



Psychoneuro Immunology (p.n.i) Of Stress

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Abstract

Considerable evidence demonstrating a relationship between stress and immune function is accumulating and a complex chain of biologic and psychologic processes are involved. An extensive network of central nervous system and endocrine system processes may be involved in the modulation of the immune system in response to stressors.

Introduction

An extensive literature links stress & the central nervous system & endocrine system. The immune system another major integrated network involved in proper adaptation. Considerable evidence demonstrates in a variety of stressful experiments of function. The present reviews experienced & clinical studies concerned with influence adverse effect on immunity as well as some of the psychologic mechanism that may be involved.

Concept of stress

Before reviewing specific aspects of the effects of stress on immune function, it is important to have a general understanding of the concept of stress. It has been used to encompass several different component of a broad frame work utilized in considering the effects of various stimuli on biological system. Stress is frequently used interchangeably with stressor to refer to an event or stimulus to which an organism is exposed. At other time, it is utilized to refer the response to a stressor & frequently, stress is defined as encompassing the process of stressor, reaction & of consequence.

The effects of stress on the body can be stressed to the work of Walter common. His experiments demonstrated the importance of the sympathetic adrenal medullary system in maintaining a steady state in the body, or homeostasis, in response to stressful psychologic events. In 1936 Seyle reported that the pituitary adrenal cortex axis also responds to stressful stimuli. Seyle subsequently developed a theory based upon series of studies which postulated that the pituitary adrenal cortex axis is also responds to stressful stimuli. Seyle subsequently developed a theory based upon the series pf studies which postulated that the pituitary adrenal cortical response was non specific and any noxious stimulus or stress or

would produce the response(1).

The emphasis on the non-specific biologic response to stressors has not been substantiated by further investigation. Mansen and other have shown that the nature of stress conditions may determined the specific pattern of response. If physical stressor for example is not perceived as noxious or alarming, the physiologic response induced may be smaller than the classical stress response or may be on the opposite direction. Both the public speaking and physical exercise produced increased plasma concentration of nor epinephrine & epinephrine. Nor epinephrine however is higher than epinephrine during exercise while epinephrine is quite higher than norepinephrine during the public speaking. Such finding emphasized the neccescity of considering the specificity of the stressor & the response also question the exclusive utilization of specific biologic responded as the basis for defining stress(2).

Recently, it has been proposed that three primary elements be delignated in a framework for considering stress, health & illness. This include an activator in the environment, the reaction to the activator, & the consequence of the reaction. A substrate of the activators is sufficiently intense or frequent to be considered as stressor. This conceptualization permits the identification of potential stressor for specific setting or individual & consideration of condition which make a potential stressor stressful. The suggestive framework also provides an approach to mediators which may be involved in the sequence of activators to reaction to consequence (4).

Stress and immune function

A variety of stressor have been found to alter humoral immune response in animals. Early studies indicated that avoidance learning stress decreased the susceptibility of mice to passive anaphylaxis and that the production of specific antibody could be suppressed in a variety of species by distressing environment stimuli such as noise, light, movement & housing conditions. Both primary & secondary antibody responses could be suppressed. However exposures to their stressor such as repeated low voltage electric shock were found to enhance antibody responses. More recent studies have tended to support the observation that while acute exposure to the stressor can suppressed humoral immune responses, repeated exposure result in an apparent adaptation of the animal to the stressor &,in some cases in an enhanced response. for example it has

been found that the restraint or crowding, presenting in single session of varying length induced suppression of antibodies responses but that after three days of repeated presentation of the stimulus the response had returned to prestress levels. Monjan & collector, using lip polysaccharides (LPS) to assess splenic B lymphocytes activity found that the exposure of mice to sound stress for up to 20 days suppressed the response, but more extended exposure resulted in an enhanced response(5). The complexity of stress effect on humoral immunity were further highlighted by Joasoo & McKenzie, who found differential effect of different stressor on antibody response in rats depending upon the sex of the animal. These studies suggest that the effect of stress on the humoral immune system is related to the nature & intensity of the stimulus as well as biologic and social characteristics of the organism.

A series of studies have investigated stress and cell mediated immune process. Monjan & collector study the effect of sound stress on the response of murine splenic lymphocytes to ConA. They found suppression of the response following short time exposure to the stressor and enhancement with extended exposure, which paralleled the findings with LPS. Reite and co-workers have studied separation experiences in primates and found decreased T cell mitogen responses following per separation for 2 weeks in pigtailed monkeys raised together from early infancy. Mitogen responses returned to base line with in several weeks of reunion. Studies from our laboratory have demonstrated a relationship between the intensity of acute stressor and the degree of suppression of T lymphocyte function in rat. A graded series of stressor applied over 18 hours including restraint in an apparatus, low level electric tail shock and high level shock, produced a progressively greater suppression of both the number of circulation lymphocytes and PHA induced stimulation of peripheral blood lymphocytes(6).

Laundenslager and Ryan (1983) have reported that stress induced suppression of lymphocyte stimulation may be related to the psychologic state of the animal. They found that PHA and Con A stimulation of lymphocyte was suppressed in rats & exposed to inescapable, uncontrollable electric shock for 80 min followed 24 hr later by several min of tail shock. Animal receiving the same total amount of shock, using a yoked paradigm, but able to terminate the stressor did not have decreased lymphocyte activity. These studies are consistent with hypothesis suggesting that the ability to cope with a stressor protects against its noxious effect (7).

Bereavement, depression and lymphocyte function

Conjugal Bereavement is among the most potentially stressful of commonly occurring life events & has been associated with increased medical mortality. The effect of Bereavement on immunity in a prospective longitudinal study of spouses of women with advanced breast carcinoma. Mitogen induced lymphocyte stimulation was measured in 15 men before & after the death of their wives.(8,9) Responses to PHA, ConA & PWM were significantly lower during the first 2 months post Bereavement compared with pre Bereavement response. The no. of peripheral blood lymphocyte and the percentage & absolute no. of T & B cells obtained during the pre Bereavement period were not significantly different from those in the post bereavement period. Follow up during the remainder of the post bereavement year revealed that mitogen responses have returned to prebereavement levels for the majority but not all of the subjects. Moreover, mitogen responses to prebereavement did not differ from those of age sex matched controls. These findings demonstrate the suppression of mitogen induced lymphocyte stimulation is a direct consequence of the bereavement event. It is important to emphasize, however that these biologic findings associated with bereavement do not adequately explain the epidemiologic findings increased morbidity and mortality following bereavement. It remains to be determined whether stress induced immune changes such as decreased mitogen responses are related to the onset or course of physical illnesses following life stress (10).

The processes linking the experience of bereavement with effects on lymphocyte activity are complex and remain to be determined. Changes in nutrition, activity & exercise levels sleep and drug uses which are often found in the widowed could influence lymphocyte function. Our subject, however, did not report major or minor persistent changes in diet or activity level or in the use of medication, alcohol, tobacco or other drugs & no significant changes in weight were noted. Further study is required to determine if subtle change on this variable related to the effects of bereavement on lymphocyte functions (11).

The effects of death of spouse on lymphocyte function could result from centrally mediated stress effects. Stressful life experiences may be related to changes in CNS activity associated with a psychologic state such as depression. Bereaved subjects have been characteristically described as manifesting depressed mood and a subgroup of bereaved individuals have been reported to have symptom patterns consistent with the presence of a major depressive disorder(12). Immune measures have recently been assessed in

clinically depressed individuals. The frequency of anti-nuclear-antibodies, which may reflect autoimmune processes, has been reported to be increased in patients with depression. More recently, investigators have begun to evaluate general measures of lymphocyte function in depression. Cappel et al reported that lymphocyte stimulation responses to PHA were lower in a group of psychotically depressed patients during the acute phase of their illness than following clinical remission. PHA responses in the depressed group did not differ, however, from those of control subjects at either time, making interpretation of findings difficult. Kronfol and coworkers reported that melancholic patients had lower lymphocyte responses to PHA, ConA and PWM than did groups of non melancholic psychiatric patients normal controls. These studies have been limited by the lack of age and sex match controls being studied stress on the same day as the depressed patients and by potential interaction between medication effects and lymphocyte functions (13).

We have conducted a series of studies to determine if depressive disorders are associated with altered immunity. Mitogen –induced lymphocyte stimulation and the number of peripheral blood lymphocyte were measured in hospitalized and ambulatory patients with major depressive disorders. Each subject was studied on the same day with an age and sex matched apparently healthy control. Depressed subjects were included if they met research diagnostic criteria (RDC) for major depressive disorder, had Hamilton depressive scale score of 18 greater, free of acute chronic medical disorders associated with immune alterations, and were drug free.

In the severely depressed hospitalized patients with major depressive disorder we have found evidence altered immunity. Lymphocyte stimulation PHA, conA and PWM was significantly lower in the group of hospitalized depressive than in the controls. The total number of T and B cells was also lower in the depressed patients, but the percentage of the cell types did not differ between the groups. The findings demonstrate that the functional activity of the lymphocyte as well as number of circulating immunocompetent cells are decreased individuals hospitalized with acute major depressive disorders(14).

In order to determine with altered immunity is associated specifically with depression and not related to hospital effects or non specifically to other psychiatric disorder. We investigated lymphocyte function in ambulatory patients with major depressive disorder and in patients hospitalized with schizophrenic disorder. Responses to PHA, ConA and

PWM were similar among depressed out patients and controls. The finding of no significant difference in mitogen responses between ambulatory depressive controls, in contrast to our previous findings of suppressed responses to same mitogen in hospitalized depressive, suggested that the decrease mitogen response in the patients depressive may be related to hospitalization severity of depression.

A group of hospitalized schizophrenic patients were studied and reported no differences between the hospitalized schizophrenic and their controls in the response to mitogen nor on any of the quantitative lymphocyte measures. The findings suggest that hospitalization on a psychiatric unit is not in itself sufficient to result in change mitogen responsiveness or the number of peripheral blood lymphocyte. It is possible, however, that schizophrenic patients are not directly comparable to inpatient depressive because they have a typical responses to hospitalization. The effect of hospitalization on lymphocyte function was therefore studied in a group of otherwise healthy patients for electric herniorrhaphy, and no significant were found between the Herniorrhaphy and match the controls.

The decreased mitogen responses in hospitalized patients with major depressive disorders but not in ambulatory depressed patients suggests that the altered immunity in depressive may be related to severity of depression symptomatology. By clinical and Hamilton rating scale measures, the ambulatory patients were less severely depressed as compared to hospitalized patients. This preliminary observation of an association between altered functions and severity of depression suggest that immune changes may be related to underlying biology processes in depression, such as a neurotransmitter defect which could be neuroendocrine dysregulation and alterations. Nor – epinephrine, for example, has been shown to have an inhibitory effect on several neuronal subsets in hypothalamus and there is evidence that nor epinephrine has a tonic inhibitory on ACTH and cortisol secretion. A norepinephrine deficiency in depressive disorder has been hypothesized to contribute to the hypercortisolemia associated with depression

Medication of stress effect on immune functions

A variety of factors may be involved in mediating the association among stress, depression and immunity. The endocrine system highly responsive to both life experiences and psychologic state and has a significant, although complicated, effect on immune processes. The most widely studied hormones are those of the hypothalamic – pituitary – adrenal(HPA)axis. A wide range of stressful experience are capable of inducing the release of

corticosteroids and, a noted, cortisol secretions is increased in major depressive disorders. Corticosteroids have extensive effects on immune the immune system. Of particular interest in relation to our findings of decreased number of lymphocyte and lower mitogen response in depression is the demonstration pharmacologic doses of glucocorticosteroids diminished mitogene induced lymphocyte stimulation and induced redistribution T cell from the circulating tools to the bone marrow. Several reports have demonstrated that recirculating lymphocyte traffic in humans is sensitive to endogenous corticosteroids and varies in relation to endogenous cortisol levels, as does the response to PHA stimulation.(15)

Secretion of corticosteroids has long been considered to the mechanism of stress induced modulation of immunity and related disease processes. The regulation of immune function in responses to stress, however may not be limited to corticosteroids. as previously noted we have shown in rats unpredictable , unavoidable tail shock suppressed immune function as measured by number of circulating lymphocyte and PHA stimulation in an effort to determine if the adrenal is required for stress – induced suppression of lymphocyte function in the rats, we investigated the effect of stressor in adrenalectomized animals. Four groups of rats were studied and consisted of non operated adrenalectomized, sham adrenalectomized, and adrenalectomized animals with home acge control. There was a progressive increase in corticosterone with increasing stress in both of the group with adrenals no corticosterone was detected in the adrenalectomized group , and concentration of corticosterone in the adrenalectomized group received the corticosterone pellets was constant. The corticosterone levels in the sham adrenalectomized group indicated that the two weeks post operative period was sufficient to allow recovery to base line corticosteroid level and that the operative procedure did not effect stress – related corticosterone response. The steroids levels adrenalectomy group confirm total adrenalectomy . the adrenalectomy plus corticostreone pellet group showed intermediate corticosterone levels which were non responsive to the stress conditions.

Both the nonoperated and the sham-operated groups, there was significantly progressive stress-induced lymphopenia. There were no stress related changes in lymphocyte number in the adrenalectomized or adrenalectomized with pellet pellet groups. Lymphopenia following exposure to stress was described as early as 1937 and has been associated with adrenal hypertrophy and involution of the thymus and spleen. It has been shown that stress induced

induced leucopenia can be prevented by adrenalectomy in mice. The findings of our study demonstrate that stress-induced lymphopenia in the rat occurs in association with stress-induced secretion of corticosteroids and can be prevented by adrenalectomy.

The stressful conditions suppressed the stimulation of lymphocytes by PHA in adrenalectomized animals. The stressors similarly suppressed PHA responses in nonoperated animals, replicating our report ,in sham – adrenalectomized rats, and in adrenalectomized animals with steroid replacement. These findings demonstrate that stress –related adrenal secretion of corticosteroids and catecholamines is not required for the stress –induced suppression of lymphocyte stimulation by the T cell mitogen PHA in the rat. It may well be the that there is an adrenal – independent stress –induced depletion of subpopulation of T cell function or a selective redistribution to lymphoid tissues. A variety of other hormonal and neurosecretory systems may be involved in the adrenal- independent stress –induced modulation of T cell function. Because corticosteroids have been reported to have differential effects on T and B cell populations. Further studies are required to investigate the role of adrenal hormones in stress effects on B cell functions.(16)

Our findings of adrenal – dependent stress – induced lymphopenia and of adrenal – independent effects on lymphocyte stimulation indicate that stress – induced modulation of immunity is a complex phenomenon involving several, if not multiple mechanisms. Changes in thyroid hormones, growth hormones, and sex steroids have been associated with exposure to stressors and all have been reported to modulate immune function. More recently, an immunoregulatory role has been suggested for a variety of stress related peptides such as beta endorphin. Further, we and others have shown that the hypothalamus, which plays a central role in neuroendocrine function, modulates both humoral and cell mediated immunity. These findings suggest that a range of neuroendocrine processes may be involved in stress – induced altered immunity.(17)

There is good evidence that influence other than hormonal are involved in CNS regulation of immunity. It has been demonstrated in hypophysectomized rats that anterior hypothalamic lesions result in an increase in the number of thymic lymphocytes and a decrease in mitogen response. A differ link between the CNS and immunocompetent tissues has been suggested by the demonstration of nerve endings in the thymus, spleen and lymph nodes. The thymus has also been shown to receive direct innervation from the nucleus

ambiguous. These findings along with the presence of adrenergic and cholinergic receptors on the lymphocyte surface further the possibility of a direct link between the CNS and the immune response to stressors and the association with psychologic states such as depression.(18)

Conclusion

Recently, it has been demonstrated that there is decreased nor-epinephrine turnover in the hypothalamus of the rat at the peak of an immune response, and it has been suggested that the immune response, exerts an inhibitory action on central noradrenergic neurons as a result of mediators released by immunologic cells. Furthermore, it has been shown that the lymphocyte can secrete an ACTH – like substance following viral infection(19). These findings suggest the presence of a neuroendocrine-immunoregulatory feedback process associated with aminergic circuits within the CNS.

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