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Endocrinology

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Hypothalamic-Pituitary-Adrenal Axis

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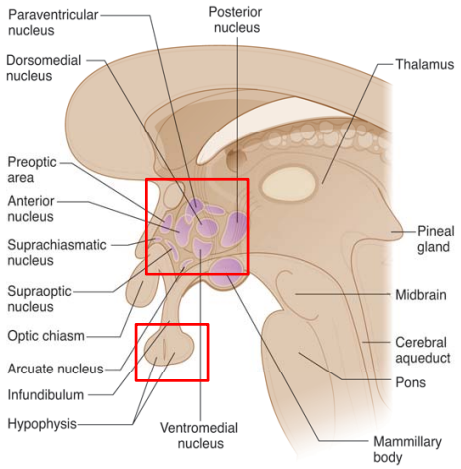
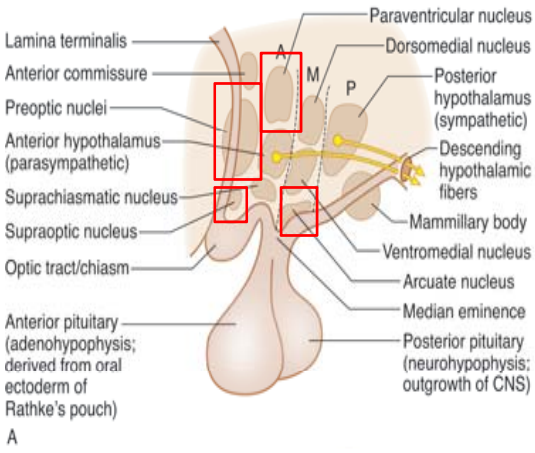
Anatomy of the Hypothalamus

- "Master gland" of the endocrine system
- Function: regulation and general homeostasis of endocrine organs
- Located above the pituitary gland
- Collection of specialized cell nuclei



Anatomy of the Hypothalamus

- Receives sensory input from inside and outside the CNS
- Hypothalamic nuclei
  - Supraoptic nucleus (ADH)
  - Paraventricular nucleus (oxytocin)
  - Arcuate nucleus (hormones and inhibitory factors)
  - Preoptic nucleus (regulates the release of GnRH)



Hypothalamic and Pituitary Hormones

- Hypothalamic hormones trigger the release of anterior pituitary hormones
- The hypothalamus synthesizes:
  - CRH
  - GHRH
  - GnRH
  - TRH
  - Prolactin-releasing factors (PRF) such as serotonin, acetylcholine, opiates, and estrogens (not produced in the hypothalamus)
  - Prolactin-inhibiting factors (PIF) such as dopamine
  - Somatostatin
- Anterior pituitary releases ACTH, GH, FSH, LH, TSH, prolactin

HYPOTHALAMUS	ACTION	PITUITARY
TRH	ACTIVATION	TSH, PROLACTIN
CRH	ACTIVATION	ACTH
GHRH	ACTIVATION	GH
GnRH	ACTIVATION	FSH, LH
PRF	ACTIVATION	PROLACTIN
PIF	INHIBITION	PROLACTIN
SOMATOSTATIN	INHIBITION	GH, TSH

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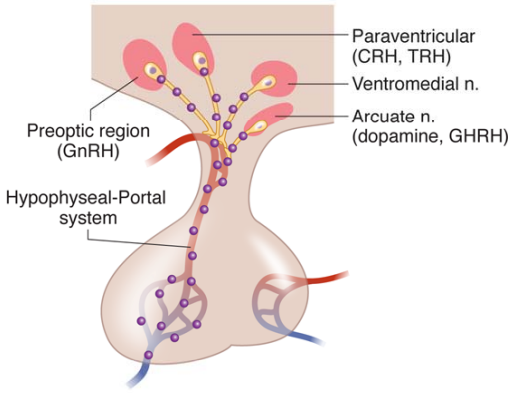
Anterior Pituitary

- Located beneath the optic chiasm and hypothalamus
- Derived from oral ectoderm
- Rathke's pouch can give rise to
  - Benign cysts
  - Craniopharyngiomas



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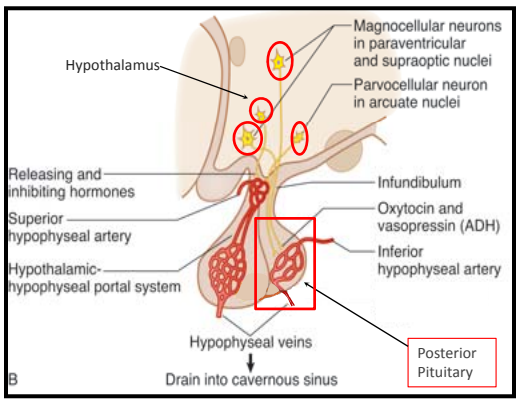
Posterior Pituitary

- Also known as the neurohypophysis
- Derived from neuroectoderm
- Cell bodies reside within the hypothalamus
  - Cell bodies synthesize antidiuretic hormone (ADH) and oxytocin
  - ADH and oxytocin are stored in the neurohypophysis



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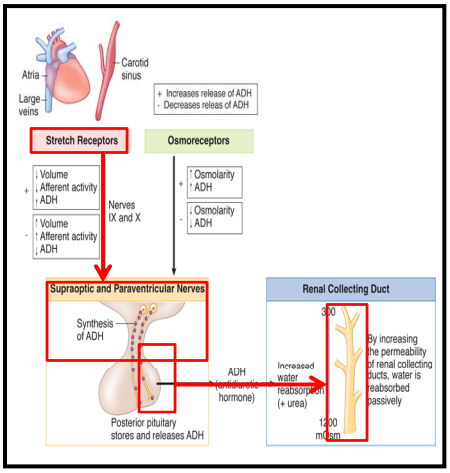
Antidiuretic Hormone

- Synthesized in the supraoptic and paraventricular nuclei
- Also known as arginine vasopressin or AVP
- Regulates blood volume by:
  - Afferent stretch receptors
  - Neural input via cranial nerves IX and X to supraoptic nucleus
  - Raises blood volume
    - Acts upon renal collecting ducts
    - Increases permeability to free water
- An increase in blood volume detected by baroreceptors inhibits ADH secretion
  - Leads to decreased free water reabsorption
  - Leads to decrease in blood pressure



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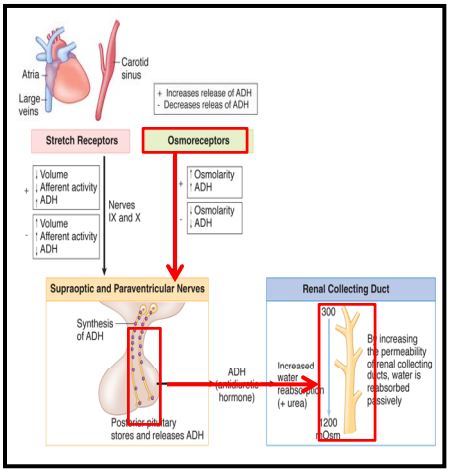
Antidiuretic Hormone

- Regulates serum osmolarity via osmoreceptors (hypothalamus)
  - Responds to change in plasma sodium concentration
  - Maintains normal serum osmotic levels
  - Change in serum osmolarity triggers release or inhibition of ADH secretion
  - Increases or decreases renal free water reabsorption
    - Brings water osmolarity back to normal



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ADH Receptor Physiology

- **V1a** (vascular smooth muscle cell receptors)
  - Found in hepatocytes, cardiac myocytes, platelets, brain, testes
  - Stimulate vasoconstriction
- **V1b or V3**
  - Found in anterior pituitary
  - Stimulate ACTH secretion
- **V2**
  - Found on basolateral membrane of principal cells of distal convoluted tubule and collecting ducts
  - Cause the insertion of aquaporin-2 in collecting ducts
  - Increase urea and Na+ chloride reabsorption (loop of Henle)
  - Increase medullary tonicity
  - Provide osmotic gradient for water absorption
  - Stimulate release of von Willebrand factor (endothelial cells)
- ADH actions upon V2 receptors are instrumental for hypothalamic regulation of osmolarity and volume

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Oxytocin

General Characteristics

- Produced in the paraventricular nucleus of the hypothalamus

Functions

- Uterine contraction during labor
- Stimulates coordinated myometrial contraction (strongest stimulant)
- Induces parturition
- Increases synthesis of uterine prostaglandin
- Induces contraction of myoepithelial cells of the breast during lactation

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Sheehan Syndrome

- Postpartum pituitary necrosis (complication of severe postpartum hemorrhage)

Signs and Symptoms

- Hypopituitarism
- Failure to lactate (most common clinical sign)
- Possible hypothyroidism and hypocortisolism
- Symptoms vary with extension and location of damage
- Posterior pituitary usually spared

Etiology

- Pituitary gland enlargement during pregnancy (particularly lactotroph cells) in response to elevated serum estrogen levels
- Delivery associated with severe blood loss causes arteriolar spasm with subsequent ischemic necrosis
- Some degree of hypopituitarism reported in 32% of women with severe postpartum hemorrhage

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Diabetes Insipidus

- A decrease in either the production or responsiveness to ADH
- Leads to an inability to concentrate urine and reabsorb free water in response to decreased blood volume or increased plasma osmolarity
- Patients experience both marked thirst and polyuria

Diabetes Insipidus

Classification

- Central or nephrogenic, depending on location of the lesion

Central Diabetes Insipidus

- Decreased ADH production from the hypothalamus, due to lesions involving:
  - Hypothalamic osmoreceptors
  - Supraoptic or paraventricular nuclei
  - Supraoptico-hypophyseal tract
- Damage to this region can be caused by:
  - Craniopharyngiomas
  - Pineal tumors
  - Head trauma
  - Iatrogenic neurosurgical injury
  - Infiltrative diseases (e.g., histiocytosis X)

Diabetes Insipidus

Nephrogenic Diabetes Insipidus

- Resistance to ADH stimulation of renal collecting duct ADH receptors
- Can be due to
  - Inherited mutation of the aquaporin gene, leading to the resistance of collecting duct epithelial cells to ADH stimulation
  - Hypercalcemia
  - Lithium
  - Demeclocycline toxicity

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Diabetes Insipidus

Clinical Presentation

- Hypotonic polyuria, dehydration, polydipsia, and hypernatremia

General Workup

- Serum and urine electrolyte panel
- Serum ADH levels
- Urine-specific gravity and sodium
- Urine and serum osmolarity

Diagnosis

- Decreased urine osmolarity
- Increased serum osmolarity (elevated serum sodium level)
- Water deprivation test
  - Fluid intake withheld the night before assessment
  - Normal: increase urine osmolarity and decreased polyuria
  - Vasopressin administration differentiates between central and nephrogenic DI

	Diabetes Insipidus	Dehydration	SIADH	Primary Polydipsia
Urine flow	↑	↓	↓	↑
Urine osmolarity	↓	↑	↑	↓
ECF volume	↓	↓	↑	↑
ECF osmolarity	↑	↑	↓	↓
ICF volume	↓	↓	↑	↑
ICF osmolarity	↑	↑	↓	↓

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Diabetes Insipidus

General management

- Replace lost free water by providing or encouraging adequate fluid intake

Central Diabetes Insipidus

- Desmopressin (ADH analogs in subcutaneous, intranasal, and oral form)
- Surgery when indicated

Nephrogenic Diabetes Insipidus

- Hydrochlorothiazide
- Amiloride
- NSAIDs
- Diuretics: increase urine sodium, which stimulates aldosterone, causing an increase in Na+ reabsorption
  - Free water absorbed with Na+
  - Less free water loss with urine

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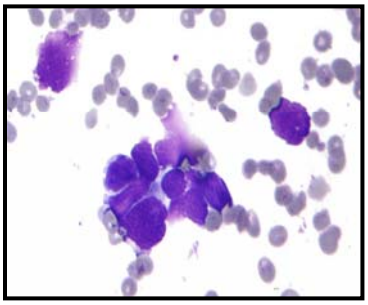
Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH)

- Abnormally high, unregulated ADH secretion by neurohypophysis and abnormal focus outside the CNS



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Etiology

- Small cell carcinoma
- Head trauma
- CNS disorders
- Pulmonary disease
- Drugs
  - Cyclophosphamide
  - SSRIs
  - Sulfonylureas
  - Vincristine
  - TCAs

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SIADH

Signs and symptoms

- Hyponatremia (depending on severity)
- Anorexia, nausea, malaise, headache, muscle cramps, seizures, change in mental status
- Additional symptoms attributable to underlying condition

Diagnosis

- Elevated urine osmolarity
- Decreased serum osmolarity
- Decreased serum sodium levels

Treatment

- Fluid restriction (800–1000 mL/day)
- Demeclocycline
- Hypertonic saline (≤0.5–1 mmol/L/h)
- Too rapid a correction leads to central pontine myelinolysis

	Diabetes Insipidus	Dehydration	SIADH	Primary Polydipsia
Urine Flow	↑	↓	↓	↑
Urine osmolarity	↓	↑	↑	↓
ECF volume	↓	↓	↑	↑
ECF osmolarity	↑	↑	↓	↓
ICF volume	↓	↓	↑	↑
ICF osmolarity	↑	↑	↓	↓

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Prolactin

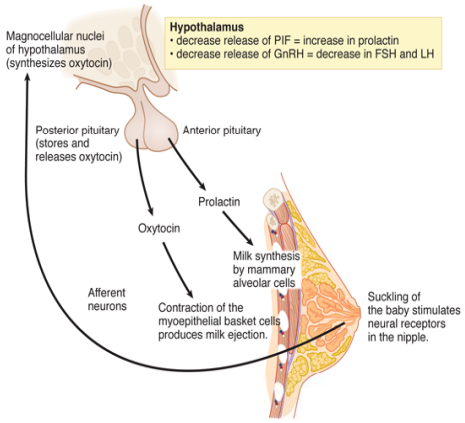
- Secreted from the anterior pituitary

Women

- Stimulated by elevated serum estrogens
- Inhibits GnRH synthesis and secretion → inhibits ovulation
- Up-regulated by nipple stimulation

Men (less significant role)

- Not part of the normal male reproductive hormone feedback loop
- Inhibition of GnRH has inhibitory influence on spermatogenesis



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Prolactin

General characteristics of prolactin regulation

- Regulated by hypothalamic dopamine (prolactin-inhibiting factor)
- Increased serum prolactin levels stimulate dopamine release from the hypothalamus inhibiting anterior pituitary secretion of prolactin
- TRH increases prolactin secretion

Prolactin physiology is altered in certain disease states and by drugs:

- Dopamine agonists: decrease prolactin
  - Bromocriptine (used in prolactinomas)
- Dopamine antagonists: increase prolactin
  - Antipsychotics
  - Synthetic estrogens (oral contraceptive pills)

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Pituitary Adenomas

Classification

- Microadenomas: <1 cm, estimated prevalence 10% in the United States
- Macroadenomas: >1 cm

General characteristics

- Prolactinomas most common
- Signs and symptoms corresponding to the overproduction of each hormone
  - ACTH overproduction: Cushing disease
  - Growth hormone: acromegaly
  - Prolactinomas: amenorrhea, galactorrhea, low libido, infertility
- Adenomas may grow to a size that causes symptoms of local mass effect:
  - Visual field defects due to impingement of the optic chiasm
  - Headaches due to elevated intracranial pressure or hemorrhage
  - Sudden hemorrhage may be due to pituitary infarction → pituitary apoplexy associated with circulatory collapse and death if not recognized and treated on time

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Pituitary Adenoma

Treatment

- Prolactinomas: dopamine agonists (e.g., bromocriptine and cabergoline)
- Other types:
  - Surgical resection
  - Radiation
- Post-therapy, pituitary hormone replacement
  - Immediate replacement of TSH, cortisol, and ADH
  - Non-immediate hormone replacement
    - Follicle-stimulating hormone
    - Luteinizing hormone
    - Growth hormone

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Growth Hormone

- Synthesized and secreted by anterior pituitary cells (somatotrophs)
- Required for normal growth

Direct catabolic effects

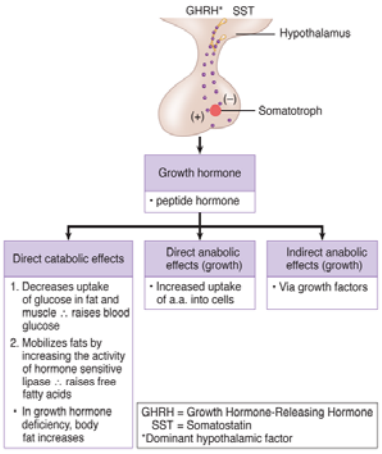
- Decreases uptake of glucose in fat and muscle
- Mobilizes fats by increasing the activity of hormone sensitive lipase (raises serum-free fatty acids)

Direct anabolic effects

- Increased uptake of amino acids into cells

Indirect anabolic effects

- Produces growth factors called somatomedins or insulin-like growth factors
  - Growth factor secretion is pulsatile, occurring mostly at night during sleep



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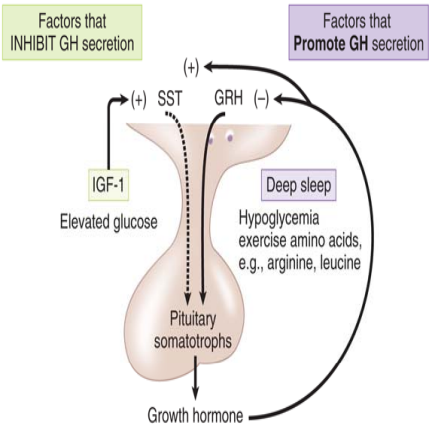
Growth Hormone

- Factors that stimulate growth hormone secretion
  - Hypoglycemia
  - Stress
  - Deep sleep
  - Exercise
  - Amino acids
- Factors that inhibit growth hormone secretion
  - Somatostatin
- Growth hormone exerts negative feedback inhibition of further growth hormone



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Growth Hormone

Indirect actions

- Stimulates production of peptide growth factors (somatomedins or insulin-like growth factors-IGF)
- Stimulates production of somatomedins via receptor-associated tyrosine kinase (JAK/STAT pathway) in liver and other tissues
  - Somatomedins have proinsulin-like structure and insulin-like activity
    - Bind to plasma proteins
    - Act via the MAP kinase (intrinsic tyrosine kinase cell signaling pathway)
    - Stimulate bone and cartilage growth during puberty
    - Increase protein synthesis for the growth and maintenance of visceral organs
    - Increase and maintain lean body mass

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Acromegaly

- Caused by excess secretion of GH
- 95% of cases due to GH-secreting pituitary adenomas
- Remaining cases due to ectopic secretion by malignant tumors
- When presenting in children, known as gigantism

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Signs and symptoms

- Insulin antagonism or resistance
- Coarse voice
- Increased risk of colonic polyps
- Macrognathia (enlarged jaw)
- Enlargement of facial bones
- Hand and feet overgrowth
- Hypertrophy of visceral organs
- Bilateral carpal tunnel syndrome

Acromegaly

Diagnosis

- Elevated serum insulin-like growth factor (used to both screen and monitor the efficacy of therapy)
- Failure to suppress serum GH following an oral glucose tolerance test

Treatment

- Goal of treatment
  - Glucose-suppressed GH concentration <2 ng/mL
  - Normalization of serum IGF-1 concentration
- Surgery first
- Medical therapy for residual disease
  - Octreotide (somatostatin analogue)

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The Thyroid

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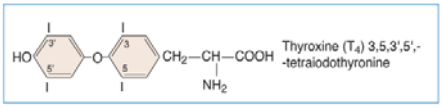
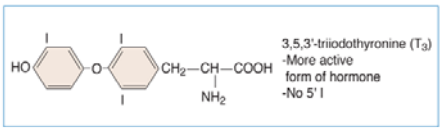
Thyroid Hormone

Characteristics

- Anabolic hormone
- Secreted in 2 forms: T3 and T4
  - Ratio of T4:T3 is 20:1
  - T3 is more active than T4





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Thyroid Hormone

Function

- ↑ metabolic rate through ↑ sodium-potassium ATPase activity, leading to :
  - ↑ oxygen consumption
  - ↑ respiratory rate
  - ↑ body temperature
- Essential for bone growth and normal brain maturation (in synergism with growth hormone)
- ↑ beta-1 receptors in the heart:
  - ↑ cardiac output, ↑ heart rate, ↑ contractility, ↑ stroke volume
- ↑ glycogenolysis, gluconeogenesis
- ↑ lipolysis, cholesterol clearance from plasma
- ↑ erythropoietin levels
- ↑ gut motility
- ↑ bone turnover

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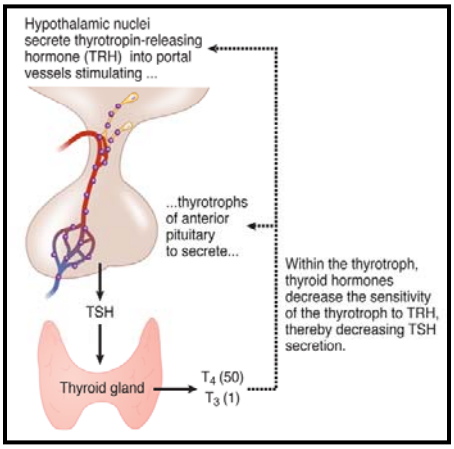
Thyroid Hormone Regulation

Steps

- Hypothalamus secretes TRH into portal vessels
- Pituitary thyrotrophs secrete TSH (into the plasma)
- Thyroid gland secretes T4 and T3
- Thyroid hormones act as negative feedback to inhibit further secretion of TRH and TSH
- T4 is responsible for most of the negative feedback



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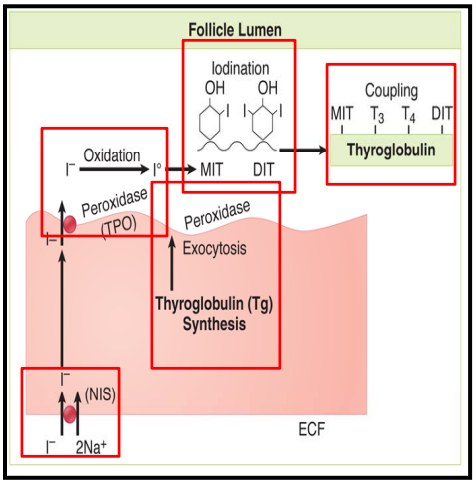
Thyroid Hormone Synthesis

- Begins with iodide (diet)
- Iodide enters the thyroid follicular cell lumen by active transport
  - Thyroperoxidase (apical border) catalyzes oxidation of iodide to iodine
  - Peroxidase catalyzes iodination of thyroglobulin (within follicle cells)
- Iodination of thyroglobulin's tyrosine residue yields 2 products:
  - *Monoiodotyrosine (MIT)*
  - *Diiodotyrosine (DIT)*
- Peroxidase also catalyzes coupling
  - 2 diiodotyrosine molecules = T4
  - Monoiodotyrosine + diiodotyrosine = T3
  - Stored in the follicular colloid
- Stored thyroid hormones can last in the body for 2–3 months



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Transport of Thyroid Hormones

- Thyroid hormones:
  - Are lipid-soluble hormones
  - Are carried in the plasma attached to plasma proteins called thyroid binding globulins (TBG)
  - Act within target tissues upon receptors inside cells, in the nucleus
  - Stimulate synthesis of new specific proteins
- 99% of circulating thyroid hormone is bound to TBG
- The amount of circulating hormone is roughly 3 times the amount normally secreted each day; therefore, the circulating protein-bound fraction serves as reservoir
- T4 has half-life of 6 days (due to higher affinity for TBG)
- T3 has half life of 1 day

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Activation and Degradation of Thyroid Hormones

- T3 and T4 bind to the same nuclear receptors at target tissues
- T3 binds with more affinity (more active form)
- Within the nucleus, they bind to an enhancer-like element in DNA to induce protein synthesis
- Many target tissues can regulate the conversion of T4 to T3, allowing for some local hormonal control
- TSH: initial *screening test* for hypo- and hyperthyroidism
- T4 levels used to *confirm diagnosis*
- Free T4 (total thyroid concentration) can vary depending on TBG levels due to:
  - Pregnancy
  - Oral contraceptive use
  - Liver failure

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General Characteristics of Hypothyroidism

Signs and symptoms

- Decreased basal metabolic rate
- Decreased oxygen consumption
- Cold intolerance
- Constipation
- Cool, dry skin
- Hyperprolactinemia secondary to increased TRH
  - In women, manifests as amenorrhea, galactorrhea or anovulatory cycles with menorrhagia
  - In men, manifests as infertility or gynecomastia

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General Characteristics of Hypothyroidism

Signs and symptoms, cont'd

- Lethargy
- Change in mental status
- Decreased food intake
- Hyperlipidemia and hypercholesterolemia
- Decreased ventilatory drive, hypercapnia, and hypoxia
- Decreased cardiac performance
- Myxedema (severe, long-standing hypothyroidism)
  - Myxedema crisis or coma, precipitated by major physiological stressors
    - Hypotension
    - Hypothermia
    - Generalized non-pitting edema
    - Hypoventilation
    - Bradycardia
    - Ileus

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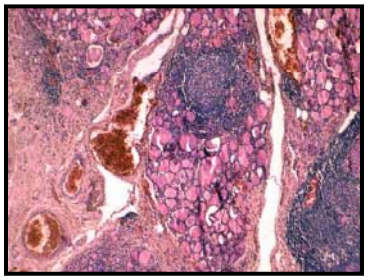
Types of Hypothyroidism



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- Hashimoto's thyroiditis
- Subacute thyroiditis (de Quervain's thyroiditis)
- Riedel's thyroiditis
- Congenital hypothyroidism (cretinism)

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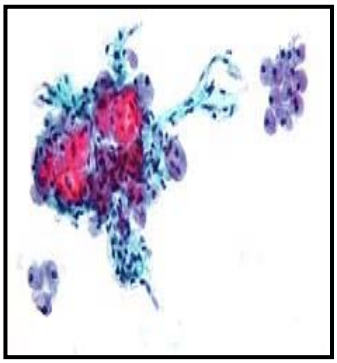
Hypothyroidism: Hashimoto Thyroiditis

Characteristics

- Most common cause of hypothyroidism
- Chronic autoimmune disorder
- Antibodies produced against:
  - Thyroid peroxidase (TPO) (microsomal antigen)
  - Thyroglobulin (Tg)
- Associated with HLA-DR5 antigen serotype
- Biopsy findings: lymphocytic infiltration (germinal centers) and Hurthle cells
- ↑ risk of non-Hodgkin B-cell lymphoma
- Specific signs and symptoms:
  - Enlarged, non-tender thyroid
  - Symptoms of hyperthyroidism prior to symptoms of hypothyroidism



Hurthle cell neoplasm, commons.wikimedia.org. Used with permission

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Hypothyroidism: de Quervain Thyroiditis

Characteristics

- Second most common cause of thyroiditis
- Self-limited form of hypothyroidism that often follows “flu-like” illness
- May also present with hyperthyroidism early in its course
- Associated with:
  - Elevated erythrocyte sedimentation rate
  - Jaw pain
  - Thyroid area tenderness
- Biopsy: granulomatous inflammation

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x1.5 EN02-12

Hypothyroidism: Riedel Thyroiditis

Characteristics

- Chronic inflammation where dense fibrosis replaces thyroid parenchyma
- Presents with a fixed, hard, painless goiter that is asymmetrically enlarged
- Etiology unknown
  - Autoimmune phenomenon or primary fibrotic disorder

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Congenital Hypothyroidism (Cretinism)

Characteristics

- Caused by iodine deficiency during intrauterine and neonatal life
  - In endemic regions, due to iodine deficiency
  - In non-endemic regions, due to thyroid dysgenesis
- Affected individuals present with:
  - Failure to thrive
  - Stunted bone growth
  - Dwarfism
  - Spasticity
  - Motor incoordination
  - Mental retardation

FA 2012: 325 • FA 2011: 298 • FA 2010: 293 • ME 3e 388

x1.5 EN02-14

General Characteristics of Hyperthyroidism

Signs and symptoms

- Heat intolerance secondary to an increase in metabolic rate and heat production
- Weight loss with increased food intake
- Protein-wasting and subsequent muscle weakness
- Diarrhea
- Decreased serum cholesterol levels
- Increased cardiac output
- Increased heart contractility
- Increased heart rate manifesting as palpitations and arrhythmias
- Tremor
- Nervousness
- Excessive sweating
- Warm, moist skin
- Fine hair
- Increased deep tendon reflexes

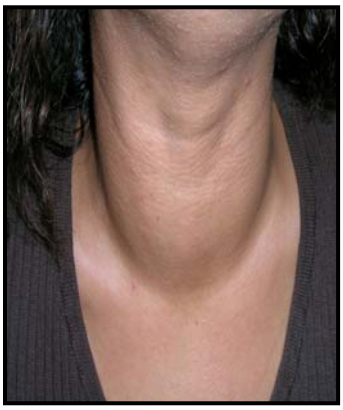
Conditions Causing Hyperthyroidism

- Graves' disease
- Toxic multinodular goiter
- Thyroid adenoma
- TSH-secreting pituitary adenoma

Hyperthyroidism: Graves' Disease

Characteristics

- Most common cause of thyrotoxicosis
- Autoimmune disease (caused by TSH receptor antibodies)
- Type II hypersensitivity reaction
- Symmetrical enlargement of the thyroid
- Hypersecretion of thyroid hormones
- Patients tend to be young women
- Common in post-partum period
- Symptoms:
  - Hyperthyroidism
  - Pretibial myxedema (glycosaminoglycans)
  - Exophthalmos
- If untreated, may lead to thyroid storm



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x1.5 EN02-17

Hyperthyroidism: Toxic Multinodular Goiter

Characteristics

- Caused by focal regions of hyperfunctioning follicular cells (independent of TSH)
- Due to a mutation of the TSH receptor
- Patchy nodules of disease involvement (hot nodules)
  - Seen on nuclear imaging (increased uptake of I^{123} or Tc^{99})
- Can be the result of chronic iodide deficiency
  - Excessive TSH stimulation induces
    - Focal hyperplasia
    - Subsequent necrosis and hemorrhage
    - Nodule formation
- Induced by excess iodide intake (Jod-Basedow syndrome)
  - Follows iodinated radiocontrast study
  - Involves abnormal adaptation of the thyroid to iodide excess
  - Treatment: cessation of excess iodine intake

[Torstein] Woman with struma, Martin Finborud (1861-1930. commons.wikimedia.org. Used with permission

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x1.5 EN02-18

Hyperthyroidism: Thyroid Adenoma

Characteristics

- Benign, monoclonal tumors
- Most commonly comprised of follicular cells
- Called “cold nodules”
  - Normal appearance on radioactive iodine uptake scan
- May become autonomous → hyperthyroidism
- Treatment: surgical thyroid lobectomy

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x1.5 EN02-19

Action and Effects of Anti-thyroid Agents

Medications known to inhibit thyroid hormone synthesis

- Propylthiouracil
- Methimazole
- Drug class: thioamides
- Used in the treatment of hyperthyroidism

Mechanism of action

- Inhibit organification of iodide
- Inhibit coupling of thyroid hormone synthesis
- Propylthiouracil also decreases peripheral conversion of T4 to T3 (similar effect seen with beta blockers)
- Thioamides do not inactivate existing T4/T3 (slow onset of action)
- Thyroid hormone bound to TBG serves as pool of thyroid hormone

Side effects

- Maculopapular rash, agranulocytosis (rare), aplastic anemia
- Propylthiouracil is safer in pregnancy as it is tightly bound to proteins

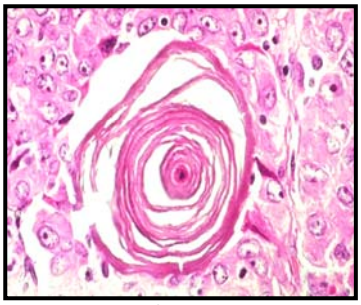
FA 2012: 334 • FA 2011: 298 • FA 2010: 299 • ME 3e 389

x1.5 EN02-20

Carcinomas of the Thyroid: Papillary Carcinoma

Characteristics

- Most common thyroid carcinoma
- Women > men
- History of radiation exposure predisposes to papillary carcinoma
- Good prognosis due to its slow-growth
- Involves metastasis to adjacent lymph nodes



AFIP Atlas of Tumor Pathology, psammoma, commons.wikimedia.org. Used with permission

Histology

- Psammoma bodies (round collections of calcium)
- Found in stroma of the tumor
- Nuclei have empty ground-glass appearance, with characteristic nuclear grooves (Orphan Annie nuclei)

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x1.5 EN02-21

Carcinomas of the Thyroid: Follicular Carcinoma

Characteristics

- Accounts for 15% of malignant thyroid tumors
- Women > men
- Involves hematogenous metastasis (bones or lungs)

Histology

- Normal-appearing, uniform follicles

FA 2012: 326 • FA 2011: 298 • FA 2010: 293 • ME 3e 389

x1.5 EN02-22

Carcinomas of the Thyroid: Medullary Carcinoma

Characteristics

- Accounts for 5% of malignant thyroid tumors
- Arises from parafollicular “C” cells
- Produces and secretes calcitonin
- Associated with MEN types 2A and 2B
- Due to a mutation in the RET proto-oncogene

Histology

- Sheets of cells in amyloid stroma

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x1.5 EN02-23

Carcinomas of the Thyroid: Anaplastic Carcinoma

Characteristics

- Common in women age >60
- Presents as firm, enlarging mass causing mass effect upon surrounding structures
- Patients may have dyspnea and dysphagia
- Tendency for early and widespread invasion and metastasis
- Carries very poor prognosis

Histology

- Undifferentiated, anaplastic, pleomorphic cells
- High mitotic activity

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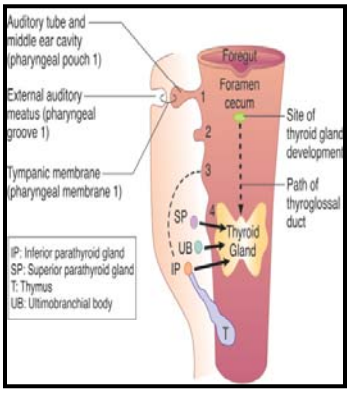
x1.5 EN02-24

Thyroglossal Duct Cyst

Embryological origin

- Develops from endodermal diverticulum at floor of the pharynx
- Migrates caudally to anterior aspect of the neck
- Remains connected to the foregut via the *thyroglossal duct* (normally obliterates)
- Foramen cecum marks former site of the duct



Ectopic thyroid tissue

- Most common site is tongue
- Not associated with hypo- or hyperfunctionality
- Cysts may be nidus for infection
- Rarely harbors carcinomas
- Before surgical removal, ensure presence of normal thyroid tissue

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x1.5 EN02-25

KAPLAN MEDICAL

The Parathyroids and Calcium Homeostasis

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x1.5

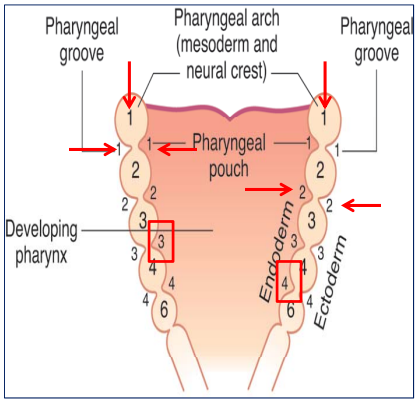
Embryologic Development of the Parathyroids

Pharyngeal apparatus

- Pharyngeal arches (mesoderm and neural crest)
- Pharyngeal pouches (endoderm)
- Pharyngeal grooves or clefts (ectoderm)

Parathyroid glands arise from:

- Pouch 3, which yields the inferior parathyroid glands
- Pouch 4, which yields the superior parathyroid glands and ultimobranchial body (parafollicular "C" cells of the thyroid)



FA 2012:135 • FA 2011: 127 • FA 2010: 128 • ME 3e 429

x1.5 EN03-2

Parathyroid Hormone

Characteristics

- Peptide hormone
- Function is to raise plasma-free calcium levels by several mechanisms
- Secretion induced by decreased plasma Ca^{2+}
- Parathyroid cells ("chief" cells) sense free calcium via calcium-sensing receptors
- Secretion dependent on subsequent rise in intracellular magnesium
- Depletion of magnesium stores can create reversible hypoparathyroidism

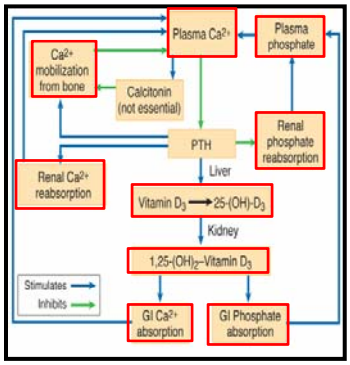
FA 2012: 320 • FA 2011: 293 • FA 2010:288 • ME 3e 383

x1.5 EN03-3

Parathyroid Hormone (PTH)

General actions

- In the bone
  - ↑ resorption calcium
  - ↑ resorption phosphate
  - ↑ production macrophage-colony stimulating factor (M-CSF)
    - Released by osteoblasts, acts on osteoclasts
- In the kidneys
  - ↑ reabsorption calcium
  - ↓ reabsorption phosphate (distal convoluted tubule)
  - ↑ production 1,25-$(OH)_2$-vitamin D (calcitriol)
  - Stimulates 1α-hydroxylase
- Small intestine
  - 1,25-$(OH)_2$-vitamin D ↑ absorption Ca^{2+} and phosphate
- Net effect: ↑ serum Ca+, ↓ serum PO_4^{3-}, ↑ urine PO_4^{3-}



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x1.5 EN03-4

PTH and Calcium Homeostasis

Phosphate

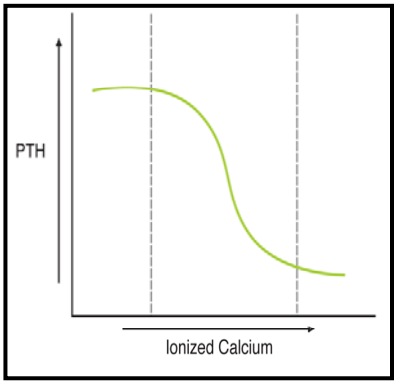
- Binds to calcium in the plasma
- Decreases available free ionized calcium concentration

PTH

- Decreases renal phosphate reabsorption
- Increases plasma concentration of ionized calcium
- Excessive phosphate will be excreted in urine

Vitamin D

- Acts as a co-regulator
- Imposes checks and balances on PTH



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x1.5 EN03-5

Vitamin D

Vitamin D

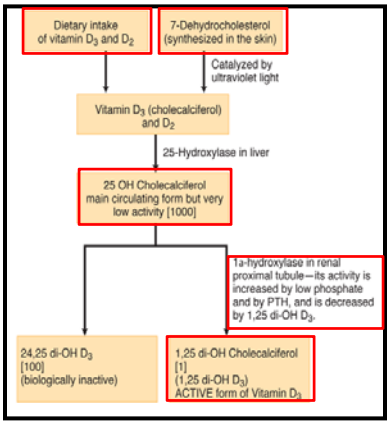
- Can functionally be considered a pro-hormone
- Vit D_2 and D_3 are obtained from the diet
- Vit D_3 (cholecalciferol) is synthesized in the skin
- Converted to 25-(OH) cholecalciferol in the liver
- Stored in body fat (best measure of body stores)

PTH

- Increases activity of 1α-hydroxylase (renal proximal tubule)
- Induces conversion of 25-(OH) cholecalciferol to 1,25-$(OH)_2$ vitamin D3 (calcitriol)

Calcitriol (active form)

- Decreases activity of 1α-hydroxylase
- Raises plasma calcium and phosphate levels
- Promotes bone deposition
- PTH net effect: ↑ serum Ca^{2+} and ↓ serum PO_4^{3-}
- Vit D net effect: ↑ serum Ca^{2+} and ↑ serum PO_4^{3-}



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x1.5 EN03-6

Hypoparathyroidism

Etiology

- Iatrogenic, as a result of surgical removal of parathyroid glands (e.g., total thyroidectomy)
- DiGeorge syndrome

Signs and symptoms

- Hypocalcemia
- Psychiatric disturbances
- Cardiac conduction defects (prolonged QT interval on EKG)
- Increased motor neuron excitability (muscular spasms and tetany)
- Chvostek sign (twitching of ipsilateral facial muscles induced by tapping)
- Trousseau sign (induction of muscular contractions by inflating BP cuff)

Treatment: calcium and vitamin D (hypocalcemia)

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x1.5 EN03-7

Pseudohypoparathyroidism

Characteristics

- Rare familial disorder
- Characterized by target tissue resistance to parathyroid hormone (particularly in the kidneys)
- Same signs and symptoms as primary hypoparathyroidism (except elevated PTH)
- Usually accompanied by:
  - Developmental defects
  - Mental retardation
  - Short and stocky stature
  - 1+ missing metacarpal or metatarsal bones (short fingers)

FA 2012: 327 • FA 2011: 299 • FA 2010: 294 • ME 3e 385

x1.5 EN03-8

DiGeorge Syndrome

Etiology

- Embryologic failure to develop third and fourth pharyngeal pouches
- Absence of parathyroid glands and thymus
- Due to a deletion on chromosome 22 at q11.2 location

Signs and symptoms

- Dysregulation of calcium homeostasis: hypocalcemia and tetany
- T-cell deficiency and recurrent infections with viral and fungal organisms
- Possible cardiac defects

Treatment: no cure; address and treat individual features

FA 2012: 327 • FA 2011: 299 • FA 2010: 294 • ME 3e 385

x1.5 EN03-9

Hyperparathyroidism

Primary hyperparathyroidism: defect lies within parathyroid glands

Etiology

- Parathyroid adenomas (most common)
  - May be associated with MEN types 1 and 2a
- Parathyroid hyperplasia
- Parathyroid carcinoma (rare)

Signs and symptoms

- Elevated calcium and PTH
- Serum chloride to phosphate ratio >33 (in those not taking thiazide diuretics)
- Often asymptomatic
- Possible kidney stones
- Osteoporosis
- Osteitis fibrosa cystica (cystic bone spaces filled with brown fibrous tissue)
- Metastatic calcification
- Neurologic changes

Treatment: surgical removal of hyperfunctioning glands

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x1.5 EN03-10

Hyperparathyroidism

Secondary hyperparathyroidism

- Caused by any disease that results in hypocalcemia
- Increased secretion of PTH by parathyroid glands

Etiology

- Chronic kidney disease (no coversion of Vit.D to active form, no excretion of PO_4, leading to formation of insoluble $CaPO_4$)
- Vitamin D deficiency
- Malabsorption syndromes

Signs and symptoms

- Hypocalcemia
- Hyperphosphatemia
- Elevated PTH

Treatment: treat underlying cause

- Dietary phosphorus restriction and vitamin D (chronic kidney disease)
- If untreated, the disease will progress to tertiary hyperparathyroidism

Tertiary hyperparathyroidism

- Caused by chronic parathyroid hormone stimulation
- Treatment: surgical removal of 3 of the parathyroid glands

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x1.5 EN03-11

Calcitonin

Characteristics

- Plays minimal role in maintaining calcium homeostasis
- Secreted by parafollicular “C” cells of thyroid gland
- Induced by elevated free serum calcium levels
- Decreases activity of osteoclasts, thus decreasing bone resorption
- Used therapeutically in some clinical contexts:
  - Acute, symptomatic hypercalcemia in conjunction with:
    - Aggressive hydration
    - Loop diuretics
    - Dialysis (if needed)
- Medullary carcinoma of the thyroid secretes calcitonin and is associated with MEN 2A and 2B

FA 2012: 321 • FA 2011: 294 • FA 2010: 289 • ME 3e 383

x1.5 EN03-12

KAPLAN MEDICAL

The Adrenals—Steroids and Catecholamines

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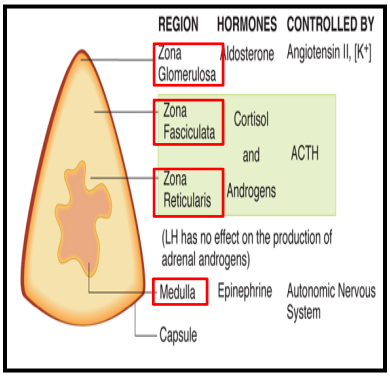
x1.5

Adrenal Glands

Encapsulated organ composed of:

- **Adrenal cortex (derived from mesoderm)**
- **Zona glomerulosa (outermost region)**
  - Regulated by renin-angiotensin system
  - Produces aldosterone
- **Zona fasciculata (between reticularis and glomerulosa)**
  - Regulated by adrenocorticotropic hormone
  - Produces cortisol and androgens
- **Zona reticularis (innermost region)**
  - Influenced by adrenocorticotropic hormone
  - Produces androgens independent of GnRH, FSH, and LH
- **Adrenal medulla (derived from neural crest cells)**
  - Influenced by preganglionic sympathetic nerve fibers
  - Produces catecholamines



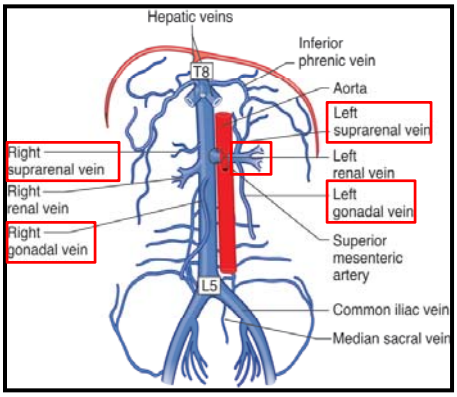
FA 2012: 314 • FA2011: 288 • FA 2010: 284 • ME 3e 372

x1.5 EN04-2

Venous Drainage of the Adrenal Glands

Venous drainage

- **Left adrenal gland**
  - Left adrenal vein → left renal vein → inferior vena cava
- **Right adrenal vein**
  - Directly into inferior vena cava
- **Right gonadal vein**
  - Directly into inferior vena cava
- **Left gonadal vein**
  - Left gonadal vein → left renal vein → inferior vena cava



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x1.5 EN04-3

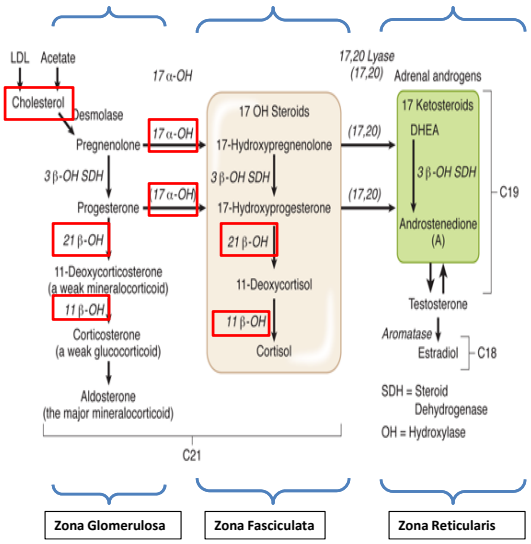
Adrenal Steroids: Synthesis Pathway

Characteristics

- Derived from cholesterol
- Aldosterone and cortisol: 21 carbons
- Androgens: 19 carbons

Enzyme deficiencies

- 17α-hydroxylase: cortisol and androgens
- 21-hydroxylase: cortisol and ALL mineralcorticoids
- 11β-hydroxylase: cortisol and aldosterone (but not all mineralcorticoids)



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x1.5 EN04-4

Adrenal Enzyme Deficiencies

- Enlargement of adrenal glands (↑ ACTH stimulation)

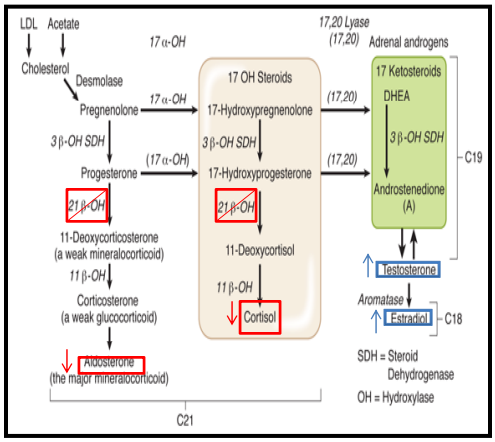
21-hydroxylase deficiency (most common)

- Decreased cortisol
- Decreased mineralocorticoid
- Increased sex hormones

Signs and symptoms

- Hypotension (decreased aldosterone)
- Sodium and volume loss
- Hyperkalemia
- Elevated plasma renin
- Women: virilization of fetus and sexual ambiguity at birth
- Men: phenotypically normal, precocious pseudo-puberty, premature epiphyseal plate closure

Treatment: replace glucocorticoids and mineralocorticoids



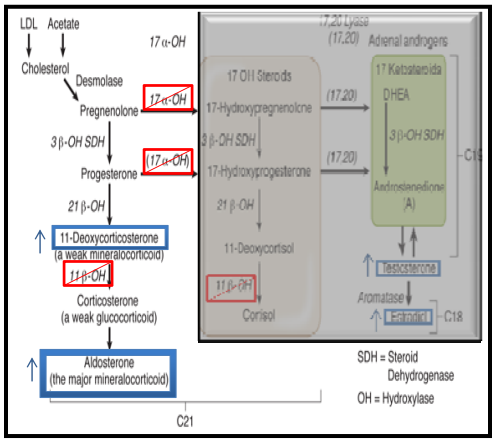
Adrenal Enzyme Deficiencies

11β-hydroxylase deficiency

- Accounts for 7% of adrenal enzyme deficiencies
- ↑ androgens
- Virilization of female fetuses
- ↑ 11-deoxycorticosterone
- Hypertension
- Hypokalemia
- Suppressed renin secretion

17α-hydroxylase deficiency

- Extremely rare
- ↓ adrenal androgens and cortisol
- Excess mineralocorticoids
- Patients diagnosed at time of puberty
- Hypertension
- Hypokalemia
- Hypogonadism



Cortisol

Characteristics

- Acts to mobilize energy stores to cope with physiologic stressors
- Promotes degradation and increased delivery of amino acids
- Promotes lipolysis and increased delivery of free fatty acids and glycerol
- Raises blood glucose
- Inhibits glucose uptake in most tissues
- Increases hepatic output of glucose via gluconeogenesis from amino acids

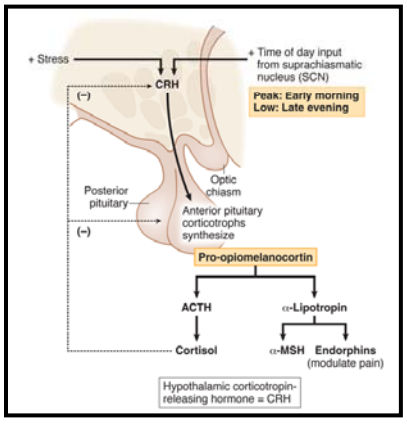
FA 2012: 319 • FA2011: 292 • FA 2010: 287 • ME 3e 372

x1.5 EN04-7

Cortisol

Characteristics, cont'd

- Enhances capacity of glucagon and catecholamines
- When decreased, is associated with circulatory collapse
- Exerts negative feedback control of CRH and ACTH secretion
- Secreted in a pulsatile fashion
- Blood levels:
  - Highest in AM, just before waking
  - Lowest at night, as CRH secretion declines slowly during the day



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x1.5 EN04-8

Cortisol

Characteristics, cont'd

- Has catabolic effect on bone
  - Long-term steroid use is a risk factor for osteoporosis and avascular necrosis of bone and bone marrow
- Is very potent immunosuppressant, useful with:
  - Auto-immune disease
  - Transplants
  - Asthma
  - Allergies
- Anti-inflammatory and immunosuppressant effects are due to:
  - Inhibition of phospholipase A2
  - Inhibition of production of IL-2

FA 2012: 319 • FA2011: 292 • FA 2010: 287 • ME 3e 372

x1.5 EN04-9

Cushing's Syndrome

Definition

- Syndrome that results from continued exposure to high levels of glucocorticoid steroids, whether endogenous or exogenous

Etiology

- Most common cause is iatrogenic (cortisol administration)
- May be due to:
  - ACTH-secreting pituitary adenoma (known as Cushing's disease)
  - Ectopic ACTH secretion (e.g., small cell lung carcinoma)
  - Adrenal adenoma
  - Adrenal carcinoma
  - Nodular adrenal hyperplasia

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x1.5 EN04-10

Cushing's Syndrome

Signs and symptoms

- Central obesity, "moon" face and "buffalo hump"
- Protein depletion due to excessive protein catabolism
- Poor wound healing
- Hyperglycemia, leading to hyperinsulinemia and insulin-resistance
- Hyperlipidemia
- Bone dissolution and osteoporosis
- Thinning of the skin with wide purple striae
- Increased adrenal androgens
  - Women: acne, mild hirsutism, amenorrhea
  - Men: decreased libido and impotence
- Salt and water retention
  - Hypertension
  - Potassium depletion
  - Hypokalemic alkalosis
  - Polydipsia, polyuria
- Anxiety, depression, and other emotional disorders

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x1.5 EN04-11

Cushing's Syndrome

Dexamethasone test measures ACTH response after exogenous dexamethasone

Cushing's disease

- ACTH-secreting pituitary adenomas
- Abnormally elevated ACTH levels
- Inhibited by high dexamethasone dose

Ectopic ACTH-secreting tissues

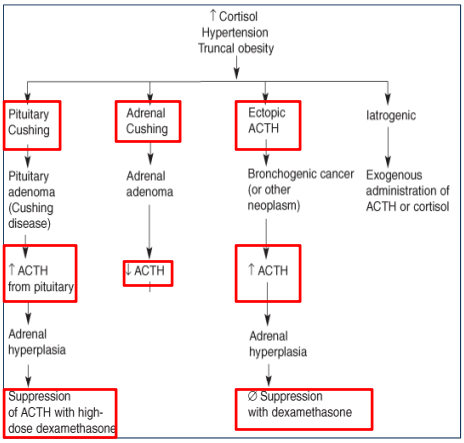
- Small-cell lung carcinoma and bronchial carcinoid
- Elevated serum ACTH levels
- Not suppressible by high-dose dexamethasone

Cushing's syndrome

- Adrenocortical adenomas
- Nodular adrenal hyperplasia
- Low ACTH levels

Treatment

- Surgery when possible
- Ketoconazole to inhibit desmolase



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x1.5 EN04-12

Addison's Disease: Primary Hypocortisolism

Characteristics of cortisol deficiencies

- Weakness, fatigue, anorexia, hypotension, hyponatremia, hypoglycemia

Etiology

- Adrenal atrophy or destruction by autoimmune disease
- Infectious disease such as TB
- Neoplasm, either primary or metastatic

Signs and symptoms

- Aldosterone deficiency (sodium-wasting and hyponatremia)
- Hyperkalemia, dehydration, hypotension, acidosis
- Loss of axillary and pubic hair, amenorrhea (in females)
- Darkening of the skin

Autoimmune-associated adrenal destruction

- Onset of symptoms is slow
- Loss of 90% of both adrenals required before symptoms
- Basal secretion is normal but does not respond to stress

Acute-onset adrenal insufficiency

- May be due to bilateral adrenal hemorrhage
- Adrenal crisis
- Hyperpigmentation (usually absent)
- Hyponatremia, hyperkalemia

Secondary Hypocortisolism

Etiology

- Decreased pituitary ACTH production due to
  - Withdrawal of exogenous glucocorticoid therapy
  - Pituitary or hypothalamic tumor

Signs and symptoms

- Cortisol deficiency
- Hypopituitarism or hormonal excess (pituitary hormone-secreting tumor)
- Atrophy of zona fasciculata and zona reticularis
- Zona glomerulosa not affected (normal aldosterone)

Treatment

- Addison and primary hypocortisolism: treat underlying condition
  - Lifelong exogenous glucocorticoids and mineralcorticoid supplementation
- Secondary hypocortisolism: treat underlying condition
  - Lifelong exogenous glucocorticoids but no mineralocorticoid supplementation required

Conn Syndrome: Primary Hyperaldosteronism

Etiology

- Aldosterone-secreting adrenal adenoma (most common)
- Bilateral adrenal hyperplasia
- Adrenal carcinoma

Signs and symptoms

- Hypertension, secondary to increased peripheral vasoconstriction
- Hypokalemia, leading to weakness and fatigue
- Metabolic alkalosis, secondary to increased hydrogen ion excretion
- Decreased plasma renin level
- Infrequent hypernatremia (due to “sodium escape”)

FA 2012: 323 • FA2011: 296 • FA 2010: 291 • ME 3e 375

x1.5 EN04-15

Secondary Hyperaldosteronism

- Appropriate increase of aldosterone in response to activation of renin-angiotensin system

Etiology

- Decrease in renal blood flow with resultant excessive secretion of renin
- Renal artery stenosis
- Renal vascular disease due to atherosclerosis or fibromuscular dysplasia
- Chronic renal failure
- Congestive heart disease
- Cirrhosis
- Nephrotic syndrome

Treatment

- Treat underlying cause
- Surgery if indicated
- Spironolactone (aldosterone receptor blocker)

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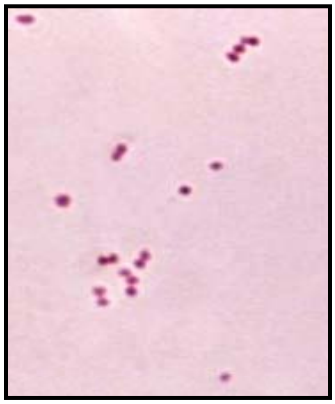
x1.5 EN04-16

Waterhouse-Friderichsen Syndrome

Etiology
- Acute primary insufficiency caused by bilateral adrenal hemorrhage
- Associated with *Neisseria meningitidis* septicemia

Signs and symptoms
- *N. meningitidis* endotoxin causes:
  - Disseminated intravascular coagulation (DIC)
  - Acute respiratory distress syndrome
  - Hypotension
  - Bilateral hemorrhagic infarction of adrenal glands
- Acute adrenal failure
- Petechial rash (sign associated with DIC)

Treatment: fatal unless rapidly recognized and treated
- Antibiotics (sepsis)
- Hormone replacement (acute adrenal insufficiency)



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x1.5 EN04-17

Pheochromocytoma

Definition
- Benign tumor of the adrenal medulla
- Derived from chromaffin cells (of neural crest origin)
- Most secrete catecholamines: epinephrine, norepinephrine, dopamine

Signs and Symptoms
- Similar to those with hyper-catecholamine secretion
- Tachycardia, palpitations, diaphoresis, anxiety, pallor, hypertension, and headaches
- **Rule of 10s**
  - 10% occur in children
  - 10% are bilateral
  - 10% occur outside the adrenal gland
  - 10% are malignant
  - 10% are familial
- Associated with MEN 2A and 2B

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x1.5 EN04-18

Pheochromocytoma

Diagnosis

- Urinary catecholamines and vanillylmandelic acid (most reliable)
- Elevated plasma catecholamines

Treatment

- Medical management of symptoms
- Alpha-antagonists (e.g., phenoxybenzamine)
- Surgical removal of tumor if indicated
  - Must give alpha-antagonists preoperatively
  - Adrenal vascular supply to tumors must be completely isolated and ligated prior to tumor resection

Other characteristics

- Also known as ***paragangliomas*** if derived from extra-adrenal chromaffin cells
- May be associated with neurofibromatosis (e.g., type 1 von Recklinghausen disease)

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x1.5 EN04-19

Multiple Endocrine Neoplasia (MEN) Syndromes

- Three syndromes:
  - MEN 1
  - MEN 2A
  - MEN 2B
- Autosomal dominant with incomplete penetrance
- Marked by hyperplasia and tumors of endocrine glands
- MEN 1 may arise sporadically due to newly acquired mutations

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x1.5 EN04-20

MEN 1

- Also known as Wermer's syndrome
- Caused by loss of function mutation of MEN 1 gene encoding for nuclear protein menin
- Manifests as neoplasias of:
  - ***P***ancreas
  - ***P***ituitary
  - ***P***arathyroid: hyperparathyroidism (most common manifestation)
    - Caused by parathyroid hyperplasia
    - 100% penetrance by age 50
    - Urolithiasis
    - Bone abnormalities
    - Generalized weakness
    - Cognitive dysfunction

3 P's

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x1.5 EN04-21

MEN 1

Pancreatic islet cell tumors (second most common manifestation)

- Tumors produce multiple peptides and biogenic amines
- Non-functioning tumors are the most common
- Functional tumors include:
  - Gastrinoma (most common) → Zollinger-Ellison syndrome
    - Gastric ulcer resistant to treatment
  - Insulinoma
  - Glucagonoma
  - VIPoma
    - Secretes vasoactive intestinal polypeptide
    - Presents with WDHA syndrome
      - Watery diarrhea, hypokalemia, achlorhydria

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x1.5 EN04-22

MEN 2

- Two distinct presentations
  - MEN 2A
  - MEN 2B
- Both caused by a mutation of the RET proto-oncogene
  - Codes for a receptor tyrosine kinase
  - Due to a gain of function mutation
    - A loss of function mutation causes Hirschsprung's disease

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x1.5 EN04-23

MEN 2

MEN 2A

- Known as Sipple's syndrome
- Carcinomas:
  - Medullary carcinoma of the thyroid
  - Pheochromocytoma
  - Parathyroid hyperplasia or adenoma

MEN 2B

- Carcinomas:
  - Medullary carcinoma of the thyroid
  - Pheochromocytoma
  - Mucocutaneous neuroma

- For carcinomas, must screen for presence of other expected neoplasms of the syndrome

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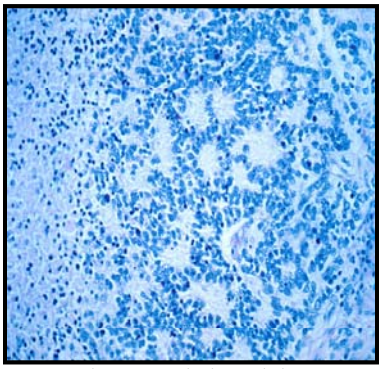
x1.5 EN04-24

Neuroblastoma

- Most common extracranial malignancy of childhood
- Poorly differentiated neoplasm derived from neural crest cells
- Affects infants and young children
- 20% are autosomally inherited
- Various karyotypic abnormalities may contribute; exact etiology unknown
- 70–80% have deletion on short arm of chromosome 1 and gain on long arm of chromosome 17
- Leads to amplification of N-myc oncogene (a nuclear transcription factor)
- Can occur anywhere along sympathetic chain



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x1.5 EN04-25

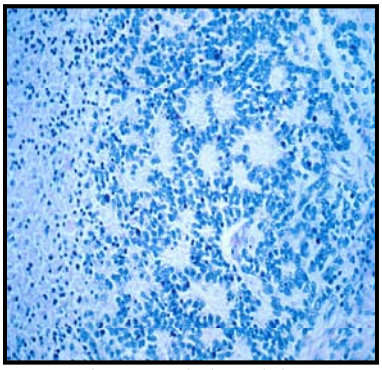
Neuroblastoma

Histology

- Round, blue cells

Signs and symptoms

- Varies depending on site of involvement
- 65% occur in abdomen (within adrenals)
- Abdominal distention or obstruction
- Bony pain (due to metastatic disease)
- Signs of sympathetic ganglia compression (Horner's syndrome)
  - Myosis
  - Anhidrosis
  - Ptosis
- Superior vena cava syndrome



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x1.5 EN04-26

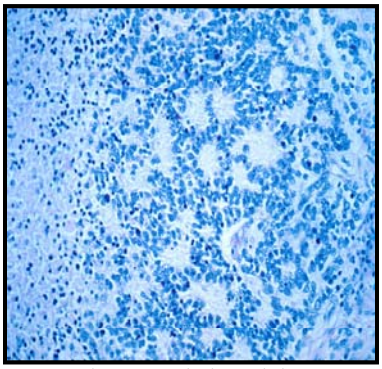
Neuroblastoma

Other characteristics

- Secretory products produced:
  - Catecholamines (most)
  - Vasoactive intestinal peptide → Kerner-Morrison syndrome
    - Intractable, secretory diarrhea
    - Hypovolemia
    - Hypokalemia

Treatment

- Surgery (if stage is low)
- Multi-agent chemotherapy
- Infants with disseminated disease have favorable outcome with chemo and surgery
- Children age >1 with late-stage disease have poor outcome



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x1.5 EN04-27

Carcinoid Syndrome

Characteristics

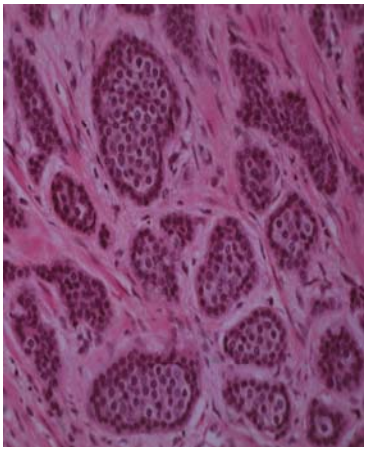
- Rare; caused by carcinoid tumors
- Most common location GI tract
- Metastasis outside portal circulation cause carcinoid syndrome

Histology

- Nests of small, uniform cells
- Tumors secrete serotonin
- Metabolized by liver when tumors are limited to GI tract

Signs and symptoms

- Diarrhea
- Cutaneous flushing
- Bronchospasm
- Wheezing
- Fibrosis
- Right-sided cardiac valvular disease



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x1.5 EN04-28

Carcinoid Syndrome

Diagnosis

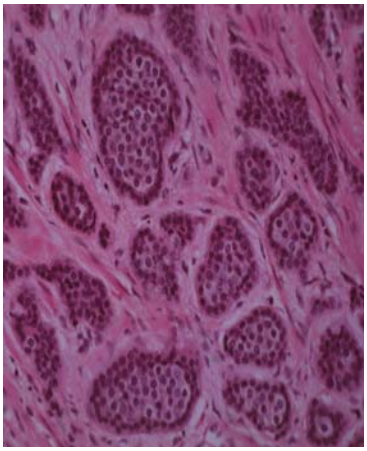
- Increased urine 5-HIAA (monoamine oxidase breakdown of serotonin)

Other characteristics

- Rule of thirds:
  - One-third metastasize
  - One-third present with second malignancy
  - One-third are multifocal

Treatment

- Surgery: resection if primary is localized
- Somatostatin (i.e., octreotide)
  - Inhibits serotonin secretion



KAPLAN MEDICAL

The Pancreas and Diabetes

Matthew B. Wilkinson, PhD, M4
Mount Sinai School of Medicine

x1.5

Functional Anatomy

Functional anatomy: endocrine and exocrine organs

Pancreatic acini

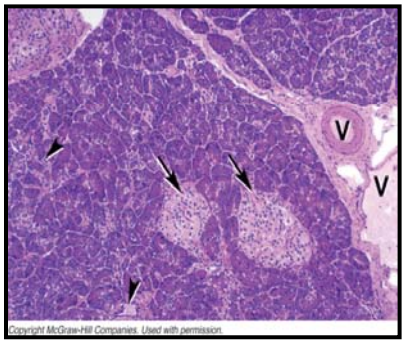
- Exocrine cells that produce digestive enzymes (proteases, lipases, amylases)

Pancreatic islets of Langerhans

- Alpha cells (20% of islet cells)
  - Secrete glucagon
  - Located near periphery
- Beta cells (60-75% of islet cells)
  - Synthesize insulin
  - Located near center
- Delta cells (5% of islet cells)
  - Secrete somatostatin
  - Interspersed between alpha and beta cells

Directionality of islet blood flow

- First, to **beta cells** to pick up insulin
- Then, to **alpha cells** to inhibit glucagon



•**Arrows**: islets of Langerhans
•**Arrowheads**: exocrine acini with ducts
•**V**: blood vessel

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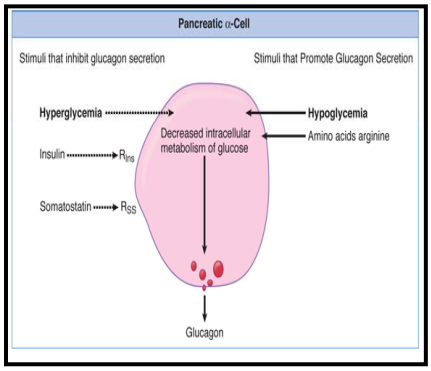
x1.5 EN05- 2

Glucagon

- Peptide hormone secreted by alpha cells
- Main stimulus for glucagon secretion: hypoglycemia
- Target of glucagon action: liver hepatocytes
- Inhibitors of glucagon secretion
  - Hyperglycemia
  - Insulin
  - Somatostatin
- Functions to raise serum glucose
- Acts through G-protein coupled receptor
  - Activates adenyl cyclase
  - Increases cAMP → protein kinase A
- Actions: ↑ glycogenolysis, gluconeogenesis, ketogenesis, ↓ lipogenesis



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x1.5 EN05- 3

Insulin

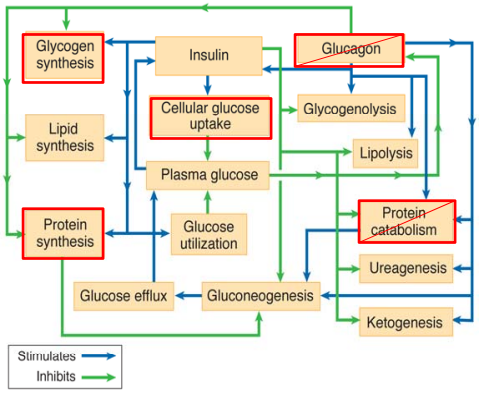
- Major anabolic hormone
- Stimulated in response to carbohydrate- and/or protein-containing meal

Effects on glucose metabolism

- Antagonistic to glucagon
- Increases glucose uptake and metabolism (muscle and fat)
- Increases glycogen synthesis (liver and muscle)

Effects on protein metabolism

- Increases amino acid uptake in muscle
- Increases protein synthesis
- Decreases protein breakdown



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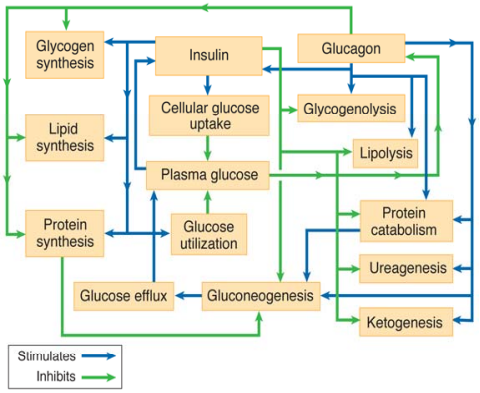
x1.5 EN05- 4

Insulin

Effects on fat metabolism

- Increases glucose and triglyceride uptake
- Increases lipogenesis and triglyceride synthesis (adipose tissue and liver)
  - By carboxylation of acetyl CoA to malonyl-CoA
- Increases number of GLUT 4 receptors on adipose tissue and muscle plasma membranes
  - Increases transport of glucose into these cells, increasing Na^+/K^+ ATPase activity
- Acts upon target tissue tyrosine kinase receptors via MAP kinase pathway



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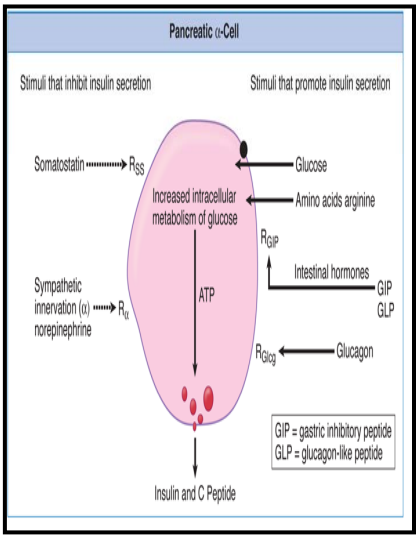
x1.5 EN05- 5

Insulin

Factors regulating insulin secretion

- Plasma glucose
  - >100 mg/dL insulin secretion is directly proportional to plasma glucose
  - Beta cell glucose uptake increases ATP
  - ATP → closes beta cell K^+ channels, leading to depolarization; this induces voltage-dependent Ca^+ channel opening
  - Increased intracellular Ca^+ → insulin exocytosis; these Ca^+ channels are drug targets
- Amino acids (e.g., arginine)
- Intestinal hormones (e.g., GIP)
- Somatostatin and sympathetic stimulation inhibit insulin secretion



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x1.5 EN05- 6

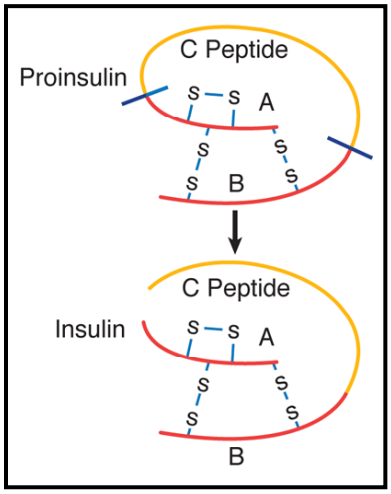
Insulin

Characteristics

- Stimulated beta cells synthesize preproinsulin
- Preproinsulin cleaved to form proinsulin
- Proinsulin splits into insulin and C-peptide
- Both stored in vesicles within beta cells

Clinical use

- Diagnose etiology of hypoglycemia
  - Factitious hypoglycemia (decreased C-peptide levels)
  - Endogenous hyperinsulinemia (diabetes type 2) (increased C-peptide levels)



Kaplan Physiology 2010: Figure X-6-2

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x1.5 EN05- 7

Diabetes Mellitus (DM)

- Chronic systemic disease marked by insulin deficiency or peripheral resistance
- Leads to hyperglycemia and nonenzymatic glycosylation of proteins
- Leading contributor to end-stage renal disease (United States)
- Leading cause of non-traumatic lower limb amputation
- Large public health burden in United States and abroad
- Confers twofold increased risk for coronary heart disease (men); three- to fourfold increase (women)
- 5–10% of patients have type I diabetes; 90–95% of patients have type II
  - Etiologies of the 2 types differ but effect is the same
    - Chronic hyperglycemia
    - Subsequent damage to organs

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x1.5 EN05- 8

DM Type 1

- Formerly called insulin-dependent or juvenile onset diabetes

Risk factors

- Northern European ancestry
- HLA types DR3, DR 4, and DQ

Etiology

- Viral or immune destruction of pancreatic beta cells → insulin-dependence
- Autoimmune reaction thought to be triggered by an infection (e.g., Coxackie B virus)

Histology

- Lymphocytic infiltration and inflammation of islets of Langerhans
- Beta cell loss and islet fibrosis

Signs and symptoms

- Polydipsia, polyuria, polyphagia, weight loss, dehydration, electrolyte imbalance, metabolic ketoacidosis, coma and death

Treatment

- Exogenous insulin replacement

DM Type 2

- Also called non-insulin dependent diabetes or adult onset diabetes

Risk factors

- Obesity
- Increasing age
- Genetic predisposition

Pathogenesis

- Reduced insulin secretion
- Reduced tissue sensitivity to insulin due to decreased receptor number

Histology

- Pancreatic islet findings are non-specific: focal atrophy and amyloid deposition

Clinical presentation

- Frequently asymptomatic at early stages
- Polydipsia, polyuria, polyphagia, hyperosmolar non-ketotic diabetic coma (progressed disease)

Treatment: multi-modal

Gestational Diabetes

- Manifests during pregnancy

Pathogenesis

- Due to diabetogenic effects of secreted:
  - Human placental lactogen
  - Placental insulinase
  - Cortisol
  - Progesterone

Other features

- 2–3% prevalence of glucose intolerance in pregnancy
- 35% of affected women develop diabetes type 2 within 5-10 yrs post-partum

Treatment: case-by-case basis

- Dietary management
- Exogenous insulin
- Glyburide (not contraindicated in pregnancy)

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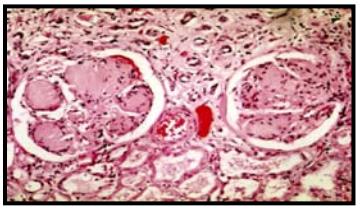
x1.5 EN05- 11

Complications of DM

Chronic complications

- Atherosclerosis (e.g., MI, peripheral vascular disease)
  - Due to nonenzymatic reaction of excess glucose with proteins, nucleotides, and lipids
  - Leads to diffuse vascular endothelial basement membrane thickening
- Renal vascular disease
  - Hyperglycemia-induced mesangial expansion
  - Glomerular basement membrane thickening
  - Glomerular sclerosis due to intraglomerular hypertension
- Diabetic retinopathy
  - Microaneurysm
  - Retinal hemorrhage
  - Neovascularization
  - Vitreous humor fibrosis
  - Retinal detachment



Nodular glomerulosclerosis.commons.wikimedia.org. Used with permission.

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x1.5 EN05- 12

Complications of DM

Chronic complications, cont'd

- Neuropathy
  - Due to glycosylation and subsequent disruption of neuronal integrity
  - Increased intracellular neuron concentration → sorbitol and fructose production and accumulation
    - Decreases membrane Na^+/K^+ ATPase activity
    - Impairs axonal transport
    - Leads to structural breakdown of nerves
  - Increased free radical production → direct blood vessel damage and nerve ischemia

Diabetic Ketoacidosis (DKA)

- State of absolute or relative insulin deficiency associated with hyperglycemia, dehydration, and acidosis
- Most common acute, life-threatening complication of type 1 DM
- May also occur in type 2 DM

Pathogenesis

- In DKA, cells perceive a hyperglycemic state as hypoglycemia
- Cells cannot utilize plasma glucose due to underlying insulin deficiency
- Release of counter-regulatory hormones (glucagon, cortisol, epinephrine, and growth hormone), which induces:
  - Lipolysis + metabolism of ketogenic amino acids → ketonemia → anion gap acidosis
  - Ketones (beta-hydroxybutyrate): nausea and vomiting
  - Acetone: fruity breath
  - Respiratory compensation → Kussmaul respiration
  - Hyperkalemia: H^+ shifts into cells in exchange for K^+
    - No change in total body potassium

Diabetic Ketoacidosis

Risk factors

- Infection: *Klebsiella pneumoniae, E. coli*
- Surgery
- Trauma
- Pregnancy
- Insufficient or interrupted insulin therapy

Diagnosis

- ↑ blood glucose
- ↑ serum ketones (acetoacetate, acetone, hydroxybutyrate)
- ↑ anion gap metabolic acidosis

Treatment

- IV insulin
- IV fluids
- Electrolyte replacement

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x1.5 EN05- 15

Hyperosmolar Nonketotic (HONK) State

- Most common in type 2 diabetics
- Characterized by severe hyperglycemia without ketosis

Risk factors

- Non-compliance of hypoglycemic medication
- Acute physiological stressor

Pathophysiology

- Hyperglycemia → glucosuria → osmotic diuresis
  - Volume depletion
  - Hyperosmolarity → intracellular dehydration
  - Hemoconcentration
  - Electrolyte loss (e.g., Na^+ and K^+)
- No ketoacidosis
  - Residual insulin thought to inhibit lipolysis

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x1.5 EN05- 16

HONK State

Diagnosis

- Increased blood glucose
- Increased serum osmolarity
- Increased BUN (pre-renal azotemia)

Treatment

- IV insulin
- IV fluids
- Electrolyte replacement

Diabetes

Diagnosis

- Fasting glucose >126 mg/dL on 2+ separate occasions
- Glucose tolerance test (no longer widely used)
  - Administer 75 gm glucose and measure serum glucose 2 hours later
  - If >300 mg/dL → diabetes mellitus
- Hemoglobin A1c ≥6.5%
  - Hemoglobin A1c is glycosylated hemoglobin produced by non-enzymatic condensation of glucose with free amino groups on globin
  - Used to follow patient compliance with treatment
  - Used to assess overall glycemic control

Diabetes

Treatment

- **DM type 1:** exogenous insulin replacement (primary)
- **DM type 2:**
  - Glycemic monitoring and management
  - Weight loss: losing 4–7% of weight improves insulin sensitivity and reduces postprandial hyperglycemia
  - Dietary modification
  - Exercise: exercising muscles does not need insulin for glucose entry but resting muscles do
  - Pharmacologic: all type 2 diabetics require oral hypoglycemic medication

Insulin Analogues

Exogenous insulin replacement (primary)

- Only used in DM type 2 for severe cases not controlled by oral agents
- Different forms of insulin work via the same mechanism (action upon insulin receptors)
  - Differences among them:
    - Time of onset
    - Time to peak action
    - Duration of action

Sulfonylureas

Characteristics

- Stimulate insulin release by blocking K^+ channels on pancreatic beta cells → depolarization and insulin release
- Metabolized by the liver
  - Cannot be used with liver-failure patients
  - Can be used with renal-failure patients

Side effects

- Weight gain
- Hypoglycemia
- Increased risk of hypoglycemia when used with cimetidine, insulin, salicylates, and sulfonamides
- Avoid EtOH with chlorpropamide → causes disulfiram-like effect by inhibiting acetaldehyde

Metformin

Characteristics

- First-line agent for DM type 2
- Increases peripheral sensitivity to insulin
- Decreases hepatic gluconeogenesis
- Does not cause hypoglycemia or weight gain
- Work synergistically with sulfonylureas which are added when monotherapy is inadequate

Side effects

- Lactic acidosis
- GI discomfort
- Renal dysfunction

Acarbose

Characteristics

- Inhibits alpha-glucosidase in small intestinal brush border, leading to:
  - ↓ formation of absorbable carbohydrates
  - ↓ post-prandial glucose load
  - ↓ demand for insulin
- Does not cause hypoglycemia

Side effects

- GI discomfort
  - Rarely used because of severe GI disturbance
- Flatulence
- Diarrhea

Thiazolidinediones

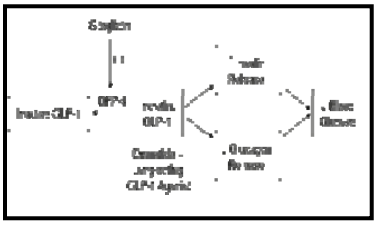
Characteristics

- Include pioglitazone and rosiglitazone
- Bind to nuclear peroxisome proliferator-activated receptors (PPARs) → transcription of insulin-responsive genes → increases tissue sensitivity to insulin
- Decrease hepatic gluconeogenesis and triglycerides
- Increase insulin-receptor numbers

Side effects

- Weight gain
- Peripheral edema

Glucagon-like Peptide-1 Receptor Agonists



Characteristics

- GLP-1 is an incretin, released from small intestine
- Augments glucose-dependent secretion

Agents

- Exenatide
  - Long-acting GLP-1 receptor agonist
  - Used in combination with other oral agents
  - Side effects:
    - Nausea
    - Hypoglycemia (when used with sulfonylurea)
- Sitagliptin
  - Inhibits dipeptidyl peptidase (DPP-4)

Treatment Algorithm for Diabetes

- Recognize signs and symptoms of hypoglycemia
  - Diaphoresis, tremor, and tachycardia
  - Anxiety, hunger
  - Altered mental status
- Confirm the diagnosis
  - Obtain serum blood glucose level
  - Measure serum insulin, C-peptide, and sulfonylurea level if:
    - Cause isn't apparent
    - Patient is non-diabetic
    - Prolonged fast
- Therapy
  - Give oral or IV glucose and reassess for correction; repeat as needed until hypoglycemia has resolved
  - With restoration of euglycemia, assess labs to determine etiology
  - Rule out insulinoma or factitious hyperinsulinism if suspected