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# Cortisol Metabolism in Healthy Young Adults: Sexual Dimorphism in Activities of A-Ring Reductases, but not 11β-Hydroxysteroid Dehydrogenases*

MARTIJN J. J. FINKEN, ROBERT C. ANDREWS, RUTH ANDREW, AND BRIAN R. WALKER

*University of Edinburgh, Endocrinology Unit, Department of Medical Sciences, Western General Hospital, Edinburgh, United Kingdom EH4 2XU*

**ABSTRACT**

Cortisol is metabolized irreversibly by A-ring reductases (5α- and 5β-reductases) and reversibly (to cortisone) by 11β-hydroxysteroid dehydrogenases (11βHSDs). In rats, estradiol down-regulates 11βHSD1 expression. In humans, ratios of urinary cortisol/cortisone metabolites differ in men and women. In this study, urinary cortisol metabolites and hepatic 11βHSD1 activity were measured in healthy young men and women at different phases of the menstrual cycle.

Ten men and 10 women with regular menstrual cycles collected a 24-h urine sample, took 250 μg oral dexamethasone at 2300 h, took 25 mg oral cortisone at 0900 h (after fasting), and had blood sampled for plasma cortisol estimation over the subsequent 150 min. Women repeated the tests in random order in menstrual, follicular, and luteal phases.

Women excreted disproportionately less A-ring-reduced metabolites of cortisol [median 5α-tetrahydrocortisol, 1811 (interquartile range, 1391–2300) μg/day in menstrual phase *vs.* 2723 (interquartile range, 2454–3154) in men ($P = 0.01$); 5β-tetrahydrocortisol, 1600 (interquartile range, 1419–1968) *vs.* 2197 (interquartile range, 1748–2995; $P = 0.03$)] but similar amounts of cortisol, cortisone, and tetrahydrocortisone. Analogous differences were observed in urinary excretion of androgen metabolites. Conversion of cortisone to cortisol on hepatic first pass metabolism was not different (peak plasma cortisol, 733 ± 60 nmol/L in women *vs.* 684 ± 53 nmol/L in men; mean ± SEM; $P = 0.55$). There were no differences in cortisol or androgen metabolism between phases of the menstrual cycle.

We conclude that sexual dimorphism in cortisol metabolite excretion is attributable to less A-ring reduction of cortisol in women, rather than less reactivation of cortisone to cortisol by 11βHSD1. This difference is not influenced acutely by gonadal steroids. 11βHSD1 has been suggested to modulate insulin sensitivity and body fat distribution, but caution must be exercised in extrapolating inferences about its regulation from rodents to man. A-Ring reductases may have an equally important influence on metabolic clearance of cortisol and intracellular cortisol concentrations. (*J Clin Endocrinol Metab* **84:** 3316–3321, 1999)

CORTISOL IS metabolized by several enzymes (Fig. 1), including irreversible inactivation by A-ring reductases (5α- and 5β-reductases) and reversible interconversion to inactive cortisone. Interconversion with cortisone is catalyzed by 11β-hydroxysteroid dehydrogenases (11βHSDs), which are now recognized to play a crucial role in modulating activation of corticosteroid receptors. 11βHSD type 2 (1, 2) inactivates cortisol in the distal nephron, thereby protecting mineralocorticoid receptors from inappropriate activation by cortisol. Congenital or acquired defects in 11βHSD2 result in cortisol-dependent mineralocorticoid excess (3–5). More recently, the role of 11βHSD type 1 (6) has been defined. This enzyme reactivates cortisone in many sites, including liver and adipose tissue (7–9), where it appears to maintain adequate exposure of glucocorticoid receptors to cortisol (10–12). Defects in 11βHSD1 result in enhanced sensitivity to insulin. Increased activity of 11βHSD1 has been postulated to be important in insulin resistance syndromes, particularly obesity (9, 13, 14).

A number of studies in rodents, many of which preceded the cloning of distinct 11βHSD1 and 11βHSD2 isozymes, have examined the regulation of these enzymes. In brief, 11βHSD2 is constitutive and appears to present an effective barrier to glucocorticoid access to mineralocorticoid receptors under all conditions. By contrast, 11βHSD1 is regulated by glucocorticoids (15), thyroid hormones (16), insulin (15), GH (17), cytokines (18), and gonadal steroids (17, 19–21). Regulation of 11βHSD1 by gonadal steroids is of particular interest, because sex-specific differences in enzyme activity could contribute to differences in body fat distribution and susceptibility to cardiovascular risk factors associated with insulin resistance.

In rats, 11βHSD1 expression and activity in liver are markedly lower in females than in males (21). Estradiol administration to gonadectomized rats potently represses 11βHSD1 expression, an effect that depends at least in part on changes in the pattern of GH secretion (17). Evidence of whether estrogen regulates 11βHSD1 in humans is surprisingly limited. In premenopausal healthy women, the ratio of urinary metabolites of cortisol to cortisone has been reported to be lower than that in men (22), but the characteristics of participants in that study were not described in detail. The same trend was observed in hypopituitary patients (23), but clearly there are potential confounding effects of hormonal

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Address all correspondence and requests for reprints to: Dr. Brian R. Walker, University of Edinburgh, Endocrinology Unit, Department of Medical Sciences, Western General Hospital, Edinburgh, United Kingdom EH4 2XU. E-mail: b.walker@ed.ac.uk.

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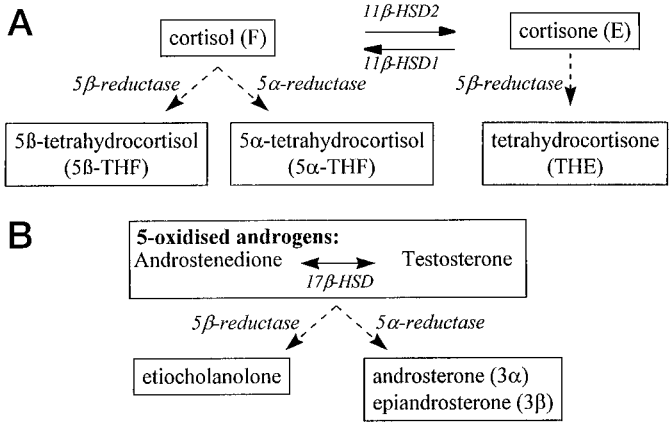


FIG. 1. Principal metabolites of cortisol (A) and androgens (B) measured in urine by gas chromatography and mass spectrometry. *Dotted arrows* indicate that more than one step is involved.

replacement therapies in this group. In healthy postmenopausal women, the ratio of cortisol/cortisone metabolites was higher than that in men and was not influenced by estrogen replacement therapy (14).

In this study, we sought to clarify whether sex-specific difference in cortisol metabolism are observed in healthy young adults and to establish whether changes in urinary cortisol/cortisone metabolites could be attributed to differences in hepatic conversion of cortisone to cortisol by 11βHSD1. In addition, we sought differences in these indexes of cortisol metabolism in different phases of the menstrual cycle.

## Experimental Subjects

Lothian Research ethics committee approval and written informed consent were obtained. All participants were white Caucasians. Ten healthy men and 10 healthy women with regular endogenous menstrual cycles (between 24–34 days) were recruited by advertisement. Their characteristics are shown in Table 1. Groups were matched for age and body mass index. Inclusion criteria were: age, 20–45 yr; blood pressure, less than 160/90 mm Hg; no regular medication; no use of glucocorticoid therapy by any route during the previous 3 months; no psychiatric illness in the previous 3 months; and no abnormality of renal, thyroid, or liver function on biochemical screening.

## Materials and Methods

### *Clinical protocol*

Men were studied on one occasion. Women were studied on three occasions, in random order, during menstrual (2–5 days after starting menstruation), follicular (19–16 days before the next expected menstruation), or luteal (9–5 days before next menstruation) phases. All studies were completed in the winter months (December to March), and men and women were studied in parallel to avoid confounding effects of seasonal changes in steroid metabolite excretion (24).

On each occasion, subjects collected a 24-h urine sample, took 250 μg oral dexamethasone at 2300 h, and attended next day at 0830 h after an overnight fast. A venous cannula was inserted, and blood was withdrawn after 25 min for cortisol and, in women, estradiol and progesterone determinations. After 30 min, 25 mg oral cortisone acetate was administered, and blood was sampled during the next 150 min for plasma cortisol determination. The dose of dexamethasone was selected to lower baseline plasma cortisol so that a rise could be readily detected after cortisone administration without giving so much that dexamethasone metabolites might interfere with cortisone metabolism (25).

### *Laboratory measurements*

Cortisol and its metabolites in urine were measured by gas chromatography and electron impact mass spectrometry after Sep-Pak $C_{18}$ extraction, hydrolysis with β-glucuronidase, and formation of methoximetrimethylsilyl derivatives as previously described (26). Epi-cortisol and epi-tetrahydrocortisol were used as internal standards, which were added to samples before extraction. Peaks of interest were quantified by the ratio of (area under the peak)/(area under neighboring internal standard peak), rather than the ratio of peak height against a line extrapolated from bracketed internal standards as used by many other groups. Ratios were compared against standard curves for each steroid included in every assay batch. The average intraassay precision for all steroids measured was less than 20% (n = 16 assays). In each assay batch, water samples were included containing standard steroids and average accuracy for all steroids varied from −4.4% to +5.5% (n = 16). Principal urinary androgen metabolites were measured using the same method, except that 5α-androstan-3α,17α-diol was used as an internal standard. Pathways of cortisol and androgen metabolism leading to these metabolites are illustrated in Fig. 1. The ratio between 5β-reduced and 5α-reduced metabolites of cortisol and androgens was closely correlated ($r = 0.80$; $P < 0.001$).

Cortisol, estradiol, and progesterone were measured in plasma by commercial RIAs.

**TABLE 1.** Characteristics of participants

| | Males (n = 10) | Females (n = 10) | *P* value (by Student's *t* test) |
|---|---|---|---|
| Age (yr) | 27.8 ± 1.5 (22–35) | 28.6 ± 1.7 (20–40) | 0.61 |
| Ht (m) | 1.80 ± 0.02 (1.73–1.91) | 1.63 ± 0.02 (1.55–1.71) | <0.0001 |
| Wt (kg) | 77.4 ± 3.7 (60.3–96.7) | 65.9 ± 3.8 (47.8–94.5) | 0.04 |
| Body mass index (kg/m$^2$) | 23.9 ± 1.0 (18.6–27.3) | 24.9 ± 1.6 (18.4–34.3) | 0.63 |
| Waist circumference (cm) | 87 ± 2 (71–99) | 76 ± 4 (61–97) | 0.02 |
| Hip circumference (cm) | 100 ± 2 (91–113) | 97 ± 3 (80–110) | 0.34 |
| Waist/hip ratio | 0.87 ± 0.01 (0.78–0.91) | 0.78 ± 0.02 (0.66–0.92) | 0.002 |

Data are the mean ± SEM (range). Values for females were recorded during the menstrual phase.

### *Statistics*

Results are presented as the mean ± SEM for normally distributed variables; groups were compared using unpaired Student's *t* tests or repeated measures ANOVA. Many of the urinary cortisol metabolites had skewed distributions, necessitating nonparametric analyses; these are presented as median (interquartile range). Data from men and women in the menstrual phase were compared by Mann-Whitney U tests; data from different phases of the menstrual cycle were compared by Friedman ANOVA. Data for men and women in luteal and follicular phases were not compared to avoid multiple statistical testing.

## Results

### *Comparison between men and women*

Men and women were well matched for age and body mass index, but men were taller and heavier, with android distribution of body fat (Table 1). Absolute excretion rates of urinary cortisol metabolites tended to be higher in men (Table 2). This was attributable principally to lower excretion of 5α-reduced and 5β-reduced metabolites of cortisol in women. Excretions of cortisol, cortisone, and tetrahydrocortisone were not different. Excretion of androgen metabolites also tended to be higher in men, accounted for by a trend toward lower excretion of 5α-reduced metabolites in women.

Table 2 shows ratios of metabolites reflecting activities of

**TABLE 2.** Twenty-four-hour urinary cortisol and androgen metabolite excretion

| | Males | Females | | | *P* males *vs.* menstrual females (Mann-Whitney U test) | *P* between menstrual phases (Friedman ANOVA) |
|---|---|---|---|---|---|---|
| | | Menstrual | Follicular | Luteal | | |
| Cortisol | 119 [85–139)] | 150 [84–204] | 163 [115–178] | 117 [71–256] | 0.50 | 0.41 |
| Cortisone | 135 [115–150] | 123 [85–145] | 116 [111–146] | 133 [122–195] | 0.36 | 0.90 |
| 5α-THF | 2723 [2454–3154] | 1811 [1391–2300] | 1950 [1698–2324] | 1943 [1765–2245] | 0.01 | 0.27 |
| 5β-THF | 2197 [1748–2995] | 1600 [1419–1968] | 1770 [1412–1965] | 2007 [1434–2259] | 0.03 | 0.74 |
| THE | 2393 [2082–2895] | 1927 [1678–2860] | 2238 [1789–2735] | 1999 [1525–2515] | 0.55 | 0.67 |
| Sum of cortisol metabolites[a] | 11879 [9963–20644] | 10140 [7360–11430] | 10321 [8811–14718] | 12568 [7068–19285] | 0.10 | 0.41 |
| Cortisol/cortisone | 0.94 [0.73–1.04] | 1.27 [0.94–1.70] | 1.16 [0.91–1.74] | 0.92 [0.73–1.37] | 0.06 | 0.49 |
| 5β/5α-THF | 0.76 [0.66–1.16] | 0.92 [0.69–1.30] | 0.86 [0.70–1.00] | 0.98 [0.79–1.07] | 0.45 | 0.50 |
| THFs/THE | 1.99 [1.70–2.62] | 1.90 [1.38–2.45] | 1.78 [1.34–2.01] | 2.06 [1.39–2.63] | 0.50 | 0.67 |
| 5α-THF/cortisol | 23.4 [20.5–27.7] | 18.8 [5.9–24.1] | 12.2 [10.4–20.2] | 17.1 [8.8–26.7] | 0.07 | 0.74 |
| 5β-THF/cortisol | 16.0 [14.6–30.4] | 12.6 [9.0–16.8] | 11.7 [7.4–15.3] | 14.2 [9.2–18.9] | 0.03 | 0.50 |
| THE/cortisone | 18.3 [14.5–22.8] | 19.4 [15.1–20.9] | 18.5 [15.8–19.9] | 13.5 [12.5–18.1] | 0.55 | 0.27 |
| 5-Oxidized androgens (androstenedione + testosterone) | 186 [106–209] | 254 [145–316] | 170 [130–245] | 255 [101–432] | 0.13 | 0.12 |
| 5α-Reduced androgens (androsterone + epiandrosterone) | 3775 [3213–4951] | 3294 [2356–3962] | 3099 [1819–4330] | 3069 [2277–3709] | 0.15 | 0.50 |
| 5β-Reduced androgens (etiocholanolone) | 2191 [1076–2566] | 1881 [1384–2492] | 1628 [1234–2571] | 2122 [1209–2651] | 0.88 | 0.74 |
| Sum of androgen metabolites[b] | 6267 [4395–7435] | 5249 [4484–6916] | 4808 [3080–7146] | 5816 [3632–6835] | 0.60 | 0.74 |
| 5β/5α-Reduced androgens | 0.53 [0.35–0.68] | 0.68 [0.55–0.98] | 0.59 [0.47–0.85] | 0.64 [0.56–0.77] | 0.11 | 0.27 |
| 5α-Reduced/5-oxidized androgens | 25.9 [20.1–32.3] | 14.2 [11.2–16.6] | 19.0 [14.9–24.3] | 15.6 [9.4–27.3] | 0.02 | 0.08 |
| 5β-Reduced/5-oxidized androgens | 10.8 [9.5–17.5] | 9.0 [7.8–11.0] | 9.7 [7.0–14.6] | 8.7 [5.8–20.4] | 0.23 | 0.50 |

Data are medians [inter-quartile range], expressed as micrograms per 24 h.

[a] Sum of urinary cortisol metabolites = 5α-THF + 5β-THF + THE + cortols + cortolones.

[b] Sum of urinary androgen metabolites = dehydroepiandrosterone + androstenedione + testosterone + androsterone + epiandrosterone + etiocholanolone.

**TABLE 3.** Plasma cortisol

| | Males | Females | | | *P* males *vs.* menstrual females (Student's *t* test) | *P* between menstrual phases (repeated measures ANOVA) |
|---|---|---|---|---|---|---|
| | | Menstrual | Follicular | Luteal | | |
| Fasting baseline plasma cortisol (nmol/L)[a,b] | 323 ± 74 | 268 ± 37 | 272 ± 43 | 270 ± 54 | 0.52 | 0.99 |
| Peak plasma cortisol (nmol/L)[a] | 684 ± 53 | 733 ± 60 | 800 ± 62 | 792 ± 58 | 0.55 | 0.49 |
| Time to peak (min) | 75 ± 8 | 111 ± 9 | 99 ± 13 | 86 ± 7 | 0.01 | 0.27 |
| Area under curve[c] | 221 ± 162 | 343 ± 139 | 305 ± 157 | 352 ± 156 | 0.10 | 0.37 |

Data are the mean ± SEM
[a] Subjects received 250 μg oral dexamethasone at 2300 h the previous evening and 25 mg oral cortisone acetate on the morning of the test.
[b] Baseline plasma cortisol was calculated as the arithmetic mean of measurements at 5 and 0 minutes before cortisone administration.
[c] Calculated by the trapezoidal rule as the average increment above baseline plasma cortisol from 15–150 min.

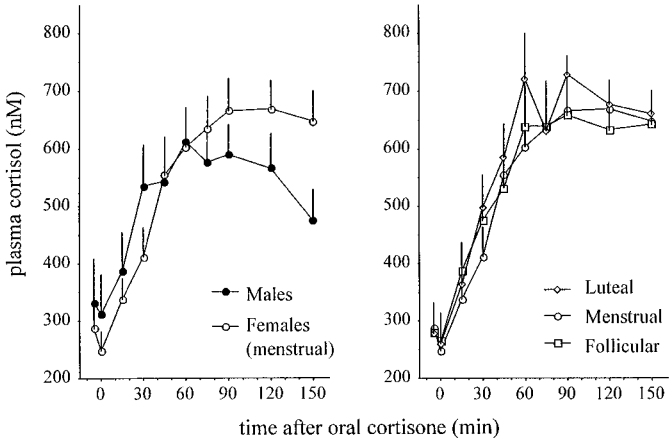


FIG. 2. Hepatic 11βHSD1 activity. Plasma cortisol was measured after overnight dexamethasone suppression (250 μg, orally, at 2300 h) and oral administration of 25 mg cortisone acetate at 0900 h. Data are the mean ± SEM for males (n = 10), and females (n = 10) in menstrual, follicular, and luteal phases of the endogenous menstrual cycle. Comparisons are given in Table 3.

different enzymes. 11βHSD activities are conventionally inferred from relative excretion of metabolites of cortisol and cortisone [cortisol/cortisone ratio reflecting principally renal 11βHSD2 activity (26, 27) and ratios of tetrahydrocortisols/tetrahydrocortisone reflecting the balance between 11βHSD1 and 11βHSD2 activities]; these ratios did not differ between men and women, although there was a trend for a lower cortisol/cortisone ratio in men. A-Ring 5α- and 5β-reductase activities can be inferred relative to each other by the ratio of 5β-tetrahydrocortisol/5α-tetrahydrocortisol and by 5β-/5α-reduced androgen metabolites, which did not differ between men and women. Provided that urinary cortisol and cortisone are not different (28), 5β-reductase activity can also be inferred from the ratios of 5β-tetrahydrocortisol/cortisol, tetrahydrocortisone/cortisone (29), and 5β-reduced/5-oxidized androgen metabolites; in women this activity was less for cortisol but not for cortisone or androgens. 5α-Reductase activity can be inferred from the ratio of 5α-tetrahydrocortisol/cortisol and 5α-reduced/5-oxidized androgens, which was lower in women.

Plasma cortisol after overnight dexamethasone suppression was not different between men and women (Table 3). The rise in plasma cortisol after oral cortisone administration is shown in Fig. 2. The rate of rise, maximum plasma cortisol, and area under the curves did not differ between men and women. However, the peak cortisol occurred earlier in men than women, apparently because cortisol was cleared from plasma more quickly in men.

*Comparison between phases of menstrual cycle in women*

Accuracy of timing of phases of the menstrual cycle was confirmed by measurements of plasma estradiol and progesterone (data not shown). For all women, estradiol was higher in the follicular than in the menstrual phase, and progesterone was only detectable in the luteal phase.

There were no differences in urinary cortisol or androgen metabolite excretion (Table 2) or conversion of oral cortisone to plasma cortisol (Fig. 2) in different phases of the menstrual cycle.

## Discussion

This study is consistent with previous observations that urinary excretion of the A-ring reduced metabolites of cortisol is lower in premenopausal women than in men (22), and that this is out of proportion to the excretion of other metabolites of cortisol in women. The disproportionality of these differences excludes technical confounders, such as incomplete urine collection. The absolute excretion rates for some cortisol metabolites, particularly 5α-tetrahydrocortisol, are somewhat higher in this group than those reported by others in healthy volunteers (3, 27, 30, 31). This may reflect differences between groups of subjects or methodological differences, for example in the choice of internal standards. In addition, this study confirms previous reports that urinary androgen excretion is only marginally higher in men than in women (30), reflecting the fact that most urinary androgen metabolites are derived from adrenal androgens.

Previously, differences in cortisol metabolite excretion between men and women have been attributed to alterations in 11β-hydroxysteroid dehydrogenases. Whether this reflects enhanced inactivation of cortisol to cortisone by 11βHSD2 or impaired reactivation of cortisone to cortisol by 11βHSD1 in women had not been tested. However, it was assumed that lesser 11βHSD1 activity in women was responsible on the basis of studies in rats suggesting that only 11βHSD1 is regulated by other hormones, including down-regulation by estrogen (17, 20, 21).

In the present study, ratios of urinary cortisol/cortisone (26, 27) suggest that conversion of cortisol to cortisone by renal 11βHSD2 activity is lower, rather than higher, in women than men. Therefore, differences in 11βHSD2 could not explain lower ratios of cortisol/cortisone metabolites; this is consistent with the hypothesis that these differences reflect sexual dimorphism in 11βHSD1 activity. However, we also made a more specific assessment of hepatic 11βHSD1 activity by measuring the conversion of cortisone adminis-

tered orally into cortisol in the peripheral circulation. The rate of appearance of cortisol is lower when 11βHSD1 is inhibited, *e.g.* by carbenoxolone (32), but is not influenced by 11βHSD2 activity (33). The lack of sexual dimorphism in the rate of appearance of cortisol in the present study suggests that 11βHSD1 activity is not different in men and women. Moreover, in marked contrast with dramatic changes over a similar time course in rats (17, 21), changes in estrogen levels in women during the menstrual cycle were not associated with alterations in any index of 11βHSD1 activity.

The present data suggest an alternative explanation for the disproportionately low excretion of tetrahydrocortisols in women. As previously described in postmenopausal (14) and hypopituitary (23) women, the excretion of cortisol and cortisone is similar or even increased in women compared with that in men; the differences are observed only in the A-ring reduced metabolites. Thus, the ratios of urinary metabolites suggest that rates of A-ring reduction of cortisol are lower in women than in men. This is substantiated by examining A-ring reduction of androgen metabolites. Lower A-ring reduction could also explain why cortisol is cleared less rapidly from plasma in women than in men after an oral dose of cortisone. Unlike postmenopausal women (14), this difference does not affect the 5β-reduction of cortisone and could therefore account both for the lower ratio of tetrahydrocortisols/tetrahydrocortisone observed in young women (22), but not postmenopausal women (14), and for the trend toward higher urinary cortisol/cortisone in women in this study.

It is not clear why A-ring reduction of cortisol should differ between men and women. The principal enzymes involved are 5β-reductase (34) and 5α-reductase types 1 and 2 (35). 5β-Reductase is expressed in liver and is involved in the metabolism of bile acids. Although there is some evidence that affinities for cortisol and cortisone/androgens can be separated by semipurification and subcellular fractionation *in vitro* (36, 37), there is no evidence that there is more than one 5β-reductase active *in vivo* in man (38). 5β-Reductase activity is lower in female than in male rat livers (39), but it is up-regulated by estrogen (40). 5α-Reductase type 1, the principal isozyme in human liver and fat (41), is usually thought to be constitutive and not regulated hormonally (42, 43), but there is some evidence that this isozyme is down-regulated by androgens (44, 45) more so than by estrogen (46), so that its activity is higher in female liver (47) and adrenal (48). 5α-Reductase type 2 is expressed mainly in the prostate and is up-regulated by androgens (35). These observations from animals predict that activities of 5β-reductase may be lower, and hepatic 5α-reductase may be higher, rather than decreased, in women. Moreover, the lack of acute effect of changes in gonadal steroids on urinary cortisol metabolite excretion in the current study suggests that the explanation for sexual dimorphism in A-ring reductases does not relate to acute gonadal steroid regulation in humans. An alternative explanation relates to the relative mass of tissues expressing A-ring reductases in men and women. It is not clear whether the prostate contributes substantially to A-ring reduction of cortisol, but, interestingly, finasteride, a relatively specific inhibitor of 5α-reductase type 2, does alter the relative excretion of cortisol metabolites in men (49). The quantity and distribution of body fat may also be important, as 5α-reductase type 1 is expressed in adipocytes and is more active in peripheral sc than central visceral fat in culture (41), although the contribution of adipose 5α-reductase activity to cortisol clearance may be small. Previous studies suggest that increased visceral fat in men may be associated with greater 5α-reductase activity (14). However, the current study is too small, and subjects within it too similar, to explore whether differences in body fat distribution might explain sexual dimorphism in cortisol metabolite excretion.

We have previously reported cortisol metabolite profiles in older subjects, in whom we found relationships between greater central/visceral obesity and enhanced activity of 5α-reductase, but not 5β-reductase (14). The pattern of differences between older men and women contrasts with the results in young subjects studied here and previously (22). Older women had higher 5α-reductase, but not 5β-reductase, activity and higher ratios of metabolites of cortisol to those of cortisone in urine compared with men. Comparing values in Table 2 with values in the older population measured by the same method (14), it appears that there is little difference between postmenopausal and premenopausal women, but that the major differences are between younger and older men. Thus, aging in men may be associated with falling activities of 5α-reductase and 11βHSD1.

Whatever the reason for sexual dimorphism of A-ring reduction of cortisol and its change with age, this observation has important implications for physiological glucocorticoid action and for interpretation of apparent pathological disruption of cortisol metabolism. Lesser A-ring reduction of cortisol in women predicts a lower MCR of cortisol, which, in turn, predicts greater feedback suppression of the hypothalamic-pituitary-adrenal axis. If A-ring reduction is increased, as in obesity (14) and probably also in polycystic ovarian syndrome (50, 51), increased ACTH drive to the adrenal cortex may contribute to excessive androgen secretion. Conversely, a decline in A-ring reduction, as may occur with normal aging in men, may contribute to the fall in adrenal androgen excretion with age (52). In addition, the extent of A-ring reduction in specific organs, including adipose tissue and liver, will influence local concentrations of cortisol independently of circulating glucocorticoid concentrations. It remains to be established whether this has a potent influence on corticosteroid receptor activation, but it may contribute to the sexual dimorphism of body fat distribution.

Arguably the most important implications of this study are that care should be exercised in extrapolating to humans from studies of regulation of 11βHSD1 in rodents, and that ratios of tetrahydrometabolites of cortisol and cortisone should be interpreted cautiously if they are not accompanied by measurements of cortisol and cortisone (26, 27). The latter has not been measured in some other studies comparing men and women (22) or in studies of polycystic ovarian syndrome (50, 51) or essential hypertension (53, 54). Arguably for this reason the inferences concerning 11βHSD activities may have been overemphasized, and the potential importance of disturbances in A-ring reduction of cortisol may have been overlooked.

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