INTRODUCTION

An extensive interrelationship exists between the endocrine, nervous, and immune systems: These systems regulate each other through complex, multidirectional channels of communication. The magnitude and diversity of this association is well-illustrated in the mucosal immune system of the gastrointestinal tract. The gastrointestinal mucosal immune system is an important component of the normal host response to bacterial, nutritional, viral, parasitic, and other environmental antigens. The mucosal immune system also plays a key role in the pathogenesis of inflammatory bowel disease and graft vs host disease.

Results from classical pituitary gland ablation and replacement studies (1,2) led to the hypothesis that development and function of the immune system is dependent on factors produced in the hypothalamic-pituitary axis. Ample evidence exists to indicate that hypothalamic releasing hormones, anterior and posterior pituitary hormones, adrenal glucocorticoid, and gonadal steroid hormones can act as modulators of immune function and thus serve as important mediators in complex communication loops that link the nervous, immune, and endocrine systems (3). Similarly, intestinal neurons, enterochromaffin-like cells, and immune effector cells release neuropeptides, hormones, and cytokines, which modulate many parameters of mucosal immunity. In this chapter the authors will review neuroendocrine immune interactions in the hypothalamic-pituitary axes and also describe neuroendocrine immune interactions, which are of major importance in the intestine and other mucosal immune tissues.
HYPOTHALAMIC-PITUITARY-IMMUNE INTERACTIONS

Cytokines interact at multiple sites in the hypothalamic-pituitary (HP)-immune axis. Cytokines produced by activated immune cells act as messengers between the immune and the endocrine systems, and convey to the brain the occurrence of immune activation. Interleukins (IL-1, IL-2, IL-4, IL-6), interferons (IFN-γ), and tumor necrosis factor (TNF-α) modulate the secretion of hypothalamic and anterior pituitary hormones in vitro and in vivo. Specific high-affinity receptors for IL-1, IL-2, and IL-6 have been identified in neuroendocrine tissues. IL-1 and IL-6 are the most thoroughly characterized cytokines that function as bidirectional regulators of neuroendocrine-immune communication (4). A common pattern of cytokine effects (IL-1, IL-6, IFN-γ, TNF-α) is an increase in adrenocorticotropin (ACTH) secretion and suppression of thyroid stimulating hormone (TSH) release, whereas the pattern for other hormones is less consistent (5). Cytokines are thus proving to be major modulators of hypothalamic-pituitary function, including HP-adrenal, HP-liver, HP-thyroid, and HP-gonadal axes.

Hypothalamic-Pituitary-Adrenal Axis and Immune Function

The hypothalamic releasing hormone, corticotropin releasing factor (CRF), may have both direct and indirect effects on immune function. Cells of the immune system respond to hypothalamic releasing hormone peptides in a manner remarkably similar to pituitary target cells. CRF induces release of ACTH from the pituitary to act on adrenal cells and immune cells, both of which can release corticosteroids (Fig. 1). CRF also induces ACTH production by leukocytes (6), and modulates the immune response to stress in the rat by inhibiting lymphocyte proliferation and natural killer cell activity (7).

Acute peripheral injection of IL-1 α or β causes dose-dependent increases in plasma ACTH and corticosterone secretion in the adult rat (8). These changes are primarily dependent upon increased release of CRF into the portal circulation, and recent studies have indicated that the paraventricular nucleus (PVN) of the hypothalamus is the main source of this CRF (9). These studies have been extended, and it has been reported that IL-1 receptors can be demonstrated on the pituitary gland (6) and that CRF can upregulate IL-1 receptors on AtT-20 cells (10).

IL-2 is the most potent regulator of pituitary ACTH secretion and is more active than the classical hypothalamic regulator, CRF. In rat pituitary cell cultures at low concentrations, IL-2 elevated ACTH, prolactin, and TSH release and inhibit the release of follicular stimulating hormone (FSH), luteinizing hormone (LH), and growth hormone (GH) from hemipituitaries in vitro. In addition to their effects on hormone secretion, both IL-2 and IL-6 may participate in anterior pituitary cell growth regulation (11). IL-2 given centrally induces a somewhat different pattern of response than the other cytokines in that it stimulated TSH release, which was inhibited by IL-1, IL-6, INF-γ, and TNF-α. As in the case of IL-1, IL-2 inhibited LH release, but it also inhibited FSH release. Thus, IL-2 has powerful actions at the hypothalamic level to alter pituitary hormone release as well as direct actions on the pituitary (5).

IL-6 is a potent stimulator of adrenal corticosteroid secretion as a consequence of CRF and cyclooxygenase-dependent eicosanoid activation of the HP-adrenal axis (12). Although prolonged stimulation is required, it directly stimulates pituitary release of ACTH (13–15). IL-6 is a more potent secretagogue for ACTH by AtT-20 pituitary tumor cells than CRF (16).