Circulating Dihydrotestosterone May Not Reflect Peripheral Formation

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Abstract

We compared the blood \( P_{b,DHT} \) and urine \( P_{u,DHT} \) production rate of dihydrotestosterone (DHT) in normal men and women to determine whether peripheral formation was totally reflected in blood. \( P_{b,DHT} \) was similar when measured at both sites in men (674±79 vs. 788±207 SE μg/d); however, \( P_{u,DHT} \) was greater than \( P_{b,DHT} \) in women (174±55 vs. 55±8 μg/d, \( P < 0.02 \)). Excretion rates of DHT and 3α-androstanediol (3α-adiol) were similar in both sexes despite major differences in blood levels. However, between sexes large differences were present in 3α-diol glucuronide (3α-adiolG) in both plasma and urine. These observations indicate that peripheral (renal) formation of DHT and probably 3α-diol were not accurately determined by measurement of these steroids in blood. The large difference between blood and urine production rates in women suggests an important role of non-testosterone precursors of 5α-reduced steroids. Measurements of 3α-adiolG may provide more insight into these peripheral events.

Introduction

Dihydrotestosterone (DHT),\(^1\) the 5α-reduced metabolite of testosterone, is the mediator of androgen action and the nuclear androgen, especially in sexual tissues (1, 2). In peripheral tissue, DHT can be further metabolized to the androstanediols, 3α or 3β, (3–5) and to 3α-androstanediol glucuronide (3α-adiolG) (6–8). Previous studies have shown that DHT, 3α-androstanediol (3α-diol), and 3α-adiolG arise from extravascular sites (9, 10), and direct secretion has also been excluded (11). It was hoped that plasma DHT might be an accurate reflection of peripheral formation; however, most observations do not support this. Plasma DHT is normal or only slightly increased in most hirsute and acne patients (7, 12, 13), whereas other in vitro studies of hair follicles or sebaceous gland tissues in hirsutism indicate marked conversion activity of testosterone, androstenedione, and other precursors to DHT (14, 15). In men with 5α-reductase deficiency that involves both peripheral and hepatic enzyme deficiency, blood levels of DHT can be normal in parallel with testosterone levels (16, 17).

In a recent study of 3α-adiolG kinetics, the calculated blood production rate of 3α-adiolG was three to four times higher than simultaneous blood production rate of DHT (\( P_{b,DHT} \)) (18). 3α-adiolG is thought to be a marker of DHT formation. Mahoudeau et al., while evaluating the origin of blood DHT and its conversion to the androstanediols, concluded that most peripheral DHT formed is probably further metabolized before entering the general circulation (3). On the basis of this indirect evidence, we designed a study to determine more directly whether total body (peripheral) DHT formation exceeds that entering the circulation.

Our study finds a large difference between the specific activity and calculated production rates of DHT in blood and urine in women, which suggests that only a fraction of DHT synthesized by target tissues enters the circulation.

Methods

Steroids

1,2\(^{3}H\)DHT (55 Ci/mM sp act), 4 \(^{14}C\)DHT (57 Ci/mM sp act), and 1,2\(^{3}H\)3α-adiol (30.1 Ci/mM sp act) from New England Nuclear, Boston, MA were purified as previously described (19). \(^{14}C\)Androstanediol was produced by treating \(^{14}C\)DHT with 3α-hydroxysteroid dehydrogenase (Sigma Chemical Co., St. Louis, MO) in phosphate buffer and NADH for 20 min. The steroid product was purified by repetitive chromatography steps to constant \(^{14}C/H\)-ratios.

Infusion study on subjects

The protocol was approved by our institutional research committee. Nine normal volunteers (four males and five females) were studied at our Clinical Research Center, and blood and urine samples were obtained under strict supervision (Table I). Subjects were infused through a forearm vein while supine with 50 μCi of \(^{3}H\)DHT in 5 ml ethanol diluted to 100 ml with sterile isotonic saline as previously described (19). A priming dose of 3–4 μCi was given at the beginning of the infusion from 8 to 9 a.m. and the infusion continued for 8 h. Normal women were studied in the early follicular phase. Blood was obtained from the opposite arm at 6 and 8 h and urine was collected for three successive days and frozen.

Steroid concentrations and diurnal variation

Plasma DHT was measured on the day before the infusion from 8 to 9 a.m. and 5 to 6 p.m. In one male and female patient, blood was also collected six times every 4 h to evaluate circadian variation. Urine was collected on the day before the radioactive infusion and in two subjects, on two separate days to evaluate day to day variation of androgen excretion rates.

Measurement of steroids

Plasma DHT and 3α-adiol were measured after ether extraction and celite chromatography by radioimmunoassay (RIA) methods previously described and validated (4, 10, 12). 15 ml urine DHT and 3α-adiol (unconjugated) from a 24-h collection were measured with internal standard for correction of losses. The unconjugated steroid was extracted with ether (three times for 3 vol). The steroids were then purified in the same

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1. Abbreviations used in this paper: DHT, dihydrotestosterone; 3α-diol, 3α-androstanediol; 3α-adiolG, 3α-diol glucuronide; 3β-diol, 3β-androstanediol; MCR, metabolic clearance rate; MCR\(^{DHT}\), MCR of DHT; \( P_{b,DHT} \), blood production rate of DHT; \( P_{u,DHT} \), urine production rate of DHT.

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way as the plasma by using cellophane chromatography, which resulted in 70% overall recovery. Characteristics of the 3αdiol and 3βdiol (e.g., sensitivity and precision) assays were similar when using either blood or urine (4, 10). Completeness of urine collection was monitored by creatinine excretion.

Each plasma and urine sample was measured in duplicate and the values reported represent the mean obtained in two or three different RIA runs. To minimize errors, the RIA evaluation of both plasma and urine samples were performed by using the same standard curve, and the amount transferred to RIA tubes was calculated on the basis of previous curve results so that plasma and urine results were read on the same part of the standard curve.

Validation of the DHT assay in urine

The characteristics of this assay used for urine analysis is fully described since comparison of blood and urine DHT was central to the study.

Sensitivity. The antibodies used (DHT antibodies obtained against 15β-carboxyethylmercapto-5 DHT–bovine serum albumin and the 3αdiol antibody, against 3αdiol–succinate-bovine throblobulin) on urine extracts were the same used for plasma and were purchased from Radioassay System Laboratories, Carson, CA. Further paper chromatography did not significantly alter the values obtained by the standard method.

Specificity. Sensitivity of the standard curves based on mean±2 SD of intercept is ±2.3 pg for DHT and method blank values are 3.2±1.1 pg/tube for DHT. The intra-assay and interassay coefficient of variation were 2 and 8.5%, respectively.

Accuracy. A test of parallelism for DHT in urine was performed with increasing urine amounts (7.5, 15, and 30 ml). A good correlation was obtained (y = 1.13 x −0.82, r = 0.9980, P < 0.001).

Purification of steroids after infusion of [3H]DHT

Unconjugated steroids with 14C indicator were extracted with ether (three times for 3 vol). After the hydrolysis step with β-glucuronidase (20), both the plasma and urine steroids together with the original steroid extract were handled identically using cellophane chromatography followed by a Bush A paper chromatography that separated the three C19 steroids from all other steroids, including 3α-androstanediol (3αdiol). Previous studies have demonstrated that these steps achieve radiochemical purity (5, 19).

Further proof of purity of both assays was demonstrated by the constancy of the 14C/[3H] ratio (2.45 vs. 2.45 for DHT and 1.07 vs. 1.10 for 3αdiol) between the two-step procedure and an additional paper chromatography. In separate studies, using 9,11[3H]3αdiolG, we demonstrated that degradation did not occur during collection or storage of samples.

In all studies, counting times (three times for 50 min) were chosen to produce errors of < 5%.

Evidence for attainment of a steady state of labeled steroids

In previous studies we have demonstrated that labeled, unconjugated [3H]C19 steroids, such as DHT given by infusion, reach a state of equilibrium in subjects by 1.5–2 h if preceded by a loading dose (4, 5). Similarly, after DHT infusion, the level of radioactive 3αdiolG in plasma reaches a steady state by 4–5 h (19). Sampling times were designed to exceed this, and differences in 6- and 8-h samples were < 10% without any trend.

Calculations

Plasma. The metabolic clearance rate (MCR) was determined by analysis of steady state [3H]DHT levels according to the formula: MCR (liters/day) = (cpm DHT infused per day)/(cpm DHT per liter). (PbDHT) was calculated as the product of the DHT averaged concentrations (nanograms per liter) for a.m. and p.m. samples and it's MCR (MCRDHT) (liters per day). The specific activity of each steroid was calculated by dividing the cpm per liter at steady state by the mean plasma levels (nanograms per liter) and expressed as cpm per nanogram.

Urine. The urinary production rate of DHT (PbDHT) was estimated as the reciprocal of the integrated DHT specific activity from 2 of collected urines (i.e., cpm infused plus loading dose divided by cpm per nanogram of DHT).

Statistics. Wilcoxon signed rank test, both one and two-tailed, was utilized using Clino facilities, University of Southern California, Los Angeles, CA.

Results

The clinical data for all study patients are noted (Table I).

Plasma. Infusion rates of [3H]DHT, and concentrations of [3H]DHT, 3αdiol, and 3βdiol as well as the concentration of nonlabeled androgens (nanograms per deciliter) previously measured in plasma as well as [3H]DHT levels (cpm per liter) at 6 and 8 h of both male and female subjects are presented in Table II and Fig. 1. Also, the calculated MCRDHT and PbDHT and specific activities of DHT, 3αdiol, and 3βdiol are shown. The levels of [3H]DHT were very similar at 6 and 8 h (80,299±26,599 vs. 84,776±25,096 and 252,300±87,868 vs. 240,750±83,140). Individual subjects demonstrated a slight circadian variation of unlabeled steroids, but values differed < 20%.

MCRDHT based on 8-h infusions was 1,306±166 liters/d in four men and 520±96 liters/d in five women. The calculated PbDHT were 674±79 μg/d and 55±7 μg/d in men and women, respectively. The specific activity was much higher in women despite similar infusion doses and it fell progressively from DHT to 3αdiol and 3βdiol in both men and women.

Urine. Most [3H]DHT (84.6±3.8%) infused appeared in the first urine collection day with only a small amount (15.4±3.8%) on the second and < 1% on the third day. Similar results were seen with [3H]3αdiol and [3H]3βdiol. Even a larger fraction of [3H]3βdiolG was excreted on the first day (93.5±1.6%), whereas the remainder appeared in the second urine collection. Excretion rates for 1 and 2 d were determined along with specific activity from combined day 1 and 2 pools to account for > 95% of excreted counts.

Table III gives the 8-h infusion rate plus the loading dose that must be used in calculating urinary production rates. Values of DHT, 3αdiol, and 3βdiolG that were measured by appropriate RIA techniques are also shown as well as the calculated specific activities and production rates (Fig. 2). Urinary DHT and 3αdiol were 115±23 and 204±27 ng/d in men and 75±33 and 152±89 ng/d in women. Minor differences (< 10%) of day to day excretion rates of the three androgens were noted.
Table II. Plasma Calculations*

<table>
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<tr>
<th></th>
<th>DHT-infusion (cpm/8 h × 10^4)</th>
<th>DHT</th>
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<th>3α-diolG</th>
<th>Specific activity</th>
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<tr>
<td></td>
<td></td>
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<td>ng/dl</td>
<td>ng/dl</td>
<td>cpm/liter</td>
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</table>

* Data on infusion rates, labeled and unlabeled steroid concentrations in plasma, and calculated clearance (MCR), production (P), and specific activities after an 8-hour infusion of [3H]DHT in men and women.

1 Represents the mean of a.m.-p.m. values.

Comparison between rates determined in blood and urine. As previously reported, there are major differences in the plasma concentration of DHT, 3α-diol, and 3α-diolG for each sex. However, no significant urinary DHT and 3α-diol differences between the sexes were apparent in this small series, and plasma differences between the sexes were much more marked than urine differences. In contrast with the unconjugated androgens, a large difference was present between 3α-diolG in urine of males and females (106±17 vs. 24±9 µg/d, P < 0.01); values did not overlap. Note that 3α-diolG values were reported as the steroid mass only for comparison with unconjugated steroids.

As was noted in plasma, the specific activities of androgens were higher in females than males and there was a reduction in specific activity between DHT and 3α-diol (Fig. 2). However, in contrast, the specific activity of 3α-diolG was higher than 3α-diol in females.

The calculated P<sub>DHT</sub> and P<sub>U</sub> showed important differences for each sex (Fig. 3). The DHT production rate in men was similar in most individuals and as a group between blood and urine (P<sub>DHT</sub> = 674±79 µg/d vs. P<sub>U</sub> = 788±207 µg/d, P = NS). Specific activities of DHT were lower in the urine of females in each case, and there was a significant difference between P<sub>DHT</sub> and P<sub>U</sub> (P<sub>DHT</sub> = 55±7 µg/d, P < 0.02). The specific activities of 3α-diolG in plasma and urine were not significantly different in either males or females, but specific activities were much lower in men despite similar injection doses of tracer DHT.

Discussion

This study was performed on normal males and females to investigate whether the specific activities and calculated P<sub>DHT</sub> and P<sub>U</sub> were derived from the same compartment or pool. Our hypothesis was that peripherally synthesized steroid hormones might at least in part be locally metabolized and that only a fraction of total body production be reflected by blood levels or blood production rates. This concept appears intuitively valid; studies of blood and tissue sex steroid levels and formation rates of androgens in females with hirsutism and acne all indirectly support this concept (21, 22). Earlier studies demonstrated that the blood production of testosterone in women was only a fraction of that calculated from analysis of urinary testosterone glucuronide, which indicates that androstenedione is a testosterone precursor in women (23, 24). This earlier work implied that peripheral formation of testosterone was much greater than that which entered the circulation; therefore, we have compared specific activities and calculated production rates of DHT. It was also appropriate to compare specific activities of 3α-diol and the putative DHT product, 3α-diolG since this metabolite appeared to more accurately reflect peripheral DHT formation than did DHT or even 3α-diol. We did not analyze blood and urine DHT glucuronide since our previous study demonstrated

![Figure 1. Concentrations of plasma DHT, 3α-diol, and 3α-diolG and specific activities of these androgens in plasma after an 8-h infusion of [3H]DHT in normal men (top) and women (bottom).](image)
that testosterone is its major precursor (19). Sampling at other sites in vivo (e.g., muscle or fat) is not practical since differences across most organs and tissues should be a low order. We assume that major differences in specific activities between urine and blood of these steroids represented the contribution of the kidney and associated sexual tissue, and there is evidence that the kidney is an active site of DHT formation (25–27).

Plasma values of DHT, 3αDiol, and 3αDiolG in our study groups were very similar to those reported from larger control series. Whereas our mean a.m. and p.m. values may be somewhat different from those derived from integrating values throughout the day, our pilot studies indicate that only minor circadian variation occurred. Previous studies and additional proof of purity performed in the present project all provide evidence that a steady state of DHT, 3αDiol, and 3αDiolG in blood is achieved during the labeled DHT infusion, and that the steroids isolated by repetitive column and paper chromatography are radiochemically pure.

The metabolic clearance and production rates given in liters per day or corrected for surface area of DHT are ~ 50% higher in both men and women than those previously reported by us and others (3, 4). This may be the result of our small numbers or reflect the much longer period of infusion in the supine position as compared with previously reported 1–2-h procedures. This is also reflected in the PbDHT of 674±79 and 55±8 μg/d in men and women in our present study. We believe these values are correct and cite the minor differences in DHT radioactivity and specific activities that were observed in 6- and 8-h blood samples as evidence for steady state conditions. However, further studies will be necessary to determine whether steady state conditions were completely attained in the earlier literature.

The progressive reduction in specific activities between infused DHT, and 3αDiol and its conjugate in plasma is compatible with the biosynthetic scheme DHT → 3αDiol → 3αDiolG. However, a progressive reduction also suggests the role of other precursors, and a pathway to 3αDiolG not exclusively via DHT and

**Table III. Urine Calculations**

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<th></th>
<th>Counts infused + loading dose × 10⁴</th>
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<th>3αDiol</th>
<th>3αDiolG</th>
<th>Specific activity</th>
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<td>ng/24 h</td>
<td>μg/24 h</td>
<td>cpm/ng</td>
<td>μg/d</td>
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<td>±89</td>
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* Data on infusion rates and loading doses of [3H]DHT, excretion rates of DHT, 3αDIOL, and 3αDIOLG as well as specific activities of these steroids and the calculated production rates from analysis of urinary DHT in men and women.

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**Figure 2.** Urinary excretion rate of DHT, 3αDiol, and 3αDiolG and specific activities of these androgens after infusion of [3H]DHT in both men and women.

**Figure 3.** Daily PbDHT and PbU calculated and specific activities of 3αDiolG in blood and urine from normal men and women.
3adiol. We have recently demonstrated that androstenedione is a precursor of 3adiolG in normal and hirsute women (28), and there may be other C19 precursors.

This study presents for the first time data on the urinary excretion of unconjugated DHT and 3adiol, and compares 3adiolG simultaneously both in blood and urine. Unexpectedly, there was about twice as much 3adiol as DHT in urine in both sexes. Only small amounts of these androgens were not bound to sex hormone binding globulin in plasma and were able to be filtered and excreted by the kidney. Perhaps the larger amount of 3adiol was a reflection of somewhat less binding of sex hormone binding globulin than DHT, but the possibility of local formation and excretion by renal tissue must also be considered. This latter possibility was strengthened by the lower specific activity noted in each subject for 3adiol vs. DHT. There were also minimal excretion rate differences for each sex as compared with plasma of both DHT and 3adiol, as has been reported in vitro in animals (25).

In both sexes, the specific activity of 3adiolG between blood and urine was not significantly different. The urinary 3adiolG mass values are similar to those reported by Wright et al. (28) and others (29, 30). Between the sex, there were major differences in the excretion rates of 3adiolG (106±17 vs. 27.6±11 μg/d, P < 0.01) as compared with DHT and 3adiol. The specific activity of 3adiol in urine of females was higher than 3adiolG, which suggests that they arose in part from different sites in the kidney and that 3adiol can be excreted without being conjugated.

The most important observation of the study relates to the differences in calculated P<sub>b</sub><sup>DHT</sup> and those determined from analysis of DHT in urine. P<sub>b</sub><sup>DHT</sup> can be determined by comparison of injected and steady state specific activities and this formula can be converted into the product of the plasma concentration of the substance and its MCR. Similarly, in urine the ratio of specific activities can be simplified into the total dose of labeled steroid that was infused or injected and the specific activities. When these calculations were made in previous studies after injecting [3H<sub>j</sub>]testosterone, the blood and urinary determinations were very similar in men, which indicates that blood testosterone and urinary testosterone glucuronide were derived from a single source or compartment. However, in women the urinary metabolite production rate was four to five times that of blood. Testosterone in urine was not a unique metabolite of secreted testosterone, but rather was derived from peripheral formation from androstenedione and other precursors.

A similar conclusion can now be made for DHT. In men, P<sub>b</sub><sup>DHT</sup> and P<sub>b</sub><sup>V</sup><sup>DHT</sup> were comparable (674±79 vs. 786±207 μg/d, P = NS). However, in women there was a major difference between the calculated production rates that were determined from the two sites (55±8 vs. 174±55 μg/d, P < 0.02). The differences in production rates were easier to visualize than the specific activities since, in blood, it was derived from an 8-h infusion, which would have had to be corrected for a 24-h infusion to make direct comparisons.

We interpret this data to be analogous to the earlier discovery on sources and sites of testosterone formation in women. A significant fraction of DHT formed in peripheral tissues must be further metabolized locally. In our study, we were probably seeing only differences generated by urogenital tissue, primarily the kidney. The differences were brought out in the female, where P<sub>b</sub><sup>DHT</sup> was low and any renal synthesis of DHT, 3adiol, and 3adiolG could more easily be detected. Other secreted C19 steroid such as androstenedione, 5-androstene-3α,17β-diol, or dehydroandrosterone could also serve as precursors.

In men, the specific activity of 3adiol and its conjugate was similar, probably because the major C19 androgen is testosterone. However, in women the specific activities of 3adiol and 3adiolG were quite different, which suggests that 3adiolG was synthesized in sites different from 3adiol or that blood 3adiol was not in equilibrium with 3adiol in sites where 3adiolG was synthesized. Urinary 3adiolG appeared to arise from the same compartment as blood 3adiolG, especially in the male, although we have recently reported that only a fraction of the blood production of this conjugate appears in urine, and thus another site of excretion or additional degradative steps must be present.

A practical outgrowth of this study is that it provides more direct proof that peripherally formed androgens are locally metabolized. Blood levels of these hormones may be an inadequate measure of total or peripheral formation and, as discussed, this appears to be the case for many disorders of androgen (and estrogen) formation and action. Markers of peripheral steroid production such as certain steroid conjugates may be of considerable value in the evaluation of disorders of peripheral formation.

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