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Review

Nongenomic effects of thyroid hormones on the immune system cells: New targets, old players

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ABSTRACT

It is now widely accepted that thyroid hormones, L-thyroxine (T_4) and 3,3′,5-triiodo-L-thyronine (T_3), act as modulators of the immune response. Immune functions such as chemotaxis, phagocytosis, generation of reactive oxygen species, and cytokine synthesis and release, are altered in hypo- and hyper-thyroid conditions, even though for many immune cells no clear correlation has been found between altered levels of T_3 or T_4 and effects on the immune responses. Integrins are extracellular matrix proteins that are important modulators of many cellular responses, and the integrin αvβ3 has been identified as a cell surface receptor for thyroid hormones. Rapid signaling via this plasma membrane binding site appears to be responsible for many nongenomic effects of thyroid hormones, independent of the classic nuclear receptors. Through the integrin αvβ3 receptor the hormone can activate both the ERK1/2 and phosphatidylinositol 3-kinase pathways, with downstream effects including intracellular protein trafficking, angiogenesis and tumor cell proliferation. It has recently become clear that an important downstream target of the thyroid hormone nongenomic pathway may be the mammalian target of rapamycin, mTOR. New results demonstrate the capability of T_3 or T_4 to induce in the short time range important responses related to the immune function, such as reactive oxygen species production and cell migration in THP-1 monocytes. Thus thyroid hormones seem to be able to modulate the immune system by a combination of rapid nongenomic responses interacting with the classical nuclear response.

Contents

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1. Introduction

The neuroendocrine and immune systems operate in a bidirectional manner and hormones and cytokines represent the main effectors of this complex cross-talk [1–5]. The endocrine system, through the synthesis and release of specific hormones, plays an important role in the regulation of metabolic responses; at the same time the immune system, through the release of cytokines, modulates the activity of immune cells [3]. However, immune as well as endocrine cells express receptors for both cytokines and hormones: immune cells can bind different hormones, neurotransmitters, and neuropeptides, while the biological activity of several neuroendocrine cells can be modulated by cytokines [3,6]. The activities of endocrine glands can be modulated through the hypothalamus–pituitary–gonadal or hypothalamus–pituitary–adrenal or thyroid axis [7,8], but interestingly also by the immune system through the release of several cytokines such as interleukin-1 (IL-1), interleukin-6 (IL-6), tumor necrosis factor alpha (TNF-α) and interferon gamma (INF-γ), which may stimulate the hypothalamus–pituitary–adrenal or thyroid axis [3].

This paper will focus on the cross-talk between the immune system cells and thyroid hormones, that have already been recognized to play a role in immune function and immune cells [3].

2. Thyroid hormones

Thyroid hormones 3,5,3′-triiodo-L-thyronine (T_3) and L-thyroxine (T_4) give rise to a wide range of effects on metabolism, growth and development affecting practically all tissues: bone, muscle, heart, brain, liver, fat, and pituitary [9]. The major form of thyroid hormone secreted from the thyroid gland is T_4 whereas T_3 is produced mainly in target tissues by deiodination of T_4 [10], but normally T_3 is considered the active form of the thyroid hormones. The effects of T_3 are mediated through binding to specific receptor proteins (TRs) that may translocate into the cell nucleus where they regulate gene expression by binding to Thyroid Hormone Response Elements (TREs) [9]; as with all genomic machinery a period of time is required for protein synthesis and for the biological responses to manifest. There are two types of receptors, TRα and TRβ; they belong to the steroid receptor family and different isoforms have been identified [9]. There is a tissue-specific expression of the isoforms: TRβ-1 is found in most tissues, whereas TRα-1 and TRα-2 are more abundant in skeletal and cardiac muscle [9]. The ligand-binding domains of both TRα and TRβ have been crystallized and structurally characterized in detail [11–13] and they are known to act as ligand-regulated transcription factors. The levels of thyroid hormones are fairly constant in the adult euthyroid subject, and this is believed to be in agreement with their typical biological role, which is to keep constant the settings of certain basal physiological activities.

Beside the classical nuclear actions, thyroid hormones also produce very rapid effects in cells (seconds to minutes), which do not depend on DNA transcriptional activity. Such nongenomic or extranuclear actions of thyroid hormone are typically initiated at the plasma membrane or in the cytoplasm [14]. Nongenomic mechanisms of thyroid hormone action rely upon rapid transduction of the hormone signal by cytoplasmic kinases such as mitogen-activated protein kinase (MAPK) [15–21] or phosphatidylinositol 3-kinase (PI3K) [22–27]. These kinases are early (upstream) factors that may give rise to specific nuclear long-term effects such as gene transcription and cell proliferation [28,29]. Thus, in some cases there is cross-talk between nongenomic and genomic actions of thyroid hormone, leading to complex cellular events. Also the extranuclear effects depend on the initial binding to a receptor; in the cytosol this can be one of the TRs interacting with other proteins. The nature of the plasma membrane receptors remained elusive for years, but in 2005 Bergh et al. [30] identified the integrin αvβ3 as a plasma membrane receptor for thyroid hormones. The interaction of the integrin with T_3 or T_4 induces a complex sequence of cellular events, leading to cell responses such as angiogenesis or tumor cell proliferation, but only a few of these events have been characterized to date [30,31].

3. Thyroid status and immune system

Hyperthyroidism is the result of excessive production and release of thyroid hormones from the thyroid. It can be caused by thyroid adenoma and multinodular goiter, and very frequently by the autoimmune Graves' disease. Hypothyroidism is instead the result of insufficient production of thyroid hormones. Both hyper- and hypofunction of the thyroid are able to affect the immune system [32,33]. In general hyperthyroidism increases the immune response, antibody production, cell migration, lymphocyte proliferation, and reactive oxygen species production, whereas it decreases the proinflammatory markers, antioxidant enzymes and their activity [5]. Hypothyroidism typically produces the opposite effects on parameters of the immune function; it decreases immune response, antibody production, cell migration, and lymphocyte proliferation [34,35]. However, in some cases contrasting results have been reported, and therefore it is quite difficult to establish a clear correlation between immune function and hyper- or hypo-thyroid conditions [36–39].

From the literature it appears that the relationship between thyroid hormones and the immune system has been studied mainly in physiopathological conditions. Hodkinson et al. [40] reported the major parameters of the immune function in 93 healthy euthyroid subjects, late-middle aged, and showed that their thyroid hormone concentrations were positively correlated to the immune function. The authors measured plasma thyroid hormone levels and calculated the mean T_3/T_4 ratio, and used these numbers to distinguish between low- and high-thyroid hormone concentration, but within the normal physiological range. They found a significant association between thyroid hormones and markers of immune function, such as the complement proteins C3 and C4, the C-reactive protein produced by the liver whose plasma level is increased during inflammation, and phagocyte activity, Natural Killer T-cell percentage expression and counts, and IL-6 expression by activated monocytes, with some differences between the T_3 and T_4 [40].

4. Direct and indirect evidence that thyroid hormones are able to affect immune cell system and function

The immunological properties of thyroid hormones were actually first found in non-immune cells. Thyroxine is able to potentiate the antiviral state induced by IFN-γ on HLA-DR expression in both CV-1 and HeLa cells, which are fibroblasts and tumor cells, respectively [16]. Although none of these cells belong to the immune system, the effects found are certainly related to it. Furthermore, both