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# Secretion of Unconjugated Androgens and Estrogens by the Normal and Abnormal Human Testis before and after Human Chorionic Gonadotropin

R. L. Weinstein, … , S. L. Kaplan, M. M. Grumbach

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**Research Article**

The secretion of androgens and estrogens by normal and abnormal testes was compared by determining the concentrations of dehydroepiandrosterone (DHEA), androstenedione ($\Delta_4$A), testosterone (T), estrone ($E_1$), and 17β-estradiol ($E_2$) in peripheral and spermatic venous plasma samples from 14 normal men and 5 men with unilateral testicular atrophy. Four normal men and one patient with unilateral atrophy of the testis were given human chorionic gonadotropin (HCG) before surgery. Plasma estrogens were determined by radioimmunoassay; plasma androgens were measured by the double-isotope dilution derivative technique. Peripheral concentrations of these steroids before and after HCG were similar in both the normal men and the patients with unilateral testicular atrophy. In normal men, the mean ±SE spermatic venous concentrations were DHEA, 73.1±11.7 ng/ml; $\Delta_4$A, 30.7±7.9 ng/ml; T, 751±114 ng/ml; $E_1$, 306±55 pg/ml; and $E_2$, 1298±216 pg/ml. Three of four subjects with unilateral testicular atrophy had greatly diminished spermatic venous levels of androgens and estrogens. HCG treatment increased the testicular secretion of DHEA and T fivefold, $\Delta_4$A threefold, $E_1$ sixfold, and $E_2$ eightfold in normal men. In the single subject with an atrophic testis who received HCG, the spermatic venous concentrations of androgens and estrogens were much less than in normal men similarly treated. We conclude that: (*a*) $E_1$ is secreted by the human testis, but testicular secretion of $E_1$ accounts for less than 5% […]



# Secretion of Unconjugated Androgens and Estrogens by the Normal and Abnormal Human Testis before and after Human Chorionic Gonadotropin

R. L. WEINSTEIN, R. P. KELCH, M. R. JENNER, S. L. KAPLAN, and M. M. GRUMBACH

*From the Clinical Investigation Center, Naval Hospital, Oakland, California, and the Department of Pediatrics, University of California, San Francisco, California 94122*

ABSTRACT The secretion of androgens and estrogens by normal and abnormal testes was compared by determining the concentrations of dehydroepiandrosterone (DHEA), androstenedione ($\Delta_4$A), testosterone (T), estrone ($E_1$), and 17$\beta$-estradiol ($E_2$) in peripheral and spermatic venous plasma samples from 14 normal men and 5 men with unilateral testicular atrophy. Four normal men and one patient with unilateral atrophy of the testis were given human chorionic gonadotropin (HCG) before surgery. Plasma estrogens were determined by radioimmunoassay; plasma androgens were measured by the double-isotope dilution derivative technique. Peripheral concentrations of these steroids before and after HCG were similar in both the normal men and the patients with unilateral testicular atrophy. In normal men, the mean ±SE spermatic venous concentrations were DHEA, 73.1±11.7 ng/ml; $\Delta_4$A, 30.7±7.9 ng/ml; T, 751±114 ng/ml; $E_1$, 306±55 pg/ml; and $E_2$, 1298±216 pg/ml. Three of four subjects with unilateral testicular atrophy had greatly diminished spermatic venous levels of androgens and estrogens. HCG treatment increased the testicular secretion of DHEA and T fivefold, $\Delta_4$A threefold, $E_1$ sixfold, and $E_2$ eightfold in normal men. In the single subject with an atrophic testis who received HCG, the spermatic venous concentrations of androgens and estrogens were much less than in normal men similarly treated. We conclude that: (*a*) $E_1$ is secreted by the human testis, but testicular secretion of $E_1$ accounts for less than 5% of $E_1$ production in normal men; (*b*) HCG stimulation produces increases in spermatic venous estrogens equal to or greater than the changes in androgens, including testosterone; and (*c*) strikingly decreased secretion of androgen and estrogen by unilateral atrophic human testes cannot be appreciated by analyses of peripheral steroid concentrations.

## INTRODUCTION

Secretion of 17$\beta$-estradiol ($E_2$)[1] by the human testis has recently been documented and compared to the secretion of testosterone (1). To clarify further the role of the normal and abnormal human testis in androgen and estrogen production, we determined the concentrations of dehydroepiandrosterone (DHEA), androstenedione ($\Delta_4$A), testosterone (T), estrone ($E_1$), and $E_2$ in peripheral and spermatic venous plasma obtained from 14 normal men and 5 men with unilateral testicular atrophy. In addition, testicular secretory responsiveness was assessed by administering human chorionic gonadotropin (HCG) before surgery to four normal men and one man with an atrophic testis.

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Dr. Weinstein's present address is: Providence Hospital, Endocrine-Metabolic Center, Oakland, California 94609.

Dr. Kelch was a trainee in Pediatric Endocrinology under a program sponsored by the National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, and his present address is the Department of Pediatrics, University of Michigan, Ann Arbor, Mich. 48104.

Dr. Jenner's present address is the Department of Pediatrics, University of Western Ontario, London, Ontario, Canada.

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[1] *Abbreviations used in this paper:* $\Delta_4$A, androstenedione; DHEA, dehydroepiandrosterone; $E_1$, estrone; $E_2$, 17$\beta$-estradiol; HCG, human chorionic gonadotropin; T, testosterone.

## METHODS

*Subjects.* Peripheral and spermatic venous blood was drawn simultaneously during an elective inguinal herniorrhaphy (13 subjects) or varicocelectomy (patient 8, Tables I and II) in 14 normal adults. Four subjects received intramuscular HCG before surgery: three 5,000 U/day for 4 days and one 5,000 U/day for 2 days. For comparison, five additional subjects with unilateral testicular atrophy (testis less than 3.0 cm in greatest diameter) were similarly studied during an elective inguinal herniorrhaphy on the side of the atrophic testis. One of these subjects (patient 19, Tables III and IV) also received HCG (5,000 U/day for 4 days) before surgery. Spermatic venous blood was collected as previously described (1). Informed consent was obtained from all subjects.

*Steroid analyses.* Plasma levels of DHEA, $\Delta_4$A, and T were determined by a modification (2) of the double-isotope dilution derivative technique combined with gas-liquid chromatography (3). Plasma concentrations of $E_2$ and $E_1$ were performed by radioimmunoassay. The details of our initial assay of $E_2$ and the modifications in methodology for simultaneous measurement of plasma $E_1$ and $E_2$ have been described in detail (1, 4). Duplicate determinations of an adult female plasma pool (10 assays) averaged 87±8.6 (SD) pg/ml for $E_1$ and 123±14.1 (SD) pg/ml for $E_2$. The concentrations of $E_1$ and $E_2$ in spermatic venous plasma were determined at four or more different dilutions to ensure parallelism with the standards.

The cross-reactivity of nonphenolic $C_{19}$ and $C_{21}$ steroids is negligible in both $E_1$ and $E_2$ radioimmunoassays. For example, T shows 0.001% cross-reactivity in the $E_1$ assay and less than 0.001% in the $E_2$ assay. In addition, the Sephadex LH-20 chromatographic system used in the estrogen assays reliably separates $C_{19}$ and $C_{21}$ plasma steroids from the $E_1$ and $E_2$ fractions (4). Nonetheless, the remarkably increased concentrations of unconjugated steroids observed in the spermatic venous samples, especially after HCG administration, prompted further validation of the techniques used in this study. DHEA, $\Delta_4$A, T, $E_1$, and $E_2$ were quantitatively recovered from a normal saline: absolute ethanol (95:5) solution that contained the following concentrations of unconjugated steroids: DHEA, 500; $\Delta_4$A, 100; T, 2,500; $E_1$, 2.0; and $E_2$, 20 ng/ml. The experimentally determined values obtained for these steroids were: (Mean±SD) DHEA, 475±8.0; $\Delta_4$A, 101±2.1, T, 2520 ±36; $E_1$, 1.99±0.8; and $E_2$, 15.9±1.8 ng/ml. In addition to the above steroids, the "simulated spermatic venous plasma sample" also contained various other steroids at the following concentrations: 5-androstene-3$\beta$, 17$\alpha$-diol, 100; 5-androstene-3$\beta$,17$\beta$-diol, 800; 4-androstene-3$\beta$,17$\alpha$diol, 100; 4-androstene-3$\beta$,17$\beta$-diol, 800; pregnenolone, 200; progesterone, 200; 17$\alpha$hydroxypregnenolone, 500; and 17$\alpha$hydroxyprogesterone, 250 ng/ml.

## RESULTS

### Normal human testis

*Androgen secretion before and after HCG.* Table I lists the results of peripheral and spermatic venous concentrations in 14 normal adults, 21–60 yr old. The values for DHEA in peripheral plasma and the concentrations of $\Delta_4$A in peripheral and spermatic venous plasma agree closely with previous reports (2, 5, 6). The mean spermatic vein concentration of DHEA is somewhat higher but this was influenced greatly by three subjects, 3, 4, and 7, who had remarkably high

TABLE I

*Peripheral and Spermatic Venous Plasma Concentrations of DHEA, Androstenedione and Testosterone in Normal Man*

| Subject | Age | DHEA | | Androstenedione | | Testosterone | |
|---|---|---|---|---|---|---|---|
| | | Peripheral | Spermatic | Peripheral | Spermatic | Peripheral | Spermatic |
| *no.* | *yr* | *ng/ml* | | *ng/ml* | | *ng/ml* | |
| 1 | 60 | 3.8 | 20.9 | 1.1 | 13.2 | 2.8 | 365 |
| 2 | 44 | 1.9 | 74.1 | 1.0 | 32.6 | 3.8 | 984 |
| 3 | 45 | 5.1 | 116.0 | 1.3 | 18.1 | 2.8 | 362 |
| 4 | 35 | 1.4 | 138.0 | 0.5 | 20.7 | 3.7 | 767 |
| 5 | 21 | 7.2 | 57.3 | 0.6 | 11.4 | 11.0 | 878 |
| 6 | 24 | 3.7 | 30.1 | 0.8 | 54.0 | 9.7 | 738 |
| 7 | 31 | 7.8 | 101.0 | 1.5 | 89.9 | 6.8 | 1,550 |
| 8 | 23 | 3.3 | 48.3 | 0.9 | 9.9 | 5.4 | 350* |
| 9 | 50 | 2.4 | 77.8 | 0.5 | 20.3 | 3.3 | 695* |
| 10 | 53 | 1.9 | 66.8 | 0.7 | 36.8 | 6.3 | 821* |
| Mean concn (±SE) | | 3.9±0.7 | 73.1±11.7 | 0.9±0.1 | 30.7±7.9 | 5.6±0.9 | 751±114 |
| | | | | HCG treatment‡ | | | |
| 11 | 40 | 6.5/7.2§ | 300 | 0.6/0.8 | 56 | 7.8/17.6 | 2,870 |
| 12 | 24 | 3.8/3.9 | 380 | 0.5/0.9 | 89 | 10.2/23.8 | 5,780 |
| 13 | 31 | 2.5/3.4 | 343 | 1.6/2.1 | 117 | 5.1/11.0 | 3,030 |
| Mean concn (±SE) | | 4.3±1.2/4.8±1.4 | 341±23.1 | 0.9±0.4/1.3±0.4 | 87±18 | 7.7±1.5/17.5±3.7 | 3,890±944 |
| 14 | 27 | 1.5/1.9 | 179 | 0.5/0.9 | 44 | 7.1/11.3 | 1,210 |

* Testosterone values reported previously (1).

‡ Subjects 11, 12 and 13: 5,000 U daily for 4 days; subject 14: 5,000 U daily for 2 days.

§ Before/after HCG.

TABLE II

*Peripheral and Spermatic Venous Plasma Concentrations of Estrone and Estradiol in Normal Men*

| Subject | Age | Estrone | | Estradiol | |
|---|---|---|---|---|---|
| | | Peripheral | Spermatic | Peripheral | Spermatic |
| *no.* | *yr* | *pg/ml* | | *pg/ml* | |
| 1 | 60 | 107 | 135 | 33 | 448 |
| 2 | 44 | 52 | 162 | 23 | 709 |
| 3 | 45 | 69 | 665 | 34 | 2,550 |
| 4 | 35 | 52 | 288 | 34 | 2,158 |
| 5 | 21 | 48 | 227 | 37 | 790 |
| 6 | 24 | 54 | 167 | 23 | 900 |
| 7 | 31 | 46 | 398 | 20 | 1,900 |
| 8 | 23 | * | * | 21 | 1,235‡ |
| 9 | 50 | * | 374 | 16 | 1,260‡ |
| 10 | 53 | * | 340 | 13 | 1,030‡ |
| Mean concn (±SE) | | 61±8 | 306±55 | 25±2.3 | 1,298±216 |
| | | HCG treatment§ | | | |
| 11 | 40 | 53/62‖ | 1,397 | 42/94 | 10,800 |
| 12 | 24 | 27/57 | 1,423 | 15/101 | 11,800 |
| 13 | 31 | 58/72 | 1,900 | 32/116 | 8,500 |
| Mean concn (±SE) | | 46±10/64±4 | 1,573±164 | 30±8/104±7 | 10,367±977 |
| 14 | 27 | */30 | 963 | */43 | 7,419 |

* Volume not sufficient.

‡ Estradiol values reported previously (1).

§ Subjects 11, 12, and 13: 5,000 U daily for 4 days; subject 14: 5,000 U daily for 2 days.

‖ Before/after HCG.

values. The range and mean spermatic venous T closely agree with values previously reported by us (1) and by Laatikainen, Laitinen, and Vihko (6) but is higher than values reported by Hudson, Coghlan, Dulmanis, and Wintour (7) and by Jeffcoate, Brooks, Lim, London, Prunty, and Spathis (8). After HCG administration to three subjects, 11, 12, and 13, changes in mean peripheral levels of DHEA (4.3 ng/ml to 4.8 ng/ml) and $\Delta_4$A (0.9 ng/ml to 1.3 ng/ml) were much smaller compared with T (7.7 ng/ml to 17.5 ng/ml). However, mean spermatic venous DHEA, $\Delta_4$A, and T increased similarly, approximately 3–5-fold. In subjects 14, only 2 days of HCG clearly increased the concentrations of DHEA, $\Delta_4$A, and T in spermatic venous plasma.

*Estrogen secretion before and after HCG.* Table II lists the peripheral and spermatic venous concentrations of $E_1$ and $E_2$ in normal subjects. Peripheral $E_1$ levels in early morning plasma samples ranged between 46 pg/ml and 107 pg/ml, while the mean concentration was 61±8 (SE) pg/ml. These values are comparable to other reports (9–11) but are slightly higher than concentrations in randomly obtained specimens in adult males not undergoing surgery (range 20–69 pg/ml; mean±SE, 40±5) (4). The concentrations of $E_2$ in peripheral plasma agree with values previously reported by us (1, 4) and others (9, 11, 12). Spermatic venous $E_1$ concentrations ranged from 135 pg/ml to 665 pg/ml. Concentrations of spermatic venous $E_2$ are slightly higher than in our previous report (1). This increase, similar to the changes in DHEA, was influenced greatly by subjects 3, 4, and 7. Concentrations of spermatic venous $E_2$ were approximately fourfold greater than spermatic venous $E_1$ levels. HCG, in subjects 11, 12, and 13, produced a slight increase in peripheral venous $E_1$ but a greater, approximately threefold, increase in $E_2$, while testicular gradients (spermatic minus peripheral) of $E_1$ and $E_2$ increased six- and eightfold, respectively. In subject 14 after only 2 days of HCG, four- and sixfold increases, respectively, in testicular gradients of $E_1$ and $E_2$ were observed.

## Abnormal human testis

*Androgen secretion before and after HCG.* Table III lists the peripheral and spermatic venous concentrations of DHEA, $\Delta_4$A, and T in five subjects, each with an atrophic testis. Peripheral DHEA, $\Delta_4$A, and T were

TABLE III

*Peripheral and Spermatic Venous Plasma Concentrations of DHEA, Androstenedione, and Testosterone in Men with a Unilateral Atrophic Testis*

| Subject | Age | DHEA | | Androstenedione | | Testosterone | |
|---|---|---|---|---|---|---|---|
| | | Peripheral | Spermatic | Peripheral | Spermatic | Peripheral | Spermatic |
| *no.* | *yr* | *ng/ml* | | *ng/ml* | | *ng/ml* | |
| 15 | 28 | 2.3 | 14.3 | 1.1 | 3.7 | 6.8 | 95.3* |
| 16 | 31 | 5.5 | 10.7 | 0.9 | 2.3 | 4.1 | 76.0 |
| 17 | 22 | 6.6 | 12.6 | 1.3 | 4.0 | 5.2 | 99.8* |
| Mean concn (±SE) | | 4.7±1.2 | 12.5±1.0 | 1.1±0.1 | 3.3±0.5 | 5.2±0.6 | 89±7.1 |
| 18 | 26 | 5.6 | 57.8 | 1.1 | 29.1 | 3.0 | 996* |
| | | HCG treatment‡ | | | | | |
| 19 | 23 | 3.7/4.4§ | 25.0 | 1.5/1.8 | 12.0 | 4.7/11.0 | 260 |

* Testosterone values reported previously (1).
‡ Subject 19: 5,000 U daily for 4 days.
§ Before/after HCG.

normal. Spermatic venous DHEA, $\Delta_4$A, and T were markedly reduced in three subjects, 15, 16, and 17, while levels in subject 18 were normal. After HCG, a normal increase in the peripheral concentrations of DHEA, $\Delta_4$A, and T was found in subject 19. However, the spermatic venous concentrations of DHEA, $\Delta_4$A, and T were much less than in normal men treated with HCG.

Table IV lists the peripheral and spermatic venous $E_1$ and $E_2$ concentrations in five subjects, each with an atrophic testis. Peripheral concentrations of $E_1$ and $E_2$ were normal. Like the concentrations of androgens, spermatic venous concentrations of $E_1$ and $E_2$ were strikingly reduced in subjects 15, 16, and 17. In subject 18, $E_1$ and $E_2$ spermatic venous concentrations were low-normal. In subject 19, the spermatic venous concentrations of $E_1$ and $E_2$ were much less than the levels found in normal men similarly treated with HCG; however, HCG produced a normal rise in peripheral $E_1$ and $E_2$.

## DISCUSSION

The concentrations of unconjugated androgens and estrogens in peripheral and spermatic venous plasma have been compared in men with normal and abnormal testes before and after HCG. In normal subjects concentrations of unconjugated $\Delta_4$A and T in spermatic venous plasma

TABLE IV

*Peripheral and Spermatic Venous Plasma Concentrations of Estrone and 17β-Estradiol in Men with a Unilateral Atrophic Testis*

| Subject | Age | Estrone | | 17β-Estradiol | |
|---|---|---|---|---|---|
| | | Peripheral | Spermatic | Peripheral | Spermatic |
| *no.* | *yr* | *pg/ml* | | *pg/ml* | |
| 15 | 28 | 66 | 84 | 24 | 280* |
| 16 | 31 | 31 | 61 | 25 | 104 |
| 17 | 22 | 36 | 102 | 28 | 186* |
| Mean concn (±SE) | | 44±11 | 72±15 | 26±1 | 190±51 |
| 18 | 26 | ‡ | 164 | 23 | 416* |
| | | HCG treatment§ | | | |
| 19 | 23 | 72/196‖ | 555 | 34/99 | 1,849 |

* Estradiol values reported previously (1).
‡ Volume not sufficient.
§ Subject 19: 5,000 U daily for 4 days.
‖ Before/after HCG.

and the responses to HCG are in agreement with values reported by Laatikainen et al. (6). However, the concentration of DHEA in spermatic venous plasma was higher. This difference can be explained, in part, by the remarkably high values in subjects 3, 4, and 7.

After HCG, peripheral levels of DHEA and $\Delta_4$A increased 50% or less, while spermatic venous concentrations increased five- and threefold, respectively. Since the major source of these steroids is adrenal and not testicular, the small increase in peripheral plasma values would be expected.

Recently secretion of $E_2$ by the normal human testis was established (1, 13), which allowed us to estimate that testicular secretion of $E_2$ accounts for at least one-fourth of $E_2$ production (1). We now present direct evidence for the testicular secretion of $E_1$ with a testicular $E_1$ gradient of 245 pg/ml. Utilizing the mean blood production rate of T, 7 mg/day for normal adult males (14), and the experimentally determined T and $E_1$ gradients from this study, we estimate testicular $E_1$ secretion to be 2.5 $\mu$g/day. A comparison of this estimate with calculated production rates of $E_1$ (45 $\mu$g/day–80 $\mu$g/day) (15, 16) indicates that testicular secretion accounts for less than 5% of $E_1$ production in normal men. Thus, nearly all of $E_1$ production is by peripheral hormonal interconversions (17, 18) and extratesticular secretion (19).

Longcope, Widrich, and Swain (20) recently reported the secretion of $E_1$ by human testes. Perhaps because Longcope et al. obtained spermatic venous plasma via renal vein catheterization and not from the spermatic plexus, their values for the spermatic venous concentrations of $E_1$, $E_2$, $\Delta_4$A, and T were lower than those of most previous reports, including the present study.

After HCG, spermatic venous $E_1$ and $E_2$ increased strikingly: $E_1$, sixfold; and $E_2$, eightfold. These responses were equal to or greater than changes observed in any of the androgens, including T. The slight increase in the peripheral concentrations of $E_1$ after HCG support our conclusion that the major sources of $E_1$ are nontesticular. In contrast, the larger rise in peripheral $E_2$ after HCG (fourfold) also indicates that the testicular secretion of $E_2$ is greater than $E_1$.

Spermatic venous concentrations of unconjugated androgens and estrogens in three subjects, 15, 16, and 17, with unilateral testicular atrophy were significantly reduced. The normal peripheral levels in these subjects suggest that the contralateral testis had compensated by secretion of greater than normal amounts of androgens and estrogens. The low values found in the spermatic venous samples in HCG-stimulated and untreated patients with unilateral atrophic testes (four of five) indicate that hormone secretion and secretory reserve are limited in these instances.

Although comparisons between the subjects in this study (treated vs. untreated and normal vs. atrophic testes) seem valid, unqualified extrapolation of these data to the normal state is unwarranted. For example, surgical stress has been shown to decrease plasma T in men (cf. peripheral T values in subjects 1 and 3) (21). Further, the effects of anesthesia on testicular blood flow and on metabolic clearance of unconjugated steroids are unclear.

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