

Endocrine

“If you skew the endocrine system, you lose the pathways to self.”

—Hilary Mantel

“Sometimes you need a little crisis to get your adrenaline flowing and help you realize your potential.”

—Jeannette Walls, *The Glass Castle*

“Chocolate causes certain endocrine glands to secrete hormones that affect your feelings and behavior by making you happy.”

—Elaine Sherman, *Book of Divine Indulgences*

► Embryology	330
► Anatomy	331
► Physiology	332
► Pathology	342
► Pharmacology	358

The endocrine system comprises widely distributed organs that work in a highly integrated manner to orchestrate a state of hormonal equilibrium within the body. Generally speaking, endocrine diseases can be classified either as diseases of underproduction or overproduction, or as conditions involving the development of mass lesions—which themselves may be associated with underproduction or overproduction of hormones. Therefore, study the endocrine system first by learning the glands, their hormones, and their regulation, and then by integrating disease manifestations with diagnosis and management. Take time to learn the multisystem connections.



► ENDOCRINE—ANATOMY

Pituitary gland**Anterior pituitary
(adenohypophysis)**

Secretes FSH, LH, ACTH, TSH, prolactin, GH, and β -endorphin. Melanotropin (MSH) secreted from intermediate lobe of pituitary. Derived from oral ectoderm (Rathke pouch).

- α subunit—hormone subunit common to TSH, LH, FSH, and hCG.
- β subunit—determines hormone specificity.

Proopiomelanocortin derivatives— β -endorphin, ACTH, and MSH. Go pro with a BAM!

FLAT PiG: FSH, LH, ACTH, TSH, PRL, GH.

B-FLAT: Basophils—FSH, LH, ACTH, TSH.

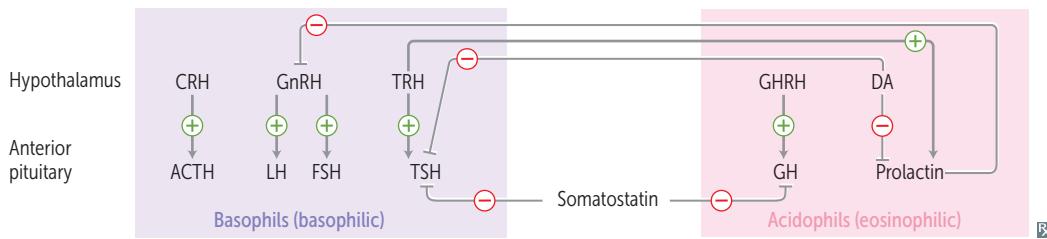
Acid PiG: Acidophils — PRL, GH.

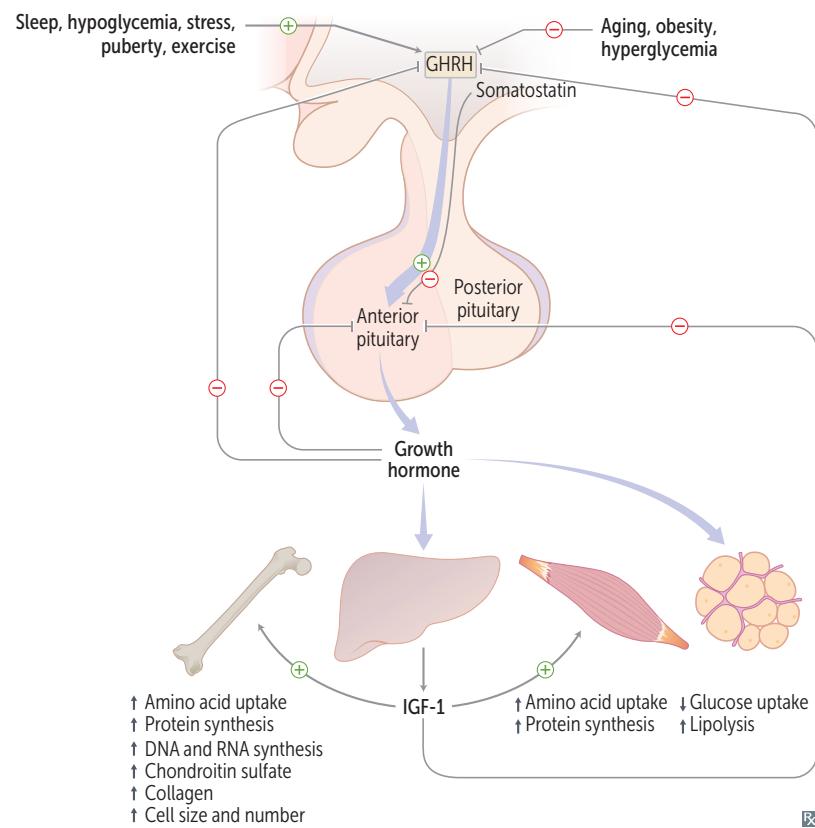
**Posterior pituitary
(neurohypophysis)**

► ENDOCRINE—PHYSIOLOGY

Hypothalamic-pituitary hormones

HORMONE	FUNCTION	CLINICAL NOTES
ADH	↑ water permeability of distal convoluted tubule and collecting duct cells in kidney to ↑ water reabsorption	Alcohol consumption → ↓ ADH secretion → polyuria and dehydration
CRH	↑ ACTH, ↑ MSH, ↑ β-endorphin	↓ in chronic glucocorticoid use
Dopamine	↓ prolactin, ↓ TSH	Also called prolactin-inhibiting factor Dopamine antagonists (eg, antipsychotics) can cause galactorrhea due to hyperprolactinemia
GHRH	↑ GH	Analog (tesamorelin) used to treat HIV-associated lipodystrophy
GnRH	↑ FSH, ↑ LH	Suppressed by hyperprolactinemia Tonic GnRH analog (eg, leuprolide) suppresses hypothalamic–pituitary–gonadal axis. Pulsatile GnRH leads to puberty, fertility
MSH	↑ melanogenesis by melanocytes	Causes hyperpigmentation in Cushing disease, as MSH and ACTH share the same precursor molecule, proopiomelanocortin
Oxytocin	Causes uterine contractions during labor. Responsible for milk letdown reflex in response to suckling.	Modulates fear, anxiety, social bonding, mood, and depression
Prolactin	↓ GnRH Stimulates lactogenesis.	Pituitary prolactinoma → amenorrhea, osteoporosis, hypogonadism, galactorrhea Breastfeeding → ↑ prolactin → ↓ GnRH → delayed postpartum ovulation (natural contraception)
Somatostatin	↓ GH, ↓ TSH	Also called growth hormone inhibiting hormone (GHIH)
TRH	↑ TSH, ↑ prolactin	↑ TRH (eg, in 1°/2° hypothyroidism) may increase prolactin secretion → galactorrhea



Growth hormone

Also called somatotropin. Secreted by anterior pituitary.

Stimulates linear growth and muscle mass through IGF-1 (somatomedin C) secretion by liver. ↑ insulin resistance (diabetogenic).

Released in pulses in response to growth hormone-releasing hormone (GHRH).

Secretion ↑ during sleep, hypoglycemia, stress, puberty, exercise.

Secretion ↓ with aging, obesity, hyperglycemia, somatostatin, somatomedin (regulatory molecule secreted by liver in response to GH acting on target tissues).

Excess secretion of GH (eg, pituitary adenoma) may cause acromegaly (adults) or gigantism (children). Treatment: somatostatin analogs (eg, octreotide) or surgery.

Antidiuretic hormone

Also called vasopressin.

SOURCE

Synthesized in hypothalamus (supraoptic and paraventricular nuclei), stored and secreted by posterior pituitary.

FUNCTION

Regulates blood pressure (V_1 -receptors) and serum osmolality (V_2 -receptors). Primary function is serum osmolality regulation (ADH ↓ serum osmolality, ↑ urine osmolality) via regulation of aquaporin channel insertion in principal cells of renal collecting duct.

ADH level is ↓ in central diabetes insipidus (DI), normal or ↑ in nephrogenic DI.

Nephrogenic DI can be caused by mutation in V_2 -receptor.

Desmopressin (ADH analog) is a treatment for central DI and nocturnal enuresis.

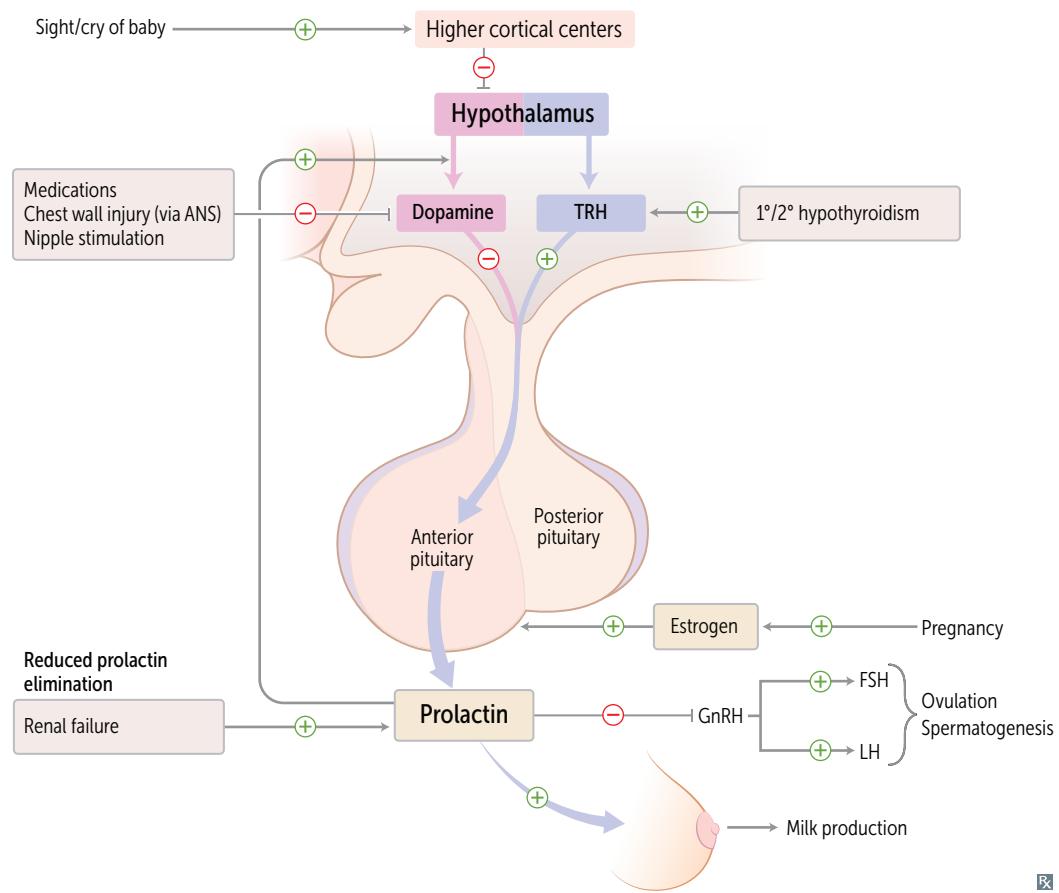
Vasopressin is also a potent **vasopressor** that can be used to increase organ perfusion in septic shock.

REGULATION

Plasma osmolality (1°); hypovolemia.

Prolactin

SOURCE	Secreted mainly by anterior pituitary.	Structurally homologous to growth hormone.
FUNCTION	Stimulates milk production in breast; inhibits ovulation in females and spermatogenesis in males by inhibiting GnRH synthesis and release.	Excessive amounts of prolactin associated with ↓ libido.
REGULATION	Prolactin secretion from anterior pituitary is tonically inhibited by dopamine from tuberoinfundibular pathway of hypothalamus. Prolactin in turn inhibits its own secretion by ↑ dopamine synthesis and secretion from hypothalamus. TRH ↑ prolactin secretion (eg, in 1° or 2° hypothyroidism). Dopamine has stronger effect on prolactin regulation than TRH does.	Dopamine agonists (eg, bromocriptine, cabergoline) inhibit prolactin secretion and can be used in treatment of prolactinoma. Dopamine antagonists (eg, most antipsychotics, metoclopramide) and estrogens (eg, OCPs, pregnancy) stimulate prolactin secretion.



Thyroid hormones

Thyroid produces triiodothyronine (T_3) and thyroxine (T_4), iodine-containing hormones that control the body's metabolic rate.

SOURCE

Follicles of thyroid. $5'$ -deiodinase converts T_4 (the major thyroid product) to T_3 in peripheral tissue (5, 4, 3). Peripheral conversion is inhibited by glucocorticoids, β -blockers, and propylthiouracil (PTU). Reverse T_3 (rT_3) is a metabolically inactive byproduct of the peripheral conversion of T_4 and its production is increased by growth hormone and glucocorticoids. Functions of thyroid peroxidase include oxidation, organification of iodine, and coupling of monoiodotyrosine (MIT) and diiodotyrosine (DIT). Inhibited by PTU and methimazole. $DIT + DIT = T_4$. $DIT + MIT = T_3$. Wolff-Chaikoff effect—protective autoregulation; sudden exposure to excess iodine temporarily turns off thyroid peroxidase $\rightarrow \downarrow T_3/T_4$ production.

FUNCTION

Only free hormone is active. T_3 binds nuclear receptor with greater affinity than T_4 . T_3 functions ~ 7 B's:

- Brain maturation
- Bone growth (synergism with GH and IGF-1)
- β -adrenergic effects. $\uparrow \beta_1$ receptors in heart $\rightarrow \uparrow CO, HR, SV$, contractility; β -blockers alleviate adrenergic symptoms in thyrotoxicosis
- Basal metabolic rate \uparrow (via $\uparrow Na^+/K^+$ -ATPase $\rightarrow \uparrow O_2$ consumption, RR, body temperature)
- Blood sugar (\uparrow glycogenolysis, gluconeogenesis)
- Break down lipids (\uparrow lipolysis)
- Stimulates surfactant synthesis in Babies

REGULATION

TRH $\rightarrow \oplus$ TSH release $\rightarrow \oplus$ follicular cells. Thyroid-stimulating immunoglobulin (TSI) may \oplus follicular cells in Graves disease.

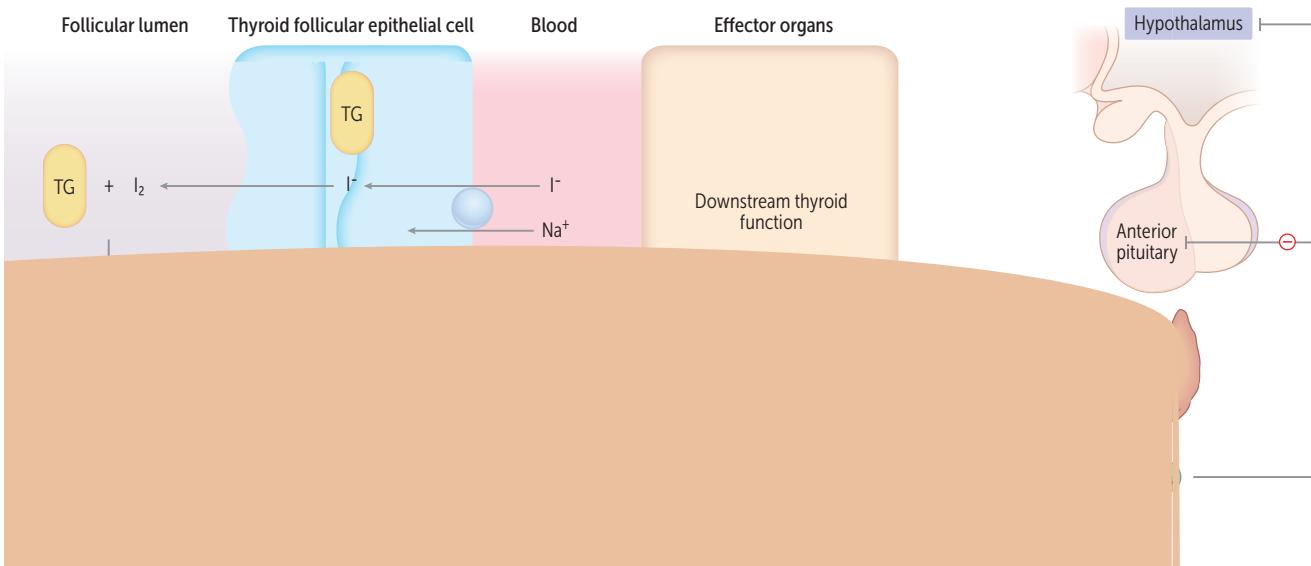
Negative feedback primarily by free T_3/T_4 :

- Anterior pituitary $\rightarrow \downarrow$ sensitivity to TRH
- Hypothalamus $\rightarrow \downarrow$ TRH secretion

Thyroxine-binding globulin (TBG) binds most T_3/T_4 in blood. Bound T_3/T_4 = inactive.

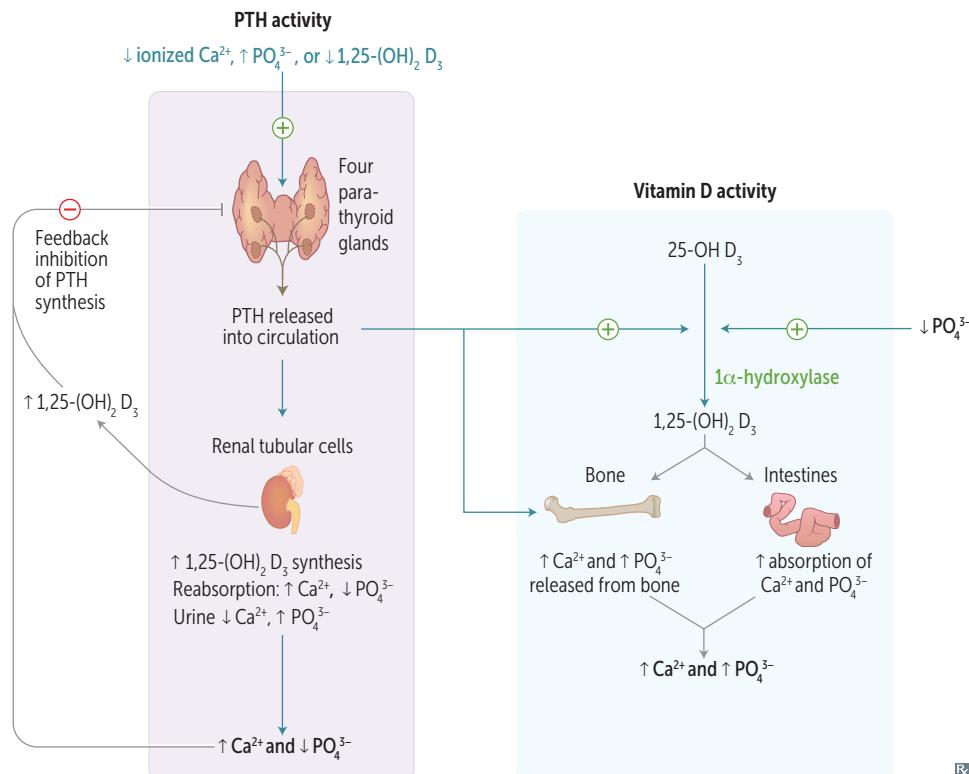
- \uparrow TBG in pregnancy, OCP use (estrogen $\rightarrow \uparrow$ TBG) $\rightarrow \uparrow$ total T_3/T_4
- \downarrow TBG in steroid use, nephrotic syndrome

T_3 and T_4 are the only lipophilic hormones with charged amino acids and require specific transporters to diffuse into the cell (facilitated diffusion).



Parathyroid hormone

SOURCE	Chief cells of parathyroid	
FUNCTION	<ul style="list-style-type: none"> ↑ free Ca^{2+} in the blood (1° function) ↑ Ca^{2+} and PO_4^{3-} absorption in GI system ↑ Ca^{2+} and PO_4^{3-} from bone resorption ↑ Ca^{2+} reabsorption from DCT ↓ PO_4^{3-} reabsorption in PCT ↑ 1,25-(OH)₂D₃ (calcitriol) production by activating 1α-hydroxylase in PCT (tri to make D₃ in the PCT) 	<ul style="list-style-type: none"> PTH ↑ serum Ca^{2+}, ↓ serum PO_4^{3-}, ↑ urine PO_4^{3-}, ↑ urine cAMP ↑ RANK-L (receptor activator of NF-κB ligand) secreted by osteoblasts and osteocytes; binds RANK (receptor) on osteoclasts and their precursors to stimulate osteoclasts and ↑ Ca^{2+} → bone resorption (intermittent PTH release can also stimulate bone formation) PTH = Phosphate-Trashing Hormone PTH-related peptide (PTHRP) functions like PTH and is commonly increased in malignancies (eg, squamous cell carcinoma of the lung, renal cell carcinoma)
REGULATION	<ul style="list-style-type: none"> ↓ serum Ca^{2+} → ↑ PTH secretion ↑ serum PO_4^{3-} → ↑ PTH secretion ↓ serum Mg^{2+} → ↑ PTH secretion ↓↓ serum Mg^{2+} → ↓ PTH secretion <p>Common causes of ↓ Mg^{2+} include diarrhea, aminoglycosides, diuretics, alcohol use disorder</p>	<ul style="list-style-type: none"> Ca²⁺ is the major regulator of PTH release



Calcium homeostasis

Plasma Ca^{2+} exists in three forms:

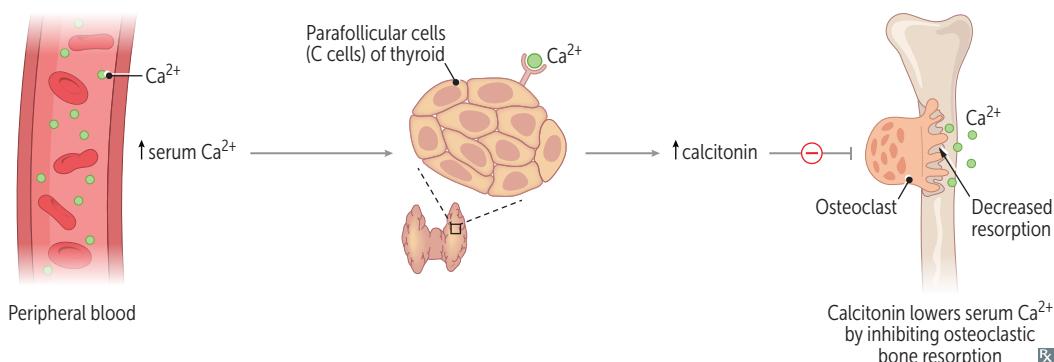
- Ionized/free (~ 45%, active form)
- Bound to albumin (~ 40%)
- Bound to anions (~ 15%)

Ionized/free Ca^{2+} is 1° regulator of PTH; changes in pH alter PTH secretion, whereas changes in albumin concentration do not

Ca^{2+} competes with H^+ to bind to albumin
 \uparrow pH (less H^+) → albumin binds more
 $\text{Ca}^{2+} \rightarrow \downarrow$ ionized Ca^{2+} (eg, cramps, pain, paresthesias, carpopedal spasm) → \uparrow PTH
 \downarrow pH (more H^+) → albumin binds less Ca^{2+}
 $\rightarrow \uparrow$ ionized $\text{Ca}^{2+} \rightarrow \downarrow$ PTH

Calcitonin

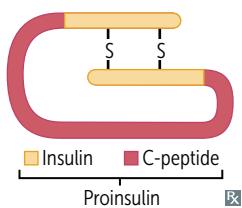
SOURCE	Parafollicular cells (C cells) of thyroid.	Calcitonin opposes actions of PTH. Not important in normal Ca^{2+} homeostasis Calcitonin tones down serum Ca^{2+} levels and keeps it in bones
FUNCTION	↓ bone resorption.	
REGULATION	↑ serum $\text{Ca}^{2+} \rightarrow \uparrow$ calcitonin secretion.	

**Glucagon**

SOURCE	Made by α cells of pancreas.
FUNCTION	Promotes glycogenolysis, gluconeogenesis, lipolysis, ketogenesis. Elevates blood sugar levels to maintain homeostasis when bloodstream glucose levels fall too low (ie, fasting state).
REGULATION	Secreted in response to hypoglycemia. Inhibited by insulin, amylin, somatostatin, hyperglycemia.

Insulin

SYNTHESIS



Preproinsulin (synthesized in RER of pancreatic β cells) \rightarrow cleavage of “presignal” \rightarrow proinsulin (stored in secretory granules) \rightarrow cleavage of proinsulin \rightarrow exocytosis of insulin and C-peptide equally. Both insulin and C-peptide are \uparrow in endogenous insulin secretion (eg, type 2 DM, insulin secretagogues, insulinoma), whereas exogenous insulin lacks C-peptide.

Insulin is synthesized in pancreas and cleared by both liver and kidneys.

FUNCTION

Binds insulin receptors (tyrosine kinase activity ①), inducing glucose uptake (carrier-mediated transport) into insulin-dependent tissue ② and gene transcription.

Anabolic effects of insulin:

- \uparrow glucose transport in skeletal muscle and adipose tissue
- \uparrow glycogen synthesis and storage
- \uparrow triglyceride synthesis
- \uparrow Na^+ retention (kidneys)
- \uparrow protein synthesis (muscles)
- \uparrow cellular uptake of K^+ and amino acids
- \downarrow glucagon release
- \downarrow lipolysis in adipose tissue

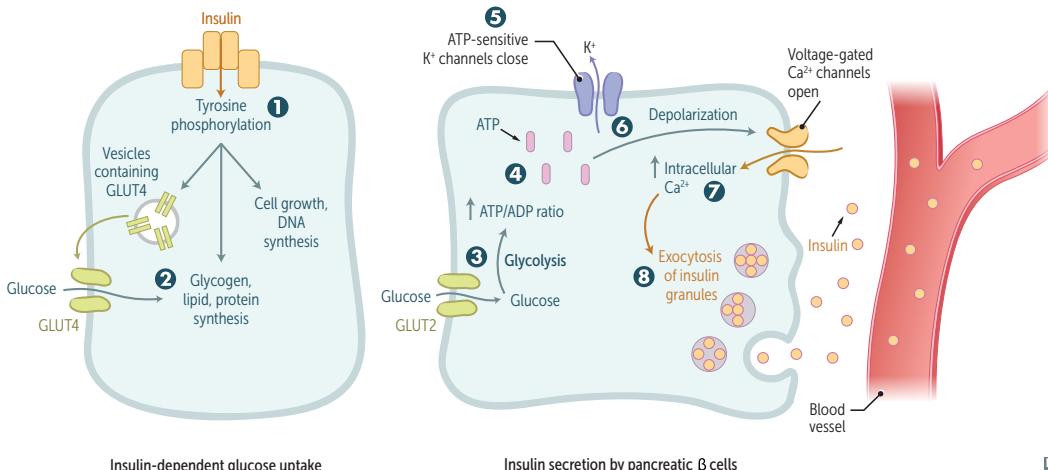
Unlike glucose, insulin does not cross placenta.

In mothers with diabetes, excess glucose can cross placenta and $\uparrow\uparrow$ fetal insulin.

REGULATION

Glucose is the major regulator of insulin release. \uparrow insulin response with oral vs IV glucose due to incretins (eg, glucagonlike peptide 1 [GLP-1], glucose-dependent insulinotropic polypeptide [GIP]), which are released after meals and \uparrow β cell sensitivity to glucose. Release \downarrow by α_2 , \uparrow by β_2 stimulation (2 = regulates insulin).

Glucose enters β cells ③ \rightarrow \uparrow ATP generated from glucose metabolism ④ closes K^+ channels (target of sulfonylureas) ⑤ and depolarizes β cell membrane ⑥. Voltage-gated Ca^{2+} channels open \rightarrow Ca^{2+} influx ⑦ and stimulation of insulin exocytosis ⑧.



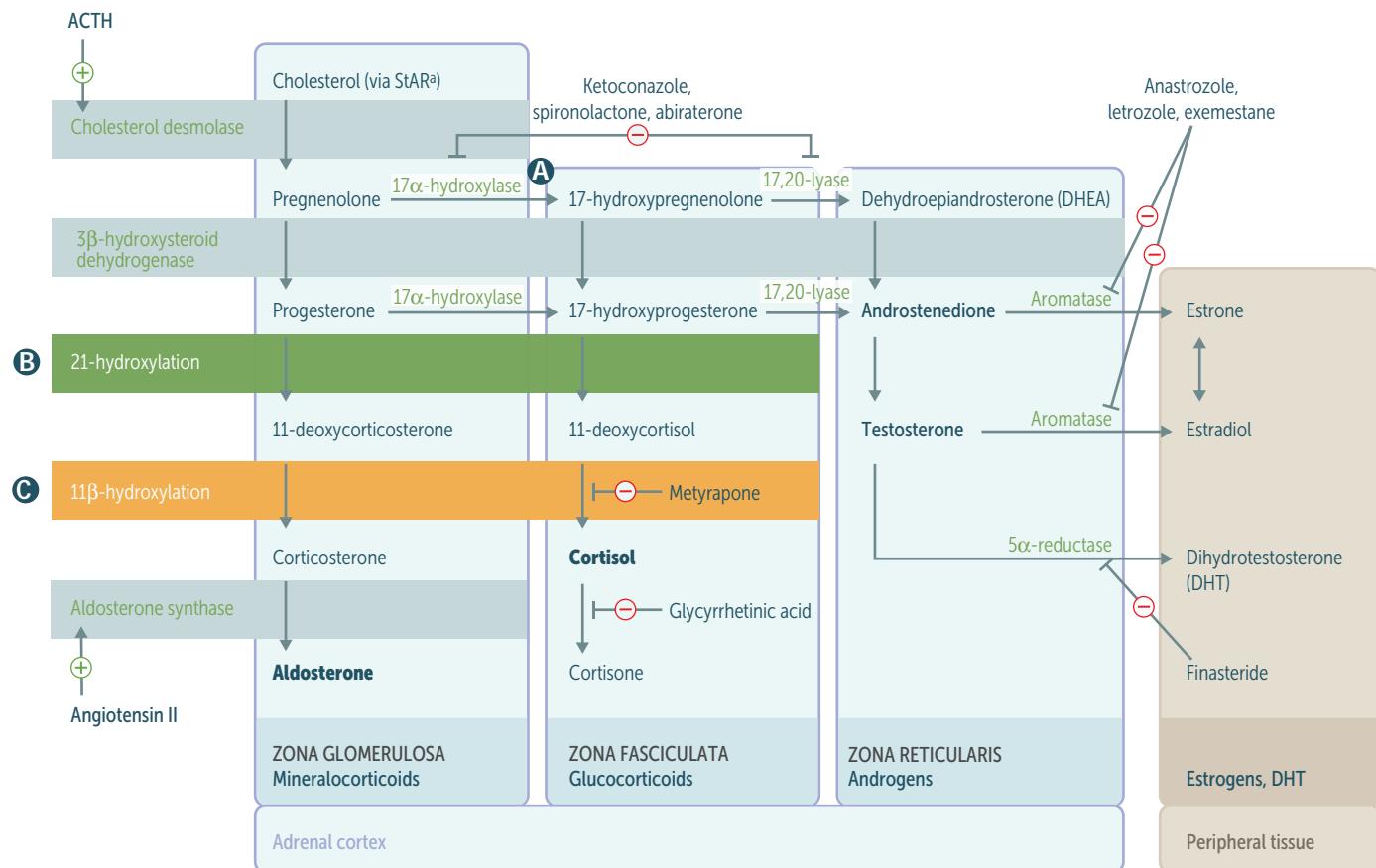
Insulin-dependent glucose transporters:

- GLUT4: adipose tissue, striated muscle (exercise can also \uparrow GLUT4 expression)
- GLUT1: RBCs, brain, cornea, placenta
- GLUT2 (bidirectional): β islet cells, liver, kidney, GI tract (think 2-way street)
- GLUT3: brain, placenta
- GLUT5 (fructose): spermatocytes, GI tract
- SGLT1/SGLT2 (Na^+ -glucose cotransporters): kidney, small intestine

Brain prefers glucose, but may use ketone bodies during starvation. RBCs utilize only glucose, as they lack mitochondria for aerobic metabolism.

BRICK LIPS (insulin-independent glucose uptake): Brain, RBCs, Intestine, Cornea, Kidney, Liver, Islet (β) cells, Placenta, Spermatocytes.

Adrenal steroids and congenital adrenal hyperplasias

^aRate-limiting step.

Rx

ENZYME DEFICIENCY	MINERALOCORTICOIDS	[K ⁺]	BP	CORTISOL	SEX HORMONES	LABS	PRESENTATION
A 17α-hydroxylase^a	↑		↓	↑	↓	↓ androstenedione	XY: atypical genitalia, undescended testes XX: lacks 2° sexual development
B 21-hydroxylase^a	↓		↑	↓	↓	↑ renin activity ↑ 17-hydroxyprogesterone	Most common Presents in infancy (salt wasting) or childhood (precocious puberty) XX: virilization
C 11β-hydroxylase^a	↓ aldosterone ↑ 11-deoxycorticosterone (results in ↑ BP)	↓	↑	↓	↑	↓ renin activity	Presents in infancy (severe hypertension) or childhood (precocious puberty) XX: virilization

^aAll congenital adrenal enzyme deficiencies are autosomal recessive disorders and most are characterized by skin hyperpigmentation (due to ↑ MSH production, which is coproduced and secreted with ACTH) and bilateral adrenal gland enlargement (due to ↑ ACTH stimulation).

If deficient enzyme starts with 1, it causes hypertension; if deficient enzyme ends with 1, it causes virilization in females.

Cortisol

SOURCE	Adrenal zona fasciculata.	Bound to corticosteroid-binding globulin.
FUNCTION	<ul style="list-style-type: none"> ↑ Appetite ↑ Blood pressure: <ul style="list-style-type: none"> ▪ Upregulates α_1-receptors on arterioles → ↑ sensitivity to norepinephrine and epinephrine (permissive action) ▪ At high concentrations, can bind to mineralocorticoid (aldosterone) receptors ↑ Insulin resistance (diabetogenic) ↑ Gluconeogenesis, lipolysis, and proteolysis (↓ glucose utilization) ↓ Fibroblast activity (poor wound healing, ↓ collagen synthesis, ↑ striae) ↓ Inflammatory and Immune responses: <ul style="list-style-type: none"> ▪ Inhibits production of leukotrienes and prostaglandins ▪ Inhibits WBC adhesion → neutrophilia ▪ Blocks histamine release from mast cells ▪ Eosinopenia, lymphopenia ▪ Blocks IL-2 production ↓ Bone formation (↓ osteoblast activity) 	Cortisol is A BIG FIB . Exogenous glucocorticoids can cause reactivation of TB and candidiasis (blocks IL-2 production).
REGULATION	CRH (hypothalamus) stimulates ACTH release (pituitary) → cortisol production in adrenal zona fasciculata. Excess cortisol ↓ CRH, ACTH, and cortisol secretion.	<pre> graph TD Stress((Stress Circadian rhythm)) -- "+" --> Hypothalamus[Hypothalamus] Hypothalamus -- "-" --> Hypothalamus Hypothalamus -- "+" --> CRH[CRH] CRH -- "+" --> AnteriorPituitary[Anterior pituitary] AnteriorPituitary -- "-" --> AnteriorPituitary AnteriorPituitary -- "+" --> ACTH[ACTH] ACTH -- "+" --> AdrenalCortex[Adrenal cortex] AdrenalCortex -- "+" --> Cortisol[Cortisol] Cortisol --> Downstream[Downstream cortisol function] Endorphins[Endorphins] --> AnteriorPituitary </pre>

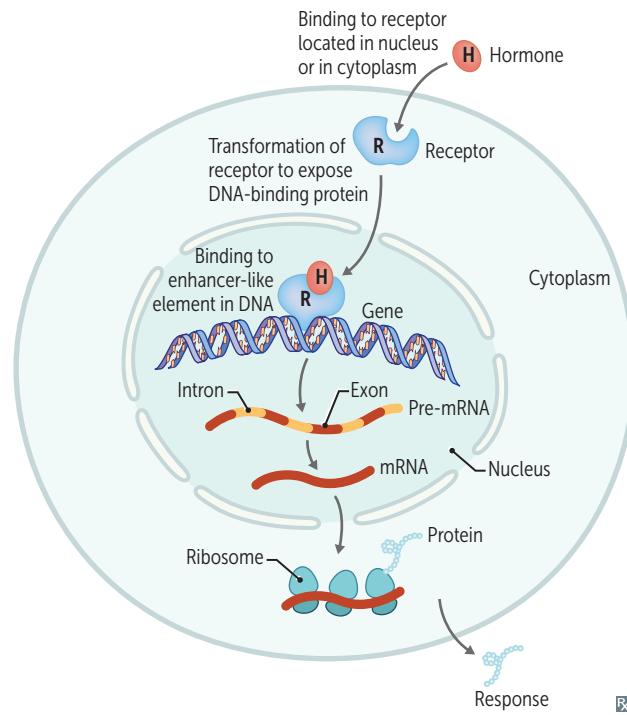
Appetite regulation

Ghrelin	<p>Stimulates hunger (orexigenic effect) and GH release (via GH secretagog receptor). Produced by stomach. Sleep deprivation, fasting, or Prader-Willi syndrome → ↑ ghrelin production.</p> <p>Ghrelin makes you <i>ghrow hungry</i>. Acts on lateral area of hypothalamus (hunger center) to ↑ appetite.</p>
Leptin	<p>Satiety hormone. Produced by adipose tissue. Mutation of leptin gene → severe obesity. Obese people have ↑ leptin due to ↑ adipose tissue but are tolerant or resistant to leptin's anorexigenic effect. Sleep deprivation or starvation → ↓ leptin production.</p> <p>Leptin keeps you thin. Acts on ventromedial area of hypothalamus (satiety center) to ↓ appetite.</p>
Endocannabinoids	<p>Act at cannabinoid receptors in hypothalamus and nucleus accumbens, two key brain areas for the homeostatic and hedonic control of food intake → ↑ appetite.</p> <p>Exogenous cannabinoids cause "the munchies."</p>

Signaling pathways of endocrine hormones

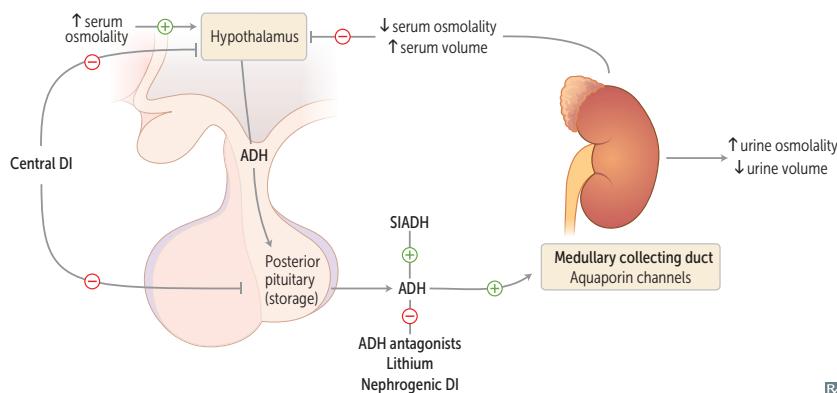
cAMP	FSH, LH, ACTH, TSH, CRH, hCG, ADH (V ₂ -receptor), MSH, PTH, Calcitonin, Histamine (H ₂ -receptor), Glucagon, GHRH	FLAT ChAMPs CHuGG
cGMP	BNP, ANP, EDRF (NO)	BAD GraMPa Think vasodilation and diuresis
IP ₃	GnRH, Oxytocin, ADH (V ₁ -receptor), TRH, Histamine (H ₁ -receptor), Angiotensin II, Gastrin	GOAT HAG
Intracellular receptor	Progesterone, Estrogen, Testosterone, Cortisol, Aldosterone, T ₃ /T ₄ , Vitamin D	PET CAT in TV
Receptor tyrosine kinase	IGF-1, FGF, PDGF, EGF, Insulin	MAP kinase pathway Get Found In the MAP
Nonreceptor tyrosine kinase	G-CSF, Erythropoietin, Thrombopoietin Prolactin, Immunomodulators (eg, cytokines IL-2, IL-6, IFN), GH	JAK/STAT pathway Think acidophils and cytokines GET a JAKed PIG

Signaling pathways of steroid hormones



Steroid hormones are lipophilic and therefore must circulate bound to specific binding globulins, which ↑ their solubility.
 In males, ↑ sex hormone–binding globulin (SHBG) lowers free testosterone → gynecomastia.
 In females, ↓ SHBG raises free testosterone → hirsutism.
 ↑ estrogen (eg, OCPs, pregnancy) → ↑ SHBG.

► ENDOCRINE—PATHOLOGY

Syndrome of inappropriate antidiuretic hormone secretion

Characterized by excessive free water retention, euvolemic hyponatremia with continued urinary Na^+ excretion, urine osmolality $>$ serum osmolality.

Body responds to water retention with ↓ aldosterone and ↑ ANP and BNP → ↑ urinary Na^+ secretion → normalization of extracellular fluid volume → euvolemic hyponatremia.

Treatment: fluid restriction (first line), salt tablets, IV hypertonic saline, diuretics, ADH antagonists (eg, conivaptan, tolvaptan, demeclocycline).

SIADH causes include (HEED-up water):

- Head trauma/CNS disorders
- Ectopic ADH (eg, small cell lung cancer)
- Exogenous hormones (eg, vasopressin, desmopressin, oxytocin)
- Lung disease
- Drugs (eg, SSRIs, carbamazepine, cyclophosphamide)

Primary polydipsia and diabetes insipidus

Characterized by the production of large amounts of dilute urine +/- thirst. Urine specific gravity < 1.006 . Urine osmolality usually $< 300 \text{ mOsm/kg}$. Central DI may be transient if damage is below hypothalamic median eminence or in the posterior pituitary (ADH in hypothalamus can still be secreted systemically via portal capillaries in median eminence).

	Primary polydipsia	Central DI	Nephrogenic DI
DEFINITION	Excessive water intake	↓ ADH release	ADH resistance
CAUSES	Psychiatric illnesses, hypothalamic lesions affecting thirst center	Idiopathic, brain injury (trauma, hypoxia, tumor, surgery, infiltrative diseases)	Hereditary (ADH receptor mutation), drugs (eg, lithium, demeclocycline), hypercalcemia, hypokalemia
SERUM OSMOLALITY	↓	↑	↑
ADH LEVEL	↓ or normal	↓	Normal or ↑
WATER RESTRICTION^a	Significant ↑ in urine osmolality ($> 700 \text{ mOsm/kg}$)	No change or slight ↑ in urine osmolality	No change or slight ↑ in urine osmolality
DESMOPRESSIN ADMINISTRATION^b	—	Significant ↑ in urine osmolality ($> 50\%$)	Minimal change in urine osmolality
TREATMENT	Water restriction	Desmopressin (DDAVP)	Manage the underlying cause; low-solute diet, HCTZ, amiloride, indomethacin

^aNo water intake for 2–3 hours followed by hourly measurements of urine volume and osmolality as well as plasma Na^+ concentration and osmolality.

^bDesmopressin (ADH analog) is administered if serum osmolality $> 295\text{--}300 \text{ mOsm/kg}$, plasma $\text{Na}^+ \geq 145 \text{ mEq/L}$, or urine osmolality does not increase despite ↑ plasma osmolality.

Hypopituitarism

Undersecretion of pituitary hormones due to

- Nonsecreting pituitary adenoma, craniopharyngioma
- **Sheehan syndrome**—ischemic infarct of pituitary following severe postpartum hemorrhage; pregnancy-induced pituitary growth → ↑ susceptibility to hypoperfusion. Usually presents with failure to lactate, amenorrhea, cold intolerance (anterior pituitary hormones mainly affected).
- **Empty sella syndrome**—atrophy or compression of pituitary (which lies in the sella turcica), often idiopathic, common in obese females; associated with idiopathic intracranial hypertension
- **Pituitary apoplexy**—sudden hemorrhage of pituitary gland, often in the presence of an existing pituitary adenoma. Usually presents with sudden onset severe headache, visual impairment (eg, bitemporal hemianopia, diplopia due to CN III palsy), and features of hypopituitarism
- Brain injury
- Radiation

Treatment: hormone replacement therapy (glucocorticoids, thyroxine, sex steroids, human growth hormone)

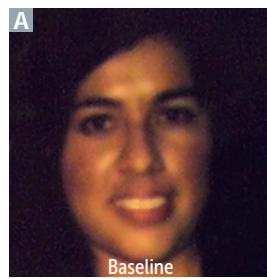
Acromegaly

Excess GH in adults. Typically caused by pituitary adenoma.

FINDINGS

Large tongue with deep furrows, frontal bossing, coarsening of facial features with aging **A**, deep voice, diaphoresis (excessive sweating), hypertrophic arthropathy, impaired glucose tolerance (insulin resistance), HTN, LVH, HFpEF (most common cause of death).

↑ GH in children → gigantism (↑ linear bone growth due to unfused epiphysis).

**DIAGNOSIS**

↑ serum IGF-1; failure to suppress serum GH following oral glucose tolerance test; pituitary mass seen on brain MRI.

TREATMENT

Pituitary adenoma resection. If not cured, treat with octreotide (somatostatin analog), pegvisomant (GH receptor antagonist), or dopamine agonists (eg, cabergoline).

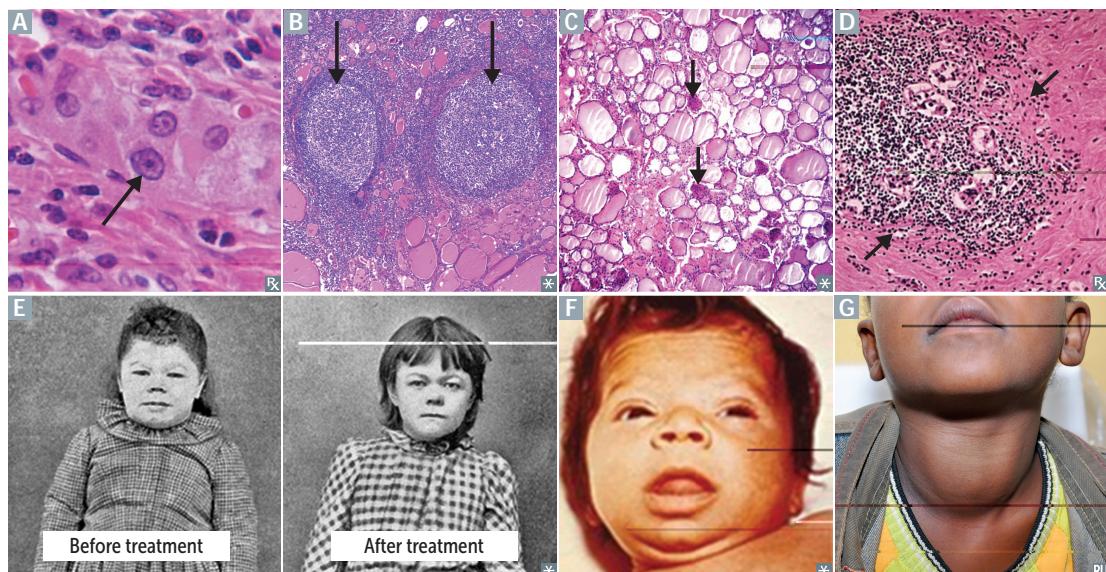
Hypothyroidism vs hyperthyroidism

	Hypothyroidism	Hyperthyroidism
METABOLIC	Cold intolerance, ↓ sweating, weight gain (↓ basal metabolic rate → ↓ calorogenesis), hyponatremia (↓ free water clearance)	Heat intolerance, ↑ sweating, weight loss (↑ synthesis of Na^+/K^+ -ATPase → ↑ basal metabolic rate → ↑ calorogenesis)
SKIN/HAIR	Dry, cool skin (due to ↓ blood flow); coarse, brittle hair; diffuse alopecia; brittle nails; puffy facies and generalized nonpitting edema (myxedema) due to ↑ GAGs in interstitial spaces → ↑ osmotic pressure → water retention	Warm, moist skin (due to vasodilation); fine hair; onycholysis (A); pretibial myxedema in Graves disease B
OCULAR	Periorbital edema C	Ophthalmopathy in Graves disease (including periorbital edema, exophthalmos), lid lag/retraction (↑ sympathetic stimulation of superior tarsal muscle)
GASTROINTESTINAL	Constipation (↓ GI motility), ↓ appetite	Hyperdefecation/diarrhea (↑ GI motility), ↑ appetite
MUSCULOSKELETAL	Hypothyroid myopathy (proximal weakness, ↑ CK), carpal tunnel syndrome, myoedema (small lump rising on the surface of a muscle when struck with a hammer)	Thyrotoxic myopathy (proximal weakness, normal CK), osteoporosis/↑ fracture rate (T_3 directly stimulates bone resorption)
REPRODUCTIVE	Abnormal uterine bleeding, ↓ libido, infertility	Abnormal uterine bleeding, gynecomastia, ↓ libido, infertility
NEUROPSYCHIATRIC	Hypoactivity, lethargy, fatigue, weakness, depressed mood, ↓ reflexes (delayed/slow relaxing)	Hyperactivity, restlessness, anxiety, insomnia, fine tremors (due to ↑ β -adrenergic activity), ↑ reflexes (brisk)
CARDIOVASCULAR	Bradycardia, dyspnea on exertion (↓ cardiac output)	Tachycardia, palpitations, dyspnea, arrhythmias (eg, atrial fibrillation), chest pain and systolic HTN due to ↑ number and sensitivity of β -adrenergic receptors, ↑ expression of cardiac sarcolemmal ATPase and ↓ expression of phospholamban
LABS	↑ TSH (if 1°) ↓ free T_3 and T_4 Hypercholesterolemia (due to ↓ LDL receptor expression)	↓ TSH (if 1°) ↑ free T_3 and T_4 ↓ LDL, HDL, and total cholesterol



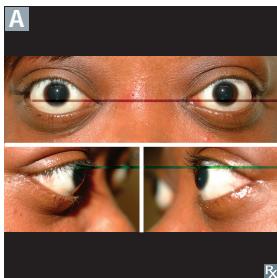
Hypothyroidism

Hashimoto thyroiditis	<p>Also called chronic autoimmune thyroiditis. Most common cause of hypothyroidism in iodine-sufficient regions. Associated with HLA-DR3 (differs by ethnicity), ↑ risk of primary thyroid lymphoma (typically diffuse large B-cell lymphoma).</p> <p>Findings: moderately enlarged, nontender thyroid. May be preceded by transient hyperthyroid state (“Hashitoxicosis”) due to follicular rupture and thyroid hormone release.</p> <p>Serology: + antithyroid peroxidase (antimicrosomal) and antithyroglobulin antibodies.</p> <p>Histology: Hürthle cells A, lymphoid aggregates with germinal centers B.</p> <p>Postpartum thyroiditis—mild, self-limited variant of Hashimoto thyroiditis arising < 1 year after delivery.</p>
Subacute granulomatous thyroiditis	<p>Also called de Quervain thyroiditis. Usually, a self-limited disease. Natural history: transient hyperthyroidism → euthyroid state → hypothyroidism → euthyroid state. Often preceded by viral infection.</p> <p>Findings: ↑ ESR, jaw pain, very tender thyroid (de Quervain is associated with pain).</p> <p>Histology: granulomatous inflammation C.</p>
Riedel thyroiditis	<p>Also called invasive fibrous thyroiditis. May occur as part of IgG₄-related disease spectrum (eg, autoimmune pancreatitis, retroperitoneal fibrosis, noninfectious aortitis). Hypothyroidism occurs in ½ of patients. Fibrosis may extend to local structures (eg, trachea, esophagus), mimicking anaplastic carcinoma.</p> <p>Findings: slowly enlarging, hard (rocklike), fixed, nontender thyroid.</p> <p>Histology: thyroid replaced by fibrous tissue and inflammatory infiltrate D.</p>
Congenital hypothyroidism	<p>Formerly called cretinism. Most commonly caused by thyroid dysgenesis (abnormal thyroid gland development; eg, agenesis, hypoplasia, ectopy) or dyshormonogenesis (abnormal thyroid hormone synthesis; eg, mutations in thyroid peroxidase) in iodine-sufficient regions.</p> <p>Findings (6 P's): pot-bellied, pale, puffy-faced child E with protruding umbilicus, protuberant tongue F, and poor brain development.</p>
Other causes	Iodine deficiency (most common cause worldwide; typically presents with goiter G), iodine excess (Wolff-Chaikoff effect), drugs (eg, amiodarone, lithium), nonthyroidal illness syndrome (also called euthyroid sick syndrome; ↓ T ₃ with normal/↓ T ₄ and TSH in critically ill patients).



Hyperthyroidism

Graves disease



Most common cause of hyperthyroidism. Thyroid-stimulating immunoglobulin (IgG, can cause transient neonatal hyperthyroidism; type II hypersensitivity) stimulates TSH receptors on thyroid (hyperthyroidism, diffuse goiter), dermal fibroblasts (pretibial myxedema), and orbital fibroblasts (Graves orbitopathy). Activation of T-cells → lymphocytic infiltration of retroorbital space → ↑ cytokines (eg, TNF- α , IFN- γ) → ↑ fibroblast secretion of hydrophilic GAGs → ↑ osmotic muscle swelling, muscle inflammation, and adipocyte count → exophthalmos **A**. Often presents during stress (eg, pregnancy). Associated with HLA-DR3 and HLA-B8. Histology: tall, crowded follicular epithelial cells; scalloped colloid.

Toxic multinodular goiter

Focal patches of hyperfunctioning follicular cells distended with colloid working independently of TSH (due to TSH receptor mutations in 60% of cases). ↑ release of T₃ and T₄. Hot nodules (hyperfunctioning nodules visualized on radioactive iodine scan) are rarely malignant.

Thyroid storm

Uncommon but serious complication that occurs when hyperthyroidism is incompletely treated/untreated and then significantly worsens in the setting of acute stress such as infection, trauma, surgery. Presents with agitation, delirium, fever, diarrhea, coma, and tachyarrhythmia (cause of death). May see ↑ LFTs. Treat with the **4 P's**: β -blockers (eg, propranolol), propylthiouracil, glucocorticoids (eg, prednisolone), potassium iodide (Lugol iodine). Iodide load → ↓ T₄ synthesis → Wolff-Chaikoff effect.

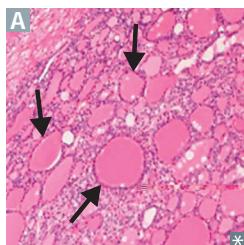
Jod-Basedow phenomenon

Iodine-induced hyperthyroidism. Occurs when a patient with iodine deficiency and partially autonomous thyroid tissue (eg, autonomous nodule) is made iodine replete. Can happen after iodine IV contrast or amiodarone use. Opposite to Wolff-Chaikoff effect.

Causes of goiter

Smooth/diffuse: Graves disease, Hashimoto thyroiditis, iodine deficiency, TSH-secreting pituitary adenoma.
Nodular: toxic multinodular goiter, thyroid adenoma, thyroid cancer, thyroid cyst.

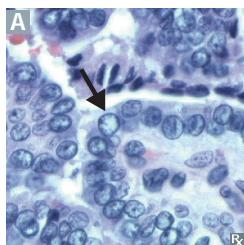
Thyroid adenoma



Benign solitary growth of the thyroid. Most are nonfunctional (“cold” on radioactive iodine scan), can rarely cause hyperthyroidism via autonomous thyroid hormone production (“hot” or “toxic”). Most common histology is follicular (arrows in **A**); absence of capsular or vascular invasion (unlike follicular carcinoma).

Thyroid cancer

Typically diagnosed with fine needle aspiration; treated with thyroidectomy. Complications of surgery include hypocalcemia (due to removal of parathyroid glands), transection of recurrent laryngeal nerve during ligation of inferior thyroid artery (leads to dysphagia and dysphonia [hoarseness]), and injury to the external branch of the superior laryngeal nerve during ligation of superior thyroid vascular pedicle (may lead to loss of tenor usually noticeable in professional voice users).

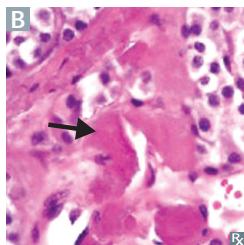
Papillary carcinoma

Most common. Empty-appearing nuclei with central clearing (“**Orphan Annie**” eyes) **A**, psammoma bodies, nuclear grooves (**Papi** and **Moma** adopted **Orphan Annie**). ↑ risk with *RET/PTC* rearrangements and *BRAF* mutations, childhood irradiation.

Papillary carcinoma: most prevalent, palpable lymph nodes. Good prognosis.

Follicular carcinoma

Good prognosis. Invades thyroid capsule and vasculature (unlike follicular adenoma), uniform follicles; hematogenous spread is common. Associated with *RAS* mutation and *PAX8-PPAR-γ* translocations. Fine needle aspiration cytology may not be able to distinguish between follicular adenoma and carcinoma.

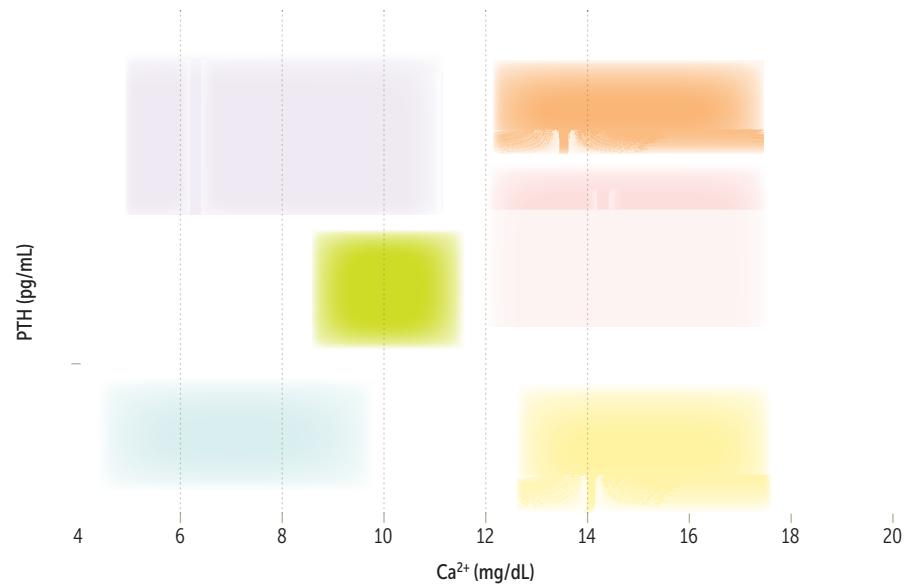
Medullary carcinoma

From parafollicular “**C** cells”; produces calcitonin, sheets of polygonal cells in an amyloid stroma **B** (stains with Congo red). Associated with MEN 2A and 2B (*RET* mutations).

Undifferentiated/anaplastic carcinoma

Older patients; presents with rapidly enlarging neck mass → compressive symptoms (eg, dyspnea, dysphagia, hoarseness); very poor prognosis. Associated with *TP53* mutation.

Diagnosing parathyroid disease



Hyperparathyroidism

Primary hyperparathyroidism



Usually due to parathyroid adenoma or hyperplasia. **Hypercalcemia**, hypercalciuria (renal **stones**), polyuria (**thrones**), hypophosphatemia, ↑ PTH, ↑ ALP, ↑ urinary cAMP. Most often asymptomatic. May present with **bone** pain, weakness, constipation (“**groans**”), abdominal/flank pain (kidney stones, acute pancreatitis), neuropsychiatric disturbances (“**psychiatric overtones**”).

Secondary hyperparathyroidism

2° hyperplasia due to ↓ Ca²⁺ absorption and/or ↑ PO₄³⁻, most often in chronic kidney disease (causes hypovitaminosis D and hyperphosphatemia → ↓ Ca²⁺). **Hypocalcemia**, hyperphosphatemia in chronic kidney disease (vs hypophosphatemia with most other causes), ↑ ALP, ↑ PTH.

Tertiary hyperparathyroidism

Refractory (autonomous) hyperparathyroidism resulting from chronic kidney disease. ↑↑ PTH, ↑ Ca²⁺.

Familial hypocalciuric hypercalcemia

Autosomal dominant. Defective G-coupled Ca²⁺-sensing receptors in multiple tissues (eg, parathyroids, kidneys). Higher than normal Ca²⁺ levels required to suppress PTH. Excessive renal Ca²⁺ reabsorption → mild hypercalcemia and hypocalciuria with normal to ↑ PTH levels.

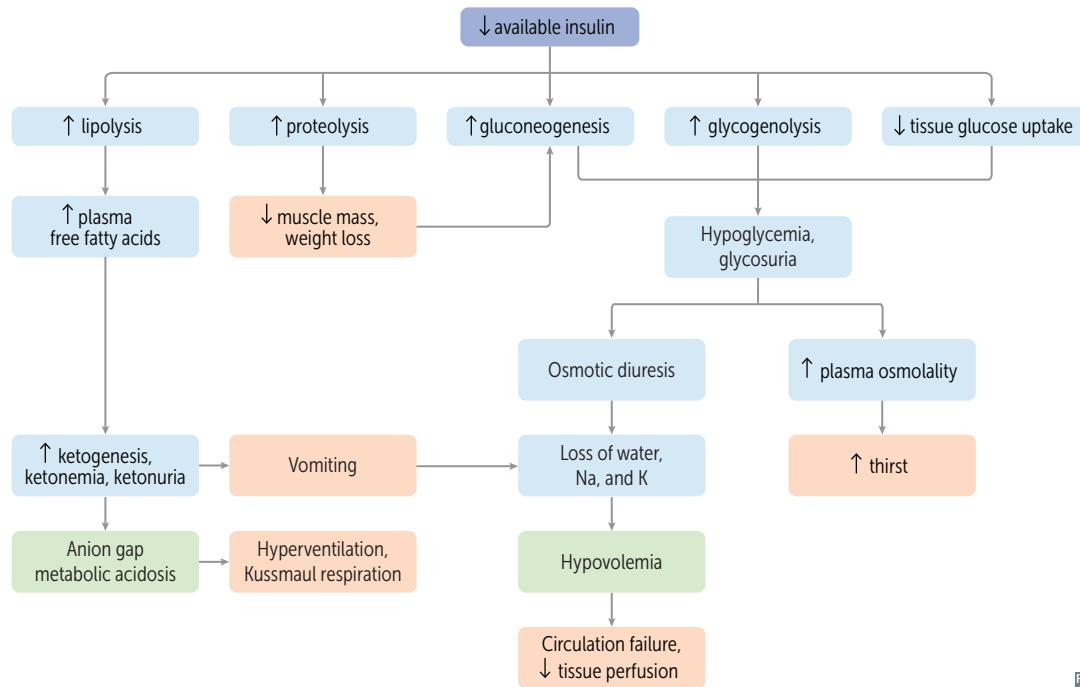
Osteitis brosa cystica—cystic **bone** spaces filled with brown fibrous tissue **A** (“brown tumor” consisting of osteoclasts and deposited hemosiderin from hemorrhages; causes bone pain). Due to ↑ PTH, classically associated with 1° (but also seen with 2°) hyperparathyroidism.

“**Stones, thrones, bones, groans**, and **psychiatric overtones**.”

Renal osteodystrophy—renal disease → 2° and 3° hyperparathyroidism → bone lesions.

Diabetes mellitus

ACUTE MANIFESTATIONS	<p>Polydipsia, polyuria, polyphagia (3 P's), weight loss, DKA (type 1), hyperosmolar hyperglycemic state (type 2).</p> <p>Rarely, can be caused by unopposed secretion of GH and epinephrine. Also seen in patients on glucocorticoid therapy (steroid diabetes).</p>		
CHRONIC COMPLICATIONS	<p>Nonenzymatic glycation:</p> <ul style="list-style-type: none"> ▪ Small vessel disease (hyaline arteriolosclerosis) → retinopathy, neuropathy, nephropathy. ▪ Large vessel disease (atherosclerosis) → CAD, cerebrovascular disease, peripheral vascular disease. MI is the most common cause of death. <p>Osmotic damage (sorbitol accumulation in organs with aldose reductase and ↓ or absent sorbitol dehydrogenase):</p> <ul style="list-style-type: none"> ▪ Neuropathy: motor, sensory (glove and stocking distribution), autonomic degeneration (eg, GERD, gastroparesis, diabetic diarrhea). ▪ Cataracts. 		
DIAGNOSIS	TEST HbA _{1c}	DIAGNOSTIC CUTOFF ≥ 6.5%	NOTES Reflects average blood glucose over prior 3 months (influenced by RBC turnover)
	Fasting plasma glucose	≥ 126 mg/dL	Fasting for > 8 hours
	2-hour oral glucose tolerance test	≥ 200 mg/dL	2 hours after consumption of 75 g of glucose in water
	Random plasma glucose	≥ 200 mg/dL	Presence of hyperglycemic symptoms is required



Type 1 vs type 2 diabetes mellitus

	Type 1	Type 2
1° DEFECT	Autoimmune T-cell-mediated destruction of β cells	↑ resistance to insulin, progressive pancreatic β-cell failure
INSULIN NECESSARY IN TREATMENT	Always	Sometimes
AGE (EXCEPTIONS COMMON)	< 30 yr	> 40 yr
ASSOCIATION WITH OBESITY	No	Yes
GENETIC PREDISPOSITION	Relatively weak (50% concordance in identical twins), polygenic	Relatively strong (90% concordance in identical twins), polygenic
ASSOCIATION WITH HLA SYSTEM	Yes, HLA-DR4 and -DR3 (4 – 3 = type 1)	No
GLUCOSE INTOLERANCE	Severe	Mild to moderate
INSULIN SENSITIVITY	High	Low
KETOACIDOSIS	Common	Rare
β-CELL NUMBERS IN THE ISLETS	↓	Variable (with amyloid deposits)
SERUM INSULIN LEVEL	↓	↑ initially, but ↓ in advanced disease
CLASSIC SYMPTOMS OF POLYURIA, POLYDIPSIA, POLYPHAGIA, WEIGHT LOSS	Common	Sometimes
HISTOLOGY	Islet leukocytic infiltrate	Islet amyloid polypeptide deposits

Hyperglycemic emergencies

	Diabetic ketoacidosis	Hyperosmolar hyperglycemic state
PATHOGENESIS	Insulin noncompliance or ↑ requirements due to ↑ stress (eg, infection) → lipolysis and oxidation of free fatty acids → ↑ ketone bodies (β-hydroxybutyrate > acetacetate). Insulin deficient, ketones present.	Profound hyperglycemia → excessive osmotic diuresis → dehydration and ↑ serum osmolality → HHS. Classically seen in older patients with type 2 DM and limited ability to drink. Insulin present, ketones deficient.
SIGNS/SYMPTOMS	DKA is Deadly: Delirium/psychosis, Kussmaul respirations (rapid, deep breathing), Abdominal pain-nausea/vomiting, Dehydration. Fruity breath odor due to exhaled acetone.	Thirst, polyuria, lethargy, focal neurologic deficits, seizures.
LABS	Hyperglycemia, ↑ H ⁺ , ↓ HCO ₃ ⁻ (↑ anion gap metabolic acidosis), ↑ urine and blood ketone levels, leukocytosis. Normal/↑ serum K ⁺ , but depleted intracellular K ⁺ due to transcellular shift from ↓ insulin and acidosis. Osmotic diuresis → ↑ K ⁺ loss in urine → total body K ⁺ depletion.	Hyperglycemia (often > 600 mg/dL), ↑ serum osmolality (> 320 mOsm/kg), normal pH (no acidosis), no ketones. Normal/↑ serum K ⁺ , ↓ intracellular K ⁺ .
COMPLICATIONS	Life-threatening mucormycosis, cerebral edema, cardiac arrhythmias.	Can progress to coma and death if untreated.
TREATMENT	IV fluids, IV insulin, and K ⁺ (to replete intracellular stores). Glucose may be required to prevent hypoglycemia from insulin therapy.	

Hypoglycemia in diabetes mellitus

Usually occurs in patients treated with insulin or insulin secretagogues (eg, sulfonylureas, meglitinides) in the setting of high-dose treatment, inadequate food intake, and/or exercise.

- Neurogenic (autonomic) symptoms: diaphoresis, tachycardia, tremor, anxiety, hunger. Allow perception of ↓ glucose (hypoglycemia awareness).
- Neuroglycopenic symptoms: altered mental status, seizures, death due to insufficient glucose in CNS. May occur in the absence of preceding neurogenic symptoms in patients with attenuated autonomic response (hypoglycemia unawareness).

Treatment: simple carbohydrates (eg, glucose tablets, fruit juice), IM glucagon, IV dextrose.

Cushing syndrome**ETIOLOGY**

↑ cortisol due to a variety of causes:

- Exogenous glucocorticoids → ↓ ACTH → bilateral adrenal atrophy. Most common cause.
- Primary adrenal adenoma, hyperplasia, or carcinoma → ↓ ACTH → atrophy of uninvolved adrenal gland.
- ACTH-secreting pituitary adenoma (Cushing disease); paraneoplastic ACTH secretion (eg, small cell lung cancer, bronchial carcinoids) → bilateral adrenal hyperplasia. Cushing disease is responsible for the majority of endogenous cases of Cushing syndrome.

FINDINGS

MOON FACIES: Metabolic syndrome (hypertension, hyperglycemia, hyperlipidemia), **O**besity

(truncal weight gain, easy bruising, moon face, hirsutism, acne, oligomenorrhea)

hages (thinning, striae

B, hyperpigmentation).

DIAGNOSIS

Screening tests include: ↑ free-cortisol on 24-hr urine, ↑

Nelson syndrome

Enlargement of pre-existing ACTH-secreting pituitary adenoma after bilateral adrenalectomy for refractory Cushing disease → ↑ ACTH (hyperpigmentation), mass effect (headaches, bitemporal hemianopia).
Treatment: transsphenoidal resection, postoperative pituitary irradiation for residual tumor.

Adrenal insufficiency

Inability of adrenal glands to generate enough glucocorticoids +/- mineralocorticoids for the body's needs. Can be acute or chronic. Symptoms include weakness, fatigue, orthostatic hypotension, muscle aches, weight loss, GI disturbances, sugar and/or salt cravings.
Treatment: glucocorticoid +/- mineralocorticoid replacement.

Primary adrenal insufficiency

↓ gland function → ↓ cortisol, ↓ aldosterone → hypotension (hyponatremic volume contraction), hyperkalemia, metabolic acidosis, skin/mucosal hyperpigmentation **A** (↑ melanin synthesis due to ↑ MSH, a byproduct of POMC cleavage). **Primary** pigments the skin/mucosa.
Addison disease—chronic 1° adrenal insufficiency; caused by adrenal atrophy or destruction. Most commonly due to autoimmune adrenalitis (high-income countries) or TB (low-income countries).

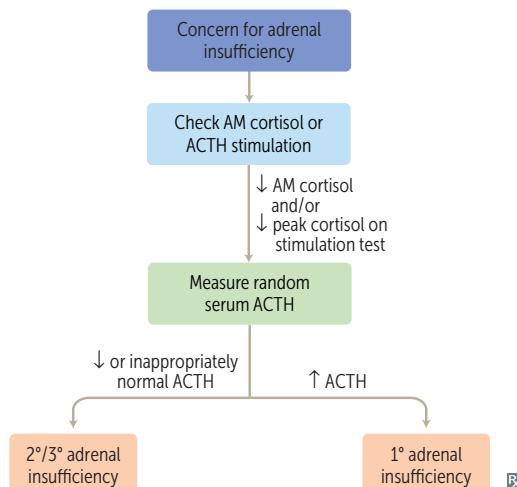
Secondary and tertiary adrenal insufficiency

↓ pituitary ACTH secretion (secondary) or ↓ hypothalamic CRH secretion (tertiary). No hyperkalemia (aldosterone synthesis preserved due to functioning adrenal gland, intact RAAS), no hyperpigmentation.
2° adrenal insufficiency is due to pituitary pathologies, 3° adrenal insufficiency is most commonly due to abrupt cessation of chronic glucocorticoid therapy (HPA suppression). **Tertiary** from treatment.

Acute adrenal insufficiency

Also called adrenal (addisonian) crisis; often precipitated by acute stressors that ↑ glucocorticoid requirements (eg, infection) in patients with pre-existing adrenal insufficiency or on glucocorticoid therapy. May present with acute abdominal pain, nausea, vomiting, altered mental status, shock.

Waterhouse-Friderichsen syndrome—bilateral adrenal hemorrhage in the setting of sepsis (eg, meningococcemia) → acute 1° adrenal insufficiency.



Hyperaldosteronism

Increased secretion of aldosterone from adrenal gland. Clinical features include hypertension, ↓ or normal K⁺, metabolic alkalosis. 1° hyperaldosteronism does not directly cause edema due to aldosterone escape mechanism. However, certain 2° causes of hyperaldosteronism (eg, heart failure) impair the aldosterone escape mechanism, leading to worsening of edema.

Primary hyperaldosteronism

Seen in patients with bilateral adrenal hyperplasia or adrenal adenoma (Conn syndrome). ↑ aldosterone, ↓ renin. Leads to treatment-resistant hypertension.

Secondary hyperaldosteronism

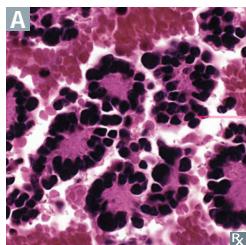
Seen in patients with renovascular hypertension, juxtaglomerular cell tumors (renin-producing), and edema (eg, cirrhosis, heart failure, nephrotic syndrome).

Neuroendocrine tumors

Heterogeneous group of neoplasms originating from neuroendocrine cells (which have traits similar to nerve cells and hormone-producing cells).

Most neoplasms occur in the GI system (eg, carcinoid, gastrinoma), pancreas (eg, insulinoma, glucagonoma), and lungs (eg, small cell carcinoma). Also in thyroid (eg, medullary carcinoma) and adrenals (eg, pheochromocytoma).

Neuroendocrine cells (eg, pancreatic β cells, enterochromaffin cells) share a common biologic function through amine precursor uptake decarboxylase (APUD) despite differences in embryologic origin, anatomic site, and secretory products (eg, chromogranin A, neuron-specific enolase [NSE], synaptophysin, serotonin, histamine, calcitonin). Treatment: surgical resection, somatostatin analogs.

Neuroblastoma

Most common tumor of the adrenal medulla in **children**, usually < 4 years old. Originates from **neural crest cells**. Occurs anywhere along the sympathetic chain.

Most common presentation is abdominal distension and a firm, irregular mass that can cross the midline (vs Wilms tumor, which is smooth and unilateral). Less likely to develop hypertension than with pheochromocytoma (**neuroblastoma is normotensive**). Can also present with opsoclonus-myoclonus syndrome (“dancing eyes-dancing feet”).

↑ HVA and VMA (catecholamine metabolites) in urine. Homer-Wright rosettes (neuroblasts surrounding a central area of neuropil **A**) characteristic of neuroblastoma and medulloblastoma. Bombesin and **NSE** \oplus . Associated with amplification of **N-myc** oncogene.

Pheochromocytoma

Etiology



Most common tumor of the adrenal medulla in **adults** (black arrow in **A**; red arrow points to bone metastases). Derived from chromaffin cells (arise from neural crest). May be associated with germline mutations (eg, NF-1, VHL, RET [MEN 2A, 2B]).

Symptoms

Most tumors secrete epinephrine, norepinephrine, and dopamine, which can cause episodic hypertension. May also secrete EPO → polycythemia. Symptoms occur in “spells”—relapse and remit.

Rule of 10's:

- 10%** malignant
- 10%** bilateral
- 10%** extra-adrenal (eg, bladder wall, organ of Zuckerkandl)
- 10%** calcify
- 10%** kids

Findings

↑ catecholamines and metanephhrines (eg, homovanillic acid, vanillylmandelic acid) in urine and plasma.

Episodic hyperadrenergic symptoms (**5 P's**):

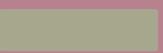
- P**ressure (\uparrow BP)
- P**ain (headache)
- P**erspiration
- P**alpitations (tachycardia)
- P**allor

Treatment

Irreversible α -antagonists (eg, phenoxybenzamine) followed by β -blockers prior to tumor resection. α -blockade must be achieved before giving β -blockers to avoid a hypertensive crisis. **A** before **B**.

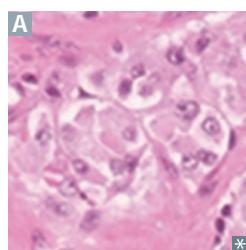
Chromogranin, synaptophysin and NSE \oplus .

Phenoxylbenzamine for **pheochromocytoma**.



Pancreatic islet cell tumors

Insulinoma	Tumor of pancreatic β cells \rightarrow overproduction of insulin \rightarrow hypoglycemia. May see Whipple triad: low blood glucose, symptoms of hypoglycemia (eg, lethargy, syncope, diplopia), and resolution of symptoms after normalization of plasma glucose levels. Symptomatic patients have \downarrow blood glucose and \uparrow C-peptide levels (vs exogenous insulin use). $\sim 10\%$ of cases associated with MEN1 syndrome. Treatment: surgical resection.
Glucagonoma	Tumor of pancreatic α cells \rightarrow overproduction of glucagon. Presents with 6 D's : dermatitis (necrolytic migratory erythema), diabetes (hyperglycemia), DVT, declining weight, depression, diarrhea. Treatment: octreotide, surgical resection.
Somatostatinoma	Tumor of pancreatic δ cells \rightarrow overproduction of somatostatin \rightarrow \downarrow secretion of secretin, cholecystokinin, glucagon, insulin, gastrin, gastric inhibitory peptide (GIP). May present with diabetes/glucose intolerance, steatorrhea, gallstones, achlorhydria. Treatment: surgical resection; somatostatin analogs (eg, octreotide) for symptom control.

Carcinoid tumors

Carcinoid tumors arise from neuroendocrine cells, most commonly in the intestine or lung.

Neuroendocrine cells secrete 5-HT, which undergoes hepatic first-pass metabolism and enzymatic breakdown by MAO in the lung. If 5-HT reaches the systemic circulation (eg, after liver metastasis), carcinoid tumor may present with **carcinoid syndrome**—episodic flushing, diarrhea, wheezing, right-sided valvular heart disease (eg, tricuspid regurgitation, pulmonic stenosis), niacin deficiency (pellagra), \uparrow urinary 5-HIAA.

Histology: rosettes **A**, chromogranin A \oplus , synaptophysin \oplus .

Treatment: surgical resection, somatostatin analog (eg, octreotide) or tryptophan hydroxylase inhibitor (eg, telotristat) for symptom control.

Rule of thirds:

1/3 metastasize

1/3 present with 2nd malignancy

1/3 are multiple

Zollinger-Ellison syndrome

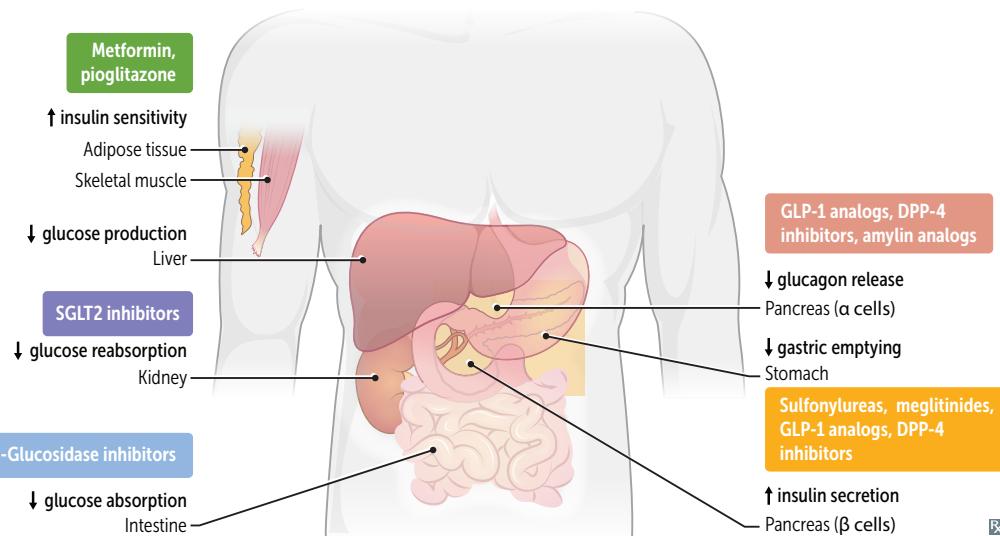
Gastrin-secreting tumor (gastrinoma) of duodenum or pancreas. Acid hypersecretion causes recurrent ulcers in duodenum and jejunum. Presents with abdominal pain (peptic ulcer disease, distal ulcers), diarrhea (malabsorption). Positive secretin stimulation test: \uparrow gastrin $\text{le t q E(r)- 199 240.9368 c0w-}$

► ENDOCRINE—PHARMACOLOGY

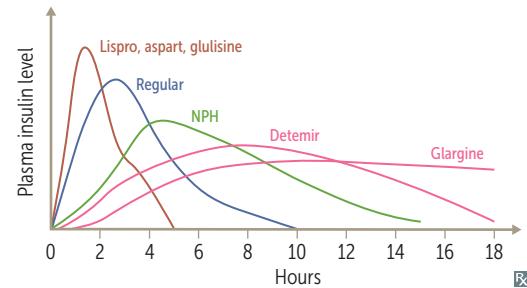
Diabetes mellitus therapy

All patients with diabetes mellitus should receive education on diet, exercise, blood glucose monitoring, and complication management. Treatment differs based on the type of diabetes and glycemic control:

- Type 1 DM—insulin replacement
 - Type 2 DM—oral agents (metformin is first line), non-insulin injectables, insulin replacement; weight loss particularly helpful in lowering blood glucose
 - Gestational DM—insulin replacement if nutrition therapy and exercise alone fail
- Regular (short-acting) insulin is preferred for DKA (IV), hyperkalemia (+ glucose), stress hyperglycemia.



DRUG	MECHANISM	ADVERSE EFFECTS
Insulin preparations		
Rapid acting (no lag): lispro, aspart, glulisine	Bind insulin receptor (tyrosine kinase activity) Liver: ↑ glucose storage as glycogen	Hypoglycemia, lipodystrophy, hypersensitivity reactions (rare), weight gain
Short acting: regular	Muscle: ↑ glycogen, protein synthesis Fat: ↑ TG storage	
Intermediate acting: NPH	Cell membrane: ↑ K ⁺ uptake	
Long acting: detemir, glargine		
Very long acting: degludec		



Diabetes mellitus therapy (continued)

DRUG	MECHANISM	ADVERSE EFFECTS
Increase insulin sensitivity		
Metformin	Inhibits mitochondrial glycerol-3-phosphate dehydrogenase (mGPD) → inhibition of hepatic gluconeogenesis and the action of glucagon. ↑ glycolysis, peripheral glucose uptake (↑ insulin sensitivity).	GI upset, lactic acidosis (use with caution in renal insufficiency), vitamin B ₁₂ deficiency. Weight loss (often desired).
Pioglitazone	Activate PPAR-γ (a nuclear receptor) → ↑ insulin sensitivity and levels of adiponectin → regulation of glucose metabolism and fatty acid storage.	Weight gain, edema, HF, ↑ risk of fractures. Delayed onset of action (several weeks).
Increase insulin secretion		
Sulfonylureas (1st gen)		
Chlorpropamide, tolbutamide		
Sulfonylureas (2nd gen)		
Glipizide, glyburide	Close K ⁺ channels in pancreatic B cell membrane → cell depolarizes → insulin release via ↑ Ca ²⁺ influx.	Disulfiram-like reaction with first-generation sulfonylureas only (rarely used). Hypoglycemia (↑ risk in renal insufficiency), weight gain.
Meglitinides		
Nateglinide, repaglinide		
Increase glucose-induced insulin secretion		
GLP-1 analogs	↓ glucagon release, ↓ gastric emptying, ↑ glucose-dependent insulin release.	Nausea, vomiting, pancreatitis. Weight loss (often desired). ↑ satiety (often desired).
Exenatide, liraglutide, semaglutide		
DPP-4 inhibitors		
Linagliptin, saxagliptin, sitagliptin	Inhibit DPP-4 enzyme that deactivates GLP-1 → ↓ glucagon release, ↓ gastric emptying. ↑ glucose-dependent insulin release.	Respiratory and urinary infections, weight neutral. ↑ satiety (often desired).
Decrease glucose absorption		
Sodium-glucose co-transporter 2 inhibitors		
Canagli ozin, dapagli ozin, empagli ozin	Block reabsorption of glucose in proximal convoluted tubule.	Glucosuria (UTIs, vulvovaginal candidiasis), dehydration (orthostatic hypotension), weight loss. Glucose flows in urine. Use with caution in renal insufficiency (↓ efficacy with ↓ GFR).
α-glucosidase inhibitors		
Acarbose, miglitol	Inhibit intestinal brush-border α-glucosidases → delayed carbohydrate hydrolysis and glucose absorption → ↓ postprandial hyperglycemia.	GI upset, bloating. Not recommended in renal insufficiency.
Others		
Amylin analogs Pramlintide	↓ glucagon release, ↓ gastric emptying.	Hypoglycemia, nausea. ↑ satiety (often desired).

Thionamides

Propylthiouracil, methimazole.

MECHANISM	Block thyroid peroxidase, inhibiting the oxidation of iodide as well as the organification and coupling of iodine → inhibition of thyroid hormone synthesis. PTU also blocks 5'-deiodinase → ↓ Peripheral conversion of T ₄ to T ₃ .
CLINICAL USE	Hyperthyroidism. PTU used in Primary (first) trimester of pregnancy (due to methimazole teratogenicity); methimazole used in second and third trimesters of pregnancy (due to risk of PTU-induced hepatotoxicity). Not used to treat Graves ophthalmopathy (treated with glucocorticoids).
ADVERSE EFFECTS	Skin rash, agranulocytosis (rare), aplastic anemia, hepatotoxicity. PTU use has been associated with ANCA-positive vasculitis. Methimazole is a possible teratogen (can cause aplasia cutis).

Levothyroxine, liothyronine

MECHANISM	Hormone replacement for T ₄ (levothyroxine; levo = 4 letters) or T ₃ (liothyronine; lio = 3 letters). Avoid levothyroxine with antacids, bile acid resins, or ferrous sulfate (↓ absorption).
CLINICAL USE	Hypothyroidism, myxedema. May be misused for weight loss. Distinguish exogenous hyperthyroidism from endogenous hyperthyroidism by using a combination of TSH receptor antibodies, radioactive iodine uptake, and/or measurement of thyroid blood flow on ultrasound.
ADVERSE EFFECTS	Tachycardia, heat intolerance, tremors, arrhythmias.

Hypothalamic/pituitary drugs

DRUG	CLINICAL USE
Conivaptan, tolvaptan	ADH antagonists SIADH (block action of ADH at V ₂ -receptor)
Demeclacycline	ADH antagonist, a tetracycline SIADH (interferes with ADH signaling)
Desmopressin	ADH analog Central DI, von Willebrand disease, sleep enuresis, hemophilia A
GH	GH deficiency, Turner syndrome
Oxytocin	Induction of labor (stimulates uterine contractions), control uterine hemorrhage
Somatostatin (octreotide)	Acromegaly, carcinoid syndrome, gastrinoma, glucagonoma, esophageal varices

Fludrocortisone

MECHANISM	Synthetic analog of aldosterone with glucocorticoid effects. Fludrocortisone retains fluid.
CLINICAL USE	Mineralocorticoid replacement in 1° adrenal insufficiency.
ADVERSE EFFECTS	Similar to glucocorticoids; also edema, exacerbation of heart failure, hyperpigmentation.

Cinacalcet

MECHANISM	Sensitizes calcium-sensing receptor (CaSR) in parathyroid gland to circulating Ca^{2+} $\rightarrow \downarrow \text{PTH}$. Pronounce “Senacalcet.”
CLINICAL USE	2° hyperparathyroidism in patients with CKD receiving hemodialysis, hypercalcemia in 1° hyperparathyroidism (if parathyroidectomy fails), or in parathyroid carcinoma.
ADVERSE EFFECTS	Hypocalcemia.

Sevelamer

MECHANISM	Nonabsorbable phosphate binder that prevents phosphate absorption from the GI tract.
CLINICAL USE	Hyperphosphatemia in CKD.
ADVERSE EFFECTS	Hypophosphatemia, GI upset.

Cation exchange resins Patiromer, sodium polystyrene sulfonate, zirconium cyclosilicate.

MECHANISM	Bind K^+ in colon in exchange for other cations (eg, Na^+ , Ca^{2+}) $\rightarrow \text{K}^+$ excreted in feces.
CLINICAL USE	Hyperkalemia.
ADVERSE EFFECTS	Hypokalemia, GI upset.