

Stress and Female Reproductive System :

Disruption of Corticotropin-Releasing Hormone/Opiate Balance by Sympathetic Nerve Traffic

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Abstract

Nowadays stress is an integral part of everyday living and the physiological and behavioral consequences of exposure to stressful situations have been extensively studied for decades. The stress response is a necessary mechanism but disrupts homeostatic process and it is sub served by a complex system located in both the central nervous system (CNS) and the periphery. Stressor-induced activation of the hypothalamus–pituitary–adrenal (HPA) axis and the sympathetic nervous system (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. Normal activation of the HPA axis is essential for reproduction, growth, metabolic homeostasis, and responses to stress and they are critical for adapting to changes in the external environment. The 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 classical feedback mechanisms in the hypothalamus and the pituitary. The present overview focuses on the neuroendocrine infrastructure of the adaptive response to stress and its effects on the female reproductive system.

Keywords: Stress, Hypothalamic-pituitary-adrenal (HPA) axis, Corticotropin-releasing hormone (CRH), Norepinephrine (NE), Opioid system, Luteinizing hormone-releasing hormone (LHRH)

1. Stress system

1.1. stress syndrome physiology and anatomic organization

The central components of the stress system 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, the CRH neurons of the paraventricular and parabrachial nuclei of the medulla, the locus ceruleus (LC) and other mostly noradrenergic (norepinephrine or NE) cell groups of the medulla and the pons (the LC/NE-sympathetic system) (1). The peripheral limbs of the stress system are the hypothalamic-pituitary-adrenal (HPA) axis along with the efferent sympathetic-adreno-medullary

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system, and components of the parasympathetic system.

1.2. Stress system: response and adaptation

Transient Adaptation: Allostasis

Physiologic systems operate within a dynamic range of steady state and maintain internal balance, or homeostasis, in terms of blood pH and electrolyte concentration. When physical or psychologic stressors challenge the body, there is activation of sympathoadrenal and adrenocortical responses that promote adaptation and survival in the short term. This has been referred to as **allostasis**, which is the reestablishment of stability (hemostasis) through change in the level of operation of physiological systems. For example, during exercise or emotional responses, there is transient activation of the sympathoadrenal and HPA systems; resulting in elevation of arterial pressure, heart rate, and circulating catecholamines and glucocorticoids. The response to stress is not stereotyped. The patterns of autonomic, neuroendocrine, and behavioral responses vary with the type of stress, the different perceptions of stress by the subject, the extent of control on the stressful stimulus, and the active or passive coping mechanisms in stress response (3). The stress system coordinates the adaptive responses of the organism to stressors of any kind (4). 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 (5). Most stressors produce specific and nonspecific responses. The specific stress responses alter an individual to the presence of the stressors, which involve neuroendocrine responses such as increased autonomic nervous system activity (6). When faced with excessive stress, whether physical or emotional, a subject's adaptive responses attain a relatively stereotypic nonspecific nature, referred to by Selye as "the general adaptation syndrome." We now know that the adaptive responses have some specificity toward the stressor that generates them, which, however, is progressively lost as the severity of the stressor increases. The adaptive response of an individual to stress is determined by a multiplicity of genetic, environmental and developmental factors (4) and prenatal life, infancy, childhood and adolescence are critical periods characterized by increased vulnerability to stressors (7). Although the entire central nervous system is directly or indirectly involved in the maintenance of the internal homeostasis and participates in the organization of the stress response, specific areas of the brain have critical roles in these mechanisms and modulation of the activity of the stress system at the level of both the hypothalamic-pituitary-adrenal axis and the central and peripheral components of the autonomic nervous system is critical for a successful adaptive response to stressors. Corticotropin-releasing hormone (CRH) is a crucial neuropeptide in the regulation of the hypothalamic-pituitary-adrenal (HPA)-axis, i.e., the final common pathway in the stress response. In addition, it has various central effects, including cardiovascular regulation, respiration, appetite control, stress-related behavior and mood, cerebral blood flow regulation (8) and stress-induced analgesia (9).

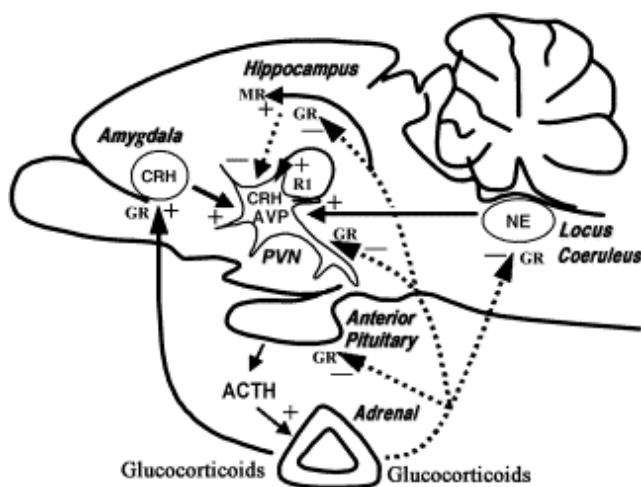


Fig 1: Multiple feedback loops activating CRH systems during chronic stress (2)

1.3. Regulation of the stress response

The orchestrated interplay of several neurotransmitter systems in the brain underlies the characteristic phenomenology of behavioral, endocrine, autonomic and immune responses to stress (10). Stress is a potent general activator of 1) CRH, 2) LC/NE system for coordinating stress response. CRH was implicated in other components of the stress response, such as arousal and autonomic activity. Supportive evidence was derived from

intracerebroventricular or selective brain administration of CRH in rodents and nonhuman primates, which precipitated several coordinated responses characteristic of stress (11). Brain administration of CRH peptide antagonists suppresses many aspects of the stress response and CRH type 1 receptor knockout mice were shown to have a markedly deficient ability to mount an effective stress response (12). CRH-binding sites are also found in various peripheral tissues, such as the adrenal medulla, heart, gut, liver, kidney, ovary, uterine, prostate and testes. The locus ceruleus and other noradrenergic cell groups of the medulla and pons are collectively known as the LC/NE system. Brain epinephrine serves globally as an alarm system that decreases neurovegetative functions, such as eating and sleeping and that contributes to accompanying increases in autonomic and neuroendocrine responses to stress, including HPA axis activation (11). The locus coeruleus also shows sexual dimorphism and contains more noradrenergic cells in females and is larger than in the male brain (13, 14).

2. Stress system and female reproductive system

2.1. HPA and the hypothalamic-pituitary-ovarian (HPO) axes

Women in the reproductive age are more vulnerable to develop affective disorders than men. This difference may attribute to anatomical differences, hormonal influences and environmental factors such as stress. However, the higher prevalence in women normalizes once menopause is established, suggesting that ovarian hormones may play an important role in the development of depression in women. Ovarian hormones such as estrogen can pass the brain-blood barrier and bind to cytoplasmic estrogen receptor alpha and beta in different areas of the limbic system. During stress, estrogen can modulate the behavioral and neurobiological response depending on the concentrations of estrogen (15). The female reproductive system is regulated by two axes: the hypothalamic-pituitary-adrenal (HPA) and hypothalamic-pituitary-ovarian (HPO) axes, that the principal regulators of these axes are CRH and GnRH that stimulates FSH and LH secretion and, subsequently, estradiol and progesterone secretion by the ovary (16). Hypothalamic target neurons of estrogen include neurosecretory neurons such as

gonadotropin-releasing hormone (GnRH) and dopamine neurons, and local circuitry neurons such as proopiomelanocortin (POMC). These and other hypothalamic neurons are involved in regulating numerous homeostatic functions including reproduction, thermoregulation, stress responses, feeding and motivated behaviors (17). The HPA axis, when activated by stress, exerts an inhibitory effect on the female reproductive system, corticotropin releasing hormone and CRH-induced proopiomelanocortin peptides, such as β -endorphin, inhibit hypothalamic GnRH secretion (18). In addition, glucocorticoids suppress gonadal axis function at the hypothalamic, pituitary and uterine level (19). Glucocorticoid administration significantly reduces the peak luteinizing hormone response to intravenous GnRH, suggesting an inhibitory effect of glucocorticoids on the pituitary gonadotroph (20) (Fig2).

2.2. Reproduction and CRH

CRH and its receptors have been identified in several female reproductive organs, including the ovaries, the endometrial glands, decidualized endometrial stroma, placental trophoblast, syncytiotrophoblast and decidua (21). Reproductive CRH participates in various reproductive functions with an aseptic inflammatory component, such as ovulation, luteolysis, implantation and parturition. Ovarian CRH is primarily found in the theca and stroma and also in the cytoplasm of the ovum (22). Corticotropin-releasing-hormone type1 (CRHR-1) receptors (similar to those of the anterior pituitary) are also detected in the ovarian stroma and theca and in the cumulus oophorus of the graafian follicle. In vitro experiments have shown that CRH exerts an inhibitory effect on ovarian steroidogenesis in a dose-dependent manner (23).

2.3. Reproduction and β -Endorphin

More than 50 years have passed since Barraclough & Sawyer (1955) first demonstrated that morphine prevents ovulation in rats (24). The most favored theory, the "endorphin hypothesis" by Morgan 1985, ascribes the psychophysical effects to changes in central opioidergic transmission (25). The importance of the preoptic area in mediating the inhibitory effects of opioid peptides is demonstrated by the observation that chronic hypothalamic infertility in female rats is associated with significant alterations of preoptic opioid receptors and then the amount of β -endorphin

found in preoptic tissues; such changes suggest there is increased activity in this opioid system (26). Endogenous opioid peptides act centrally to inhibit the release of gonadotrophin-releasing hormone (GnRH) and thereby the secretion of luteinizing hormone and both stressors, fasting and excessive exercise, delay the onset of the luteinising hormone (LH) surge, preliminary results suggests that opioids mediate these effects and also clinical manifestations

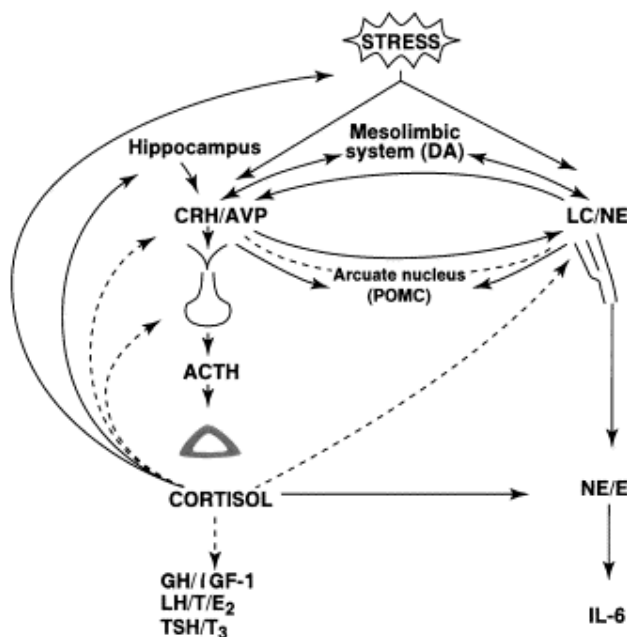


Fig 2: A simplified schematic representation of the central and peripheral components of the stress system, their functional interrelations and their relations to other central systems involved in the stress response. The CRH/AVP neurons and central catecholaminergic neurons of the LC/NE system reciprocally innervate and activate each other. The HPA axis is controlled by several feedback loops that tend to normalize the time-integrated secretion of cortisol, yet glucocorticoids stimulate the fear centers in the amygdala. Activation of the HPA axis leads to suppression of the GH/IGF-1, LH/testosterone/E₂ and TSH/T₃ axes; activation of the sympathetic system increases IL-6 secretion. Solid lines indicate stimulation; dashed lines indicate inhibition (10).

range from luteal phase deficiency to anovulation, amenorrhea, and even delayed menarch, most cases are reversible with dietary and exercise modifications (27).

2.4. Reproduction and CRH/ β -Endorphin/NE

In female reproductive system, CRH can inhibit hypothalamic gonadotropin-releasing hormone (GnRH) secretion, and glucocorticoids inhibit pituitary luteinizing hormone and ovarian estrogen and progesterone secretion. These effects are responsible for the "hypothalamic" amenorrhea of stress, which is observed in anxiety and depression, malnutrition, eating disorders and chronic excessive exercise, and the hypogonadism of the Cushing syndrome. Endogenous opioids have modulating role on catecholamine secretion, and studies of these effect show that, opioids inhibit the release of catecholamine during stress (28). In peripherally the analyzed relationship between sympathetic and opioid system in pathogenesis of stress demonstrates a protective role by the peripheral mu-opioid receptors and was associated with decrease in an activity of sympathico-adrenal system and this phenomena in the heart leads to a increase in stress heart damage via an increase in sympathetic influence on the myocardium and now, how does this pathogenesis process affect reproductive system? Both reproductive physiology and sexual behaviors are influenced by stress, with changes in the activity of GnRH, neurons in the forebrain, whereas the suppression of sexual behaviors appears to be due, at least in part, to decrease estrogen receptor in the ventromediate hypothalamus. The mu-opioid receptor appears to be the permissive for the LH surge because; the studies suggest a role of opioid peptide systems in controlling timing of the surge, which entrained to the circadian rhythm (29).

2.5. Stress and infertility

In general, acute, transient challenges that trigger active (fight or flight) adaptation produce a short-term response referred to as the defense reaction consisting primarily of sympathoadrenal activation. In this allostatic response, the principal brain effectors are the PVN neurons synthesizing CRH/AVP and the Locus ceruleus norepinephrine neurons. Acting together, these two neuronal groups initiate an adaptation response that includes improved alertness and attention span, decreased reflex time, antinociception, suppression of feeding and sexual

behavior and activation of the sympathoadrenal and HPA systems. These transient allostatic responses are adaptive and result in energy mobilization, increased traffic of immune cells and promotion of memory storage (due to effect of glucocorticoids in the hippocampus). In normal conditions, this allostatic response is shut off during the recovery after stress. In contrast, chronic stress states produce anxiety and passive or withdrawal coping mechanisms elicit a long-term response referred to as the vigilance or defeat reaction characterized by chronic activation of HPA system. The consequences of over activity of the allostatic load occur in 4 main settings: 1) chronic stress due to repeated hits by multiple novel stressors; 2) lack of adaptation to repetition of the same stressors; 3) prolonged response due to inability to shut down the allostatic response; and 4) inadequate response, leading to compensatory hyperactivity of other systems. Allostatic load is maladaptive and leads to obesity, diabetes, hypertension and muscle wasting, increased susceptibility to infection and impairment of memory (from damaging effects of chronically elevated glucocorticoid values on hippocampus cells) (3). Increased CRH and beta-End in the hypothalamus and also the tonic inhibitory effect of beta-End on sympathetic tone in stressful situations (30), inhibits the secretion of gonadotropins, oxytocin and vasopressin, this may lead to amenorrhea, which often is a consequence of intensive training or psychological stress (31) and can disrupt parturition and lactation (32). Oestradiol and progesterone increase beta-End concentrations in the luteal phase of menstrual cycle and this is followed by a rapid fall at menstruation and pulsatile gonadotropin secretion is inhibited by stress and by administered morphine, but morphine dose not block the estrogen-induced preovulatory surge in primates. Accordingly, impaired follicular development appears to be the most common cause of reproductive dysfunction attributable to stress in the humans female. The reduction in endogenous GnRH/LH secretion utility deprives the ovarian follicular of adequate gonadotropin support leading to reduced oestradiol production by slower growing follicles. Interestingly, several components of the HPA axis and their receptors are present in reproductive tissues as autocrine regulators of their various functions. These include ovarian and endometrial CRH, which may participate in the inflammatory processes of the ovary estrogen directly, stimulates the CRH gene, which may explain the slight hypercortisolism of female and

the preponderance of depressive anxiety and eating disorders as well as cushing disease in women. Thus there is a level of interference by stressors at the ovary (33).

2.6. Stress and disruption of the CRH/opioid balance by sympathetic nerve traffic

Corticotropine-releasing hormone (CRH) is the hypothalamic neurohormone that initiates release of adrenocorticotropin in response to stress. CRH has marked kindling and glucocorticoids have strong consolidating properties, hence both of these hormones are crucial in development and can produce the stress syndrome alone. The activation of CRH neurons, increases ACTH biosynthesis and it is the best marker in endocrine axis which reaches a maximum in the first hour and cortisol is highest during the second hour of stress (34). ACTH may play a crucial, perhaps direct, role in the regulation of catecholamine (CA) biosynthetic enzymes in sympathetic nervous system, especially during stress, since administration of ACTH was as effective as immobilization stress in increasing expression of catecholamine biosynthetic enzymes tyrosine hydroxylase (TH) and dopamine β -hydroxylase (DBH) in male rat superior cervical ganglia (SCG) (35). Injections of adrenocorticotrophic hormone (ACTH) elicited induction of the interaction between CRH and endogenous opioids within the pontine nucleus in LC, as a target in response to stress and opiates, disruption in CRH/opioid balance as a result of hyperactivity, hyperresponsiveness of the LC-NA system and co-regulation of LC-NA system by CRH and opioids all may be important in acute adaptation stress (36). In rodents, the locus ceruleus (LC) participates in the regulation of the estrous cycle and luteinizing hormone (LH) release on the afternoon of proestrus in oophorectomized rats (37) and LC plays an important role in triggering the preovulatory surge of gonadotropin. LC activation may be required for depolarization of LHRH neurons and consequent LH surge (38, 39). Reduction of GnRH/LH deprives the ovarian follicular of adequate gonadotropin support leading to reduced oestradiol production by slower growing follicles, thus there is an interference between sympathetic overactivity, opioid system and ovary. This interference in animal model of polycystic ovary (PCO) is considerable. Central neuronal activity in norepinephrine (NE) neurons is increased in rats with estradiol valerate induced (EV) polycystic ovary (PCO) suggesting increased central

sympathetic outflow and downregulation of the β_2 adrenergic receptor (40) and electro-acupuncture (EA) inhibits hyperactivity in the sympathetic nervous system (41). In the last decade, study on mRNA levels of tyrosine hydroxylase (TH) and dopamine β hydroxylase (DBH) in central and periphery shows that stresses include foot shock, restraint or immobilization, chronic social stress and forced walking induces a maximum elevation of TH and dopamine β hydroxylase (DBH) mRNA levels in sympathetic ganglia and LC (the primary site of the major noradrenergic cell bodies in the brain) (31) and Previous reports about the rat ovary have shown that vesicular release of NE from ovarian noradrenergic nerves begins to operate by the third week of postnatal life, becoming fully functional near the time of puberty (42). Also the sympathetic nervous system (SNS) is capable of responding to stressors during fetal life (43), because participates in several stress responses. Therefore, exposures to various stressors during fetal or neonatal life might affect development of sympathetic innervations or its regulation and organizing effects during fetal life as well as activating effects of sex hormones on the HPA-axis have been reported. Dorfman's results suggest that chronic stress, through an intraovarian neurotrophin-mediated sympathetic activation, produces changes in follicular development that could lead to an impairment of reproductive function (44).

3. Summary and concluding remarks

The stress response is mediated by the hypothalamo-pituitary-adrenal (HPA) system. Activity of the corticotropin-releasing hormone (CRH) neurons in the hypothalamic paraventricular nucleus (PVN) forms the basis of the activity of the HPA-axis. The CRH neurons induce adrenocorticotropin (ACTH) release from the pituitary, which subsequently causes cortisol release from the adrenal cortex. In stressful situation, the activity of HPA axis, LC- NE system and inhibitory tone of opiates are increased and this significant deactivation in μ -opioid neurotransmission can result in over activity of sympathetic nervous system (SNS) and increased gene expression and elevate TH mRNA levels in response to stress. In adaptation to stress the hyperactivity of SNS, hyper responsiveness of the LC-NA system and co-regulation of LC-NA system by CRH and opioids can disrupt this balance especially in LC. Studies show that exposures to various stressors during fetal or neonatal life might

affect development of sympathetic innervations or its regulation. Activating effects of sex hormones on the HPA-axis have been reported and also LC activation is necessary for depolarization of LHRH neurons and consequent LH surge. As a conclusion, time and intensity of stress and age of life can induce significant changes on function of central and periphery sympathetic nerve traffic in HPA axis.

This finding suggests that ovarian CRH has anti-reproductive actions that might be related to the earlier ovarian failure observed in women exposed to high psychosocial stress.

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