HYPOTHALAMUS – PITUITARY-THYROID AXIS

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Learning objectives

- Describe the morphology and biological role of the thyroid gland.
- Explain the structure of thyroid hormones, their synthesis and secretion by follicular cells.
- Describe how plasma thyroid hormone levels are regulated by the hypothalamus-pituitary axis, by deiodinases, and by carriers. Why is serum TSH level used as indicator of thyroid gland function?
- Describe the mechanism of action of thyroid hormones.
- Explain the effect of hyper- and hypo-secretion of thyroid hormone on basal metabolism. What happens to thyroid hormone in prolonged fasting and in restricted diets?

INTRODUCTION

The thyroid hormones are trophic hormones that regulate basal metabolism, and are essential in the early development of the CNS, skeletal growth, and for "permissive actions" on body tissues. They are synthesized and secreted by the thyroid gland as two active forms, thyroxin (T4) and triiodothyronine (T3) (Fig 1). The thyroid contains 3-4 months supply of stored hormone.

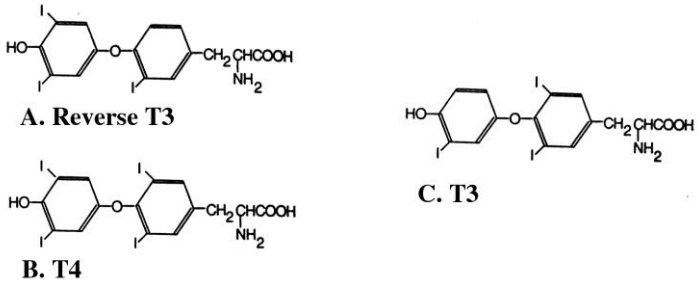

Figure 1. Thyroid hormones are derivatives of tyrosine. Their relative activity is T3> T4>> rT3 (inactive). Both iodine atoms on the inner ring and one on the outer ring are essential.

SYNTHESIS, SECRETION AND STORAGE

Synthesis of thyroid hormone takes place in the thyroid follicular cells. The preprohormone, thyroglobulin (330,000 Da), is synthesized on rough endoplasmic reticulum (RER) and then secreted into the lumen of the follicles for storage (Fig 2). At the cell-lumen boundary, iodine is added covalently and a coupling reaction occurs to form the precursors of T3 and T4. Thyroglobulin and the thyroid hormones are the only iodinated proteins made in the body.
***** In the absence of iodide, thyroid hormones are not made**.

Dietary iodide enters the thyroid follicular cell by a Na^+/I^- transporter. This is a secondary active transport coupled to the activity of the Na-K ATPase also located on the basal surface of these cells. Under normal conditions, the thyroid/serum (T/S) ratio is 25:1. However, the Na+/I- transporter can be stimulated by TSH to concentrate iodide raising the T/S ratio to at least 250:1.

The thyroid gland is the only gland in the human body that stores iodine. Therefore the activity of the gland can be measured by ^{131}I uptake. This is used clinically to determine the activity of the gland.

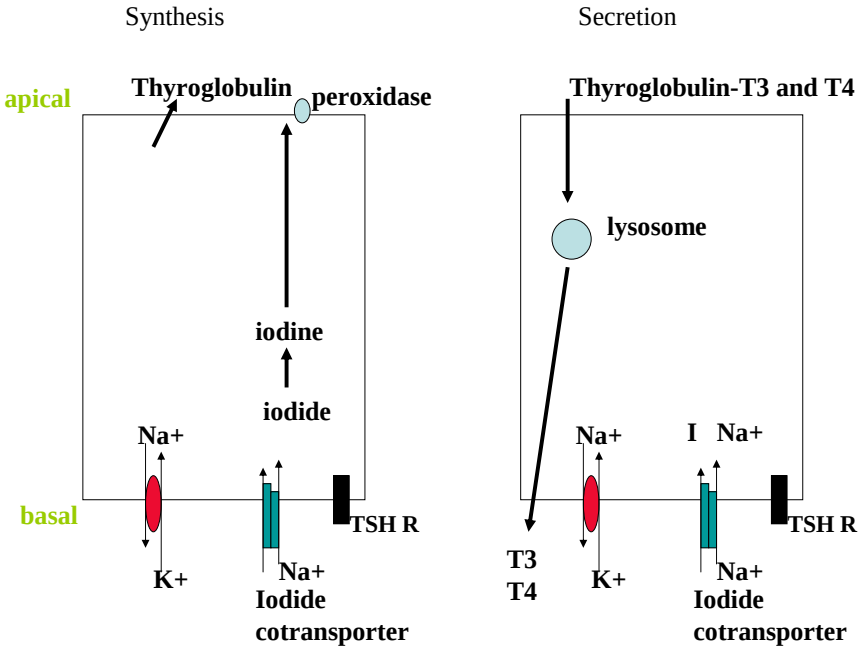

Figure 2. Synthesis and secretion of thyroid hormone is regulated by TSH which binds to its receptor (TSH R) on the basal surface of the follicular cells.

Thyroid hormone synthesis is controlled by the hypothalamus-pituitary axis. Thyroid stimulating hormone (TSH) from the pituitary stimulates both the synthesis and secretion of thyroid hormone. In turn, TSH is regulated by thyroid releasing hormone (TRH) secreted from the hypothalamus. TRH and TSH secretions are inhibited by high blood levels of thyroid hormone in a classical negative feedback loop (Fig 3). Thyroid hormone axis is sensitive to external factors such as cold and stress. These factors increase TSH secretion and thereby the synthesis and secretion of T3 and T4 to raise basal metabolic rate (BMR).

TRANSPORT BY CARRIERS IN BLOOD

Thyroid hormones are not soluble in the plasma. They are transported by specific carriers (thyroid binding globulin). Only free T3 and T4 are biologically active. They enter target cells by facilitated diffusion. Under normal conditions, carrier bound T4 and T3 circulate in the blood in a ratio of about 20:1. T3 is more active than T4.

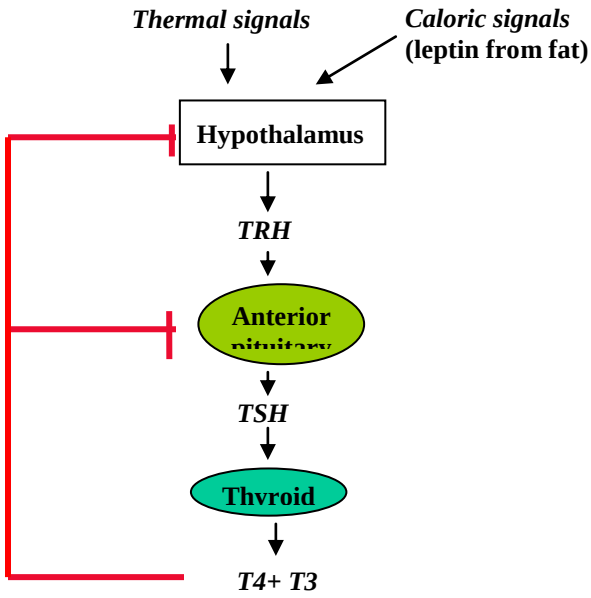

Figure 3. Negative feedback loops regulate secretion of thyroid hormones.

CONVERSION IN PERIPHERAL TISSUES

T4 is the prohormone which can be converted to T3 by an enzyme called deiodinase. During starvation or prolonged fasting, the deiodinase activity is inhibited (Fig 4) in most peripheral tissues but not in the brain, skeletal muscles, heart and thyroid gland. Why is this important? [*answer*. *The brain, heart and thyroid gland are the critical organs for maintenance of homeostasis. Skeletal muscle is usually the largest mass in the body. Its metabolism directly affects body temperature (both shivering and non-shivering thermogenesis*).]

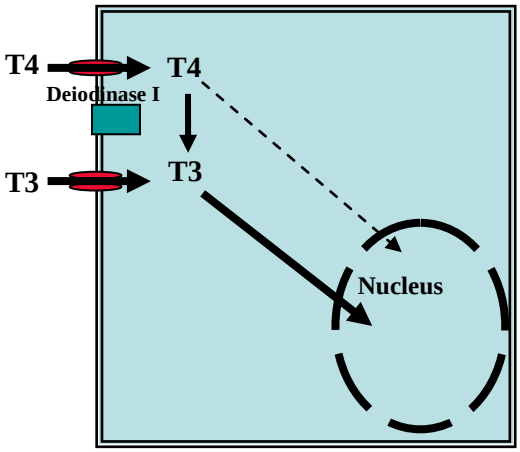

Figure 4. Deiodinase activity in peripheral target tissues converts T4 to T3. Deiodinase I, expressed on most peripheral tissues, is down-regulated by starvation. Deiodinase II, expressed in the CNS, heart, thyroid and skeletal muscle, is not regulated by diet.

SITES AND MECHANISM OF ACTION

Thyroid hormone activates gene transcription in all tissues. The thyroid hormone binds to the thyroid hormone receptor (THR) which resides on DNA in the nucleus. Transcription of two important genes, the Na-K ATPase and the beta 1 adrenergic receptor, are increased by TH action. Increased adrenergic receptor activity in turn leads to an increase in the expression of uncoupling proteins in mitochondria which generates heat.

PATHOPHYSIOLOGY

Too Little: Congenital hypothyroidism occurs with insufficient levels of TH at birth. This state results in growth disturbances and severe mental retardation which is irreversible.

Too little: Hypothyroidism leads to weight gain due to decreased metabolism, hair loss, mental sluggishness, and decreased tolerance to cold.

Too much: Hyperthyroidism leads to muscle wasting, nervousness, weight loss due to increased metabolism and decreased tolerance for heat. A common sign of hyperthyroidism is a rapid heart rate. Why?

Too much: Grave's disease is an autoimmune disease in which circulating antibodies (IgG) bind to and activate the TSH receptor on the thyroid gland follicular cells. This leads to increased secretion of T3 and T4. Would TSH levels be increased in this condition? Why?

Iodine deficiency can lead to an enlarged gland called a **goiter**. Frank iodine deficiency has been virtually eliminated by iodine supplementation of salt. Predict the levels of TSH when the diet is deficient in iodine [increased, decreased, no change].

KEY CONCEPTS

1. T3 and T4 are synthesized and secreted by the thyroid gland in response to TSH.
2. Thyroid hormones are formed from hydrolysis of iodinated thyroglobulin.
3. Dietary iodine is essential for synthesis of the thyroid hormones.
4. Under normal conditions, the majority of T3 is made in peripheral tissues from T4. This is an important regulatory site governing basal metabolic rate (BMR).
5. Thyroid hormones are essential for development of the central nervous system, for normal body growth, and to regulate basal energy and temperature.

QUESTION

A 20 year old student had been taking pills containing 5 times the normal dose of triiodothyronine (T3). When examined she had increased:

A. Basal metabolic rate (BMR)
B. T4 levels in her blood
C. TSH levels in her blood

ANSWER

A. basal metabolic rate increased