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Review Article

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 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.

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Role of Thyroid Hormone in Metabolic Homeostasis

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ABBREVIATIONS

TH: Thyroid Hormone; SNS: Sympathetic Nervous System; WAT: While Adipose Tissue; BAT: Brown Adipose Tissue; UCP1: Uncoupling Protein 1; ARC: Arcuate Nucleus; PVH: Paraventricular Nucleus; SO: Supraoptic Nucleus; VMH: Ventromedial Nucleus; T4: Thyroixine; 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 thyroid 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 hormoneplays 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 SNS activity, where norepinerphine binds to β3-adrenergic receptors and triggers cellular pathways that culminate in mitochondrial heat production through creation of 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 in hypothalamic areas that modulate energy balance and peripheral metabolismsuch 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 thyroixine (T4) 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 AMP-Activated Protein Kinase (AMPK) activity. Inhibition of hypothalamic AMPK pathwayresults 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-medicated 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

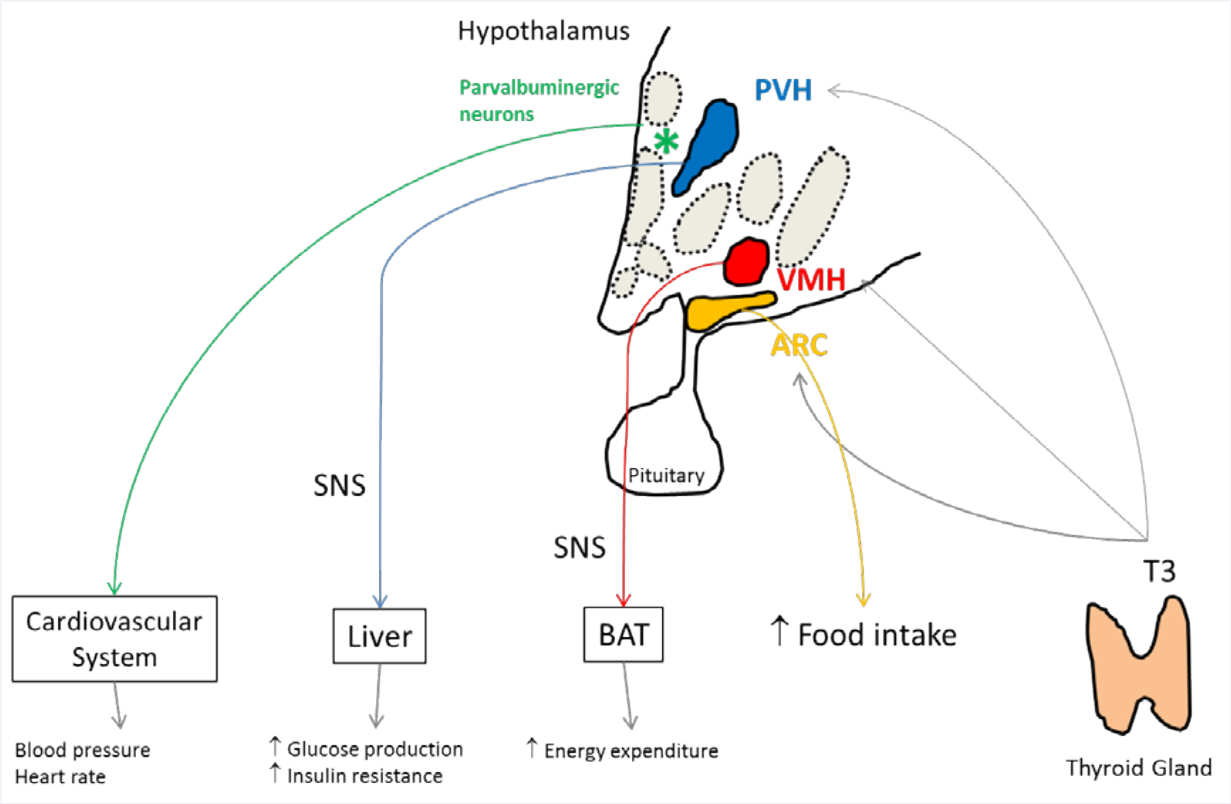

Figure 1 Central actions of thyroid hormone regulating metabolic homeostasis. TH actions in hypothalamic nuclei results in specific metabolic responses. T3 modulates hepatic glucose production and insulin sensitivity via SNS-mediated action in PVH. T3 modulates thermogenic program via stimulation of lipogenesis in VMH. Central T3 regulates appetite through activation of mTOR and UCP2 that regulate orexigenic/anorexigenic ARC nucleus neuropetides. TH is required for development of parvalbuminergic neurons in anterior hyopothalamus (* 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 modulates 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 neuropetides.

Thyroid hormone and central regulation of cardiovascular functions

There is recent evidence demonstrating central action of TH in regulation of cardiovascular function. Thyroid hormoneaction is required for the development of a previously unknown population of parvalbumin ergic neurons in the anterior hypothalamus involved in autonomic control of cardiovascular functions [11]. Mice with heterozygous 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 parvalbuminergic neurons 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

1. Brent GA. Mechanisms of thyroid hormone action. J Clin Invest. 2012; 122: 3035-3043.
2. Kim B. Thyroid hormone as a determinant of energy expenditure and the basal metabolic rate. Thyroid. 2008; 18: 141-144.
3. Mullur R, Liu YY, Brent GA. Thyroid hormone regulation of metabolism. Physiol Rev. 2014; 94: 355-382.
4. Silva JE. Thermogenic mechanisms and their hormonal regulation. Physiol Rev. 2006; 86: 435-464.
5. Cannon B, Nedergaard J. Brown adipose tissue: function and physiological significance. Physiol Rev. 2004; 84: 277-359.
6. Alkemade A, Vuijst CL, Unmehopa UA, Bakker O, Vennström B, Wiersinga WM, et al. Thyroid hormone receptor expression in the human hypothalamus and anterior pituitary. J Clin Endocrinol Metab. 2005; 90: 904-912.
7. López M, Varela L, Vázquez MJ, Rodríguez-Cuenca S, González CR, Velagapudi VR, et al. Hypothalamic AMPK and fatty acid metabolism mediate thyroid regulation of energy balance. Nat Med. 2010; 16: 1001-1008.
8. Alkemade A, Friesema EC, Unmehopa UA, Fabriek BO, Kuiper GG, Leonard JL, et al. Neuroanatomical pathways for thyroid hormone feedback in the human hypothalamus. J Clin Endocrinol Metab. 2005; 90: 4322-4334.
9. Coppola A, Liu ZW, Andrews ZB, Paradis E, Roy MC, Friedman JM, et al. A central thermogenic-like mechanism in feeding regulation: an interplay between arcuate nucleus T3 and UCP2. Cell Metab. 2007; 5: 21-33.
10. Varela L, Martínez-Sánchez N, Gallego R, Vázquez MJ, Roa J, Gándara M, et al. Hypothalamic mTOR pathway mediates thyroid hormone-induced hyperphagia in hyperthyroidism. J Pathol. 2012; 227: 209-222.
11. Mittag J, Lyons DJ, Sällström J, Vujovic M, Dudazy-Gralla S, Warner A, et al. Thyroid hormone is required for hypothalamic neurons regulating cardiovascular functions. J Clin Invest. 2013; 123: 509-516.
12. Fliers E, Klieverik LP, Kalsbeek A. Novel neural pathways for metabolic effects of thyroid hormone. Trends Endocrinol Metab. 2010; 21: 230-236.
13. Klieverik LP, Sauerwein HP, Ackermans MT, Boelen A, Kalsbeek A, Fliers E. Effects of thyrotoxicosis and selective hepatic autonomic denervation on hepatic glucose metabolism in rats. Am J Physiol

Endocrinol Metab. 2008; 294: E513-520.

14. Klieverik LP, Janssen SF, van Riel A, Foppen E, Bisschop PH, Serlie MJ, et al. Thyroid hormone modulates glucose production via a sympathetic pathway from the hypothalamic paraventricular nucleus to the liver. Proc Natl Acad Sci U S A. 2009; 106: 5966-5971.

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