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SHORT COMMUNICATION

Methodological considerations in use of the cortisol/DHEA(S) ratio in adolescent populations

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Summary
Objective: The cortisol/DHEA(S) ratio has demonstrated utility in studies of HPA activity and psychopathology. However, use of the cortisol/DHEA(S) ratio in adolescent populations requires additional consideration of differential changes in DHEA(S) and cortisol during the course of puberty. This study examines the relationship between pubertal status and individual cortisol and DHEAS levels as well as with the cortisol/DHEAS ratio.
Method: Morning salivary cortisol and urinary DHEAS levels were obtained for 267 young adolescents at three time points, each approximately one year apart. Growth curve modeling and repeated measures ANOVA were used to assess the effect of adrenal development on individual hormone levels and on the total ratio.
Results: Pubic hair development was a significant predictor of change over time in DHEAS but not cortisol. Development was also a significant predictor of the cortisol/DHEAS ratio when raw cortisol and DHEAS values were used.
Conclusions: Our findings indicate that, when DHEAS levels were adjusted to control for pubertal status, the ratio demonstrated stability over time. This finding is in line with the hypothesis that the ratio may tap stable individual differences in HPA functioning.

1. Introduction

Burgeoning research on links between the hypothalamic—pituitary—adrenal (HPA) system and psychopathology has focused extensively on the cortisol stress response. However, recent studies suggest that dehydroepiandrosterone (DHEA)

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and its sulfate (DHEAS) also play a role in the stress system. The relative level of cortisol to DHEA(S) has been examined as an indicator of HPA axis functioning that accounts for the neurotropic effects of each hormone (for review, see Maninger et al., 2009). However, comparison of findings across age groups is complicated by the differential impact of adrenal development on these hormones; specifically, DHEA(S) levels are known to increase with adrenarche whereas effects of puberty on cortisol are unclear. Yet, the few studies examining the cortisol/DHEA(S) ratio in adolescents have neglected to control for hormonal changes associated with adrenarche.

Both cortisol and DHEA(S) are synthesized from pregnenolone in response to adrenocorticotropic hormone release. It has been suggested that the ratio of cortisol and DHEA(S) taps preferential production of one hormone or the other such that markedly higher or lower ratios may reflect physiological vulnerabilities for psychopathology. In particular, significantly higher or lower cortisol/DHEA(S) ratios have been associated with depression (Angold, 2003) and aggression (Pajer et al., 2006), respectively.

Both cortisol and DHEA(S) demonstrate developmental changes throughout the lifetime (Goodyer et al., 2001). Several studies have reported developmentally-related increases in basal cortisol levels from childhood through adolescence (Gunnar and Vasquez, 2006), but others have found this effect only in females (Schiefelbein and Susman, 2006) or not at all (Knuttson et al., 1997). A recent 6-year longitudinal study by Shirtcliff et al., 2012 found a decrease in cortisol and identified this change as being driven by age rather than puberty. In contrast, DHEA(S) increases significantly beginning at adrenarche continuing throughout puberty (Rege and Rainey, 2012).

As indicated, the only identified studies on the cortisol/DHEA(S) ratio in adolescents have failed to control for puberty prior to calculating the ratio beyond simply classifying participants as "pre-pubertal" or "post-pubertal" (e.g., Netherton et al., 2004). In young children and in adults, variations in DHEA(S) associated with puberty are less important because the entire sample is either pre- or post-pubertal. For adolescent samples, individuals are at varying stages of adrenarche and therefore have significantly different reference ranges for DHEA(S) (Rege and Rainey, 2012). For example, Identifying an individual as having a lower cortisol/DHEA(S) ratio could indicate preferential production of DHEA(S) over cortisol or that the individual has developed earlier than his/her peers (and vice versa for high cortisol/DHEAS). This difference is notable because early pubertal maturation has also been identified as a risk factor for psychopathology in adolescents (Graber et al., 2010).

The purpose of the current study is to examine the relationship between pubertal development, adrenal hormones, and their ratio in a community sample of children seen annually during the transition from childhood into adolescence.

2. Methods

Two hundred sixty-seven pre- to early-adolescent boys and girls (Ngirls = 138, Nboys = 129; M age = 9.2 years, SD = 0.70 at Time 1) were seen annually for 3 years. The racial/ethnic makeup of the participants at enrollment was 39% Caucasian, 32% African-American, 12% Hispanic, and 17% multiracial or other. One hundred ninety-four participants (Ngirls = 92, Nboys = 102) provided data at Time 2 (27% attrition; M age = 10.9 years, SD = 0.77). As all participants were contacted at each assessment, 202 children (Ngirls = 111, Nboys = 91) participated at Time 3 (24% attrition from enrollment; M age = 12.0 years, SD = 0.77). Male participants were more likely than females, and white were less likely than non-white participants to have discontinued participation (T1 to T3). No significant differences were found in attrition based on T1 cortisol, DHEAS values, or pubertal status.

2.1. Procedure

The girls' and boys' studies were not conducted concurrently and some procedures differed between studies; however, procedures were consistent within gender over time. Procedures were approved by the IRB of Teachers College, Columbia University. Saliva samples and overnight urine samples were collected each morning for two (boys) or three (girls) days at home to assess hormone levels. Morning salivary samples for cortisol were collected immediately upon the child's natural waking time, before eating, drinking, or brushing teeth. Because DHEAS assays for saliva collected with salivette devices were not available at the time assays were conducted, morning urine samples were used for DHEAS sampling instead. Overnight urine collection for DHEAS included first morning void and any voids between bedtime and waking. Parents labeled samples with time and date of collection.

2.2. Cortisol

Salivary cortisol was assayed in duplicate using radioimmunoassay developed by Kirschbaum and colleagues (Diagnostic Products Company) with a lower detection limit of 0.02 μg/dl per 200 μl of saliva. The inter- and intra-assay variation coefficients were less than 3% and 5%, respectively. Cortisol values for each of the two (boys) or three (girls) samples were averaged at each time point.

2.3. DHEAS

DHEAS level was determined using a commercial solid-phase, competitive chemiluminescent immunoassay (Immulite, Siemens, Los Angeles, CA) with a sensitivity of 3 g/dl. The inter- and intra-assay variation coefficients were less than 8.2% and 12.0%, respectively. Urinary DHEAS was standardized using creatinin; however, no significant differences were found in the raw and creatinin-standardized DHEAS values. Hence, raw values were used in this study. DHEAS levels for each of the two (boys) or three (girls) samples were averaged at each time point.

2.4. Pubertal status

Mothers rated Tanner stage of pubic hair growth (TannerPH) from drawings (1—5, from no development to complete adult stage of development; Morris and Udry, 1980); child report was obtained in cases where mothers indicated they were not able to complete ratings. While Tanner staging also includes a