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Review

Immune-Endocrine Interactions of the Hypothalamus-Pituitary-Thyroid Axis: Integration, Communication and Homeostasis

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Imagination is more important than knowledge
Albert Einstein

Abstract. The immune and neuroendocrine systems are two essential physiological components of mammalian organisms. Although each is primarily committed to a set of tasks involved, on the one hand, in the protection from infection and disease, and on the other hand, in the regulation of metabolism and other physiological activities, there is also evidence indicating that active and dynamic collaborations exist between those systems in the execution of their designated functions. These interactions occur at many stages of embryonic and neonatal development, and they are a continual part of the normal homeostatic balance needed to maintain health. The present review discusses various historical and contemporary perspectives of immune-endocrine interactions involving the hypothalamus-pituitary-thyroid axis, and offers a hypothesis of how this aspect of the neuroendocrine system participates directly in the immune response to antigenic challenge, infection and disease.

Key words: immune-endocrine; hormone; antigen-presenting cells; pituitary-thyroid; lymphocytes; immunity.

Introduction

In its most elemental form, homeostasis can be viewed as a state of equilibrium between various physiological and chemical processes. It is therefore reasonable, in fact essential, to assume that homeostasis at the organismic level is a composite of its many interactive component parts – the totality of factors and events, whether structural, regulatory or effector in nature, which impinge upon the physiological operation of the organism. In that context, the immune system and the neuroendocrine system are inextricably linked, though many of the specific details of how this occurs have yet to be fully elucidated or remain incomplete. This is due, at least in part, to the sheer complexity of the immune and neuroendocrine systems individually and to the inherent amplification of those complexities when viewed as a whole.

Abbreviations used: APC – antigen-presenting cell, HPT – hypothalamus-pituitary-thyroid, TSH – thyroid-stimulating hormone (thyrotropin), IL – interleukin, IEL – intraepithelial lymphocyte, TCR – T cell receptor, TEC – thymus epithelial cell, TRH – thryrotropin-releasing hormone, TNF – tumor necrosis factor.

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Yet both systems share basic common properties in curiously similar ways. Consider, for example, that each consists of highlyinteractive components that are widely dispersed throughout nearly all tissues of the organism. Moreover, both are wonderfully modular, each containing specialized parts designed to perform specific tasks, for example, the delivery of a given hormone to a particular hormone-responsive tissue in precisely the right amount at precisely the right time, or the selective secretion of immunoregulatory cytokines in a dedicated and controlled fashion.

The immune and neuroendocrine systems are also fundamentally regulatory in nature. In the case of the neuroendocrine system, this involves the control over nearly all aspects of growth and development, broad--spectrum metabolic regulation and the responsiveness to stress, and the activation and balance of various hormone-mediated processes, such as reproduction. In the case of the immune system, this involves a complex set of internal regulatory elements (cells, molecules and mediators) used to adjust the duration and amplitude of the immune response according to the type of threat confronting the organism. Moreover, a key feature of both systems is a process of homeostatic regulatory feedback that involves the shunting of signals used to perpetuate, accelerate or terminate a response as needed.

Finally, and perhaps most importantly, both systems have highlydeveloped sensory elements consisting of cell-borne receptors selectively distributed on tissues throughout the organisms; these serve as exquisite mechanisms for focusing biological activity along operationally defined pathways. Consequently, secretion or expression of a functionally-relevant molecule by the neuroendocrine and immune systems has significance only in the context of those receptor-bearing cells, thereby establishing a process of "information" transfer with a remarkable degree of specificity. In fact, perhaps nowhere else in the mammalian organism is this distinction more handsomely drawn than within the immune system, consisting of no less than two hundred and fifty cell surface molecules that govern a panoplia of immunological activities and functions that regulate hematopoietic cell development and differentiation.

Immune-Endocrine Interactions Mediated by Thyroid-Stimulating Hormone: Evidence for an Intrinsic Autocrine/Paracrine Hormone Network

Thyrotropin (thyroid-stimulating hormone – TSH), a glycoprotein hormone produced by the anterior pituitary and released into the blood upon induction by hypothalamic-derived thyrotropin-releasing hormone (TRH), is composed of disulfide-linked α/β heterodimeric components[17]. The biological activity and specificity of TSH resides in the TSH β-chain molecule, whereas the α-chain is shared by other glycoprotein hormones, including luteinizing hormone, follicle-stimulating hormone and human chorionic gonadotropin[17]. Within the hypothalamus-pituitary-thyroid (HPT) axis, TSH is involved in the regulation of the thyroid hormones T_3 (tri-iodothyroxine) and T_4 (tetra-iodothyronine) and, conversely, thyroid hormones exert both positive and negative effects on the transcription of the TSH β-chain genes in the anterior pituitary, thus establishing a hormone-mediated cycle of self-regulatory control. Although the activity of TSH is traditionally regarded to be confined to the HPT axis, it is clear that the effects of TSH reach beyond the neuroendocrine system.

TSH receptor expression within the immune system

Receptors for a wide range of neuropeptides and hormones are now known to be expressed on hematopoietic cells of mice, rats and humans (reviewed in ref.[32]). Although relatively few studies have specifically examined TSH receptor (TSHr) expression, there is, nonetheless, convincing evidence linking the presence of TSHr to specific cells of the mammalian immune system. An early study, using radiolabeled TSH binding assays with peripheral blood leukocytes enriched by density gradient centrifugation, found TSH to preferentially bind to phagocytic cells, in particular monocytes and polymorphonuclear leukocytes[4]. These findings have been confirmed and extended in studies of phenotypically-defined human peripheral blood leukocytes, which demonstrated high level TSH binding to Leu-M3$^+$ monocytic/macrophage cells, as well as to the macrophage cell line U937[5]. Similarly, studies from our laboratory indicate that ~30–50% of CD11b$^+$/CD11c$^+$ adherent cells from the spleen and lymph nodes are TSHr$^+$ cells (Fig. 1A). Taken together, those findings provide a strong consensus for a process of TSH utilization by professional antigen-presenting cells (APCs), in particular dendritic cells and macrophages. Perhaps most importantly, however, this locates TSH-responsive cells at the core of both the adaptive and innate immune responses, a potentially important fact given the central role of APCs in the overall scheme of immune activation and regulation. However, because APCs are known to be phenotypically heterogeneous, additional analyses of TSHr expression on murine cells defined by cell

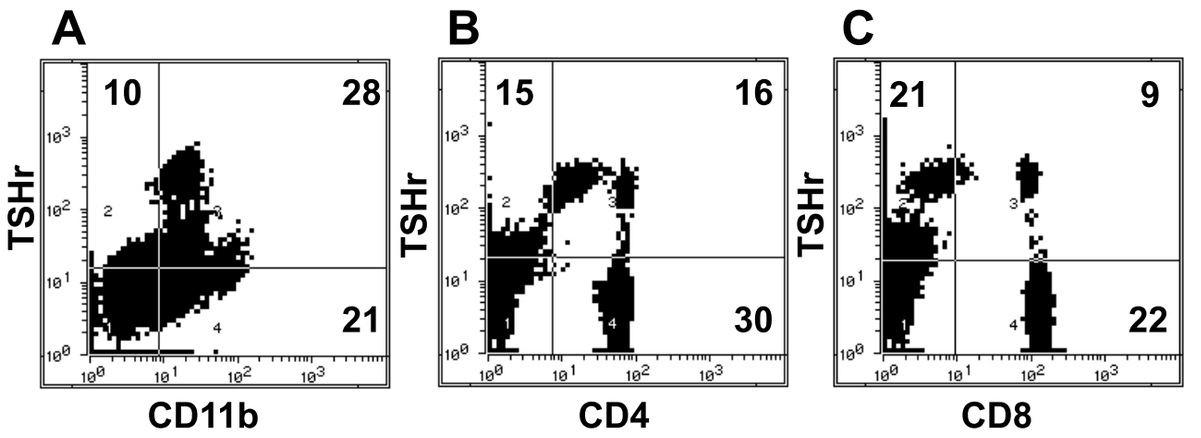

Fig. 1. Flow cytometric analyses of TSHr expression on purified murine CD11b splenic adherent cells (**A**), and whole lymph node lymphocytes stained for CD4 expression (**B**), and CD8 expression (**C**)

surface markers 33D1, DEC-205, CD8a, Sca-2, CD24 and c-kit, which are to varying degrees expressed on dendritic cells and/or macrophages[27], should help considerably in defining TSH-responsive APCs.

The extent to which the TSHr is expressed on lymphoid cells is less clear. Using human peripheral blood leukocytes and tonsillar lymphocytes defined by CD4, CD5, CD8 or CD19 expression, little or no binding to resting T cells or B cells was observed[5]. Likewise, human T cells stimulated with the T cell mitogen phytohemagglutinin[5] or murine T cells stimulated with staphylococcal enterotoxin-A (SEA)[11] remained unable to bind TSH. In contrast to T cells, activated but not resting B cells showed an increased ability to bind TSH[5,11], a finding in line with an earlier study using human B cell lines[18] and implying a functional role for TSH in the generation of a humoral immune response shortly after the initial activating steps have occurred.

Studies in our laboratory using murine lymphocytes find little or no TSH binding to resting splenic T cells or B cells. Interestingly, however, a subset of $CD45RB^{hi}$, $CD69^{-}$ lymph node T cells bearing a phenotype of naïve non-activated cells, including both $CD4^{+}8^{-}$ and $CD4^{-}8^{+}$ cells, express high levels of TSHr (Fig. 1B and C), suggesting that there are anatomical differences in TSH utilization by peripheral lymphoid cells. While the meaning of the difference in TSHr expression between splenic and lymph node T cells in mice is at present not fully known, it may have relevance for understanding immune-endocrine interactions within and between peripheral lymphoid tissues. Consider, for example, that the spleen serves primarily as an immunological filter for the blood, whereas lymph nodes are sites in which tissue-derived antigens are imported and delivered to T cells and B cells by APCs. Furthermore, these immunological interactions in lymph nodes are most critical during the generation of a primary immune response leading to the activation of naïve T cells, and are of less importance for the re-activation of effector or memory cells[26]. In that context, studies using TSHr-defective animals such as C.RF*TSHr*$^{hyt/hyt}$, mice may help considerably for elucidating the impact of TSH on APC-mediated responses during primary versus secondary immune challenge.

Two other hematopoietic cell populations in mice have recently been demonstrated to express TSHr. Intestinal intraepithelial lymphocytes (IEL), a lymphoid cell population consisting of T cells and a small but significant set of resident dendritic cells and macrophages, express surface TSHr as predicted from binding studies and based on expression of TSHr gene transcripts[29]. In this system, TSH has been shown to functionally influence the differentiation and/or the redistribution of IEL subsets within the intestinal epithelium, as discussed in detail below. Similarly, based on gene expression, the TSHr was found to be expressed on hematopoietic cells of the bone marrow, though the relationship of specific $TSHr^{+}$ stem cell subsets to mature leukocytes has not been determined[33].

Extra-pituitary production of TSH

The awareness that cells of the immune system utilize TSH prompts many questions, not the least of which is the source of TSH that is used by the immune

system. Clearly, blood-borne TSH could serve in this capacity. In that case, however, serum-derived TSH levels would be largely dictated by the needs of the thyroid rather than the immune system. Thus, the possibility exists that extra-pituitary TSH is produced by cells of the immune system itself. First evidence for this was provided in experiments from SMITH and colleagues[23]. Using density-gradient purified human mononuclear cells, up to 50% of SEA-stimulated cells contained intracellular TSH that was immunologically indistinguishable from pituitary-derived TSH. TSH also has been shown to be produced by human T cell lines stimulated with SEA or TRH[10]. Using purified populations of murine splenic mononuclear cells defined by flow cytometry with markers specific for APCs, T cells and B cells, we have found TSH-producing cells to reside among APCs, particularly dendritic cells, based on intracellular staining with anti-TSHβ-specific antisera, and TSHβ secretion detected by enzyme-linked immunoassays (EIA). Moreover, the activity of TSHβ increased after dendritic cell activation upon stimulation with anti-CD40 antibody in the presence of IL-4, whereas murine T cells and B cells did not produce significant amounts of TSH regardless of their state of activation (BAGRIACIK and KLEIN, unpublished).

Involvement of HPT hormones in immune system function

Effects within the peripheral immune system. A role for TSH in antibody synthesis by B cells has been demonstrated in several laboratories[5, 11, 15, 16]. Using human and murine lymphocytes or cell lines, 2–7-fold increases in immunoglobulin production have been reported following *in vitro* co-culture of mitogen-activated B cells with TSH. Similar positive effects on immunoglobulin production have been noted in TRH--supplemented spleen cell cultures, in which there was a concomitant release of TSH[16]. Although the cellular source of TSH in those cultures was not determined, the presence of TRH receptors on lymphoid cells has been inferred from studies demonstrating TRH receptor gene transcripts in rat and human cells[20], further suggesting an intrinsic TRH→TSH pathway leading to a TSH-mediated intracellular signal. Moreover, because TSH stimulation of B cells did not result in enhanced B cell proliferation, the effect of TSH on antibody production could not be attributed to an increase in the numbers of B cells. Using the T cell-independent antigen, *Brucella abortus*-trinitrophenol (BA-TNP), the costimulatory effects of TSH were augmented by macrophages and, curiously, were found to be strictly dependent upon T cells[15]. Although at first glance the latter finding seems difficult to reconcile for a T cell-independent antigen, it rather makes a strong case for the likelihood that TSH is acting not on B cells, but that it is directed to accessory cells and possibly T cells, a scenario consistent with the notion of wide-spread TSHr expression among APCs as discussed earlier.

Effects on the intestinal immune system. The intestinal mucosa constitutes an important host barrier to the entry and dissemination of foreign antigen. It is, thus, not surprising that the intestinal immune system has developed mechanisms of immunological protection that differ from those found in lymphoid tissues elsewhere in the animal. Studies over the past two decades reveal a remarkable level of phenotypic complexity of intestinal IELs, including several cell populations that are unique to the intestine. In mice, murine IELs are almost exclusively of $CD8^+$ T cells comprised of either TCRαβ or TCRγδ cells in roughly equal proportions[14]. Moreover, ~75–80% of the IELs utilize a CD8αα homodimer rather than the CD8αβ heterodimer found on most other peripheral T cells[9,21]. That feature has been hypothesized to discriminate IELs along developmental lineages such that CD8αα IELs are considered to be extrathymic T cells that have matured locally within the intestine, whereas CD8αβ IEL are believed to be mature thymus-derived T cells recruited into the gut from the periphery.

The distinction between CD8 expression and IEL development becomes more dubious, however, in the light of studies indicating that HPT hormone can influence the phenotypic composition of cells in the gut epithelium. Mice thymectomized as neonates and treated with TRH or TSH for three weeks beginning at six weeks of age were found to have increases in the numbers and proportions of CD8αβ IELs[29,30], i.e. the IEL population generally considered to be "thymus-dependent" T cells (Fig. 2). Because the effect of TRH/TSH treatment occurred in the absence of direct immune augmentation and could not be accounted for by increased proliferation of the small numbers of extant CD8αβ cells present in athymic mice, it was reasoned that the effect of hormone treatment was to compensate for the disruption by thymectomy of an immune-endocrine circuit that is needed for proper maturation of the intestinal epithelium as a site for immunological development[29,31].

Effects on bone marrow stem cells. The influence of TSH also can be seen in the bone marrow. Bone marrow hematopoietic cells cultured *in vitro* with either purified TSH or antibodies to the TSHr result in rapid but selective cytokine production as determined by EIA

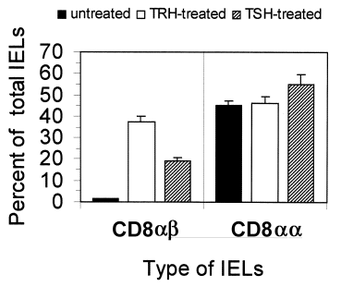

Fig. 2. Percent of CD8αα and CD8αβ intestinal IELs from nine week old neonatally-thymectomized mice without hormone treatment, and from neonatally-thymectomized mice treated with TRH or TSH for three weeks beginning at six weeks of age. Note the increase in numbers of CD8αβ$^+$ IELs following TRH or TSH treatment

and cytokine gene transcription in RNase protection assays[33]. Thus, gene activation and/or cytokine production for interleukin (IL)-6, tumor necrosis factor (TNF)-α, TNF-β, lymphotoxin-β, interferon-β, and transforming growth factor-β2, but not IL-1β, IL-2, IL-12, or interferon-γ, were observed[33]. Also of interest in those studies was the finding that TSH stimulation of bone marrow cells resulted in rapid phosphorylation of the JAK2 protein kinase with concomitant increase in cAMP levels, implying that novel intracellular signaling events may be used in the course of TSH activation.

The Thymus-Thyroid Connection

Regulation of thymus function and peripheral immunity by thyroid hormones

A role for the thyroid in the regulation of thymus activity can be seen during many stages of development and aging. For example, although it is well known that mice which are athymic during fetal and/or early neonatal life undergo a wasting process characterized by loss of weight and a generalized failure to thrive, a process similar to wasting can be induced when pituitary--thyroid hormone activities are suppressed in neonatal euthymic mice[19]. Although wasting likely reflects, to a large degree, an inability of the animal to mount an effective T cell-mediated response to infection, the ability to prevent wasting through thyroid supplementation without thymus intervention further underscores a basic role for the thyroid in the expression of immunity.

While the mode of action of thyroid hormones on thymus activity is undoubtedly complex, potentially affecting many cellular activities, some of this appears to reflect the modulation of thymus-derived thymulin as seen by correlations between T_3 levels and circulating thymulin[22]. Those findings are supported by other studies indicating that naturallyoccurring hypothyroid human infants, as well as mice treated experimentally with 6N-propyl-2-thiouracyl as an inhibitor of thyroid hormone synthesis, have depressed thymulin levels[22]. Furthermore, although circulating thymulin levels display age-dependent differences in humans, ranging from high levels by the second decade of life to low levels by the 6th decade of life, hypothyroidism in young adults depresses thymulin to levels similar to those found in aged persons, while hyperthyroidism in older adults leads to elevated thymulin levels resembling that of young adults[8].

These observations, while tantalizing, by themselves provide only indirect evidence of a thyroid→thymus regulatory event: one which may be secondary to a process of enhancement or suppression of metabolic activities broadly controlled by thyroid hormones. To circumvent that problem, investigators have used cultured human or rat thymic epithelial cells (TECs) and have measured secreted thymulin in the presence and absence of thyroid hormone, in this case T_3. Beginning 3–5 days after culture, thymulin levels were significantly and continually elevated in T_3-supplemented cultures, implying a direct effect of thyroid hormone on TECs[6]. Although those studies have not been extended to other thymus-derived peptides and mediators produced by TECs, the potential for extensive immunomodulating effects exerted by thyroid hormones on intrathymic T cell development warrants further study.

Additional direct evidence for thyroid regulation of immunity comes from experiments using the autoimmune gastritis model in day 3 neonatally-thymectomized mice. In that system, organ-specific autoimmune diseases of the stomach and reproductive tissues, with onset in young adult mice between 6 to 9 weeks of age, can be elicited following neonatal thymectomy between days 1 and 3 post-birth[24]. Disease is mediated primarily by CD4$^+$ T cells and autoantibodies, and expression of disease is closely linked to whether or not the thymus is present during a critical phase of immunological (and neuroendocrine) maturation[24]. Hence, mice lacking a thymus throughout fetal life, i.e. congenitally athymic nude mice, rarely develop those autoimmunities; mice thymectomized on or after day 5 post--birth are similarly unaffected. Because T cells are produced in mice beginning at the time of birth, it has been speculated that thymus removal during that period leads to perturbations in regulatory T cell subsets that are critical for maintaining peripheral self tolerance[3].

With that model, it was demonstrated that day 1–3 neonatally-thymectomized mice treated with T_4 just prior to the time of disease onset had lower incidences and severity of gastritis compared with untreated mice or with mice treated with TSH or TRH[28]. This is to say that, exposure to exogenous T_4 as the autoimmune response is developing appears to compensate for an inherent thymus-associated immune deficiency resulting from thymectomy during the immediate post-birth period.

Inflammatory cytokines and thyroid function

Immune system cytokines, in particular inflammatory cytokines such as IL-1β, IL-6, and TNF-α, have pleiotropic effects on thyroid cell growth and function as measured by modulation in thyroglobulin production and cAMP levels in primary thyroid cells and cell lines such as FRTL-5 cells. An early study by DUBUIS et. al.[7] reported a precipitous decline in serum TSH levels within 5 h of a single injection of recombinant human IL-1β. Recovery to normal TSH levels occurred within 12–24 h, but was followed by a concomitant decrease in total serum T_4 and an increase in free T_4[28]. Similar findings have been observed in rats undergoing continuous infusion of IL-1 and IL-6, as well as with TNF-α exposure, even in the face of TSH supplementation[12], suggesting that in those situations adjustments in thyroid activity may not be mediated through the conventional hypothalamus-pituitary feedback loop, but may be regulated from within the immune system itself. Possibly the most interesting aspect of the above studies, however, is that all the cytokines in question are produced by professional APCs and all have properties tied to the regulation of inflammatory responses. Still other studies report gene transcripts for IL-1α, IL-6, IL-8, IL-12, IL-13 and IL-15 in thyroid follicular cells from patients with thyroid dysfunction and in normal thyroid tissues (reviewed in ref. 1).

A Model for TSH-Mediated Immune-Endocrine Interactions in Health and Disease

The information presented here demonstrates the dynamic manner by which the immune system and the endocrine system interact and communicate, and how those physiological entities function to regulate each other. How, then, might these interactions have biological significance in the broader scheme of immunity? Recall that professional APCs consist of cells that can produce and utilize TSH, though not necessarily by the same subsets, thus establishing a TSH-driven response system wholly contained within the immune system. With that, we envision a process whereby both the adaptive and innate branches of immunity converge through the use of TSH, particularly in response to a strong antigenic challenge. Although TRH might serve as an activating signal in this pathway, induction by antigens such as bacterial endotoxin is more feasible from an immunological perspective. Rapid release of TSH from cytoplasmic endosomes then would be available for local use by appropriate APCs, T cells and B cells, thereby enhancing cytokine synthesis, T cell activity and antibody responses from B cells.

Further amplification of the effects of these immune-endocrine interactions would be manifest in a number of ways. TSH-mediated enhancement of the APC-derived cytokines, IL-1β and IL-6, would provide an additional level of protection to the host by inducing a febrile state upon direct stimulation of the hypothalamus[13] and would suppress thyroid activity[25]. This would be accompanied by a transient decline in serum thyroid hormone levels during the days immediately following antigen exposure. Such changes in thyroid hormone levels have been reported in mice following systemic antigen challenge (ref.[2], and BAGRIACIK and KLEIN, unpublished), although the mechanism(s) which account for that are currently obscure.

Immune-endocrine changes of this type have many features consistent with extant observations pertaining to the natural immune response. For example, the malaise frequently experienced during the early period following virus or bacterial infection may be due to a drop in thyroid hormone levels, forcing the host into a period of inactivity. Yet, this could be deleterious to the host if the biological activity of the immune response were simultaneously compromised. Interestingly, however, we have observed that slightly lower levels of thyroid hormones favor the production of IFN-γ, a Th1 cytokine that is involved in early events leading to immune activation and also has anti-viral and anti-bacterial activities.

Finally, we predict that suppression of thyroid hormone activity is subsequently compensated for by dendritic cells or other TSH-producing APCs which migrate to the thyroid, rather than by regulation from pituitary-derived TSH. In this pathway, therefore, TSH plays a critical role at two levels, the first being within the immune system itself as an endogenous mediator of immune activity, the second being as a molecular signal used by the immune system to communicate with the thyroid. Clearly, as is true for other types of immune-endocrine interactions, many aspects of this system remain to be explored empirically.

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