Immune System-Central Nervous System Interactions: Effect and Immunomodulatory Consequences of Immune System Mediators on the Brain

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The field of psychoneuroimmunology deals with brain-immune system interactions. Studies involving various stress paradigms have revealed that the brain can influence the immune system through its various neuropeptides, neurohormones, and neurotransmitters. In the accompanying minireview (6), the consequences of stress on the immune system were reviewed; in general, immune suppression results from acute stress (6).

Substantial evidence now indicates that a bidirectional circuit exists between the brain and the immune system. Feedback from the immune system is effected by immune and/or inflammatory mediators released from activated immune cells which affect the brain. In this minireview, I review such interactions and the evidence that the brain plays a role in regulating the immune system through the hypothalamic-pituitary-adrenal (HPA) axis. I also consider the consequences of dysregulation of the HPA axis with respect to certain infectious, immunoloic, or psychiatric diseases. In addition, I consider whether stress plays a role in determining the resistance of the organism to exogenous infection or to disease resulting from reactivation of latent infectious agents.

IMMUNE SYSTEM-BRAIN INTERACTIONS

In the accompanying article (6), I considered the evidence indicating that various neuromediator molecules are released in response to stress and affect the immune system. I now consider whether and how products of immune cells are released and influence the brain. It has long been known that inoculation of foreign antigens induces a classic stress response in animals (18, 32), with elevated corticosteroid (22, 47) and catecholamine levels and increased catecholamine turnover in the brain and periphery (4, 22). The levels of circulating corticosteroids were maximal at the peak of an immune response to an antigenic challenge (5, 47). This occurred only in responding animals, i.e., those animals undergoing a strong immune response (5). Such corticosteroid levels are immunosuppressive (5). In other experiments, inoculation of the supernatent from a mixed lymphocyte reaction produced elevated levels of corticosteroids in blood (2). The pituitary gland and the hypothalamus are required for this corticosteroid response (20).

It was also observed that increased electrophysiologic activity (firing rates) occurred in the neurons of the medial hypothalamus in the area of the paraventricular nucleus and in the locus ceruleus at the height of an immune response (3). Further study indicated that norepinephrine metabolism was stimulated with an increased turnover rate, resulting in less norepinephrine in the hypothalamic and brain stem nuclei;

animals responding with a large antibody immune response, as determined by a greater plaque-forming capacity of B cells, had more norepinephrine depletion in the hypothalamic and brain stem nuclei (34). These findings of stimulated norepinephrine metabolism and turnover were thought to be indicative of increased neurogenic activity of neurons containing norepinephrine (34). They were similar to those seen with stress and were likely to be due to stimulation of neurons that release corticotropin-releasing factor (CRF), with the subsequent activation by CRF of sympathetic nuclei in the hypothalamus and locus ceruleus. I now consider the likely mechanism(s) that is responsible for these changes in corticosteroid and norepinephrine metabolism.

CYTOKINES AND THE CRF RESPONSE

It is now known that cytokines such as interleukin-1 (IL-1), tumor necrosis factor alpha (TNF-α), and IL-6, which are released from immune cells, specifically, macrophages during immune system activation, affect the brain. Although a blood-brain barrier exists to exclude water-soluble substances such as circulating peptides and proteins from the brain, this barrier is lacking in the area of the preoptic nucleus of the hypothalamus (1, 57). Certain neurons in the preoptic nucleus have receptors for IL-1, TNF-α, and IL-6, to which the cytokines bind and thereby pass from the circulation to the brain (57). Preoptic neurons communicate with another hypothalamic nucleus, the paraventricular nucleus, which contains neurons that release CRF. As described in the accompanying minireview (6), CRF induces expression of proopiomelanocortin in the anterior pituitary gland, resulting in the synthesis of corticotropin (ACTH) and β-endorphin. ACTH stimulates the adrenal gland to produce corticosteroids. It is also likely that CRF stimulation of the autonomic nuclei in the hypothalamus and brain stem is responsible for the increased firing of these nuclei during an immune reaction. CRF, therefore, mediates the central nervous system response to immunization and, presumably, infection as well, as it does the response to an environmental, physiologic, or psychological stress. Thus, an ongoing immune response results in elevated corticosteroid, catecholamine, and certain endogenous opiate levels in blood, which explains the findings in the previous section. Activated immune cells may also synthesize small quantities of a number of neurotransmitters, neuropeptides, neurohormones such as CRF, ACTH, vasoactive intestinal polypeptide, somatostatin, thyrotropin, growth hormone, prolactin, and β-endorphin (8). The roles of these molecules in immune system modulation are not known. CRF may act locally in an autocrine or paracrine manner as an inflammatory cytokine. The increased corticosteroid levels induced by the superna-

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tant of a mixed lymphocyte reaction was found to be due to the presence of IL-1 in the supernatant (2).

A number of experiments, done mainly with IL-1, strengthen the argument that IL-1 acts via CRF. IL-1 induces CRF in a dose-dependent fashion (9). Human recombinant IL-1 inoculated intracerebrally into rat brain produces immune suppression. The effect is blocked by antibody to CRF and CRF antagonists; it is also blocked by α-melanocyte-stimulating hormone, which inhibits IL-1 (20, 21, 56). Similar experiments have been done with TNF-α. For example, TNF-α inoculated intravenously into dogs produces elevated norepinephrine, epinephrine, and corticosteroid levels, presumably because of increased CRF levels (49). IL-6 inoculated intracerebrally also produces similar effects which are blocked by antibody to CRF (31). In addition, other cytokines, e.g., IL-8, act to increase CRF (31). Moreover, certain interferons (IFNs), such as alpha interferon (IFN-α) and IFN-γ, may act similarly to IL-1, TNF-α, and IL-6 (57). There is also some evidence that IL-2 and IL-3 activate the HPA axis (25). Activation of CRF by these cytokines should lead to a decrease in growth hormone levels and prolactin secretion by mechanisms discussed in the accompanying minireview (6). Such decreases in the levels of these immunoenhancing hormones would be beneficial to the organism if the desired effect of the cytokines on the HPA axis was to down regulate an activated immune system.

Although most evidence indicates that cytokines stimulate CRF, cytokines may also act directly on anterior pituitary cells. These cells have receptors for cytokines such as IL-1, TNF-α, IL-6, IL-2, and IFN-γ (13, 58). Cytokine-activated cells would be expected to synthesize proopiomelanocortin, as is the case with CRF stimulation. One might question what effect cytokine activation might have on growth hormone and prolactin secretion. In a number of studies, it has been shown either that IL-1 has little to no effect on the release of prolactin or growth hormone in activated pituitary adenoma cells (20, 34) or that it causes a marked decrease in prolactin secretion in basal or vasopressin-stimulated adenoma cells (57). IL-1 as well as IL-2 induce somatostatin release by cultured diencephalon cells (31), and somatostatin acts to decrease growth hormone release. TNF-α induces the release of several hormones from normal pituitary cells in culture, but these did not include prolactin; growth hormone as well as ACTH were released by TNF-α stimulation alone, but growth hormone was inhibited when somatostatin was added to culture (49). Thus, although most aspects of the response to the different stresses (i.e., environmental-, physiologic-, or psychological-induced stress versus cytokine-induced stress) are similar, there is little to no increase in growth hormone or prolactin levels in organisms with cytokine-induced stress. Certainly, studies must be done to investigate growth hormone and prolactin levels at the time of maximal elevation of corticosteroid and catecholamine levels to definitively establish this. The net effect of the immunosuppression induced by the cytokines would be to turn off or down regulate the immune response. This is likely to occur with most immune system reactions and would indicate that the brain, via the HPA axis, is an important controlling factor in immune system reactions.

DISORDERS OF THE HPA AXIS

If CRF is an important regulator of the HPA axis, it is possible that dysfunction or dysregulation of this axis, either in the immune system-generated signals or in the hypothal-

amus or pituitary gland itself, may be associated with certain diseases (10, 15, 60). For example, a certain strain of rat (Lewis) is susceptible to a wide variety of inflammatory and autoimmune diseases (60). In response to inflammatory cytokines, most notably IL-1, the Lewis rat produces markedly diminished ACTH and corticosteroid levels (61). When the rat is challenged with CRF, the response is also subnormal. There is apparently a defect in the hypothalamus in the synthesis and/or secretion of CRF which may be due to an inappropriate regulation of the CRF gene (61). The immune system is apparently turned on or, more appropriately, is not turned off because of this defect in the hypothalamic feedback loop. It is of interest that Lewis rats subjected to various physical stresses (cold, restraint, ether, or open field), in addition to low ACTH and corticosteroid responses, did not develop any of the behavioral characteristics (behavioral adaptation) of stress that other rats that were not susceptible to these inflammatory and autoimmune diseases displayed (59).

Insufficient functioning of the HPA axis also may be involved in other diseases. In a recent study of patients with chronic fatigue syndrome, in which the immune system is also activated, low CRF levels and hypofunctioning of the HPA axis were also found (19). It would be of interest to determine whether failure of central nervous system regulation of the immune response is a factor in the etiology of certain autoimmune diseases. I considered, in the section on catecholamines in the accompanying minireview (6), evidence indicating that the loss of sympathetic nervous system activity enhances autoimmunity, again suggesting that disease may result from insufficient HPA axis down regulation of immune function.

Sustained hyperactivity of the HPA axis has been associated with several psychiatric disorders, most notably, major depression (15, 27, 51). Marked hypersecretion of ACTH and corticosteroids, which is not appropriately suppressible by dexamethasone, occurs in approximately 40 to 50% of patients with major depression (62). CRF levels may also be elevated in such patients. It is of interest that a statistically significant percentage of patients with major depression have depressed immune function, but there is no correlation between immune system dysfunction and failure of dexamethasone suppression (42). Much current thinking supports the view that major depression represents a generalized stress response that has escaped its usual counterregulation (15, 27, 51).

STRESS AND RESISTANCE TO INFECTIOUS DISEASES

The fact that stress can alter immune system function raises the question of whether there is an association between stress and increased susceptibility to infectious diseases and, if so, whether immune system dysfunction is the important intervening variable. Studies with both viral and bacterial pathogens have been carried out in both animals and humans. A number of stressors for animals, mostly rodents, have been used. These include forced exercise, high-intensity sound, restraint, transportation, differential housing (crowding), and cold temperatures. Such studies have generally revealed that stressed animals had greater mortality from a variety of infections induced by both viruses and bacteria than did nonstressed animals. The effect was most pronounced when the stressor was administered at the time of challenge (see references 17 and 53 for reviews).

In humans, the vast majority of studies have been concerned with the effect of psychological stress, brought on by

disruptive life events and determined by a number of psychometric instruments, on the course of various infectious diseases. These instruments assessed stress most commonly arising from situations of personal failure, divorce, separation, or a change in social status (53). Three main types of infections have been studied: upper respiratory infections, reactivation of latent herpesvirus infections, and bacterial infections.

Several retrospective studies indicate that stress (i.e., stressful life events) increases risk for contracting an upper respiratory infection. Many of these studies were self-reported, however (see below). In viral challenge studies, recent life stress was found to significantly increase symptomatic infection by rhinoviruses (30, 63). Personality traits may also have played a role, since in one of these studies introverts were more susceptible and had more severe infections than extroverts (63). A recent very well controlled study involved viral challenge of a large cohort of approximately 400 men and women with one of five respiratory viruses (16). Infection was documented by virus isolation, specific antibody rises, or both. Psychological stress, as determined by questionnaires, was associated in a dose-response relationship with an increased risk of acute infectious respiratory disease, and the risk was associated with increased rates of infection. Neither leukocyte counts nor initial total or virus-specific immunoglobulin levels explained the relationship. Therefore, if immunity had been a determining factor, it would have had to have been one of the components not measured, such as natural killer cell function or cytokine production (62).

In studies of reactivation of latent herpesvirus infection, the evidence that disease episodes were preceded by emotional distress is suggestive but not conclusive (17). Although the evidence from retrospective studies is mixed, in prospective studies, support for stress-induced reactivation comes from two studies of oral herpesvirus infection (24, 36) and two studies of genital herpesvirus infection (28, 46). In three of these studies (24, 36, 46) as well as in another study (43), fewer episodes of disease were found in those with well-developed social networking, i.e., those with social competence and social support.

Some inherent problems relating stress to reactivation of disease may be due to individual differences among subjects with respect to activation and clinical evidence of disease. This is based on the findings in stress studies of medical students taking examinations (26) as well as studies of recently separated women (38), separated and divorced men (40), caregivers of patients with Alzheimer's disease (39), and depressed patients (12, 55). It is clear from these data that stress can result in activation of herpes simplex virus type 1, cytomegalovirus, and Epstein-Barr virus, as determined by increases in specific antibody titer but, in most instances, without the clinical manifestations of disease. Presumably, stress altered the cell-mediated immune containment of the latent infection, viral replication occurred, and an antibody response was elicited; cell-mediated immune reactions are apparently more sensitive to stress than antibody production. Thus, activation can occur without clinical evidence of disease, and if the end point of evaluation was disease, the reactivation rate would be erroneously low.

Stress may also affect primary infection with a herpesvirus (35). Fourteen hundred West Point cadets who were seronegative for Epstein-Barr virus at the start of the study were followed prospectively for 4 years. Cadets who were under more stress because of a high level of motivation and poor academic performance were more likely to seroconvert, to develop clinical infectious mononucleosis if they seroconverted, and to spend more time in the hospital if they developed clinical infection (35).

The studies of bacterial infection, although limited, again indicate a retrospective relationship between stressful life events and a variety of bacterial infections such as tuberculosis, verified cases of Vincent's disease, and dental caries (17, 53). In the only longitudinal study, the effect of stress on the pathogenesis of group A streptococcal disease was studied. An increased level of acquisition of the illness was found in family members who experienced a variety of psychological stressors, e.g., loss of a family member, illness in the family, or divorce (48). Only one challenge study has been carried out; by using exposure to tularemia, a greater severity of illness was documented in individuals who were psychologically vulnerable, a measure of psychological distress involving hypochondriasis, morale loss, and ego strength, than in those who were psychologically nonvulnerable, as determined by a questionnaire administered 2 days prior to exposure (11).

The aforementioned studies indicate that stress is quite likely a factor in the pathogenesis of certain infectious diseases. A number of qualifiers regarding these studies should be mentioned, since substantial limitations exist in several of the studies with both human and animal models (17, 53). More prospective studies are needed with larger, more representative samples. Problems inherent in self-reporting of symptomatology and whether symptoms indicated disease in stressed versus nonstressed patients characterized several of the retrospective studies of upper respiratory infections; confirmatory viral isolation frequently was not done in the studies. Several of the herpesvirus reactivation studies lacked proper controls, and the prospective studies of reactivation of genital herpesvirus infection had methodologic limitations (17). Those studies are difficult to control, and confounding variables that were due to the sex of the subject, level of sleep deprivation, altered nutrition, medication usage, and alcohol consumption were not always considered (53). Last, the nature of the stressor and its effect, as well as its timing and duration and whether it was acute or chronic, must also be further characterized since many of the animal stressors have been physical, involving exercise and pain, while human stressors have frequently been psychological. Are the large variety of stressors acting similarly and, if so, by what mechanisms?

The last point raises, perhaps, the greatest criticism, which involves the mechanism or pathway by which stress enhances the pathogenesis of infectious disease. It seems clear that stress induces immunosuppression and that stress enhances disease acquisition or reactivation of latent disease; whether the former is the important intervening variable for the latter relationship is not apparent in the vast majority of studies. A few studies have examined immune pathways. For example, McClelland et al. (45) found more respiratory infections and diminished salivary immunoglobulin A levels in a population of prisoners who had high levels of inhibited power motivation and self-reported power-related life stress. Future studies should resolve the relationship between stress-altered immune system function and resistance to infectious disease.

CONCLUSIONS AND IMPLICATIONS

One can conclude from the information presented in this and the accompanying minireview (6) that the brain and

immune system are mutually interactive; stress affects the immune system through the HPA axis, and the immune system, by cytokine elaboration, affects the brain through this same axis. Furthermore, I hypothesize that similar molecules induced by CRF are elaborated by HPA axis stimulation by both stress and cytokines; the net effect is immunosuppression. Growth hormone and prolactin, which enhance immune system function, are apparently down regulated in both situations after a transient elevation at the onset of stress. The brain therefore has the capacity to fine-tune the immune response. Thus, the immune system can no longer be considered autonomous. Together with immune regulatory factors, such as CD8 suppressor cells and anti-idiotypic antibody, which down regulate its function, it is evident that central nervous system-induced down regulation may also play an important role. Insufficient down regulation because of HPA axis dysregulation may contribute to the development of autoimmune disease as well as other diseases with hyperactive immune cells such as chronic fatigue syndrome. Hyperfunctioning of the HPA axis may be operative in the pathogenesis of major depression or in the hypercorticoid-induced immunosuppressed state in aged individuals (6).

One may question the role of the HPA axis in regulating the immune system when there is a continuous need for immune system function, such as in patients with subacute or chronic infections. Down regulation of immunity in individuals with these conditions would not be advantageous to the host. Cytokines are liberated and reach the brain in individuals with such infections since they are responsible for fever as well as other manifestations of sickness behavior (37), and corticosteroids are elevated as well, indicating a responsive HPA axis. The nature of the HPA axis function as well as the presence or absence of other components of the negative-feedback loop during persistent infection, which are incompletely understood at present, need to be further delineated.

Recent studies indicate that stress in animals can cause cytokine (IL-1) secretion from macrophages (33). Liberated cytokines such as IL-1 are proinflammatory and are the earliest molecules involved in the inflammatory response. IL-1 as well as other cytokines, particularly IL-6 and TNF-α, induce acute-phase reactants in the liver. Acute-phase reactants contribute to the inflammatory reaction and are also released by stress, presumably through cytokine activation (50, 64). Therefore, the early, essential elements which induce an inflammatory response can be activated by stress. This raises the question of whether stress can induce inflammatory reactions and be a factor in the etiology and/or progression of certain human inflammatory diseases, such as rheumatoid arthritis, for which no etiology is known. In this respect, IL-1 has been repeatedly implicated in the pathogenesis of rheumatoid arthritis (9, 14), and some current therapies involve the use of IL-1 receptor antagonists.

Cytokines (IL-1 [41, 52], TNF-α [23, 29], and IL-6 [54]) can act on the long terminal repeat of the integrated provirus of human immunodeficiency virus (HIV), promoting transcription of the provirus of HIV and the replication of HIV. More precisely, cytokines activate NF-κB in the cytoplasm, which acts on the long terminal repeat of the integrated provirus of HIV to promote transcription. Corticosteroids can also activate transcription of the provirus of HIV (44). Therefore, by inducing cytokines and corticosteroids, stress, which can promote HIV replication, may act as a cofactor in the progression of HIV infection to clinical AIDS (see reference 7 for review).

Psychoneuroimmunology involves many medical disciplines: psychiatry, neurology, neuroendocrinology, and immunology. Because stress alters resistance to infection, it involves infectious diseases as well. Recent advances in research on microbial pathogenesis together with some of the progress in psychoneuroimmunology described in this minireview should together give greater insight into the cellular and molecular basis of stress-induced influences on the pathogenesis of infectious disease (53).

SUMMARY

A bidirectional circuit exists between the central nervous system and the immune system, since activation of the immune system results in the elaboration of cytokines and inflammatory mediators; these mediators induce hypothalamic CRF, which stimulates the release of the same immunosuppressive molecules that mediate the response to stress. The brain, therefore, is likely to be involved in immune system regulation. Hypofunctioning of the HPA axis with insufficient down regulation may be involved in autoimmune or other diseases with excessive immune system activation. Hyperfunctioning of the HPA axis, which is not appropriately suppressed, has been found in a large number of patients with major depression. Evidence that stress is an important factor in both lowering resistance to infectious agents and contributing to the reactivation of latent viruses is discussed. Also discussed is the evidence that stress induces proinflammatory cytokines which may contribute to both the pathogenesis of inflammatory diseases of unknown etiology and the progression of HIV infection to AIDS by activation of HIV replication.

ACKNOWLEDGMENTS

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