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Brief Naturalistic Stressors Cause Shift of TH1 to TH2 Cytokine Response and Increase Disease Susceptibility

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Abstract: In this study, a typical psycho-neuro-endocrino-immune network has been developed in which, Corticotrophin Releasing Hormone (CRH), adrenocorticotrophic hormone (ACTH), glucocorticoids (GC), β-endorphin (β-end) and met-enkephalin (Met-enk) 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-γ) 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, brief naturalistic stressors have different immune modulatory activities such as, cause shift of TH1 to TH2 cytokine response which is harmful to one's homeostasis and increase disease susceptibility.

Key words: POMC, HPA axis, glucocorticoids, cortisol, β-endorphin, met-enkephalin

INTRODUCTION

The mechanistic view of traditional medical science evolved by neglecting the folk wisdom which suggests that stressful events take a toll on health (Glaser and Kiecolt-Glaser, 2005) and good thoughts can influence disease and healing (Simon, 1997). This narrow focus has also tended to obscure the importance of the interactions between mind and body and to overshadow the possible importance of mind in producing and alleviating disease.

During the last two decades through a lot of researches, researchers proved that our mental state influences our physical state or well being (Maier *et al*., 1994; Marucha *et al*., 1998). Sternberg (2000) showed that the central nervous system, the endocrine system and immune system are interacting with each other any division is merely the hallucination of somewhat blinkered theorists. This has invented a new scientific field, psychoneuroimmunology (PNI), which describes some aspects of joined-up-ness of these three systems (Biondi and Zannino, 1997).

For the key mechanistic evidences of stress on immune modulation now it is clear that psyche and soma are constantly interacting. Stress is a complex process involving social, psychological and physiological elements. Stress can be defined as an environmental or psychological challenge that disrupts homeostasis and requires adaptation, coping and defense (Zimbardo, 1992; Mahbub-E-Sobhani *et al*., 2006). According to psychobiological theories stress is determined by the balance between the perceived demands from the environment and the individual's resources to meet those demands. More broadly, psychobiological stress ensues when events or environmental demands exceed an individual's perceived ability to cope (Cohen *et al*., 1998).

It is perhaps better termed a stressor, a challenge resulting in psychobiological strain or distress. Stress is a personal matter. How much stress we experience is determined by the quality and intensity of a combination of variables: the dimensions of the stressor, the way we interpret the meaning of the stressor, the resources are available to deal with the stressor and the amount and nature of the total strain placed on the individual

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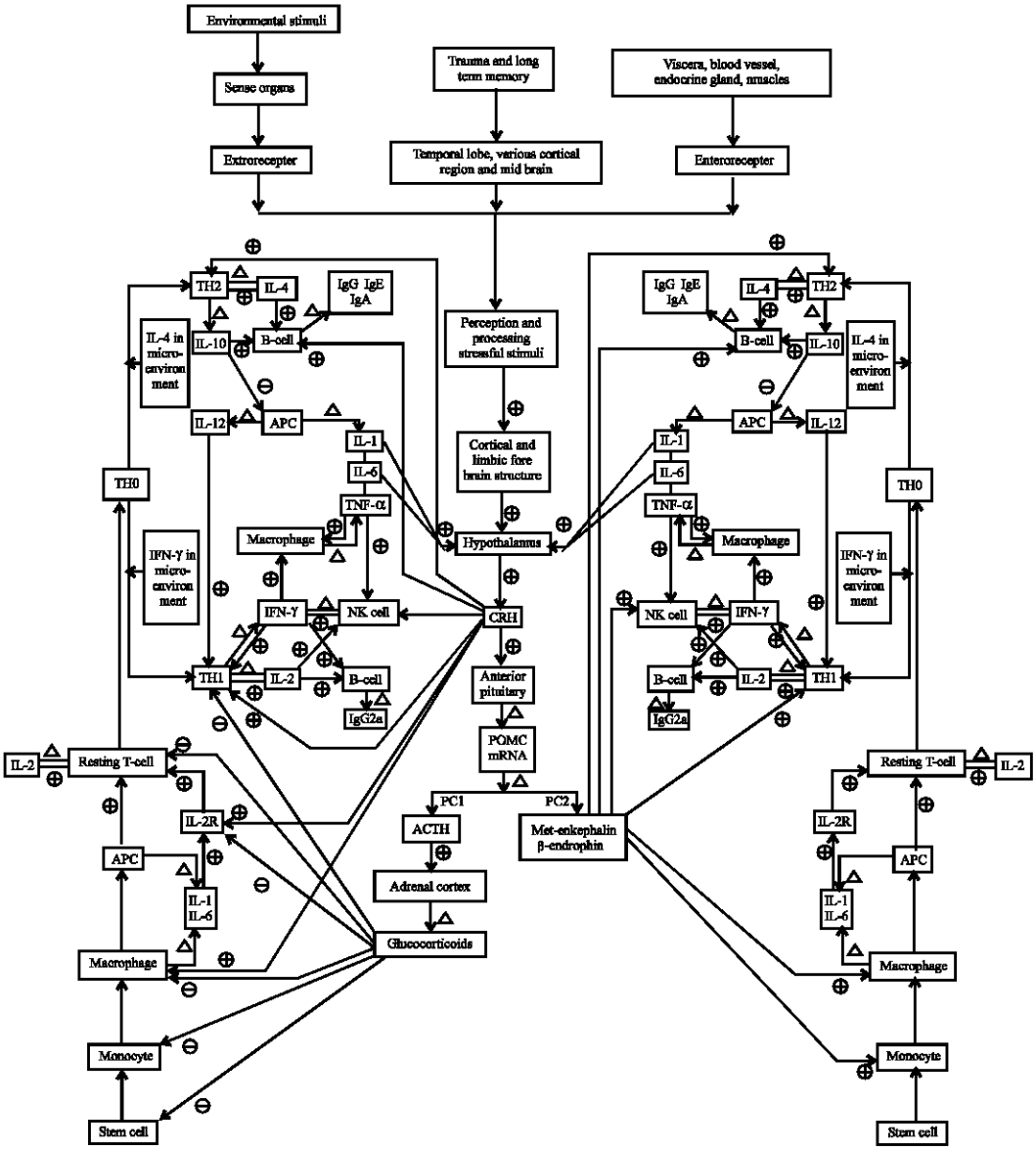

Fig. 1: A typical psycho-neuro-endocrine-immune network, (⊕: Activating reaction; ⊖: Inhibiting reaction; Δ: Releasing activity)

(Zimbardo, 1992). Ursin and Eriksen (2004) proposed that the level of the physiological response depends on the expectancy of the outcome of the stress stimuli and the specific responses available for coping. Thus, expectation of a positive outcome has an arousal lowering effects, whereas uncertainty or lack of predictability of the outcome produces a strong physiological arousal (feelings of helplessness and hopelessness).

Stress or stressors can be categorized in so many ways. In this study Elliot and Eisdorfer's (1982) taxonomy to characterize these stressors has been evolved, in which stressors have been categorized on two important dimensions: duration and course. According to them brief naturalistic stressors involve a person confronting a real-life short-term challenge such as academic examinations (Segerstrom and Miller, 2004). The studies undertaken during last two decades have provided the evidence that any type of stressor (Acute time limited stressors to chronic stressors) may cause immune modulation (Glaser and Kiecolt-Glaser, 2005). On the basis of the findings of these researches in this study through a typical psycho-neuro-endocrine-immune network (Fig. 1). It has been shown that mind has a great influence on body and brief naturalistic stressors cause shift of TH1 to TH2 cytokine response and increase disease susceptibility.

PSYCHO NEUROENDOCRINE NETWORK

Modulation of the immune response by the Central Nervous System (CNS) is mediated by a complex network among the nervous system, the endocrine system and the immune system. Over the past decade, the most intensive investigations of neural signaling of the immune system during stressful states have focused on the Hypothalamus-Pituitary-adrenal (HPA) axis and the Sympathetic Adrenal Medullary (SAM) axis, the two most prominent components of the stress response (Glaser and Kiecolt-Glaser, 2005). Evidence from the past decade has demonstrated that numerous neuroendocrine signals can modulate immune responses and subsequent disease outcomes. In addition, direct nerve fiber connections have been found between the SAM and the both primary and secondary lymphoid organs (Felten and Maida, 2000). From many studies it has been found that catecholamines (adrenalin and noradrenalin) are the product of SAM axis and glucocorticoids (corticosterone in rodents and cortisol in primates) are the product of HPA axis (Glaser and Kiecolt-Glaser, 2005).

The classical markers for acute stress are cortisol, adrenalin, heart rate and blood pressure, which will increase rapidly to stress exposure. Adrenalin is regarded as maybe the best indicator of the intensity of the stressor. However, a disadvantage with adrenalin, heart rate and blood pressure is that these measures will not reflect the emotional value of the stressor and are rather nonspecific. Also activation associated with positive mood and pleasant activities will increase the levels of these measures. Peters *et al.* (1998) proposed that cortisol is a better marker if the emotional value is of interest and increased cortisol levels should be associated with inability to cope, lack of control of the stress situations and depressive mood. Though the empirical evidence for this hypothesis is so far limited in this study, cortisol has been taken as the key component of stress and described its effect on immune modulation. And this immune modulation due to stress has been described through the pathway of HPA axis.

All organisms, from bacteria to primate humans, have evolved mechanisms to deal with significant changes in their external or internal environments, that is, stressors. According to the Russian Schools of Physiology all of the bodily changes following stress originate in the cerebral cortex. From there the stimuli reach the hypothalamic region through limbic system to produce changes in the autonomic nervous system and in the neuroendocrine apparatus. As a result hypothalamus secretes stress hormone CRH (Corticotropin releasing hormone) (Chrousos, 1995). CRH of the hypothalamus is a 41-residue peptide that plays the major role in regulation of pituitary corticotrope trophic activity, (Gertz *et al.*, 1987) POMC (proopiomelanocortin) gene transcription (Autelitano *et al.*, 1990). CRH is the major physiologic regulator of the basal and stress-induced release of POMC-derived peptides from the anterior pituitary (Dunn and Berridge, 1990; Owens and Nemeroff, 1991).

POMC is an ultra-cool 260 amino acid protein which gets glycosylated (sugars added, probably at select arginine residues as for prolactin) and then cleaved to give a number of neurohormones. The anterior pituitary hormones ACTH (adrenocorticotrophic hormone) and LPH (lipotropin hormone, weak lipid-degrading hormone) are derived from POMC in the pars distalis of the anterior pituitary. In the pars intermedia area of the anterior pituitary, the ACTH derived from cleavage of POMC is cleaved further to produce γ-MSH (melanocyte-stimulating hormone). Thus, POMC is processed differently in different areas of the pituitary. We can also get beta-endorphin out of POMC cleavage, which means POMC is a source of an endogenous opioid peptide. In fact, POMC is the precursor to ACTH, α-, α -, γ-MSH, α-, α-, γ-end (endorphin), b-lipoprotein and met-enk (enkephalin). Besides the hypophysis (pituitary), the brain, gastrointestinal system, immune cells, placenta and gonads are able to synthesize POMC products (Foye *et al.*, 2002).

ACTH regulates steroid synthesis by the Adrenal Cortex. ACTH stimulates the secretion of glucocorticoids, (Chrousos, 1995) corticosterone in rodents and cortisol in primates by the cells of the adrenal cortex (Munck *et al.*, 1984). Glucocorticoids help maintain blood pressure 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.*, 2002).

REGULATORY ACTIVITY OF ENDOCRINE COMPONENTS ON IMMUNE SYSTEM

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 responses to immunological agents through its coordinated actions in the nervous, endocrine and immune systems (Owens and Nemeroff, 1991). CRH has direct effects on immune function and

inflammatory processes. CRH induces the secretion of POMC derived peptides such as ACTH and β-end in human peripheral blood and mouse splenic leukocytes. Furthermore, CRH stimulates the secretion of IL (interleukin)-1 and IL-2, as well as lymphocyte proliferation and IL-2 receptor expression in peripheral blood leukocytes (De Souza, 1995). CRH also stimulates B cell proliferation and NK (natural killer) cell activity and IL-6 production (Leu and Singh, 1992). Receptors for CRH have been found on immune cells (Webster *et al*., 1990), providing a mechanism for these effects.

The increase in β-end actually causes the increase in the count of NK cells and also increases cytotoxicity in a dose dependent manner and that the effects seem to be mediated by μ and δ opioid receptors. Thus an increase in endogenous opioids leads to an increase in NK cells which may enhance one's immunity. On the other hand the Met-enk stimulates B and T-cell proliferation (Kowalski, 1998) and also able to stimulate the migration of monocytes, lymphocytes and neutrophils *in vitro* towards the site of injection (Weigent and Blalock, 1997). Met-enk stimulates the release of proinflammatory cytokines such as IL-6. Moreover, pro-enk mRNA levels in peripheral human blood monocytes are increased in response to IL-6 (Kamphuis *et al*., 1998). Met-enk also influences intracellular signal transduction with T-cells, as the Ca^{2+} levels were lower in T-cells incubated with met-enk, as compared with controls (Sorensen and Claesson, 1998). Prepro-enk mRNA and Met-enk are present at higher levels in TH2 cultures compared with TH1 cultures, thus prepro-enk has a role in enhancing TH2 cell function. Met-enk is now considered as a new cytokine, probably implicated as a pro-inflammatory signal in the immune response (Stefano *et al*., 1998). However, high concentration of Met-enk inhibits the inflammatory response like do the POMC derived peptides such as ACTH and MSH (Lipton and Catania, 1997).

Glucocorticoids also have immune modulatory activity. Macrophage functions are relatively sensitive to glucocorticoids inhibitory action (Parrillo and Fauci, 1979). Glucocorticoids alter macrophage functions that effect cell function. Glucocorticoids induce a monocytopenia, suppressed committed marrow monocyte forming stem cells and block the differentiation of monocytes into macrophages. By blocking the production of IFN (interferon)-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. So, it can block the ability of the monocytes to bind to antibody coated cells, elicit bactericidal activity and cytotoxicity (Parrillo and Fauci, 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. Glucocorticoids block the production of IFNã and TNF (tumor necrosis factor)-α by T cells and their actions on macrophages (Munck *et al*., 1984). They suppress T lymphocyte production of IFN-γ and IL-2 and they inhibit NK cell activity (Munck *et al*., 1984). Glucocorticoids do not suppress ADCC (antibody dependent cellular cytotoxicity) of human cells (Parrillo and Fauci, 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 (Parrillo and Fauci, 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). Thus, glucocorticoid's effects on B cell functions are very modest. Cortisol and other glucocorticoids increase glucose production, inhibit protein synthesis and increase protein breakdown, stimulate lipolysis and affect immunological and inflammatory responses (Foye *et al*., 2002).

EFFECTS OF BRIEF NATURALISTIC STRESSOR ON IMMUNE SYSTEM

Data from a number of studies have shown that various stressors can adversely affect immune function. 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 (Maier *et al*., 1994; Marucha *et al*., 1998). Moreover, glucocorticoid stress hormones are regarded widely as being immunosuppressive and are used clinically as antiinflammatory agents (Munck *et al*., 1984). In this study, we briefly review some of the immunological changes that have been associated with brief naturalistic stressors.

Brief naturalistic stressors 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 are thought to have important antiviral and antitumor functions (Sheridan *et al*., 1994). In some studies, dramatic decreases in gamma interferon production by lymphocytes during examinations were found (Glaser *et al*., 2005).

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).

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*., 1999).

The 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. Glaser *et al*. (1999) were also 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.

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) (Segerstrom and Miller, 2004).

DISCUSSION

Brief naturalistic stressor decrease NK cell activity; and IFN-γ production (Sheridan *et al*. 1994). 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 and thus inhibit NK cell activity. 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 stressors reduce resistance to latent HSV, EBV and CMV in depressed patients and increase production of antibody to them (Lycke *et al*., 1974). 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; although counterintuitive, elevated antibody titers to a latent HSV reflect poorer cellular immune system control over virus latency (Glaser *et al*., 1999).

Brief naturalistic stressor also changes cytokine production that indicates a shift away from cellular immunity (TH1) and toward humoral immunity (TH2) (Segerstrom and Miller, 2004). This may be occurred by changing 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 (Maes *et al*., 1999), which stimulates natural and humoral immune functions and IL-10 (Kiecolt-Glaser *et al*., 2002), which inhibits TH1 cytokine production.

From the study, it has been found that Brief naturalistic stressors cause decrease of TH1 type cytokine IFN-γ and increases TH2 type cytokine IL-6. These also increase the production of IL-10 which inhibits TH1 cytokine production. At that time production of IL-12 also decreased, as a result NK-cell activity inhibited. Brief naturalistic stressors thus cause shift of TH1 to TH2 cytokine response or cellular to humoral immunity.

As the cellular immunity shifts from cellular to humoral immunity, the latent virus got the chance to synthesis virus or virus protein. Beside these brief naturalistic stressors decrease the production of lymphocyte or immune cell. So, finally it can be concluded that, brief naturalistic stressors cause shift of TH1 to TH2 cytokine response and reduces production of immune cell and thus make us vulnerable to disease.

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