Nociception and the Neuroendocrine-Immune Connection

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Linking the Central Nervous and Immune System

There are several pathways through which the central nervous system (CNS) and the immune system interact (1, 2). For example, there are nerve endings in lymphoid organs such as the spleen and lymph nodes and some of these nerve terminals have direct contact with T-lymphocytes. The endocrine system is also an important mediator between the CNS and the immune systems; certain hormones such as cortisol and prolactin can regulate some aspects of cellular immunity (3-5). Receptors to neuropeptides such as adrenocorticotropic hormone (ACTH) have been identified on the surface of lymphocytes, and lymphocytes produce certain hormones such as ACTH and prolactin (5, 6). The demonstration of neuroimmunomodulation may partially explain anecdotal observations in animals and humans suggesting that certain kinds of stressors may increase risk for infectious disease and cancer. This area of study has included the examination of the immune response in association with severe affective states such as depression, as well as minor stressors like academic examinations (7-9).

Psychological stress can result in changes in a variety of hormones. It is thought that response to emotional stress is initiated in the hypothalamus, which ultimately modulates the release of pituitary hormones (10, 11). In addition, catecholamines are released and initiate a secondary cascade of hormonal effects. McCabe and Schneiderman (12) provide a model of host coping in which individual differences in coping responses may lead to differences in neuroendocrine profiles following exposure to stressors. Specifically, elevations in plasma catecholamines and cortisol associated with stressful events are often accompanied by decreases in cell-mediated immunity. For example, epinephrine infusions in humans produce decreases in leukocyte number and lymphocyte proliferation in vitro, probably mediated by increased cyclic AMP (cAMP) levels (13). Our previous research has found elevations in cAMP in peripheral blood leukocytes (PBLs) in studies measuring the impact of academic stress on cellular immunity (14). This is significant in that it has been shown that intracellular cAMP down-regulates lymphocyte proliferation and cytotoxic function (13), as well as increases herpes virus reactivation and shedding (15).

Plasma corticosteroids and catecholamines can be elevated by stressors; however, additional hormones such as growth hormone, somatotropin (16), ACTH (17), melanocyte-stimulating hormone (18), prolactin (19), thyroxin, glucagon, renin, erythropoietin, and gastrin also appear to be modulated by stress (7, 20). The impact of changes of these hormones on the immune response in animals is reviewed by Landsberg (21). These changes include progressive atrophy of lymphoid organs, reduction in natural killer (NK) cell activity, depression in the blastogenic response of lymphocytes, and changes in the percentage of lymphocytes and subpopulations of
lymphocytes. Many of these inhibitory effects can occur even in the presence of low concentrations of hormones (22).

Another mechanism of CNS/endocrine induced immune impairment involves corticosteroids, such as cortisol, which inhibits cellular immunity by impairing production of cytokines such as interleukin-1 (IL-1), interleukin-2 (IL-2), gamma-interferon (γ-IFN), and macrophage migration inhibitory factor (MIF) (23-25). By altering these important lymphokines, a disruption in normal immune system communication results and impairs an effective expression of the immune response.

Detrimental consequences may result from such immunosuppression: in, for example, Epstein-Barr virus (EBV) and Human Immunodeficiency virus (HIV) infected individuals. Progressive loss of cellular immunity increases the likelihood of latent EBV reactivation and subsequent disease progression from uncomplicated HIV seropositivity to AIDS-related complex and AIDS. It has been shown that hydrocortisone can induce latent EBV and enhance CMV replication in vitro (26-29) as well as enhance HIV replication (30). Therefore, as investigations of the behavioral stress—CNS—endocrine—immune—viral reactivation pathway progress, the more we find how complex these multiple interactions are. Simple cause and effect relationships are very difficult to show, although theoretically, the contribution of behavioral stress to viral reactivation seems plausible.

Stress and Infectious Disease

Several studies have found relationships between infectious disease and life stress. For example, Meyer and Haggerty (31) found that chronic stress was related to an increase in streptococcal infection. In another study, Jacobs, Spilken, and Norman (32) selected students who were either healthy or displayed symptoms of respiratory infection and found that the ill subjects reported a higher number of life events involving personal failure or role crisis and more unpleasant affect—more depression, hostility, and anxiety—compared to their healthy counterparts. Similarly, McClelland, Alexander, and Marks (33) found that prisoners who were experiencing a high degree of self-reported stress (i.e., aggravations, worries, upsets, obstacles, and sources of tension and stress) had more severe upper respiratory illnesses than did other prisoners reporting lower levels of stress. In general, psychological stressors such as life change stress, dissatisfaction with life, family related stress, or emotional stress have all been associated with risk for infectious disease (reviewed in 34).

Since psychosocial factors affect immunity, such factors might also be related to the incidence of acute infections. For example, Hinkle and Plummer (35) showed that the greater the degree of dissatisfaction, the greater the number of acute respiratory illnesses telephone company employees reported. In a subsequent study, Hinkle (36) followed telephone operators once a week for 6 months. The subjects were examined and interviewed by a physician, and viral and bacterial cultures were obtained; color photographs of their noses and throats were also obtained to measure
clinical changes. In addition, the subjects kept daily records of events and situations in their lives. The findings suggested that past experience with respiratory illness predicted the incidence of such illness during the study, and life events that occurred with self-reported sadness were likely to be followed by an acute respiratory illness.

Other relevant research has focused on children, who have a greater incidence of infectious disease than adults, probably due to increased contact in day care, school, and other activities. Meyer and Haggerty (31) followed 16 lower-middle-class families for 12 months, each with two or more children, recording life events that were distressing to the family or to particular members. They also collected throat cultures every 3 weeks, analyzed them for evidence of streptococcal infection, and had medical personnel conduct examinations to detect clinical signs and symptoms of streptococcal respiratory illness. Among family members, particularly children 2 years of age or older, a greater degree of family-related stress occurred during the 2-week intervals before both documented infection and clinical acute respiratory illness than had occurred during the 2-week intervals after such infection and clinical disease.

Collectively, these studies suggest that chronic stress may contribute to the development of an opportunistic infectious disease. In the last 30 years, a number of studies have examined the relationship of psychosocial factors with the etiology and course of infectious mononucleosis in a college population. Greenfield, Roessier, and Crosley (37) investigated the length of recovery from infectious mononucleosis among 38 patients at a university health service. Using medical records which included white blood cell counts, percentage of lymphocytes, and the presence of atypical lymphocytes, the investigators were able to classify the patients as having a slow or a quick recovery from the disease. It was found that the quick recovery group scored higher on psychological inventories (i.e., greater mental health) administered 6 months after recovery of the disease than did the slow recovery group. Although these data suggest that psychological factors may affect recovery from infectious mononucleosis, it is equally possible that the length of recovery affected the psychological health of the individuals.

In a related study, Kasl, Evans, and Niederman (38) investigated the relationship between stress and duration of clinically diagnosed EBV-associated infectious mononucleosis. The study involved 1400 incoming students at the West Point Military Academy. The students were classified as EBV sero-positive or negative and therefore either susceptible (if antibody negative) or immune to EBV infection (if antibody positive). From this study, the investigators were able to observe the interactions between motivation and performance in terms of the effect of stress. That is, having a high motivation for a military career was associated with developing clinical disease among cadets whose academic performance was poor. In addition, Kasl and colleagues (38) also reported that they were able to predict seroconversion among susceptible students (who did not actually manifest clinical disease) as well as the length of hospitalization among those who did manifest the disease. These data, consistent with the Greenfield et al. (37) study, suggest that psychosocial factors can affect the length
of recovery from an infectious disease.

Recently, the contributions of psychological stress on the pathogenesis of infectious disease have been examined in greater detail (34, 39). For example, Cohen, Tyrrell, and Smith (40) studied the effect of psychological stress on host resistance to infection to a variety of respiratory viruses. Psychological stress was associated in a dose-response manner with an increased rate of acute infection and clinical colds, as opposed to an increased frequency of symptoms after infection, as typically investigated. Strengthening this claim, the associations observed were similar for each of five virus strains, and were independent of health behaviors (e.g., smoking, alcohol consumption, exercise, diet, sleep) or other confounds (e.g., age, sex, allergic status, weight).

We recently studied the effect of examination stress and social support on the ability to generate an antibody response to the recombinant hepatitis B surface antigen (HBsAg) vaccine (41). Students who reported high levels of stress and anxiety showed a delay in seroconversion to the HBsAg compared to their low stress and anxious counterparts. In addition, following seroconversion, those who reported less social support had a poorer immune response to the HBsAg, as determined by both antibody titers and the blastogenic response to the HBsAg. These data suggest that psychological stress can modulate the specific immune response to a number of viruses which may impact on the infection rate as well as the rate of seroconversion to a standard vaccination protocol.

Investigating one possible mechanism which might explain the stress-infectious disease relationship, Levy and colleagues (42) measured plasma beta-endorphin levels prospectively in an attempt to explain infectious illness outcome variance in subjects with low NK activity. Their findings suggest that the low NK activity might be related to circulating beta-endorphin, since lowered endorphin levels predicted lowered NK activity which in turn predicted greater illness morbidity.

It appears that psychological stress may have alter both the pathogenesis as well as the symptomatology of infectious illness. Data from these studies highlight the interactions between family, academic stress, and general life stressors with streptococcal infections, rhinovirus infections, infectious mononucleosis, and response to a vaccine. Collectively, there appears to be growing evidence that stress impacts on the morbidity of infectious illness, and this relationship may be mediated via the immune and endocrine systems.

**Stress and Herpes Virus Latency**

The reactivation of latent EBV and other herpes viruses is not well understood. Normally, after the primary herpesvirus infection, the virus latently infects certain target cells where the viral genome is maintained for life. In individuals who become immune suppressed, either naturally by infection with other viruses or, for example, after radiation therapy in cancer patients, antibody titers to one or more of the herpes viruses, including HSV-1, EBV, and CMV, often increase. These antibody increases are thought to be the result of the humoral (memory) immune response to the elevation in virus-specific antigens after
reactivation. There may or may not be clinical signs of disease. It is thought that the cellular immune response is very important for the limitation of the primary infection and controlling the expression of latent herpes viruses because clinical disease can occur in the presence of high levels of circulating antibody in the serum (43-45). Following infection, EBV has the capacity to infect B-cells and epithelial cells in the nasopharynx. It is the responsibility of memory T cells to keep latently infected B cell growth under control and to limit the replication of latent virus.

Using a prospective design, Glaser, Kiecolt-Glaser, Speicher and Holliday (46) studied stress-associated reactivation of EBV. A significant change in EBV virus capsid antigen (VCA), CMV, and HSV-1 antibody titers across three sample points was observed. In addition, high-loneliness subjects had significantly higher EBV-VCA antibody titers than low-loneliness subjects, suggesting greater virus reactivation. Because it was possible that fluctuations in total IgG antibody (polyclonal activation) could have explained the above differences, antibody titers to poliovirus type 2 were assessed. No significant change in antibody titers to poliovirus type 2 was found in the same samples in which changes to the three herpes viruses was found, supporting the hypothesis that the herpesvirus data reflect stress-related changes in virus latency and reactivation.

This data were confirmed in several studies investigating both chronic and acute physiological stress. Using an examinations stress model, Fittschen and colleagues (47) reported that subjects who reported high levels of stress (i.e., challenge) during the examination periods evidenced the highest levels of antibody to HSV-1. Similarly, McKinnon and colleagues (48) reported that individuals living near the damaged Three-Mile Island nuclear reactor plant for more than six years had higher antibody titers to both CMV and HSV-1 compared to controls living near a coal-burning plant, and these antibody titers could not be explained by total IgG, IgM or antibody to rubella virus. Together, these data suggest that under high perceived levels of stress, there is greater reactivation of several latent herpes viruses.

Recently, Esterling, Antoni, Kumar and Schneiderman (49) investigated other individual difference measures (i.e., repression and sensitization) to determine chronic differences in latent EBV reactivation. Those individuals with personalities characterized as overbearing, aggressive, rivalrous and confident, had a low level of frustration tolerance, and who are quick to express their negative feelings (i.e., Sensitizers) had the lowest levels of antibody to EBV, suggesting the highest physiological control over latent EBV. In contrast, those individuals who were characterized as having an inner need to deny negative feelings to themselves and others, who tended to appear content in the face of problems, and who attempted to please others with self-sacrificing behaviors (i.e., Repressors) had the highest levels of antibody to EBV. It was hypothesized that subjects who abstained from disclosing emotional material, and similarly, those subjects with psychometrically-derived Repressive interpersonal styles on a laboratory task, would have the highest levels of antibody to EBV. Controlling for immunological confounds those individuals classified as Sensitizers had the lowest levels of antibody (i.e., highest control of latent EBV) if they disclosed high
frequencies of emotional words when given the opportunity to express their stressful event in a written format. In contrast, those individuals classified as Repressors as well as those with the former personality structure but who showed low levels of emotional disclosure on the behavioral task had the higher EBV levels of antibody.

While this evidence suggests that control of latent EBV in individuals differs as a function of ruminative style, there is evidence that EBV may affect mood directly. A possible mechanism that could explain these observations is as follows; stimulated lymphocytes reacting to EBV produce as yet uncharacterized molecules that substantially alter norepinephrine activity in the hypothalamus (50). Activated lymphocytes secrete soluble factors (i.e., interleukins) that stimulate cortisol secretion not only through the hypothalamus (50), but also directly via the adrenal gland (lymphoid-adrenal axis) (51). Biological changes associated with depression include altered norepinephrine activity in the brain and elevated serum cortisol levels (52) and may underlie the mood alterations found with EBV infection. In addition, individuals with depressive symptoms, there is a positive correlation between repressive behavior, personality pathology as measured on the Minnesota Multiphasic Personality Inventory (MMPI), and plasma cortisol secretion rate following a stressful event (53). This finding may be relevant since it has been shown that cortisol impairs several components of cell-mediated immunity (7, 23). Vickers (53) reviewed 5 studies (54-58) which showed that over 16% of the variance in cortisol levels could be predicted from emotionality scores. These studies provide evidence for one possible neuroendocrine mechanism that could explain these observations.

In support of the Repressive personality hypothesis, Jamner, Schwartz and Leigh (59) found that individuals characterized as Repressors had decreased monocyte and eosinophile counts, as well as serum glucose levels. In addition, Broadbent, Broadbent and Hildopen (60) investigated the association between psychological factors and rhinovirus shedding following rhinovirus and influenza virus challenge. Assessments of virus shedding showed a higher degree of infection by rhinovirus in the subjects classified as introverts than in those classified as extraverts classified by the Eysenck Personality Questionnaire. Subjects with higher obsessional symptom scores had increased nasal secretion after infection by either type of virus. Together these data suggest a plausible role for a Repressive personality style in the control of virus infection (EBV, rhinovirus, influenza virus) as well as general cellular immune disregulation.

Immune function generally declines with age both in humans and in laboratory animals. For example, T-lymphocyte-mediated immune function for the production of certain autoantibodies, such as antinuclear antibodies, tends to increase with aging (61-64). For example, although there are no changes in plasma levels of IgM, two other immunoglobulins IgG and IgA, are elevated in older individuals (62). In order to examine another aspect of cellular immunity and control of the latent EBV genome under natural conditions in otherwise healthy individuals, Glaser, et al. (65) examined EBV reactivation in a geriatric population. EBV-VCA IgG and
IgA as well as EBV early antigen (EA) IgG were assayed to determine if there were any differences in the antibody patterns to these antigens when compared to a younger population, the medical students. The EBV-EA geometric mean titer (GMT) in the medical students was lower than the EBV-EA GMT of the geriatric group. A similar significant difference was found between EBV-VCA IgG as well as IgA GMTs in the two populations as well. At no time during the course of the study did any of the geriatric participants complain of any health problems. The data suggest that there may be some loss of control over latent EBV in geriatric individuals, presumably because of a less efficient cellular immune response; a similar observation was made for CMV (66). Overall, the data suggest that down-regulation of the cellular immune response, due to aging or because of psychological factors such as academic stress, can result in reactivation of latent herpes viruses.

Following this line of reasoning, Glaser, and colleagues (14) investigated the linkages among distress and changes in antibody titer to EBV and EBV-specific T cell killing. Consistent with prior work, antibody titers to EBV increased during examinations periods. In addition, T-cell killing by EBV-specific memory T lymphocytes declined during examination periods compared to baseline levels.

In exploring the antibody response to EBV, it is possible that changes in antibody levels could reflect complete or partial activation of the EBV genome. In order to determine if increases in antibody titers in a healthy population could be due to partial reactivation, the antibody response to specific EBV polypeptides were assessed as a function of examination stress (67). Although EBV-VCA antibody titers increased as traditionally measured by immunofluorescence (IF) during examinations compared to baseline, no significant changes in antibody titers were observed in two late viral proteins (the 125 Kd VCA polypeptide and the Gp 350/300 membrane antigen), or an early protein (the 85 Kd EA-R). However, antibody titers to the diffuse early antigen (EA-D 52/50 Kd protein) were modulated over the course of the study, supporting a partial activation hypothesis. Some individuals who did not have antibody titers (i.e., <1:2) to the 52/50 Kd EA-D polypeptide became antibody positive and vice-versa over the course of the study. This suggested that the expression of the gene encoding for this protein was down-regulated sufficiently to cease the production of this protein, or alternatively, that the production of the protein was sufficiently down-regulated to reduce the amount of antigen available to stimulate antibody production. Since the antibody data for the 52/50 Kd EA-D polypeptide was not identical to that of the IF data, it is probable that other proteins were modulated at different time points which were reflected by the ability to measure antibody titers by IF.

Several studies from our laboratory have found significant decreases in NK cell activity using both K562 cells and MOLT-4 cells (68, 69). In these same studies, changes in total IFN production by concanavalin A (Con-A)-stimulated PBLs taken at baseline and at the time of examination were measured. The production of IFNs by Con-A-stimulated lymphocytes declined sharply from baseline to
the examination samples, although no measurable plasma levels could be detected in either sample point, as expected (68). These data were confirmed in a second study in which the ability of Con-A-stimulated PBLs to synthesize γ-IFN was markedly inhibited during the examination periods as compared to baseline controls (14). These data demonstrate a very large and significant decrease in the amount of γ-IFN produced by Con-A-stimulated PBLs obtained from medical students during a psychological stressor (i.e., examinations) compared to baseline values obtained 6 weeks earlier. Since certain “stress hormones” such as cortisol have been shown to reactivate latent EBV and enhance virus replication in vitro as already discussed, and since a variety of hormones increase during stressful events, it is not unreasonable to propose that these events are interrelated and could account for stress-associated reactivation of latent herpes viruses. Future studies are necessary to explore this scenario.

Stress-Management

Healthy Subjects

Since stressful events such as examination, restraint, emotional inhibition, and depression may lead to viral reactivation, it seems plausible to explore the idea that by managing stress one may modulate such reactivation. Relaxation is one effective treatment component of stress-management. Since stress is a major factor in psychosomatic illness and a contributing factor in psychiatric conditions, the idea of using stress-management as a buffer to the experience of stress has been used in the treatment of stress-related disorders, anxiety, and behavior disorders related to tension.

Since data from several laboratories suggest that a variety of stressors may affect the immune response, Kiecolt-Glaser, et al. (70) assessed the enhancement of two measures of immune function, NK activity and antibody titers to HSV-1 as a reflection of cellular immune control of this latent virus. They employed either relaxation or just social contact in a geriatric population. At the end of a one-month intervention, the relaxation group showed an increase in NK cell activity, and a significant decrease in antibody titers to HSV-1 and self-rated distress. The social contact and control groups showed nonsignificant changes. In addition, there was an increase in the T lymphocyte response to PHA stimulation at the end of the intervention, with greater change at lower mitogen concentrations. This study was one of the first to show that cellular immunocompetence may be modulated (enhanced) by a relaxation intervention.

As a follow-up to this study, Kiecolt-Glaser, et al. (71) assessed the psychosocial modulation (using a hypnotic relaxation training intervention) of certain aspects of cellular immunity in medical student volunteers. By collecting blood one month before, and on the last day of examinations, these investigators were able to explore the interaction of stress (i.e., examination) and relaxation training. Significant declines in the percentage of helper/inducer T lymphocytes, in the helper/inducer—suppressor/cytotoxic-cell ratio, and in NK cell activity in the blood samples obtained on the day of examinations compared to baseline levels were found. In addition to specific distress-buffering effects in those who practiced this technique, frequency of relaxation practice was a significant predictor of higher percentages of helper/inducer cells during
examinations.

At-Risk Subjects

In a population at risk for HIV infection, Antoni, et al. (72) investigated the ability of a cognitive behavioral stress management (CBSM) group intervention to buffer the affective distress and immune suppression associated with HIV serostatus notification. In this design, healthy gay men were randomly assigned to a CBSM condition or a control condition 5 weeks prior to notification. Blood was collected 72 hours before serostatus notification and one week after notification. It was found that CBSM was effective as a buffer of both psychological distress in individuals exposed to the acute, life-threatening stressor of notification, as well as up-regulating components of the cellular immune response. Specifically, the immunoenhancing buffering effect included increases in helper/inducer (CD4+) and NK (CD56+) cell counts as well as a slight increment in proliferative responses to PHA.

Although not investigating mechanisms of viral activation, Burnette and colleagues (73) investigated the clinical recurrence rate (an indirect measure of viral activation) of genital herpes using a multiple baseline across subjects design. After a minimum of 3 months of daily baseline recording of the presence of a herpes related lesion, subjects were individually trained in standard progressive muscle relaxation and were instructed to use the skill whenever they felt stressed. After 3 months of practice, 5 of the 8 subjects showed a decrease in recurrence frequency of 40% or greater. Similarly, relaxation training was compared to social support and a waiting-list control in the control of latent virus activity (74). After 6 consecutive weekly 90-minute group treatment sessions, individuals receiving the relaxation intervention reported significantly greater reductions in herpetic lesions, and significant improvements of emotional distress, social support, and cognitive measures when compared with the other individuals. These results suggest that stress reduction strategies may be effective to some extent in modulating HSV reactivation.

In addition to relaxation training, there is evidence that aerobic exercise training may also have immune enhancing effects which may buffer stress-induced deteriorations in physical health (75, 76). Aerobic exercise has been proposed as an important resistance resource against illness which may act by decreasing or buffering life stress (77, 78). Brown and Siegel (79) investigated stress and well-being in adolescents to examine the ability of exercise to buffer stress-induced deteriorations in physical health. The negative impact of stressful life events on health declined as exercise levels increased; exercise may be one resource for combating life stress.

Recent evidence from a study with an HIV seropositive population is consistent with the above findings. LaPerriere, et al. (80) investigated the effects of an aerobic exercise training program on stress reduction and immune function for individuals at risk for AIDS. Following aerobic exercise training, subjects showed a significant increase in CD4+ cells and the inducer subset (CD45RA+CD4+) which activate suppressor/cytotoxic (CD8+) cells. Interestingly, the increases noted are comparable to that achieved by the AIDS drug
azidothymidine (AZT), but without the accompanying side effects. In another study, the impact of aerobic exercise training as a buffer of the immune decrements found concomitant with the notification of HIV antibody status in an AIDS risk group was studied (81). After 5 weeks of aerobic exercise training, the HIV seropositive controls showed significant decrements in NK cell number following notification, whereas HIV seropositive exercisers showed no similar changes and in fact, resembled the virus seronegative groups. The data suggest that further studies explaining these interesting observations on attenuated effects by an experimentally-manipulated aerobic exercise training intervention be performed. In investigating the effects of aerobic exercise training on lymphocyte subpopulations, aerobic exercise training results in a significant increase in predicted maximal oxygen consumption and is accompanied by increases in total T cells (CD2+), CD4+, CD45RA+CD4+, CD8+ and B (CD20+) cell counts (75).

Aerobic exercise training may also improve autonomic reactivity allowing the aerobically-trained individual to cope more effectively with psychosocial stressors (82), improve social support, decrease anxiety and depression (83-85), and increase self-esteem (86). Aerobic exercise training may also buffer the impact of anxiety and depression in response to notification of a positive HIV serologic finding in an HIV seropositive cohort (80).

Because of the evidence that there may be buffering effects of CBSM and aerobic exercise on immunological and psychological endpoints as noted earlier, we were interested in determining whether these interventions could have implications for control of latent viruses. We investigated whether the CBSM and exercise interventions could attenuate reactivation of EBV or Human Herpesvirus-6, (HHV-6) in a sample of HIV-1 seropositive (HIV+) and seronegative (HIV−) gay men (87). As expected from the literature (88), the HIV+ men had higher levels of antibody to EBV-VCA, compared to the HIV− counterparts at each of six measurement times throughout a 10 week study period. In comparison, no significant differences were noted for antibodies to HHV-6, although both the HIV+ and HIV− subjects had significantly higher antibody titers than a group of laboratory controls. The HIV+ subjects were found to have lower CD4 cells, CD4:CD8 ratios, and a poorer blastogenic response to PHA, as well as higher CD8 cells at baseline. No differences were found, however, between the HIV+ and HIV− subjects in levels of anxiety or depression at baseline.

When investigating the effects of this intervention, it was found that the HIV+ and HIV− subjects, respectively, who participated in either the CBSM or aerobic exercise groups had significant decreases in antibody to EBV-VCA and HHV-6 over the 10 week study period. However, those subjects assigned to the assessment-only control group had no significant change over the same time period, and remained consistently higher than either behavioral intervention group. These data are consistent with our earlier study with geriatric individuals (70). In order to determine whether these effects were due to specific changes in antibody titers to these herpes viruses or to a nonspecific modulation of IgG antibody to EBV or HHV-6, polyclonal B cell activation (as indicated by Forssman antibody titers) and changes in IgG levels were assessed. The
changes within the HIV+ and HIV− cohorts appeared to be independent of total serum IgG and degree of polyclonal B cell activation. These data suggest that the behavioral interventions employed in these studies were modulating control over latent EBV and HHV-6 differently since EBV antibody titers consistently decreased over the 10 week period, whereas significant decreases in HHV-6 antibody titers were not apparent until week 8. Since the greatest changes occurred between baseline and week 10 for each virus, we correlated changes in immune (CD4, CD8, CD4:CD8 ratio and PHA stimulation) and distress-related measures (state depression and anxiety) with pre–post changes in EBV-VCA and HHV-6 titers respectively. There were no relationships between any of these immune or distress-related markers and EBV-VCA or HHV-6 titers, suggesting that the mechanisms underlying reactivation of EBV and HHV-6 were not directly related to the above mentioned measures, but could be due to some other, yet to be studied, immune or psychological variables.

Stress-modifying strategies can reduce perceptions of stress and increase quality of life, and may also modulate parameters of the immune system that could have ramifications for virus latency. The data from these studies provide some evidence for this relationship, but it is clear that future confirmatory studies are needed to validate the stress-virus reactivation hypothesis.

Summary

This chapter explored evidence linking behavioral stress and latent herpesvirus reactivation. Data were presented that provided a theoretical model whereby the CNS interacts with the immune system both through direct contact as well as through endocrine mediators. Further, evidence was explored which investigated the relationship between stress (e.g., family distress, unpleasant affect, role conflict) and frequency of infectious disease symptoms and viral reactivation to several herpes viruses, particularly EBV. These data suggest a relationship between psychosocial stressors and immune variance, but that a consequence of higher levels of stress may be translated into herpesvirus reactivation as well as disease endpoints. The most compelling evidence for this relationship comes from intervention studies where the stress response can be modified. Recent work suggests that behavioral interventions alter the ways in which individuals process and handle stress, and the immune responses and immunologic control over these viruses may be modified, both in healthy as well as immunologically impaired individuals (e.g., HIV-1 infected individuals, geriatric individuals). Future work will be needed to investigate and confirm mechanisms of the stress-virus reactivation hypothesis; that is, to explore other psychosocial correlates (e.g., personality, self-efficacy, avoidant vs. intrusive thoughts, social support) and immune mediators (e.g., cytokines, catecholamines) which might impact on the modulation of virus reactivation. It is only through the understanding of the mechanisms of the relationship that specific intervention paradigms may be designed for clinical applications.
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