Adaptive Contribution of Thyroid Hormones in Obesity

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Abstract

Nowadays, obesity is seriously threatening healthy life in all societies, especially in developed societies. Obesity is showing its likely effects through biologically active substances called adipokines. The most familiar of these is leptin. Leptin is synthesized in directly proportional to the amount of adipose tissue and reduced appetite by stimulating the satiety center. This status is like a protective mechanism that tries to reverse severe pathological process. Similar to this behavior of leptin, thyroid hormones are increasing in the advanced stages of obesity, increasing the resting energy expenditure (REE). The accelerating oxidative phosphorylation causes the use of energy as heat, the energy that has not transformed into ATP, together with ATP synthesis. This situation, the significant portion of energy provides to consumed instead of storing as fat. In addition, finding that T3 accelerates glucose transport and the TCA cycle without changing the rate of ATP synthesis in skeletal muscles suggests that thyroid hormones may be an effective tool in standing against obesity. In addition of that, the presence of studies indicating that thyroid hormones have an increasing tendency in the advanced stages of obesity is likely thought to be a rescuer mechanism to increase the effectiveness of suppressed thyroid hormones. On the contrary of these ideas, having been reported suppressing 5'-deiodinease enzyme activity in chronic diseases causes anxiety about the effectiveness of thyroid hormones in obesity. Based on available information, we aimed to prepare a review evaluating of this adaptive condition of thyroid hormones.

Introduction

Nowadays, obesity has become the leading health problem with its increasing prevalence day by day. Because of the effects on all systems in the advanced stages of obesity is seriously threatening healthy life. In addition, thereby obesity cause significant effects on endocrine, cardiovascular, respiratory, gastrointestinal and leukomotor systems, increasing the morbidity and mortality of the society. With a simple definition is that obesity is an observed situation a result of taking more energy than needed. Genetic structure, endocrine conditions affecting the metabolism (such as Cushing's disease, hypothyroidism and polycystic ovary syndrome), nutritional habits, the psycho-social and cultural factors the interaction of one or more these factors are the main causes of obesity. Obesity, which is characterized by an abnormal increase in the amount of adipose tissue, is the most common chronic disease of our age in developed and developing countries [1,2]. According to the latest data shared by the World Health Organization (WHO), the incidence of obesity is increasing among European countries as in the USA. It was found that obesity, having become a serious public health problem in developed societies was associated with insulin resistance, diabetes, atherosclerosis, hypertension, chronic kidney disease, and increasing cardiovascular morbidity and mortality [3, 4].

The main role of adipose tissue is to store energy. It fulfills this role by storing fat transported through lipoproteins or by synthesizing fatty acid from glucose [5]. In addition, physical preservation, as well as the storage of fat-soluble vitamins (vitamin A, D, E and K) and providing body temperature hemostasis are the other roles of adipose tissue.

Synthesis and Effects of Adipokines in Adipocytes

Adipose tissues are composed from adipocytes, fibroblasts, leukocytes and macrophage cells. There are two types of adipose tissue in the body: white adipose tissue and brown adipose tissue. The fact that leptin from adipokines having been found first time in 1994 showed that white adipose tissue was also an endocrine organ [6]. Since then, white adipose tissue has been found to release many adipokines having several functions. Interleukin 6 (IL-6) and tumor necrosis factor alpha (TNF-α) secreted from macrophages in adipose tissue were also counted among adipokines. IL-6 has been found to have a regulating effect on other adipokines and reported that decrease adiponectin levels [7]. Likewise, TNF-α has been found to have regulatory effects on other adipokines (reducing adiponectin levels and increasing leptin levels). With reduced the development of obesity, and decreased insulin and leptin levels have been reported in animal studies in which the effect of TNF-α was blocked [8, 9].

Recently, adipokines have been found to be secreted from other cells, except for adipocyte cells. Furthermore, adipokines associated with adipose tissue were indicated to have an important role in progression of insulin resistance, hypertension, inflammation, cardiovascular diseases. The recent year studies have been confirmed that white adipose tissue is an active endocrine organ that secretes adipokines, which are bioactive polypeptides. The complexity of the effects of adipokines on the body caused many researchers to have different or even contradictory results. It has been reported that adipokines affect insulin sensitivity, oxidative capacity and lipid intake in the peripheral, while regulating appetite and energy expenditure in the central [10-15]. After the emergence that adipose tissue produces/secretes a group of bioactive polypeptides, which are defined as adipokines, studies on the negative effects of obesity through these mediators have accelerated. However, on the contrary of other, the presence of adipokines, such as leptin (with its inhibitory effect against weight gain) than other adipokines, has brought a different dimension to the discussions. Thus, leptin is mainly produced from adipocytes in subcutaneous white adipose tissue and it has been thought to control the growth of adipose tissue by affecting the satiety center in the central nervous system [16-18].

Studies in animals with gene mutation responsible for leptin production have shown that obesity develops due to gene mutation, and again weight gain is stopped and even weight loss occurs when leptin is administered to these animals. These findings suggested that leptin may be an important mediator in controlling obesity. In another recent study, founding high levels of blood leptin in a significant proportion of obese patients suggested that there might

be a rescuer endocrine response developed by the body's adipose tissue against obesity. In this context, the presence of obese patients with increased weight despite hyperleptinemia suggests that resistance to endogenous leptin may develop. In studies supporting this idea, have been found that some proteins increase with causing resistance against to endogenous leptin and inhibiting leptin-dependent stimulation. These mechanisms are indicated by the fact that leptin cannot act on the target neurons and does not cross the blood-brain barrier (BBB). A clinical-based study reported that leptin contributed to the regulation of blood glucose levels and increased insulin sensitivity [13, 19]. In addition it has also been shown that leptin is associated with the formation of TNF-α and reactive oxygen products, macrophage activation and synthesis of nitric oxide synthase. These findings [20-22], also shows that obesity-related hyperleptinemia may have a harmful effect on the cardiovascular system.

In a study investigating the association of adipose tissue amount and location with circulating adiponectin levels, it was shown that adiponectin concentration decreased with obesity and increasing amount of visceral adipose tissue, but increased adiponectin concentration with weight loss [23]. In addition, adipose tissue may also release different mediators or markers than adipokine that may be associated with obesity. Ghrelin, serum amyloid A, resistin, retinol binding protein 4 (RBP-4), vaspin, visfatin, omentin and chemerin are among these mediators. An example is the fact that plasminogen activator inhibitor-1 (PAI-1), which is primarily secreted from hepatocytes and endothelium, has been reported to be secreted from visceral white adipose tissue. In a study of patients have central obesity have found that the high level of PAI-1 concentration and the PAI-1 concentrations decrease in weight loss [24, 25], also support this finding. In a different study on PAI-1 deficient mice, obesity and insulin resistance were not observed. This condition supports the relationship between PAI-1 levels and adipose tissue [26]. In a multicenter insulin resistance-atherosclerosis study involving different ethnic groups aimed at investigating the relationships between insulin resistance, cardiovascular risk factors and disease, a correlation was found between increased plasminogen activator inhibitor-1 levels and the development of type 2 diabetes [27]. All these findings suggest that people with high amount of adipose tissue are prone to thrombosis (thrombophilia). This information explains why obesity has a high mortality risk.

Energy Consumption in Obesity and the Relationship with Thyroid Hormone

It is known that TRH, TSH and T3 are actively involved in the regulation of the release of thyroid hormones (Figure 1). The hypothalamic-pituitary-thyroid (HPT) axis has also been shown to be regulated by adipose tissue-dependent leptin and nutritional status [18, 28, 29]. In such a regulation, upon considering the regulatory effect of the thyroid on thermogenesis, it has been suggested that thyroid hormones might be effective in preventing of the development of obesity [18, 30]. It is known that TSH is significant on energy metabolism, especially in 3,5-diiodo-l-thyronine (3,5-T2), T3 and T4 levels [30, 31]. However, conclusive evidences about its obesity-inhibiting contributions are needed.

Major factors that determine the body's energy need include resting basal metabolic activity, physical processes, BMI, nutrition frequency, and gender [32]. This basal metabolic rate, an important parameter of energy requirement, is significantly associated to thyroid hormones. Moreover, there are evidences revealing thyroid hormone-dependent energy requirement is associated with adaptive thermogenesis [30, 33]. The adaptive thermogenesis in question here defines the balance between heat loss and gain. The heat requirement in this equilibrium is associated with oxidative phosphorylation related to locally produced thyroid hormones in brown adipose tissue, which is more pronounced in some animals (such as the bear). And what's more, thyroid hormones are partially effective on the energy requirement of the skeletal muscle [34]. The fact that thyroid hormones promote increased energy expenditure during rest may be considered a function preventing the storage of energy as fat. The detection that adaptive thermogenesis due to thyroid hormones affects the energy expenditure during rest [35, 36], strengthens this idea. This relationship between obesity and thyroid functions contributes to the progress of researches in this direction.
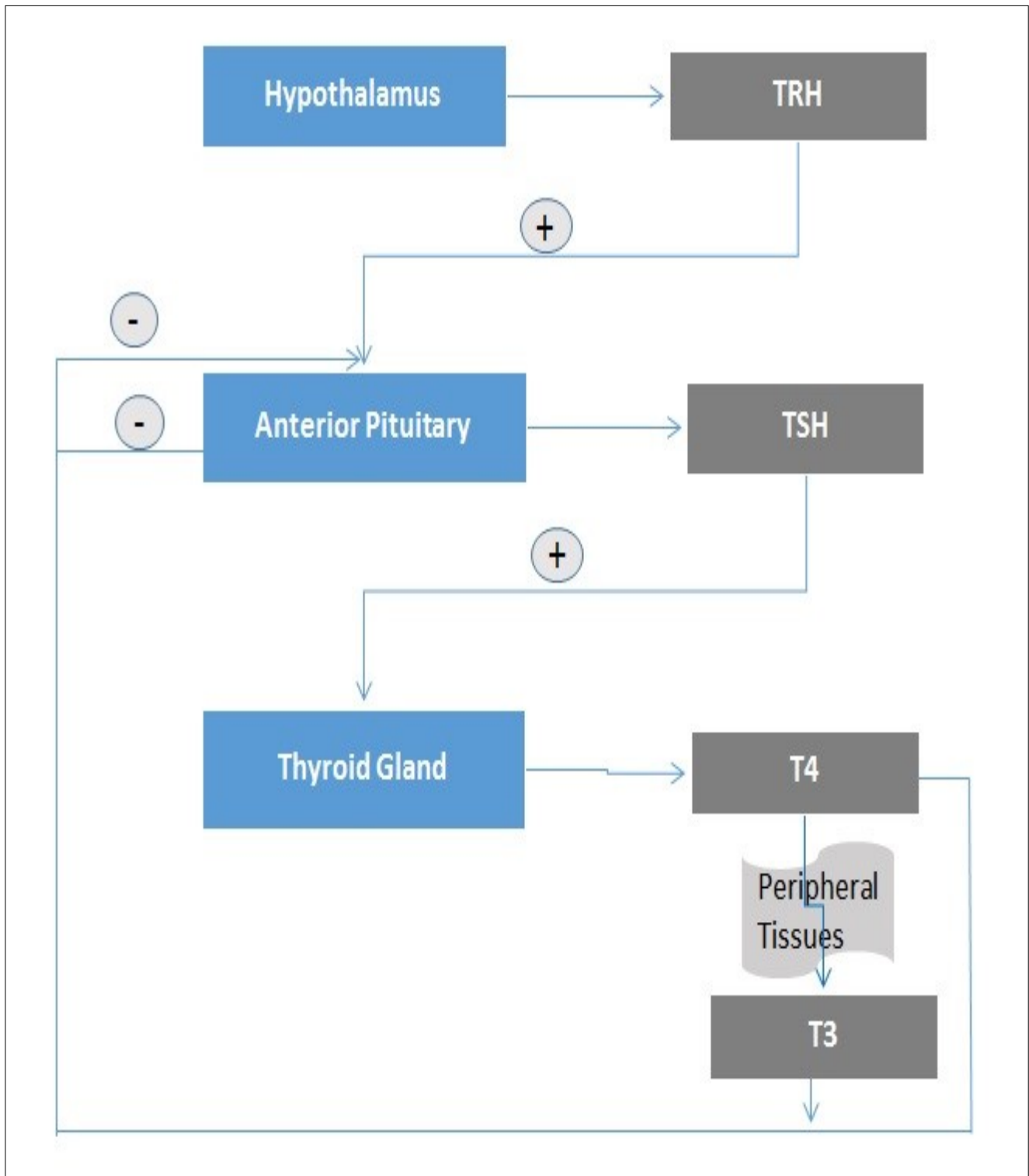
Figure 1. Thyroid hormones synthesis. The synthesis of thyroid hormones begins with hypothalamic stimulation. Increased level of T4 or T3 hormones suppress basal TSH levels by negative feedback and inhibit the TSH response to TRH.

Deiodinase Activity in Obesity and Chronic Diseases

Under normal conditions, 3,5,3',5'-tetraiodo-L-tyronine (T4) is synthesized more than 3,5,3'-triiodo-L-tironine (T3) in the thyroid gland. The majority of T3 in the blood is formed by removal of iodine from the outer ring of T4 with the 5'-deiodinase enzymes commonly found in peripheral tissues other than thyroid. While the less common 5-deiodinase enzymes by catalyzes the separation of iodine from the inner ring of T4, providing the formation of inactive reverse T3 (rT3). These deiodinase enzymes are classified into three types (D1, D2 and D3) according to their activity and synthesis in different organs. D1 is mainly expressed in the liver and shows its predominant activity on the outer ring of T4. The potent inhibition of D1 by anti-thyroid drug propylthiouracil (PTU) is an important feature that differentiates D1 from other deiodinases. It has been reported to be active in D2, central nervous system, pituitary, brown adipose tissue and skeletal muscle that can show its effect only on the outer ring. The expression of D2 is aimed at preserving tissue T3 levels against plasma levels of T4 and T3, which vary depending on the changes in thyroid function. D3, which is mainly expressed from the brain, has only the inner ring deionization activity and mediates the degradation of thyroid hormone. Therefore, brain tissue is considered to be the main site for the plasma T3 to be transformed by inactivation (cleaning) and plasma rT3 production [37-41]. TSH and 5'-deiodinase enzyme activity may be suppressed when basal metabolic rate decreases in cases, which metabolism slows down (prolonged fasting, calorie restriction and some chronic diseases such as renal and liver failure), thus, T3 formation from T4 in peripheral tissues may be inhibited. In some studies, it has been reported that a relatively large amount of rT3 is formed in fetus, chronic diseases, carbohydrate starvation and diabetes mellitus [42-45]. Based on these findings; obesity, which is commonly seen in chronic diseases, will probably be negatively affected by the transformation of T4 to T3 since D2 is suppressed (Figure 2). Therefore, more rT3 formation will occur. However, more conclusive evidence is needed.

Important in Energy Metabolism of Thyroid Hormones

It is known that thyroid hormones play an important role in energy metabolism and alter the functions of other endocrine glands. The effect of thyroid hormones on insulin secretion function of the pancreas is not known yet, but its association with
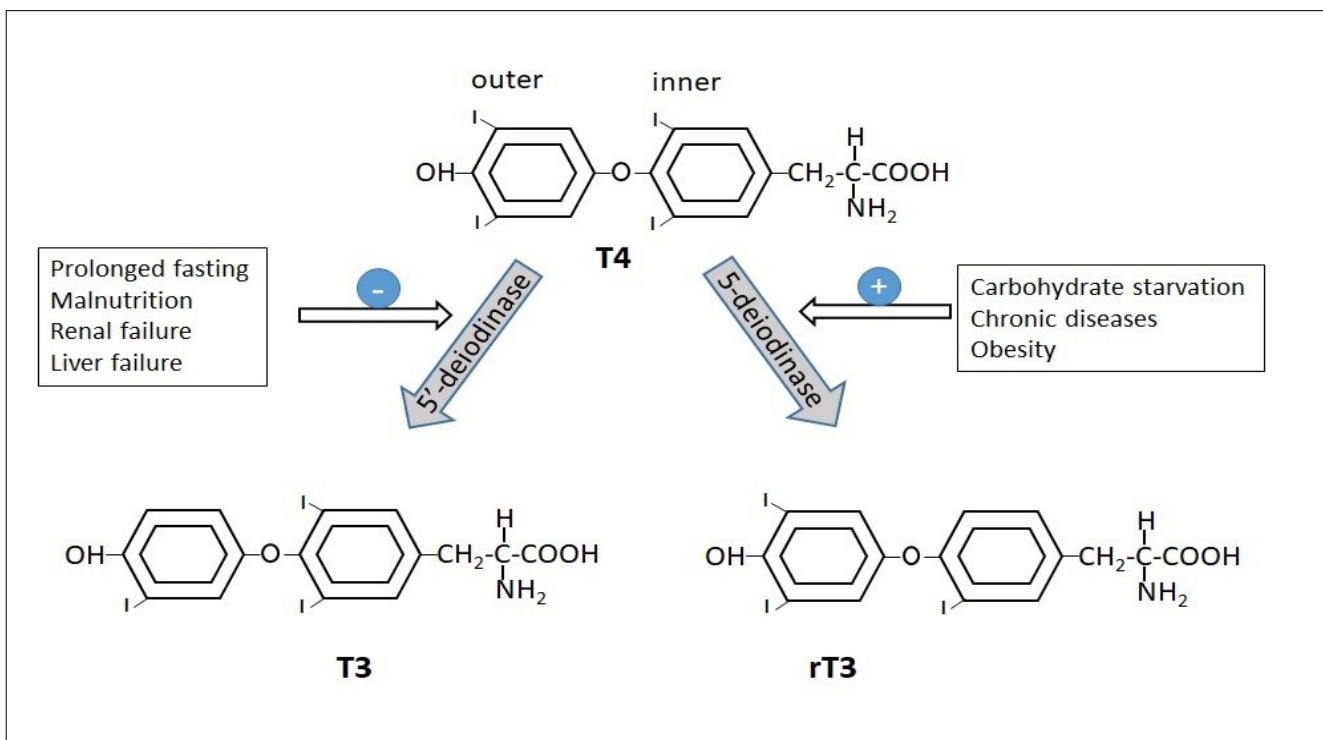

Figure 2. The 5' and 5-deiodinase enzyme activity in obesity, prolonged fasting and chronic diseases.

diabetes is detected. Studies on thyroid hormones focused on fat degradation, glucose oxidation and oxidative phosphorylation acceleration and other metabolic effects. In particular, thyroid hormones-mediated increased energy metabolism and insulin function have been highly emphasized. Recent studies suggest that thyroid hormones play an important role in the islet pathology of diabetes and have non-genomic effects on kinases or calmodulin, Ca^{+2}-ATPase, adenylate cyclase and glucose transporters. However, it is assumed that T3 shows its most important effect through the regulation of thyroid receptors-mediated via target gene transcription found in the nucleus [46-48]. Studies in adult rat have shown that T3 plays an important role in coordinated regulation of lipogenesis and lipolysis, basal oxygen consumption and storage of fats [49, 50]. For all these reasons, the use of thyroid hormones in the treatment of obesity and diabetes continues to be a current topic.

Although there are studies indicating that there are elevated levels of leptin in parallel with fat ratios in hypothyroid rats and that thyroid hormones affect serum leptin concentrations, there is no conclusive evidence explaining the mechanism of relationship between leptin and hyper / hypothyroidism [51-55].

Many studies have reported that the increased leptin levels in rats with hypothyroidism are observed, and thyroid hormones affect serum leptin concentrations. However, there is no conclusive evidence defining the mechanism of the relationship between leptin and hyper / hypothyroidism.

Thyroid Hormone Levels in Obesity and its Contribution to ATP Consumption

In our study conducted in obese patients, we observed that there is a strong correlation between the severity of nonalcoholic fatty liver disease (NAFLD) and insulin resistance (IR) and blood TT3, fT3 and adiponectin levels. In this study, IR and NAFLD severity increased, especially fT3 levels decreased and then increased. We considered the possible cause of this last increase as the body's protection mechanism against severe pathology [56]. In a recent study [34] reporting moderate TSH elevation (T3 is normal or slightly above normal) in obese individuals supports our finding.

Clinical studies have indicated that there are many causes of moderate TSH elevation in obese people. These reasons; a) subclinical hypothyroidism due to iodine deficiency or autoimmune thyroiditis, b) dysfunction of the hypothalamic-pituitary axis, c) thyroid hormone resistance and d) an adaptation process to increased energy consumption [57-61]. In a large-scale cohort study, moderate levels of TSH elevation were found in many obese patients without any thyroid disease, but it was reported that some of the obese children and adults participating in the study had autoimmune thyroiditis [62, 63].

T4 release and blood T4 levels are rapidly suppressed during fasting. This suppression contributes to the adaptive reduction of the metabolic rate helping preservation of energy and reinforcing survival. The mechanism underlying this response has been associated with the dramatic reduction of circulating leptin during fasting. Prevention of the decrease in thyroid hormone levels associated with systemic administration of leptin during fasting [64, 65], this confirms the relation.

Considering the effects of thyroid hormones on metabolism, the relationship between obesity and thyroid hormone will be better understood. That is, the effect of T3 on Na^+/K^+-ATPase is well known [66] and T3 increases the ATP consumption by accelerating the activity of Na+/K+-ATPase in almost all tissues. Accelerating oxidative phosphorylation leads to the use of energy as heat instead of converted to ATP, as well as the synthesis of ATP. Therefore, O2 consumption and metabolic rate will increase [67]. Thus, it will be ensured that the excess energy is consumed instead of storing it as fat.

Thyroid hormones increase the sensitivity of β-adrenergic receptors to catecholamines and then stimulate respiration, heart rate and systole (Figure 3). To achieve this, the rate of glucose metabolism through glycogenolysis and gluconeogenesis will increase. In animal studies, prolonged administration of T3 has been reported to stimulate GLUT4 expression and glucose transport in the skeletal muscle [68]. It is thought that thyroid hormones can regulate glucose metabolism, and this is achieved through the glucose transporter (GLUT-4) via the T3-sensitive control point. In a clinical study, it was reported that the TCA cycle (without
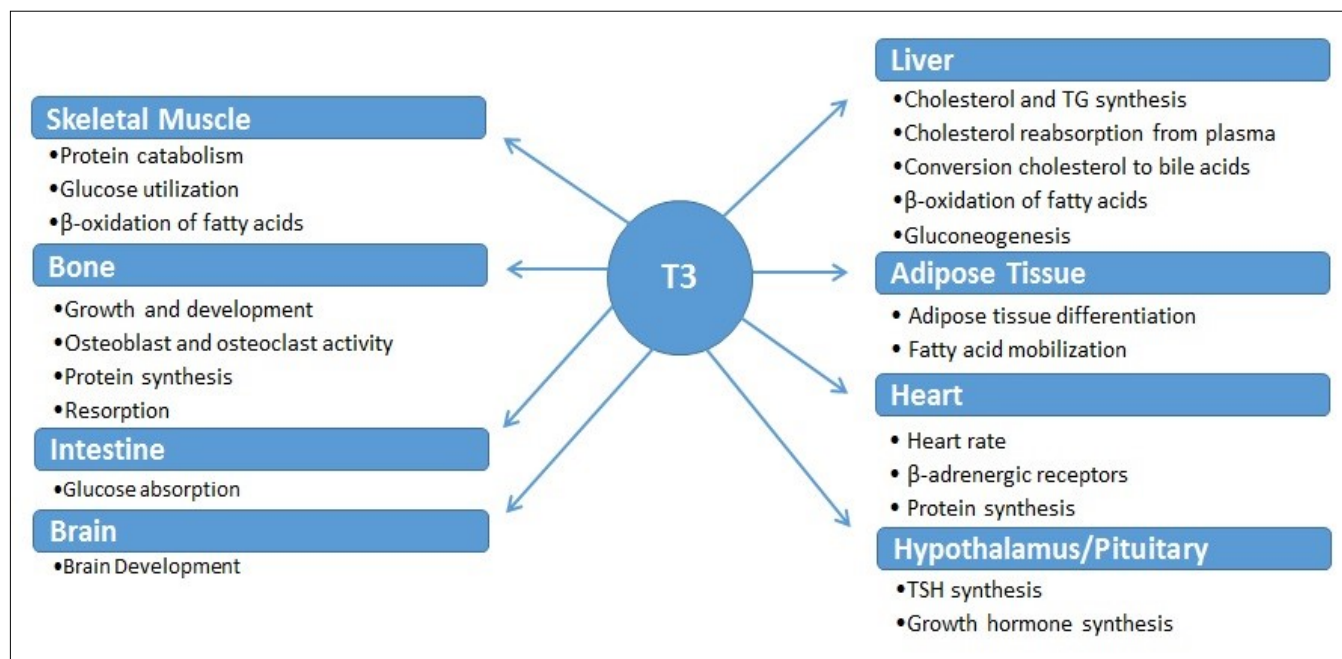
Figure 3. Specific functions of thyroid hormones on target organs.

altering the rate of ATP synthesis) was accelerated by short-term administration of T3 to healthy individuals, accelerating the transport of glucose in skeletal muscles by T3-effective separation [69].

Under normal conditions, thyroid hormones stimulate protein synthesis (Figure 3). In the presence of excess thyroid hormone, protein synthesis is slowed down and negative nitrogen balance is observed [70]. While thyroid hormones stimulate lipid synthesis in a similar way to protein, it is also reporting that it increases the activity of hormone-sensitive lipase at the same time. It is decreasing fat deposits by increasing fatty acid oxidation to form ATP for use in thermogenesis [71]. Overproduction of thyroid hormones has been associated with hyperthermia, tachycardia, sweating and hypertension. However, heart rate deceleration, drowsiness, weight gain, constipation, high cholesterol level, slowing the basal metabolism rate, cold intolerance and psycho-somatic disorders are attributed to decreased thyroid hormone production [72].

Conclusion

Similar to leptin behavior, thereby it is understood that thyroid hormones increase in advanced stages of obesity and increase energy consumption at rest. Accelerating oxidative phosphorylation, with ATP synthesis, is thought to be the use of energy that is not transformed into ATP as heat, so it can be consumed instead of storing excess energy as fat. In addition, T3 hormone in the skeletal muscles without changing the rate of ATP synthesis of glucose transport and the TCA cycle of finding that the thyroid hormones may be an effective tool to stand against obesity. However, reporting that 5'-iodinease activity is suppressed in chronic diseases causes anxiety about in the efficacy of thyroid hormones in obesity. The increasing tendency of thyroid hormones in the advanced stages of obesity is probably a rescuer mechanism to increase the effectiveness of suppressed thyroid hormones.

As a result, in the advanced stages of obesity, increased in thyroid hormones supports to enhance energy consumption of the body by increasing the energy need during rest, thus offering an alternative rescuer way to the body against obesity risk. This situation is a rescuer adaptive contribution similar to the impact that leptin, which correlates with the amount of adipose tissue in obesity, inhibits feeding by affecting the satiety center.

Disclosure

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