Pharmacology 4th year
Pituitary and Thyroid hormones

The neuroendocrine system, which is 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 much broader range of response time than do nerve impulses, requiring from seconds to days, or longer, to cause a response that may last for weeks or months. The two regulatory systems are closely interrelated. For example, the release of hormones is stimulated or inhibited by the nervous system, and some hormones can stimulate or inhibit nerve impulses.

Hypothalamic 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. These are produced in cell bodies in the hypothalamus, and they reach the cells of the pituitary by the hypophysial portal system . The interaction of the releasing hormones with their receptors results in the activation of genes that promote the synthesis of protein precursors. These are then processed posttranslationally to the hormones and are released into the circulation. 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 (that is, to determine pituitary insufficiency). [Note: The hypothalamus also synthesizes the precursor proteins of the hormones vasopressin and oxytocin, which are transported to the posterior pituitary, where they are stored until released.] Although a number of pituitary hormone preparations are currently used therapeutically for specific hormonal deficiencies Hormones of the anterior and posterior pituitary are administered either intramuscularly (IM), subcutaneously, or intranasally, but not orally, because their peptidyl nature makes them susceptible to destruction by the proteolytic enzymes of the digestive tract.

Adrenocorticotropic hormone (corticotropin):-

Corticotropin-releasing hormone (CRH) is responsible for the synthesis and release of the peptide proopiomelanocortin by the hypothalamus . Adrenocorticotropic hormone (ACTH), or corticotropin is a product of the posttranslational processing of this precursor polypeptide. Other products of proopiomelanocortin are γ-melanocyte stimulating hormone and α-lipotropin, the latter being the precursor of the endorphins.

Normally, 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 evening. Stress stimulates its secretion, whereas cortisol acting via negative feedback suppresses its release.

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 cyclic adenosine monophosphate (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 .

Therapeutic uses: The availability of synthetic adrenocorticosteroids with specific properties has limited the use of corticotropin mainly to serving as a diagnostic tool for differentiating between primary adrenal insufficiency (Addison's disease, associated with adrenal atrophy) and secondary adrenal insufficiency (caused by the inadequate secretion of ACTH by the pituitary). Therapeutic corticotropin preparations are extracts from the anterior pituitaries of domestic animals or synthetic human ACTH. The latter, cosyntropin , is preferred for the diagnosis of adrenal insufficiency.

Adverse effects: Toxicities are similar to those of glucocorticoids. Antibodies can form against ACTH derived from animal sources.

Growth hormone (somatotropin):-

Somatotropin is a large polypeptide that is 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. With increasing age, GH secretion decreases, being accompanied by a decrease in lean muscle mass. Human GH is produced synthetically by recombinant DNA technology. Somatotropin influences a wide variety of biochemical processes; for example, through stimulation of protein synthetic processes, cell proliferation and bone growth are promoted. Increased formation of hydroxyproline from proline boosts cartilage synthesis.

Mechanism of action: Although many physiologic effects of GH are exerted directly at its targets, others are mediated through the somatomedins-insulin-like growth factors I and II (IGF-I and IGF-II). [Note: In acromegaly, IGF-I levels are consistently high, reflecting elevated GH.]

Therapeutic uses: Somatotropin is used in the treatment of GH deficiency in children. A therapeutically equivalent drug, somatrem , contains an extra terminal methionyl residue not found in somatotropin. Although the half-lives of these drugs are short (approximately 25 minutes), they induce the release from the liver of IGF-I (formerly somatomedin C), which is responsible for subsequent GH-like actions.

Growth hormone-inhibiting hormone (somatostatin):-

In the pituitary, somatostatin binds to distinct receptors, SSTR2 and SSTR5, which suppress GH and thyroid-stimulating hormone release. Originally isolated from the hypothalamus, somatostatin is a small polypeptide that is also found in neurons throughout the body as well as in the intestine and pancreas. Somatostatin therefore has a number of actions. For example, it not only inhibits the release of GH but, also, that of insulin, glucagon, and gastrin. **Octreotide** is a synthetic analog of somatostatin. Its half-life is longer than that of the natural compound, and a depot form is also available. The two forms suppress GH and IGF-I for 12 hours and 6 weeks, respectively. They have found use in the treatment of acromegaly caused by hormone-secreting tumors.

Adverse effects of **octreotide** treatment are flatulence, nausea. Gallbladder emptying is delayed, and asymptomatic cholesterol gallstones can occur with long-term treatment. [Note: An analog of human GH , **pegvisomant** , is being employed in the treatment of acromegaly that is refractory to other modes of surgical, radiologic, or pharmacologic intervention. It acts as an antagonist at one of the GH receptors and results in the normalization of IGF-I levels.

Gonadotropin-releasing hormone/luteinizing hormone-releasing hormone

Gonadotropin-releasing hormone (GnRH), also called gonadorelin, is a decapeptide 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, whereas continuous administration inhibits gonadotropin release. GnRH is employed to stimulate gonadal hormone production in hypogonadism. A number of synthetic analogs, such as **leuprolide** , **goserelin** , **nafarelin** , and **histrelin**, act as agonists at GnRH receptors .These are effective in suppressing production of the gonadal hormones and, thus, are effective in the treatment of prostatic cancer, endometriosis, and precocious puberty.

Adverse effects of gonadorelin include hypersensitivity, dermatitis, and headache. In women, the analogs may cause hot flushes and sweating as well as diminished libido, depression, and ovarian cysts. They are contraindicated in pregnancy and breast-feeding. In men, they initially

cause a rise in testosterone that can result in bone pain; hot flushes, edema, and diminished libido also occur.

Gonadotropins: Human menopausal gonadotropin, follicle-stimulating hormone, and human chorionic gonadotropin

The gonadotropins are glycoproteins that are produced in the anterior pituitary. The regulation of gonadal steroid hormones depends on these agents. They find use in the treatment of infertility in men and women. Menotropins (human menopausal gonadotropins, or hMG) are obtained from the urine of menopausal women and contain FSH and luteinizing hormone LH. Chorionic gonadotropin (hCG) is a placental hormone and an LH agonist, to which it is structurally related. It is also excreted in the urine. **Urofollitropin** is FSH obtained from menopausal women and is devoid of LH. **Follitropin** beta is human FSH manufactured by recombinant DNA technology. All of these hormones are injected IM. 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.

Adverse effects include ovarian enlargement and possible hypovolemia. Multiple births are not uncommon. Men may develop gynecomastia.

Prolactin

Prolactin is a peptide hormone similar in structure to GH, and is also secreted by the anterior pituitary. Its secretion is inhibited by dopamine acting at D_2 receptors. Its primary function is to stimulate and maintain lactation. In addition, it decreases sexual drive and reproductive function. There is no preparation available for hypoprolactinemic conditions. On the other hand, hyperprolactinemia, which is associated with galactorrhea and hypogonadism, is usually treated with D_2-receptor agonists, such as **bromocriptine and cabergoline**. They not only act at the D_2 receptor to inhibit prolactin secretion but also cause increased hypothalamic dopamine by decreasing its turnover.

Hormones of the Posterior Pituitary

In contrast to the hormones of the anterior lobe of the pituitary, those of the posterior lobe, vasopressin and oxytocin, are not regulated by releasing hormones. Instead, they are synthesized in the hypothalamus, transported to the posterior pituitary, and released in response to specific physiologic signals, such as high plasma osmolarity or parturition. They are susceptible to proteolytic cleavage and, thus, are given parenterally. Both hormones have very short half-lives.

Oxytocin

Oxytocin , originally extracted from animal posterior pituitaries, is now chemically synthesized. Its only use is in obstetrics, where it is employed to stimulate uterine contraction to induce or reinforce labor or to promote ejection of breast milk. [Note: The sensitivity of the uterus to oxytocin increases with the duration of pregnancy when it is under estrogenic dominance. To induce labor, the drug is administered intravenously. Oxytocin causes milk ejection by contracting the myoepithelial cells around the mammary alveoli.

Although toxicities are uncommon when the drug is used properly, hypertensive crises, uterine rupture, water retention, and fetal death have been reported.

[Note: Oxytocin is contraindicated in abnormal fetal presentation, fetal distress, and premature births.]

Vasopressin:-

Vasopressin (antidiuretic hormone), is structurally related to oxytocin. The chemically synthesized nonapeptide has replaced that extracted from animal posterior pituitaries. Vasopressin has both antidiuretic and vasopressor effects . In the kidney, it binds to the V_2 receptor to increase water permeability and resorption in the collecting tubules. Thus, the major use of vasopressin is to treat diabetes insipidus. Other effects of vasopressin are mediated by the V_1 receptor, which is found in liver, vascular smooth muscle (where it causes constriction). As might be expected, the major toxicities are water intoxication and hyponatremia.

Desmopressin:-

Because of its pressor properties, vasopressin has been modified to desmopressin which has minimal activity at the V_1 receptor, making it largely free of pressor effects. This analog is now preferred for diabetes insipidus and nocturnal enuresis and is longer-acting than vasopressin. Desmopressin is conveniently administered intranasally. local irritation may occur.

Thyroid Hormones:-

The thyroid gland facilitates normal growth and maturation by maintaining a level of metabolism in the tissues that is optimal for their normal function. The two major thyroid hormones are triiodothyronine (T3; the most active form) and thyroxine (T4). Although the thyroid gland is not essential for life, inadequate secretion of thyroid hormone (hypothyroidism) results in bradycardia, poor resistance to cold, and mental and physical slowing (in children, this can cause mental retardation and dwarfism). If, an excess of thyroid hormones is secreted (hyperthyroidism), then tachycardia and cardiac arrhythmias, body wasting, nervousness, tremor, and excess

heat production can occur. [Note: The thyroid gland also secretes the hormone calcitonin-a serum calcium-lowering hormone.]

Thyroid hormone synthesis and secretion:-

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

Regulation of synthesis: Thyroid function is controlled by a tropic hormone, thyroid-stimulating hormone (TSH; thyrotropin). TSH is a glycoprotein, structurally related to LH and FSH, which is synthesized by the anterior pituitary . TSH generation is governed by the hypothalamic thyrotropin-releasing hormone (TRH). TSH action is mediated by cAMP and leads to stimulation of iodide (I^-) uptake. Oxidation to iodine (I_2) by a peroxidase is followed by iodination of tyrosines on thyroglobulin. Condensation of two diiodotyrosine residues gives rise to T4, whereas condensation of a monoiodotyrosine residue with a diiodotyrosine residue generates T3. The hormones are released following proteolytic cleavage of the thyroglobulin.

Regulation of secretion: Secretion of TSH by the anterior pituitary is stimulated by the hypothalamic TRH. Feedback inhibition of TRH occurs with high levels of circulating thyroid hormone. [Note: 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.

Mechanism of action:-

Both T4 and T3 must dissociate from thyroxine-binding plasma proteins prior to entry into cells, either by diffusion or by active transport. In the cell, T4 is enzymatically deiodinated to T3, which enters the nucleus and attaches to specific receptors. The activation of these receptors promotes the formation of RNA and subsequent protein synthesis, which is responsible for the effects of T_4.

Pharmacokinetics:-

Both T4 and T3 are absorbed after oral administration. Food, calcium preparations, and aluminum-containing antacids can decrease the absorption of T4 but not of T3. T4 is converted to T3 by one of two distinct deiodinases, depending on the tissue. 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.

Treatment of hypothyroidism:-

Hypothyroidism usually results from autoimmune destruction of the gland or the peroxidase and is diagnosed by elevated TSH. It is treated with levothyroxine (T4) . The drug is 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 and manifests itself as nervousness, heart palpitations and tachycardia, intolerance to heat, and 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. In these situations, TSH levels are reduced. The goal of therapy is to decrease synthesis and/or release of additional hormone. This can be accomplished by removing part or all of the thyroid gland, by inhibiting synthesis of the hormones, or by blocking release of the hormones from the follicle.

Removal of part or all of the thyroid: This 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 , whereas the opposite is the case in elderly patients. Most patients become hypothyroid as a result of this drug and require treatment with levothyroxine.

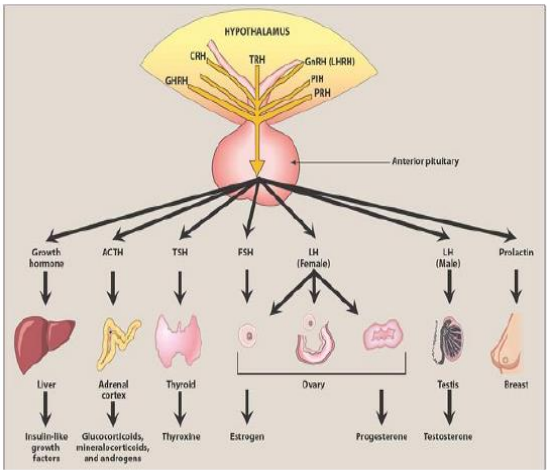
Inhibition of thyroid hormone synthesis: The thioamides, propylthiouracil (PTU) and methimazole , are concentrated in the thyroid, where they inhibit both the oxidative processes required for iodination of tyrosyl groups and the coupling of iodotyrosines to form T3 and T4 . PTU can also block the conversion of T4 to T3 [Note: These drugs have no effect on the thyroglobulin already stored in the gland; therefore, observation of any clinical effects of these drugs may be delayed until thyroglobulin stores are depleted.] The thioamides are well absorbed from the gastrointestinal tract, but they have short half-lives. Several doses of PTU are required per day, whereas a single dose of methimazole suffices due to the duration of its antithyroid effect. The effects of these drugs are slow in onset; thus, they are not effective in the treatment of thyroid storm . Relapse may occur. Relatively rare adverse effects include agranulocytosis, rash, and edema.

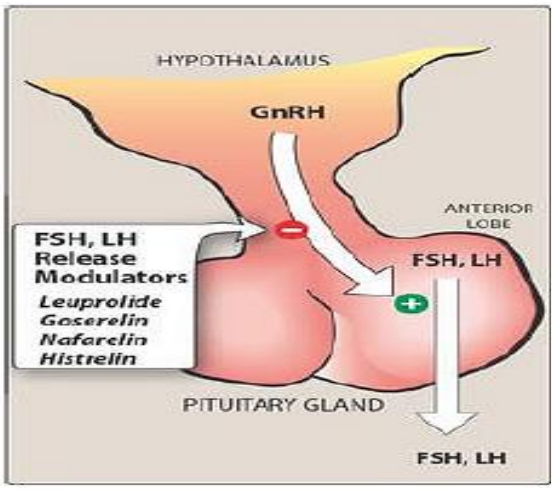
Thyroid storm: β-Blockers that lack sympathomimetic activity, such as propranolol, are effective in blunting the widespread sympathetic stimulation that occurs in hyperthyroidism. Intravenous administration is effective in treating thyroid storm. An alternative in patients suffering from severe heart failure or asthma is the calcium-channel blocker, diltiazem. Other agents used in the treatment of thyroid storm include PTU (because it inhibits the peripheral conversion of T_4 to T3 but methimazole does not), iodides, and glucocorticoids (to protect against shock).

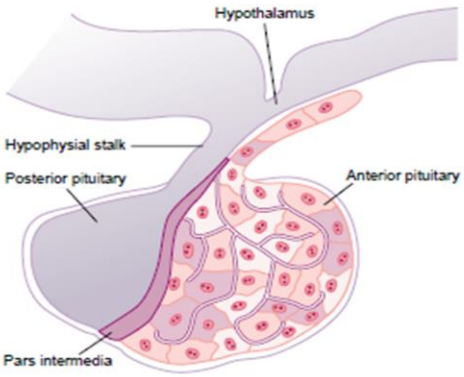
Blockade of hormone release: A pharmacologic dose of iodide inhibits the iodination of tyrosines (the so-called -acute Wolff-Chaikoff effect-),

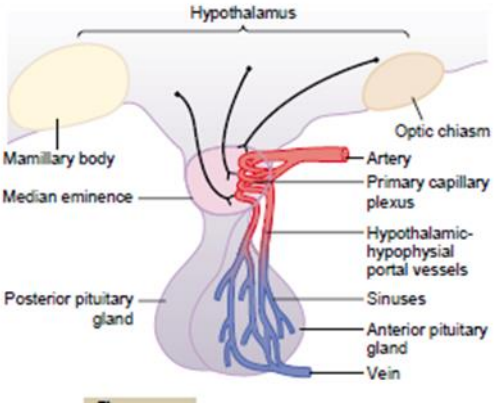
but this effect lasts only a few days. What is more important, iodide inhibits the release of thyroid hormones from thyroglobulin by mechanisms not yet understood. Today, iodide is rarely used as the sole therapy. However, it is employed to treat potentially fatal thyrotoxic crisis (thyroid storm) or 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. Iodide is administered orally.

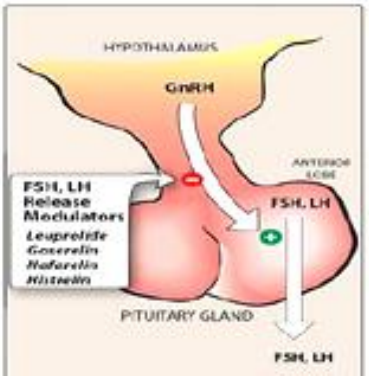
Adverse effects are relatively minor and include sore mouth and throat, swelling of the tongue or larynx, rashes, ulcerations of mucous membranes, and a metallic taste in the mouth.

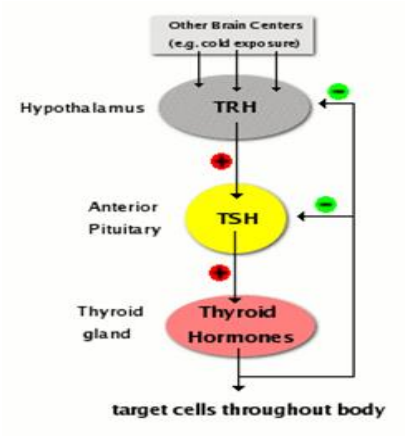


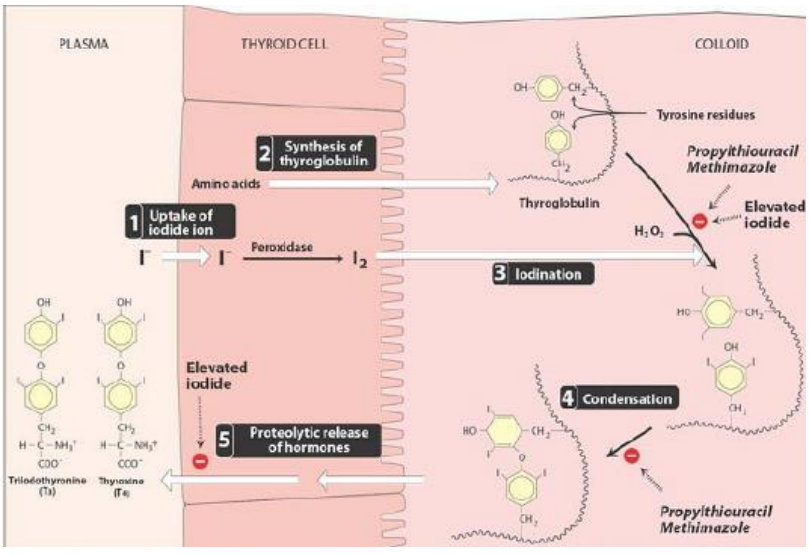


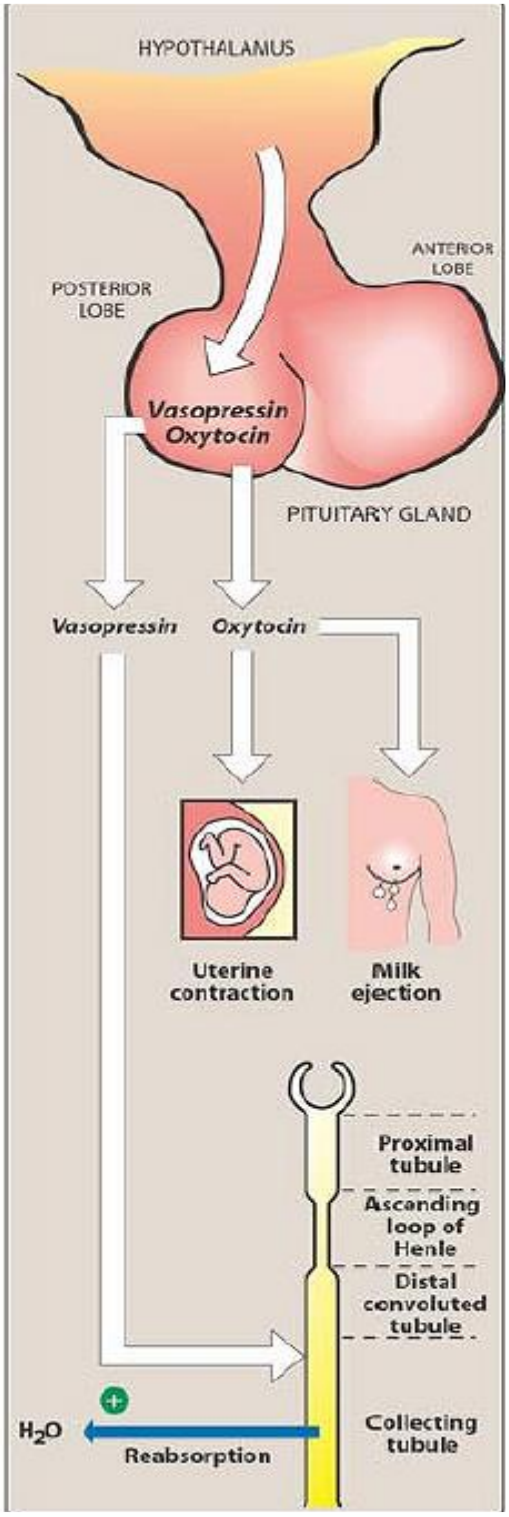

Hypothalamus
Hypophysial stalk
Posterior pituitary
Anterior pituitary
Pars intermedia

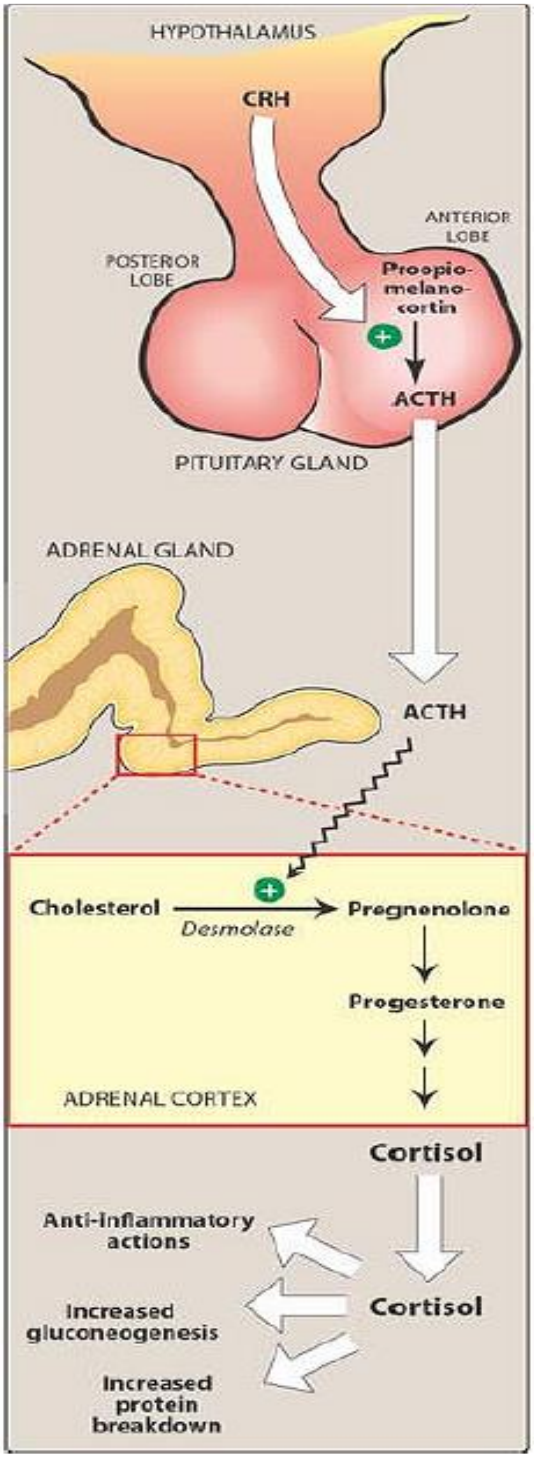

Hypothalamus
Optic chiasm
Mamillary body
Artery
Primary capillary plexus
Median eminence
Hypothalamic-hypophysial portal vessels
Posterior pituitary gland
Sinuses
Anterior pituitary gland
Vein


HYPOTHALAMUS
GnRH
FSH, LH Release Modulators
Leuprolide
Goserelin
Nafarelin
Histrelin
FSH, LH
PITUITARY GLAND
FSH, LH


Other Brain Centers (e.g. cold exposure)
Hypothalamus
TRH
Anterior Pituitary
TSH
Thyroid gland
Thyroid Hormones
target cells throughout body


PLASMA
THYROID CELL
COLLOID
Tyrosine residues
2 Synthesis of thyroglobulin
Amino acids
Thyroglobulin
Propylthiouracil
Methimazole
1 Uptake of iodide ion
Elevated iodide
H_2O_2
Peroxidase
I^-
I_2
3 Iodination
Elevated iodide
4 Condensation
5 Proteolytic release of hormones
Propylthiouracil
Methimazole


HYPOTHALAMUS
POSTERIOR LOBE
ANTERIOR LOBE
Vasopressin
Oxytocin
PITUITARY GLAND
Vasopressin
Oxytocin
Uterine contraction
Milk ejection
Proximal tubule
Ascending loop of Henle
Distal convoluted tubule
Collecting tubule
H_2O
Reabsorption


HYPOTHALAMUS
CRH
ANTERIOR LOBE
POSTERIOR LOBE
Proopio-melano-cortin
ACTH
PITUITARY GLAND
ADRENAL GLAND
ACTH
Cholesterol
Desmolase
Pregnenolone
Progesterone
ADRENAL CORTEX
Cortisol
Anti-inflammatory actions
Increased gluconeogenesis
Increased protein breakdown
Cortisol