MINIREVIEW

The Immune System as a Regulator of Thyroid Hormone Activity

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It has been known for decades that the neuroendocrine system can both directly and indirectly influence the developmental and functional activity of the immune system. In contrast, far less is known about the extent to which the immune system collaborates in the regulation of endocrine activity. This is particularly true for immune–endocrine interactions of the hypothalamus-pituitary-thyroid axis. Although thyroid-stimulating hormone (TSH) can be produced by many types of extra-pituitary cells—including T cells, B cells, splenic dendritic cells, bone marrow hematopoietic cells, intestinal epithelial cells, and lymphocytes—the functional significance of those TSH pathways remains elusive and historically has been largely ignored from a research perspective. There is now, however, evidence linking cells of the immune system to the regulation of thyroid hormone activity in normal physiological conditions as well as during times of immunological stress. Although the mechanisms behind this are poorly understood, they appear to reflect a process of local intrathyroidal synthesis of TSH mediated by a population of bone marrow cells that traffic to the thyroid. This hitherto undescribed cell population has the potential to microregulate thyroid hormone secretion leading to critical alterations in metabolic activity independent of pituitary TSH output, and it has expansive implications for understanding mechanisms by which the immune system may act to modulate neuroendocrine function during times of host stress. In this article, the basic underpinnings of the hematopoietic-thyroid connection are described, and a model is presented in which the immune system participates in the regulation of thyroid hormone activity during acute infection. Exp Biol Med 231:229–236, 2006

Key words: immune-endocrine; homeostasis; metabolic; infection; hormone

Synthesis and Use of Thyroid-Stimulating Hormone (TSH) by Hematopoietic Cells

TSH-Producing Cells of the Immune System. The primary function of the hypothalamus-pituitary-thyroid (HPT) axis is to regulate thyroid hormone synthesis and production. Thyrotropin-releasing hormone (TRH)—a tripeptide hormone produced by the hypothalamus—serves as an inductive signal for the release of thyrotropin (TSH) from the anterior pituitary. Similar to other glycoprotein hormones, TSH is a heterodimer consisting of α-chain and β-chain molecules. Because the α chain is shared with follicle-stimulating hormone, luteinizing hormone, and chorionic gonadotropin, the TSHβ component is responsible for conferring hormone activity and specificity on TSH. Once released from the anterior pituitary and disseminated *via* the blood to the thyroid, its target tissue, TSH induces the release of thyroxine (T_4) and triiodothyronine (T_3) (1). T_4 may be converted into the more biologically active T_3 form in target tissues. Levels of circulating thyroid hormones provide feedback mechanisms, in both positive and negative ways, that contribute to the regulation of TRH and TSH synthesis (2).

Evidence for the production of TSH by cells of the immune system was first demonstrated over 20 years ago (3, 4). Initial studies used human leukocytes, which produced TSH following stimulation with staphylococcus enterotoxin A or on exposure to TRH (3–5). Thyroid hormones also may serve as negative regulators of hematopoietic TSH in a

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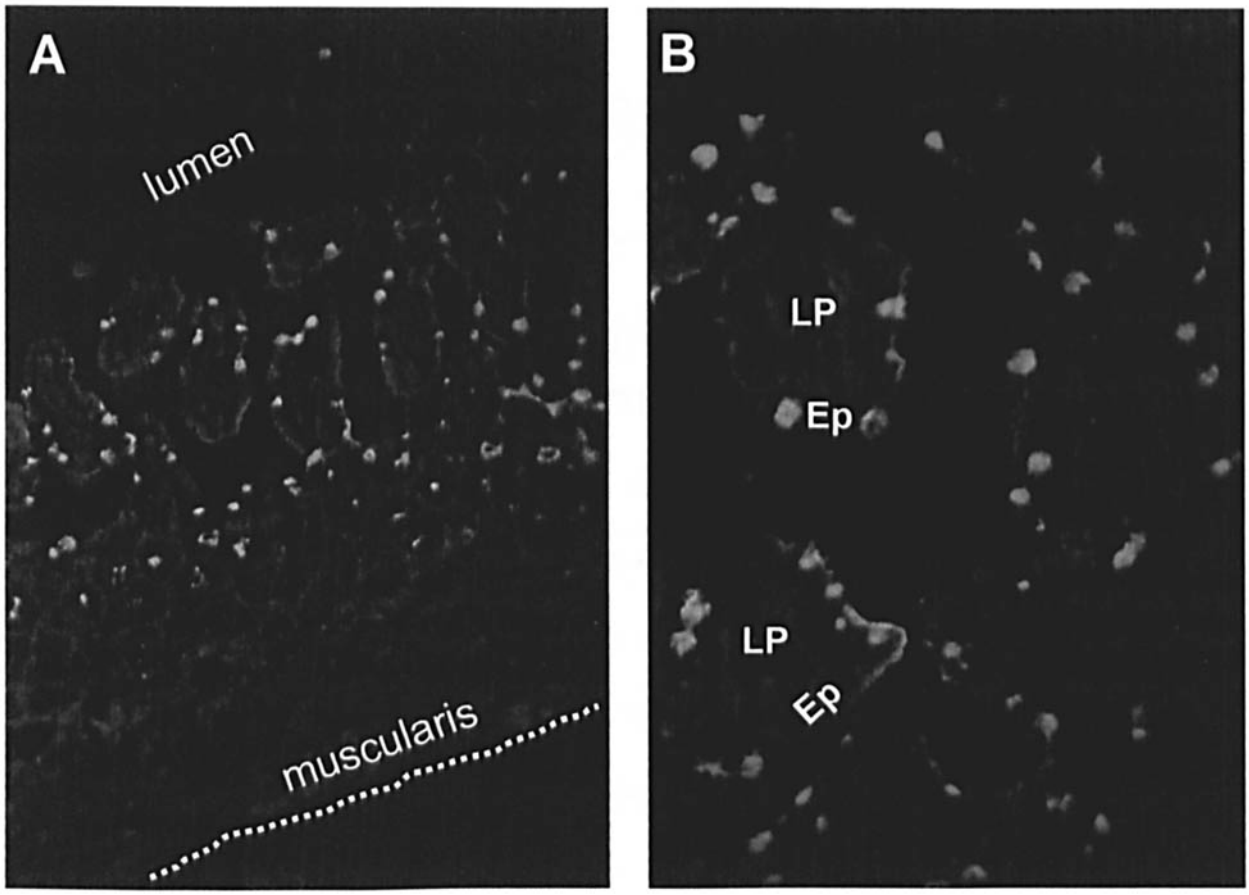

Figure 1. Small intestinal jejunum section from a Day 4 reovirus serotype 3–infected mouse stained with biotinylated anti-TSHβ antibody 1B11 (10) and streptavidin fluorescein isothiocyanate. Note the predominance of TSH^+ cells in the intestinal epithelium. Staining was rare in epithelial regions of noninfected mice or using isotype control antibody (data not shown).

fashion similar to that of the HPT axis (6). In secondary lymphoid tissues, splenic dendritic cells (DCs) have been shown to be a particularly strong source of TSH. Following *in vitro* culture in medium without stimulation or when cultured with staphylococcus enterotoxin B, DCs produced three to six times more TSH than was produced by purified B cells or T cells (7). The capacity of DCs to produce TSH was confirmed *in vivo* by immunofluorescence staining of splenic tissues from normal mice, which revealed that the majority of TSH-producing cells were localized in the marginal zones surrounding T-cell areas and in germinal centers where DCs are enriched (8). Additionally, studies in our laboratory demonstrate that the number of TSH-producing cells in the marginal zone of the spleen and lymph nodes is markedly increased following *in vivo* challenge with bacterial lipopolysaccharide (LPS) (unpublished observation), suggesting that TSH-producing cells of the immune system respond to strong antigenic stimuli with an aggressive burst of TSH production.

TSH has been shown to be produced by a subpopulation of bone marrow hematopoietic cells. This has been demonstrated by intracellular staining in combination with CD45 (leukocyte-common antigen [LCA]) or CD11b staining. TSH^+ bone marrow cells were exclusively associated with the LCA^+ cells (9); thus, they were not bone marrow stromal cells. Moreover, most TSH^+ cell belonged to a $CD11b^+$ monocyte/macrophage precursor or granulocyte precursor population; considerably fewer TSH^+ cells were lymphocyte precursors (9). That bone marrow cells actively secreted TSH was confirmed using cell-sorted $CD11b^+$ bone marrow cells in an enzyme-linked assay with anti-mouse TSH antibody (9, 10). Although both $CD11b^+$ and $CD11b^-$ cells produced TSH, the $CD11b^+$ population was the predominant TSH-producing cell population (9), a finding that will have significance later in this article.

The small intestine in mice also has been shown to be a site of active TSH synthesis as documented at both the transcriptional and the cell surface levels for intestinal epithelial cells and intestinal T cells and the presence of the TSH receptor (TSHR) on intestinal cells (11). TSH synthesis is localized in subvillus crypt regions (12)—a site where local T-cell development occurs (13)—and also in focal areas of the epithelium (12). Moreover, during acute rotavirus infection, TSH staining in the epithelium increases considerably, particularly in areas of virus infection (12). Similar findings now have been observed in our laboratory during acute intestinal reovirus infection (Fig. 1). Given the potential involvement of TSH in immune regulation of the intestine

Table 1. Sources of Extrapituitary TSH

Cells	Stimulus	Reference
Leukocytes	SEA,[a] TRH,[b] and immune activation	3–5
Dendritic cells	SEB[c]	7
Bone marrow cells	Spontaneous	9
Intestinal epithelial cells and T cells	Spontaneous and virus induced	11
$CD11b^+$ intrathyroidal cells	Spontaneous; possibly after activation	8

[a] SEA, staphylococcus enterotoxin A.
[b] TRH, thyrotropin-releasing hormone.
[c] SEB, staphylococcus enterotoxin B.

(14, 15), those studies provide evidence for local paracrine action of TSH, and thus they lend credence to the likelihood that immune system–derived TSH may operate in a paracrine manner elsewhere in the organism, as will be discussed for the thyroid. These findings are summarized in Table 1.

Two Venues for TSH Modulation of Immune Function. Despite evidence for a hematopoietic source of TSH, questions remain as to how immune system TSH participates in the immunophysiological process during health and disease. There are at least two ways through which extra-pituitary TSH could exert an effect on cells of the body: one being a direct effect of TSH on cells of the immune system, the other being an indirect effect mediated by TSH-induced thyroid hormone.

Inasmuch as TSH can be produced by leukocytes, it is reasonable to assume that TSH may act as a cytokine-like regulatory molecule within the immune system. Support for this comes from studies demonstrating the expression of TSHR on lymphoid and myeloid cells (16, 17) and as inferred from studies demonstrating the ability of TSH to influence lymphocyte functional behavior (18, 19). TSH has been shown to elicit elevated antibody responses in *in vitro* plaque assays (4, 5, 20) and to have potentiating effects on concanavalin-A- and phytohemagglutinin-induced proliferation of lymphocytes (21). TSH also has co-stimulatory activity for natural killer cells in combination with interleukin (IL)-2 (21). TSH stimulation of splenic DCs results in a stronger phagocytic response *in vitro* and increases the cytokine activity of IL-1β and IL-12 in the presence of phagocytic stimuli (17). In the bone marrow, the TSHR is expressed on some but not all lymphocyte, monocyte, and granulocyte precursors, and stimulation of bone marrow cells with TSH results in increased secretion of TNFα by the $CD11b^-$ population (9, 22). TSH stimulation of bone marrow cells results in a classical cAMP response and rapid phosphorylation of the Jak2 kinase (22). Because those studies used *in vitro* systems and thus were less affected by secondary or ancillary events mediated by TSH *in vivo*, the likelihood is high that they reflected direct activity of TSH on $TSHR^+$ immune cells.

Alternatively, TSH also could act indirectly on the immune system by altering T_3 and T_4 release from the thyroid, which then would affect the functional or developmental activity of cells in the bone marrow and/or in secondary lymphoid tissues. Evidence for this comes from studies showing impaired immune function in situations of low circulating thyroid hormones. In the TSHR defective C.RF-*hyt/hyt* mouse, which are unable to use TSH and consequently are severely hypothyroidic, B-cell development in the bone marrow is curtailed (23, 24). Administration of T_4 to C.RF-*hyt/hyt* mice increased the percent and absolute numbers of pro-B cells in cell cycle (23). Similarly, mice with gene deletion in the T_3 receptors α1 and α2 had significantly reduced numbers of cells in the bone marrow, thymus, and the spleen, with all leukocyte populations in the spleen (B cells, T cells, granulocytes, and macrophages) being affected (25). Taken together, these studies point to a range of activities exerted by TSH and thyroid hormone on central and peripheral immune function.

A Novel Role for Hematopoietic Cell–Derived TSH in Metabolic Regulation. The targeted effects of TSH on immunological function notwithstanding, an additional role of immune system TSH may be to microregulate thyroid hormone synthesis. This would occur under highly specialized conditions in which there is a fundamental necessity for communication between the immune system and the thyroid. Several suppositions would need to be fulfilled for this to occur:

1. There must exist a TSH-producing cell with the potential to traffic to the thyroid. This could consist of a cell of known characteristics and properties, possibly one of the TSH-producing cells described in the previous section, or it could involve novel hematopoietic cells with a dedicated function aimed at thyroid regulation.

2. The operative cell must migrate to the thyroid with the primary purpose of producing intrathyroidal TSH.

3. There must be a rationale for a system such as this to be maintained.

In the following sections, the empirical and conceptual underpinnings of an immune-thyroid communication network are laid out.

Immune-Thyroid Networks

To begin to understand how immune system TSH might be involved in thyroid hormone regulation, it will be necessary to predict the biological context in which this would occur. There are at present several examples by which immune-thyroid interactions might come into play

under natural or experimental conditions. Two of these are described here.

Nonthyroidal Illness—A Complex and Enigmatic Process That Involves Multiple Interactive Physiological Events with Salient Features of an Immune Regulated Process. Nonthyroidal illness, also known as euthyroid sick syndrome (ESS), is a hypothyroidic condition of humans that occurs in the absence of overt thyroid disease. In mild forms, ESS is characterized by a reduction in circulating T_3, usually resulting from a failure to convert T_4 to T_3 in the liver or kidneys (2, 26, 27). In severe forms, however, levels of both T_3 and T_4 can be reduced, the latter caused by impaired T_4 output from the thyroid (2). ESS can result from a wide variety of causes, including fasting, infection, sepsis, trauma, myocardial infarction, coronary artery bypass surgery, and bone marrow transplantation (27–31). Although the full significance of ESS is not known, it may represent a basic host mechanism used to conserve energy during periods of physiological stress (27, 32, 33), and it likely represents an essential, albeit poorly understood, phase of the host immunophysiological defense against infection. The mechanisms responsible for the hypothyroidic state in ESS differ depending on the inducing stimuli. During fasting, suppressed serum leptin levels lead to lower TRH and TSH levels with a concomitant lowering of T_3 and T_4 output and suppressed host metabolic activity (34–37). After the cessation of fasting, leptin levels increase, and the physiological process is reversed, resulting in increased metabolic activity.

The mechanistic pathway involved in ESS during infection is different from that of fasting in that, among other things, it is not significantly regulated by leptin (38–41). In experimental systems involving infection or exposure to lipopolysaccharide (LPS), two mechanisms (not necessarily mutually exclusive) have been described that could account for suppressed TSH levels. First, infusion of rats with the proinflammatory cytokines, IL-1, IL-6, or TNFα, has been shown to lower serum TSH levels (42–45). Thus, the mere presence of those potent inflammatory mediators could indirectly influence thyroid hormone synthesis. Second, studies have demonstrated that, following LPS exposure, T_4 is converted to T_3 in tanycytes of the third ventricle near the hypothalamic median eminence, thereby causing a surge in T_3 locally (33, 36). This, in essence, would constitute a localized T_3 feedback mechanism that would suppress TRH and TSH output and curtail the release of thyroid hormones. As yet, however, there is no known compensatory mechanism to account for the increase in T_3/T_4 synthesis during the recovery phase of infection. Thus, a critical question remains as to how the neuroendocrine system "perceives" that the time is right to readjust thyroid hormone production. The hypothesis proposed here, drawn from extant empirical evidence, is that it is the immune system—not the endocrine system—that restarts the process of thyroid hormone output. The immune system, which is indeed capable of TSH production, would be well suited to determine the optimal time to initiate the thyroid hormone recovery phase. A critical factor in this would be the inherent ability of the immune system to continually assess the status of the infectious condition and thus to determine whether it is safe for the host to return to a state of normal metabolic activity.

Thyroid Activity Following Bone Marrow Transplantation. A substantial body of literature has accumulated over the years demonstrating a relationship between thyroid hormone dysfunction and bone marrow transplantation. This can occur following total body irradiation (46–53) or after chemotherapy in the absence of irradiation (53, 54). In both situations, an ESS-like condition is commonly observed. Characteristically, T_3 and occasionally T_4 levels are low even though TSH output may be only marginally altered. Because the thyroid is primarily resistant to the effects of clinical radiation (55), the basis for changes in thyroid hormone levels is not well understood; however, they are not likely due to damage to the thyroid gland by the immunosuppressive treatment itself. Furthermore, it is unclear why thyroid hormone levels in bone marrow transplant patients continue to be suppressed in the face of otherwise normal circulating TSH levels. Indeed, as is frequently observed in ESS, the effects of available circulating TSH appear to have minimal influence on thyroid hormone levels in bone marrow transplant patients. Thus, the question emerges as to whether—as a consequence of bone marrow transplantation—there is a disturbance of a bone marrow cell population vested with TSH production.

Experimental Evidence for Immune-Thyroid Interactions

Following Immunological Stress, Mice Display a Precipitous Though Transient Drop in Circulating Thyroid Hormone Levels. In experimental systems using rodents, several studies have reported a drop in circulating thyroid hormones following systemic exposure to natural or synthetic antigens (e.g., sheep red blood cells or trinitrophenyl hemocyanin; Ref. 56) as well as to tumor-inducing agents, such as methylcholanthrene or dimethylbenzanthracene (57). Studies in our laboratory have explored this phenomenon in two experimental murine systems (7). In the first, the effects of acute antigen exposure on circulating thyroid hormone levels were evaluated in mice primed intraperitoneally with allogeneic lymphoid cells—a situation that most closely approximates the condition that occurs in humans following transplantation with nonautologous bone marrow. In the second experimental system, mice expressing a transgenic T-cell receptor for hen-egg lysozyme (HEL) were primed with HEL. That system was selected since it represented a strong T cell–mediated response to a nominal antigen. Serum T_3 and T_4 levels were monitored daily in mice after antigen priming (7). Notably, in both experimental models, there was a sharp though transient drop in circulating T_3 and T_4 24–48 hrs after antigen exposure; recovery in circulating

thyroid hormone levels began 3–4 days postantigen challenge (7). As with ESS, there was minimal change in levels of circulating TSH during or after the hypothyroidic phase (7), and thus these findings replicated experimentally using defined antigen systems the general observations seen in ESS. The reason for the immune-modulating effects of those stimuli on circulating thyroid hormone levels remains unclear, although a key feature of all is that they involve some type of acute immunological stress.

A Compensatory Response in Thyroid Hormone Production Arising *via* an Extrapituitary Pathway. Because circulating TSH levels did not fluctuate significantly during the hypothyroidic period in the experimental systems described previously, the question emerges as to what mechanisms might be responsible for the recovery of thyroid hormone activity. One possibility is that this occurs from a natural source of extra-pituitary TSH. To test that hypothesis, experiments were done in which hypophysectomized (HPX) mice were used for *in vivo* alloantigen challenge (7). Because HPX mice are incapable of producing pituitary-derived TSH, an increase in thyroid hormone levels following antigen priming would have to come from an extra-pituitary pool of TSH. Sera were collected from tail veins of HPX mice immediately before alloantigen injection and also at the time of sacrifice on Days 1, 2, 3, or 4 after antigen priming, and comparisons were made of T_4 levels in matched pre- and postchallenge sera for each animal (7). Findings from those experiments were remarkable in that there was a significant increase in serum T_4 in all HPX mice after antigen priming compared to preantigen-challenge levels (7). Most important, because HPX mice were unable to synthesize pituitary TSH, the increase in serum T_4 following antigen exposure must have been due to a compensatory event similar to that observed in non-HPX mice during Days 3–4 postantigen challenge (7).

A Bone Marrow–Thyroid TSH Network

Bone Marrow–Derived TSH-Producing Cells Actively Traffic to the Thyroid. As described previously, there is now evidence that bone marrow cells are an active source of extrapituitary TSH, that the predominant TSH-producing cell population is a $CD11b^+$ subset (9), and that those cells routinely migrate to the thyroid (8). When thyroid tissue sections from normal mice were stained with a panel of antibodies to lymphoid and myeloid cell surface markers, there were a surprisingly high number of cells clustering near thyroid follicles that expressed CD11b but lacked expression of CD3, CD8α, CD11c, CD19, CD40, Ly-6G, and F4/80 (8). That particularly unusual phenotype suggested that the intrathyroidal $CD11b^+$ cells were not conventional macrophages, plasmacytoid or lymphoid dendritic cells, activated dendritic cells, T cells, or B cells but rather that they may be a novel, previously uncharacterized type of hematopoietic cell.

To trace the origins of those cells, bone marrow chimeras were constructed in which normal mice were exposed to 900 rad total body irradiation to destroy host hematopoietic cell precursors, and the immune system was reconstituted using bone marrow from syngeneic mice that expressed an enhanced-green fluorescent protein (EGFP) transgene (58). By using EGFP donor bone marrow, it was possible to accurately follow the trafficking of cells to the thyroid and to confirm that they were of donor origin. Thyroid tissue sections from chimeric mice were studied from 1–20 weeks after bone marrow transfer using immunofluorescence microscopy to monitor the appearance of $EGFP^+$ cells. The striking finding from these experiments was the rapid accumulation of $EGFP^+$ cells in the thyroid after bone marrow transfer and the presence of $EGFP^+$ cells throughout the 20-week period of study (8). Moreover, the location and basic morphological features of the $EGFP^+$ cells suggested that they were identical to the $CD11b^+$ intrathyroidal cells found in normal non-chimeric mice (8).

Evidence for Intrathyroidal TSH Synthesis by Bone Marrow–Derived Cells. Clearly, the presence of migrating bone marrow cells in the thyroid would not, of itself, be proof of intrathyroidal TSH synthesis. Compelling evidence of this came in the form of two empirical observations. First, RT-PCR analysis of thyroid tissues revealed gene expression of the TSHβ gene, thus providing evidence that *in situ* TSH production occurs (8). Second, active production of intrathyroidal TSH was confirmed by *in situ* staining using an anti-mouse TSHβ antibody that revealed $TSH\beta^+$ cells with morphological features similar to the $CD11b^+$ cells and the migratory $EGFP^+$ cells found in the thyroid (8). Since there is no *a priori* evidence for TSH synthesis by thyrocytes themselves, expression of the TSHβ gene and TSHβ staining in thyroid tissues strongly favor a process of local intrathyroidal production by hematopoietic cells. Collectively, these findings make a strong case for the likelihood that there is a unique population of bone marrow–derived hematopoietic cells that traffic to the thyroid for the purpose of intrathyroidal TSH synthesis. Clearly, this system would operate on a paracrine basis involving the local synthesis and utilization of thyroid hormone. The best evidence to date that TSH has the potential to act through a paracrine rather than an endocrine delivery system comes from the experiments of rotavirus infection in mice, as described earlier, in which local TSH synthesis was tracked to areas of virus infection (12), with the awareness that TSH has been shown to modulate immune activity in the intestine (11, 14, 15). Additional studies will be needed to confirm that locally produced TSH directly participates in thyroid hormone regulation.

A Model of Immune Regulation of Thyroid Hormone Synthesis

How, then, do all these observations bear on a potential role for hematopoietic TSH regulation of thyroid hormone activity? Perhaps the best example comes from the

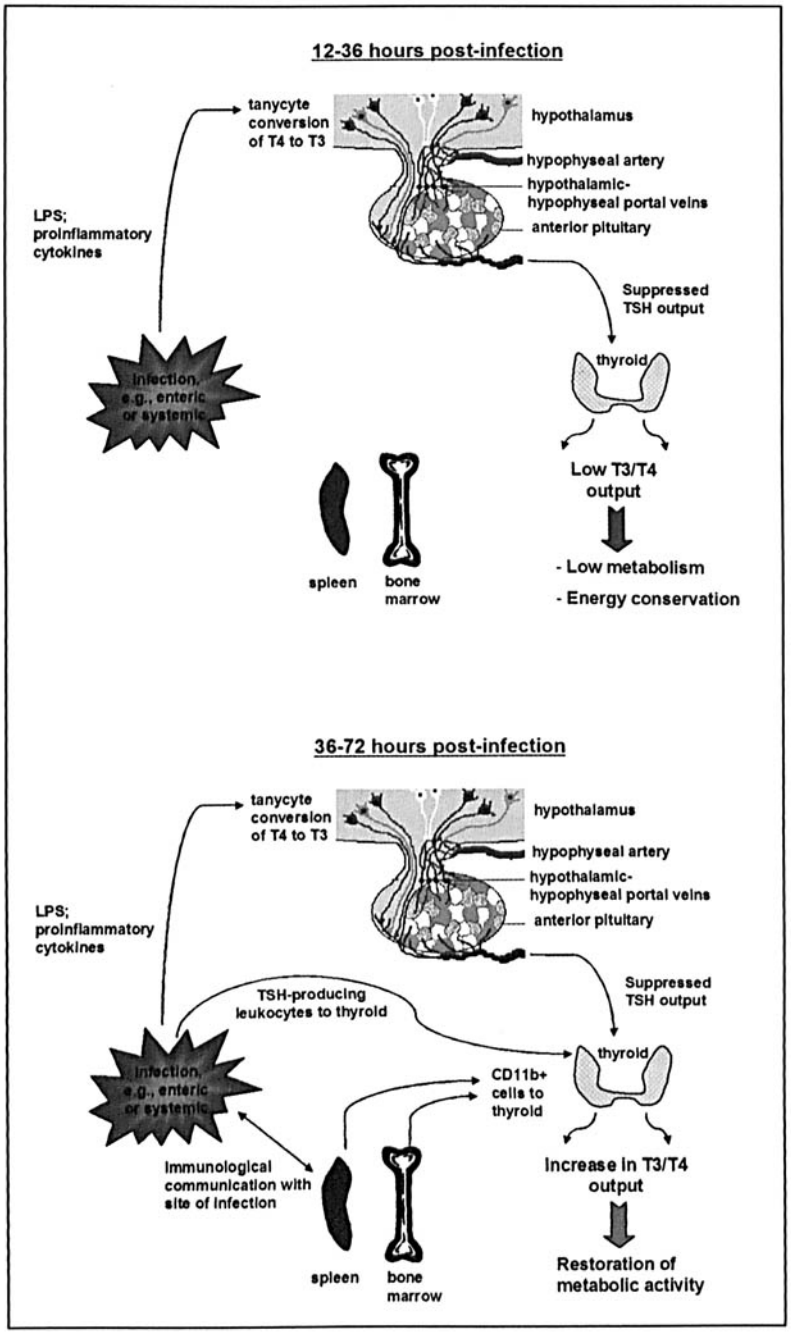

Figure 2. Model of immune regulation of thyroid hormone activity during acute infection. (A) During the early phase of infection (12–36 hrs), such as with enteric virus infection (e.g., rotavirus or reovirus [12] or systemic viral or bacterial infection), proinflammatory cytokines and/or bacterial-derived products stimulate the conversion of T_4 to T_3 in tanycytes of the third ventricle, causing suppression of TRH and TSH release and a decrease in T_3 and T_4 output. A general sense of malaise ensues because of curtailed metabolic activity, leading to energy conservation at a critical time of host physiological stress. (B) The immune system responds to the infectious process through the generation of innate and adaptive immune responses. As the infection is controlled, $CD11b^+$ cells selectively mobilized in the bone marrow, in peripheral lymphoid tissues, and possibly in the site of infection itself traffic to the thyroid, where they secrete TSH, prompting thyroid hormone release, which in turn leads to an elevation of metabolic activity. A critical feature of this model pertains to the readjustment in thyroid hormone activity by the immune system since it is the immune system that would be most capable of determining the optimal time for this to occur in the context of the host's response to infectious challenge.

infectious model as detailed in Figure 2. During acute infection, inflammatory mediators released into the circulation would stimulate the conversion of T_4 to T_3 in tanycytes of the third ventricle. This in turn would hold TSH in check, lowering thyroid hormone output. Physiologically, this would initiate and sustain an overall condition of curtailed metabolic activity. Low metabolic activity would encourage energy conservation by the host and discourage attempts to overexert during the period of infection—a time when rest would be important. Once the infection is under

control through the generation of innate and adaptive immune responses, the immune system would provide the initial signal (through intrathyroidal TSH synthesis by $CD11b^{+}$ cells from the bone marrow and possibly also from the peripheral immune system) that would lead to an adjustment in thyroid hormone activity with concomitant recovery in metabolic activity. This system offers the added advantage, particularly during times of acute infection, of drawing on the inherent power of the immune system into the process of metabolic regulation in ways that could not be accomplished solely through classical HPT circuitry. Furthermore, many aspects of this model are amenable to additional experimental study, such as a detailed analysis of the intrathyroidal TSH-producing hematopoietic cell(s), which may be the key element in understanding the immune-thyroid pathway.

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