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Metabolic Systemic Effects Triiodothyronine

Abstract

Triiodothyronine (T_3, 3,5,3'-L-triiodothyronine) is a thyroid hormone (thyroid), the secretion of which is carried out directly both by the gland (to a lesser extent) and outside it (the main amount; as a result of peripheral deiodination of thyroxine (T_4)). Getting into the nuclei of cells, T_3 interacts with specific nuclear receptors of target tissues, which determines its biological activity. This interaction leads to the activation of transcription of a number of genes.

In the pituitary gland and peripheral tissues, the action of thyroid hormones is modulated by local deiodinases, which convert T_4 to more active T_3, the molecular effects of which in individual tissues depend on subtypes of T_3 receptors and their interaction with other ligands, coactivators and corepressors, as well as on the activation or repression of specific genes. The reason for the lack of T_3 production is primarily a deficiency of iodine in the diet, less often, a defect in the genes encoding the proteins that are involved in T_3 biosynthesis. As a result of the low intake of iodide in the body, the so-called adaptive mechanism is activated, which consists in increasing the proportion of synthesized T_3, which increases the metabolic efficiency of thyroid homones. With a deficiency in the diet of such a trace element as selenium, the conversion of T_4 to T_3 is reduced.

Thyroid hormones play a vital role in the regulation of homeostasis and the metabolic rate of cells and tissues of humans and mammals. They are necessary for physical and mental development. Their insufficient production at the stage of formation of the internal organs of the fetus and in childhood can lead to various pathologies, primarily to pathology of the central nervous system, and as a result, growth retardation and mental retardation. In adulthood, hypothyroidism leads to a decrease in metabolism, memory impairment, depressive disorders, impaired fertility. Many discussions and ambiguous conclusions have been obtained regarding combination drugs (sodium levothyroxine + lyothironon) for the treatment of hypothyroidism. This article will examine the metabolic effects of T_3, the thyroid hormone with the highest activity.

Key words: *thyroid gland, triiodothyronine, triiodothyronine isoforms*

Conflict of interests

The authors declare no conflict of interests

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D_I, D_{II}, D_{III} — deiodinases, DIT — diiodothyrosine, ESS — euthyroid sick syndrome, GPX — glutathione peroxidase, HF — heart failure, LT_3 — liothyronine, MIT — monoiodothyrosine, NCOR1 — nuclear receptor coregulator 1, rT_3 — reverse T_3, T_3 — triiodothyronine, T_4 — thyroxine, TBG — thyroxine-binding globulin, TG — thyroid gland, THrα — thyroid hormone receptor alpha, THrß — thyroid hormone receptor beta

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The history of the discovery of thyroid hormones

In the 20th century, important discoveries were made in the field of the biochemistry of thyroid hormones. In 1915, E. C. Kendall, an American biochemist, isolated a hormone called thyroxine (T_4) from the thyroid gland (TG). A little later, in 1927, C. R. Harington and G. Barger synthesized the hormone. Another great event was the isolation and synthesis of triiodothyronine (T_3) by J. Gross and R. Pitt-Rivers in 1953. In 1955, R. Pitt-Rivers and her colleagues suggested that T_3 is produced in vivo through T_4 conversion, but this theory remained unproven for a long time.

In 1970, L. E. Braverman et al. demonstrated the conversion of T_4 to T_3 in individuals with no TG, and Anne Fausto-Sterling et al. revealed the same in healthy subjects. Over the next decade, T_4 detection methods were improved; specially-developed radioimmune analysis allowed to determine the level of reverse T_3 (rT_3, inactive) and to understand its physiological role. In 1975, D. Chopra et al. found mutual changes in T_3 and rT_3 levels in the presence of systemic diseases — somatic non-thyroid disease leads to decreased T_3 and increased rT_3. In 1977, K. D. Burman et al. developed a radioimmunoassay for rT_3 detection, which confirmed its presence in the blood serum of healthy individuals. It was also found that rT_3 level is lower in patients with hypothyroidism who take minimal daily doses of levothyroxine sodium. Conversely, rT_3 level was high in patients with hyperthyroidism who received large doses of levothyroxine sodium. The late 70s were marked by a surge in interest in T_3 metabolites, including the development of radioimmunoassay for 3,3′-diiodothyronine (3–3′T_2) [1].

T_3 biosynthesis and metabolism

T_3 is formed as a result of the combination of diiodothyrosine (DIT) and monoiodothyrosine (MIT) molecules. It then accumulates inside the follicle in the form of a colloid. T_3 is secreted with colloid resorption with the help of proteolytic enzymes. MIT, DIT, and T_3, which enters the bloodstream [2], are formed as a result. TG produces no more than 20% of T_3 circulating in the human body. The rest of it and rT_3 (95–98%) result from the peripheral conversion of T_4 by deiodination [1]. The effect of T_3 is about five times higher than that of T_4. T_3 half-life ($T_{1/2}$) is 1–2 days. If T_4 conversion to T_3 is impaired, rT_3 level increases [2].

About 40% of T_4 metabolizes to form T_3 and rT_3 (Fig. 1) [2].

The T_4 molecule has four iodine atoms; the loss of one atom leads to the formation of T_3 or rT_3 depending on which atom is lost. Iodine removal from position 5′ on the outer ring leads to the formation of T_3 — the most active thyroid hormone, which is produced at a rate of 30–40 μg per day. Conversely, when T_4 loses the iodine atom from position 5 on the inner ring, rT_3 is formed at a rate slightly lower than that of T_3, i.e., from 28 to 40 μg per day. rT_3 is inactive. Both T_3 and rT_3 can give up more iodine atoms to form various isomers of T_2, T_1, and, ultimately, T_0. Other pathways of thyroid hormone metabolism include glucuronidation, sulfation, oxidative deamination and cleavage of the ether bond [1].

Reactions of T_3 formation are catalyzed by three types of enzymes (deiodinases):

***D*$_I$** — participates in the deiodination of inner and outer T4 rings, supplies T3 to peripheral tissues. This enzyme provides the formation of most of T3 in plasma by converting T4 into active T3, and also deactivates it; it is localized mainly in the liver, kidneys, TG, and pituitary gland, and in a smaller amount — in the central nervous system [1, 3].

***D*$_{II}$** — catalyzes the conversion of T_4 into T_3, having effect exclusively on the outer ring of thyroid hormones, and falls in the category of

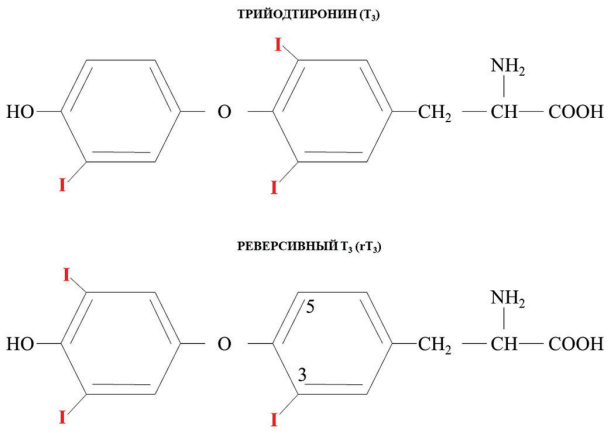

Figure 1. *Forms of triiodothyronine (Adapted from Troshina E.A., 2012)*

essential enzymes. D_{II} provides constant concentration of intracellular T_3; it is synthesized in the central nervous system, pituitary gland, brown adipose tissue, TG, placenta, skeletal muscles and the heart [1, 4].

D_{III} — is responsible for the transformation of T_4 into rT_3, deactivates T_3 and T_4 by catalyzing iodine removal from the inner ring. An inactive form — 3,3-diiodothyronine — is produced as a result. D_{III} synthesis takes place in the central nervous system, skin, hemangiomas, fetal liver, placenta, and fetal tissues [1, 3].

Free T_3 concentration in plasma is relatively constant; however, its concentration in tissues varies depending on the amount of hormone transferred and the activity of local deiodinases. The effect of T_3 depends on the duration of its binding to the nuclear receptor and the number of receptors. Under these conditions, deiodinases play an important role in maintaining concentrations of thyroid hormones in tissues and cells; signal transduction here can vary regardless of their serum concentrations. For example, T_3 production in the central nervous system by local D_{II} is crucial for maintaining T_3 homeostasis. According to Maia A. L. et al. (2011), D_{II}, which is expressed in human TG, plays an important role in maintaining T_3 level in plasma [1–3]. There is a theory that increased expression of D_{II} in enlarged TG leads to a relatively high level of circulating T_3 with certain underlying thyroid diseases, such as McCune—Albright syndrome, T_3-thyrotoxicosis in Graves' disease, abnormalities in thyroglobulin gene. Deiodinases also modulate tissue-specific T_3 concentrations in response to iodine deficiency and changes in thyroid function. In a developing brain, D_{II} locally converts T_4 into T_3. Iodine deficiency and hypothyroidism lead to increased D_{II} activity in tissues, especially in brain tissue, and, as a result, T_4 conversion into T_3 is locally increased [1]. In cases of hyperthyroidism, excessive expression of D_I contributes to the relatively excessive production of T_3, while the activation of D_{III} in the brain protects the central nervous system from excessive amounts of thyroid hormones. D_{III} is the main physiological inactivator of thyroid hormones and plays a major role in protecting tissues from the excessive amount thereof. This mechanism is crucial for fetal development and explains the high expression of D_{III} in the placenta and human fetal tissue. D_{II} and D_{III} regulate T_3 availability in the course of brain development. In tissues of adult individuals, the importance of D_{III} in the regulation of thyroid hormone homeostasis becomes apparent in the cases of certain pathophysiological conditions, such as non-thyroid diseases and malnutrition. Whenever a decrease in metabolism is "homeostatically desirable", for example, in intensive care unit patients or during fasting, T_3 formation decreases and rT_3 formation increases [1, 4, 5]. D_{III} is also activated during fetal hypoxia during delivery [6].

T_3 transport

Most of circulating T_3 is bound to plasma proteins (total T_3), and only 0.4% is free (unbound) T_3 that enters target cells [7].

Thyroxin-binding globulin (TBG), transthyretin and albumin are the main transport proteins.

In case of TBG deficiency, total T_3 concentration decreases. However, the level of free T_3 remains normal. The following may cause impaired hormone binding to protein: congenital TBG synthesis defects, taking medications (androgens, glucocorticoids, danazol, L-asparaginase), certain physiological and pathological conditions (most systemic diseases).

Excessive TBG can be caused by congenital malformations, pregnancy, estrogen-producing tumors, treatment with estrogens, 5-fluoro-uracil. TBG concentration in plasma and total T_3 level increase in this case.

In comparison with T_4, transthyretin has less affinity for T_3.

Among the abovementioned proteins, albumin has the lowest power of binding to T_3, but due to its high concentration, it binds about 15% of the hormone in plasma. Due to the rapid dissociation of the protein-hormone complex, albumin is the main source of free T_3. In cases of renal failure or liver cirrhosis accompanied by hypoalbuminemia, total T_3 level is lower, but free T_3 level remains normal [7].

Diagnostic value of total T_3 and free T_3

Total T3 has diagnostic value only in cases when the binding ability of proteins remains constant. Said constancy changes when taking certain

medications, and during severe general (non-thyroid) diseases. Therefore the determination of free T3 is more significant.

Total T_3 level correlates with total T_4 in most clinical cases. The determination of total T_3 is most reasonable with underlying thyrotoxicosis, since in some cases the total T_4 level shows no significant changes, and total T_3 concentration in serum increases sharply, which allows considering the latter as a more appropriate and objective parameter. In particular, in the absence of TBG binding disorder and with normal total T_3, thyrotoxicosis can be almost excluded.

Patients with myeloma, which produces a large amount of immunoglobulin G, or with severe liver diseases demonstrate falsely high total T_3. Total T_3 may decrease after different surgical interventions, in cases of chronic and acute somatic diseases (for example, diabetes mellitus; HIV infection; myocardial infarction; cirrhosis; anorexia; sepsis; nephrotic syndrome, etc.).

When diagnosing possible thyroid dysfunction, the determination of total T_3 is not enough, especially in patients with hypothyroidism, when in some cases, total T_3 level remains within reference values. The following are indications for determining total and free T_3: differential diagnosis of T_3 thyrotoxicosis; initial thyroid hyperfunction, in particular, in the presence of functional autonomy; relapse of thyrotoxicosis, symptomatically increased T_3; drug-induced thyrotoxicosis [8].

Reverse T_3

Reverse triiodothyronine (3,3',5'-triiodothyronine, reverse T_3, or rT_3) is a T_3 isomer. However, due to its inability to bind nuclear receptors of thyroid hormones, it is usually considered biologically inactive. Reverse T_3 suppresses the effect of nuclear T_3. This is a result of its ability to reduce T_4 conversion into T_3 in D_{II}-expressing tissues, such as the brain. According to Rastogi L. et al. (2018), rT_3 has a neuroprotective effect during ischemic reperfusion injury in vivo and in vitro [9]. In cases of severe general diseases, rT_3 level can increase rapidly, which can also be observed in newborns, with underlying liver failure, after taking certain drugs (beta-blockers, corticosteroids, antiarrhythmic drugs) [8]. Oxidative stress, apoptosis and inflammation are the primary mediators of tissue damage in stroke. It was noted that rT_3 reduces the induction of oxidative stress and apoptosis signaling after ischemic stroke [9]. According to Salazar P. et al. (2019), patients with Alzheimer's disease have high rT_3 and a high rT_3 to T_4 ratio in cerebrospinal fluid with a normal level of thyroid hormones in serum. T_3 inhibits the transcriptional activity of the β-amyloid precursor protein (APP) gene, which is an important risk factor for Alzheimer's disease [10].

Overall, the determination of rT_3 in serum had no clinical significance for the diagnosis of hypothyroidism in patients with systemic diseases. A retrospective study by L. A. Burmeister (1995) demonstrated that somatic non-thyroid pathology complicates the interpretation of thyroid function tests, and measuring rT_3 in serum does not allow to reliably distinguish a patient with hypothyroidism from a patient with euthyroidism. According to L. A. Burmeister, diagnosis requires the evaluation of clinical symptoms, determination of levels of free T_4 and thyroid-stimulating hormone (TSH), and patient monitoring [1]. rT_3 measurement is required only in some clinical situations. Its determination can be performed for differential diagnosis between hypothyroidism and euthyroid sick syndrome: rT_3 should always be considered in combination with TSH, free T_3 and free T_4, taking into account clinical evidence. Table 1 shows changes in the levels of thyroid hormones depending on the severity of systemic disease (as non-thyroid pathology progresses, more significant changes in thyroid function are registered; disease severity is defined conventionally; ultimately, everything depends on the initial and underlying disease).

The utility of determining rT_3 in an outpatient setting is debatable. Sometimes it is difficult to make a differential diagnosis between hypothyroidism and non-thyroidal illness syndrome in intensive care units. rT_3 can be low, normal or high regardless of thyroid function. Also, endogenous changes in the hypothalamus — pituitary — thyroid axis can be exacerbated by drugs commonly used in intensive care units, such as dopamine and glucocorticoids. Changes in thyroid function should be evaluated based on clinical evidence. However, regardless of the T_3 level, thyroid hormone replacement therapy should not be prescribed without taking into account the general clinical status of the patient; controlled

Table 1. *Changes in the levels of thyroid hormones depending on the severity of systemic disease*

Severity of disease	TSH	Total T_3	Free T_4	Reverse T_3	Probable cause
mild	no changes	slightly decreased	no changes	slightly increased	D_I, D_{II} slightly decreased
moderate	no changes or slightly decreased	decreased	no changes or moderately increased or decreased	increased	D_I, D_{II} decreased; slightly increased D_{III} is possible
severe	decreased	significantly decreased	slightly decreased	slightly increased	D_I, D_{II} decreased; slightly increased D_{III} is possible
recovery	slightly increased	slightly decreased	slightly decreased	slightly increased	unknown

Note: TSH — thyroid-stimulating hormone; total T_3 — total triiodothyronine; free T_4 — free thyroxine; reverse T_3 — reverse triiodothyronine

studies showed no evidence that such therapy is beneficial [1]. In cases of mild non-thyroidal somatic diseases, concentrations of free T_3 and TSH may be low. Patients often have abnormal rT_3 levels in blood serum even though TSH is within reference values. Therefore, it makes no sense to determine rT_3. The only relevant test for initiating or adjusting treatment with levothyroxine sodium is the measurement of the TSH level. If the decision to prescribe replacement therapy is based on rT_3 only, always consider the possibility of drug overdose, which can lead to subclinical or even clinical thyrotoxicosis. The discovery of molecular mechanisms that lead to D_{III} reactivation in cases of different diseases, such as HIV infection, chronic heart failure (CHF), and anorexia, is an important field of research today [1].

Effect of thyroid hormones on the development of the central nervous system

Physiological concentrations of thyroid hormones in brain tissue are crucial for pre- and postnatal development and for the regulation of the most important cellular mechanisms. Hypothyroidism in pregnant women significantly increases the risk of autism in the child, and low perinatal levels of thyroid hormones are associated with persistent cognitive impairment and attention deficit. Biosynthesis of T_4, its conversion to T_3 and activation of thyroid hormone receptors are vital processes for normal brain development.

In the developing fetal brain, D_{II} locally converts T_4 to T_3. D_{III} is responsible for the decrease in the cellular level of T_3.

There are two types of thyroid hormone receptors: THrα and THrß. THrα is widely expressed in the brain, THrß — mainly in subcortical areas. Alternative splicing leads to the formation of two variants of THrα — α1 and α2. T_3-dependent transcription is mediated by THrα1. THrα2 does not bind to T_3 and suppresses T_3-dependent transcription. The effect of thyroid hormones at the brain formation and development stages can be increased or decreased by changing the expression levels of THrα1 and THrα2.

Transcriptional coregulators (activators/repressors) can adjust T_3-dependent transcription. Nuclear receptor coregulator 1 (NCOR1) is particularly important for regulating the action of thyroid hormones in vivo. Coactivator MED1 (mediator of RNA polymerase II transcription subunit 1) induces T_3-dependent transcription, which can enhance the effect of thyroid hormones and counteract NCOR1. Local activation of thyroid hormone signaling is achieved at the early stage of development and during brain formation by increasing the activity of D_{II}, THαr1 and MED1. The activation of D_{III}, THrα2 and NCOR1 at the final stage of brain formation can inhibit the action of thyroid hormones and changes in gene expression.

TG dysfunction at an early age can significantly impact cerebellar-mediated motor function. Hypothyroidism leads to functional and structural changes within the cerebellum, hippocampus, cortex, and subcortical nuclei. Abnormal formation of cerebellar-cortical connections leads to autism. Normal TG function in the perinatal period is vital for the development of various behavior in vertebrates. According to Törel Ergür

A. (2012), perinatal levels of thyroid hormones are the basis for the development of various behavior in humans, rodents, birds, and fish [10, 11].

Children with congenital hypothyroidism are characterized by cognitive disorders, impaired speech and motor function. According to the study performed by Törel Ergür A. (2012), subclinical hypothyroidism in children and adolescents correlates with attention deficit. The study performed by Resch U. (2002) demonstrated that low levels of thyroid hormones in patients with manifest and subclinical hypothyroidism are associated with the development of oxidative stress [10]. Mechanisms underlying it have not been studied yet [10].

T_3 and iodine deficiency disorders

Iodine is an essential trace element for the synthesis of thyroid hormones that regulate metabolic processes in most cells and play a key role in the growth and development of the human body.

Iodine deficiency disorders (IDD) are a global public health problem. Their prevention is primarily associated with the prevention of brain formation disorders at the embryonic development stage. Additional intake of iodine preparations in early pregnancy and lactation allows eliminating the adverse effects of iodine deficiency [11].

Severe, prolonged iodine deficiency results in impaired synthesis and secretion of thyroid hormones. Iodine deficiency and decreased production of thyroid hormones lead to the increase of the MIT/DIT ratio in thyroglobulin and to the increase of T_3 secreted by TG. The hypothalamic-pituitary system responds by increasing TSH levels, which is accompanied by an increase in TG size. Due to this compensatory mechanism, hypothyroidism is briefly compensated. It is extremely important to note that thyroid hormone deficiency in newborns and infants leads to irreversible damage to the nervous system and other systems [11].

In addition to the formation of the central nervous system (CNS), other vital functions of T_3 should be noted:

- T_3 regulates the development of bone zones of fetal development and linear bone growth, and is also responsible for endochondral ossification and maturation of epiphyseal centers of ossification after birth. In adults, T_3 participates in bone remodeling and ensures the degradation of mucopolysaccharides and fibronectin in extracellular connective tissue.
- T_3 stimulates the breathing rate at rest and minute pulmonary ventilation, thereby normalizing oxygen concentration in arterial blood as compensation for the increase in oxidation rate. T_3 also contributes to the delivery of oxygen to tissues, simulating the production of erythropoietin and hemoglobin. It also facilitates the absorption of folate and cobalamin in the gastrointestinal tract [12].

Euthyroid sick syndrome or hypothyroidism?

Some patients with several pathologies, such as coronary heart disease (CHD), liver disease (decompensated cirrhosis), chronic kidney disease (CKD), sepsis, mental illness (including food deprivation), trauma, HIV infection, etc., and with no thyroid pathology, demonstrated low T_3, low or normal T_4, and normal TSH. These abnormalities are classified as the so-called euthyroid sick syndrome (ESS, low T_3 syndrome, non-thyroidal illness syndrome, thyroid pseudodysfunction syndrome). The first reports about it emerged around 1976 when methods for determining rT_3 were not widely available. However, some researchers associated this syndrome with high rT_3. In 1982, L. Wartofsky and K.D. Burman analyzed thyroid dysfunction in patients with severe systemic diseases and found a number of factors that can cause changes in thyroid function, such as age, stress, and various drugs [1].

Many somatic diseases are characterized by changes in thyroid hormones, but there are no clinical signs of thyroid dysfunction in such cases. Thyroid hormone levels are restored as the underlying disease is treated. The severity of changes in the thyroid hormone levels depends on the severity of the nonthyroidal disease. These abnormalities are the adaptive response to the pathological mechanisms of the underlying disease. ESS is associated with the impaired deiodination of T_4 in the liver, increased or decreased binding of thyroid hormones to plasma proteins, and impaired TSH production.

The role of D_{III} in the development of ESS was considered relatively recently. D_{III}, which is usually

undetectable in mature tissues, is reactivated in different types of cells in response to damage and is responsible for the decrease of T_3 in serum. Hypoxia induces the activity of D_{III} and messenger RNA in vitro and in vivo. The study by Wajner S. M. et al. (2011) discussed the role of cytokines in ESS. Interleukin-6 lowers the activity of D_I and D_{II} and increases activity of D_{III} in vitro [1].

Differential diagnosis of ESS with true thyroid pathology is important in clinical practice. Routine determination of thyroid function is not recommended for patients in the early postoperative period, as well as for patients who are in intensive care or trauma unit [1, 2, 13, 14].

Chronic heart failure and low T_3 syndrome

The supposed relationship between cardiovascular diseases and thyropathies was for the first time established more than 200 years ago by C. H. Parry, an English physician, who described a patient with goiter and palpitations.

Many patients with cardiac pathology have thyroid dysfunction (hypothyroidism, thyrotoxicosis), but these conditions are often underestimated and are not taken into account by clinicians.

Many direct and indirect effects of thyroid hormones on the heart and blood vessels are described. There is no conversion of T_4 to T_3 in the heart muscle. Therefore, only T_3 in serum has an effect on the myocardium. The primary transporters of thyroid hormones (mainly T_3) into myocytes are monocarboxylate transporters: MCT8 and MCT10. T_3 is an important regulator of the expression of cardiac genes, such as genes that encode contractile proteins, α-myosin heavy chain (MHC) and β-MHC, sodium-calcium exchanger (NCX1), sarcoplasmic reticulum calcium ATPase (SERCA2), β-adrenergic receptor. These mechanisms control changes in the contractile function of the heart, the calcium cycle, and diastolic relaxation of the myocardium. T_3 increases contractility and reduces systemic vascular resistance due to the dilation of peripheral resistance arterioles. Thus, T_3 has a direct effect on the heart and vasculature and an indirect effect on cardiovascular hemodynamics. Figure 2 shows the mechanisms of T_3 action at the level of heart muscle cells (cardiomyocytes).

There are several mechanisms of impairment of T_4 conversion to T_3. One of them is decreased D_I activity and increased expression and activity of D_{III}. Increased D_{III} gene expression may result from hypoxia and inflammation. There is a theory that the dysfunction of deiodinases may be associated with oxidative stress and selenium (Se) deficiency, which is also observed in cases of heart failure (HF). Glutathione peroxidase (GPX) is a marker of protection against oxidative stress. Se levels correlate with GPX enzyme activity. Deiodinases and GPX are selenium-containing proteins competing for Se uptake. In this case, Se deficiency can lead to both GPX deficiency and decreased T_4 conversion to T_3. According to some literature sources, these patterns can be caused by severe HF. On the other hand, oxidative stress and the so-called low T_3 syndrome can contribute to the progression of HF [15].

Low T_3 syndrome, which accompanies HF, can cause many disorders. Thyroid hormone deficiency may result in decreased expression of the α-myosin heavy chain (α-MHC) gene (MYH6), which leads to the deterioration of heart systolic function. Thyroid hormone deficiency contributes to the lowering of the sarcoplasmic/endoplasmic reticulum of calcium ATPase2 (SERCa2) due to the suppression of the ATP2A2 gene. Thyroid hormones activate phosphatidylinositol-3-kinase (PI3K) and serine/threonine protein kinase (AKT) signaling pathways through non-genomic action, inducing the production of endothelial nitric oxide. Also, both hormones (especially T_3) have a direct vasodilating effect that depends on their concentration. Low hormone levels can affect the function of ion channels, which leads to arrhythmia. Thyroid hormone deficiency affects the biogenesis of cardiac muscle mitochondria [15]. According to several studies, low T_3 syndrome is a predictor of death in patients with heart diseases. At the same time, low levels of T_3 are associated with HF severity (they are more often observed with underlying III–IV functional class, according to the New York Heart Association (NYHA) classification). Low concentration of free T_3 may have the same prognostic value as the N-terminal pro-B-type natriuretic peptide (NT-proBNP) in chronic and acute HF. The coincidence of low T_3 syndrome and Se deficiency in patients with HF is also interesting. In a recent study performed by Fraczek-Jucha M. et al. (2019), it was demonstrated that low

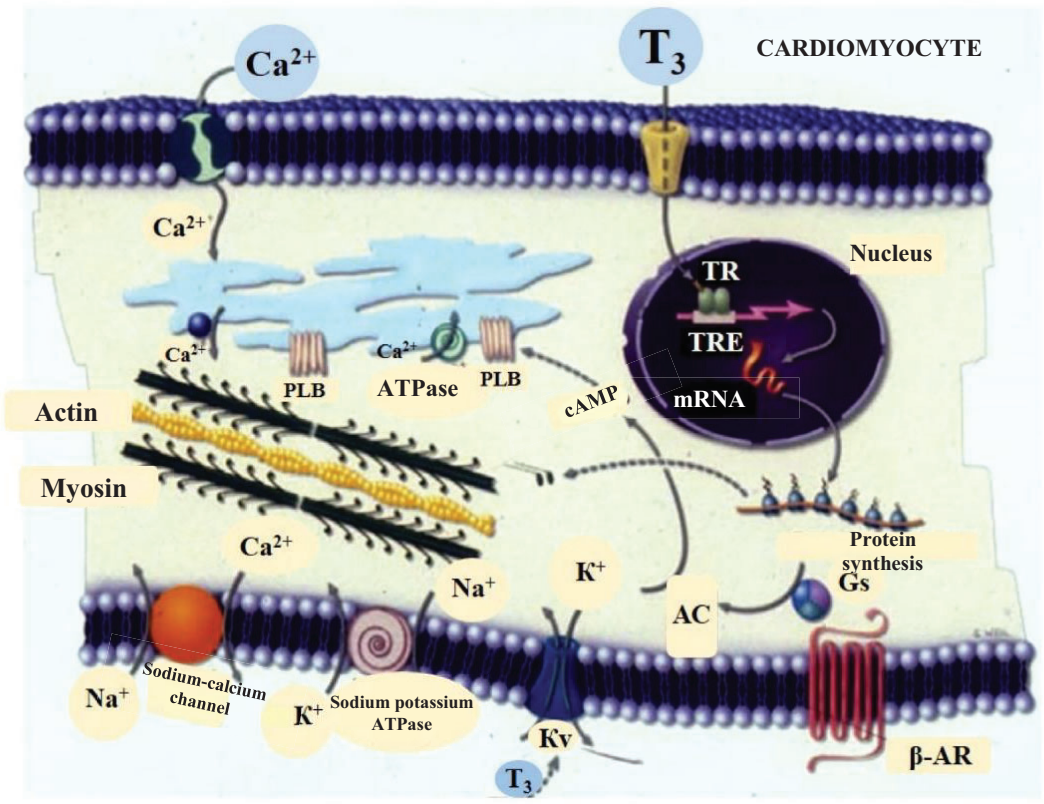

Figure 2. *Mechanisms of T3 action on the cardiomyocyte. T3 is involved in both genomic and non-genomic processes in the cell. Genomic mechanisms include the binding of T3 to thyroid hormone receptors in the heart muscle, which regulate the transcription of certain heart genes. Non-genomic processes are associated with continuous modulation of membrane ion channels.*

Note: TR — thyroid receptors; TRE — thyroid response element; Gs — guanine nucleotide binding protein; β-AR — beta-adrenergic receptor; Kv — voltage-dependent potassium channels; AC — adenylate cyclase; PLB — hydrophobic phosphoprotein of the sarcoplasmic reticulum of heart muscle (Adapted from Danzi S. et al., 2020 [17])

concentration of free T_3 is often found in patients with severe HF (15.3%). The same study revealed a significant number of cases of Se deficiency (74.6%). However, the correlation between Se concentration and free T_3 level was not proven [16].

The study by Pingitore A. et al. (2016) noted that parenteral intravenous administration of T_3 led to a lower heart rate, increased diastolic volume of the left ventricle and stroke volume, as well as improvement of the neurohormonal profile: decreased noradrenaline level in plasma, NT-proBNP and aldosterone [15, 16].

Synthetic triiodothyronine

Synthetic T_3 (liothyronine, LT_3) is classified as a thyroid hormone preparation and is used in replacement therapy for various forms of hypothyroidism solely as an experimental method of treatment. In contrast to sodium levothyroxine, the administration of liothyronine leads to short-term drug-induced thyrotoxicosis due to a sharp increase of T_3 in blood. According to several studies [17, 18], combination drugs (sodium levothyroxine + liothyronine) contribute to the improvement of clinical symptoms of hypothyroidism and patients' quality of life. However, this issue is still debatable. Many studies [14, 19–25] demonstrated that combination therapy (sodium levothyroxine + liothyronine) has no advantage over monotherapy with levothyroxine sodium. According to European Thyroid Association, "combination therapy should be considered solely as an experimental treatment modality" [26]. General limitations for LT_3 are its short half-life, risk of cardiovascular complications and mineral and bone metabolism disorders in the presence of hyperthyroidism or drug overdose [27–30].

According to Hoermann R. et al. (2019), there is a prolonged form of LT_3 (with slow release) with better pharmacological characteristics compared

with conventional LT_3. However, at present, this new formulated product is not available due to the lack of convincing evidence of drug efficacy. Large-scale randomized controlled clinical trials are required for the further recommendation of the use of this drug in clinical practice [31–32].

Conclusion

T_3 is a biologically active thyroid hormone. It is primarily formed by the conversion of T_4 to T_3 in extrathyroid peripheral tissues. Today, there are several known mechanisms of impairment of the conversion of T_4 to T_3, which in most cases are associated with iodine deficiency in the diet, as well as, possibly, with the deficiency of other trace elements, such as selenium, etc. These disorders can also be caused by severe somatic non-thyroidal diseases that require differential diagnosis with true thyroid pathology. Maintaining the physiological concentration of T_3 is extremely important for preventing the development and progression of HF, the formation of antimicrobial and antitumor immunity, and limiting autoimmune inflammation. Combination therapy for hypothyroidism — sodium levothyroxine + liothyronine — is still of great interest. Most of the studies performed revealed no advantages of this therapy compared with monotherapy with levothyroxine sodium. However, according to some studies, combination therapy has significant efficacy in the form of improved neurocognitive function and quality of life in general. Combination therapy may be preferable for certain categories of patients. However, high-quality, large-scale clinical trials are required for the substantiation of these conclusions and the creation of the corresponding evidence base.

Author Contribution:

All the authors contributed significantly to the study and the article, read and approved the final version of the article before publication.

Troshina E.A. (ORCID ID: https://orcid.org/0000-0002-8520-8702): development of the concept and design of the study

Senyushkina E.S. (ORCID ID: https://orcid.org/0000-0001-7960-8315): data collection, analysis and interpretation; substantiation and writing of the manuscript

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