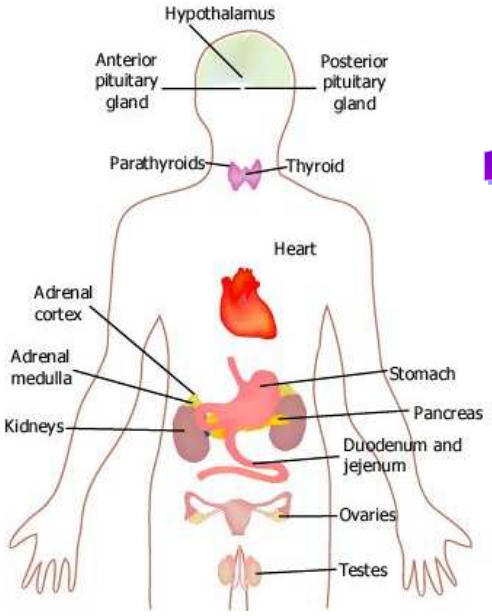


Endocrine System

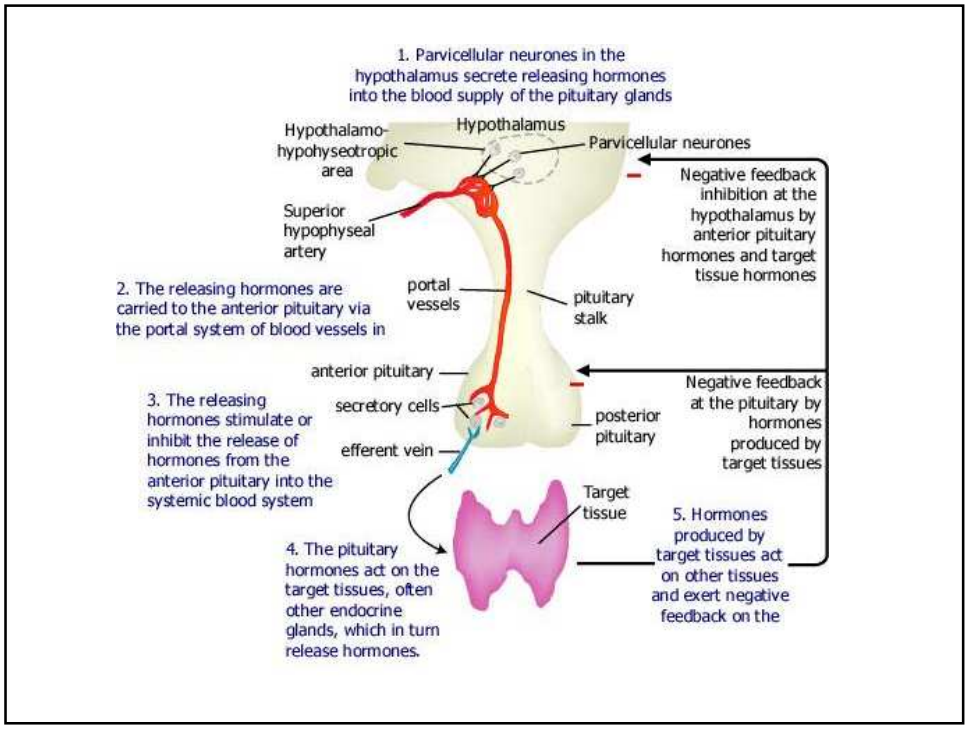
Endocrine gland	Hormone	Main tissues acted on by hormone	Main function of hormones
Hypothalamus	**Thyrotrophin releasing hormone (TRH)**	**Anterior pituitary**	Stimulates release of thyroid stimulating hormone (TSH) from the anterior pituitary
	Somatostatin	**Anterior pituitary**	Inhibitory hormone that prevents release of hormones such as growth hormone from the anterior pituitary
	Gonadotrophin releasing hormone (GnRH)	**Anterior pituitary**	Stimulates release of follicle stimulating hormone (FSH) and luteinising hormone (LH) from the anterior pituitary
	Corticotrophin releasing hormone (CRH)	**Anterior pituitary**	Stimulates adrenocorticotrophic hormone (ACTH) release from the anterior pituitary.
	Growth Hormone Releasing Hormone (GHRH)	**Anterior pituitary**	Stimulates release of growth hormone (GH) form the anterior pituitary

Anterior pituitary	**Thyroid stimulating hormone (TSH)**	**Thyroid gland**	Stimulates release of thyroxine and tri-iodothyronine from the thyroid gland
	Luteinising hormone (LH)	**Ovary/Testis**	Females: promotes ovulation of the egg and stimulates oestrogen and progesterone production Males: promotes testosterone release from the testis
	Follicle stimulating hormone (FSH)	**Ovary/Testis**	Females: promotes development of eggs and follicles in the ovary prior to ovulationMales: promotes production of testosterone from testis
	Growth Hormone (GH)	**Bones, cartilage, muscle, fat, liver, heart**	Acts to promote growth of bones and organs
	Prolactin (PRL)	**Breasts, brain**	Stimulates milk production in the breasts and plays a role in sexual behaviour
	Adrenocortico-trophic hormone (ACTH)	**Adrenal glands**	Stimulates the adrenal glands to produce mainly cortisol
Posterior pituitary	**Vasopressin (anti-diuretic hormone, ADH)**	**Kidney, blood vessels, blood components**	Acts to maintain blood pressure by causing the kidney to retain fluid and by constricting blood vessels
	Oxytocin	**Uterus, milk ducts of breasts**	Causes ejection of milk from the milk ducts and causes constriction of the uterus during labour

The anterior pituitary

contains a number of secretory cells that release hormones, the main ones being:

- adrenocorticotrophic hormone (ACTH)
- thyroid stimulating hormone (TSH)
- growth hormone (GH)
- follicle stimulating hormone (FSH)
- luteinising hormone (LH)
- prolactin (PRL)



Anterior pituitary hormone	Hypothalamic releasing hormone	Stimulatory or inhibitory	Stimuli for activation of the system
Adrenocorticotrophic hormone (ACTH)	Corticotrophin releasing hormone (CRH)	Stimulatory	Stress (e.g. pain, fever, hypoglycaemia, low BP)
	Vasopressin	Stimulatory	
Thyroid stimulating hormone (TSH)	Thyrotrophin releasing hormone (TRH)	Stimulatory	Rhythmic activity in the hypothalamus
Follicle stimulating hormone (FSH) and Luteinising hormone (LH)	Gonadotrophin releasing hormone (GnRH)	Stimulatory	Rhythmic activity in the hypothalamus
Growth hormone (GH)	Growth hormone releasing hormone (GHRH)	Stimulatory	Exercise, stress, hypoglycaemia, arginine administration, high amino acid levels
	Somatostatin	Inhibitory	
Prolactin (PRL)	Dopamine	Inhibitory	Sleep, stress, suckling stimulus
	Thyrotrophin releasing hormone (TRH)	Stimulatory	

Growth Hormone

Growth hormone, also known as *somatotropin*, is a protein hormone of about 190 amino acids that is synthesized and secreted by cells called *somatotrophs* in the anterior pituitary. It is a major participant in control of several complex physiologic processes, including growth and metabolism. Growth hormone is also of considerable interest as a drug used in both humans and animals.

Control of Growth Hormone Secretion

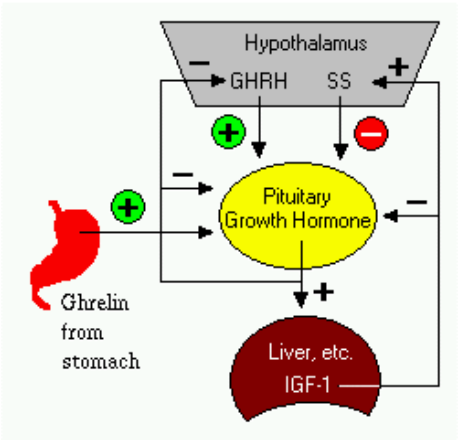
Production of growth hormone is modulated by many factors, including stress, exercise, nutrition, sleep and growth hormone itself.

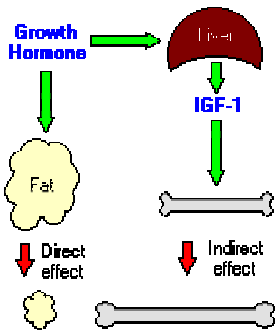
However, its primary controllers are :

➢**Growth hormone-releasing hormone (GHRH) is a hypothalamic peptide that stimulates both the synthesis and secretion of growth hormone.**

➢**Somatostatin (SS) is a peptide produced by several tissues in the body, including the hypothalamus.** Somatostatin inhibits growth hormone release in response to GHRH and to other stimulatory factors such as low blood glucose concentration.

➢**Ghrelin is a peptide hormone secreted from the stomach.** Ghrelin binds to receptors on somatotrophs and potently stimulates secretion of growth hormone.





•**Direct effects** are the result of growth hormone binding its receptor on target cells. Fat cells (adipocytes), for example, have growth hormone receptors, and growth hormone stimulates them to break down triglyceride and supresses their ability to take up and accumulate circulating lipids.

•**Indirect effects** are mediated primarily by a **insulin-like growth factor-1 (IGF-1)**, a hormone that is secreted from the liver and other tissues in response to growth hormone. A majority of the growth promoting effects of growth hormone is actually due to IGF-1 acting on its target cells.

All of the effects of GH are the ultimate result of its binding to a specific cell surface receptor which is widely distributed throughout the body. The mature GH receptor is a transmembrane glyciprotein of 620 amino acid residues.

Recent evidence shows that, in spite of the absence of intrinsic tyrosine kinase activity in the growth hormone receptor, the binding of the hormone leads to an **increase in the phosporylation of intracellular proteins on tyrosine residues**. These initial events are mediated by certain cytoplasmic protein tyrosine kinases that physically associate with the ligand-bound GH receptor and become activated as a consequence of this association.

Anabolic and growth-depending effects are mediated by IGFs. The IGF-1 receptor is structurally related to the insulin receptor and has intrinsic tyrosine kinase activity.

IGF-1 receptor also can bind insulin and IGF-2. Insulin receptors also are capable of binding IGF-1 and IGF-2, whereas the IGF-2 receptor does not bind insulin but can bind IGF-1.

Metabolic Effects

- **Protein metabolism: In general, growth hormone stimulates protein anabolism in many tissues.** This effect reflects increased amino acid uptake, increased protein synthesis and decreased oxidation of proteins.

- **Fat metabolism: Growth hormone enhances the utilization of fat by stimulating triglyceride breakdown and oxidation in adipocytes.**

- **Carbohydrate metabolism: Growth hormone is one of a battery of hormones that serves to maintain blood glucose within a normal range. Growth hormone is often said to have anti-insulin activity, because it supresses the abilities of insulin to stimulate uptake of glucose in peripheral tissues and enhance glucose synthesis in the liver. Somewhat paradoxically, administration of growth hormone stimulates insulin secretion, leading to hyperinsulinemia.**

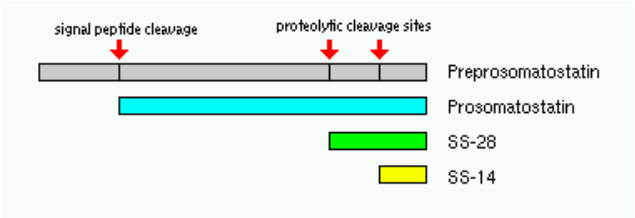
Drugs used in the Treatment of Syndromes of Growth Hormone Excess

Dopamine agonists (bromocriptine)

Somatostatin and analogues

Somatostatin and analogues: octreotide, lanreotide, vapreotide

Two forms of somatostatin are synthesized. They are referred to as SS-14 and SS-28, reflecting their amino acid chain length. Both forms of somatostatin are generated by proteolytic cleavage of prosomatostatin, which itself is derived from preprosomatostatin. Two cysteine residules in SS-14 allow the peptide to form an internal disulfide bond.



The relative amounts of SS-14 versus SS-28 secreted depends upon the tissue. For example, SS-14 is the predominant form produced in the nervous system and apparently the sole form secreted from pancreas, whereas the intestine secretes mostly SS-28.
In addition to tissue-specific differences in secretion of SS-14 and SS-28, the two forms of this hormone can have different biological potencies. SS-28 is roughly ten-fold more potent in inhibition of growth hormone secretion, but less potent that SS-14 in inhibiting glucagon release. **Five stomatostatin receptors have been identified and characterized, all of which are members of the G protein-coupled receptor superfamily.** Each of the receptors activates distinct signalling mechanisms within cells, although all inhibit adenylyl cyclase. Four of the five receptors do not differentiate SS-14 from SS-28.

Pharmaceutical and Biotechnological Uses of Growth Hormone

In years past, growth hormone purified from human cadaver pituitaries was used to treat children with severe growth retardation. More recently, the virtually unlimited supply of recombinant growth hormone has lead to several other applications to human and animal populations.
Human growth hormone is commonly used to treat children of pathologically short stature. There is concern that this practice will be extended to treatment of essentially normal children - so called "enhancement therapy" or growth hormone on demand. Similarly, growth hormone has been used by some to enhance atheletic performance. Although growth hormone therapy is generally safe, it is not as safe as no therapy and does entail unpredictable health risks. Parents that request growth hormone therapy for children of essentially-normal stature are clearly misguided.
The role of growth hormone in normal aging remains poorly understood, but some of the cosmetic symptoms of aging appear to be amenable to growth hormone therapy. This is an active area of research, and additional information and recommendations about risks and benefits will undoubtedly surface in the near future.

DAIRY CATTLE

Growth hormone is currently approved and marketed for enhancing milk production in dairy cattle. There is no doubt that administration of bovine somatotropin to lactating cows results in increased milk yield, and, depending on the way the cows are managed, can be an economically-viable therapy. However, this treatment engenders abundant controversy, even among dairy farmers. One thing that appears clear is that drinking milk from cattle treated with bovine growth hormone does not pose a risk to human health.

Another application of growth hormone in animal agriculture is treatment of growing pigs with porcine growth hormone. Such treatment has been demonstrated to significantly stimulate muscle growth and reduce deposition of fat.

Growth hormone-releasing hormone (GHRH)

Is a single polypeptide chain of 44 amino acid residues derived from a 108 amino acid residue precursor.

The binding of GHRH to its cognate receptor (a member of the G-protein-coupled receptor family) results in the activation od adenyl cyclase and increased cyclic AMP levels in somatotropes, resulting in a stimulation of the synthesis, via increased transcription of the GHRH gene, and release of GHRH.

GHRH is used mainly as a diagnostic agent (hypothalamic or pituitary growth deficit?)

Prolactin

Prolactin is a single-chain protein hormone closely related to growth hormone. It is secreted by so-called *lactotrophs* in the anterior pituitary. It is also synthesized and secreted by a broad range of other cells in the body, most prominently various immune cells, the brain and the decidua of the pregnant uterus.
Prolactin is synthesized as a prohormone. Following cleavage of the signal peptide, the length of the mature hormone is between 194 and 199 amino acids, depending on species. Hormone structure is stabilized by three intramolecular disulfide bonds.

Mammary Gland Development, Milk Production and Reproduction

In the 1920's it was found that extracts of the pituitary gland, when injected into virgin rabbits, induced milk production. Subsequent research demonstrated that prolactin has two major roles in milk production:

- **Prolactin induces lobuloalveolar growth of the mammary gland. Alveoli are the clusters of cells in the mammary gland that actually secrete milk.**

- **Prolactin stimulates lactogenesis or milk production after giving birth. Prolactin, along with cortisol and insulin, act together to stimulate transcription of the genes that encode milk proteins.**

The critical role of prolactin in lactation has been confirmed in mice with targeted deletions in the prolactin gene. Female mice that are heterozygous for the deleted prolactin gene (and produce roughly half the normal amount of prolactin) show failure to lactate after their first pregnancy.

Prolactin also appears important in several non-lactational aspects of reproduction. In some species (rodents, dogs, skunks), prolactin is necessary for maintainance of corpora lutea (ovarian structures that secrete progesterone, the "hormone of pregnancy"). Mice that are homozygous for an inactivated prolactin gene and thus incapable of secreting prolactin are infertile due to defects in ovulation, fertilization, preimplantation development and implantation.

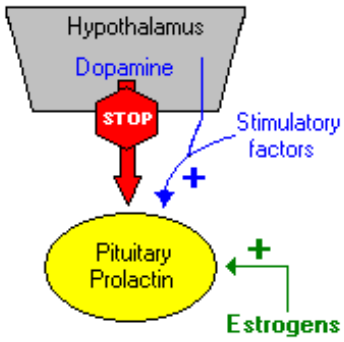
Finally, prolactin appears to have stimulatory effects in some species on reproductive or maternal behaviors such as nest building and retrieval of scattered young.

Effects on Immune Function

The prolactin receptor is widely expressed by immune cells, and some types of lymphocytes synthesize and secrete prolactin. These observations suggest that prolactin may act as an autocrine or paracrine modulator of immune activity. Interestingly, mice with homozygous deletions of the prolactin gene fail to show significant abnormalities in immune responses.
A considerable amount of research is in progress to delineate the role of prolactin in normal and pathologic immune responses. It appears that prolactin has a modulatory role in several aspects of immune function, but is not strictly required for these responses.

Control of Prolactin Secretion

In contrast to what is seen with all the other pituitary hormones, the hypothalamus tonically suppresses prolactin secretion from the pituitary. In other words, there is usually a hypothalamic "brake" set on the lactotroph, and prolactin is secreted only when the brake is released. If the pituitary stalk is cut, prolactin secretion increases, while secretion of all the other pituitary hormones fall dramatically due to loss of hypothalamic releasing hormones.

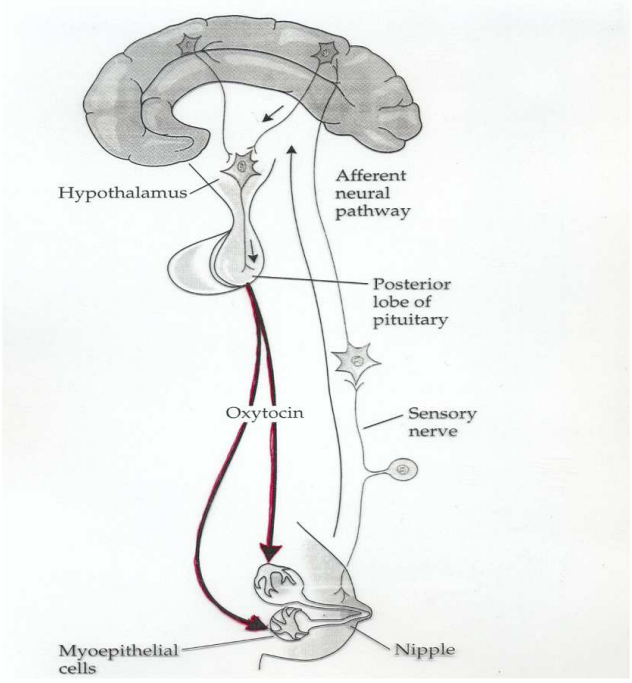


Dopamine serves as the major prolactin-inhibiting factor or brake on prolactin secretion. Dopamine is secreted into portal blood by hypothalamic neurons, binds to receptors on lactotrophs, and inhibits both the synthesis and secretion of prolactin. Agents and drugs that interfere with dopamine secretion or receptor binding lead to enhanced secretion of prolactin.

In addition to tonic inhibition by dopamine, prolactin secretion is **positively regulated** by several hormones, including **thyroid-releasing hormone**, **gonadotropin-releasing hormone** and **vasoactive intestinal polypeptide**.

Stimulation of the nipples and mammary gland, as occurs during nursing, leads to prolactin release. This effect appears to be due to a spinal reflex arc that causes release of prolactin-stimulating hormones from the hypothalamus.

Estrogens provide a well-studied positive control over prolactin synthesis and secretion. The increasing blood concentrations of estrogen during late pregnancy appear responsible for the elevated levels of prolactin that are necessary to prepare the mammary gland for lactation at the end of gestation.



Hyperprolactinemia

Excessive secretion of prolactin is a relative common disorder in humans. This condition has numerous causes, including prolactin-secreting tumors and therapy with certain drugs.

Dopamine-receptor agonists

Bromocriptine is used to treat amenorrhea, a condition in which the menstrual period does not occur; infertility (inability to get pregnant) in women; abnormal discharge of milk from the breast; hypogonadism; Parkinson's disease; and acromegaly, a condition in which too much growth hormone is in the body. T ½: 2-8 hrs.

Pergolide is used with another medication to treat the symptoms of Parkinson's disease (a disorder of the nervous system that causes difficulties with movement, muscle control, and balance). Pergolide is in a class of medications called dopamine agonists. It works by acting in place of dopamine, a natural substance in the brain that is needed to control movement.

Cabergoline is used to treat different types of medical problems that occur when too much of the hormone prolactin is produced. It can be used to treat certain menstrual problems, fertility problems in men and women, and pituitary prolactinomas (tumors of the pituitary gland). T ½: 65 hrs.

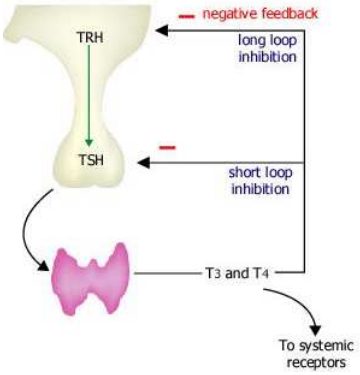
Quinagolide prevents the production of a chemical called *prolactin.* It is therefore helpful in preventing or reducing milk production for medical reasons, treating some types of infertility, breast problems and menstrual problems. It also affects the production of growth hormone and has been used for the treatment of conditions such as *acromegaly*, a disease which causes enlargement of the hands, feet and face. T ½: 22 hrs.

Thyroid-stimulating hormone

Thyroid-stimulating hormone, also known as thyrotropin, is secreted from cells in the anterior pituitary called *thyrotrophs*, finds its receptors on epithelial cells in the thyroid gland, and stimulates that gland to synthesize and release thyroid hormones.

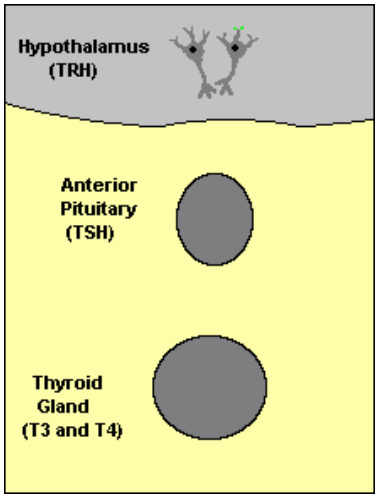
The most important controller of TSH secretion is thyroid-releasing hormone. Thyroid-releasing hormone is secreted by hypothalamic neurons into hypothalamic-hypophyseal portal blood, finds its receptors on thyrotrophs in the anterior pituitary and stimulates secretion of TSH.

Secretion of thyroid-releasing hormone, and hence, TSH, is inhibited by high blood levels of thyroid hormones in a classical negative feedback loop.



Thyroid gland	**Thyroxine (T4)**	**Most tissues**	Acts to regulate the body's metabolic rate
	Tri-iodothyronine (T3)	**Most tissues**	Acts to regulate the body's metabolic rate

Feedback loops are used extensively to regulate secretion of hormones in the hypothalamic-pituitary axis. An important example of a negative feedback loop is seen in control of thyroid hormone secretion. The thyroid hormones thyroxine and triiodothyronine ("T4 and T3") are synthesized and secreted by thyroid glands and affect metabolism throughout the body. The basic mechanisms for control in this system (illustrated to the right) are:



•Neurons in the hypothalamus secrete thyroid releasing hormone (TRH), which stimulates cells in the anterior pituitary to secrete thyroid-stimulating hormone (TSH).

•TSH binds to receptors on epithelial cells in the thyroid gland, stimulating synthesis and secretion of thyroid hormones, which affect probably all cells in the body.

•When blood concentrations of thyroid hormones increase above a certain threshold, TRH-secreting neurons in the hypothalamus are inhibited and stop secreting TRH. ***This is an example of "negative feedback".***

Inhibition of TRH secretion leads to shut-off of TSH secretion, which leads to shut-off of thyroid hormone secretion. As thyroid hormone levels decay below the threshold, negative feedback is relieved, TRH secretion starts again, leading to TSH secretion ...

Constructing Thyroid Hormones

The entire synthetic process occurs in three major steps, which are, at least in some ways:

- **Production and accumulation of the raw materials**
- **Fabrication or synthesis of the hormones on a backbone or scaffold of precursor**
- **Release of the free hormones from the scaffold and secretion into blood**

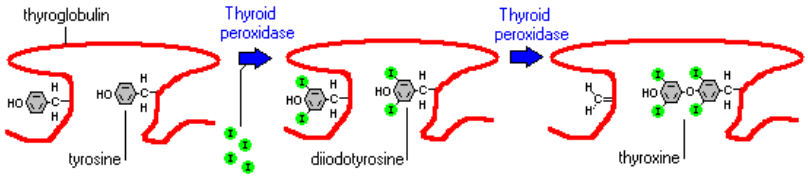
The recipe for making thyroid hormones calls for two principle raw materials:

- **Tyrosines are provided from a large glycoprotein scaffold called thyroglobulin, which is synthesized by thyroid epithelial cells and secreted into the lumen of the follicle - colloid is essentially a pool of thyroglobulin. A molecule of thyroglobulin contains 134 tyrosines, although only a handful of these are actually used to synthesize T4 and T3.**

- **Iodine, or more accurately iodide (I^-)**, is avidly taken up from blood by thyroid epithelial cells, which have on their outer plasma membrane a sodium-iodide symporter or "*iodine trap*". Once inside the cell, iodide is transported into the lumen of the follicle along with thyroglobulin.

Fabrication of thyroid hormones is conducted by the enzyme thyroid peroxidase, an integral membrane protein present in the apical (colloid-facing) plasma membrane of thyroid epithelial cells. Thyroid peroxidase catalyzes two sequential reactions:

1. Iodination of tyrosines on thyroglobulin (also known as "organification of iodide").
2. Synthesis of thyroxine (or triiodothyronine) from two iodotyrosines.



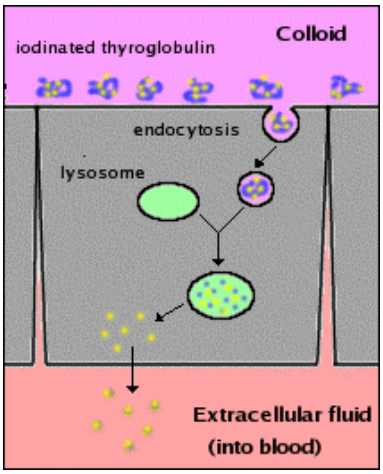
Through the action of thyroid peroxidase, thyroid hormones accumulate in colloid, on the surface of thyroid epithelial cells. *Remember that hormone is still tied up in molecules of thyroglobulin - the task remaining is to liberate it from the scaffold and secrete free hormone into blood.*

Thyroid hormones are excised from their thyroglobulin scaffold by digestion in lysosomes of thyroid epithelial cells. This final act in thyroid hormone synthesis proceeds in the following steps:

•Thyroid epithelial cells ingest colloid by endocytosis from their apical borders - that colloid contains thyroglobulin decorated with thyroid hormone.

•Colloid-laden endosomes fuse with lysosomes, which contain hydrolytic enzymes that digest thyroglobluin, thereby liberating free thyroid hormones.

•Finally, free thyroid hormones apparently diffuse out of lysosomes, through the basal plasma membrane of the cell, and into blood where they quickly bind to carrier proteins for transport to target cells.



Receptors for thyroid hormones are intracellular DNA-binding proteins that function as hormone-responsive transcription factors, very similar conceptually to the receptors for steroid hormones.
Despite being derived from an amino acid, thyroid hormones are hydrophobic in character and appear to enter cells and nuclei by diffusion through cell membranes. Once inside the nucleus, the hormone binds its receptor, and **the hormone-receptor complex interacts with specific sequences of DNA in the promoters of responsive genes. The effect of receptor binding to DNA is to modulate gene expression, either by stimulating or inhibiting transcription of specific genes.**

Mammalian thyroid hormone receptors are encoded by two genes, designated alpha and beta. Further, the primary transcript for each gene can be alternatively spliced, generating different alpha and beta receptor isoforms. Currently, four different thyroid hormone receptors are recognized: alpha-1, alpha-2, beta-1 and beta-2.

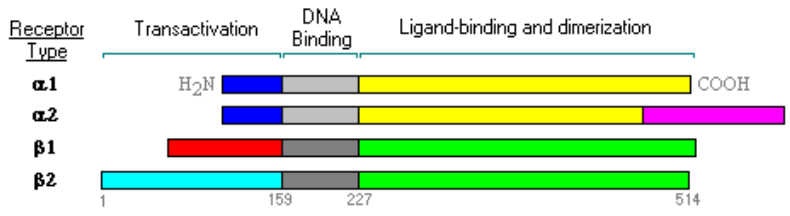
Like other members of the nuclear receptor superfamily, thyroid hormone receptors encapsulate three functional domains:

- A **transactivation domain** **at the amino terminus that interacts with other transcription factors to form complexes that repress or activate transcription. There is considerable divergence in sequence of the transactivation domains of alpha and beta isoforms and between the two beta isoforms of the receptor.**

- A **DNA-binding domain** **that binds to sequences of promoter DNA known as hormone response elements.**

- A **ligand-binding and dimerization domain** **at the carboxy-terminus.**

The DNA-binding domains of the different receptor isoforms are very similar, but there is considerable divergence among transactivation and ligand-binding domains. *Most notably, the alpha-2 isoform has a unique carboxy-terminus and does not bind triiodothyronine* (T3).



The different forms of thyroid receptors have patterns of expression that vary by tissue and by developmental stage.

Physiologic Effects of Thyroid Hormones

It is likely that all cells in the body are targets for thyroid hormones. While not strictly necessary for life, thyroid hormones have profound effects on many "big time" physiologic processes, such as development, growth and metabolism.

Metabolism: **Thyroid hormones stimulate diverse metabolic activities most tissues, leading to an increase in basal metabolic rate. One consequence of this activity is to increase body heat production, which seems to result, at least in part, from increased oxygen consumption and rates of ATP hydrolysis.** *By way of analogy, the action of thyroid hormones is akin to blowing on a smouldering fire.* A few examples of specific metabolic effects of thyroid hormones include:

- **Lipid metabolism: Increased thyroid hormone levels stimulate fat mobilization, leading to increased concentrations of fatty acids in plasma. They also enhance oxidation of fatty acids in many tissues. Finally, plasma concentrations of cholesterol and triglycerides are inversely correlated with thyroid hormone levels - one diagnostic indiction of hypothyroidism is increased blood cholesterol concentration.**

- **Carbohydrate metabolism: Thyroid hormones stimulate almost all aspects of carbohydrate metabolism, including enhancement of insulin-dependent entry of glucose into cells and increased gluconeogenesis and glycogenolysis to generate free glucose.**

Growth: **Thyroid hormones are clearly necessary for normal growth in children and young animals, as evidenced by the growth-retardation observed in thyroid deficiency.** Not surprisingly, the growth-promoting effect of thyroid hormones is intimately intertwined with that of growth hormone, a clear indiction that complex physiologic processes like growth depend upon multiple endocrine controls.

Development: **A classical experiment in endocrinology was the demonstration that tadpoles deprived of thyroid hormone failed to undergo metamorphosis into frogs. Of critical importance in mammals is the fact that normal levels of thyroid hormone are essential to the development of the fetal and neonatal brain.**

Other Effects: **As mentioned above, there do not seem to be organs and tissues that are not affected by thyroid hormones. A few additional, well-documented effects of thyroid hormones include:**

- **Cardiovascular system: Thyroid hormones increases heart rate, cardiac contractility and cardiac output. They also promote vasodilation, which leads to enhanced blood flow to many organs.**
- **Central nervous system: Both decreased and increased concentrations of thyroid hormones lead to alterations in mental state. Too little thyroid hormone, and the individual tends to feel mentally sluggish, while too much induces anxiety and nervousness.**
- **Reproductive system: Normal reproductive behavior and physiology is dependent on having essentially normal levels of thyroid hormone. Hypothyroidism in particular is commonly associated with infertility.**

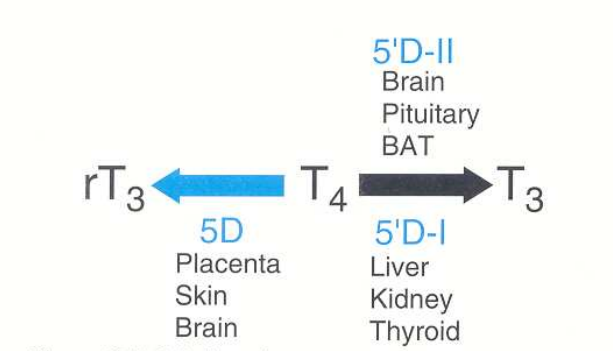


Figure 56–5. Deiodinase isozymes.

Abbreviations are as follows: 5′D-I, type I iodothyronine 5′-deiodinase; 5′D-II, type II iodothyronine 5′-deiodinase; 5D, type III iodothyronine 5-deiodinase; BAT, brown adipose tissue.

Factors that alter binding of Thyroxine to Thyroxine-binding globulin

INCREASE BINDING	DECREASE BINDING
Drugs	
Estrogens	Glucocorticoids
Methadone	Androgens
Clofibrate	L-Asparaginase
5-Fluorouracile	Salicylates
Heroin	Mefenamic Acid
Tamoxifen	Antiseizures medications (Phenyoin, carbamazepine)
	Furosemide
Systemic factors	
Liver diesease	Inheritance
Porphyria	Acute and chronic illness
HIV infection	
Inheritance	

The antithyroid drugs most frequently used today are chemicals known as **thioureylenes**, which belong to the thionamide family. Thioureylene compounds include **propylthiouracil (PTU)** and **methimazole** . In Great Britain and Europe, **carbimazole**, a derivative of methimazole is most often used. The active ingredient in both compounds is the same.

Other ATDs include aniline derivatives such as **sulfonamides** and polyhdric phenols such as **resorcinol**.
Other compounds with antithyroid properties include **lithium salts**, high concentrations of **saturated potassium iodine**, **thiouracil derivatives**, **oral imaging contrast dyes**, some anticonvulsant drugs and iodide transport (ionic) inhibitors such as **perchlorate**.

Thioureylenes

Antithyroid drugs inhibit the formation of thyroid hormones by interfering with the incorporation of iodine into tyroyl resideus of thyroglobulin.

They also inhibit the coupling of these iodotyrosyl residues to form iodothyrosines. This implies that they interfere with the oxidation of iodide ion and iodotyrosyl groups.

Drugs inhibit the peroxidase enzyme, thereby preventing oxidation of iodide or iodotyrosyl groups to the required active state: antithyroid drugs bind to and inactivate the peroxidase only when the heme of the enzyme is in the oxidized state.

Antithyroid Compounds

PROCESS AFFECTED	EXAMPLES OF INHIBITORS
Active transport of iodide	Complex anions: perchlorate, fluoborate, pertechnetate, thiocyanate
Iodination of thyroglobulin	Thionamides: propylthiouracil, methimazole, carbimazole
	Thiocyanate
	Aniline derivatives; sulfonamides
	Iodide
Coupling reaction	Thionamides
	Sulfonamides
	?All other inhibitors of iodination
Hormone release	Lithium salts
	Iodide
Iodotyrosine deiodination	Nitrotyrosines
Peripheral iodothyronine deiodination	Thiouracil derivatives
	Oral cholecystographic agents
	Amiodarone
Hormone excretion/ inactivation	Inducers of hepatic drug-metabolizing enzymes: phenobarbital, rifampin, carbamazepine, phenytoin
Hormone action	Thyroxine analogs
	Amiodarone
	?Phenytoin

Ionic Inhibitors

The term designates the substances that interfere with the concentration of iodide by the thyroid gland.
The effective agents are themeselves anions that in some ways resemble iodide; they are all monovalent, hydrated anions of a size similar to that of iodide.
The most studied example, thiocyanate, differs from the others qualitatively; it is not concentrated by the gland, and in large amounts it inhibits the organification of iodine.
Perchlorate in 10 times as active as thiocyanate, but it causes fatal aplastic anemia when given in excessive amounts. Fluoborate is effective as perchlorate.
Lithium decreases secretion of T4 and T3.

Commonly Used Iodine-Containing Drugs

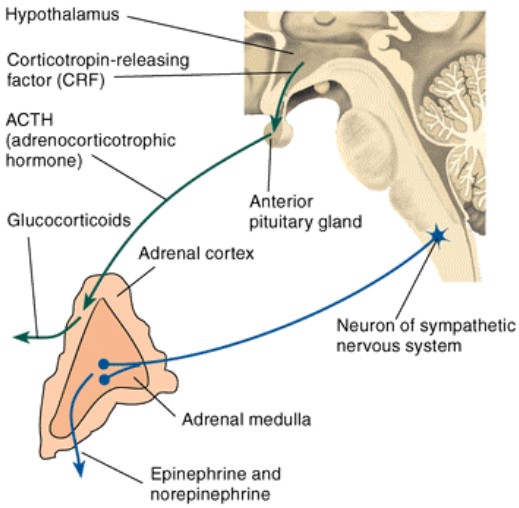
DRUGS	IODINE CONTENT
Oral or local	
Amiodarone	75 mg/tablet
Calcium iodide (*e.g.*, CALCIDRINE SYRUP)	26 mg/ml
Iodoquinol (diiodohydroxyquin)	134–416 mg/tablet
Echothiophate iodide ophthalmic solution	5–41 μg/drop
Hydriodic acid syrup	13–15 mg/ml
Iodochlohydroxyquin	104 mg/tablet
Iodine-containing vitamins	0.15 mg/tablet
Iodinated glycerol	15 mg/tablet
Idoxuridine ophthalmic solution	18 μg/drop
Kelp	0.15 mg/tablet
Potassium iodide (*e.g.*, QUADRINAL)	145 mg/tablet
Lugol's solution	6.3 mg/drop
Niacinamide hydroiodide + potassium iodide (*e.g.*, IODO-NIACIN)	115 mg/tablet
PONARIS nasal emollient	5 mg/0.8 ml
Saturated solution of potassium iodide	38 mg/drop
Parenteral preparations	
Sodium iodide, 10% solution	85 mg/ml
Topical antiseptics	
Iodoquinol (diiodohydroxyquin) cream	6 mg/g
Iodine tincture	40 mg/ml
Iodochlorhydroxyquin cream	12 mg/g
Iodoform gauze	4.8 mg/100 mg gauze
Povidone iodine	10 mg/ml
Radiology contrast agents	
Diatrizoate meglumine sodium	370 mg/ml
Propyliodone	340 mg/ml
Iopanoic acid	333 mg/tablet
Ipodate	308 mg/capsule
Iothalamate	480 mg/ml
Metrizamide	483 mg/ml before dilution
Iohexol	463 mg/ml

SOURCE: Adapted from Braverman, 1994.

Adrenocorticotropic hormone

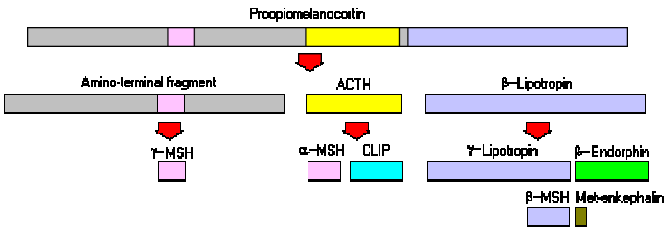
Adrenocorticotropic hormone, as its name implies, stimulates the adrenal cortex. More specifically, it stimulates secretion of glucocorticoids such as cortisol, and has little control over secretion of aldosterone, the other major steroid hormone from the adrenal cortex. Another name for ACTH is *corticotropin*.

► **Control of the Secretion of Glucocorticoids by the Adrenal Cortex and of Catecholamines by the Adrenal Medulla**



ACTH is secreted from the anterior pituitary in response to corticotropin-releasing hormone from the hypothalamus. corticotropin-releasing hormone is secreted in response to many types of stress, which makes sense in view of the "stress management" functions of glucocorticoids. Corticotropin-releasing hormone itself is inhibited by glucocorticoids, making it part of a classical negative feedback loop.

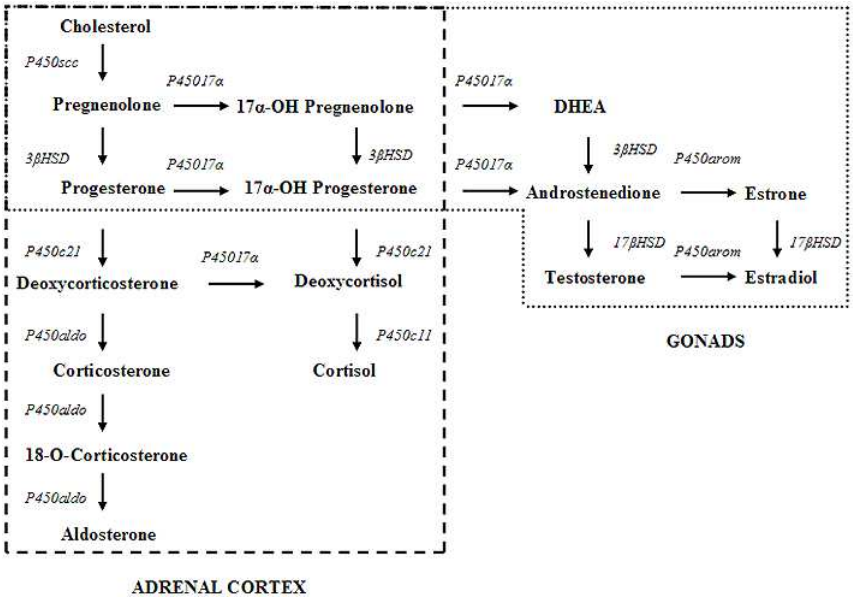
Within the pituitary gland, ACTH is produced in a process that also generates several other hormones. A large precursor protein named proopiomelanocortin (POMC, "Big Mama") is synthesized and proteolytically chopped into several fragments as depicted below. Not all of the cleavages occur in all species and some occur only in the intermediate lobe of the pituitary.



The major attributes of the hormones other than ACTH that are produced in this process are summarized as follows:

- **Lipotropin: Originally described as having weak lipolytic effects, its major importance is as the precursor to beta-endorphin.**
- **Beta-endorphin and Met-enkephalin: Opioid peptides with pain-alleviation and euphoric effects.**
- **Melanocyte-stimulating hormone (MSH): Known to control melanin pigmentation in the skin of most vertebrates.**

The adrenal cortex synthesizes two classes of steroids:
the corticosteroids (*glucocosrticoids* and *mineralcorticoids*), which have 21 carbon atoms, and the androgens, which have 19.



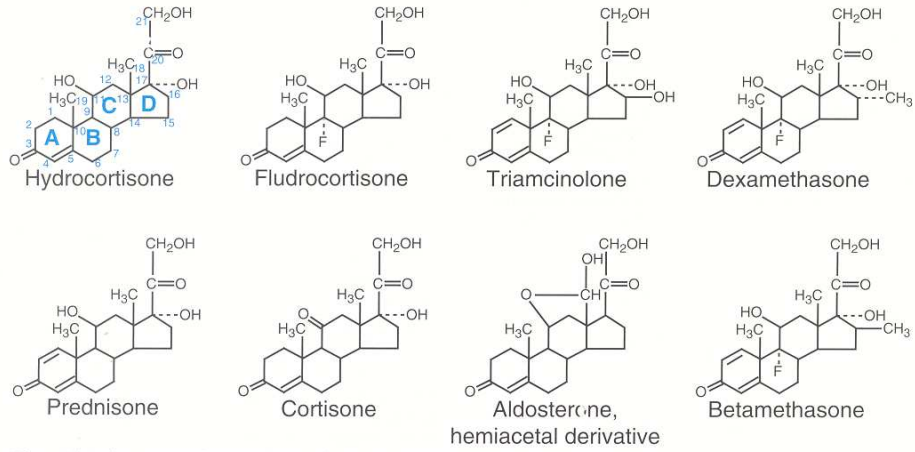


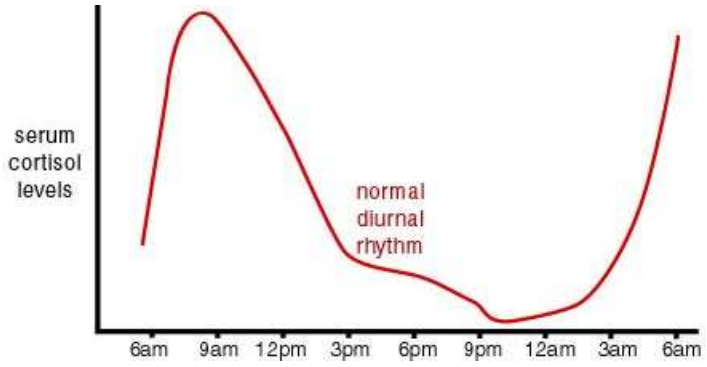
Figure 59–7. Structure and nomenclature of corticosteroid products and selected synthetic derivatives.

The structure of hydrocortisone is represented in two dimensions. It should be noted that the steroid ring system is not completely planar and that the orientation of the groups attached to the steroid rings is an important determinant of the biological activity. The methyl groups at C 18 and C 19 and the hydroxyl group at C 11 project upward (*forward* in the two-dimensional representation and shown by a solid line connecting the atoms) and are designated β. The hydroxyl at C 17 projects below the plane (*behind* in the two-dimensional representation, and represented by the dashed line connecting the atoms) and is designated α.

Adrenal cortex	**Cortisol**	**Most tissues**	**Involved in a huge array of physiological functions including blood pressure regulation, immune system functioning and blood glucose regulation.**
	Aldosterone	**Kidney**	**Acts to maintain blood pressure by causing salt and water retention.**
	Androgens	**Most tissues**	**Steroid hormones that promote development of male characteristics. Physiological function unclear.**
Adrenal medulla	**Adrenaline and noradrenaline (the catecholamines)**	**Most tissues**	**Involved in many physiological systems including blood pressure regulation, gastrointestinal movement and patency of the airways.**

Normal Daily Production Rates and Circulating Levels of the Predominant Corticosteroids

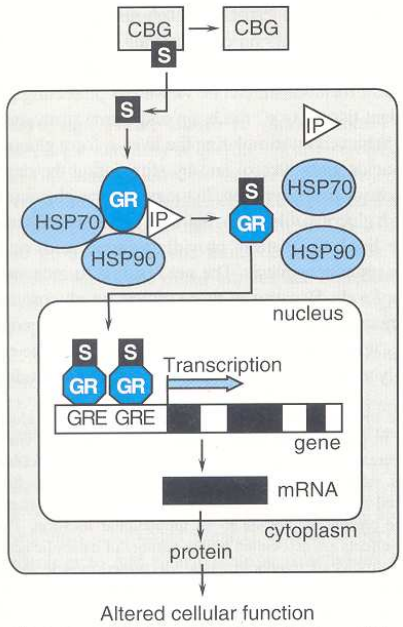
	CORTISOL	ALDOSTERONE
Rate of secretion under optimal conditions	10 mg/day	0.125 mg/day
Concentration in peripheral plasma:		
8 A.M.	16 μg/100 ml	0.01 μg/100 ml
4 P.M.	4 μg/100 ml	0.01 μg/100 ml



Relative Potencies and Equivalent Doses of Representative Corticosteroids

COMPOUND	ANTI-INFLAMMATORY POTENCY	Na^+-RETAINING POTENCY	DURATION OF ACTION*	EQUIVALENT DOSE†, mg
Cortisol	1	1	S	20
Cortisone	0.8	0.8	S	25
Fludrocortisone	10	125	S	‡
Prednisone	4	0.8	I	5
Prednisolone	4	0.8	I	5
6α-methylprednisolone	5	0.5	I	4
Triamcinolone	5	0	I	4
Betamethasone	25	0	L	0.75
Dexamethasone	25	0	L	0.75

* S, short (*i.e.*, 8–12 hour biological half-life); I, intermediate (*i.e.*, 12–36 hour biological half-life); L, long (*i.e.* 36–72 hour biological half-life).
† These dose relationships apply only to oral or intravenous administration, as glucocorticoid potencies may differ greatly following intramuscular or intraarticular administration.
‡ This agent is not used for glucocorticoid effects.



The molecular pathway by which glucocorticoid steroids (labeled S) enter cells and interact with the glucocorticoid receptor to change the GR conformation (indicated by the change in shape of the GR), induce GR nuclear translocation, and activate transcription of target genes is shown. The example shown is one in which glucocorticoids activate expression of target genes; the expression of certain genes, including pro-opiomelanocortin (POMC) expression by corticotropes, is inhibited by glucocorticoid treatment. CBG, corticosteroid binding globulin; GR, glucocorticoid receptor; S, steroid hormone; HSP90 the 90-kDa heat shock protein; HSP70, the 70-kDa heat shock protein; IP, the 56-kDa immunophilin; GRE, glucocorticoid-response elements in the DNA that recognize and bind the GR, thus providing specificity to induction of gene transcription by glucocorticoids. Within the gene are introns (unshaded) and exons (shaded); transcription and mRNA processing leads to splicing and removal of introns and assembly of exons into mRNA.

Figure 59–5. Intracellular mechanism of action of the glucocorticoid receptor.

Effects

Carbohydrate and Protein metabolism

Glucocorticoids protect glucose-dependent tissues (brain and heart) from starvation. This is achieved by stimulating the liver to form glucose from amino acids and glycerol and by stimulating the deposition of glucose as liver glycogen.

In the periphery, glucocorticoids diminish glucose utilization, increase protein breakdown, and activate lipolysis, thereby providing amino acids and glycerol for gluconeogenesis. The net result is to increase blood glucose levels.

Effects

Lipid metabolism

Glucocorticoids have two effects firmly established. The first is the dramatic redistribution of body fat that occurs in settings of hypercorticism such as Cushing's syndrome. The other is the permissive facilitation of the effect of other agents, such as growth hormone and β- adrenergic receptor agonists, in inducing lipolysis in adipocytes, with a resultant increase in free fatty acids following glucocorticoid administration.

Effects

Electrolyte and Water balance

Aldosterone is by far the most potent naturally occurring corticosteroid with respect to fluid and electrolyte balance. Mineralcorticoids act on the distal tubules and collecting ducts of the kidney to enhance reabsorption of Na^+ from tubular fluid; they also increase the urinary excretion of both K^+ or H^+, although the molecular mechanism of monovalent cation handling is not a simple 1:1 exchange of cations in the renale tubule.

Glucocorticoids also exert effects on fluid and electrolyte balance, largely due to to permissive effects on tubular function and actions that maintain gloerular filtration rate, having a permissive role in the renal excretion of free water and Ca^{2+}.

Effects

Cardiovascular system

The most striking effects of corticosteroids result from mineralcorticoid-induced changes in renal Na^+ excretion as is evident in primary aldosteronism. The resultant hypertension can lead to a diverse group od adverse effects on the cardiovascular system, icluding increased atherosclerosis, cerebral hemorhage, stroke, and hypertensive cardiomyoppathy.

The second major action on the CVS is to enhance vascular reactivity to other vasoactive substances. Hypoadrenalism generally is associated with hypotension and reduced response to vasoconstrictors such as norepinephrine and angiotensin II.

Effects

Skeletal muscle

Permissive concentrations of corticosteroids are required for the normal function of skeletal muscle; diminished work capacity is a prominent sign of adrenocortical insufficiency.

Effects

Central Nervous System

Glucocorticoids exert a number of indirect effects on CNS, through maintenance of blood pressure, plasma glucose concentrations, and electrolyte concentrations. Improved awareness of the distribution and function of steroid receptors in the brain has led to increasing recognition of direct effects of corticosteroids on the CNS, including effects on mood, behavior, and brain excitability.

Effects

Formed elements of blood

Glucocorticoids exert minor effects on hemoglobin and erythrocyte content of blood, as evidenced by the frequent occurrence of plycythemia in Cushing's syndrome and of normochromic, normocytic anemia in Addison's disease. More profound effects are seen in the setting of autoimmune hemolytic anemia, where the immunosuppressive effects of glucocorticoids can diminish the self-destruction of erythrocytes. Corticosteroids also affect circulating white blood cells. The administration of glucocorticoids leads to a decreased number of circulating lymphocytes, eosinophils, monocytes, and basophils.

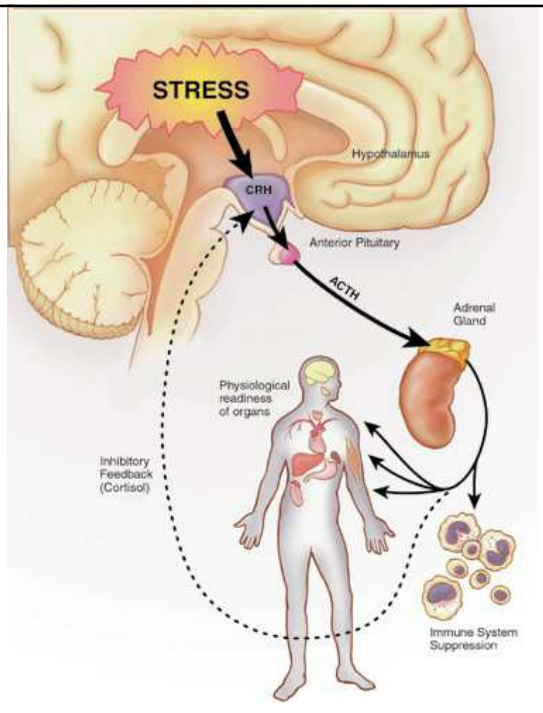
Effects

Anti-inflammatory and immunosuppressive actions

In addition to their effects on lymphocyte number, corticosteroids profoundly alter the immune responses of lymphocytes. These effects are an important facet of the anti-inflammatory and immunosuppressive actions of the glucocorticoids. They can prevent or suppress inflammation in response to multiple inciting events, including radiant, mechanical, chemical, infectious, and immunological stimuli.

Effects of Glucocorticoids on Components of Inflammatory/Immune Responses

CELL TYPE	FACTOR	COMMENTS
Macrophages and monocytes	Arachidonic acid and its metabolites (prostaglandins and leukotrienes)	Inhibited in part by glucocorticoid induction of a protein (lipocortin) that inhibits phospholipase A2.
	Cytokines, including: Interleukin (IL)-1, IL-6, and TNF-α	Production and release are blocked. The cytokines exert multiple effects on inflammation (*e.g.*, activation of T cells, stimulation of fibroblast proliferation.
	Acute phase reactants	These include the third component of complement.
Endothelial cells	Endothelial leukocyte adhesion molecule-1 (ELAM-1) and intracellular adhesion molecule-1 (ICAM-1)	ELAM-1 and ICAM-1 are intracellular adhesion molecules that are critical for leukocyte localization.
	Acute phase reactants	Same as above, for macrophages and monocytes.
	Cytokines (*e.g.*, IL-1)	Same as above, for macrophages and monocytes.
	Arachidonic acid derivatives	Same as above, for macrophages and monocytes.
Basophils	Histamine Leukotriene C4	IgE-dependent release inhibited by glucocorticoids.
Fibroblasts	Arachidonic acid metabolites	Same as above for macrophages and monocytes. Glucocorticoids also suppress growth factor-induced DNA synthesis and fibroblast proliferation.
Lymphocytes	Cytokines (IL-1, IL-2, IL-3, IL-6, TNF-α, GM-CSF, interferon gamma)	Same as above for macrophages and monocytes.



Toxicity of Adrenocortical Steroids

Two categories of toxic effects result from the therapeutic use of corticosteroids: those resulting from withdrawal of steroid therapy (iatrogenic acute adrenal insufficiency in long-term treatment) and those resulting from continued use of supraphysiological doses (hypokalemic alkalosis, edema, hypertension, susceptibility to infection or reactivation of latent illness, risk of peptic ulcers, myopathy, behavioral changes, cataracts, osteoporosis, osteonecrosis, growth retardation).

Therapeutic Uses

With the exception of replacement therapy in deficiency states, the use of glucocrticoids largely is empirical.
Replacement therapy (acute adrenal insufficiency, chronic primary adrenal insuffciency, secondary adrenal insufficency, congenital adrenal hyperplasia); nonendocrine disease (rheumatic disorders, allergic diseases, bronchial asthma, infectious diseases, ocular, renal, skin, hepatic, gastrointestinal disease, malignancies, cerebral edema, sarcoidosis, thrombocytopenia, autoimmune destruction of erythrocytes, organ transplantation, stroke and spinal cord injury).

Inhibitors of the biosynthesis and action of adrenocortical steroids

Mitotane (o,p'-DDD) (chemically similar to insecticides DDT)
Metyrapone
Aminoglutethimide } (CYP450 inhibitors)
Ketoconazole
Trilostane (inhibitor of 3β-hydroxisteroid dehydrogenase)
Metyrapone (inhibitor of $CYP450_{11\beta}$ 11β– hydroxylation)

Mifepristone, progesterone receptor antagonist, acts as antiglucocorticoid agent. At higher doses, it inhibits the glucocorticoid receptor, blocking feedback regulation of the HPA axis and increasing endogenous ACTH and cortisol levels.

Luteinizing hormone (LH)

Follicle-stimulating hormone (FSH)

Luteinizing hormone (LH) and follicle-stimulating hormone (FSH) are called gonadotropins because stimulate the gonads - in males, the testes, and in females, the ovaries. They are not necessary for life, but are essential for reproduction. These two hormones are secreted from cells in the anterior pituitary called *gonadotrophs*. Most gonadotrophs secrete only LH or FSH, but some appear to secrete both hormones.

LH and FSH are large glycoproteins composed of alpha and beta subunits. The alpha subunit is identical in all three of these anterior pituitary hormones, while the beta subunit is unique and endows each hormone with the ability to bind its own receptor.

Luteinizing Hormone

In both sexes, LH stimulates secretion of sex steroids from the gonads. In the testes, LH binds to receptors on Leydig cells, stimulating synthesis and secretion of testosterone. Theca cells in the ovary respond to LH stimulation by secretion of testosterone, which is converted into estrogen by adjacent granulosa cells.

In females, ovulation of mature follicles on the ovary is induced by a large burst of LH secretion known as the preovulatory LH surge. Residual cells within ovulated follicles proliferate to form corpora lutea, which secrete the steroid hormones progesterone and estradiol. Progesterone is necessary for maintenance of pregnancy, and, in most mammals, LH is required for continued development and function of corpora lutea. The name luteinizing hormone derives from this effect of inducing luteinization of ovarian follicles.

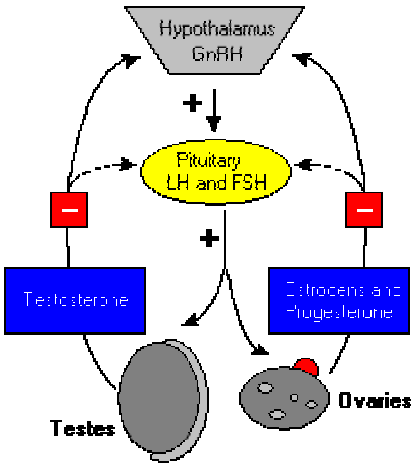
Follicle-Stimulating Hormone

As its name implies, FSH stimulates the maturation of ovarian follicles. Administration of FSH to humans and animals induces "superovulation", or development of more than the usual number of mature follicles and hence, an increased number of mature gametes.
FSH is also critical for sperm production. It supports the function of Sertoli cells, which in turn support many aspects of sperm cell maturation.

Control of Gonadotropin Secretion

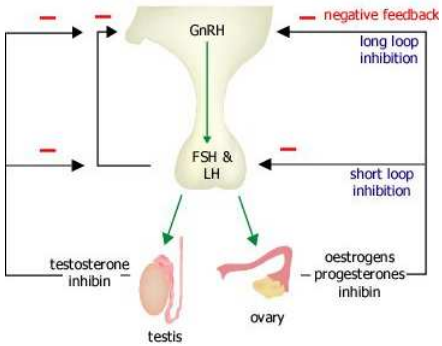
The principle regulator of LH and FSH secretion is gonadotropin-releasing hormone or GnRH (also known as LH-releasing hormone). GnRH is a ten amino acid peptide that is synthesized and secreted from hypothalamic neurons and binds to receptors on gonadotrophs.

GnRH stimultes secretion of LH, which in turn stimulates gonadal secretion of the sex steroids testosterone, estrogen and progesterone. **In a classical negative feedback loop, sex steroids inhibit secretion of GnRH and also appear to have direct negative effects on gonadotrophs.**



This regulatory loop leads to pulsatile secretion of LH and, to a much lesser extent, FSH. The number of pulses of GnRH and LH varies from a few per day to one or more per hour. In females, pulse frequency is clearly related to stage of the cycle.

Numerous hormones influence GnRH secretion, and positive and negative control over GnRH and gonadotropin secretion is actually considerably more complex than depicted in the figure. For example, the gonads secrete at least two additional hormones - inhibin and activin - which selectively inhibit and activate FSH secretion from the pituitary.



Ovary	**Oestrogens**	Breast, Uterus, Internal and external genitalia	Acts to promote development of female primary and secondary sexual characteristics. Important role in preparing the uterus for implantation of embryo.
	Progesterone	BreastUterus	Affects female sexual characteristics and important in the maintenance of pregnancy.
Testis	**Testosterone**	Sexual organs	Promotes the development of male sexual characteristics including sperm development

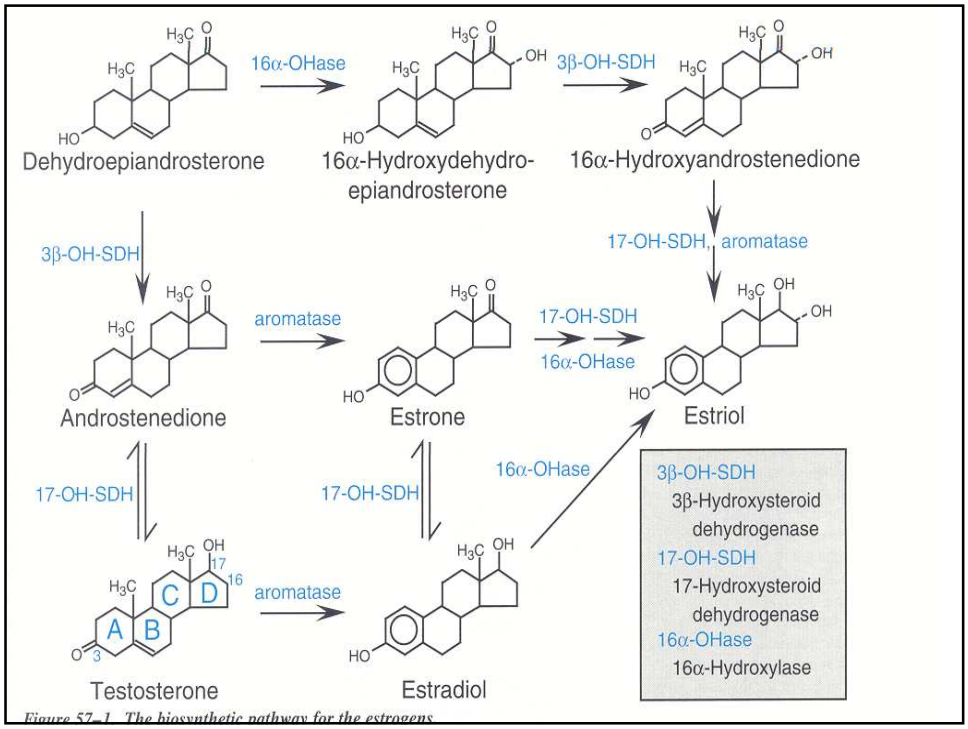


Figure 57–1. The biosynthetic pathway for the estrogens.

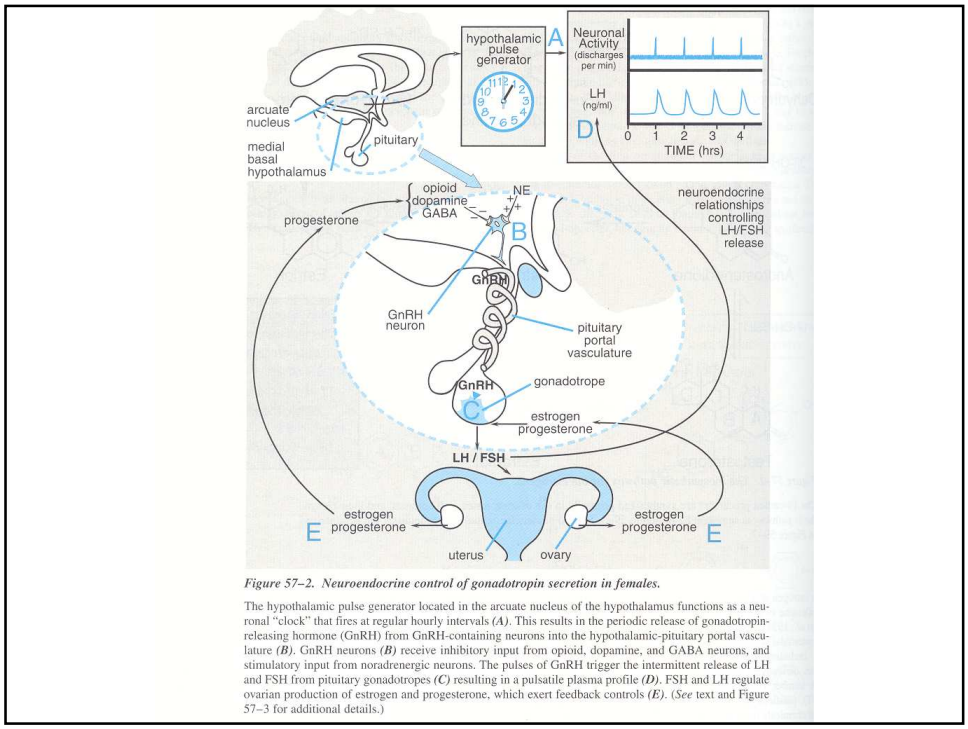
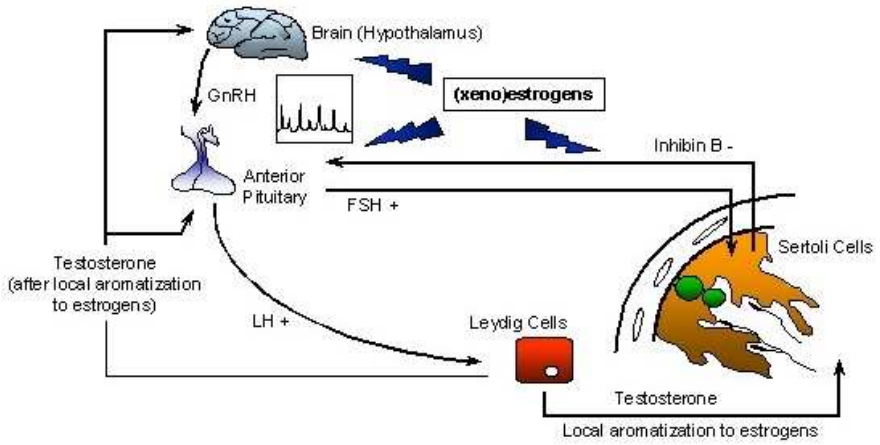


Figure 57–2. Neuroendocrine control of gonadotropin secretion in females.

The hypothalamic pulse generator located in the arcuate nucleus of the hypothalamus functions as a neuronal "clock" that fires at regular hourly intervals ***(A)***. This results in the periodic release of gonadotropin-releasing hormone (GnRH) from GnRH-containing neurons into the hypothalamic-pituitary portal vasculature ***(B)***. GnRH neurons ***(B)*** receive inhibitory input from opioid, dopamine, and GABA neurons, and stimulatory input from noradrenergic neurons. The pulses of GnRH trigger the intermittent release of LH and FSH from pituitary gonadotropes ***(C)*** resulting in a pulsatile plasma profile ***(D)***. FSH and LH regulate ovarian production of estrogen and progesterone, which exert feedback controls ***(E)***. (*See* text and Figure 57–3 for additional details.)



Disease States

Diminished secretion of LH or FSH can result in failure of gonadal function (hypogonadism). This condition is typically manifest in males as failure in production of normal numbers of sperm. In females, cessation of reproductive cycles is commonly observed.
Elevated blood levels of gonadotropins usually reflect lack of steroid negative feedback. Removal of the gonads from either males or females, as is commonly done to animals, leads to persistent elevation in LH and FSH. In humans, excessive secretion of FSH and/or LH most commonly the result of gonadal failure or pituitary tumors. In general, elevated levels of gonadotropins per se have no biological effect.

Pharmacologic Manipulation of Gonadotropin Secretion

Normal patterns of gonadotropin secretion are absolutely required for reproduction, and interfering particularly with LH secretion is a widely-used strategy for contraception. Oral contraceptive pills contain a progestin (progesterone-mimicking compound), usually combined with an estrogen. As discussed above, progesterone and estrogen inhibit LH secretion, and oral contraceptives are effective because they inhibit the LH surge that induces ovulation.
Another route to suppressing gonadotropin secretion is to block the GnRH receptor. GnRH receptor antagonists have potent contraceptive effects in both males and females, but have not been widely deployed for that purpose.

Gonadotropin-releasing hormone (GnRH) analogues

Buserelin – Goserelin - Leuprorelin acetate – Nafarelin - Triptorelin

Administration of **gonadorelin analogues** produces an initial phase of stimulation; continued administration is followed by down-regulation of gonadotropin-releasing hormone receptors, thereby reducing the release of gonadotrophins (follicle stimulating hormone and luteinising hormone) which in turn leads to inhibition of androgen and estrogen production. Gonadorelin analogues are used in the treatment of **endometriosis, infertility, anaemia due to uterine fibroids (together with iron supplementation), breast cancer , prostate cancer , and before intra-uterine surgery**. Use of leuprorelin and triptorelin for 3 to 4 months before surgery reduces the uterine volume, fibroid size and associated bleeding. For women undergoing hysterectomy or myomectomy, a vaginal procedure is made more feasible following the use of a gonadorelin analogue.

Drugs affecting gonadotrophins

Danazol is a synthetic steroid derived from ethisterone. It is antiestrogenic and weakly androgenic. It inhibits pituitary gonadotrophins; it combines androgenic activity with antioestrogenic and antiprogestogenic activity. It is used in the treatment of **endometriosis** and has also been used for **mammary dysplasia** and **gynaecomastia** where other measures have proved unsatisfactory; it has been used for **menorrhagia** and other menstrual disorders but in view of its side effects, treatment with other drugs may be preferable.
Gestrinone (GnRH-antagonist) has general actions similar to those of danazol and is indicated for the treatment of **endometriosis**.
Cetrorelix and **ganirelix** are luteinising hormone releasing hormone antagonists and inhibit the releasing of gonadotrophins. They are used in **assisted reproduction**.

Estrogens

Estrogens affect many tissues and have many metabolic actions (positive effects on bone mass; lipid metabolism; glucose and insulin levels; increase of hormone binding proteins; effects on clotting cascade). They act primarily by regulating gene expression. These lipophilic hormones diffuse passively through cellular membranes and bind to a receptor present in the nucleus that is highly homologous with receptor for the other steroid hormones, thyroid hormine, vitamin D, and retinoids.

The reptor interacts with specific nucleotide sequences termed estrogen response elements (EREs) present in target genes, and this interaction increases, or in some cases decreases, transcription of hormone-regulated genes.

They have role in the neuroendocrine control of the menstrual cycle. They have developmental actions at puberty in girls and are responsible for the secondary sexual characteristics of females.

Therapeutic Uses

- Contraceptive use
- Postmenopausal Hormone Replacement Therapy
- Failure of Ovarian Development

Concern about carcinogenic actions

About 1980, epidemiological studies indicated that estrogen replacement therapy was associated with large increase in the incidence of endometrial carcinoma, presumably due in part to the continuous stimulation of endometrial hyperplasia by **unopposed estrogens**.
This realization led to the use of HRT that includes both an estrogen, for its beneficial effects, and a progestin to limit endometrial hyperplasia.

Progestins

The progestins include the naturally occurring hormone progesterone, which rarely is used therapeutically, and a number of frequently used synthetic compounds that have progestational activity.

They are quite lipophilic and diffuse freely into cells, where they bind to the progesterone receptor, a ligand-activated nuclear transcription factor that interacts with progesterone response element in target genes to regulate thier expression.

Progesterone has neuroendocrine actions, producing several physiological effects in the luteal phase of the cycle. It decreases estrogen-driven endometrial proliferation and leads to the development of a secretory endometrium. It influences the endocervical glands activity. Acting with estrogen, it brings about a proliferation of the acini of mammary gland. It has also effects on termoregulation and on lipid and glucose metabolism.

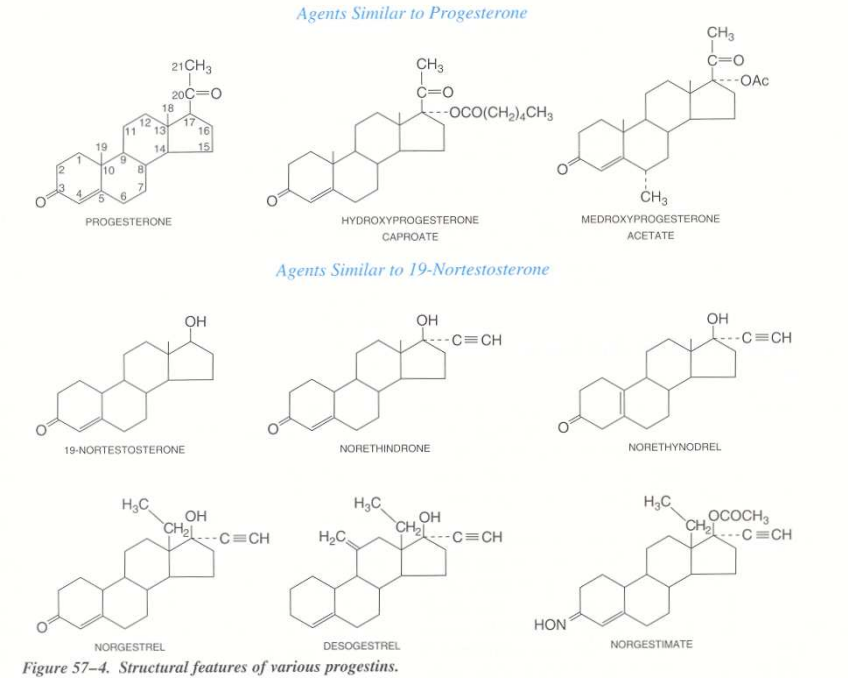


Figure 57–4. Structural features of various progestins.

Therapeutic Uses

The two most frequent uses of progestins are for contraception, either alone or with estradiol or mestranol in oral contraceptives, and combined with estrogen for hormone replacement therapy of postmenopausal women.
Progestins also are used in several settings for ovarian suppression, e.g., dysmenorrhea, endometriosis, hirsutism, and uterine bleeding. Among the oral progestins used besides medroxyprogesterone acetate in these settings are norethindrone and norethindrone acetate.

Estrogen-Progestin Contraceptives

Therapeutic Use

- Oral contraceptive that is taken every day
  - **Monophasic contraceptives: contain the same amount of progestin throughout cycle.**
  - **Biphasic and triphasic contraceptives: the amount of progestin increases after the first third of the cycle to mimic the natural estrogen:progesterone ratio changes that occur in the menstrual cycle.**
  - Pills containing no hormones are given for 7 days to allow the uterine lining to disintegrate and menstruation to occur.
- High-doses of birth control pills can be used up to 72 hours after intercourse to prevent implantation

Mechanism of Action

- Estrogens and progestins inhibit ovulation by inhibiting the release of FSH and LH.
  - Without FSH, the follicle will not grow and release estradiol.
  - Without the LH surge, ovulation will not occur.
- Progestins make the lining of the uterus less hospitable to implantation of the fertilized egg. They also thicken the cervical mucus so that it acts as a barrier to sperm.

Adverse Effects

- **Thromboembolytic disease (deep vein thrombosis, pulmonary embolism, stroke) is increased up to 6-fold in oral contraceptive users. The risk is much higher in smokers than nonsmokers, and also increases with age.**
  - Women with heart disease should not use oral contraceptives.
  - Smokers over age 35 should not use oral contraceptives.
- **Hypertension may occur - blood pressure should be monitored.**
- Oral contraceptives can stimulate growth of **pre-existing reproductive system cancers (e.g. breast cancer). Women who have or have had these cancers should not take oral contraceptives.**
- Oral contraceptives cause **birth defects and should not be taken by someone who thinks she is pregnant!**
- Oral contraceptives can worsen liver and gallbladder disease.
- Oral contraceptives interact with many drugs, some of which make the contraceptives potentially ineffective and pregnancy can occur!
- Oral contraceptives may increase the risk of a woman getting cervical cancer, probably do not increase the risk of breast cancer (if given before menopause), and decrease the risk of endometrial and ovarian cancer.
- Non-life-threatening side effects that usually go away after several months or can be decreased by changing the contraceptive dose/formulation include: cramps, breakthrough bleeding, nausea/vomiting, dizziness, fluid retention, weight gain, loss of appetite, stimulation of appetite, breast enlargement, changes in sex drive, headaches, and fatigue.

Progestin-Only Contraceptives

Therapeutic Use

- Long-term contraceptives:
  - Injections (Depo-Provera® - lasts months)
  - Intrauterine devices (Mirena® IUD - lasts 5 years): T-shaped devices, implanted in uterus, which slowly release progesterone.
- Emergency contraception after intercourse (Plan B®)
- Progestin "mini-pills" are used to treat **endometriosis (overgrowth of the lining of the uterus) but are not routinely used for contraception because they are less effective than estrogen-progestin contraceptives.**
  - An exception to this is that progestin mini-pills are sometimes used by women who are breastfeeding because they do not decrease milk supply as much as the estrogen-progestin contraceptives do.

Mechanism of Action

- Injected and oral progestins act primarily by suppressing the LH surge that stimulates ovulation. They also make the lining of the uterus less hospitable to implantation and thicken the cervical mucus.
  - This is the same mechanism that progestins have in the estrogen-progestin oral contraceptives!
  - The amount of progestin in the mini-pill is not high enough to consistently inhibit ovulation. This is why it is less effective!
- Progestin-containing IUDs have mainly local effects on the lining of the uterus - they make the lining of the uterus less hospitable to implantation and thicken the cervical mucus. They inhibit ovulation in only a small percentage of women.

Adverse Effects

- For oral and injected progestins, the adverse effects are similar to those of combined estrogen-progestin oral contraceptives:
  - **Elevated risk of thromboembolytic disease**
  - Stimulation of **growth of pre-existing reproductive system tumors**
  - **Birth defects - do not use if pregnancy is suspected**
  - Menstrual irregularity
  - Many other adverse effects are similar to estrgen-progestin contraceptives. Too many to list here.
- For the IUD, the major side effects are localized at the uterus:
  - Increased risk of **uterine infection**
  - Increased risk of **ectopic pregnancy** **(fertilized egg implants outside the uterus)**

Antiestrogens

SERMs (Selective Estrogen Receptor Modulators): Tamoxifen and Clomiphene are used primarily for the treatment of breast cancer and female infertility, respectively. These agents are used therapeutically for their antiestrogenic actions, but they can produce estrogenic as well as antiestrogenic effects. Clomiphene is used for ovulation induction. Both agents competitively block estradiol binding to its receptor.Toremifene also is used for its effects on breast tissue. Raloxifene is used in the treatment of postmenopausal osteoporosis.

Estrogen synthesis inhibitors can be used to decrease the effects of endogenous estrogens by blocking thier synthesis. Gonadotropin-releasing hormone (GnRH) or the use of long-acting GnRH agonists prevent ovarian synthesis of estrogens, but not the peripheral synthesis of estrogens from adrenal androgens.

Aromatase Inhibitors (AIs)

Another approach to anti-estrogen therapy is to lower the amount of estrogen being produced by the body. **Aromatase:** An enzyme involved in the production of estrogen that acts by catalyzing the conversion of testosterone to estradiol. Aromatase is located in estrogen-producing cells in the adrenal glands, ovaries, placenta, testicles, adipose (fat) tissue, and brain.

AIs do not block estrogen production by the ovaries, but they can block other tissues from making this hormone. Currently, three AIs are approved by the U.S. Food and Drug Administration: anastrazole, exemestane, and letrozole, used primarily for post-menopausal women with metastatic breast cancer (cancer that has spread beyond the breast).

Antiprogestins

Mifepristone, derivate of the 19-nor progestin norethindrone, is a potent competitive antagonist of both progesterone and glucocorticoid binding to thier respective receptors.

In the presence of progestins, mifepristone acts as a competitive receptor antagonist, but it is a partial agonist with weak activity when present alone.

Post-Implantation Contraceptives

Mifepristone (RU486)

Therapeutic Use

- Used as a post-implantation contraceptive "abortion pill" in early pregnancy (up to 7 weeks gestation)

Mechanism of Action

- Acts as an antagonist of progesterone receptors.
- Since progesterone stimulates development of the uterine lining, blocking progesterone's effect causes breakdown of uterine lining and detachment of implanted embryo or fetus.
- Another drug is given 24 hours after mifepristone to stimulate uterine contractions to expel the fetus.

Adverse Effects

- **GI upset: diarrhea, nausea, vomiting,**
- **Uterine cramping and pain**
- **Heavy uterine bleeding for 1 -2 weeks; uterine hemmhorage occurs in 5%**
- Mifepristone can also cause headache, dizziness, and fatigue.

Androgens

Testosterone is converted by steroid 5α-reductases in dihydrotestosterone, the active form of the hormone.

The enzyme is located largely in nongenital skin and liver, and is present principally in the urogenital tract of the male and in the genital skin of both sexes.

Testosterone and dihydrotestosterone binds to an intracellualr protein receptor, and the hormone-receptor complex is attached in the nucleus to specific hormone regulatory elements on the chromosomes and acts to increase the synthesis of specific RNAs and proteins.

Therapeutic Uses

- **Hypogonadism**
- **Nitrogen balance and muscle development**
- **Stimulation of Erythropoiesis**
- **Hereditary Angioneurotic Edema (low levels or lak of the first component of complement)**

Antiandrogens

Inhibitors of Androgen Synthesis

Gonadotropin-releasing hormone (GnRH) or agonists such as leuprolide or gonadorelin.
Antifungal agents of the imidazole class inhibit CYP450 enzymes involved in steroid hormone biosynthesis.
Spironolactone, an aldosterone antagonist, acts as a weak inhibitor of the binding of androgen to the androgen receptor but primarily inhibits androgen biosynthesis. It is used in treatment of female hirsutism.

5α-reductases Inhibitors

Finasteride preferentially blocks enzyme 2 but inhibits also enzyme 1. It causes a consistent decrease in prostate size in prostatic hyperplasia patients.

Androgen-receptor Antagonists

Ciproterone Acetate. Progesterone itself is a weak antiandrogen, and in the search for orally active progestogens, Cyproterone acetate was found to be a potent androgen antagonist. It also possesses progestational activity and suppresses the secretion of gonadotropins. The agent competes with dihydrotestosterone for binding to the androgen receptor.

Flutamide. It is a nonsteroidal antiandrogen that is devoid of other hormonal activity; it probably acts after conversion in vivo to 2-hydroxyflutamide, which is a potent competitive inhibitor of binding of dihydrotestosterone to the androgen receptor.

Male Contraceptives

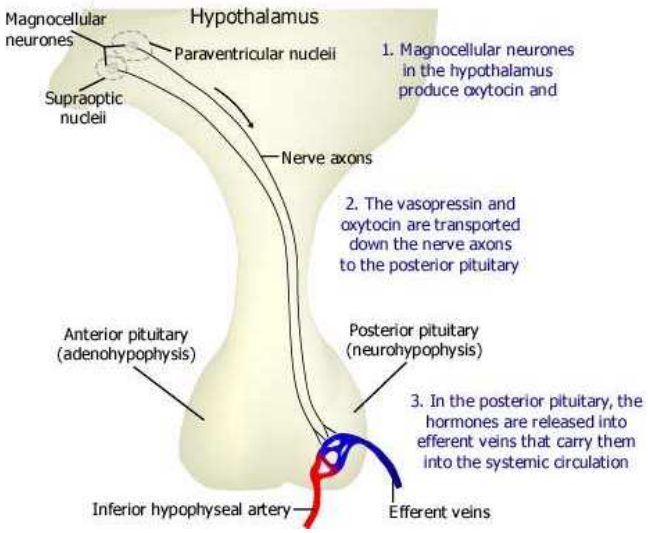
A variety of compounds, i naddition to the antiandrogens discussed above, can inhibit spermatogenesis.

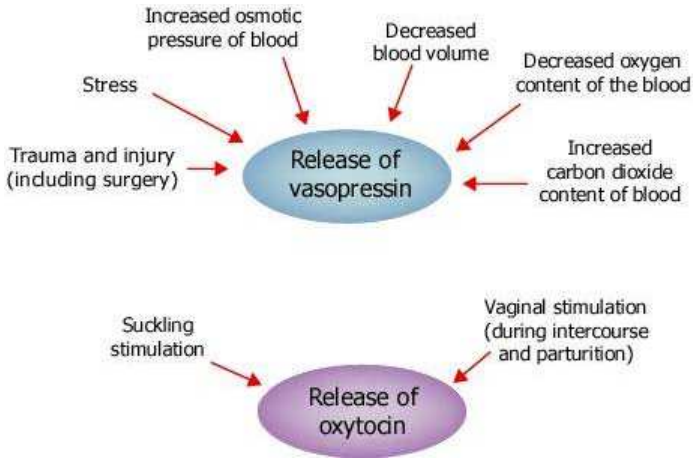
Gossypol, a phenolic compound extracted from the cotton plant, reduces sperm density. It causes hypokalemia and weakness.
Gonadal steroids can suppress secretion of FSH and LH, which are required for spermatogenesis and the syntheis of testosterone by the testes. While estrogens and progestinis are effective contraceptives in men, suppression of testosterone decreases both libido and potency; gynecomastia also may occur.
Potent agonists and antagonists of GnRH can inhibit secretion of gonadotropins and can be administered together with testosterone.

The posterior pituitary

This part of the pituitary secretes two main hormones:

- oxytocin
- vasopressin (also known as anti-diuretic hormone, ADH)


Hypothalamus
Magnocellular neurones
Paraventricular nuclei
Supraoptic nuclei
1. Magnocellular neurones in the hypothalamus produce oxytocin and
Nerve axons
2. The vasopressin and oxytocin are transported down the nerve axons to the posterior pituitary
Anterior pituitary (adenohypophysis)
Posterior pituitary (neurohypophysis)
3. In the posterior pituitary, the hormones are released into efferent veins that carry them into the systemic circulation
Inferior hypophyseal artery
Efferent veins


Increased osmotic pressure of blood
Decreased blood volume
Decreased oxygen content of the blood
Stress
Trauma and injury (including surgery)
Release of vasopressin
Increased carbon dioxide content of blood
Suckling stimulation
Vaginal stimulation (during intercourse and parturition)
Release of oxytocin

Parathyroid glands	Parathyroid hormone (PTH)	Kidney, Bone cells	Increases blood calcium levels in the blood when they are low
	Calcitonin	Kidney, Bone cells	Decreases blood calcium levels when they are high

Stomach	Gastrin	Stomach	Promotes acid secretion in the stomach
	Serotonin (5-HT)	Stomach	Causes constriction of the stomach muscles
Duodenum and jejunum	Secretin	Stomach, Liver	Inhibits secretions from the stomach and increases bile production
	Cholecystokinin (CCK)	Liver, Pancreas	Stimulates release of bile from the gall bladder and causes the pancreas to release digestive enzymes

Pancreas	Insulin	Muscle, fat tissue	Acts to lower blood glucose levels
	Glucagon	Liver	Acts to raise blood glucose levels
	Somatostatin	Pancreas	Acts to inhibit glucagon and insulin release

References:

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