



STRESS INDUCED NEURO-ENDOCRINE-IMMUNE SYSTEM ALTERATION AND ITS RELATION WITH AUTOIMMUNE/INFLAMMATORY DISEASES: A REVIEW

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KUS-05/25-110905

Manuscript received: September 11, 2005; Accepted: February 2, 2006

Abstract: In recent years a novel scientific discipline called psychoneuroimmunology has emerged that examines complex interdependence of the mind, brain, endocrine and immune system in health and disease. Homeostasis (a self-referral phenomenon) plays an important role in keeping a person healthy and it has a fundamental role in host defense. Many studies show that stress (acute or chronic) creates disorder especially in the immune regulation. In this study a typical nervous-endocrine and immune network has been shown in case of stress. From this network Corticotrophin Releasing Factor (CRF), Adrenocorticotrophic Hormone (ACTH), Growth Hormone(GH), prolactin (PRL), Glucocorticoids (GC) and catecholamine are found as important endocrine factors and T cells, B cells, monocytes/macrophages, Natural Killer(NK) cells and their cytokines that is Tumor Necrosis Factor- α (TNF- α), Gamma Interferon (IFN- γ) and interleukins such as IL-1, IL-2, IL-4, IL-6, IL-10 etc. are found as important immune factors in most stress related studies. Finally, autoimmune/ inflammatory disease is shown in relation to above endocrine and immune factors. In summary, we have demonstrated psychoneuroimmune alteration in stress and its association with autoimmune/inflammatory disease. The present study suggests the importance of restoring self-referral organization in the body.

Key words: Stress, cortisol, HPA axis, autoimmune disease, neuro endocrine immune system, inflammation

Introduction

Stress can be defined as an environmental or psychological challenge that disrupts homeostasis and requires adaptation, coping and defense. 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 we have available to deal with the stressor, and the amount and nature of the total strain placed on the individual (Zimbardo, 1992).

Types of Stress

The causes of stress (stressors) are multiple and varied, but they can be divided into two general categories – external and internal (Geddes and Groset, 1997) as shown in Table 1. These factors generate various

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DOI: <https://doi.org/10.53808/KUS.2006.7.1.0525-L>

symptoms of emotional and mental stress, the most common including: anger, anxiety, worry, fear, and depression (Geddes and Groset, 1997).

Table 1. Type of stress.

External stressors	Internal stressors
Physical environment –noise, bright lights, heat, confined spaces.	Lifestyle choices-caffeine, not enough sleep, overloaded schedule.
Social interaction –rudeness, bossiness or aggressiveness by others.	Negative self-talk –pessimistic thinking, self-criticism, over-analyzing
Organizational –rule, regulations, ‘red tape’, deadlines.	Mind traps-unrealistic expectations, taking things personally, all-or-nothing thinking, exaggerating, rigid thinking.
Major life events –death of a relative, lost job, promotion, new baby.	Stressful personality traits –type A, perfectionist, workaholic.
Daily hassles-commuting, misplacing keys, mechanical breakdowns.	

Homeostasis as Self-Referral and Stress as Object Referral Aspect

Homeostasis refers to the ability of an organism to maintain stability of its internal environment by adjusting the physiological process. Each cell, tissue and body organ functions within a range of values suitable to support life (Graaft *et al.*, 1997).

However, mind is deeply connected with the body. The different levels of the mind–ego, emotions, intellect, thinking mind, and senses emerge sequentially in the process of unfoldment of “Pure Consciousness”. The ego is the sit of our sense of ‘I,’ the ‘experiencer’ that integrates and synthesizes the ceaseless input of experience. The level of emotions denotes the mental processes associated with feelings, motivation, intuition, creativity, and basic values. The level of the intellect represents the properties of discrimination and decision-making. Memory and association are linked with the next level, the conscious mind, which is the mind in its limited connotation as a specific faculty of mental functioning. Lastly, the senses process environmental information, serving as a link between the individual and the world (Sharma, 1999).

From this view, we can say that mind posses a self-referral phenomenon that identifies the ego and all other levels with ‘Pure Consciousness’. These self-referral phenomenon are found as homeostatic biofeedback system that prevails in DNA and entrance up to the whole body. In contrast, object referral is a process of relinquishing the identity of one’s self to some object of reference, which may be an event, a person, or a thing. Once this has taken place –once the self has been exchanged for an external image, we begin to forget the true wholeness of our nature (Simon, 1997).

Earlier, we have showed various types of stressors. These factors shift our perception from self-referrality to object-referrality. However, since homeostasis maintains a stable internal environment from various challenges, we refer homeostasis as the self-referral aspect that is keeping in pace with memory of wholeness. In contrast, we refer stress in general with the object referral aspect since it disturbs homeostatic feedback system in our body.

The Neuro-Endocrine-Immune Network Onset of Stress

The field of psychoneuroimmunology (PNI) examines the complex interactions between the nervous system and immune system (Berk *et al.*, 2001). 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 central nervous system (CNS) and the parenchyma and vasculature of both primary and secondary lymphoid organs (Felten and Maida, 2000). Post-ganglionic nor-adrenergic sympathetic nerve fibers are major contributors to this signaling, but numerous neuropeptidergic neural-immune connections also have been identified. These neurotransmitters also exert extensive regulatory control over immune responses (Bellinger *et al.*, 1994).

Immuno-regulation by the nervous system occurs through two distinct pathways: the hypothalamic pituitary adrenal Axis (HPA axis) and the sympathetic division of the autonomic nervous system. The latter directly innervates lymphoid organs (Ader *et al.*, 1995). Following the perception and processing of stressful stimuli by higher cortical and limbic forebrain structures, the corticotrophin-releasing factor (CRF) neurons of the paraventricular nucleus of the hypothalamus are activated, which induces secretion of corticotrophin (ACTH)

from the anterior pituitary, resulting in the secretion of cortisol by the adrenal cortex into the systemic circulation (Johnson *et al.*, 1992).

Complex feedback loops within the endocrine and immune systems serve to further regulate HPA function. Increased cortisol levels tend to suppress activation of the axis at the level of the anterior pituitary and the hypothalamus. Corticotropin release also is mediated by arginine, vasopressin, oxytocin, and thymic peptides; arginine vasopressin can synergize with CRF to further activate ACTH and cortisol. Cytokines such as IL-1 and IL-6 can modulate HPA activity via activation of CRF neurons in the paraventricular nucleus (Fulsochi *et al.*, 1999). Furthermore, ACTH and CRF receptors exist on some subsets of lymphocytes and other lymphoid cells, and some activated immunocytes are capable of secreting hormones including ACTH, thyroid stimulating hormone (TSH), growth hormone (GH), prolactin (PRL) and endorphins (Blalock, 1994).

Modulation of CRF mRNA and proenkephalin A mRNA in the paraventricular nucleus and pro-opiomelanocortin (POMC)-mRNA in the anterior pituitary are stimulus dependent (Harbuz and Lightman, 1989), suggesting a disassociation among stress hormone component responses. Further support is provided by the finding that POMC, a neuropeptide precursor molecule cleaved by endopeptidases to yield ACTH, beta-endorphin and beta-lipotrophin, undergoes tissue-specific posttranslational processing (Castro and Morrison, 1997). In addition, POMC-derived ACTH, beta-endorphin, and alpha-melanocyte-stimulating hormone from the anterior and intermediate lobes of the pituitary have been found to be differentially regulated (Kjaer *et al.*, 1995). It therefore appears that individual hormones in the "stress hormone" profile are subject to independent regulation and are controlled by separate signaling mechanisms.

Cortisol is not universally immunosuppressive, nor is the result of cortisol secretion always detrimental to health. 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. In addition, Sternberg *et al.* (1989) have demonstrated that blocking of corticosteroid activity with RU486 in rodent strains that are not susceptible genetically to induced autoimmunity (Fischer 344 rat) results in a switch in their susceptibility to an extent equivalent to the genetically susceptible strains (e.g. Lewis/N - rats).

Typical human TH1 cytokines include gamma-interferon (IFN- γ), tumor necrosis factor- α (TNF- α) and IL-12; TH1 cells are involved in cell-mediated responses. Several TH1 cytokines activate cytotoxic, inflammatory, and delayed hypersensitivity reactions. By contrast, TH2 cells are typified by the production of IL-4 and IL-5, with IL-6, IL-9, IL-10, and IL-13 also commonly produced. Furthermore, TH2 cells encourage production of antibodies, especially IgE, and TH2 cytokines are associated with regulation of strong antibody allergic responses. Cytokines from TH1 cells usually can inhibit the actions of TH2 cells, and vice versa. Immune responses often are characterized as TH1- or TH2-dominant responses.

The TH1/TH2 decision is crucial to effective immunity; it is likely that many interlocking factors contribute to that decision. Many signals may influence the differentiation of CD4+ helper T cells. Relevant to the neuroendocrine findings is the activity of co-stimulatory molecules and hormones present in the local environment. For example, glucocorticoids such as cortisol tend to drive the developing response toward TH2. Derivatives of dehydroepiandrosterone tend to oppose this effect and favor a TH1 response (Hechter *et al.*, 1997). Levels of these adrenal hormones are regulated both systemically and by local metabolism within target organs. Therefore, the balance between cortisol and dehydroepiandrosterone concentrations within lymphoid organs and sites of pathology may be a critical determinant of the response type.

IFN- γ has numerous important immunoregulatory actions and plays a major role relative to TH1 cell-mediated reactions. Its primary sources are antigen specific T cells and NK cells, and its principal targets are lymphocytes, monocytes, NK cells and tissue cells. Its effects are exerted through specific saturable binding to a single class of high-affinity receptors found in myelomonocytic cells, lymphoid cells, mast cells, endothelial cells, fibroblasts, neuronal cells, and melanocytes. It is, however, the most potent inducer of macrophage activation and class II molecules on tissue cells. In this and other functions, it synergizes with TNF- α and TNF- β . IFN- γ also can regulate proliferation, differentiation, and activation of T and B cells, and can activate NK cell activity (Rook and Balkwill, 1998) (Fig. 1).

Possible Missing Link Bridge of Stress Perception

It is important to link between perception of stress by higher cortical and limbic forebrain structures. As stress is, a conscious activity by our brain it is related with the consciousness researches.

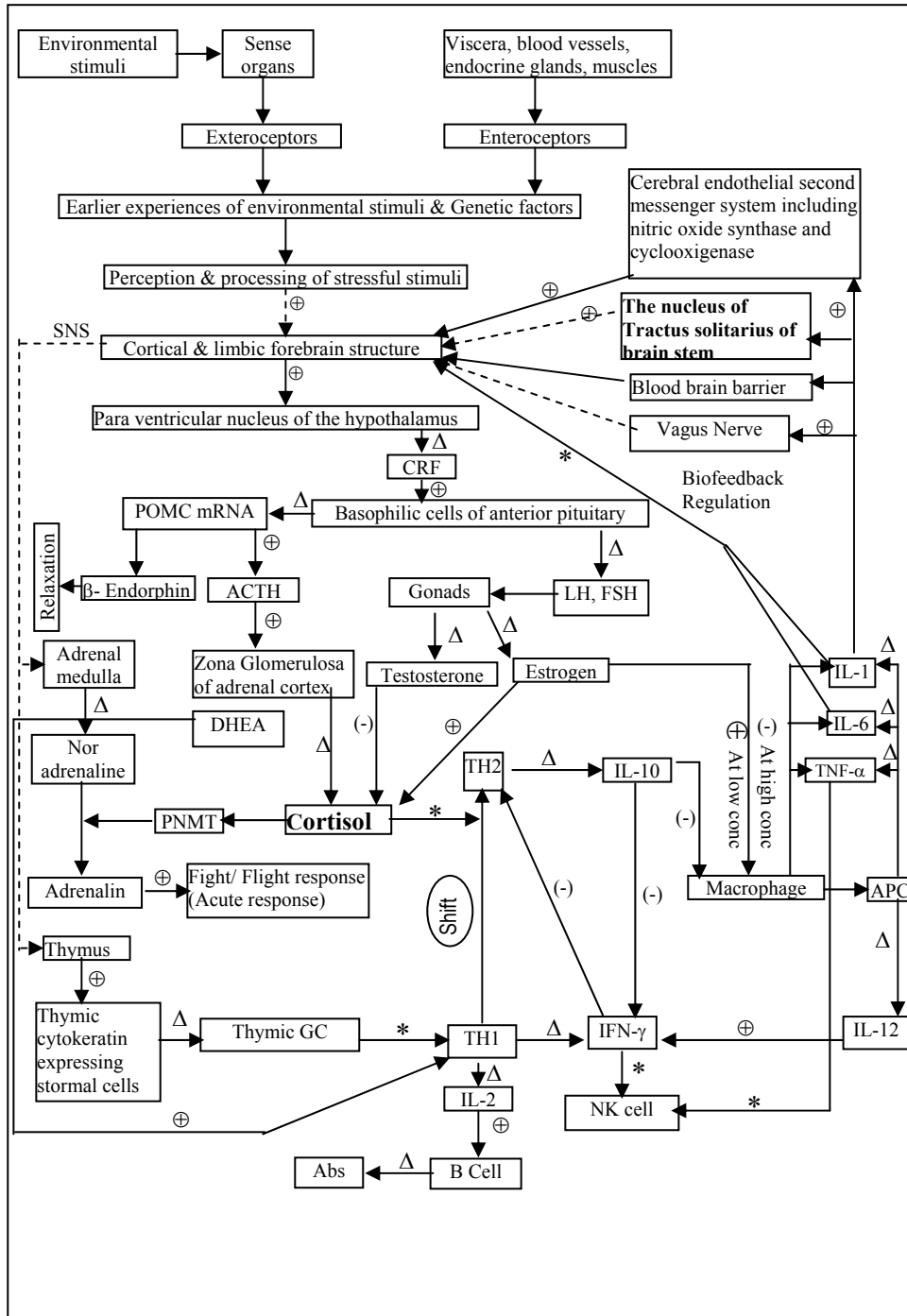


Fig. 1. The figure shows a typical mind-brain-endocrine-immune network. [⊕ : activating reaction; ⊖: inhibiting reaction; *: regulating reaction; Δ: releasing activity. The dotted line indicates that the path has connection with brain.]

To suggest and explain for how consciousness could arise in brains, we could look at the typical wave patterns seen on the EEG, which are believed to record sub-threshold (pre-firing) oscillations on neuron cell walls, vary depending on one's state of consciousness and the activity in which the brain is engaged. Four distinct patterns have been recognized: alpha, beta, delta and theta. In the normal human brain, the beta waves, which are associated with organized, conceptual thinking, dominate at the EEG pattern during working hours.

Fröhlich's (1968) 'pumped system' demonstrated that beyond a certain threshold, any additional energy pumped onto the system causes the molecules in the cell walls of living tissue to vibrate in unison. They do so increasingly until they pull themselves in to the most ordered form of condensed phase possible – a 'Bose-Einstein condensate'.

The crucial distinguishing feature of Bose-Einstein condensates is that the many parts which go to make up an ordered system not only behave as a whole, but they become whole- their identities merge or overlap in such a way that they lose their individuality entirely.

Evidence for coherent states (Bose-Einstein condensates) in biological tissue is abundant, and the interpretation of its meaning lies at the cutting edge of exciting breakthroughs in our understanding of what distinguishes life from non-life. Dana Johar suggests that the Fröhlich style Bose-Einstein condensation amongst neuron constituents is what distinguishes the conscious from the non-conscious, and it is the physical basis of consciousness (Zohar, 1991).

Stress and Autoimmune/Inflammatory Disease

Interactions between the immune and central nervous systems (CNS) play an important role in modulating host susceptibility and resistance to inflammatory and infectious disease (Sternberg, 1997a). During inflammation, a bi-direction signaling between the immune and CNS is set into play, in which cytokines from the periphery can initiate the cycle by crossing the blood-brain barrier actively or at leaky sites in the blood-brain barrier, the circumventricular organs. They can also activate cerebral endothelial cell second messenger systems, including nitric oxide synthase and cyclooxygenase, and thus indirectly stimulate CNS functions. In addition, cytokines such as IL-1 can signal the central nervous system through stimulation of the vagus nerve and activation of brainstem regions such as the nucleus of the tractus solitarius (Warkins *et al.*, 1994). Such immune signaling of the CNS causes activation of the HPA axis, with release of corticotrophin releasing hormone (CRH) from the hypothalamus and ACTH from the pituitary gland which, in turn through the generally immunosuppressive effects of the glucocorticoids released from the adrenals, inhibits inflammation.

Both excess and inadequate stress, hormone responses are associated with disease: excess with enhanced susceptibility to infection, and inadequate stress hormone responses with enhanced susceptibility to inflammatory, autoimmune and allergic diseases. Thus, chronic HPA axis over-activation, as occurs during stress, can affect susceptibility to or severity of infectious disease through the immunosuppressive effects of the glucocorticoids. In contrast, blunted HPA axis responses are associated with enhanced susceptibility to autoimmune inflammatory disease (Sternberg, 1997b).

The HPA axis modulates inflammation through the generally anti-inflammatory action of glucocorticoids released from the adrenal cortex after HPA axis stimulation. Initially, glucocorticoids were thought to have a mainly immunosuppressive effect (Cupps and Fauci, 1982). Indeed, pharmacological doses of glucocorticoids are immunosuppressive at virtually every level of immune and inflammatory responses, including during activation of the innate immune response and in both cellular and humoral acquired immune response. Thus, glucocorticoids suppress cell adhesion, margination and migration, macrophage activation, antigen presentation, T cell receptor expression, T lymphocyte activation, proliferation, differentiation and mature cell function, including cytotoxicity, and B cell function including antibody production. Recent studies, however, indicate that physiological levels of glucocorticoids are immunomodulatory rather than solely immunosuppressive, causing a shift of cytokine production from a primarily pro-inflammatory to an anti-inflammatory pattern (Ashwell *et al.*, 2000).

Glucocorticoids also regulate immune function at the level of immune organs such as the thymus. The entire synthetic enzyme machinery for glucocorticoid production has been identified in the thymus, as have

glucocorticoid hormones and their precursors (Vacchio and Ashwell, 1997). Studies show that these local glucocorticoids play a role in thymic T cell selection. Depending on the concentration of glucocorticoid produced relative to the concentration of antigen, T cells undergo negative or positive selection, that is they may be shunted to the death pathway and die by apoptosis or they may undergo clonal proliferation. Thymic glucocorticoids are produced by thymic cytokeratin expressing stromal cells, rather than by differentiating T cells. It is not known whether this local glucocorticoid production is under hypothalamic-pituitary control or is independent. Thus, it is not known whether circadian or stress-related variations in ACTH can affect this route of glucocorticoid-related thymic selection.

Discussion

The further back in the causal chain of events we can begin treating the problem, the more powerful can be the healing. Ideally, a problem can be addressed at many levels simultaneously. The opposite is also true: if we treat only the apparent problem without also dealing with the underlying causes, then (1) new problem may occur, (2) the old problem may recur or persist, and (3) treatments tend to be more difficult, expensive, and invasive, with greater side effects than if the underlying causes were also addressed (Ornish, 1996). So, dealing with various diseases we have to look into the root causes of stress.

Molecular biologists and physicists support the fact that beyond molecules there remains integrations of information, intelligence and energy at the level of 'Pure Consciousness'. Both mind and body are different vibrational states of these fundamental field of 'Pure Existences'. However, the human physiology is structured in layers of self-referral wholeness (e.g. homeostasis); the property of self-interaction forms the basis of holistic integrations and functioning of the physiology. At all levels of emerging wholeness, it is a self-referral dynamism that coordinates and harmonizes the activity of parts in relation to wholes.

The perception of stress at the cerebral cortex is one avenue through which the physiology is mediated. The body responds instantaneously to experience our interpretation of and reaction to the environment is the key element in a domino chain of interrelated processes that shape our physiological status at any given moment. During stress that ultimately tends to disease shifts our perception from self-referral to object referral. In this stage the value of pure consciousness is obscured as the mind becomes absorbed in the objects of perception and memory of its own essential nature is overshadowed. Because the physiology is a precipitated expression of pure consciousness, this creates a shadow in the mind – body wholeness. The result is impaired self-regulation, which in turn leads to reduced order and co-ordination in the functioning of the system. Individual cells on other elements of the physiology begin to lose their connection to the whole of the physiology. Once this happens, the seed of disease has been sown.

Conclusion

Finally, we have seen in this review that autoimmune diseases are expressions of an internal dialogue of threat and alienation that results in self-destructive hostility; cancer and susceptibility to infection are immune-system's expressions of internal conflicts that result in desperation and hopelessness; health, however, is a state of flexibility that integrates all challenges and experiences into a meaningful response.

An ancient Vedic expression declares, "Infinite flexibility is the secret of immortality." The stability of the body's immune system depends upon the flexibility of our responses to the challenges of daily experience. Stability is built upon the foundation of dynamic nonchange in the midst of numberless swirling and chaotic influences. The essential feature of a healthy immune system is the capability to mount a dynamic response while maintaining stability and integrity.

The healing traditions of the world have always asserted the mind's influence on the body, but modern science is just beginning to understand how thoughts, feelings and perceptual interpretations of the world can influence well being. When our lives are in balance and our internal dialogue is harmonious, our immune system and every other aspect of our being receive the message of health.

Acknowledgements

Authors would like to thank Noor Jahan of Biotechnology and Genetic Engineering Discipline of Khulna University, Bangladesh, for her technical support and Janice K. Kiecolt-Glaser, Ph.D, of Ohio State University Collage of Medicine to provide us all her outstanding research articles.

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