Thyroid Hormone and Central Control of Metabolic Homeostasis

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Abstract

Thyroid Hormone (TH) regulates energy balance, lipid metabolism and cardiovascular function. These effects are largely due to direct action of TH on peripheral target tissues. However, there is increasing evidence for a direct central action of TH modulating metabolic processes, including regulation of thermogenesis, food intake, hepatic glucose metabolism and cardiovascular tone through direct action in the brain. Here, we review the current understanding of mechanisms including key hypothalamic signaling involved in central TH regulation of energy balance and metabolism.

ABBREVIATIONS

TH: Thyroid Hormone; SNS: Sympathetic Nervous System; WAT: White Adipose Tissue; BAT: Brown Adipose Tissue; UCP1: Uncoupling Protein 1; ARC: Arcuate Nucleus; PVH: Paraventricular Nucleus; S0: Supraoptic Nucleus; VMH: Ventromedial Nucleus; T4: Thyroxine; T3: Triiodothyronine; MCT8: Monocarboxylate Transporter 8; AMPK: AMP-activated Protein Kinase; NPY: Neuropeptide Y; AgRP: Agouti-Related Protein; POMC: Proopiomelanocortin; α-MSH: Alpha-Melanocyte-Stimulating Hormone; CART: Cocaine and Amphetamine Regulated Transcript; mTOR: Mammalian Target of Rapamycin; D2: Deiodinase 2; PSNS: Parasympathetic Nervous System

INTRODUCTION

It is well defined that Thyroid Hormone (TH) regulates energy balance, lipid metabolism and cardiovascular function [1]. Excessive TH levels (hyperthyroidism) lead to hypermetabolic state characterized by increased energy expenditure and weight loss despite increased food intake. Decreased TH levels (hypothyroidism), by contrast, is associated with decreased metabolic rate and weight gain despite reduced food intake [2]. Most of these effects are due to the direct action of thyroxine hormones on target tissues, such as liver, white and brown adipose tissues (WAT and BAT, respectively), heart and skeletal muscle via modulation of adrenergic nervous system and direct actions on genes expression [reviewed in [3]]. However, there is increasing body of evidence for a direct central action of TH modulating metabolic processes. Here, we review current understanding of the mechanisms for TH regulation of thermogenesis, food intake, cardiovascular tone, and hepatic glucose metabolism through direct action in the brain.

Thyroid Hormone and Central Regulation of Energy Expenditure

In a thermoneutral environment the body can maintain temperature through obligatory thermogenesis, i.e. generation of heat that accompanies metabolic processes. When ambient temperature falls below thermoneutral (23°C in humans) there is activation of heat-saving mechanisms (vasoconstriction, piloerection, rounded position, mobility reduction) and adaptive thermogenesis (generation of heat by shivering and by BAT) [4]. Thyroid hormone plays a major role in regulating both obligatory and adaptive thermogenesis by increasing basal metabolic rate and by modulating Sympathetic Nervous System (SNS)-activation of BAT, respectively [4]. Thyroid hormones increase metabolic rate by increasing ATP utilization and turnover, and by reducing the efficiency with which a cell captures energy substrate in ATP thus dissipating more of it as heat. Heat generation in BAT occurs via so-called ucp1-mediated proton-motive force by uncoupling protein 1 (UCP1). Thyroid hormones increases thermogenesis in BAT by augmenting responsiveness to norepinephrine, as well as enhancing the cAMP-mediated acute rise in ucp1 gene expression [5].

In addition to the above mentioned peripheral mechanisms through which THs modulate thermogenesis, there is evidence that THs modulates BAT through direct action in the brain. Initial indication for a role of TH in central regulation comes from observation that Thyroid Receptor (TR) isoforms α1, α2, β1 and β2 are widely located in brain, including hypothalamic areas that modulate energy balance and peripheral metabolism as well as...
the Arcuate (ARC), Paraventricular (PVH), Supraoptic (SO), and Ventromedial (VMH) hypothalamic nuclei [6,7]. The hypothalamus also expresses deiodinases that regulate conversion of TH to its active form triiodothyronine (T3), and expresses TH active transporter Monocarboxylate Transporter 8 (MCT8) [8]. The molecular mechanisms for TH central regulation of energy balance has been investigated by Lopez et al [7]. They demonstrate that central administration of triiodothyronine (T3) in rats leads to SNS activation and upregulation of BAT thermogenesis via reduction in hypothalamic AMPK activity. Inhibition of hypothalamic AMPK pathway results in activation of lipogenic enzyme acetyl-CoA carboxylase and subsequent activation of its downstream targets acetyl-CoA carboxylase and fatty acid synthase as well as inhibition of CPT1, resulting in de novo lipogenesis specifically in the hypothalamus but not in other brain regions, such as cortex and cerebellum. This T3-mediated alteration in hypothalamic lipogenesis works as a “global energy gauge” causing weight loss via SNS-mediated increased energy dissipation in BAT. Genetic inhibition of TH signaling using adenoviral injection of a dominant negative TR in the VMH reversed the effects of hyperthyroidism on energy balance, inactivating thermogenic program in BAT and therefore preventing weight loss associated with hyperthyroidism. The effects of TH on AMPK signaling are specific to VMH, as inactivation of hypothalamic fat metabolism in VMH by selective ablation of AMPK induced weight loss and increased BAT activation, while stereotaxical treatment with adenovirus harboring constitutively active AMPK reduced activation of BAT and prevented weight loss associated with hyperthyroidism without increased feeding. Taken together, the above data provides solid basis and increasing understanding of TH-mediated central control of negative energy balance through its effects in energy dissipation.

Thyroid hormone and central regulation of appetite

Hypothalamic nuclei, especially ARC, are the center for food intake control. ARC integrates peripheral signals and regulates food intake through expression of orexigenic factors (appetite stimulation) such as neuropeptide Y (NPY) and agouti-related protein (AgRP), as well as expression of anorexigenic factors (appetite inhibition) such as Proopiomelanocortin (POMC) which encodes for alpha-melanocyte-stimulating hormone (α-MSH), and Cocaine and Amphetamine Regulated Transcript (CART). Hyperthyroidism-induced increase in food intake is associated with dysregulation of hypothalamic neuropeptide system, including increased NPY and AgRP expression, and decreased POMC expression in ARC [7].

Mechanisms underlying central regulation of TH-induced changes in hypothalamic neuropeptides have been investigated, and include deiodinase 2, UCP2 and mTOR signaling in hypothalamic ARC. Deiodinase 2 (D2) catalyzes the conversion of T3 to T4, which is required for development of parvalbuminergic neurons in anterior hypothalamus (* location in Figure is arbitrary) that modulate central autonomic control of blood pressure and heart rate.
of T4 to T3. D2 activity is particularly high in ARC, where it is expressed within glial cells in direct contact with NPY/AgRP neurons. Food deprivation increases D2 activity in ARC neurons with resulting local rise in T3 levels and increases UCP2-dependent mitochondrial uncoupling. UCP2 activation results in mitochondrial proliferation in NPY/AgRP neurons, leading to excitability of these orexigenic neurons and increased appetite. UCP2 expression and activity are also increased by central injection of T3, but reduced in hypothyroidism [9]. Hypothalamic mammalian target of rapamycin (mTOR) also mediates TH-mediated control of feeding. Central administration of T3 activates mTOR signaling pathway and is associated with increased expression of AgRP and NPY, and decreased POMC expression in hypothalamic ARC, an area where mTOR co-localizes with TRα. Hyperthyroidism-induced increase in food intake is reversed by central treatment with specific mTOR inhibitor rapamycin, resulting in weight loss [10]. These studies demonstrate that T3 levels in hypothalamus regulate feeding through mTOR signaling and expression of orexigenic/anorexigenic ARC nucleus neuropeptides.

**Thyroid hormone and central regulation of cardiovascular functions**

There is recent evidence demonstrating central action of TH in regulation of cardiovascular function. Thyroid hormone action is required for the development of a previously unknown population of parvalbuminergic neurons in the anterior hypothalamus involved in autonomic control of cardiovascular functions [11]. Mice with heterozygotic inactivation of TRα have a reduced number of parvalbuminergic neurons in the anterior hypothalamus. Targeted ablation of this hypothalamic parvalbuminergic neurons results in hypertension and temperature-dependent tachycardia, indicating their role in the central autonomic control of blood pressure and heart rate. These findings suggest that perinatal developmental of anterior hypothalamic parvalbuminergic neurons depends on intact signaling of thyroid receptor isoforms, and that developmental hypothyroidism may represent a previously unknown risk factor for cardiovascular disorders, although a higher frequency of hypertension in adult patients with congenital hypothyroidism has not been reported.

**Thyroid hormone and central regulation of hepatic glucose metabolism**

THs influence several aspects of glucose metabolism, mainly hepatic glucose output and insulin sensitivity. Thyrotoxicosis is often associated with impaired glucose tolerance or frank hyperglycemia at least in part due to increased glucose production in the liver and reduction in hepatic insulin sensitivity [12]. A study performing selective denervation of the hepatic SNS or parasympathetic nervous system (PSNS) in euthyroid and thyrotoxic rats showed that TH modulates hepatic glucose production via sympathetic pathway from the hypothalamus. While in euthyroid rats selective hepatic sympathectomy or parasympathectomy did not affect glucose metabolism, in thyrotoxic rats sympathectomy attenuated the increased hepatic glucose production observed in hyperthyroidism and parasympathectomy did not affect hepatic glucose production but worsened insulin resistance [13]. T3 administration in hypothalamic PVH increased hepatic glucose production independent of plasma T3, insulin, glucagon and corticosterone [14] and this effect was abolished by selective hepatic sympathectomy. These studies show that T3-sensitive neurons in PVN mediate liver glucose production via sympathetic projections on the liver.

**SUMMARY AND CONCLUSION**

THs are important modulators of energy balance and metabolism, through effects in peripheral tissues and also actions in hypothalamus. TH has very distinct and dissociated actions in VMH, ARC, PVH and paraventriculineurons in the hypothalamus modulating specific metabolic processes. Understanding these central pathways and mechanisms may reveal molecular targets to treat energy balance disorders such as cachexia and obesity.

**REFERENCES**

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