

PHARMACOLOGY

Pharmacology of Endocrine System: Thyroid Hormone & Anti-thyroid Drugs

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Keywords

thyroid hormone, thyronine, thyroglobulin, liothyronine.

The thyroid gland is the source of two different types of hormones:

1. Triiodothyronine (T_3) and Tetraiodothyronine(T_4) which regulate the normal growth and development.
2. Calcitonin which is important for the regulation of calcium metabolism and is secreted by parafollicular “C” cells

Iodide Metabolism

Both T_4 and T_3 are iodine containing derivatives of the condensation product of the amino acid tyrosine which is called thyronine. The recommended daily intake of iodide is about 100-150micro grams.

Biosynthesis

- (1) **Uptake:** Iodide is taken up in the gland by a follicle cell basement membrane protein called sodium/iodide symporter. (NIS). This can be inhibited by various anions as SCN^- , ClO_4^- .(Fig.1) The NIS is also controlled by an autoregulatory mechanism whereby decreased thyroid iodine stores increase uptake due to TSH mediated stimulation of NIS and vice versa i.e. increased intrathyroidal iodine decreasing NIS protein expression.
- (2) **Oxidation and iodination:** Iodide thus taken up is oxidized by thyroidal peroxidase (TPO) to iodinium ions or hypoiodous acid or enzyme linked hypoiodate in the presence of hydrogen peroxide. These forms which form iodinate tyrosine residues in thyroglobulin molecule to form monoiodotyrosine (MIT) and diiodotyrosine (DIT) by the process of iodide organification. TPO is blocked transiently by high intrathyroidal iodide and persistently by thioamide drugs.(Fig.1)
- (3) **Coupling and Release:** Two molecules of DIT combine within the thyroglobulin molecule to form T_4 (l-thyroxine). One molecule of MIT and one molecule of DIT combine to form T_3 (liothyronine). T_4 , T_3 , MIT and DIT are released from thyroglobulin by endocytosis and proteolysis of thyroglobulin at the apical border of follicular cells. T_4 and T_3 are released into the circulation while MIT and DIT are deiodinated within the gland and the iodine is reutilized. The process of proteolysis is also blocked by high levels of intrathyroidal iodide.
- (4) **Conversion of T_4 to T_3 in periphery:** Almost 80% of the T_3 is derived from the sequential monodeiodination of thyroxine in the peripheral tissues, primarily liver by the enzyme iodothyronine 5' deiodinase. Iodothyronine 5' deiodinase exists in two forms, type I is present in the liver and is responsible for circulating T_3 while type II is found primarily in brain and pituitary and is responsible for local production of T_3 in these tissues. Another enzyme 5 deiodinase may form reverse T_3 ($r T_3$). Most tissues utilize the circulatory T_3 except brain and pituitary where local generation of T_3 is the major source of intracellular hormone.

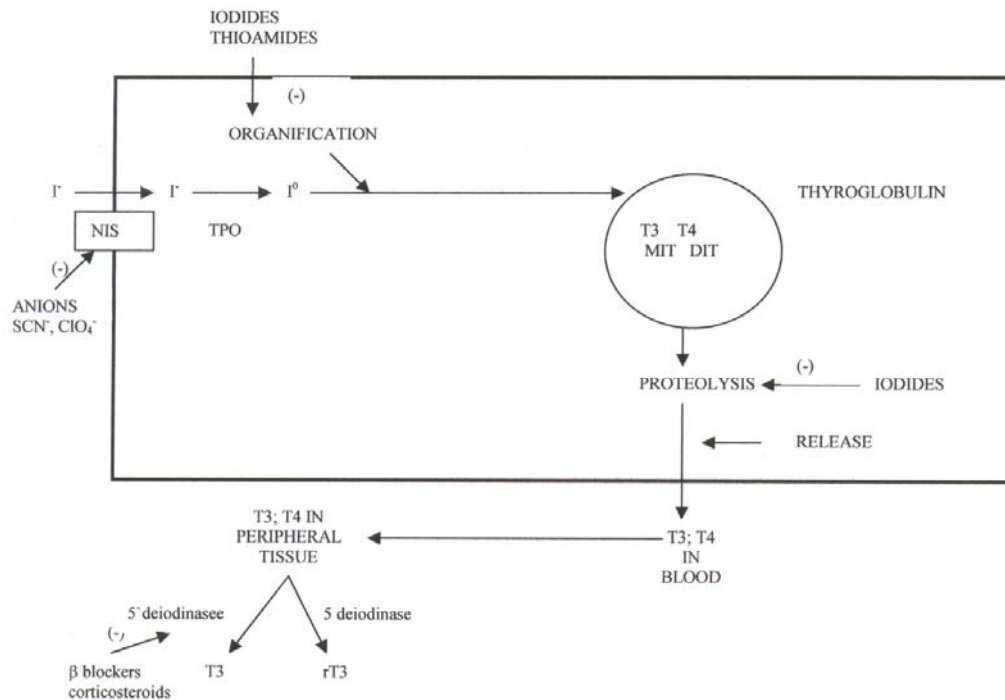


Fig.1 THYROID HORMONE BIOSYNTHESIS

Transport and Metabolism

T₄ and T₃ in plasma are reversibly bound to the plasma proteins primarily the thyroxine binding globulin (TBG). The protein binding protects the hormones from metabolism and excretion resulting in their long half lives in the circulation. Only about 0.03% of total T₄ and 0.3% of T₃ exist in the “free” form which is the form in which the hormones have metabolic activity. Beside TBG, transthyretin and albumin can also bind the thyroxine.

Thyroxine has a half life of 6-8 days and the same for T₃ is 1- 2 days. The half lives are increased in hypothyroidism and decreased in hyperthyroidism because of altered rates of metabolism. In condition where TBG is increased such as pregnancy or by contraceptives or estrogens, the concentration of total and bound hormone will increase but the concentration of free hormone and steady state elimination will be normal.

Regulation of Thyroid Function

As is seen in Fig. 2, hypothalamus secretes thyrotropin releasing hormone (TRH) into the pituitary portal venous system. TRH stimulates the synthesis and release of thyroid stimulating hormone (TSH). TSH increases the synthesis and released of T₄ and T₃ via an adenylyl cyclase cAMP pathway. T₄ and T₃ act in a negative feedback fashion in the pituitary and hypothalamus to block the secretion of TSH and TRH respectively. Besides this, others drugs such as dopamine, steroids etc. also affect the thyroid function.

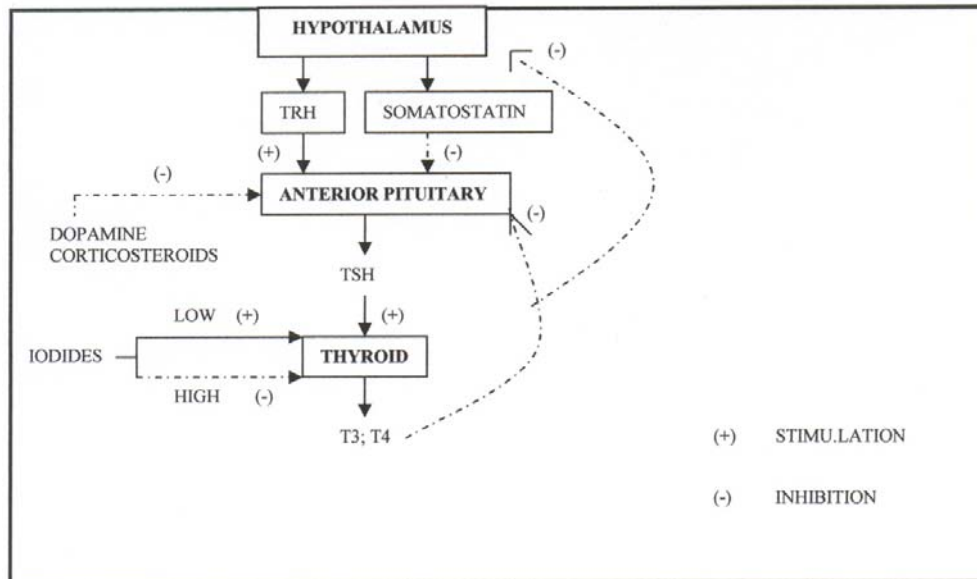


Fig.2 REGULATION OF THYROID

Besides the hypothalamus-pituitary-thyroid axis autoregulation is also very important in the case of thyroid for its normal functioning.

Actions of Thyroid hormones

Mechanism of Action: Most actions of thyroid hormones seem to be mediated by nuclear receptors. T₃ binds to nuclear receptors which bind to thyroid hormone response elements situated in the regulatory region of target genes. So T₃ modulates gene transcription and therefore, protein synthesis. In contrast to T₃, T₄ does not alter gene transcription. It may serve as a “prohormone”

1. Growth and development: Thyroid hormones are responsible for optimal growth and development. Irreversible mental retardation occurs if thyroid hormones are absent during active neurogenesis and morphological alterations like disturbed axonal projections and decreased synapse formation are seen in the brain

2. Calorigenic effects: There is an increase in oxygen consumption out of which up to 40% is because of increased cardiac contractility. Organs such as brain, gonads and spleen are unresponsive to the calorigenic effects of thyroid hormones. The mechanism by which this is mediated is not known.

3. Cardiovascular effects: Hyperthyroidism is characterized by tachycardia, increased stroke volume, cardiac hypertrophy, decreased peripheral vascular resistance and increased pulse pressure. At least two mechanisms seem to be operating for these effects:

a) Direct effect on myosin Ca^{2+} -ATPase and

b) As a result increased number of β receptors and enhanced amplification of β receptor signal. It is not because of increased catecholamine levels. T₃ also has a direct vasodilating effect on vascular smooth muscle.

4. Metabolic effects: Thyroid hormones stimulate mainly the metabolism of cholesterol to bile acids. They enhance the lipolytic effect of other hormones (eg catecholamines). Also, in hyperthyroidism there is depletion of glycogen stores, enhanced gluconeogenesis and increased absorption of glucose from the gut which manifests as an insulin resistant state. Negative nitrogen balance leading to weight loss and decreased mucoprotein synthesis resulting in myxoedema characterize hyper and hypothyroidism respectively.

5. Other effects: Besides the above-mentioned actions thyroid hormones also affect skeletal muscle contraction, propulsive activity of gastrointestinal system and are required for maintenance of pregnancy & lactation.

Preparations

The thyroid preparations may be synthetic or of animal origin. The synthetic levothyroxine (T_4) is used most frequently for thyroid replacement and suppression because it is cheap, less allergic, and stable and has a long duration of action whereas liothyronine (T_3) is used in case of myxoedema coma because of its prompt action. A mixture of thyroxine and liothyronine (liotrix) in a ratio of 4:1 is available but is very expensive.

Uses

1. Cretinism: Irreversible mental retardation occurs if thyroid hormones are not present during neurogenesis. So, success depends on the age at which therapy is started and hence therapy should be started as early as possible. Thyroxine (6-8 $\mu\text{g/kg/d}$) is started and the guides for appropriate hormone replacement therapy include physical growth, motor development, bone maturation etc.

2. Adult hypothyroidism: - Treatment with l- thyroxine is started with initial low dose (50 μg) and gradually increasing it till the optimal level is attained (dose regulated by clinical response). Cautious approach is needed in older patients because heart is sensitive to the level of circulating thyroxine and angina may be precipitated.

3. Nodular thyroid disease: - TSH suppressive therapy with the levothyroxine is started for a benign solitary nodule which then decreases in the size because of reduced TSH stimulation. Therapy is continued till the nodule continues to decrease in size though it should be observed for any recurrent growth.

4. Myxoedema coma: - It is medical emergency seen in the elderly characterized by hypothermia, respiratory depression, unconsciousness, bradycardia, delayed reflexes and dilutional hyponatremia. Treatment includes supportive care, ventilatory support, rewarming and treatment of precipitating incident. Parental administration of T_3 (liothyronine) is necessary due to uncertain absorption through gut. However if T_3 is not available, parenteral T_4 can be given. T_3 is preferred because of its rapid onset of action. Intravenous steroids are also recommended because of coexistent decreased adrenal reserve in about 10% patients.

5. Thyroid cancer: - Only some cases of papillary type of thyroid cancer respond to TSH suppression by l-thyroxine. Surgery is the mainstay of treatment for the rest.

Antithyroid Agents

The antithyroid drugs reduce the thyroid activity by the following mechanisms:-

a) Modifying the tissue response to thyroid hormones

- b) Interfering with the production of thyroid hormones
- c) Destruction of the gland by radiation or surgery

Classification

1. **Thioamides:** Propylthiouracil, Methimazole, Carbimazole
2. **Ionic Inhibitors:** Thiocyanate, Perchlorate
3. **Hormone Release Inhibitors:** Iodine, Iodides of potassium and sodium, Iodinated contrast media
4. **Drugs Destroying Thyroid Tissue:** Radioactive iodines eg. ^{131}I , ^{125}I
5. **Miscellaneous:** Adrenergic blockers

Thioamides

Methimazole is much more potent as compared to propylthiouracil. The major mechanism of its action is the inhibition of thyroid peroxidase catalyzed reactions and iodine organification. The coupling of iodotyrosines is also blocked. Propylthiouracil also blocks the peripheral conversion of T_4 to the more active T_3 and hence has a rapid onset of action. Therefore it is more suitable for the management of thyroid storm. These drugs require up to 4 weeks for their effect because this is the time taken by the already synthesized hormones to be used up. During this period symptoms can be controlled by using β blockers.

Pharmacokinetics: Carbimazole acts by getting converted into methimazole. Both propylthiouracil and methimazole are rapidly absorbed orally. Both these drugs have volume of distribution equal to that of total body water and are excreted in the urine. The plasma half lives of propylthiouracil and methimazole are 75min and 6 hours respectively. Since both the drugs are accumulated in the thyroid, so their dosing is not influenced by their short plasma half lives. Though both drugs cross the placenta and enter the milk, propylthiouracil is preferred in pregnancy because it crosses the placenta less readily owing to its high protein binding.

Adverse Effects: Untoward effects occur in 3-8% of the patients receiving the drug. A papular urticarial rash is the commonest side effect. Other frequent side effects include pain and stiffness of joints, headache, nausea, cholestatic jaundice, loss and graying of hair and lymphadenopathy. Agranulocytosis is the most dangerous complication though it is rare and fortunately reversible. Patient should immediately consult if fever or sore throat develops in them.

Uses:

1. **Definitive therapy:** These drugs are most useful in young patients with small goiter and mild disease. It is also used in grave's disease till spontaneous remission occurs. Though long periods of treatment and observation are required but the distinct advantage is that they leave an intact thyroid gland and if hypothyroidism occurs, it is readily reversible.
2. **In conjunction with radioactive iodine:** It is used along with ^{131}I because the response to radioactive iodine takes time and so for the initial control, thioamides are used. However they should be stopped for few days before administering radioactive iodine so that the uptake of radioactive iodine is not impaired.

3. **Prior to surgery:** patients requiring surgery are rendered euthyroid before operating upon them by the use of these drugs.

Anion Inhibitors

Anion inhibitors such as perchlorate (ClO_4^-) and thiocyanate (SCN^-) act by competing with the iodide transport mechanism. Though their effect is unpredictable but this group is important in the treatment of iodide induced hyperthyroidism (e.g. amiodarone induced hyperthyroidism) and in some cases of Grave's disease. This group is used infrequently because of its hepatotoxicity and bone marrow toxicity.

Iodides

Iodides act as rapid and efficacious drugs in thyrotoxicosis because high iodide plasma concentration results in inhibition of the release of thyroid hormones. Acute inhibition of the synthesis of iodotyrosines and iodothyronines by iodide is also known as Wolff chaikoff effect. Iodides also decrease vascularity and size of a hyperplastic gland making this useful in a patient prior to surgery. The only disadvantage is that the gland 'escapes' from the iodide block in 1-2 months. So, thioamides should be used prior to the use of iodides. Also there is a risk of development of fetal goiter if it is given in pregnant women. Iodides may also be used to protect thyroid from subsequent damage from radiation exposure in nuclear accidents.

Adverse Effects: Iodism is the condition caused due to chronic iodide overdose. Its features include headache, swelling of salivary glands, sneezing, increased lacrimation, rash and gastric irritation. In addition hypersensitivity to iodide may present acutely characterized by angioedema, cutaneous hemorrhage, lymphadenopathy, arthralgia and thrombocytopenia.

Iodinated Contrast Media

The iodinated agents like ipodate and iopanoic acid taken orally or diazotate intravenously inhibit the conversion of T_4 to T_3 in the liver, kidney, pituitary and the brain. They also inhibit hormone release. They are used as adjunctive drugs in thyroid storm. Their safety in pregnancy is unknown.

Radioactive Iodine

Out of the many radioisotopes which are present, only ^{131}I which has a half life of 8 days is used. It is administered orally. Another radioactive iodine preparation is ^{125}I having a short half life of 13 hrs. It emits only γ rays and is used for diagnostic purposes. ^{131}I is trapped efficiently inside the thyroid where it emits β particles resulting in follicular disruption, necrosis of follicular cells and finally the fibrosis of the gland. It also emits γ rays which pass through the tissues and can be detected easily. Its advantages include easy administration, cheap, absence of pain and minimal injury to adjacent tissues. It should not be given in pregnant women because it crosses the placenta and is excreted in breast milk. The only disadvantage is permanent hypothyroidism which follows its use. In some patients it can precipitate thyroid storm due to release of thyroid hormones as a result of gland destruction. It is indicated in the treatment of hyperthyroidism especially older patients and in those with heart disease. It is also useful in patients with toxic nodular goiter since it does not go in spontaneous remission easily.

Adrenergic Blockers

The beta blockers without intrinsic sympathomimetic activity are effective in alleviating symptoms in thyrotoxicosis because most of these symptoms resemble sympathetic stimulation. Propranolol is the most frequently used drug in this category. These drugs also inhibit the conversion of T_4 to T_3 to some extent which may also account for the beneficial effect.

Suggested Reading

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