Interrelationships between Hormones, Behavior, and Affect during Adolescence

Complex Relationships Exist between Reproductive Hormones, Stress-Related Hormones, and the Activity of Neural Systems That Regulate Behavioral Affect

Comments on Part III

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ABSTRACT: Adolescence is a period in life marked by change, encompassing physiological changes associated with pubertal development, changes in social status and the social stresses that an individual faces, and changes in behavioral affect regulation. The interactions between activity in the reproductive axis, the neural systems that regulate stress, hormones produced in response to stress, and neural systems governing behavioral affect regulation are complex and multifaceted. Although our understanding of these interactions remains rudimentary, we do know that stress can suppress activity of the reproductive axis, that reproductive hormones can modulate the activity of neural systems that govern the body's responses to stress, that both reproductive function and stress responsiveness can be altered in depressed individuals, and that the function of some of the key neural systems regulating behavioral affect (i.e., serotonergic, noradrenergic, dopaminergic systems) are modulated by both gonadal steroid hormones and adrenal steroid hormones. This summary reviews the central interactions discussed in this session on the interrelationships between hormones, behavior, and affect during adolescence and identifies key topics that require further investigation in order to understand the role that pubertal changes in reproductive function, interacting with increased exposure to life stresses, play in modulating behavioral affect regulation during the adolescent period.

KEYWORDS: stress; monoamines; cortisol; estrogen; psychopathology

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INTRODUCTION

Not only is adolescence a time of remarkable change in the functioning of the reproductive axis, but also, as many of the other articles in this volume detail, adolescence is a time when persons face an increased number of challenges and life stresses. The interactions between activity in the reproductive axis, the neural systems that regulate stress, hormones produced in response to stress, and neural systems governing behavioral affect regulation are complex and multifaceted. Although our understanding of these interactions remains rudimentary at this time, we do know that stress can suppress activity of the reproductive axis, that reproductive hormones can modulate the activity of neural systems that govern the body's responses to stress, that both reproductive function and stress-responsiveness can be altered in depressed persons, and that functions of some of the key neural systems regulating behavioral affect (i.e., serotonergic, noradrenergic, dopaminergic systems) are modulated by both gonadal steroid hormones and adrenal steroid hormones. The paper by Dr. Young in this section, and that of Dr. McEwen at the conference, analyze these complex interactions in clinical studies of normal and depressed men and women and in basic animal models. This summary reviews the central interactions discussed in these presentations and identifies key topics that will require further investigation in order to understand the role that pubertal changes in reproductive function, interacting with increased exposure to life stresses, play in modulating behavioral affect regulation during the adolescent period.

MANY TYPES OF STRESS CAN MODULATE ACTIVITY OF THE REPRODUCTIVE AXIS AND THE TIMING OF PUBERTY

Many forms of stress, including psychosocial stress and a host of physical stressors (e.g., energy restriction, increased energy expenditure with exercise, temperature stress, infection, pain and injury) can lead to suppression of reproductive hormone secretion and, if sustained, to a suppression of fertility.[1–4] Stress-induced reproductive dysfunction can occur in both females and males. In adulthood, stress-induced reproductive impairment in females is characterized by a lengthening of the menstrual cycle and a suppression of ovulation, followed eventually by a loss of ovarian cyclicity and amenorrhea. In males, the reproductive impairment is characterized by a decrease in testosterone secretion and thus a decrease in spermatogenesis and hormonal support for secondary sexual characteristics, as well as a loss of libido. Chronic stress, occurring during the process of pubertal development, can impair the progression of puberty in both females and males, leading in some cases to a very marked delay in the pubertal development of reproductive capacity and the accompanying development of secondary sexual characteristics.[5] Pubertal delay resulting from undernutrition[6,7] and exercise[8,9] have been clearly documented in humans, as well as in a variety of animal species.

The primary site of disruption of the reproductive axis with all forms of stress studied in detail to date appears to be at the level of the GnRH neurons, which provide the central neural drive to the reproductive axis. Using animal models of various stresses, it has been shown for at least some stresses that GnRH secretion is impaired.[10] However, more typically, it is inferred that GnRH secretion is impaired un-

der conditions of stress, when a suppression of pituitary gonadotropin secretion is measured. This is further supported by the finding that in all conditions of stress-induced reproductive dysfunction studied to date, administration of exogenous GnRH can stimulate the function of the reproductive axis, indicating that stress is not acting to directly suppress pituitary or gonadal activity.[11] The mechanisms by which various forms of stress impair reproductive axis activity appear to have some common elements, but there also appear to be mechanisms that are specific to each type of stress. For example, many forms of stress can activate the hypothalamic-pituitary-adrenal axis, and experimental studies have shown several mechanisms by which activation of the HPA axis can impair the central neural drive to the reproductive axis.[12,13] On the other hand, certain aspects of stress, such as decreased fuel availability, only occur with some forms of stress and are likely to impair the activity of the reproductive axis via relatively specific mechanisms.[4]

The influence of psychological and social stresses on the activity of the reproductive axis is of particular relevance to understanding the interaction between reproduction, stress, and changes in behavioral affect in adolescence. There is strong evidence, both in clinical studies and in animal models, that exposure to psychosocial stresses can impair activity of the reproductive axis. One of the best characterized forms of psychosocial stress-induced reproductive dysfunction comes from studies of women who present to infertility clinics with functional hypothalamic amenorrhea (FHA), a form of stress-induced reproductive dysfunction.[14,15] Women with FHA experience more psychological stress than other women: although they do not experience more stressful life events, they react more profoundly to the stressful events they do experience.[16] They also show increased activation of physiological systems that respond to stress, including increased HPA axis activity.[17] Treatment of these patients with cognitive behavior therapy, or with drugs that reduce the activity of some central neural systems that are activated by stress, can restore fertility, although not in all cases.[17,18] In animal studies, both acute exposure to psychosocial stresses[19–21] and exposure to chronic social stress[22] can suppress activity of the reproductive axis. However, not all persons respond to psychosocial stresses with a suppression of reproductive function, and there appear to be a number of factors underlying the individual differences in responsiveness to stress, including perception of stress, social status of the individual experiencing the stress, aggressiveness of the

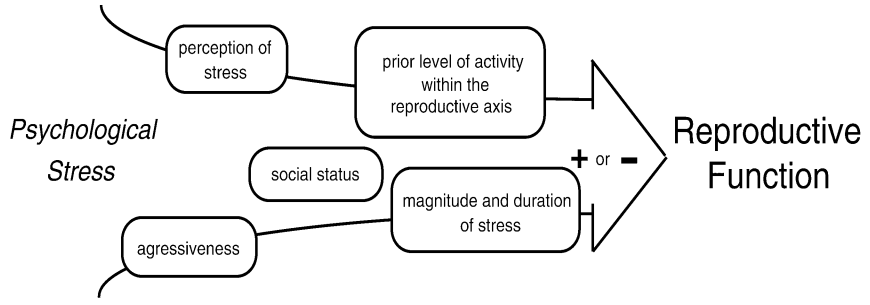

FIGURE 1. Schematic diagram of the factors that mediate the effects of psychological stress on the activity of the hypothalamic-pituitary-gonadal axis. (Redrawn from Cameron.[23])

individual experiencing the stress, the magnitude and duration of the stress, and the level of activity within the reproductive axis prior to exposure to stress (FIG. 1).[3,23]

Although the majority of studies examining the effects of psychosocial stress on reproduction have documented stress-induced suppression of reproductive function, some studies have reported that girls who have grown up under conditions of family stress (e.g., in homes in which the father is absent or there has been family conflict, or when parents have divorced) enter puberty at a significantly earlier age.[24–26] However, neural mechanisms by which such exposure to stress would advance the onset of puberty remain to be determined. It is possible that early exposure to stress does not *cause* advancement of puberty, but rather, that the likelihood of early puberty and exposure to early life family stresses may simply be correlated because they are both influenced by a common factor(s). For example, one of the factors governing the age of menarche is the age of the girl's mother at menarche.[27] Thus it is possible that mothers who experienced early menarche are more likely to have family conflict or divorce when their children are young and to have daughters who will have early menarche; but the conflict would not cause the early menarche in the daughters.

REPRODUCTIVE HORMONES INFLUENCE STRUCTURE AND FUNCTION OF STRESS-RESPONSIVE SYSTEMS IN THE BRAIN

One of the primary brain systems responding to a wide variety of stresses is the hypothalamic-pituitary-adrenal (HPA) axis, which releases the neuroendocrine neurotransmitter, corticotrophin-releasing hormone (CRH), from cells in the paraventricular nucleus of the hypothalamus to cause release of adrenocorticotropin-releasing hormone (ACTH) from the pituitary. ACTH stimulates the adrenal gland to increase synthesis and secretion of glucocorticoid hormones (cortisol in primates and corticosterone in rodents). Specific receptors for glucocorticoids are located in a number of brain regions, thus allowing glucocorticoids to have a negative feedback action to limit activation of the HPA axis as well as to influence a number of brain functions. The other brain system that is activated by exposure to stress and mediates many stress responses is the sympathetic nervous system, which involves increased release of the neurotransmitter, norepinephrine, both centrally and peripherally. Bruce McEwen has written extensively about the role of these two neural/hormonal systems in mediating allostasis (the process of adaptation to events in daily life, defined as the body processes responsible for maintaining stability, or homeostasis, through change).[28,29] These mediators of allostasis promote adaptation and play generally beneficial roles when they are released in an acute manner, but when they are released chronically, their cumulative influence leads to "wear and tear" on the body and brain that is referred to as "allostatic load."[29]

Gender differences in stress responsiveness exist. Female rats generally show higher basal levels of glucocorticoids and have greater HPA responsiveness to stress compared to males.[30] However, in human studies, males have often been shown to have greater HPA axis reactivity to stresses such as public speaking and mental arithmetic,[30] and Dorn *et al*.[31] reported that male adolescents have greater secretion of ACTH to an exogenous bolus of CRH. It has been proposed that at least part of this

divergence between preclinical and clinical studies reflects a gender difference in humans with regard to the type of test that is perceived as stressful, and there is evidence that men show greater HPA reactivity to achievement challenges while women show greater HPA reactivity to social rejection challenges.[30] Estrogen modulation of the HPA axis reactivity to stress has been reported in both experimental animals and in humans by Dr. Young and others. In rats, short-term exposure to low doses of estrogen appears to suppress HPA axis responses to stress, while more prolonged treatment and high doses of estrogen appear to enhance HPA axis responses to stress.[32–34] In post-menopausal women estrogen has been shown to blunt HPA axis responsiveness to several forms of stress.[35,36]

High densities of glucocorticoid receptors are located in the hippocampus and the amygdala. In the hippocampus, low levels of glucocorticoids are associated with enhancement of hippocampal-mediated learning and memory tasks,[37] whereas high levels impair hippocampal functions.[38] At a structural level, stress impairs neurogenesis in the dentate gyrus of the hippocampus,[39] and reduces branching and length of several types of hippocampal neurons via glucocorticoid-mediated mechanisms.[40,41] Clinical studies by Dr. Young and others have shown that evening levels of cortisol are increased in depression,[42,43] a neuropsychiatric disease strongly linked to stress. And neuroimaging studies have found a decrease in hippocampal volume in depressed patients, related to the duration of depression.[44,45] In contrast, estrogen induces synaptogenesis on dendritic spines of hippocampal CA1 neurons.[46,47] And, whereas male monkeys and rats show CA3 neuron loss in the hippocampus upon prolonged exposure to stress, a similar loss is not found in stress-exposed females.[48,49] Female rats also do not show stress-induced atrophy of CA3 neurons,[50] and they have a larger dentate gyrus and more extensively branched CA3 neuron dendrites than male rats.[51,52] Estrogen treatment has also been shown to improve performance of ovariectomized rats in spatial memory tasks that are dependent on hippocampal function,[53] although changes in performance on spatial tasks have not been seen to vary across the ovarian cycle or in women on estrogen treatment.[54]

Taken together, there is a wealth of data to suggest that both the changes in reproductive hormones occurring with pubertal development, and increased exposure to life stresses over the adolescent period, could potentially modulate both the structure and function of neurons in the brain that make up the circuits involved in learning, memory, and detection and regulation of emotion. Since there are virtually no studies examining the effects of either gonadal or adrenal steroid hormones on these neural circuits over the adolescent period, this area is ripe for investigation.

AN INTERPLAY BETWEEN REPRODUCTIVE HORMONES, STRESS-SENSITIVE SYSTEMS, AND NEURAL SYSTEMS REGULATING BEHAVIORAL AFFECT

The interplay between reproductive hormones, neural systems regulated by stress, and the neural systems that regulate behavioral affect is multi-faceted. As discussed in the overview to this section, gonadal steroid hormones, in particular estrogen, can modulate expression of a number of genes integral to the brain monoamine

systems (serotonin and norepinephrine) that play important roles in regulating behavioral affect. Moreover, there is evidence that estrogen alters responsiveness to antidepressant medications. These same systems are profoundly influenced by exposure to stress, with both systems showing activation in response to acute stress exposure,[34] but states of chronic stress exposure and a number of psychiatric diseases associated with lower activity in the serotonin system.[55,56] Glucocorticoids act on neural circuits, such as the hippocampus, in concert with norepinephrine and serotonin, and also regulate activity in these monoaminergic systems.[29] There is also evidence that activity in each of these systems may be linked to the sensitivity or resilience of an individual to stress exposure. Evidence is rapidly accumulating that indicates that an interplay between genetic factors and environmental exposure to stresses act together to influence the likelihood of an individual developing stress-related psychopathologies.[34,57] With each of these systems showing alterations in function over the period of adolescent development, and the increase in stress-associated psychopathologies such as depression showing profound gender differences in this period, much more work is needed to understand the interplay between these systems during the transition from childhood to adulthood, and the degree to which they influence changes in behavioral affect associated with adolescence.

STRATEGIES FOR FUTURE RESEARCH

As highlighted in this section, within the broader frame of understanding adolescent brain development, it is important to consider the multiple influences which pubertal maturation may have. Puberty encompasses maturational changes in at least three separate neuroendocrine axes: the reproductive axis, the adrenal axis, and the growth axis. Moreoever, each of these systems is influenced by exposure to life stresses, and many of the hormones which increase at puberty can in turn modulate the systems in the brain that respond to stress. Research to date has focused on describing the developmental processes within each of these neuroendocrine systems and understanding the mechanisms underlying maturation of each system. Other lines of research have examined the influence of hormones on the brain in adulthood, showing profound influences of these hormones on brain circuits that are integral to the processes of learning, memory, and the regulation of emotion and behavioral affect. However, there has been virtually no research examining how shifts in the function of various neuroendocrine axes at puberty modulate these brain processes over the adolescent period. A strategy for undertaking this daunting task has been proposed by Ron Dahl, a co-organizer of this meeting.[58] As discussed by Dahl, understanding how pubertal processes influence adolescent brain maturation requires consideration of the component processes of puberty including: (*a*) pubertal brain changes that *antedate* (and contribute to) the cascade of hormone changes; (*b*) pubertal brain changes that are *caused* by maturational hormonal increases; (*c*) maturational brain changes that occur relatively independent of puberty; and (*d*) maturational processes linked to puberty only in indirect ways (e.g., new experiences that occur as a result of sexual maturation). Well-controlled studies, both basic animal studies and clinical studies, are needed to directly address which aspects of adolescent development are specifically linked to which specific aspects of puberty.

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