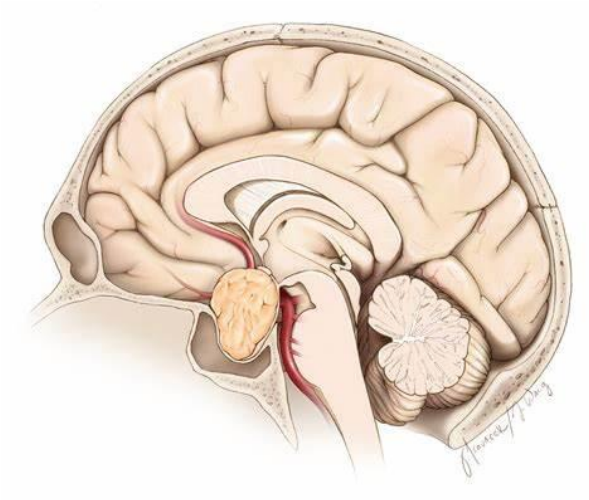
Pituitary and Thyroid



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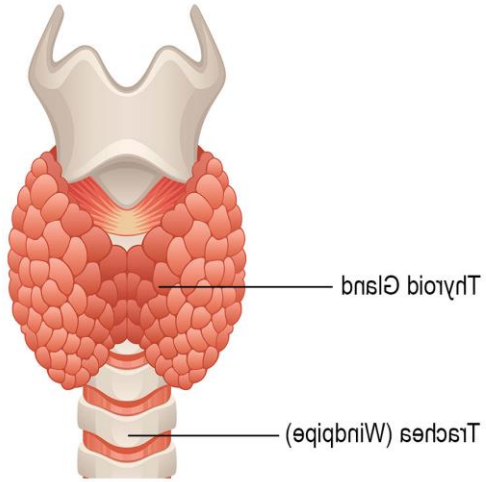
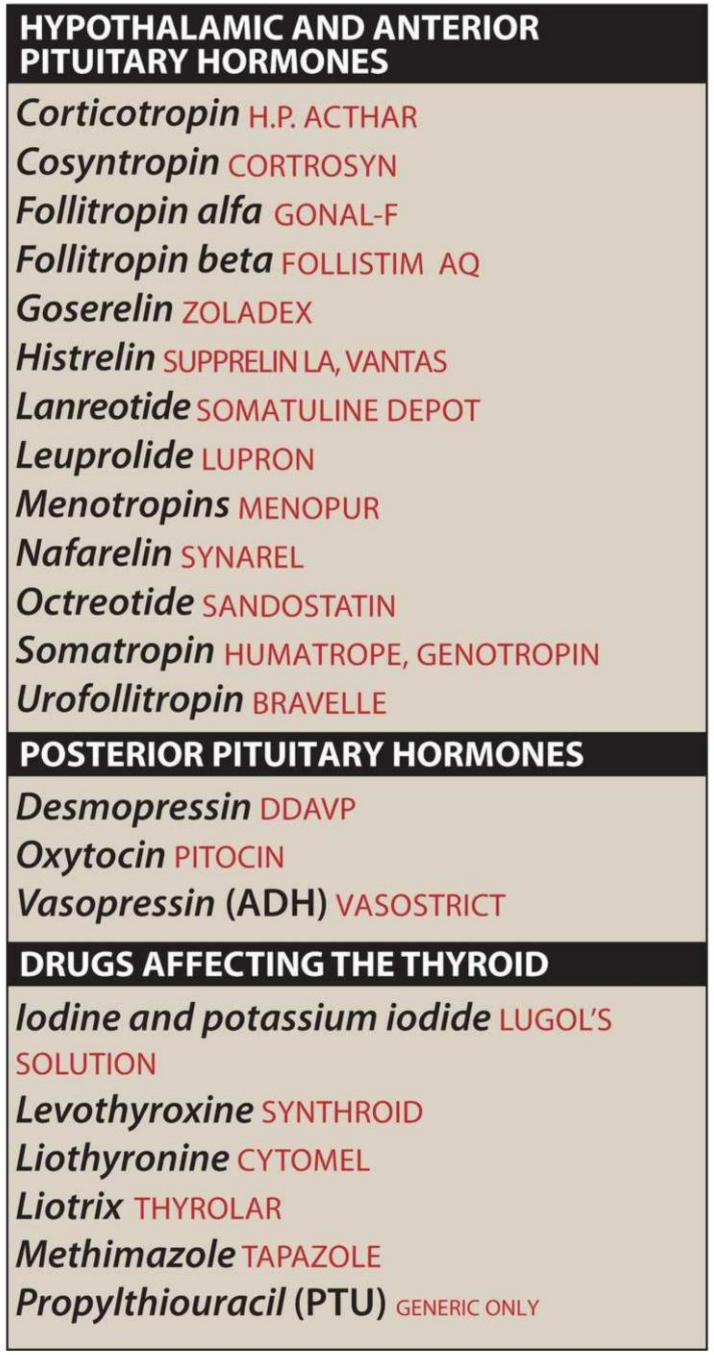


2023 -2024

- The endocrine system releases hormones into the bloodstream, which carries chemical messengers to target cells throughout the body.
- Hormones have a much broader range of response time than do nerve impulses, requiring from **seconds to days, or longer**, to cause a response that may last for **weeks or months**.
- [Note: Nerve impulses generally act within milliseconds.] An important function of the hypothalamus is to connect the nervous system with the endocrine system via the pituitary gland. 23.1).



II. Hypothalamic and Anterior Pituitary Hormones

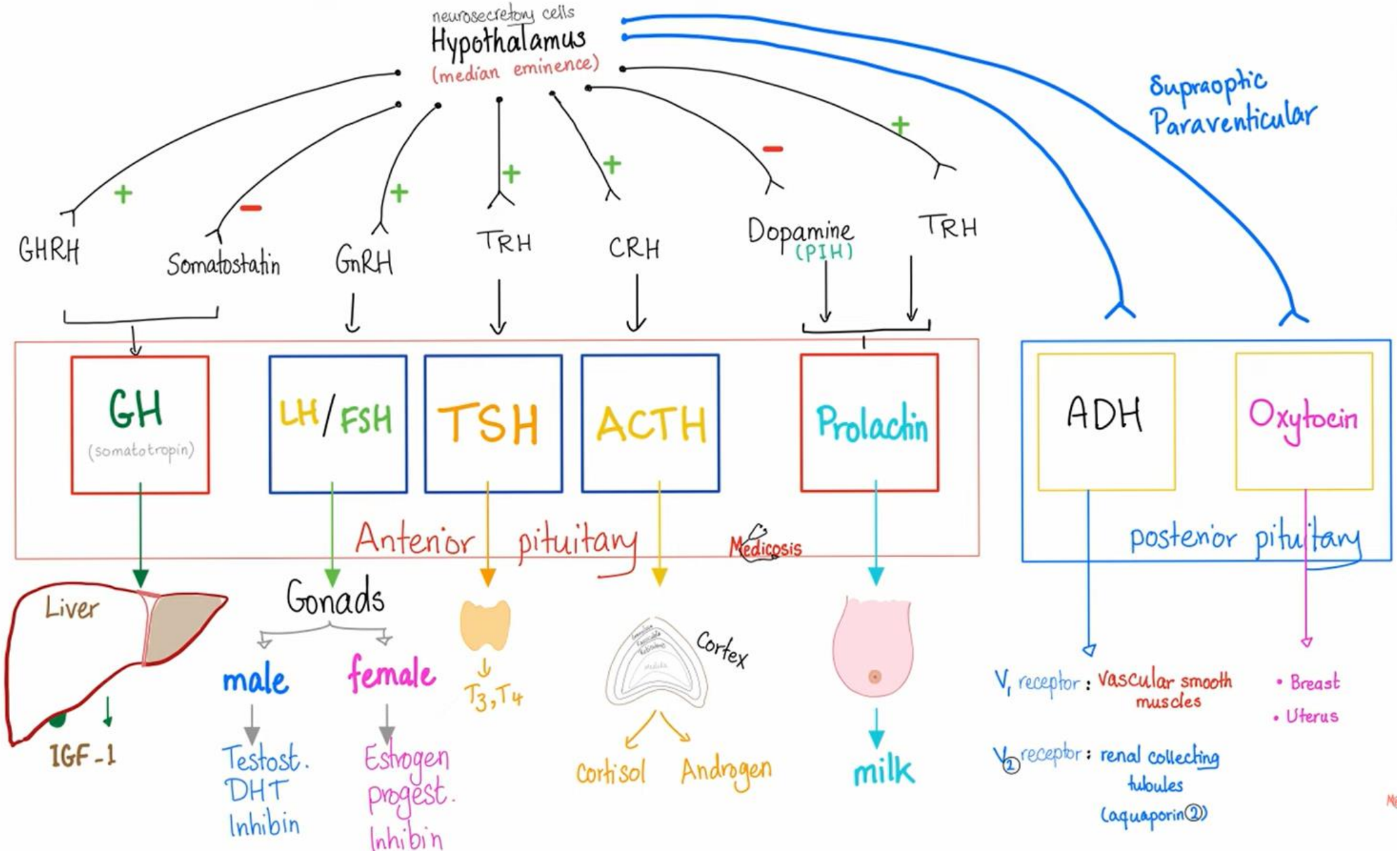
The hormones secreted by the hypothalamus and the pituitary are **peptides or glycoproteins** that act by binding to specific receptor sites on target tissues.

The hormones of the anterior pituitary are regulated by neuropeptides that are called either **“releasing” or “inhibiting” factors or hormones.** These are produced in the hypothalamus, and they reach the pituitary by the **hypophyseal portal system.**

- The interaction of the releasing hormones with receptors results in the activation of genes that promote the synthesis of protein precursors. The protein precursors then undergo posttranslational modification to produce hormones, which are released into the circulation.

  Each hypothalamic regulatory hormone controls the release of a specific hormone from the anterior pituitary.

  Pituitary hormone preparations are currently used for specific hormonal deficiencies, although most of the agents have limited therapeutic applications. Hormones of the anterior pituitary are administered **intramuscularly (IM), subcutaneously, or intranasally** because their peptidyl nature makes them susceptible to destruction by proteolytic enzymes of the digestive tract.


neurosecretory cells
Hypothalamus
(median eminence)
Supraoptic
Paraventricular
GHRH
Somatostatin
GnRH
TRH
CRH
Dopamine
(PIH)
TRH
+
−
+
+
+
−
+
GH
(somatotropin)
LH/FSH
TSH
ACTH
Prolactin
ADH
Oxytocin
Anterior pituitary
Medicosis
posterior pituitary
Liver
IGF-1
Gonads
male
female
Testost.
DHT
Inhibin
Estrogen
progest.
Inhibin
T3, T4
Cortex
Cortisol
Androgen
milk
V1 receptor : vascular smooth muscles
V2 receptor : renal collecting tubules (aquaporin②)
• Breast
• Uterus

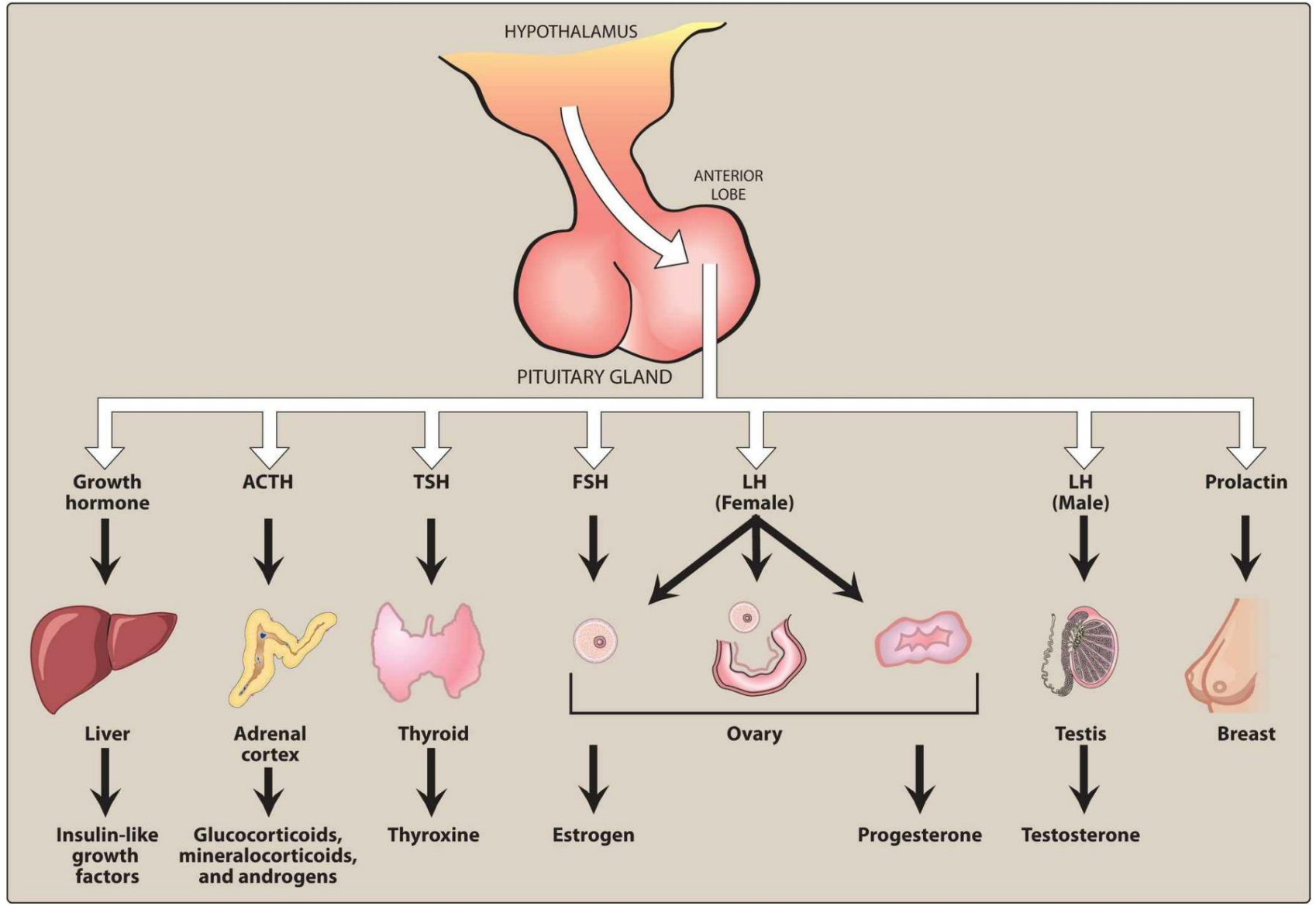
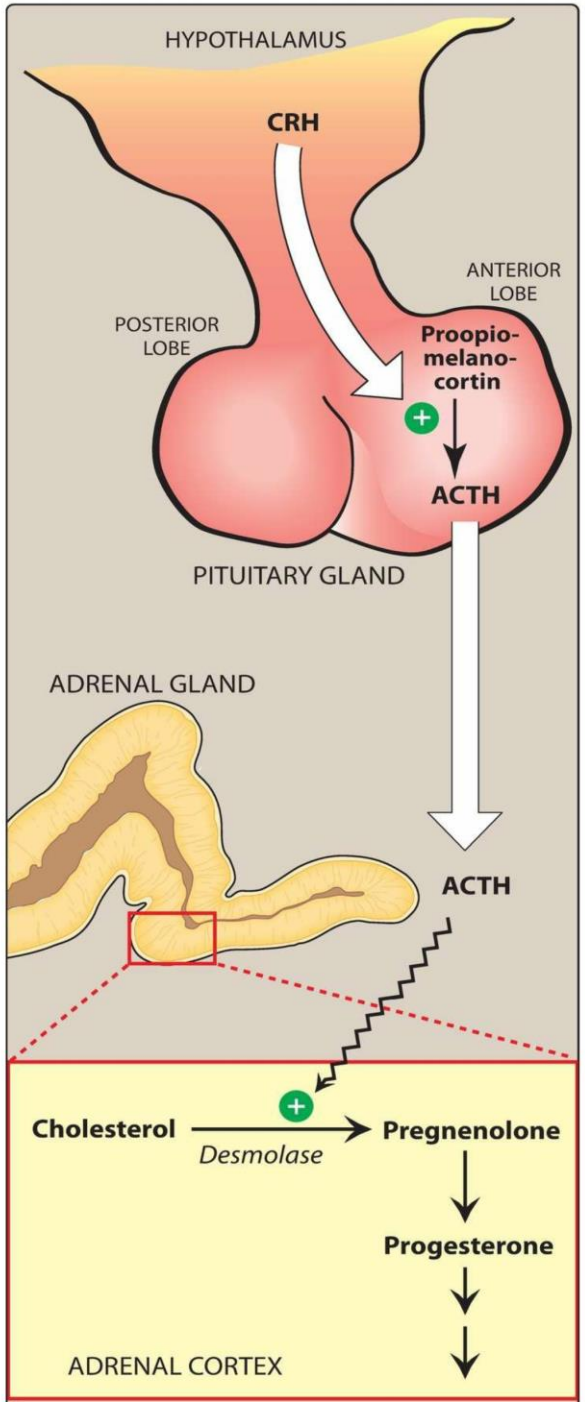
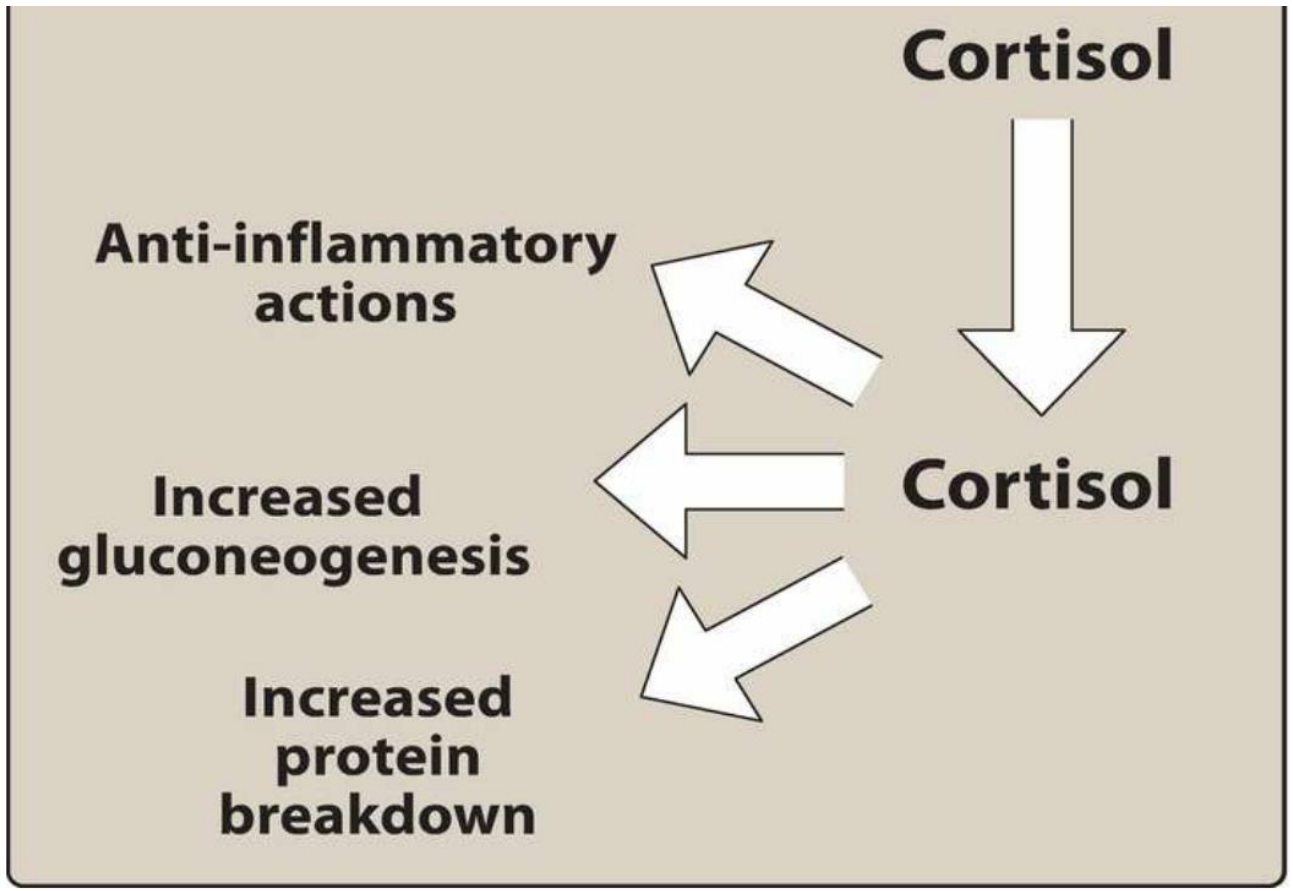


Figure 23.2 Anterior pituitary hormones. ACTH = adrenocorticotropic hormone; TSH = thyroid-stimulating hormone; FSH = follicle-stimulating hormone; LH = luteinizing hormone.

- **A. Adrenocorticotropic hormone (corticotropin)**
  Corticotropin-releasing hormone (CRH) is responsible for the synthesis and release of the peptide **proopiomelanocortin** by the pituitary (Figure 23.3). *Adrenocorticotropic hormone* (ACTH) or *corticotropin* [kor-tikoe-TROE-pin] is a product of the posttranslational processing of this precursor polypeptide. ***[Note: CRH is used diagnostically to differentiate between Cushing syndrome and ectopic ACTH-producing cells.]***
- Normally, ACTH is released from the pituitary in pulses with an overriding diurnal rhythm, with the ***highest concentration occurring in early morning and the lowest in late evening.*** Stress stimulates its secretion, whereas cortisol acting via negative feedback suppresses its release.
  1. Mechanism of action
  ACTH binds to receptors on the surface of the adrenal cortex, thereby activating G protein–coupled processes that ultimately stimulate the rate-limiting step in the adrenocorticosteroid synthetic pathway (cholesterol to pregnenolone; Figure 23.3). This pathway ends with the synthesis and release of adrenocorticosteroids and the adrenal androgens.

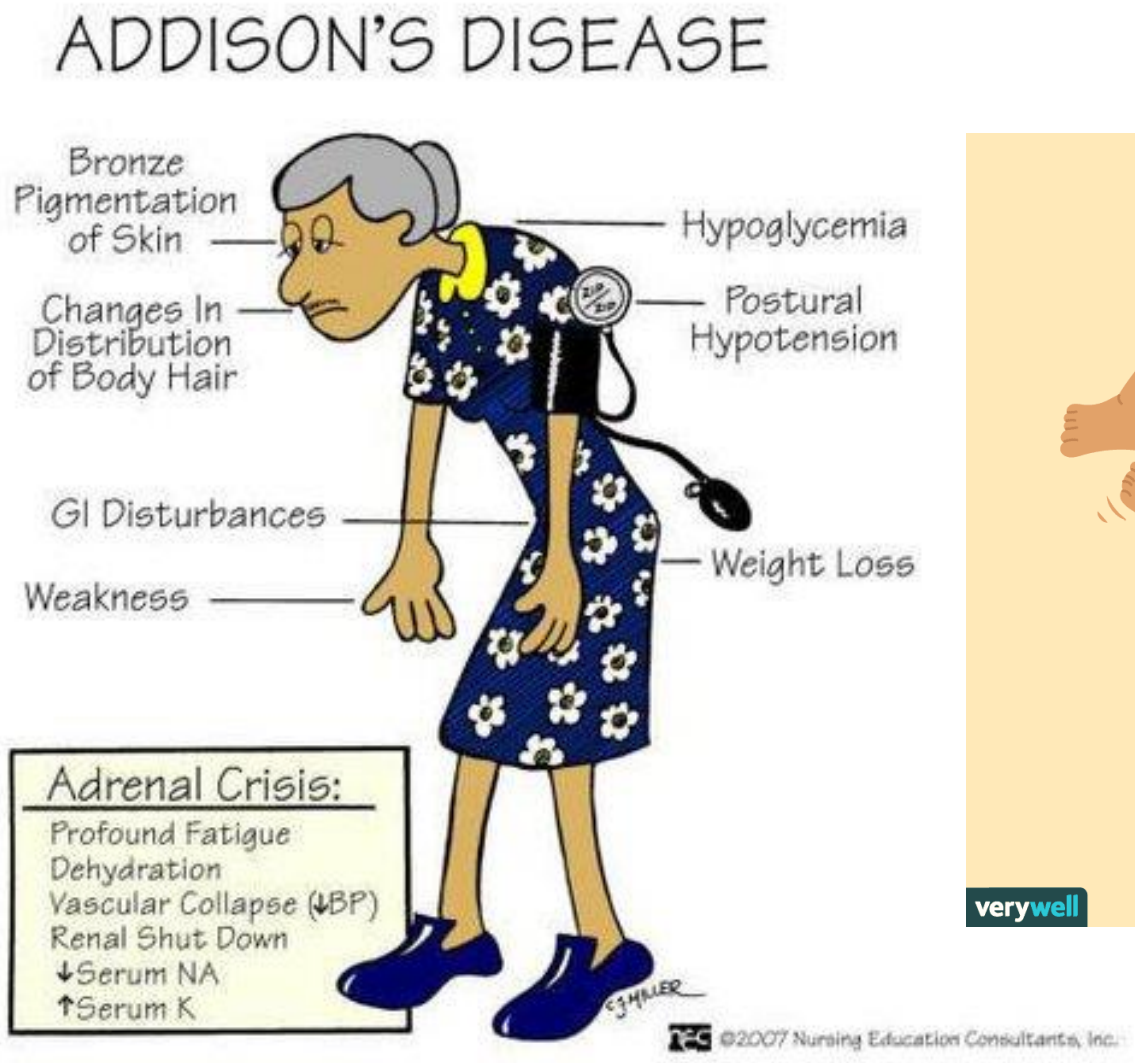

HYPOTHALAMUS
CRH
ANTERIOR LOBE
POSTERIOR LOBE
Proopio-melano-cortin
ACTH
PITUITARY GLAND
ADRENAL GLAND
ACTH
Cholesterol
Desmolase
Pregnenolone
Progesterone
ADRENAL CORTEX


Cortisol
Anti-inflammatory actions
Increased gluconeogenesis
Increased protein breakdown
Cortisol

- **2. Therapeutic uses**
  The availability of synthetic adrenocorticosteroids with specific properties has limited the use of *corticotropin* mainly to serving as a diagnostic tool for differentiating between primary adrenal insufficiency (***Addison disease, associated with adrenal atrophy) and secondary adrenal insufficiency (caused by inadequate secretion of ACTH by the pituitary).***
- Therapeutic *corticotropin* preparations are extracts from the anterior pituitaries of domestic animals or synthetic human ACTH.
- The latter, ***cosyntropin*** [ko-sin-TROE-pin], is preferred for the diagnosis of adrenal insufficiency. **ACTH is also used in the treatment of infantile spasms and multiple sclerosis.**

3. Adverse effects

Short-term use of ACTH for diagnostic purposes is usually well tolerated. With longer use, toxicities are similar to glucocorticoids and **include hypertension, peripheral edema, hypokalemia, emotional disturbances, and increased risk of infection.**


ADDISON'S DISEASE
Bronze Pigmentation of Skin
Changes In Distribution of Body Hair
GI Disturbances
Weakness
Hypoglycemia
Postural Hypotension
Weight Loss
Adrenal Crisis:
Profound Fatigue
Dehydration
Vascular Collapse (↓BP)
Renal Shut Down
↓Serum NA
↑Serum K
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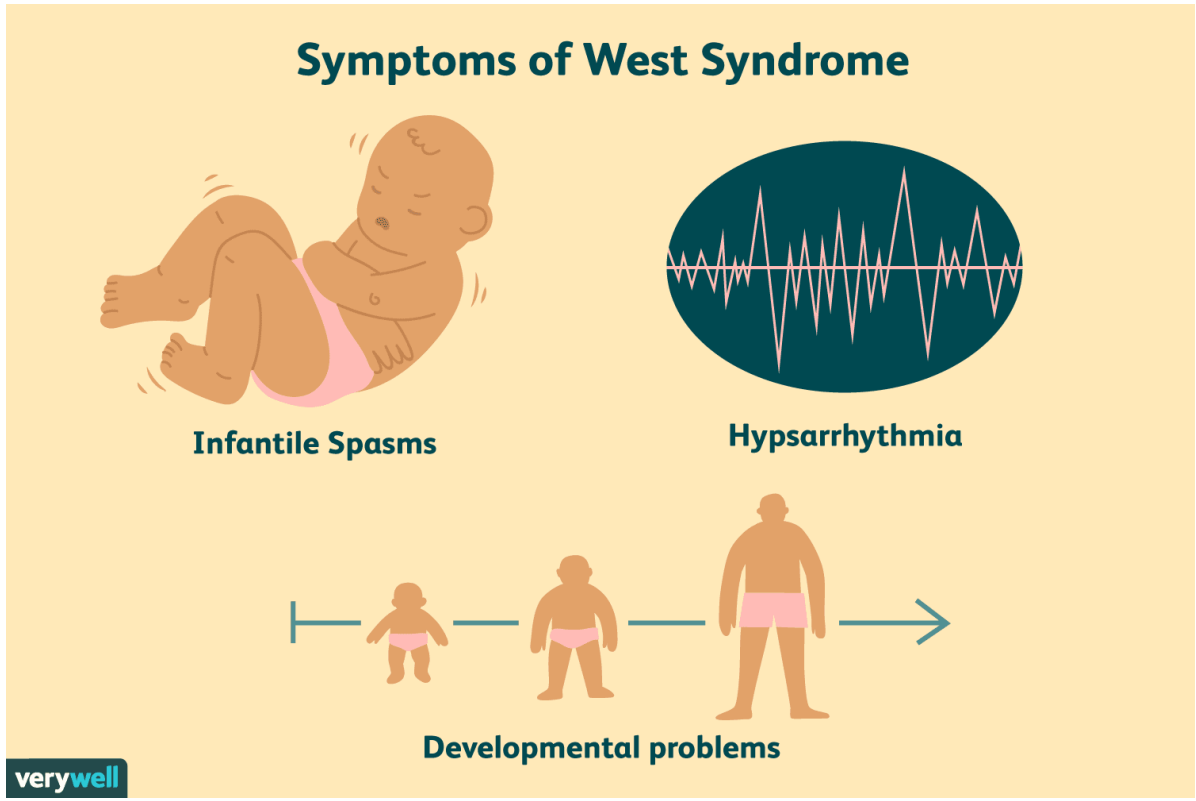

Symptoms of West Syndrome
Infantile Spasms
Hypsarrhythmia
Developmental problems
verywell

- **B. Growth hormone (somatotropin)**
  Somatotropin is released by the anterior pituitary in response to growth hormone (GH)-releasing hormone (Figure 23.4). Conversely, secretion of GH is inhibited by the hormone **somatostatin** (see below). GH is released in a pulsatile manner, with the ***highest levels occurring during sleep.***
- With increasing age, GH secretion decreases, accompanied by a decrease in lean muscle mass. Somatotropin influences a wide variety of biochemical processes (for example, cell proliferation and bone growth). Synthetic human GH (***somatropin*** [soe-mah-TROE-pin]) is produced using recombinant DNA technology.

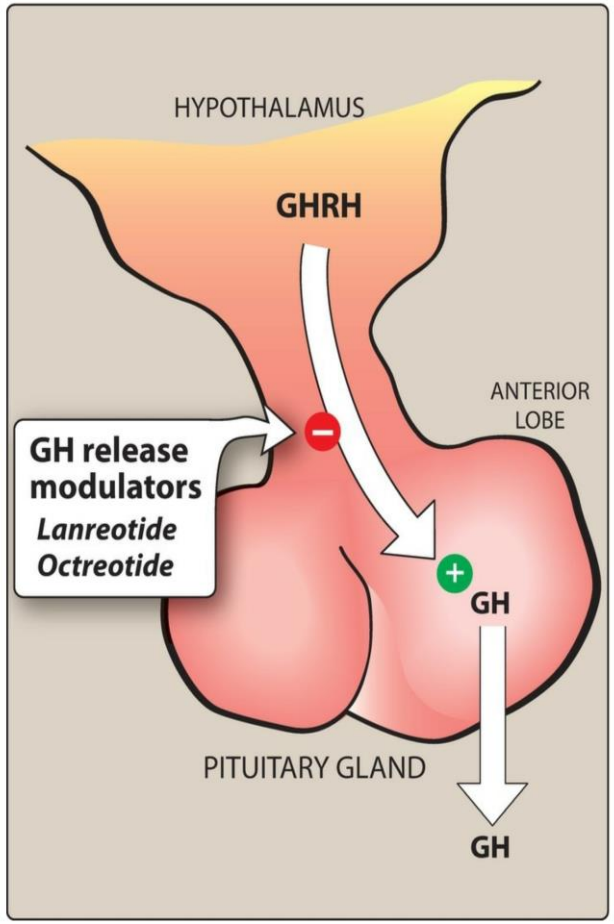


Figure 23.4 Secretion of growth hormone (GH). GHRH = growth hormone–releasing hormone.

- **1. Mechanism of action**
  Although many physiologic effects of GH are exerted directly at its targets, others are mediated through the **somatomedins—insulin-like growth factors 1 and 2 (IGF-1 and IGF-2).**
- [Note: In acromegaly (a syndrome of excess GH due to hormone-secreting tumors), IGF-1 levels are consistently high, reflecting elevated GH.]
- GH **is a large peptide**, the exogenous one, synthesized by gene technology and used as injection; the animal one is **ineffective** for human.
- Over secretion of GH before puberty causes **Gigantism**
- Over secretion of GH after puberty causes **Acromegaly**
- Reduced secretion of GH causes **Dwarfism**.

- **GH has the following functions:**
- 1- Glycogenolysis (catabolism of glycogen)→↑ blood sugar
- 2- Lipolysis (catabolism of lipid)
- 3- protein synthesis
- 4- Increase the no of cells and their density including bone and cartilage.

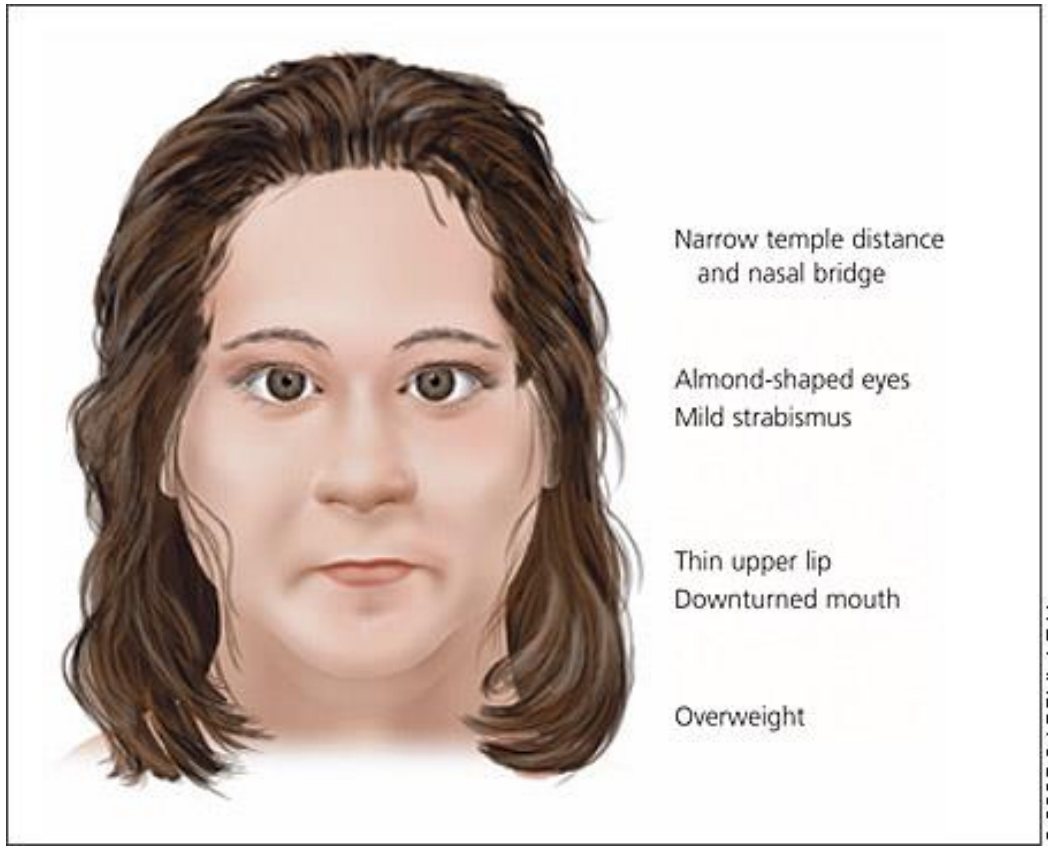
➢**Therapeutic uses:** Somatropin is used in the treatment of:

- **1- GH deficiency,**
- **2- Growth failure in children,**
- **3-treatment of HIV patients with cachexia, and**
- **4-GH replacement in adults with confirmed deficiency.**
- **The synthetic GH** (somatrem has longer t1/2 =25 min than natural GH, this drug is given to dwarf patients **before** puberty because after puberty the closure of long bones epiphysis occur, so administration of GH after puberty causes acromegaly, which characterized by thick skin & bone ,large nose and lower jaw and extremities specially fingers.

- 3. **Adverse effects:** Adverse effects of somatropin include pain at the injection site, edema, arthralgias, myalgias, nausea, and an increased risk of diabetes. Somatropin should not be used in pediatric patients with **closed epiphyses**, patients with **diabetic retinopathy**, or obese patients with **Prader-Willi syndrome**.

What is Prader-Willi Syndrome?

- A spontaneous, congenital, genetic disorder.
- Occurs equally across genders and races.
- Range of estimated prevalence: 1:8,000 to 1:25,000.
- There is no cure.
- Prader-Willi Syndrome Association of USA states most likely prevalence: 1:15,000 (PWSA, 2012).
- One of the ten most common syndromes seen in genetic clinics (Utah Prader-Willi Association, n.d.).



- **C. Somatostatin (growth hormone–inhibiting hormone)**

  In the pituitary, somatostatin binds to receptors that suppress GH and thyroid-stimulating hormone (TSH) release. Originally isolated from the hypothalamus, somatostatin is a small polypeptide found in neurons throughout the body as well as in the intestine, stomach, and pancreas. Somatostatin not only inhibits release of GH but also insulin, glucagon, and gastrin.

- **Octreotide** and **lanreotide** are synthetic analogs of somatostatin with longer halflives. Depot formulations of these agents allow for **administration every 4 weeks**. They have found use **in the treatment of acromegaly and in severe diarrhea/flushing episodes associated with carcinoid tumors**. An intravenous infusion of octreotide is also used for the treatment of **bleeding esophageal varices**.

Adverse effects of octreotide include **bradycardia, diarrhea, abdominal pain, flatulence, nausea, and steatorrhea**. Gallbladder emptying is delayed, and asymptomatic cholesterol gallstones can occur with long-term treatment.

- **D. Gonadotropin-releasing hormone**

  Pulsatile secretion of gonadotropin-releasing hormone (GnRH) from the hypothalamus is essential for release of the gonadotropins follicle-stimulating hormone (FSH) and luteinizing hormone (LH) from the anterior pituitary.

  However, **continuous administration of GnRH inhibits gonadotropin release through down-regulation of GnRH receptors on the pituitary**.

- Continuous administration of synthetic GnRH analogs, such as ***leuprolide*** [loo-PROElide], is effective in suppressing production of FSH and LH (Figure 23.5). Suppression of gonadotropins, in turn, leads to reduced production of gonadal steroid hormones (androgens and estrogens). Thus, these agents are effective

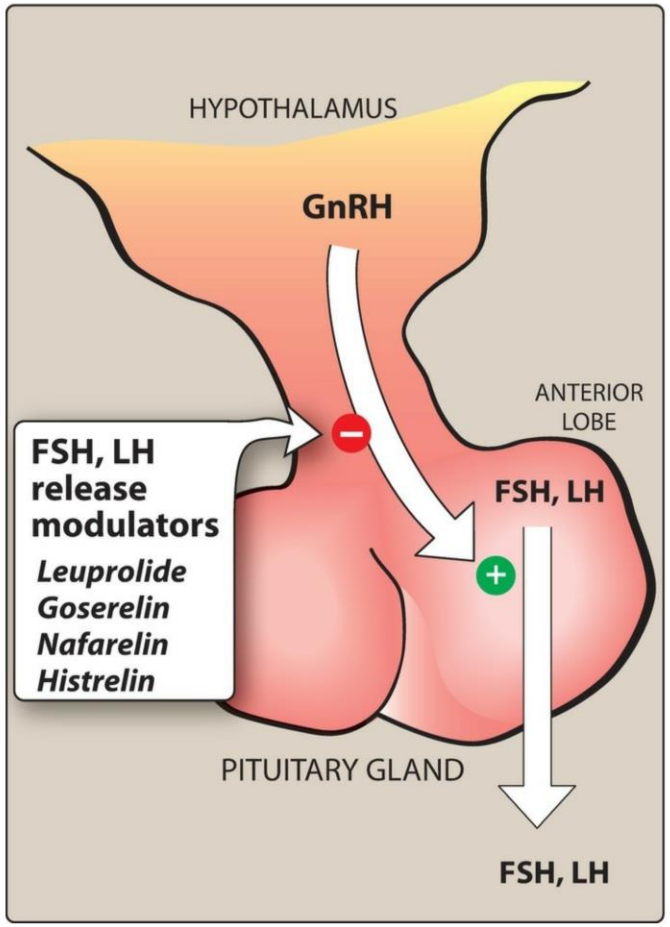


Figure 23.5 Secretion of follicle-stimulating hormone (FSH) and luteinizing hormone (LH). GnRH = gonadotropin-releasing hormone.

- **in the treatment of prostate cancer, endometriosis, and precocious puberty.**

  Leuprolide is also used to suppress the LH surge and prevent premature ovulation in women undergoing controlled ovarian stimulation protocols for the treatment of infertility. [Note: GnRH antagonists such as ***cetrorelix*** (set-roe-REL-iks) and ***ganirelix*** (ga-ni-REL-iks) can also be used to inhibit LH secretion in infertility protocols.]

- In women, the GnRH analogs may cause **hot flushes and sweating**, as well as **diminished libido, depression, and ovarian cysts**.

- They are **contraindicated in pregnancy and breast-feeding**.

- In men, they **initially cause a rise in testosterone that can result in bone pain.**

  Hot flushes, edema, gynecomastia, and diminished libido may also occur.

• E. Gonadotropins

The gonadotropins (FSH and LH) are produced in the anterior pituitary. The regulation of gonadal steroid hormones depends on these agents. They **used in the treatment of infertility**.

- **Menotropins** (also known as human menopausal gonadotropins or **hMG**) are obtained from urine of postmenopausal women and marketed under trade name (**pergonal** R) and contain both **FSH and LH**. **Urofollitropin** is **FSH obtained** from postmenopausal women and is devoid of LH.
- **Follitropin alfa** and **follitropin beta** are human **FSH products** manufactured using recombinant DNA technology.
- **Human chorionic gonadotropin (hCG)** is a placental hormone that is excreted in urine of pregnant women isolated and marketed under trade name R(**pregenyl**).The effects of hCG and **choriogonadotropin** alfa (made using recombinant DNA technology) are essentially identical to those of **LH**.

- Both preparations administered as IM injection as follow:
- **For infertile women:**
- Give menotropin at 5-12 days of menstrual cycle (for growth and maturation of follicals) followed by HCG at day 13-15 from period for ovulation.
- **For infertile men:**
- Give HCG for maturation of external sexual organs followed by menotropin for induction of spermatogenesis.
- Adverse effects include **ovarian enlargement and possible ovarian hyperstimulation syndrome,** which may be life threatening. **Multiple births** can occur.

Prygnyl

Pergonal

- **F. Prolactin**
  Prolactin is a peptide hormone secreted by the anterior pituitary. Its primary function is to stimulate and maintain lactation. In addition, it decreases sexual drive and reproductive function. **Thyrotropin releasing hormone stimulates the release of prolactin**, and secretion is **inhibited by dopamine acting at D2 receptors** (Figure 23.6).
- [Note: Drugs that act as dopamine antagonists (for example, ***metoclopramide*** and some antipsychotics) can **increase the secretion of prolactin**.] Hyperprolactinemia, which is associated with galactorrhea and hypogonadism, is treated **with D2 receptor agonists**, such as ***bromocriptine*** **and** ***cabergoline***.

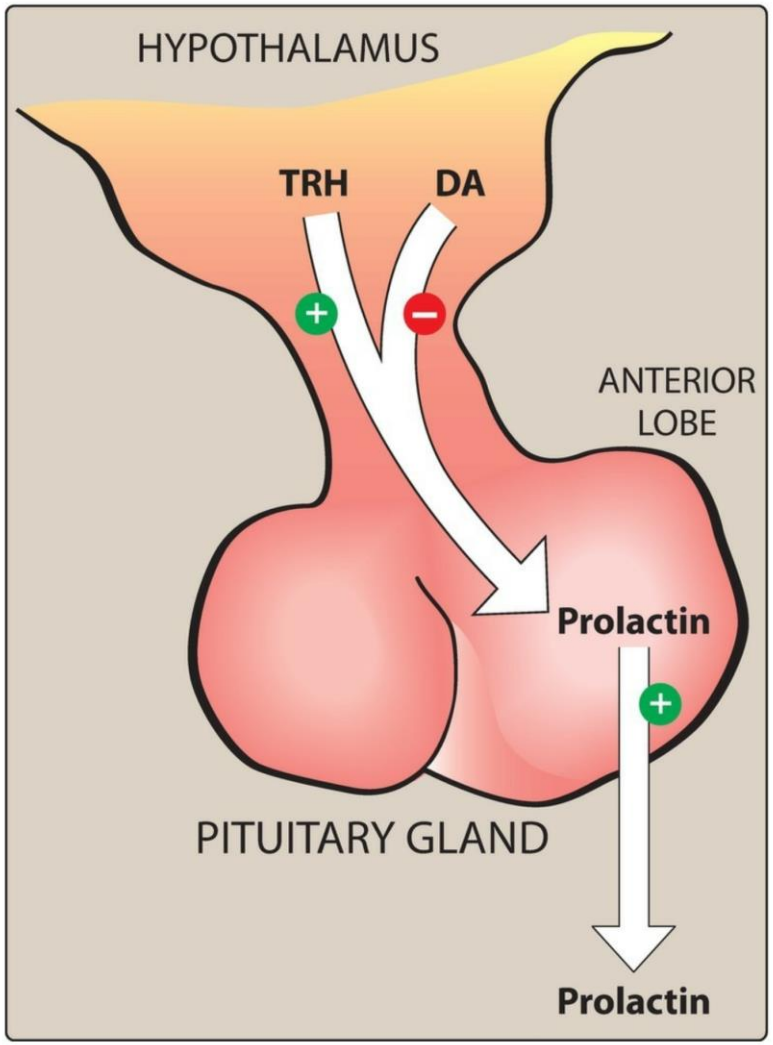
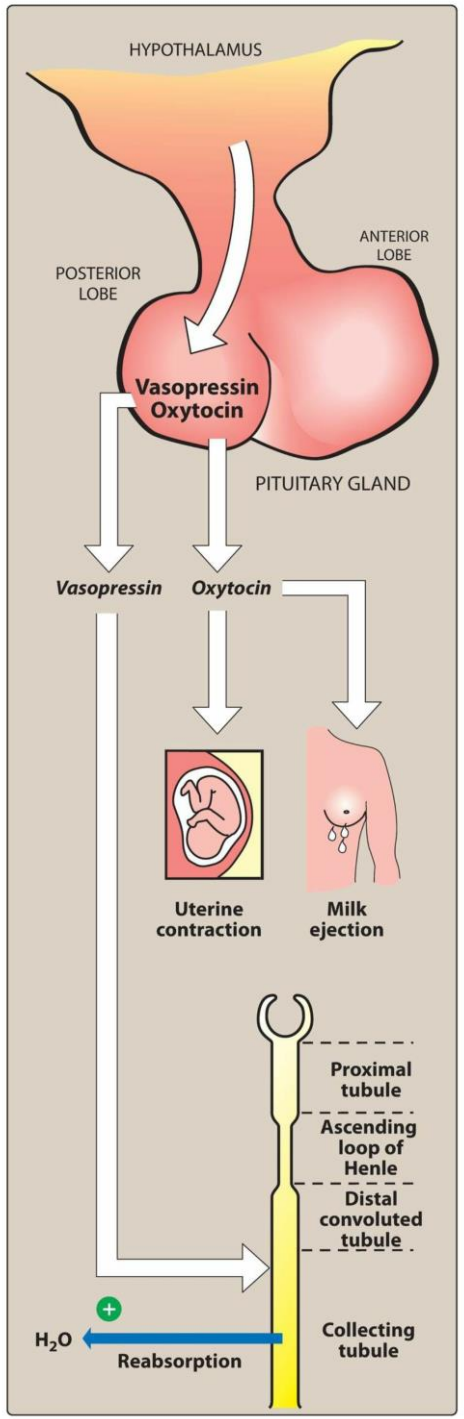


Figure 23.6 Secretion and action of prolactin. DA = dopamine; TRH = thyrotropin-releasing hormone.

- Both of these agents also find ***use in the treatment of pituitary microadenomas.***
- ***Bromocriptine*** is also indicated for treatment of type 2 diabetes. Among their adverse effects are nausea, headache and, less frequently, psychosis.

- **III. Hormones of the Posterior Pituitary**

  In contrast to the hormones of the anterior lobe of the pituitary, those of the posterior lobe, ***vasopressin*** and ***oxytocin***, are not regulated by releasing hormones. Instead, they are synthesized in the hypothalamus, transported to the posterior pituitary, and released in response to specific physiologic signals, such as high plasma osmolarity or parturition. Both hormones are administered **intravenously** and have **very short half-lives**. Their actions are summarized in Figure 23.7.



- **A. Oxytocin**
  Oxytocin [ok-se-TOE-sin] is used in **obstetrics to stimulate uterine contraction and induce labor**. *Oxytocin* also
  causes milk ejection by contracting the myoepithelial cells around the mammary alveoli. Although toxicities are uncommon with proper drug use, hypertension, uterine rupture, water retention, and fetal death may occur. Its antidiuretic and pressor activities are much less than those of *vasopressin*.
- **B. *Vasopressin***
  Vasopressin [vas-oh-PRESS-in] (antidiuretic hormone) is structurally related to *oxytocin*. *Vasopressin* has both **antidiuretic and vasopressor effects** (Figure 23.7). In the **kidney**, it binds to the **V2 receptor** to increase water permeability and reabsorption in the collecting tubules. Thus, the major use of *vasopressin* is to treat diabetes insipidus.

- It also finds use in septic shock and in controlling bleeding due to esophageal varices. Other effects of ***vasopressin*** are mediated by the **V1 receptor**, which is found in the liver, **vascular smooth muscle** (where it causes constriction), and other tissues. The major toxicities of *vasopressin* are water intoxication and hyponatremia. Abdominal pain, tremor, and vertigo can also occur. ***Desmopressin*** [des-moe-PRESS-in], an analog of *vasopressin*, has minimal activity at the V1 receptor, making it largely free of pressor effects.

- This analog is longer acting than *vasopressin* and is preferred for the ***treatment of diabetes insipidus and nocturnal enuresis.*** For these indications, *desmopressin* is administered intranasally or orally. [Note: The nasal spray should not be used for enuresis due to reports of seizures in children using this formulation.] Local irritation may occur with the nasal spray.


FERRING
Minirin MELT 60mcg
Desmopressin Oral Lyophilisate
30


FERRING
PHARMACEUTICALS
Desmopressin
Nasal Spray
Minirin
Nasal spray
0.1mg/ml
1 Vial of 2.5ml


Minirin
मिनिरीन
10 microg/dose
Each ml contains :
Desmopressin Acetate...0.1 mg
(equivalent to
Desmopressin.....89 microg)
Excipients.....q.s.
Purified water..... to 1 ml
Manufactured by :
FERRING GmbH
Wittland 11,
D-24109 Kiel, Germany.
Imported and Marketed by :
FERRING
PHARMACEUTICALS PVT. LTD.
Building No. B4, Gala No. 1 & 2,
City Link Warehousing Complex,
Vadape Village, Bhiwandi,
Thane - 421302, India.
1 Vial of 2.5ml

- **IV. Thyroid Hormones**

- The thyroid gland facilitates normal growth and maturation by maintaining a level of metabolism in the tissues that is optimal for normal function. The two major thyroid hormones are **triiodothyronine** (T3; the most active form) and **thyroxine** (T4).
- • Normal TH concentration called **Euthyroid**
- • High TH concentration called **hyperthyroidism** or **Graves** ' disease or
- **thyrotoxicosis**.
- • Low TH concentration called **cretinism** in children.
- • Low TH concentration called **myxoedema** in adults.
- **NOTE**: Hyper **or** hypothyroidism may **or** not associated with **goiter** formation. **The t1/2 of T3 is 2days, while the:**

- **The t1/2 of T4 in euthroid is 7 days The t1/2 of T4 in hyperthyroidism is 3 days The t1/2 of T4 in hypothyroidism is 14 days**

- **A. Thyroid hormone synthesis and secretion**
- The thyroid gland is made up of multiple follicles that consist of a single layer of epithelial cells surrounding a lumen filled with thyroglobulin (the storage form of thyroid hormone). Thyroid function is controlled by TSH (thyrotropin), which is synthesized by the anterior pituitary.
- [Note: The hypothalamic thyrotropin-releasing hormone (TRH) governs the generation of TSH.] TSH action is mediated by cAMP and leads to stimulation of iodide

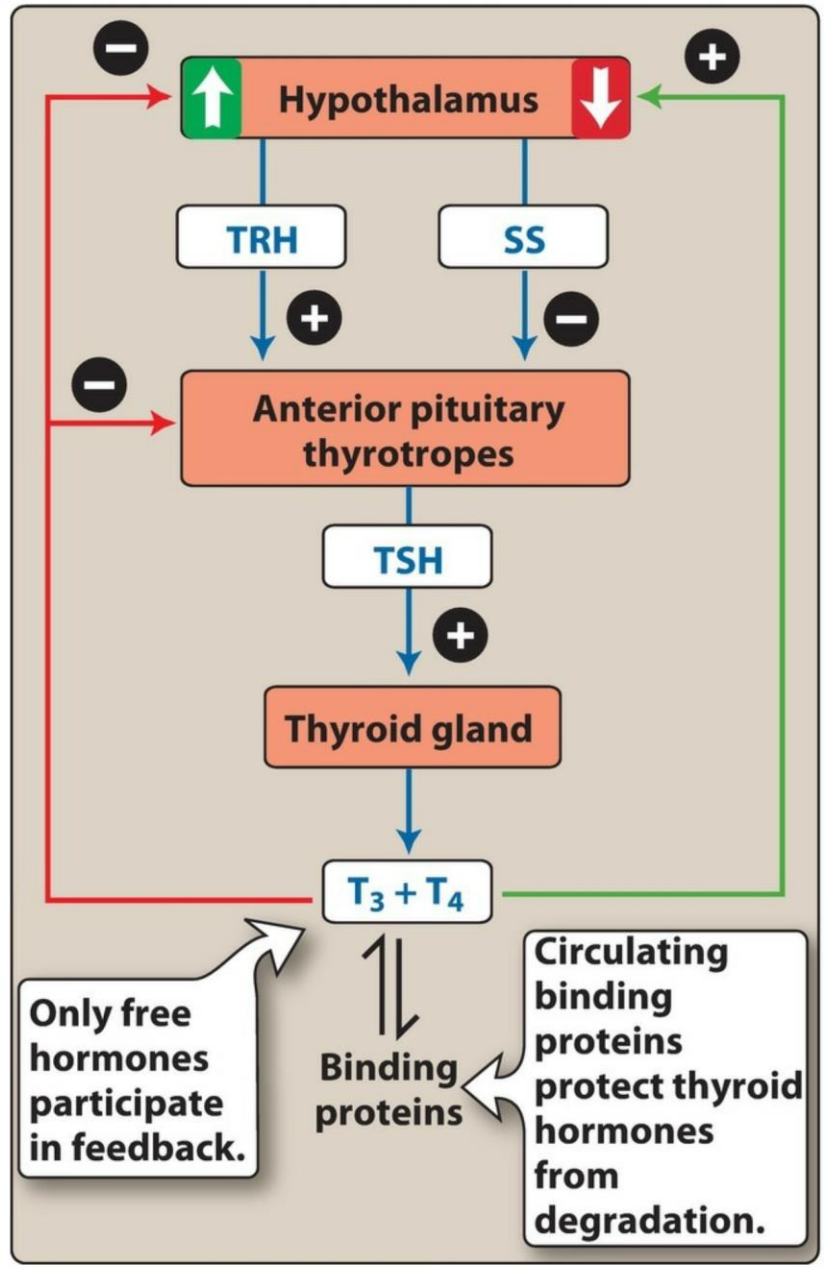


Figure 23.8 Feedback regulation of thyroid hormone release. SS = somatostatin; T_3 = triiodothyronine; T_4 = thyroxine; TRH = thyrotropin-releasing hormone; TSH = thyroid-stimulating hormone.

- **Steps of TH synthesis**:
- **1-**iodide trapping: active uptake of iodide from circulation into thyroid cells. The concentration of iodide in the thyroid gland is 25 times more than concentration in the blood.
- **2-** Oxidation of iodide to iodine……. **2 I- = I2**
- **3-** Coupling of iodide with tyrosine (a.a) forming mono iodic tyrosine in the presence of peroxidase enzyme.
- **4-** Condensation of 2 molecules of mono iodic tyrosine forming di-iodic tyrosine and then **tri iodic tyrosine** and **tetra-iodic tyrosine** in the presence of peroxidase enzyme.
- • About 80% 0f T4 converted to T3 which is biologically 5 times more active than T4
- • Both T3 and T4 are highly protein binding forming thyroglobulin (TG), especially
- T4.
- • Both are metabolized by cytochrome p-450 in the liver so they affected by enzyme
- inducers and inhibitors……

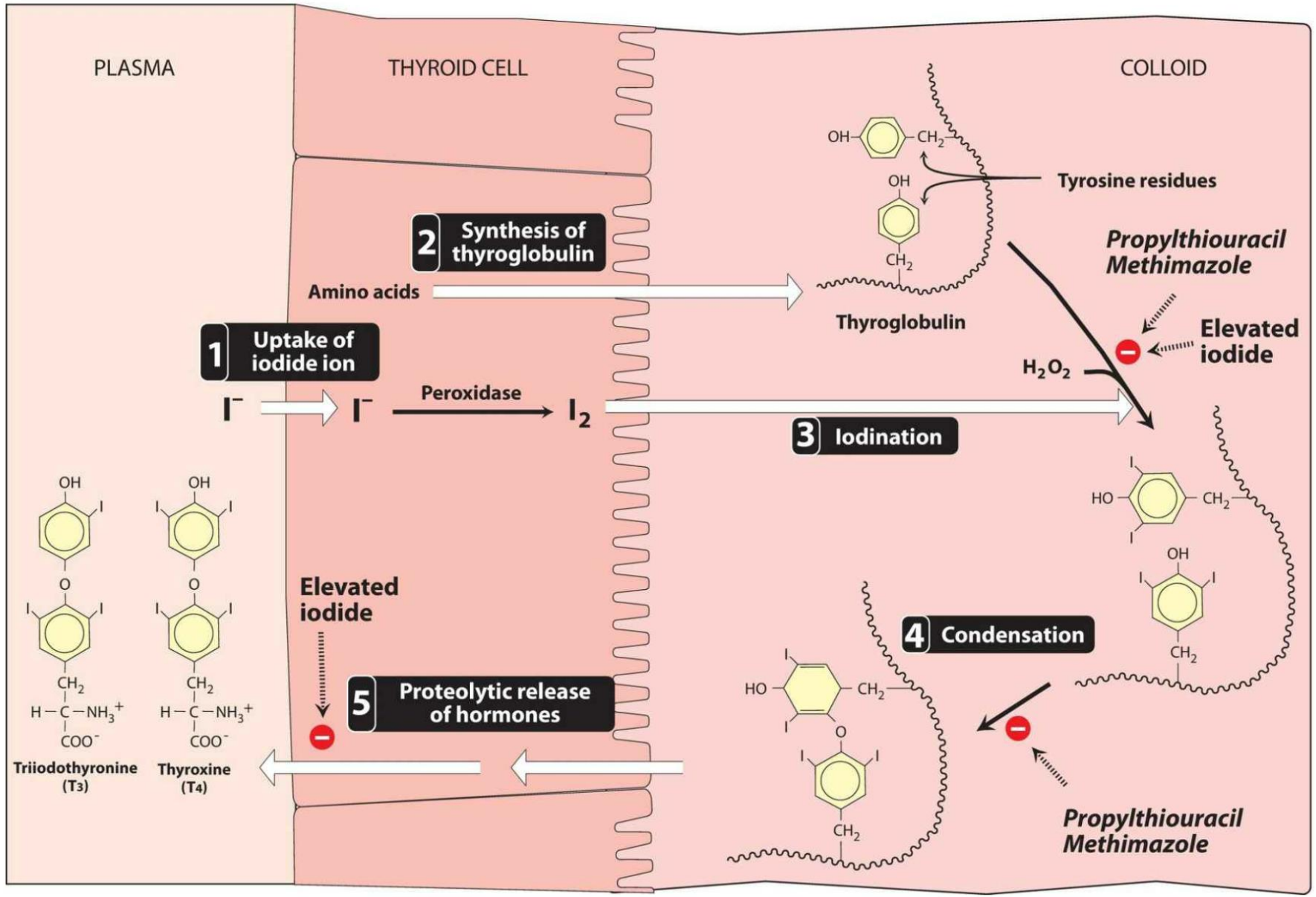


Figure 23.9 Biosynthesis of thyroid hormones.

- **B. Mechanism of action**

  Most circulating T3 and T4 is bound to thyroxine-binding globulin in the plasma. The hormones must dissociate from thyroxine-binding globulin prior to entry into cells. In the cell, T4 is enzymatically de iodinated to T3, which enters the nucleus and attaches to specific receptors. The activation of these receptors promotes the formation of RNA and subsequent protein synthesis, which is responsible for the effects of T4.

- **C. Pharmacokinetics**

  Both T4 and T3 are absorbed after oral administration. ***Food, calcium preparations, iron salts, and aluminum containing antacids can decrease the absorption of T4***.

  Deiodination is the major route of metabolism of T4. T3 also undergoes sequential deiodination. The hormones are also metabolized via conjugation with glucuronides and sulfates and excreted into bile.

- **D. Treatment of hypothyroidism** Hypothyroidism usually results from autoimmune destruction of the gland and is diagnosed by elevated TSH. **Levothyroxine (T4)** is **preferred** over **T3 (liothyronine)** or T3/T4 combination products (**liotrix**) for the treatment of hypothyroidism.

- Levothyroxine is **better tolerated** than T3 preparations and has a **longer half-life**. It is **dosed once daily, and steady state is achieved in 6 to 8 weeks.** Toxicity is directly related to T4 level and manifests as nervousness, palpitations and tachycardia, heat intolerance, and unexplained weight loss. Drugs that induce the cytochrome P-450 enzymes, such as phenytoin, rifampin, and phenobarbital, accelerate metabolism of thyroid hormones and may decrease the effectiveness.

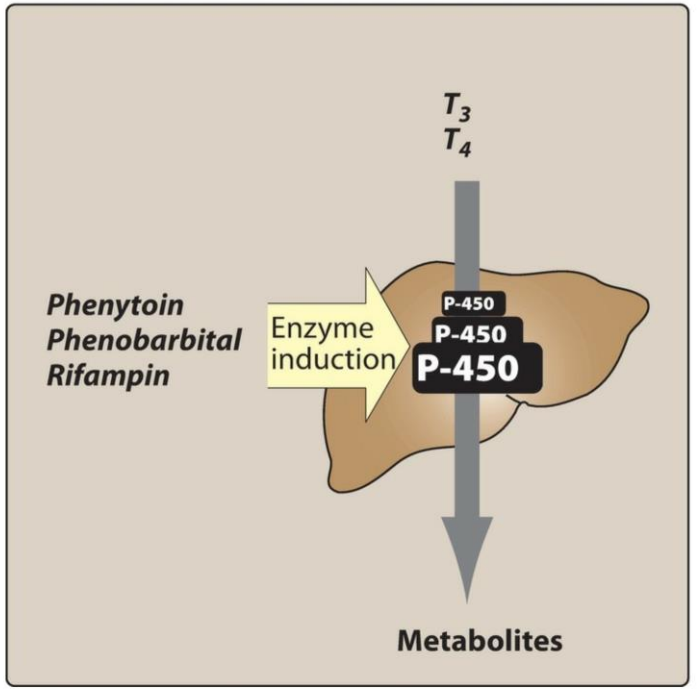


Figure 23.10 Enzyme induction can increase the metabolism of the thyroid hormones. T_3 = triiodothyronine; T_4 = thyroxine.

- **E. Treatment of hyperthyroidism (thyrotoxicosis)**
  Graves disease, an autoimmune disease that affects the thyroid, is the most common cause of hyperthyroidism. In these situations, TSH levels are low due to negative feedback. **[Note: Feedback inhibition of TRH occurs with high levels of circulating thyroid hormone, which, in turn, decreases secretion of TSH.]**
- The goal of therapy is to decrease synthesis and/or release of additional hormone. This can be accomplished by **removing part or all of the thyroid gland, by inhibiting synthesis of the hormones, or by blocking release of hormones from the follicle.**
  1. Removal of the thyroid
  This can be accomplished surgically or by destruction of the gland with radioactive iodine (131I), which is selectively taken up by the thyroid follicular cells. Most patients become hypothyroid after radioactive iodine and require treatment with ***levothyroxine***.

- **2. Inhibition of thyroid hormone synthesis**
- The thioamides, ***propylthiouracil*** [proe-pil-thye-oh-YOOR-ah-sil] (*PTU*) and *methimazole* [me-THIM-ah-zole], are ***concentrated in the thyroid, where they inhibit both the oxidative processes required for iodination of tyrosyl groups and the condensation (coupling) of iodotyrosines to form T3 and T4 (Figure 23.9). PTU also blocks the peripheral conversion of T4 to T3.***
- [Note: These drugs have no effect on thyroglobulin already stored in the gland. Therefore, clinical effects may be delayed until thyroglobulin stores are depleted (Figure 23.11).] ***Methimazole*** **is preferred over *PTU* because it has a longer half-life, allowing for once-daily dosing, and a lower incidence of adverse effects. However, *PTU* is recommended during the first trimester of pregnancy due to a greater risk of teratogenic effects with *methimazole***. *PTU* has been associated with hepatotoxicity and, rarely, agranulocytosis.

3. Blockade of hormone release

A pharmacologic dose of *iodide* inhibits the iodination of tyrosines ("Wolff-Chaikoff effect"), but this effect lasts only a few days. More importantly, *iodide* inhibits the release of thyroid hormones from thyroglobulin by mechanisms not yet understood.

Iodide is employed to treat thyroid storm or prior to surgery, because it decreases the vascularity of the thyroid gland. *Iodide*, administered orally, is not useful for long-term therapy; the thyroid ceases to respond to the drug after a few weeks. Adverse effects include sore mouth and throat, swelling of the tongue or larynx, rashes, ulcerations of mucous membranes, and metallic taste.

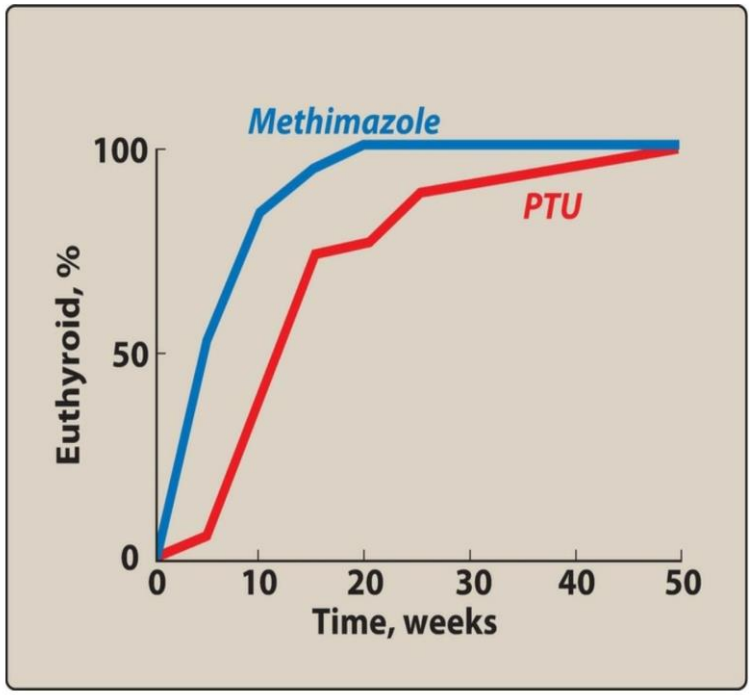


Figure 23.11 Time required for patients with Graves hyperthyroidism to become euthyroid with normal serum T_4 and T_3 concentrations.

- ***4.*** **Thyroid storm**

  Thyroid storm presents with extreme symptoms of hyperthyroidism. The treatment of thyroid storm is the same as for

  hyperthyroidism, except that the drugs are given in higher doses and more frequently. **β-blockers**, such as metoprolol or propranolol, are effective in blunting the widespread sympathetic stimulation that occurs in hyperthyroidism. but beta blockers can't be considered as anti- hyperthyroid drugs because:

  1- B-Blockers don't change the lab-biochemical test results.

- 2- B-Blockers don't treat or block all metabolic effects of TH.
- 3- B-Blockers don't change the course of disease.

Good luck