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New insights into thyroid hormone action☆

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ABSTRACT

Thyroid hormones (TH) are endocrine messengers essential for normal development and function of virtually every vertebrate. The hypothalamic-pituitary-thyroid axis is exquisitely modulated to maintain nearly constant TH (T4 and T3) levels in circulation. However peripheral tissues and the CNS control the intracellular availability of TH, suggesting that circulating concentrations of TH are not fully representative of what each cell type sees. Indeed, recent work in the field has identified that TH transporters, deiodinases and thyroid hormone receptor coregulators can strongly control tissue-specific sensitivity to a set amount of TH. Furthermore, the mechanism by which the thyroid hormone receptors regulate target gene expression can vary by gene, tissue and cellular context. This review will highlight novel insights into the machinery that controls the cellular response to TH, which include unique signaling cascades. These findings shed new light into the pathophysiology of human diseases caused by abnormal TH signaling.

Contents

Abbreviations: TH, thyroid hormones; T4, thyroxine; T3, triiodothyronine; CNS, central nervous system; HPT, hypothalamic-pituitary-thyroid axis; TRH, thyrotropin-releasing hormone; PVN, paraventricular nucleus; CART, cocaine- and amphetamine-regulated transcript; CRH, corticotrophin releasing hormone; TSH, thyroid stimulating hormone; GWAS, genome-wide association studies; PDE8B, Phosphodiesterase 8B; PDE10A, Phosphodiesterase 10A; CAPZB, Capping Actin Protein of Muscle Z-line Beta subunit; MAF/LOC440389, V-Maf Avian Musculoaponeurotic Fibrosarcoma Oncogene Homolog; VEGFA, Vascular Endothelial Growth Factor A; NR3C2, Nuclear Receptor Subfamily 3 Group C Member 2; IGFBP5, Insulin Like Growth Factor Binding Protein 5; NFIA, Nuclear Factor I A; SOX9, SRY-Box 9; PRDM11, PR Domain 11; FGF7, Fibroblast Growth Factor 7; INSR, Insulin Receptor; ABO, ABO Blood Group; MIR1179, MicroRNA 1179; NRG1, Neuregulin 1; MBIP, MAP3K12 Binding Inhibitory Protein 1; ITPK1, Inositol-Tetrakisphosphate 1-Kinase; SASH1, SAM And SH3 Domain Containing 1; GLIS3, GLIS Family Zinc Finger 3; DIO1, Deiodinase, Iodothyronine Type I; LHX3, LIM Homeobox 3; FOXE1, Forkhead Box E1; AADAT, Aminoadipate Aminotransferase; NETO1/FBXO15, Neuropilin and Tolloid Like 1/F-Box Protein 15; LPCAT2/CAPNS2, Lysophosphatidylcholine Acyltransferase 2/Calpain Small Subunit 2; FT4, free thyroxine; MCT8, monocarboxylate transporter 8; MCT10, monocarboxylate transporter 10; OATP1, organic anion transporter; LAT, L-type amino acid transporter; AHS, Allan-Hendon Dudley syndrome; SNP, single nucleotide polymorphism; TRIAC, 3,5,3′-triiodothyroacetic acid; TETRAC, tetraiodothyroacetic acid; DITPA, 3,5-diiodothyropropionic acid; LPS, lipopolysaccharide; LAT2, L-type amino acid transporter 2; D2, type 2 deiodinase; D3, type 3 deiodinase; IRD, inner-ring deiodination; ORD, outer ring deiodination; D1, type 1 deiodinase; EGL, external germinal layers; IGL, internal germinal layers; CTX, cardiotoxin analogue III; WSB-1, WD Repeat and SOCS Box Containing 1; OA, osteoarthritis; ADAMTS5, ADAM Metallopeptidase with Thrombospondin Type 1 Motif 5; TR, thyroid hormone receptor; LBD, ligand binding domain; TRβ1, thyroid hormone receptor beta 1; TRβ2, thyroid hormone receptor beta 2; TRα1, thyroid hormone receptor alpha 1; RTHB, resistance to thyroid hormone beta; RTH, resistance to thyroid hormones; GI, gastrointestinal; RXRα, retinoic X receptor alpha; GFP, green fluorescent protein; RNF166, Ring Finger Protein 166; PI3K, Fosfoinositol 3-quinasa; NCoR1, Nuclear receptor corepressor 1; SMRT, silencing mediator of retinoic acid and thyroid hormone receptor; HDAC3, Histone Deacetylase 3; SRC-1, steroid receptor coactivator 1; CBP, CREB-binding protein; NCORΔID, Nuclear receptor corepressor 1 that lacks nuclear receptor interaction domains; SRC-2, steroid receptor coactivator 2; FBXO21, F-Box Protein 21; Gsta1, Glutathione S-Transferase Alpha 1.

☆ Conflict of Interest: The authors declare that there are no conflicts of interest.

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1. Introduction

Thyroid hormones modulate gene expression in virtually every vertebrate tissue; their actions are finely tuned by a series of conserved pathways, which orchestrate the onset of crucial physiological processes for normal development, growth and energy metabolism. Since the cloning of the thyroid hormone receptors in 1986 three decades of intense research have enlightened our knowledge on the molecular basis of thyroid hormone action. In the present review we will address the new insights into thyroid hormone action that have been published within the last four years.

2. The hypothalamic-pituitary-thyroid axis

Thyroid hormones (TH) are essential for growth and development in virtually every vertebrate including humans. TH synthesis and secretion is finely modulated by the hypothalamic-pituitary-thyroid (HPT) axis. It is well appreciated that thyroid hormone production is governed by this central axis that begins in the paraventricular nucleus of the hypothalamus and proceeds through the pituitary before engaging the thyroid. Indeed, human mutations have been described at every level of the axis and all cause hypothyroidism (Medici, Visser, Visser, & Peeters, 2015). Importantly, circulating thyroid hormones (TH) negatively feedback to the central components of the axis to regulate levels. Today, pituitary-secreted thyroid-stimulating hormone (TSH) remains the most important and universal biomarker of TH action in humans.

The hypothalamic section of the axis is represented by the thyrotropin-releasing hormone (TRH)-neurons in the paraventricular nucleus (PVN), which secrete TRH in response to a series of environmental and physiological stimuli. Interestingly, TRH neurons in the PVN co-secrete the neuropeptide cocaine- and amphetamine-related transcript (CART) but its role remains unclear (Hollenberg, 2008). Several other important neuronal populations exist in the PVN including corticotropin-releasing hormone (CRH), vasopressin and oxytocin neurons, which each have an important endocrine function. The TRH gene encodes a prepro-hormone that is ultimately processed to a tripeptide with the sequence of glu-his-pro (Nillni & Sevarino, 1999). Released into the median eminence, TRH induces the secretion of thyroid-stimulating hormone (TSH) from the anterior pituitary, which in turn accentuates the synthesis and secretion of thyroid hormones from the thyroid gland into the circulation (Fig. 1). TRH released into the median eminence acts on the TRH-receptor located in the membrane of thyrotrophs, the TSH-producing cell in the pituitary. Thyrotrophs lose their ability to secrete TSH when disaggregated in cell culture, suggesting a functional role for the architecture of the anterior hypophysis of the pituitary and the possible participation of other signaling factors to modulate thyrotroph sensitivity to TRH *in vivo* (Bargi-Souza et al., 2015). The HPT axis plays the major role in maintaining the homeostasis of circulating TH levels as circulating T4 and T3 feed back to both the hypothalamus and the pituitary to regulate TRH and TSH production (see 'Negative regulation by thyroid hormone).

Remarkably, the set point of the HPT axis differs between individuals (Fitzgerald & Bean, 2016). This is likely due to genetic factors. Genome-wide association studies (GWAS) analyzing different populations of euthyroid humans have identified polymorphisms associated with differences in circulating levels of TSH and T4 within the normal range of concentration. The loci associated with TSH levels are PDE8B, PDE10A, CAPZB, MAF/LOC440389, VEGFA, NR3C2, IGFBP5, NFIA, SOX9, PRDM11, FGF7, INSR, ABO, MIR1179, NRG1, MBIP, ITPK1, SASH1, and GLIS3, whereas free T4 (FT4) was associated with DIO1, LHX3, FOXE1, AADAT, NETO1/FBXO15, and LPCAT2/CAPNS2, (Malinowski et al., 2014; Porcu et al., 2013; Taylor et al., 2015; Zhan et al., 2014). The role of these polymorphisms in the modulation of TSH and FT4 are just starting to be elucidated, however many of these genes appear to have their actions in the thyroid. For example, polymorphisms in PDE8B, a phosphodiesterase expressed in the thyroid, are associated with high

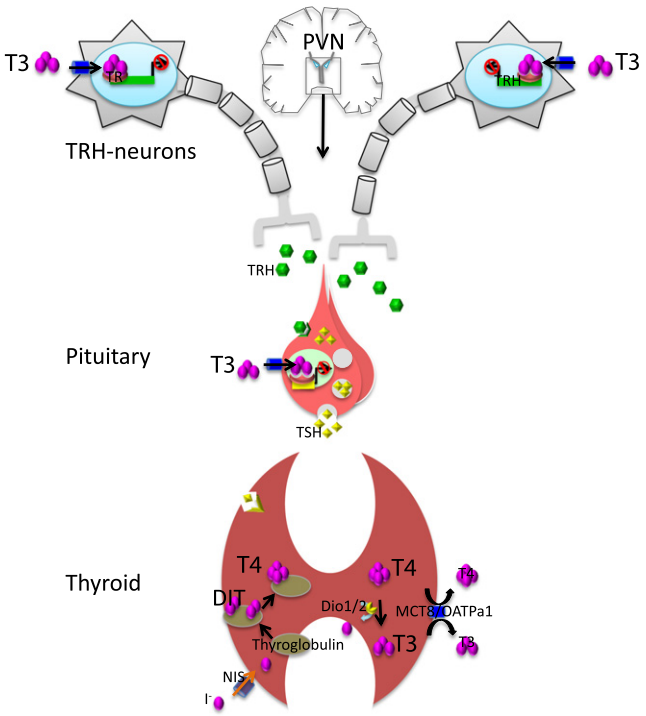

Fig. 1. The hypothalamus-pituitary-thyroid (HPT) axis maintains thyroid hormone homeostasis. The PVN neurons secrete TRH in response to low circulating T3/T4 levels. In turn, TRH signaling in the pituitary stimulates the secretion of TSH, which triggers the release of T4 and T3 from the thyroid gland into the bloodstream. T3 negative feedback on expression of TRH and TSH genes in the PVN and the pituitary respectively keeps the T3/T4 ratio virtually constant in circulation.

circulating levels of TSH together with slightly decreased FT4 levels (Roef et al., 2013b). This is consistent with PDE8B regulating TSH action in regulating the synthesis of thyroid hormone (Fig. 2). In thyroid tumor patients only, polymorphisms in another thyroid specific gene CAPZB were found to be associated with lower TSH levels (Feng et al., 2015). Polymorphisms in NRG1 and FOXE1 were associated with a risk of follicular adenoma (Rogounovitch et al., 2015). Polymorphisms in FOXE1 are also associated with congenital hypothyroidism (Carre et al., 2014). Some polymorphisms have little to no effect in patient care such as the type 1 deiodinase (DIO1), which does not change the dose of T4 required for TSH suppression in thyroidectimized patients (Santoro et al., 2014). Recently, hypothyroidism has been associated with both neurological disease and a longer life span. Levels of TSH have been associated with longevity, schizophrenia or bipolar disorder in two independent studies, suggesting that octogenarians and/or patients with schizophrenia have higher concentrations of circulating TSH (Jansen et al., 2015; Wysokinski & Kloszewska, 2014). Despite the fact that TSH has long been interpreted as a major marker of thyroid status it only reflects the effects of thyroid hormone signaling in the hypothalamus and pituitary, thus identifying that novel markers of thyroid hormone action in the periphery becomes paramount.

3. Thyroid hormone transporters

Thyroid hormones (T4 and T3) are primarily protein bound moieties in the circulation and are in equilibrium with free T4 and T3, which are biologically active (Fig. 3). The ratio of protein bound T4 to FT4 is higher than T3, which partly explains its much longer half-life and role as a prohormone. In recent years, it has become clear that circulating T4 and T3 do not passively cross cell membranes such as those present in liver, thyroid follicular cells or astrocytes and neurons in the brain. Several