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Stress and the Immune System in the Etiology of Anxiety and Depression

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LEONARD, B. E. AND C. SONG. *Stress and the immune system in the etiology of anxiety and depression.* PHARMACOL BIOCHEM BEHAV **54**(1) 299-303, 1996.—There is clinical and experimental evidence that various aspects of the immune and endocrine systems are severely compromised in chronic stress and depression. For example, it has been shown that a reduced lymphocyte response occurs to mitogens in depressed patients, effects that are not reversed by chronic antidepressant treatment. By contrast, monocyte phagocytosis is increased, while neutrophil phagocytosis is decreased in depressed patients. Such changes are normalized by effective antidepressant treatment. The results of such studies and others that demonstrate alterations in noncellular immune processed in depression indicate that the changes in immune function correlate with the severity and duration of the external and/or internal stressful stimuli. There is evidence that some of the immune changes are a reflection of increased plasma glucocorticoids that characterize both stress and depression. However, it is also apparent that the cytokines, prostaglandins, and corticotrophic releasing factor (CRF) also play an important role in initiating the behavioral and pathophysiological changes that are characteristic of both depression and chronic stress. This review attempts to critically assess the interplay between CRF, the immune and neurotransmitter systems, and behavior in chronic stress and depression.

CRF Neurotransmitters Cortisol Immune function Stress Depression

NEARLY a decade has passed since Ader (2) reviewed the evidence that complex interactions occurred between the brain and the immune system. It is now widely accepted that psychological stress and psychiatric illness can compromise immune function, thereby suggesting that the psychological state may influence the susceptiblility of an individual to illness or modify the course of the illness and its prognosis. In addition, there is increasing evidence to suggest that the humoral components of the immune system can directly affect brain function and thereby alter the behaviors that might be important in the adaptive response of the individual to the illness. It is well known that, in addition to subtle cell-cell interactions and cellular specificity, only the brain and the immune system possess a cellular memory and a well-developed network of communications that is operated by neurotransmitters, and lymphokines, which may be considered as immunotransmitters. In addition to the bidirectional interactions between the brain and the endocrine system and between the endocrine and the immune system, it has also been shown that the brain can interact directly with the immune system and vice versa. The purpose of this review is to first consider the effect of stress on immune function, as there is unequivocal evidence that stress is both causally related to and a concommitant of most major psychiatric illnesses. The changes in the immune system that are associated with depression and anxiety will then be discussed.

INTERACTION BETWEEN THE CENTRAL NERVOUS SYSTEM AND IMMUNE SYSTEM IN STRESS AND DEPRESSION

The monoamine hypothesis of depression proposes that a deficit of brain noradrenaline (NA) and/or serotonin (5-HT) may be causally involved in the symptoms of illness (7). Another theory of depression suggests that the disorder in hypothalamus-pituitary-adrenal (HPA) axis causes an increase in secretion of corticotropin-releasing factor (CRF), which stimulates adrenocorticotrophic hormone (ACTH) and cortisol release (8). Recently, the macrophage theory of depression has also been proposed. In this hypothesis, the evidence of abnormal secretion of some cytokines, interleukin-1 (IL-1) and interferon-alpha (INF-alpha), results in disordered secretions of CRF, ACTH, prolactin, and cortisol, and a depressive syndrome are presented in detail (62). These three hypotheses may be linked. Whatever changes in the central nervous system (CNS) or in the endocrine system occur, different aspects of immune function are affected. It is known that noradrener-

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gic and cholinergic terminals innervate the thymus gland and bone marrow and there are different neuropeptide, neurotransmitter, and hormone receptors on lymphocytes and monocytes. In addition, cytokines produced by immune cells and microglia exert different effects on the CNS and on the endocrine and immune systems (11,23,36,47,74).

A number of studies have shown that stress and depression are associated with an impairment in immune function (40). At the cellular level, a reduction in mitogen-stimulated lymphocyte proliferation and neutrophil phagocytosis and elevated monocyte activity has been reported in stress and depression (45,50,56). An increase in total white cell number and an abnormality in differential white blood cell (WBC) count (for example, increase in the percentage of neutrophil and decrease in lymphocytes) has also been found after stress or in depressed patients (48). Recently, leucocyte adhesiveness/aggregation (LAA) has also been reported to be increased during stress, and this has been suggested as a marker of stress (5).

At the subcellular level, it has been reported that serum and plasma concentrations of immunoglobin (Ig), complement (C), and acute phase proteins are changed in depressed patients (29,40,49). For example, IgA, IgM, complement C3, C4, and positive acute phase proteins are increased in depression, while negative acute phase proteins are decreased. The concentrations of cytokines IL-1, INF-alpha, and tumor necrosis factor are raised and interleukin-2 (IL-2) is reduced in the depressed patient (34,53,62). At the organ and system level it has been reported that the weights of thymus gland and spleen are reduced and adrenal is increased during stress (19). Histological studies reveal that a stress-induced rise in corticosterone, or exogenous injection of corticosterone, causes cortical atrophy and lymphocyte necrosis in the thymus gland of rats (19).

However, despite the circumstantial evidence implicating an interaction between neurotransmitter, endocrine, and immune changes, a causal relationship between these changes has yet to be proven.

STRESS AND THE IMMUNE SYSTEM

There is a large and relatively consistent literature on the effects of stressful life events on predisposition to both physical illness and infections. While the correlations between such life events and illness are not large, generally accounting for only about 10% of the variance (71), the effects are consistent across populations and different types of life events.

Bereavement stress has been the subject of several important studies. There is also evidence that risks to health associated with separation and divorce are greater than with bereavement (9). For example, Kiecolt-Glaser et al. (38) showed that separated or divorced women had a poorer immune function on five of the six immunological variables studied than matched married women. Somewhat similar findings were reported for separated or divorced men (39). It should be emphasized that the sample sizes in these studies was quite small, but such data does serve to emphasize the impact of severe life events on the immunological status and consequent health of normal individuals.

The effect of chronic stress on individuals caring for patients with Alzheimer's disease has also been the subject of several studies. It has been shown, for example, that such individuals show a high risk of depression (17,24). In addition to the greater physical and emotional distress shown by the carers, there is also evidence of impaired immune function (38). Other studies of those subject to chronic environmental stress (for example, living in the vicinity of Three Mile Island in the USA, the site of a nuclear power plant accident some years ago) showed that the residents had fewer T-suppressor cells, β-lymphocytes, and natural killer cells than a comparable group living in a normal environment (18). The conclusion of these studies is that chronic stress in man does not necessarily lead to immunological adaptation. Clearly, there are marked differences between the stress-induced changes in rodents and those reported in man. Thus, in rodents, acute stress appears to be immunosuppressive, whereas chronic stress is associated with adaptative changes or even enhancement of the immune response (16,51).

Examination stress in University students has been the subject of several studies in the United States. Thus, a decrease in natural killer cell number and function has been reported by several groups of investigators (27,37), effects that were to attributable to poor nutritional status of the students. In addition, academic stress has been associated with significant changes in antibody titers to latent herpes viruses, suggesting changes in cellular immunity. In particular, elevated antibody titers to the Epstein Barr virus (the causal agent for infective mononucleosis), herpes simplex virus type I (that causes cold sores), and cytomegalovirus (which causes the monucleosis syndrome) were raised prior to examinations but returned to normal levels following the vacation (26). There were additional changes in mitogen stimulated lymphocyte replication associated with academic stress. Thus, the incidence of self-reported infectious illness was also increased in these individuals. The effect of relaxation techniques on these immune paramaters was also studied and showed that although the percentage of helper T-cells did not decline so markedly in those subjects that were given relaxation exercises, natural killer cell activity was unaffected by such an intervention. It may be concluded from these studies of the effects of stress and adverse life events that adaptive changes in the immune system are not pronounced in man.

One of the major problems arising from the clinical studies lies in the difficulty in adequately defining stress, because the same event may have different effects on different individuals. Furthermore, most of the components of the immune system normally vary within wide limits, thereby making the small, but important, changes difficult to detect. Added to these problems is the difficulty in deciding which parameter accurately reflects the true status of the individuals immune defences.

ANIMAL MODELS OF STRESS AND DEPRESSION

There are several animal models of depression that have been developed in the past 4 decades. Reversal of the behavioral and physiological effects of the monoamine-deleting drug reserpine was the earliest animal model of depression (73). The reserpine-induced syndrome is reversed by tricyclic antidepressants and monoamine oxidase inhibitors (MAOIs), but this model failed to detect many of the newer antidepressants, such as mianserin, that differ structurally from the tricyclic compounds (30,44). Learned helplessness follows the exposure of animals to uncontrollable stress (70). The symptomatic overlap between learned helplessness and depression is striking, and it has been suggested that such a model would meet some of the criteria for major depression (18). However, most of the effects of uncontrollable stress are transient, with recovery within several hours or days (27,51), while clinical diagnosis of depression requires at least 2 weeks of abnormal symptomatology.

Olfactory bulbectomized (OB) rats have been developed as a model of depression over the past 20 years. Four weeks following bilateral olfactory bulbectomy, changes in behavioral, neurotransmitter, and endocrine aspects are qualitatively similar to those occurring in depressed patients (28,69). For example, OB rats show a hyperactivity in a novel environment (open field), the concentration of NA is decreased in the limbic system, and the serum level of corticosterone is abnormally elevated during the dark phase of the light-dark cycle (13,35). In addition, a reduction in neutrophil phagocytosis has been found in the OB rat, which also occurs in depressed patients (55). A number of studies have demonstrated that chronic treatment with most antidepressants reverse the hyperactivity of OB rats in the open-field apparatus (14,69).

The thymus gland is the first organ to age in the human and animal body. Many investigations have focussed on the relationship between thymus, aging, and immune disease. Recently, it was found that thymectomy caused psychological changes in man (10,52). In the rat, following thymectomy, changes in brain neurotransmitters are similar to those occurring in the aging brain (63). Regarding the relationship between the macrophage theory of depression with thymus aging, it seems possible that the thymus gland aging results in an impairment in cytokines production, which causes abnormalities in neurotransmitter and hormonal function.

IS CRF A CENTRAL MEDIATOR IN STRESS AND DEPRESSION?

In 1995, Saffran and Schally (47) demonstrated the existence of a factor derived from the hypothalamus that could elicit adrenocortricortrophin (ACTH) secretion from the pituitaries in intact rats; the factor was called corticotrophin-releasing factor (CRF). In the past 10 years, CRF was found as a predominantly excitatory neurotransmitter and to play an important role in behavioral, neurochemical, endocrine, and immunological aspects of stress (15). CRF is hypersecreted in depressed patients, and a downregulation of CRF receptor was found in the cortex of depressed patients and suicide victims (42).

In the experimental studies, the effects of CRF on behavior appear to vary according to the dose and time for which CRF is administered. For example, it was reported that a low dose (0.01 μg) of CRF intracerebroventricular (ICV) administration significantly increased locomotor activity in rats placed in a novel environment (43), whereas a higher dose of CRF (1 μg) decreased locomotor and rearing behavior. By contrast, Sherman et al. (61) reported that (3.0 μg) CRF increased locomotor activity but decreased the rearing behavior. Rats given CRF (9.1–20 μg) spent less time on the open arms of an elevated plus-maze than vehicle-treated animals (1). Acute administration of CRF (ICV) increased the concentrations of 3-methoxy-4-hydroxyphenylglycol (MHPG), 2-5-dihydrophenyl-acetic acid (DOPAC), homovanillic acid (HVA), dopamine (DA), and 5-hydroxyindoleacetic acid (5-HIAA) in the limbic system (20,21,46). However, few investigators have found any changes in the concentrations of noradrenaline (NA) following CRF administration.

It is well established that different types of stress can suppress immune function in man. Changes in the immune system include impaired neutrophil phagocytosis (56), increased neutrophil, and decreased lymphocyte number and percentage (32), reduced lymphocyte proliferation (51,60), and natural killer (NK) cell activity (22) and changed macrophage activity (50). Many of these events are believed to be mediated by glucocorticoids. However, with the demonstration that stress-induced immunosuppression occurs not only in normal but also in adrenalectomized rats, it became evident that other factors may be implicated, including neurotransmitters, neuropeptide-Y, neurotensin, and CRF. To date, no single key factor of the neuroimmunomodulatory responses to stress has been found (33). In 1991, Jain et al. (32) reported that electroshock, or IV or ICV administration of CRF (4 days), significantly suppressed lymphocyte proliferation and NK cell cytotoxicity in both intact and adrenalectomized rats. They also reported that if animals were pretreated with CRF antibody or CRF antagonist, the shock-induced suppression of lymphocyte and NK cell activities were markedly reversed. Strausbaugh and Irwin (68) reported that CRF administration resulted in a reduction in lymphocyte proliferation and NK cell activity, with no significant change in the total number of lymphocytes. Few investigators to date have studied the effects of CRF on other immune functions, which are changed during stress. However, an increase in leucocyte adhesiveness/aggregation (LAA) has been identified as a stress marker in both animals and humans (5,65), while CRF administration has been shown to significantly elevate plasma corticosterone and decrease lymphocyte proliferation in experimental animals (12,54). Such subacute effects of CRF may represent the type of changes found following chronic stress and in patients with depression.

Changes in the concentrations of biogenic amine neurotransmitters were also found in the brains of rats treated subchronically with CRF. Thus, the release of noradrenaline has been shown to be increased following subchronic CRF (41), while we (66) and others (21) have shown that the concentrations of dopamine and 5-hydroxyindoleacetic acid are also increased in the hypothalamus. The changes in the noradrenaline concentration would appear to reflect the subchronic effects of CRF, as we have found that a single injection of CRF did not change the brain noradrenaline concentration (Song and Leonard, unpublished observations). Presumably, these changes in neurotransmitter concentrations are a reflection of the activity of the CRF receptors that are highly concentrated in the paraventricular nuclei of the hypothalamus (25,58), an area of the brain that is the principal integrative center for the endocrine, immune, and neurotransmitter systems.

From the immunological studies, it would appear that the administration of CRF causes an impairment of immune function resembling those observed in stress and depression. Thus, previous investigations regarding the effects of CRF on immune function mostly focussed on the lymphocyte proliferation and NK cell activity. For example, Jain et al. (32) found that CRF could suppress lymphocyte proliferation and NK cell cytotoxicity in adrenalectomized and hypophysectomized rats. They speculated that POMC-derived peptides, such as ACTH, are not likely to play a significant part in CRF-mediated immunosuppression. However, CRF-induced secretion of ACTH and corticosterone may exert an important role on the mediation of immunosuppression because it has been reported that stress-induced increase in glucocorticoids will increase in the number of granulocytes in bone marrow of mice. In support of this finding, no change in granulocyte number has been found in the adrenalectomized rats (8). It has also been demonstrated that mild and severe, short- and long-term stress induced increases in the concentrations of ACTH and corticosterone directly, caused decreased lymphocyte proliferation, total number of WBC and lymphocytes, but an increased number of neutrophils. These impaired immune functions were largely attenuated following adrenalectomy (64).

The results of our investigation of the effects of subchronic CRF also suggest that corticosterone may indirectly suppress such immune functions as neutrophil phagocytosis, leucocyte adhesiveness and aggregation (LAA), and the WBC count (64). We have shown that the LAA percentage was significantly increased in the CRF-treated animals compared with controls (3,64). Arber et al. (6) demonstrated that an increase in LAA was inversely correlated with the concentrations of corticosterone and NA in the blood following NA, DA, or insulin infusion into the dog. Therefore, the increase in LAA percentage may be a consequence of elevated concentrations of NA and corticosterone caused by CRF administration.

To conclude, it is apparent from experimental studies that subchronic administration of CRF produces a time- and dose-dependent change in behavior, immune function, and neurotransmitter concentrations in the hypothalamus. Such changes that occur following ICV CRF administration qualitatively resemble those observed in stress and depression, and suggest that CRF may play a key role in the psychopathological factors that underline this condition.

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