Stress and the Adolescent Brain: Plasticity of Reproductive Behaviors in Female

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Abstract
Early life events influence life-long patterns of emotionality and stress responsiveness and alter the rate of brain and body aging. Much research attention has focused on the programming effects of the hypothalamus pituitary axis (HPA) in early life and on understanding HPA function in response to stressors in adulthood. In comparison, there has been relatively little research on adolescence, a time of significant brain development particularly in the frontal lobe and a time which is of great importance for mental and physical health. The hippocampus, amygdala, and prefrontal cortex undergo stress-induced structural remodeling, which alters behavioral and physiological responses. During adolescence, HPA function is characterized by a prolonged activation in response to stressors compared to adulthood, which may render ongoing development of the brain vulnerable. Stress reactivity is markedly influenced by both the pubertal maturation and the experience of the individual. The frequency of the pulses is increased in chronic stress, since the neuroendocrine system is such a good candidate for mediators of many diseases linked to chronic stress. The activity of HPA axis in life time of female, sex maturity, pregnancy or lactation is a plasticity of the diurnal rhythm of pulse amplitude; chronic stress can change this program formation disorder in behavioral and physiological responses.

Keywords: Stress, Adolescence, Brain, Plasticity, Female reproductive system

1. Stress System
1.1. Stress system: Stress Syndrome Phenomenology
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 cause a hazardous or even lethal effect on the body, increasing the risk of obesity, heart disease, depression (1), cutaneous diseases (2) and a variety of other illnesses.

1.2. Stress: Homeostasis and Allostasis
Homeostasis, in a strict sense, applies to a limited
number of systems like pH, body temperature and oxygen tension, components of the internal milieu, which are truly essential for life and are, therefore, maintained over a narrow range, as a result of their critical role for survival. These systems are not activated or varied in order to help the individual adapt to its environment. Allostasis is a term introduced by Sterling and Eyer to characterize how blood pressure and heart rate responses (3). Allostasis is the process of adaptation to challenge that maintains stability, or homeostasis, through an active process that may change the operating set points or range of systems that participate in adaptation (2) and allostatic load is the wear and tear produced by the repeated activation of allostatic or adaptive mechanisms (3).

1.3. Allostasis Load
Life exists by maintaining a complex dynamic equilibrium or homeostasis.t hat is constantly challenged by intrinsic or extrinsic adverse forces, the stressors. According to Hans Selye, stressors include mental and psychologic or sociologic factors that all disturb stable internal environment of body, that may contribute directly to the production of disease or development of a behavior, which increases the risk of disease. The process that counteracts this disruption and maintains homeostasis is termed allostasis and to be successful may activate a wide range of both general and specific physiological systems and behavioral coping mechanisms. The amount of work carried out during allostasis is termed the allostatic load and represents the cost(s) of responding to the stimulus. Over the past decade, these terms have been introduced to human stress research to differentiate between adaptation, allostasis and the end result, homeostasis, with the aim of producing a measurement of allostatic load that can be used to compare the effects of a wide range of stimuli. Beyond the "flight-or-fight" response to acute stress, there are events in daily life that produce a type of chronic stress and lead over time to wear and tear on the body ("allostatic load"). Yet, hormones associated with stress protect the body in the short-run and promote adaptation ("allostasis"). The brain is a target of stress, and the hippocampus is the first brain region, besides the hypothalamus, to be recognized as a target for glucocorticoids. Stress and stress hormones produce both adaptive and maladaptive effects on this brain region throughout the life course (4). Four types of allostatic load have been identified. These consist of 1) repeated challenges, for example, chronic stress, 2) failure to habituate with repeated challenges, 3) failure to shut off the response after the challenge is past, and 4) failure to mount an adequate response (5).

1.4. Stress System: Response
Stressor-induced activation of the 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 necessary physiologic and metabolic changes required to cope with the demands of a homeostatic challenge (6). Most of the stressors produce specific and nonspecific responses. The specific stress responses alter an individual in the presence of the stressors, which involve neuroendocrine responses such as increased autonomic nervous system activity (7). When faced with excessive stress, whether physical or emotional, subject's adaptive response 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 (8) and prenatal life, infancy, childhood and adolescence are critical periods characterized by increased vulnerability to stressors (9).

2. Adolescence
Adolescence is a transitional time from childhood to adulthood that involves the maturation of social and cognitive behavior (10). For example, adolescence is the time in which adult-typical social behavior of males and risk-taking behaviors emerge (11). There are marked differences in the behavior of adolescents compared to adults. For example, adolescents have greater levels of novelty-seeking and impulsivity and reduced stress and anxiety in response to novelty than adults (12).

Puberty, or attainment of sexual / reproductive maturity, is attained during adolescence and involves augmented pulsatile gonadotropin-releasing hormone secretion and activation of the hypothalamic – pituitary – gonadal axis (13). Adolescence is increasingly being viewed as a significant period of developmental vulnerabilities. For instance, puberty is marked by an increase in the morbidity and susceptibility
to various psychological disorders, such as anxiety and depression (14). During adolescence the brain shows remarkable changes in both structure and function. The plasticity exhibited by the brain during this pubertal period may make individuals more vulnerable to perturbations, such as stress (15). Two factors may render the prepubertal brain especially vulnerable to stress. First, the prepubertal brain may be more sensitive to corticosterone, as a recent study showed an equivalent dose of corticosterone increased hippocampal N-methyl-D-aspartate (NMDA) receptor subunit expression (e.g., NR2A and NR2B) to a greater degree in prepubertal than adult males (16). Second, brain regions that continue to mature during adolescence, such as hippocampus (17), medial prefrontal cortex (mPFC) (18) and amygdala (19). Thus, upon encountering a similar stressor, the immature, and possibly more sensitive, prepubertal brain experiences differential exposure to corticosterone compared to the more fully developed adult brain (20).

2.1. Adolescence: A time of Heightened Plasticity

During adolescence the brain shows remarkable changes in both structure and function. The plasticity exhibited by the brain during this pubertal period may make individuals more vulnerable to perturbations, such as stress (15). When exposed to chronic stress, the HPA axis can show both response ‘habitation’ and response ‘facilitation’. ‘Habitation’ 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 (21). The central nervous system is remarkably flexible. There is a great deal of plasticity in the adult CNS. Much of this plasticity is localized at dendritic spines, the postsynaptic sites of excitatory connections. Changes in spine density, morphology, and motility have been shown to occur with paradigms that induce synaptic plasticity. Spines are dynamic structures, but the functional consequences of dynamic changes in these structures in the mature brain are unclear. Spines fall into two groups: those that are large and for the most part stable (facilitation) and those that are more transient and smaller (habituation).

These changes potentially lead to an alteration in synaptic connectivity and strength between neuronal partners, affecting the efficacy of synaptic communication (22).

2.2. HPA and Plasticity

In the context of plasticity, Kasai et al. (2003) have proposed that small spines represent “learning spines” that can either retract or become stabilized in the context of learning. In this view, large spines are “memory spines” that are stabilized and retain information over the long term (23). Glucocorticoids are important regulators of brain development and neuronal plasticity: They can influence virtually all aspects of neural development, including neurogenesis, synaptogenesis and dendritic morphology and cell death (24). The factors that selected to analyze stress and behaviour responses are: (1) Source of stress, (2) Stressor duration, (2) Stressor intensity (3), Stressor timing. The studies show the prefrontal cortex (PFC) plays an important role in the regulation of stress-induced hypothalamic–pituitary–adrenal (HPA) activity. The anatomical areas in brain: limbic system, and in particular the hippocampus and the medial prefrontal cortex (mPFC) serve pivotal roles in the regulation of the hypothalamic – pituitary – adrenal (HPA) axis. Accumulating evidence shows that corticosteroid modulation of hippocampal and mPFC activity and plasticity may underlie some aspects of the physiological and behavioral effects of chronic stress. The medial PFC also contains high levels of glucocorticoid receptors and regulates HPA activity under behaviorally stressful conditions. The mPFC is a target site for the negative – feedback effects of glucocorticoids on stress-induced HPA activity, and that this effect is dependent upon the nature of the stress (25). There are three types of plasticity in the hippocampal formation in which adrenal steroids play a role. First, adrenal steroids reversibly and biphasically modulate excitability of hippocampal neurons and influence the magnitude of long-term potentiation, as well as producing long-term depression (26). Second, adrenal steroids participate along with excitatory amino acids in regulating neurogenesis of the dentate gyrus granule neuron, in which acute stressful experiences can suppress the ongoing neurogenesis (27). Third, adrenal steroids participate along with excitatory amino acids in a reversible stress-induced remodeling of dendrites in the CA3 region of hippocampus. Glucocorticoid administration can mimic the effects of stress to cause remodeling and n-methyl d-aspartate (NMDA) receptor blocker prevents the remodeling (28). The ability of repeated stress to produce structural changes in hippocampus is an example of allostatic load, as will be described below.
2.3. Allostasis Load and Plasticity

Allostasis is the process of adaptation to challenge that maintains stability or homeostasis, through an active process that may change the operating set points or range of systems that participate in adaptation. Repeated stress and or dysregulation of the HPA axis and of excitatory amino acids, that results in adaptive plasticity of hippocampal nerve cells also leads to conditions that may result in permanent damage to the hippocampus of limbic system. One of four types of allostatic load is chronic stress that in hippocamp involving excitatory amino acid release. Under restraint stress, rats show increased extracellular levels of glutamate in hippocampus, as determined by microdialysis, and adrenalectomy markedly attenuates this elevation (28). Glucocorticoids appear to be involved in potentiating the increased extracellular levels of excitatory amino acids under stress (29). In mPFC, repeated stress affects on learning through differential effects on spine number and morphology (30). This suggests that repeated stress may impair mPFC-dependent learning through an inability of spines to undergo plasticity-induced shifts from the smaller “learning” to larger “memory” phenotypes (31). Holmes and colleagues have shown that shorter intervals of stress are also capable of impairing the extinction of fear conditioning, a form of learning that is also dependent on the mPFC (32).

2.4. HPA and Puberty / Adolescence

Puberty and adolescence mark the metamorphosis of the child into the adult. Biologists have typically viewed puberty from an endocrine perspective because the overt signs of reproductive maturation are driven by hormonal changes occurring during this period of development. Over the past four decades, an appreciation for the neural control of hormone secretion and a gradual awareness of extensive brain remodeling during adolescence have shifted the emphasis to a neural basis for reproductive maturational. The terms puberty and adolescence are often used interchangeably. To specialists, however, puberty refers to the activation of the hypothalamic-pituitary – gonadal axis that culminates in gonadal maturation. Adolescence refers to the maturation of adult social and cognitive behaviours. These nuances of terminology capture the two essential elements of adulthood: production of gametes and a behavioral means for bringing male and female gametes together. The gonadal maturation and behavioural matura-

tion are two distinct brain-driven processes with separate timing and neurobiological mechanisms, but they are intimately coupled through iterative interactions between the nervous system and gonadal steroid hormones (33). Males and females often initiate and end puberty at different times and if the maturational component of puberty is a clock mechanism, then there must be key regulatory genes that are an integral part of the developmental process. More recent reports have nominated G-protein coupled receptor-54 (GPR54) as the ‘puberty gene.’ GPR54 encodes a G protein – coupled receptor, and mutations in the gene lead to the absence of increased GnRH secretion at puberty (34, 35). Adolescence refers to the maturation of adult social and cognitive behaviours and the timing of adolescent behavioural maturation depends on the timing of gonadal maturation because steroid hormones are required for the overt expression of reproductive behaviour. However, it is clear that some important aspects of behavioural maturation are not driven solely by the appearance of steroid hormones at the time of puberty, because hormone treatment fails to fully activate copulatory behaviour in prepubertal animals, indicating a need for further maturation of central and peripheral tissues before behaviour can be expressed. Thus, as with puberty, there appears to be a developmental clock that times behavioural maturation during adolescence and that limits the age at which fully mature adult reproductive behaviour can be expressed. A critical question is whether the developmental clock timing behavioural maturation is the same as that timing gonadal maturation (36, 37). During adolescence the brain shows remarkable changes in both structure and function. The plasticity exhibited by the brain during this pubertal period may make individuals more vulnerable to perturbations, such as stress. Although much is known about how exposure to stress and stress hormones during perinatal development and adulthood affect the structure and function of the brain, relatively little is known about how the pubertal brain responds to stress. Furthermore, it is not clear whether stressors experienced during adolescence lead to altered physiological and behavioural potentials in adulthood, as has been shown for perinatal development (38). Throughout an individual’s life span, both the magnitude and the duration of the hormonal stress response change dramatically. For instance, neonates show reduced stress reactivity in response to stressors that typically elicit robust stress responses in adults.
(39). Conversely, aged adults show heightened and more prolonged stress responses compared with younger adults (40). The reduced stress reactivity experienced by neonates has been posited to protect the developing organism from the damaging effects of stress hormones (39), whereas the extended exposure to stress hormones in the aged may contribute to the age-related decline in neurophysiological function and contribute to fat deposition, bone mineral loss, and impaired immune function in the elderly (40). Thus, parameters that change stress reactivity, such as development, may have profound consequences as to whether stressors lead to adaptive or maladaptive responses. Although stress responsiveness in neonatal and adult life stages has been well characterized, little is known about how stress reactivity changes during puberty. In addition to development, experience with stressors can influence stress reactivity. For instance, in adults, repeated exposure to a stressor leads to habituation of the stress response, such that stress hormone levels are blunted (41). However, changes in the brain over adolescence may be required for the regulation of HPA function by sex hormones, as other research indicates that the prolonged corticosterone release in response to stressors.

**Adolescence: Glucocorticoids / Estradiol**

Gonadal steroids regulate several aspects of hypothalamic-pituitary-adrenal (HPA) function. Brain sexual differentiation is time- and dose-dependent and can be blocked by removal of the testis in males or by administration of an estrogen antagonist. Sex differences exist in HPA activity and estrogen is the active agent of periodic estrogen-induced synaptic plasticity (EISP) that drives the estrogen-induced gonadotropin surge (EIGS) also causes further differentiation of the females synaptology toward that of the male, whose brain is differentiated during the perinatal period (42). In rodents, 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 adrenocorticotropic hormone (ACTH) response to stress, faster onset of corticosterone secretion after stress, and a faster rate of rise of corticosterone (43). 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 oophorectomized 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 activation components of the system at either the corticotropin hormone (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 HPA responsiveness under basal conditions. But in stress condition, chronic stress can have a deleterious effect on the HPA 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 Limbic-HPA (LHPA) axis (44). Stress-like concentrations of cortisol increase the negative feedback potency of estradiol in castrated male sheep. A similar cortisol – dependent response in female sheep might be expected to suppress gonadotropin secretion and impair follicular development and ovulation (45). Stress – like concentrations of cortisol interfere with follicular phase endocrine events of the ewe by suppressing pulsatile luteinizing hormone (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 (46). 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 folli-
cular 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 (47). These results provide new insight into the means by which gonadal steroids, and possibly reproductive status, modulate neuroendocrine responses to stress and estrogen is time – and dose – dependent and determine the reproductive life history of female.

Summary

Aging is defined as a period with decreased ability to maintain homeostasis, increased activation of the hypothalamic-pituitary-adrenal (HPA) axis following stress and impaired behavioral adaptation. HPA function differs in adolescence in comparison to adulthood in responses to both acute and chronic stressors and in its regulation by gonadal hormones. As indicated above, one consequence of exposure to stressors in adolescence appears to be more prolonged exposure to glucocorticoids, hormones that influence ongoing brain development and program future behavioral and physiological responses and E2 potentiates the increase in serum ACTH and corticosterone following stress. The adolescent brain is continuing to mature and develop; the consequences of exposure to stressors may be different from or greater than in adulthood. Thus, there is increasing evidence that adolescence is a time of heightened plasticity, and may indeed be a sensitive period of development similar to the perinatal period for the effects of stressors (48). However, much more research is required on the effects of stressors in adolescence to uncover at which ages / stages of maturation in adolescence are females and males most vulnerable to stressors and to which type of stressors. The neural regions implicated in the control of the HPA axis such as the medial prefrontal cortex, bed nucleus of the stria terminalis, hippocampus, and amygdala are undergoing developmental changes over adolescence and are potentially involved in the increase in sensitivity of the HPA axis to sex hormones (49). The activity of HPA axis in life time of female, sex maturity, pregnancy or lactation is a plastic duration of the diurnal rhythm of pulse amplitude and chronic stress can changes this programming and current results highlight that sex, age and gonadal hormone state should be considered in stress research because these variables can impact the results and may have important consequences for understanding stress related disorders and diseases.

References

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