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Immune Modulation in Response to Stress and Relaxation

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Abstract: Traditional medical science has kept the mind separate from the body. Recently people realize the effect of mind on health and psychoneuroimmunology is the new evolved science that describes the interactions between psyche and soma. In this review through a typical psycho-neuro-endocrino-immune network the effects of psychological stress (acute, brief naturalistic and chronic) and relaxation on immune modulation has been shown. From this network Corticotrophin Releasing Factor (CRF), Adrenocorticotrophic Hormone (ACTH), Glucocorticoids (GC), α-endorphin and Met-enkephalin are found as important endocrine components and T cells, B cells, monocytes/macrophages, Natural Killer (NK) cells and their cytokines that is Tumor Necrosis Factor-α (TNF-α), Interferon Gamma (IFN-α) and interleukins such as IL-1, IL-2, IL-4, IL-6, IL-10, IL-12 etc. are found as important immune components. Finally, it has been shown that, acute, brief naturalistic and chronic stress have different immune modulatory activities which are harmful to one's homeostasis and relaxation can help to maintain that homeostasis.

Key words: Psychoneuroimmunology, stress, HPA axis, glucocorticoids, α-endorphin, Met-enkephalin

INTRODUCTION

The modern medical science describes mind and body as separate entities that permitted medical science the freedom to explore and experiment on the body. As a result the medicines that evolved from this focus on the body and its processes have yielded extraordinary discoveries about the nature and treatment of disease states.

However, this narrow focus has tended to obscure the importance of the interactions between mind and body and to overshadow the possible importance of the mind in producing and alleviating disease. Moreover, the reductionism also led us into the trap of supposing that the autonomic nervous system, the endocrine, immune and neuropeptide systems were independent and autonomous self-regulating structures (Sternberg, 2000) and as a result we have failed to find out the real causes of disease.

During the past 30 years, there has been a powerful scientific movement to explore the mind's capacity to affect the body and to rediscover the ways in which it permeates and is being affected by all of the body's functions. It also has been shown that autonomic nervous system, the endocrine, immune and neuropeptide systems constitute a cybernetic whole (Sternberg, 2000); any division is merely the hallucination of somewhat blinkered theorists. As a result an understanding is now emerging of a complex world of interactions between our mental and emotional selves and our neural, endocrine and immune functions. A new word to describe some aspects of this joined-up-ness is psychoneuroimmunology which was coined by Ader (2000).

Psychoneuroimmunology research over the past 30 years established that the brain and the immune system are inextricably linked through a variety of pathways that include the Hypothalamus-Pituitary-Adrenal (HPA) axis and other endocrine organs, including the thyroid, gonads and adrenal medulla as well as autonomic nervous system components (Webster *et al*., 2002). Although their neuroendocrine pathways are not identical, both anxiety (Sadeghi *et al*., 2007) and depressive states are associated with similar biological and chemical effects on both regulatory and effector immune components (Koh, 1998).

Moreover, several clinical and pre-clinical research indicates that psychological stress suppresses various aspects of innate and adaptive immune function and can ultimately impact upon disease onset and/or progression (Kemeny and Schedlowski, 2007). Specifically, evidence indicates that psychological stress suppresses a range of immune parameters, results in impaired host resistance to infectious disease, results in reduced responses to vaccinations, inhibits wound healing and increases the progression of cancer (Glaser and Kiecolt-Glaser, 2005). In general, the impact of stress on functioning of the immune system is thought to depend on the severity and duration of the stressful situation (Kemeny and Schedlowski 2007).

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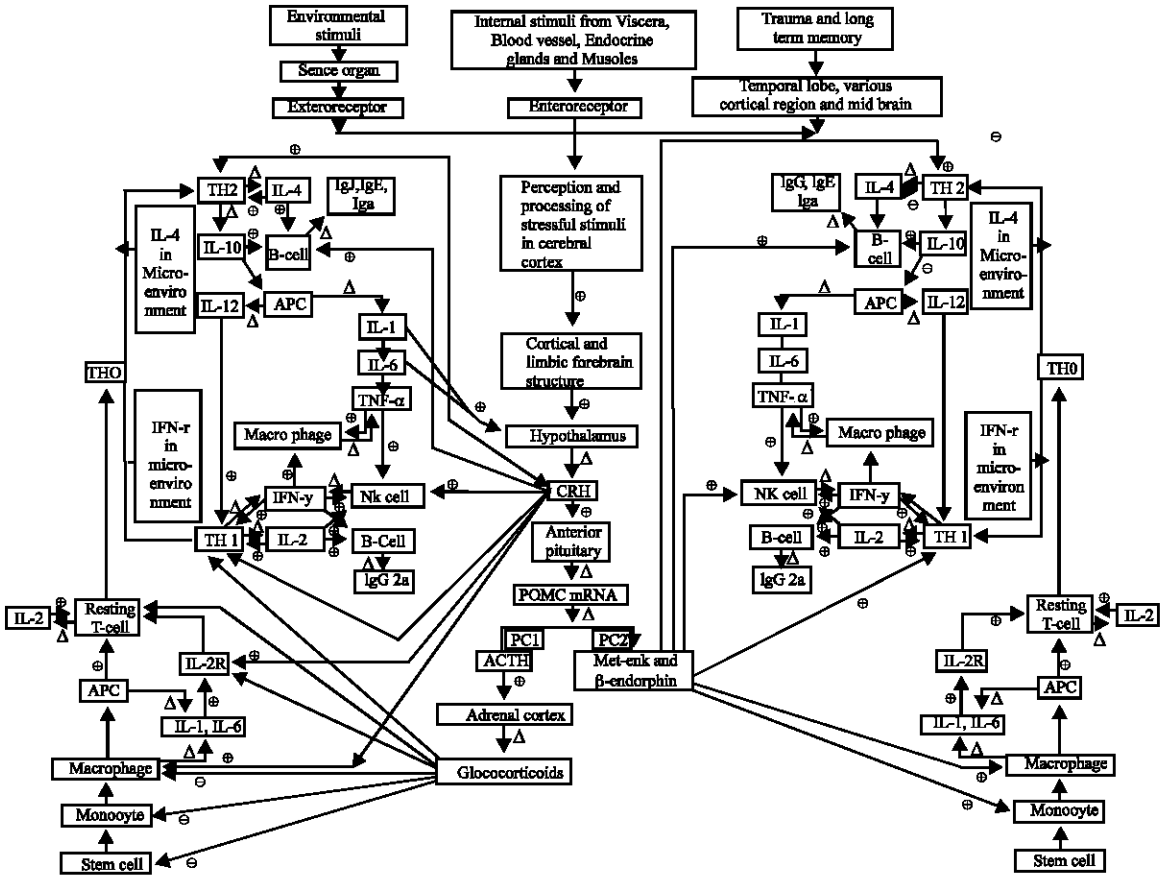

Fig. 1: A typical psycho-neuro-endocrine-immune network. (⊕ : activating reaction; ⊖: inhibiting reaction; Δ: releasing activity)

In this review the general pathway of immune system is described and the effects of stress and relaxation on immune system are shown by developing a pathway of psychoneuroendocrinoimmune interaction (Fig. 1). Corticotropin releasing hormone (CRH) and glucocorticoids are considered as key components to show the effect of stress. On the other hand Met-enkephalin and β-endorphin are considered as key components in this review as products of relaxation.

The main objective of this review is to change our reductive view to holistic view by showing that mind has a great influence on body infact mindbody is a single whole system.

PSYCHONEUROENDOCRINE NETWORK

First the environmental and psychological stresses are perceived and processed in the cerebral cortex of the forebrain. Then through cortical and limbic forebrain structure hypothalamus is stimulated. As a result hypothalamus secretes stress hormone CRH. CRH activates the HPA axis, inducing the secretion of ACTH by the anterior pituitary (Montoro *et al*., 2009).

ACTH regulates steroid synthesis by the Adrenal Cortex. ACTH stimulates the secretion of glucocorticoids (Smith-Rohrberg, 2000), corticosterone in rodents and cortisol in primates by the cells of the adrenal cortex (Munck *et al*., 1984; Endo *et al*., 2011). Cortisol and other glucocorticoids increase glucose production, inhibit protein synthesis and increase protein breakdown, stimulate lipolysis and affect immunological and inflammatory responses. Cortisol induces thymus involution which is a decline in normal thymus function that in part accounts for its ability to decrease immune system response. Glucocorticoids help maintain blood pressure (Chamani *et al*., 2006) and form an essential component of the body's response to stress. Cortisol feeds back to the pituitary and hypothalamus to suppress levels of ACTH and CRH. Under basal (non-stress) conditions, cortisol is secreted with a pronounced circadian rhythm, with higher levels early in the morning and low levels late in the evening. Under stressful

conditions, the circadian variation is blunted (Foye *et al*., 1995).

IMMUNE REGULATORY ACTIVITY OF CRH

CRH is a mediator of endocrine, autonomic and immune responses to stress (Dunn and Berridge, 1990; De Souza, 1995). CRH plays a significant role in integrating the stress-related and inflammatory responses to immunological agents such as viruses, bacteria, or tumor cells through its coordinated actions in the nervous, endocrine and immune systems (Owens and Nemeroff, 1991; Webster *et al*., 1991). CRH has direct effects on immune function and inflammatory processes. CRH induces the secretion of POMC derived peptides such as ACTH and β-endorphin in human peripheral blood and mouse splenic leukocytes. Furthermore, CRH stimulates the secretion of IL-1 and IL-2, as well as lymphocyte proliferation and IL-2 receptor expression in peripheral blood leukocytes. These actions of CRH are mediated through functional receptors present on resident macrophages in mouse spleen and human peripheral blood monocytes (De Souza and Grigoriadis, 2002). CRH also stimulates B cell proliferation and NK cell activity and IL-6 production (Leu and Singh, 1992). Receptors for CRF have been found on immune cells (Webster *et al*., 1990), providing a mechanism for these effects. Several sources of endogenous CRH may be important in regulating immune function. Immunoreactive CRH and CRH mRNA are expressed in human peripheral blood leukocytes. CRH immunoreactivity is also present in primary sensory afferent nerves and in the dorsal sensory and sympathetic intermediolateral columns of the spinal cord. Sensory afferents and sympathetic efferent nerve fibers strongly influence inflammatory responses (De Souza and Grigoriadis, 2002).

IMMUNE REGULATORY ACTIVITY OF GLUCOCORTICOIDS

A number of specific lymphocyte functions are blocked by the steroids without cell death and there are variations in sensitivity. For, instance, the lymphocyte proliferative response to some but not other antigens can be suppressed. The proliferative responses to antigens are more readily suppressed than are those to mitogens (Parrillo and Fauchi, 1979). Nevertheless, blockage of some T cell mitogenic responses have been observed; this may be due to steroid actions that block the release of T cell growth factor (IL-2) (Munck *et al*., 1984). IL-2 is important for clonal expansion of cells early on but not later (Munck *et al*., 1984). Glucocorticoids also alter macrophage functions that effect cell function. They suppress T lymphocyte production of IFN-γ and IL-12 and they inhibit NK cell activity (Munck *et al*., 1984). Glucocorticoids do not suppress ADCC of human cells (Parrillo and Fauchi, 1979). Antibody production by B cells results from a series of steps involving early activation, later, B cell growth factor mediated proliferation, and final differentiation to the antibody producing state. These steps are affected by suppressor cell and helper cell functions and can be suppressed by glucocorticoids (Baxter and Rousseau, 1979). Studies in vitro, glucocorticoids affect substantially the early activation , have a lesser effect on the B cell growth factor response and do not affect the final step (Cupps *et al*., 1985). Because of varying sensitivities and complex accessory cell effects on B and/or T cell function, it is possible to observe a variety of effects, either stimulatory or inhibitory. Inhibition of suppressor cell function may explain why in sarcoidosis with energy (that may be due in part to increased suppressor activity), glucocorticoids may increase immune responsiveness (Saxon *et al*., 1978). Macrophage functions are relatively sensitive to glucocorticoids inhibitory action (Parrillo and Fauchi, 1979). Glucocorticoids induce a monocytopenia, suppressed committed marrow monocyte forming stem cells and block the differentiation of monocytes into macrophages (Bar-Shavit *et al*., 1984). By blocking the production of IFN-γ, glucocorticoids can also decrease the levels of Fc receptors on monocyte and macrophages; (Larsen and Henson, 1983) these receptors facilitate the phagocytosis of particular antigens and other functions of the cells in the inflammatory responses (Swanson and Hoppe, 2004). Steroids can block the ability of the monocytes to bind to antibody coated cells, elicit bactericidal activity and cytotoxicity (Parrillo and Fauchi, 1979). Glucocorticoids suppress macrophage production of IL-1, which is involved in T cell mitogenesis and of chemokines that prevent the exit of macrophages from inflammatory sites (Fahey *et al*. 1981). Glucocorticoids block the production of IFNγ and TNF-α by T cells and their actions on macrophages (Munck *et al*., 1984). Thus, glucocorticoid's effects on B cell functions are very modest. High dose corticosteroid therapy causes a small decrease in antibody levels as a result of both decreased synthesis and increased catabolism (Butler and Rossen, 1973).

IMMUNE REGULATORY ACTIVITY OF MET-ENKEPHALIN AND B-ENDORPHINS

In mammals, pro-enkephalin mRNA and its derived peptides are found in many types of immune cells,

including T-lymphocytes and monocytes (Salzet and Tasiemski, 2001). In rodents, pro-enkephalin gene expression was detected in fetal thymocytes and in normal B and T-lymphocytes (Kamphuis *et al*., 1998). Kowalski (1998) demonstrated that the Met-enk stimulates B- and T-cell proliferation and leu-enk, while its degradation fragments stimulate the production of T helper and T cytotoxic cells (Padros *et al*., 1989; Sizemore *et al*., 1991). Met-enk is also able to stimulate the migration of monocytes, lymphocytes and neutrophils *in vitro* towards the site of injection (Stefano *et al*., 1996; Weigent and Blalock, 1997). Injection of Met-enk and its metabolites Tyr-Gly-Gly increased the production of NK cells and mitogen-induced proliferation of T and B-lymphocytes that was blocked by naloxone, thus demonstrating that the action is opiate-mediated (Kamphuis *et al*., 1998). Met-enk also influences the intracellular signal transduction with T-cells, as the levels and increase of Ca^{2+} is low in T-cells incubated with Met-enk (Sorensen and Claesson, 1998; Li, 1998). Prepro-enkephalin mRNA expression has been detected in many cells of the immune system including $CD4^+$ TH2 and TH1 lymphocyte subpopulations. Prepro-enkephalin mRNA and Met-enk are present at higher levels in TH2 cultures compared with TH1 cultures. Lymphocytes from prepro-enk deficient mice show that cultures containing IL-4 do not require prepro-enkfor TH2 differentiation (Hook *et al*., 1999). However, in the airway eosinophilia model, Hook and colleagues observed that although the accumulation of lymphocytes in the airways of prepro-enkephalin-deficient mice was similar to that induced in control mice, IL-5 production and eosinophil infiltration were reduced. They concluded that prepro-enkephalin has a role in enhancing TH2 cell function (Hook *et al*., 2000). Met-enk and its analogs, such as Leu enkephalin and Metenkephalin-Arg-Phe stimulate the release of proinflammatory cytokines such as interleukin-6 (Goumon *et al*., 1998). Moreover, pro-enkephalin mRNA levels in peripheral human blood monocytes are increased in response to IL-6 (Kamphuis *et al*. 1998). Met enkephalin is now considered as a new cytokine (Plotnikoff *et al*., 1997), probably implicated as a pro-inflammatory signal in the immune response (Tasiemski *et al*., 2000; Salzet *et al*., 2000). However, high concentration of Met-Enkephalin inhibits the inflammatory response like do the POMC derived peptides such as ACTH [1–39] and MSH:ACTH [1–13] (Lipton and Catania, 1997).

It is known that the increase in β-endorphins during exercise actually causes the increase in NK cells because when naloxone antagonist to β-endorphins is administered to a subject before exercise, the NK count did not increase after exercise, while there was a definite increase for the control group that wasn't pre-treated with naloxone. Other research has shown that β-endorphin increases cytotoxicity in a dose dependent manner and that the effects seem to be mediated by μ and δ opioid receptors (Jonsdottir *et al*., 1997). Thus an increase in endogenous opioids leads to an increase in NK cells which may enhance one's immunity.

EFFECTS OF STRESS AND RELAXATION

Data from a number of studies have shown that various stressors can adversely affect immune function (Ader *et al*., 2001; Graham *et al*., 2006). Stress has long been suspected of playing a role in the etiology of many diseases, and numerous studies have shown that stress can be immunosuppressive and hence may be detrimental to health (Herbert and Cohen, 1993; Kiecolt-Glaser *et al*., 1996; Marucha *et al*., 1998). Moreover, glucocorticoid stress hormones are regarded widely as being immunosuppressive (Munck *et al*., 1984) and are used clinically as antiinflammatory agents (Schleimer *et al*., 1989). In this study we have briefly reviewed some of the immunological changes that have been associated with stress as well as evidence for the efficacy of various interventions.

Acute time stress: Acute stressors elicite various patterns of immune change across a wide spectrum of durations ranging from 5 to 100 min and irrespective of whether they involved social (e.g., public speaking), cognitive (e.g., mental arithmetic), or experiential (e.g., parachute jumping) forms of stressful experience (Segerstrom and Miller, 2004). Secretory immunoglobulin A (sIgA), measured in saliva, is a convenient and much used indicator of immune status. Measurement of this parameter is thought to be indicative of the functional status of the entire mucosal immune system (Mestecky, 1993). Numerous studies have shown that salivary sIgA is sensitive to psychological variables. Recent studies show that the acute response to a psychological challenge is a rise in sIgA, albeit transient (Evans *et al*., 1997). This mobilisation of sIgA has been reported in response to acute laboratory psychophysiological stress tests, such as public speaking (Bristow *et al*., 1997), computer game challenge (Carroll *et al*., 1996), cold pressure task and mental arithmetic (Willemsen *et al*., 1998). However, the study of Carroll *et al*. (1996) revealed that the sIgA response only characterised novice players. Following and acute stressor, increase in both sIgA and cortisol were found in several findings (Evans *et al*., 1994).

Reliable effects of acute stress on the immune system include increase in immune parameters, especially natural immunity. The most robust effect of this kind of experience was a marked increase in the number of NK cells and large granular lymphocytes in peripheral blood (Segerstrom and Miller, 2004). This effect is consistent with the view that acute stressors cause immune cells to redistribute into the compartments in which they will be most effective (Dhabhar and McEwen, 1997). However, other types of lymphocytes do not show robust redistribution effects: whereas, B cells and T-helper cells show a very little change (Segerstrom and Miller, 2004). T-cytotoxic lymphocytes tend to increase reliably in peripheral blood, though to a lesser degree than their natural immunity counterparts; this increase drives a reliable decline in the T-helper:T-cytotoxic ratio (Segerstrom and Miller, 2004). Other indicators of upregulated natural immunity include increased neutrophil numbers in peripheral blood, increased production of a proinflammatory cytokine (IL-6) (Maes *et al*., 1999; Lutgendorf *et al*., 1999), and increased production of a cytokine (IFN-γ) that potently stimulates macrophages and NK cells as well as T cells (Segerstrom and Miller, 2004). The only exception to this pattern is the increased secretion of IgA antibody, which is a product of the specific immune response (Segerstrom and Miller, 2004). The data for acute stressors, therefore, support an upregulation of natural immunity (Dhabhar and McEwen, 1999; Dopp *et al*., 2000), as reflected by increased number of NK cells in peripheral blood and potential down regulation of specific immunity, as reflected by decreased proliferative responses (Segerstrom and Miller, 2004).

Brief naturalistic stressors: Stressful events can alter a wide range of immunological activities. For example, even common place aversive events such as academic examinations are associated with transient immunological changes. Some immunological study on medical students during examination time showed significant declines in NK cell activity; these cells arethought to have important antiviral and antitumor functions (Kiecolt-Glaser and Glaser, 1992; Sheridan *et al*., 1994). Gamma interferon, a lymphokine that serves as a major regulator of NK cells by stimulating their growth and differentiation, also enhances their ability to destroy target cells (Herberman *et al*., 1982). In two separate studies, dramatic decreases in gamma interferon production by lymphocytes during examinations were found (Glaser *et al*., 1986).

The first association between psychological distress and reduced resistance to herpes virus (HSV) was reported by Lycke *et al*. (1974) in the form of increased antibodies to the latent HSV, Epstein-Barr virus (EBV) and Cytomegalovirus (CMV) in depressed patients. Subsequent investigators confirmed this association in medical students at exam time and in spouses about to divorce (Gruzelier, 1999). From then the large and reliable changes in antibody titers to latent HSV during exams, particularly EBV and HSV type-1, are also thought to reflect alterations in the competence of the cellular immune response. The characteristic elevations in EBV antibody titers during exams are thought to occur in response to the increased synthesis of the virus or virus proteins (Glaser *et al*., 1991); although counterintuitive, elevated antibody titers to a latent HSV reflect poorer cellular immune system control over virus latency (Henle and Henle, 1982). Consistent with the elevations in HSV antibody titers, specific T cell killing of EBV infected target cells decreased during examinations and a HSV-relevant lymphokine was also altered (Glaser *et al*., 1987).

The proliferative response of lymphocytes cultured with a mitogen, a substance that stimulates cell replication, is thought to provide a model of the immune system's ability to respond to infectious agents, such as bacteria or viruses. Medical students show a poorer proliferative response to mitogens during examinations, compared with non-exam taker (Sheridan *et al*., 1994).

IL-2 is a lymphokine that is important for T-lymphocyte proliferation and the IL-2 receptor (the part of the cell to which IL-2 binds) is an important mediator of this response. The percentage of peripheral blood T-lymphocytes expressing the IL-2 receptor was lower during exams compared with lower stress baseline periods in three independent medical student studies. Moreover, the level of messenger RNA to the IL-2 receptor in peripheral blood leukocytes decreased during examinations in a subset of these students (Glaser *et al*., 1990).

These are the first data suggesting that stress-associated decrements in immunity may be observed at the level of gene expression. Examination stress alters phorbol ester inhibition of radiation-induced apoptosis in human Peripheral Blood Leukocytes (PBLs) (Tomei *et al*., 1990). Apoptosis is the process of genetically programmed alterations in cell structure that leads to the failure of proliferation and differentiation and eventually to cell death. Apoptosis may be induced by a variety of toxic insults, including growth factor deprivation and ionizing radiation, and it is thought to help protect against the appearance of heritable phenotypic changes in cells. These data and others suggest possible connections between stress and carcinogenesis Kiecolt-Glaser *et al*. (1985).

In contrast to the acute time-limited stressors, examination stress did not markedly affect the number or percentage of cells in peripheral blood. Instead, the largest effects are on functional parameters, particularly changes in cytokine production that indicate a shift away from cellular immunity (TH1) and toward humoral immunity (TH2). Brief stressors reliably change the profile of cytokine production via a decrease in a TH1-type cytokine, IFN-γ, which stimulates natural and cellular immune functions and increases in the TH2-type cytokines IL-6 (Dentino *et al*., 1999; Lutgendorf *et al*., 1999), which stimulates natural and humoral immune functions, and IL-10 (Kiecolt-Glaser *et al*., 2002), which inhibits TH1 cytokine production. IFN-γ and IL-6 share the property of stimulating natural immunity but differentially stimulate cytotoxic versus inflammatory effector mechanisms. Their dissociation after brief naturalistic stress indicates differential effects between TH1 and TH2 responses rather than natural and specific responses. (Segerstrom and Miller, 2004).

Chronic stressors: Other studies have addressed the question of whether longer-term adaptation occurs when a stressor is more chronic, such as living near a damaged nuclear reactor (McKinnon *et al.,* 1989) or caregiving for a family member with a progressive dementia (Kiecolt-Glaser *et al*., 1991). The weight of the evidence to date suggests that chronic stressors are associated with continued down-regulation of immune function rather than adaptation (Kiecolt-Glaser *et al*., 1991).

Chronic stressors include dementia caregiving, living with a handicap, and unemployment. Like other nonacute stressors, they do not have any systematic relationship with enumerative measures of the immune system. They do, however, have negative effects on almost all functional measures of the immune system. Both natural and specific immunity were negatively affected, as were TH1 (e.g., T cell proliferative responses) and TH2 (e.g., antibody to influenza vaccine) parameters (Segerstrom and Miller, 2004).

There are common genetic influences for depression and neuroendocrine dysregulation, sufficiently stressful circumstances can also produce clinically significant immune and endocrine dysregulation in individuals who are not at risk. For example, the chronic strains of dementia spousal caregiving are related to the onset of syndromal depressive disorders in older adults who have no prior evidence of vulnerability through either personal or family history (Dura *et al*., 1990). Moreover, although only a minority of caregivers develop syndromal disorders, men and women who provide long-term care for a spouse or parent with Alzheimer's disease typically report high levels of distress as they attempt to cope with the family member's problematic behaviors; this stressor has been associated with prolonged endocrine and immune dysregulation, as well as health changes, including alterations in vaccine response and wound healing (Glaser *et al*., 1998; Wu *et al*., 1999).

Relaxation: Recent studies found that at the time of exercise (Thoren *et al*., 1990; Taylor *et al*., 1994; Jonsdottir *et al*., 1997) and meditation (Harte *et al*., 1995) there is an increase in β-endorphin secretion. Secreted β-endorphins during exercise actually cause the increase in NK cells (Jonsdottir *et al*., 1997). Thus an increase in endogenous opioids leads to an increase in NK cells and enhance one's immunity.

Another study looked at a six week structured group intervention (health education, problem solving skills regarding diagnosis, stress management and psychological support) in patients with stage I or II malignant melanoma. Short term effects included a reduction in psychological stress and increased number and activity of NK cells. Follow up at six years showed reduced recurrence and mortality rates in the intervention compared with the control group (Fawzy *et al*., 1993). Group therapy and self hypnosis for women with metastatic breast cancer has been shown to extend survival by an average of 18 months (Spiegel *et al*., 1989).

DISCUSSION

In this review we have found that at the time of *acute stress* the number of natural killer cells and large granular lymphocytes in peripheral blood increase (Segerstrom and Miller, 2004). Moreover, acute time stress increases the production of a proinflammatory cytokine IL-6 (Dentino *et al*., 1999; Lutgendorf *et al*., 1999; Maes *et al*., 1999) and cytokine IFN-γ that potently stimulates macrophages and natural killer cells as well as T cells (Segerstrom and Miller, 2004). That means acute stressor up-regulate the natural immunity (Sobhani *et al*., 2011).

This up-regulation may be occurred due to the action of CRH and CRH induced secretion of POMC-derived peptides such as metenkephalin and β-endorphin. Just after the perception of stress, CRH level in the blood becomes high. Immunoreactive CRH and CRH mRNA are expressed in human peripheral blood leukocytes (De Souza and Grigoriadis, 2002). The CRH has direct effects on immune function and inflammatory processes (De Souza and Grigoriadis, 2002) and receptors for CRH have been found on immune cells (Webster *et al*., 1990) which may facilitate the mechanism of inflammatory

responses by the immune cells (Kane *et al*., 2006). Furthermore, CRH stimulates the secretion of IL-1, IL-2 and IL-6 as well as lymphocyte proliferation and IL-2 receptor expression in peripheral blood leukocytes (De Souza and Grigoriadis, 2002). It may activate the immune cells and facilitate their proliferation.

On the other hand POMC derived Met-enk is also found to be able to stimulate the migration of monocytes, lymphocytes and neutrophils in vitro towards the site of injection (Stefano *et al*., 1996) and also stimulate the release of proinflammatory cytokines such as IL-6 (Gounon *et al*., 1998). Met-enk is probably implicated as a pro-inflammatory signal in the immune response (Stefano *et al*., 1998; Salzet *et al*., 2000).

The only exception to this pattern is the increased secretion of IgA antibody, which is a product of the specific immune response (Evans *et al*., 1997). But the timeframe of these acute stressors is too short for the a significant mount of new antibody; therefore, this increase is probably due to the release of already synthesized antibody from plasma cells and increased translocation of antibody across the epithelium and into saliva (Bosch *et al*., 2002). This effect therefore represents relocation, albeit of an immune protein rather than immune cells.

Brief naturalistic stressor decrease Natural Killer (NK) cell activity (Glaser *et al*., 1987; Sheridan *et al*,. 1994) and IFN-γ production (Herberman *et al*. 1982). At the period of brief naturalistic stressor, the proliferative response of lymphocytes, cultured with a mitogen, show a poorer proliferative response (Sheridan *et al*., 1994). That means, it decrease cellular immunity.

Decrease in cellular immunity may be due to the action of glucocorticoids. Glucocorticoids alter macrophage functions that affect cell function. They also suppress T lymphocyte production of IFN-γ and IL-12 (Elenkov *et al*., 2006) and thus inhibit NK cell activity (Munck *et al*., 1984). The poorer proliferative responses of lymphocytes in culture to mitogens may be due to steroid actions that block the release of lymphocyte growth factor IL-2. IL-2 is important for clonal expansion of cells early on but not later (Munck *et al*., 1984). The percentage of peripheral blood T-lymphocytes expressing the IL-2 receptor and the level of mRNA to the IL-2 receptor in peripheral blood leukocytes decrease at brief naturalistic stressor (i.e., during examinations) (Glaser *et al*., 1990). Thus the lesser production of IL-2 and the expression of IL-2 receptors may reduce the proliferative response of lymphocyte and that inhibitory action is done by glucocorticoids, which is produced as a result of stress.

Brief naturalistic stressor also changes cytokine production that indicates a shift away from cellular immunity (TH1) and toward humoral immunity (TH2) (Sobhani *et al*., 2008) this may be done by blocking the production of TH1-type cytokine, IFN-γ, which stimulate natural and cellular immune functions. Brief naturalistric stressors reduce resistance to latent HSV, EBV and CMV in depressed patients and increase production of antibody to them (Gruzelier, 1999). Hence it reflects alterations in the competence of the cellular immune response (Glaser *et al*., 1991) and shows poorer cellular immune system control over virus latency (Henle and Henle, 1982). Consistent with the elevations in HSV antibody titers, specific T cell killing of EBV infected target cells decreased during examinations and a HSV-relevant lymphokine is also altered Glaser *et al*. (1987).

Evidence to date suggests that *chronic stressors* are associated with continued down-regulation of immune function rather than adaptation Kiecolt-Glaser *et al*. (1991). Chronic stressors include dementia caregiving, living with a handicap and unemployment. Both natural and specific immunity are negatively affected, which are seen from TH1 and TH2 parameters (Segerstrom and Miller, 2004).

The down regulation of the immune system as a result of chronic stress may be due to the regulatory action of both CRH and glucocorticoids. After perception of stress, CRH is released from hypothalamus. CRH has direct effect on the immune regulatory functions and facilitate the inflammatory process. It also stimulates the production of IL-1, IL-2 and IL-2R (De Souza and Grigoriadis, 2002) and thus facilitates the activation and proliferation of immune cells. Moreover, CRH stimulates B cell proliferation and NK cell activity and IL-6 production (Leu and Singh, 1992).

But, when the stress becomes chronic, glucocorticoids produced from the adrenal medulla as a response of CRH is followed by ACTH. Glucocorticoids block the release of T cell growth factor (IL-2) by steroid actions. IL-2 is important for clonal expansion of cells early on but not later (Munck *et al*. 1984). Glucocorticoids also alter cellular activity of macrophage. Glucocorticoids induce a monocytopenia, suppressed committed marrow monocyte forming stem cells and blockthe differentiation of monocytes into macrophages (Bar-Shavit *et al*., 1984). By blocking the production of IFN-γ, glucocorticoids can also decrease the expression of Fc receptors on monocyte and macrophages (Larsen and Henson, 1983) and thus block the ability of monocytes to bind to antibody coated cells, elicit bactericidal activity and cytotoxicity

(Parrillo and Fauchi, 1979). Glucocorticoids suppress macrophage production of IL-1, which is involved in T cell mitogenesis and of chemokines that prevent the exit of macrophages from inflammatory sites (Fahey *et al*., 1981). Glucocorticoids block the production of IFN-γ and TNF-α by T cells and their actions on macrophages (Munck *et al*., 1984). They also suppress T lymphocyte production of IFN-γ and IL-12 and inhibit NK cell activity (Fahey *et al*., 1981; Munck *et al*., 1984). Studies *in vitro* shows, glucocorticoids affect substantially the early activation, have a lesser effect on the B cell growth factor response and do not affect the final step (Cupps *et al*., 1985). High dose corticosteroid therapy causes a small decrease in antibody levels as a result of it's decreased synthesis and increased catabolism (Butler and Rossen, 1973). Therefore, it becomes clear that glucocorticoids down-regulate the cellular immunity by blocking the activity of monocyte, macrophage, NK cells and T-helper and T-cytotoxic cells.

Most of the T and B effector cells produced during an immune response must be eliminated after they have done their job. As antigen levels fall and the responses subside, effector cells are deprived of the antigen and cytokine stimulation that they need to survive and the majority of the cells die by apoptosis; but only memory cells and some long-lived effector cells survive (Alberts *et al*., 2002). At the time of acute stress the immune cells become active and the T and B cells mature into effector cells. But if the stress becomes chronic, CRH make the cells (T and B) active; but glucocorticoids, as they inhibit the production of cytokines, the cells cannot survive. Moreover, new cells are also not formed due to the action of glucocorticoids. Thus chronic stress down regulates both cellular and humoral immunity through CRH and glucocorticoids.

On the other hand at *relaxed state* there is an increase in β-endorphin secretion which causes the increase in NK cells (Jonsdottir *et al*., 1997) and thus enhance one's immunity. Short term effects of relaxation included a reduction in psychological stress and increased number and activity of NK cells; long term effects shows reduced recurrence and mortality rates (Fawzy *et al*., 1993) and extend survival time of women with metastatic breast cancer (Spiegel *et al*., 1989).

The enhancement of the immunity may be due to the action of Met-enk and β-endorphin. Met-enk stimulates B- and T-cell proliferation (Kowalski, 1998) and leu-enk; while its degradation fragments stimulate the production of T helper and T cytotoxic cells (Sizemore *et al*., 1991). Met-enk is also able to stimulate the migration of monocytes, lymphocytes and neutrophils in vitro towards the site of injection (Stefano *et al*., 1996; Weigent and Blalock, 1997). Moreover, prepro-enkephalin has a role in enhancing TH2 cell function (Hook *et al*., 2000). Met-enk and its analogs, such as Leu-enkephalin and Met-enk-Arg-Phe stimulate the release of proinflammatory cytokines such as IL-6 (Goumon *et al*., 1998). Pro-enkephalin mRNA levels in peripheral human blood monocytes are increased in response to IL-6 (Kamphuis *et al*., 1998). Met-enk probably implicated as a pro-inflammatory signal in the immune response (Tasiemski *et al*., 2000).

From the above discussion it might seem that glucocorticoids are universal immuno down regulating component, where as β-endorphin and Met-enk are immuno enhancing components. Cortisol is not always immunosuppressive, nor the result of cortisol secretion is always detrimental to health (Sobhani *et al*., 2006). Adequate cortisol levels are essential for the maintenance of normal immune responses and physiological levels of cortisol can influence helper T cell cytokine production in favor of humoral (TH2) as opposed to cell-mediated (TH1) responses (Berk *et al*., 2001). Moreover, corticosteroid secretion may be an essential physiological component in a normal immune response that prevents uncontrolled proliferation of unwanted clones of immunocytes (Besedovsky *et al*., 1975). This hormone is also necessary for suppressing immune responses by turning off the production of proinflammatory cytokines before they are overproduced. That means, at the time of normal immune function glucocorticoids shows bio feedback regulation, and is friendly to the immune system; but when it is a product of stress, it down regulates the immune system, and becomes harmful.

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