



Thyroid hormones and the mechanisms of adaptation to cold

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Abstract

The thyroid gland plays a crucial role in the regulation of metabolism, oxygen consumption, and the release of energy in the form of heat to maintain the body. Even at rest, these processes are sensitive to changes in thyroid function. This means that along with the adrenergic system, thyroid function determines the organism's ability to adapt to cold. Cold adaptation causes deiodination of thyroxine (T₄) and thus promotes an increase in blood triiodothyronine (T₃) levels in humans and animals. Triiodothyronine is an inductor of iodothyronine deiodinase expression in brown fat, liver, and kidney. Iodothyronine deiodinase plays an important role in adaptation of the organism to cold by contributing to high adrenergic reactivity of brown fat. T₃ also leads to an increase in expression of uncoupling proteins and uncoupling oxidative phosphorylation and an increase in heat production. The aim of this article is to review the available literature regarding the role of thyroid hormones in adaptation to cold and to present the current knowledge of the understanding of the molecular mechanism underlying their action during cold adaptation.

Keywords Cold · Adaptation to cold · Thyroid hormones UCP · Iodothyronine deiodinase · T₃Rβ-RXR

Introduction

In 1964, Leblanc and Pouliot, working with a group of 15 rats, obtained evidence of norepinephrine involvement in cold acclimatization [1]. The rats were divided into three groups: (1) control animals, (2) rats exposed to chronic cold (6 °C, 45 days), and (3) rats with a daily injection of norepinephrine (45 days). It was found that adaptation to cold increases oxygen consumption at 30 °C, while daily administration of norepinephrine does not have this effect. In response to subcutaneous injections of norepinephrine, oxygen consumption in the control animals increased by 40%, in adapted rats by 75%, and in animals receiving norepinephrine by 100% [1]. After 12 h at −20 °C, all of the euthyroid rats died. Among the rats that received norepinephrine, 70% of the animals died and only 20% of the adapted rats. The presented data suggests that norepinephrine mimics the calorogenic effect of cold

acclimatization. However, the results of this study indicate that catecholamines are not the only humoral factors that ensure adaptation to cold, since the mortality from cold in the rats receiving noradrenaline remained high. It has been demonstrated that thyroid hormones play the second most important role in adaptation to cold after the adrenergic system (AS). Indeed, as far back as 1950, it was shown that thyroidectomized rats survive only a few days at 1.5 °C, while euthyroid animals survive and eventually adapt to cold [2]. Later, it was found that hypothyroid rats survive only for 3 to 4 days at 4 °C, while euthyroid animals do not die at this temperature and adapt to cold for a month [3]. Severe hypothermia developed in hypothyroid mice at 4 °C for 8 h, while euthyroid animals had a lower temperature decrease [4]. In 2002, Zaninovich et al. [5] obtained data provided new insight into the role of thyroid hormones in cold acclimatization. They performed thyroidectomy in rats after 2 months of cold adaptation, after which the rats were again placed in an environment with a temperature of 4 °C for 2 months. All thyroidectomized rats survived: they maintained a high mass of interscapular fat, which plays an important role in thermogenesis [6]. Indeed, cold acclimatization increased skeletal muscle respiration by 35%, that of the liver by 18%, and that of brown adipose tissue (BAT) by 450% [7]. According to Zaninovich et al. [5], after thyroidectomy in adapted rats, a large amount of uncoupling protein-1 (UCP-1) remained in brown fat [5].

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As is known, uncoupling proteins provide the following: (a) uncoupling of oxidative phosphorylation and (b) increased heat production by mitochondria [8]: the increased expression of UCP-1 thus indicates adaptation to cold. The authors concluded [7] that thyroid hormones play an important role in adaptation to cold, but not in maintenance of increased tolerance to low temperatures. It was shown that short-term exposure to cold in rabbits increases T_3 in serum, which the authors identified as an outcome similar to that observed in hyperthyroidism [9]. Ketzer et al. observed an increase in oxygen consumption and heat production during Ca^{2+} transport by cardiac sarcoplasmic reticulum as in hyperthyroidism, caused by T_4 administration for 10 days, and during short-term exposure to cold (4 °C, 72 h) [9]. Short-term exposures to cold and hyperthyroidism caused an increase in the activity of sarcoplasmic reticulum Ca^{2+} -ATPase (SERCA2a). In contrast, both mitochondrial respiration and heat derived from calcium transport were reduced in rabbits with hypothyroidism after use of propylthiouracil. Changes in the functional state of the heart, oxygen consumption, and SERCA2a activity, detected during short-term exposure to cold, were not observed after prolonged adaptation to cold (4 °C, 10 days). The authors suggest that a short-term increase in serum T_3 levels contributes to the same short-term response to cold exposure, which is not observed with exposure to cold for 10 days [9]. It should be noted that cold adaptation reaches its maximum with longer cold exposure, lasting 1 month. Hypothyroidism is characterized by increased sensitivity to cold and an increase in body weight, which indicates changes in energy expenditure and a response to exposure to cold. Indeed, it has been shown that restoration of thyroid function in humans with hypothyroidism significantly increases cold-induced thermogenesis [10].

Thyroid hormone alterations in adaptation to cold

Animal studies

One of the first articles worthy of attention and, which was devoted to the role of thyroid hormones in cold adaptation, is the article by Straw and Fregly, which was published in 1967 [11]. They found that chronic exposure to cold (6 °C, 52 days) causes an increase in thyroid mass, which reaches a maximum on the 28th day of adaptation. Thyroid function was assessed by uptake of radioactive ^{131}I . It was shown that the thyroid gland of adapted rats captures ^{131}I faster and accumulates it in a larger quantity compared with the thyroid gland of euthyroid animals. In women who have practiced cold water swimming for 6–10 years, in 100% of cases hypertrophy of the thyroid gland was observed; in men, this figure was only 67% [12]. An increase in thyroid mass after cold adaptation has been shown by other investigators [13]. Increased T_4 and T_3 levels

after cold adaptation were confirmed by Kühn et al. [14], Moriya [15], and other investigators [13, 16–20]. According to Fregly et al. [21], after adaptation to cold in rats, T_3 concentrations in serum increased, but concentrations of T_4 decreased due to constant levels of thyroid stimulating hormone (TSH). It is possible that such changes in hormone levels occur due to increased conversion of T_4 to T_3 . An increase in T_4 to T_3 conversion was shown when rabbits were adapted to cold (4 °C; 7 weeks) [22]. We found that continuous exposure to cold (4 °C, 24 h/day, 4 weeks) leads to an increase in T_3 levels in serum in rats [23]. Long-term (4 °C, 8 h/day, 4 weeks) intermittent cold exposures increased T_4 levels. At the same time, there is a certain pattern in the distribution of thyroid hormones: exposure to cold causes a decrease in thyroid hormone levels in the hypothalamus of rats, while their levels at the periphery increase [24]. When adapting to cold, thyroid hormone levels increased not only in the blood but also in the tissues. Thus, according to Gaikwad et al. [16], after rats stayed in 4 °C for 30–35 days, T_3 levels in BAT increased 10-fold. Héroux and Brauer hypothesized that the reason for a decrease in T_4 levels in rats is the greater loss of this hormone with feces in cold-adapted rats than in non-adapted animals [25]. In another study, rats were exposed to cold (4 °C, 14 days). The animals were administered ^{131}I - T_3 and ^{125}I - T_4 [26]. Clearance of labeled T_4 with urine and feces increased 2-fold, while clearance of labeled T_3 increased 1.5-fold.

It has been established that in some cases a change in secretion of thyroid hormones can occur without any change in TSH level. It was shown that in old (22 months) rats, serum T_3 levels and T_4 levels were reduced, compared with young (7 months) rats [27]. In response to short-term exposure to cold (4 °C, 5 h), there was an increase in free T_3 and T_4 levels both in old and young rats, but in old rats, T_3 and T_4 levels were lower than in young animals. The authors failed to detect any increase in TSH levels in response to cold exposure in either young or old rats.

However, some investigators have failed to detect a rise in T_3 levels in blood plasma of cold-adapted rats [28], although in response to acute cold exposure (− 15 °C), they recorded a 2-fold rise in T_4 levels both in adapted and in unadapted animals.

Thyrotropin-releasing hormone (TRH) may also be involved in cold adaptation. In 2018, TRH administration into the paraventricular nucleus of the hypothalamus of rats significantly mimicked metabolic and behavioral changes caused by exposure to cold, indicating a potential link between TRH release in the hypothalamus and protection from cold [29].

Thyroid hormones have widespread cellular effects. They increase energy expenditure which can be balanced by increased food intake [10]. Lopez M et al. demonstrated that either whole-body hyperthyroidism or central administration of T_3 decreases the activity of hypothalamic AMP-activated protein kinase (AMPK), increases sympathetic nervous

system (SNS) activity, and upregulates thermogenic markers in BAT [30]. Inhibition of the lipogenesis pathway in the ventromedial nucleus (VN) of the hypothalamus prevents CNS-mediated activation of BAT by thyroid hormones and reverses the weight loss associated with hyperthyroidism. Similarly, inhibition of thyroid hormone receptors in the VN reverses weight loss associated with hyperthyroidism. This regulatory mechanism depends on AMPK inactivation, as genetic inhibition of this enzyme in the VN of euthyroid rats induces feeding-independent weight loss and increases expression of thermogenic markers in BAT. These effects were reversed by pharmacological blockade of the SNS. Thus, thyroid hormone-induced modulation of AMPK activity and lipid metabolism in the hypothalamus is a major regulator of whole-body energy homeostasis [30].

Human studies

In 1974, a study was published reporting an increase in the levels of T_3 and T_4 in the blood of volunteers as they adapted to cold was published [31]. About three decades later, it was shown that people living in rural areas of Japan and doing agricultural work had higher plasma T_3 levels in winter compared to a summer period [32]. Significant differences in the levels of thyroid hormones and concentrations of TSH between summer and winter in urban residents were not detected. Increased T_4 and T_3 levels in humans after cold adaptation was confirmed by several investigators [33–36]. Sometimes changes in thyroid hormone levels are multidirectional. It has been shown that prolonged exposure of the human body to cold in combination with severe physical exertion leads to an increase in serum T_3 levels while simultaneously reducing the concentration of thyroxine, while TSH level does not change [37]. In soldiers who were serving in Alaska, the maximum level of total T_4 to T_3 conversion was recorded in winter and maximum conversion of free T_4 to T_3 in early spring [35]. In a study conducted in Finland in healthy volunteers, it was shown that the level of serum free T_3 was reduced in winter, while urine T_3 levels, by contrast, increased in winter and decreased in summer [38]. Total T_3 , total T_4 , and free T_4 concentration in urine did not undergo seasonal changes [38]. The level of TSH was significantly increased only in December.

During observations of participants of an Antarctic expedition, it was found that after 5 months and 10 months of stay in the Antarctic, there was no significant change in serum thyroxine levels, while free T_3 levels decreased after 10 months [39]. The concentration of TSH in serum, on the contrary, increased and reached a maximum at 10 months of observations. It is possible that such a dynamic of T_3 indicates the occurrence of thyroid insufficiency and maladaptation to chronic cold exposure. However, a decrease in serum T_3 and T_4 levels was also observed with a 21-day human adaptation

to cold [40]. A decrease in total T_3 and T_4 levels in workers working at a temperature of -40 to -20 °C was observed by Solter et al. [41]. Possibly, this also concerns a case of thyroid dysfunction. Solter et al. did not determine TSH levels; thus, to evaluate whether such a dysfunction is present or not is not necessary. In 1992, studies on volunteers showed that 2-month adaptation to cold does not affect TSH levels, total plasma T_3 , total T_4 , or free T_4 , but it causes a decrease in free T_3 [42]. A study performed in 2016 showed that people living in Antarctic conditions have a decrease in free plasma T_4 , total T_3 , and total T_4 , while TSH levels have not changed [43]. Surprisingly, being in Arctic conditions led to a decrease in plasma norepinephrine and epinephrine levels [43]. The authors did not offer an explanation for this paradoxical effect. During the observation of participants of another Antarctic expedition, it was found that in the first month of stay in the Antarctica, total plasma T_3 levels decrease compared to baseline (before the expedition), whereas thyroxine and TSH levels do not differ from initial values [44]. A decrease in the concentration of free T_3 or total T_3 is, apparently, is due to increased T_3 accumulation in tissues. Indeed, in a study performed in cold-adapted volunteers, who received per os T_3 , it was shown [45] that adaptation leads to an increase in the rate of removal of this hormone from blood. During observation of participants of an Antarctic expedition who took T_3 per os, it was shown that they also increased the binding of T_3 by tissues [46]. In 1998, the results of observations of inhabitants of the Arctic Circle were published [47]. They showed that their free T_3 levels were significantly reduced in February compared with summer time. Free T_3 levels correlated with ambient temperature during the previous month. The authors called such a change in free T_3 the “polar T_3 syndrome.” TSH levels were significantly increased in December compared to the summer period. According to these investigators, a detected decrease in free T_3 is a consequence of increased accumulation of this hormone in tissues and not the result of a violation of synthesis of thyroid hormones [47]. Other investigators during observations of participants of an Antarctic expedition confirmed the presence of the polar T_3 syndrome [48]. They found that in polar workers, simultaneously with an increase in serum TSH levels, production of T_3 and clearance of T_3 increased. In addition, a decrease in the free T_4 level in serum was detected, apparently due to an increase in its accumulation in tissues.

Heinen et al. found that intravenous administration of TRH can increase BAT activity in humans during cold exposure [49]. BAT activity was assessed by ^{18}F -fluorodeoxyglucose (^{18}F -FDG) accumulation, which was measured using positron emission tomography (PET). After moderate exposure to cold (17 °C), 44% of volunteers experienced an increase in fatty tissue uptake by ^{18}F -FDG after administration of TRH compared with placebo [49].

Kralova Lesna et al. in their investigation studied the effect of cold adaptation on cardiovascular risk factors, thyroid hormones, and the capacity to eliminate the damaging effect of oxidative stress [50]. Ten well cold-adapted winter swimmers and 16 non-adapted individuals (controls) were enrolled in this study. It was shown that higher T₃ levels were observed in the cold-adapted group compared to the control group, but TSH and other thyroid hormones did not differ between the two groups. It was found that cold adaptation induced the improvement of cardiovascular risk factors. A decrease in apolipoprotein B/apolipoprotein A1 (ApoB/ApoA1) ratio and a decrease in plasma homocysteine level in cold-adapted subjects were detected, which points to the positive effect of cold adaptation [50].

Thus, adaptation to cold leads to a transient increase in T₃ and T₄ levels in humans and animals; the observed changes in thyroid hormone levels are most likely due to an increased turnover of these hormones in humans. Cold exposure lasting a month or more can cause a decrease in the concentration of total and free T₃ in human blood due to increased clearance of this hormone. A similar response of the thyroid system is characteristic of humans, which, as mentioned above, has been called the polar T₃ syndrome.

The role of thyroxine deiodination in adaptation to cold

In 1980, Scammell et al. [51] found that in the liver of cold-adapted rats, the deiodination rate of T₄ to T₃ increases by 40%. The important role of deiodination in adaptation to cold was shown in a study by Gabrielsen et al. [52] performed in polar bears (*Ursus maritimus*) during the winter season. In this regard, it should be noted that currently, T₄ is considered to be a prohormone, which has an effect on the cell after transformation into T₃, which occurs via the action of intracellular enzyme iodothyronine deiodinase D2 (thyroxine-5'-deiodinase II) [53]. D2, in turn, is induced by cold and hypothyroidism. For this reason, the more cells express thyroxine-5'-deiodinase II, the more sensitive they are to thyroxine [53]. The key role of 5'-deiodinase in a thyroid-dependent calorogenic response to cold is indicated by a study by Carvalho et al. [54]. Scammell et al. attempted to elucidate the mechanism of cold enhancement of deiodination [55]. They showed that after chronic exposure to cold, deiodination of T₄ to T₃ in the liver increases by 53% and in the kidneys by 71%. Chronic administration of isoproterenol did not affect deiodination, while prolonged administration of thyroxine increased deiodination in the liver by 300% and in the kidneys by 200%. The coadministration of isoproterenol, the β -adrenergic receptor (AR) agonist, and thyroxine had the same effect as administration of thyroxine alone [55]. The conclusion drawn was that cold-induced conversion of T₄ to T₃ did

not depend on catecholamines. However, this conclusion is too hasty, because the authors did not use chronic administration of the α -AR agonist phenylephrine and did not use α - and β -AR antagonists during acclimatization. In 1983, Silva and Larsen [56] found that administration of norepinephrine to rats or cold stress (4 °C for 4 h) caused an increase in iodothyronine deiodinase D2 activity in brown fat. If endogenous catecholamine reserves were depleted after application of α -methyl-p-tyrosine, a tyrosine hydroxylase inhibitor, then the cold effect did not affect the activity of deiodinase D2, and norepinephrine increased its activity. The α_1 -AR antagonist prazosin eliminated the effect of both norepinephrine and cold stress on deiodinase D2. The β -AR antagonist propranolol or the α_2 -AR antagonist yohimbine did not affect the stimulatory effect of cold and norepinephrine on this enzyme [56]. These facts indicate that endogenous catecholamines may increase the activity of iodothyronine deiodinase D2 in brown fat by stimulating α_1 -AR. In 1985, the same group [19] found that acclimatization of rats to cold leads to an 8-fold increase in iodothyronine deiodinase D2 activity in brown fat as compared with non-adapted animals, while enzyme activity values in the liver and kidneys do not differ from control values. Moreover, the authors obtained evidence that during chronic exposure to cold, brown fat becomes an important source of T₃ circulating in blood. Other investigators share the view that iodothyronine deiodinase is a source of T₃ circulating in blood in humans and mammals [57]. In addition, it was shown that daily administration of the α_1 -AR antagonist prazosin in rats during adaptation to cold abolished an increase in the activity of iodothyronine-deiodinase in brown fat adipocytes [19]. This fact suggests that endogenous catecholamines regulate the functional state of the endocrine system in the process of adaptation to cold due to α_1 -AR activation.

In 1986, Nunes and Bianco [58], performing experiments with rat liver and kidney homogenate, found that conversion of T₄ to T₃ decreases in rats with hypothyroidism and increases in animals with hyperthyroidism. These data suggest that thyroid hormones themselves can be inducers of iodothyronine deiodinase expression (type 1). It has been established that cold acclimatization leads to an 80-fold increase in the activity of iodothyronine deiodinase in BAT [59]. Similar results were obtained by other investigators [60]. Bianco and Silva [61] obtained indirect data in favor of activation of brown fat iodothyronine deiodinase. However, according to a study by Gaikwad et al. [16], the activity of iodothyronine deiodinase in BAT increased only 3-fold. These facts testify to the important role of this enzyme in cold adaptation. In experiments on gophers, it was shown that during adaptation to cold, a correlation is observed between iodothyronine deiodinase activation and an increase in UCP-1 mRNA levels in BAT [62]. In experiments in mice with deletion of the dopamine D(2) receptor gene, it was shown that T₃ levels in these animals do not differ from the norm

[63]. Mild hypothermia developed in wild-type mice for 24 h in 4 °C, and pronounced hypothermia appeared in the knocked out animals. For a specified period of time in 4 °C in knocked out mice, the serum creatine kinase levels were increased by 2-fold compared with initial values, which indicates cell death due to necrosis. In wild-type mice in these conditions, creatine kinase levels did not change. After exposure to cold, animals without iodothyronine deiodinase showed a decrease in body weight, while in wild-type mice, their body weight increased slightly [63]. In euthyroid animals, in response to norepinephrine infusion, the temperature of interscapular brown fat increased by 1 °C, and in knockout animals, only by 0.4 °C. In experiments on adipocytes isolated from brown fat of knockout mice, norepinephrine increased cell respiration 2-fold and in experiments with cells of wild-type animals 5-fold. The selective β_3 -AR agonist CL316,243 also acted more weakly in experiments with knockout mouse cells. Forskolin-induced respiration was reduced in adipocytes lacking iodothyronine deiodinase, where forskolin is an adenylate cyclase activator [63]. A similar pattern was observed for norepinephrine-, CL316,243-, and forskolin-induced lipolysis in adipocytes. T_3 injection in knockout mice restored all of the listed indicators. It was mentioned above that UCP-1 levels in brown fat cells are the same in naïve and in knockout mice. A completely different situation was observed after application of norepinephrine, which increased UCP-1 mRNA levels 4-fold in adipose tissue of naïve mice, while in adipocytes with deletion of the iodothyronine deiodinase gene, this indicator increased 2-fold. Triiodothyronine restored norepinephrine-induced synthesis of UCP-1 mRNA in knockout adipocytes to normal values. From the presented data, it can be concluded that T_3 and iodothyronine deiodinase provide a high adrenergic response of brown fat. The important role of iodothyronine deiodinase D2 was confirmed in later studies [64].

Moreover, cold exposure may enhance T_3 production by deiodination of T_4 in skeletal muscle, which may enhance heat production in muscle via a change in muscle fiber type [65].

The adipokine adipocyte fatty acid-binding protein (A-FABP) has been implicated in obesity-related cardiometabolic complications. Shu et al. showed that A-FABP increases thermogenesis by promoting conversion of T_4 to T_3 in brown adipocytes [66]. The authors demonstrated that A-FABP levels are increased in both white adipose tissue and in BAT as well as in blood in response to thermogenic stimuli. A-FABP knockout mice have reduced thermogenesis and whole-body energy expenditure after cold exposure or after being fed a high-fat diet, which can be reversed by infusion of recombinant A-FABP. A-FABP induced type-II iodothyronine deiodinase expression in BAT via inhibition of the nuclear receptor liver X receptor α , thereby leading to conversion of inactive T_4 to active T_3 . A thermogenic response to T_4 was abrogated in A-FABP knockout mice. It is thus evident

that A-FABP acts as a physiological regulator of BAT-mediated adaptive thermogenesis [66].

Therefore, endogenous catecholamines can provide an increase in iodothyronine deiodinase D2 activity in BAT by stimulating α_1 -AR. T_3 is an inducer of iodothyronine deiodinase expression in BAT, liver, and kidney. The presented data indicate that iodothyronine deiodinase D2 plays an important role in adaptation to cold, providing a high adrenergic response of brown fat.

The role of T_3 receptors and uncoupling proteins in the calorogenic effect of thyroid hormones

Animal studies

The cellular effects of T_3 are known to be associated with activation of thyroid hormone receptors (TR α or TR β) [53]. In 1986, it was shown that adaptation to cold does not affect a number of these receptors and their affinity (Kd) for T_3 [67]. One of these is the specific mitochondrial T_3 receptor p43 [68]. In 2016, the results of a study on mice that lacked the p43 receptor were published. It was demonstrated that a genetic defect of this type does not affect tolerance to cold and does not cause any defects in thermogenesis [68]. Consequently, the adaptive effect of prolonged exposure to cold is not associated with changes in the number and properties of nuclear and mitochondrial T_3 receptors. Similar data were obtained by other investigators [61]. The positive role of thyroid hormones in adaptation appears to be in enhancing UCP-1 expression [69]. In experiments on thyroidectomized rats, it was shown that in these animals, in response to cold exposure (4 °C, 15 h), there is no increase in uncoupling UCP-1 protein level in BAT. The authors associated the high lethality of thyroidectomized rats in cold conditions with the lack of increased expression of this protein. Regular subcutaneous administration of thyroxine, as with exposure to cold, increases UCP-1 levels in BAT [69]. In 1989, Park et al. [70] showed that in thyroidectomized rats, in response to acute cold exposure (4 °C, 15 h), UCP-1 expression was not increased. After administration of small doses of T_4 or T_3 , cold-induced expression of the *UCP-1* gene was restored. In 1995, Rabelo et al. [71], performing experiments on JEG-3, HIP-1B cells, and brown fat adipocytes, found two T_3 receptor binding sites (thyroid hormone-responsive elements) next to a *UCP* gene enhancer. Investigators in experiments on HIP-1B cells showed that, in the absence of T_3 , T_3 receptor β (TR β) is associated with TREs, which leads to inhibition of *UCP-1* gene transcription [72]. When T_3 is added to the incubation medium, homodimers are separated from DNA, which break up, followed by TR β -RXR heterodimer formation, where RXR is the nuclear retinoid X receptor. Heterodimers contain

bound T_3 ; they interact with DNA and enhance transcription of the gene encoding UCP.

Based on these published studies, we can conclude that the following event chain is built up in cells: increase in T_3 concentration leads to interaction of T_3 with $T_3R\beta$ and formation of $T_3R\beta$ -RXR heterodimers, which bind of $T_3R\beta$ -RXR to DNA. Increased transcription of the UCP-1 gene leads to an increase in the amount of UCP1-protein, which provides oxidative phosphorylation uncoupling and, as a result, increase heat production (Fig. 1).

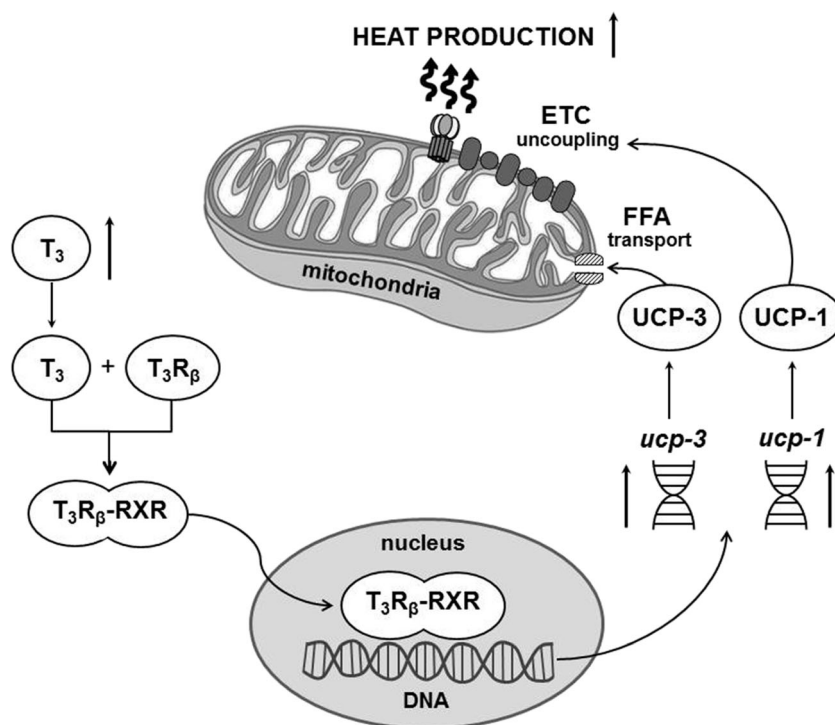
If T_3 or a $T_3R\beta$ agonist GC-1 was injected into hypothyroid mice, UCP-1 expression returned to normal values. However, at 4 °C, hypothermia developed in mice receiving GC-1. A normal temperature was maintained in animals receiving T_3 [4]. In mice with hypothyroidism, bradycardia developed, which disappeared after the course of administration of T_3 , whereas it persisted after the application of GC-1. In hypothyroid mice in 4 °C for 8 h, pronounced hypothermia occurred. In mice treated with T_3 , the temperature decrease was less significant [4]. The course of administration of T_3 to the hypothyroid mice restored a body's normal response to a decrease in ambient temperature; GC-1 did not have this effect.

Apparently, the role of thyroid hormones in adaptation to cold is not limited only to enhancing UCP-1 expression and $T_3R\beta$ activation but includes stimulation of other T_3 receptors and other adaptive mechanisms. In 2010, Martinez de Mena et al. [73] obtained data that confirm this opinion. In experiments on cultured brown fat adipocytes, they studied the effect of T_3 , a $T_3R\beta$ 1 GC-1 agonist, and a $T_3R\alpha$ 1 CO23 agonist on

adrenergic induction of UCP-1 synthesis and iodothyronine deiodinase D2. Triiodothyronine and GC-1 in the presence of norepinephrine induced UCP-1 expression, while CO23 was weaker in this respect. In the presence of norepinephrine, CO23 did not affect iodothyronine deiodinase D2 activity in adipocytes. Triiodothyronine had a concentration-dependent effect; at a concentration of 10 nM, it increased enzyme activity, and at a concentration of 100 nM, it inhibited it. The $T_3R\beta$ 1 GC-1 agonist, in the presence of norepinephrine, increased the iodothyronine deiodinase D2 activity. In this respect, it acted more strongly than T_3 [73]. The authors concluded that T_3 enhances adrenergic expression of UCP-1 and iodothyronine deiodinase D2, mainly due to $T_3R\beta$ 1 stimulation. The biphasic effect of T_3 seems to be associated with activation of two different subtypes of T_3 receptors; when the first receptor is activated, it appears that $T_3R\beta$ 1 increases iodothyronine deiodinase expression, and when the second receptor is activated, inhibition occurs.

In 1997, Gong et al. [74] showed that UCP-1 is not the only protein whose levels are regulated by thyroid hormones. It was found that hypothyroidism leads to a decrease in the amount of UCP-3 protein, which is a fatty acid transporter, in skeletal muscles by approximately 70%, while hyperthyroidism contributes to a 6-fold increase in UCP-3 levels, in comparison with naïve animals. Investigators have found that a T_3 injection causes a 5-fold increase in the amount of UCP-3 protein in skeletal muscle and a 4-fold increase in white and brown fat [75]. Acute cold exposure (4 °C) caused a 2-fold increase in the amount of UCP-3 protein in brown fat and in

Fig. 1 The involvement of $T_3R\beta$ -RXR and mitochondria in calorigenic effect of thyroid hormones



white fat a 3-fold increase; by contrast, the amount of UCP-3 in skeletal muscles decreased by approximately 70% [75]. The presented data indicate that triiodothyronine causes increased UCP-3 expression in skeletal muscle and in brown and white fat. Unfortunately, the authors did not study the effect of prolonged cold exposure on UCP-3 expression. It is possible that this protein expression during acclimatization to cold is enhanced in all of the listed tissues; otherwise, it is difficult to explain the observed increased respiration of skeletal muscles of adapted animals [7].

In Wen's study, it was shown that cold acclimatization (5 °C, 4 weeks) and administration of L-thyroxine to hamsters (*Cricetulus barabensis*) caused an increase in serum T₃ levels, which was accompanied by an increase in food intake and metabolic rate [76]. Acclimatization at 5 °C enhanced non-contractile thermogenesis, increased *UCP-1* gene expression in BAT, and reduced body fat. L-Thyroxine caused an increase in basal metabolism, but had no significant effect on UCP-1 expression and non-contractile thermogenesis. These observations indirectly indicate that other factors, such as catecholamines, may be involved in adapting to cold. Finally, cold exposure (5 °C) reduced the effect of L-thyroxine on energy metabolism.

In 2013, Mittag's group demonstrated that TR α mutation actually causes increased BAT activity in mice, as it prevents vasoconstriction and thus protection against heat loss [77]. Mice heterozygous for a point mutation in TR α 1 displayed increased thermogenesis as a consequence of sympathetic brown fat stimulation. Despite hypermetabolism, their body temperature was not elevated. The authors used isolated tail arteries and showed that defective TR α 1 signaling impairs acetylcholine-mediated vascular relaxation as well as phenylephrine-induced vasoconstriction. Using infrared thermography on conscious animals, they demonstrate that these defects severely interfere with appropriate peripheral heat conservation and dissipation, which in turn leads to compensatory alterations in BAT activity. Consequently, when a vasoconstrictive defect in mice heterozygous for a point mutation in TR α 1 was reversed with the selective adrenergic receptor α 1 agonist midodrine, inappropriate heat loss over their tail surface was reduced, normalizing BAT activity and energy expenditure. These data demonstrate that thyroid hormones play a key role in vascular heat conservation and dissipation processes, adding a unique aspect to their functions in thermoregulation [77].

Human studies

It should be noted that not all authors agree that thyroid hormones play a key role in regulating the functional state of adipose tissue under cold exposure. We have already mentioned above Wen's study in which it was shown that administration of thyroxine cannot fully imitate the effects of cold

adaptation. In 2017, it was shown that increased uptake of ¹⁸F-FDG by brown adipose tissue in response to cold exposure persists in patients with hypothyroidism [78].

Analysis of the presented data allows us to conclude that the following event chain is built up in cells, presented in Fig. 1: increase in T₃ concentration leads to T₃ interaction with T₃R β and T₃R β -RXR heterodimer formation and T₃R β -RXR binding to DNA. UCP-1 and UCP-3 gene transcription enhancement increases in amount of UCP-1 and UCP-3 proteins, which provides uncoupling of oxidative phosphorylation and, as a result, increase in heat production.

Thyroid-adrenergic interactions in cold adaptation

In 1986, Sato et al. [79] demonstrated that rats with chemically induced hypothyroidism (using propylthiouracil) are able to survive at 6 °C for a month. It should be noted that the authors, who reported that thyroidectomized animals do not survive in cold conditions, used lower temperatures (1.5 °C and 4 °C) [2, 3]. When exposed to cold, rats with hypothyroidism had significantly increased dopamine- β -hydroxylase activity, which is involved in the synthesis of catecholamines. The authors concluded that thyroid insufficiency during cold exposure leads to a compensatory enhancement of synthesis of catecholamines by the adrenal glands. Apparently, the adrenergic and endocrine systems are synergistic in adapting to cold. Investigators have shown [80] that hypothyroidism leads to a 3-fold decrease in β -AR density in BAT, with unchanged affinity (K_d) of receptors for the ligand. Two days after T₃ injection to hypothyroid rats, rapid recovery of β -AR density occurred in brown fat adipocytes. Hypothyroidism led to a 7-fold decrease in norepinephrine-induced cAMP synthesis in BAT. T₃ administration to hypothyroid rats contributed to recovery of cAMP synthesis to normal values [80]. In another paper, the same group of authors showed that in hypothyroid rats, the density of β ₁-AR in brown fat decreases, while the density of β ₂-AR remains at the level typical for euthyroid animals [81]. Hypothyroidism leads to a decrease in the ability of norepinephrine and β ₃-AR agonists to induce cAMP synthesis in BAT. cAMP synthesis induced by forskolin in brown adipose tissue decreased by approximately 80%. This fact suggests that deficiency of thyroid hormones not only disrupts β ₁-AR expression but also causes a decrease in adenylate cyclase activity. Three days after T₃ injection, the density of β ₁-AR and forskolin-induced cAMP synthesis in adipocytes was restored to normal values [81]. In 1995, Rabelo et al. [71] in a study with JEG-3, HIP-1B, and brown fat adipocytes showed that forskolin increases UCP expression 4-fold, while T₃ also acts; and when they are used together, UCP expression is enhanced 12-fold. This observation suggests that catecholamines and thyroid hormones act as synergists. Investigators

conducting experiments in hypothyroid mice attempted to study the nature of interaction of the endocrine and adrenergic systems [4].

In hypothyroid mice, infusion of norepinephrine did not cause an increase in the temperature of interscapular brown fat, while in mice treated with T_3 , recovery of the hyperthermic response to norepinephrine infusion was noted. In hypothyroid mice injected with the $T_3R\beta$ GC-1 agonist, a similar recovery in the calorogenic effect of norepinephrine was not observed. In a study on isolated adipocytes of brown fat of hypothyroid mice, it was demonstrated that norepinephrine-induced increase in cAMP was almost 50% lower than in euthyroid animals. In isolated brown fat adipocytes, forskolin-induced cAMP synthesis was impaired, T_3 application restored the adenylate cyclase activity, and administration of the $T_3R\beta$ agonist GC-1 had no effect [4]. Consequently, thyroid hormones provide a normal adrenergic response of brown fat and this effect is not associated with $T_3R\beta$ stimulation. It is believed that $T_3R\alpha$ activation is required to maintain normal adrenergic response of brown fat [63]. Tight functional integration of the endocrine and adrenergic systems was shown in de Jesus's study [63] and in Martinez de Mena's study [73].

In 2005, Marrif et al. [82], performing experiments in mice with deletion of the $T3R\alpha$ gene, showed that at 6 °C, the body temperature of wild-type mice decreases by 1 °C over 16 h, and by 4 °C in knockout mice. At the same time, UCP-1 levels in BAT remained within the normal range, as was the concentration of T_3 and T_4 in the blood [82]. In response to acute cold exposure (6 °C, 16 h), UCP-1 mRNA levels and iodothyronine deiodinase D2 activity in BAT increased equally in wild-type mice and in animals with deletion of the $T3R\alpha$ gene. In response to norepinephrine infusion, the temperature of brown fat in normal rats increased by 8 °C and that of knockout mice by only 2 °C. After using norepinephrine, the body temperature of wild-type mice increased by 7 °C, and in mice lacking the $T3R\alpha$ gene, it increased by 2 °C. This fact suggests that $T_3R\alpha$ provides normal adrenergic response of adipocytes of brown fat. The chain of signal events is outlined in Figure 2. There are many unknowns in this signal pathway. For example, it is not known which gene transcription is enhanced, due to which there is an increase in adrenergic

response of adipocytes. However, these data are evidence of the tight integration of the adrenergic and endocrine systems.

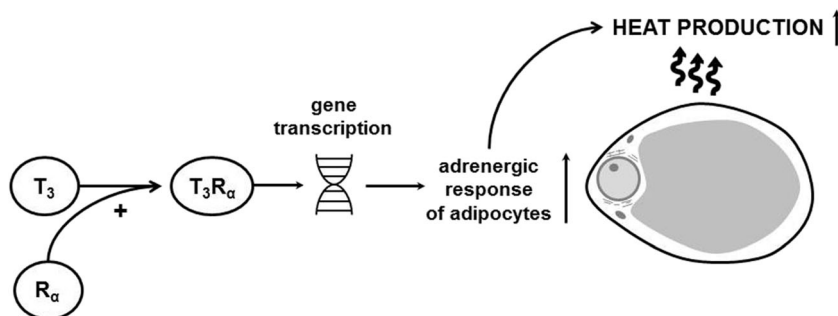
As noted above, Silva and Larsen [19, 56] found that acute cold exposure or acclimatization of rats to cold leads to an increase in iodothyronine deiodinase D2 activity in brown fat. Administration of the α_1 -AR antagonist prazosin to rats before cold stress or during cold adaptation eliminates this effect [19]. This fact suggests that not only thyroid hormones regulate adrenergic response of tissues but also the adrenergic system regulates the functional state of the endocrine system in a process of adaptation to cold.

Thus, T_3 increases a β_1 -AR density in brown fat adipocytes and increases the adenylate cyclase activity in these cells. Forskolin and T_3 act as synergists in the regulation of UCP expression. Triiodothyronine facilitates normal adrenergic response of brown fat, apparently due to $T_3R\alpha$ activation. Figure 2 illustrates the apparent chain of signal events that occurs. The adrenergic system regulates the functional state of the endocrine system in a process of adaptation to cold due to α_1 -AR activation. The above observations indicate that the adrenergic and thyroid systems are synergistic in adaptation to cold.

Concluding remarks

Analysis of the presented data suggests that the endocrine system plays an important role in adaptation to cold. Prolonged exposure to cold leads to an increase in T_3 and T_4 levels in blood of both humans and animals. An increase in thyroid hormone levels can occur without a synchronous increase in TSH level. Cold exposure lasting 30 days or more can cause a decrease in the concentration of total and free T_3 in human blood due to increased clearance of this hormone. A similar response of the endocrine system is characteristic of humans, which has been named the “polar T_3 syndrome”. Endogenous catecholamines increase the iodothyronine deiodinase D2 activity in BAT by stimulating α_1 -AR during adaptation to cold. T_3 is a trigger of iodothyronine deiodinase expression in brown fat, liver, and kidney. The presented data indicate that iodothyronine deiodinase D2 plays an important role in adaptation to cold providing a high adrenergic response

Fig. 2 The involvement of adipocytes and adrenergic receptors in calorogenic effect of thyroid hormones



of BAT. A chain of events during adaptation to cold is built up in cells, as shown in Figure 1. Triiodothyronine increases β_1 -AR density in brown fat adipocytes and increases adenylate cyclase activity in these cells. Forskolin and T_3 act as synergists in the regulation of UCP expression. Triiodothyronine facilitates normal adrenergic response of BAT, apparently due to $T_3R\alpha$ activation. Figure 2 illustrates the apparent chain of signal events that occurs. The adrenergic system regulates the functional state of the endocrine system in a process of adaptation to cold. The adrenergic and endocrine systems act as synergists in adaptation to cold.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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