of calcium homeostasis misses

hypercalcaemia (too much)

1. GROANS (constipation)
2. MOANS (fatigue, lethargy)
3. BONES bone pain
4. STONES kidney
5. psychiatric overTONES (depression)

hypocalcaemia (too little)

CATS:

1. Convulsions
2. Arrhythmias
3. Tetany
4. Spasms, seizures, stridor

## 8 Fluid balance

55 percent of person is water. 2/3rds is in cell (ICF). 1/3rd is ECF. 75 percent of that is interstitial. 25 percent is in plasma. Intake 2.2 L of water a day, produces like 0.3 L a day. Urinate approximately 1.5L a day. Sweat, breath losses at about 0.9 L a day. Not enough water means less ECF, and lower blood pressure.

### 8.1 How is urine produced

blood goes into kidneys, filtered at nephrons. becomes urine. leaves through the ureter. in nephron: 1500 litres a day of blood comes in, filtered through. Most gets reabsorbed. some gets secreted. 180 L of filtrate is formed. 1.8L of urine day (1 percent of total filtrate). Nephron is responsible for vitamin D (via PTH). also pH, electrolytes, etc.

### 8.2 Urine hormones

vasopressin (ADH, or anti urinating) synthesized in brain (hypothalamus) secreted from posterior pituitary. increases water reabsorption in kidneys, tells them to conserve body water. and also increases blood volume and pressure. regulates permeability of kidney cells. **stimulus:** osmolarity (most common). with high plasma osmolarity or “saltiness”, wants to dilute it, so it conserves water inside. Can also be triggered by low blood pressure. High osmolarity gives you feelings of thirst through hormone secretion. Vasopressin in blood binds to receptor releases cAMP. signal cascade into aquaporin 2 water pores sitting in cells. then bind to inside of nephron. into collecting duct lumen

### 8.3 Aldosterone

Aldosterone is the principal mineralocorticoid steroid hormone, synthesized by the zona glomerulosa of the adrenal cortex. It acts on the distal nephron, colon and sweat glands to conserve sodium and excrete potassium, thereby regulating extracellular fluid volume and blood pressure.

- Regulation:

- *Stimuli for release:*
    - \* ↑ Plasma  $[K^+]$
    - \* Angiotensin II (RAAS)
    - \* ↓ Blood pressure / ↓ renal perfusion
  - *Negative feedback:*
    - \* Restored sodium balance and blood pressure
    - \* ↓ Plasma  $[K^+]$
  - *Inhibition:* High ECF osmolarity
  - *Half-life:* roughly 15 minutes

- **RAAS Cascade:**

1. Low blood pressure or sympathetic tone → juxtaglomerular cells release renin.
2. Renin cleaves liver-derived angiotensinogen → angiotensin I.
3. ACE (lung endothelium) converts angiotensin I → angiotensin II.
4. Angiotensin II:
  - Stimulates aldosterone release.
  - Vasoconstricts arterioles ( $\uparrow$  BP).
  - Acts on hypothalamus → thirst, ADH release.

- **Mechanism of Action:**

- Aldosterone diffuses into target cell → binds cytosolic mineralocorticoid receptor.
- Hormone-receptor complex translocates to nucleus → binds hormone response elements.
- Upregulates transcription of:
  - \* Epithelial  $\text{Na}^+$  channels (ENaC) in the apical membrane.
  - \*  $\text{Na}^+/\text{K}^+$ -ATPase in the basolateral membrane.
  - \*  $\text{K}^+$  channels for secretion.
- Net effect:  $\uparrow \text{Na}^+$  reabsorption (and passive water retention),  $\uparrow \text{K}^+$  secretion.

## 8.4 Natriuretic Peptides

The natriuretic peptides (ANP, BNP, CNP) are cardiac- and endothelium-derived hormones that lower blood volume and pressure by promoting natriuresis and vasodilation.

- **Sources:**

- ANP: atrial myocytes (stimulated by atrial stretch)
- BNP: ventricular myocytes ( $\uparrow$  in heart failure)
- CNP: vascular endothelium (paracrine)

- **Receptors & Signaling:**

- NPR-A/B: particulate guanylyl cyclase →  $\uparrow$  cGMP.
- NPR-C: clearance receptor.

- **Actions:**

- *Kidney:*
  - \*  $\uparrow$  GFR via afferent dilation / efferent constriction.
  - \*  $\uparrow$  natriuresis and diuresis ( $\downarrow \text{Na}^+$  and water reabsorption).
  - \* Inhibit renin and aldosterone secretion.
- *Vascular:*
  - \* Direct vasodilation →  $\downarrow$  systemic vascular resistance.
- *Heart:*
  - \* Inhibit cardiac hypertrophy and fibrosis (BNP).

- **Physiological Role:** Protects against volume overload and hypertension by counterbalancing the RAAS and sympathetic nervous system.

## 9 Adrenal Gland

The paired adrenal glands sit atop the kidneys in the retroperitoneum. Each gland is composed of an outer cortex and an inner medulla, which derive from different embryologic tissues and secrete distinct hormones.

## 9.1 Adrenal Medulla

- **Origin:** Neural crest (sympathoadrenal lineage).
- **Control:** Direct innervation by preganglionic sympathetic fibers (“fight-or-flight”).
- **Principal hormones:**
  - *Epinephrine* (roughly 80%): via phenylethanolamine N-methyltransferase (PNMT).
  - *Norepinephrine* (roughly 20%).
- **Actions:**
  - ↑ Heart rate and contractility, ↓ peripheral resistance (via  $\beta_2$ -mediated vasodilation).
  - ↑ glycogenolysis, lipolysis, bronchodilation.
  - Clinical: EpiPen for anaphylaxis.

## 9.2 Adrenal Cortex

Covered by a fibrous capsule, the cortex contains three concentric zones:

### 1. Zona glomerulosa

- *Hormone:* Aldosterone (mineralocorticoid)
- *Regulation:* RAAS ( $\uparrow K^+$ , low BP)

### 2. Zona fasciculata

- *Hormone:* Cortisol (glucocorticoid)
- *Regulation:* CRH  $\rightarrow$  ACTH (negative feedback to hypothalamus & pituitary)

### 3. Zona reticularis

- *Hormones:* DHEA, androstenedione (weak androgens)
- *Role:* Precursor pool for peripheral sex steroid synthesis

All steroid hormones are synthesized from cholesterol via cytochrome P450 enzymes.

## 9.3 Androgens (DHEA, Androstenedione)

- **Source:** Zona reticularis.
- **Functions:**
  - *Males:* Prenatal differentiation of external genitalia, puberty growth spurts.
  - *Females:* Libido, pubic/axillary hair, peripheral conversion to estrogens.

## 9.4 Cortisol

- **Source:** Zona fasciculata.
- **Regulation:**

Hypothalamus  $\xrightarrow{CRH}$  Anterior pituitary  $\xrightarrow{ACTH}$  Adrenal cortex  $\xrightarrow{\text{cortisol}}$

with negative feedback at hypothalamus and pituitary.
- **Actions:**
  - ↑ Gluconeogenesis, protein catabolism, lipolysis.
  - Anti-inflammatory and immunosuppressive.
  - Chronic excess  $\rightarrow$  muscle wasting, osteoporosis, hyperglycemia.

## 9.5 Addison's Disease (Primary Adrenal Insufficiency)

- **Etiology:** Autoimmune destruction, infections, metastases.
- **Features:**
  - ↓ Aldosterone → hyponatremia, hyperkalemia, hypotension.
  - ↓ Cortisol → hypoglycemia, weight loss, fatigue.
  - ↑ ACTH → hyperpigmentation.
- **Treatment:** Lifelong glucocorticoid and mineralocorticoid replacement.

## 9.6 Cushing's Syndrome (Cortisol Excess)

- **Etiologies:**
  - ↑ ACTH (pituitary adenoma = Cushing's disease, ectopic ACTH).
  - Adrenal adenoma/carcinoma.
  - Exogenous glucocorticoids.
- **Clinical signs:** Central obesity, moon face, buffalo hump, skin striae, muscle weakness, osteoporosis, glucose intolerance.

# 10 Pancreas

## 10.1 Metabolism

- Basal metabolic rate (BMR): energy expenditure at rest, thermoneutrality, fasted
- Anabolism: synthesis of large molecules from smaller ones
- Catabolism: breakdown of large molecules into smaller ones
- Energy balance controlled by caloric intake and exercise

## 10.2 Metabolic Processes in Fed and Fasted States

- **Fed (absorptive) state:** anabolic; primary fuel = glucose
- **Fasted (post-absorptive) state:** catabolic; fuels = glucose, fatty acids
- Key pathways:
  - Glycolysis, TCA cycle, oxidative phosphorylation
  - Glycogenesis vs. glycogenolysis
  - Lipogenesis vs. lipolysis ( $\beta$ -oxidation)
  - Gluconeogenesis
  - Protein synthesis vs. degradation

## 10.3 Hormones of the Endocrine Pancreas

- **Insulin and Glucagon:** coordinate fed vs. fasting metabolism
- **GLP-1 and GIP:** incretin hormones that modulate insulin/glucagon
- Exocrine pancreas produces digestive enzymes and bicarbonate

## 10.4 Insulin

### General:

- Peptide hormone; binds receptor tyrosine kinase
- Lowers blood glucose; promotes anabolic pathways (glycogen, fat, protein synthesis)
- Enhances cell proliferation

### Mechanisms of Action:

- ↑ GLUT4 translocation (muscle, adipose)
- ↑ hexokinase activity (liver; GLUT2 transporter)
- Activates glycogenesis, lipogenesis, protein synthesis
- Inhibits glycogenolysis, gluconeogenesis, lipolysis

### Regulation of Secretion:

#### • Stimulators:

1. ↑ plasma glucose
2. Incretins (GLP-1, GIP)
3. ↑ plasma amino acids
4. Parasympathetic activity

#### • Inhibitor:

1. Sympathetic activity

## 10.5 Glucagon

### General:

- Secreted by pancreatic  $\alpha$ -cells; G-protein coupled receptor
- Counter-regulatory to insulin; prevents hypoglycemia

### Mechanism:

- Stimulates hepatic glycogenolysis and gluconeogenesis via cAMP cascade
- Permissive effects of cortisol and epinephrine

### Regulation of Secretion:

#### • Stimulators:

1. ↓ plasma glucose
2. ↑ plasma amino acids
3. Sympathetic activity

#### • Inhibitor:

1. GLP-1

## 10.6 GLP-1 (Glucagon-Like Peptide-1)

- Secreted by intestinal L-cells in response to nutrients
- ↑ insulin secretion, ↑  $\beta$ -cell mass, anorexigenic
- ↓ glucagon secretion, ↓ gastric emptying

## 10.7 Diabetes Mellitus

- **Type 1 (10%):** autoimmune  $\beta$ -cell destruction; treated with insulin
- **Type 2 (90%):** insulin resistance + relative insulin deficiency; diet, exercise, oral agents, sometimes insulin
- Uncontrolled Type 1 summary:
  1. No insulin  $\rightarrow$  no GLUT4  $\rightarrow$  hyperglycemia
  2. Glucosuria  $\rightarrow$  osmotic diuresis  $\rightarrow$  volume depletion  $\rightarrow$   $\uparrow$  ADH
  3. Ketogenesis  $\rightarrow$  acidosis  $\rightarrow$  hyperventilation
  4. Polyphagia, polydipsia, polyuria

## Review Questions

1. One hour after a meal, which would you expect?
  - (a) Gluconeogenesis in the liver.
  - (b) Lipolysis in fat cells.
  - (c) Protein synthesis in muscle.
  - (d) Glycogenolysis in the liver.
2. In Type 1 diabetes with excess insulin injection, you would observe:
  - (a) Release of ADH.
  - (b) Hyperglycemia.
  - (c) Fewer GLUT4 on membranes.
  - (d) Release of glucagon.
3. In severe hypoglycemia (e.g. blood glucose 2.5 mg/dL), the immediate treatment is:
  - (a) Insulin injection.
  - (b) **Glucagon injection.**
  - (c) GLP-1 injection.
  - (d) Vitamin D injection.

## 11 Growth and Thyroid hormones

### 11.1 Hypothalamic–Pituitary Axis

- **Posterior pituitary:** neural tissue; stores/secretes ADH (vasopressin) and oxytocin
- **Anterior pituitary:** endocrine tissue; secretes:
  - Prolactin
  - Thyrotropin (TSH)
  - Adrenocorticotropic hormone (ACTH)
  - Growth hormone (GH)
  - Follicle-stimulating hormone (FSH)
  - Luteinizing hormone (LH)
- Hypothalamic releasing/inhibiting hormones reach anterior pituitary via portal system

## 11.2 Growth Hormone (GH)

- **Regulation:**

- GHRH stimulates GH release
- Somatostatin (GHIH) inhibits GH release
- GH → liver → IGF-1 (insulin-like growth factor 1)
- **IGF-1 effects:** recruitment/proliferation of chondrocytes; bone and soft tissue growth
- **Physiologic factors for normal growth:**
  - GH, thyroid hormones, insulin, sex steroids
  - Adequate nutrition; absence of chronic stress

- **Pathologies:**

- *Gigantism:* GH excess in childhood
- *Acromegaly:* GH excess in adulthood

## 11.3 Thyroid Hormone (T3, T4)

**Synthesis:**

- Na<sup>+</sup>/I<sup>-</sup> symporter imports iodide
- Pendrin transports iodide into colloid
- Thyroglobulin synthesis; iodination by thyroid peroxidase → MIT, DIT
- Coupling: MIT+DIT → T3; DIT+DIT → T4
- Endocytosis of thyroglobulin; proteolytic release of free T3, T4

**Mechanism of Action:**

- Circulate bound to plasma proteins; T3 roughly 3–5× potency of T4
- T4 → T3 conversion in target tissues
- Nuclear receptors (thyroid receptor homodimers or heterodimers with RAR)
- Modulate gene transcription

**Physiologic Effects:**

- ↑ Basal metabolic rate, O<sub>2</sub> consumption, heat production
- ↑ Protein degradation, lipolysis
- CNS: ↑ speech, cognition, reflexes
- Growth and development (synergy with GH)
- Cardiovascular: ↑ heart rate, contractility; ↑ β-adrenergic receptors
- Muscular: excess → muscle weakness

## 11.4 Thyroid Hormone Regulation

- TRH (hypothalamus) → TSH (anterior pituitary) → T3/T4 (thyroid)
- Negative feedback by circulating T3/T4 on TRH/TSH

## 11.5 Thyroid Pathologies

- **Hyperthyroidism:**

- Causes: tumours; thyroid-stimulating immunoglobulins (Graves' disease)
- Symptoms: goiter, nervousness, insomnia, anxiety, tachycardia, exophthalmos, weight loss
- Treatments: partial thyroidectomy; antithyroid drugs; block T4→T3 conversion

- **Graves' Disease:**

- Autoimmune TSH-receptor antibodies
- Most common hyperthyroidism; goiter in developed countries

- **Hypothyroidism:**

- Causes: iodine deficiency; autoimmune destruction; underactive gland
- Symptoms: goiter, bradycardia, slowed speech, fatigue, cold intolerance, weight gain; cretinism in infants
- Treatment: exogenous T4 (thyroxine)

- **Cretinism (Infants):**

- Iodine deficiency → T3/T4 ↓ → ↑ TSH → thyroid growth (goiter)
- Global prevalence: 2 billion iodine deficient; 50 million symptomatic
- Public health: \$0.05/person/year for iodization

## 11.6 Review Question

1. A man is iodine deficient. Predict his TRH, TSH, and T3/T4 levels compared to normal.