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A Review on Immunomodulation triggered by psychological stress and its effects on health

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Abstract:
Our daily lives are filled with stress and stressful events, and these unpleasant circumstances cause intricate modifications in the biological system. These stress reactions affect the immunological, neuroendocrine, and cerebral systems. They also affect the chest rate, which can either raise or diminish the organism's capacity to withstand these stressors. Peripheral reactions to stress are regulated by the brain through the expression of intricate behavioural paradigms, and there is a bidirectional relationship in the modulation of stress effects. Anxiety disorders can arise from both acute and chronic stress exposure, as anxiety is a typical neurobehavioral correlate of a wide range of stressors. The relationship between the immune system and the brain is known as psycho neuroimmunology, and there is growing evidence that the immune system may influence how the brain and body react to stress. Anxiogenesis and immunomodulation during stress may be related, according to studies demonstrating the potential influence of the brain and its intricate neurotransmitter networks on immunological function. The current study provides an overview of the link between stress, anxiety, and immunological response. Physiological and pharmacological studies have underlined this idea.

Keywords:
Immunomodulation, Anxiety, Anxiogenesis, Neuroimmunology, Neurobehavioral.

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I. Introduction:

Psycho neuroimmunology (PNI) is a discipline that has attracted a great deal of interest from researchers and clinicians due to studies on how stress affects the immune system. The study of PNI focuses on how behaviour affects the interactions between the immune system, endocrine system, and central nervous system (CNS), as well as how these connections affect health. It has long been known that the CNS can alter the immune system. A sophisticated network of signals that facilitates bidirectional communication between the immunological, endocrine, and neurological systems controls how the central nervous system (CNS) modulates the immune system. According to recent research, psychological stress can dysregulate or downregulate immune responses by causing this network's signals to become dysregulated. Psychological stress modulates the immune system through two "pathways": the sympathetic-adrenal medullary (SAM) axis and the hypothalamic-pituitary-adrenal (HPA) axis. Furthermore, the autonomic nervous system innervates both primary and secondary lymphoid tissues. Through the production of biological mediators, these pathways interact and impact immune system cellular components. We go over how cellular immune function is affected by psychological stress in this review. We discuss research on stress and its impact on the immune response to infectious pathogens in humans and animals within the context of this study, highlighting the significance of these effects on health. An

overview of the nature of the interactions between the immune system, endocrine system, and central nervous system will be given. The research that clarified how psychological stress affects the immune system will be covered. We will conclude by quickly going over the detrimental impact that daily psychological stress can have on the immune system and how it can affect the healing of wounds and infectious diseases. [1] [2]

Stress and The Immune System

According to research on stress and immunity in humans and experimental animals, psychological difficulties can alter many aspects of the immune response (MacQueen & Bienenstock, 2006; Padgett & Glaser, 2003). Research utilising animal models has demonstrated that stress modifies autoimmune disorders, decreases wound healing, increases the pathogenicity of viruses and bacteria, and reduces vaccine responses (Yang & Glaser, 2000). According to these studies (Glaser, Rabin, Chesney, Cohen, & Natelson, 1999; Yang & Glaser, 2002a), stress hormones inhibit the trafficking of neutrophils, macrophages, antigen-presenting cells, natural killer (NK) cells, T and B lymphocytes, and they downregulate the production of cytokines required for the generation of adaptive immune responses. They also impair the effector functions of macrophages, NK cells, and lymphocytes. Different stresses may affect immunity differently—acute vs. chronic. In the findings of Dhabhar and McEwen (1997), rats' acute and chronic exposure to radiation seems to have opposing effects on their delayed type hypersensitivity (DTH) reactions. In other words, DTH responses in the skin were increased after a single session of restriction before the challenge, but they were decreased after repeated sessions of chronic restraint in comparison to control mice. These effects might be mediated by the adrenal hormones corticosterone and epinephrine. According to certain theories, acute stress may cause peripheral blood lymphocytes to "redeploy" to the skin, which would be an adaptive reaction that occurs during the "flight and fight" response (Glaser et al., 1999; Yang & Glaser, 2002b). Rat lymphocytes' mitogen responses were also inhibited after a single intermittent foot shock session, but this suppression only occurred when beta endorphin was produced; it was unaffected by the higher levels of corticosterone that were seen with both intermittent and continuous shock. Mice that had a single foot shock treatment had their plaque for Ming cell responses and serum antibody titers to sheep red blood cell immunisation inhibited. Furthermore, several researchers have looked into how acute stressors affect the cytotoxicity of NK cells. Acute stress nearly always has a suppressive effect on natural killer (NK) cell function, as these cells lyse cancer and virally-infected cells on their own. IFNγ can also boost the action of these cells. (Dhabhar, Miller, McEwen, & Spencer, 1995; Petticrew & Hunter, 1999).In rodent and nonhuman primate models, as well as in humans, prolonged stress is generally linked to the inhibition of NK cell responses and antigen-specific immune responses. According to Brosschot et al. (1998), immune function deficiencies caused by stress should put people at risk for weakened immunological responses after viral infections. It has been demonstrated that after contracting a rhinovirus in a lab, those who felt more stressed out had greater infection rates. According to more recent research, people with low levels of NK cells were more likely to self-report upper respiratory infections at times of high stress as opposed to lowstress. The introduction of stressors can change the balance between Th1 and Th2cell activity or cytokine production (Kim & Maes, 2003). There is no change in the production of IL-2 or IFN-γ, but there is a highly substantial elevation of Th2 cytokine IL-4 specific to keyhole limpet hemocyanin (KLH) during exposure to the odours produced by stressed BALB/c mice. It's interesting to note that elevated serum IgM and IgG anti-KLH antibodies were linked to this rise in IL-4 production (Calcagni &Elenkov, 2006). Furthermore, after being stimulated with T-cell mitogen, lymphocytes from rats that had an involuntary tail shock generated less IFN-γ. On the other hand, chronic RS was found to dramatically reduce the Th1- (IL-2 and IFN-γ) and Th2-derived (IL-10) cytokine responses after the influenza virus infection of C57B1/6 mice in another investigation. Differed neuroendocrine responses that cause alterations in one kind of Th cell, but not necessarily both, may account for part of the observed varied effects of stressors on immunological parameters (Kiank et al., 2006; Reiche, Nunes, & Morimoto, 2004). According to Wilckens and De Rijk (1997), glucocorticoids seem to play a key role in regulating each person's unique repertoire of immunological responses, including the strength and course of those reactions. Infection, trauma, and other immunologically linked stressors can resolve if glucocorticoid-dependent processes are appropriately balanced (Jessop &Harbuz, 2003). Disruption or failure of these dynamic interactions, however, may lead to an acute inflammatory response that is deadly or may put one at risk for autoimmunity or atopic reactions. Glucocorticoid receptors are found on many immune cells, where they bind cortisol and disrupt NF-κB, an enzyme that controls the activity of immune cells that produce cytokines (Riccardi, Bruscoli, &Migliorati, 2002). By binding to both norepinephrine and adrenaline, as well as activating the c-AMP response element binding protein, adrenaline receptors stimulate transcription of genes that code for a range of cytokines. Dysregulating immune function can result from glucocorticoid hormones and catecholamines-mediated modifications in gene expression (Leonard, 2006). There is evidence to support the hypothesis that immunity and the brain are related. Immune homeostasis is maintained via communication between the neurological and immune systems, according to data. The immune system and the central nervous system (CNS) are bidirectionally regulated because immune system activation leads to the production of cytokines and inflammatory mediators. These mediators cause the release of hypothalamic CRF, which in turn

triggers the release of the same immunosuppressive molecules that mediate the stress response (Haddad, Saade, & Safieh-Garabedian, 2002). According to Huang, Pang, Karalis, and Theoharides (2003), the antibody response has been shown to trigger metabolic changes in the central and peripheral nervous systems for ACh, NA, 5-HT, and DA. These changes can subsequently impact immune function by binding to neurotransmitter-relevant receptors on immunocytes.

Central Nervous system, Anxiety & Behaviour

The brain plays a crucial role in perceiving and reacting to potentially stressful situations. Stress hormones, especially glucocorticoids, act on the brain. Unavoidable, acute, and traumatic stressors can alter behaviour and the brain in long-term ways (Joca, Ferreira, & Guimaraes, 2007). The hippocampus, amygdala, and prefrontal cortex have all been shown to have neurological correlates for the behavioural deficiencies. These correlates include features of cell proliferation and structural remodelling, as well as modifications to the amine, neuropeptide, and corticosteroid systems (Herman et al., 2003). Stress exposure sets off a cascade of coordinated reactions that may alter how the brain functions. Stress-induced activation of the brain's neurotransmitter systems, including signal transduction pathways mediated by neurotransmitter receptors, is responsible for the majority of the alterations in brain function. Stress-induced alterations in neuronal functioning are ultimately caused by the signal transduction pathways. However, depending on the type and length of stressful stimuli, some of these alterations may be advantageous. Negative changes in neural processes, on the other hand, may result in several illnesses.It is important to consider how the brain responds to both short-term and long-term stress in terms of its ability to exhibit adaptive plasticity. Research conducted in numerous labs has demonstrated that the hippocampal neurons express receptors for circulating adrenal steroids. These receptors mediate a range of effects on neuronal excitability, neurochemistry, and structural plasticity (McLaughlin, Gomez, Baran, & Conrad, 2007). The replacement of nerve cells in the dentate gyrus and the control of dendritic branching and length in the pyramidal cells of Ammon's horn are examples of these effects involving hormone-mediated effects on gene expression (Sandi et al., 2003). Many of these hormone effects are part of ongoing neural activity rather than occurring in isolation. Specifically, serotonin, NMDA receptors, and excitatory amino acids contribute significantly to the morphological and functional alterations in the hippocampus formation brought about by steroid hormones. In addition, the hippocampus has intracellular oestrogen and androgen receptors and is gonadal hormone sensitive (Karst & Joels, 2003). In addition to developing mental events like sexual differentiation and the effects of early stressful life experiences, gonadal and adrenal hormones play a role in the functional and structural changes that occur in adulthood (Adamec, 2003). Both humans and animals may have long-lasting behavioural changes in response to severe stress. It's interesting to note that recurring seizures can cause long-lasting emotional alterations in humans and animals, such as behavioural changes and kindling, by infiltrating the limbic system circuitry (Adamec & Young). Decreases in glucocorticoid receptor mRNA expression in the dorsal hippocampus's CA1 subdivision are linked to these behavioural alterations. Numerous studies have shown that the amygdala is essential to the brain circuitry that underlies stress and anxiety in addition to being crucial for emotional learning. The amygdala may contain the molecular substrates for stress-induced alterations in emotional behaviour, according to recent research (Rademacher et al., 2008). A crucial element in the chain of molecular processes connecting the development of anxiety-like behaviour and recurrent restraint stress (RS)-induced plasticity has been found to be the serine protease tissue plasminogen activator in the amygdala (Bennur et al., 2007). Research suggests that the same prolonged immobilisation stress that results in dendritic hypertrophy in the basolateral amygdala might also produce dendritic atrophy in hippocampal CA3 pyramidal neurons. More significantly, the type of stressor that causes this type of dendritic remodelling in the basolateral amygdala is critical: long-term immobilisation stress, but not long-term unpredictable stress, causes dendritic remodelling of spiny neurons in the basolateral amygdale (Vyas, Mitra, Shankaranarayana Rao, &Chattarji, 2002). According to Pawlak et al. (2005), an acute stress episode may set off a series of chemical events linked to structural modelling in the amygdala within hours, which may ultimately result in the development of anxiety. A complicated illness, depression manifests as a collection of related clinical symptoms. Anatomical research has demonstrated that reversible alterations in hippocampus volume are associated with clinical symptoms in certain patients. These volume variations were thought to be connected to stress-induced decreases in dentate gyrus neurogenesis and adult proliferation. Remarkably, antidepressant tianeptine reverses the suppression of proliferation brought on by stress (Czeh et al., 2001). It is currently unknown whether the identification of responsive target genes indicates that the effects of long-term or recurrent stressors on hippocampal remodelling occur directly through MR- (mineralocorticoid receptor) and GR- (glucocorticoid receptor)-mediated actions on structural and cell cycle genes in neurons. To distinguish between GR- and MR-mediated effects, a variety of chaperones, auxiliary proteins, coregulators, and interacting transcription factors are involved in the complex corticosteroid signalling cascade. After extended periods of stress, this could change (Garcia, Steiner, Kronenberg, Bick-Sander, &Kempermann, 2004). Apart from the corticosteroid receptors, there are other mediators that have been linked to altered brain function following chronic stress, including growth factors and the central monoaminergic system. Noradrenaline and

CRH reciprocally increase each other's activity in the amygdala-locus coeruleus circuitry during prolonged stress. Chronic stress reduces the pleasant effects of activating the mesocortical dopaminergic system and decreases dopamine release in a number of terminal regions, including the hypothalamus, especially when coping is impossible (Holsboer, 2000). Corticosteroid receptors and the monoaminergic system work together to create alterations in the brain. GRs are rather resistant to the effects of prolonged stress, hence it is likely that brain MRs are the primary mechanism for this. Additionally, modifying the hippocampus's noradrenergic, peptidergic, and 5-HT inputs increases the expression of MR in particular. Given that the MR is a critical regulator of dentate gyrus neurogenesis and cell death, this could have a significant impact on the integrity of the dentate gyrus. Consequently, antidepressant-induced MRs may mediate the recently documented pharmacological effects on neurogenesis (Sabban &Kvetnansky, 2001). Few research exist that include female patients and show that males and females can respond differently, or even in the opposite way, from one another, despite the majority of studies using animal models of depression and behavioural response to antidepressants (McEwen, 2003). To fully comprehend the behavioural variations between males and females in response to both acute and chronic stressors, more research is necessary.

The process underlying the stress response

When one is exposed to adverse environments, often known as stressors, the body mounts a coordinated defence mechanism designed to increase the likelihood of surviving. Often called "stress responses," these coordinated reactions include changes in behaviour, autonomic function, and the release of several hormones, such as oxytocin, prolactin, renin, adrenal catecholamines, and adrenocorticotropin hormone (ACTH) and cortisol/corticosterone (Gold &Chrousos, 2002). In order to maintain brain and muscle function, the body releases energy during a stress response. Other physiological changes include: (i) increased cerebral perfusion rates and local cerebral glucose utilisation; (ii) sharpened and focused attention on the perceived threat; (iv) enhanced cardiovascular output and respiration, and redistribution of blood flow, increasing substrate and energy delivery to the brain and muscles; (v) immune function modulation; (vi) inhibition of reproductive physiology and sexual behaviour; and (vii) decreased feeding and appetite. These premeditated reactions are designed to change the internal environment in a way that raises the likelihood of survival.Stressors can be broadly classified into four categories: (a) psychological stressors, which stem from a learned reaction to the possibility of an unfavourable situation (fear, anxiety, exposure to an unfamiliar or unpredictable environment); (b) physical stressors, which involve a physical stimulus and have a significant psychological component (pain, foot shock, immobilisation); (c) cardiovascular stressors, which involve physical exertion, exercise, heat exposure, orthostatic stress/upright tilt, haemorrhage, and so on); and (d) social stressors, which involve interpersonal interactions among individuals (death of a partner, divorce, joblessness, etc.). It is thought that the neuroendocrine reactions to stresses are crucial survival mechanisms when faced with potentially fatal events.Stressors can be classified as either (a) acute stressors (single, intermittent, time-dependent exposure) or (b) chronic or recurring stressors (intermittent long-term exposure and continuous long-term protracted exposure).

Relationships between the immunological, endocrine, and neurological systems:

It is well known that there are bidirectional interactions between the immune systems and the central nervous system (CNS) that lead to immune system control. By causing the pituitary gland to release neuroendocrine hormones, stress-induced activation of the HPA axis affects the immune system. Lymphoid and myeloid cells can react to signals from the HPA axis by activating or downregulating their activity, which is mediated via receptors for neuroendocrine hormones and neuropeptides. Furthermore, the catecholamine receptors on these cells, which include norepinephrine and adrenaline, allow them to react to signals coming from the SAM axis. Interleukin 1 (IL-1) and other cytokines that can be prompted to be released by immune cells can then cause the hypothalamus to produce more corticotrophin-releasing hormone (CRH). The pituitary gland and the adrenal cortex, respectively, release corticotrophin-releasing hormone and adrenocorticotropic hormone (ACTH) and corticosterone or cortisol in response to this stimulus. Subsequently, these "stress" hormones may dysregulate immune responses and have adverse health repercussions. It has been demonstrated that lymphocytes are capable of producing hormones such as prolactin, growth hormone, and ACTH in addition to cytokines. It's interesting to note that glucocorticoids and peptides like ACTH, endorphins, substance P, and somatostatin have also been shown to influence a number of immune response-related processes, including the growth of B and T cells, the production of cytokines and antibodies, the chemotaxis of monocytes and neutrophils, and the cytotoxicity of natural killer (NK) cells.Furthermore, noradrenergic sympathetic and peptidergic nerve fibres of the autonomic nervous system innervate main and secondary lymphoid organs such as the bone marrow, thymus, spleen, and lymph nodes. Through the creation of neuroeffector junctions, the intimate relationship between these nerve terminals and immune cells enables direct neural–immune interaction. These connections cause the production of neurotransmitters such as substance P and norepinephrine, which can then impact immune cells nearby or far away, such as in the lymph node's microenvironment, and alter how they

operate. Collectively, findings suggest that stresses might trigger the release of multiple "stress hormones" from the CNS, HPA, and SAM axis, which can modulate immune cell activity and cell trafficking.

Dysregulation of immunological response and cytokine production brought on by stress

Numerousneurotransmitter receptors have been found on lymphocytes, monocytes/macrophages, and granulocytes. Through the modulation of cAMP levels, catecholamines have been shown to indirectly affect immunological processes such as lymphocyte trafficking and proliferation, antibody formation, and cell lysis. Furthermore, it has been demonstrated that administering catecholamines to peripheral blood leukocytes (PBLs) in vitro causes an increase in IL-10 synthesis while suppressing IL-12 synthesis. T-helper (Th) cells may become less involved in cell-mediated immunity (Th1 cells) and more involved in the generation of antibodies (Th2 cells) as a result of this. These in vitro investigations are supported by recent research that employ an academic stress paradigm. Marshall et al.'s observations [28] indicate that the psychological strain brought on by medical students' exams may cause a shift in the Th1/Th2 cytokine balance in favour of a Th2 response. According to their findings, PBLs isolated from healthy medical students who were under stress from medical school exams produced more IL-10, a Th2 cytokine, and less interferon-gamma (IFN-g). This led to a decrease in the IFN-g/IL-10 ratio during the post-exam (stress) period compared to the pre-exam (non-stress) period. It is postulated that this downregulation of the Th1 cytokine response may lead to a reduction in cell-mediated immunity, hence raising the risk of viral, fungal, and mycobacterial infections. In animal studies, this stress-induced Th1/Th2 transition has also been noted. According to a constraint stress model applied in mouse studies, stress is also responsible for a shift in the Th1/Th2 balance in favour of Th2 dominance. After 24 hours of restriction, there was a notable drop-in NK cell activity, a reduction in IFN-g production by Concanavalin A (Con A)-stimulated splenocytes, and a simultaneous rise in serum corticosterone levels. Furthermore, it was found that the ability of Con A-stimulated splenocytes to generate IL-4 was unaffected by restraint stress.According to a different study, when Listeria monocytogenes is present, constraint stress can reduce leukocyte migration and Th1 cytokine production while increasing Th2 cytokine expression. Research conducted in our group has demonstrated that exam stress can lower NK cell function, PBLs' sensitivity to mitogens, Con PBL-stimulated IFN-g production, a decline in the hepatitis B vaccination-induced antibody and virus-specific T-cell response, and alterations in the immune system's capacity to regulate the expression of latent herpesviruses like Epstein-Barr virus (EBV) and herpes simplex virus type 1 (HSV-1). [29] Additionally, these medical students mentioned that taking exams was linked to a higher frequency of upper respiratory tract infections.Additionally, compared to baseline and control levels, it has been demonstrated that extended durations of academic stress were linked to a considerable decrease in salivary IgA secretion upon awakening. This implies that those under stress related to their studies have fewer first-line defences against microorganisms that invade the gastrointestinal tract's mucosal lining, making them more vulnerable to infectious diseases. We compared a group of patients caring for a spouse with dementia, including Alzheimer's disease (AD), to non-caregiver controls in order to investigate the effects of long-term stress on the immune system. Stress-related deregulation or downregulation of cellular immune responses was observed in dementia carers. For example, PBLs from the carers showed decreased NK cell response to recombinant IL-2 and IFN-g, suppression of T-cell responses to Con A, PHA, an antibody to the T-cell receptor, and a poorer proliferative (memory) response to HSV-1. Documents created by physicians also indicated that carers had a greater frequency of respiratory infections. Comparing spouse carers of dementia patients to well-matched controls, we also recently discovered that plasma levels of nerve growth factor (NGF) were linked to high levels of subjective stress and despair. This demonstrates even further how the nervous system plays a role in the HPA axis' activity. More proof that psychological stress leads to the dysregulation of proinflammatory cytokines comes from recent data on IL-6 levels. Human stress and depression have been linked to higher levels of serum IL-6, as demonstrated by Maes et al. These outcomes are in line with those of rats that, following exposure to different stressors, show elevated levels of plasma IL-6. The rise in plasma corticosterone was accompanied by the observed elevation in plasma IL-6. All of these findings are consistent with the hypothesis that IL-6 and other proinflammatory cytokines contribute to the HPA axis' activation in response to psychological stress. [29] [30] [31] [32]

II. Conclusion:

In conclusion, this review paper has delved into the intricate relationship between psychological stress, immunomodulation, and their profound impacts on health. Through an extensive exploration of existing literature, it is evident that stress, whether acute or chronic, can significantly influence the immune system, leading to a cascade of immunomodulatory responses that can either enhance or impair immune function.The bidirectional communication between the brain and the immune system, mediated by various pathways such as the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system (SNS), plays a pivotal role in modulating immune responses during stress. Furthermore, the influence of stress on inflammatory cytokines, immune cell trafficking, and the balance between pro-inflammatory and anti-inflammatory processes has been

thoroughly discussed, highlighting the intricate mechanisms by which stress can shape immune function.Importantly, the impact of stress-induced immunomodulation on health outcomes has been elucidated, with evidence suggesting that chronic stress and dysregulated immune responses are associated with an increased risk of various health conditions, including autoimmune diseases, cardiovascular disorders, and mental health disorders. Conversely, strategies aimed at mitigating stress, such as mindfulness-based interventions, cognitive-behavioural therapy, and stress management techniques, have shown promise in restoring immune homeostasis and improving overall health outcomes.In light of these findings, it is imperative to recognize the complex interplay between psychological stress and the immune system and to implement holistic approaches that address both mental well-being and immune health. Future research endeavors should focus on elucidating the underlying mechanisms linking stress, immunomodulation, and disease pathogenesis, as well as developing targeted interventions that optimize immune function and promote resilience in the face of stressors. By fostering a deeper understanding of this intricate relationship, we can pave the way for innovative strategies to enhance immune resilience and improve health outcomes in individuals facing psychological stress.

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