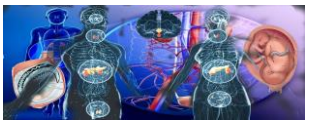
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Metabolic Effects of Thyroid Hormone: A Review

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Abstract

The thyroid hormone is well known for controlling metabolism, growth, and many other bodily functions. The thyroid gland, anterior pituitary gland, and hypothalamus comprise a self-regulatory circuit called the hypothalamic-pituitary-thyroid axis. The main hormones produced by the thyroid gland are thyroxine or tetraiodothyronine (T4) and triiodothyronine (T3). Thyrotropin-releasing hormone (TRH) from the hypothalamus, thyroid-stimulating hormone (TSH) from the anterior pituitary gland, and T4 work in synchronous harmony to maintain proper feedback mechanism and homeostasis. Hypothyroidism, caused by an underactive thyroid gland, typically manifests as bradycardia, cold intolerance, and weight gain. constipation, fatigue,

Keywords: Thyroid hormone synthesis; Iodine deficiency; myxedema coma; cretinism; periventricular nucleus; thyroid-stimulating hormone

Introduction

The thyroid hormone is well known for controlling metabolism, growth, and many other bodily functions. The thyroid gland, anterior pituitary gland, and hypothalamus comprise a self-regulatory circuit called the hypothalamic-pituitary-thyroid axis. The main hormones produced by the thyroid gland are thyroxine or tetraiodothyronine (T4) and triiodothyronine (T3). Thyrotropin-releasing hormone (TRH) from the hypothalamus, thyroid-stimulating hormone (TSH) from the anterior pituitary gland, and T4 work in synchronous harmony to maintain proper feedback mechanism and homeostasis. Iodine is an essential trace element absorbed in the small intestine. It is an integral part of T3 and T4. Sources of iodine include iodized table salt, seafood, seaweed, and vegetables. Decreased iodine intake can cause iodine deficiency and decreased thyroid hormone synthesis. Iodine deficiency can cause cretinism, goiter, myxedema coma, and hypothyroidism.

Cellular Level

Regulation of thyroid hormone starts at the hypothalamus. The hypothalamus releases thyrotropin-releasing hormone (TRH) into the hypothalamic-hypophyseal portal system to the anterior pituitary gland. TRH stimulates thyrotropin cells in the anterior pituitary to the release of thyroid-stimulating hormone (TSH). TRH is a peptide hormone created by the cell bodies in the periventricular nucleus (PVN) of the hypothalamus. These cell bodies project their neurosecretory neurons down to the hypophyseal portal circulation, where TRH can concentrate before reaching the anterior pituitary.

TRH is a tropic hormone, meaning that it indirectly affects cells by stimulating other endocrine glands first. It binds to the TRH receptors on the anterior pituitary gland, causing a signal cascade mediated by a G-protein coupled receptor. Activation of Gq protein leads to the activation of phosphoinositide-specific phospholipase C (PLC). PLC hydrolyzes phosphatidylinositol 4,5-P(PIP) into inositol 1,4,5-triphosphate (IP) and 1,2-diacylglycerol (DAG). These second messengers mobilize intracellular calcium stores and activate protein kinase C, leading to downstream gene activation and transcription of TSH.

TSH is released into the blood and binds to the thyroid-releasing hormone receptor (TSH-R) on the basolateral aspect of the thyroid follicular cell. The TSH-R is a Gs-protein coupled receptor, and its activation leads to the activation of adenylyl cyclase and intracellular levels of cAMP. The increased cAMP activates protein kinase A (PKA). PKA phosphorylates different proteins to modify their functions. The five steps of thyroid synthesis are below:

1. **Synthesis of Thyroglobulin**: Thyrocytes in the thyroid follicles produce a protein called thyroglobulin (TG). TG does not contain any iodine, and it is a precursor protein stored in the lumen of follicles. It is produced in the rough endoplasmic reticulum. Golgi apparatus pack it into the vesicles, and then it enters the follicular lumen through exocytosis.
2. **Iodide uptake**: Protein kinase A phosphorylation causes increased activity of basolateral Na+-I- symporters, driven by Na+-K+-ATPase, to bring iodide from the circulation into the thyrocytes. Iodide then diffuses from the basolateral side to the apex of the cell, where it is transported into the colloid through the pendrin transporter.
3. **Iodination of thyroglobulin**: Protein kinase A also phosphorylates and activates the enzyme thyroid peroxidase (TPO). TPO has three functions: oxidation, organification, and coupling reaction.

Transport and bioavailability of thyroid hormones

T3 is the biologically active hormone, while T4, which is the major hormone secreted by the thyroid, is considered a precursor of T3 or a prohormone. T3 is approximately four times more potent than T4, but its circulating concentration and plasma half-life are much lower than T4. The deiodination of T4 in peripheral tissues (e.g. in the liver) by the action of deiodinases (D1, D2, and D3) leads to the production of T3 and/or reverse T3 (rT3).

T3 and T4 enter the target cell by diffusion or by carrier-mediated transport involving membrane transporters, such as MCT8, MCT10, and Oatp1a2. Within the target cell, THs perform their function directly by activating their nuclear receptors, stimulating or repressing the expression of transcription genes that are dependent on retinoic acid X receptor dimerization (RXR) and/or the recruitment of coactivators, such as steroid receptor coactivator (SRC)

Bioavailability of thyroid hormones during pregnancy

The transfer of THs from mother to fetus during pregnancy varies between women and animals. This process is dependent on the type of placenta, which will influence the expression of transporter molecules, binding proteins, and D3 activity. D3 has high expression in the uterus, placenta, and amniotic membrane, where it plays an important role as an enzymatic barrier to the excessive transfer of maternal THs to the developing fetus.

Effect of thyroid hormones on other hormones and growth factors

Sex steroids

Disorders of reproductive behavior and cycling in females caused by thyroid dysfunctions are associated with changes in the bioavailability and metabolism of other hormones, such as sex steroids and their transport proteins. It is known that the blood transport of sex steroids (testosterone, dihydrotestosterone, and estradiol) occurs through the action of sex hormone-binding globulin (SHBG) and that THs affect the production of this transporter protein by altering the production of hepatic SHBG via hepatocyte nuclear factor-4α (HNF4α).

Conclusion

Thyroid hormones are involved in the regulation of various physiological processes, and changes in their serum concentrations compromise the proper functioning of the whole organism, particularly the reproductive system. Well-documented sequelae of maternal thyroid dysfunctions include subfertility or infertility, menstrual/estrous irregularity, anovulation, abortion, preterm delivery, intrauterine growth restriction, and mental retardation in children. Therefore, in recent years, several studies have been carried out involving prospective and retrospective studies of women with thyroid dysfunction, as well as in vivo and in vitro studies of hypo- and hyperthyroidism using animal models and/or ovarian, uterine, and placental cell cultures.

The thyroid hormone is well known for controlling metabolism, growth, and many other bodily functions. The thyroid gland, anterior pituitary gland, and hypothalamus comprise a self-regulatory circuit called the hypothalamic-pituitary-thyroid axis. The main hormones produced by the thyroid gland are thyroxine or tetraiodothyronine (T4) and triiodothyronine (T3). Thyrotropin-releasing hormone (TRH) from the hypothalamus, thyroid-stimulating hormone (TSH) from the anterior pituitary gland, and T4 work in synchronous harmony to maintain proper feedback mechanism and homeostasis. Iodine is an essential trace element absorbed in the small intestine. It is an integral part of T3 and T4. Sources of iodine include iodized table salt, seafood, seaweed, and vegetables. Decreased iodine intake can cause iodine deficiency and decreased thyroid hormone synthesis. Iodine deficiency can cause cretinism, goiter, myxedema coma, and hypothyroidism.

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