Production Rates of Testosterone and of Dihydrotestosterone in Female Pattern Hair Loss

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Production rates of testosterone (T) and of dihydrotestosterone (DHT) were determined in young women (n = 8, age, 23 to 40 years) with female-pattern hair loss using the stable isotope dilution technique and mass spectrometry. 1α,2α-D-testosterone and 2,3,4-^{13}C-dihydro-testosterone were infused for 10 hours at a dose of 2 μg/h each and blood samples were obtained at 20-minute intervals during the last 4 hours of the observation period. In the presence of normal metabolic clearance rates (MCRs), production rates of T were increased (9.4 ± 5.0 μg/h; normal, 4.3 ± 1.9 μg/h, *P* < .05). MCRs of DHT (8.0 ± 3.4 L/h; normal, 25.9 ± 12.3 L/h, *P* < .002) were subnormal in all women and the production rates of DHT were within or below the normal range (mean, 1.6 ± 0.6 μg/h; normal, 2.9 ± 1.1 μg/h, *P* < .02). Unlike men with male-pattern baldness, women with female-pattern baldness are characterized by increased production rates of T, but not of DHT. These results are compatible with the idea that 5α-reductase inhibition is of no therapeutical value in female-pattern baldness.

ALTHOUGH there appears to be a genetic component to male-pattern baldness and to female-pattern baldness, the 2 disorders occur in different families and are thought to have different etiologies.[1] In the majority of men with male-pattern baldness, endogenous production of dihydrotestosterone (DHT) is increased in the presence of normal production rates of testosterone (T).[2] Whether a similar increase in DHT production rates is present in women with early-onset female-pattern hair loss is unknown. Since this would provide a rationale for therapeutical 5α-reductase inhibition[3,4] in these patients, we have studied endogenous production rates of T and of DHT in a group of young women with early-onset female-pattern baldness using the stable isotope dilution technique and mass spectrometry.[2,5]

MATERIALS AND METHODS

Experimental Protocol

Eight otherwise healthy, non-obese (body mass index [BMI], 23.3 ± 3.3 kg/m^2), nonhirsute women (aged 27 to 40 years) with early-onset female-pattern baldness who had been carefully informed about the aims and the possible risks of the investigation gave their consent to participate. They were off any medication that could have interfered with the study results. None of these patients suffered from hirsutism and/or acne and all but one had regular menses. The investigation was not standardized to any phase of the patient's menstrual cycle. Their mean BMI was 23.3 ± 3.3 kg/m^2 (range, 19.1 to 26.2 kg/m^2). Serum concentrations of sex hormone–binding globulin (SHBG) were in the normal range (56.5 ± 22.5 nmol/L; normal, 30 to 95 nmol/L).

On the day of the experiments an indwelling catheter was inserted at 8 AM into an antecubital vein. Subsequently women received an intravenous, continuous (Infusomat, Braun-Melsungen, Germany; 40 mL/h, t = 10 hours) infusion of 500 mL 0.9% saline containing 25 μg 1α,2α-D-testosterone (CIL Isotopes, Andover, MA), 25 μg 2,3,4-^{13}C-dihydro-testosterone, and 2 mL of the individual's own blood. In order to correct for losses by adsorption, samples of the infusate were obtained at the beginning and at the end of each infusion from the end of the infusion line. After an equilibration period of 6 hours (at 2 PM), a second indwelling catheter was inserted into the contralateral arm and blood samples (5 mL) were obtained at 20-minute intervals for 4 hours (ie, until 6 PM). Blood samples were subsequently pooled for the whole period of 4 hours. These pooled samples were used for analysis by gas chromatography–mass spectrometry (GC-MS).

Analogous investigations were performed in 7 healthy, non-obese women (aged 22 to 38 years) as reported previously.[2]

Materials

All organic solvents were of high-performance liquid chromatography (HPLC) grade and purchased from Baker Chemicals, Phillipsburg, NJ. Nonactive T (4-androsten-17ß-ol-3-one) and DHT (4-androstan-17ß-ol-3-one) were obtained from Steraloids Inc. (Wilton, NH). Radioactive [^{3}H]1,2,6,7-testosterone (specific activity, 95 Ci/mmol) and radioactive [^{3}H]1,2,4,5,6,7-dihydrotestosterone (specific activity, 110 Ci/mmol) were purchased from New England Nuclear, Boston, MA. Stable-labeled 1,2-d-testosterone (isotopic enrichment: 99.0%) was purchased from CIL. Stable-labeled 2,3,4-^{13}C-dihydro-testosterone (isotopic enrichment, 99.0%)[5,6] was obtained from Steroko Chemicals, Vienna, Austria.

Sample Preparation and Analysis by GC-MS

The sample preparation for the GC-MS analysis and of dihydrotestosterone and of testosterone has been described previously.[2,5]

Calculation of DHT and T Production Rates

Production rates (PR) of DHT and of T were calculated from the product of the known infusion rate (Rt) and the ratio of tracer infusate enrichment (Et) to tracer dilution in the plasma (Es): (PR = Rt × [Et/Es − 1]).[8] Metabolic clearance rates (MCRs) were calculated by dividing the respective production rates by the plasma concentration of native T or DHT, respectively.

Statistics

Data in the text and in the tables are given as means ± SD. Student's *t* test (2-tailed) for unmatched pairs was used for statistical evaluation.

RESULTS

As shown in Table 1 the plasma concentrations of both T (50.2 ± 3.6 ng/dL) and dihydrotestosterone (21.8 ± 5.5 ng/dL), while still within the normal range, were higher than those

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Table 1. Plasma Concentrations, Calculated Metabolic Clearance Rates, and Production Rates of T and of DHT in Eight Women With Female-Pattern Baldness

Patients			T			DHT		
No.	Age (yr)	BMI (kg/m^2)	PC (ng/dL)	MCR (L/h)	PR (μg/h)	PC (ng/dL)	MCR (L/h)	PR (μg/h)
1	33	22.7	52.0	30.9	16.1	29.8	5.5	1.6
2	32	29.7	54.2	28.4	15.4	24.8	8.8	2.2
3	31	22.2	58.3	21.9	12.8	18.1	6.7	1.2
4	36	19.1	39.3	23.2	9.1	20.7	5.0	1.0
5	40	20.7	34.4	22.7	7.8	12.0	13.0	1.6
6	32	23.5	48.7	12.0	6.8	26.8	3.1	0.8
7	27	26.2	84.7	4.9	4.1	19.8	10.3	2.0
8	23	21.9	29.9	9.8	2.9	22.6	11.2	2.5
All patients (mean ± SD)			50.2 ± 3.6	19.5 ± 9.0	9.4 ± 5.0	21.8 ± 5.5	8.0 ± 3.4	1.6 ± 0.6
Healthy women (mean ± SD)			19.3 ± 3.6	21.4 ± 7.8	4.3 ± 1.9	12.1 ± 3.8	25.9 ± 12.3	2.9 ± 1.1
P value (2-tailed)			<.01	—	<.05	<.01	<.002	<.02

Abbreviations: T, testosterone; DHT, dihydrotestosterone; BMI, body mass index; PC, plasma concentration determined by gas chromatography–mass spectometry; MCR, metabolic clearance rate; PR, production rate (2 PM to 6 PM).

estimated in the healthy female controls. In the presence of normal MCRs of T (19.5 ± 9.0 L/h; healthy women, 21.4 ± 7.8 L/h), production rates of T of women with female-pattern baldness were increased (9.4 ± 5.0 μg/h; healthy women, 4.3 ± 1.9 μg/h, $P < .05$). Subnormal MCRs of DHT (8.0 ± 3.4 L/h; healthy women, 25.9 ± 12.3 L/h, $P < .002$) were seen in all women with female-pattern baldness and production rates of DHT were within or below the normal range (mean, 1.6 ± 0.6 μg/h; healthy women, 2.9 ± 1.1 μg/h, $P < .02$).

DISCUSSION

Hair follicles are active sites of the 5α-reduction of T to DHT.[9] The affinity of DHT to the androgen receptor is about 5 times higher than that of T.[10] Increased formation of DHT has been recognized as a causative factor in male-pattern baldness. The enhanced local activity of 5α-reductase in the hair follicles of men with male-pattern baldness,[11] which is reflected by an increased blood production rate of DHT,[2] explains or is at least in keeping with the effectiveness of 5α-reductase inhibition[3,4] in male-pattern baldness.[12,13]

Although female-pattern hair loss has been described in the virtual absence of androgens due to hypopituitarism,[14] there is no doubt that the disorder is commonly seen in women virilized by high androgen concentrations.[15] The psychosocial consequences of alopecia are equally pronounced in both genders.[16,17] Unlike balding men, however, women with female-pattern baldness do not respond favorably to 5α-reductase inhibition: despite the substantial reduction in serum DHT, treatment with the 5α-reductase inhibitor, finasteride, for 1 year was not superior to placebo.[18] Indeed, since the predominantly androgen-dependent nature of these women's baldness has not been ascertained the previously used term "androgenetic alopecia" has been replaced by "female-pattern hair loss" of early or late onset. These apparent differences in the pathogenesis of hair loss between young men and women and the various clinical patterns of baldness in men and women—believed by others to reflect quantitative differences in the levels of 5α-reductase[19]—suggested to us that relationship between the production rates of T and DHT in young, balding women would be different from that in young men with male-pattern hair loss. The results of the present study demonstrate that this is indeed the case. Whereas the majority of balding young men present normal production rates of T but a marked rise in the production rates of DHT and consequently with a shift of the ratio between the production rates of T and DHT towards DHT,[2] the findings in early-onset female-pattern hair loss is quite the opposite. The majority of these women are characterized by subnormal to low-normal production rates of DHT, but an increase in the production rate of T. Thus, the mechanisms leading to male- and female-pattern baldness are not quite as similar as recently suggested.[10]

T and DHT are both biologically active androgens, their biological nonequivalency being due to the more rapid binding of DHT to the androgen receptor.[10] However the local effects of testosterone are equal to those of DHT if concentrations of T are raised to high enough concentrations.[20] An increased production of T is therefore compatible with female-pattern hair loss, even in the absence of enhanced DHT production characteristic for male-pattern hair loss. In our patients with female-pattern hair loss serum concentrations of both DHT and T were higher than in healthy women. It is possible that the combined action of the 2 androgens at the androgen receptor of these patients promotes their hair loss. In addition, it cannot be excluded that the decreased MCR of DHT may, in the presence of normal DHT production rates, contribute to the loss of hair. Furthermore the interindividual variability in the production rates of T among our patients with female-pattern hair loss may indicate etiological differences of this disorder. Finally is remains to be investigated whether our results, obtained in premenopausal women, also apply to women in the postmenopause.

The reason why the increased production of T in these

non-obese women resulted in female-pattern hair loss but not in clinically apparent hirsutism is unclear. Potential explanations include differences in the androgen sensitity of hair follicles in different body areas and/or a different time-pattern in the manifestation of T-dependent hair loss and hirsutism, respectively.

In summary, patients with female-pattern baldness have increased production rates of T but not of DHT. Therefore, pharmacological inhibition of 5α-reductase in this disorder does not hold therapeutical promise.

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