Modulation of cellular immunity by psychological stress

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Abstract

Data from prospective studies suggest that even commonplace stressful events are associated with changes in a number of facets of the cellular immune response. We have used first- and second-year medical students to study the effects of academic stress on immune function. Our medical students have seven or eight 3-day examination blocks during their first 2 years of medical school. Thus, the preclinical medical student classes cycle as a group through these higher-stress examination periods, as well as through lower-stress periods when there are no examinations. We have used examination stress as a model for examining the response to commonplace stressful events.

We found significant declines in natural killer (NK) cell activity in blood samples obtained from 75 medical student subjects during final examinations, in contrast to baseline blood samples collected 1 month previously. This significant decrease in NK cell activity was replicated in two follow-up studies. We also found that production of gamma interferon is decreased during examinations [1].

It is noteworthy that we have also found changes in antibody titers to latent herpesviruses, reflecting stress-related changes in the competence of the cellular immune response. We have followed students across the academic year, across three lower stress baseline and three higher stress examination periods. Antibody titers to Epstein-Barr virus (EBV) virus capsid antigen (VCA) were reliably elevated during examinations [2]. In this same study we found that the ability of EBV specific memory (cytotoxic) T-lymphocytes to inhibit the outgrowth of EBV-infected autologous B-lymphocytes fluctuated with examination stress, with less cell killing observed at the time of examinations. In a subsequent study we found evidence for incomplete reactivation of latent EBV, with only selective expression of the latent virus genome [2].

In an attempt to explore the cell/cell interactions affected by psychological stress, we explored the expression of a receptor for an important lymphokine, the interleukin-2 receptor (IL-2R). We also measured the synthesis of IL-2R mRNA by peripheral blood leukocytes (PBLs) obtained from medical students in three independent studies. The PBLs obtained at low-stress baseline periods had significantly higher percentages of IL-2R positive cells when compared with cells obtained from the same individuals during examinations. Moreover, in one study,
IL-2R mRNA in the PBLs decreased significantly during examinations in a subset of 13 of these students.

Thus, there is good evidence that academic stress can modulate a wide range of immunological activities.

Introduction

The interaction among the central nervous system (CNS), endocrine and immune systems is a complex interaction involving "hard wiring" among cells and chemical messengers such as hormones, lymphokines and neuropeptides. It is therefore not surprising that factors which modulate the CNS have impact on this axis. There is an extensive literature demonstrating that different kinds of psychological stress in human studies, and a variety of physical stressors, in animal studies, can modulate the interactions between these three systems in a significant way [3]. Two central questions in the field of psychoneuroimmunology are:

1. What are the mechanisms whereby these three systems interact with each other?
2. What are the health implications of these interactions?

Intuitively, it is reasonable to conclude that a variety of psychological stressors, both short- and long-term, which have impact on the immune response, could have implications for risk for infectious disease and perhaps cancer, two groups of illnesses for which the immune system plays a major role protecting the individual. However, there are few studies that provide well-controlled evidence for this relationship.

There are many problems in trying to establish a linkage between stress-associated immune modulation and illness. For example, individuals have a very broad range of lifestyles which could have implications for increased risk for illness, such as alcohol and drug abuse, inadequate sleep, poor nutrition and insufficient exercise. Compounding these relationships are the variable rates of exposure to infectious pathogens.

Studies on the impact of academic stress on the immune response in medical students

Our laboratory has focused for several years on an everyday stressor, academic stress in medical students, as a means to explore the impact of this stressor on the cellular immune response (reviewed in [4]). In this model, first and second year medical students at The Ohio State University Medical Center have been studied. The curriculum in the first and second year at Ohio State University College of Medicine is such that the medical students do not take examinations at random; examinations are given over a series of six or seven 2- or 3-day examination blocks across the academic year. Thus, as a class, the medical students are cycling through examination blocks as a group, resulting in periods of less and greater stress. We have obtained blood samples for immune assays to evaluate the impact of academic stress on cellular immunity at a baseline period approximately 1 month before an examination block, and again on a day during the examination block. The design is a within-subjects design in which we are following the same medical students across the academic year, matching values obtained at baseline periods and comparing those values, both psychological and immunological, to the values obtained during examination periods. In all of the studies with our medical students, we have confirmed that the students were more stressed and had greater anxiety at the time of examinations than at the baseline periods, using several psychological measures. A variety of other factors were also measured that could have health implications, such as caffeine intake, sleep deprivation, weight gain or loss, cigarette smoking, and alcohol intake.

In these studies we have found significant downregulation of natural killer (NK) cell activity in blood samples obtained from different groups of medical students when the values at baseline were compared to the values obtained during examinations. These changes have been replicated in two follow-up studies, and include evidence that a decrease in the percentage of NK cells may have contributed to these deficits. The studies were performed using two different target cells, K-562 or MOLT-4. Subsequently we found that peripheral blood leukocytes (PBLs) obtained from the medical students at baseline and examination periods, when stimulated in vitro with Concanavalin A (Con A) to induce interferon, showed a significant downregulation of the ability of the PBLs to synthesize gamma interferon. In one of these studies, we simultaneously measured plasma and intracellular cyclic AMP (cAMP) levels, and found significant increases in both. These data are consistent with a downregulation of T-cell function. We also were able to demonstrate that the response of PBLs to both Con A and phytohemagglutinin (PHA) was also downregulated in association with examination stress (reviewed in [4]).

In an attempt to explore some of the cell-to-cell interactions affected by psychological stress, we studied the expression of the interleukin-2 receptor (IL-2R) [5]. In three separate studies with three separate medical student classes, we found that the expression of the IL-2R was downregulated in PBLs obtained at the time of examinations, as compared to the baseline blood samples. In the third study, we simultaneously measured IL-2R mRNA and IL-2 in the supernatants in the same cell cultures. Concomitant with the downregulation of the IL-2R, we found a significant decrease in the amount of IL-2R mRNA in the PBLs examined. Surprisingly, when IL-2 was measured in the same cell cultures, a significant increase was observed. The data suggest:

a) that the physiological changes associated with psychological stress can downregulate an important receptor for T-cell function at the level of mRNA synthesis (gene expression); and

b) that the mechanisms involved in this modification of T-cell function is probably more complex than simply linking these interactions to glucocorticoids, which are known to downregulate these functions. The fact that we simultaneously found an increase in IL-2, which is normally inhibited by glucocorticoids,
suggests that this is a complex interaction and perhaps involves other hormones and/or neuropeptides [5]. Whether further inhibition or modification of the protein composing the IL-2R takes place post-translationally has not been determined.

Impact of psychological stress on herpesvirus latency

After a primary infection, herpesviruses latently infect a variety of target cells, depending on the strain of herpesvirus involved in the infection [6]. It is known that the cellular immune response plays a major role in controlling the spread of reactivated virus from the latent state. It is also known that hormones, e.g., glucocorticoids, can reactivate latent herpesviruses, and that glucocorticoids fall into the group of “stress hormones”. When herpesviruses are reactivated, this is reflected in the following possible combinations of clinical symptoms:

- an increase in antibody titer to the virus, reflecting an increase in virus proteins associated with virus reactivation;
- an increase in antibody titers associated with the ability to recover infectious virus from, e.g., the urine or saliva in the absence of lesions or disease;
- an increase in antibody titer, recovery of infectious virus, and the presence of virus-specific lesions and disease, and occasionally, if sufficiently severe, death [6].

In our studies with the medical students, as well as studies with other human populations [1,7,8], we have explored the stress-associated down-regulation of cellular immunity and its impact on the ability of a person to maintain control over a latent herpesvirus. Toward this goal, we have examined antibody titers to Epstein-Barr virus (EBV) and herpes simplex virus type 1 (HSV-1). The EBV causes infectious mononucleosis, and HSV-1 causes cold sores and occasionally encephalitis. We have found large and reliable changes in antibody titers to EBV virus capsid antigen (VCA) and HSV-1 in medical students at the time of examinations, compared to the baseline periods [1,2,7].

There is evidence that the changes observed in EBV latency in the medical students could have implications for disease. In a study by Kasl and co-workers [9] with West Point cadets, data suggest possible clinical significance of the changes observed in EBV VCA antibody titers in our study. Kasl et al. [9] followed West Point cadets that were EBV seronegative upon entrance to the Academy and therefore not latently infected with the virus. The data collected on the cadets over a 4-year period demonstrated that a triad of social risk factors, including poor academic performance, high levels of motivation for a military career, and having a father who was an “over-achiever”, was associated with three different illness indices: a greater risk for EBV seroconversion, i.e., infection, longer hospitalizations following seroconversion, and higher EBV antibody titers in those cadets who did seroconvert, but who did not have clinical symptoms of infectious mononucleosis. Other studies have also shown that similar convergence for psychological stress and immune function occurred with HSV-induced lesions [10].

In a recent study, we have explored the possibility that academic stress could have an impact on the ability of the students to respond to a primary antigen. In order to perform this study, we inoculated the medical students with the recombinant hepatitis B vaccine [11]. We found that medical students who were less anxious and less stressed seroconverted earlier than more stressed medical students, and had a greater T-cell response (as measured by blastogenesis to a purified hepatitis B viral protein) at the end of a 6-month study. The data have health implications for individuals who receive vaccinations to pathogens and who never are followed in order to determine whether they actually have seroconverted or whether they have sufficient antibody levels to a particular pathogen. With individuals such as health-care workers, who are at risk, for example, to hepatitis B virus, any delay in the appearance of antibody or in insufficient levels of antibody could have implications for risk. In addition, men and women in the military who are sent overseas to participate in a war, such as the recent Gulf war, and who are vaccinated with a variety of vaccines and then are subsequently put into an extremely stressful situation (much more stressful than the stress associated with taking examinations), might not be as protected against pathogens contacted in the field as one might expect. Since infectious disease plays a very important role in the effectiveness of an army, this could have important implications and should be explored.

The studies outlined in this chapter suggest that the impact of psychological stress on the CNS/immune/endocrine axis has implications for changes in the immune response. The studies in our laboratory on the medical students and in studies in which family caregivers of Alzheimer’s disease patients have been studied as a model of long-term chronic stress [8], have supported the hypothesis that immune changes associated with psychological stress could have health implications. Additional long-term longitudinal studies examining these associations are necessary and important to continue to explore this very interesting relationship.

References

The sequelae of chronic stress: Immunity and health

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Abstract

To examine the interactions among social support, chronic stress, immune function, and infectious illness in older adults, we assessed changes in immune function and health in 69 spouses who had been providing care for a husband or wife with Alzheimer’s disease for an average of 5 years and 69 sociodemographically-matched control subjects. Data were collected at two points in time, the initial sample (“intake”) and follow-up, an average of 13 months later. We also assessed social support and depression. Depression was assessed using the Structured Clinical Interview for DSM-III-R and the Hamilton Depression Rating Scale. Immunological assays included three functional assays, blastogenesis using concanavalin and phytohemagglutinin, and antibody titers to Epstein-Barr virus as a measure of the effectiveness of the cellular immune response to control latent virus.

Caregivers showed decrements relative to control subjects on all three measures of cellular immunity. Caregivers also reported significantly more days of infectious illness, primarily upper respiratory tract infections. Caregivers had a much greater incidence of depressive disorders than controls, with 25% of follow-up, compared to no cases among controls at intake and 6% at follow-up. Caregivers who reported lower levels of social support at intake and who were most distressed by dementia-related behaviors showed the greatest and most uniformly negative changes in immune function at follow-up.

These findings may be particularly important for older adults, since immune function declines with age. For individuals who are more chronically stressed, there could be longer-term, potentially important consequences for health.

Introduction

Considerable evidence has suggested an association between the occurrence of short-term stressful events and downregulation of immune function. In particular, studies from our laboratory showed decrements in a variety of immune function in blood samples drawn during an examination series, in contrast to lower stress “baseline” samples drawn about 1 month previously when students were not taking examinations [1–3]. The range of immune functions that appear to be affected by