A century ago pathologists noted first that the size of the thymus was profoundly influenced by emotional events and by neuroendocrine aberrations. Hans Selye discovered (1936) that when the hypothalamus-pituitary-adrenal axis is activated, it leads to the rapid involution of the thymus. Following that, Andor Szentivanyi and colleagues showed (1949) the regulatory power of the nervous system over immune reactions.

Cytokines, especially interleukin (IL)-2, IL-6, tumor necrosis factor (TNF)-α and interferon (IFN)-γ were shown to regulate the secretion of pituitary hormones during systemic immune/inflammatory reactions. It is also clear that nerves have immunoregulatory function and provide feedback signals from lymphoid organs and from sites of immune/inflammatory reactions towards the central nervous system. Now, it is well known that the nervous system plays a role in organizing, adapting and restraining the systemic inflammatory reactions via a complex cascade of mechanisms (Table 1).

NEURAL REGULATION OF IMMUNE FUNCTIONS

The nervous system can modulate the immune system in two ways:

I- Anterior pituitary hormones are under the neuroendocrine control of the hypothalamus, and their secretion can be influenced by suprahypothalamic stimuli such as environmental signals, sleep rhythms, and physical and emotional stress. Each of these hormones has either a direct or an indirect effect on the immune response through the secretions of its respective target gland.

II- The neural regulation of immune function is through the sympathetic nervous system by the release of catecholamines at autonomic nerve endings and from the adrenal medulla.

Pituitary-Immune System Interactions

1- Immune augmenting effects of pituitary hormones: Antibody-mediated, T-cell mediated and autoimmune reactions are impaired in hypophysectomized animals.

2- Immune inhibitory effects of pituitary hormones: ACTH, released from pituitary, causes release of glucocorticosteroids from the adrenal cortex, which are potent immunosuppressive agents.

3- Yin-yang effects: ACTH opposes the actions of prolactin and growth hormone. The immune-augmenting effects of prolactin and growth hormone are antagonized by concomitant administration of ACTH in the animal.

4- Feedback: Since pituitary hormones both augment and inhibit the immune response,
Table 1: The Complex Bidirectional Communication Pathway Between the Central Nervous System (CNS), The Endocrine System, and The Immune System:

<table>
<thead>
<tr>
<th>CENTRAL NERVOUS SYSTEM</th>
<th>BRAIN</th>
<th>SPINALCORD PARASYM. NS SYMPATHETIC NS</th>
<th>CYTOKINES IL-1α, IL-1β, IL-2, IL-6, IL-12, TNF-α, TNF-β, IFN-α, IFN-γ, LIF, MIF, COMPLEMENT IMMUNOLOGOBULINS</th>
</tr>
</thead>
<tbody>
<tr>
<td>ENDOCRINE SYSTEM</td>
<td>ENDOCRINE GLANDS ADRENAL CORTEX/MEDULLA</td>
<td>ADENOHYPOPHYSIS PRL, FSH, LH, GH, TSH, ACTH CATECHOLAMINS/CORTICOSTEROIDS T3, T4 INSULIN/GLUCAGON ESTROGEN/PROGESTERONE</td>
<td></td>
</tr>
<tr>
<td>IMMUNE SYSTEM</td>
<td>SECONDARY LYMP. ORGANS THYMUS, THYMIC HORMONES BONE MARROW</td>
<td>B CELLS, ACTIVATED MACROPHAGES ANTIGEN-PRESENTING CELL T CELLS</td>
<td></td>
</tr>
</tbody>
</table>

products released by cells of the immune system might be expected to increase or decrease pituitary function.

Interactions between the Sympathetic Nervous System (SNS) and the Immune System:

The lymphoid organs, lymph nodes, spleen, thymus, and gut-associated lymphoid tissue receive an extensive sympathetic intraparenchymal innervation. SNS nerve endings contact T cells, monocytes, and B cells. The function of SNS nerves within the lymphoid organs is regulated by products of immune system cells, while neurotransmitters and neuropeptides released by SNS nerves alter immune system cell responses. In the absence of sympathetic innervation, the severity of experimental autoimmune diseases such as experimental allergic encephalomyelitis (EAE) and experimental autoimmune myastenia gravis (EAMG) are more severe than controls. In patients with progressive multiple sclerosis (MS), β2 adrenergic receptors are two-to threefold increased on CD8-positive, CD28-negative T cells but values are normal in stable MS patients. An increased number of β adrenergic receptors in progressive MS patients suggests that either SNS input to the lymphoid organs is deficient, or the immune system is persistently activated, or both.

THE EFFECTS OF IMMUNE SYSTEM ON NEUROENDOCRINE FUNCTION

The immune system has the capacity not only to sense the presence of foreign
molecules but also communicate this information to the brain and neuroendocrine system. This interaction described by Blalock as the "bidirectional communication" between the immune and neuroendocrine systems, is most evident in the increase of secretion by the pituitary and adrenal glands that follows inflammation or infection. IL-1, IL-6, and TNF-α directly stimulate the synthesis and secretion of corticotropin-releasing hormone and vasopressin at the level of the hypothalamus. The consequent activation of the pituitary-adrenal axis reduces the intensity of the immune response, because virtually all the components of the immune response are inhibited by cortisol.

It has been suggested that psychological stress may promote the onset and/or exacerbation of chronic inflammatory diseases such as autoimmune rheumatoid arthritis, MS and systemic lupus erythematosus (SLE). However, there is no clear evidence of a causal relationship between chronic stress or major life events and the onset of autoimmune disease. It has been shown that stress may have a bidirectional effect on the immune system depending on whether it is acute or chronic. Acute stressors augment the immune response and result in redistribution of immune cells from the blood into the bone marrow, lymph nodes, and skin, enhance antigen-specific cell-mediated immunity and alter T cell subsets. In contrast to this, chronic stressors are thought to suppress the ability of the immune system to respond to challenge and thus increase susceptibility to infectious disease and neoplasia. The effects of stress have also been shown in experimental autoimmune encephalomyelitis and Thielers virus infection, both of which are accepted as experimental models of MS.

Bousios and colleagues have shown that under basal conditions, steroid receptor co-activator (SRC)-1 is expressed at higher levels in the hippocampus and the pituitary of male, compared to female rats. Acute stress results in

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**TABLE 2- Modulation of immune function by hormones**

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Thymic</th>
<th>Progesterone</th>
<th>Cortisol</th>
<th>Testosterone</th>
<th>Estrogen</th>
<th>PTH</th>
<th>CRH</th>
<th>Melatonin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thyroid</td>
<td>Decrease</td>
<td>Decrease</td>
<td>Decrease</td>
<td>Decrease</td>
<td>a</td>
<td>Decrease</td>
<td>Increase</td>
<td>Decrease</td>
</tr>
<tr>
<td>Prolactin</td>
<td>?</td>
<td>Increase</td>
<td>?</td>
<td>Decrease</td>
<td>?</td>
<td>Decrease</td>
<td>Increase</td>
<td>?</td>
</tr>
<tr>
<td>Vitamin D</td>
<td>Increase</td>
<td>?</td>
<td>?</td>
<td>Decrease</td>
<td>?</td>
<td>Decrease</td>
<td>Increase</td>
<td>?</td>
</tr>
<tr>
<td>Growth hormone</td>
<td>?</td>
<td>Increase</td>
<td>?</td>
<td>Decrease</td>
<td>?</td>
<td>Decrease</td>
<td>Increase</td>
<td>?</td>
</tr>
</tbody>
</table>

CRH: corticotropin releasing hormone, DHEA: dehydroepiandrosterone, PTH: parathyroid hormone.
decreased SRC-1 levels in the hypothalamus of both sexes, in the pituitary and frontal cortex of male rats, and in increased SRC-1 levels in the hippocampus of female rats. The mechanism of the stress-induced increase in SRC-1 expression in female hippocampus remains unknown. The authors suggested that a physiological consequence of this finding could be an enhanced ability of female system to cope with stress.

During reproductive ages, there is a distinct female preponderance of autoimmune diseases, including MS, rheumatoid arthritis (RA), SLE, MG, Sjögren's syndrome and Hashimoto's thyroiditis. Gender differences in animal models of autoimmunity, studied predominantly in murine species that spontaneously develop SLE or IDDM, show a more rapid disease progression in females. Sex hormones or sex-linked gene inheritance may be responsible for the enhanced susceptibility of women to these autoimmune diseases. A role for sex hormones in susceptibility to autoimmune disease is supported by observations of alterations in disease symptomatology with alterations in sex hormone levels during pregnancy, menopause, exogenous hormone replacement therapy or oral contraceptive use. In some disease models, administration of androgens can delay the onset of the disease in females, indicating a direct role of sex steroids. Clinical disease activity of several T cell-mediated autoimmune disorders, such as RA, Crohn's disease or MS, decreases during pregnancy but flares in the post-partum period. As disease activity in these disorders is often associated with increased Th1-type cytokine responses, it was suggested that a cytokine shift during pregnancy may be protective. Gestation is associated with a transient depression of maternal cell-mediated immunity to protect the semi-allogeneic embryo from rejection. The hallmark of this immune tolerance is a profound modulation of T cell responses characterized by a shift from Th1 to a Th2 type cytokine responses. It was demonstrated that a failure in the generation of Th2-type cytokine responses is associated with recurrent abortions, complications and poor outcome of pregnancy. This systemic shift toward Th2 immunity during pregnancy may also underlie observations that Th1-mediated autoimmune diseases improve during pregnancy whereas Th2-mediated autoimmune diseases are exacerbated.

Some premenopausal female patients with chronic inflammatory diseases also demonstrate changes in disease activity during the menstrual cycle. Konecna et al. showed oscillation of serum IL-6 concentration during menstrual cycle and the marked menstrual cycle-dependent modulation of IL-6 secretion by sex hormones.

In conclusion, the features of neuroendocrine-immune relations can be summarized as follows:

- Immune system cells can synthesize biologically active neuroendocrine peptide hormones,
- Immune cells also possess receptors for many of these peptides,
- Neuroendocrine hormones can influence immune functions,
- Lymphokines can influence neuroendocrine tissue.

The proper functioning of both HPA axis and the sympathetic nervous system is crucial for survival and maintenance of health, it is not surprising that their regulation is developmentally plastic and complex, multilevel and redundant. Unraveling the significant complexity of brain-immune-endocrine interactions could provide essential new insight and potential treatment considerations for the clinical neurosciences.

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