Is Dihydrotestosterone a Classic Hormone?

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In 1968, Brochovsky and Wilson (1, 2) published the first two papers describing dihydrotestosterone (DHT). Wilson and colleagues (3) subsequently demonstrated that 5-α reduction of testosterone to DHT was essential for the normal male fetal genital and prostatic development. As a result of this seminal work, DHT has been regarded as one of the three major sex steroid hormones in men (joining testosterone and estradiol).

The traditional definition of a hormone is a substance that is secreted by an endocrine gland and is distributed in the circulatory system to cause effects in target organs. Testosterone is a sex steroid that acts as a hormone in men (and likely in women). Deficiency in testosterone secretion from the testes results in low serum concentrations and end-organ effects such as loss of muscle and decreased erythropoiesis. Some of the effects of testosterone deficiency, such as loss of bone mass and increased fat mass, result from lack of substrate for local aromatization of testosterone to estradiol, but these effects are still due to low serum testosterone concentrations (4).

In this issue of *Endocrine Reviews*, Swerdloff *et al.* (5) review the human and animal data regarding the physiological and clinical implications of elevated blood concentrations of DHT in men and women. All exogenous testosterone formulations increase serum DHT concentrations above physiologically normal serum concentrations. Because testosterone therapy is commonly prescribed to men, understanding the physiological effects (beneficial and adverse) of supranormal DHT concentrations is clinically important (6, 7). Although the focus of their review is on the physiological and clinical effects of supraphysiological serum DHT concentrations, they also review the effects of pharmacological suppression of DHT.

A primary concern about supraphysiological serum DHT concentrations is the potential risks of prostatic disease (benign prostatic hyperplasia and prostate cancer). A lesser concern is androgenic alopecia. These concerns stem principally from the fact that 5α-reductase inhibitors are used to treat benign prostate hyperplasia and androgenic alopecia and (more controversially) might be effective in chemoprevention of prostate cancer. The syllogism is the following: "if 5α-reductase inhibitors that reduce serum DHT are useful in the treatment (or prevention) of these diseases, then supraphysiological serum DHT concentrations would increase the incidence of these diseases."

In healthy, eugonadal men, the prostate synthesizes DHT from circulating testosterone (that diffuses into the prostate as a substrate). However, the prostate also produces DHT directly (via the "backdoor pathway") from progestins (17-hydroxypregnenolone and 17-hydroxyprogesterone) in serial steps to several intermediates to 5α-androstane-3α, 17β-diol and eventually DHT (Figure 3 of Swerdloff review). In a third pathway, dehydroepiandrosterone (DHEA) and DHEA sulfate from the adrenal glands can be converted to serial steps directly to DHT or to testosterone and then to DHT (8). In normal men, local prostatic production of DHT results in concentrations that are ~10-fold higher than serum concentrations. Pharmacological suppression of serum testosterone concentrations to levels associated with castration results decreased prostatic DHT concentrations, but prostatic DHT concentrations remain 20-fold higher than serum DHT concentrations (9).

As a result of the prostatic pathways for DHT production, modest decreases in serum testosterone result in no change in normal prostatic DHT concentration. In a study of healthy eugonadal men who were medically castrated for 12 weeks and then divided into groups treated with variable dosages of testosterone gel (1.25 to 15 g 1% daily), prostatic DHT concentrations were similar across groups even in the group treated with the lowest dosage (1.25 g 1% daily) that resulted in a very low average serum testosterone concentration (~190 ng/dL) (10).

Two studies of eugonadal men have demonstrated that exogenous testosterone gel administration (at normal to high-normal dosages for treatment of hypogonadism) raises serum DHT concentrations significantly (about threefold to fivefold), but these increases in serum DHT concentrations do not affect prostatic DHT concentrations (10, 11). Administration

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of DHT sufficient to increase serum DHT concentrations sevenfold also does not affect prostatic DHT concentrations (12).

Collectively, these data indicate that the prostate self-regulates DHT concentrations independently of serum DHT concentrations. Within a broad range from low to high-normal serum testosterone concentrations, prostatic DHT concentrations remain stable. It is likely that even high dosages of testosterone would not affect prostatic DHT concentrations through passive diffusion; serum DHT concentrations would have to exceed normal prostatic DHT concentrations that are typically 10-fold higher than circulating DHT concentrations. However, very high dosages of testosterone could elevate prostatic DHT concentrations by providing more substrate (testosterone) for prostatic synthesis of DHT. For the prostate, DHT is a paracrine and intracrine hormone, not a classic circulating hormone.

The skin also synthesizes DHT from testosterone (via a different 5α-reductase than the prostatic reductase), and there is little correlation between circulating and skin DHT concentrations in men or women. Although 5α-reductase inhibitors are effective in treating male androgenic alopecia, DHT does not appear to play a primary role in the pathogenesis of male or female androgenic alopecia or acne. Androgen receptor polymorphisms and differences in androgen receptor concentrations and steroid-converting enzymes are the principal contributors to male androgenic alopecia (5). There is no correlation between serum DHT concentrations and the androgenic alopecia or acne. Clinical evidence supports this observation: increased incidence of these effects was not reported in a 2-year placebo-controlled study of high-dosage exogenous DHT in middle-aged to older men (13).

Thus, DHT acts as a paracrine independently of circulating DHT concentrations for the two principal target organs in adults: prostate and skin. It remains possible, however, that DHT might have specific effects as a classic hormone. Although DHT binds to the same androgen receptor (there is only one known androgen receptor) as testosterone, DHT has physiologically different effects than testosterone due to differences in receptor binding avidity and differences in interaction with the androgen receptor and its function and turnover rate. Circulating DHT concentrations might have direct effects on tissues other than prostate and skin. Swerdloff *et al.* examine the modest literature on DHT and extraprostatic and extradermal effects. Broadly speaking, the evidence suggests that DHT may directly modulate sexual function, but the evidence is insufficient to conclude that DHT has clinically significant specific effects (that are unique to DHT *vs* testosterone) on a variety of outcomes and functions, including cardiovascular health, cognitive function, immune function, erythropoiesis, and glucose and lipid metabolism.

As noted by the authors, it is not possible to examine the effects of DHT in isolation because of the interaction between testosterone, estradiol, and DHT. Administration of DHT results in suppression of testosterone and estradiol (via feedback on the hypothalamopituitary/gonadal axis), and suppression of endogenous DHT production also affects testosterone and estradiol production. Administration of 5α-reductase inhibitors suppresses tissue DHT production and circulating DHT concentrations, but 5α-reductase inhibition raises tissue and circulating testosterone (due to decreased metabolism) and estradiol (due to shunting) concentrations. Nonetheless, data from trials of 5α-reductase inhibitors have demonstrated that DHT does not appear to be necessary for the direct effects of testosterone on muscle function and erythropoiesis and the indirect effects of testosterone (via aromatization to estradiol) on bone and fat (4, 14–17). Suppression of circulating and tissue DHT concentrations is associated with decreases in libido and erectile function in some men ($<$10%) and a small decrease in average sperm concentration (16, 18–23).

Administration of high-dosage DHT maintains most androgenic effects of exogenous testosterone in men with androgen insufficiency with the notable exception of libido and bone mineral density. A 2-year study of daily application of high-dosage DHT gel (that increased serum DHT by ~10-fold) in middle-aged to older healthy eugonadal men demonstrated that exogenous DHT markedly suppressed serum testosterone and estradiol concentrations, increased lean mass and erythropoiesis and decreased fat mass, but it did not affect prostate volume (13). Vertebral bone mass and overall sexual desire decreased modestly, but significantly, during the 2-year period (13, 24).

DHT was the last major sex hormone to be described. There remain significant gaps of its role in human physiology. We need a more complete understanding of the physiological effects of DHT, including its specific role in cardiovascular health, sexual function, and bone health. Long-term clinical trials examining the effects of exogenous DHT on outcomes in cardiovascular, prostate, and bone health would be useful to define the potential role of DHT and nonaromatizable selective androgen modulators in the treatment of male hypogonadism and the development of male hormonal contraceptives.

In the meantime, the review by Swerdloff *et al.* (5) demonstrates that DHT is principally a paracrine hormone. Circulating DHT concentrations have little relationship to prostatic and skin DHT concentrations. In addition, within a broad range of serum testosterone concentrations, raising or lowering serum testosterone concentrations has little effect on prostatic DHT concentrations. It is unlikely that exogenous testerosterone therapy used for treatment of male hypogonadism or for future development of androgen-based male hormonal contraceptives will appreciably alter the prostate hormonal milieu and the potential risk of incident prostate cancer.

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Abbreviation

DHT, dihydrotestosterone.