Research over the past several decades has provided with ample evidence to suggest the existence of a highly complex and interactive system known as neuroimmunoendocrinology. The evidence suggests that the immune system is not a closed circuit that functions autonomously and whose regulation is limited strictly to the actions of its own members. The neuroendocrine system also provides a level of regulation of immune function either directly through neurotransmitters or indirectly through centrally controlled neuroendocrine hormones. The fact that there is direct communication or a “hard wired” circuitry between the neuroendocrine and the immune systems is logical because the majority of lymphoid tissue is innervated. The major discovery in recent years, however, has been that the communication between the two systems is not one way but bi-directional in that the immune system is capable of modulating neuroendocrine function. This bi-directional communication is facilitated on a molecular basis by the production of similar ligands and receptors by both the neuroendocrine and the immune systems, thus providing for a complete regulatory loop (Eskandari & Sternberg, 2002; Ader,
and Cohen, 1991). This chapter discusses how do neuroendocrine and immune systems interact and communicate with each other.

**Neuromodulation by Immune System**

Immune system has its effects on central nervous system (CNS) principally by the release of peripheral soluble factors known as cytokines by cells of the immune system. Cytokines are released both by cells providing innate immunity *i.e.* T-helper cells and acquired immunity *i.e.* polymorphs and macrophages. Cytokines function as hormones to affect the central nervous system. They can affect the CNS directly by crossing the blood brain barrier or indirectly by stimulation of vagus nerve. Cytokines directly influence the electrophysiological functions of neurons in the central nervous system, this is especially true during the inflammation of brain. Chemokines, a related family of proteins is associated with the trafficking of leucocytes in physiological immune surveillance and inflammatory cell recruitment in host defense. Besides their well-established role in immune system, they also play a role in central nervous system. In fact they are expressed constitutively by microglial cells, astrocytes and neurons. Their expression can be increased after induction with inflammatory mediators. Chemokines can modulate neuronal signaling through the inhibition of neuronal calcium currents (Oh, Endoht, Simen, & Ren, 2002).

Cytokines released by the immune system have wide range of actions both on the central and peripheral nervous system, which can be described as follows:

Pro-inflammatory cytokines can activate the hypothalamic-pituitary-adrenal (HPA) axis and induce sickness behaviour during the acute phase response, *e.g.*

(a.) Fever: Interleukin-6 (IL-6), IL-1 by their actions the level of hypothalamus.

(b.) Sickness behaviour: which includes weakness, malaise, listlessness, inability to concentrate, decreased food and water
intake. These actions are induced by IL-1B and Tumour Necrosis Factor (TNF) are mediated by binding to the vagus nerve.

These signs and symptoms produced by peripheral cytokines can be abolished by vagotomy.

(c.) Nausea and Vomiting—IL-1B diffuses across the brain blood barrier and activates area postrema (this is an area in the brain stem, which activates the HPA axis and gives rise to feelings of nausea). It is explained in figure given blow:

FIGURE 1

**Immune system and sickness behaviour**
There is an overwhelming evidence that cytokines, peptide hormones and neurotransmitters, as well as their receptors, are present in the brain, endocrine and immune systems (Ader & Cohen, 1991). The structure and pattern of synthesis of these peptides by leukocytes appear similar to those synthesized in the neuroendocrine system, although some differences exist. Once secreted, these peptide hormones may function as endogenous regulators inside of each system and also in bi-directional communication between the immune and neuroendocrine system. Such communication suggests an immunoregulatory role for the brain and a sensory function for the immune system, which may sense stimuli that are not recognized by the central and peripheral nervous systems (non-cognitive stimuli). The plasma hormone concentrations contributed by lymphocytes usually do not reach the levels required when the pituitary gland is the target, but because immune cells are mobile, they have the potential to deposit the hormone locally at the target site. Several immunoregulatory cytokines, including IL-1, IL-2, IL-6, IFN-gamma and TNF are produced not only in the immune system but in the neuroendocrine system as well. They have profound effects on neuroendocrine functions especially on hypothalamic pituitary axis (Ferencik, & Stvrtinova, 1997).

Organisms respond to infection with complex adaptations involving bi-directional communication between the immune and neuroendocrine systems. The idea of intercellular communication between the neuroendocrine and immune systems via common signal molecules has provided a conceptual framework for such crosswalk. The studies till date show that cells of the immune system contain receptors for neuroendocrine hormones and can also be considered a source of pituitary and hypothalamic peptides (Webesfer, Tonelliand & Sternberg, 2002). The structure and pattern of synthesis of these peptides by leukocytes appear similar
to neuroendocrine hormones, although some differences exist. Once secreted, these peptide hormones may function as endogenous regulators of the immune system as well as conveyors of information from the immune to the neuroendocrine system. The plasma hormone concentrations contributed by lymphocytes usually do not reach the levels adequate enough to reach the target. The immune cells are mobile and deposit the hormone at the target site. Likewise, the cells of the neuroendocrine system contain receptors for cytokines and can also be considered a source of cytokines, particularly interleukin-1 (IL-1) and IL-6. In the pituitary IL-1 beta coexists with thyroid stimulating hormone in a subpopulation of thyrotropes, suggesting it may have a role as a pituitary paracrine factor. The cytokines, including IL-1, IL-2, IL-6, interferon-gamma and tumour necrosis factor, exert profound effects on hypothalamic pituitary axis. This information to the neuroendocrine system represents sensory function for the immune system wherein leukocytes recognize stimuli that are not recognizable by the central and peripheral nervous systems (i.e., bacteria, tumours, viruses, and antigens). The recognition of such non-cognitive stimuli by immunocytes is then converted into information and a physiological change occurs. (Weigent, & Blalock, 1995)

Activation of Pituitary and Adrenal Glands by Immune Function Modulators (Cytokines):

Immune system not only senses the foreign molecules but also passes on this information to brain and neuroendocrine system. This “bi-directional communication” between the two systems is evident by increase in secretion by pituitary and adrenals that follows inflammation and/or infection. As illustrated in the Fig-2 below, cytokines (IL-1,2,3,6 and TNF) directly stimulate secretion of corticotrophin hormone (CRH) and vasopresin by the hypothalamus. CRH activates the pituitary -adrenal axis and
cortisol is secreted by the adrenals. Cortisol in turn inhibits all components of immune response. It suppresses the release of INF-\(\gamma\), GM-CSF, IL-1, 2,3,6, TNF- and eicosanoids, bradykinin, serotonin and histamine. It ultimately reduces the intensity of the immune response.

FIGURE 2
Cytokine Regulation of HPA axis
The hypothesis that pituitary-adrenal response prevents over exuberant immune reactions has been supported by study of immune responses in a strain of rats. Lewis-strain rats have a genetic defect in synthesis of CRH. Acute arthritis develops in these rats on being injected with streptococcal cell wall suspensions. It does not develop in Fischer strain rats, in which responses of HPA axis are normal. Administration of glucocorticoids to Lewis rats suppresses the inflammation and prevents the development of arthritis (Blalock, 1989; Sternberg, et al., 1992).

The relevance of HPA response to inflammation in humans is being evaluated. In patients with chronic fatigue syndrome, reduced pituitary and adrenal responses to CRH and slightly reduced plasma cortisol have been reported (Demitrack, Date and Straus 1991). Whether the pituitary and adrenal changes precede the disorder or are a consequence of it, is not known. Further many patients too have reduced pituitary and adrenal responses to CRH, though their plasma concentrations are slightly elevated.

**Cytokines Induced Thyroid Abnormalities:**

Patients in much different illnesses have abnormality of thyroid function, such as low T3, low T4, and inappropriately low thyrotropin concentration. If the concentration of thyroid hormones (T3, T4) is low, that of thyrotropin should be higher by feedback-loop. Low plasma thyrotropin concentration in these patients suggests that hypothalamic-pituitary feedback response to low T3 and T4 is impaired. Inflammatory cytokines act on the hypothalamus to inhibit secretion of Thyrotropin Releasing Hormone (TRH) and enhance somatostatin secretion. The thyrotropin response to TRH too is reduced by TNF. Within the pituitary itself bacterial endotoxins induce the synthesis of both IL-1 and IL-6, which may inhibit thyrotropin secretion through a

**Cytokines Induced Abnormalities of Gonadal Function:**

Cytokines suppress reproductive function at several levels. IL-1 can be induced within the testes and ovaries in inflammatory illnesses of gonads such as sepsis, burns, and trauma. It inhibits the synthesis of male and female sexual hormones. Under normal circumstances low levels of T- or B-Lymphocytes leads to increased secretion of gonadotropins, TSH and LH, through activation of hypothalamus-pituitary adrenal (HPA) axis. This however does not occur because IL-1 inhibits the pulsatile secretion of Gonadolropin Releasing Hormone by hypothalamus. Nothing is known till date about the functional importance of gonadal suppression. Teleologically one could argue that inflammation—induced gonadal dysfunction prevents reproduction in sick persons (Skinner, 1991; Adashi, 1990; Rivier, & Rivest, 1991; Shalts, Feng & Ferin, 1992).

**Immunomodulation by Neuroendocrine System**

So far we have discussed how the immune system modulates the neuroendocrine system. The brain can in turn regulate immunocompetence also. A number of changes occur in systemic immune function by manipulations of the central nervous system. Evidence for this comes from the following findings:

- Lesions of anterior hypothalamus modify asthma (Mrazek, and Klinnert, 1991) and reduce humoral and cellular responses to foreign antigens (Felten, et al., 1991).
• Rats with hereditary defects of hypothalamic CRH are more vulnerable to inflammatory arthritis (Kidd, Mapp & Gibson, 1989).

• Experimental destruction of sensory innervation of its joints reduces the intensity of inflammatory arthritis (Kidd, et al., 1989).

• Intracerebral injection of HIV-GP 120 decreases function of peripheral blood lymphocytes suggesting that AIDS encephalopathy may further compromise the cell-mediated immunity (Sundar, Cierpial & Kamaraju, 1991).

• In post head-injury several inflammatory cytokines appear in the circulation (McClain, et al., 1991).

• Men and boys with dyslexia and left handedness have a higher incidence of autoimmune disease than other men and boys (Geschwind & Behan, 1982).

The primary hormonal pathway by which the CNS regulates the immune system is the hypothalamic-pituitary-adrenal axis, through the hormones of the neuroendocrine stress response. The sympathetic nervous system regulates the function of the immune system primarily via adrenergic neurotransmitters released through neuronal routes. Neuroendocrine regulation of immune function is essential for survival during stress or infection and to modulate immune responses in inflammatory disease. Glucocorticoids are the main effector endpoint of this neuroendocrine system and through the glucocorticoid, receptors have multiple effects on immune cells and molecules (Webster, Tonelli and Sternberg, 2001).

Further each of the hormone of anterior pituitary has either a direct or an indirect effect on the immune response through the secretions of its respective target gland. The immunoregulatory effects of several hormones are illustrated in the Table 1.
TABLE 1

Immunoregulatory Effects of Endocrine Hormones

<table>
<thead>
<tr>
<th>Hormone or Peptide</th>
<th>Effect on Immune System</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inhibitory</strong></td>
<td></td>
</tr>
<tr>
<td>Glucocorticoids</td>
<td>Synthesis of lymphokines, inflammation</td>
</tr>
<tr>
<td>Corticotropin and interferon</td>
<td>Activation of macrophages, synthesis of IgG</td>
</tr>
<tr>
<td>Choronic gonadotropin</td>
<td>Activity of T cells and natural killer cells</td>
</tr>
<tr>
<td>Endorphin</td>
<td>IgG synthesis, T-cell proliferation</td>
</tr>
<tr>
<td>Somatostatin</td>
<td>Proliferation of T-cells, inflammatory cascade</td>
</tr>
<tr>
<td>Vasoactive intestinal peptide</td>
<td>Proliferation of T-cells</td>
</tr>
<tr>
<td><strong>Stimulatory</strong></td>
<td></td>
</tr>
<tr>
<td>Estrogens</td>
<td>Proliferation of lymphocyte</td>
</tr>
<tr>
<td>Growth hormone</td>
<td>Thymic growth, lymphocyte reactivity</td>
</tr>
<tr>
<td>Prolactin</td>
<td>Thymic activity, lymphocyte proliferation</td>
</tr>
<tr>
<td>Thyrotropin</td>
<td>Synthesis of IgG</td>
</tr>
<tr>
<td>Endorphin</td>
<td>Activity of T, B, and natural killer cells</td>
</tr>
<tr>
<td>Substance P</td>
<td>Proliferation of T cells and macrophages, inflammatory cascade</td>
</tr>
<tr>
<td>Corticotropin-releasing hormone</td>
<td>Proliferation and activation of lymphocytes and monocytes</td>
</tr>
</tbody>
</table>

Adopted from Blalock (1989).

**Neuroregulators and Receptors Common to Immunocompetent and Neuroendocrine Cells**

The ‘B’ and ‘T’ lymphocytes, mononuclear macrophages, polymorphs, leukocytes, mast cells are all immunocompetent cells. The immunocompetent cells of the immune system not only protect against extrinsic pathogens but also against intrinsic pathological changes in cells and tissues that result in alterations
of cell surface molecules producing carcinogenic cells. These cells too contain a number of hormones and peptides, which have been classically associated with the neuroendocrine system cells. A list of the hormones and neuropeptides found in immunocompetent cells are: T lymphocytes—growth hormone, hyrotropin, chorionic gonadotropin; β-Lymphocytes—corticotropin, enkephalins; Mononuclear cells—prolactin, vasoactive intestinal peptide, somatostatin; Thymus—vasopressin, oxytocin, neurophysin.

It has been suggested (Sternberg et.al., 1992) that secretion of hormones and neuropeptides by immunocompetent cells may exert important paracrine and autocrine effects. VIP (vasoactive intestinal peptide) can modulate immune function by regulating traffic of immunocompetent cells through the small bowel (Ottaway, 1991). CRH is secreted at sites of inflammation by monocytes and has proinflammatory actions (Crofford, Sano & Karalis, 1992). Lymphocytes contain m-RNA coding for growth hormone and prolactin and reportedly secrete these hormones (Weigent, & Blalock, 1990; Kelley, Arkins & Li, 1992). Despite the evidence of secretion of neuroendocrine hormones by the immunocompetent cells, it still remains to be established whether these secretions have any systemic effects.

**SUMMARY AND CONCLUSION**

There is evidence to support a molecular basis for bi-directional communication between the immune and neuroendocrine systems (Weigent, & Blalock, 1987). The main findings can be summarized as follows: First, cells of the immune system can synthesize biologically active neuroendocrine peptide hormones. Second, immune cells also possess receptors for many of these peptides. Third, these same neuroendocrine hormones can influence immune function; and fourth, lymphokines can influence neuroendocrine tissues. Although recent studies have begun to unravel the biochemistry of bi-directional communication
between the immune and neuroendocrine systems, there are still missing parts in this puzzle. Among the important questions that must be resolved is the identification of factors that trigger the synthesis of neuroendocrine hormones by immune cells. Are these events operating similar to or in balance with pituitary cells? Should that drugs that interfere with either pathway may be useful? Further, it will be of value to understand the factors controlling neuroendocrine hormone receptor expression on immune cells. A better understanding of the spectrum of positive and negative regulatory events for both systems may determine the ultimate behaviour of immune and neuroendocrine cells. In addition, since leukocytes can produce hormones and also have receptors for the same hormones (e.g., ACTH and GH), it is possible that these immunocytes may also influence their own function in an autocrine-like fashion. The immune system can serve as a sensory organ for external stimuli that cannot be detected by the nervous system. Thus the immune system recognizes stimuli such as bacteria, viruses etc. The contribution of extra-pituitary sites of hormone production and function may provide new cues to define psychological and/or pathological states in the pathophysiology of infectious disease and tumours.

REFERENCES


Neuroendocrine System and Immune Functions


