**Thyroid Gland**

**Characteristics**

--only endocrine gland that stores its hormone
--Composed of follicles (sac of stored hormone/collod surrounded by follicle cells that produced it
--Parafollicular cells: secrete calcitonin (reduces calcium conc. in body fluids when levels elevate)

**Thyroid Hormones**

--Transported in: blood
--Bind with: intracellular NUCLEAR receptor and initiate new protein synthesis
--Amino Acid (tyrosine) hormone
--Actions:
  a. increase rate of glucose, fat, protein metabolism
  b. increase body temperature

**Types of Thyroid Hormones**

1. Triiodothyronine (T₃)
   *most potent form (liver, kidney, pituitary convert T₄ to T₃)
2. Tetraiodothyronine (T₄, thyroxine)
   *predominantly secreted form
3. T₃ and T₄
   *Secreted by: follicular cells
   *Action: metabolic rate, protein metabolism, breakdown of fats, use of glucose for ATP production
   *CALORIGENIC
4. Calcitonin
   *Secreted by: parafollicular cells
   *Action: building of bone and stops reabsorption of bone (lowers blood Ca levels)

**Formation of Thyroid Hormone**

a. TGB (thyroglobulin, a large glycoprotein): synthesized in the RER, glycosylated in the Golgi, packaged in secretory vesicles and released on the apical side into the colloid
b. TGB has numerous tyrosine residues which will be iodinated to form the hormones
c. Iodide trap: Na⁺/I⁻ symporter (secondary active transport) on basal side; activity increased by TSH
d. Oxidation of iodide to iodine (I₂) by thyroid peroxidase (hydrogen
peroxide is the electron acceptor
*thyroid peroxidase is inhibited by propythiouracil (PTU) which blocks all steps (oxidation, organification, and coupling); use it in hyperthyroidism

e. Organification of iodine by thyroid peroxidase; I combines with tyrosine on TGB to form moniodotyrosine (MIT) and diiodotyrosine (DIT) which remain attached to TGB until the thyroid gland is stimulated to secrete

f. Coupling reaction: catalyzed by thyroid peroxidase; 2 DIT couple to form T₄ or 1 DIT and 1 MIT form T₃ (T₄ faster and more of this is formed)
g. After coupling TGB contains MIT, DIT, T₃ and T₄

h. Pinocytosis: when thyroid gland is stimulated by TSH (from the pituitary), TGB is taken up by pinocytosis as part of the colloid, and pinocytic vesicles fuse with lysosomes

i. Hydrolysis of MIT, DIT, T₃, and T₄ occurs. T₃ and T₄ are transported across basal membrane: MIT and DIT are recycled (deiodinated by thyroid deiodinase, I recycled and tyrosines are used for synthesis of TGB)

j. T₃ and T₄ circulate in the plasma free or bound to TGB

k. Free T₃ and T₄ available for binding to receptors

l. Tissue iodinases converts T₄ to T₃

--Effects of Thyroid Hormones (increase metabolic rate and heat production)
a. Calorigenic action: increase oxygen consumption in all tissues except: brain, testes, uterus, lymph nodes, spleen, pituitary

b. CNS effects
   *development of CNS (cretinism—low thyroid during infancy)
   *reflexes: reflex time as a tool to diagnose hypo or hyper-thyroidism
   *catecholamine: increase synthesis of beta adrenergic receptors (increase heart responsiveness to epi) leading to increase in cardiac output

c. Heart: affect the type of myosin present (alpha myoglobin chain with higher ATPase activity)

b. Respiratory effects: increase resting respiratory rate, minute ventilation

e. CHO metabolism: increase rate of absorption from intestine

f. Cholesterol metabolism: lower cholesterol level in plasma

g. Growth: bone growth and maturation

--Control of T₃ and T₄
   *negative feedback system
   *low blood levels of hormones stimulate hypothalamus
   *stimulates pituitary to relase TSH
   *TSH stimulates gland to raise blood levels
--Thyroid Hormone Hypo and Hypersecretion

<table>
<thead>
<tr>
<th></th>
<th><strong>Hyperthyroidism</strong></th>
<th><strong>Hypothyroidism</strong></th>
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</thead>
<tbody>
<tr>
<td><strong>Symptoms:</strong></td>
<td>Increased metabolic rate</td>
<td>Decreased metabolic rate</td>
</tr>
<tr>
<td></td>
<td>Weight loss, increased appetite</td>
<td>Weight gain, reduced appetite</td>
</tr>
<tr>
<td></td>
<td>Warm flushed skin</td>
<td>Dry and cold skin</td>
</tr>
<tr>
<td></td>
<td>Weak muscles that exhibit tremors</td>
<td>Weak, flabby skeletal muscles, sluggish</td>
</tr>
<tr>
<td></td>
<td>Hyper-reflexia</td>
<td>Myxedema (edema)</td>
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<tr>
<td><strong>Exopthalmos</strong></td>
<td>(edema behind eye balls)</td>
<td>Apathetic, somnolent</td>
</tr>
<tr>
<td></td>
<td>Hyperactivity, insomnia</td>
<td>Coarse hair, rough dry skin</td>
</tr>
<tr>
<td></td>
<td>Soft smooth hair and skin</td>
<td>Decreased iodide uptake</td>
</tr>
<tr>
<td></td>
<td>Increased iodide uptake</td>
<td>Possible goiter</td>
</tr>
<tr>
<td></td>
<td>Almost always develops goiter</td>
<td>Cretinism (starts at birth)</td>
</tr>
<tr>
<td><strong>Causes:</strong></td>
<td>Graves’ Disease (autoimmune disorder—Ab activate TSH receptors)</td>
<td>Thyroiditis (Hashimoto’s thyroditis)</td>
</tr>
<tr>
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<td>Thyroiditis (Hashimoto’s thyroditis)</td>
<td>Cretinism</td>
</tr>
<tr>
<td><strong>TSH levels:</strong></td>
<td>May increase or decrease</td>
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</tr>
<tr>
<td><strong>Treatment:</strong></td>
<td>Propylthiouracil (inhibits peroxidase enzyme and thyroid hormone synthesis)</td>
<td>Hormone replacement therapy</td>
</tr>
<tr>
<td></td>
<td>Antithyroid drugs: thiourylenes</td>
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<td>Natural goitrogens—cabbage goiters</td>
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</table>
Adrenal Glands

Characteristics

--Cortex: from mesoderm (80-90%)
  a. Zona glomerulosa: secretes mineralcorticoids (aldosterone)
  b. Zona fasciculate: secretes glucocorticoids (cortisol)
  c. Zona reticularis: secretes androgens (dehydroepiandrosterone/DHEA)
--Medulla: from ectoderm (neural crest cells)

Hormones of Adrenal Cortex

--Steroid hormones: carried in plasma by binding proteins, have cytosolic receptors, regulate gene expressions
--Mineralcorticoids/ALDOSTERONE
  *secreted by zona glomerulosa
  *Aldosterone: produced in greatest amounts, increases rate of sodium reabsorption by kidneys, increasing sodium blood levels
  *Functions:
    a. increase reabsorption of sodium with Cl, HCO₃⁻, and H₂O
    b. promotes excretion of K⁺ and H⁺ (pH regulation)
    c. adjusts blood pressure and blood volume
  *Regulation of Aldosterone: Renin-angiotensin-aldosterone pathway (pic)
  *5 factors stimulate aldosterone release
    a. ACTH
    b. Conversion of angiotensin I to angiotensin II
    c. Hyperkalemia
    d. Hyponatremia
    e. Decrease in BP
  *Hypersecretion: tumor producing aldosteronism → high blood pressure caused by retention of Na⁺ and water in blood
--Glucocorticoids/CORTISOL
  *Secreted by: zona fasciculata
  *Cortisol: increases fat and protein breakdown, increasing glucose synthesis,
decreases inflammatory response (also corticosterone and cortisone)

*Functions: help regulate metabolism, increase glucose
  a. increase rate of protein catabolism (breakdown)
  b. conversion of amino acids to glucose (gluconeogenesis)
  c. stimulate lipolysis
  d. provide resistance to stress by making nutrients available for ATP production
  e. raise BP by vasoconstriction
  f. anti-inflammatory effects (skin cream) → reduce release of histamine from mast cells, decrease capillary permeability, depress phagocytosis
  g. depress immune responses (organ transplant patients)
  h. diurnal fluctuations: high 6am to noon

*Hormone released in response to chronic stress
*Cortisol has permissive effect on glucagon and epinephrine
*Regulation: negative feedback

--Androgens

*Secreted by: Zona reticularis
*DHEA: androgens converted to other steroids
  a. insignificant in males
  b. contribute to sex drive in females (libido)
  c. converted to estrogens which have feminizing effects; it is the only source of estrogen in postmenopausal females
  d. stimulate growth of axillary and pubic hair in boys and girls
  e. contributes to growth spur during puberty

*Stimulated by: ACTH

**Disorders of the Adrenal Gland**

--Congenital adrenal hyperplasia

*genetic disorder, defective cortisol synthesis; no negative feedback; high ACTH secretion by anterior pituitary; ACTH leads to enlargement of the adrenal cortex and accumulation of cortisol precursors; some precursors can be converted to testosterone → masculinization = virilism

*In females: virilism causes growth of a beard and male distribution of body hair, deeper voice, atrophy of breasts, growth of clitoris (may resemble a penis)

--Primary hyperaldosteronism/Conn’s syndrome

*Increased: total Na, ECF volume, plasma volume, BP, pH
*Decreased: K, rennin, angiotension II

--Primary adrenal hyperplasia/Cushing’s syndrome

* hypersecretion fo cortisol due to increased ACTH levels or adrenal tumors &hyperglycermia, osteoporosis, virilization and menstrual disorders
--Primary hypoaldosteronism/Addison’s disease
  *Increased: K, rennin, angiotensin II
  *Decreased: Na, ECF volume, plasma volume, BP, pH

**Adrenal Medulla**

--Chromaffin cells receive direct innervation from sympathetic nervous system (develop from same tissue as postganglionic neurons)
--Produce epinephrine and norepinephrine (neurohormones w/ short half lifes)
--Sympathomimetic: effects mimic those of sympathetic NS, cause fight/flight behavior, reduce activity of organs not essential for physical activity, increase blood flow and metabolism of organs needed
--Acetylcholine increase hormone secretion by adrenal medulla
--Cause release of Epinephrine:
  a. exercise
  b. emergencies
  c. exposure to cold

**Pancreas**

**Characteristics**

--Cell types in Pancreatic Islets:
  a. Alpha cells (20%): produce glucagon
  b. Beta cells (70%): produce insulin
  c. Delta cells (5%): produce somatostatin
  d. F cells (5%): produce pancreatic polypeptide

**Hormones**

--Insulin effects on glucose metabolism:
  *On Muscle:
    a. Glucose uptake by muscle: promotes muscle glucose uptake and metabolism; resting muscle fibers are only slightly permeable to glucose. Insulin increases permeability, permeability also increased during heavy exercise
    b. Glycogenesis: promotes storage of glycogen in muscle
  *On Liver: (promotes liver uptake, storage, and use of glucose)
    a. inactivates liver phosphorylase (splits glycogen into glucose)
    b. increase activity of glycogen synthase
    c. increase glucose uptake
    d. increases activity of glucokinase (phosphorylates glucose, trapping)
    e. promotes conversion of glucose into FA and triglycerides
--Insulin levels decrease b/w meals (reverse events)
  a. activation of phosphoylase
b. activation of glucose phosphatase

**No effect of insulin on brain**

--Insulin effects on lipid metabolism: (promotes fat synthesis and storage)

*On liver:
  a. after enough glycogen is formed, glucose is used to synthesize lipids
  b. FA secreted by liver via VLDLs and reach adipose capillaries where
     insulin has activated lipoprotein lipase (breaks down the
     triglycerides for absorption)

*Within Adipose cells:
  a. stimulates glucose uptake
  b. stimulates triglyceride uptake
  c. increase conversion of CHO into fat
  d. inhibits lipases to prevent fat catabolism and induces the formation
     of glycerol phosphate (needed for triglyceride synthesis)
  e. decrease ketone body production

--Insulin lack results in:
  a. lipolysis of stored fat and release of free FA by activating hormone
     sensitive lipase
  b. Increased free FA in plasma, promotes synthesis of cholesterol and
     phospholipids in liver which are released into circulation-
     arteriosclerosis
  c. Liver produces excess acetoacetic acid (ketone body) from condensation of
     acetylCoA (from oxidation of free FA), it is released from liver and used for
     synthesis of ketone bodies in tissues-ketosis

--Insulin Effects on Protein Metabolism (promotes protein synthesis):
  a. stimulates amino acid uptake by tissues
  b. increases protein translation from mRNA (turns on ribosome machinery)
  c. regulates gene expression
  d. inhibits protein catabolism
  e. decreases gluconeogenesis (from AA)
  f. interacts synergistically (not simply additive effects) with hGH

--Insulin Lack and protein metabolism:
  *protein degradation and increased plasma levels of AA

--Factors Affecting Insulin Secretion

<table>
<thead>
<tr>
<th>Stimulatory Factors</th>
<th>Inhibitory Factors</th>
</tr>
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<tbody>
<tr>
<td>Increased glucose</td>
<td>Decreased glucose</td>
</tr>
<tr>
<td>Increased AA</td>
<td>Fasting</td>
</tr>
<tr>
<td>Increased FA</td>
<td>Exercise</td>
</tr>
<tr>
<td>Growth hormone</td>
<td></td>
</tr>
<tr>
<td>Cortisol</td>
<td></td>
</tr>
<tr>
<td>Gastric inhibitory peptide (GIP)</td>
<td></td>
</tr>
</tbody>
</table>
- Regulation of Insulin: picture
- Effects of Insulin on Nutrient Flow
  a. Glucose, Fatty acids, ketoacids, amino acids: DECREASED

**Glucagon**

- Secreted by: alpha cells
- Actions:
  a. stimulates liver glycogenolysis
     * activates adenyl cyclase $\rightarrow$ increase cAMP
     * increase protein kinase regulatory proteins
     * which activate phosphorylase b kinase
     * converts phosphorylase b to a
     * phosphorylase a splits glycogen into glu-1-P $\rightarrow$ de-P and removed from liver
  b. increase gluconeogenesis in liver
     * increase AA uptake and synthesis of glucose, activates necessary enzymes
  c. stimulates lipolysis
     * activates lipases in adipose cells $\rightarrow$ FA available for energy to preserve glucose
  d. NET INCREASE glucose availability to other tissues

- Effects of Glucagon on Nutrient Flow
  * glucose, fatty acids, ketoacids: INCREASED

- Factors Affecting Glucagon Secretion

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<thead>
<tr>
<th>Stimulatory factors</th>
<th>Inhibitory factors</th>
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<tbody>
<tr>
<td>Decreased glucose in blood</td>
<td>Insulin</td>
</tr>
<tr>
<td>Increased AA in blood</td>
<td>Somatostatin</td>
</tr>
<tr>
<td>Exercise</td>
<td>Glucose</td>
</tr>
<tr>
<td>Fasting</td>
<td>Free FA</td>
</tr>
<tr>
<td>ACh, beta-adrenergic agonists</td>
<td>ketones</td>
</tr>
</tbody>
</table>

- Major Actions of Glucagon and Effect on Blood Levels

<table>
<thead>
<tr>
<th>Action of Glucagon</th>
<th>Effect on Blood Level</th>
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<tbody>
<tr>
<td>Increases glycogenolysis</td>
<td>Increases blood glucose</td>
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<tr>
<td>Increases gluconeogenesis</td>
<td>Increases blood glucose</td>
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</table>
Increases lipolysis
Increases blood fatty acids
Increases ketoacid formation
Increases blood ketoacids

--Regulation of Glucagon and Insulin Secretion
  * low blood glucose stimulates release of glucagon
  * high blood glucose stimulates secretion of insulin

--Insulin vs. Glucagon

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<thead>
<tr>
<th></th>
<th>Insulin</th>
<th>Glucagon</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target tissues</td>
<td>Liver, adipose tissue, muscle, and satiety center of hypothalamus</td>
<td>Liver</td>
</tr>
<tr>
<td>Result</td>
<td>Increases uptake of glucose and amino acids by cells</td>
<td>Causes breakdown of glycogen and fats for energy</td>
</tr>
</tbody>
</table>

Somatostatin (GHIH)

--Secreted by: delta cells
--Actions:
  a. Inhibits glucagon and insulin secretion
  b. decreases motility of stomach, duodenum, and gallbladder
  c. decreases secretion and absorption in GI

Disorders of Pancreas

--Diabetes Mellitus
  * results from inadequate secretion of insulin or inability of tissues to respond to insulin

  * Type I: low insulin because of defective B-cells; glucose levels in blood reach very high levels
    a. glucose in urine: dehydration (direct effect on cell, indirect effect on kidney = osmotic diuresis), polyurea, intracellular + extracellular dehydration, thirst \(\rightarrow\) secondary effect= hypertension
    b. increased utilization of fats (ketoadcidosis) \(\rightarrow\) secondary effect increased cholesterol in blood (atherosclerosis)
    c. protein breakdown: weight loss, hunger
    d. Treatment: insulin therapy

  * Type II: decrease in sensitivity to insulin/insulin resistance
    a. obese patients—easier to treat with diet, caloric restriction
    b. Drugs that increase sensitivity: thiazolidinediones and metformin
    c. Drugs that increase insulin secretion: sulfonylureas
Miscellaneous Hormones: Eicosanoids

--local hormones released by all body cells
--2 broad families
  a. Leukotrienes: influences WBCs and inflammation
  b. Prostaglandins: alter
     *smooth muscle contraction (major role), glandular secretion, blood flow, platelet function, nerve transmission, metabolism
     *ibuprofen and other nonsteroidal anti-inflammatory drugs treat pain, fever, and inflammation by inhibiting prostaglandin synthesis
     *first to be discovered (E and F series)
     *Localized actions of PGE/F on the microcirculation adjust local blood flow in response to changing metabolic requirements of the tissue
--Nonsteroidal Anti-inflammatory drugs
  *inhibit a key enzyme in prostaglandin synthesis without affecting the synthesis of leukotrienes
  *treats a variety of inflammatory disorders: rheumatoid arthritis
  *usefulness of aspirin to treat fever and pain implies prostaglandins are responsible for those symptoms
--Prostacyclins: PGI
  *produced by blood vessel wall—blood endothelium may be considered an endocrine tissue
  *potent inhibitors of platelet aggregation (PGI₂ most potent)—maintains vascular flow
  *exert effect via increase levels of cAMP
--Thromboxanes
  *produced by platelets (A₂)
  *elevated during clotting
  *may play a role as Ca ionophore to increase Ca conc.; Ca in turn may regulate the changes in cellular shape needed for platelet aggregation
--Leukotrienes
  *made in leukocytes; leukocytes may be considered wandering endocrine cells
  *potent vasoconstrictors
  *increase vascular permeability
  *induce inflammation or allergic response in sites of injury or invasion by foreign proteins
--Thymus Gland
  *important role in maturation of T cells
*hormones produced by thymus gland: thymosin, thymic humoral factor, thymic factor, thymopoietin

--Growth Factors
*substances with mitogenic qualities (cause cell growth from cell division)
*many act locally as autocrines or paracrines
*Some growth factors: epidermal GF, platelet-derived GF, fibroblast GF, nerve GF, tumor angiogenesis factors, transforming GF

**Calcium Homeostasis**

--Bone is the major storage site for calcium in the body
*calcium moves into bone as osteoblasts build new bone
*calcium moves out of the bone as osteoclasts break down bone
*when osteoclast and osteoblast activity is balanced, movement even

--Calcium ions involved with many body systems
*nerve and muscle cell fuction
*blood clotting
*enzyme function in many biochemical reactions

--Small changes in blood levels of Ca++ can be deadly
*plasma level maintained 9-11mg/100mL
*cardiac arrest if too high
*respiratory arrest if too low

--Ca exists in 3 pools:
a. Bound form: in plasma, nondiffusible across capillaries (41%)
b. non-ionized but bound to anions, diffusible (9%)
c. ionized Ca: diffusible, most important physiologically (50%)

--Regulation of Calcium Ions
*Regulated within narrow range
a. elevated extracellular Ca levels prevent membrane depolarization
b. decreased elveles lead to spontaneous action potential generation

*Terms
a. hypocalcemia
   --NS excitement
   --low extracellular Ca conc. causes an increase in membrane permeability to Na, depolarizing membranes to threshold
   --hyperreflexia: spontaneous twitching, muscle cramps
b. hypercalcemia
   --depresses NS and neuromuscular reflexes; hyporeflexia
   --decreases muscle activity; lethargy
   --decreases QT interval
   --constipation, lack of appetite
   --CaPO$_4$ start to precipitate at high Ca levels

*PTH increases Ca++ extracellular levels and decreases extracellular
phosphate levels
*Vitamin D stimulates Ca++ uptake in intestines
*Calcitonin decreases extracellular Ca++ levels
**Minor changes in Ca have powerful effects on PTH and calcitonin secretion

--Vitamin D stimulates:
a. synthesis of Ca-binding protein in intestinal cells maintains Ca gradient
b. Ca-ATPase to pump it out of cells into capillaries
*small decreases in plasma Ca has dramatic effect on formation of Vit D

--3 Mjnor organs necessary for the production of vitamin D₃
a. Skin
b. Liver
c. Kidneys

--Regulation of Phosphate Ions
a. under normal conditions, reabsorption of phosphate occurs at maximum rate in the nephron
b. an increase in plasma phosphate increases amount of phosphate in nephron beyond that which can be reabsorbed; excess is lost in urine

--People with Hyperparathyroidism
a. Stones: from hypercalciurea
b. Bones: from bone resorption
c. Graons: from constipation