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MINIREVIEWS

Central Nervous System-Immune System Interactions: Psychoneuroendocrinology of Stress and Its Immune Consequences

PAUL H. BLACK*

Department of Microbiology, Boston University School of Medicine, Boston, Massachusetts 02118

The past 20 years has witnessed the emergence of the field of psychoneuroimmunology (48). This field deals with the influence of the central nervous system (CNS) on the immune system, or more specifically, whether and how thoughts and emotions affect immune function. Studies have concentrated, for the most part, on the effects of stress on the immune system. Stress is defined as a state of disharmony or threatened homeostasis provoked by a psychological, environmental, or physiologic stressor (12, 40). It has also become apparent from these studies that the immune system can influence the CNS, and thus, a circuit exists between these two systems. Regulatory molecules or cytokines elaborated from activated immune cells evoke a CNS response which, in turn, affects the immune system (26). It is likely, therefore, that the brain is normally part of the immunoregulatory network. Investigators postulate that the events which occur in the brain, specifically at the hypothalamic-pituitary-adrenal (HPA) axis, in response to stress are similar to those which occur in response to internal immune system events; in both instances, the effect of HPA axis stimulation is a down regulation of immune system function.

In this minireview, I discuss the evidence for CNS-immune system interactions, the neuroendocrinologic response of the organism to stress, and the major stress-induced neuromediators which affect the immune system. In the accompanying minireview (6), I consider the events that occur at the HPA axis in response to an ongoing immune reaction, whereby the brain may modulate the immune response, and whether HPA axis dysfunction may be a factor operative in certain infectious, immunologic, and psychiatric disorders (6). I also consider whether and how the immunologic effects of stress may render the host susceptible to infection (6).

EVIDENCE FOR BRAIN-IMMUNE SYSTEM INTERACTIONS

Much of the influence of the brain on immune events is exerted through the HPA axis. The hypothalamus occupies a small area of the diencephalon and regulates vegetative functions such as growth, reproduction, thyroid function, appetite, and sleep. It is rich in neural connections to the limbic system, which is involved in adaptation and in the neuroendocrine and emotional responses to stress. The hypothalamus is the efferent link of the visceral brain, receiving information from the periphery, integrating it with the internal environment, and adjusting certain functions such as sympathetic nervous system function and endocrine secretion (28). The hypothalamus influences the pituitary gland through a variety of polypeptide "releasing factors," for example, corticotropin-releasing factor (CRF), which controls the release of corticotropin (ACTH) from the anterior pituitary gland. Other hypothalamic releasing hormones (RHs) include thyrotropin RH, growth hormone RH, and luteinizing hormone RH; these control the release of thyrotropin, growth hormone, gonadotropin, and luteinizing hormone from the anterior pituitary gland. In addition, hypothalamic somatostatin and dopamine inhibit the release of growth hormone and prolactin, respectively, from the anterior pituitary gland.

Evidence for CNS-immune system interactions has been derived from the following studies. Electrolytic lesions of certain areas of the hypothalamus produce either enhancement or inhibition of various immune functions (25). These changes, both facilitatory and inhibitory, are prevented by hypophysectomy, indicating that pituitary function mediates the hypothalamic effect (28). Lesioning of the pituitary gland can also inhibit or stimulate certain immune system functions. The facts that both the hypothalamus and the pituitary gland can produce both immune-enhancing and immune-suppressive effects and, furthermore, that the pituitary is under hypothalamic control provide a mechanism for tightly regulating the immune response in both magnitude and duration (2). Further evidence for a CNS-immune system interaction is derived from the observation that certain neurotransmitters, neuropeptides, and neurohormones affect immune function both in vivo and in vitro; receptors for these molecules are present on lymphocytes and/or macrophages (7, 25). Cytokines, in turn, elaborated from activated immune cells can alter HPA axis function, thereby closing a negative-feedback loop. In other studies, the sympathetic nervous system has been found to innervate both primary (thymus, bone marrow) and secondary (spleen, lymph node, Peyer's patches) lymphoid tissues (19, 20); this indicates that states of arousal can be transmitted neurogenically to lymphoid tissue. In addition, a number of studies indicate that the immune system can be conditioned. For example, conditioned immunosuppression occurs when a sensory stimulus is paired with an immunosuppressive drug; subsequent exposure to the sensory (conditioned) stimulus results in immunosuppression (1). Thus, a substantial body of evidence exists for bidirectional interactions between the CNS and the immune system.

* Corresponding author.

THE STRESS RESPONSE

Distress resulting from a psychological, environmental, or physiologic stressor induces the "fight-or-flight reaction," both centrally and peripherally, as described by Cannon et al. (9). Centrally, neural pathways which mediate arousal, improved alertness and attention span, vigilance, and appropriate aggression (behavioral adaptation) together with a concurrent inhibition of vegetative functions such as feeding, sexual behavior, growth, and reproduction are facilitated. Peripheral changes prepare an animal to respond to the stressor and include increases in heart rate, blood pressure, and respiration and the redirection of oxygen and nutrients to organs which require additional energy to function with stress; these include the brain and organs involved in fight-or-flight activities. These changes have collectively been called the "General Adaptational Syndrome" by Selye (47). Although the physiologic changes that make up this response have been thoroughly investigated, far less is known about immune system function, which, together with the vegetative functions, is suppressed in response to stress.

CRF AND THE STRESS RESPONSE

Much evidence indicates that CRF is the coordinator of the response to stress (17). Although neurons containing CRF are found throughout the brain, the largest concentration of CRF-containing neurons is found in the paraventricular nucleus of the hypothalamus (31). Diverse peripheral stimuli reach the paraventricular nucleus via various arousal pathways. Stressful thoughts and emotions may reach the hypothalamus by axons relayed by neurons from the limbic system or from the forebrain. Somatic and viscerosensory stimuli such as pain or stressful mechanical stimuli may come to the hypothalamus by spinal and cranial sensory nerve fibers (35). Norepinephrine, serotonin, and acetylcholine are important neurotransmitters which mediate much of the neurogenic stimulation of CRF production (12, 31, 50) (see Fig. 1).

Within minutes of an acute stress, increased CRF mRNA and then CRF appear in the paraventricular nucleus (35). CRF then moves along the axon to the medial eminence of the hypothalamus; there, the axons terminate and CRF is secreted into fenestrated capillaries of the hypophyseal-portal venous plexus which courses to the anterior pituitary gland (30). CRF then acts on the basophilic cells of the anterior pituitary gland to induce proopiomelanocortin, a polyprotein which is subsequently cleaved to form ACTH, β-endorphin, and α-melanocyte-stimulating hormone. ACTH stimulates the production of corticosteroids from the adrenal gland, one of the major classes of stress hormones.

Axons from the paraventricular nucleus of the hypothalamus ramify widely to autonomic nuclei in the brain stem, but particularly to a very dense nucleus in the brain stem, the locus ceruleus, where approximately 50% of the sympathetic, norepinephrine-producing neurons of the brain are located. Locus ceruleus neurons have receptors for CRF (34, 51, 52). With stress, CRF stimulates the production of tyrosine hydroxylase, the rate-limiting enzyme in the synthesis of norepinephrine (34); norepinephrine is then synthesized and secreted. Autonomic nervous system activation by CRF further results in the release of norepinephrine from peripheral sympathetic nerve terminals; in addition, norepinephrine, but particularly epinephrine, are secreted in the adrenal medulla. Elevated norepinephrine and epinephrine levels are invariably present during stress and represent the second major class of stress hormones. It is of interest that intraventricular infusion of CRF produces all of these changes, i.e., the increases in corticosteroids, norepinephrine, and epinephrine and the arousal behavior described above. Antibody to CRF or CRF antagonists prevents the increases in catecholamines and corticosteroids and the stress-induced arousal behavior (24).

NEUROENDOCRINOLOGY OF THE STRESS RESPONSE

In addition to the elevation of CRF, corticosteroids, and the catecholamines with stress, levels of β-endorphin, which is derived from cleavage of the proopiomelanocortin polyprotein, are also elevated, as are the levels of several other opioids. Opiates would function to alleviate pain during a fight-or-flight encounter. Arginine vasopressin secretion from the hypothalamus is also increased, and AVP acts synergistically with CRF to induce proopiomelanocortin gene expression, as well as to induce norepinephrine expression from the locus ceruleus (12) (Fig. 1). CRF also induces somatostatin (53) and dopamine release from the hypothalamus (4, 17). During the adaptational response to stress discussed above, the systems regulating growth, reproduction, thyroid function, and immunity are down regulated; these functions, while necessary for the long-term function of the animal or preservation of the species, provide an organism little survival advantage during an acute life-threatening event.

Two anterior pituitary hormones, growth hormone and prolactin, should be mentioned in greater detail because these are immunoenhancing (27, 33). Growth hormone levels are elevated at the onset of stress, but growth hormone secretion is inhibited with prolonged activation; corticosteroids and somatostatin have been implicated in this inhibition (22). Prolactin levels are also elevated early, but prolactin is subsequently inhibited by the dopamine released from the hypothalamus (4). Certain other neurotransmitters, neuropeptides, and neurohormones which are affected by stress may also interact with the immune system. An abbreviated list of these is given in Table 1. While all of these cannot be considered in this minireview, certain molecules mentioned above have important immunologic effects and will be considered in further detail; these include the corticosteroids, catecholamines, certain opioids, growth hormone, and prolactin.

EFFECTS OF STRESS ON THE IMMUNE RESPONSE

Corticosteroids. Many studies have indicated that the corticosteroids, whose levels are elevated with stress, have profound immunosuppressive effects on the lymphoreticular system; they also have marked antiallergic and anti-inflammatory effects as well. Corticosteroids inhibit many functions of lymphocytes, macrophages, and leukocytes and may affect their trafficking patterns. In addition, they decrease the production of many cytokines and mediators of inflammation and decrease the effect(s) of certain inflammatory molecules on various target tissues (12, 37, 38). Removal of adrenal function by adrenalectomy or suppression of corticosteroid synthesis with metapyrone, for example, with subsequent stress, eliminates many, but not all, of the immunosuppressive effects of stress, indicating that other molecules mediate stress-induced immunologic effects as well (14).

It is of interest that aged rats are unusually sensitive to

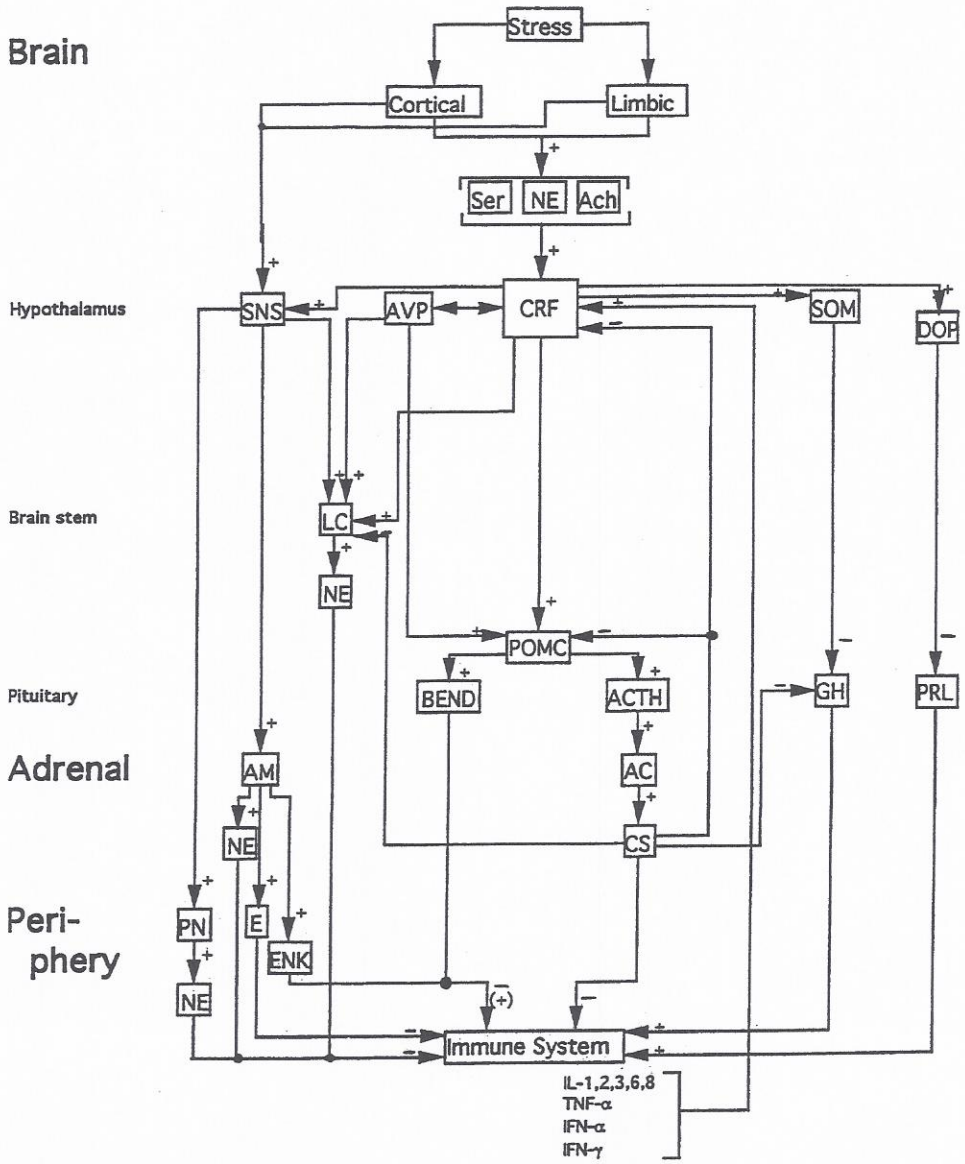

FIG. 1. Schematic representation of the neuroendocrine response to stress. The anatomic and functional interrelationships of the components of the stress system are shown. CRF, corticotropin-releasing factor; Ser, serotonin; Ach, acetylcholine; POMC, proopiomelanocortin; SNS, sympathetic nervous system; NE, norepinephrine; E, epinephrine; LC, locus ceruleus; AVP, arginine vasopressin; DOP, dopamine; SOM, somatostatin; GH, growth hormone; PRL, prolactin; ACTH, corticotropin; CS, corticosteroid; BEND (β end); β endorphin; ENK, enkephalin; IL, interleukin; TNF-α, tumor necrosis factor alpha; IFN-α, alpha interferon; IFN-γ, gamma interferon; PN, peripheral nerve; AM, adrenal medulla; AC, adrenal cortex.

stress, and their brains respond by producing very high levels of corticosteroids. Successful transplantation of tumor cells occurred to a greater extent in stressed aged mice, presumably because of the immunosuppressive effects of the elevated corticosteroid levels, than in stressed young mice. Similar tumor cell growth could be achieved in young stressed mice by giving them corticosteroids so that the levels of corticosteroids were equal to those in older stressed mice. The hypercorticoid state in aged mice was thought to be due to a deficiency in the negative-feedback regulation by the HPA axis (45). Elevated corticosteroid levels normally feed back and down regulate CRF and ACTH production (Fig. 1). A dysregulated HPA axis, therefore, might result in elevated corticosteroid levels (see below).

Catecholamines. Elevation of norepinephrine and epinephrine levels, which accompanies stress, may produce changes in lymphocyte, monocyte, and leukocyte functions (16). Although increased corticosteroid levels may also be a contributing factor, evidence from a number of stress experiments suggests that the plasma epinephrine level is in-

TABLE 1. Some neurotransmitters, neuropeptides, neurohormones, or neuroendocrine effector molecules which both are affected by stress and can modulate immune system function[a]

Molecule
Neurotransmitters
Norepinephrine
5-Hydroxytryptamine (serotonin)
Acetylcholine
Opiates
Dopamine
Neuropeptides
Arginine vasopressin
Substance P
Vasoactive intestinal polypeptide
Cholecystokinin
Oxytocin
Melatonin
Neurohormones
CRF
Corticotropin
Corticosteroid
Growth hormone
Prolactin
Somatostatin
Neuroendocrine effector molecules
Epinephrine
Sex steroids
Thyroxine
Tri-iodothyronine

[a] These categories are not mutually exclusive. For example, the neuropeptides oxytocin and arginine vasopressin are also considered to be neurohormones.

versely related to specific immune system functions (14, 29). Both lymphocytes and macrophages have β_2-adrenergic receptors, and norepinephrine, epinephrine, and β-adrenergic agonists generally down regulate immune system function. When β-agonists are systemically administered to an animal before or at the start of an immune response, some functions such as antibody production may be stimulated early; late in the immune response, however, a decrease in the production of and response to cytokines and general inhibition of macrophage and lymphocyte function occur (2). β-Agonists potentiate the suppression; β-receptor antagonists potentiate the immune response (10). Thus, catecholamines are generally immunosuppressive, especially late in the immune response.

It is of interest that surgical ablation of the sympathetic nervous system results in the up regulation of a variety of immune responses to various challenges (10). Moreover, in the absence of sympathetic nervous system function, there is a significant augmentation of several autoimmune diseases in mice such as experimental allergic encephalitis, experimental autoimmune multiple sclerosis, and experimental autoimmune myesthenia gravis (2). Consistent with these data are the findings that the β-agonist isoproterenol protects rats against experimental allergic encephalitis and β-adrenergic antagonists worsen the disease (11). Results of those studies provide additional evidence that sympathetic nervous system activity generally down regulates immunity. The absence of sympathetic nervous system activity apparently enhances autoimmunity (see below).

Endogenous opiates. The opiates are a large group of peptides which have been isolated from the brain and pituitary gland and which have antinociceptive or analgesic effects. The following three large groups of endogenous opiates exist. (i) One of the endorphins, β-endorphin, is released from the proopiomelanocortin gene product in the pituitary, while α- and γ-endorphins are likely to be derived from β-endorphin; (ii) met-enkephalin and leu-enkephalin are pentapeptides which are present predominantly in the brain and adrenal medulla and share homology with β-endorphin; and (iii) dynorphins coexist in hypothalamic neurons that secrete CRF and arginine vasopressin. The opiates interact with three well-characterized and specific opiate receptors (mu, delta, kappa).

The levels of opiates are increased in the brain during stress (28). Stress also results in stimulation of the sympathetic fiber-containing splanchnic nerve which innervates the adrenal medulla, which is rich in enkephalins; these are cosecreted in response to the same stimuli that induce catecholamine secretion, resulting in increased blood opiate levels (32).

A large amount of information on the effects of opiates on immune system function has accumulated in the literature, with somewhat conflicting results (23); in general, however, the effects are reported to be immunosuppressive. In a number of experiments in which intermittent inescapable foot shock was used, natural killer cell activity decreased; this was prevented if naltrexone, an opiate receptor antagonist, was administered prior to the shock. It is likely to be mediated centrally since endogenous opiates are released in the periaqueductal grey matter of the brain, an area rich in opiate receptors. Indeed, the changes in natural killer cell activity can be mimicked by administering morphine intracranially; this can also be blocked with naltrexone (14). Endorphins and/or enkephalins have also been shown to prevent lymphokine release (gamma interferon) from lymphocytes during an immune reaction (41), prevent mitogenesis in lymphocytes stimulated with various mitogens (23), decrease antibody response to antigens (22), and dysregulate cytoskeletal organization, phagocytosis, and display of class II antigens in monocytes (42). Moreover, various opioids that react with each of the three types of opiate receptors have produced decreased lymphocyte mitogenesis as well as antibody formation (44).

Fewer studies, however, report that opiates have immunostimulatory effects. Some of the discrepancies of the effects of opioids on the immune system may well have to do with various experimental details. These would include in vivo versus in vitro experimentation (21), differences in the species, strain, or sex of an animal (8), different assay systems and/or experimental conditions (8), the neuropeptide dosage used (36), the time course of the observed finding (36), and the type of opioid, cell receptor, or cell used (39, 46, 49).

Growth hormone and prolactin. It has long been known that immunoenhancing factors are present in the pituitary gland. Growth hormone was first implicated in the modulation of the immune system response in pituitary dwarf mice (3); administration of growth hormone alleviated the immune system dysfunction (14). Hypophysectomized animals are also immunosuppressed. Immune system function is restored by administering growth hormone and prolactin (14). Both of these hormones are immunoenhancing (27, 33) and are necessary for normal immune system function and resistance to infection. For example, animals deprived of either growth hormone or prolactin, or both, are far more sensitive than control animals to the lethal effects of exper-

imental *Salmonella typhimurium* and *Listeria monocytogenes* infections (18).

Receptors for both growth hormone and prolactin are present on lymphocytes and macrophages (27, 33). Growth hormone has been shown to regulate the activities of T lymphocytes, monocytes, and stem cells (22, 27), while prolactin is required for various T-lymphocyte and macrophage activities (5, 13). Both hormones also are likely to have important functions in thymus cell differentiation, since receptors for both growth hormone and prolactin are present on thymus epithelial cells (15).

The levels of both growth hormone and prolactin are elevated early in the stress response in humans (28), and this has been thought to provide an immune "restorative" function to buffer the immunosuppressive effects of stress (14). This is unlikely, since the levels of both growth hormone and prolactin are decreased late in the stress response and with recurrent or chronic stress (22, 54). These neurohormones have many similarities. Both growth hormone and prolactin, which are related phylogenetically and which have similar structures, are secreted from the lactotrophs (acidophiles) of the pituitary gland and are under control by both releasing and inhibitory hormones from the hypothalamus (4, 22). TRH is thought to act as an RH for prolactin, but other molecules such as arginine vasopressin, vasoactive intestinal polypeptide, serotonin, and oxytocin may contribute to prolactin release as well (43). Other anterior pituitary hormones such as ACTH, thyrotropin, gonadotropin, and luteinizing hormone are controlled only by RHs. As mentioned above, CRF stimulates somatostatin release, which inhibits growth hormone secretion, and corticosteroids contribute to this inhibition (53); CRF also stimulates dopamine, the prolactin "inhibiting factor" in the hypothalamus, which normally exerts tonic inhibition of prolactin release; this would further inhibit prolactin secretion (4, 17). Thus, the concentrations of both growth hormone and prolactin, which are elevated early, may decline after the onset of stress; this would, of course, contribute further to the immunosuppression seen with stress.

SUMMARY

Psychoneuroimmunology is a relatively new discipline which deals with CNS-immune system interactions. The evidence for such interactions was reviewed, as was the neuroendocrinologic response to stress. Recent evidence indicates that the behavioral, nervous system, and neuroendocrine responses to stress are mediated by hypothalamic CRF, which acts on both the sympathetic nervous system and the HPA axis, resulting in increased levels of corticosteroids, catecholamines, and certain opiates, substances which are generally immunosuppressive. Concentrations of growth hormone and prolactin, which are immunoenhancing, are elevated early during the response to stress but are later suppressed. Although several other neuromediators may also be released with stress, the net effect of a variety of acute stressors is down regulation of the immune system function. In the following minireview, I consider whether stress alters the resistance of the host to infection as well as the immunomodulatory effects of released immune system mediators on the brain (6).

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