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Immune Deregulation Caused by Stress: Implications for Cancer, Infectious Disease and Wound Healing

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ABSTRACT

The nervous, endocrine, and immune systems are connected through a complex network of bidirectional signals, allowing for communication between them. The field of Psychoneuroimmunology (PNI) has shed new light on the pathophysiological processes related to the immune system. Research in PNI has shown that psychological stress disrupts the functional interaction between the nervous and immune systems, resulting in immune dysregulation. This stress-induced immune dysregulation can have significant health consequences, including reduced immune response to vaccines, slower wound healing, reactivation of latent herpesviruses like Epstein-Barr Virus (EBV), and an increased risk for severe infectious diseases. Chronic stress and depression can increase the production of proinflammatory Cytokines like Interleukin-6 (IL-6) in the peripheral system. High levels of IL-6 in the serum have been linked to several conditions, including cardiovascular disease, type 2 diabetes, mental health disorders, and certain cancers. In summary, this article will examine the evidence suggesting that psychological stress can promote immune dysfunction that hurts human health.

Keywords: Stress, Cancer. Oncology, Infectious disease, Wound healing

INTRODUCTION

Psychological stress is the perception of stress that affects an individual's ability to cope with life events. It has been established that psychological stress has a significant impact on immune function and overall health. However, the duration and course of the stress are the key factors that determine the nature of stress-induced immune change and its health-related outcome.

In certain circumstances, short-term stressors can enhance certain aspects of immune function, which can either be beneficial or detrimental. For instance, the "fight or flight response" triggered by activation of both the Hypothalamic-Pituitary-Adrenal (HPA) axis and the Sympathetic Nervous System (SNS) helps organisms deal with threats by increasing heart rate, blood flow to skeletal muscle, and glucose metabolism. This acute activation of HPA- and SNS-mediated pathways increases leukocyte trafficking and enhances adaptive (B-cell) immune responses. Studies have shown that acute stress improved the delayed-type hypersensitivity response in mice, which was considered a protective mechanism against wound infection following an aggressive encounter. However, there is a negative side to acute stress, which is associated with hyperimmune responses in asthma, allergic responses, and latent viral reactivation. Thus, the effect of acute stress on the immune system is a complex interaction that requires further investigation.

On the other hand, chronic or excessive stress has a deleterious effect on immunity. This is evident from studies showing that psychological stress delays the wound healing process, increases the severity and duration of infectious disease, promotes the reactivation of latent viruses, and may even be a cofactor for tumor development and progression. In particular, chronic stress can increase the peripheral production of proinflammatory cytokines such as interleukin (IL)-6. High serum levels of IL-6 have been linked to various health conditions such as cardiovascular disease, type 2 diabetes, mental health complications, and certain cancers.

In conclusion, while short-term stressors may have beneficial or detrimental effects on immune function, chronic or excessive stress has a negative impact on immunity and overall health. Therefore, it is important to manage stress effectively to minimize its harmful effects on the immune system and to maintain good health.

LITERATURE REVIEW

Healing of Wounds

New research has shown that when the body is under physiological stress, it can impair the wound-healing process. This is because stress can affect the first phase of wound healing, which is cell-mediated and relies on interactions between chemokines, cytokines, and growth factors to recruit phagocytes and fibroblasts to the wound site and promote the repair of damaged tissue [1].

This initial response is crucial because if it is impaired, the entire healing process can be disrupted. This is a significant clinical concern because when stress-induced deficits in wound healing occur, it can lead to longer hospitalization and an increase in complications following surgical procedures [2].

Several human studies have shown that psychological stress can cause a significant delay in wound healing. For example, a study found that older women who were primary caregivers of a demented spouse experienced attenuated wound healing, taking an average of nine days longer to heal compared to controls. In another study, dental students who underwent oral mucosal wounds during an examination period experienced a delay in wound healing by approximately 40%. Additionally, hostile marital relationships have been found to delay wound healing by 60% [3].

These studies suggest that psychological stress significantly prolongs the time it takes for wounds to heal, possibly through a mechanism involving the reduction of the cell-mediated inflammatory response at the wound site. One potential explanation for this delay is that stress stimulates the production of Glucocorticoid (GC) hormones through the HPA axis. Adrenocorticotropic Hormone (ACTH) stimulation of the adrenal gland promotes the release of GCs, which can influence immune cells by suppressing differentiation and proliferation, regulating gene transcription, and reducing the expression of cell adhesion molecules that are involved in immune cell trafficking [4].

In terms of wound healing, cortisol, a type of GC hormone, functions as an anti-inflammatory agent and modulates Th1-mediated immune responses essential for the initial healing phase. Studies have shown that individuals with higher perceived stress levels had elevated levels of salivary cortisol and decreased concentrations of inflammatory cytokines at wound sites, which are necessary for the initial inflammatory phase of wound healing [5].

Furthermore, stress has been found to shift the cytokine profile away from a Th1 profile and towards a Th 2 profile, with an increase in IL-10 synthesizing T cells. Microarray analysis of neutrophils at the wound site in medical students experiencing examination stress revealed a transcriptional profile consistent with the suppression of neutrophil activity. These findings collectively indicate that psychological stress impairs normal cell-mediated immunity at the wound site, causing a significant delay in the healing process [6].

Studies conducted in mouse models have provided significant insight into the mechanisms underlying how stress attenuates wound healing. Similar to human studies, inflammatory cytokines were found to be down-regulated in the early phase of wound healing in stressed mice, and the glucocorticoid hormone, corticosterone, played a major role in the delayed healing response. For example, restraint stress caused wounds to heal approximately 27% slower than wounds in control mice, which was associated with decreased leukocyte infiltration to the wound site at 1 to 3 days post-wounding [7].

Corticosterone levels were elevated 4-fold in restraint-stressed mice. When corticosterone signaling was blocked with the glucocorticoid inhibitor RU4055, wound healing rates of restraint-stressed mice returned to baseline values. Glucocorticoid hormones can suppress inflammatory cytokine production by modulating the activity of the transcription factor, Nuclear Factor Kappa B (NFκB). NFκB is a potent activator of proinflammatory gene

transcription, and its activity is modulated by GCs via several mechanisms, including increased transcription of the inhibitor of NFκB (IκB), competition for inflammatory gene promoter sites, and reduction of active NFκB translocation into the nucleus. Therefore, high cortisol levels associated with stress may limit NFκB transcriptional activity and subsequently, reduce proinflammatory gene expression at the wound site [8].

Infectious Disease

Psychological stress is known to cause negative emotions such as anxiety and depression. These emotions can impair the immune system's ability to fight off infections and diseases, specifically B-cell and T-cell-mediated immune responses. This is significant because stress-induced immune dysfunction has been associated with an increase in both the severity and duration of infectious diseases [9,10].

One example of this is the risk of developing clinical symptoms of rhinovirus infection due to psychological stress. Research has also shown that higher perceived stress scores were associated with the severity of clinical symptoms associated with respiratory virus infections, and stress caused a delay in the recovery from these infections.

Stress can also influence the pathogenesis of the Human Immunodeficiency Virus (HIV). For instance, psychological stress related to the concealment of sexuality in HIV-positive males was associated with a more rapid progression into AIDS. In studies with monkeys, the stress of an unstable living environment was associated with higher Simian Immunodeficiency Virus (SIV)-RNA levels in plasma after virus inoculation, indicating stress-enhanced viral replication [11,12].

Additionally, psychological stress impairs the immune response to several antiviral/bacterial vaccines, including hepatitis B virus, pneumococcal bacteria, rubella virus, meningitis virus, and influenza virus. This is biologically significant because immune responses to vaccinations are good indicators of how a person would respond to a pathogen.

Research has shown that individuals who had attenuated immune responses against influenza virus vaccination also experienced higher rates of clinical illness and longer clinical episodes. Caregivers of a demented spouse showed dramatic deficits in both cellular and humoral immune responses to an influenza virus vaccine compared with non-caregivers. These impaired immune responses to the influenza virus vaccination are paralleled in stress studies. Moreover, caregivers with poorer antibody responses to influenza virus vaccination had elevated concentrations of salivary cortisol that were correlated with higher perceived stress scores [13,14].

Therefore, prolonged HPA axis-dependent production of glucocorticoids is thought to play a role in the relationship between psychological stress and impaired immune responses. Mouse studies using restraint stress have shown that glucocorticoids were markedly elevated by stress. In this restraint model, stress impaired antibody production to influenza virus 2 weeks following vaccination and caused deficits in cell-mediated immunity with decreased IL-2 production [15-18].

Latent Virus Reactivation

There is increasing evidence to suggest that psychological stress can have a significant impact on the development, duration, and recurrence of viral infections, including Herpes Simplex Virus type 1 (HSV-1) and Epstein-Barr Virus (EBV). The cellular immune response plays a vital role in controlling the pathophysiology of both lytic herpesvirus infections and the expression/replication of latent herpesviruses. When cellular immunity is impaired, one or more herpesviruses can be reactivated, which often leads to severe infection and even death [19-21].

Studies have shown that psychological stressors are associated with an increased frequency of lesions in women infected with HSV-1 or HSV-2, as well as longer recurrences of genital herpes in women, and an increased incidence of herpes zoster virus in older individuals. Furthermore, HSV-1 reactivation and impaired immunity to HSV-1 infection has been demonstrated in mouse models of stress [22,23].

EBV is a gamma herpesvirus and the etiological agent for infectious mononucleosis, and it is also a human tumor virus implicated in several malignant diseases. Stress has been shown to promote latent EBV reactivation, which is reflected in higher antibody titers to EBV antigens such as the Virus Capsid Antigen (VCA). Academic stress has been found to cause a reduction in EBV-specific CTL-mediated killing of B cells latently infected with EBV. PBLs

isolated from stressed EBV-positive individuals also showed reduced proliferation to purified EBV polypeptides, indicating a reduction in the memory T cell response to the virus [24,25].

EBV and several other latent herpesviruses, including VZV and Cytomegalovirus (CMV), are reactivated by the psychological stress associated with spaceflight. The highest levels of salivary EBV DNA were found during spaceflight, and cortisol and catecholamines were also elevated on the day of landing. Furthermore, in West Point cadets, the stress of final exams promoted EBV reactivation, whereas the more physical stressor of survival training did not. These data suggest that there may be differences in the physiological effects induced by diverse manifestations of stressors resulting in different health outcomes [26,27].

Collectively, these findings support the notion that stress-induced changes in the cellular immune response are associated with the reactivation of latent herpesviruses. The mechanism of how latent viruses are reactivated in vivo is not well understood. The stress-induced shift in the cytokine profile away from a Th1 toward a Th2 profile favors virus-induced pathogenesis and survival because it down-regulates the production of cytokines important for the T cell response to the virus. Although EBV reactivation and replication are enhanced by glucocorticoids in vitro, in vivo circulating cortisol levels, in a study from our laboratory, did not correlate with EBV reactivation, i.e., antibody titers to this virus [28,29].

It is believed that this mechanism is more complicated than a direct relationship between absolute glucocorticoid serum levels and latent EBV reactivation. One critical factor may be how an individual responds to a stressor. For instance, a recent study demonstrated that viral reactivation was influenced by whether a person was a high or low responder to stress. Although levels of circulating cortisol were similar in subjects with high and low cortisol responses, those with high cortisol responses showed a greater increase in antibody titers to EBV VCA IgG after a stressor. This suggests that individual differences in the stress response, rather than just the presence of stress, may play a critical role in the reactivation of latent herpesviruses [30].

Cancer

While the scientific literature on the connection between stress and cancer may not be as extensive as that on wound healing or infectious diseases, studies have suggested that the physiological changes brought on by stress may play a role in both the initiation and progression of tumors. In particular, some researchers have theorized that stress may reactivate latent tumor-promoting viruses [31].

As we have discussed, the Epstein-Barr Virus (EBV) has been associated with several cancers, including nasopharyngeal carcinoma, Burkitt's lymphoma, non-Hodgkin's lymphoma, and post-transplant lymphomas. Because stress has been shown to promote the reactivation of latent viruses, it is plausible that there may be a relationship between stress and EBV-associated tumors [32].

Furthermore, stress has been linked to a reduction in the activity of Natural Killer (NK) cells and cytotoxic T cells, both of which are essential for targeting abnormally growing cells for destruction. In addition, stress-induced changes in the balance of cytokine profiles may promote virus replication and thereby increase the frequency of tumor promotion [33,34].

Taken together, these findings suggest that stress-induced immune dysregulation may act as a cofactor in increasing the risk of tumor promotion, particularly in cases where oncogenic viruses are involved in the development of cancer. While more research is needed to fully understand the connection between stress and cancer, these studies offer valuable insights into potential mechanisms underlying this complex relationship [35,36].

CONCLUSION

Over the years, researchers have made significant progress in understanding how psychological stress affects the immune system. Both clinical and experimental evidence suggest that stress can hinder the wound healing process and also contribute to the reactivation of latent herpesviruses which lead to infectious diseases. Furthermore, stress may also act as a cofactor in both the development and progression of tumors. Therefore, it is crucial to understand the mechanisms by which stress affects immune function to develop behavioral and pharmacological interventions that can lower the incidence of stress-induced immune dysfunction.

Various interventions, including nutrition, exercise, and stress-reducing protocols such as muscle relaxation and yoga, may provide a way to counteract the harmful effects of stress on the immune system and overall health. For instance, recent research has demonstrated that moderate exercise can improve wound healing in older adults, while marital support can reduce stress-related immune impairments in individuals experiencing hostile marital relationships. Implementing such interventions to reduce stress can be essential in restoring immune function and improving health outcomes, particularly when used in conjunction with appropriate medical management.

DECLARATIONS

Conflict of Interest

The authors declared no potential conflicts of interest concerning the research, authorship, and/or publication of this article.

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