Nociception and the Neuroendocrine-Immune Connection

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PSYCHOLOGICAL INFLUENCES ON IMMUNE AND ENDOCRINE FUNCTION

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Introduction

Since the emergence of such immunosuppressive diseases as Acquired Immune Deficiency (AIDS), there has been growing public interest in the function and influence of the immune system on the human body. In addition, there has been widespread interest how such diseases are acquired, as well as variables that might separate those individuals who become infected from individuals who never develop an infection. It has long been thought that both psychological and environmental factors have played a major role in the etiology of physical illness. The area of research known as psychoneuroimmunology focuses on the relationship among behavior, the immune system, and physical illness (i.e., infectious disease, cancer, allergies, and autoimmune diseases).

In recent years, a variety of animal and human studies have assessed the impact of behavior on the immune system. These studies have included clinical studies that have sought possible immunological markers for certain psychiatric disorders, and research that has examined the effects of both real life and laboratory stressors on specific immune functions. Many of the psychological factors that may modulate the immune system have been associated with the stress process; these include negative mood, social support, coping styles, and stressful life events (1).

In addition to psychosocial influences on the immune system, many researchers have also focused on the ways that the central nervous system, endocrine system, and behavior interact to influence the immune system and disease states. Some of the effects of psychological states on the immune system are mediated via the central nervous system which in turn may stimulate immunological changes through the hypothalamic-pituitary axis (2); it has become increasingly apparent that the endocrine system plays a significant role in the regulation of the immune system (3). This chapter discusses the interactions between psychosocial variables on various components of the immune system, as well as studies that highlight the role of the endocrine system as a key mediator of behavioral influences on immunity.

Depression and Dysphoria

Substantial research has been conducted to assess immunity in relation to depression and dysphoria. Generally, these studies indicate that depression and dysphoria have adverse effects on immunocompetence (4).

In order to study the effects of depression on the immune system, researchers have studied both clinically depressed and non-clinically depressed populations. Studies examining clinically depressed populations have reported
lower lymphocyte stimulation responses to PHA in hospitalized depressed patients during the acute phase of their illness as compared to their responses following clinical remission (5). A decrease in lymphocyte responses to mitogens (6), and a depression of circulating lymphocytes (7) has been observed in patients with major depressive disorders. Another study examined the relationship between natural killer (NK) cell activity and severity of depression in a group of bereaved women who were not clinically depressed (8).

NK cells are a subpopulation of leukocytes that can nonspecifically kill certain target cells such as virus infected cells and tumor cells. There are significant relationships between severity of depression symptoms and impairment of NK cell activity, absolute numbers of suppressor/cytotoxic cells, and an increase in the ratio of T helper to T suppressor/cytotoxic cells. Helper T cells stimulate important immunological activities, (e.g., the production of antibody by B lymphocytes) which are important for defense against infectious agents. Suppressor T cells act to downregulate the activity of helper cells when sufficient antibody has been produced. A lower ratio has been associated with immune deficiency (9).

Schleifer, Keller, Stein and their colleagues have examined major depression and immune function. Their initial studies showed significantly lower mitogen responses in a depressed population as compared to age and sex-matched controls; lymphocyte proliferation in response to mitogens has been widely used as one method of assessing general immunocompetence. However, subsequent studies in their laboratory showed no significant differences between depressed patients and controls across a number of immunological markers including total peripheral blood lymphocytes, T and B lymphocytes, and NK cell activity (10). Multiple regression analyses showed significant age-related differences between the depressed patients and controls with regards to mitogen responses and number of T4 lymphocytes. Severity of depression was also associated with immune changes. That is, immune changes were more likely in the older, more severely depressed patients than the younger, less severely depressed patients.

Various studies have shown possible relations among unhappiness, loneliness, and alterations in both immunocompetence and certain aspects of infectious disease. For example, Luborsky, Mintz, Brightman, and Katcher (11) found that general unhappiness in a population of student nurses was a good predictor of the frequency of occurrence of herpes labialis. Loneliness, as well as unhappiness, has also been linked with altered immune function. Kiecolt-Glaser et al. (12) found a significant relationship between higher loneliness and low NK activity in a group of medical students with similar findings in a group of newly admitted psychiatric inpatients (13). They also observed significantly poorer T-lymphocyte response to PHA stimulation in association with higher scores on loneliness in a psychiatric population. In another study using medical students subjects, they found significantly higher Epstein-Barr virus (EBV) antibody titers in the high-loneliness subjects as compared with the low-loneliness subjects (14), suggesting that cellular immunity was less competent in controlling virus latency in the high-loneliness group. Furthermore, other studies have shown correlations between high
levels of depressive mood, anxiety, and hostility and lower proportions of suppressor-cytotoxic T cells in a group of patients with recurrent genital herpes simplex virus (15). The same relationships with anxiety and hostility were found to produce lower NK cell activity (16, 17), total white blood cell counts, and the number of polymorphonuclear leukocytes and lymphocytes on differential counts in a group of AIDS patients (18).

Although there is evidence that depression or dysphoria is immunosuppressive, many of the studies thus far point to the possible relationship between these emotional states and modulation of the immune system. It is important to note, however, that other issues must be taken into account when studying depression and the immune system. Examples include the age of the individual, nutritional status, severity of the disorder, and in particular, the nature of the depression (19).

Major Life Events

Bereavement

Loss of a loved one is one of the most common and potentially stressful life events. Along with the various behavioral changes that one may observe, researchers have also found links between bereavement and altered immunity. Bartrop and his group (20) first found that a group of bereaved individuals showed decreased lymphocyte function as compared with a group of controls. Similarly, a longitudinal study of husbands of women with advanced breast cancer found significantly lower lymphocyte stimulation two months post-death as compared with the same measures prior to their wives’ deaths (21). Lin, Lin, and Jensen (22) found reduced lymphocyte responses to PHA only in a group of bereaved subjects that scored highest on a depression subscale. Natural killer cell activity was measured in another study in which women whose husbands were being treated for cancer were compared with a group of women whose husbands had died from cancer, and women who had healthy spouses (23); the bereaved women had lower NK cell activity than the other two groups, consistent with the other studies described earlier.

The process of linking the experience of bereavement with effects on the immune system are complex. Changes in appetite, sleeping habits, drug and alcohol use, and depression may all contribute to the suppression of particular immune functions (24). Therefore, it remains to be determined whether stress-induced changes in the immune system are related in any way to the onset or course of an illness following a life stressor such as the lose of a loved one. Certainly, it has been shown that bereavement does effect particular functions of the immune system; however, further study is required to find out what dimensions of bereavement are affecting the immune system and if these changes can be linked with mortality and morbidity.

Divorce/Separation

Studies on marital disruption through separation and divorce are also consistent with the idea that negative emotionally significant life events have adverse effects on the immune system. One study compared the immune function of a group of 38 separated and divorced women with a socio-demographically matched group of married women. The
separated/divorced women had lower responses to two mitogens, lower helper T-cell percentages, and higher antibody titers to EBV. Women who had been separated from their mates for longer periods fared better with regard to the immune parameters than more recently separated women. Moreover, the greater the continuing preoccupation or attachment to the ex-spouse, the poorer the immune system responses (25).

In addition, marital disruption has been associated with increased morbidity and mortality compared to married individuals. Studies comparing married and separated/divorced individuals have shown that divorced individuals are six times more likely to die due to pneumonia than married individuals (26), and that separated women are more likely to visit their physicians and report more acute illness than their married counterparts (27).

While one might assume that married individuals are healthier than single or separated individuals, studies suggest that the quality of married life is also a factor in the health and immune function of the individual. Renne (28) found that unhappily married individuals reported poorer health than either happily married or divorced individuals. Also, within the group of married women who were studied by Kiecolt-Glaser and associates (25), those who rated their marriages as poorer were found to more depressed and had a poorer response across three function measures of immunity.

Academic Stress

Changes in immunity can also be studied in naturally occurring, less severe stress situations such as the stress associated with taking examinations (academic stress). Dorian, et al. (29) examined 8 trainees in psychiatry before and after their oral fellowship exams. They found transiently elevated numbers of T and B lymphocytes prior to exam time, as well as a reduction in plaque forming cells and mitogen responses.

Other studies examining the effect of examination stress on immunocompetence have been done with groups of medical students. A study in which blood was drawn from 75 first-year medical students one month prior to and during an examination block over 3 days found alterations in immunocompetence during the exam period as compared with baseline measures (12). Natural killer cell activity declined from baseline to exam. Alterations in the percentage of helper and suppressor cells were also found. Similar studies with medical students found higher plasma IgG, IgM, and IgA during examinations (30), and lower percentages of total T-lymphocytes, helper T-cells, and suppressor T-cells; the response of T-lymphocytes to stimulation by two mitogens also declined during examination as compared to baseline (31). In two separate studies, a change in interferon (gamma) production by lymphocytes stimulated by Con A was found during examinations (30, 32). Gamma interferon is an important immune modulator, e.g. it is a major regulator of NK cell activity, and enhances their ability to destroy target cells (33). These data suggest that even a common, naturally occurring stressor, like examination stress can alter immune function.

Caregiving

The effect of chronic stress on behavior and
immunity is another area of interest to investigators. Examining the effects of stress over long periods of time can help determine if these effects are similar to acute stress, or whether some sort of adaptive mechanism exists in the human body that allows the body to adjust itself to the stressor. Applying chronic stress to an individual is virtually impossible from an ethical standpoint; however, researchers have turned to studying populations that experience naturally occurring chronic stressors, such as family caregivers for Alzheimer’s disease patients. The process of taking care of a demented family member with an unpredictable and uncontrollable disease has been conceptualized as a chronic stressor (34).

One study examined 34 men and women who were providing long-term care for a family member with Alzheimer’s disease (35). They found that caregivers had significantly lower percentages of total T-lymphocytes, helper T-lymphocytes, and helper/Suppressor cell ratios than sociodemographically-matched controls. Con A and PHA responses were down as well. They also found that these same group of caregivers had significantly higher antibody titers to EBV as compared to controls. In a longitudinal study, 69 spousal caregivers and 69 sociodemographical-matched controls were followed for 13 months (36). Caregivers had greater decrements across three measures of cellular immunity compared to controls, and the former also reported more days of infectious illness than the latter.

It is important to consider that the effects of caregiving on the immune system may be more complex than simply representing a response to a chronic stressor. AD caregivers have much higher rates of depression than sociodemographically-matched controls (37), and the effects of depression on the immune system were reviewed in an earlier section. In addition, as the need for caregiving increases, the amount of time the caregiver has for her/himself decreases; caregiving time demands often diminish other relationships and other support networks that individual may have had (34). These studies examining the effects of caregiving for dementia patients suggest that chronic stress does not lead to immunological adaptation in humans (37).

**Acute Laboratory Stress**

Although psychosocial variables can affect immunocompetence, few studies have examined how acute psychological challenges may affect immune function. These studies provide another way to study how the immune system responds during psychological stress.

Landmann et al. (38) used the Stroop color word conflict task to examine the effects of such a psychological stressor on both quantitative and qualitative changes of blood lymphocytes, monocytes, and granulocytes in a group of 15 young men and women. The numbers of circulating monocytes, B cells, and NK cells increased after the stressor compared to baseline measures.

Another study examined the effects of an acute laboratory stressor, mental arithmetic, and aging on the immune system in younger and older women (39). Their brief psychological stressor was associated with rapid immunological changes. In both the young and older groups, increases in numbers of circulating CD (8) suppressor/cytotoxic T cells
and NK lymphocytes followed the mental arithmetic task; NK cell activity increased in response to the stressor, but only in young women. The authors hypothesized that the absence of such an increase in the older population may indicate a difference in NK cell mobilization and cell lysis, as well as up-regulation of NK activity responses to stress related to aging.

Finally, a study using both the mental arithmetic and the Stroop color-word tasks found effects of these acute stressors on lymphocyte subpopulations and T-lymphocyte mitogenesis in a group of 25 males (40). These subjects were exposed to a 20-minute laboratory stressor in which the two psychological tasks were alternated every five minutes following a baseline period. Catecholamine and cardiovascular reactivity were also measured before and during the stressors. It is interesting to note however, that these stress-related changes in immune function were only observed in the subgroup of individuals who also experienced heightened catecholamine and cardiovascular reactions to stress. The researchers suggest that much of the variability of individuals' physiologic responses to stress may be related to behaviorally-evoked differences in sympathetic nervous system activation.

Mediation via the Endocrine System

It is now widely accepted that the biological effects of stress and other behaviors on the immune system are multifaceted and include complex neuroendocrine and neurotransmitter interactions. The response of the endocrine system to a variety of life experiences and psychological states is well documented. The most widely-studied hormonal connection with regard to stress and immune system modulation is the hypothalamic-pituitary-adrenal axis (41). However, recent studies point to other hormonal pathways that may be involved in the regulation of stress-induced immune system responses (42, 43).

**Hypothalamic-Pituitary-Adrenal Axis**

Many studies have examined the effects of hormones from the adrenal cortex on the immune system (44). One major group of stress hormones involved with immunosuppression are the glucocorticoids (3). The release of glucocorticoids, in which cortisol is predominant in humans, is regulated by a feedback system which begins at the level of the hypothalamus. During stress, signals to the hypothalamus stimulate the production Corticotropin-Releasing Factor (CRF). CRF works on the anterior pituitary to secrete the hormone adrenocorticotropic (ACTH), which stimulates the adrenal cortex to produce glucocorticoids.

Although most of the effects of CRF and ACTH on immunity are mediated by the glucocorticoids, there is some evidence that suggests both of these peptides may act alone to directly influence the immune system. Receptors for ACTH have been found on lymphocytes (45) as well as human and animal mononuclear cells (46). Administration of ACTH depresses antibody formation (47), produces atrophy of lymphoid tissue (48), suppresses inflammation (49), and prolongs survival of skin grafts (50). Inhibition of antibody responses to T-cell dependent and independent antigens and suppression of mitogen induction of interferon (gamma) by spleen cells due to ACTH in vitro have also
been observed (45, 51). Johnson et al. (51) discovered that lymphocytes have the ability to produce ACTH. Because of this finding, Blalock et al. (46) believe that CRF signals lymphocytes to produce ACTH when an organism’s immune system encounters a pathogen or other antigens. This neural signaling may be one of the ways in which the neuroendocrine system and immune system communicate.

Recent evidence suggests that CRF plays a modulatory role in NK cytotoxicity. Investigators found that intraventricular administration of CRF suppressed NK-cell activity, and this suppression could be antagonized by central preadministration of CRF antagonist (8).

Several investigators have shown that glucocorticoids have effects on various immune functions. Suppression of mitogen-induced lymphocyte stimulation (52) and induction of a redistribution of T cells and T-helper cells from the circulating pool in bone marrow (53) have been related to glucocorticoids. Others have found that recirculating lymphocyte traffic and response to PHA stimulation are sensitive to corticosteroids (54). Furthermore, these adrenal cortex hormones also exert effects on the production of such cytokines as tumor necrosis factor, IL-1 and 2, and interferon (gamma) (19). The discovery that both types of adrenal steroid receptors are expressed on immune tissues suggests that these hormones can influence the immune system directly (55).

There is also evidence that glucocorticoids are not necessary for stress-related immunosuppression. Keller and colleagues (56) found that adrenalectomy did not effect suppression of PHA-induced mitogenesis of T cells. A similar study showed that PHA-stimulated mitogenesis, NK activity, and IL-2 and interferon production were profoundly suppressed regardless of the animal’s ability to secrete adrenal hormones (57). The authors believe that while adrenal hormones may play a role in stress-induced suppression of the cellular immune response, secretion of adrenal hormones is not required to produce suppression. Therefore, despite the extensive ways in which glucocorticoids can influence and modulate immune function, attributing all immunological consequences of altered behavioral states to the adrenal cortex hormones oversimplifies the connection between the endocrine and immune systems.

Other hormonal activities

In addition to the HPA axis, changes in growth hormone, prolactin, endogenous opioids, and estrogen have been associated with both exposure to stress and modulation of the immune system.

1. Growth Hormone (GH) and Prolactin (PRL)

While the immunosuppressive effects of the glucocorticoids are well-known, prolactin and growth hormone can stimulate immune function. Studies in which animals have had their pituitary glands removed show deficits in both cell mediated and humoral immunological functions. These same studies demonstrate that either PRL or GH replacement therapy corrects for these deficiencies (3).

Growth hormone, secreted by the anterior pituitary, is involved in the stimulation of growth of body cells. The secretion of GH is
influenced by many factors. However, its release is mainly stimulated by growth hormone-releasing hormone (GHRH) from the hypothalamus. Elevations in growth hormone in humans have been observed during several different types of stressors. For example, the stress of surgery, electroshock therapy, physical exercise, and anxiety-provoking performance tests all enhance GH secretion (41).

With regard to immune function, deficiencies in GH are associated with depressed T-cell function, NK activity, and antibody responses, and some of these deficiencies can be repaired with administration of GH to the animals (42). Furthermore, a number of investigators have reported that lymphocytes have high-affinity GH-binding sites, therefore suggesting possible direct effects of the hormone on the immune system (3).

Prolactin (PRL), secreted by the anterior pituitary, is involved with the promotion of milk secretion by the mammary glands. Many types of physical and psychological stressors can elicit a surge in prolactin (41); the release of PRL is probably mediated via prolactin-releasing hormones from the hypothalamus, and regulated by other factors such as endogenous opioids and estrogen (43).

Russell and coworkers (58) showed that PRL can stimulate cells involved in immunity in vitro. In one study, NK cells from human blood were cultured in serum-supplemented medium containing PRL (59). The cytotoxic activity of the NK cells was found to increase. Additionally, similar to GH, many studies have reported the existence of PRL receptors on both lymphocytes and monocytes. Russell, et al. (60) isolated T and B lymphocytes from human spleens and found high-affinity PRL-binding sites. In a recent study from our laboratory, it was found that human peripheral blood mononuclear cells synthesize and secrete a PRL-like molecule. This molecule was observed to function in an autocrine loop, as a growth factor for lymphoproliferation (61). Other studies have shown that PRL- and GH-like compounds can be synthesized and secreted directly from cells that are involved in immune function (62).

Thus, the evidence to date indicate that PRL and GH are important regulators of the immune system and are secreted during stress. Although the evidence is conflicting, it appears that both hormones are capable of directly influencing cells of the immune system. More research examining the effects of GH and PRL on the human immune system is needed to understand the physiological significance of their influence as well as the importance of the synthesis of such products by immune cells.

2. Endogenous Opioids

Opioid peptides can alter such components of the immune system as antibody production, NK cell activity, and mitogen-stimulated lymphocyte proliferation (63). Further evidence that opioids have effects on the immune system comes from studies that show opiate addicts appear to be more susceptible to infections and have deficits in immune function (57).

Endogenous opioids can be released under a variety of stress-related circumstances (41). Studies of stress-induced analgesia show that stress can be a physiological trigger for intrinsic analgesia mediated by an opioid peptide mechanism or by a non-opioid
mechanism; these two interactions are produced by different types of stressors and stress situations. Physiological and behavioral differences have been observed between the two types of analgesia as well (64). Therefore, the type of stressor may affect the presence and levels of certain hormones and thus affect the type of immune modulation.

Foot shock paradigms are often used to examine the effects of opioid versus non-opioid stressors on various physiological and behavioral consequences. One study compared female rats that were exposed to intermittent foot shocks (producing opioid analgesia) with female rats that received continuous foot shocks (producing non-opioid analgesia) (65); exposure to the opioid, but not the non-opioid, form of foot shock stress resulted in significant suppression of NK cell activity, and this suppression was prevented by administration of naltrexone (an opioid antagonist). Similar studies have shown that morphine injections and single exposures to opioid form shock or a single morphine injection also produce suppression in NK cell activity (66).

It is important to mention that several physiological mechanisms may account for changes in the immune system seen during both morphine presentation and endogenous opiate release. First, the peptides released during stress may act directly on opiate receptors on various cells of the immune system. The effects of these peptides on NK cell activity may also be modulated via the autonomic nervous system. Finally, they may effect NK cell activity by their effect on hormone release such as ACTH. In this regard, the immunosuppressive effects of ACTH have already been mentioned, and opioids have been implicated in mediating the release of this hormone by activating the HPA axis (67).

Other studies examining the immunological consequences of endogenous opioids have focused on tumor growth. These studies show that rats subjected to opioid and not non-opioid foot shock stress prior to implantation of tumors have a reduced survival time and percent survival compared to nonstressed animals (68). Some tumor cells have opioid receptors. It is possible that opioids which are released during stress can affect tumor growth directly; however, it may also be that the mechanism involved in tumor growth enhancement is via the affect opioids have directly on the immune system, specifically on NK cell activity mentioned earlier.

Whatever the reason, exposure to opioids affects NK cell activity and tumor growth (65, 68). There is also evidence of opioid receptors located directly on various immune system tissues and cells (43). However, much work is still needed to examine how opioids affect the immune system, and the levels that these hormones have their effects.

3. Estrogen

The effect of female reproductive hormones on components of the immune system has become an important area of study in immunology because male and females differ with regard to some immune responses. Higher plasma immunoglobulin levels (69) and higher primary and secondary responses to a number of antigens (70, 71) have been observed in females compared to males. Females have a higher incidence of autoimmune disease such as
rheumatoid arthritis and systemic lupus erythematosus (72). Females are more likely than males to experience allergies after puberty (onset of menstruation); before puberty, males are more likely to experience allergies (73). These sex differences in occurrence of such immune disorders may be due to the increase reactivity of the female immune system, and that this hyperreactivity may be due, in part, to female reproductive hormones.

Estrogen, produced by the female ovary, and regulated by a feedback mechanism from the hypothalamus and anterior pituitary, is one of the major hormones of the female reproductive system. Estrogen has a depressive effect on both cell-mediated and humoral immunity. One study examining the effect of long-term treatment with synthetic estrogen found depressed mitogen responsiveness in female mice receiving estrogen compared to female mice not receiving estrogen (74). In addition, reduced NK cell activity has been associated with estrogen treatment (75).

Estrogen can have direct impact on many types of immune cells and tissues. Receptors for estrogen have been identified on the thymus of humans, mice, and rats (76), and estrogen may have direct effects on the action of lymphocytes. Paavonen, Andersson, and Adlercreutz (77) showed that immunoglobulin synthesis of B-cells stimulated by pokeweed mitogen (PWM) increased following estrogen inhibition of T-cell-mediated suppression. They also found similar increases in the number of plaque-forming cells induced by PWM-stimulation of human peripheral blood mononuclear cells. Furthermore, estrogen can mediate immune function indirectly by effecting other hormones (43). Elevations in estrogen influences growth hormone secretion, increases prolactin secretion, and suppresses glucocorticoid production (78). All of these hormones have been associated with the modulation of various components of the immune system, as discussed earlier in this section.

In addition to the effect of estrogen on the immune system, there have been several studies that have examined estrogen and stress responsivity. Estrogen, in particular estradiol, may actually work to attenuate both cardiovascular and endocrine responses to stress. Studies comparing responses to various stressors across different menstrual cycle phases or comparing pre- and post-menopausal females in have been conducted. Although the results are conflicting, there is some evidence that supports the idea that estrogen may decrease responsivity to stress (79).

Saab et al. (80) compared pre- and post-menopausal females and their response to various stressors. They found that post-menopausal females had significantly higher systolic blood pressure (SBP) responses to stress compared to pre-menopausal females. Another study found a negative relationship between SBP responses and estrogen levels during a mental arithmetic challenge in both normal menstruating and ovariectomized females (81). Estrogen replacement studies in post-menopausal females show post-menopausal females who are taking estrogen replacement therapy (ERT) have lower systolic blood pressure (82) and less hypertension (83) compared with post-menopausal females of equivalent ages who were not taking estrogen. Finally, studies comparing sex differences in reactivity to stressors have generally found that
females have significantly lower SBP responses to the stressors compared to males (84).

Since stress affects immunocompetence and estrogen may affect stress reactivity, it may be important to examine estrogen's role in the modulation of the immune system response during stress. However, there are very few studies that have examined estrogen's contribution to stress reactivity and the immune system, especially in humans.

In summary, there is good evidence that estrogen is involved either directly or indirectly in mediating some components of the immune system. These effects may provide one explanation for the sex differences that some investigators have observed in both immune reactivity and the incidence of autoimmune disease. In addition, there is also evidence that suggests the estrogen may act to attenuate stress reactivity, at least with regard to the cardiovascular and endocrine systems. Therefore, menstrual cycle phase and the presence of such female sex hormones as estrogen may be important contributors to the modulation of immune system response during stressful situations.

Conclusions

Although much remains to be discovered about the complex interactions between the immune system and psychological factors, the links between psychological distress and suppressed immune function are increasingly well-recognized. Reasons for individual variability in severity and duration of symptomatology and occurrence of infectious diseases are not well understood. However, various psychological factors may play a role in producing these individual differences.

In addition, a variety of studies have shown that stress is associated with alterations of immune function in both laboratory animals and humans, and several factors play an important role in determining these effects, including stress chronicity, the timing of stress application, stress intensity, and stress controllability. Studies comparing non-opioid and opioid forms of stress-induced analgesia also suggest that different types of stressors elicit different responses from the immune system.

Finally, the endocrine system serves as one mediator of immune function, particularly during stress. Prolactin, growth hormone, glucocorticoids, and estrogen all influence the immune system. Although the interactions are complex, many investigators believe that the immune system can be influenced by hormones from various endocrine tissues.
REFERENCES


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