

Effects of Psychological Stress on Immune System

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Abstract

Background: Stress is the most influential entity of our lives today. Our body's defence system allows us to withstand stressful conditions. This ability might get altered if the person lives in a stressed environment over an extended time period. The objective of this review article is to understand how psychological stress impacts our immune system. **Methodology:** The study was conducted during the period May-June 2020. The literature review was made using online libraries like PubMed and Google Scholar. **Result:** It was thus understood that psychological stress would suppress the immune system by shifting from Th1 subset to Th2 subset of cells and through the actions of hypothalamus-pituitary-adrenal axis and sympathetic nervous system. Thus, making the body vulnerable to many diseases and unable to respond adequately to certain infections, injury or vaccinations. **Conclusion:** Chronic stress can lead to potential adverse effects on the immune system. The interventional methods for stress management might be helpful in improving immune responses of stressed patients.

Key words: Psychological Stress, Immunity, Cytokines, HPA Axis, Chronic

Introduction

Stress can be distinguished as acute and chronic stress. For example, the nervousness in a student just prior to entering the examination room could be understood as acute stress, while the stress experienced by him during the preparation period can be called as chronic. Chronic stress can also be best studied in people taking care of chronically or terminally ill patients. It is necessary to differentiate acute from chronic stress as the immune response of our body varies accordingly. When the person faces stress initially, the response of the immune system is actually protective to his body. The problem arises when this stress is experienced for longer durations. It is then

that the body's immune response starts getting suppressed. This occurs through collaborated actions of central nervous system and the immune system (*Vitlic et al, 2014*). As the immunity is weakened eventually, the body becomes prone to many abnormalities like impaired wound healing, infection to latent viruses, ineffective vaccination, skin disorders, cancer, etc.

Integrative Functioning of CNS and Immune System

As the body is exposed to the stress initially, the sympathetic response of fight-and-flight is exhibited by the release of catecholamines (sympathetic-adrenal-medullary axis). The hypothalamus-

pituitary-adrenal axis involves hypothalamic release of CRH which signals anterior pituitary for release of ACTH. This is the stimulation for the adrenal cortex to release corticosteroids (Vitlic *et al*, 2014). The corticosteroids, particularly cortisol, causes glucose to mobilize out of the cells. The rise in plasma glucose levels thus not only provides energy to cope up with the acute stress, but also stimulates the release of IL-6, a proinflammatory cytokine (Priyadarshini and Aich, 2012). It is also crucial to note that IL-6 is able to move across the blood-brain-barrier and stimulate the HPA axis (Hall *et al*, 2012). Moreover, norepinephrine potentiates the expression of NF- κ B gene, a transcription factor responsible for expression of genes of several inflammatory proteins. Thus, NF- κ B could be one way by which psychological stress gets transformed into chronic immune activation (Gouin *et al*, 2008).

As this stress gets chronic, the cortisol response starts diminishing via the negative feedback on the release of hormones from CNS (Priyadarshini and Aich, 2012). Another possible idea is that the mineralocorticoid receptors have more affinity for glucocorticoids paradoxically than the glucocorticoid receptors. Thus, initially during acute stress, they show pro-inflammatory actions. As the chronic stress follows, the mineralocorticoid receptors get fully occupied and the glucocorticoid receptors can regulate the anti-inflammatory actions (Vitlic *et al*, 2014).

During acute stress there are high levels of IL-6, IL-1 β , TNF α and IFN- γ . These are Th-1 or proinflammatory cytokines. When these cytokines are released for very long durations, they may produce harmful conditions, like septic shock. To counter this situation, there is a Th1-Th2 subset shift. Now, the Th-2 cells start releasing anti-inflammatory cytokines like IL-10, IL-13, IL-4. This is how the systemic inflammatory response syndrome

is transformed into compensatory anti-inflammatory syndrome (Priyadarshini and Aich, 2012).

Thus, the initial immune action in response to acute stress is immunoenhancing. This could be beneficial when exaggerated immune response is required, but deleterious in case of allergies and autoimmune diseases. The prolonged compensatory response generated during chronic stress could also lead to obesity and hypertension (Vitlic *et al*, 2014).

Wound Healing

Wound healing is studied as divided into three phases. The first phase, the inflammatory phase shows vasoconstriction and blood coagulation occurs. Also, there is a rise in inflammatory cytokines like IL-1, TNF- α and TGF- β . IL-1 further induces Th-1 cells to secrete IL-2, IL-6 and IL-8, which also contribute in the process of healing. IL-1 also stimulates matrix metalloproteinases (MMPs) and fibroblast chemotaxis at the injury site. IL-1, TNF- α and TNF- β attract phagocytes and other cells, thereby starting the proliferative phase in which there is cell replication and tissue regeneration. Finally, in the remodelling phase, there is realignment of collagen and wound contraction due to fibroblast activity (Gouin *et al*, 2011).

Psychological stress decelerates wound healing by affecting the inflammatory phase. The synthesis of IL-1 β m-RNA falls. The levels of other inflammatory cytokines also decrease in response to stress. Catecholamines released in high anxiety states can delay wound healing. The glucocorticoids diminish the expression of IL-1, TNF- α and PGDF, hence suppress the healing. Furthermore, oxytocin can be credited for enhanced wound healing by alleviating stress-induced cortisone production, as it was seen that the individuals who were taken care by their loved ones showed better healing.

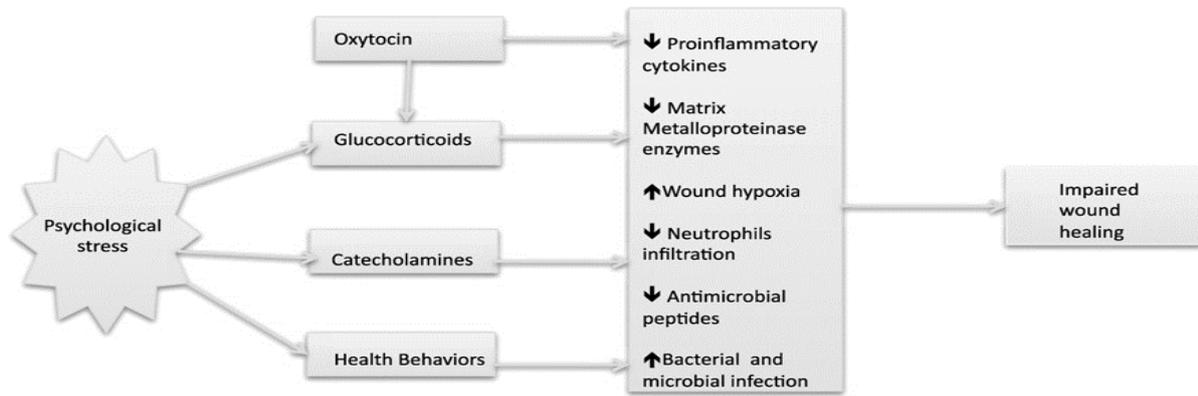


Figure.1 (Gouin, J. P., & Kiecolt-Glaser, J. K. (2011). The impact of psychological stress on wound healing: methods and mechanisms. *Immunology and Allergy Clinics*, 31(1), 81-93) shows impaired wound healing due to psychological stress

In women, higher plasma level of vasopressin is also concerned with faster healing. Psychological stress also induces wound hypoxia and reduced infiltration of cells at the injury site (Gouin et al, 2011).

Cancer Metabolism

Chronic stress suppresses multiple aspects of protective immune response which increases susceptibility to cancer. Psychological stress exacerbates chronic inflammation and enhances immune-suppressive pathways as well. Chronic inflammation is critical for tumour initiation, progression and metastasis. It causes mutations in DNA, oxidative stress, release of factors like MMPs which leads to tumour invasion, and factors that promote angiogenesis and metastasis. Chronic stress is seen to suppress expression of gene responsible for cutaneous-T-cell-attracting chemokine (CTACK/CCL27) that recruits T cells for immune activation. This is due to suppression of infiltration of CD4+ and CD8+ T cells along with the suppression of Th-1 cytokines, thus inhibiting immune-protection. In addition, chronic stress enhances immunosuppression by proliferation of suppressor/regulatory T cells (CD4+CD25+) in the tumour and in the circulation (Antoni and Dhabhar, 2019).

Chronic stress induced glucocorticoids and catecholamines

mediated mechanisms also suppress immune responses against cancer. Breast cancer patients with higher cortisol concentrations and more depressive symptoms showed significantly weak cell mediated immunity. Lower anxiety states showed higher synthesis of IL-2 followed by anti-CD3 (T-cell receptor) induction, while happier mood resulted in rise in IL-12 and IFN- γ levels. In patients with ovarian cancer, depression caused retardation of NK cell cytotoxicity (NKCC) and production of T-cell cytokines (Antoni and Dhabhar, 2019).

Cutaneous Response to Stress

A variety of psych dermatologic disorders have been reported, for example, rosacea, lichen planus, alopecia areata, pruritis and atopic dermatitis. The skin also has a parallel HPA axis that functions in tune with that of CNS. Human skin expresses CRH and its receptors. CRH-R1 α is predominant in skin and expressed mainly in epidermis, dermis and subcutis. While, CRH-R2 is predominant in hair follicles, eccrine and sebaceous glands and muscles. Alopecia patients under stress have shown higher CRH-R2 expression around the hair follicles of the affected areas, while CRH-R1 was upregulated in patients suffering from urticaria and contact dermatitis (Hall et al, 2012).

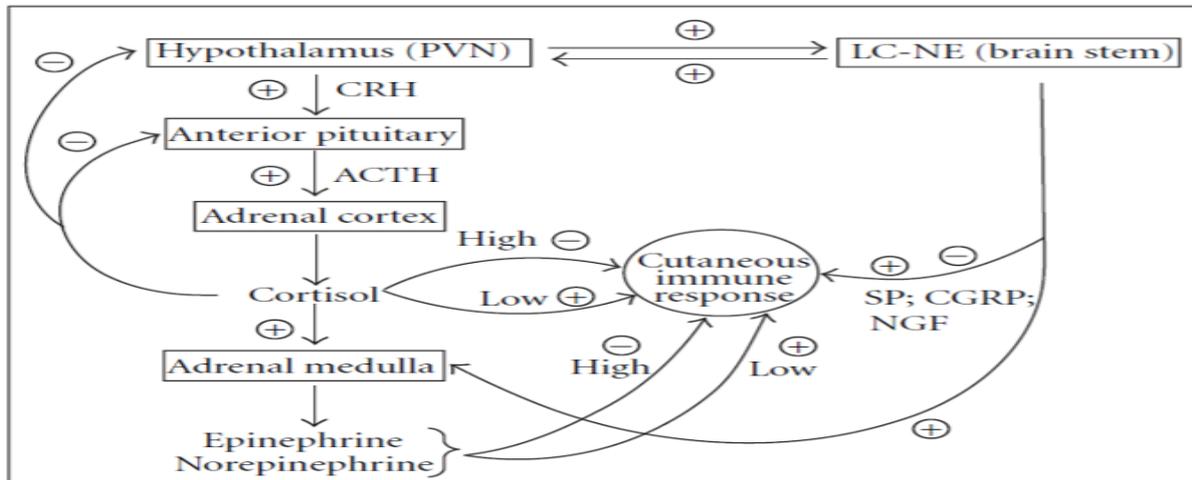


Figure.2 (Antoni, M. H., & Dhabhar, F. S. (2019). The impact of psychosocial stress and stress management on immune responses in patients with cancer. *Cancer*, 125(9), 1417-1431) shows altered immune response in cancer patients under acute and chronic stress.

CRH, when binds to CRH-1, stimulates the release of proopiomelanocortin protein (POMC) and its peptides that leads to an increase in ACTH, melanocyte stimulating hormone (MSH), and β -endorphin from the pituitary gland. Additionally, skin is innervated by abundant sensory fibres derived from dorsal root ganglion (Arck *et al*, 2006). Psychological stress causes increase in levels of nerve growth factor (NGF) in skin, which performs a variety of functions that include axonal growth of sympathetic and peptidergic neurons, enhancing interaction between neurons, glial cells, and cells of immune system, and promoting movement of macrophages across vascular endothelium. Is also upregulates calcitonin gene-related peptide (CGRP), a strong vasodilator. Mast cells are also found on the dermis and express CRH receptors. ACTH and CRH can activate mast cells. The expression of CRH-1 receptors on mast cells is by substance-P. Acute psychological stress stimulates mast cells to release IL-6 (Hall *et al*, 2012).

Chronic stress leads to immunosuppression, even in skin graft rejection. Also, chronically released glucocorticoids cause apoptosis of Langerhans cells. Glucocorticoids also retard the release of IL-12 from dendritic

cells. The suppression of IL-12 would switch the Th1/Th2 balance towards Th-2, thereby modulating immune response. Moreover, CGRP affects antigen presentation by Langerhans cells by causing antigen presentation to Th-2 subset instead of Th-1 subset. In addition, substance-P also binds to Langerhans cells leading to impaired antigen presentation and T-cell responses (Hall *et al*, 2012).

Vaccination Responses

Psychological stress also renders the patient with an inability to respond adequately to certain vaccinations, like tetanus immunization, influenza virus immunization, etc. this could be due to dysregulated cortisol production, inadequate antibody production and suppressed T- and B-cell functions. Such observations have been made in depressed people like those taking care of dementia patients or the ones in an unhappy marriage. Chronic stress mediated impaired vaccine responses might continue to exist even after removing stress stimuli (Gouin *et al*, 2008).

Latent Viral Infections

Certain viruses, like Herpes virus, are known to cause latent infection after

the primary infection. Such viruses might get reactivated if the host's cellular immunity is diminished. Chronic stress can be associated with poor defence against latent viruses. This could be mediated by decreased Ig-G antibody production and T-cell responses (*Gouin et al, 2008*).

Prenatal and Early Life Stress

Anxiety in pregnant women, especially during third trimester, is seen to be linked with asthma in children born to them. Infants born to women exposed to any kind of violence, direct or indirect, have higher chances of developing asthma. Not only during pregnancy, but psychological stress during any time of life (e.g., neglect in childhood or adolescence, violence by partner, rape, witnessing family violence, physical abuse, depression) have shown rise in plasma levels of C-Reactive protein (CRP), a systemic inflammation biomarker. Higher CRP levels in women have resulted in greater chances of asthma in their children by the age of 3 years. Interestingly, boys are assumed to be more vulnerable to prenatal stress, while girls are more affected by postnatal stress (*Rosa et al, 2018*).

Early life stress could be seen in case of maltreatment, maternal separation, abuse, etc. such children are reported to have greater inflammatory processes in later life. Early life stress might cause greater reaction to immune and psychosocial challenges. The inflammatory biomarkers (like CRP, fibrinogen, WBCs) were seen to be elevated in maltreated children. Such elevation in inflammatory responses is known to be related with the development of major psychological abnormalities like schizophrenia, bipolar disorder, etc. Children with major depression have shown higher IL-6 levels and NF- κ B binding with DNA. Psychological stress might also impair the development of acquired immunity (*Danese and Lewis, 2017*).

Telomere and Cell Senescence

Telomeres are capped at both the chromosomal ends and ensure chromosomal stability and regulate lifespan of replication of the cell. Telomeric length is shortened with every subsequent replication. Telomerase can only partially reconstruct the telomeres after each cycle. Once the telomeres are reduced up to a certain length, the cell enters the phase of senescence. This is associated with the normal aging process. Chronic stress causes shortening of telomere length, reduced telomerase activity and increased oxidative stress. Shorter telomeres have been observed in PBMCs and T-cells. This could explain the accelerated senescence of immune system under chronic stress (*Gouin et al, 2008*).

Conclusion

Psychological stress can significantly suppress the immune system and cause chronic inflammation. This could result in the development of severe disorders, like asthma in neonates and certain dermatologic disorders. It also retards defensive response against cancer and latent viral infections and even cause ineffective vaccination response and delayed wound healing. Interventional methods for stress management could be an aid to improve immunity in stressed patients. Such methods have shown positive outcomes in cancer patients and others. There is still a need for a better understanding to how reduction in stress could be employed to the benefits of enhancing immunity in a broader spectrum of patients.

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