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Review Article

STRESS AND IMMUNITY: BRIEF REVIEW OF MECHANISMS IN PSYCHONEUROIMMUNOLOGY

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ABSTRACT

Psychoneuroimmunology is the term used for the interaction of the psychological stimulus with the immune system. The main objective of this paper is to have a thorough review of the mechanisms behind the immune changes during stress. This review includes various studies and methodologies forming a basis in understanding how a stressed individual would have immune suppression with increased susceptibility to various diseases. Understanding of these concepts over the years has now resulted in treatment modalities like immune checkpoint therapy for various illnesses like cancer and how they are modulated by the psychic stimuli. This study emphasises on the need for providing support and creating a positive environment around diseased individuals to enhance their immunity and have a great relief from any knid of stress.

keywords: Immunity, Psychoneuroimmunology, Stress.

INTRODUCTION

In a healthy individual, a normal physiologic process occurs between the brain, endocrine system, and the immunologic responses. When a person undergoes various emotional changes, this normal physiology maybe disrupted and thus indirectly alters the normal functioning of the immune system. Recent studies reveal that the physiologic changes occurring in our brain during different emotional changes affect both the innate and acquired immunity of an individual through the Hypothalamus-Pituitary-Adrenal (HPA) axis and the sympathetic nervous system [1]. This complex relationship was pointed out by Steven Maier in people who stay with wet hair for a long time in winters with more susceptibility to common cold. Maier concluded that the common cold is basically due to the stress created by the cold environment. This stress causes immunosuppression leading to the symptoms of the common cold. The stressor activates the first line of immune defense resulting in sickness response with a series of physiological and behavioral changes including fever, changes in liver metabolism, reduced food and water intake, reduced sexual activity and increased anxiety. This sickness response also releases stress hormones like cortisol. Macrophages are the cells which are involved in the first line of defense against infections. These macrophages process the antigens and release pro-inflammatory cytokines like interleukin 1, interleukin 6, tumor necrosis factor alpha. These pro-inflammatory cytokines have receptors on the brain to which they combine and cause the sickness response. When Maier and his colleagues blocked these receptors in the brain, there was no sign of infection even though the infection existed. But these pro-inflammatory cytokines are too big to pass through the blood-brain barrier. The message moves through the bloodstream to the vagus nerve which transmits the signals to the brain. The vagal paraganglia have receptors for interleukins. These interleukins released by macrophages get attached to the receptors on the paraganglia. Then neurotransmitters released by stimulated vagus nerve transmit the signal to the brain. On reception of these signals, brain, in turn, releases interleukin 1 thus increasing its concentration and enhancing the sickness response. This is a bidirectional and complete process is also called the immune brain loop. During stress, the same circuit gets activated but starts with the brain. Maier has found out that during stress there is a massive increase in interleukin 1 levels released by the hippocampus which in turn stimulate the sickness response. This indicates that stress can induce a similar condition that is induced by sickness [2]. Thus stress enhances the functioning of our innate immunity or non-specific immunity.

MEDIATORS INVOLVED IN PSYCHONEUROIMMUNOLOGY:

The alterations in normal psychic pattern due to stress and anxiety can lead to depression[3]. Studies show that stress activates proinflammatory cytokines and their signaling pathways in the peripheral and central nervous system. In laboratory animals, a variety of psychological stressors increased the concentrations of proinflammatory cytokines including IL-β and TNF-α in the brain [4,5]. The stressors thus induce depression by the mediation of pro-inflammatory cytokines, the immune signaling molecules that promote inflammation such as tumor necrosis α and interferon γ[6]. Undoubtedly, the chronic treatment with interferons also leads to depression.

Studies in laboratory animals show that inflammatory cytokines induce a sickness syndrome that has features of depression, anhedonia (inability to experience pleasure), anorexia, inability to sleep and decreased locomotor activity [7]. These changes are due to alterations in the metabolism of epinephrine, serotonin, and dopamine in the brain regions essential for regulating emotions. Thus at a neurobiological level, alterations in the neurotransmitter functioning which involves serotonin, norepinephrine, and dopamine are well known to induce depression [8]. Hypersecretion of Corticotrophic Releasing Hormone (CRH) is also noted in depressed patients [9]. In addition to hyperactivity of CRH, there is also hyperactivity of sympathetic nervous system and HPA axis. The role of the HPA axis in the causation of stress-related diseases is shown in fig 1[10].

ENDOCRINE RESPONSE TO PSYCHIC FACTORS LIKE STRESS

The psychological factors will modulate the activity in the HPA axis. The HPA axis is a chain of interactions occurring between our nervous and endocrine systems. The Adrenocorticotrophic hormone (ACTH) that is released when the adenohypophysis of the pituitary gland is stimulated by the hypothalamic Corticotropic Releasing Hormone stimulates the adrenal cortex. The secretions of adrenal cortex, particularly glucocorticoids are steroidal in nature which is immunosuppressive in large doses. Cortisol is an important stress hormone but when its amount is increased above normal, the homeostasis is disturbed leading to immunomodulation. During stress, there is also release of proinflammatory cytokines which can

induce inflammation. These changes happen when there are repeated events of acute stress or when there is chronic stress. In case of acute stress, there is suppression of the cell mediated but the humoral mediated immunity is maintained. In events of chronic stress, both the types of immunity are suppressed.

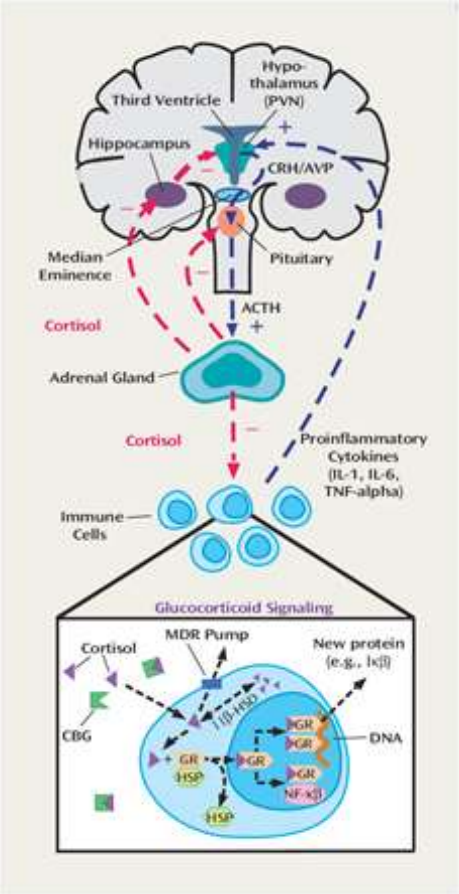

Fig 1: HPA axis

The study done in Stressed Dartmouth students deprived of sleep with more consumption of caffeine found that caffeine is capable of inducing the release of cortisol. Cortisol has a weakening action on the immune system as it inhibits the proliferation of T-lymphocytes by preventing them from recognizing the interleukin signals. It also hinders inflammation by inhibition of histamine secretion leading to a more stressful event. A clear relation between stress, caffeine and cortisol hadn't been established yet but it is believed that increased caffeine levels can confuse the Hypothalamus – Pituitary – Adrenal axis leading to the release of cortisol. Thus when the students are stressed and consume more amounts of caffeine to deprive themselves of sleep, there is an exaggeration of the responses leads to increase secretion of cortisol with immunosuppression in those individuals. Often students decide to celebrate after a stressful event by consuming more amount of alcohol. Studies show markedly increased glucocorticoids levels following the consumption of alcohol in comparison to the stressful event which via negative feedback mechanism may inhibit the HPA axis [11].

NEURAL RESPONSE TO PSYCHIC FACTORS LIKE STRESS

The body's physiologic response to stress is also by the activation of the sympathetic nervous system which releases catecholamine mainly Norepinephrine. The adrenaline in our body is mainly secreted from the adrenal medulla. Although catecholamines are helping to acutely withstand stress, they are capable of affecting lymphocytes, monocytes, macrophages, and granulocytes each to a varying degree. The receptors usually present on the surface of immune cells are β2 adrenergic receptors. Adrenaline and noradrenaline have direct or indirect effects on the immune system. The direct effect may cause a change in cellular trafficking, proliferation, antibody production and cytokine secretion [12]. Indirectly they can cause the mobilization of immune cells by demargination of lymphocytes from the vascular endothelium. This demargination is due to the action of adrenaline which increases the blood pressure which in turn causes an increase in demargination of lymphocytes from the vascular endothelium [13].

Elenkov et al (2000) suggested that the main effect of catecholamines on the Th subsets is the control of the varying cytokines that cause the activation of them. Both Th1 and Th2 subsets originate from Th0 cell based on how they are activated. Th1 cells play a major role in innate cell-mediated immune response while Th2 cells play an important role in humoral mediated immune response [14]. When there is a stress, there is an increase in favour of one of the subsets [15]. Therefore when one pathway is stimulated, the other pathway is usually inhibited. This can be because of the production of pro-inflammatory cytokines by Th1 and anti-inflammatory cytokines by Th2 cells [16]. The varying degrees of changes caused in the two types of Th cells are based on the number of receptors present on their cell surface. Mohede et al suggested that Th1 cells have a number of β adrenergic receptors on their surface. Hence the cell-mediated immunity is suppressed. There are comparatively less number of receptors for catecholamines on the surface of Th2 cells due to which the catecholamines can't directly affect the humoral mediated immunity [17]. Elenkov et al suggested that adrenaline and noradrenaline directly act on the Th2 cells which in turn stimulate B-cell proliferation ultimately resulting in increased antibody production. But since there are only a few receptors present on the surface of Th2 cells, this increase in the humoral immunity is less prominent than the suppression of cell-mediated immunity which is dominant [18]. So overall the effect with sympathetic stimulation will be immune-suppression in the individual.

Thus by the endocrine or neural response, the stress will lead to immune suppression which lead an individual more vulnerable to various diseases or disorders. This concept can be clinically implemented to the patients who are suffering from one of the most stressful journeys of cancers. Cancer is a group of diseases involving abnormal cell growth and those cells acquire the capacity to infiltrate various tissues and acquire the capacity to metastasize. Inflammation has been identified as an essential factor in the growth and metastasis of tumor cells [19, 20]. Cytokines, chemokines, macrophages, and leukocyte infiltrates contribute to tumor progression by promoting invasion, migration, and angiogenesis [21-25].

Experimental and clinical studies suggest that downstream activation of the sympathetic nervous system and the hypothalamic-pituitary-adrenal axis exerts selective physiologic pressures that initiate molecular signaling pathways involved in DNA repair, angiogenesis, cell survival, inflammation, invasion, metastasis, and resistance to therapy [26-29]. Effect of stress in tumor microenvironment is depicted in the following picture [27].

Neuroendocrine receptor-mediated signalling has the documented ability to regulate leukocyte gene expression, molecular processes, and functional characteristics of cells within microenvironments [30-35]. Neuroendocrine hormones activate oncogenic viruses and alter several aspects of immune function including antibody production, cell trafficking, and the production and release of proinflammatory cytokines [36, 37]. Catecholamines bind to α-adrenergic receptors and β-adrenergic receptors found on tumor cells and stromal compartments within the microenvironment [38]. Examples of observed effects include promotion of tumor cell growth, migration and invasive capacity, and stimulation of angiogenesis by inducing production of pro-angiogenic cytokines [36, 37].

Thus the progression of cancer is correlated with the psychosocial factors. The catecholamines and the proinflammatory cytokines that are released during stress have been proved to have the capacity to promote tumor growth [39]. Fig 2 indicates the neural, endocrine and the bio behavioral factors involved in cancer progression [40].

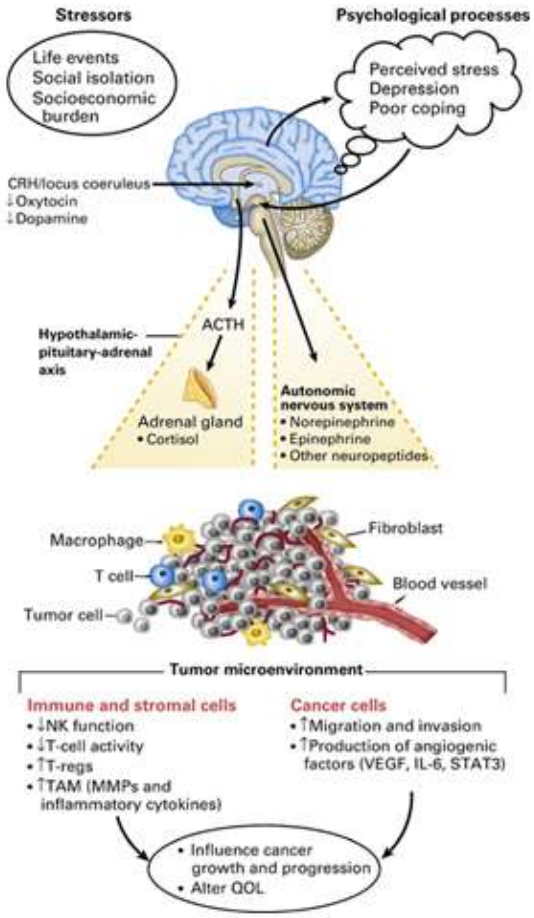

Fig.2: Psychic and immunologic factors in cancer progression

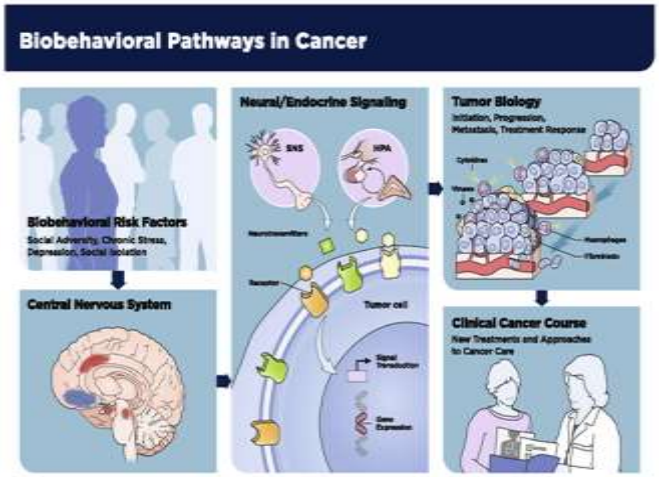

Fig 3: Biobehavioral pathways in cancer

Proinflammatory cytokines such as IL-8 and IL-6 promote angiogenesis whereas norepinephrine induces the production of IL-6 and IL-8 in ovarian cancer patients and melanoma cell lines. Researches show that women who were not receiving proper social support were showing large serum levels of IL-6 compared to those who received proper social support. This leads to more rigorous angiogenesis and tumor growth. Thus it is very important to comfort the cancer patients by psychological support so that the stress can be minimised and tumor progression can be reduced.

CONCLUSION

Stress is unavoidable. Immune suppression during stress with release of various substances can induce cell growth and angiogenesis which can worsen the condition like cancer. Thus, approaches towards decreasing stress like social support can also decrease the progression of cancer in patients. This field of psychoneuroimmunology is thus creating physiological basis for the reduction of stress among such individuals. Interesting research is going on in this field can be a dawn in the medical field enabling the prevention of various diseases caused due to the chemistry of various emotions.

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