Endocrine drugs

Drugs affecting the endocrine system

- Drugs Affecting Pituitary and Thyroid
- Drugs for Diabetes
- Estrogens and Androgens
- Adrenal Hormones

Hormone Pharmacotherapy

- Hormones are used as
  - Replacement therapy
  - Antineoplastics
  - Natural therapeutic effects
    - Exaggerated response or suppression of body defenses
- Hormone blockers are used to inhibit actions of certain hormones

Drugs Affecting Pituitary and Thyroid

- The neuroendocrine system, controlled by the pituitary and hypothalamus, coordinates body functions by transmitting messages between individual cells and tissues
- The endocrine system releases hormones into the bloodstream, which carries these chemical messengers to target cells throughout the body
- Hormones have a longer response time than nerve impulses, requiring from seconds to days, or longer, to cause a response that may last for weeks or months

- The nervous system and the endocrine system are closely interrelated
- The release of hormones could be stimulated or inhibited by the nervous system, and some hormones can stimulate or inhibit nerve impulses

Hypothalamus and anterior pituitary hormones

- The hormones secreted by the hypothalamus and the pituitary are all peptides or low-molecular-weight proteins that act by binding to specific receptor sites on their target tissues

- The hormones of the anterior pituitary are regulated by neuropeptides that are called either “releasing” or “inhibiting” factors or hormones produced in the hypothalamus

Hypothalamus and anterior pituitary hormones

- The interaction of the releasing hormones with their receptors results in the activation of genes that promote the synthesis of protein precursors

- The protein precursors then undergo post-translational modification to produce hormones released into the circulation

Hypothalamus and anterior pituitary hormones

- Each hypothalamic regulatory hormone controls the release of a specific hormone from the anterior pituitary
- The hypothalamic-releasing hormones are primarily used for diagnostic purposes (to determine pituitary insufficiency)
- The hypothalamus also synthesizes the precursor proteins of vasopressin and oxytocin, which are stored in the posterior pituitary

Hypothalamus and anterior pituitary hormones

- Some pituitary hormone preparations are used therapeutically for specific hormonal deficiencies but most have limited therapeutic applications

- Hormones of the anterior and posterior pituitary are administered either IM, SC, or intranasally but not orally, because their peptidyl nature makes them susceptible to destruction by the proteolytic enzymes in GIT

Hypothalamus and anterior pituitary hormones

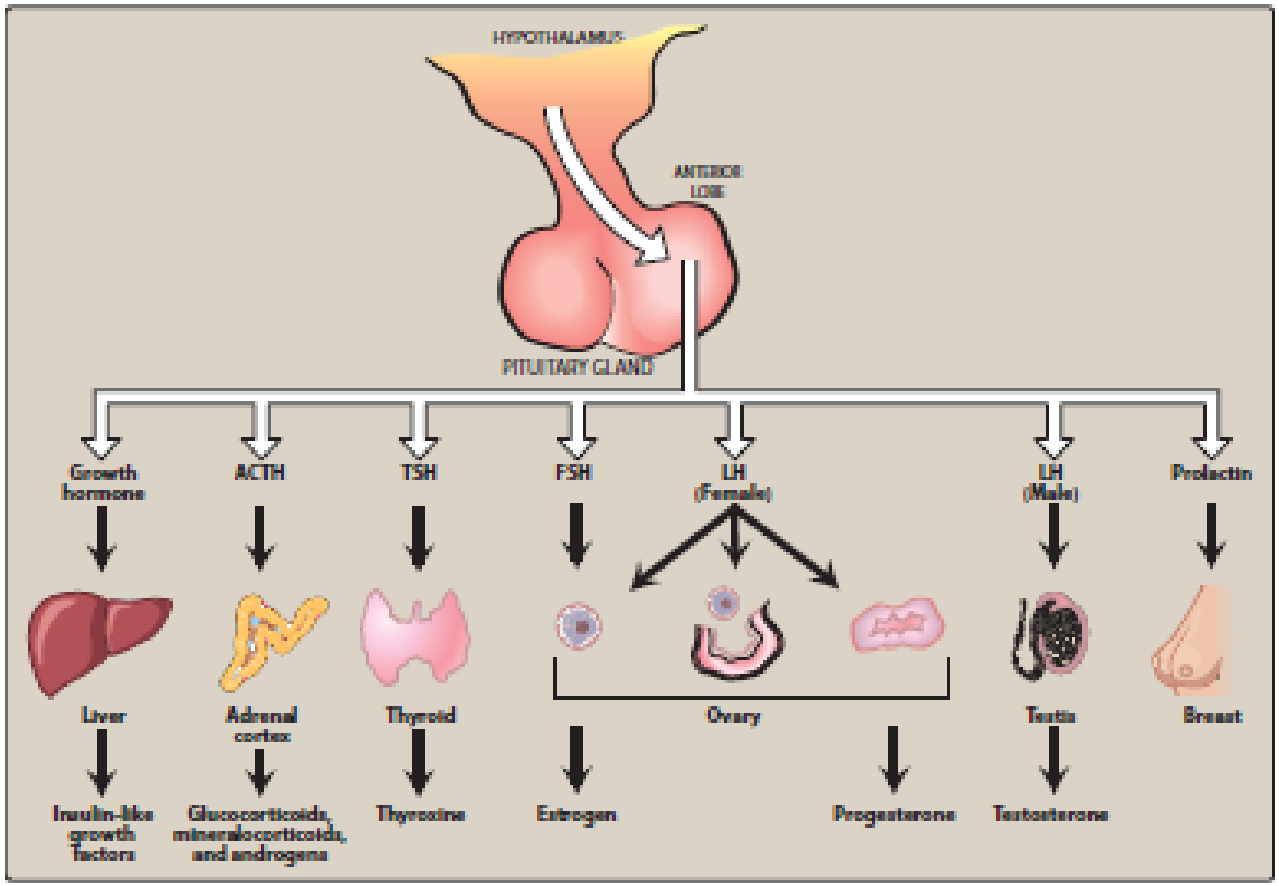
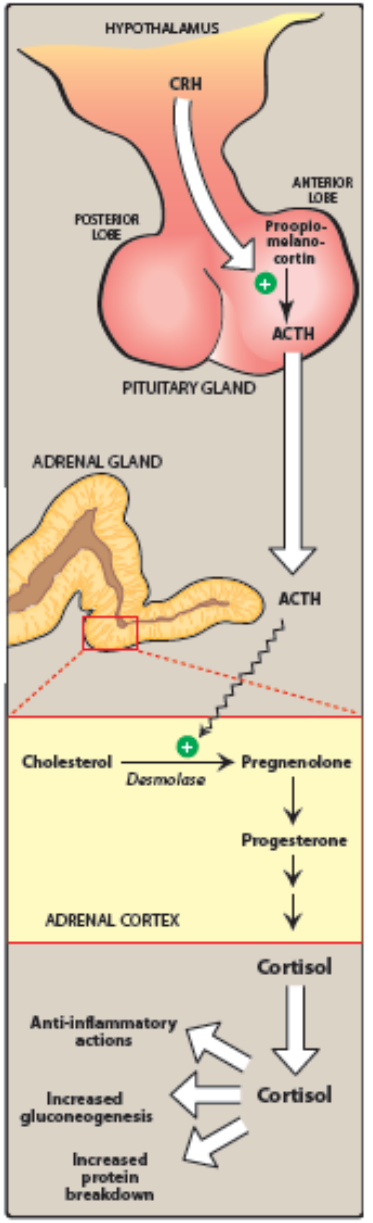


Figure 24.2
Anterior pituitary hormones. ACTH = adrenocorticotropic hormone; TSH = thyroid-stimulating hormone; FSH = follicle-stimulating hormone; LH = luteinizing hormone.

Adrenocorticotropic hormone (corticotropin)

- Corticotropin-releasing hormone (CRH) is responsible for the synthesis and release of the peptide pro-opiomelanocortin by the pituitary

- Adrenocorticotropic hormone (ACTH), or corticotropin is a product of the posttranslational processing of this precursor polypeptide



Adrenocorticotropic hormone (corticotropin)

- CRH is used diagnostically to differentiate between Cushing syndrome and ectopic ACTH-producing cells
- ACTH is released from the pituitary in pulses with an overriding diurnal rhythm, with the highest concentration occurring at approximately 6 AM and the lowest in the late evening
- Stress stimulates ACTH secretion, whereas cortisol acting via negative feedback suppresses its release

Adrenocorticotropic hormone (corticotropin)

Mechanism of action:

- The target organ of ACTH is the adrenal cortex, where it binds to specific receptors on the cell surfaces

- The occupied receptors activate G protein–coupled processes to increase cAMP, which in turn stimulates the rate-limiting step in the adrenocorticosteroid synthetic pathway (cholesterol to pregnenolone)

- This pathway ends with the synthesis and release of the adrenocorticosteroids and the adrenal androgens

Adrenocorticotropic hormone (corticotropin)

Therapeutic uses:

- Diagnostic use for differentiating between primary adrenal insufficiency (Addison disease, associated with adrenal atrophy) and secondary adrenal insufficiency (caused by the inadequate secretion of ACTH by the pituitary)

- ACTH is used in the treatment of multiple sclerosis and infantile spasm (West syndrome)

Adrenocorticotropic hormone (corticotropin)

Adverse effects:

- Similar to those of glucocorticoids
  - Osteoporosis
  - Hypertension
  - Peripheral edema
  - Hypokalemia
  - Emotional disturbances
  - Increased risk of infection

Growth hormone (GH) (somatotropin)

- A large polypeptide released by the anterior pituitary in response to growth hormone (GH)-releasing hormone produced by the hypothalamus
- Secretion of GH is inhibited by another pituitary hormone, somatostatin
- GH is released in a pulsatile manner, with the highest levels occurring during sleep
- With increasing age, GH secretion decreases, being accompanied by a decrease in lean muscle mass

Growth hormone (GH) (somatotropin)

- Somatotropin influences a wide variety of biochemical processes:
  - Stimulation of protein synthetic processes, cell proliferation and bone growth
  - Increased formation of hydroxyproline from proline boosting cartilage synthesis
  - Stimulates lipolysis
  - Antagonize insulin so as to elevate blood sugar level

Growth hormone (GH) (somatotropin)

- Synthetic human GH is produced using recombinant DNA technology and is called somatropin

Mechanism of action:

- Physiologic effects of GH are exerted directly at its targets
- Others are mediated through the somatomedins—insulin-like growth factors I and II (IGF-I and IGF-II)

Somatostatin

- Somatostatin: Growth hormone–inhibiting hormone
- In the pituitary somatostatin binds to distinct receptors, SSTR2 and SSTR5, which suppress GH and thyroid-stimulating hormone release
- Actions:
  - Inhibits the release of GH, insulin, glucagon, and gastrin

Octreotide

- A synthetic analog of somatostatin with a longer half-life
- The injectable solution and the depot formulation suppress GH and IGF-I for 12 hours and 6 weeks respectively
- Uses
  - Treatment of acromegaly caused by hormone-secreting tumors
  - Secretory diarrhea associated with tumors producing vasoactive intestinal peptide (VIPomas)

Octreotide

- Adverse effects:
  - Abdominal pain, flatulence, nausea, and steatorrhea
  - Delayed gallbladder emptying and asymptomatic cholesterol gallstones with long-term treatment

Pegvisomant

- An analog of human GH with polyethylene

glycol polymers attached

- Used for treatment of acromegaly that is refractory to other modes of surgical, radiologic, or pharmacologic intervention
- Mechanism of action: an antagonist at the GH receptor that normalizes IGF-I levels

Gonadotropin releasing hormone (GnRH)

- Obtained from the hypothalamus
- Pulsatile secretion of GnRH is essential for the release of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) from the pituitary
- Continuous administration inhibits gonadotropin release

GnRH analogs

Leuprolide

Goserelin

Nafarelin

Histrelin

- GnRH synthetic analogs act as agonists at GnRH receptors
- Effective in suppressing production of the gonadal hormones when administered continuously
- Effective in the treatment of prostatic cancer, endometriosis, and precocious puberty

GnRH analogs adverse effects, C/I

- In women, the analogs may cause hot flushes, sweating, diminished libido, depression, and ovarian cysts
- Contraindicated in pregnancy and breast-feeding
- In men
  - Initially cause a rise in testosterone that can result in bone pain
  - Hot flushes, edema, gynecomastia, and diminished libido

Gonadotropins

- Menotropins (human menopausal gonadotropins, or hMG) are obtained from the urine of postmenopausal women and contain FSH and LH
- Chorionic gonadotropin (hCG) is a placental hormone structurally related to LH which is an LH receptor agonist
- Urofollitropin: FSH obtained from postmenopausal women and is devoid of LH
- Follitropin alpha and follitropin beta are human FSH products manufactured using recombinant DNA technology

Gonadotropins

- Menotropins
- hCG
- Urofollitropin
- Follitropin alpha and follitropin beta
- All of these hormones are injected IM or SC
- Injection of hMG or FSH over a period of 5 to 12 days causes ovarian follicular growth and maturation, and with subsequent injection of hCG, ovulation occurs
- In men who are lacking gonadotropins, treatment with hCG causes external sexual maturation, and with the subsequent injection of hMG or follitropin, spermatogenesis occurs
- Multiple births can occur

Gonadotropins

- In females adverse effects include ovarian enlargement and possible hypovolemia
- Men may develop gynecomastia

Prolactin

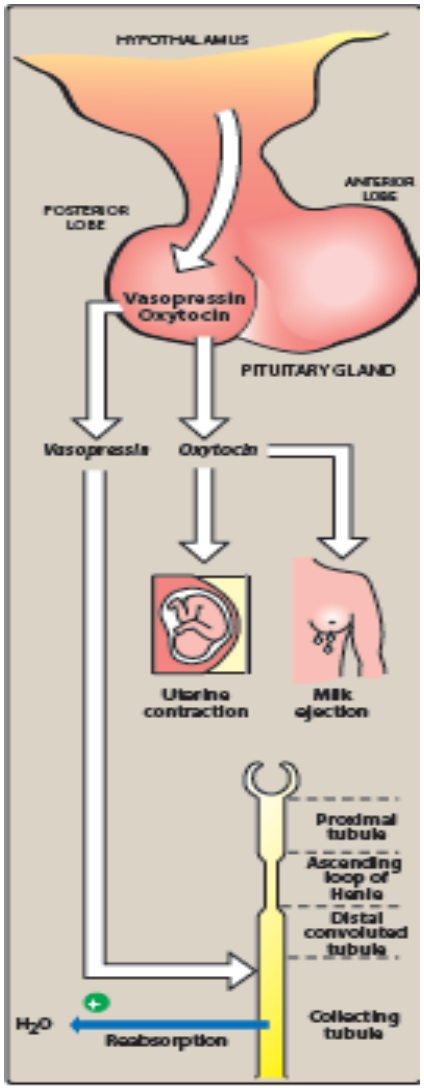
- Secreted by the anterior pituitary
- Its secretion is inhibited by dopamine acting at D2 receptors
- Its primary function is to stimulate and maintain lactation
- Decreases sexual drive and reproductive function
- The hormone binds to a transmembrane receptor which activates a tyrosine kinase to promote tyrosine phosphorylation and gene activation

Prolactin

- There is no preparation available for hypoprolactinemic conditions
- Hyperprolactinemia, which is associated with galactorrhea and hypogonadism, is usually treated with D2-receptor agonists, such as **bromocriptine and cabergoline**
- Bromocriptine and cabergoline can be used for treatment of pituitary microadenomas, macroprolactinomas and hyperprolactinemia
- Adverse effects of bromocriptine and cabergoline:
  - Nausea, headache, and sometimes psychiatric problems

Hormones of the posterior pituitary

- Vasopressin and oxytocin
- Not regulated by releasing hormones
- Synthesized in the hypothalamus, transported to the posterior pituitary, and released in response to specific physiologic signals:
  - High plasma osmolarity
  - Parturition



Hormones of the posterior pituitary

- Vasopressin and oxytocin
- Each is a nonapeptide with a circular structure due to a disulfide bridge
- Reduction of the disulfide inactivates these hormones
- Given parenterally because they are susceptible to proteolytic cleavage

Oxytocin

- Used IV is in obstetrics to stimulate uterine contraction to induce or reinforce labour
- The sensitivity of the uterus to oxytocin increases with the duration of pregnancy when it is under estrogenic dominance
- Oxytocin causes milk ejection by contracting the myoepithelial cells around the mammary alveoli
- Toxicities are uncommon when the drug is used properly
- Hypertension, uterine rupture, water retention, and fetal death have been reported

- Oxytocin antagonist: **Atosiban**
  - An inhibitor of the hormones oxytocin and vasopressin
  - Used as an intravenous medication as a labor repressant (tocolytic) to halt premature labor

Vasopressin

- Antidiuretic hormone
- In the kidney it binds to the V2 receptor to increase water permeability and reabsorption in the collecting tubules
- Has antidiuretic and vasopressor effects
- Some effects of vasopressin are mediated by the V1 receptor, which is found in liver, vascular smooth muscle (causing constriction)

Vasopressin

- Therapeutic use:
  - Treatment of diabetes insipidus
  - Management of cardiac arrest and in controlling bleeding due to esophageal varices or colonic diverticula

Vasopressin

- Adverse effects:
  - Water intoxication
  - Hyponatremia
  - Headache
  - Bronchoconstriction
  - Tremor

- Caution must be used when treating patients with coronary artery disease, epilepsy, and asthma

Desmopressin

- Vasopressin analog
- Has minimal activity at the V1 receptor making it largely free of pressor effects
- Longer duration of action than vasopressin
- Used for diabetes insipidus and nocturnal enuresis
- Administered intranasally or orally
- Local irritation may occur with the nasal spray
- The nasal formulation is no longer indicated for enuresis due to reports of seizures in children using the nasal spray

- **Conivaptan** (vasopressin receptor antagonist)
  - A non-peptide inhibitor of ADH, inhibits vasopressin receptor and used in SIADH
- Other drugs used in syndrome of inappropriate ADH (SIADH): Lithium, Demeclocyline
- Drugs used in the treatment of nephrogenic diabetes insipidus :
  - Thiazides, amiloride

Thyroid hormones

- The thyroid gland facilitates normal growth and maturation by maintaining optimum levels of metabolism in tissues for their normal function

- The thyroid gland is made up of multiple follicles that consist of a single layer of epithelial cells surrounding a lumen filled with thyroglobulin, which is the storage form of thyroid hormone

- The two major thyroid hormones are triiodothyronine (T_3) and thyroxine (T_4)

Thyroid hormones

- Euthyroidism: normal thyroid function

- Hypothyroidism, inadequate secretion of thyroid hormone, results in:
  - Bradycardia, poor resistance to cold, and mental and physical slowing
  - In children, this can cause mental retardation and dwarfism

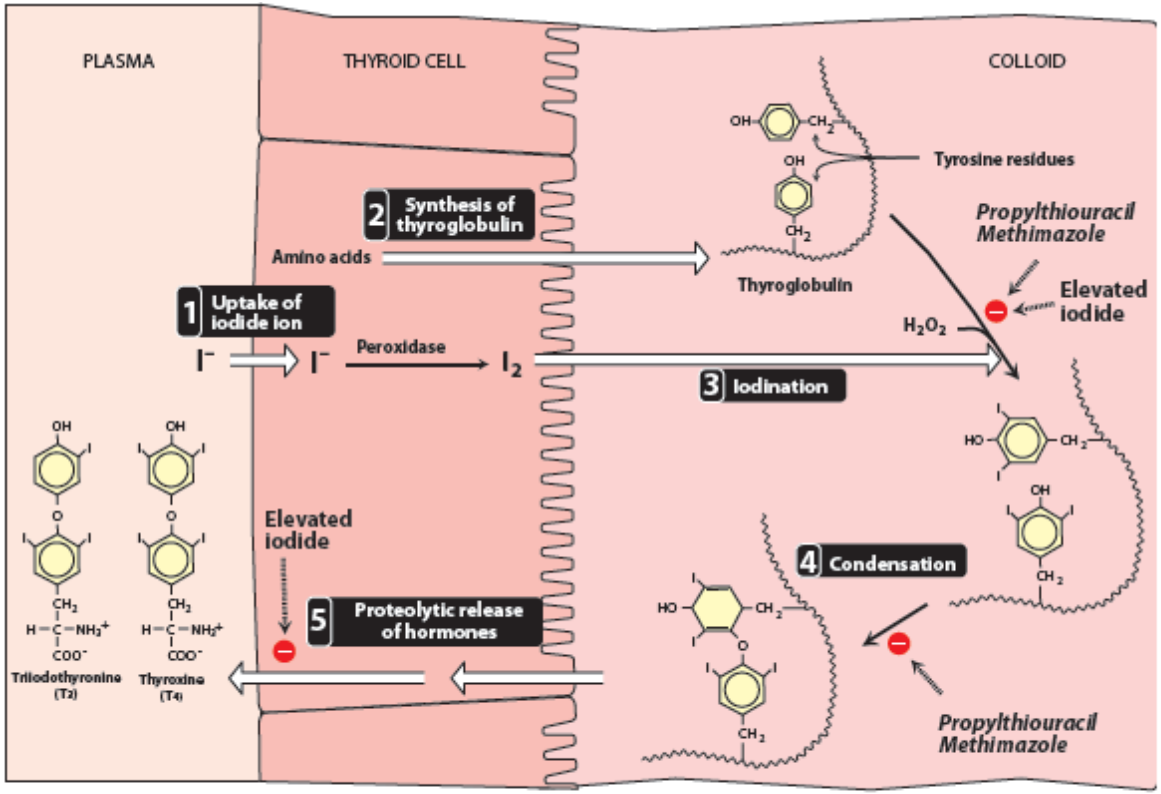
- Hyperthyroidism, an excess of thyroid hormones secretion, causing:
  - Tachycardia and cardiac arrhythmias, body wasting, nervousness, tremor, and excess heat production

Thyroid hormones synthesis & secretion

1. **Regulation of synthesis:**

- Thyroid function is controlled by TSH (thyrotropin)
- TSH action is mediated by cAMP and leads to stimulation of iodide (I^-) uptake
- Oxidation to I_2 by a peroxidase is followed by iodination of tyrosines on thyroglobulin
- Condensation
- The hormones are released following proteolytic cleavage of the thyroglobulin

Biosynthesis of thyroid hormones



Thyroid hormones synthesis & secretion

2. Regulation of secretion:

- Secretion of TSH by the anterior pituitary is stimulated by hypothalamic TRH
- Feedback inhibition of TRH occurs with high levels of circulating thyroid hormone
- At pharmacologic doses, dopamine, somatostatin, or glucocorticoids can also suppress TSH secretion
- Most of the hormone (T3 and T4) is bound to thyroxine-binding globulin in the plasma

Thyroid hormones

Mechanism of action

- T_4 and T_3 must dissociate from thyroxine-binding plasma proteins prior to entry into cells, either by diffusion or by active transport
- In the cell, T_4 is enzymatically deiodinated to T_3, 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 T_4

Thyroid hormones

- Both T_4 and T_3 are absorbed after oral administration
- Food, Ca, Al can decrease the absorption of T_4 but not of T_3
- T_4 is converted to T_3 by deiodinases
- The hormones are metabolized through the microsomal P450 system
- Drugs that induce the P450 enzymes such as phenytoin rifampin and phenobarbital accelerate metabolism of the thyroid hormones

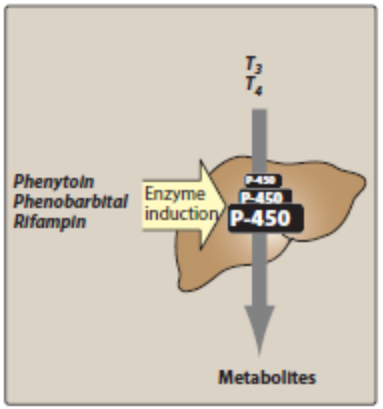


Figure 24.8
Enzyme induction can increase the metabolism of the thyroid hormones. T_3 = triiodothyronine; T_4 = thyroxine.

Thyroid Hormones: Actions

1. General metabolic effects: Increase oxygen consumption, metabolic rate, heat production (thermogenesis)
2. Increase glucose utilization and oxidation by muscles, increase hepatic gluconeogenesis
3. CNS: Influence growth and development, axon proliferation, mylein sheath formation
4. CVS: Increase cardiac output and heart rate, decrease peripheral resistance
5. G.I. tract and kidneys: Important for function, increases intestinal motility

Treatment of hypothyroidism

- Hypothyroidism usually results from autoimmune destruction of the gland or the peroxidase
- Diagnosed by elevated TSH
- Condition presented at birth: Cretinism: Impaired mental and skeletal development
- Condition presented at adulthood: Myxedema: Muscle weakness, decreased appetite, fatigue, and lethargy

Treatment of hypothyroidism

- Levothyroxine (T4) is used for hypothyroidism treatment
  - Given once daily because of its long half life
  - Steady state is achieved in 6 to 8 weeks
  - Toxicity is directly related to T4 levels
    - Nervousness
    - Heart palpitations
    - Tachycardia
    - Intolerance to heat
    - Unexplained weight loss

Treatment of hyperthyroidism (thyrotoxicosis)

- Excessive amounts of thyroid hormones in the circulation are associated with a number of disease states, including Graves disease, toxic adenoma, and goiter

- TSH levels are reduced due to negative feedback

Treatment of hyperthyroidism (thyrotoxicosis)

- The goal of therapy is to decrease synthesis and/or release of additional hormone by:
  - Removing part or all of the thyroid gland
  - Inhibiting synthesis of the hormones
  - Blocking release of the hormones from the follicle

Treatment of hyperthyroidism (thyrotoxicosis)

1. Removal of part or all of the thyroid:

- Can be accomplished either surgically or by destruction of the gland by beta particles emitted by radioactive iodine (^{131}I), which is selectively taken up by the thyroid follicular cells
- Younger patients are treated with the isotope without prior pretreatment with methimazole, the opposite is done in elderly patients
- Most patients become hypothyroid and require treatment with levothyroxine

Treatment of hyperthyroidism (thyrotoxicosis)

2. **Inhibition of thyroid hormone synthesis:**

- The thioamides: propylthiouracil (PTU) and methimazole
- Inhibit oxidative processes for iodination of tyrosyl groups and the condensation (coupling) of iodotyrosines to form T3 and T4
- PTU can also block the conversion of T4 to T3
- Clinical effects of these drugs may be delayed

Treatment of hyperthyroidism (thyrotoxicosis)

2. **Inhibition of thyroid hormone synthesis: (Cont'd)**

- PTU, methimazole
- Adverse effects include agranulocytosis, rash, edema
- PTU can cause liver toxicity or liver failure and should be reserved for patients who are intolerant of methimazole
- PTU is safer in first trimester of pregnancy

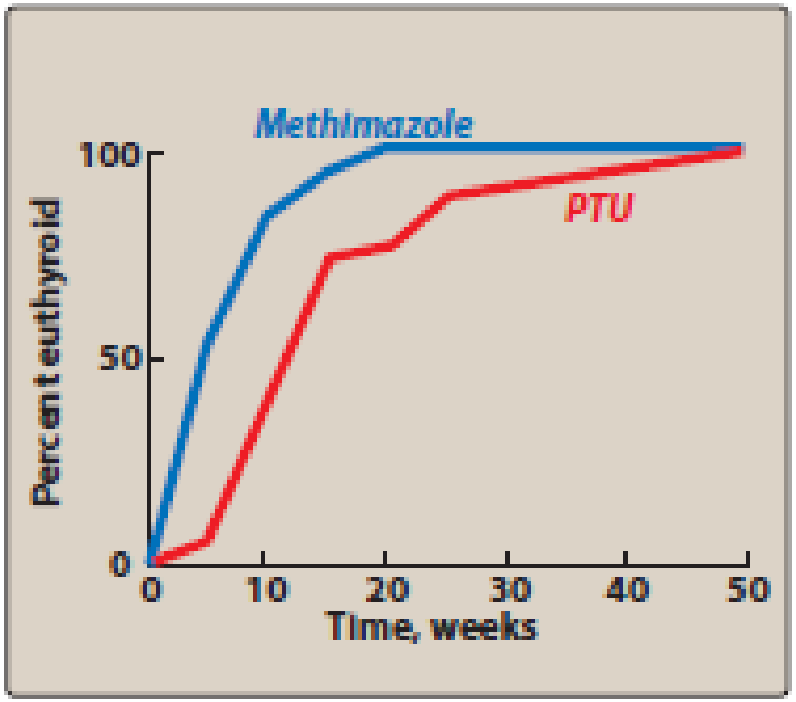


Figure 24.9

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

Treatment of hyperthyroidism (thyrotoxicosis)

3. Blockade of hormone release:

- A pharmacologic dose of iodide inhibits the iodination of tyrosines “acute Wolff-Chaikoff effect” but this effect lasts only a few days
- Iodide inhibits the release of thyroid hormones from thyroglobulin by unknown mechanisms
- Iodide is rarely used as the sole therapy
- It is employed to treat potentially fatal thyroid storm or prior to surgery, because it decreases the vascularity of the thyroid gland
- Iodide is not useful for long-term therapy, because the thyroid ceases to respond to the drug after a few weeks

Treatment of hyperthyroidism (thyrotoxicosis)

3. Blockade of hormone release: (Cont'd)

- Iodide is administered orally
- Adverse effects
  - Sore mouth and throat
  - Swelling of the tongue or larynx
  - Rashes
  - Ulcerations of mucous membranes
  - Metallic taste in the mouth

Treatment of hyperthyroidism (thyrotoxicosis)

4. Thyroid storm:

- Presents with extreme symptoms of hyperthyroidism
- Same therapy as hyperthyroidism, given in higher doses and more frequently
- β-Blockers that lack sympathomimetic activity, such as propranolol, are effective in blunting the sympathetic stimulation
  - An alternative in patients suffering from severe heart failure or asthma is the calcium-channel blocker, diltiazem

Treatment of hyperthyroidism (thyrotoxicosis)

- Other agents used in the treatment of thyroid storm include:
  - PTU
  - Iodides
  - Iodinated contrast media (which rapidly inhibits the conversion of T4 to T3)
  - Glucocorticoids (to protect against shock)