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Dihydrotestosterone Is a Peripheral Paracrine Hormone

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ABSTRACT: Androgen action in sexual tissues, especially skin and the prostate, is expressed by dihydrotestosterone (DHT) acting at the nuclear level. Dihydrotestosterone in the circulation and target tissues is almost solely derived from the peripheral conversion of secreted testosterone (T) in men and androstenedione in women. The general pathway is testosterone → DHT ⇌ androstanediol (3α diol). However, a number of studies suggest that blood DHT or 3α diol are not reliable indicators of peripheral DHT formation. This is particularly suggested by discrepancies in the specific activity of DHT in blood and urine following infusion of labeled DHT, suggesting that total body DHT formation is not reflected by blood levels. Thus, DHT should be thought of as a paracrine hormone formed and acting primarily in target tissues. 3α androstanediol glucuronide (3α diol G) is a major metabolite of DHT. An important site of its formation is the skin. Levels in blood and urine are increased in hirsutism and acne, and blood levels closely parallel pubertal development. 3α diol G levels are especially increased in adrenal disorders of androgenicity such as andrenogenital syndrome; it is also a good marker of response to therapy. Levels are reduced in various forms of male pseudohermaphroditism. 3α androstanediol glucuronide appears to be the best marker available of DHT formation in target tissues such as skin.

Key words: dihydrotestosterone, androstanediol, androstanediol glucuronide, hirsutism, adrenogenital syndrome, pseudohermaphroditism.

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Although the concept of paracrine–autocrine formation and action of hormones is well established, it is only now being suggested for certain steroids. Nevertheless, it is documented that androgen in women and estrogens in men are largely derived from the peripheral conversion of precursor steroids such as the interconverting pair androstenedione to testosterone (Horton and Tait, 1966) and testosterone to estradiol (Longcope et al, 1969). Another system is the peripheral conversion of progesterone to desoxycorticosterone (Antonipillai et al, 1983).

The nuclear androgen in sexual tissue and in some other organs is dihydrotestosterone (DHT) (Wilson, 1972). This potent androgen is the growth factor for sexual hair, is required for prostate development, and is formed peripherally from testosterone in the man and from secreted androstenedione in the woman (Ito and Horton, 1971; Mahoudeau et al, 1971). Earlier work suggested that the pathway in men for testosterone is I → DHT ⇌ androstanediol (3α diol). Note that the testosterone-DHT conversion (5α reduction) is irreversible; however, the DHT ⇌ -androstanediol (3α diol) involving 3α reduction/oxidation is reversible. It is of interest that all of these steroids are present in peripheral blood and could be measured, it was hoped, as a marker and reflection of blood and total body production (Ito and Horton, 1970; Horton et al, 1982; Fig 1). Blood levels of most steroid hormones such as cortisol and aldosterone reflect production rates. The measurement of DHT in blood became of more interest as it was shown by MacDonald's group and ourselves that most circulating DHT in blood was from the peripheral conversion of testosterone in the man and androstenedione in the woman (Fig 2). In the case of DHT, negligible amounts are secreted by Leydig cells; and the liver, although capable of forming DHT (5α reductase activity), does not secrete any net DHT into the general circulation (Ishimaru et al, 1978; Fig 3).

Thus the stage was set to measure DHT in blood along with its precursors in the study of disorders of sexual development and androgen action. This was not destined to be very useful. In studies of hirsutism in women or acne in men, DHT or androstanediol levels did not reflect the clinical state, in contrast to *in vitro* skin or hair follicle formation of 5α-reduced steroids. Particularly striking was the polycystic ovary (PCO) syndrome, in which DHT levels did not significantly differ in patients with or without hirsutism (Lobo et al, 1983). In the 5α reductase deficiency syndrome, the level of DHT in blood, although reduced, did not fully reflect the absence of 5α reductase activity measurable in peripheral tissues (Imperato-McGinley et al, 1982). These conclusions are not altered by the effects of

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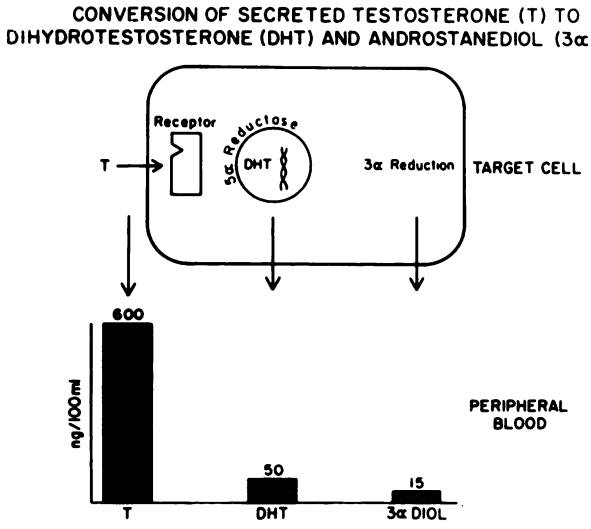

FIG. 1. Overall conversion by peripheral tissue of blood androgens to dihydrotestosterone (DHT) in men by 5α reductase and further 3α oxidoreduction to androstanediol (3αdiol). DHT then binds to a receptor and acts in the nucleus. These steroids are present in peripheral blood and might reflect tissue events. In women, the major precursor is androstenedione.

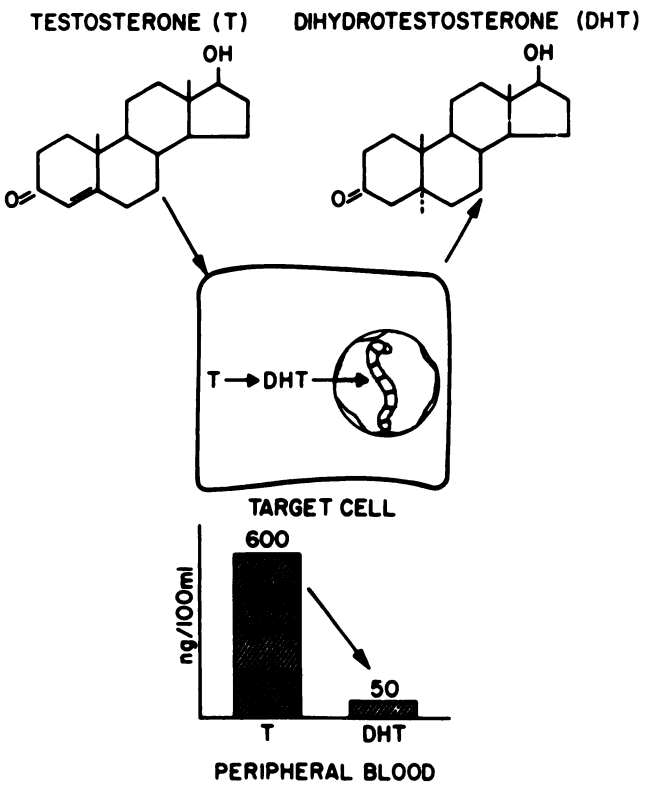

FIG. 2. Testosterone (T) in plasma is the major source of circulating DHT via peripheral 5α reduction in men. This was demonstrated by steady-state infusion of labeled T in men or androstenedione in women. Nearly all of the DHT (50 mg/dl) in men is from peripheral conversion of T or (not shown) from androstenedione in women.

sex hormone-binding globulin (SHBG) on DHT or 3α diol binding. 3α diol G is not bound by SHBG.

We recently approached the questions of whether peripherally formed DHT directly enters the circulation without being metabolized in target tissues, and whether the blood production is an integrated reflection of tissue formation. Since DHT is formed in the kidney, we reasoned that, in a steady state, the specific activity of DHT in blood would be the same in all body fluids. Tritiated DHT was infused into men and women, and the concentration and radioactivity measured by radioimmunoassay (RIA) and scintillation counting after repetitive chromatography to radiochemical purity. The concentrations of DHT and 3α diol, as well as the blood production rates, were similar to those previously reported by our group and others. Unconjugated DHT and 3α diol was present in urine. The specific activity of DHT in blood and urine was similar in men. However, it was significantly lower in female urine, and calculated production rates in women were much higher when determined from urinary (renal) DHT. We conclude that the blood production rate is less than total body formation, and that this is most striking in women (Toscano and Horton, 1987). The formation of DHT by renal tissue reduced the specific activity and increased calculated production rates, and was not reflected in blood. Dihydrotestosterone is formed and acts as a paracrine/autocrine hormone. Blood levels probably provide only a hint of the level in tissues, and this may vary from organ to organ.

Since a major fraction of peripheral DHT must be metabolized locally prior to its appearance in the circulation, the question arises as to the fate of peripheral DHT. Unconjugated androstanediol is a potential metabolite, but the levels in blood and the production rate are less than body production of DHT (Kinouchi and Horton, 1974). Initially, Baulieu observed that androstanediol glucuronide (3α diol 6) was a metabolite of androgenic steroids in urine (Baulieu and Mauvais-Jarvis, 1964). Mauvais-Jarvis and his colleagues then reported that there was a major sex difference in excretion: values were low before puberty and excretion rates were much reduced in male pseudohermaphrodites (Mauvais-Jarvis et al, 1973; Kuttenn et al, 1977). In a series of studies, we have concluded that 3α diol G is a major metabolite of DHT in men and women; a working model in skin for this concept is presented in Figure 4. A large fraction of labeled DHT is converted to 3α diol G (Moghissi et al, 1984).

Androstanediol glucuronide is present in blood primarily as the 17β glucuronide, which is the expected site of conjugation if DHT is the immediate precursor (Rao et al, 1987). Steady-state intravenous infusions of ^{3}H-DHT were

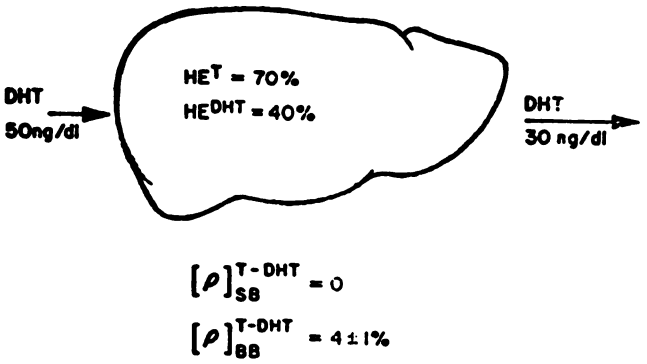

FIG. 3. During steady-state infusions of DHT or T to patients undergoing indicated right heart catheterizations, blood could be drawn from the thoracic aorta and hepatic vein. Analysis of steroid concentration and specific activity (SA) allowed calculation of hepatic extraction, (HE), mass, and SA. No net production of DHT occurs across the liver. The rho value ([ρ]) represents the conversion of precursor to product T to DHT in blood (BB), and is 4% overall from peripheral conversion, but undetectable $[\rho]_{SB}^{T\text{-}DHT}$ across splanchnic tissue.

achieved in young and elderly men prior to indicated cardiac catheterization procedures. Blood was drawn nearly simultaneously from the thoracic aorta and the hepatic vein. No net gradient in the level of 3α diol G measured by specific RIA was determined, nor was there a change in the specific activity of 3α diol G entering or leaving the liver (Kinouchi and Horton, 1974). In other studies, we infused various C19 androgen steroids, and concluded that DHT is a major precursor (Moghissi et al, 1984; Fig 5). Dihydrotestosterone originates via peripheral conversion of testosterone in men and androstenedione in women. Recent studies by Rittmaster and Giapulli et al also suggest that dehydroisoandrosterone is a precursor in women (Rittmaster and Thompson, 1990; Giapulli et al, 1989; Horton, 1983.

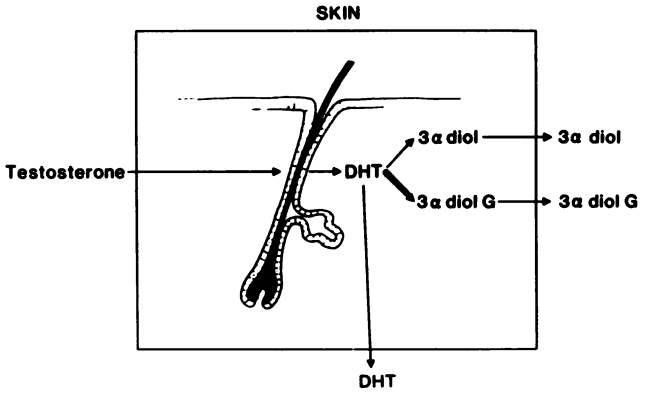

FIG. 4. A model for peripheral metabolism of DHT. Only a fraction of formed DHT enters the circulation. Some is metabolized to 3α diol, whereas a larger fraction is converted to androstanediol glucuronide (3α diol G), which appears in the circulation. Our studies in skin indicate that conversion is DHT → 3α diol → 3α diol G.

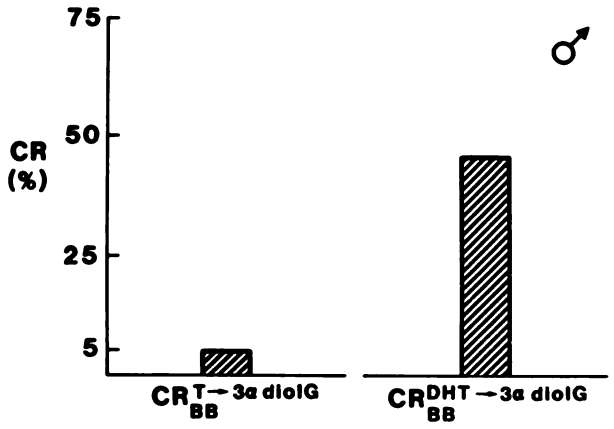

FIG. 5. Steady-state conversions of testosterone (T) and dihydrotestosterone (DHT) to 3α diol glucuronide (3α diol G). Conversion ratios (CR) of T → 3α diol G and DHT to 3α diol G. DHT is efficiently converted to 3α diol G in men.

In our initial clinical studies, we measured plasma 3α diol G levels in patients with idiopathic hirsutism. These cases had moderate to severe hirsutism, and almost all had increased plasma 3α diol G (Horton et al, 1982). It appeared to be a better marker than total or free testosterone. Subsequent studies on more diverse populations continue to support these observations, although a minority of patients have normal 3α diol G and free testosterone levels, or have elevated free testosterone levels only. The measurement of free testosterone (fT) and 3α diol G might be useful in evaluating the relative role of increased delivery of androgen to skin (fT) and the formation of DHT by 5α reduction and metabolism to the conjugate (3α diol G). These observations were further strengthened in a study by Lobo et al in which PCO cases had increased 3α diol when hirsute but normal levels of the conjugate in the clinical absence of hirsutism (Lobo et al, 1983).

Our conclusion is that 3α diol G levels reflect the peripheral formation of DHT, and that most peripheral DHT is metabolized locally before entering the circulation. We also measured 3α diol G in patients with pseudohermaphroditism due to either androgen resistance or 5α reductase deficiency. Despite normal levels of testosterone in plasma, 3α diol G levels were low (Horton, 1983; Ertel et al, 1989). This is the most dramatic example of normal blood levels of a potent androgen, but with impaired formation of peripheral androgens (DHT) via 5α reductase and reduced levels of the DHT metabolite (Fig 6). These clinical observations are strengthened by comparing 3α diol G plasma levels with measurements of 5α reductase activity obtained from sexual skin biopsy tissue. A good correlation exists between the clinical degree of hirsutism, blood levels of the metabolite, and estimates of 5α reductase activity (Lobo et al, 1987; Paulson et al, 1986).

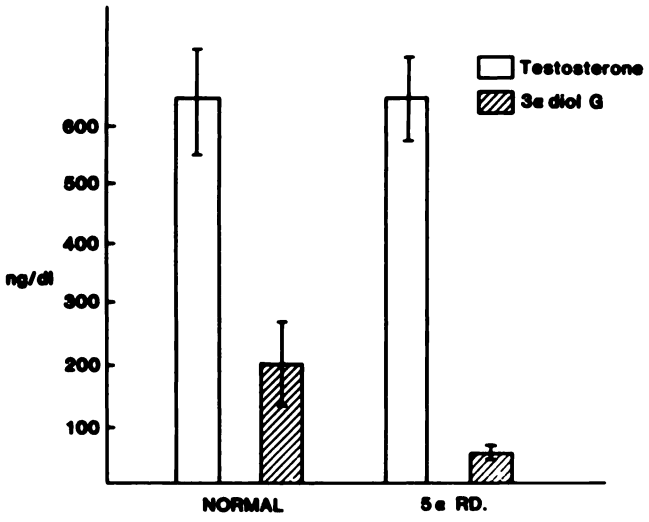

FIG. 6. Plasma testosterone (T) and androstanediol glucuronide (3α diol G) in five patients with 5α reductase deficiency, demonstrating that 3α diol G levels in plasma are lower than normal despite similar values of T. Study in collaboration with J. Imperato-McGinley.

Literature by other investigators has further established the clinical utility of 3α diol G measurements. This is especially so of hirsutism of various types (Table 1). Levels rise early, paralleling pubertal development (Belanger et al, 1986). Androstanediol glucuronide levels are elevated in patients with adrenogenital syndrome, and it may be the best reflection of therapeutic effectiveness (Reiner et al, 1989; Riddick et al, 1991). It may also be a marker of adrenal function in precocious puberty. A recent report suggests that 3α diol G levels reflect body hairiness and acne. A highly significant correlation between blood 3α diol G levels and chest hairiness and acne in men was observed (Lookingbill et al, 1988).

The observations that a peripherally formed steroid may be locally metabolized prior to entering the circulation has clarified a number of mysteries about androgens. Biologic mechanisms are frequently used in other systems. The formation and regulation of androgens in the prostate and estrogen in the breast and uterus may also be found to involve similar systems, as endocrinologists free themselves from the dogma that hormonal levels in biologic fluid are invariably accurate reflections of body and tissue production.

Table 1. *References to studies on plasma androstanediol glucuronide levels in patients with hirsutism and acne*

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