Review

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The key roles of thyroid hormone in mitochondrial regulation, at interface of human health and disease

https://doi.org/10.1515/jbcpp-2024-0108
Received June 28, 2024; accepted July 6, 2024;
published online July 19, 2024

Abstract: Mitochondria are highly plastic and dynamic organelles long known as the powerhouse of cellular bioenergetics, but also endowed with a critical role in stress responses and homeostasis maintenance, supporting and integrating activities across multifaced cellular processes. As a such, mitochondria dysfunctions are leading causes of a wide range of diseases and pathologies. Thyroid hormones (THs) are endocrine regulators of cellular metabolism, regulating intracellular nutrients fueling of sugars, amino acids and fatty acids. For instance, THs regulate the balance between the anabolism and catabolism of all the macro-molecules, influencing energy homeostasis during different nutritional conditions. Noteworthy, not only most of the TH-dependent metabolic modulations act via the mitochondria, but also THs have been proved to regulate the mitochondrial biosynthesis, dynamics and function. The significance of such an interplay is different in the context of specific tissues and strongly impacts on cellular homeostasis. Thus, a comprehensive understanding of THs-dependent mitochondrial functions and dynamics is required to develop more precise strategies for targeting mitochondrial function. Herein, we describe the mechanisms of TH-dependent metabolic regulation with a focus on mitochondrial action, in different tissue contexts, thus providing new insights for targeted modulation of mitochondrial dynamics.

Keywords: thyroid hormone; metabolism; mitochondria

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Introduction

Thyroid hormones synthesis and metabolism

Thyroid hormones (THs) action is critical for the development of many tissues and for the regulation of their function in the adult [1, 2]. Indeed, THs influence numerous aspects of cell physiology such as cell growth, differentiation, and apoptosis and are key regulators of cell energy metabolism and thermogenesis [3]. THs increase oxygen consumption and heat production, while hypothyroidism has the opposite effects [3]. In addition to its influence on oxygen consumption, mitochondrial function is deeply affected by the thyroid state. The biological action of THs (T3 and T4) is mediated through the interaction of T3, a biologically active hormone, with nuclear thyroid hormone receptors (TRs) determining enhancement or inhibition of the expression of target genes. The TR isoforms, α and β, ligand-dependent transcription factors and members of the nuclear receptor gene superfamily, are differentially expressed in tissues and have distinct roles in TH signaling [1, 4]. In addition to the canonical genomic action, THs also exert a non-genomic action, which is responsible for rapid effects. The non-genomic action does not involve T3 binding to TRs but is mediated by the interaction with receptors on the cell membrane, as in the case of integrin αvβ3, or with intracellular molecules to activate intracellular cascade pathways [5, 6].

Serum THs levels are regulated by the hypothalamic–pituitary–thyroid (HPT) axis, which maintains stable TH levels through the actions of TSH and TSH-releasing hormone (TRH). The thyroid gland produces an excess of the inactive hormone T4 compared to the active hormone T3. Thus, most of the T3 intracellular availability derives from the local regulation of THs metabolism. Without perturbing serum concentrations, the intracellular THs levels can be modified by the deiodinases, a family of enzymes composed of three members: type 1 (D1), type 2 (D2) and type 3 deiodinase (D3) [7]. The three enzymes are expressed in a tissue-specific manner in fetal and adult life [8] and differentially catalyze THs activation or inactivation [9, 10]. D1 and D2

catalyze the activation pathway: the conversion of T4 to T3, with more affinity than T4 for nuclear receptors, whereas D1 and D3 inactivate both T4 and T3 [11]. Moreover, THs can enter the cells via membrane transporter proteins, including MCT8 and MCT10 [12]. Therefore, the final extent of THs function is determined by the fine-tuned balance between different tissue deiodinases, the receptors and the transporters in the target cells [13, 14].

Thyroid hormones and energy homeostasis

Experimental studies revealed how several TH-induced processes contribute to regulating metabolic homeostasis in humans [15]. Nuclear and non-genomic action of THs affect the key metabolic pathways that control energy balance by regulating energy expenditure and accumulation through both central and peripheral actions [16]. THs facilitate adaptive thermogenesis via the brown adipose tissue, modulate appetite and food intake and regulate the body weight [17, 18]. Indeed, it is well known that in healthy individuals, variations in serum TSH are associated with changes in body weight in both men and women [19]. Moreover, THs influence insulin signaling, glucose uptake and lipid metabolism, thus promoting adipocyte differentiation, lipogenesis and lipolysis, depending on metabolic state [20], in both white adipose tissue (WAT) and brown adipose tissue (BAT), although BAT is predominantly involved in energy expenditure. THs in high doses can also induce catabolism of proteins [21]. Dysregulation of the thyroid state leads to considerable alterations in energy balance, indeed, the importance of the THs-mediated homeostatic control of energy metabolism is evident in patients with thyroid dysfunction [22]. Hyperthyroidism, a clinical syndrome that causes an excess of TH, promotes a hypermetabolic state characterized by increased energy expenditure at rest, weight loss despite increased food intake, reduced cholesterol levels, increased lipolysis and gluconeogenesis [23]. By contrast, hypothyroidism is associated with hypometabolism characterized by decreased metabolic rate, weight gain despite reduced food intake, increased cholesterol levels, reduced lipolysis, and decreased gluconeogenesis [24]. The intolerance to cold and heat are hallmark features of hypothyroid and hyperthyroid patients, respectively. Typically, the metabolic regulation of TH has been attributed to the acceleration of both anabolic and catabolic reactions [20]. Therefore, the action of TH turns out to promote the *futile cycles* that contribute significantly to the increase in the oxygen consumption as observed in thyrotoxicosis [3]. Briefly, THs maintain basal metabolic rate (BMR), by increasing ATP production for metabolic processes and by generating and maintaining ion gradients [25]. In particular, they preserve BMR by decoupling oxidative phosphorylation in mitochondria [26] through up-regulation of UCP-1, activating the mitochondrial permeability transition pores and modulating the ADP/ATP translocase [27]. The action of TH also has a significant effect on mitochondrial respiration through promoting mitochondrial biogenesis [28] and stimulating the transcription of PGC-1α [29], which is considered the main regulator of aerobic respiration.

Thyroid hormones regulation of cellular metabolism in illness

The effects of THs on cellular metabolism are exacerbated in different pathological conditions [30]. For instance, hypothyroidism is associated with metabolic deregulations, such as hypercholesterolemia and increased low-density lipoprotein (LDL) levels, representing a risk factor for developing diabetes mellitus (DM) and cardiovascular complications [31–36]. Hyperthyroidism is associated with various cardiovascular events mostly as a significant risk of heart failure, even in individuals without a history of cardiovascular disease. An excess of THs stimulates venous return, increases blood volume and heart rhythm [37]. This causes circulatory congestion by relaxing vascular smooth muscle cells, which can reduce vascular resistance by up to 70 % [38]. A recent report showed that hyperthyroid individuals without diabetes have an increased risk of developing Type 2 DM, indicating that thyroid dysfunction may precede diabetogenic processes [39]. In this line, while hyperthyroid patients show increased basal hepatic glucose production and elevated fasting insulin levels compared to healthy individuals, hyperthyroid patients treated with methimazole show significantly reduced levels of the same parameters, reaching the levels of healthy controls [40]. Several studies have shown that elevated circulating TSH levels are associated with an increased prevalence of metabolic syndrome and obesity [41]. Hepatic insulin resistance in hypothyroid individuals has been shown to result in increased gluconeogenesis and subsequent accumulation of hepatic glucose [42, 43]. Thus, given the central role of insulin action in the regulation of hepatic gluconeogenesis and glycogenolysis [44], impaired insulin sensitivity caused by altered THs levels may per se have important consequences on glucose homeostasis. Moreover, since TH significantly affects energy metabolism, tissues with high metabolic demand, such as skeletal muscle, show serious effects in hypothyroid and hyperthyroid patients. For example, studies aimed at determining the physiological and pathological role of TH in skeletal muscle have shown that patients

with hypothyroidism exhibit muscle damage, as evidenced by high levels of creatine kinase [45]. Also, hyperthyroid individuals show muscle weakness, notably muscle strength and muscle cross-sectional area increase when TH function is normalized in these patients [46].

Alterations in THs status leading to different forms of hyperthyroidism and hypothyroidism are associated not only with the onset of metabolic syndromes such as diabetes mellitus, but also with the cancer. Indeed, patients with high prevalence of pathologies related to thyroid status, such as diabetes, obesity, as well as nonalcoholic steatohepatitis (NASH), one of the most common chronic liver diseases characterized by inflammation and hepatic fibrosis, are also predisposed to develop hepatocellular carcinoma (HCC), however the association between THs and HCC may also be independent of these comorbidities [47, 48]. Indeed, clinical evidence has shown that hypothyroidism predisposes to the development of HCC, suggesting that dysfunctional THs may be a risk factor for this type of cancer [48, 49]. In this regard, a link between THs and the pathophysiology of various types of cancer has been established by more than a century of research. Both *in vitro* studies and research in animal models have shown an effect T3 and T4 on cancer proliferation, apoptosis, invasiveness and angiogenesis [50]. Also in humans, accumulating evidence clearly indicates that the deregulation of TH signaling occurs in different types of cancer [11, 51]. THs mediate their effects on the cancer cell through both genomic and non-genomic pathways and a dysregulation of intra-tumoral THs is involved in cancer initiation and progression. The modulation of deiodinases expression in tumor can affect cancer cells behavior [52]. A differential modulation of D2 and D3 has been demonstrated at specific stages of carcinogenesis in squamous cell carcinoma (SCC) [53]. Altered TH levels are also associated with metabolic reprogramming and angiogenesis of malignant cells, thereby promoting metastasis *in vivo* [54]. In this line, the critical role of intra-tumoral modulation of TH by deiodinases D3 and D2 has been demonstrated not only in skin, but also in other epithelial tumors, including colon and prostate cancer (PCa) [55–57].

In summary, both hyperthyroidism and hypothyroidism are associated with the risk of developing various pathologies such as diabetes and cancer, highlighting the complexity of the mechanisms controlled by TH. The regulation of physiological and pathophysiological processes by TH is highly complex and tissue-specific, depending on the metabolic status of the cells and their sensitivity to THs signal determined by deiodinases, receptors and transporters expression.

Effects of thyroid hormones on mitochondria

The evidence that THs greatly affect mitochondria functioning goes back a long way. However, despite this and the increasing knowledge of the physiology and mechanism of THs-dependent mitochondria regulation, several aspects of such effects remain to be elucidated. The current evidence is focused on two possible mechanisms that might underlie the effects of THs on mitochondrial respiration: i. a mechanism involving their nuclear action and ii. a mechanism involving a direct effect of THs on mitochondria (Figure 1). The transcriptional activity of THs trough the T3-TRs complexes is potently involved in mitochondrial regulation. For instance, THs are major regulators of mitochondrial biogenesis and consequently of mitochondrial activity, through the transcriptional induction of PGC1α and the nuclear respiratory factor 1 (NRF-1) [58], which in turn promote the expression of genes encoding the mitochondrial transcription factors (TFAM, TFB1M, TFB2M), and, subsequently, activate mitochondrial OXPHOS gene expression [59]. THs also directly induce mitochondrial OXPHOS genes, as they increase gene and protein expression of mitochondrial-encoded subunit 1 of cytochrome c oxidase (MTCO1), a subunit of respiratory chain complex IV and TFAM [60]. In addition, THs increase the transcription of the ROS scavenger SOD2 (superoxide dismutase 2) [61]. In detail, THs exert a dose-dependent control on the dynamics of ROS, thus reducing the production of ROS via SOD2 under physiological circumstances while increasing the production of ROS and apoptosis under thyrotoxicosis conditions [61]. Thus, mitochondrial metabolism and redox state are profoundly regulated by the nuclear action of THs (Table 1).

In addition to nuclear pathways, since many mitochondrial genes that are endogenously regulated by T3 lack of thyroid responsive elements in their regulatory elements, a TR-independent pathway of T3-mediated gene regulation is likely. Indeed, TH can directly affect mitochondrial replication, through the truncated forms of TRα1 [62] and TRβ1 [63] that are specifically imported into the mitochondria and stimulate the transcription of the mitochondrial genome. In general, mitochondrial binding sites specific to T3 have been demonstrated over the years, thus acting directly on mitochondrial modulation [64]. The existence of these mitochondrial binding sites for T3 shows that T3 plays very important physiological roles in the regulation of the mitochondrial transcription apparatus, thus regulating mitochondrial biogenesis by acting in synchrony with the nuclear genome.

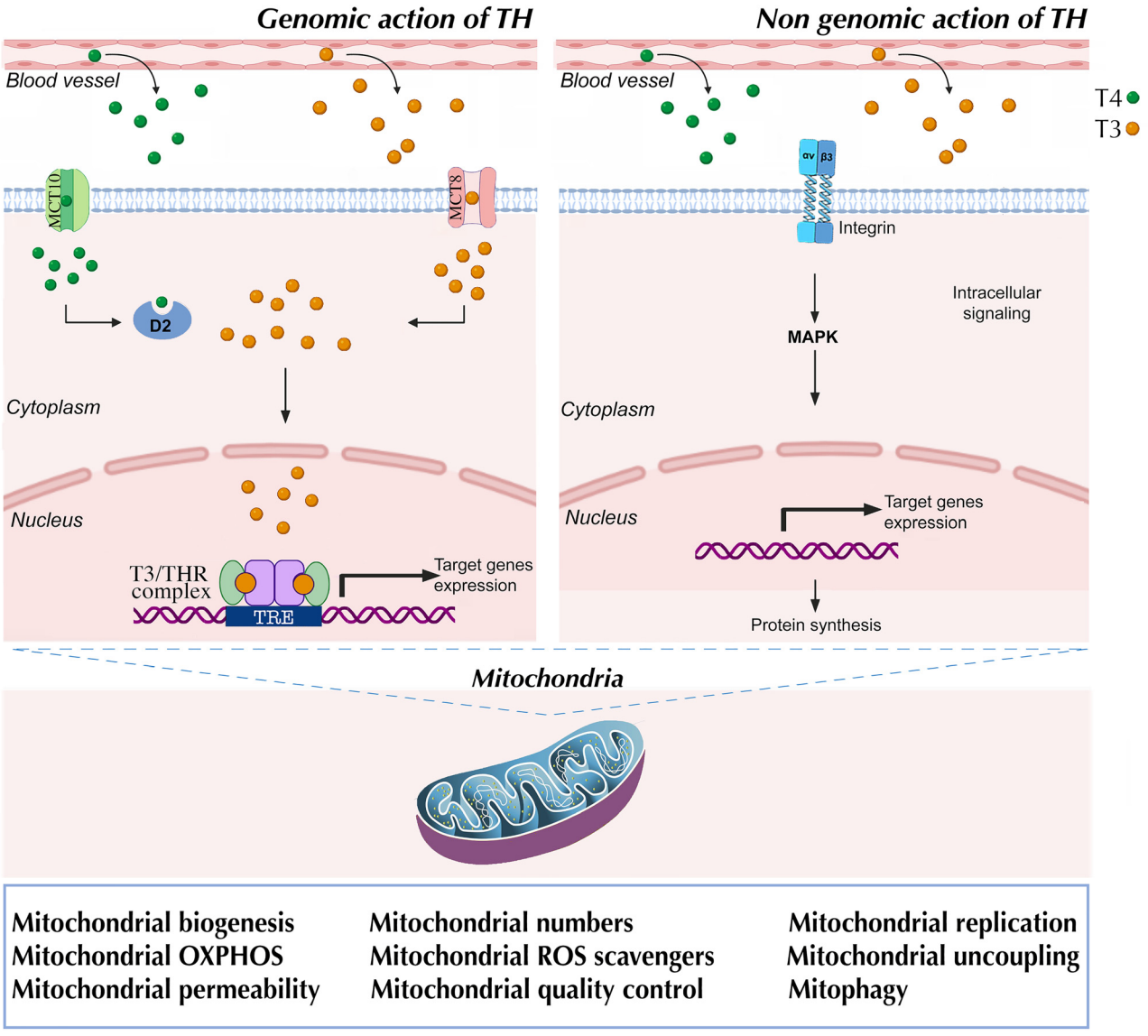

Figure 1: Thyroid Hormones have a deep influence on mitochondria functioning via genomic and non-genomic mechanisms.

Table 1: Key genes under thyroid hormone control involved in mitochondrial regulation.

Gene	Regulation by TH	Role	References
UCP-1	Up-regulation	Uncoupling	[27]
PGC1a	Up-regulation	Mitochondrial biogenesis	[29]
NRF-1	Up-regulation	Mitochondrial biogenesis	[58]
OXPHOS	Activation	Aerobic metabolism	[59]
MTCO1	Up-regulation	Mitochondrial oxidative phosphorylation	[60]
TFAM	Up-regulation	Mitochondrial replication	[60]
SOD2	Up-regulation	ROS balance	[61]
AMPK	Activation	Mitochondrial biogenesis	[79]
UCP3	Up-regulation	Uncoupling	[81]

All the cited evidence highlights the intimate link between THs and mitochondria and have pointed out that, acting through the classical nuclear action or via the direct mitochondrial regulation, THs can play tissue-specific effects on mitochondrial biogenesis, dynamics and functioning. Herein, we describe the effects of THs on mitochondria at single tissue level.

Skeletal muscle

Skeletal muscle (SKM) is among the most important tissues for energy expenditure and glucose and lipid homeostasis [65, 66]. SKM shows remarkable plasticity in response to physiological stimuli such as exercise, fasting and hormonal signals, including THs. Indeed, changes in thyroid status affect SKM metabolic processes as well as mitochondrial activity and biogenesis, leading to changes in mitochondrial mass, structure and contractility [67]. THs also regulate the expression of key genes involved in muscle myogenesis and regeneration [65, 68, 69]. All TH signaling components, transporters, TRs and the deiodinases D2 and D3 are expressed in rodent and human skeletal muscle [70, 71]. Although expressed at very low level in SKM, D2 and D3 have a physiological relevance for SKM, as demonstrated by loss of function studies. For instance, D2 null mice show a delay in the differentiation of muscle stem cells and this impacts on the muscle regeneration process, as seen in experimental models of cardiotoxin induced muscle damage [9, 10, 69]. Moreover, the D2-mediated T3 activation stimulates the slow-to-fast muscle fiber type switch [68, 72]. The transition from a glycolytic to an oxidative fiber increase both mitochondrial content and mitochondrial fusion, forming elongated mitochondria [73]. The role of T3 in stimulating PGC1α and oxidative pathways has a particular importance in SKM, since it is strictly linked to the insulin signaling [74]. In addition, D2 expression and activity is critical for the muscle locomotory performance as indicated by the concomitant stimulation of PGC1α and D2 in exercised muscles [75]. AMP-activated kinase (AMPK) regulates the expression of genes involved in mitochondrial biogenesis, as well as phosphorylated and active PGC1α [76, 77]. Chronic and acute administration of T3 to euthyroid [78] and hypothyroid [79, 80] rats has been shown to induce activation of AMPK, which may mediate the effect of T3 on mitochondrial biogenesis in SKM. The mechanisms by which T3 induces mitochondrial activity and oxygen consumption in muscle are also related to the stimulation of the transcription of the mitochondrial enzymes and of the uncoupling protein 3 (UCP3) [81, 82], which promotes mitochondrial uncoupling in muscle, thereby dissipating energy in the form of heat and reducing the energy efficiency of the cell. Interestingly, D2 is early upregulated in muscle after acute cold exposure indicating a role of TH in the thermogenic activity of SKM [83].

Finally, considering that through autophagy, cells select and specifically target damaged organelles, such as mitochondria, to lysosomes for their degradation [84], modulation of autophagy is a key strategy for improving muscle performance and treating degenerative conditions such as various dystrophic diseases [85]. In contrast, autophagic hyperactivity or inhibition leads to significant loss of muscle mass, myopathies, and muscle injury [86, 87]. Therefore, homeostasis of the autophagic process is critical to ensure both functionality and mitochondrial content in SKM. Recently, Lesmana and colleagues have shown that TH-induced mitochondrial biogenesis and activity is dependent on T3-induced autophagy [88], consistent with previous studies showing a link between autophagic induction and mitochondrial function during exercise [89, 90].

Liver

The liver represents a major target for THs, which regulate liver function by modulating the basal metabolic rate of hepatocytes; the liver, in turn, metabolizes THs and regulates their systemic endocrine effects [91]. For example, TH plays an important role in the regulation of hepatic glucose, lipid and cholesterol metabolism and homeostasis [92]. In addition, THs play a key role in lipophagy, mitochondrial quality control and regulation of metabolic genes. As mentioned above, TH induces the maintenance of mitochondrial homeostasis, indeed promotes the process of “mitophagy” to prevent cell damage due to excessive ROS production [93], during nutrient deprivation and exposure to inflammatory or pro-apoptotic stimuli [94]. In liver, THs are known to be potent inducers of hepatic autophagy and mitochondrial function [95] and have also beneficial effects on lipid homeostasis, reducing serum levels of cholesterol and triglycerides. In addition, hypothyroidism has been associated with non-alcoholic fatty liver disease (NAFLD) and vice versa [96], both hypothyroidism and NAFLD are associated with the development of fatty liver, obesity and insulin resistance [96]. In this context, regulation of autophagy represents a new strategy for the treatment of several important liver diseases [97], including NAFLD [98]. Indeed, TH-induced mitophagy [99] may help to counteract the excessive oxidative stress and consequent mitochondrial damage caused by the lipotoxic intermediates present in NAFLD. Although it is well described that TH stimulates the transport of free fatty acids into mitochondria [100], the processes leading to the generation of free fatty acids are not

well understood. Recently, studies have suggested that TH-induced lipophagy, one of the major pathways of lipid mobilization in hepatocytes, may be useful in reducing hepatic lipid accumulation and increasing mitochondrial β-oxidation [101]. Therefore, thyroid dysfunction may lead to intrahepatic and systemic dysregulation thus impairing not only hepatic but also whole body energy metabolism. However, the use of THs in clinical settings is severely limited because THs can cause side effects such as atrial arrhythmias, osteoporosis and hyperthermia. To avoid these effects, TH mimetics targeting the liver have been developed and have considerable therapeutic potential [102].

Thyrotoxicosis is characterized by an excessive energy consumption and heat production in the mitochondria [103]. It has long been known that mitochondria in the liver of hyperthyroid rats appear swollen [104]. This morphological change appears to protect the hyperthyroid liver from increased oxidative damage. Indeed, in the presence of Ca^{2+}, the oxidative modification of inner membrane proteins has been shown to promote greater permeabilization of the inner membrane [105], which determines mitochondrial swelling. Mitochondria with high levels of ROS keep pores open and are discarded, while organelles with low ROS production survive [67]. Therefore, the regulation of mitochondria ROS levels can be deciphered as a survival mechanism. Hepatic mitochondria in hyperthyroid rats show increased swelling [106], balancing cellular production of ROS, thus suggesting that TH plays a central role as a mitochondrial preservative agent. Additionally, it is also worth mentioning the effects of oxidative stress, mitochondrial dysfunction and ROS production in liver disease but also in liver cancer. The liver is capable of regeneration, but it is subject to pathologies that can lead to cancer, such as fibrosis, cirrhosis and non-alcoholic fatty liver disease. The immediate consequences of oxidative stress and ROS production include enhanced D3 activity, leading to reduced T3 production, and increased rT3 levels, stimulating tumor cell proliferation [107, 108].

Brain

THs are involved in many processes that regulate the metabolism and development of the central nervous system (CNS). In fact, THs stimulate the growth and differentiation of neurons to ensure optimal brain function and are also essential for normal brain development: they influence neurogenesis, neuronal and glial cell differentiation and migration, synaptogenesis and myelination. Their deficiency may severely affect the brain during fetal and postnatal development, causing retarded maturation, intellectual deficits, and neurological impairment [109]. Consequently, the importance of TH effects in the mature brain is underscored by the variety of neurological and psychiatric disorders that result from thyroid dysfunction in adults. These include anxiety, lethargy, sleep disturbances, mood disorders, cognitive deficits, and seizures [110]. Moreover, considering the beneficial effects of THs on axonal maturation, myelination and on synaptic plasticity, alterations of systemic THs levels have a deep impact on neuronal stroke [111].

Mitochondria in neuronal tissue are fundamental to their unique function as major energy producers, and THs are critical in regulating this function. Alterations in THs levels can lead to mitochondrial dysfunction, which is implicated in several neurological disorders, demonstrating potential causal relationships between oxidative stress and cognitive functions, including cognitive performance, intelligence, memory, reaction time, and language [112]. TH may also promote recovery and neuronal regeneration after brain injury [113]. An important role in neuroprotection is played by mitochondrial metabolism in astrocytes. Mitochondrial energy production is rapidly increased after T3 treatment via a mitochondrially targeted TH receptor [114]. Therefore, an effective strategy to enhance neuroprotection may be to target astrocyte metabolism to increase ATP levels in the brain. Thus, of growing interest is the role of THs and mitochondria in some neurodegenerative and neurocognitive disorders, like in Alzheimer's disease, in depression and anxiety.

Conclusions

Thyroid Hormones control nutrient fueling and metabolic rate via diverse pathways. Mitochondria, as the prime metabolic platform, are site target of THs. The cellular mechanisms underlying the THs-dependent mitochondrial regulation have been widely investigated. However, still many aspects of the complex relationship between THs and mitochondria remain to be fully elucidated, as well as the impact of hyper- and hypothyroidism in mitochondrial dysfunctions.

Multiple aspects contribute to such a complexity: the double ability of THs to act at short- and long-term regulation by integrating genomic and non-genomic molecular processes; the interaction of TH receptors with different co-repressor or co-activator partners in specific cellular contexts; the countless genes and pathways under the transcriptional or non-transcriptional regulation of THs; the differential contribution of THs to metabolic regulation in each target tissue.

Here, we review the effects of thyroid hormones on mitochondrial energetics with a particular emphasis on the differential contribution of THs in specific cellular districts. The whole picture emerging indicates THs as master regulators for mitochondria synthesis and function. Indeed, the effects of THs range from modulating inner membrane proteins and lipids composition to balancing the ATP production/uncoupling processes ratio to the fine tuning the reactive oxygen species production and scavenging. In conclusion, intensive research studies are still needed for a clear understanding of the multiple function of THs in mitochondria in order to provide critical benefits on overall whole-body metabolism in healthy and disease.

Research ethics: Not applicable.
Informed consent: Not applicable.
Author contributions: All authors have accepted responsibility for the entire content of this manuscript and approved its submission.
Competing interests: Authors state no conflict of interest.
Research funding: This work was supported by grants from AIRC to M.D. (IG 29242), by Telethon to M.D. (GMR22T1020) and by a PRIN-2022 grant from MIUR awarded to M.D. (2022HB54P9).
Data availability: Not applicable.

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