Gender differences in stress response: Role of developmental and biological determinants

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Abstract

Stress response is associated with manifestations of various psychosomatic and psychiatric disorders. Hence, it is important to understand the underlying mechanisms that influence this association. Moreover, men and women tend to react differently with stress—both psychologically and biologically. These differences also need to be studied in order to have a better understanding in the gender difference observed for many disorders, which are likely to be contributed by the gender difference in stress reactivity and responses. Such an understanding would have a significant impact on our understanding about how adult health is set during early life and how adult disease could be prevented in men and women.

Keywords: Gender, psychiatric disorders, stress response

Stress can be defined as a real or interpreted threat to the physiological or psychological integrity of an individual that results in physiological and behavioral responses. In Eastern cultures, stress has been viewed as an absence of inner peace. On the other hand, the Western culture has viewed stress as a loss of control.

Gender is an important determinant of human health, and there is a clear pattern for the sex-specific prevalence rates of various mental and physical disorders. Susceptibility to infectious diseases, hypertension, aggressive behavior, and drug abuse is generally observed to be higher in men. Conditions such as autoimmune diseases, chronic pain, depression, and anxiety disorders are relatively more prevalent among women.[1–4] The observed gender-specific disease pattern may be partly attributed to effects of sex hormones as some of these gender differences emerge during reproductive years and gradually diminish after menopause.[5] Individual differences in stress reactivity have been proposed as a potentially important risk factor for gender-specific health problems in men and women.[6,7]

HYPOTHALAMIC-PITUITARY-ADRENAL AXIS AND AUTONOMIC NERVOUS SYSTEM

Assessment of gender differences in stress reactivity relies primarily on measuring physiological responses to acute stressors in laboratory settings. This includes activities of the Hypothalamic-Pituitary-Adrenal (HPA) axis (eg, cortisol) and sympathetic nervous system (eg, heart rate and blood pressure). Greater acute HPA and autonomic responses have been found in adult men as compared to adult women, with the help of standard performance-related psychosocial stressors such as public speaking.[8,9] Pathogenesis of cardiovascular disease, aggression, and immune suppression in men are likely to be influenced by this greater sympathoadrenal responsiveness.[4,7]

HPA response patterns differ markedly between males and females. This has been demonstrated in both animal and human studies. The biochemical profile of human beings varied from that of rodents with regard to stress-related neurochemicals such as basal Adrenocorticotropic Hormone (ACTH) and corticosterone levels.[10] While the basal level as well as variance in response to stress is uniformly higher in females of rodents, the picture is more complex in humans. A relatively higher secretion of ACTH with comparable total cortisol levels under basal conditions has been observed in men. This finding reflects an increased sensitivity of the adrenal cortex in women as compared to men.[11] However, no gender differences are observed at the pituitary level on challenging with synthetic Human Corticotropin-Releasing Factor (h-CRF) with or without pretreatment with dexamethasone.[10,11] The response is different to ovine CRF[12] or a combination of h-CRF and vasopressin with respect to ACTH secretion, with women being more responsive.[11]

GONADAL STEROIDS AND MENSTRUAL CYCLE

Female sex hormones attenuate the sympathoadrenal and HPA responsiveness. This leads to sluggish cortisol feedback on the brain and less or delayed containment of the stress response. Tendency of women to develop depression is related to the compromised cortisol feedback effects on HPA arousal.[2,6] Ovariectomy leads to attenuated HPA responses, whereas estradiol substitution induces HPA stimulation in animal studies.[13] An increased HPA-axis response to stress in females is observed in gonadectomized or neonatally estrogenized rats. This effect is independent of differences in circulating gonadal steroid levels.[14] This suggests an innate or organized difference in the HPA-axis response to stress. Genomic differences, organizationally or developmentally programmed effects (caused by earlier differential gonadal steroid exposure), and/or acute, activational effects of recent gonadal steroid exposure are some of the possible underlying mechanisms reflected in the observed sex differences in the central nervous system function. The sex differences in HPA axis responses would be expected to disappear if gonadal steroids were removed. On the contrary, sexual dimorphism would persist if the responses were not dependent on the concurrent gonadal steroids. Low levels of estradiol are observed in the early follicular phase, which peak shortly before or during ovulation and slowly decrease throughout the luteal phase. Basal as well as stimulated ACTH and corticosterone levels are the highest around the time of ovulation in rats.[15] Human studies have produced inconsistent results with respect to possible changes in the HPA activity during the menstrual cycle.[16]

PSYCHONEUROIMMUNOLOGICAL MARKERS

There is a difference in susceptibility of women and men to specific immunological disorders. This suggests gender dimorphism of the immune system. Gender may exert differential effects on the immune system by modulating Glucocorticoid (GC) sensitivity of proinflammatory cytokine production.[17] The HPA axis can be activated by a wide variety of psychosocial and physiological stressors. This results in the secretion of GCs and modulation of specific immune responses. Psychosocial stress, such as academic examinations, leads to decreased cellular immune function.[18] This is mediated by profound changes in cytokine secretion. GCs suppress major type 1 cytokines, interferon-alpha, and Interleukin (IL)-2, produced by TH1 helper cells. However, type 2 cytokines, IL-4, and IL-10 remain unchanged. Humoral immune responses are favoured, while cell-mediated immunity is suppressed by this shift toward a type 2 cytokine pattern.[19] GCs specifically inhibit the production of proinflammatory cytokines (IL-6, IL-1, and Tumor Necrosis Factor (TNF)-alpha) in monocytes and macrophages. The anti-inflammatory cytokines remain unaffected or are even elevated.[20]
There is a difference in the stress response exhibited by men and women. It is characterized by ‘fight-or-flight’ in men and ‘tend-and-befriend’ in women. [26] This hypothesis is supported by neuroendocrine and behavioral evidence. The physiological stress response typically involves activation of the sympathetic nervous system and the HPA axis in both genders. However, the stress response specifically builds on attachment care-giving processes in females. This tends to buffer the sympathetic and HPA arousal.

It was observed that the RFFC is activated and Left Orbitofrontal Cortex (LOF) is suppressed by stress. RFFC is an important part of both the negative emotion and vigilance systems and LOF is associated with positive emotion and hedonic goals. [27] The hypothesis that stress responses in men may be primarily characterized as “fight-or-flight” is supported by the observation that RFFC activation and LOF deactivation with stress is predominantly observed in the male brain. Involvement of the limbic system including ventral striatum, putamen, insula, and cingulate cortex underlies the stress response in females. [28] The observed limbic activation to stress in female subjects is more consistent with a ‘tend-and-befriend’ model of stress response. This is in contrast to the stress response observed in males, which is characterized by ‘fight-or-flight’ behavior. [29] There are several neurophysiological and neuroendocrine mechanisms underlying these gender differences in stress response.

The role of ventral striatum along with several limbic regions has been implicated in learning, reward, motivation, and emotion. [30] The observed gender differences in central stress responses might be a result of computational roles subserved by these brain regions.

The general trend of greater acute HPA and autonomous responses in males as compared to females by using performance stress paradigms is supported by the neuroimaging findings. Gender differences in autonomic and endocrine responses are related to sex differences in stress response. [31] However, this effect was observed only for the mild stressors rather than the severe life events. [32] This could be a result from greater sensitivity to depression-inducing effects of SLEs among some individuals as compared to others. [33] Personality traits such as neuroticism, [34] childhood adversity, [35] and indirect measures of genetic risk for depression and anxiety, derived from twin or family studies, play a role in stress reactivity. [36] A length polymorphism in the gene encoding the serotonin transporter (5-HTTLPR) could be responsible for the moderating effect of genetic risk on the relationship between life events and depression. [37] However, this effect was observed only for the mild stressors rather than the severe life events. [38] An interaction between a genetic polymorphism and a stable psychological trait to experience the environment as stressful may be the manifested sign of an underlying interaction between a genetic polymorphism and SLEs. Additionally, the 5-HTTLPR genotype may moderate the association between depressive disorder and the tendency to experience the environment as stressful.

Patients with depression or anxiety tend to score higher on neuroticism, extraversion, and facets of agreeableness and conscientiousness than individuals without these conditions. [39] Neuroticism has been associated with social phobia, agoraphobia, panic disorder, obsessive–compulsive disorder, and major depression. Introspection has been associated with social phobia and agoraphobia. Neuroticism not only predicts the onset of depressive symptoms and depressive disorder but also increases the risk of exposure to SLEs. [40]–[45]

COGNITIVE STRUCTURE

As characterized by Beck, sociotropy reflects a high need for interpersonal relationships with a focus on ‘pleasing others to avoid disapproval’ in order to secure attachments. However, a greater degree of emotional ‘rewinding’ (melancholy thinking) or reflection of own emotional traits is also increased. [46] Beck postulates that elevated levels of sociotropy and autonomy increase one’s sensitivity to the depressogenic effects of certain types of stressful life events.

Cognitive styles reflect a ‘concern about disapproval’ and ‘need for control’ pose significant risk for depression independent of the effects of stressful life events. [47] Individuals rating higher on these two cognitive styles are likely to be at greater risk for depression in the presence of stressful life events. [48] Kendler et al. reported that women are more sensitive to depressogenic effects of interpersonal problems with individuals within their proximal network. [49] Ruminative thinking is also more common in women and is associated with an increased risk of depression. [50]

FIGHT-OR-FLIGHT V/S TEND-AND-BEFRIEND MODEL

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bephriend’ rather than a ‘fight-or-flight’ model.

However, it is noteworthy that ventral striatum activation is not a unique marker for the involvement of the reward system and has been implicated in numerous processes. [65] Also, the isolated fMRI environment is hostile to the formation of social attachment under stress. Some authors have suggested that the gender difference in emotionality per se may be an ill-posed question. [65, 66]

**DEVELOPMENTAL IMPACT**

Attachment theory proposed by Bowlby provides a biological basis for understanding close, protective relationships. [65, 66] The attachment theory is based on the premise that a child’s desire for proximity to his/her mother is a biological drive, which has been selected in evolution. An infant maintains proximity to her or his mother through a complex system of communications and behaviors, which increase its probability of survival. An insecure attachment may increase perceived stress. Also, it may affect the intensity or duration of the physiological stress response. Finally, it may determine the success of social support in buffering stress.

A high prevalence of past psychological trauma, including sexual abuse, is reported by individuals with various physical conditions including gastrointestinal disorders, fibromyalgia, and pain syndromes. Small size at birth is associated with a higher prevalence of cardiovascular and metabolic disease in a child’s later life. [71]

Animal and human studies have suggested that in utero resetting of the Hypothalamic–Pituitary–Adrenal (HPA) axis may be an important change initiating the metabolic syndrome. A sexually dimorphic response to programming of the HPA axis has been found in animal studies. Female rats are more sensitive than male rats to activation of the HPA axis following fetal alcohol exposure or prenatal stress. Moreover, the HPA activation associated glucose tolerance and insulin sensitivity has been found to be impaired in female guinea pigs. Association between the simple measurement of fasting plasma cortisol with birthweight and the metabolic syndrome has been found in both men and women. However, most of the published cross-sectional studies exploring the role of cortisol levels in cardiovascular risk factors have been conducted in men. [75, 76] A difference in metabolic clearance rates of cortisol among males and females is reflected in the fact that urinary cortisol metabolite excretion differs between them. [77] Prematurity at the time of birth affects the cortisol metabolite excretion rate only in women. [78] Also prematurely born women exhibiting lower cortisol responses to stress. [79, 80] A more recent study failed to find a correlation between birth size and the adrenal response to synthetic ACTH. [86]

**ASSOCIATION WITH DISORDERS**

Manifestations of psychosomatic and psychiatric disorders has been found to be associated with a dysfunctional HPA axis. [81] HPA hyperactivity is a common finding in major depression. [82] Social phobia, panic disorder, generalized anxiety, obsessive–compulsive disorder susceptibility to infectious diseases and cardiovascular disorders. [88] Evidence of hypercortisolism is one of the most consistent biological findings among psychiatric patients. [89–91] Different diagnostic subtypes of depression may be characterized by different types of stress system pathology. Melancholic depression is associated with HPA axis hyperactivity. [92] On the other hand, atypical depression is associated with HPA axis downregulation. [93] Lupus erythematosus, multiple sclerosis, and neurodermatitis are associated with hyporeactivity of the HPA system. A clear relationship between stressful life events and the onset of breast cancer has not yet been established. [97] However, a few studies suggest that stress may influence the progression and recurrence of cancer. Severe life event stress is associated with an increased rate of early HIV disease progression. [98] Specific types of chronic difficulty such as caring for a relative with dementia can be associated with increased cortisol secretion. [99, 100] A study found lowered plasma tryptophan levels and increased cortisol secretion in carers of patients with clinical dementia. [100]

A noteworthy point here is that some studies have found that patients suffering from depression hypersecrete cortisol. Also, elevated cortisol levels after life events are not necessarily associated with the development of depressive disorder. In addition, the majority of patients suffering from moderate depression in the community probably do not hypersecrete cortisol.

**CONCLUSION**

Prevention of emergence of various disorders could be helped significantly by improving our understanding in the psychobiological impact of stress. Men and women tend to react differently to stress—both psychologically and biologically. The neurobiological underpinnings of this difference continue to be explored. At the same time, the research needs to explore the determinants of the environmental influence on the stress reaction. Better planned and designed interventions would help individuals deal more effectively with stress in their lives.

**Footnotes**

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