

## Hypothalamic/Pituitary Axis: Adrenals and Thyroid.

### section I. Adrenocorticotrophic hormone (ACTH)

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## **Adrenocorticotrophic hormone (ACTH; Corticotropin)**

### 1. Overview of ACTH function:

- \* The major physiological stimulus for glucocorticoid production is the peptide hormone ACTH.
- \* ACTH stimulates the synthesis and the release of the glucocorticoids (as well as some androgens and mineralcorticoids) from the adrenal cortex.
- \* The release of ACTH is mainly regulated by Corticotropin-Releasing Hormone (CRH) a peptide hormone from the hypothalamus.
- \* CRH release is in turn regulated by negative feedback effects of plasma glucocorticoids and by neural factors.

### 2. A Brief Review of Glucocorticoids:

- \* The adrenal cortex produces two principal steroids, the 21-carbon corticosteroids (glucocorticoids and mineralcorticoids) and the 19-carbon androgens.
- \* The glucocorticoids (such as hydrocortisone and corticosterone) affect carbohydrate and protein metabolism. Some glucocorticoids also affect water and electrolyte balance.
- \* These molecules have anti-inflammatory and immunosuppressive activity- for which they are most commonly prescribed.

- \* The glucocorticoids are ligands for a transcription factor called the glucocorticoid receptor and some of their actions are at the level of gene regulation.
- \* Addison's disease is a deficiency in corticosteroid production. Symptoms include muscle weakness, depression, lowered blood pressure and loss of weight.
- \* Cushing's syndrome is marked by excessive glucocorticoid activity. The prolonged effects of glucocorticoid excess may cause symptoms among which are euphoria, thinning skin, increased abdominal fat, easy bruising and poor wound healing, and muscle wasting.

### 3. Structure and Chemistry of ACTH:

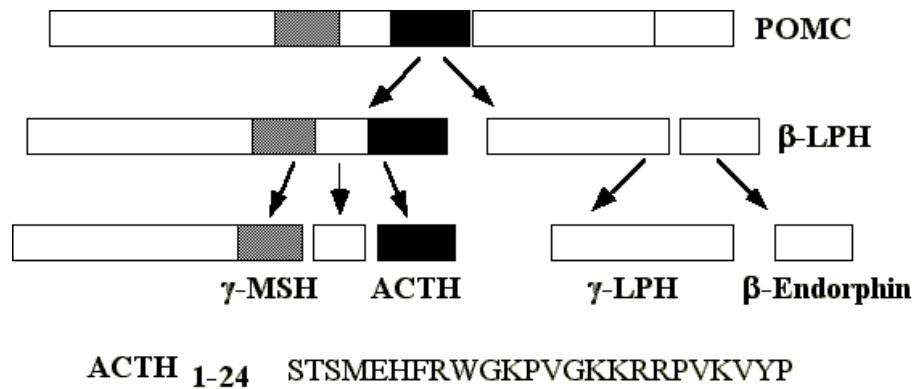


Figure 1. Proopiomelanocortin (POMC) is proteolytically converted to ACTH and other peptides in the anterior pituitary. Other peptide hormones derived from POMC include those related to ACTH (such as melanocyte stimulating hormone or  $\gamma$ -MSH) and lipotropins and endorphins. The sequence of the first 24 residues of ACTH is shown.

Human ACTH is a 39-amino acid polypeptide hormone derived from POMC (see figure 1). A peptide consisting of only the first 20 residues from the N-terminus retains full biological activity. The remaining residues (25-39) confer species specificity. Removal of even one residue from the N-terminus, however, substantially reduces function.

Corticotropin (ACTH) administration can provoke antibody response- mainly to the immunogenic residues in the C-terminus. Instead, Cosyntropin, a synthetic peptide that consists of the first 24 residues of ACTH is used in therapy.

### 4. Pharmacokinetics and Pharmacodynamics of ACTH:

Corticotropin and Cosyntropin can not be administered orally because of their rapid proteolysis in the gastrointestinal tract. These molecules are well absorbed by the intramuscular route.

These molecules exhibit biological half-lives in the order of 15-20 minutes (enzymatic hydrolysis). Tissue uptake occurs in liver and kidneys. ACTH is not excreted in significant amounts in the urine.

ACTH, like many peptide hormones, binds to a G protein-coupled receptor (in the adrenal cortex). This binding activates adenylyl cyclase and increases intracellular cAMP. cAMP is the second messenger for most of the ACTH effects on steroidogenesis.

Adrenocortical cells respond to ACTH in two distinct phases. In the acute phase (seconds to minutes in duration) there is an increase in the supply of cholesterol (the substrate) to the steroidogenic enzymes. The mechanism by which ACTH stimulates translocation of cholesterol to the inner mitochondrial membrane remains unknown. In the chronic phase (hours to days) there is an increase in the transcription of genes encoding the steroidogenic enzymes such as steroid hydroxylases.

#### 5. Regulation of ACTH Secretion:

There is a diurnal variation in the release of ACTH, and a subsequent variation in the concentration of endogenous corticosteroids. The levels of both are higher during the early morning hours.

##### A. Regulation by **Corticotropin-Releasing Hormone (CRH)**:

Fluctuations in glucocorticoids secretions mirror the fluctuations in ACTH release by the pituitary corticotropes. These corticotropes are regulated primarily by CRH- a peptide released by CRH neurons of the endocrine hypothalamus.

CRH is the primary secretagogue of ACTH. CRH is a peptide of 41 amino-acid residues that is also derived from a larger precursor protein by proteolysis. CRH is made in the paraventricular nucleus.

CRH also acts through a G-coupled receptor to stimulate adenylyl cyclase to raise cAMP in corticotropes.

The CNS integrates a number of + and - signals that converge on the CRH neurons-which are clustered in the paraventricular hypothalamic nucleus. Once CRH is released into the hypophyseal plexus, it travels to the pituitary where it binds its receptor.

##### B. Arginine Vasopressin:

The action of CRH is significantly potentiated by Arginine Vasopressin (AVP) via G-proteins, Phospholipase C, and the secondary messengers diacylglycerol and 1,4,5-inositol triphosphate. These messengers release ACTH.

##### C. Negative Feedback Effects on the Anterior Pituitary and Hypothalamus:

Endogenous as well as clinically administered glucocorticoids have a negative feedback effect on the secretion of both ACTH and CRH. Administration of exogenous

glucocorticoids inhibits the secretion of endogenous glucocorticoids and may lead to atrophy of the adrenal cortex.

The long-loop and short-loop negative feedback systems on hypothalamic neurons are shown in Figure 2. In the long-loop, the decreased release of CRH (rapid-minutes) appears to be mediated by membrane receptors for cortisol and/or steroid intermediates. In addition, the decreased synthesis of CRH (slow effect, hours) is probably mediated by the glucocorticoid nuclear receptor.

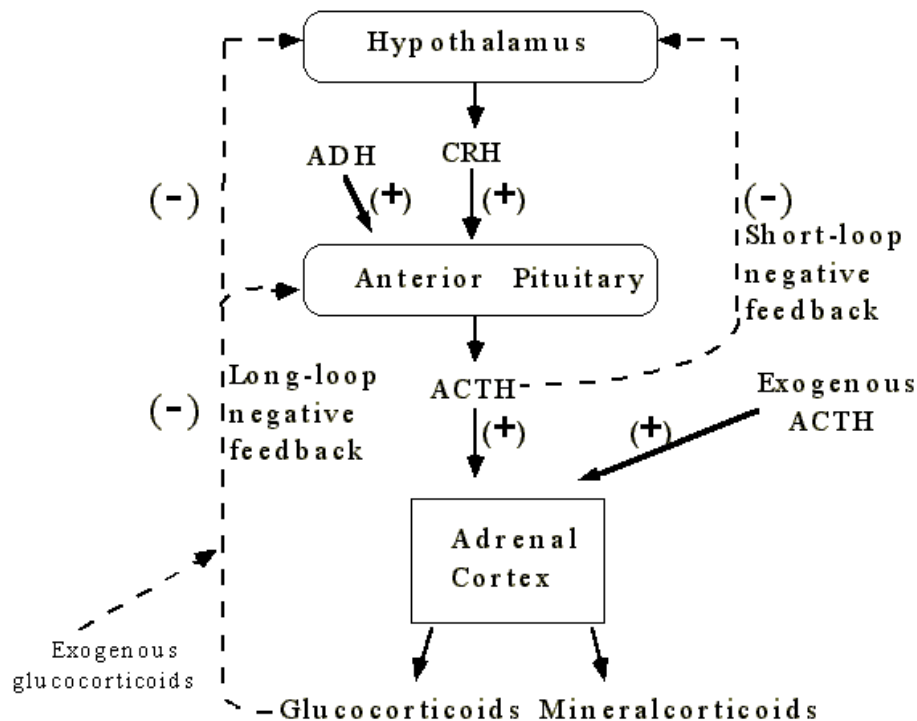


Figure 2: Regulation of synthesis and secretion of adrenal corticosteroids. The long and short negative feedback loops are shown. AHD = antidiuretic hormone (vasopressin).

Low plasma ACTH and a relative absence of adrenal responsiveness to ACTH can thus be caused by high glucocorticoid levels (for example from adrenal tumors or therapeutic administration).

#### D. The Stress Response:

Stress signals (e.g. injury, hemorrhage, severe infection, hypoglycemia, cold, pain and fear) can overcome negative feedback regulation of the HPA axis, leading to a substantial increase in corticosteroid production. Glucocorticoid secretion appears to be important for maintaining homeostasis in some stress situations. Although the mechanisms

underlying this stress response are not well understood, it is possible that complex interactions with the immune response may be of relevance.

## 6. Actions of ACTH:

The primary endocrine function of ACTH is to stimulate the synthesis and release of adrenocortical hormones. This occurs at higher physiological concentrations. It is believed that the actions of ACTH to increase steroid levels are at the level of *de-novo* biosynthesis. For example, ACTH increases the activity of cholesterol esterase, the enzyme that catalyzes the rate-limiting step of steroid hormone synthesis: cholesterol to pregnenolone. As discussed above, the actions of ACTH derive from second messengers produced through the interactions of ACTH with the ACTH receptor (a member of the G-coupled receptor superfamily).

In addition, there are trophic effects on the adrenal cortex at low physiological concentrations. In this way, it maintains the cell mass, cell number, and the integrity of the adrenal cortex.

Low ACTH levels may suggest destruction of pituicytes or defects in the synthesis/secretion of CRH. In contrast, high ACTH levels in the plasma indicate problems upstream- such as pituitary adenoma or an ectopic tumor secreting ACTH or CRH. Elevation of ACTH lead to adrenal hyperplasia and hypertrophy (e.g. congenital virilizing adrenal hyperplasia; Cushing's disease).

## 7. Diagnostic and Therapeutic Uses:

Although corticotropin can be used therapeutically, its primary usefulness is in the assessment of adrenocortical responsiveness.

ACTH stimulation of the adrenals will fail to elicit response in states of adrenal insufficiency. A useful test for adrenal insufficiency is to administer cosyntropin and measure plasma cortisol levels before and shortly after injection. A subnormal response indicates adrenocortical insufficiency.

Corticotropin may be prescribe for patients with normal adrenal function to increase their glucocorticoid concentrations. Adverse effects should be carefully considered since their effectiveness is similar. On balance, the disadvantages of ACTH outweigh its advantages, making glucocorticoids ore useful for anti-inflammatory or immunosuppressive therapy.

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## Thyroid Hormones

### 1. Chemistry of Thyroid Hormones:

Figure 1 shows the structures of the two active thyroid hormones thyroxine ( $T_4$ ) and triiodothyronine ( $T_3$ ), in addition to the metabolically inert reverse triiodothyronine ( $rT_3$ ).

Although both  $T_3$  and  $T_4$  are important for normal growth and development and energy metabolism,  $T_3$  is three-five times more active than  $T_4$ . All three naturally occurring molecules are iodinated forms of thyronine.

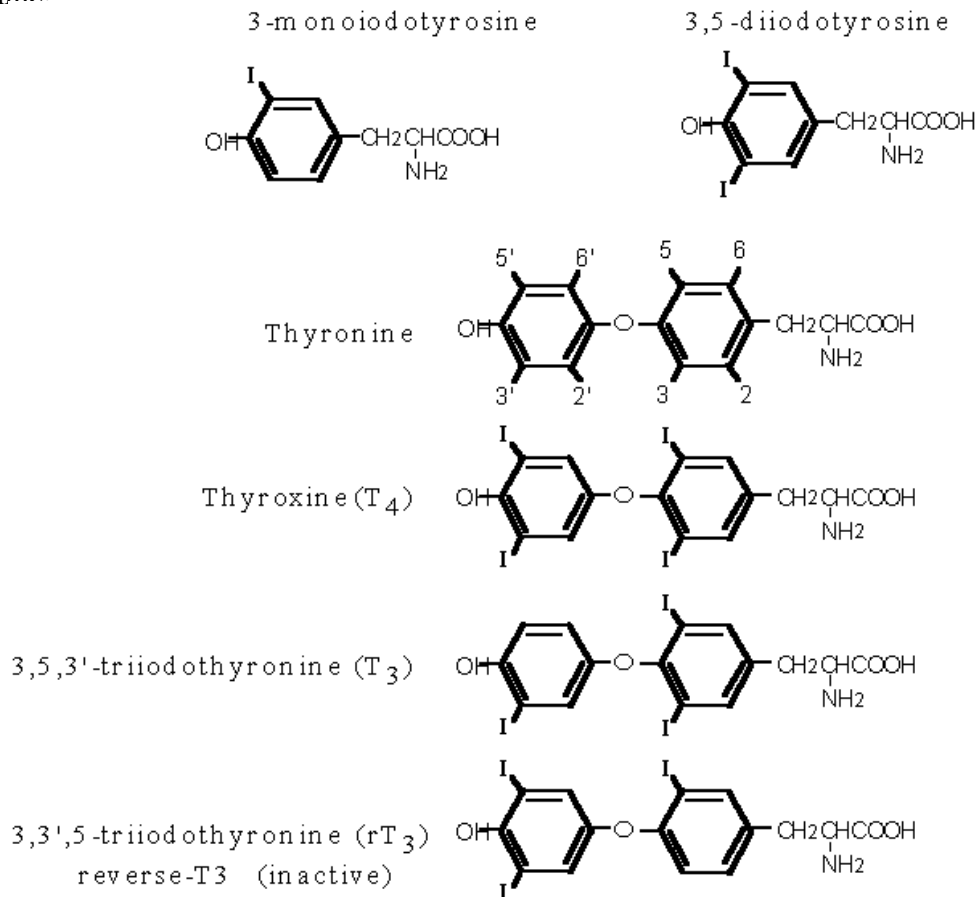


Figure 1. Thyroid hormones and their iodotyrosine precursors.

## 2. Synthesis of Thyroid Hormones:

Synthesis is complex and inefficient.

The functional unit of the thyroid is the follicle. The follicle lumen is filled with a thick colloid which predominantly contains thyroglobulin. The synthesis of the thyroid hormones begins with the tyrosyl amino-acid residues of thyroglobulin.

Thyroglobulin is a highly glycosylated protein of two subunits, each of 330 kDa. The subunit contains 115 tyrosine residues. This way, the thyroid gland maintains a large reservoir of potential hormone.

The main steps in the synthesis, storage and secretion of thyroid hormones are as follows (see Figure 2):

- \* Iodine ingested in diet reaches the circulation in form of iodide ( $I^-$ ).
- \* Uptake of iodide by the follicle cells of the gland by active transport. Iodide is concentrated 20-200 fold over plasma in the gland (stimulated by thyroid-stimulating hormone TSH).
- \* Oxidation of iodide to hypoiodate ( $OI^-$ ) by the membrane bound thyroid peroxidase and  $H_2O_2$ , and the subsequent iodination of tyrosine residues of the thyroglobulin.
- \* Coupling of iodotyrosine residues by ether linkage to generated iodothyronines (see Figure1).
- \* The proteolysis of thyroglobulin and release of thyroid hormones into the blood.
- \* The conversion of  $T_4$  to  $T_3$  in peripheral tissues.

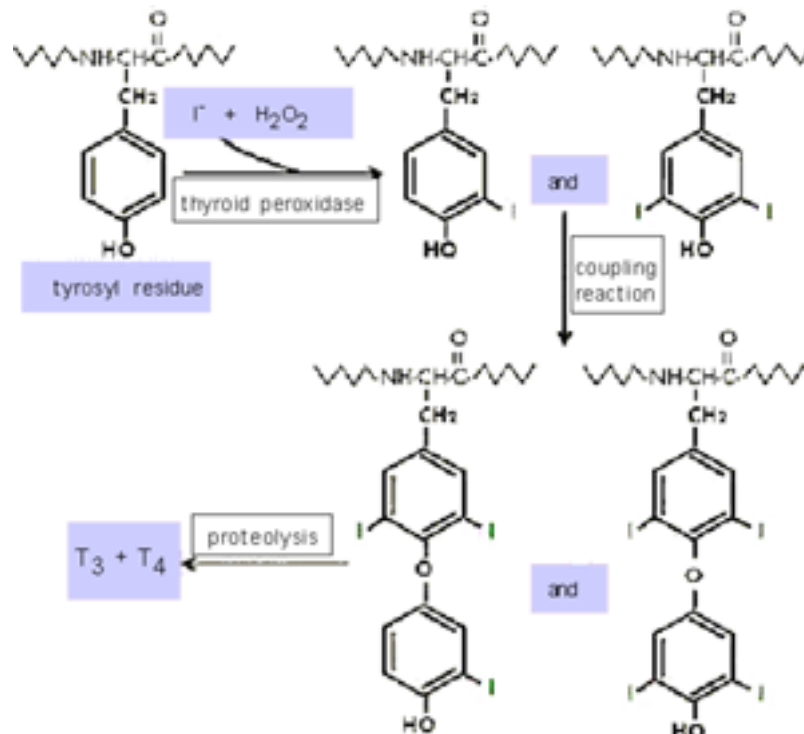


Figure 2. Formation of protein-bound thyroxine and triiodothyronine. The oxidative coupling reactions of two diiodotyrosyl residues to form thyroxine, or of a monoiodotyrosine and a diiodotyrosine to form  $T_3$  is believed to be also catalyzed by the thyroid peroxidase.

### 3. Secretion of Thyroid Hormones.

- \* Secretion is stimulated by TSH.
- \* Secretion is initiated by endocytosis of thyroglobulin by the follicle cells. This starts with formation of pseudopods which engulf some of the colloid in the lumen. The endocytic vesicles then fuse with lysosomes to proteolyze thyroglobulin.
- \*  $T_3$  and  $T_4$  are then released and secreted into the plasma.
- \*  $T_4 : T_3$  ratio coming out of the gland is about 3-6 : 1, but some 80% of circulating  $T_3$  is derived from metabolism of  $T_4$  (via monodeiodination) in peripheral tissues (see below).

### 4. Transport of Thyroid Hormones in the Blood.

- \* Virtually all of the  $T_4$  and  $T_3$  in the circulation is bound to plasma protein.
- \* Thyroxine-binding globulin (TBG) is the major carrier of thyroid hormones, carrying some 75% of circulating thyroxine.
- \* TBG has limited capacity, but high affinity for  $T_4$ . Its affinity for  $T_3$  is considerably lower, which is responsible for the shorter plasma half-life of  $T_3$ .
- \* Transthyretin (thyroxine-binding prealbumin or TBPA)- has higher capacity, but lower affinity (again affinity for  $T_3$  is lower than that for  $T_4$ ).
- \* Synthesis and plasma concentrations of thyroid hormones are increased by estrogens including oral contraceptives.

### 5. Metabolism of Thyroid Hormones:

- \* The major site of thyroxine conversion outside of the thyroid is in the liver. Thus, when thyroxine is administered to patients in doses that produce normal [thyroxine] plasma, the [ $T_3$ ] also reaches the normal levels.
- \*  $T_4$  is converted to  $T_3$  by specific 5'-deiodinases. This represents activation of the hormone.
- \* Type-1 enzyme in liver, kidney, and other tissues. These are inhibited by propylthiouracil but not methimazole (see discussion of these drugs below). Type-II enzyme, in the pituitary, has very high affinity for  $T_4$ , and is important for feedback inhibition of TSH secretion that is mediated by  $T_3$ .

- \* Inactivation of hormone activity by removal of iodine from the 5 position (not 5', see Figure 1) leads to so called “reverse” T<sub>3</sub> and 3,3'-diiodothyronine (derived from T<sub>3</sub>). The enzyme involved has not been identified.
- \* Hepatic metabolism - mainly conjugation of phenolic -OH with glucuronic or sulfuric acid followed by biliary secretion. A large portion of these conjugates are cleaved in the intestine with reabsorption of active hormones, but some 40% of T<sub>4</sub> ends up in feces.
- \* Plasma half-life of T<sub>4</sub> is 6-7 days in adults; for T<sub>3</sub> it is less than 2 days. In contrast, the half-life of T<sub>4</sub> is prolonged to 9-10 days in *hypothyroid* cases, and shortened to 3-4 days in *hyperthyroidism*.

## 6. Action of Thyroid Hormones.

### A. The thyroid hormone receptor:

T<sub>4</sub> and T<sub>3</sub> bind to a nuclear receptor called the thyroid hormone receptor (TR) shown in Figure 3. This transcription factor in turn regulates gene expression. TR is a member of the nuclear receptor superfamily, the largest known superfamily of eukaryotic transcription factors (with over 150 other members). Other nuclear receptors include the glucocorticoid receptor, estrogen receptor, retinoid receptors, vitamin D<sub>3</sub> receptor, etc.

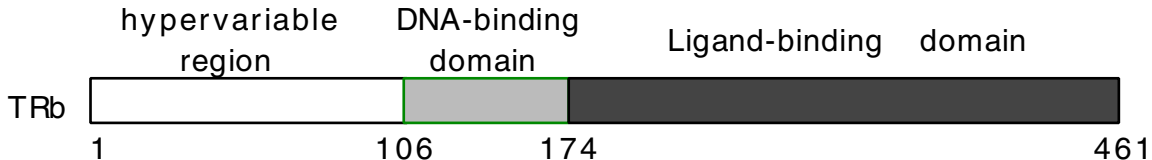


Figure 3. The architecture of a human thyroid receptor (TR,  $\beta$ -isotype), a member of the nuclear receptor superfamily. These receptors have a modular architecture with distinct domains for DNA- and ligand-binding. The DNA-binding domains of the nuclear receptors share 40-50% sequence identity, and are the basis for inclusion in the family. The TR binds to specific DNA sequences known as hormone response elements, through which it up- or down-regulates transcription of its target genes in response to its ligand occupancy. Its affinity for T<sub>4</sub> is 10-fold lower than for T<sub>3</sub>.

TR exists as a heterodimeric protein with RXR- the nuclear receptor for 9-*cis* retinoic acid.

There are several isotypes of TR, and one form is believed to be exclusively formed in the pituitary.

The hormonal response leads to changes in the synthesis of various mRNAs, leading to specific protein syntheses. The resulting proteins exert their effects on mitochondria, which increase in their number and size, and stimulate mitochondrial protein synthesis.

TR is also referred to as c-erbA. An oncogenic variant, v-erbA has also been identified.

B. The chemical findings in hypo- or hyperthyroidism are the result of the actions of products of a variety of genes- all of whose expression is regulated by thyroid hormones.

C. Thyroid hormones are essential for the normal growth and development, especially for the development of the CNS. Congenital thyroid deficiency results in cretinism, which includes dwarfism and mental retardation.

D. There are *calorigenic effects* induced by the thyroid hormones. They increase the basal metabolic rate (oxygen consumption) in most tissues. There are marked effects in heart, skeletal muscle, liver, and kidney. The mechanisms here are not properly understood yet. The whole body oxygen consumption results from cardiac stimulation and enhanced breakdown and re-synthesis of triglycerides (futile cycle).

E. The thyroid hormones also exhibit *Cardiovascular effects*. They increase the rate, force, and output of the heart. The thyroid hormones appear to alter the expression of myosin isozymes so that calcium and actin-activated ATPase activity of cardiac myosin is enhanced. This increases the velocity of muscle fiber shortening. Therefore, *administration of B-adrenergic blockers* must be an important aspect of the initial treatment of severe thyrotoxicosis (also called *thyroid 'storm'*).

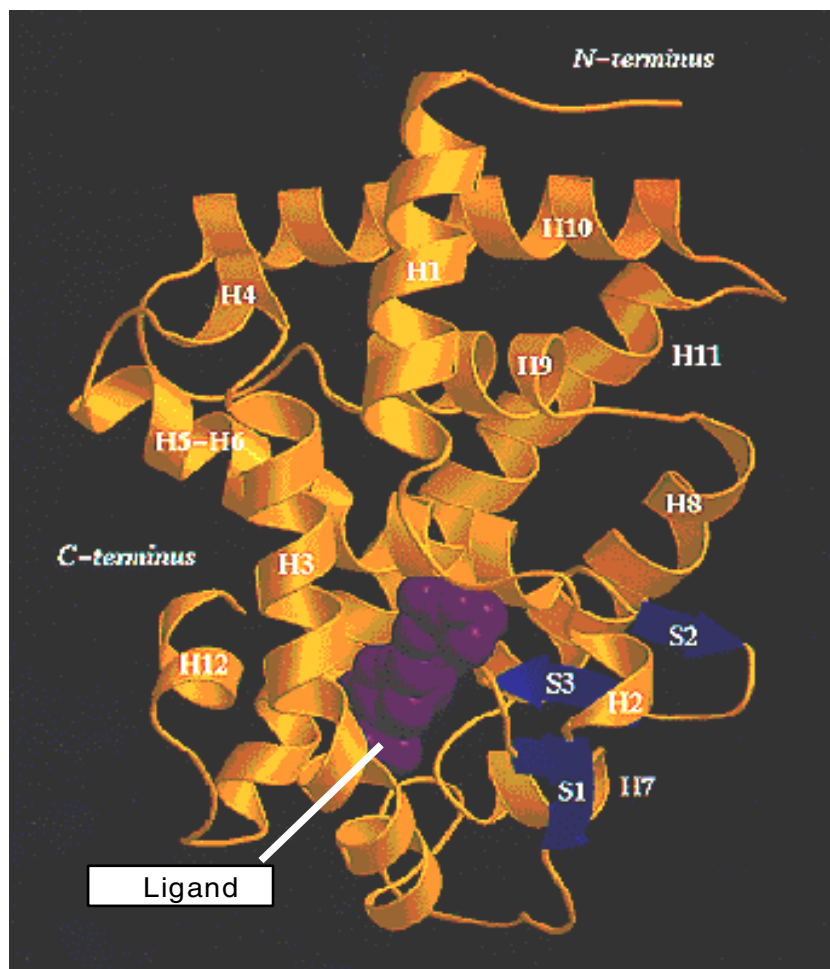


Figure 4. The crystal structure of the TR ligand-binding domain bound to a thyroid hormone. The hormone is recognized in an interior hydrophobic cavity, and makes a number of van der Waals contacts with the hydrophobic amino-acids in the protein core.

F. There are additional (miscellaneous) metabolic effects: these include the reduction of plasma cholesterol (via increase in LDL receptors and enhanced conversion of cholesterol to bile acids). Also, there is an enhancement of intestinal glucose transport.

G. Mutations in the ligand-binding domain of TR (see Figure 3) can lead to generalized resistance to thyroid hormones (See Figure 4). Children with this disorder have a high incidence of attention-deficit-hyperactivity disorder (ADHD).

H. The close inverse relationship between serum  $T_3$  and TSH concentrations is an elegant example of a negative feedback loop (see below). The mechanism: the  $T_3$  / TR complex negatively regulates the expression of genes encoding TSH subunits.

I. Effects of excessive thyroid hormone

increased oxygen consumption, hyperphagia, weight loss, psychiatric disturbances, widened pulse pressure, tachycardia, enhanced cardiac contractility with decreased SVR (increased CO), risk of cardiac hypertrophy. Atrial fibrillation 10% to 25% prevalence. Bone loss in post-menopausal women only.

J. Effects of excessive adrenergic stimulation

Tachycardia, tremor, increased systolic blood pressure, hyperreflexia, eyelid lag, staring, palpitations, depression, nervousness, anxiety.

## 7. The Regulation of Thyroid Function

Overview. The main controlling mechanism is through thyrotropin (thyroid-stimulating hormone, **TSH**), a glycoprotein released from the thyrotroph cells of the anterior pituitary under the influence of the hypothalamic hormone **TRH** (thyrotropin-releasing hormone, or protirelin). See Figure 5.

The production of TSH is also influenced by a negative feedback effect of the thyroid hormones (see Figure 5). The control of the secretion of TSH thus depends on the balance between the actions of thyroid hormones and TRH, and probably also on somatostatin action on the pituitary.

A. The primary secretagogue of TSH is TRH. TRH is a tripeptide (pyroGlu-His-Pro-NH<sub>2</sub>) made by the neurons in the paraventricular nucleus.

B. TRH receptors are linked to the hydrolysis of  $\text{PIP}_2$  - and lead to accumulation of  $\text{IP}_3$ , DAG,  $\text{Ca}^{2+}$ , etc.

TRH is metabolized to His-Pro-NH<sub>2</sub> and then to His-Pro-diketopiperazine.

C. In the negative feedback by thyroid hormones,  $\text{T}_3$  is the more potent species. The dominant mechanism is at the level of the pituitary thyrotrope; where there is a local conversion of  $\text{T}_4$  to  $\text{T}_3$  and protein synthesis. See Figure 5.

In addition, there is another mechanism of feedback (not shown in Figure 5) at the level of hypothalamus also mediated by  $\text{T}_3$ .

D. The actions of TSH on the thyroid gland occur primarily through cAMP.

TSH rapidly increases the release of thyroid hormones in the circulation. Nearly all phases of hormone synthesis and release are eventually stimulated (e.g. iodide uptake, synthesis of thyroglobulin, endocytosis, proteolysis of the colloid).

“Trophic” effects include maintaining the structure and the responsiveness of the thyroid gland at normal levels of TSH. Excess TSH down-regulates TSH receptors.

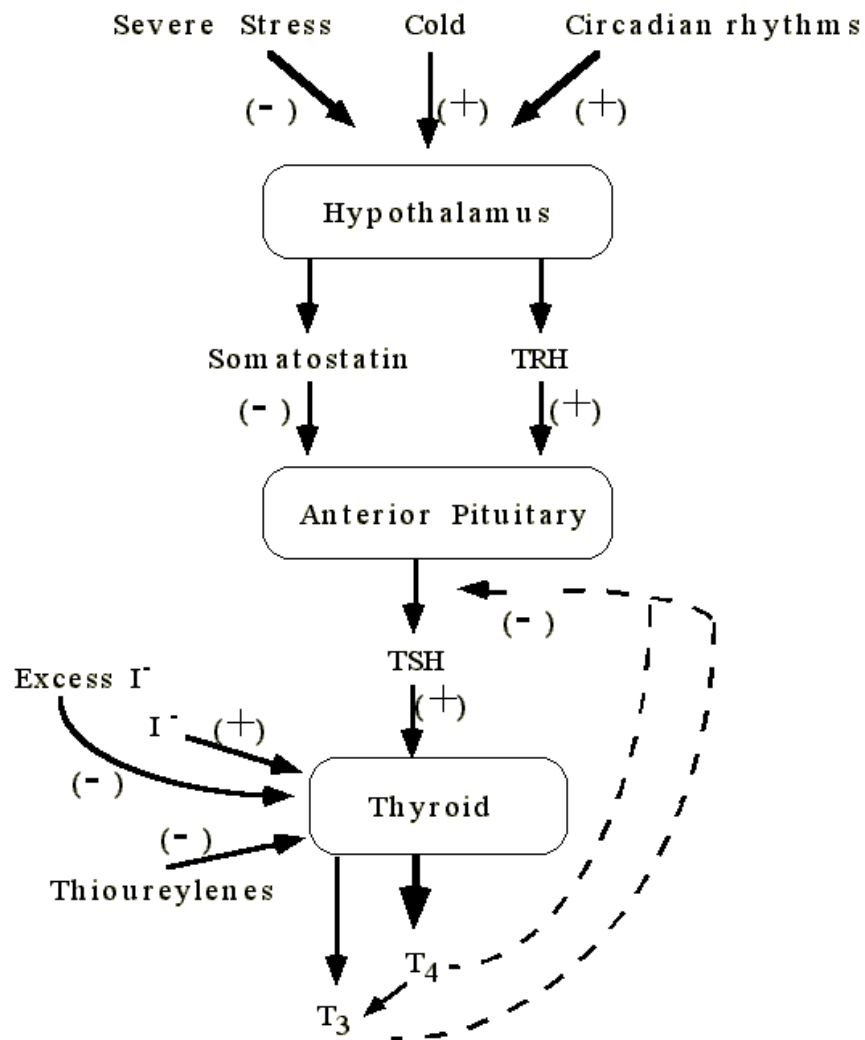


Figure 5. Factors that regulate thyroid hormone secretion.

## 8. Thyroid Function Tests

### a. Serum TSH

Sensitive methods use labeled monoclonal antibodies. Will be low in hyperthyroidism except for rare TSH-induced hyperthyroidism.

### b. Serum T4, Serum T3

Elevated in hyperthyroidism

Serum level increased in increased thyroidbinding globulin states (e.g. pregnancy), but free levels will be normal. T3 rises earlier and more markedly than T4 in hyperthyroid states.

### c. Radioiodine Uptake Scan

High in most cases of hyperthyroidism; low in cases where thyroid is not actively synthesizing hormone, e.g.

- inflammatory thyroiditis (see below)
- ingestion of thyroid hormone

## 9. Graves Hyperthyroidism

### a. Epidemiology:

This is the most common cause of hyperthyroidism.

The second most common cause is excessive thyroid replacement

### b. Pathogenesis

Graves disease is an autoimmune hyperthyroidism caused by the production of IgG antibodies to the TSH receptors. 90% of patients with active Graves Disease have serum IgG with thyroid-stimulating activity. These molecules were formerly called “LATS” for long-acting thyroid stimulating substance, but now are called thyroid stimulating immunoglobulins, or TSI. The antibodies are probably also responsible for Graves ophthalmopathy (against extra-ocular muscle antigens).

The antibodies are obviously not subject to feedback inhibition by thyroid hormones- but the circulating TSH is severely depressed because of the elevation in circulating thyroid hormones.

### c. The Strategy for treatment of Graves disease.

No direct immunomodulation therapy is presently available. Therefore, the strategy is to control symptoms of adrenergic stimulation, with beta-blockers decrease production of thyroid hormone, by temporary treatment with *thioureylenes* (see next section), in hopes of remission. There is definitive treatment with radioiodine (see section on this topic below) or surgery (also see the section on this topic below), at risk of hypothyroidism. Treat with  $^{131}\text{I}$  before planned pregnancy to avoid need for treatment during pregnancy.

## 10. Antithyroid drugs: Thioureylenes (Propylthiouracil and Methimazole, see Figure 6)

1. Mechanism: These drugs can inhibit synthesis of thyroid hormones by inhibiting the peroxidase enzyme discussed earlier, and may be immunomodulatory (anti-TSH receptor Ab are decreased and suppresser T-cell activity increased). Addition of thyroxine to regimens may increase remission rate.

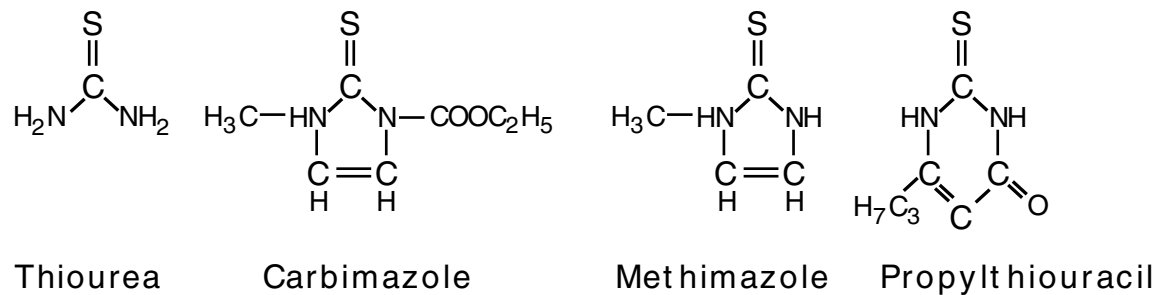


Figure 6. Thioureylene Drugs are related to thiourea (the thiocarbamide group is essential for their anti-thyroid activities).

Prognosis: Treating for 12 to 18 months will give remission rates of 14% to 80%.  
 Relapses after discontinuation usually occur within 6 months, but may be years later.  
 Monitor T<sub>4</sub> and T<sub>3</sub> since TSH may remain suppressed even after T<sub>4</sub> levels are corrected..

#### Propylthiouracil

- inhibits hepatic conversion of T<sub>4</sub> to T<sub>3</sub> -thus good for rapid lowering of serum T<sub>3</sub>
- preferred for pregnant or breast-feeding women
- half-life of 2 hours

#### Methimazole

- lower risk of agranulocytosis with low dose methimazole.
- half-life of 3-5 hours.

## 11. Radioactive Iodine

### Overview:

Radioactive iodine is used for both diagnosis and for the treatment of hyperthyroidism or thyroid carcinoma.

Sodium iodide containing <sup>123</sup>I is used only for diagnostic scans - it emits X-rays that can be detected externally and has a half-life of 13 hours.

Carrier free <sup>131</sup>I sodium iodide emits both X-rays and  $\beta$ -particles. Its half-life is 8 days (99% lost in 56 days). It is efficiently 'trapped' by the thyroid and incorporated into thyroglobulin. The soft  $\beta$ -particles exert a destructive effect almost exclusively on the parenchymal cells of the thyroid gland.

a. Uses of  $^{131}\text{I}$ :

Preferred Graves therapy for young adults and older patients and is the most common treatment for Graves. But 50 to 80% risk of hypothyroidism (something we should always watch out for).

b. Method of use:

Because of delay in effect, treat with thioureyline drug and/or beta-blocker for immediate management. Some stop thioureyline drug 4-5 days before treatment.

Monitor follow-up  $T_3$  and  $T_4$  levels closely for hypothyroidism.

Tracer uptake studies are not generally necessary since dose calculations using uptake data haven't been shown to be better at avoiding hypothyroidism than just using a standard dose (5 to 15mCi).

Pregnancy and breast-feeding are contraindications ( $^{131}\text{I}$  crosses placenta and can cause fetal hypothyroidism); Avoid pregnancy for 4 months after treatment.

c. Prognosis

Symptoms should improve in 4 to 6 weeks. If not improved in 3 to 6 months, repeat same or larger dose.

d. Complications:

Main complication is dose-dependent risk of long term hypothyroidism (50% to 80%); hypothyroidism in first 6 months may be temporary. Radiation dose to gonads is similar to an abdominal CT scan or barium enema. Radiation thyroiditis is uncommon; thyroid storm from this is very rare. No apparent increased thyroid cancer risk.

## 12. Surgical Thyroidectomy (modified subtotal)

a. Indications:

- obstructing goiters
- allergy to anti-thyroid drugs
- refusal to take  $^{131}\text{I}$
- thyroid cancer

b. Method:

Usual practice is to make euthyroid with propylthiouracil or methimazole and inorganic iodine (Lugol's) over 4 to 7 days before surgery; or use beta-blockers with or without

### c. Prognosis

In one 4 year prospective study of 55 patients, 90% were euthyroid at 4 years. Treat for one year if thyroxine needed, then re-check. Other studies: 5% permanent hypothyroid after one year, 50% by 25 years. (papillary) thyroid cancer more common in surgerized Graves.

### 13. Non-radioactive Iodine (in addition to goiter prophylaxis)

Large doses of Lugol's solution ( $I_2 + NaI$ ) are given to prepare patients for subtotal thyroidectomy because it reduces the vascularity of the gland and makes it harder and less friable. Iodine inhibits release of thyroid hormones for a few days or weeks, then effect is lost. Iodine is not a commonly used treatment.

#### Indications:

pre-operative restoration of euthyroid state.

thyroid storm after  $^{131}I$  to hasten fall of  $T_4$  and  $T_3$ .

### 14. Management of Nodular Goiter

Does not spontaneously remit.

40% of patients over 60 have atrial fibrillation.

$^{131}I$  is preferred therapy. Low incidence of post-treatment hypothyroidism, especially with solitary adenomas, since normal thyroid tissue usually recovers. May need a higher dose (10 to 50 mCi) and/or repeat treatment. Should err on side of overtreating

### 15. Management of Thyroiditis

Caused by inflammation- mediated release of pre-formed hormones from thyroid gland. Disease is acute, generally mild and self-limited to a few weeks so definitive therapy is rarely needed.

Use beta-blockers to treat symptoms of adrenergic over-stimulation.

May become transiently hypothyroid (1 to 4 months) during recovery. If treatment with L-thyroxine is required (see below), discontinue and recheck thyroid status after 6 months.

Short-term salicylate may be required for relief of painful thyroiditis

Up to 1/3 of post partum cases become hypothyroid permanently.

### 16. Therapeutic Use of Thyroid Hormones- treatment for thyroid hypofunction:

a. Levothyroxine sodium (l-thyroxine,  $T_4$ ) is best choice since dosage can be more reliably controlled than with other preparations of desiccated, defatted whole porcine

thyroid glands, or of the derived thyroglobulin. The advantage of using thyroxine is that the serum T<sub>3</sub> concentration is physiologically controlled.

- usually given orally, 30-40% never reaches the circulation and is excreted in feces.
- can be given parenterally (i.v.) in higher doses for fast action in urgent situations.
- onset of its action depends on the dose administered (at best 6-24 hours).

b. Liothyronine sodium (T<sub>3</sub>) is sometimes used for quicker action. Only oral preparations are available for use.

c. Liotrix is an expensive 4:1 mixture of T<sub>4</sub> and T<sub>3</sub> that is supposed to mimic the normal secretion of the thyroid gland.

## 17. References

[1] Klein I, Becker DV, Levey GS. Treatment of Hyperthyroid Disease. *Annals of Internal Medicine* 1994; 121:281-288. Abstract

[2] Franklyn JA. Drug Therapy: The Management of Hyperthyroidism. *New England Journal of Medicine* 1994; 330(24):1731-1738. Abstract

[3] Sawin CT, Geller A, Wolf PA, et al. Low Serum Thyrotropin Concentrations as a risk factor for atrial fibrillation in older persons. *New England Journal of Medicine* 1994;331(19):1249-52. Abstract

## Summary of Compounds and Drugs

ACTH

CRH

Tri-iodothyronine (T<sub>3</sub>)

Thyroxine (T<sub>4</sub>)

TSH

TRH

Propylthiouracil

Methimazole

Carbimazole

<sup>131</sup>Iodine

<sup>123</sup>Iodine

Lugol's solution