The Endocrine System

Overview of Endocrine System

• Endocrine glands secrete into extracellular space, secretion (hormones) diffuses to circulatory system

• Includes primary glands - pituitary, thyroid, parathyroid, adrenal, & pineal glands

• Accessory structures with glandular function as well as others - hypothalamus, thymus, pancreas, ovaries, testes, kidneys, small intestine heart & placenta (and others)

• Provides homeostasis control along with nervous system
  – Hormonal control usually slower and longer lasting - dependent on blood supply and receptors
  – Control metabolism, growth & development and reproduction

• In some cases the two interact together
  – May stimulate or inhibit the other, or modulate the effect of the other (smooth & cardiac muscle, some glands)
  – Some neurotransmitters are also hormones

Endocrine Tissues (graphic)

Hormonal Chemistry

• Lipid soluble vs. water soluble hormones
  – Lipid soluble - steroids, T₃ & T₄ thyroid hormones, nitric oxide
  – Water soluble - amines, peptides/proteins, eicosanoids

• May be circulating or local hormones
  – Local may be paracrines or autocrines and are typically short-lived
  – Circulating typically destroyed by liver and excreted by kidney

• Steroids (lipid) - derived from cholesterol, differences in side chains of 4-ring structure
  – Secretory cells derived from mesoderm
  – Produced by adrenal cortex, kidneys, testes/ovaries

• Thyroid hormones - combination of two molecules of tyrosine bound to iodine
  – Produced by thyroid gland

• Nitric oxide – NO synthase

• Amines - derived from amino acids
  – Catecholamines (epi, norepi & dopamine) - derived from tyrosine
  – Histamine - derived from histidine
  – Serotonin & melatonin - from tryptophan
  – Produced by adrenal medulla, mast cells, platelets (serotonin), pineal

• Peptides/proteins - 3-200 amino acids, some are glycoproteins (e.g. TSH)
  – Produced by hypothalamus, pituitary, pancreas, parathyroids, thyroid, stomach, & small intestine, kidneys and adipose tissue
- Eicosanoids - derived from arachidonic acid (20-C fatty acid) including prostaglandins and leukotrienes
  - Primary local activity
  - Produced by most cells (except RBCs)

**Hormone Types (graphic)**

**Hormone Transport**
- Water-soluble free in blood
- Lipid-soluble largely attached to transport proteins except for a small free fraction (0.1-10%)
  - Transport proteins produced in liver
  - When attached to transport protein, hormone is less likely to leave CV system (including loss in kidney)

**Hormonal Effects**
- Effects include synthesis of new molecules, changed membrane permeability, stimulated transport of molecules across cell membrane, rate of metabolic reactions, contraction of smooth or cardiac muscle
- Effect dependent on target cell - those cells with receptors for hormone
  - Effect may change depending on target cells - e.g. insulin → synthesis of glycogen in liver cells or triglycerides in adipose cells
- Some receptors on cell membrane - water soluble hormones (catecholamines & peptide/proteins)
- Some receptors inside cells - lipid soluble hormones (steroids & thyroid hormones)
- Solubility and digestibility determines how hormonal drugs are given - e.g. insulin is water soluble and digestible and must be injected
- Number of receptors changes - altered level of response
  - Excess hormone level - down-regulation
  - Deficient hormone level - up-regulation
  - Interactions between hormones may be related to up or down-regulation

**Lipid-soluble Hormones**
- Interact with receptors in cytosol or nucleus
- Activated receptor activates or inactivates genetic expression
- Changed genetic expression, alters protein manufacture (usually an enzyme) and ultimately cell’s activity related to protein

**Lipid-soluble Hormone Action (graphic)**

**Water-soluble Hormones**
- Interact with surface receptors (first messenger)
- Activated external receptor initiates second messenger
  - Frequently cAMP - formed from ATP by adenylate cyclase (activated by G-proteins in cell membrane)
- Activity of second messenger dependent on target cell
– cAMP stimulates break down of triglycerides in adipose cells while increasing secretion of thyroid hormone in thyroid cells
– cAMP activates protein kinase → phosphorylates target cell enzymes which activates or inactivates enzyme → altered cell activity (regulation of other enzymes, secretion, protein synthesis, membrane permeability)
– Phosphodiesterase ultimately inactivates cAMP
– Some hormones decrease cAMP

• Other secondary messengers include Ca^{2+}, cGMP, inositol triphosphate (IP3), and diacylglycerol (DAG)

**Water-soluble Hormone Action (graphic)**

**Other Hormone Action**

• Enzymatic amplification of hormones
  – single hormone molecule → multiple G-proteins activated → adenylate cyclase → multiple cAMP → protein kinase

• Hormonal interactions
  – Permissive effect - activity of some hormones requires recent or simultaneous presence of another hormone (e.g. thyroid hormones and cortisol support action of other hormones) via up-regulation or required presence of enzyme
  – Synergistic effect - activity of two hormones together greater than either one alone (e.g. estrogen and LH (or FSH) required for oocyte production)
  – Antagonistic effect - opposite activity of hormone action (e.g. insulin → synthesis of glycogen in liver, glucagon → catabolism of glycogen in liver)

**Hormone Secretion**

• Frequently in bursts rather than steady flow
  – Why? - delayed response, minimizes down-regulation

• Stimulus for secretion - neural, sensed changes in blood, other hormones

• Homeostatic control mechanisms usually negative feedback systems
  – But sometimes positive feedback (e.g. oxytocin bringing on childbirth, LH bringing on ovulation)

**Hypothalamus and Pituitary**

• Pituitary primarily controlled by hypothalamus - major link between neural and endocrine function

• Hypothalamus receives input from limbic system, cortex, thalamus and RAS, plus visceral sensory and probable visual input

• Hypothalamus controls ANS, regulates body temp, thirst, hunger, sexual behavior and defensive emotions

• At least 9 hormones from hypothalamus, 7 from pituitary

**Pituitary**

• Anterior and posterior - developmentally different (ectodermal hypophyseal pouch and neurohypophyseal bud respectively), third pars intermedia is embryonic
• Suspended in sella turcica by infundibulum
• Posterior pituitary primarily neurosecretory with cell bodies in hypothalamus

**Anterior Pituitary**
• Secrete hormones under control of releasing or inhibiting hormones of the hypothalamus
• Hypothalamic hormones transported via specialized hypophyseal portal system
  – Internal carotid and communicating arteries supply blood
  – Primary plexus - capillary bed at base of hypothalamus where neurosecretory cells release hormones
  – Hypophyseal portal veins
  – Secondary plexus in anterior pituitary
• Five secretory cell types
  – Somatotrophs - hGH (somatotropin) - growth and metabolism through intermediate IGFs
  – Thyrotrophs - TSH - activity of thyroid glands
  – Gonadotrophs - FSH & LH - secretion of estrogens & progesterones and maturation in ovaries or secretion of testosterone and sperm production in testes
  – Lactotrophs - prolactin (PRL) - begins milk production
  – Corticotrophs - adrenocorticotrophic hormone (ACTH) and MSH - secretion of glucocorticoids in adrenal cortex and skin pigmentation respectively
• Hormones that affect other endocrine secretions - tropins
  – FSH, LH, TSH, ACTH released by pituitary
  – Hypothalamic tropins act on pituitary - hypophysiotropic hormones
• Ant. pituitary secretion also affected by negative feedback from hormones of target organs

**Pituitary Blood Supply (graphic)**

**Human Growth Hormone (hGH)**
• Controls growth and metabolism of cells
  – Much of hGH effect by secretion of insulin-like growth factors (IGF) from liver, muscle, cartilage, bone, etc.
  – May be carried by blood from liver or act as autocrine or paracrine
  – Increases permeability of cell membrane to amino acids, stimulates protein synthesis, inhibits protein catabolism - results in skeletal and muscle growth, tissue repair
• IGFs alters molecular energy source by stimulating lypolysis (triglycerides) and reducing use of glucose for energy production - important for periods of starvation
  • Glucose in short supply used by neurons
  • May stimulate glucose to be released by liver cells - insulin antagonist
• Excessive secretion can be diabetogenic (beta cell burnout) – reduced insulin secretion
• Hypothalamic tropin (GHRH or GHIH) release regulated by blood glucose
  – Low glucose increases GHRH
• Other factors that increase secretion
  – Decreased fatty acids or elevated amino acids in blood
  – Stage 3 & 4 NREM sleep
  – Increase sympathetic activity
  – Other hormones - glucagon, estrogens, cortisol, insulin
• Other factors that decrease secretion
  – Increased fatty acids or lowered amino acids in blood
  – REM sleep
  – Emotional deprivation
  – Obesity
  – Low thyroid hormones
• Abnormal secretory levels
  – Pituitary dwarfism - low during childhood
  – Gigantism - high during childhood
  – Acromegaly (thickened bones in hands, feet and face, enlarged facial features, thickened skin) - high during adulthood

**Hypothalamic Control of hGH (graphic)**

**Thyroid Stim. Hormone (TSH)**

• Also thyrotropin
• Stimulates secretion of triiodothyronine (T₃) and thyroxine (T₄) by thyroid gland
• Secretion controlled by thyrotropin releasing hormone (TRH) from hypothalamus based on TSH, T₃, blood glucose level and metabolic rate

**Hypothalamic Control of TSH (graphic)**

**Follicle Stim. Hormone (FSH)**

• In females - stimulates ovarian follicular growth in monthly cycle and follicular cells to secrete estrogen
• In males - stimulates sperm production
• Secretion controlled by gonadotropin releasing hormone (GnRH) from hypothalamus based on blood estrogen or testosterone levels

**Luteinizing Hormone (LH)**

• In females - stimulates follicular cells to secrete estrogen, initiates ovulation, formation of corpus luteum in ovary (after ovulation) and corpus luteal release of progesterone
  – Both estrogen and progesterone important in development of uterine lining for implantation of egg and preparation of mammary glands for milk secretion
• In males - stimulates testicular interstitial cell development and release of testosterone
• Secretion controlled by GnRH

**Prolactin (PRL)**
• Initiates and maintains milk production
• Effect of prolactin only after preparation of mammary glands by other hormones (estrogen, progesterone, glucocorticoids, hGH, thyroxine and insulin)
• Secretion controlled by prolactin inhibiting hormone (PIH, dopamine) from hypothalamus based on estrogen and progesterone levels
  – Declining estrogen and progesterone levels as menstruation begins and infant suckling activity retards secretion of PIH
• Secretion also controlled by prolactin releasing hormone (PRH) from hypothalamus during pregnancy

**Adrenocorticotropic Hormone (ACTH)**
• Also corticotropin
• Precursor to ACTH (and MSH) is pro-opiomelanocortin (POMC) produced by corticotrophs; subsequently fragmented to ACTH (and MSH)
• Controls production and release of glucocorticoids (primarily cortisol) by adrenal cortex
• Secretion controlled by corticotropin releasing hormone (CRH) from hypothalamus based on glucocorticoid levels
  – And also low blood glucose, physical trauma, and interleukin produced by macrophages

**Hypothalamic Control of ACTH (graphic)**

**Melanocyte-Stim. Hormone (MSH)**
• Darkens skin through melanocyte activity
• Secretion enhanced by CRH and inhibited by dopamine from hypothalamus

**Posterior Pituitary Gland**
• Site of storage (in nerve terminals) and release of oxytocin (OT) and antidiuretic hormone (ADH or vasopressin)
• Secretory neurons descend from hypothalamic nuclei via hypothalamohypophyseal tract
• Blood flow - inferior hypophyseal arteries → plexus of the infundibular process → posterior hypophyseal veins

**Neurosecretion (graphic)**

**Oxytocin (OT)**
• Increases contraction of smooth muscle in uterine wall during childbirth in response to stretching of cervix - positive feedback
• Increases contraction of smooth muscle around mammary gland cells postpartum causing ejection of milk in response to nipple stimulation (which also enhances prolactin release)
• Both are examples of neuroendocrine reflex
• Importance unclear at other times and in males

**Antidiuretic Hormone (ADH)**
• Conserves water by increasing kidney reabsorption and reduced sweating
  – Without ADH, kidneys would produce 20 liters of urine/day instead of 1-2
• Increases blood pressure by smooth muscle vasoconstriction in blood vessels when blood volume has declined
• Secretion controlled by activity of osmoreceptors in hypothalamus
• Secretion affected by other stimuli - pain, stress, nicotine, various drugs and alcohol
  – Alcohol inhibits ADH secretion causing dehydration
• Diabetes insipidus with symptoms of substantial, dilute urine production
  – Neurogenic (reduced secretion) vs. nephrogenic (reduced kidney response to ADH)

**Hypothalamic Control of ADH (graphic)**

**Thyroid**
• Lateral lobe and isthmus with substantial blood supply via branches of internal carotid arteries and jugular veins
• Ultrastructure - thyroid follicle with follicular and parafollicular cells (C cells)
• Follicular cells produce thyroxine (tetraiodothyronine or T₄) and triiodothyronine (T₃), parafollicular cells produce calcitonin
• Thyroid only gland to store substantial quantities of hormones (100 days)

**Thyroid/Parathyroid Glands (graphic)**

**Thyroid Ultrastructure (graphic)**

**Thyroid Follicular Structure (graphic)**

**Production of T₃ and T₄**
• From blood - active transport of iodide (20-40 times greater)
• Within follicular cells - production of precursor - thyroglobulin (TGB) and oxidation of iodide to iodine
• Follicular lumen (storage site) - iodination of tyrosine portion of TGB with 1 or 2 iodine (T₁ or T₂) and coupling to form T₃ and T₄ (1:4 ratio)
• Within follicular cells - lysosome digestion of TGB to cleave off T₃ & T₄, remnants recycled
  – T₃ more active than T₄
• Secretion via lipid soluble diffusion into blood and transported in blood by thyroxine-binding globulin (TBG)
  . Upon entering target cell, T₄ frequently converted to T₃

**T₃/T₄ Production (graphic)**

**T₃ and T₄ Action**
• Increase BMR (use of O₂) via increase production of Na⁺/K⁺ ATPase for electrogentic pump, heat increases body temperature (calorigenic effect)
• Increased cellular metabolism via increased protein synthesis, increased use of glucose as ATP source, increased lipolysis (including elevated cholesterol in bile which enhances lipid digestion)
• Regulates growth and development (in addition to hGH & insulin), particularly the nervous & reproductive system
• Up-regulates $\beta$ receptors of catecholamines (epi & norepi)
• Secretion controlled by hypothalamus based (thryrotropin RH) on low metabolic rate or low levels of T$_3$ or T$_4$ in blood
• Check effects of hypo- or hypersecretion

Calcitonin (CT)
• Produced by parafollicular cells
• Lowers blood calcium and phosphates by decreasing activity of osteoclasts
  – Loss of calcitonin production has little effect - reason unknown

Parathyroid Glands
• Bilateral superior and inferior parathyroid glands attached to thyroid
• Composed of two cell types - principal and oxyphil cells
  – Principal cells produce parathyroid hormone (PTH or parathormone)
  – Function of oxyphil cells unknown

Parathyroid Hormone (PTH)
• Increases bone reabsorption (and calcium and phosphate in blood) via increased osteoclasts and their activity
• Increases kidney reabsorption of Ca$^{2+}$ and Mg$^{2+}$
• Inhibits kidney phosphate (HPO$_4^{2-}$) reabsorption - effect ultimately lowers phosphate level in blood
• Stimulates kidney manufacture of calcitriol from Vit. D which enhances Ca$^{2+}$, HPO$_4^{2-}$, and Mg$^{2+}$ absorption by digestive tract
• Secretion controlled by Ca$^{2+}$ level in blood

Ca$^{2+}$ Homeostasis (graphic)

Adrenal Cortex
• Adrenal gland structurally and functionally divided into cortex and medulla
• Develops from mesoderm
• Cortex consists of three layers, each secreting different hormones
  – Outer layer - zona glomerulosa produces mineralocorticoids that control mineral homeostasis
  – Middle layer - zona fasiculata produces glucocorticoids that control glucose homeostasis
  – Inner layer - zona reticularis produces androgens (male sex hormones)

Layers of Adrenal Cortex (graphic)

Mineralocorticoids
• Primarily (95%) aldosterone
• Increases kidney tubular reabsorption of $\text{Na}^+$ which secondarily increases reabsorption of $\text{Cl}^-$ and $\text{HCO}_3^-$ and water retention
• Increases kidney excretion of $\text{K}^+$ and $\text{H}^+$
• Secretion controlled by renin-angiotensin pathway based on dehydration, low $\text{Na}^+$ or hemorrhage
• Or $\text{K}^+$ at adrenal cortex

**Renin/Angiotensin Pathway (graphic)**

**Glucocorticoids**

• Primarily (95%) cortisol (hydrocortisone)
• Increases protein catabolism primarily in muscle, ↑ amino acids in blood
• Stimulates gluconeogenesis in liver from amino acids or lactic acid
• Stimulates lypolysis in adipose cells
• Provides an anti-inflammatory effect by reducing # of mast cells that produce histamine, decrease lysosomal release of enzymes, lower permeability of capillaries and retard phagocytosis and thus also slow wound healing
• Depress immune response (decreases tissue rejection in transplant cases)
• Secretion controlled by hypothalamus (corticotropin releasing hormone (CRH)) based on cortisol level in blood
• Increased release in response to stress, increasing availability of ATP and heightened response to vasoconstrictors
• Hyposcretion - Addison’s disease
• Hypersecretion - Cushing’s syndrome

**Regulation of Cortisol (graphic)**

**Androgens**

• Primarily dehyroepiandrosterone (DEHA)
• Androgen secretion appears more significant in females (sex drive and behavior), post-menopausal estrogen source (converted) and in prepubertal growth and pubertal maturation in both sexes
• Secretion probably controlled by ACTH
• In males, largest proportion of androgens from testes

**Adrenal Medulla**

• Develops from ectoderm
• Composed primarily of chromaffin cells which are innervated by preganglionic neurons of sympathetic NS (thus chromaffin cells are specialized postganglionic cells)
• Neurotransmitter epi (80%) and norepi
• Increases blood pressure (increased HR, force of contraction, vasoconstriction in some areas)
• Vasodilation in heart, liver, skeletal muscle and adipose tissue
• Dilates air passages to lungs
• Decreases digestion, increase blood glucose, and stimulate metabolism
• Secretion based on neural input from hypothalamus

**Pancreas**

• Both exocrine (structurally as acini, digestive function) and endocrine function
• About 1% of cells are pancreatic islets (islets of Langerhans)
• Four different hormone secreting cell types
  – Alpha (A) cells (20%) - glucagon
    • Increases blood glucose
  – Beta (B) cells (70%) - insulin
    • Decreases blood glucose
  – Delta (D) cells (5%) - somatostatin (same as GHIH)
    • Inhibits release of insulin & glucagon (paracrine activity on alpha & beta cells), and retards nutrient absorption in GI tract
  – F cells - pancreatic polypeptide
    • Inhibits release of somatostatin, gallbladder contraction, and pancreatic digestive enzymes

• Antagonistic control of blood glucose by glucagon and insulin
• Diabetes mellitus - review causes and symptoms for Type I & II

**Pancreatic Ultrastructure (graphic)**

**Islet of Langerhans (graphic)**

**Glucose Regulation (graphic)**

**Many Other Hormones**

• Ovaries - estrogens, progesterone, inhibin, relaxin
• Testes - testosterone, inhibin
• Pineal gland - melatonin
• Thymus - thymosin, thymic humoral factor (THF), thymic factor, thymopoietin
• Eicosanoid (largely prostaglandins and leukotrienes) secretors
• A variety of growth factor sources - mitogenic

**Hormones & Stress**

• Homeostatic control vs. response to prolonged or extreme stress (general adaptation syndrome - GAS)
  – GAS results in resetting of normal control conditions via hypothalamus
• Alarm reaction - sympathetic action
• Resistance reaction - hypothalamus/anterior pituitary action starting with CRH, GHRH, and TRH
• Exhaustion

**General Adaptation Syndrome (GAS) (graphic)**