# Stress and Immunity: Implications for Viral Disease and Wound Healing

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*It is now well established that psychological stress can downregulate the cellular immune response. Communication between the central nervous system and the immune system occurs via a complex network of bidirectional signals linking the nervous, endocrine, and immune systems. Stress disrupts the homeostasis of this network, which in turn, alters immune function. In this review, we discuss the role of stress in modulating cellular immune function and the potential health implications of this downregulation.* J Periodontol 1999;70:786-792.

**KEY WORDS**

**Immune response; stress, psychological; viral diseases/pathogenesis; wound healing.**

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There is increasing evidence that the central nervous system (CNS) can influence the immune response via a complex network of bidirectional signals linking the nervous, endocrine, and immune systems. Psychological stress can downregulate immune responses by altering the signals within this network.[1] In this review, we discuss how psychological stress modulates cellular immune function. We also review the possible health implications of these changes, focusing on viral disease and wound healing.

Psychoneuroimmunology (PNI) is an emerging field concerned with the influence of behavior on brain-immune interactions, and how this affects health. Since the landmark discoveries of these interactions by Solomon and Moos[2] and Ader and Cohen,[3] researchers have been striving to understand the underlying mechanisms. It is known that two main pathways link the brain and immune system: the hypothalamic-pituitary-adrenal (HPA) axis, and direct neuronal fiber connections from the autonomic nervous system. Both pathways produce biologically important mediators capable of interacting with cells of the immune system.[1]

Neuroendocrine hormones released from the pituitary gland by the activation of the HPA axis influence the immune system. Both lymphoid and myeloid cells express receptors for these hormones and neuropeptides, and several studies have demonstrated that lymphocytes can also synthesize hormones such as prolactin, growth hormone, and adrenocorticotropic hormone (ACTH).[4-7] Furthermore, neurohormones, e.g., glucocorticoids, and peptides such as ACTH, endorphins, substance P, and somatostatin are able to modulate many aspects of the immune response, including cytokine production, B- and T-cell proliferation, antibody production, chemotaxis of monocytes and neutrophils, and natural killer (NK) cell activity.[8]

In addition to neuroendocrine signals from the HPA axis, noradrenergic sympathetic and peptidergic nerve fibers have been detected in both primary and secondary lymphoid organs including bone marrow, thymus, spleen, and lymph nodes.[9] The close association of these nerve terminals with immune cells results in

the formation of neuroeffector junctions and direct neural-immune interaction. Neurotransmitters such as epinephrine and substance P that are released at these junctions can then interact directly with an associated immune cell or at a distant site, thereby affecting surrounding cells.

Lymphocytes, monocytes/macrophages, and granulocytes possess receptors for many neurotransmitters,[10] and these neurotransmitters alone are capable of immune regulation. For example, the catecholamines (epinephrine and norepinephrine) regulate lymphocyte cyclic-AMP levels, which in turn, alter immune responses such as cellular migration, lymphocyte proliferation, antibody secretion, and cell lysis.[11] A recent report by Elenkov and colleagues[12] shows that the addition of catecholamines to human whole blood resulted in the suppression of interleukin 12 (IL-12) production, with a concomitant increase in interleukin 10 (IL-10) production. This cytokine shift caused a T-helper (Th) cell shift from Th1 cells involved with cell-mediated inflammatory reactions to Th2 cells that produce cytokines which encourage antibody production. Elenkov et al.[12] suggest that stress may suppress Th1 function and cause a shift towards a Th2 cytokine pattern, thus increasing the susceptibility of the host to infectious pathogens that require a cellular response, e.g., viral infections. This may also have important implications for progression of periodontitis that has been hypothesized to be a Th2 lesion.[13]

These bidirectional pathways between the CNS and immune system provide a feedback mechanism for immune regulation.[14-16] For example, IL-1 released from activated immune/inflammatory cells stimulates the hypothalamus to produce more corticotrophin-releasing hormone (CRH), which in turn, triggers the release of two "stress" hormones, ACTH from the pituitary gland and corticosterone from the adrenal cortex. These stress hormones can downregulate immune responses. Thus, physical or psychological stressors can activate the CNS and HPA axis to release catecholamines and glucocorticoids that alter these feedback mechanisms and disrupt homeostasis. The oral cavity is a potential target for neuroendocrine regulation as well. Free cortisol is present in saliva at the same concentration as the plasma and thus may regulate oral inflammatory reactions including oral wound healing. The recent finding of cortisol in gingival crevicular fluid also suggests that cortisol produced as a result of stress may play a role in periodontitis.[17] Thus, understanding how stress modulates the immune system will further our understanding of oral wound healing and oral diseases, like periodontitis.

## STRESS-ASSOCIATED IMMUNE MODULATION

Studies from our laboratory first focused on the impact of examination stress on young healthy medical students. As summarized in Figure 1, a number of immune changes were found in response to this relatively mild stressor, including decreases in NK cell activity, a decrease in the response of peripheral blood leukocytes (PBL) to mitogens, a decrease in the synthesis of gamma-interferon (IFN-γ) after stimulation of PBL with concanavalin A (ConA), a decrease in the antibody and T-cell responses to hepatitis B (Hep B) vaccination, and changes in the ability of the immune system to maintain control over the latent herpesviruses, Epstein Barr virus (EBV) and herpes simplex type 1 virus (HSV-1).[18-24] These immune changes were observed concomitantly with an increase in self-reported upper respiratory tract infections. Interestingly, Deinzer et al.[25] have recently shown that IL-1ß is elevated in gingival crevicular fluid after examinations in experimental gingivitis sites. Thus, stress can alter the balance between host responses and bacteria in the periodontium.

*Figure 1.*

**Immune changes associated with academic stress in medical students**

1. *Decreased percentages of total $CD3^+$, $CD4^+$, and $CD8^+$ T lymphocytes*
2. *Decrements in NK cell activity*
3. *Decreased proliferative responses of lymphocytes to mitogens (ConA, PHA)*
4. *Decreased production of gamma-interferon by lymphocytes after stimulation with ConA*
5. *Decreased interleukin 2 receptor (IL-2R) positive lymphocytes and IL-2R mRNA after mitogen stimulation*
6. *Evidence for reactivation of latent herpesviruses, e.g., EBV, HSV-1*
7. *Decrements in memory T-cell killing of EBV-transformed autologous B lymphocytes*
8. *Decrements in memory T-cell response to purified EBV polypeptides*
9. *Decreased antibody and T-cell response to Hep B vaccination*

Speculating that stress-associated immunosuppression may have a greater health impact on those individuals whose immune function is already impaired, we chose to study older adults because of the age-related decrements in immune function. We focused on the impact of both aging and chronic psychological stress on immunity and health in individuals caring for a spouse with Alzheimer's disease (AD).[26-31]

***Figure 2.***

**Immune and endocrine changes associated with the stress of caregiving for a dementia victim as compared to well-matched control subjects**

*Caregivers show:*

1. *Decrements in NK cell activity in response to:*
   *a) recombinant IFN-γ*
   *b) recombinant IL-2*
2. *Decreased proliferative responses of lymphocytes to mitogens (ConA, PHA)*
3. *Poorer T-cell receptor-induced blastogenic response to a monoclonal antibody against the T-cell receptor*
4. *Decreased IL-2 receptor positive lymphocytes after mitogen stimulation*
5. *Evidence for reactivation of latent herpesviruses, e.g., EBV, HSV-1*
6. *Decrements in memory T-cell proliferation to HSV-1*
7. *Higher plasma ACTH levels*
8. *Decreased production of IL-1ß by lymphocytes after stimulation with LPS*
9. *Poorer antibody and T-cell responses to an influenza virus vaccination*
10. *More respiratory infections and more days ill*

Spousal caregivers showed reduced responses on a number of immune measures as compared to well-matched control subjects (Fig. 2). For example, PBL obtained from caregivers showed poorer blastogenic responses to mitogens, poorer proliferation in response to a viral antigen (HSV-1),[31] and an inhibition of the ability of NK cells to respond to recombinant IL-2 and IFN-γ. The AD caregivers also had more respiratory infections and more days ill than the control subjects.[26]

The data from these studies suggest that psychological stress can alter specific parameters of immune function. This immune modulation may be most detrimental to those individuals whose immune function may already be impaired such as the elderly, the medically immunosuppressed, and those with immunosuppressive diseases such as AIDS.[32-34]

## IMPACT OF STRESS ON LATENT HERPESVIRUSES

Recurrent herpes simplex virus infections are a common sequelae of surgical and other traumatic procedures in the oral cavity. Unlike common cold viruses, which often cause acute infections and are effectively eliminated by the immune system, herpesviruses latently infect target cells where the viral genome resides for life. In individuals who are immunosuppressed due to medical treatments (i.e., organ transplantation), or immunosuppressive diseases, one or more latent herpesviruses are commonly reactivated. In severely immune-compromised patients, these viruses can induce severe complications and death.[35] Among normal individuals, reactivation of one of the herpes viruses may result in a clinical outcome, e.g., a cold sore caused by HSV-1. However, evidence for the reactivation of a latent herpes virus may be more subtle, i.e., a rise in the IgG class of antibodies to various viral proteins in the absence of clinical symptoms or infectious virus.[36,37] It is believed that the loss of immunological control over viral latency is associated with changes in the cellular immune response. It is the increase in viral antigens synthesized after reactivation which induces memory B cells to increase antibody production.

Several studies also show that pharmacological and, more importantly, physiological levels of glucocorticoid hormones can reactivate certain latent herpesviruses from virus genome-positive cells in vitro.[38-41] Increases in glucocorticoids associated with stress can result in some degree of suppression of the cellular immune response. Thus, reactivation of latent herpesviruses could be the result of a combination of immunosuppression and changes in the steady state expression of the latent virus induced directly by the hormones.[40]

In a series of human studies, we examined the effect of psychological stress on the steady state expression of latent EBV and HSV-1. First- and second-year medical students from The Ohio State University College of Medicine were assessed over less stressful periods (baseline) and during highly stressful examination blocks (several 2- to 3-day examination periods throughout the academic year). Students completed questionnaires at the time of blood sampling to provide data on anxiety and perceived stress. In this longitudinal study, a within-subject design was used so that each student served as his/her own control. In addition to the cellular immune changes summarized in Figure 1, we also found that examination stress was associated with changes in the steady state expression of latent EBV and HSV-1.[22,42] The data showed that examination stress resulted in higher plasma IgG antibody titers to EBV viral capsid antigen (VCA) IgG as compared to levels found at baseline. Concurrently, we also observed a significant decrease in the ability of EBV-specific cytotoxic T cells obtained during examinations to kill EBV-infected autologous B lymphocytes,[22] and a decrease in the virus-specific memory response of PBL to 5 purified EBV polypeptides.[43]

In the AD caregiver study, we confirmed that the stress associated with caring for a spouse with AD could also affect the expression of latent EBV. AD

caregivers had higher plasma EBV VCA IgG antibody titers than well-matched controls.[26] The average age of both AD caregivers and controls was approximately 70; therefore, antibody titer differences were not due to aging alone. However, other studies using healthy geriatric subjects have shown that aging does result in some loss of immunological control over latent EBV[44] and cytomegalovirus (CMV),[45] possibly due to age-related decrements in the cellular immune responses. Varicella-zoster virus (VZV), another herpesvirus, is the causative agent of the acute primary disease varicella (chicken pox) and also the painful vesicular disease called shingles (herpes zoster). Zoster is caused by VZV reactivation, and the incidence of zoster greatly increases with age and immunosuppression.[46] Stress has also been reported as a risk factor for reactivation of VZV and development of zoster, especially in older adults.[47] Modulation of latent HSV-1 was also observed in AD caregivers.[31] Caregivers had significantly higher IgG antibody titers to HSV-1 than well-matched control subjects, and the HSV-1 specific memory T-cell response was significantly reduced in the caregivers. These above studies were recently supported by data that show evidence for reactivation of latent CMV in AD caregivers.[48] The data provide additional evidence that psychological stress can be associated with poorer control over latent herpesviruses.

## IMPACT OF STRESS ON VIRAL INFECTIONS

Exposure to an infectious pathogen such as a virus does not always result in manifestation of clinical disease. The health of the individual prior to pathogen exposure, especially with regards to immune function, plays a major role in the pathogenicity of the infection. We can hypothesize that individuals whose immune system is already impaired would be at greater risk for developing an infectious illness or having more severe clinical symptoms if stress further downregulated immune function. Inoculating with a viral vaccine provides one way to test this hypothesis and control for pathogen exposure.

Accordingly, 48 medical students were given a recombinant Hep B vaccine to study how academic stress might affect the students' ability to respond to a primary viral antigen. The vaccine was administered in a series of 3 injections over 6 months, with each injection coinciding with a 3-day examination block.[23] We found that the students who were more stressed showed a delay in production of antibodies, and lower antibody titers to the vaccine after seroconversion. They also showed a decrease in the in vitro virus-specific T-cell response to the Hep B surface antigen. These results were confirmed in a later study conducted in The Netherlands.[49]

We subsequently administered an influenza virus vaccine to 64 AD caregivers and controls (mean age, 73).[50] Relative to the well-matched control subjects, AD caregivers had a poorer antibody response to the influenza virus vaccine as measured by two independent methods, ELISA and hemagglutinin inhibition (HAI). PBL from AD caregivers also produced less IL-2 in response to in vitro stimulation with influenza viral antigen, showing an inhibition of the virus-specific T-cell response. Moreover, after stimulation with lipopolysaccharide (LPS), PBL from caregivers produced less IL-1ß than that obtained from well-matched controls. The data obtained from these studies suggest that psychological stress is capable of modulating immune responses to vaccines, therefore placing individuals at risk for developing infectious diseases.

Although a vaccination mimics exposure to viral antigens, the ability of the immune system to eradicate an infectious pathogen cannot be measured because most vaccines are made from killed viruses, or components of viruses. Therefore, inoculating subjects with live virus is the best way to study the impact of stress on infections. Cohen and colleagues[51] inoculated 420 healthy human volunteers with 1 of 5 common strains of respiratory virus or a placebo. Clinical disease was verified by severity of cold symptoms, serologic status as compared to baseline, and/or viral isolation from nasal-wash samples. Psychological stress was associated in a dose-response manner with an increased risk of acute infectious respiratory illness, but not increased frequency of symptoms after infection.

## STRESS AND WOUND HEALING

The cellular immune response plays a major role in wound healing. Not only does it protect the wound site from infection, it also prepares the wound for healing and regulates its repair. Cytokines such as IL-1, IL-8, and tumor necrosis factor (TNF) are extremely important in recruiting phagocytic cells to clear away the damaged tissue and to regulate the rebuilding by fibroblasts and epithelial cells.[52,53] A decrease in expression in any of these cytokines could theoretically impair wound healing. We previously discussed how stress could suppress certain aspects of the cellular immune response such as mitogen stimulation, antibody and cytokine production, and NK cell activity. We chose to study how psychological stress and the associated changes in the cellular immune responses impact on wound healing.

In this study, 13 female caregivers of dementia victims and 13 female control subjects (mean age, 61) were given a uniform 3.5 mm full-thickness punch biopsy wound on the forearm, approximately 4 cm below the elbow. The wound was covered with a hydrocolloid dressing for one week. Photographs of the wound against a standardized dot were taken approximately every 2 to 3 days. Slides were digitized and wound size was expressed as the ratio of the wounded area to the standardized dot measurement. Hydrogen peroxide was applied daily to clean the wound and assess the foaming reaction. The functional barrier of the epithelium was verified, and the wound considered healed, when the site no longer foamed following the application of hydrogen peroxide. IL-1ß mRNA was measured in an ex vivo whole blood culture system.

Complete wound healing took significantly longer in the caregiver subjects than in the well-matched controls, with means of 48.7 days and 39.3 days, respectively.[54] That is, it took caregivers an average of 9 days (24% longer) to heal as compared to the control subjects. Both the wound size and the peroxide reaction were associated with caregiving stress. In addition, PBL from caregivers produced significantly less IL-1ß mRNA in response to LPS stimulation than PBL from the control subjects. These mRNA cytokine data were consistent with a previous finding from the influenza virus vaccine study,[50] where PBL from caregivers secreted less IL-1ß than that from the control subjects. IL-1ß produced soon after tissue injury is important in recruitment of inflammatory cells, mediating the remodeling of the connective tissue matrix, as well as fibroblast recruitment and the production of collagen.[53,55,56] Decreased levels of this important cytokine may therefore be linked with delayed wound healing.[57] Decreased wound healing, especially in the context of immunosuppression caused by stress, may have serious sequelae including increased infection, scarring, a poor esthetic outcome, and poor regenerative potential.

In conclusion, the studies reviewed above support the hypothesis that stress can have a significant impact on immune function, ranging from the down-regulation of B- and T-cell responses to decreases in cytokine production. These changes have been shown to be associated with reactivation of 3 latent herpesviruses, a decrease in the antibody and T-cell responses to 2 viral vaccines, an increased risk for clinical symptoms of colds, and delays in wound healing. The data suggest that the immune changes induced by stress appear to be large enough to be a health risk. Furthermore, since stress dysregulates inflammatory and immune responses, stress can alter the course of oral wound healing and affect the management of other oral diseases, e.g., periodontitis.

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