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Review

Modulating the function of the immune system by thyroid hormones and thyrotropin

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ABSTRACT

Accumulating evidence suggests a close bidirectional communication and regulation between the neuroendocrine and immune systems. Thyroid hormones (THs) can exert responses in various immune cells, e.g., monocytes, macrophages, natural killer cells, and lymphocytes, affecting several inflammation-related processes (such as, chemotaxis, phagocytosis, reactive oxygen species generation, and cytokines production). The interactions between the endocrine and immune systems have been shown to contribute to pathophysiological conditions, including sepsis, inflammation, autoimmune diseases and viral infections. Under these conditions, TH therapy could contribute to restoring normal physiological functions. Here we discuss the effects of THs and thyroid stimulating hormone (TSH) on the immune system and the contribution to inflammation and pathogen clearance, as well as the consequences of thyroid pathologies over the function of the immune system.

Contents

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1. THs and TSH: background

Thyroxine (T_4) and 3,5,3'-triiodo-L-thyronine (T_3), two thyroid hormones (THs), regulate numerous mammalian metabolic processes [1]. Blood TH levels are finely regulated by the hypothalamus-pituitary-thyroid axis, which secretes the thyrotropin-releasing hormone to maintain adequate blood TH levels. In turn, pituitary-gland secretion of the thyroid-stimulating hormone (TSH) is triggered with this hormone, then activating its receptor (TSHR) in the thyroid gland to stimulate TH synthesis and secretion [2].

The effects of TSH are mediated by TSHR, a seven-transmembrane domain G-protein coupled receptor expressed by the thyroid gland [3]. This receptor is also expressed by a variety of external thyroid tissues, including the anterior pituitary, hypothalamus, ovary, testis, skin, kidney, immune cells, bone marrow, peripheral blood cells, white and brown adipose tissue, preadipocytes, fibroblasts and bone [4]. While TSHR expression is low outside the thyroid gland, the binding affinity for TSH and the ability to produce cAMP in response to TSH stimulation has a Kd $\approx$ 0.3 nM and an EC50 $\approx$ 3 nM. Therefore, TSHR could function and activate a cellular response even at low TSH levels [5]. Although currently there is no evidence for other receptor(s) acting in the extra thyroidal effects of TSH, this possibility cannot be definitively excluded.

TSHRs couple to $G\alpha_s$ and $G\alpha_q$, which work as signaling transducing molecules. $G\alpha_s$ activation triggers the cAMP-protein kinase A signal transduction pathway [6] and together with adenylate cyclase stimulates iodine uptake, thyroglobulin transcription, thyroid peroxidase activity and the sodium-iodine symporter in the thyroid cell [6,7]. The activation of phosphoinositide phospholipase C increases intracellular Ca^{2+} and regulates iodide efflux, H_2O_2 production and thyroglobulin iodination. Despite that, analyses using TSHR photoaffinity labelling with azido-GTP and subsequent immunoprecipitation have suggested that Gα, Gαi/o, Gαq/11 and Gα12/13 can interact with TSHR, only $G\alpha_s$ and $G\alpha_q$ are known to contribute to TSHR signaling [8].

An alternative ligand for TSHR is thyrostimulin, that binds to TSHR with an affinity similar to TSH, in addition to presenting thyroid-stimulating activity *in vivo* [9]. This ligand is present in the anterior pituitary gland, an area known to express TSHR, suggesting a paracrine action mechanism [10]. The effects of thyrostimulin on immune cells remain unknown. Then further research is needed to define a potential modulatory effect by this molecule over the immune response.

T_4 and T_3 derived from the blood are incorporated into cells via TH-specific transporters [11]. There are several transporter families, but only the monocarboxylate transporters MCT8 and MCT10 and the organic anion-transporting polypeptide OATP1C1 are highly specific for THs [12]. At the cytoplasm, T_4 is converted into T_3 by deiodinases located in the endoplasmic reticulum or the plasma membrane [13,14]. Among these enzymes, the most significant are the iodothyronine deiodinases types I, II and III (D1, D2 and D3 respectively) [15]. While D2 is located at the endoplasmic reticulum membrane, D1 and D3 are found in the plasma membrane [16]. In addition to T_4 to T_3 conversion, D1 and D3 can also inactivate T_4 through conversion to reverse T_3 (rT_3) [15].

In humans, approximately 20% of circulating T_3 originates from thyroidal production, while the remaining 80% derives from a peripheral conversion of T_4 to T_3 through D1 and D2 activities [15]. In rodents, the contribution of peripheral conversion is approximately 60%, with the remaining 40% secreted by the thyroid gland [15]. In macrophages, inflammation-induced D2 expression in the liver occurs in conjunction with expression of the selective thyroid hormone transporter MCT10 [17].

TH effects are mainly mediated by genomic mechanisms, however there is a growing body of experimental evidence indicating that THs can also function through non-genomic mechanisms [18]. The genomic actions of THs are mainly carried out by T_3, TH considered biologically active. Specifically, T_3 binds thyroid hormone receptors (THRs) of nuclear hormone receptor superfamily, which includes receptors for steroids, retinoids and the vitamin D3 [19]. These receptors are transcription factors that positively or negatively regulate target gene expression [20,21]. For example, the expressions of genes encoding for TSHB and TRH (thyrotropin-releasing hormone) are negatively regulated by T_3 [22].

The human TRα and TRβ proteins are transcribed from two separate genes, THRA and THRB, each of which has a homologue gene in the mouse, known as *Thra* and *Thrb*, respectively. Three mRNA species are transcribed from the THRA gene located at human chromosome 17 (TRα1, TRα2 and TRα3 mRNAs). TRα1 protein binds T_3 and can form dimers with the truncated THRA gene products, the TRα2 and TRα3 proteins. Meanwhile, TRα2 and TRα3 proteins can not bind this hormone [13]. Although the exact physiological importance of these truncated proteins remains unknown, heterodimerization of these isoforms with full-length TRα1 protein *in vitro* antagonizes the transcriptional activation induced by T_3 [23,24]. On the other hand, the THRB gene is located at the human chromosome 3 and expresses two protein isoforms, TRβ1 and TRβ2 proteins, which bind T_3. TRβ3, a third protein isoform is found only in rats [25]. The expression of these THR isoforms is tissue-dependent and developmentally regulated [26–28]. While TRα1 mRNA is constitutively expressed during embryonic development, TRβ1 mRNA is preferentially expressed at later developmental stages [27]. TRβ1 protein is widely expressed; TRβ2 protein is expressed in the retina, brain and inner ear [25,29] and TRβ3 protein, a functional receptor is expressed in the kidney, the liver and the lung. Finally, the TRα1 and TRα2 protein isoforms are highly expressed in the brain and, to a lesser extent, in the kidneys, skeletal muscle, lungs, bone, heart, testes and liver [25]. It is noteworthy that TRβ1 protein can be expressed by dendritic cells (DCs) [30] and other antigen-presenting cells, such as macrophages [31], an observation reported by scientists from the Nuclear Receptor Signaling Atlas research program.

Clinical research and animal-model studies have provided support to the notion of a close communication between the neuroendocrine and the immune system [2,32]. Of note, homeostatic regulation of the immune system involves several factors, including hormones [33]. Indeed, thyroid activity and the hypothalamic-pituitary-thyroid axis play pivotal roles at modulating the function of the immune system [33].

In this article we have focused on the contribution of THs to the regulation of immune cell functions, as well as on the importance of THs for the control of sepsis, inflammation, autoimmunity and viral infection.

2. Effects of thyroid hormones on immune system cells

Previous reports indicate that alterations in TH levels can affect the immune system [34]. Patients with hyperthyroidism frequently manifest unbalanced immune responses, including abnormal antibody production (either increased or decreased) [35], increased migration of polymorphonuclear leukocytes [36], lymphocyte proliferation [37] and increased reactive oxygen species (ROS) production by macrophages, specifically hydrogen peroxide and superoxide [38,39]. Additionally, these patients may show reduced levels of pro-inflammatory markers and lower antioxidant enzyme activity. In contrast, patients with hypothyroidism display an opposite phenotype [40,41]. However, in some cases, contrasting results have been reported and therefore it is difficult to establish a clear