Chronic Stress and Limbic-Hypothalamopituitary-Adrenal Axis (LHPA) Response in Female Reproductive system

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Abstract
The hypothalamo-pituitary-adrenocortical (HPA) axis is a critical adaptive system that maximizes survival potential in the face of physical or psychological challenge. The principal end products of the HPA axis, glucocorticoid hormones, act on multiple organ systems, including the brain, to maintain homeostatic balance. The brain is a target of stress, and the hippocampus is the first brain region, besides the hypothalamus, to be recognized as a target of glucocorticoids. These anatomical areas in brain are limbic system, and in particular the hippocampus, medial prefrontal cortex (mPFC) and amigdal that have multiple control points in regulation of the hypothalamic–pituitary–adrenal (HPA) axis. The studies show the prefrontal cortex (PFC) plays an important role in the regulation of stress-induced hypothalamic–pituitary–adrenal (HPA) activity and regulation of gonadal function in men and women is under the control of the HPA. This regulation is complex and sex steroids are important regulators of GnRH and gonadotropin release through classic feedback mechanisms in the hypothalamus and pituitary gland. Chronic stress can have a deleterious effect on the reproductive axis that, for females, is manifested in reduced pulsatile gonadotropin secretion and increased incidence of ovulatory abnormalities and infertility. The limbic–hypothalamic–pituitary–adrenal (LHPA) axis suggests a functional role for gonadal steroids in the regulation of a female's response to stress.

Keywords: Chronic stress, Limbic-hypothalamopituitary-adrenal (LHPA) axis, Female reproductive system, Glucocorticoids, Estradiol

1. Stress system

1.1. Stress system & homeostasis

The concept of stress is as old as medical history itself, dating back at least to the time of Hippocrates who referred both to the suffering associated with disease (pathos) and to the toil (ponos) — the fight of the body to restore itself to normal position (1). In more recent history, both Walter Cannon (2) and Claude Bernard (3) described the ability of all organisms to maintain a constancy of their internal milieu or homeostasis, and 70 years ago Hans Selye, the pioneer of contemporary stress research, first described the General Adaptation Syndrome (GAS) as a chronological development of the response to stressors when their action is prolonged (4). While

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we will return to the concept of generalized biological responses to stress and stress response adaptation as a context to understand pathophysiologic processes for neurosteroids in depressive disorders, it is of historical interest to point out here that Selye was the first to document the relatively immediate (within minutes) anesthetic and anticonvulsant properties of progesterone and related compounds administered itraperitoneally to rats (5, 6). Therefore As pointed out for the first time by Hans Selye in Nature in 1936, stress or 'noxious agents' initiate a reaction in the body, which he called the 'general adaptation syndrome' (GAS). Selye distinguished three stages that the body passes when responding to stress in the GAS: 1) the first stage is an 'alarm reaction', in which the body prepares itself for 'fight or flight'; 2) the second stage of adaptation (provided the organism survives the first stage), is one in which a resistance to the stress is built; and 3) finally, if the duration of the stress is sufficiently long, the body enters a stage of exhaustion, a sort of aging, due to 'wear and tear'. Although the stress response of the body is meant to maintain stability or homeostasis, long-term activation of the stress system can have a hazardous or even lethal effect on the body, increasing the risk of obesity, heart disease, depression, and a variety of other illnesses (7). Life exists by maintaining a complex dynamic equilibrium or homeostasis that is constantly challenged by intrinsic or extrinsic adverse forces, the stressors. 1. GP Chrousos and PW Gold, The concepts of stress system disorders: overview of behavioral and physical homeostasis. JAMA, J Am Med Assoc 267 (1992), pp. 1244–1252. View Record in Scopus | Cited By in Scopus (1163According to Hans Sely, stressors include physical and psychologic or socialogic that all disturb homeostasis stable internal environment of body, that may contribute directly to the production of disease or it contribute to the development of behavior, which increases the risk of disease (8).

1.2. Stress response

The stress response is mediated by a sequence of neurological and endocrine messages involving the secretion of corticotropin releasing factor (CRF) and arginine vasopressin (AVP) by the paraventricular nucleus (PVN) of the hypothalamus, which in turn stimulates the release of adrenocorticotropic hormone (ACTH) from the anterior pituitary lobe. ACTH stimulates release of glucocorticoid (GC) and some mineralocorticoid steroid hormones from the adrenal glands (9). These stress hormones secreted by the HPA axis indirectly control their own secretion through a classic neuroendocrine negative feedback loop. That is, the glucocorticoids feedback on the PVN and many other extrahypothalamic sites, in particular, the hippocampus and medial prefrontal cortex (mPFC), to inhibit further release of CRH. Corticosteroids enhance catabolic, and suppress anabolic processes by increasing circulating levels of energy substrates—glucose, free fatty acids and free amino acids. The major GC in rodents is corticosterone (CORT), and in humans, cortisol. In addition, the immune response and processes involving cellular growth and reproduction are temporarily inhibited, to allow the animal to utilize resources for action. While short-term activation of the hypothalamic–pituitary–adrenal (HPA) axis allows for rapid mobilization of energy stores, in the long run, suppression of anabolic processes, depletion of energy stores and suppression of the immune system can be devastating to the organism (10).

1.3. Different types of stress

Stress management can be complicated and confusing because there are different types of stress: acute stress, episodic acute stress, and chronic stress, each with its own characteristics: intensity, duration, symptoms, and treatment approaches.

1) Acute Stress

Acute stress is the most common form of stress. It comes from demands and pressures of the recent past and anticipated demands and pressures of the near future. Acute stress is thrilling and exciting in small doses, but too much is exhausting.

2) Episodic Acute Stress

The symptoms of episodic acute stress are the symptoms of extended over arousal: persistent tension headaches, migraines, hypertension, chest pain, and heart disease. Treating episodic acute stress requires intervention on a number of levels, generally requiring professional help, which may take many months.

3) Chronic Stress

While acute stress can be thrilling and exciting, chronic stress is not. This is the grinding stress that wears people away day after day, year after year. Chronic stress destroys bodies, minds and lives.

Chronic stress kills through suicide, violence, heart attack, stroke, and, perhaps, even cancer. Because physical and mental resources are depleted through long-term attrition, the symptoms of chronic stress are difficult to treat and may require extended medical as well as behavioral treatment and stress management (11).

1.4. Stress and two axes: HPA, SNS

Disruptions in homeostasis (i.e., stress) place demands on the body that are met by the activation of two systems, the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system (SNS). Stressor-induced activation of the HPA axis and the SNS results in a series of neural and endocrine adaptations known as the "stress response" or "stress cascade." The stress cascade is responsible for allowing the body to make the necessary physiological and metabolic changes required to cope with the demands of a homeostatic challenge (12). Stress induced release of noradrenaline (NE) from postganglionic sympathetic neurons and epinephrine predominantly from the adrenal medulla. In the brain, the majority of the NE neurons activated by stress originate from the locus coeruleus (LC). Locus coeruleus (LC) is the primary site of the major noradrenergic cell bodies in the brain and a target in response to stress (13). Both electrophysiological and neurochemical studies (i.e., in vivo microdialysis) have shown that the brain noradrenergic system is phasically and robustly activated by a diverse array of acutely stressful stimuli, including immobilization, loud noise, immune challenge, electric shock, hypoglycemia, hypotension, cold exposure, bladder distension forced activity, and others (14, 15).Abercrombie and Jacobs, 1987 E.D. Abercrombie and B.L. Jacobs, Single-unit response of noradrenergic neurons in the locus coeruleus of freely moving cats: I. Acutely presented stressful and nonstressful stimuli, J. Neurosci. 7 (1987), pp. 2837–2843. View Record in Scopus | Cited By in Scopus (142) ..

2.1. HPA axis

Historical Context: In 1936, Hans Selye reported a historic series of studies on severe stress in rats. Exposure to bacterial infection, toxic chemicals, and other life threatening insults consistently caused adrenal gland enlargement with high levels of corticosterone secretion, atrophy of the immune organs, and gastric ulcers. All three components of this nonspecific stress response are caused by prolonged activation of the hypothalamic–pituitary-adrenocortical axis (HPAC), resulting in secretion of stress levels of adrenocorticotropin (ACTH) and glucocorticoids. In spite of these harmful effects, glucocorticoids in normal levels are necessary for sustaining life (16).

2.2. HPA and stress system

The central control stations of the stress system by HPA are located in the hypothalamus and the brain stem and include the parvocellular corticotropin-releasing hormone (CRH) and arginine–vasopressin (AVP) neurons of the paraventricular nuclei (PVN) of the hypothalamus, and the locus ceruleus (LC)–norepinephrine system (central sympathetic system) (17). Activation of the hypothalamus–pituitary–adrenal (HPA) axis, with the subsequent release of ACTH and glucocorticoids into blood, is one of the prototypical responses to all stressful situations either systemic or emotional.

2.3. HPA and Limbic System

Given the connection between stress and affective disorders, it is important to note that the hippocampus, prefrontal cortex and amygdala are also implicated in HPA axis regulation. The structure of limbic: hippocampus, prefrontal cortex and amygdala implicated in neuropsychiatric disease states also play a major role in stress control. Given the link between limbic regions, stress and psychosis, it is important to determine the role these structures play in stress integration. The HPA axis is controlled by a discrete set of hypophysiotrophic neurons in the medial parvocellular division of the hypothalamic paraventricular nucleus (PVN). These neurons synthesize and secrete corticotropin releasing hormone (CRH), the primary secretagogue for ACTH (18). Then the key CNS site integrating the neuroendocrine adjustments to stress is the hypothalamic paraventricular nucleus (PVN). This nucleus is comprised of two major neurosecretory components: the magnocellular (mPVN) and parvocellular (pPVN) subdivisions (19). The mPVN together with the supraoptic (SON) nuclei of the hypothalamus constitute the neurohypophysial system that is the primary source of AVP and the related peptide oxytocin (Oxt) released into the systemic circulation from neurons terminating in the posterior pituitary. Neurons in the more medially situated pPVN are the principal CNS source of

corticotropin-releasing hormone (CRH), which is a major physiological regulator of pituitary ACTH secretion. Under basal conditions about 50% of these neurons also express Avp (20). CRH and AVP stimulate ACTH secretion and there is evidence that AVP may become the dominant ACTH secretagogue in some chronic stress situations. If an acute stress is repeated over a number of days, adaptation or desensitization of the HPA axis can occur resulting in diminished responsiveness to this (homotypic) stressor. During acute stress, the amplitude and synchronization of the CRH and AVP pulsations in the hypophyseal portal system markedly increases, resulting in increases of ACTH and Glucocorticoid secretory episodes (21). Glucocorticoid secretion is also driven by internally perceived disruptions of homeostasis, cued by cardiovascular, respiratory or visceral stimuli. These disruptions appear to be relayed to the PVN by way of brainstem neurons, located in the region of the nucleus of the solitary tract and to a lesser extent, the ventrolateral medulla, a substantial population of these excitatory neurons are noradrenergic or adrenergic (22). Monoaminergic neural systems were among the first to be identified as stress sensitive, both to acute and chronic stress and noradrenergic input from brainstem nuclei, such as the locus coeruleus (LC) and nucleus tractus solitarius (NTS), during stress may reflect up-regulation of CRH1 receptor mRNA in the PVN(Fig.1) (23).

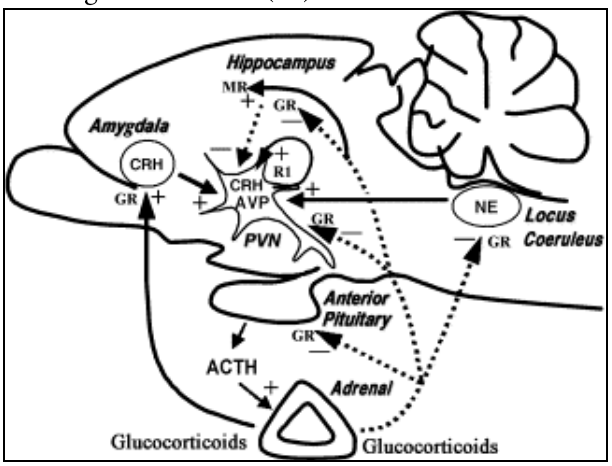
2.4. Limbic system

The anatomical limbic system suggest a functional role for gonadal steroids in the regulation of a female's response to stress and LHPA axis has a multiple control points in this response.

2.4.1. Hippocampus

Hippocampal stimulation decreases glucocorticoid secretion in rat and human and Rubin et al., 1966 R.T. Rubin, A.J. Mandell and P.H. Crandall, Corticosteroid responses to limbic stimulation in man: localization of stimulation sites, Science 153 (1966), pp. 1212–1215. suggesting that this region is sufficient to inhibit HPA activation. HPA response to stress depends on the kinds of stress, for example chronic stress, long-term high dose corticosteroid treatment and aging are all associated with hippocampal neuroimpairment, decreased levels of hippocampal corticosteroid receptors and prolonged stress responses, suggesting a connection between decreased hippocampal glucocorticoid signaling and HPA inhibition(24).

Figure1: Multiple feedback loops activating CRH systems during chronic stress. Stress initially activates the hypothalamic CRH system (i.e., CRH in the PVN), resulting in the hypersecretion of glucocorticoids from the adrenal gland. In addition, the psychological component of the stressor stimulates the amygdaloid CRH system (i.e., CRH in the central nucleus of the amygdala). Glucocorticoids exert GR-mediated negative feedback effects on the biosynthesis and release of CRH in the PVN and ACTH in the anterior pituitary (AP) directly or indirectly through the brainstem catecholaminergic nuclei such as the LC, resulting in the termination of stress-induced HPA axis activation. In the chronic phase of stress, down-regulation of GR in the PVN and other brain structures such as the LC fails to restrain hyperfunction of the HPA axis. Increased CRH in the PVN also induces a putative ultrashort positive feedback effects on its own biosynthesis through up-regulation of PVN CRHr-1. The persistent activation of the HPA axis further up-regulates the amygdaloid CRH system involved in the expression of fear and anxiety, and the amygdala may have stimulatory effects on the HPA axis. Thus, the hypothalamic and the amygdaloid CRH systems cooperatively constitute stress-responsive,anxiety-producing neurocircuitry during chronic stress (23).



2.4.2. Medial prefrontal cortex(mPFC)

The medial prefrontal cortex is also implicated in stress regulation. Functional imaging studies in humans suggest that medial prefrontal cortex (mPFC) dysfunction is correlated with abnormalities in neuroendocrine regulation as well as with cognitive and affective changes that are symptomatic in many stress-related mental illnesses(25). Detailed investigation of how repeated stress affects neuronal morphology in the mPFC may provide a cellular and synaptic basis for the neuroendocrine and behavioral manifestations of stress, particularly with respect to long-lasting pathology. Several reports have shown that repeated stress induces the retraction and debranching of apical, but not basal, dendrites in mPFC pyramidal neurons(26). Howevere both acute and repeated stress-induced mPFC-dependent learning impairments corresponded to decreased apical dendritic arborization in pyramidal neurons in this region and lesions of the anterior cingulate and prelimbic divisions of the medial prefrontal cortex enhance ACTH and corticosterone secretion(27).

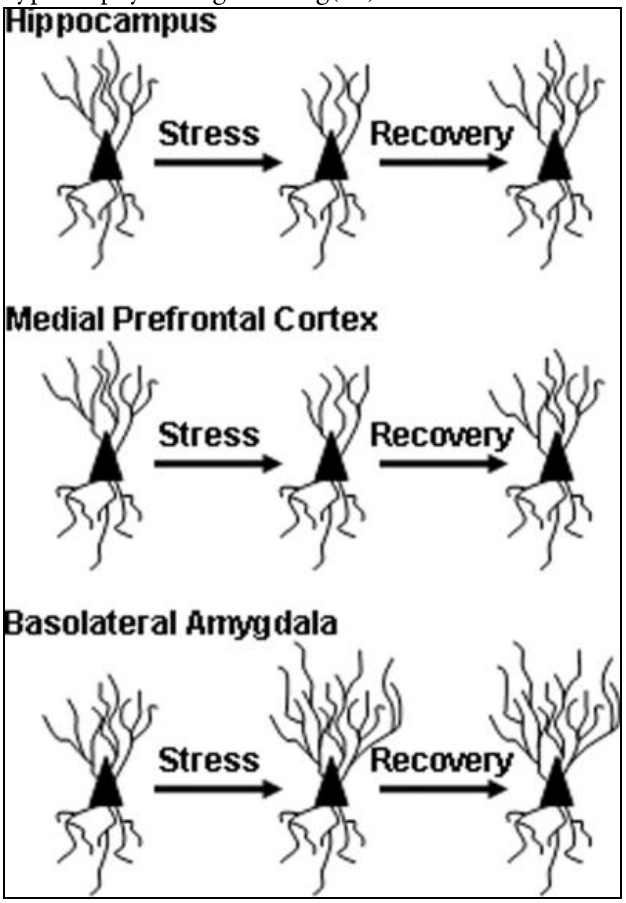
2.4.3. Amygdala

The amygdala is also a potential target for glucocorticoids. Like other limbic regions, the influence of the amygdala on the HPA axis is stressor- and region-specific. The influence of the amygdala on the HPA system is largely mediated by the medial and central amygdaloid nuclei, representing the principle amygdalar projection neurons to basal forebrain, hypothalamic and brainstem structures. Large amygdaloid lesions or lesions of the central or medial amygdaloid nuclei reduce ACTH and/or corticosterone secretion following stress. Overall, the data have led to the intriguing hypothesis that amygdalar glucocorticoid receptors play a 'feed forward' role in stress regulation, serving to potentiate rather than inhibit HPA responses (26). The analysis of how chronic stress modifies dendritic spine morphology may help in elucidating the cellular mechanisms that give rise to such Limbic-dependent behavioral alterations(Fig.2) (27).

2.4.4. LHPA axis and glucocorticoids

Cognitive responses to stress follow the temporally dependent pattern originally established by Selye (28) where in short-term stressors elicit adaptive responses whereas continued stress (chronic) results in maladaptive changes deleterious effects on

Figure2: Schematic diagrams of dendritic remodeling in the adult hippocampus (top), mPFC (middle), and basolateral amygdala (bottom). Note that the dendritic remodeling of both the hippocampus and mPFC are reversible, while basolateral amygdala dendritic hypertrophy is longer lasting(27).



physiological systems and impaired cognition. Females show different cognitive responses to stress. In contrast to impaired cognition in males after chronic stress, female rodents show enhanced performance on the same memory tasks after the same stress. Not only cognition, but anxiety, shows sex-dependent changes following chronic stress – stress is anxiolytic in males and anxiogenic in females (29). A broad range of studies show that 1) neurones are adversely affected in the frontal cortex, hippocampus and amigdala and show altered dendritic arbours (generally a pruning) and structural remodelling of synaptic connectivity. 2) Activities of monoaminergic systems in both cell bodies in the hindbrain and terminals throughout the brain are

changed (30). 3) Receptors for glucocorticoids are generally down regulated in hippocampus (31), which leads to greater release of corticosterone and an escalation in the adverse changes as long as the stressor is present. Functional indices of neurones are also affected, and include impairments in cognitive function and changes in anxiety level. In the few animal studies where female brains have been examined, a different pattern of stress effects is seen than in males with respect to morphology, where females show dendritic pruning in basal, not apical, hippocampal CA3 pyramidal neurones (32) and an increase in dendritic spine heads in CA1 pyramidal neurones (33). Glucocorticoid receptors are increased (up-regulation) in CA1 of females (31) as well as levels of some monoamines (34). Because there was a decrease in plasma corticosteroid-binding globulin levels in female rats during the restraint stress, while there was no change in male rats throughout the experiment. Then the sensitivity of animals and humans (male/ female) to cognitive function and stress by glucocorticoid in LHPA is not constant. When exposed to chronic stress, the HPA axis can show both response 'habituation' and 'facilitation'. 'Habituation' occurs when the same (homotypic) stressor is delivered repeatedly, and is characterized by progressive diminution of glucocorticoid responses to the stimulus. 'Facilitation' is observed when animals repeatedly exposed to one stimulus are presented with a novel (heterotypic) stressor. Habituation and facilitation (sencitisation) are two models of plasticity in central nervous system (CNS). The CNS is remarkably flexible and there is a great deal of plasticity in the adult CNS. Facilitation can occur in the context of chronic stress-induced elevations in resting glucocorticoids levels, suggesting that this process involves a bypass or override of negative feedback signals in LHPA area (35).

2.4.5. LHPA: Glucocorticoids/Estradiol

The endocrine-stress axis can be defined as the biological interface for neural and humoral communication between CNS and peripheral glands or organs responsible for mobilizing the stress response. Gonadal steroids regulate several aspects of hypothalamic-pituitary-adrenal (HPA) function. Sex differences exist in HPA activity, female rats have higher levels of total plasma corticosterone and also have higher plasma corticosterone binding globulin levels. Compared with male rats, female rats have a greater ACTH response to stress, faster onset of corticosterone secretion after stress, and a faster rate of rise of corticosterone (36). Studies in rat show that in the physiological range estradiol is an important inhibitory factor in the hypothalamic-pituitary-adrenal stress response of females and several studies suggest that estradiol plays a role in enhanced stress responses in female rats, based on increased HPA axis responses to stress when the ovariectomized rats are treated with estradiol. Decreased ACTH response to stress following estradiol treatment could either be due to enhanced negative feedback or to decreases in the activational components of the system at either the CRH or ACTH level. The increase in ACTH and corticosterone following restraint stress or exposure to a novel environment is enhanced by estradiol (E2) and also E2 potentiates the increase in serum ACTH and corticosterone following restraint stress.The foregoing suggests that most but not all data indicate that E2 may facilitate LHPA responsiveness under basal conditions. But in stress condition, chronic stress can have a deleterious effect on the LHPA and reproductive axis that, for females, is manifested in an increased incidence of infertility. However, gonadal steroids may, in turn, affect a female's response to stress as measured by activity within the LHPA axis (37). Stress-like concentrations of cortisol increase the negative feedback potency of oestradiol in castrated male sheep. A similar cortisol-dependent response in female sheep might be expected to suppress gonadotrophin secretion and impair follicular development and ovulation (38). Stress-like concentrations of cortisol interfere with follicular phase endocrine events of the ewe by suppressing pulsatile LH secretion, which is essential for subsequent steps in the preovulatory sequence. Cortisol was infused during the early to midfollicular phase, elevating plasma cortisol concentrations to one third, one half, or the maximal value induced by isolation, a commonly used model of psychosocial stress. All cortisol treatments compromised at least some aspect of reproductive hormone secretion in follicular phase ewes. First, cortisol significantly suppressed LH pulse frequency by as much as 35%, thus attenuating the high frequency LH pulses typical of the preovulatory period. Second, cortisol interfered with timely generation of the follicular phase estradiol rise, either preventing it or delaying the estradiol peak by as much as 20 h. Third, cortisol delayed or blocked the preovulatory LH and FSH surges.Moreover, the suppression of LH pulse

frequency provides indirect evidence that cortisol acts centrally to suppress pulsatile GnRH secretion in follicular-phase ewes (39). In sheep, cortisol acts at the pituitary to reduce responsiveness to GnRH but does not affect GnRH pulse frequency in the absence of ovarian hormones. However, in ewes during the follicular phase of the estrous cycle, cortisol reduces LH pulse frequency. To test the hypothesis that cortisol reduces GnRH pulse frequency in the presence of ovarian steroids, the effect of cortisol on GnRH secretion was monitored directly in pituitary portal blood of follicular phase sheep in the presence and absence of a cortisol treatment that elevated plasma cortisol to a level observed during stress (40). These results provide new insight into the means by which gonadal steroids, and possibly reproductive status, modulate neuroendocrine responses to stress.

Summary

Stress is the major epigenetic factor that contributes to the etiology, pathophysiology, and treatment outcome of most psychiatric disorders.The hippocampus, prefrontal cortex and amygdala, are three brain areas that show morphological changes as a result of stress-related disorders. The physiological levels of estradiol are inhibitory on stress responsiveness and that blocking estradiol in gonadally intact, normally cycling female rats leads to exaggerated stress responsiveness. It is important to note that link of Limbic and HPA activation in turn influences gonadal systems and stress-induced alteration of gonadal systems may also be involved in some of the enduring effects of stressors on a wide range of behaviours. The prefrontal cortex (PFC) plays an important role in the regulation of stress-induced HPA activity and regulation of gonadal function in men and women is under the control of the HPA. The effect of mPFC is a target for glucocorticoids involved in the stress response and repeated restraint stress on dendritic spine number in the mPFC with dendritic atrophy and spine loss may be important cellular features of stress-related psychiatric disorders where the PFC is functionally impaired (41). It is now well established that chronic stress has a profound impact on neural plasticity in a number of corticolimbic structures and affects the etiology, pathophysiology, and therapeutic outcome of most psychiatric disorders. The effect of this plasticity in limbic area and the link of this system with HPA activation in stress show that, Estrogen (E2) and glucocorticoid negative feedback have a critical role in regulation of LHPA axis in stress condition. E2 potentiates the increase ACTH and corticosterone following psychosocial stress and cortisol reduces LH pulse frequency.

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