

PHYSIOLOGY - ENDOCRINE

INTRODUCTION TO ENDOCRINE PHYSIOLOGY

Nervous system: one of the two major control systems for physiological integration of organ systems.

Processed communication through synapses → neurotransmitters bind receptors → coordinates activity of the whole body

Endocrine system: the second major control system. Secretes hormones that diffuse from cells and travel through the bloodstream.

Chemical messengers (hormones) travel through the bloodstream → bind to specific receptors on tissues → triggers specific response → coordinated activity of the whole body.

- Consists of the hypothalamus, thyroid, pituitary, parathyroid, adrenal, endocrine pancreas, ovaries, and testis.
- Classical endocrine glands are hormone producers.

Two types of secretions:

1. Exocrine: made by cells that secrete into lumen and travel to their distant location through ducts.
2. Endocrine: secretes hormones that diffuse into bloodstream and travel to their effector organ.

Modes of intercellular communication:

Endocrine signaling

Paracrine signaling

Autocrine signaling

HORMONES: extracellular chemical messengers produced and secreted by endocrine cells. Hormones bind to and activate highly specific receptors, which are either on or inside the target cell.

Hormone's function is to maintain and regulate:

- Growth and development (linear growth, coordination of organ growth)
- Internal environment/adaptation (allows maintenance of homeostasis)
- Energy production, storage, and utilization (digestion, metabolism)
- Reproduction

Peptide (protein) hormones: bind to cell surface receptors and act through second messengers, first messenger being the hormone. Made up of amino acid chains of varying lengths.

- Thyroid stimulation hormone, **insulin**, **growth hormone**, etc.

Steroid hormones: bind to intracellular receptors (ligand-activated transcription factors). Derived from cholesterol, which is a lipid, allowing steroid hormones to diffuse through the plasma membrane.

- **Estrogen**, **cortisol**, testosterone, **aldosterone**, etc.

Amino acid derivatives: mixed. Derived from tyrosine or tryptophan.

- Dopamine (binds cell surface receptor) and **thyroid hormones** (binds intracellular receptor)

PEPTIDE HORMONES

STEROID HORMONES

Hypothalamic-Pituitary Axis (HPA): controls many endocrine organs.

NEGATIVE FEEDBACK is the major physiologic mechanism regulating the HPA and keeps hormone levels within regulatory range.

GROWTH HORMONE (SOMATOTROPIN): peptide hormone secreted by the anterior pituitary. Essential for normal growth during child and adolescence (not responsible for growth of embryo) and plays a role in regulating metabolism in adults. Stimulates the expression of insulin-like growth factor 1 (IGF-1) in many different tissues.

IGF-1 (Somatomedin): mediates effect of growth hormone on linear growth. Potent mitogen (increases cell division) and differentiation factor.

- Released by many cell types in response to stimulation by growth hormone.
- Most circulating IGF-1 comes from the liver.

Actions of Growth Hormone

Regulation of Growth Hormone

Excess Growth Hormone

Acromegaly: results from excessive secretion of growth hormone in **adults**, usually the result of benign pituitary tumors (production of GH in a dysregulated way).

- Changes to face due to cartilage being responsive to excess GH (facial bones, nose, ears)
- Enlargement of the feet and hands
- No increased linear growth.

Giantism: the result of excessive growth hormone secretion that begins in **young children or adolescents**. Results in excessive linear growth. Very rare and typically resulting from a pituitary tumor.

Growth Hormone Deficiency

Pituitary dwarfism: GH deficiency in children if untreated.

- Mid-20th century: GH extracted from cadavers to treat GH deficiency → unsuccessful
- Mid 1980s: Genentech optimized protocols for producing recombinant human GH in bacteria. Isolated GH to conserve its biological function.
- GH is broken down in the gut, so GH replacement therapy is administered by injection.
- GH levels decline with age.

THYROID HORMONES AND ADRENAL CORTICAL HORMONES

THYROID HORMONES: regulate body growth and cellular metabolism.

Most cells of the body express receptors for thyroid hormones.

Thyroid disorders are very common, especially in women.

Thyroid follicles: store thyroid hormone.

Follicular cells: produce thyroid hormone.

Thyroid hormones require **iodine** in order to be active.

No iodine → no biological activity.

Thyroid follicular cells release:

T3: 90%. Has greater biological activity than T4.

- Binds with higher affinity and more potent.

T4: 10%. Converted to T3 inside target cells.

- Cells have enzymes that clip 4th iodine.

Thyroid hormones are unusual because:

- They are derived from amino acids, so they resemble peptide hormones.
- Chemical structure resembles that of steroid hormones.
- Thyroid hormones bind to nuclear receptors and regulate gene expression in their target cell similarly to steroid hormones.

SYNTHESIS OF THYROGLOBULIN AND THE RELEASE OF THYROID HORMONES

Negative Feedback Control of Thyroid Hormone Secretion

ACTIONS OF THYROID HORMONES ON TARGETS CELLS

During embryonic development and childhood:

- Regulate the timing of cellular differentiation.
- Critical role in the central nervous system.
- Contribute to the regulation of somatic growth during childhood.
- The absence of thyroid hormone can cause permanent, irreversible intellectual disability and dwarfism.

Throughout life:

- Increase basal metabolic rate.
- Regulate protein, fat, and carbohydrate metabolism.

Hyperthyroidism: autoantibodies bind and stimulate TSH receptors (**Graves Disease**). Autoantibodies mimic hormone and bind TSH receptors causing constant release of thyroid hormone.

Symptoms include:

- Anxiety, emotional lability, weakness, tremor, palpitations, **heat intolerance**, increased perspiration, and unintended weight loss despite normal or increased diet.
- Inability to concentrate (scattered thoughts) that interferes with work performance.
- Enlarged thyroid gland or goiter.
- Alterations to menstrual cycle or absence of menstruation in reproductive age women.
 - Underrecognized because symptom can be confused with menopause.
- **Grave's orbitopathy**: "protruding stare" – eyeballs protrude forward, and blinking is reduced. Present in 20-30% of patients.

Hypothyroidism:

Pathogenesis:

- May be congenital or acquired.
- Most common cause of acquired is Hashimoto or autoimmune thyroiditis (immune system attacks thyroid causing decrease in thyroid hormone production).
- Irradiation of thyroid gland or surgical removal of thyroid tissue (less common).
- Iodine deficiency – more common in poorer, landlocked (no access to seafood), mountainous countries (above shallow seas, no iodine in soil).

Clinical Manifestations:

- Decreased basal metabolic rate – decreased activity in all body systems.
 - Weakness, lethargy, cold intolerance, decreased appetite, bradycardia, and mild/moderate weight gain.
- Dry skin, constipation due to slowly of digestive system, depression and difficulties with memory, loss of (lateral) eyebrows, increased hair breakage due to dryness, menstrual irregularity.

Cretinism: combines intellectual impairment, dwarfism, and distinctive facial traits. Characterized by thyroid deficiency in embryonic development.

ADRENAL HORMONES

ALDOSTERONE: required for the maintenance of normal extracellular fluid volume. Regulates the volume of blood, and thus systemic blood pressure.

- Stimulated **Na⁺ reabsorption** and **K⁺ secretion** at the distal tubule.

CORTISOL: secreted in response to **stress** – trauma, infection, illness, temperature change, and mental stress.

- Helps the body cope with stress.
- Mobilizes glucose, amino acids, and fatty acids.
- Reduces inflammation.
- Follows a circadian rhythm – levels are highest in the morning and lowest in the evening.
 - Experience the most stress and change in the morning when our body is waking up.
 - Helps the body become alert in the morning and in reducing activity prior to sleep/

Hypercortisolism or Cushing's Syndrome: excess cortisol causes changes in fat concentration and skin.

- Fat gets reconcentrated to abdomen.
- Poor wound healing and easy bruising.
- Moon face with red cheeks
- Thinning of the skin and muscle wasting.
- Hypertension.
- Cataracts

Key points: Thyroid Hormones

Thyroid hormone secretion is regulated by hormones from **hypothalamus AND pituitary gland**, through a negative-feedback pathway.

Thyroid hormones require **iodine** to be biologically active. Iodine deficiency → thyroid hormone deficiency.

- Deficiency during embryonic development has devastating consequences.

Thyroid hormones regulate the activities of cells in all organs, so symptoms are diverse.

Most common cause of thyroid disorders are **autoimmune**. Hypo = Hashimoto's. Hyper = Grave's Disease.

Key Points: Adrenal Hormones

The cortex of the adrenal gland has a layered structure, with different zones specializing in the production of different steroid hormones.

Aldosterone, from the **zona glomerulosa**, has a key role in regulating Na⁺ and K⁺ levels, and thus water loss/reabsorption from the kidney, and thus total blood volume and blood pressure.

Cortisol, from the **zona fasciculata**, is one of the major "stress response" hormones, and regulates metabolism, inflammation, and wakefulness.

Cortisol work in opposition to **insulin** by mobilizing stored glucose and increased blood glucose levels.

BLOOD GLUCOSE REGULATION

It is important to maintain the concentration of glucose in the blood within a specific range because our body is constantly needed energy that is supplied from glucose.

- Body transitions between feeding and fasting states. Body utilizes glucose that is being consumed when feeding and stores excess as glycogen. Glycogen is broken down and glucose is released for energy during fasting states.'

Hypoglycemia: decreased glucose. May result in clumsiness, confusion, loss of consciousness, seizures, or death.

Hyperglycemia: increased glucose. Chronic can damage the vessels that supply blood to important organs, like the heart, brain, kidneys, eyes, and nerves.

- This leads to increased risk of heart attack, stroke, kidney failure, blindness, amputation, and chronic pain.

The pancreatic hormones insulin and glucagon are the most important hormones that control the blood glucose concentration.

INSULIN: promotes uptake of glucose by target cells, and utilization of glucose as an energy substrate.

GLUCAGON: promotes mobilization of stored glucose and increase in blood glucose levels. Breaks down glycogen and releases glucose.

PANCREAS

ISLETS OF LANGERHANS

SYNTHESIS AND STORAGE OF INSULIN WITHIN B ISLET CELLS

REGULATED SECRETION OF INSULIN

Net effect of insulin receptor activation in target cells:

In liver: increased storage of glucose as glycogen, increased storage of lipids, and increased synthesis of proteins.

In muscle: increased uptake of glucose via GLUT 4. Glucose may be stored as glycogen OR broken down for use in the citric acid cycle.

In adipocytes: increased uptake and breakdown of glucose.

Hormones that act in OPPOSITION to insulin:

1. Glucagon: from the islet alpha cells and intestinal L cells.
 - a. Stimulates breakdown of glycogen into glucose that can be used by cells when fasting.
2. Catecholamines (epinephrin and norepinephrine): from adrenal medulla
 - a. Moves stored glucose into blood
3. Cortisol: from the adrenal cortex.
 - a. Stress response. Moves stored glucose back into blood.
4. Growth Hormone: from the pituitary gland.
 - a. Important role in metabolism to mobilize glucose out of stored form to protect protein from being used for energy.

Fed State

Fasting State

Type 1 Diabetes

Type 2 Diabetes

Type 1 Diabetes Mellitus: characterized by destruction of the beta cells of the pancreas. Results in absolute insulin deficiency.

- Usually diagnosed between 5 and 20 years of age.
- Immune mediated (recognize proteins on B-islet cells as foreign) or idiopathic (no autoantibodies. Removal of pancreas).

Glucose levels rise, lead to **polyuria** (increased urination), **polydipsia** (thirst), and **polyphagia** (hunger).

Treatment: insulin injections

Untreated: patients die due to combined effects of dehydration and ketoacidosis.

- Ketoacidosis: liver breaks down fat and proteins to provide energy substrates and converts fatty acids to ketone bodies that are acidic. Excessive ketones cause metabolic acidosis.

Diagnosis: oral glucose tolerance test.

Type 2 Diabetes Mellitus: problem starts with insulin resistance and can lead to B cell exhaustion and the cells start to degenerate. Not a pancreas defect but defect in the responsiveness of the target cells.

- Most common form of DM.
- Non-white and elderly disproportionately affected.
- Overweight and obese individuals have a much greater risk than normal weight individuals.

Glycated Hemoglobin: hemoglobin A1C. Used as a bio-indicator of poorly controlled blood glucose. DECREASE in hemoglobin A1C correlates with INCREASED glucose reabsorption by the body.

Chronic Diabetes Complications:

- Microvascular disease
 - Nephropathy, neuropathy, and retinopathy.
- Macrovascular disease
 - Coronary artery disease, cerebrovascular disease, and peripheral vascular disease.
- Associated complications
 - Foot ulcers (can lead to amputation)
 - Infections that are harder to treat.

Role of Stress in Diabetic Patients

Illness, infection, or psychological stress → increased stress hormones (cortisol and catecholamines) → increase production of glucose in the liver → hyperglycemia.

- Diabetic patients need to follow “sick day rules” so that stress does not seriously worsen their existing condition.

Type 1 Diabetes vs. Type 2 Diabetes

Key Points:

Multiple hormones act to regulate the levels of blood glucose in response to feeding and fasting.

Insulin promotes the uptake and storage of glucose following a meal.

Glycogen (and several other hormones) act to liberate stored glucose during periods of fasting.

In Type 1 Diabetes, the B cells of the pancreas are damaged and unable to make sufficient amounts of insulin, so that chronic hyperglycemia results.

In Type 2 Diabetes, the target cells of insulin become unresponsive, leading to chronic hyperglycemia.

- The complications of long-term, chronic hyperglycemia include increased risk of stroke, heart attack, blindness, limb amputation and chronic pain.

CALCIUM HOMEOSTASIS

Role of Calcium:

- Muscle Contractility: an increase in cytosolic calcium allows actin filaments to bind myosin, promoting contraction.
- Synaptic transmission: an influx of calcium allows synaptic vesicles to dock at the membrane and release neurotransmitter.
- Blood clotting: requires the presence of calcium in blood plasma.
- Many other types of vesicle fusion require an influx of calcium.

Extracellular calcium levels must be maintained within special limits.

BONES: major reservoir of calcium because of the calcium-and-phosphate rich hydroxyapatite crystals that provide mechanical strength to the bone.

Osteoblasts: build bone. Deposit bone matrix, which stores large amounts of calcium.

Osteoclasts: carve bone. Remove bone matrix, liberating stored calcium into the extracellular fluid. Form a tight seal with matrix and scrape away at it.

Osteocyte: osteoblasts that are stuck in bone.

Calcium in Extracellular Fluid – ionic calcium is biologically active form.

PARATHYROID HORMONE (PTH): is essential for life. Peptide hormone synthesized in chief cells of the parathyroid glands. The physiological function of PTH is to increase plasma calcium.

- PTH secretion is controlled primarily by circulating levels of ionized calcium.

Serum calcium → PTH secretion (5-fold)

Plasma calcium → PTH secretion rapidly

Parathyroid Hormone-Related Peptide (PTH-RP): present in everyone but increased levels are discovered in people with malignancies.

Pathological role – increased humoral hypercalcemia of malignancy mostly in tumors of the lung, head, and neck. PTH-RP mimics PTH but has a decreased effect.

Effects – same as PTH at the bone and kidney but less likely to stimulate 1,25-(OH)₂-D formation, so had less effect at the gut.

Physiological role – teeth eruption, mammary gland development, and lactation.

CALCITONIN: peptide hormone secreted by parafollicular cells of the thyroid.

Effects – opposes the effect of PTH at bone, kidney, and gut. Overall effect is to decrease serum calcium.

- Not a major factor in calcium homeostasis OR in calcium disorder because it's not very potent.
- Marker for monitoring for medullary thyroid cancer recurrence.

DIHYDROXY VITAMIN D: functions as a steroid hormone. Vitamin D exists as D2 and D3. VD2 is obtained in the diet, largely from vegetables and VD3 is made in the skin, in a reaction that requires UV light. VD3 is available from dietary sources and fortified milk.

The biologically active form of vitamin D is neither D2 nor D3, but rather a dihydroxylated metabolite of either one.

Vitamin D deficiency: results in weak bones in children and causes [rickets](#). When vitamin D levels are low, absorption of dietary calcium is very inefficient, PTH levels are high, osteoclasts are active and bone mineralization is poor.

- Bones are growing but not hardening causing deformities due to body weight.
- In the US, milk and some other foods are now supplemented with vitamin D.

Hyperparathyroidism: increase in parathyroid hormone causing increased rates of bone reabsorption.

Causes: idiopathic, genetic, parathyroid adenoma, and chronic renal failure.

Clinical manifestations: many patients are asymptomatic. “Stones (calcifications), bones (osteoporosis), groans, thrones (change in bathroom habits), and psychiatric overtones.”

Kidney failure induces hyperparathyroidism

Hypoparathyroidism: rare. Causes “neuromuscular instability” – irregular heartbeat, muscle twitching, possibly tetany or bronchial spasm, possibly numbness or tingling in lips or finger.

Etiology and pathogenesis:

- May be idiopathic, autoimmune, or congenital.
- Secondary: parathyroid or thyroid surgery. May be temporary or permanent.

KEY POINTS:

Ion calcium must be maintained within a specific physiologic range for proper functioning of the nervous system, appropriate contractility of muscle, normal blood clotting, and functioning of secretory cells.

Two key hormones regulate calcium levels in humans: **parathyroid** and **1,25-(OH)2D**

1. **Parathyroid hormone** is secreted by chief cells of the parathyroid glands in response to low levels of calcium in the plasma and interstitial fluid.
 - a. Acts to mobilize stored calcium from bone, decrease calcium loss in urine, and increase the levels of biologically active **1,25-(OH)2D**.
2. **1,25-(OH)2D** arises by sequential hydroxylation's of Vitamin D within the liver and kidney.
 - a. Acts primarily to increase calcium absorption in the small intestine.

REPRODUCTIVE ENDOCRINOLOGY

MENSTRUAL CYCLES: serve to synchronize events in ovary and uterus. Makes sure endometrium is thicken, with good blood supply and prepared for fertilization and implantation.

- Most mammals reabsorb the uterine lining instead of shedding it.
- Most mammals time their fertility seasonally, whereas humans have monthly fertility.

The menstrual cycle lasts an average of 28 days and involves:

1. Menstruation: shedding of endometrial lining of the uterus from the previous cycle (Day 1-5). First day of bleeding.
2. Follicular (ovary)/Proliferative (endometrium) phase: **estrogen dominated**. Growth and maturation of the follicles. Proliferation of the endometrial lining (day 6-14). Estrogen acts on endometrial lining by thickening it.
3. Ovulation: discharge of ovum (day 14-15).
4. Luteal/Secretory phase: **progesterone dominated**. Follicle remnants converted to corpus luteum. Endometrial lining develops secretory glands.

GONADOTROPIN RELEASING HORMONE: dipeptide that stimulates **LH** and **FSH** production. Released in pulsatile fashion into portal blood vessels from hypothalamus.

- Low frequency pulses favor FSH.
- High frequency pulses favor LH.

Ovarian Steroidogenesis: 2 Cells and 2 Gonadotropins

Early to Mid-Follicular

Late Follicular through Ovulation

Menstruation or Menses: towards the end of luteal/secretory phase, circulating concentrations of **estrogen** and **progesterone** decline.

- In absence of hormonal maintenance, there is constriction of the spiral arteries supplying the endometrium.
- Blood vessels rupture, producing hemorrhage and sloughing off of cells.

If pregnancy does not occur: **lack of LH** leads to the degeneration of the corpus luteum, and thus a decline in the levels of progesterone and estrogen, leading to menses.

If pregnancy does occur: the developing placenta begins to secrete **human chorionic gonadotropin (hCG)** on day 7-8 post-conception to prevent menses.

HUMAN CHORIONIC GONADOTROPIN: closely resembles LH, and binds to the LH receptor, stimulating the corpus luteum to make progesterone and maintain endometrium.

- Maintaining corpus luteum causes it to continue secreting hormones, which is necessary to maintain pregnancy.
- By 8 weeks of gestation, the placenta takes over as the major source of steroid hormone and the corpus luteum is no longer needed.
 - Placenta acts as temporary endocrine organ.

By manipulating female reproductive hormones, ovulation (and thus conception) can be prevented.

Hormonal contraception is the most common form of contraception in the US.

- Synthetic estrogens and progestins, or progestin alone in some types of pills, exert negative feedback at the level of the hypothalamus and pituitary to suppress folliculogenesis and ovulation.
 - Both FSH and LH levels are kept low. No follicle development.

MALE REPRODUCTIVE ENDOCRINOLOGY

Gonadotropins regulate testicular functions.

- The targets for LH are the Leydig cells.
- The targets for FSH are the Sertoli cells.

There are bidirectional interactions between Sertoli cells and Leydig cells that are required for normal function of the male reproductive system.

Sertoli cells CANNOT synthesize testosterone, but they express abundant androgen receptor.

- Testosterone in the Sertoli cell is required for spermatogenesis.

Testosterone is synthesized in the Leydig cell, diffuses to the Sertoli cell, binds to ABP, and is concentrated there.

Major Functions of Androgens:

- Promotion of sexual maturation at puberty.
- Stimulation of spermatogenesis.
- Effects on psychology and sexual behavior.
- Formation of the male phenotype during sexual differentiation.

KEY POINTS

Production of estrogen by the ovary requires two cells" theca and granulosa.

Prolactin stimulates breast development and milk production, while oxytocin stimulates the release of milk.

Leydig cells of the testis produce testosterone, while the Sertoli cells require it to support spermatogenesis.

The default gender for a developing embryo is female, and a function testis is required to generate male phenotype.