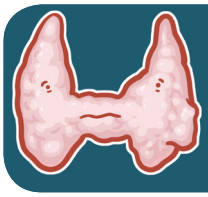

NOTES
PITUITARY HORMONES

GENERALLY, WHAT ARE THEY?

- *Pituitary gland:* AKA hypophyseal gland/ hypophysis
- Connected to hypothalamus via pituitary stalk (infundibulum) which controls pituitary secretory actions
- Consists of two embryologically, functionally different parts that secrete different hormones

ANTERIOR PITUITARY (ADENOHYPOPHYSIS)

- Connects to hypothalamus via blood vessels (hypophyseal portal system)
- Hypothalamus produces releasing hormones → pituitary secretes tropic hormones that regulate target tissues

Corticotropin-releasing hormone (CRH)

- Adrenocorticotropic hormone (ACTH) → adrenal medulla

Gonadotropin-releasing hormone (GnRH)

- Luteinizing hormone (LH), follicle-stimulating hormone (FSH) → ovaries, testes

Growth hormone releasing hormone (GHRH)

- Stimulates release of somatotropin/ growth hormone (GH) → various tissues throughout body

Thyrotropin-releasing hormone (TRH)

- Thyroid-stimulating hormone → thyroid gland

Prolactin (PL)

- Acts on breasts (lactogenesis)
  - Hypothalamus inhibits prolactin production via dopamine
  - TRH, estrogen, progesterone, oxytocin stimulate prolactin

POSTERIOR PITUITARY (NEUROHYPOPHYSIS)

- Represents an extension of hypothalamus
- Does not secrete its own hormones
- Stores, releases neurohormones synthesized in hypothalamus

Vasopressin/antidiuretic hormone (ADH)

- Acts on kidney tubules, arterioles

Oxytocin

- Acts on uterus, breasts

ADRENOCORTICOTROPIC HORMONE (ACTH)

osms.it/adrenocorticotropic-hormone

- Hormone secreted by anterior pituitary corticotropic cells
- Main action of ACTH involves stimulating adrenocortical cells of zona fasciculata of the adrenal cortex to secrete glucocorticoids (primarily cortisol)
  - Anti-inflammatory effects
  - Increases blood glucose levels
  - Increases fat and protein breakdown

SYNTHESIS

- Pre-pro-opiomelanocortin (pre-POMC) → proopiomelanocortin (POMC) → ACTH, gamma lipotropin, beta endorphin, melanocyte-stimulating hormone

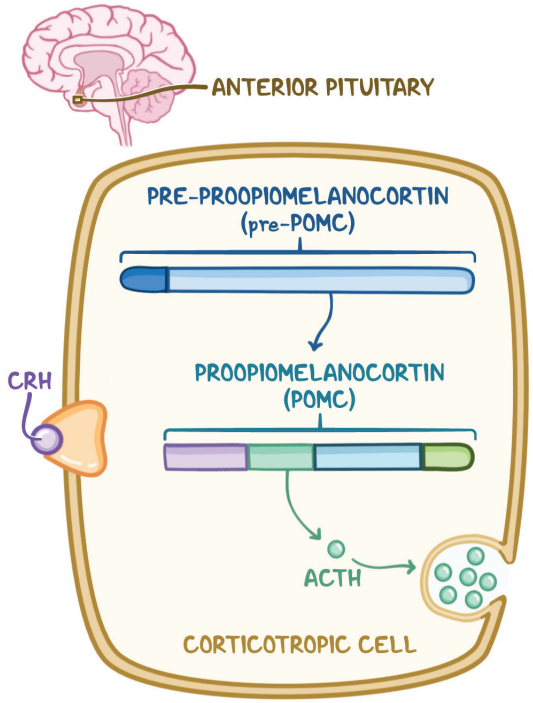

Figure 32.1 Synthesis of ACTH in the anterior pituitary. Corticotropin releasing hormone (CRH) stimulates the cell to release ACTH.

STIMULATION OF ACTH RELEASE

- Corticotropin releasing hormone (CRH) secreted by hypothalamus
  - Stress, low blood glucose, low glucocorticoid levels, increased sympathetic activity, normal diurnal rhythm
  - Release of ACTH demonstrates circadian rhythm affected by suprachiasmatic nucleus → low evening concentrations, high in morning

ACTH RELEASE REGULATION

- ACTH release is regulated by hypothalamic-pituitary-adrenal axis negative feedback
  - Hypothalamus releases CRH → CRH stimulates pituitary to release ACTH → ACTH stimulates adrenal cortex to secrete cortisol → ↑ cortisol inhibits hypothalamic release of CRH → ↓CRH decreases ACTH secretion → closed loop

ACTH SIGNALING PATHWAY

- ACTH binds to ACTH receptor on adrenal cortex adrenocorticotropic cells, primarily zona fasciculata; also expressed in skin, both white, brown adipocytes
- ACTH receptor is a seven-membrane-spanning G-coupled receptor
- ACTH binds to receptor → activates G_s protein → α subunit released → activates adenylate cyclase → ↑ cAMP → activates protein kinase A → phosphorylation cascade → transcription factor activation → effects

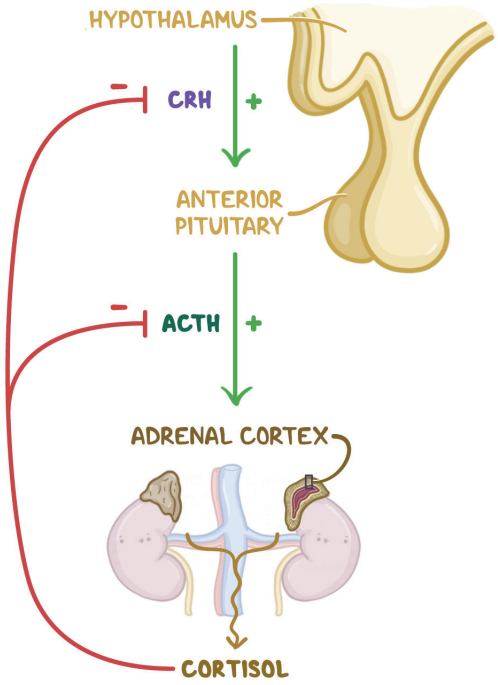

Figure 32.2 The negative feedback loop which regulates ACTH release.

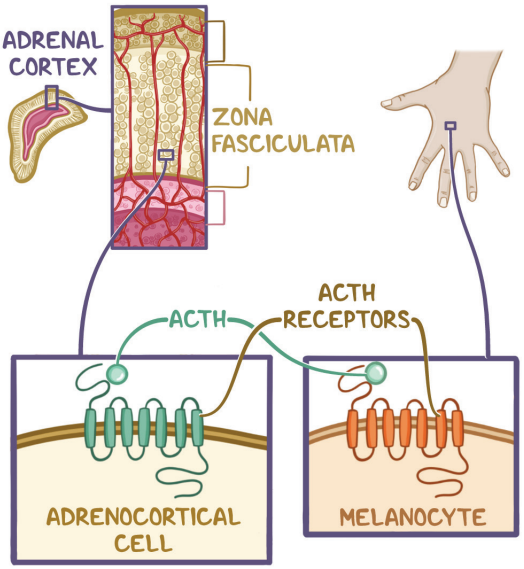

Figure 32.3 ACTH receptors are found on adrenocortical cells in the zona fasciculata of the adrenal cortex, as well as on melanocytes in the skin.

GROWTH HORMONE (GH)

osms.it/growth-hormone

- AKA somatotropin
- Peptide hormone secreted by somatotropic cells of anterior pituitary
  - Regulates tissue growth
- Released in pulsatile manner every two hours; peaks one hour after falling asleep

REGULATION OF SECRETION

Induction of GH release

- Hypoglycemia, ↑ estrogen, testosterone (puberty), stress (e.g. trauma, fever), exercise, sleep stages III, IV

Three negative feedback loops

- ↓ GH stimulates hypothalamus to release GHRH → ↑ GHRH stimulates pituitary to release GH → ↑ GH inhibits release of GHRH → absence of GHRH inhibits GH release → closed loop
- ↑ GH stimulates somatomedins production in the liver, bones, muscles → somatomedins inhibit GH release
- ↑ GH and somatomedins stimulate somatostatin production in hypothalamus → somatostatin inhibits GH release

GH SIGNALING PATHWAY

- Growth hormone receptor (GHR) belongs to cytokine receptor family
- To activate intracellular signaling, GH must bind to two GH receptors → dimerization of GHR
- GH binds to receptor → conformational change → key tyrosine residue phosphorylation → activation of tyrosine kinase JAK2 → STAT5, Src family kinases, insulin receptor substrate (IRSs) signalling molecule activation → gene transcription, effects

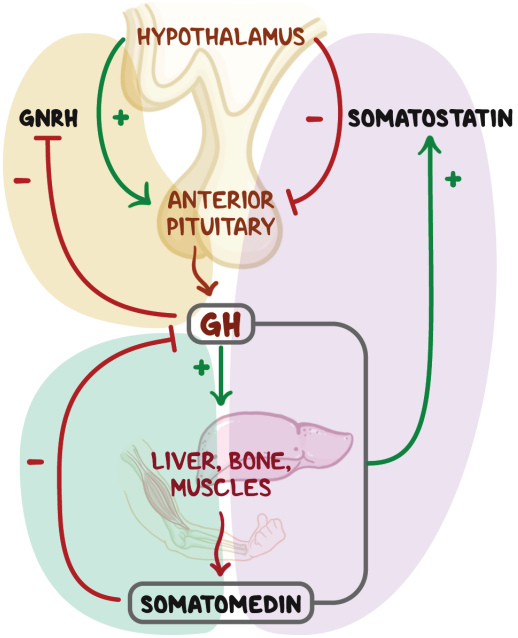

Figure 32.4 The three negative feedback loops that regulate GH secretion, each highlighted in a different colour. GH and somatomedin together stimulate somatostatin production in the hypothalamus, which inhibits GH release.

EFFECTS OF GH

- Primary effect of GH is cell metabolism stimulation, growth, division

Direct effects

- Anti-insulin-like effects
- *Carbohydrates:* ↑ blood glucose levels
  - Stimulates gluconeogenesis, glycogenolysis in liver
  - Increases tissue insulin resistance
- *Fats:* ↑ fatty acids in blood
  - Stimulates adipose tissue lipolysis

Indirect effect

- Insulin-like effects through insulin-like growth factors (e.g. somatomedins like *IGF-1*)
- Stimulates cell growth, division, and differentiation; reduces apoptosis

- *Proteins:* anabolic effect
  - Stimulates amino acid, protein uptake
  - Stimulates protein synthesis
  - Decreases protein breakdown
- Epiphyseal plates, cartilage
  - Stimulates bone osteoblast activity, cartilage chondrocyte activity → increased linear growth

THYROID-STIMULATING HORMONE (TSH)

osms.it/thyroid-hormone

- AKA thyrotropin
- Glycoprotein hormone secreted by pituitary gland
- Main action of TSH involves stimulating thyroid gland growth, thyroid hormone synthesis, release

STIMULATION OF TSH RELEASE

- Thyrotropin-releasing hormone (TRH) secreted by hypothalamus
  - Low T_3, T_4 blood levels
  - Decreased metabolism
  - Cold stress
  - Conditions that increase ATP demand

REGULATION OF SECRETION

- TRH secreted by hypothalamus, stimulates pituitary thyrotropic cells to release TSH
- Thyroid hormones, specifically T_3, down-regulate TRH receptors on thyrotropic cells, inhibiting TSH secretion
- TSH release, thyroid hormone is regulated by negative feedback loop
  - Hypothalamus releases TRH → TRH stimulates pituitary to release TSH → TSH travels to thyroid follicle → stimulates thyroid hormones synthesis, secretion → thyroid hormones inhibit both TRH, TSH release → absence of TRH, TSH inhibits further thyroid hormone secretion → closed loop

TSH SIGNALING PATHWAY

- TSH binds TSH receptor primarily found on thyroid gland follicular cells
  - Also found on adipose tissue, fibroblasts
- TSH receptor is integral membrane receptor coupled with G_s protein
- TSH binds to receptor → activates G_s protein → α subunit released → activates adenylate cyclase → ↑ cAMP → activates protein kinase A → phosphorylation cascade → transcription factor activation → effects

EFFECTS OF TSH

- TSH has two effects on the thyroid gland
  - Stimulates all the steps in thyroid hormone synthesis, secretion
  - *Trophic effect:* increases growth of thyroid gland

THYROID HORMONE

osms.it/thyroid-hormone

- Glycoprotein hormones T_3 (triiodothyronine), T_4 (tetraiodothyronine) secreted by thyroid follicular epithelial cells
- Less active form thyroid hormone (T_4) is secreted, converted in target tissue into more active form (T_3)

SYNTHESIS OF THYROID HORMONES

Six steps

- Thyroglobulin (TG) synthesized in follicular cell rough endoplasmic reticulum (RER), secreted into lumen (colloid)
- Iodine from blood enters follicular cells on basolateral side via Na^+/I^- symport
- Iodine exits cell on apical side via transporter pendrin
- Inside follicle lumen at apical side, iodine oxidized by enzyme thyroid peroxidase ($I^- \rightarrow I_2$)
- I_2 iodinates TG tyrosyl residues (organification of I_2), catalyzed by thyroid peroxidase, forms monoiodotyrosine (MIT), diiodotyrosine (DIT)
- On TG, two DIT molecules coupled to form T_4 (faster reaction); MIT coupled with DIT to form T_3 → TG now contains T_3, T_4, MIT, DIT residues

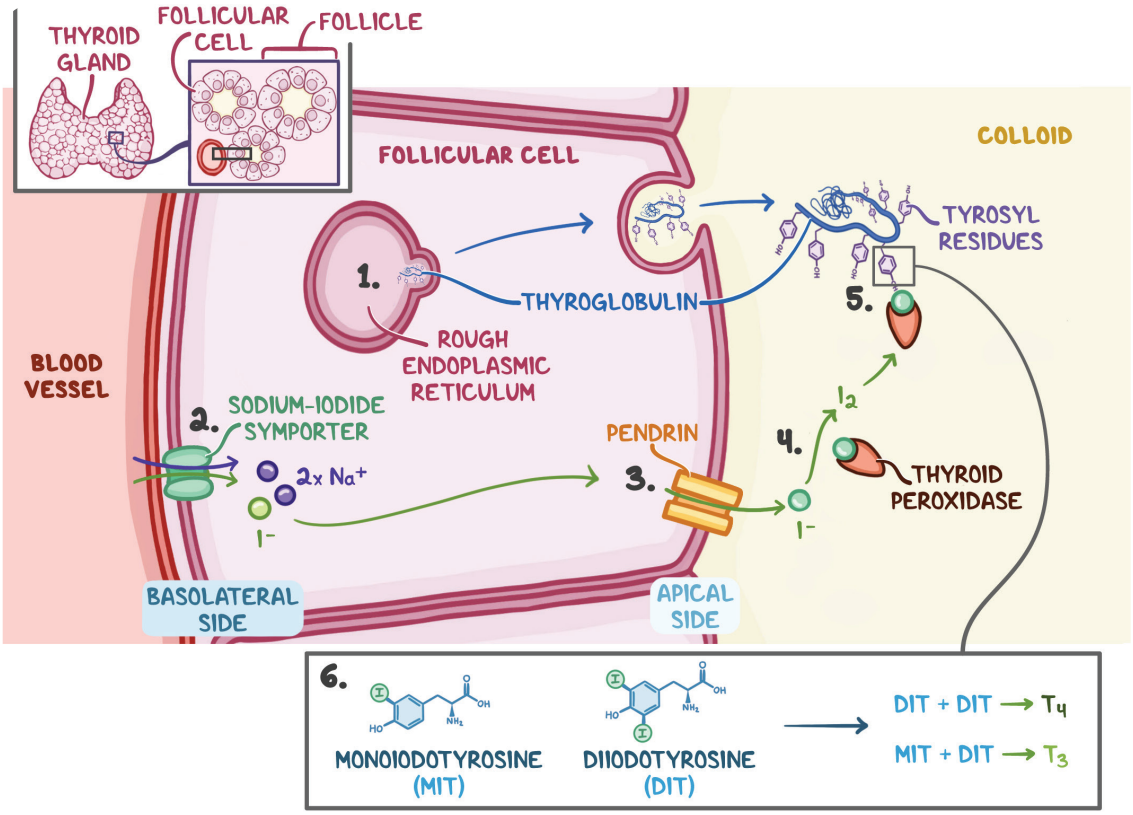

Figure 32.5 Thyroid hormone synthesis overview. **1.** Thyroglobulin (TG) is synthesized in rough endoplasmic reticulum, secreted into colloid. **2.** Iodine enters cell from blood via Na^+/I^- symporter. **3.** Iodine exits cell into colloid via pendrin. **4.** Iodine is oxidized by thyroid peroxidase, become I_2 **5.** I_2 iodinates tyrosyl residues on TG, forming monoiodotyrosine (MIT), diiodotyrosine (DIT). **6.** Two DITs combine to form T_4; MIT combines with DIT to form T_3.

THYROID HORMONE SECRETION AND TRANSPORT

Thyroid hormone secretion

- Thyroid hormones stored in colloid until stimulated for secretion
  - TSH stimulation → endocytosis of iodinated TG by follicular epithelial cells → TG transportation to basal membrane → TG fuses with lysosome → TG hydrolysis, T_3, T_4, MIT, DIT residue release → T_3 (10%), T_4 (90%) secreted into circulation
  - Iodide from MIT, DIT residues recycled for next synthesis

Transport of thyroid hormones

- Once in circulation, most thyroid hormones travel bound to thyroxine-binding protein (TBP)
  - Some bound to prealbumin, albumin
- Small fraction travels unbound → physiologically active forms

Activation of T4

- 90% of secreted thyroid hormone is in less active T4 form
- T_4 activated in target tissue by 5'-deiodinase → removes one atom of I_2 → T_4 gets converted to T_3
- Starvation inhibits 5'-deiodinase in target tissue, except in brain → lowers O_2 consumption, basal metabolic rate (BMR)

REGULATION OF SECRETION

Negative feedback loop

- Regulated by negative feedback loop in hypothalamic-pituitary-thyroid axis
  - Thyrotropin-releasing hormone (TRH) secreted by hypothalamus, stimulates thyrotropic cells of pituitary to release thyroid-stimulating hormone (TSH)

Effects of TSH on thyroid gland

- Two effects
  - Stimulates all steps in thyroid gland synthesis, secretion
  - *Trophic effect:* increases thyroid gland growth

Other regulatory factors

- Iodine deficiency
- Excessive iodine intake (Wolff–Chaikoff effect)
  - Inhibits iodine organification
- 5'-deiodinase deficiency (e.g. starvation)
- ↓ TBP synthesis (e.g. liver failure)
  - Increases unbound (active) thyroid hormones fraction

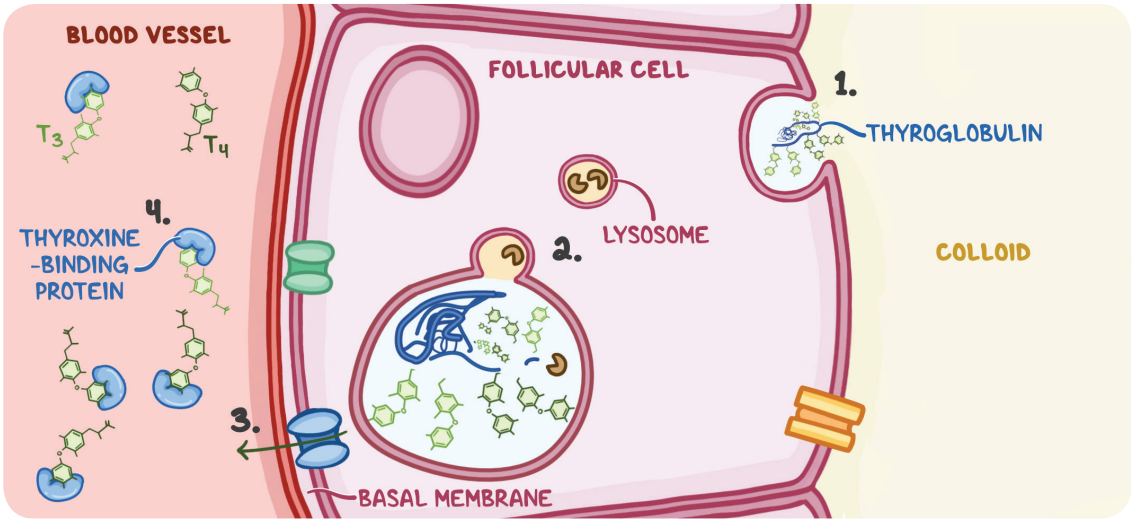

Figure 32.6 Thyroid hormone secretion overview. **1.** TG in colloid is endocytosed into follicular cell. **2.** Lysosome fuses with vesicle; thyroid hormones are cleaved from TG. **3.** Hormones are released into blood. **4.** In blood, most thyroid hormones travel bound to a protein, thyroxine-binding protein being most common.

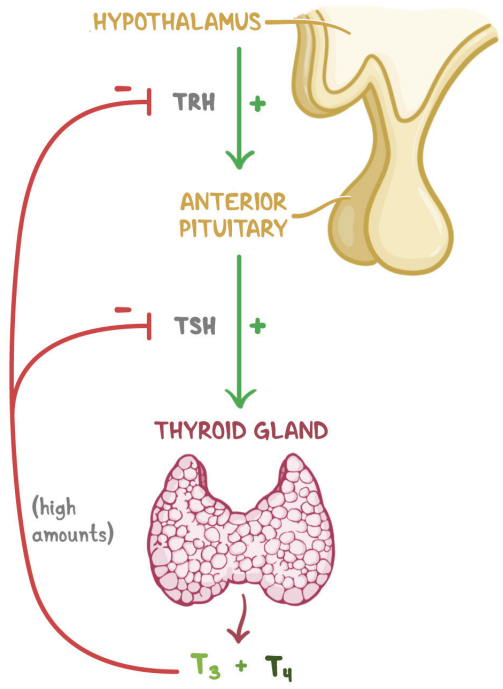

Figure 32.7 The negative feedback loop which regulates thyroid hormone secretion.

SIGNALING PATHWAY

- Thyroid hormones act on all organ systems
- Inside target cells, T_4 converts to T_3 → T_3 enters nucleus, binds nuclear receptor → T_3 receptor complex binds DNA, stimulates transcription → translation → protein synthesis
- T_3 stimulates synthesis of Na^+-K^+ ATPase, Ca^{2+} ATPase, transport proteins, proteolytic, lysosomal enzymes, β1 adrenergic receptors, structural proteins

EFFECTS OF THYROID HORMONE

- Key hormone in regulating body metabolism; also important for embryological growth
- *General effect:* all tissues except brain, spleen and gonads
  - ↑ Na^+-K^+ ATPase → ↑ oxygen consumption → ↑ basal metabolic rate (BMR), body temperature
- *Catabolic effect:* metabolism of macromolecules
  - ↑ transport proteins → ↑ glucose absorption from GI tract
  - ↑ catecholamine, glucagon, growth hormone activity → ↑ proteolysis, lipolysis, gluconeogenesis
- Cardiovascular system
  - ↑ β1 adrenergic receptors, Ca^{2+} ATPase → ↑ inotropic (contractility), chronotropic (heart rate) effect → ↑ cardiac output
- Central nervous system (CNS)
  - Gestational period → CNS development
  - Adult period → ↑ brain activity, attention span, memory
- Growth
  - ↑ osteoblast, osteoclast activity → ↑ bone formation, maturation

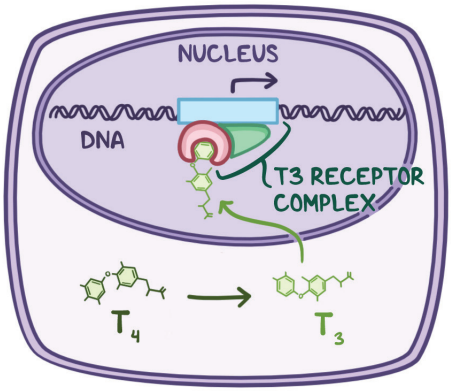

Figure 32.8 In the target cell, T_4 is converted to T_3, which enters the nucleus and binds to a receptor. The receptor complex binds to DNA to stimulate transcription.