Sexual dimorphism in cortisol secretion starts after age 10 in healthy children: urinary cortisol metabolite excretion rates during growth

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Wudy SA, Hartmann MF, Remer T. Sexual dimorphism in cortisol secretion starts after age 10 in healthy children: urinary cortisol metabolite excretion rates during growth. Am J Physiol Endocrinol Metab 293:E970–E976, 2007. First published July 17, 2007; doi:10.1152/ajpendo.00495.2006.—Detailed data on the physiological pattern of adrenocortical activity during normal growth are lacking. An established method to determine adrenocortical glucocorticoid secretion is the measurement of 24-h excretion rates of major urinary cortisol metabolites (C21). To test the hypothesis that the frequently reported higher cortisol secretion in men than in women develops during puberty, we examined C21 together with excretions of combined urinary free and conjugated cortisol (Fcomb) in 400 healthy boys and girls aged 3–18 yr using GC-MS. Daily excretion rates of C21, Fcomb, and body surface area (BSA)-corrected Fcomb significantly increased with age in both sexes. In contrast, C21/BSA (µg·m⁻²·day⁻¹) declined from the age of 3–4 yr to 7–8 yr in boys and girls (P < 0.01; e.g., in boys: from 3,991 ± 1,167 to 3,193 ± 804), then increased in both sexes, and finally became discordant after the age of 11–12 yr with a further rise in males only (17- to 18-yr-olds: boys, 5,275 ± 1,414; girls, 3,939 ± 1,586, P < 0.01). This pattern was associated with the occurrence of a lower index for 5α-reductase activity (allopregnanolone/5α-dihydrotestosterone) in females compared with males. Our results demonstrate dynamic changes in adrenocortical activity in healthy children resulting in an emerging sexual dimorphism in cortisol secretion after age 11. The latter can be explained, at least partly, by diverging 5α-reductase activities in boys and girls. Fcomb, a frequently analyzed GC-MS parameter, proved not to reflect dynamic changes in cortisol secretion. In conclusion, the varying metabolic need for cortisol during normal growth may have implications for future improvements in glucocorticoid replacement therapy.

steroid; glucocorticoid; gas chromatography; mass spectrometry

IT HAS SO FAR BEEN ASSUMED that cortisol secretion corrected for body surface area is constant throughout childhood and adolescence. This assumption has been based on studies investigating urinary excretion rates of selected glucocorticoid metabolites in mostly small samples of children (2, 15, 17). However, detailed data on the physiological pattern of daily cortisol secretion, i.e., of adrenocortical activity during normal growth, are lacking.

Assessment of cortisol secretion in a huge sample of healthy children and adolescents requires not only a nonstressful and noninvasive protocol but also a practical approach to permit successful realization. The application of invasive techniques based on isotope dilution requires venipuncture and infusions of either stable or radioactively labeled cortisol in specialized hospitals or research units with subsequent sampling of blood and/or urine to recover labeled metabolites (19, 22, 50). Additionally, administration of isotope-labeled tracers might influence endogenous cortisol production by negative feedback (18). However, it has been shown that determination of urinary excretion rates of the major endogenous glucocorticoid metabolites provides a suitable alternative to isotopic methods for the determination of cortisol secretion (15, 19, 50) and gas chromatography-mass spectrometry (GC-MS) urinary steroid profiling has been successfully used in determining cortisol secretion in preterm infants (14).

Meanwhile, measurement of urinary 24-h major cortisol metabolites is an established method used by numerous endocrine research groups (9, 16, 23, 29, 39, 41, 43, 49) to examine adrenocortical activity and/or glucocorticoid metabolism in healthy and ill children and adults. This relies on the fact that the sum of the seven major urinary cortisol metabolites (for details see SUBJECTS AND METHODS) encompasses almost 80% of the cortisol secreted per day by the adrenal gland (27, 40).

Although recent observations in children with congenital adrenal hyperplasia have suggested an increased cortisol clearance at puberty and have shown problems with glucocorticoid replacement therapy (6, 7), possible changes in cortisol secretion and cortisol metabolism in normal growing children have not been specifically investigated so far. In addition, it is unclear at what time the known sexual dimorphism with higher cortisol secretion rates in men than in women develops. This sexual dimorphism has been demonstrated in adults with stable-isotope tracer infusions (45) as well as with 24-h urinary cortisol metabolite excretion measurements (1, 30, 38).

To examine the dynamics in cortisol secretion during growth and to test the hypothesis that the higher cortisol secretion in men than in women develops during puberty, we determined urinary glucocorticoid metabolite excretion rates noninvasively in a large sample of healthy children of the DONALD (Dortmund Nutritional and Anthropometric Longitudinally Designed) study (4, 34).

SUBJECTS AND METHODS

Subjects and urine collections. The study group comprised 400 healthy children and adolescents (200 boys, 200 girls aged 3–18 yr) participating in the DONALD study (4, 34). Data from these 400 children on urinary markers of adrenarche have already been published (32). Fifty 24-h urine samples (25 from boys and 25 from girls) were randomly selected for each of the eight equally wide age groups. The study was approved by the Institutional Review Board of the...
Research Institute for Child Nutrition Dortmund, and parental consent and children’s assent were obtained before entry into the study. The participating children and their parents received instruction and written guidance to ensure compliance in the 24-h urine collection, which was performed at home by each subject (31, 34).

Metabolism of cortisol. Major catabolic products are the tetrahydro-reduced compounds tetrahydrocortisol (THF; \(\text{m/z} \quad 652\)), tetrahydrocortisone (THE; \(\text{m/z} \quad 523\)), and its hexahydro-reduced metabolites \(\alpha\)-cortol, \(\beta\)-cortol, \(\alpha\)-cortolone and \(\beta\)-cortolone. HSD, hydroxysteroid dehydrogenase. Black dots indicate intermediate metabolite products.

Fig. 1. Metabolism of cortisol. Major catabolic products are the tetrahydro-reduced compounds tetrahydrocortisol (THF; \(m/z \quad 652\)), tetrahydrocortisone (THE; \(m/z \quad 523\)) and hexahydro-reduced compounds \(\alpha\)-cortol, \(\beta\)-cortol, \(\alpha\)-cortolone and \(\beta\)-cortolone. HSD, hydroxysteroid dehydrogenase. Black dots indicate intermediate metabolite products.

Statistical analysis. Data are presented as means ± SD and/or median and percentiles. Overall sex and age group effects were tested by two-way ANOVA. Subsequent analyses of the influence of age on hormonal and enzymatic variables during specific periods of \(\approx 4\) yr duration were done (with age as a continuous predictor) using regression analysis. Sex differences in particular age groups were tested by unpaired t-test. \(P < 0.05\) was considered statistically significant. All tests were two tailed. Calculations and analyses were performed using SAS for Windows (v. 8.2; Statistical Analysis System, Cary, NC).

RESULTS

Mean values ± SD for BMI, BSA, daily energy intake, and urine volume of the subjects according to age and sex are shown in Table 1. These data reflect normal developmental

Table 1. Characteristics of the 400 children and adolescents

<table>
<thead>
<tr>
<th>Age, yr</th>
<th>BMI, kg/m²</th>
<th>Body Mass Index</th>
<th>Daily Energy Intake, calories/day</th>
<th>Urine Volume, ml/day</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Boys (n = 200)</td>
<td></td>
<td></td>
<td>Girls (n = 200)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3–4</td>
<td>15.5 ± 1.12</td>
<td>0.70 ± 0.06</td>
<td>1,403 ± 235</td>
<td>543 ± 182</td>
</tr>
<tr>
<td>5–6</td>
<td>15.2 ± 1.06</td>
<td>0.83 ± 0.07</td>
<td>1,531 ± 278</td>
<td>485 ± 205</td>
</tr>
<tr>
<td>7–8</td>
<td>16.3 ± 1.77</td>
<td>0.97 ± 0.12</td>
<td>1,825 ± 271</td>
<td>710 ± 209</td>
</tr>
<tr>
<td>9–10</td>
<td>17.3 ± 2.00</td>
<td>1.18 ± 0.13</td>
<td>1,991 ± 365</td>
<td>767 ± 257</td>
</tr>
<tr>
<td>11–12</td>
<td>18.9 ± 3.15</td>
<td>1.39 ± 0.17</td>
<td>2,081 ± 395</td>
<td>922 ± 413</td>
</tr>
<tr>
<td>13–14</td>
<td>19.8 ± 1.81</td>
<td>1.56 ± 0.16</td>
<td>2,272 ± 368</td>
<td>871 ± 243</td>
</tr>
<tr>
<td>15–16</td>
<td>20.4 ± 2.19</td>
<td>1.75 ± 0.15</td>
<td>2,554 ± 685</td>
<td>1,108 ± 422</td>
</tr>
<tr>
<td>17–18</td>
<td>22.5 ± 3.04</td>
<td>1.92 ± 0.14</td>
<td>2,722 ± 483</td>
<td>1,204 ± 596</td>
</tr>
</tbody>
</table>

Data are presented as means ± SD. Each age group comprised 25 boys and 25 girls. BMI, body mass index; BSA, body surface area.
changes in the corresponding basic characteristics of healthy children and adolescents.

In Table 2, 24-h urinary excretion rates of the three most important single glucocorticoid metabolites, THE, THF, and α-THF, are given according to age and sex. Table 3 shows the sums of total daily renal output (C21) of all seven major glucocorticoid metabolites (THF, α-THF, α-cortol, β-cortol, THE, α-cortolone, β-cortolone), reflecting overall cortisol secretion. Significant overall effects of age and sex were observed by two-way ANOVA for all individual glucocorticoid metabolites and the sums of metabolites presented in Tables 2 and 3. Age and sex remained strong predictors for cortisol secretion, when corrected for BSA (C21/BSA), is by no means constant during childhood and showed a U-shaped course in both sexes. To assess age-dependent changes in the activity of the glucocorticoid-catabolic 5α-reductase, we conventionally determined the α-THF/THF ratio, which in the first instance could therefore imply a decrease in 5α-reductase activity. Increases in this ratio could therefore imply a decrease in 5β-reductase or an increase in 5α-reductase. However, since the 5β-metabolites THF and THE do not decline in our children (relative to total cortisol secretion; compare Tables 2 and 3), changes in the ratio α-THF/THF represent altered 5α-reductase activity. Figure 3B shows that a dissociation emerges for 5α-reductase between boys and girls after age 11–12 yr (sex difference: P < 0.05 in 15- to 16-yr-olds and P < 0.01 in 17- to 18-yr-olds).

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constant throughout childhood and adolescence but shows a dynamic pattern, with a nadir around the age of 7–8 yr. Therefore, C21/BSA starts to rise again in boys and in girls, and after the age of 11–12 yr it becomes divergent between the sexes, with significantly higher levels in males.

No such dynamics is discernible for urinary cortisol (Fcomb) as conventionally measured by GC-MS. Fcomb/BSA was relatively constant over a wide age range in both sexes, especially during the period with the most dynamic changes in cortisol secretion, i.e., between age 3 and 15 yr. Since Fcomb is a combined parameter consisting only partly of urinary free cortisol, it is comprehensible that Fcomb/BSA is not necessarily totally age independent, as might be expected if this measure closely reflected integrated plasma free (bioactive) cortisol over 24 h. A considerable part of Fcomb consists of glucuronidated and sulfated cortisol, implying that changes in hepatic conjugation activity during growth may confound Fcomb/BSA as an accurate index for the noninvasive assessment of circulating bioactive free cortisol.

Our results corroborate the hypothesis that the reported higher cortisol secretion of men compared with women develops during puberty, a period during which the rough indicator of bioactive free cortisol in circulation Fcomb/BSA remains fairly constant. This strongly suggests that metabolic differences between males and females, which emerge during puberty, may be responsible. In accord with this, significant differences between the sexes were discernible for the index of 5α-reductase activity that we assessed too (see below).

Measurement and summation of the major GC metabolites of 24-h urine samples (C21) allows a time-integrated, stress-free, in vivo examination of the overall amount of cortisol and cortisone originally secreted by the adrenal gland in large samples of healthy and/or ill subjects (9, 16, 23, 29, 39, 41, 43). This is the reason that we could confirm, in healthy children and adolescents, stable-isotope infusion results (hitherto obtained mostly in small groups of normal and obese adults) that suggest that daily cortisol production rates vary considerably between individuals (10, 44, 45). Vierhapper et al. (45), for example, found daily cortisol production rates ranging between 1,680 and 7,440 μg · m⁻² · day⁻¹ in 7 healthy women. This range corresponds closely with the variation range that we observed (Fig. 2). In line with a commonly large interindividual variability are other results by stable-isotope dilution methodology, demonstrating that patients with proven Cushing’s syndrome can have normal and patients without clinical and biochemical symptoms can have elevated cortisol productions (36). The large interindividual variation in cortisol status parameters can be explained by genetic (8, 11, 20) and metabolic factors. Shifts in glucocorticoid metabolism are frequently responsible for marked changes in cortisol secretion in various illnesses. For example, elevated α-THF and normal THF excretion rates in patients with hyperthyroidism indicate an increased 5α-reductase activity and thus a reduction in cortisol half-life (16). This stimulated cortisol degradation explains why these patients frequently show an elevated cortisol secretion, necessary to maintain an appropriate bioactive free cortisol level in the circulation. A similar mechanism operates in patients with polycystic ovary syndrome (43).

Earliest estimates of cortisol production rates in normal children and adolescents using isotope dilution with intrave-
Increased cortisol production (mg·m⁻²·day⁻¹) in boys and girls was determined. In this (22) and further studies (5, 10), cortisol production was not found to vary with sex or pubertal stage, probably because of the small numbers of studies (5, 10). Cortisol production was not found to vary with sex or pubertal stage, probably because of the small numbers of studies (5, 10). In a further investigation (45) using stable-isotope dilution with deuterium-labeled cortisol and analysis by GC-MS (11.5 ± 2.2 vs. 5.3 ± 1.9 mg·m⁻²·day⁻¹ in men and women, respectively). However, concerning the dynamic course of cortisol secretion throughout childhood and adolescence, our study is the first report on the point of time, i.e., the age of 11–12 yr, when this divergence in cortisol secretion begins. Earlier investigations on 24-h urinary steroid excretions in children (2, 15) did not report corresponding dynamic variations, probably due to inhomogeneous study population (hospitalized and nonhospitalized children; partly small numbers in certain age groups) and the fact that only selected glucocorticoid metabolites were evaluated.

Several studies in adults have tried to relate the observed sexual dimorphism to a change in 11β-HSD-dependent cortisol metabolism (30, 42, 46). However, the strictly parallel behavior of 11β-HSD that we observed in both sexes does not allow any plausible explanation for the sexual dimorphism in cortisol secretion in adolescence. Therefore, our results do not support concepts explaining the sexual dimorphism in human cortisol metabolism on the basis of sex-specific regulation of 11β-HSD. Our findings are consistent with previous observations of cortisol metabolite excretion in young adults (12) showing that differences in cortisol metabolite excretion between men and women could not be attributed to alterations in 11β-HSD.

Concerning further cortisol metabolizing enzymatic systems, studies in adults have shown a predominance of 5α-reduced cortisol metabolites over 5β-reduced metabolites in males (12, 30, 42). Our data showed (Fig. 2B) that net activity of 5α/5β-reductases did not differ between boys and girls below the age of 11–12 yr. Thereafter, it became different between sexes with a higher ratio of 5α- to 5β-metabolites in males, thus confirming the above-mentioned observations in adults. Consequently, our findings corroborate the hypothesis that sexual dimorphism in cortisol metabolite excretion is attributable to less 5α-reductase activity in women, which means that cortisol is cleared less rapidly from plasma in women than in men (12). The fact that we observed the start of divergence in net activity of 5α-reductases around the beginning of puberty suggests an influence of gonadal steroids. In an earlier study, a higher increase in 5α-metabolites of testosterone compared with 5β-metabolites was observed after administration of human chorionic gonadotropin in humans (25), indicating that androgens might increase 5α-reductase activity. However, data on the regulation of 5α/5β-reductases by sex steroids are scarce, frequently inconsistent, and mostly originating from animal experiments (12).

In summary, we have measured urinary markers of cortisol secretion and metabolism in children and adolescents by use of GC-MS. We found that overall cortisol secretion varies considerably with age and sex despite adjustment for BSA. Decreases of BSA-corrected C21 excretion rates in prepubertal children and diverging increases in adolescent males and females suggest that development- and sex-dependent changes in steroid profiles by high-resolution GC (30). The authors found higher total cortisol metabolites in men than in women (mg·m⁻²·day⁻¹, mean ± SD: men: 4.2 ± 1.4; women: 2.9 ± 1.0). These values were similar to those found in our adolescents 17–18 yr of age. Similar sex differences in urinary excretion rates of cortisol metabolites measured by GC were documented in another study in adults (38) and in a further investigation (45) using stable-isotope dilution with deuterium-labeled cortisol and analysis by GC-MS (11.5 ± 2.2 vs. 5.3 ± 1.9 mg·m⁻²·day⁻¹ in men and women, respectively). However, concerning the dynamic course of cortisol secretion throughout childhood and adolescence, our study is the first report on the point of time, i.e., the age of 11–12 yr, when this divergence in cortisol secretion begins. Earlier investigations on 24-h urinary steroid excretions in children (2, 15) did not report corresponding dynamic variations, probably due to inhomogeneous study population (hospitalized and nonhospitalized children; partly small numbers in certain age groups) and the fact that only selected glucocorticoid metabolites were evaluated.

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cortisol secretion exist during normal childhood and adolescence. Our results corroborate the hypothesis that the sexual dimorphism of cortisol secretion reported for adults develops during puberty. Changes in steroid-metabolizing enzymes appear to be at least partly responsible. The findings point to a varying metabolic need for cortisol during growth and may bear importance for glucocorticoid replacement therapy.

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REFERENCES