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Research Paper

Patterns of neuroendocrine coupling in 9-year-old children: Effects of sex, body-mass index, and life stress

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ABSTRACT

Previous investigations have explored stress and pubertal hormones in parallel; it has been a recent development, however, to explore the relationships between different hormones during puberty, and how this hormonal cross-talk may be influenced by the environment. The current study investigated neuroendocrine coupling, or the extent to which hormones are correlated within the individual, and also investigated early life stressors that may influence coupling. Participants were 405 adrenarcheal children (mean Tanner stage = 1.73 for girls and 1.38 for boys) from a longitudinal study who provided saliva samples for analysis of cortisol, dehydroepiandrosterone (DHEA), and testosterone. Saliva was collected when children were 9-years-old, while early life stressors were assessed at each longitudinal assessment (ages 3, 6, and 9). Results from multi-level modeling (MLM) analyses provided evidence of positive cortisol-dehydroepiandrosterone (DHEA) and cortisol-testosterone coupling in middle childhood, and identified body mass index as a predictor of the strength of hormone coordination. While exposure to stressful life events did not impact cortisol-DHEA coupling patterns, stress interacted with sex to predict looser cortisol-testosterone coupling in girls, but not boys. The current study adds to the existing literature on the development of neuroendocrine coupling, and provided further evidence of sex differences in the impact of stress. Furthermore, hormone coupling may be investigated in the future as a mechanism by which puberty is associated with negative behavioral outcomes.

1. Introduction

Puberty, the transition from childhood to adulthood, is not a singular event, but rather a series of hormonal, neural, psychological, and social changes taking place over many years. While all healthy adolescents experience these changes, there has been growing interest in individual differences that may alter or disrupt typical developmental processes during puberty. In large part, this has been motivated by research showing that the rates of many negative outcomes, including psychological disorders and serious risk-taking behaviors, rise during and closely after puberty (Downing & Bellis, 2009; Graber, 2003; Hyde, Mezulis, & Abramson, 2008).

The myriad events of puberty are primarily initiated through hormonal changes, many of which occur well before puberty is outwardly apparent, and occur as two separate but related processes. Adrenarche begins when the adrenal gland matures and releases dehydroepiandrosterone (DHEA), typically between the ages of 6 and 8 for girls and ages 7 and 9 for boys (Auchus & Rainey, 2004). DHEA, which is an adrenal androgen largely regulated by the HPA axis, plays a role in the physical maturation associated with puberty, as rising levels of the hormone are associated with the development of pubic hair, oily skin, and voice changes. While DHEA has an important role as a sex hormone during puberty (Azziz et al., 2004; Byrne et al., 2017), it also has significant effects on brain development, especially during adrenarche (Campbell, 2011). Specifically, DHEA has been shown to promote neurogenesis (Maninger, Wolkowitz, Reus, Epel, & Mellon, 2009) as well as play a neuroprotective role during periods when the brain is especially vulnerable to environmental insults (Campbell, 2011). Throughout the lifespan, DHEA also acts in concert with cortisol during times of stress (Hucklebridge, Hussain, Evans, & Clow, 2005), largely in a neuroprotective function (Dismukes et al., 2016).

The second phase of puberty occurs when the hypothalamic-pituitary-gonadal (HPG) axis initiates a cascade of hormonal changes, which ultimately lead to the release of sex hormones (testosterone and estrogen) from the gonads. These hormones are responsible for both secondary sex characteristics and neural maturation during adolescence; the release of sex hormones and subsequent physical changes are known as gonadarche (Rosenfield, Cooke, & Radovick, 2008; Saenger &

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Dimartino-Nardi, 2001; Styne, 2004). Gonadarche occurs later than adrenarche, beginning normatively as early as ages 9 or 10 for girls, and approximately 1 year later for boys (Grumbach & Styne, 2003).

Although most investigations of puberty have considered hormones in isolation, recent studies have highlighted the relationship *between* hormone levels across time, also known as neuroendocrine coupling (Marceau et al., 2015; Mehta & Prasad, 2015; Simmons et al., 2015; Turan, Tackett, Lechtreck, & Browning, 2015). Results from both cross-sectional and longitudinal studies in adult human and animal samples suggest that the HPG and HPA axes regulate one another, although the direction of this effect has been inconsistent (Chichinadze & Chichinadze, 2008; Hardy et al., 2005). Further exploration into these inconsistencies has revealed that while HPG axis hormones increase in response to acute stress (Lennartsson, Kushnir, Bergquist, Billig, & Jonsdottir, 2012; Phan et al., 2017), exposure to chronic stress may result in decreases in sex steroid hormones, such that HPG axis functioning is inhibited when higher concentrations of HPA hormones are present, and vice versa (Elias, 1981; Roy, Kirschbaum, & Steptoe, 2003; Viau, 2002; Zilioli & Watson, 2012). This arrangement is advantageous as steroid hormones, such as testosterone, can protect the organism against the deleterious effects of excessive cortisol during times of acute stress (including memory deficits, cognitive dysfunction, and deficits in processing of emotional information; Lupien, Maheu, Tu, Fiocco, & Schramek, 2007; Prickaerts & Steckler, 2005). Conversely, during times of high chronic stress, gonadal functioning may be inhibited in favor of survival activities (Gomez, Manalo, & Dallman, 2004; Handa et al., 1994).

During childhood and adolescence, however, "positive" (i.e., higher levels of one hormone predicting higher levels of another hormone) or even null coupling between testosterone and cortisol may be developmentally advantageous, as it would be counterproductive for one hormone to inhibit another during times of growth and development (Shirtcliff & Ruttle, 2010). Research in pre-pubertal male rats found that testosterone levels are unaffected by HPA functioning and vice versa, which may be beneficial because biological resources are not being used to regulate reproductive functioning during times of stress (Gomez, Houshyar, & Dallman, 2002; Gomez et al., 2004; Lürzel, Kaiser, Krüger, & Sachser, 2011; Romeo, Lee, Chhua, McPherson, & McEwen, 2004). In early and middle adolescence, however, the pattern may begin to change to favor positive cortisol-testosterone coupling (Dismukes, Johnson, Vitacco, Iturri, & Shirtcliff, 2014; Johnson et al., 2014; Marceau et al., 2015; Turan, Tackett, Lechtreck, & Browning, 2015). For example, in a mixed-sex human sample (mean age = 13.7 years, range = 11-16 years), Marceau et al. (2015) found that cortisol and testosterone were overall positively coupled, although the magnitude of the coupling was stronger for female participants.

In contrast, DHEA-cortisol coupling is hypothesized to become more positive as adolescents transition into adulthood (Hucklebridge, Hussain, Evans, & Clow, 2005; Ruttle et al., 2015; Tung et al., 2004). For example, Oskis, Clow, Thorn, Loveday, and Hucklebridge (2012) found only a trend-level evidence of positive cortisol and DHEA coupling in a sample of 10–18 year olds. However, DHEA and cortisol are positively coupled in adults (Hucklebridge, Hussain, Evans, & Clow, 2005). While the relationship between DHEA and cortisol remains positive across the lifespan, looser coupling during childhood and adolescence may lead to greater adaptability of the hormone systems to react to pubertal changes and stressful events, which is especially important during such active periods of neural growth (Campbell, 2011).

There is growing evidence that environmental stress can impact the pubertal transition and related hormones (Belsky et al., 2007; Ellis & Garber, 2000; Graber et al., 1995; Romans et al., 2003 Romans, Martin, Gendall, & Herbison, 2003; Saxbe & Repetti, 2009). Research suggests that early exposure to negative life events, including maltreatment, abuse, or neglect, is related to HPA axis dysregulation (Essex, Klein, Cho, & Kalin, 2002; Miller, Chen, & Zhou, 2007; Tarullo & Gunnar, 2006), with effects on both cortisol and DHEA (Ellis & Essex, 2007). With regard to hormone interactions, Simmons et al. (2015) found that observed maternal aggression significantly moderated cortisol's influence on testosterone and DHEA's influence on both cortisol and testosterone levels in both girls and boys (mean age = 15.56 years), although the nature of these relationships differed between the sexes. In girls, cortisol and testosterone, as well as cortisol and DHEA, were only positively associated in girls who had experienced low or average levels of maternal aggression three years prior to the hormone collection; girls who had experienced higher levels of maternal aggression demonstrated no relationship between the hormones. In boys, however, high levels of maternal aggression predicted positive correlations between cortisol and testosterone, and cortisol and DHEA, while low levels of maternal aggression predicted a *negative* relationship between the two sets of hormones.

Ruttle et al. (2015) assessed stress in children prospectively between the ages of 1 month and 4.5 years old, and measured cortisol, DHEA, and testosterone levels at ages 11, 13, and 15 years. Overall, cortisol-DHEA coupling was positive at age 11, and became progressively more positive through age 15, while cortisol-testosterone coupling was positive at age 11, but became negative at ages 13 and 15. Exposure to stress played a significant role in hormone functioning, however. Similar to non-exposed children, children exposed to higher levels of early stress displayed positive cortisol-DHEA coupling at age 11, but by age 13 cortisol and DHEA were more tightly positively coupled in exposed children than non-exposed children; by age 15, cortisol-DHEA coupling had plateaued for the exposed children, while it continued to become more tightly positively coupled in non-exposed children.

While cortisol-DHEA coupling was impacted by stress in both sexes, a significant sex effect emerged when assessing the impact of early life stress on cortisol-testosterone coupling. Specifically, cortisol-testosterone coupling was not impacted by early life stress in boys at any age, but girls who were exposed to stress displayed more adult–like (negative) coupling earlier in development; however, this specific difference between exposed and non-exposed girls did not emerge until age 13. Prior to age 13, exposed girls demonstrated tighter positive coupling than non-exposed girls, who demonstrated positive coupling that was somewhat weaker in magnitude. These age effects are noteworthy especially when considering that gender differences in hormone pathways differ between childhood and adolescence. Specifically, while hormone pathways are similar for male and female children, adolescent male hormone development is marked by a rapid rise in testosterone, while adolescent female hormone development features a more gradual rise in testosterone and cyclic changes in other steroid hormones (Granger, Schwartz, Booth, & Arentz, 1999; Grumbach & Styne, 2003). Taken together, the two previous studies support the hypotheses that there are sex differences with regard to the impact of stress on neuroendocrine coupling, which may be further impacted by both age at stress exposure and developmental stage at hormone collection.

Neuroendocrine coupling has not been investigated in adrenarcheal children, which is notable considering some research pointing to adrenarche as a period of specific vulnerability for brain development and later negative outcomes (Byrne et al., 2017) Hence, the current study was undertaken to examine cortisol-DHEA and cortisol-testosterone coupling in a prospective community sample of 9-year-old children. We extended prior research by determining whether the same pattern of findings demonstrated in Ruttle et al. (2015) are present during adrenarche but prior to gonadarche. Extrapolating from Ruttle et al.'s findings, we tentatively hypothesized that both cortisol-DHEA and cortisol-testosterone coupling would be positive in our sample.

We also tested the relationship of pubertal development and body mass index (BMI) to hormone coupling. Although previous studies have examined the relationship between pubertal development and hormone coupling, the restricted age range of participants in the current study allows us to test the effect of pubertal development while minimizing the confound of age. Furthermore, to our knowledge, no previous study has examined the relationship of BMI and coupling, which is