Stress Damages Immune System and Health

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There is an extensive body of scientific literature related to the field of research called psychoneuroimmunology. Clinical studies, backed up by mechanism studies, have provided convincing evidence that the central nervous system (CNS) interacts with the endocrine and immune systems and that these interactions are bi-directional. Stress has been a focal point in this body of literature because it is known that stress can induce immune dysregulation across many aspects of the humoral and cellular immune responses. These studies have dated back to the 1960s and 1970s, and have included some very elegant studies involving animal models. The important outcome of this research is that stress-induced immune dysregulation can produce changes that are not only statistically significant but, most importantly, biologically significant in terms of health risk.

Introduction

It is now well established that there are very complex bi-directional interactions between the CNS and the immune system mediated by the endocrine system. Two important aspects of these interactions include the production of stress hormones by the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic-adrenal-medullary (SAM) axis. The interactions between immune cells also take place through the production of cytokines. Hormones can modulate immune function by binding to their receptors, which are expressed on virtually every type of immune cell. The modulation of cytokines has been shown to feedback to the brain, producing changes in the HPA axis, as well as inducing sickness behavior such as fever, loss of appetite, changes in sleep patterns and depression. One example of this feedback loop is through the impact of interleukin-1 (IL-1) on the production of corticotropin releasing hormone (CRH) by the hypothalamus. CRH can affect the HPA axis by triggering an increase in stress hormone levels. These are very complex interactions, but researchers working in the field of psychoneuroimmunology are making good progress in understanding the complexities that underlie mind/body interactions (Rabin, 1999; Padgett and Glaser, 2003; Ader et al., 2001).

How Do We Assess Various Stressors?

Researchers who do studies on behavior and stress have various ways to measure and quantitate the many aspects and dimensions associated with what we call psychological stress. One way to define psychological stress is by its occurrence in people who experience events or environmental demands that exceed their ability to cope. When researchers study stress and immunity, they will often study negative mood that is associated with general distress anxiety or depression. They may also study the number and types of life events that may have taken place near the time of the stressor, or they may ask their subjects to rate their perception of

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stress using psychological scales.

Experimental stressors have also been used to explore the interaction between stress and the immune system. Models, such as medical students taking examinations (thereby dealing with examination stress, a short-term stressor) or a spouse caring for a person with dementia, e.g., Alzheimer's disease (a long-term chronic stressor), have been used by many laboratories to study the interaction between chronic stress, aging, the immune response, and health. Studies of people who have survived major catastrophes, such as hurricanes and earthquakes, have provided insight into the impact of those kinds of stressors on health. Parts of these complex interactions include the ability of people to learn how to cope with stressful situations and how long it takes for a person's stress hormones to return to baseline. Stress hormones, the most typically studied aspect of this kind of research, include glucocorticoid and the catecholamine hormones, epinephrine and norepinephrine (Segerstrom and Miller, 2004).

Stress-induced Immune Dysregulation and Infectious Disease

Because the immune system plays an important role in defending the body against a variety of infectious organisms, any abnormalities or changes in the ability of the immune system to perform normally can have implications for either more severe illness or a greater risk of mortality following infection. An extensive body of literature involving animal models and studies with human subjects has examined the relationship between stress-induced immune dysregulation and infectious disease, particularly with virus infections. Mouse models have been used by several laboratories and have been very important in providing a way to explore these interactions.

One of the common stressors used by researchers doing studies with stress and mice is restraint stress. Mice are placed in plastic tubes, such that they can move forward and backward, but they cannot turn around. Holes are drilled in the sides of the tube to allow air to enter and to ensure that the mice do not overheat. In a series of studies using influenza virus, the results showed that restraint stress was able to alter the innate and adaptive immune responses to the virus. These changes included levels of antibody produced to the virus over time and suppression of both proinflammatory and anti-inflammatory cytokines. What was really interesting about this series of studies was that when the researchers used a drug (RU486) that blocked the glucocorticoid receptor on lymphocytes, the effect of stress was blocked and the animals looked like the unstressed controls. Studies like this clearly show the role of stress hormones in the modulation of the immune response in general and in response to an infectious pathogen, such as influenza virus (Ader et al., 2001).

Studies With Vaccines

A growing amount of literature, primarily focusing on viral vaccines, has shown that the changes in the immune response, modulated by psychological stress, can impact both the antibody and T-cell responses to virus vaccines. This is important because in order to be protected against a virus infection, one needs to have both an antibody and a virus-specific T-cell response to the virus sufficient to protect an individual against severe infection and perhaps death. The first vaccine study to demonstrate this relationship with stress was a study that was performed with medical students experiencing academic stress. Medical students were inoculated with the hepatitis B virus vaccine. Antibody titers were obtained along with data from experiments in which the virus-specific T-cell response was also measured over a period of six months. Both the antibody and the virus specific T-cell responses were down-regulated in those medical students who had less stress and anxiety and more social support.

In a follow-up study, spousal caregivers of patients with dementia (mean age=70) were inoculated with an influenza virus vaccine. Well-matched control subjects who were not caregiving served as the comparison group. The results showed that chronic stress from caregiving was associated with a weaker antibody and virus-specific T-cell response to the vaccine in caregivers as compared to controls. A study performed in England confirmed these results. A similar outcome was obtained in a study in which a rubella virus vaccine was used.

Two studies have examined the possibility that the observations made with viral vaccines might apply to bacterial vaccines as well. One study utilized a pneumococcal vaccine. Using the spousal caregiver of dementia chronic stress model, it was shown that caregivers produced lower levels of IgG antibodies to the

vaccine than the well-matched control subjects. Similar results were obtained with a meningitis conjugate vaccine.

These vaccine studies show that individuals who are more distressed or anxious will be at greater risk for weakened responses to both viral and bacterial vaccines. It is reasonable to assume that these same individuals would be more likely to respond more poorly to these pathogens, thus placing them at greater risk for infection and more severe illness. This is especially true in older individuals who already have a less vigorous immune system than younger ones. Supporting this hypothesis are data that show that adults who have poorer immune responses to vaccines also experience higher rates of clinical illness. It will be useful to keep these studies in mind as we begin to utilize cancer vaccines. Patients will need to be able to respond to such vaccines as strongly as possible. Stress reduction protocols might be useful prior to entering cancer patients in a vaccine trial (Ader et al., 2001; Glaser and Kiecolt-Glaser, 2005).

Stress-induced Immune Dysregulation and the Pathophysiology of HIV

Data from both human and animal studies suggest that stress plays a role in the pathophysiology of HIV and herpesvirus infections. Using rhesus macaques and simian immunodeficiency virus (SIV) for studying HIV-associated disease, it was possible to assess the impact of social stress on SIV infection. Animals that were assigned to a group experiencing a stable social condition, in which the same three animals met everyday, had lower concentrations of SIV RNA in plasma after inoculation than animals in an unstable social condition group where different 2-3 and 4 member groups were formed daily. The animals also survived longer.

In a longitudinal study involving HIV-infected men, all asymptomatic upon entry into the study, there was a faster progression of AIDS in those with more stressful life events and less social or interpersonal support. Approximately five years after entry into the study, the chance of developing AIDS was two-to-threefold higher in men who were found to be above the median level for stress or below the median level for social support compared to those who were below the median level for stress and above the median level for support (Ader et al., 2001).

The Impact of Stress on the Pathophysiology of Herpesviruses

A large number of studies were performed on the impact of stress on the pathophysiology of herpes simplex virus type I (HSV-1) infection and Epstein-Barr virus (EBV) latency. A series of studies employing mouse models have been performed in which the effect of restraint stress on the immune responses to both primary and secondary HSV-1 infections have been explored. Mice that had been inoculated with HSV-1 and also restraint-stressed showed that the ability to generate primary HSV-1-specific cytotoxic T-lymphocytes (CTLs) was inhibited. The suppression of CTL production was blocked by the surgical removal of the adrenal gland, showing that the relationship between restraint stress and CTL production was associated with the production of corticosterone. There was also an affect on natural killer (NK) cell activity, which diminished in stressed mice. These deficits in the immune response to infection by HSV-1 were associated with an increase in the level of infectious virus at the site of inoculation (the foot pad) in restraint-stressed mice. A latency model using mice was also developed for HSV-1. Mice that were exposed to a social stressor showed reactivation of latent HSV-1. The non-stress controls showed no reactivation. It is important to keep in mind that these experiments were carried out using mice in a laboratory setting. Nevertheless, the data from these studies provide insight as to how stress could modulate the immune response to a virus infection like HSV (Rabin, 1999; Ader et al., 2001; Cohen et al., 1999).

Psychological stressors have been shown to be associated with more frequent recurrences of lesions in individuals who are latently infected with HSV-1 or HSV-2. In one study, women who reported greater persistent stress that lasted more than one week also had more occurrences of genital herpes. In addition, individuals who were more chronically stressed had more frequent recurrences of reactivation of HSV-1 and HSV-2 (Ader et al., 2001; Glaser and Kiecolt-Glaser, 2005; Cohen, 1999).

Stress and EBV Latency

A series of studies on stress and latency have been performed with EBV, the etiological agent for infectious mononucleosis and a human tumor virus.

Using an academic stress model with medical students, antibody titers to EBV were higher in medical students at the time of taking examinations (high stress period) when compared to low stress baseline periods approximately one month prior to examinations. Moreover, academic stress was associated with a significant decrease in the ability of EBV-specific CTLs to kill EBV-infected autologous B-cells.

Other types of stressful situations including the chronic stress of caregiving for a spouse with dementia or the stress associated with space flights by astronauts were associated with the reactivation of latent EBV and latent cytomegalovirus (CMV).

The studies with both animal models and human subjects show that stress can modulate the steady state expression of several latent herpesviruses while simultaneously down-regulating the specific CTL response to the virus. While the mechanisms that underlie stress-associated reactivation of latent viruses are not fully understood, it is thought that glucocorticoid hormones play a role in the reactivation of the virus [Ader et al., 2001; Glaser and Kiecolt-Glaser, 2005).

Stress and Wound Healing

Wound repair progresses through several overlapping stages and any delay or inhibition of any one of the stages can slow down the complete phase of the wound healing process. The immune system plays an important role, particularly in the early stages of the wound healing cascade, by the production of the important proinflammatory cytokines, such as IL-1α, IL-1β, IL-8, IL-6, IL-2, and TNF-α.

Stress can disrupt the production of proinflammatory cytokines and thus potentially affect wound healing. An example of this is a study that was performed with spousal caregivers of Alzheimer's disease patients, a model already discussed. This is a chronic stress model and because of the age of the spousal caregivers, there is an aging/chronic stress interaction. Indeed, caregivers, compared to very well matched control subjects, took 24% longer than well matched controls to heal a small standardized dermal wound. In addition, IL-1β mRNA levels in stimulated peripheral blood leukocytes were lower in the caregivers when compared to control subjects, suggesting a possible explanation for the results. As already discussed, both IL-1α and IL-1β play important roles in the wound healing process. In a study performed with dental students experiencing academic stress, wounds healed 40% more slowly in the students when induced just prior to examinations compared to the same medical students during vacation. Once again, a decrease in IL-1β mRNA levels was found in stimulated peripheral blood leukocytes.

Stress also slowed wound healing in a series of mouse studies confirming the human subject studies. Stress inhibited wound healing by approximately 27% when compared to control animals and blocking the glucocorticoid receptor in restraint-stressed animals resulted in healing rates that were similar to those in the control animals. These data show that disruption of neuroendocrine homeostasis can modulate the early stages of wound healing (Glaser and Kiecolt-Glaser, 2005; Padgett et al., 1998).

Stress and Inflammation

As already discussed, there is good evidence that stress can induce immune dysregulation partly through the alterations in the production of proinflammatory cytokines. It has been shown that both psychological and physical stressors can up-regulate the synthesis of IL-6. Negative moods, such as depression and anxiety, can also up-regulate the production of IL-6. In fact, the data suggest that both stress and depression can sensitize an individual to subsequent antigen challenges. In a study from our laboratory, individuals who reported more depressive symptoms showed increases in serum IL-6 levels two weeks following an antigen challenge i.e., vaccination with an influenza virus vaccine. The outcome of the study showed that there was little change in IL-6 levels in those individuals who reported little or no symptoms of stress or depression while individuals who reported more depressive symptoms showed an increase in serum IL-6 levels two weeks after the vaccination when compared to controls.

These data are consistent with other evidence showing sensitization between cytokines and stressors in humans and animals. Individuals who have a history of being stressed demonstrate a higher cytokine response when re-exposed to a stressor. These data have significant health implications because inflammation is associated with a variety of diseases, particularly in older

individuals. For example, IL-6 has been linked to several diseases and conditions in older individuals including cardiovascular disease, osteoporosis, arthritis, type 2 diabetes, frailty, and certain cancers, such as chronic lymphocytic leukemia (CLL) (Glaser and Kiecolt-Glaser, 2005; Marx, 2004; Maes et al., 2001).

Stress, Inflammation and Aging

In a recent study from our laboratory, the interaction between stress, inflammation and aging was explored by measuring the average annual rate of increase in serum IL-6 levels in Alzheimer's disease caregivers versus control subjects over six years. It was found that serum IL-6 levels were about four-fold higher in men and women who were chronically stressed by caregiving for a spouse with dementia when compared to similar individuals who did not have caregiving responsibilities.

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Studies showing the up-regulation of IL-6 by different kinds of psychological stressors, including depression, provide evidence of a mechanism through which chronic stressors might accelerate the risk for developing any age-related diseases by "premature aging" of the immune response and cancer (Glaser and Kiecolt-Glaser, 2005; Maes et al., 2001; Kiecolt-Glaser et al., 2003).

Conclusion

The research focusing on psychological stress and neuroimmune dysregulation has provided data that aides our understanding of the complex physiological changes that occur in stressful situations. This information will provide new insights into clinical applications of the research being performed and the potential for new approaches for treating patients.

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