Production Rates of Cortisol in Men With Hypogonadism

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Healthy men have a larger endogenous cortisol production rate (PR) than healthy women. To investigate whether this sex-specific difference is maintained in men with low serum testosterone concentrations the endogenous PRs (2 PM to 6 PM) of testosterone, dihydrotestosterone (DHT), and cortisol were simultaneously determined in 10 hypogonadal men. As expected, hypogonadal men were characterized by subnormal PRs of testosterone (19.6 ± 5.7 μg/h; normal, 180 to 346 μg/h) and of DHT (1.6 ± 1.1 μg/h; normal, 11 to 20 μg/h). In hypogonadal patients with an intact pituitary-adrenal axis (n = 8), plasma concentrations (7.3 ± 1.8 μg/dL), metabolic clearance rates (MCRs) (10.0 ± 4.6 L/h), and endogenous PRs (0.6 ± 0.2 mg/h) of cortisol were comparable to those seen in eugonadal men. Hence, the sex-specific difference in endogenous cortisol PRs does not depend on the prevailing serum concentrations and on the endogenous PRs of testosterone.

URINARY EXCRETION of cortisol[1] and the endogenous production rate (PR) of cortisol[2] are higher in men than in women. This sexual dimorphism in cortisol production has been explained by differences between men and women in the activity of 11β-hydroxysteroid dehydrogenase type I (11β-HSD1), the enzyme responsible for the conversion of cortisone to cortisol.[3,4] While this effect does not appear to be estrogen-dependent,[4] corticotrophin (ACTH)-stimulated secretion of cortisol is enhanced in testosterone-treated women.[5] This direct or indirect effect of male sex hormones on adrenal steroidogenesis could become apparent in men with low testosterone concentrations, in whom one might expect to find lower than normal cortisol PRs. To test this hypothesis we have investigated endogenous PRs of cortisol in a group of hypogonadal man.

MATERIALS AND METHODS

Endogenous PRs of testosterone, dihydrotestosterone (DHT), and of cortisol were determined in 10 hypogonadal men. As shown in Tables 1 and 2, 4 patients suffered from hypergonadotropic hypogonadism. In 4 patients with hypogonadotropic hypogonadism, including 2 individuals with anosmia (Kallmann's syndrome), a pituitary disorder was excluded biochemically (by pituitary stimulation tests) and morphologically (by magnetic resonance tomography [MRT] of the sellar region). Among 2 men with hypogonadotropic hypogonadism due to a pituitary tumor, 1 individual was suffering from panhypopituitarism but was unsubstituted at the time of the investigation. The study was approved by the local ethics committee. On the day of the investigation an indwelling catheter was inserted into an antecubital vein and a constant (40 mL/h) intravenous infusion of 500 mL 0.9% saline containing 2.0 mg 1a,2α-D-cortisol, 250 μg 1a,2α-D-testosterone and 250 μg 2,3,4-^{13}C-DHT was started at 8 AM. At the beginning and at the end of each infusion, a sample of the infusate from the end of the infusion line was obtained to determine losses by adsorption. After an equilibration period of 6 hours (at 2 PM) a second indwelling catheter was inserted into the contralateral arm and blood samples were obtained from 2 PM until 6 PM at 20-minute intervals. These blood samples were pooled and pooled samples were used for analysis.

Materials

All organic solvents were of high-performance liquid chromatography (HPLC) grade and purchased from Baker Chemicals (Phillipsburg, NJ). Nonactive cortisol (11β,17,21-trihydroxy-4-pregnene-3-20-dione) was obtained from Sigma (St Louis, MO), and radioactive [^{3}H]1,2,6,7-cortisol (specific activity, 60 Ci/mmol) and stable-labeled 1a,2a-D-cortisol (isotopic enrichment, 99.0%) were purchased from Amersham (Amersham, UK) and from CIL (Andover, MA), respectively. Nonactive testosterone (4-androsten-17β-ol-3-one) and DHT (4-androstan-17β-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-DHT (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-DHT (isotopic enrichment, 99.0%) was obtained from Steroko Chemicals (Vienna, Austria).

Sample Preparation and Analysis by Gas Chromatography/Mass Spectometry

Plasma samples (5.0 mL) were processed and PRs of cortisol, testosterone, and DHT were calculated as reported previously.[2,6,7] To test for reproducibility, samples of 12 individuals were reanalyzed after a period of 1 to 2 years, resulting in a coefficient of variation of less than 3.0%.

Statistics

Data are given as means ± SD. Student's *t* test (2-tailed) was used for statistical analysis.

RESULTS

As shown in Table 1, the plasma concentrations of testosterone were subnormal in all patients with hypogonadism. In all but 1 patient the metabolic clearance rate (MCR) of testosterone was normal or low and hence the calculated endogenous PR of testosterone was also low. This also applies to one morbidly obese, hypogonadal man (no. 6; body mass index [BMI], 58 kg/m^2) in whom the MRC of testosterone was markedly elevated (136 L/h). In all hypogonadal men plasma concentrations of DHT were borderline low or below normal, as were MCRs and PRs of DHT (Table 1).

Plasma concentrations, MCRs, and PRs of cortisol are summarized in Table 2. The results in the 8 hypogonadal men with an intact pituitary-adrenal axis were comparable to those seen in eugonadal men.[2,8,9] Specifically, PRs of cortisol in hypogon-

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Table 1. Age, Clinical Diagnosis, Body Mass Index, Serum Concentrations Metabolic Clearance Rates, and Production Rates of Testosterone and Dihydrotestosterone in Hypogonadal Men

Patient No.	Age (yr)	Clinical Diagnosis	Underlying Disorder	BMI (kg/m^2)	T (ng/dL)	MCR (T) (L/h)	PR (T) (μg/h)	DHT (ng/dL)	MCR (DHT) (1/h)	PR (DHT) (μg/h)
1	43	Hypergonadotropic	Bilateral orchiectomy	28.4	66.8	31.7	21.2	9.9	14.9	1.5
2	57	Hypergonadotropic	Klinefelter's	21.5	121.1	9.2	11.2	13.8	5.0	0.7
3	38	Hypergonadotropic	Klinefelter's	31.0	56.8	30.0	17.1	6.4	61.9	3.9
4	24	Hypergonadotropic	Idiopathic	23.6	62.3	23.1	14.4	19.2	11.3	2.2
5	25	Hypogonadotropic	Kallmann's	22.6	3.2	10.7	3.4	3.2	26.0	0.8
6	33	Hypogonadotropic	Kallmann's	58.6	47.7	136.4	65.1	n.d.	n.d.	n.d.
7	57	Hypogonadotropic	Hypothalamic	31.2	43.3	29.1	12.2	15.3	17.8	2.7
8	34	Hypogonadotropic	Hypothalamic	18.1	11.6	18.3	20.1	6.1	18.6	1.1
9	54	Hypogonadotropic	Prolactinoma	45.9	87.0	34.5	30.0	7.4	10.9	1.5
10	39	Hypogonadotropic	Craniopharyngeoma	29.6	4.1	18.6	0.8	3.1	8.2	0.3
Eugonadal men (n = 29), range ($\pm$1 SD)[6,7,9]					440-780	28-62	180-346 (19.6 $\pm$ 5.7)			
Eugonadal men (n = 11), range ($\pm$1 SD)[7]								19.4-49.8	34-68	11-20 (1.6 $\pm$ 1.1)

NOTE. Serum concentrations of T and DHT determined my mass spectometry (2-6 PM).
Abbreviations: BMI, body mass index; T, testosterone; MCR, metabolic clearance rate; PR, production rate; DHT, dihydrotestosterone.

dal men were 0.6 $\pm$ 0.2 mg/h (eugonadal men, 0.7 $\pm$ 0.3 mg/h; difference not significant [NS]). After correction for BMI, the PRs of cortisol were 0.3 $\pm$ 0.1 mg/m^2 $\cdot$ h in hypogonadal men and 0.4 $\pm$ 0.1 mg/m^2 $\cdot$ h in eugonadal individuals (NS). A very low serum concentration and PR of cortisol was seen only in the single patient (no. 10) with established panhypopituitarism. Two patients with hypogonotropic hypogonadism but otherwise biochemically and morphologically normal anterior pituitaries (no. 7 and 8) had a marginally below-normal PR of cortisol.

DISCUSSION

By definition, hypogonadal men were characterized by subnormal plasma concentrations of testosterone. MCRs of testosterone were in the normal range and the calculated PRs were therefore subnormal. Only in 1 morbidly obese (BMI, 59 kg/m^2) hypogonadal man was the MCR of testosterone markedly increased (136 L/h). Hence, this patient had a comparatively high, albeit still subnormal PR of testosterone. This finding is in keeping with data obtained in obese, eugonadal men, who have normal PRs but decreased plasma concentrations of testosterone due to an increased MCR of testosterone.[10-14] Plasma concentrations and PRs of DHT were also subnormal in our hypogonadal men. Again, this was expected and only served to document the hypogonadal state in our patients. However, in contrast to the normal MRC of testosterone, the MRC of DHT was subnormal. The reason for this discrepancy between the MCRs of testosterone and DHT is not clear.

A sexual dimorphism in the activity of 11β-HSD1, the enzyme responsible for the conversion of cortisone to cortisol,[3,4] has been proposed as the cause of the sex-specific differences in cortisol excretion[1] and the endogenous PRs of cortisol. Based on the ratio of the main urinary 11-hydroxy/11-keto glucocorticoid metabolites in hypopituitary men and women,[3] the activity of this enzyme appears to be marginally higher in men then in women, albeit with a very substantial overlap between the 2 groups.[3,4]

Neither does this sex-specific difference in 11β-HSD1 activity seem to be estrogen-dependent—as it persists in menopausal women[4]—nor does short-term administration of testosterone in women influence adrenal cortisol secretion.[15] However, a dependency of cortisol secretion on sex hormone concentrations is suggested by the observation of enhanced

Table 2. Age, Clinical Diagnosis, Body Mass Index, Serum Concentrations Metabolic Clearance Rates, and Production Rates of Cortisol in Hypogonadal Men

Patient No.	Age (yr)	Clinical Diagnosis	Underlying Disorder	BMI	Cortisol (μg/dL)	MCR (L/h)	PR (mg/h)
1	43	Hypergonadotropic	bilat.Orchiectomy	28.4	10.9	8.0	0.87
2	57	Hypergonadotropic	Klinefelter's	21.5	5.9	7.3	0.43
3	38	Hypergonadotropic	Klinefelter's	31.0	6.4	7.9	0.51
4	24	Hypergonadotropic	Idiopathic	23.6	8.2	9.0	0.74
5	25	Hypogonadotropic	Kallmann's	22.6	6.0	9.2	0.55
6	33	Hypogonadotropic	Kallmann's	58.6	5.5	15.8	0.87
7	57	Hypogonadotropic	Hypothalamic	31.2	8.2	4.6	0.37
8	34	Hypogonadotropic	Hypothalamic	18.1	7.5	18.3	0.29
Mean $\pm$ SD (n = 8)					7.3 $\pm$ 1.8	10.0 $\pm$ 4.6	0.6 $\pm$ 0.2
9	54	Hypogonadotropic	Prolactinoma	45.9	12.4	8.1	1.00
10	39	Hypogonadotropic	Craniopharyngeoma	29.6	0.4	18.6	0.02
Eugonadal men (n = 23), range ($\pm$1 SD)[2,8,9]					6.0-10.4	5.0-13.0	0.4-1.0

NOTE. Serum concentrations of cortisol determined by mass spectometry (2-6 PM).

ACTH-stimulated secretion of cortisol in women receiving prolonged testosterone treatment.[5] We wished to investigate whether this putative effect of testosterone on cortisol production would result in lower than normal PR of cortisol in hypogonadal men. The results suggest that it does not. One of our patients had a very low PR of cortisol, but his hypogonadism was part of his hypopituitarism, including a deficiency of the pituitary-adrenal axis, and his low PR only serves to validate the used technology but cannot be interpreted as a sequel to testosterone deficiency. In the remaining patients with hypogonadotopic hypogonadism and normal pituitary morphology and function, as well as in 4 additional patients with hypergondotropic hypogonadism, the serum cocentrations, MCRs, and PRs of cortisol were normal. Taken together our results do not provide support for a major role of testosterone, either direct or indirect, in the control of cortisol production in men. It appears unlikely that this mechanism is the decisive factor for the sexual dimorphism in cortisol production.

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