PHYSIOLOGY AND NEUROBIOLOGY OF STRESS AND THE IMPLICATIONS FOR PHYSICAL HEALTH

Dr. Sukanto Sarkar * Dr. Sivaprakash B **

Stress is a word used to describe experiences that are emotionally and physiologically challenging. "Good stress," or eustress, generally refers to those experiences that a person can master and which leave a sense of accomplishment, whereas "bad stress", "distress" or "being stressed out," refers to experiences where a sense of control and mastery is lacking and which are often prolonged or recurrent, emotionally draining, and physically exhausting and detrimental to health[1]. A hallmark of the stress response is the activation of the sympathetic-autonomic nervous system (SAM) and hypothalamic-pituitary-adrenal (HPA) axis[2]. The"fight-or-flight" response is the classical behavioral and physiological response to a threat from a dangerous situation. This is an evolutionary response and is mediated by the autonomic nervous system[3].

Stress, a response to aversive stimuli, is a concept that is difficult to define fully because its interpretation tends to vary according to individual disciplines. Hans Selye, a pioneer in addressing general principles of physiology and pathophysiology in the exploration of stress, defined stress as "the non-specific response of the body to any demand " [4]. He emphasized the role of an integratedresponse of multiple systems rather than isolated reflexes. He gave the concept of general adaptation syndrome (GAS). It involves three stages i.e. the Alarm Reaction, the Stage of Resistance and the Stage of Exhaustion [5]. Although virtually all organs are affected by exposure to stress, the neuroendocrine, cardiovascular, immune and gastrointestinal systems are the first to experience functional changes.

Neuroendocrine response to stress

Exposure to variousstressors results in a series of coordinated responses often referred to as "stress responses," and are composed of alterations in behaviour, autonomic function and the secretion of multiple hormones including adrenocorticotropin hormone (ACTH) and cortisol/corticosterone, adrenal catecholamines, oxytocin, prolactin and renin[5]. Some of the physiological changes associated with the stress response include: (a) mobilization of energy to maintain brain and muscle function; (b) sharpened and focused attention on the perceived threat; (c) increased cerebral perfusion rates and local cerebral glucose utilization; (d) enhanced cardiovascular output and respiration, and redistribution of blood flow, increasing substrate and energy delivery to the brain and muscles; (e) modulation of immune function; (f) inhibition of reproductive physiology and sexual behaviour; (g) decreased feeding and appetite[6].

There is general agreement regarding the role of the hypothalamic–pituitary–adrenal axis and adrenal catecholamines in maintaining energy balance, as well as the role of the renin–angiotensin system in redistributing blood flow towards the brain and other vital organs[6, 7]. Many brain structures are involved in the response to psychologically and physically stressful stimuli. Activation of the hypothalamic–pituitary–adrenal axis leads to a rapid secretion of ACTH from corticotrophs in the anterior pituitary and increase in circulating glucocorticoids[7]. Initially, it was thought that corticotropin- releasing factor (CRF) is the sole means of releasing ACTH from the pituitary gland but other factors also contribute to regulate ACTH release from the pituitary gland[8]. CRF plays a prominent role in mediating the effect of stressors on the hypothalamic–pituitary adrenocortical axis, and in coordinating the endocrine, autonomic, behavioral and immune responses to stress[6].

Oxytocin and prolactin isalso secreted in both males and females in response to aversive stimuli implicating them as "stress hormones," thus suggesting that they play other important roles that are important for survival. Oxytocin has been reported to play a role in sodium balance and in a

*** Dr. Sukanto Sarkar, Assistant Professor of Psychiatry, ** Dr. Sivaprakash B, Professor of Psychiatry**
Mahatma Gandhi Medical College and Research Institute, Puducherry 607402, India.

central anxiolytic circuit[9], whileprolactin has been reported to modulate immune function[10].

Neuroanatomy of the stress response

Various brain circuits participate in the regulation of the neuroendocrine responses to various stressors. Among these are the hypothalamus, septohippocampal system, amygdala, cingulate and prefrontal cortices, hindbrain regions such as the brainstem catecholamine cell body groups (A2/C2 cell groups in the nucleus of the tractus solitarius; A1/C1 cell groups in the ventrolateral medulla; A6 cell groups in the locus coeruleus), the parabrachial nucleus, cuneiform nucleus and dorsal raphe nucleus[11]. During a stressful event, sensory inputs from peripheral sense organs pass through either the reticular activating system or the thalamus, which function as relay stations, to the amygdala and sensory cortex[12]. The sensory cortex communicates to the hippocampus and with the lateral amygdala through the perirhinal cortex [13]. The lateral and the basolateral nuclei of the amygdala play a major role by integrating sensory inputs from the thalamus, and cognitiveinformation from the cortex and hippocampus[6]. The amygdala also stimulates the dorsal raphe nucleus andadrenergic nuclei located in the brainstem, which, in turn innervate CRF neurons in the hypothalamic paraventricular nucleus [5]. Thus, the hypothalamic pathway is believed to play a key role in the adrenocortical response via a complex pathway. Glucocorticoids play a key regulatory role in the neuroendocrine control of the hypothalamic–pituitary–adrenocortical axis and it terminates the stress response by exerting negative feedback at the levels of hypothalamus and pituitary[14]. Also, by stimulating the GABA-ergic neurons, mineralocorticoid receptors in the hippocampusinhibit the activity of the hypothalamic–pituitary–adrenocortical axis, thus regulating this pathway [15].

Neuroimmune mechanism of Stress

Stressors in various forms at various intensities dysregulates the immune system. The interaction between the CNS, endocrine and the immune system forms the broad interdisciplinary research field known as psychoneuroimmunology [16]. Dysregulation ofthe immune system leads to susceptibility to infections, physical ill-health and to a spectrum of stress-related disorder such as diabetes, asthma, hypertension etc. The release of cortisol perhaps plays the final role to provoke various immunological changes like the release of cytokines (IFN), interleukins and TNFs. The SAM axis also innervates the lymphoid organs that produce NK cells and other T lymphocytes[17].

Impact on immune cells: Stress increases monocytes, neutrophils and B cells in the spleen and causes redistribution of myeloid and lymphoid cells from the bone marrow[18]. There is impaired function of thymus, spleen and lymph nodes under severe stress. Of these,the thymus is very sensitive to stress and thus uncontrolled stress can suppress cellular immunity[17].

Impact on cytokines: Chronic stress elevates serum glucocorticoids which leads to an increase in serum interferonsand interleukins. Glucocorticoids can influence the growth and maturation of leukocytes, downregulates cytokines such as IFN-γ, TGF-β, TNF-α, IL-12 mediated by cell immunity while upregulating the expression of various interleukins (IL-4,10,13) mediated by humoral immunity[19, 20].

Stress and Physical disorders

Chronic diseases like diabetes, obesity, cardiovascular diseases are the leading cause of death and disability (Centre for Disease Control). Psychosocial factors including stress are implicated as etiological factors, maintenance factors and factors that hinder recovery from these disorders. Mind-body medicine deals with such areas exploring the interaction between brain, mind, body and behaviour[21].

Cardiovascular diseases (CVD) are the leading cause of death worldwide. Apart from various psychosocial factors such as emotional distress, Type D personality, depressive symptoms, stressors play an important role in the etiology of CVD[22]. Acute stress causes vasoconstriction and vasospasm, mechanical straining, endothelial tearing and plaque rupture. Chronic stress leads to thrombogenesis causing increased platelet aggregation. Elevated cytokines and IL-6 are also associated with chronic stress which is strongly associated with platelet instability[22, 23].

Metabolic Syndrome has increased alarmingly over the last two decades and it includes three major disorders viz. obesity, hyperlipidaemia and diabetes. Glucose intolerance, insulin resistance and hypertension are also associated with this syndrome[24, 25]. Evidence shows that chronic psychological stress correlates with the metabolic syndrome, particularly abdominal obesity. Cortisol hypersecretion in chronic stress increases visceral obesity as cortisol binds to glucocorticoid receptors in the fat cells and activates the enzyme lipoprotein lipase which converts triglycerides to free fatty acids[26]. Cytokines and other interleukins increase insulin resistance through an inflammatory response,leading to diabetes[27].

Rheumatoid Arthritis (RA) is an autoimmune disorder of the joints and stress is recognised as a key risk factor in the pathogenesis of RA. Immune dysregulation triggered by stress via cytokine amplification and other complex mechanism leads to an autoimmune process that produces RA[28]. The treatment of RA currently focuses on stress reduction, life-style modification and improving quality of life.

Asthma is often triggered by stress. Findings suggest that acute stressors activate the sympathetic nervous system that leads to bronchospasm and subsequent attacks of asthma. Emotional distress can constrict the smooth muscles of the airways in the lungs producing wheezing, coughing and chest tightness. Chronic stressors cause immune system activation and can exacerbate asthma via inflammatory pathways[29].

Functional gastrointestinal (GI) disorders are very common in the general population and are one of the most prevalent disorders in patients attending gastroenterology clinics. Irritable Bowel Syndrome, a prototypical functional GI disorder has symptoms of abdominal pain associated with alteration of bowel habits in absence of identifiable organic disease to explain the above symptoms(30). Stress alters the neuroendocrine and the immune system causing the release of various neuropeptides and interleukins that affects the GI motility, visceral perception and increased intestinal permeability,leading to IBS[31,32].

Stress management techniques

Various stress management techniques are used to tackle stress in different settings. The most common methods supported by research evidenceinclude progressive muscle relaxation, meditation, biofeedback, cognitive-behavioral skills, stress inoculation techniques and cognitive behavioural therapy[33]. Mindfulness-based stress reduction (MBSR) is a new and clinically standardized meditation that has shown consistent efficacy for many mental and physical disorders[33, 34]. A recent article exploring systematic review on yoga in reducing stress (based on eight randomised control trials and clinical controlled trials) indicated a positive effect of yoga in reducing stress levels or stress related symptoms[35]. Also Sudarshan Kriya yogic breathing has shown to reduce stress and anxiety symptoms significantly[36].

To conclude, stress has a major impact on our life and its pathological form can contribute to the etiology of various physical disorders. As a health care provider, we should broaden our horizons and consider psychological stress as an etiological factor in various conditions and include stress management as a part and parcel of the treatment of such disorders. Let us keep in mind Sir William Osler's (1849-1919) famous lines "It is much more important to know what sort of patient has a disease than what sort of disease the patient has" [21].

References

1. McEwen BS. Physiology and neurobiology of stress and adaptation: central role of the brain. Physiol Rev 2007;87(3):873-904.
2. Ulrich-Lai YM, Herman JP. Neural regulation of endocrine and autonomic stress responses. Nat Rev Neurosci 2009; 10(6):397-409.
3. Koob GF. Corticotropin-releasing factor, norepinephrine, and stress. Biol. Psychiatry 1999; 46:1167–80.
4. Seyle H. Stress and the general adaptation syndrome. Br Med J 1950;1(4667):1383-92.
5. Carrasco GA, Van de Kar LD. Neuroendocrine pharmacology of stress. Eur J Pharmacol. 2003;463(1-3):235-72.
6. Van de Kar LD, Blair ML. Forebrain pathways mediating stress induced hormone secretion. Front Neuroendocrinol 1999; 20: 1- 48.

7. Aguilera G, Rabadan-Diehl C, Nikodemova M. Regulation of pituitary corticotropin releasing hormone receptors. Peptides 2001; 22:769-74.
8. Levens NR. Control of renal function by intrarenal angiotensin II in the dog. J Cardiovasc Pharmacol 1990; 16: S65– S69.
9. Gimpl G, Fahrenholz F. The oxytocin receptor system: structure, function, and regulation. Physiol Rev 2001; 81:629–83.
10. Neidhart M. Prolactin in autoimmune diseases. Proc Soc ExpBiol Med 1998; 217: 408– 19.
11. Herman JP, Cullinan WE. Neurocircuitry of stress: central control of the hypothalamo-pituitary-adrenocortical axis. Trends Neurosci 1997;20(2):78-84.
12. Pezzone, MA, Lee WS, Hoffman GE, Rabin BS. Induction of c-fos immunoreactivity in the rat forebrain by conditioned and unconditioned aversive stimuli. Brain Res 1992; 597: 41– 50.
13. LeDoux JE. Emotion: clues from the brain. Annu Rev Psychol 1995;46: 209-35.
14. De Kloet ER. Steroids, stability and stress. Front Neuroendocrinol 1995;16: 416-25.
15. Gesing A, Bilang-Bleuel A, Droste, S.K, Linthorst ACE, Holsboer F, Reul JMHM. Psychological stress increases hippocampal mineralocorticoid receptor levels: involvement of corticotropin-releasing hormone. J Neurosci 2001; 21: 4822-29.
16. Schneiderman N, Ironson G, Siegel SD. Stress and health: psychological, behavioral, and biological determinants. Annu Rev Clin Psychol 2005;1:607-28.
17. Yan W. Impact of prenatal stress and adulthood stress on immune system: A review.Biomedical Research 2012; 23 (3): 315-320.
18. Engler H, Bailey MT, Engler A, Sheridan JF. Effects of repeated social stress on leukocyte distribution in bone marrow, peripheral blood and spleen. J Neuroimmunol 2004; 148 (1-2): 106-15.
19. Carpentier PA, Palmer TD. Immune influence on adult neural stem cell regulation and function. Neuron 2009;64(1): 79-92.
20. Segerstrom SC, Miller GE. Psychological stress and the human immune system: a meta-analytic study of 30 years of inquiry. Psychol Bull 2004;130(4):601-30.
21. Purdy J. Chronic physical illness: a psychophysiological approach for chronic physical illness. Yale J Biol Med 2013; 86(1):15-28.
22. Hamer M. Psychosocial stress and cardiovascular disease risk: the role of physical activity. Psychosom Med 2012;74(9):896-903.
23. Herman JP, McKlveen JM, Solomon MB, Carvalho-Netto E, Myers B. Neural regulation of the stress response: glucocorticoid feedback mechanisms. Braz J Med Biol Res 2012;45(4):292-8.
24. Alberti KG, Zimmet P, Shaw J. Metabolic syndrome--a new world-wide definition. A Consensus Statement from the International Diabetes Federation. Diabet Med 2006;23(5):469-80.
25. Edwards EM, Stuver SO, Heeren TC, Fredman L. Job strain and incident metabolic syndrome over 5 years of follow-up: the coronary artery risk development in young adults study. J Occup Environ Med 2012;54(12):1447-52.
26. Koch FS, Sepa A, Ludvigsson J. Psychological stress and obesity. J Pediatr. 2008;153(6):839-44.
27. Chang JS, You YH, Park SY, Kim JW, Kim HS, Yoon KH, Cho JH. Pattern of Stress-Induced Hyperglycemia according to Type of Diabetes: A Predator Stress Model. Diabetes Metab J 2013;37(6):475-83.
28. Cutolo M, Straub RH.Stress as a risk factor in the pathogenesis of rheumatoid arthritis. Neuroimmunomodulation 2006;13(5-6):277-82.
29. Chen E, Miller GE. Stress and inflammation in exacerbations of asthma. Brain Behav Immun 2007; 21(8):993-9.
30. El-Salhy M, Gundersen D, Gilja OH, Hatlebakk JG, Hausken T. Is irritable bowel syndrome an organic disorder? World J Gastroenterol 2014; 20(2):384-400.
31. Barbara G, Cremon C, Carini G, Bellacosa L, Zecchi L, De Giorgio R, Corinaldesi R, Stanghellini V. The immune system in irritable bowel syndrome. J Neurogastroenterol Motil 2011;17(4):349-59.
32. Sugaya N, Izawa S, Kimura K, Ogawa N, Yamada KC, Shirotsuki K, Mikami I, Hirata K, Nagano Y, Nomura S, Shimada H. Adrenal hormone response and psychophysiological correlates under psychosocial stress in individuals with irritable bowel syndrome. Int J Psychophysiol 2012; 84(1):39-44.
33. Chiesa A, Serretti A. Mindfulness-based stress reduction for stress management in healthy people: a review and meta-analysis. J Altern Complement Med 2009; 15(5):593-600.
34. Praissman S. Mindfulness-based stress reduction: a literature review and clinician's guide. J Am Acad Nurse Pract 2008;20(4):212-6.
35. Chong CS, Tsunaka M, Tsang HW, Chan EP, Cheung WM. Effects of yoga on stress management in healthy adults: A systematic review. Altern Ther Health Med 2011;17(1):32-8.
36. Brown RP, Gerbarg PL. Sudarshan Kriya Yogic breathing in the treatment of stress, anxiety, and depression. Part II--clinical applications and guidelines. J Altern Complement Med 2005; 11(4):711-7.