

Neuroendocrine aspects of pediatric aggression: Can hormone measures be clinically useful?

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Abstract: Pediatric aggression is common in human societies, mainly presenting as impulsive aggression or predatory aggression. Numerous psychiatric disorders can contain aggression as a symptom, leading to difficulties in diagnosis and treatment. This review focuses on the biological systems that affect pediatric aggression. We review the hypothalamic–pituitary–adrenal (HPA) axis, the hypothalamic–pituitary–gonadal (HPG) axis, and the mechanisms by which these axes influence the body and mind of aggressive children and adolescents. Although this review focuses on the HPA and HPG axes, it is important to note that other biological systems have relationships with these two axes. Based on the results of the studies reviewed, elevated cortisol concentrations were associated with impulsive aggression, whereas, low levels of cortisol were associated with callous-unemotional traits similar to predatory aggression. Higher levels of dehydroepiandrosterone were correlated with higher levels of aggression as were higher levels of testosterone. However, there have been discrepancies in the results between various studies, indicating the need for more research on hormonal levels and pediatric aggression. In the future, hormonal levels may be useful in determining what treatments will work best for certain pediatric patients.

Keywords: youth, cortisol, adrenocorticotropin-releasing hormone, corticotropin-releasing hormone, HPA axis, HPG axis

Introduction

Though difficult to define, aggression is ubiquitous in human societies and transcends age, race, and societal milieu. In children, differentiating between pathologic aggressive behavior and developmentally-bound aggression can be difficult. To this end, many children may exhibit aggression in the context of tantrums or angry outbursts. There may be problems in differentiating between this developmentally-bound aggression of a child and pathological pediatric aggression.¹ Pathologic pediatric aggression may be more severe than developmentally-bound aggression, in terms of incidence, length, and amount of aggression.¹

In the pediatric population, pathologic aggression can be physical or verbal and may be directed towards self or others. Physical aggression can be further characterized as impulsive, reactive, predatory, or premeditated. Impulsive aggression usually occurs in response to a stimulus, whereas predatory aggression is usually planned in advance of the act.² Thus, pediatric aggression is a nonspecific symptom that transcends a number of psychiatric disorders. The diagnostic complexity of child and adolescent aggression further relates to the fact that multiple illnesses may involve aggression. Aggressive behaviors may be seen in attention-deficit or hyperactivity

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disorder (ADHD), posttraumatic stress disorder (PTSD), and oppositional defiant disorder.³ It can be challenging to determine the primary psychiatric diagnosis and what kind of predominant aggressive pattern (impulsive or premeditated) exists. This dilemma may complicate the treatment of the two different types of aggression as they may be approached in different ways.⁴

Treatment of pediatric aggression is often complicated by difficulties related to diagnostic issues, multiple medications used by clinicians, and the variety of psychological and environmental factors, which may directly affect the expression of aggression in youth. Psychopharmacologic treatment may require a long period, empiric trials of multiple medications until desired effects are attained. Thus, the main causes of the aggression need to be targeted and treated for the aggression to abate.⁵ A myriad of medications can be used to treat pediatric aggression, including antipsychotics, antidepressants, antiadrenergics, and mood stabilizers. Moreover, a number of nonpsychopharmacologic interventions, including different psychotherapies, are available for the treatment of pediatric aggression associated with a number of mental illnesses.

Aggressive behavior in children can result from a variety of experiences. Accumulating evidence from both clinical studies and investigations conducted in lower animals suggests that early life stress is a significant risk factor for the development of pathologic aggression.^{6–10} Early life stress can take many forms including early social deprivation or exposure to trauma, abuse, or neglect.⁶ Many studies have found functional and structural differences in the brains of those exposed to maltreatment.¹¹ Biological factors of pediatric aggression can be related to neuroendocrine abnormalities, genetics, and substance abuse.¹² Moreover, deficits in social skills have also been linked to pediatric aggression.¹³ Children who are not able to adjust to a social environment may act out in an aggressive manner.

Although it is evident that pediatric aggression has many causes and contributing factors, a number of biological findings have been associated with pediatric aggression and will be reviewed in the context of selected aspects of neuroendocrine function and dysfunction.

Neurochemical systems and pediatric aggression

A constellation of neurochemical systems have been implicated in the physiology of aggression. Although herein we will focus primarily on the hypothalamic–pituitary–adrenal (HPA) axis, this system has a number of intimate relationships with other neuroendocrine systems, which are important for

clinicians and neurobiologists to consider. In this review, the central monoaminergic systems (eg, norepinephrine and dopamine) and the serotonin system will be briefly reviewed with regard to their relationships with both aggression and the HPA axis.

The dopaminergic system consists of cell bodies that are primarily localized in the ventral tegmental area of the midbrain and the nucleus accumbens. These nuclei give rise to a number of tracts that project throughout various brain regions, which functionally subserve emotional regulation, motor command, cognitive processing, and neuroendocrine control. With regard to the issue of neuroendocrine control, the anterior pituitary, which ultimately modulates the release of the end products of the major hormones (the focus of this review), is coated with dopamine receptors highlighting the influence of the dopamine system on the HPA and hypothalamic–pituitary–gonadal (HPG) axes. In fact, the relationship between central nervous system dopamine release and elaborates of the HPA axis is complicated and likely reflects bidirectional influences and common stimuli. For example, both preclinical and clinical studies document cortisol-induced increases in central dopaminergic activity.¹⁴ With specific regard to impulsive aggression, a study of adults, which assessed cerebral blood flow using single photon emission computed tomography, suggests that regional blood flow may be increased in the nucleus accumbens, which itself directs important fibers to limbic regions;¹⁵ however, it remains unknown whether individuals without PTSD but with impulsive aggression would have similar increases in this region. Interestingly, from a neurochemical standpoint, cerebrospinal fluid sampling studies in adults have consistently linked high levels of the major dopamine metabolite, homovanillic acid, a finding consistent with high dopamine turnover, with higher levels of aggression in violent forensic samples.¹⁶ Moreover, the same has been observed in men convicted of murder.¹⁷ Similarly, levels of this compound are also abnormal in youth with aggression and comorbid ADHD.¹⁸ Indirect clinical evidence for the role of dopamine in the involvement of aggression includes the observation that patients, both youth and adults, who ingest cocaine (which increases postsynaptic effects of dopamine) become aggressive.¹⁹ In addition, drugs that block central dopamine receptors (eg, first and second generation antipsychotics) often have antiaggressive effects.

The catecholamine norepinephrine plays a critical role as one of the principal mediators of the mammalian response to stress. Thus, it is not surprising that it plays a central role in the modulation of aggression in both humans and lower animals.

Central norepinephrine production occurs in the locus coeruleus, whose cell bodies project to a constellation of structures that are altered or implicated in the pathophysiology of aggression, including the prefrontal cortex, amygdala, hippocampus, hypothalamus, periaqueductal gray matter and the thalamus.²⁰ As with the dopaminergic system, the relationship between norepinephrine and other systems, which have been linked to aggression, is complicated. For example, administration of β -receptor agonists increases secretion of adrenocorticotropin-releasing hormone (ACTH), and in many conditions, the concentrations of cortisol and norepinephrine covary with one another. With regard to studies of aggression and its relationship with the concentrations of plasma norepinephrine, concentrations of this catecholamine have been found to be higher in healthy subjects with high-normal aggression than in those with low-normal aggressiveness²¹; however, not all studies of peripheral norepinephrine have observed these effects,²² which is likely related to the fact that concentrations of peripheral norepinephrine are poorly reflective of central norepinephrine concentrations.^{20,23} Further indirect support for the involvement of this system in aggression is provided by the clinically used postsynaptic β -receptor antagonists and presynaptic α_2 receptor agonists to attenuate central noradrenergic tone, which are often used to decrease aggressive behaviors in youth with certain mental illnesses.²⁴

Nearly, a quarter century of accumulating evidence has firmly established a link between the serotonergic system and the aggression^{16,18,25} and have been reviewed extensively in the literature.²⁶ The serotonin system, whose cell bodies reside in the raphe nuclei of the brainstem, projects both rostrally and caudally and innervate a diverse group of brain regions including diencephalic and cortical structures, many of which have also been linked to aggression with functional imaging studies of aggressive adults and youth.^{27–29} Although an oversimplified summary neglects many nuances specific to individual history, individual attachment, individual psychopathology, etc, the serotonergic system is generally thought to be in a state of hypofunction in aggressive individuals. In a recent study of violent offenders, low cerebrospinal fluid concentrations of the major serotonin metabolite, and marker of serotonergic neurotransmission, 5-hydroxyindolacetic acid, were found to be high suggesting a link between “the outward-directed aggression of psychopathy to serotonergic hypofunctioning”.¹⁶ Importantly, the serotonergic system operates in concert with many of the other systems described in this review and elsewhere, which have been implicated or could theoretically be involved in aggression, including the

vigilance-promoting and arousal-regulating peptide orexin,³⁰ the aggression modulating steroid hormone testosterone,³¹ thyroid function,³² and the covarying monoamine dopamine.²³ Finally, from a pharmacologic standpoint, the distribution of brain 5-HT_{2a} receptors is markedly different in adults with histories of impulsive aggression as compared with those without, and agents, which act at these receptors (eg, second-generation antipsychotics), are often used clinically in treating symptoms of impulsive aggression.³³

The HPA axis and pediatric aggression

Despite the significance of these monoaminergic systems, the HPA axis, which links the central nervous system with the peripheral response to stress,³⁴ has been the focus of many studies of pediatric aggression because it is one of the main regulators of stress in the body.³⁵ The HPA axis instigates a cascade effect that eventually results in the production of cortisol.³⁵ In times of stress and in certain psychiatric conditions, the hypothalamus releases the peptide hormone called corticotrophin-releasing hormone (CRH), which stimulates the pituitary to secrete ACTH (Figure 1A). In response to the ACTH, the adrenal cortex releases glucocorticoids. Of these glucocorticoids, cortisol is perhaps the most studied and has intimate relationships with a diverse number of systems, including the immune system and the reproductive system, and even effects respiratory and cardiac functions. Moreover, this system is regulated through a series of negative feedback loops both at the level of the hypothalamus and pituitary wherein cortisol secretion inhibits release of CRH and ACTH, respectively.³⁴

Several studies have examined the function of HPA axis and the concentrations of cortisol in pediatric aggression. However, the results from the various studies have not been consistent. One study found that prepubertal children (aged 8–12 years, male and female) with disruptive behavior disorders had lower cortisol levels associated with a stress-inducing challenge.³⁶ However, this study did not characterize the severity of aggression or type. The exact mechanisms involved with low levels of HPA axis activity are unknown. Therefore, it cannot be said how this would affect hormone concentrations in the body. McBurnett et al³⁷ examined the relationship between plasma cortisol concentrations and aggression in 38 subjects (aged 7–12 years; male and female) and observed that low cortisol levels were associated with patterns of aggression and early onset of aggression in male children.³⁷ Interestingly, a low variability with low cortisol levels over the long

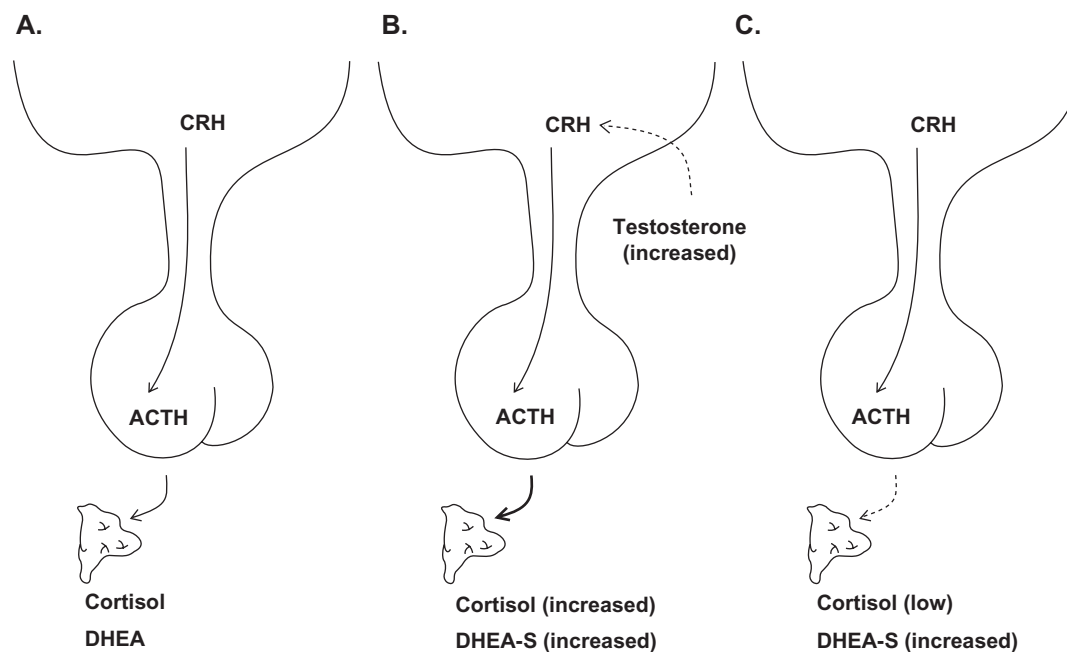


Figure 1 **A)** Neuroendocrine function among healthy children and adolescents; **B)** Children and adolescents with impulsive aggression; **C)** Children and adolescents with callous, unemotional traits. Solid arrows represent stimulation and dashed lines represent inhibitory pathways.

Abbreviations: CRH, corticotrophin-releasing hormone; ACTH, adrenocorticotropin-releasing hormone; DHEA, dehydroepiandrosterone; DHEA-S, dehydroepiandrosterone sulfate.

term (collected at the second and fourth year of the study) was predictive of severe persistent pediatric aggression.³⁷ In a subsequent study that focused on pediatric aggression rather than disruptive behavior disorders diminished postchallenge cortisol secretion corresponded to higher levels of aggression in 10 to 14-year-old children, but only in the presence of low sympathetic nervous system activity, as assessed by salivary α -amylase concentrations, a surrogate of noradrenergic activity.³⁸ This study provided evidence for the need to study more than one system at a time since biological systems are connected. Interestingly, in a study of males aged 10–12 years, it was noted that low cortisol levels correlated with aggressive behavior and impulsivity 5 years later (at ages 15–17 years).³⁹ However, to our knowledge, the potential predictive value of cortisol has not been assessed with regard to subsequent short-term aggression.

In an important study of the type of pediatric aggression and cortisol levels, Lopez-Duran et al⁴⁰ evaluated cortisol reactivity in 73 6- to 7-year-old children and noted that subjects with patterns of reactive aggression had higher cortisol reactivity than the children with no aggression or proactive aggression.⁴⁰ Moreover, in another study, Loney et al⁴¹ found that low basal cortisol levels were correlated with callous unemotional traits in male adolescents, but a similar relationship was not observed in female adolescents.⁴¹

This finding was consistent with their hypothesis that callous unemotional traits would be associated with low resting cortisol levels due to the low emotional reactivity. Serum cortisol concentrations can be considered biomarkers of “emotional reactivity”, and thus, levels of cortisol may potentially help to predict the type of aggression and help with diagnosis and treatment.⁴¹

In contrast to the aforementioned studies, Sondejker et al did not find a relationship between circulating cortisol concentrations and aggressive or disruptive behaviors.⁴² However, the children in this study were from the general population, instead of high-risk children with more severe behavioral problems. Hence, it would be important to carefully consider the characteristics of the groups of children to be studied when measuring hormonal levels. In future pediatric studies, three groups including a low-risk clinical group, a high-risk clinical group, and a control nonclinical group would allow researchers to determine how cortisol levels differ between children with a range of risk for aggression (from none to high levels). The level of risk for potential pediatric aggression and violence in child psychiatry inpatient units could be measured using the brief rating of aggression by children and adolescents.⁴³ In future neuroendocrine pediatric aggression studies, it is also important to differentiate between patterns of callous unemotional aggression and impulsive aggression.

Given the above findings, it is important to consider the etiology of the HPA pathology and pediatric aggression. In response to certain types of early life stress, the HPA axis may become dysregulated. This HPA dysregulation may result in a vulnerability for the development of psychopathology and antisocial behavior.⁴⁴ To this end, structural neuroanatomic differences in those exposed to maltreatment may be related to increased cortisol concentrations, which specifically alter the structure of glucocorticoid sensitive areas of the brain.⁴⁵

The neurobiology of attachment is highly relevant for understanding hormones and pediatric aggression. Disorganized attachment, in which a child has no ability to organize a response to elicit care under stress, is a risk factor for the development of aggressive behavior in school-aged children.⁴⁶ Several studies have also shown a correlation between cortisol levels and attachment pattern. A study investigating prenatal cortisol exposure found that increased amniotic fluid levels of cortisol negatively impacted infants' cognitive ability, but this effect only persisted if the infant-mother dyad developed an insecure attachment.⁴⁷ Infants whose mothers had high-quality maternal behavior have more normal cortisol recovery in response to stress.⁴⁸ Understanding the neurobiological mechanism of attachment-related pathology may help design treatments to abate HPA dysregulation. Accordingly, a recent study demonstrated that attachment-based psychotherapeutic interventions in children in foster care resulted in normalization of cortisol levels in response to social stressors.⁴⁹

The effects of sex hormones and their precursors on pediatric aggression

Dehydroepiandrosterone (DHEA), a neurosteroid produced by the adrenal cortex and the brain,^{50,51} is a precursor to sex hormones, such as testosterone and estrogen. A more stable and sulfated form of this compound, dehydroepiandrosterone sulfate (DHEA-S), is commonly measured secondary to its inherent stability. Circulating DHEA levels increase quickly (around 7 years old in females and around 9 years old in males) and then decline later in life.⁵¹

Not surprisingly, DHEA-S has been studied in child and adolescent psychiatry to understand its effect on aggressive behavior. In a study of 16 adolescents with conduct disorder, the circulating DHEA-S concentrations were measured in relation to observed aggression (as measured using the Overt Aggression Scales and the Child Behavior Checklist).

Higher DHEA-S levels were found in the adolescents with conduct disorder as compared with a healthy group of adolescents.⁵¹ Another study found that in male children (aged 8–12 years) with pathological aggression and conduct disorder, the DHEA-S levels were significantly higher than control subjects. Using ratings by parents and teachers, this study found that the high DHEA-S levels were associated with antisocial behaviors and aggression in these school-aged children.⁵² Similar results were found in a German study that compared DHEA-S levels in 28 boys aged 10–18 years with conduct disorder and 13 comparison subjects.⁵³ The subjects with conduct disorder had high DHEA-S concentrations as compared with the comparison subjects.

Testosterone, an androgen that circulates throughout human blood and readily crosses the blood–brain barrier, is present in both males and females but is commonly known as the male sex hormone.⁵⁴ Fluctuations of testosterone concentration may be associated with aggression and mood changes.⁵⁵ Scerbo and Kolko⁵⁶ evaluated salivary testosterone and cortisol concentrations in 40 children, aged 7–14 years (37 boys and three girls), with aggressive behaviors and observed an association between higher testosterone levels and aggressive behaviors. In addition, the higher cortisol concentrations were associated with internalizing behaviors.⁵⁶ Similarly, in adolescent males, higher testosterone levels were associated with provoked verbal and physical aggression, a finding suggesting that reactive impulsive aggression is correlated with higher testosterone levels.⁵⁴

Importantly, however, not all studies have observed differences in serum testosterone levels between aggressive and nonaggressive boys.⁵⁷ In this study of 4- to 10-year olds, there was no evidence to suggest a relationship between testosterone levels and aggressive behaviors in prepubertal children. To our surprise, the relationship between aggressive behavior and testosterone or gonadal function remains to be developed and, thus, suggests a more limited potential for testosterone as a biomarker for pediatric aggression.

Future directions

The existing data suggest that hormonal levels (eg, in saliva, serum, plasma, urine, etc) could be of potential clinical utility in that concentrations might assist in clarifying the subtype of pediatric aggression, which directly relates to subtype-specific psychopharmacologic or psychotherapeutic treatments. Thus, given the evidence that certain hormonal concentrations are associated with pediatric aggression and may be specific to the type of pediatric aggression, it is not

unreasonable to suppose that salivary hormone assays can help in identifying pediatric patients that would respond best to certain treatments.

Disclosure

The authors report no conflicts of interest in this work.

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