ENDOCRINE SYSTEM PHYSIOLOGY 3

A. Pineal Gland

Melatonin

B. Thymus Gland

Thymosins

C. Pituitary Gland: Lactotrophs

Prolactin

D. Thyroid Gland

Thyroxine, Trioiodothyronine

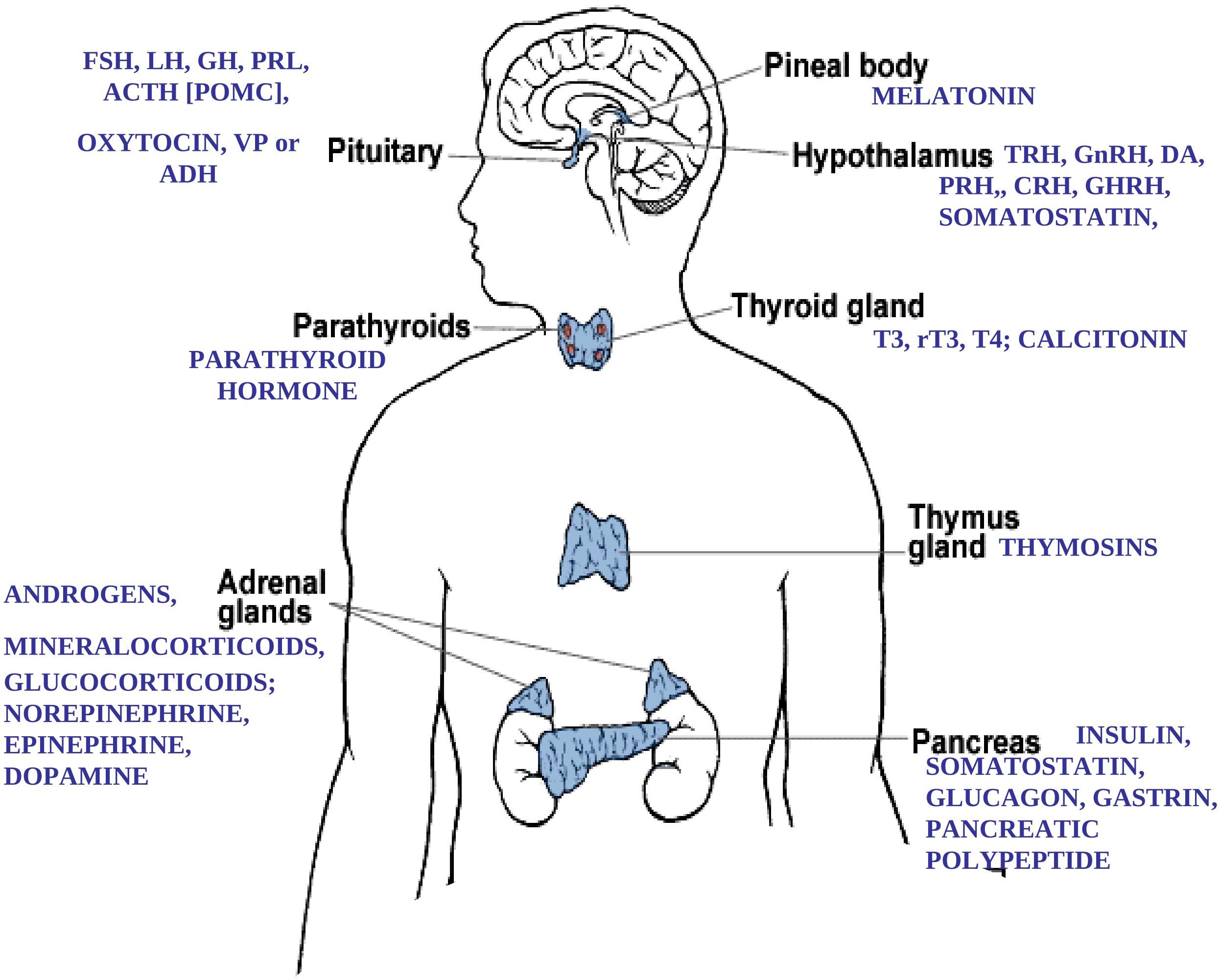
E. Adrenal Gland: Cortex

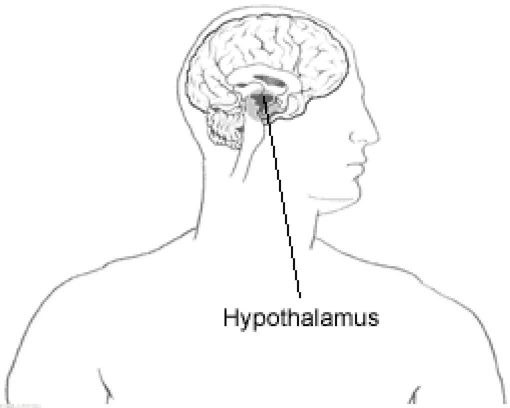
Cortisol

Adrenal Androgens

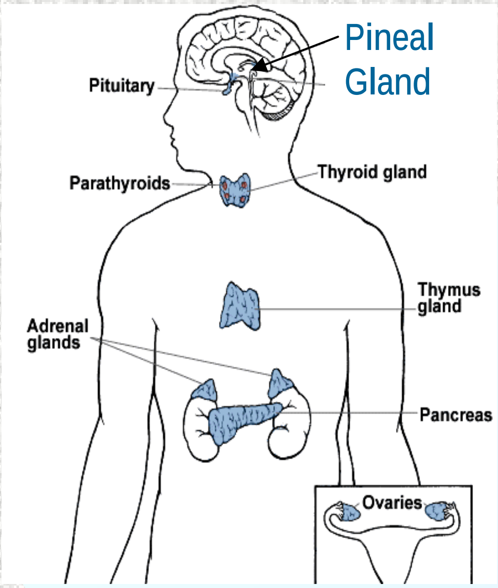
Aldosterone

F. Hormone - Receptor Binding Interactions


FSH, LH, GH, PRL,
ACTH [POMC],
OXYTOCIN, VP or ADH
Pituitary
Pineal body
MELATONIN
Hypothalamus TRH, GnRH, DA,
PRH,, CRH, GHRH,
SOMATOSTATIN,
Parathyroids
PARATHYROID HORMONE
Thyroid gland
T3, rT3, T4; CALCITONIN
Thymus gland THYMOSINS
ANDROGENS,
Adrenal glands
MINERALOCORTICOIDS,
GLUCOCORTICOIDS;
NOREPINEPHRINE,
EPINEPHRINE,
DOPAMINE
Pancreas INSULIN,
SOMATOSTATIN,
GLUCAGON, GASTRIN,
PANCREATIC
POLYPEPTIDE


Hypothalamus

MELATONIN is involved in daily biological cycles.



Melatonin secretion is associated with the body's circaidian rhythm, the sleep cycle, the light/dark cycle, the thermoregulatory cycle, the reproductive cycle, gonadal development, and immune cell functioning.

Melatonin is not stored but produced and released from pinealocytes in the pineal gland (into the bloodstream) upon activation. Light input is transmitted through the retina to the suprachiasmatic nucleus (SCN) in the hypothalamus which functions as the central circadian pacemaker of the body.

During the dark period, the SCN stimulates the release of NE from superior cervical ganglion. NE is an activator of melatonin secretion.

Melatonin has endocrine, autocrine and paracrine actions, and some of these actions are receptor-mediated events. Most melatonin receptors are found in the SCN and the pars tuberalis of the adenophysis.

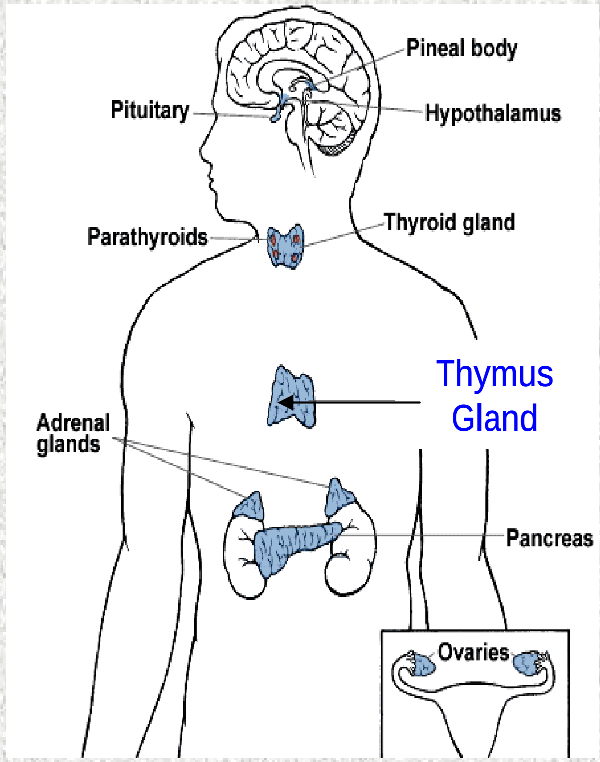
Although melatonin is present in plasma of newborns, the circadian rhythm of melatonin does not exist at birth. It appears at 9-12 weeks of age and is fully established by 5-6 months of age. Melatonin reaches high values at 1-3 years.

The secretion of melatonin is also associated with the **thermoregulatory** cycle. The circadian rhythm of melatonin inversely correlates with the temperature rhythm in humans; melatonin levels in blood increase as core body temperature decreases.

In humans, melatonin secretion is inversely correlated with **gonadal development**; peak melatonin levels fall just prior to the onset of puberty and higher levels of plasma melatonin have been noted in women with amenorrhea. Taken together, these findings suggest an inhibitory effect of melatonin on the **reproductive rhythm**.

Evidence suggests an **immunoenhancing** function for melatonin, stimulation of natural killer cell activity, cytokine expression, and inhibition of immune cell apoptosis have been reported.

Melatonin: pineal gland, pinealocytes. Actions: sleep, temperature, and reproduction. Positive regulation: cervical ganglion NE, dark, sleep; negative regulation: light.



THE THYMUS GLAND

The thymus gland plays a role in the body's immune system.

The thymus gland also has an important role in the maturation of the ovaries and other endocrine functions. Hormones like the gluco-corticoids, androgens, and estrogens can reduce the size of the thymus gland.

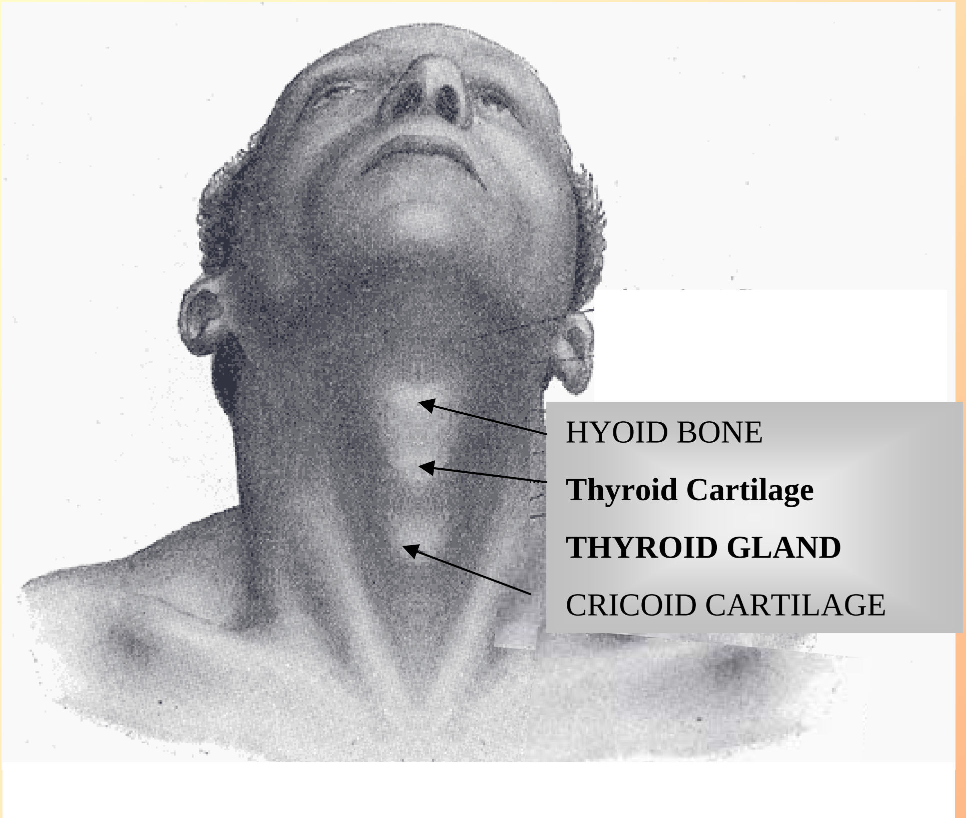
PROLACTIN

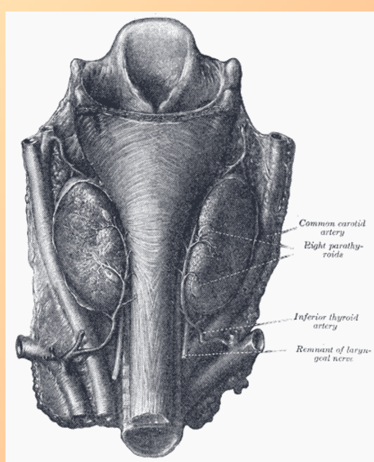
Prolactin (PRL) secretion is normally suppressed by dopamine (DA). Drugs that block the effects of DA at the pituitary or deplete DA stores in the brain release this inhibition and allow PRL to be secreted from the pituitary.

Examples of drugs that suppress DA are: major tranquilizers trifluoperazine (Stelazine) and haloperidol (Haldol); metoclopramide (Reglan), used to treat gastroesophageal reflux and certain anti-cancer drug side-effects like nausea.

Increased prolactin levels often accompany hypothyroidism. PRL levels are frequently checked in patients who have hypothyroidism.

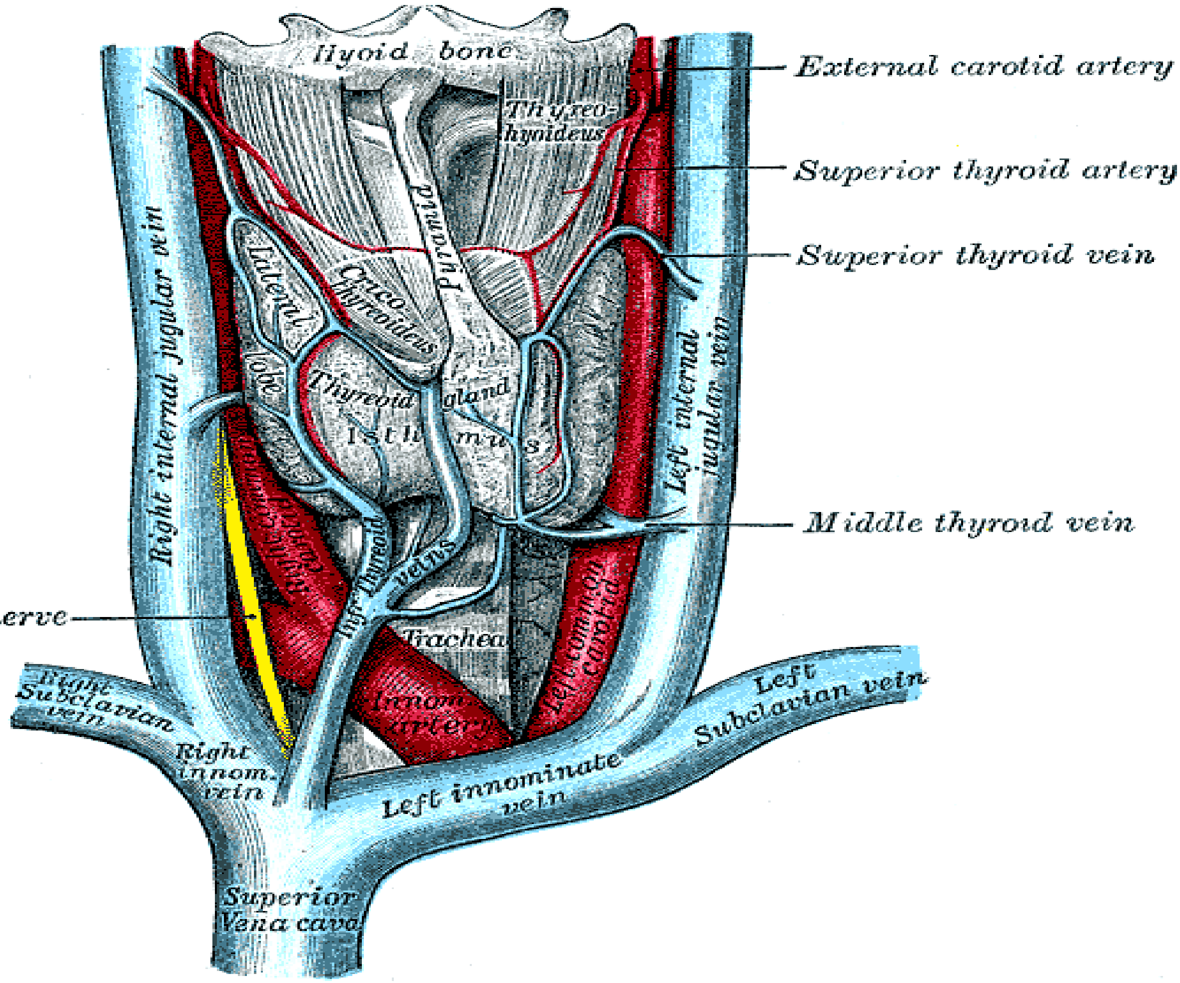
THE THYROID GLAND





Parathyroid glands

THE THYROID GLAND



The thyroid gland is a highly vascular organ, situated at the front and sides of the neck; it consists of right and left lobes connected across the middle line by an isthmus. Its weight is usually about 30 grams.

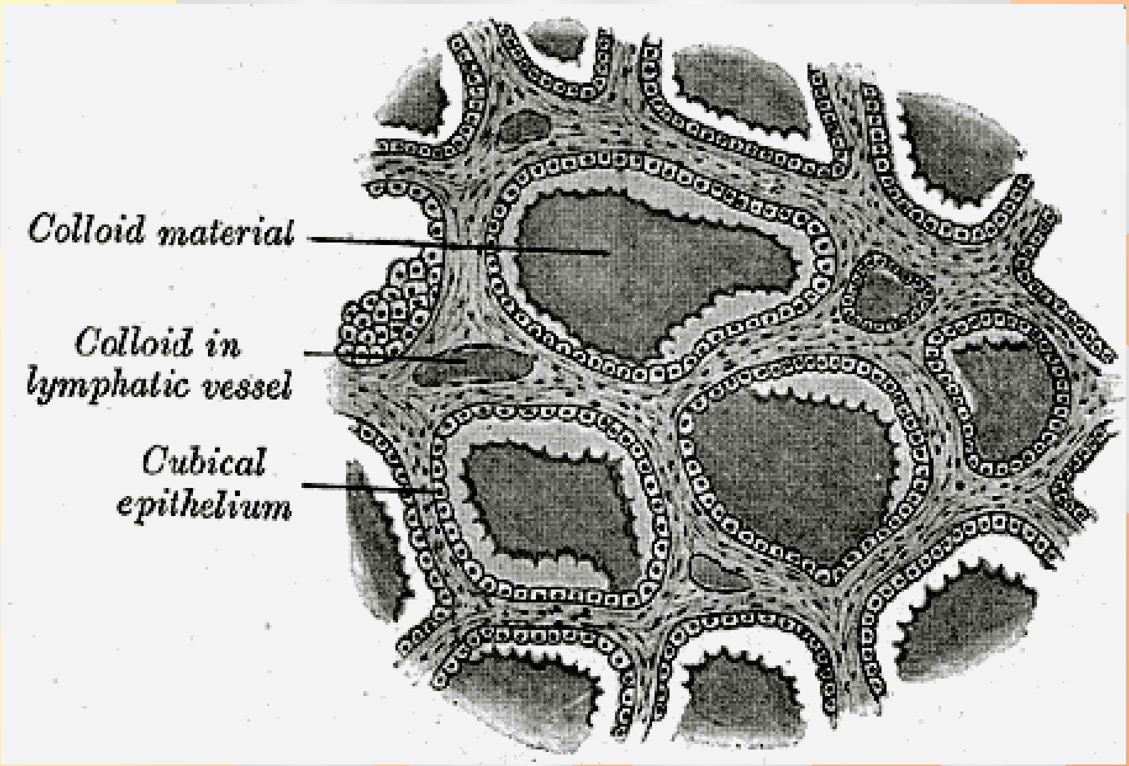
It is slightly heavier in the female, in whom it becomes enlarged during menstruation and pregnancy.

The lobes are conical in shape, the apex of each being directed upward and lateralward as far as the junction of the middle with the lower third of the thyroid cartilage; the base looks downward, and is on a level with the fifth or sixth tracheal ring. Each lobe is about 5 cm. long.

THE THYROID GLAND

The vesicles of the thyroid are of various sizes and shapes, and contain as a normal product a viscid semifluid: the colloid material, red blood cells in in various stages of disintegration, and iodine.

Section of thyroid gland of sheep



This internal secretion of the thyroid gland contains hormones which act to increase the metabolism of other tissues.

TSH

TSH stimulates the follicular cells of the thyroid gland.

All reactions necessary for the formation of T_3 and T_4 are influenced and controlled by TSH, also called thyrotropin, TSH binds to a plasma membrane receptor on the external surface of the thyroid follicular cell and activates adenylate cyclase, thus increasing the formation of cAMP, the nucleotide that mediates the intracellular effects of TSH.

Pituitary TSH secretion is controlled by a negative feedback mechanism modulated by the level of free T_4 and free T_3 in circulation. Increased levels of free thyroid hormones (T_4 and T_3) feedback negatively to inhibit TSH secretion from the anterior pituitary, whereas decreased levels of T_4 and T_3 result in an increase in TSH release from the anterior pituitary.

TSH secretion is also influenced by TRH, a 3-amino acid peptide synthesized in the hypothalamus.

TRH, released into the portal system between the hypothalamus and pituitary, binds to a specific TRH receptor on the anterior pituitary thyrotrophs and stimulates the pituitary to release TSH. [The precise regulation of TRH synthesis and release is not clear, although thyroid hormones do play a role.]

Physiologic effects of thyroid hormones:

(1) They increase protein synthesis in virtually every body tissue. T_3 and T_4 enter cells, where T_3, which is derived from the circulation and from conversion of T_4 to T_3 within the cell, binds to nuclear receptors to induce target gene transcription.

(2) T_3 increases O_2 consumption by increasing the activity of the Na+, K+-ATPase (Na pump) in tissues responsible for basal O_2 consumption (ie, liver, kidney, heart, and skeletal muscle). T_3 is believed to be the active thyroid hormone.

TRH Tests: Serum TSH is measured before and after an IV injection of synthetic TRH. Normally, TSH levels [5 to 25 µU/mL] increase within 30 min and returning to normal by 120 min. This rise is exaggerated in primary *hypo*thyroidism.

The TRH test may also be useful in distinguishing pituitary from hypothalamic hypothyroidism. Patients with hypothyroidism secondary to a pituitary deficiency won't show a change in TSH whereas those with a hypothalamic disorder (i.e. deficient TRH) and a normal pituitary will respond to a TRH challenge by releasing TSH.

In hyperthyroidism, TSH release remains suppressed, even though TRH is injected. This is because the elevated levels of free T_4 and free T_3 that are seen in hyperthyroidism feedback negatively on the anterior pituitary.

THYROID HORMONE SYNTHESIS

The follicular cells of the thyroid gland produce and secrete thyroid hormones, mainly thyroxine or T_4 [80%], and triiodothyronine or T_3 [20%].

Note that the relative concentrations of these hormones may vary with disease and nutritional deficiencies.

T_3 is the biologically active form. Its activities are mediated by binding to the thyroid hormone receptor: TR

Most T_3 in circulation derives from peripheral T_4 to T_3 conversion although intrathyroidal T_4 to T_3 conversion also takes place within the thyroid gland itself.

Nearly all of the T_3 and T_4 that are in circulation are bound to proteins [i.e. thyroid binding globulin, TBG] and only 0.02 to 0.03% is free (and thus active).

THYROID HORMONE REGULATION

Estrogens (pregnancy-level estrogens, estrogen-containing medications) cause TBG concentrations to increase (less free hormone is available).

Hypothyroid patients receiving estrogen replacement therapy may need higher doses of T_4, for example
androgens, glucocorticoids, and malnutrition cause TBG concentrations to decrease.

Glucocorticoids inhibit pulsatile TSH secretion.

Dopamine and retinoids decrease TSH. Some selective serotonin reuptake inhibitors [SSRIs] accelerate T_4 metabolism thereby lowering T_4 levels in circulation.

Some drugs, like Dilantin (phenytoin) and Aspirin (salicylates) cause T_3- and T_4-TBG binding to decrease.

THE IODINE TRAP

The thyroid gland has the unique ability to concentrate iodine.

This is made possible by the presence of a symporter called the sodium-iodide symporter or NIS.

The NIS is able to concentrate iodide to levels which are 40- to 60 times greater in the colloid (present inside of the follicular cells of the thyroid gland) then the levels found outside, in the serum.

The NIS gene is regulated by TSH (or thyrotropin).

Thyroglobulin (TG) is the precursor for all thyroid hormones. It is a protein that contains 140 tyrosine residues. These tyrosines are iodinated and coupled to form thyroid hormones.

THYROID HORMONE SYNTHESIS AND DEGRADATION

Iodine is added to tyrosine residues in the thyroid colloid forming either monoiodotyrosines [MIT] or 3,5-diiodotyrosines [DIT].

★ Thyroid peroxidase catalyzes the coupling between them such that:
one MIT and one DIT combine to form T_3; and,
two DITs [DIT and DIT] are coupled to form T_4.

TSH stimulates a cleavage process allowing some of the T_4 and T_3 to be released into the bloodstream.

Thyroid hormone metabolism can follow different pathways. In the predominant metabolic pathway the progressive deiodination of T_4 to T_3 or to rT_3, and then to T_2, T_1, and T_0 occurs.

★ T_4 is first deiodinated to form T_3 or reverse T_3, rT_3. The enzyme 5'-monodeiodinase converts T_4 into T_3, whereas the 5-monodeiodinase enzyme converts T_4 into rT_3.
★ The T_3 that is formed by the peripheral monodeiodination of T_4 is the biologically active form.

DEIODINATION

★ By contrast, rT_3 is inactive.

★ This means that the initial deiodination step, and the factors that determine it, have the capacity to form a potent compound: T_3 OR an inactive one: rT_3.

During fasting, starvation, or significant illness, the activity of the 5'-monodeiodinase enzyme is lower, T_3 conversion from T_4 decreases, and the basal metabolic rate slows down.

TERMS and ABBREVIATIONS

thyroxine = T_4;	iodide = I-
triiodothyronine = T_3;	reverse T_3 = rT_3
thyroid binding globulin = TBG;	thyroglobulin = TG
monoiodotyrosines = MIT;	**3,5-diiodotyrosines = DIT**

sodium-iodide symporter = NIS

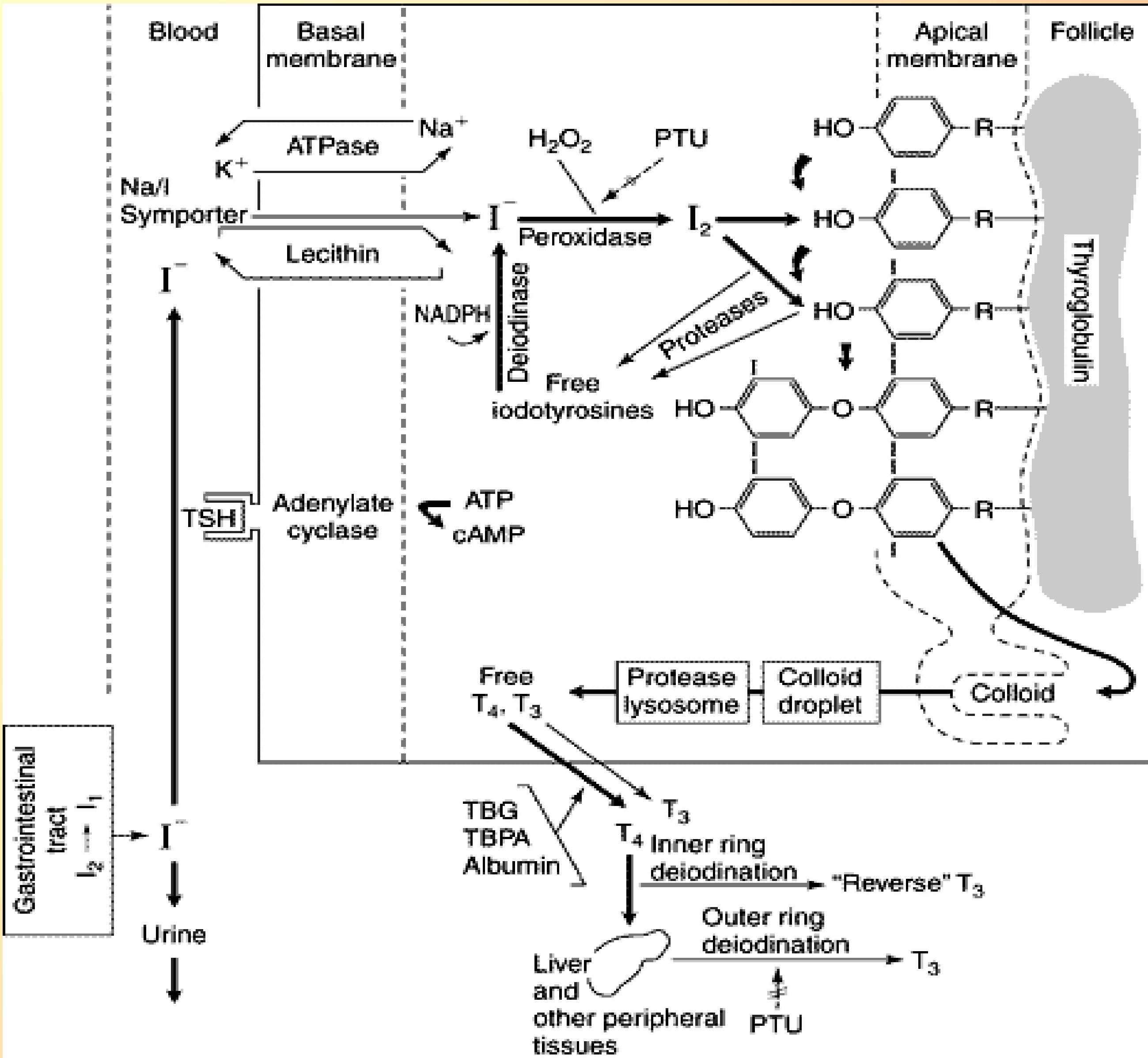
thyroid stimulating hormone = TSH ≡ thyrotropin

thyroid peroxidase;

thyroid follicular cells;

colloid

Biosynthesis of thyroid hormones.



ATP = adenosine triphosphate; cAMP = adenosine 3´:5´-cyclic phosphate; I = iodide; NADPH = the reduced form of nicotinamide-adenine dinucleotide phosphate; PTU = propylthiouracil; T_3 = triiodothyronine; T_4 thyroxine; TBG = thyroxine-binding globulin; TBPA = thyroxine-binding prealbumin (transthyretin); TSH = thyroid-stimulating hormone.

★

HORMONES OF THE ADRENAL CORTEX

Section of a part of an adrenal gland

ganglion

CAPSULE

Zona Glomerulosa → **Mineralocorticoids**

(Ex.: Aldosterone)

Zona Fasiculata → **Glucocorticoids**

(Ex.: Cortisol)

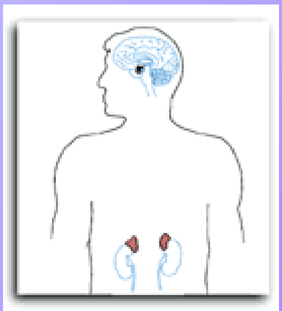
Zona Reticularis → **Androgens**

.. (Ex.: Androstenedione)

Medulla → **Catecholamines:**

(Exs.: Norepinephrine, Epinephrine)

CORTISOL



CORTISOL is normally produced by the adrenal glands.

It belongs to a class of hormones called GLUCO-CORTICOIDS, which affect almost every organ and tissue in the body.

Cortisol's actions include:

- *stress* responses
- *blood pressure* maintenance
- *cardiovascular* functioning
- *anti inflammatory* responses
- *catabolic* effects on protein, CHO, and fat metabolism
- *Insulin antagonism*
- *arousal* and *well-being*

CORTISOL is regulated by the hypo-thalamic and pituitary hormones.

The hypothalamus sends CRH to the anterior pituitary which responds by releasing ACTH (adrenocorticotropin), from POMC.

ACTH stimulates the adrenal glands to produce cortisol.

When blood cortisol levels rise, they signal the anterior pituitary to lower ACTH secretion.

This is an example of a negative feedback loop in the hypothalamic-hypophyseal-adrenal axis.

ACTH

Adrenocorticotropic hormone, also known as corticotropin, is a single-chain polypeptide containing 39 amino acids. Biologic activity resides in the N-terminal 20 amino acids. CRH is the primary agent that stimulates ACTH release, and ACTH stimulates the adrenal cortex to secrete cortisol and several weak androgens.

Cortisol and other corticosteroids (including medically administered steroids) circulating in the plasma exert a feedback inhibition of the secretion of the CRH and ACTH.

The ***CRH-ACTH-cortisol axis*** is central in the response to stress. In the absence of ACTH, the adrenal cortex atrophies and cortisol secretion virtually ceases.

Several peptide hormones are derived from a common precursor, pro-opiomelanocortin (POMC), which gives rise to ACTH, -melanocyte-stimulating hormone (MSH), enkephalins, and endorphins.

POMC

POMC is present in the anterior lobe and in cells derived from the intermediate lobe of the pituitary as well as in the hypothalamus, but the active hormones formed from POMC differ in each site where POMC is present, depending on variations in enzymatic processing. Thus, ACTH and -endorphin) are the predominant hormones synthesized in the anterior lobe.

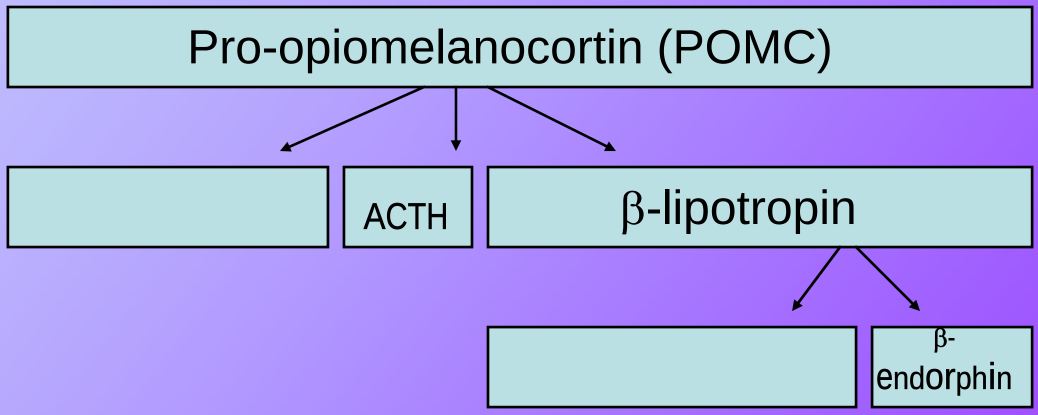
Almost all -endorphin, and ACTH is cleaved to form corticotropin-like intermediate lobe peptide (corresponding to ACTH 18-39) and -MSH (corresponding to ACTH 1-13) in the cells derived from the intermediate lobe.

In addition, the formation of POMC by the intermediate lobe cells appears to be regulated primarily by dopamine and serotonin, whereas CRH is the important regulatory agent in the anterior lobe.

POMC and MSH can cause hyperpigmentation of the skin and are only significant clinically in disorders in which ACTH levels are markedly elevated (ie, Addison's disease and Nelson syndrome). Enkephalins and endorphins are considered endogenous opioids and bind to and activate opioid receptors throughout the CNS.

P O M C

After POMC is synthesized and released from the anterior pituitary, it undergoes enzymatic cleavage reactions that result in the simultaneous release of: ACTH, β-endorphin, and other peptide. This means that for each molecule of ACTH that is released a molecule of b-endorphin will also be secreted. The cosecretion of these hormones has important implications for their physiologic functions in pathologic conditions.



Aldosterone

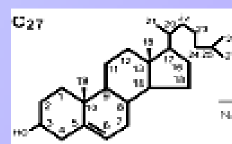
Aldosterone belongs to a class of hormones called mineralocorticoids, also produced by the adrenal glands.

Aldosterone helps maintain blood pressure and water and salt balance in the body by helping the kidney retain sodium and excrete potassium.

When aldosterone production falls too low, the kidneys are not able to regulate salt and water balance, causing blood volume and blood pressure to drop.

BIOSYNTHESIS OF HORMONES IN THE ADRENAL CORTEX BEGINS WITH CHOLESTEROL

C H O L E S T E R O L



Pregnenolone

DeHydroEpiAndrosterone

Progesterone

17-OH-Progesterone

ANDROSTENEDIONE

Corticosterone

CORTISOL

ALDOSTERONE

M I N E R ALOCORTICOIDS

G L U C O C O R T I C O I D S

A N D R O G E N S

Hormones from the adrenal cortex must first bind to intracellular receptors which travel into the nucleus in order to mediate their actions.

- Intracellular receptors belong to a large superfamily of proteins called the "Steroid/Nuclear Receptor Superfamily".

- Aldosterone binds to the *Mineralocorticoid Receptor* (MR), androgens, like testosterone, bind to the *Androgen Receptor* (AR), and cortisol binds to the *Glucocorticoid Receptor* (GR).

- Mineralocorticoids (such as aldosterone) androgens (like androstenedione and testosterone), and glucocorticoids (like cortisol) are referred to as "ligands" with regard to the receptors they bind.

Once the hormone or *ligand* binds to its receptor, the receptor-ligand complex enters the nucleus* and binds to specific DNA sequences on target genes.

These DNA-bound receptor-ligand complex is then able to induce or inhibit the expression of a particular gene (or target gene). In this way it act as a ‘transcription factor’ .

*Note that some of the receptors in the *Steroid/ Nuclear Receptor Superfamily* reside in the nucleus, while others translocate from the cytoplasm to the nucleus after ligand binding.

Hormones other than those produced by the adrenal cortex also bind and act through intracellular/nuclear receptors.

These include…

OTHER HORMONES THAT BIND TO INTRACELLULAR/NUCLEAR RECEPTORS include:

◇ Thyroid hormones:

T_3 and T_4, which bind to the *thyroid receptor* (TR),

◇ Vitamin D_3, which binds to the *vitamin* D_3 *receptor* (VDR),

◇ Estrogens:

E_2, E_1, E_3, which bind to the *estrogen receptor* (ER), and

◇ Progesterone, 17-hydroxyprogesterone, which binds to the *progesterone receptor* (PR).