The Endocrine System

- Endocrine and nervous systems work together
- Endocrine system
  - hormones released into the bloodstream travel throughout the body
  - results may take hours, but last longer
- Nervous system
  - certain parts release hormones into blood
  - rest releases neurotransmitters excite or inhibit nerve, muscle & gland cells
  - results in milliseconds, brief duration of effects

General Functions of Hormones

- Help regulate:
  - extracellular fluid
  - metabolism
  - biological clock
  - contraction of cardiac & smooth muscle
  - glandular secretion
  - some immune functions
- Growth & development
- Reproduction

Endocrine Glands Defined

- Exocrine glands
  - secrete products into ducts which empty into body cavities or body surface
  - sweat, oil, mucous, & digestive glands
- Endocrine glands
  - secrete products (hormones) into bloodstream
  - pituitary, thyroid, parathyroid, adrenal, pineal
  - other organs secrete hormones as a 2nd function
    » hypothalamus, thymus, pancreas, ovaries, testes, kidneys, stomach, liver, small intestine, skin, heart & placenta

Hormone Receptors

- Hormones only affect target cells with specific membrane proteins called receptors

Role of Hormone Receptors

- Constantly being synthesized & broken down
- A range of 2000-100,000 receptors / target cell
- Down-regulation
  - excess hormone, produces a decrease in number of receptors
    • receptors undergo endocytosis and are degraded
  - decreases sensitivity of target cell to hormone
- Up-regulation
  - deficiency of hormone, produces an increase in the number of receptors
  - target tissue more sensitive to the hormone
Blocking Hormone Receptors

- Synthetic hormones that block receptors for naturally occurring hormones
  - RU486 (mifepristone) binds to the receptors for progesterone preventing it from maintaining the uterus in a pregnant woman
    - used to induce abortion
    - brings on menstrual cycle
- Hormone is prevented from interacting with its receptors and can not perform its normal functions

Circulating & Local Hormones

- Circulating hormones
  - act on distant targets
  - travel in blood
- Local hormones
  - paracrine act on neighboring cells
  - autocrine act on same cell that secreted them

Lipid-soluble Hormones

- Steroids
  - lipids derived from cholesterol on SER
  - different functional groups attached to core of structure provide uniqueness
- Thyroid hormones
  - tyrosine ring plus attached iodines are lipid-soluble
- Nitric oxide is gas

Water-soluble Hormones

- Amine, peptide and protein hormones
  - modified amino acids or amino acids put together
  - serotonin, melatonin, histamine, epinephrine
  - some glycoproteins
- Eicosanoids
  - derived from arachidonic acid (fatty acid)
  - prostaglandins or leukotrienes

Biogenic amines

![Triodothyronine (T₃)](image)

Peptides and proteins

![Peptide and protein structures](image)

Eicosanoids

![Eicosanoid structures](image)
Hormone Transport in Blood

- Protein hormones circulate in free form in blood
- Steroid (lipid) & thyroid hormones must attach to transport proteins synthesized by liver
  - improve transport by making them water-soluble
  - slow loss of hormone by filtration within kidney
  - create reserve of hormone
    - only .1 to 10% of hormone is not bound to transport protein = free fraction

General Mechanisms of Hormone Action

- Hormone binds to cell surface or receptor inside target cell
- Cell may then
  - synthesize new molecules
  - change permeability of membrane
  - alter rates of reactions
- Each target cell responds to hormone differently
  - liver cells---insulin stimulates glycogen synthesis
  - adipose---insulin stimulates triglyceride synthesis

Action of Lipid-Soluble Hormones

- Hormone diffuses through phospholipid bilayer & into cell
- Binds to receptor turning on/off specific genes
- New mRNA is formed & directs synthesis of new proteins
- New protein alters cell’s activity

Action of Water-Soluble Hormones

- Can not diffuse through plasma membrane
- Hormone receptors are integral membrane proteins
  - act as first messenger
- Receptor protein activates G-protein in membrane
- G-protein activates adenylate cyclase to convert ATP to cAMP in the cytosol
- Cyclic AMP is the 2nd messenger
- Activates kinases in the cytosol to speed up/slow down physiological responses
- Phosphodiesterase inactivates cAMP quickly
- Cell response is turned off unless new hormone molecules arrive

Second Messengers

- Some hormones exert their influence by increasing the synthesis of cAMP
  - ADH, TSH, ACTH, glucagon and epinephrine
- Some exert their influence by decreasing the level of cAMP
  - growth hormone inhibiting hormone
- Other substances can act as 2nd messengers
– calcium ions
– cGMP

• Same hormone may use different 2nd messengers in different target cells

  Amplification of Hormone Effects

• Single molecule of hormone binds to receptor
• Activates 100 G-proteins
• Each activates an adenylate cyclase molecule which then produces 1000 cAMP
• Each cAMP activates a protein kinase, which may act upon 1000’s of substrate molecules
• One molecule of epinephrine may result in breakdown of millions of glycogen molecules into glucose molecules

  Hormonal Interactions

• Permissive effect
  – a second hormone, strengthens the effects of the first
  – thyroid strengthens epinephrine’s effect upon lipolysis

• Synergistic effect
  – two hormones acting together for greater effect
  – estrogen & LH are both needed for oocyte production

• Antagonistic effects
  – two hormones with opposite effects
  – insulin promotes glycogen formation & glucagon stimulates glycogen breakdown

  Control of Hormone Secretion

• Regulated by signals from nervous system, chemical changes in the blood or by other hormones
• Negative feedback control (most common)
  – decrease/increase in blood level is reversed
• Positive feedback control
  – the change produced by the hormone causes more hormone to be released
• Disorders involve either hyposecretion or hypersecretion of a hormone

  Negative Feedback Systems

• Decrease in blood levels
• Receptors in hypothalamus & thyroid
• Cells activated to secrete more TSH or more T3 & T4
• Blood levels increase

  Positive Feedback

• Oxytocin stimulates uterine contractions
• Uterine contractions stimulate oxytocin release
Hypothalamus and Pituitary Gland

- Both are master endocrine glands since their hormones control other endocrine glands
- Hypothalamus is a section of brain above where pituitary gland is suspended from stalk
- Hypothalamus receives input from cortex, thalamus, limbic system & internal organs
- Hypothalamus controls pituitary gland with 9 different releasing & inhibiting hormones

Anatomy of Pituitary Gland

- Pea-shaped, 1/2 inch gland found in sella turcica of sphenoid
- Infundibulum attaches it to brain
- Anterior lobe = 75%
  - develops from roof of mouth
- Posterior lobe = 25%
  - ends of axons of 10,000 neurons found in hypothalamus
  - neuroglial cells called pituicytes

Flow of Blood to Anterior Pituitary

- Controlling hormones enter blood
- Travel through portal veins
- Enter anterior pituitary at capillaries

Growth Hormone

- Produced by somatotrophs
- Within target cells increases synthesis of insulinlike growth factors that act locally or enter bloodstream
  - common target cells are liver, skeletal muscle, cartilage and bone
  - increases cell growth & cell division by increasing their uptake of amino acids & synthesis of proteins
  - stimulate lipolysis in adipose so fatty acids used for ATP
  - retard use of glucose for ATP production so blood glucose levels remain high enough to supply brain

Regulation of GH

- Low blood sugar stimulates release of GNRH from hypothalamus
  - anterior pituitary releases more GH, more glycogen broken down into glucose by liver cells
- High blood sugar stimulates release of GHIH from hypothalamus
  - less GH from anterior pituitary, glycogen does not breakdown into glucose
Diabetogenic Effect of Growth Hormone

- Excess of growth hormone
  - raises blood glucose concentration
  - pancreas releases insulin continually
  - beta-cell burnout
- Diabetogenic effect
  - causes diabetes mellitus if no insulin activity can occur eventually

Thyroid Stimulating Hormone (TSH)

- Hypothalamus regulates thyrotroph cells
- Thyrotroph cells produce TSH
- TSH stimulates the synthesis & secretion of T3 and T4
- Metabolic rate stimulated

Follicle Stimulating Hormone (FSH)

- Releasing hormone from hypothalamus controls gonadotrophs
- Gonadotrophs release follicle stimulating hormone
- FSH functions
  - initiates the formation of follicles within the ovary
  - stimulates follicle cells to secrete estrogen
  - stimulates sperm production in testes

Luteinizing Hormone (LH)

- Releasing hormones from hypothalamus stimulate gonadotrophs
- Gonadotrophs produce LH
- In females, LH stimulates
  - secretion of estrogen
  - ovulation of 2nd oocyte from ovary
  - formation of corpus luteum
  - secretion of progesterone
- In males, stimulates interstitial cells to secrete testosterone

Prolactin (PRL)

- Hypothalamus regulates lactotroph cells
- Lactotrophs produce prolactin
- Under right conditions, prolactin causes milk production
- Suckling reduces levels of hypothalamic inhibition and prolactin levels rise along with milk production
- Nursing ceases & milk production slows

Adrenocorticotropic Hormone

- Hypothalamus releasing hormones stimulate corticotrophs
- Corticotrophs secrete ACTH & MSH
- ACTH stimulates cells of the adrenal cortex that produce glucocorticoids
Melanocyte-Stimulating Hormone

- Secreted by corticotroph cells
- Releasing hormone from hypothalamus increases its release from the anterior pituitary
- Function not certain in humans (increase skin pigmentation in frogs)

Posterior Pituitary Gland (Neurohypophysis)

- Does not synthesize hormones
- Consists of axon terminals of hypothalamic neurons
- Neurons release two neurotransmitters that enter capillaries
  - antidiuretic hormone
  - oxytocin

Oxytocin

- Two target tissues both involved in neuroendocrine reflexes
  - During delivery
    - baby’s head stretches cervix
    - hormone release enhances uterine muscle contraction
    - baby & placenta are delivered
  - After delivery
    - suckling & hearing baby’s cry stimulates milk ejection
    - hormone causes muscle contraction & milk ejection

Oxytocin during Labor

- Stimulation of uterus by baby
- Hormone release from posterior pituitary
- Uterine smooth muscle contracts until birth of baby
- Baby pushed into cervix, increase hormone release
- More muscle contraction occurs
- When baby is born, positive feedback ceases

Antidiuretic Hormone (ADH)

- Known as vasopressin
- Functions
  - decrease urine production
  - decrease sweating
  - increase BP

Regulation of ADH

- Dehydration
  - ADH released
- Overhydration
  - ADH inhibited
**Thyroid Gland**

- On each side of trachea is lobe of thyroid
- Weighs 1 oz & has rich blood supply

**Histology of Thyroid Gland**

- Follicle = sac of stored hormone (colloid) surrounded by follicle cells that produced it
  - T3 & T4
- Inactive cells are short
- In between cells called parafollicular cells
  - produce calcitonin

**Photomicrograph of Thyroid Gland**

**Actions of Thyroid Hormones**

- T3 & T4 = thyroid hormones responsible for our metabolic rate, synthesis of protein, breakdown of fats, use of glucose for ATP production
- Calcitonin = responsible for building of bone & stops reabsorption of bone (lower blood levels of Calcium)

**Control of T3 & T4 Secretion**

- Negative feedback system
- Low blood levels of hormones stimulate hypothalamus
- It stimulates pituitary to release TSH
- TSH stimulates gland to raise blood levels

**Parathyroid Glands**

- 4 pea-sized glands found on back of thyroid gland

**Histology of Parathyroid Gland**

- Principal cells produce parathyroid hormone (PTH)
- Oxyphil cell function is unknown
Parathyroid Hormone

• Raise blood calcium levels
  – increase activity of osteoclasts
  – increases reabsorption of Ca+2 by kidney
  – inhibits reabsorption of phosphate (HPO4) -2
  – promote formation of calcitriol (vitamin D3) by kidney which increases absorption of Ca+2 and Mg+2 by intestinal tract

• Opposite function of calcitonin

Regulation of Calcium Blood Levels

• High or low blood levels of Ca+2 stimulate the release of different hormones --- PTH or CT
Mineralocorticoids

- 95% of hormonal activity due to aldosterone
- Functions
  - increase reabsorption of Na+ with Cl-, bicarbonate and water following it
  - promotes excretion of K+ and H+
- Hypersecretion = tumor producing aldosteronism
  - high blood pressure caused by retention of Na+ and water in blood

**Regulation of Aldosterone**

Glucocorticoids

- 95% of hormonal activity is due to cortisol
- Functions = help regulate metabolism
  - increase rate of protein catabolism & lipolysis
  - conversion of amino acids to glucose
  - stimulate lipolysis
  - provide resistance to stress by making nutrients available for ATP production
  - raise BP by vasoconstriction
  - anti-inflammatory effects reduced (skin cream)
    - reduce release of histamine from mast cells
    - decrease capillary permeability
    - depress phagocytosis

**Regulation of Glucocorticoids**

- Negative feedback

Androgens from Zona Reticularis

- Small amount of male hormone produced
  - insignificant in males
  - may contribute to sex drive in females
  - is converted to estrogen in postmenopausal females
Adrenal Medulla
- Chromaffin cells receive direct innervation from sympathetic nervous system
  - develop from same tissue as postganglionic neurons
- Produce epinephrine & norepinephrine
- Hormones are sympathomimetic
  - effects mimic those of sympathetic NS
  - cause fight-flight behavior
- Acetylcholine increase hormone secretion by adrenal medulla

Anatomy of Pancreas
- Organ (5 inches) consists of head, body & tail
- Cells (99%) in acini produce digestive enzymes
- Endocrine cells in pancreatic islets produce hormones

Cell Organization in Pancreas
- Exocrine acinar cells surround a small duct
- Endocrine cells secrete near a capillary

Histology of the Pancreas
- 1 to 2 million pancreatic islets
- Contains 4 types of endocrine cells

Cell Types in the Pancreatic Islets
- Alpha cells (20%) produce glucagon
- Beta cells (70%) produce insulin
- Delta cells (5%) produce somatostatin
- F cells produce pancreatic polypeptide

Regulation of Glucagon & Insulin Secretion
- Low blood glucose stimulates release of glucagon
- High blood glucose stimulates secretion of insulin

Ovaries and Testes
- Ovaries
  - estrogen, progesterone, relaxin & inhibin
  - regulate reproductive cycle, maintain pregnancy & prepare mammary glands for lactation

1. Low blood glucose (hypoglycemia) stimulates release of glucagon
2. Glucagon acts on hepatocytes: glucose synthesis
   - increase glycogen synthesis
   - increase triacylglycerol synthesis
3. High blood glucose (hyperglycemia) stimulates release of insulin
4. Insulin acts on various body cells: glucose metabolism
   - increase glycogen synthesis
   - increase triacylglycerol synthesis
5. Blood glucose level falls
   - if blood glucose continues to fall, hypoglycemia inhibits release of glucagon
• Testes
  – produce testosterone
  – regulate sperm production & 2nd sexual characteristics

  **Pineal Gland**

• Small gland attached to 3rd ventricle of brain
• Consists of pinealocytes & neuroglia
• Melatonin responsible for setting of biological clock
• Jet lag & SAD treatment is bright light

  **Effect of Light on Pineal Gland**

• Melatonin secretion producing sleepiness occurs during darkness due to lack of stimulation from sympathetic ganglion

  **Thymus Gland**

• Important role in maturation of T cells
• Hormones produced by gland promote the proliferation & maturation of T cells
  – thymosin
  – thymic humoral factor
  – thymic factor
  – thymopoietin

  **Miscellaneous Hormones Eicosanoids**

• Local hormones released by all body cells
• Leukotrienes influence WBCs & inflammation
• Prostaglandins alter
  – smooth muscle contraction, glandular secretion, blood flow, platelet function, nerve transmission, metabolism etc.
• Ibuprofen & other nonsteroidal anti-inflammatory drugs treat pain, fever & inflammation by inhibiting prostaglandin synthesis

  **Nonsteroidal Anti-inflammatory Drugs**

• Answer to how aspirin or ibuprofen works was discovered in 1971
  – inhibit a key enzyme in prostaglandin synthesis without affecting the synthesis of leukotrienes
• Treat a variety of inflammatory disorders
  – rheumatoid arthritis
• Usefulness of aspirin to treat fever & pain implies prostaglandins are responsible for those symptoms

  **Growth Factors**

• Substances with mitogenic qualities
  – cause cell growth from cell division
• Many act locally as autocrines or paracrines

  Selected list of growth factors
  – epidermal growth factor
    – platelet-derived growth factor
    – fibroblast growth factor
    – nerve growth factor