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Review Article

A REVIEW ON IMPACT OF PSYCHOLOGICAL STRESS IN IMMUNE RESPONSES IN DIFFERENT PATHOLOGICAL AND PHYSIOLOGICAL CONDITIONS

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Abstract:

Stress is the common psychological discomfort. Stress generally physical, psychological, acute stress and chronic stress. The factors which cause the mental stress are called stressors. Stress can affect various organ systems in our body.

Mental stress may alter immune system and cause vulnerability to infections. It affects both cell mediated and humoral immunity.

Physical and psychological stress causes the activation of Hypothalamic pituitary adrenal axis. And hypothalamus increase the release of corticotrophin releasing hormone [CRH] and anterior pituitary release adrenocorticotrophin hormone. Thus, increase serum levels of corticosteroids.

Psychological stress can promote the infectious diseases like tuberculosis. Also, Herpes simplex and Epstein Barr virus infection may re-activate because of mental stress.

The psychological stress has high impact on immune system in various levels. Because novel diseases like COVID – 19 largely effected by psychological stress. The research and practice on stress reduction techniques are highly relevant can be considered as useful prevention method.

Keywords: Psychological stress, Immune system

Introduction:

According to William C Stress is a physical, mental, or emotional factor that causes bodily or mental tension.[1] Stress is the common psychological discomfort. Stress generally physical, psychological, acute stress and chronic stress. The factors which cause the mental stress is called stressors. Mainly stress is caused by emotional factors, health issues, work pressure, academics, bereavement, financial or environmental factors.

Commonly stress produce symptoms like confusion, restlessness, nausea, vomiting, headache etc. Excessive stress may form diabetes, ulcer, cardiovascular disorders.[2]

Psychosocial factors are the major influence of many diseases. Stress can affect various organ systems in our body. Mental stress may alter immune system and cause vulnerability to infections.[3]The main role of immune system in our body to differentiate self and non - self agents. The immune system, detect antigens like viruses, bacteria and protect our body by production of antibodies.[4]

Various type of stresses differently effect production of stress hormones. [5]Most of cases immune system downregulated by mental stress. But some cases inter-individual variation takes place.[6] Stress induced immune modifications mainly by increased production of glucocorticoids. [7]

It effects both cell mediated and humoral immunity. Stress causes changes in T- Lymphocytes, Natural

killer [NK] cells, Nerve Growth Factor [NGF], C - reactive proteins etc. [5]The immune system effected mainly by Wiring system in lymphoid organs and soluble connection in neuro endocrine system.[3]

The immunological system changes mainly effect on in the case of infectious diseases. Also reduce wound healing, failure in vaccine responses, chance of cancer or other diseases.[8]

Stress has detrimental effect on neuroendocrine immune system by various aspects. The persons who have psychological stress must be assessed and preventive measures to take reduce detrimental alteration in immune system.

Self-assessment tools or questionnaires by health professionals can apply to mind-fulness based stress reduction [MBSR], progressive muscle relaxation, nutritional interventions, better sleep techniques can apply to reduce the psychological stress. [5]But the stress induced multiorgan system changes less discussed and underestimated.

1.Effect of stress on neuroendocrine system

Physical and psychological stress causes the activation of Hypothalamic-pituitary adrenal axis. And hypothalamus increase the release of corticotrophin releasing hormone [CRH] and anterior pituitary release adrenocorticotrophin hormone. Thus, increase serum levels of corticosteroids.

Also, the stress induced activation of sympathetic system will produce increased level of catecholamines in blood. They bind to G protein coupled glucocorticoid receptors and increase Camp. So that immune down regulation takes place.

The Prolactin and Growth hormone secretion increased in stress; it has immune-stimulating mechanism.[5]

Effect of stress on T – Lymphocytes

Natural killer cells, N K Cells are part of T lymphocyte. It has role in killing of virus, bacteria etc. Their activity increase level of interferon -gamma and Interleukin 2. In stress conditions decreased production of NK cells and subjects are prone to infections. For example, stress increase chance of footpad infection by Herpes simplex virus [HSV-1] [9]

T lymphocytes are main part of cell -mediated immunity. These are T helper cells, cytotoxic T cells [CD 8+ CELLS] secrete cytokines. They also activate B lymphocytes. Psychological stress in different population the significant reduction in T helper cells takes place. Memory of T cells to kill Epstein – Barr virus also decreases. [10]

Effect of stress on B lymphocytes

Engulfment of foreign antigens by antibodies is the function of B lymphocytes. T cells producing cytokines promote B cell activation. The Ig A levels are increased and Ig G, Ig M and salivary IgA levels as unchanged.[11] In some studies Ig G, 1,2, Ig M and Ig A levels increased due to stress. [12]

Effect of stress on cytokines

Cytokines are important part of innate and adaptive immune system. Cytokines include Interleukins, Tumor necrosis factor etc. The caregivers of Alzheimer's patients having high stress and IL-6 found to be higher.[13] IL-6 production also high in dermatological patients with marital stress.[14] IL-6 also increased in the time influenza vaccination in persons having stress compared to normal persons.[15]

Effect of C reactive proteins

C reactive protein formed in liver after the inflammation. High C reactive protein level in the persons who have stress compared to other persons.[16]

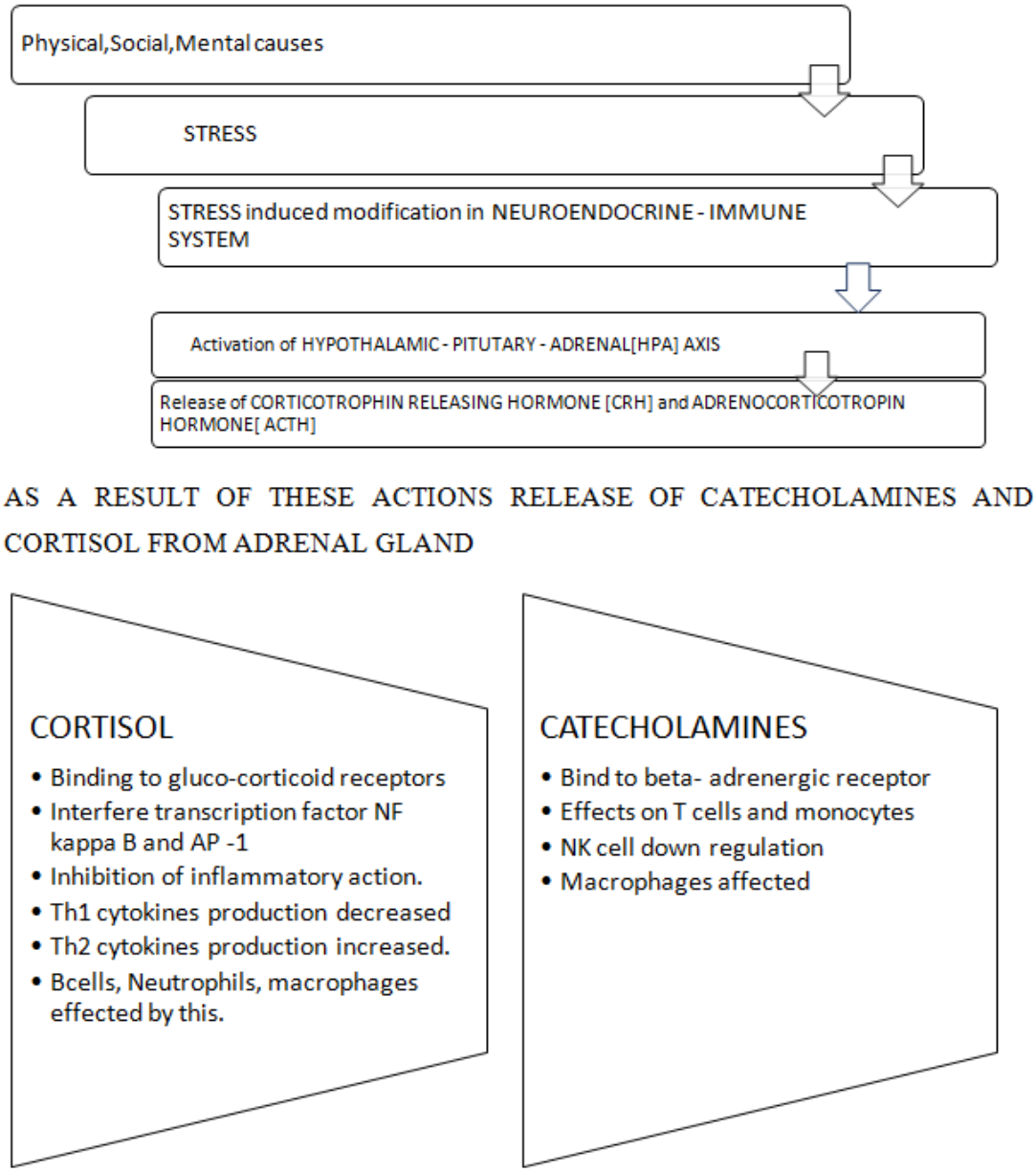

Figure 1.1: Modifications of immune system by psychological stress[5]

2. Effect of stress on infective diseases

Stress can suppress immunological reactions. Psychological stress can promote the infectious diseases like tuberculosis. Also, Herpes simplex and Epstein Barr virus infection may re-activate because of mental stress. In various studies reactivation of latent viruses like cytomegalovirus [CMV], Herpes virus formed the persons having stress by bereavement, marital problems, caregiving activity to Alzheimer's patients.[17,18,19]

Effect of stress on viral infections and COVID 19

The stress induced immunological downregulation cause increase chance of virus to overcome human immune system. The first line defense mechanism like lysozyme / mucosal Ig A are inhibited by psychosocial factors[20].

The prolonged stress will make vulnerable to viral infections like Coxsackievirus by entrance through mucous membranes[21]. Rhinovirus and corona virus have same effect on stressed individuals [stress o

The Human-Immuno Deficiency virus induced CD 4+ count decline, disease progression and mortality are significantly affected by stress. Rapid worsening of disease conditions of AIDS in stressed individuals. The HIV treatment mainly depends on viral load and CD 4+ declining.

The corona virus will exploit the Angiotensin converting enzyme 2 [ACE-2] in pneumocytes. Entrance to Pneumocytes is major obstacle to alveoli. The stress also this mechanism of COVID -19[22].

In case of innate immune system, the sympathetic system activated by stress, thus reduction of innate immune system activity occurs. The depletion of type 1 interferon system in lymphoid organs[23].So in viral diseases especially COVID -19 interferon therapy is a part of treatment[24].

In stressed individuals, cortisol production forms more vulnerability to respiratory infections by reduction of NK cells [25].

Besides downregulation of proinflammatory cytokines by alteration of NFKB receptor by glucocorticoids[26].

In viral infection the high cortisol production in long time may be downregulate the glucocorticoid receptors and increasing production of proinflammatory cytokines [27]. It is named as cytokine storm also found in COVID -19 patients. The antibody production against viruses is reduced by cortisol production[28]. The patients with cytokine storm in COVID-19 efficiently responds to treatments. Cytokine storm increase production of IL-1, IL-6 and Tumor Necrosis Factor [TNF][29]. But the prolonged effect of stress induced cytokine storm leads to immune-compromisation. The resistance of glucocorticoids can be treated by high dose exogenous steroids[30].

In obese patients with stress have a tendency to produce high amount of IL-6 in relatively low -grade infections. That produce detrimental effect [31]. The high production of IL-6 cause reduction in CD8+ cells and NK cells. It forms increase severity of COVID-19 infection[32]. Stress will also produce pile-up of immature myeloid derived suppressor cells [33]. It also counter-act the production of NK cells and CD 8 + cells[34]. Stress in obese patients forms high IL-6 associated reduction in CD 8+ cells important role in COVID -19[30].

Obesity leads to diabetes and cardiovascular diseases 30. Obese patients with diabetes are highly susceptible for COVID -19 Infections[30]. Stressed patients with obesity, old age and nicotine use increase severity of COVID -19 infection[35].

3. Stress induced alteration of immune reaction in vaccination

In case of viral vaccines response of immune system through both antibodies and specific T cell response. And in case of bacterial vaccine antibody response only. Four-fold increase of Ig G antibodies is considered limit of protection. But in case of Psychological stress no adequate increase in number of antibodies. After the 1-2 month of vaccination and 6 month of vaccination antibodies are counted. But there is no significant increase in antibodies.[36]

A study on medical students having stress found that the significant low level of antibody response and T cell response after Hepatitis B vaccination.[37]

Decrease the stability of Ig G antibody response in the time of Pneumococcal vaccination in persons having high amount of stress. Specific T cell mediated response to vaccination also small in caregivers of dementia patients.[36]

There is significant reduction in natural killer cell cytotoxicity and lymphocyte proliferation to mitogen after influenza vaccination in persons having any type of stress. Also, reduction in antibody titer per month in case of stress.

Persons suffering stress events have no increase in antibody concentration after influenza vaccination to meet the protection criteria.[38]

4. Effect of stress on Alzheimer's disease

Stress has major role in formation and progression of inflammatory and neurodegenerative disorders. Alzheimer's disease caused by neuroinflammation and degeneration. Stress induced inflammation in hypothalamus and amygdala takes place. By the

activation of microglia and immune system phosphorylation of Taue, production of proinflammatory cytokines, microvascular damages are produced. These lead to significant loss of neurons.

The stress induced immune reactions causing release of histamine and production of neuroinflammation. These may lead to Migraine and headache.[39]

5. Effect of stress on periodontitis

Stress induced adrenergic stimulation promotes differentiation and maturation of T cells.

By activation of different autonomic nervous system pathways and release of hormones & neuropeptides reduction in immunological reaction. It leads to more chance for bacterial gingivitis and periodontitis.[40]

The interleukin 1 beta have major role in periodontal disease. It is the major osteoclast activating factor. Psychological stress events increase plaque induced IL 1 beta levels. And also decrease in salivary Ig A leads to risk of bone resorption and periodontal disease.[41]

6. Relationship between stress and cancer

By the exposure of carcinogen DNA mutation takes occur and uncontrolled growth occur in cancer. The tumor cells killed by NK cells in human body. But the persons who have stress have low level of NK cells leads to rapid growth of tumors.

And the sympathetic nerve stimulation leads to production of cytokines. Cytokines like matrix metalloproteinase 2 [MPP-2], MMP-9 and Vascular endothelial factor forming high invasion of cancer cells.[42]

7. Stress on Wound healing

First stages of inflammation like phagocytosis by neutrophils are part of wound healing. In case of stress high cortisol level leads to slows down wound healing process by reduction of proinflammatory cytokines, decrease cellularization etc.[43]

In case of blister wound the reduction of growth hormone and low level of IL -1 alpha and IL-8 forms reduction in healing rate.[44,45]

Age related stress effects on immune system

Aging process effect the stress induced immunosuppression. These effects more effected in older than younger persons. And also, pre-natal or young age stress may produce malabsorptive immune responses in further ages.[46]

Stress on primary defense mechanism

The act as a barrier for foreign substances. But stress directly decrease skin hydration level. Besides histamine released from mast cells and other increased cytokines by stress also reduce barrier function[47].

The skin barrier function highly influenced by HPA axis modification by stress[48]. The skin barrier dysfunction also by modification in nicotine receptors in epithelial cells.[49]

Effect on other diseases

Stress induced increase in IL -6 also cause chance of diabetes, cardiovascular disorders and mental diseases.[50]

Conclusion

The psychological stress has high impact on immune system in various levels. Various individual differences in severity of disease have a psychological stress alteration. The study on immune system changes related to stress is an ongoing process. Because novel diseases like COVID – 19 largely effected by psychological stress. The research and practice on stress reduction techniques are highly relevant can be considered as useful prevention method.

References

1. 1.William C. Definition of stress [internet]. MedicineNet [accessed 2016 June 24]. Available from: https://www.medicinenet.com/script/main/art.asp?articlekey=20104.
2. Dimsdale JE. Psychological stress and cardiovascular disease. Journal of the American College of Cardiology. 2008 Apr 1;51(13):1237-46
3. Ballieux RE. Impact of mental stress on the immune response. Journal of clinical periodontology. 1991 Jul;18(6):427-30

4. Leonard B. Stress, depression and the activation of the immune system. The World Journal of Biological Psychiatry. 2000 Jan 1;1(1):17-25.
5. J.I. Webster, L. Tonelli, E.M. Sternberg, Neuroendocrine regulation of immunity, Annu. Rev. Immunol. 20 (2002) 125–163
6. Marsland AL, Manuck SB, Fazzari TV, Stewart CJ, Rabin BS. Stability of individual differences in cellular immune responses to acute psychological stress. Psychosomatic Medicine. 1995 May 1;57(3):295-8
7. 7.Mahani S, Panchal P. Evaluation of Knowledge, Attitude and Practice Regarding Stress Management among Undergraduate Medical Students at Tertiary Care Teaching Hospital. Journal of Clinical & Diagnostic Research. 2019 Aug 1;13(8)
8. Croiset G, Heijnen CJ, Veldhuis HD, de Wied D, Ballieux RE. Modulation of the immune response by emotional stress. Life sciences. 1987 Feb 23;40(8):775-82
9. J.K. Kiecolt-Glaser, R. Glaser, E.C. Strain, J.C. Stout, K.L. Tarr, J.E. Holliday, C.E. Speicher, Modulation of cellular immunity in medical students, J. Behav. Med. 9 (1986) 5–21.
10. R. Glaser, J. Rice, J. Sheridan, R. Fertel, J. Stout, C. Speicher, D. Pinsky, M. Kotur, A. Post, M. Beck, J. Kiecolt-Glaser, Stressrelated immune suppression: health implications, Brain Behav. Immun. 1 (1987) 7–20.
11. 8] J.K. Kiecolt-Glaser, W. Garner, C. Speicher, G.M. Penn, J. Holliday, R. Glaser, Psychosocial modifiers of immunocompetence in medical students, Psychosom. Med. 46 (1984) 7–14.
12. R. Glaser, V.S. Mehl, G. Penn, C.E. Speicher, J.K. Kiecolt-Glaser, Stress-associated changes in plasma immunoglobulin levels, Int. J. Psychosom. 33 (1986) 41–42.
13. 13.J.K. Kiecolt-Glaser, K.J. Preacher, R.C. MacCallum, C. Atkinson, W.B. Malarkey, R. Glaser, Chronic stress and age-related increases in the proinflammatory cytokine IL-6, Proc. Natl. Acad. Sci. USA 100 (2003) 9090–9095.
14. J.K. Kiecolt-Glaser, T.J. Loving, J.R. Stowell, W.B. Malarkey, S. Lemeshow, S.L. Dickinson, R. Glaser, Hostile marital interactions, proinflammatory cytokine production, and wound healing, Arch. Gen. Psychiatry 62 (2005) 1377–1384.
15. R. Glaser, T.F. Robles, J. Sheridan, W.B. Malarkey, J.K. KiecoltGlaser, Mild depressive symptoms are associated with amplified and prolonged inflammatory responses after influenza virus vaccination in older adults, Arch. Gen. Psychiatry 60 (2003) 1009–1014
16. J.E. Graham, T.F. Robles, J.K. Kiecolt-Glaser, W.B. Malarkey, M.G. Bissell, R. Glaser, Hostility and pain are related to inflammation in older adults, Brain Behav. Immun. 20 (2006) 389–400.
17. R. Glaser, J. Rice, J. Sheridan, R. Fertel, J. Stout, C. Speicher, D. Pinsky, M. Kotur, A. Post, M. Beck, J. Kiecolt-Glaser, Stressrelated immune suppression: health implications, Brain Behav. Immun. 1 (1987) 7–20.
18. 18.R. Glaser, J.K. Kiecolt-Glaser, C.E. Speicher, J.E. Holliday, Stress, loneliness, and changes in herpesvirus latency, J. Behav. Med. 8 (1985) 249–260.
19. R. Glaser, J.K. Kiecolt-Glaser, Chronic stress modulates the virusspecific immune response to latent herpes simplex virus type 1, Ann. Behav. Med. 19 (1997) 78–82.
20. Maarouf M, Maarouf CL, Yosipovitch G, Shi VY. The impact of stress on epidermal barrier function: an evidence-based review. British Journal of Dermatology. 2019 Dec;181(6):1129-37
21. 21.Jensen, MM, Rasmussen, AF,1963. Stress and susceptibility to viral infection.1 .Response of adrenals ,liver ,thymus, spleen and peripheral leukocyte counts to sounds stress.J.immunol. 90, 17-20.
22. Zhang Z, Yao W, Wang Y, Long C, Fu X. Wuhan and Hubei COVID-19 mortality analysis reveals the critical role of timely supply of medical resources. Journal of Infection. 2020 Jul 1;81(1):147-78
23. Durbin RK, Kotenko SV, Durbin JE. Interferon induction and function at the mucosal surface. Immunological reviews. 2013 Sep;255(1):25-39
24. Khan S, Siddique R, Shereen MA, Ali A, Liu J, Bai Q, Bashir N, Xue M. Emergence of a novel coronavirus, severe acute respiratory syndrome

coronavirus 2: biology and therapeutic options. Journal of clinical microbiology. 2020 Apr 23;58(5).
25. Janicki-Deverts D, Cohen S, Turner RB, Doyle WJ. Basal salivary cortisol secretion and susceptibility to upper respiratory infection. Brain, behavior, and immunity. 2016 Mar 1;53:255-61
26. Newton, R., 2000. Molecular mechanisms of glucocorticoid action: what is important? Thorax 55, 603–613.
27. Cohen, S., et al., 2012. Chronic stress, glucocorticoid receptor resistance, inflammation, and disease risk. Proc. Natl. Acad. Sci. U. S. A. 109, 5995–5999.
28. Miller, G.E., et al., 2004. Psychological stress and antibody response to influenza vaccination: when is the critical period for stress, and how does it get inside the body? Psychosom. Med. 66, 215–223.
29. Dhabhar, F.S., 2018. The short-term stress response - mother nature's mechanism for enhancing protection and performance under conditions of threat, challenge, and opportunity. Front. Neuroendocrinol. 49, 175–192
30. Peters EM, Schedlowski M, Watzl C, Gimsa U. To stress or not to stress: Brain-behavior-immune interaction may weaken or promote the immune response to SARS-CoV-2. Neurobiology of stress. 2021 May 1;14:100296
31. McInnis, C.M., et al., 2014. Measures of adiposity predict interleukin-6 responses to repeated psychosocial stress. Brain Behav. Immun. 42, 33–40.
32. Hou, W., et al., 2014. Interleukin-6 (IL-6) and IL-17 synergistically promote viral persistence by inhibiting cellular apoptosis and cytotoxic T cell function. J. Virol. 88, 8479–8489.
33. Mohammadpour, H., et al., 2019. beta2 adrenergic receptor-mediated signaling regulates the immunosuppressive potential of myeloid-derived suppressor cells. J. Clin. Invest. 129, 5537–5552.
34. Bao, Y., et al., 2015. Increased monocytic CD14(+)HLADRlow/- myeloid-derived suppressor cells in obesity. Mol. Med. Rep. 11, 2322–2328.
35. Guan, W.J., et al., 2020. Comorbidity and its impact on 1590 patients with Covid-19 in China: a nationwide analysis. Eur. Respir. J. 55, 2000547.
36. R. Glaser, J. Sheridan, W.B. Malarkey, R.C. MacCallum, J.K. Kiecolt-Glaser, Chronic stress modulates the immune response to a J.I. Webster Marketon, R. Glaser / Cellular Immunology 252 (2008) 16–26 25 pneumococcal pneumonia vaccine, Psychosom. Med. 62 (2000) 804– 807.
37. Phillips AC, Carroll D, Burns VE, Ring C, Macleod J, Drayson M. Bereavement and marriage are associated with antibody response to influenza vaccination in the elderly. Brain, behavior, and immunity. 2006 May 1;20(3):279-89
38. R. Glaser, J.K. Kiecolt-Glaser, R.H. Bonneau, W. Malarkey, S. Kennedy, J. Hughes, Stress-induced modulation of the immune response to recombinant hepatitis B vaccine, Psychosom. Med. 54 (1992) 22–29
39. Kempuraj D, Ahmed ME, Selvakumar GP, Thangavel R, Raikwar SP, Zaheer SA, Iyer SS, Burton C, James D, Zaheer A. Psychological stress–induced immune response and risk of Alzheimer's disease in veterans from operation enduring freedom and operation Iraqi freedom. Clinical therapeutics. 2020 Jun 1;42(6):974-82
40. Breivik T, Thrane PS, Murison R, Gjermo P. Emotional stress effects on immunity, gingivitis and periodontitis. European journal of oral sciences. 1996 Aug;104(4):327-34.
41. Deinzer R, Kottmann W, Förster P, Herforth A, Stiller-Winkler R, Idel H. After-effects of stress on crevicular interleukin-1ß. Journal of clinical periodontology. 2000 Jan;27(1):74-7
42. E.V. Yang, A.K. Sood, M. Chen, Y. Li, T.D. Eubank, C.B. Marsh, S. Jewell, N.A. Flavahan, C. Morrison, P.E. Yeh, S. Lemeshow, R. Glaser, Norepinephrine up-regulates the expression of vascular endothelial growth factor matrix metalloproteinase (MMP)-2 and MMP-9 in nasopharyngeal carcinoma tumor cells, Cancer Res. 66 (2006) 10357–10364.
43. J.K. Kiecolt-Glaser, T.J. Loving, J.R. Stowell, W.B. Malarkey, S. Lemeshow, S.L. Dickinson, R. Glaser, Hostile marital interactions,

proinflammatory cytokine production, and wound healing, Arch. Gen. Psychiatry 62 (2005) 1377–1384

44. R. Glaser, J.K. Kiecolt-Glaser, P.T. Marucha, R.C. MacCallum, B.F. Laskowski, W.B. Malarkey, Stress-related changes in proinflammatory cytokine production in wounds, Arch. Gen. Psychiatry 56 (1999) 450–456.
45. S. Roy, S. Khanna, P.E. Yeh, C. Rink, W.B. Malarkey, J. KiecoltGlaser, B. Laskowski, R. Glaser, C.K. Sen, Wound site neutrophil transcriptome in response to psychological stress in young men, Gene Expr. 12 (2005) 273–287.
46. Graham JE, Christian LM, Kiecolt-Glaser JK. Stress, age, and immune function: toward a lifespan approach. Journal of behavioral medicine. 2006 Aug;29(4):389-400
47. 47.Kempuraj D, Selvakumar GP, Ahmed ME, Raikwar SP, Thangavel R, Khan A, Zaheer SA, Iyer SS, Burton C, James D, Zaheer A. COVID-19, mast cells, cytokine storm, psychological stress, and neuroinflammation. The Neuroscientist. 2020 Oct;26(5-6):402-14
48. Blake KJ, Jiang XR, Chiu IM. Neuronal regulation of immunity in the skin and lungs. Trends in neurosciences. 2019 Aug 1;42(8):537-51
49. Curtis, B.J., et al., 2012. Nicotinic acetylcholine receptor stimulation impairs epidermal permeability barrier function and recovery and modulates cornified envelope proteins. Life Sci. 91, 1070–1076.
50. Godbout JP, Glaser R. Stress-induced immune dysregulation: implications for wound healing, infectious disease and cancer. Journal of Neuroimmune Pharmacology. 2006 Dec;1(4): 421