Advances in Knowledge of Androgens: How Intentional and Accidental Neurosteroid Changes Inform Us of Their Action and Role

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Abstract

Purpose of Review Here, we summarize current knowledge of androgens' action gained over the recent years.

Recent Findings Neurosteroids are produced in the brain and peripheral nerves, independent of endocrine glands have been investigated for how they are regulated, and have actions via non-steroid receptor targets to mediate social, affective, and cognitive behavior and to protect the brain. Androgens' organizing actions in the peri-natal period have effects throughout the lifetime that may be recapitulated later in life during critical periods and at times of challenge. Developmental changes in androgens occur during mid-childhood, adrenarche, puberty, adolescence, young adulthood, middle age, and andropause. Changes in androgens with a 5 α -reductase inhibitor, such as finasteride, result in disruptions in organizational and activational functions of androgens that can be unremitting.

Summary Normal developmental or perturbation in androgens through other means can cause changes in androgen-sensitive phenotypes throughout the lifespan, in part through actions of neurosteroids.

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Highlights

- Androgens have perinatal effects to masculinize and defeminize individuals; some of these organizing effects of androgens may occur at other key critical periods.
- Finasteride has the capacity to interfere with many downstream or alternative pathways for production, metabolism, or actions of (neuro) steroids and can produce psychopathologies that are unremitting in some individuals.
- Shunting one pathway increases activity of other enzymes to increase or decrease neurosteroids, which have many effects and may occur as a result of interference with the brain through environmental exposures (endocrine disruptors), pharmacological exposures (finasterides), or accidents such as Traumatic Brain Injury (TBI).

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Introduction

The purpose of this paper is to provide an update on various mechanisms of androgens that have bearing on their effects on stress, sex, and other important functions. First, an overview of neurosteroids' action will be discussed, then the relevance for masculinization and feminization, and developmental changes in androgens. Second, how finasteride can induce feminization and demasculinization is discussed, then its effects on androgens, neurosteroids, and the brain; direct effects on T and DHT, and 5 α -reductase expression and distribution; and neuroendocrine effects of post-finasteride syndrome, neurosteroids, and receptor targets, including GABA, dopamine, glutamate, glycine, ER β receptors, and genetic targets. Third, the clinical effects of post-finasteride syndrome and physical, cognitive, emotional, and sexual function will be discussed and compared with the effects of mild traumatic brain injury. Our hypothesis is that many of the substrates that underlie mild traumatic brain injury may be analogous to pathological effects of finasteride.

Overview of Neurosteroid Action in the Brain

Now, it is generally accepted that cholesterol-based, steroid hormones can be produced outside of traditional steroid organs (gonads, adrenals, placenta) in the brain and peripheral nerves (termed neurosteroids) [1]. Neurosteroids influence autonomic function (hindbrain), reward (midbrain), emotions (limbic system), learning (hippocampus, cerebellum), executive function (prefrontal cortex), and procedural memory (cerebellum). The biosynthetic pathway for neurosteroid production involves the 18 kDa translocator protein (TSPO) and steroidogenic acute regulatory (StAR) proteins which transport cholesterol into the mitochondria. Pregnenolone X receptor (PXR) homeostatically regulates cholesterol biosynthesis and cytochrome P450-dependent C27 side chain cleavage enzymes (P450_{scc}). 3 β - and 3 α -hydroxysteroid dehydrogenases (3 β -HSD) and 5 α -reductase (5 α -R) are oxidized by P450_{scc} to form pregnanolone, which is then metabolized by 3 β -HSD to progesterone, which then can be metabolized to form testosterone (T). A pathway to form 3 α -androstane-20-one (3 α -diol) from T involves sequential actions of 5 α -R, an irreversible action that forms dihydrotestosterone (DHT), and then 3 α -diol. These steroidogenic factors are expressed in the spinal cord, cerebellum, pons, medulla, ventral tegmentum, prefrontal cortex, hippocampus, basal ganglia, hypothalamus, and thalamus, in an age-, sex-, and hormone-dependent manner [2–4], as early as prenatal day 7, which imply their critical role in function.

Androgens, and their synthetic variants (selective androgen receptor modulators (SARMs)), have varied actions through androgen receptors (ARs). DHT has a tenfold greater potency of inducing AR signaling than T [5]. 3 α -diol and 3 β -diol, unlike T and DHT, do not have actions via ARs. Instead, 3 α -diol has affinity for neurotransmitter targets, such as gamma-aminobutyric acid (GABA)_A receptors [6, 7]. 3 α -diol and 3 β -diol have affinity for estrogen-receptor (ER β) [8] to mediate behavioral and physiological effects of androgens [9–12]. Androgens can also have actions through dopamine pathways involved in movement, reward, and motivation [9–14]. Humans and animals will work to get access to androgens, an effect that is dampened with naloxone [10]. Androgens will condition a place preference [15]. The pattern of these effects in humans has been modeled in rodents [16, 17]. It is notable that some neurodevelopmental (e.g., autism spectrum disorders), neuropsychiatric [18], and neurodegenerative (i.e., Alzheimer's, all-cause dementia, and seizure) [19–24] disorders are associated with differences in androgen levels. We will discuss these findings in the context of recent progress made by our research lab, clinic, and others.

Mechanisms of Masculinization and Feminization in Males

Androgens have well-known pleiotropic effects to regulate growth and functional aspects of the reproductive, central nervous, skeletal, and cardiovascular systems throughout the lifespan. However, these robust actions of androgens occur much earlier in development when we consider sexual differentiation. The presence of androgens typically early in development results in pervasive effects throughout the lifespan on the typical pattern of androgen secretion. Supported by early investigations in the field [25], the capacity of androgens that are secreted from the testes during early pre- or peri-natal development is thought to “organize” the central nervous system, including the neural control of post-pubertal patterns of androgen release, as well as the sensitivity of specific brain structures to androgens later in life for behaviors. We call this patterning of androgen secretion early on that organizes later adult responses as sexual differentiation.

Sexual Organization

Genetics Becoming a male or a female mammal depends upon the development of many different types of sexual characteristics/features: chromosomal, genetic, gonadal, hormonal, and behavioral. Sex determination begins this process; that is, the

presence of the Y chromosome after conception has the individual develop as a male (i.e., genetic sex). In this, the genetic sex related to the *sry* gene on the Y chromosome becomes active and starts the development of the testes from the primordial, undifferentiated gonads. When the testes develop, hormonal sex develops. Specifically, from the testes, T and anti-Müllerian hormone are secreted, which actively suppresses the female phenotype (defeminization). Testosterone and its metabolites are important for masculinization even at this early stage of development. Anti-Müllerian hormones inhibit the female typical pathway of development (defeminizing effects). These hormones in males in utero then begin to have actions on the body and brain during development, which ends up leading to behavioral sex/gender differences later on. In XX individuals, genetic females, the lack of *sry* begets the lack of testes and hormones from it; the Müllerian system develops as does the internal and external female genitalia and the brain. These are considered both feminizing and demasculinizing effects. In early development, without the presence of androgens, the female phenotype develops; however, this can also happen when there are deficits in androgen metabolism or with actions of androgens at targets, such as ARs early on.

Methods for Studying Androgens

The classic approach in behavioral neuroendocrinology is to determine the role of a hormone for a behavioral process by assessing endogenous changes in the hormone, extirpation of the hormone (i.e., removal of the gonads), and replacement back of the hormone. Endogenous changes are used to assess the extent to which levels of the hormone in question vary with the behavioral endpoint of interest. This is usually assessed in males by investigating behaviors and androgens that vary (1) from females (which typically have lower levels of androgens), (2) by season (e.g., seasonal breeders), and (3) across the lifespan (post-pubertal, with androgen decline in advanced aging).

Changes Across the Lifespan Many of the targets of androgens have been highlighted by changes in the tissues' functions with alterations in androgens across time. At puberty, T is important for enlargement of vocal cords, penis, and scrotum; changes in musculature; and initiation of spermatogenesis. At puberty, DHT is involved in growth of facial and body hair. Later in life, DHT is important for male pattern baldness (MPB) and disorders of the prostate, such as benign prostate hyperplasia (BPH) and prostate cancer. At puberty, androgen levels increase and remain high until midlife when androgen levels begin to decline. In humans, this is often assessed by determining age-related changes in function. Unlike the

precipitous decline in ovarian function with reproductive senescence that is observed among women, men experience a decade-by-decade decline in androgens. This decline is often termed “andropause” and, although the nature of the decline in steroids is different from that observed during the menopause of women, both situations have clear symptomology associated with steroid decline. For example, decline in bioactive androgens in men with aging is associated with diminished libido, fatigue, decreased muscle mass, osteoporosis, depression, anxiety, and/or cognitive dysfunctions.

Aging men can experience decline in gonadal, sexual, cognitive, and affective function and the role and mechanisms of androgens for these effects have been studied extensively. Androgen levels begin to rise after puberty and remain high until midlife [26], when a decade-by-decade decline in endogenous androgen levels occurs among men [27]. On average, this decline involves an annual 0.4% reduction in total T and a 1.2% reduction in biologically free T, such that concentrations at age 70 are approximately half of what is observed at ages 20–29 [28, 29]. Some behavioral sequelae associated with aging and decreased androgens include poorer performance in spatial tasks, greater anxiety and depression, and decreased sexual motivation [30–35]. In addition to androgen-sensitive changes in behavior, there are physiological changes, such as increased risk for BPH and prostate cancer [36]. These physiological changes worsen with aging, as frequency of moderate urinary symptoms related to BPH rise from 13% in the fifth to 28% in the eighth decade of life [37]. Thus, advanced aging is another example of effects of low androgen levels on many tissues of the body, including the brain, with reproductive and cognitive consequences.

Older male rodents demonstrate similar behavioral decline to that of aging men. Aged rodents display decreased sexual behavior and impaired cognitive performance in spatial tasks, and increased depression-like behavior [38–41]. Extirpation of the testes, a primary source of androgens, via gonadectomy (GDX) can reduce plasma levels of androgens similar to the low levels in advanced aging and can be considered a model of age-related androgen decline [40, 42]. Separate studies have shown that GDX of rodents produces behavioral effects similar to those seen with aging, including decreased sexual behavior and impaired cognitive performance and increased anxiety and depressive behavior [43–46]. Moreover, chronic mild unpredictable stress produces greater depression-like behavior of GDX rats coincident with decreased proliferation of new cells in the hippocampus, decreased neurogenesis, and lower expression of the protein polysialylated neural cell adhesion molecule, which is associated with neural plasticity [47].

Disruptions of Hormones Consequences of very low androgen levels are clear. Simply, when androgen concentrations are low, demasculinization is observed. For example, in humans,

low fetal levels of DHT in individuals with a deficiency in the type II isoenzyme of 5 α -R produce birth defects in male external genitalia [48]. Also, it was noted that male pattern baldness (MPB) is rare in these individuals, which in the general population of men is prevalent (up to 70% of men will experience MPB at some point in their lives [49]). Importantly, the drug finasteride, which is used to treat MPB, blocks 5 α -reduction of T to DHT. As such, changes to the androgen levels, as described herein, also result from exposure to finasteride. Clinical and adverse effects of this drug as reported [50] are consistent with the robust effects of changes in available androgens demonstrated in the literature with changes in androgen levels.

When we think about how steroids produce male- or female-typical phenotypes, there is masculinization along with defeminization in males, and demasculinization and feminization in females. Finasteride causes certain male individuals to show symptoms of demasculinization and feminization after exposure. Androgens produce masculinization and estradiol (E₂) and progestogens, like allopregnanolone (3 α ,5 α -THP), produce feminization. There is a shunting of metabolism via 5 α -R with finasteride. This produces acute and persistent effects on other steroid pathways, such that T and 3 α -diol are increased, but DHT is decreased [51, 52]. Furthermore, there are reductions in the pregnane neurosteroid, 3 α ,5 α -THP, in which 5 α -R is a rate-limiting step in its production [51, 52]. Indeed, among Fischer 344 rats, levels of T and its 5 α -reduced, but not aromatized, metabolites decline with aging (coincident with age-related changes in brain function and the body [40]). Among aging men, E₂ levels remain unchanged or increase, resulting in a decrease in the ratio of T to E₂ [29, 53]. A clear example of feminizing effects of finasteride is gynecomastia, enlargement of the breast tissues.

Use of Finasteride to Study Androgens

Finasteride alters the metabolism of T to its aromatase pathways vis-a-vis its inhibition of DHT synthesis; the end result here is an increased ratio of E₂ to T/DHT producing gynecomastia [54] and changes in pregnane steroids. Gynecomastia is a robust and irreversible feminizing change in the body. The sum of these changes is that you can have feminizing and demasculinizing effects of finasteride among men (which look similar to aging, e.g., reduced musculature, changes in fat deposition, and increased breast development) and results in effects typically associated with aging (feminization and demasculinization).

There are also feminizing effects of finasteride for brain function. The clearest examples here relate to the robust psychological effects of finasteride use among men. That is, they report an increase in female-typical symptoms and

disorders—anxiety and depression. Times of great changes in hormones among women are associated with increased incidence of anxiety and depression disorders, such as postpartum depression, premenstrual dysphoric disorder, and peri-menopausal depression [55, 56]. In these disorders, it is not low levels per se that seem to predispose women to them, but the changes in circulating hormone levels [55–57]. Also, in the case of finasteride exposure and resulting anxiety and depression, there are impairments in neurosteroids; the role of neurosteroids specifically for mood and its disorders has been a topic of interest in many laboratories including our own [56]. Table 1 summarizes some of the symptoms of post-finasteride syndrome (PFS) that most clearly align with evidence of its demasculinizing and feminizing effects. Post-finasteride syndrome is a condition characterized by altered circulating and brain steroid levels and adverse physical and psychological effects that occur even after finasteride treatment is ceased [50, 54, 58–62].

Clinical Use of Finasteride Finasteride is the first approved 5 α -R inhibitor for treatment of benign prostate hyperplasia (BPH) and MPB (aka androgenetic alopecia) [63]. Finasteride was first marketed by Merck as Proscar (for BPH) and Propecia (for MPB) in 1992 and 1997, respectively [64]. These clinical applications are based on the ability of finasteride to inhibit the 5 α -R enzyme with resulting reductions of T's metabolism to DHT. However, off-label uses can include reduction of side effects of anabolic androgenic steroid use or to promote demasculinization and feminization among transgender women [65]; some of these types of usages entered the public knowledge with the news of a joint effort between Florida and New York to clamp down on illegal steroid trafficking [66]. Just as off-label use of finasteride prevails, before it was approved for MPB, it was being used for this off-label, and produced profound effects on neurological function through inhibiting neurosteroidogenesis. Indeed, one of our patients with catamenial epilepsy nearly succumbed to intractable seizures when her uncle, a dermatologist, prescribed finasteride for off-label use [23]. Although it was first thought that 5 α -R (the enzyme that finasteride targets) was not expressed in the brain, more recent research has shown this is not true. 5 α -Reductase has expression in other tissues as well [67, 68]. As such, the effects of the drug go beyond just the scalp for the male MPB effect.

Finasteride Beyond the Scalp and in the Brain Research from our lab has demonstrated that finasteride alters behavior of male rodents. Gonadectomized or gonadally intact rats were administered T-containing, or empty, silastic capsules in conjunction with a 5 α -R inhibitor or an aromatase inhibitor. All rats were tested for reproductive, social, cognitive, and affective behavior; prostate mass was determined; and androgens were measured in plasma and brain. Blocking T's metabolism

Table 1 Finasteride significantly decreased prostate weight, increased latency to vote, time spent in overall social interaction, latencies to finding the hidden platform 2 in a water maze, number of entries to the light side, and the light/dark transition task

	Gonad condition							
	Gonadectomized				Intact			
	Androgen condition							
	Vehicle		Testosterone		Vehicle		Testosterone	
	Inhibitor condition							
	Veh	Fin	Veh	Fin	Veh	Fin	Veh	Fin
Prostate weight (g)	0.4	0.3	0.5	0.4	0.5	0.4	0.6	0.4
Latency to mate (s)	550	600	500	600	300	350	250	300
Secs spent in social interaction (% time with novel object)	35 ± 6	29 ± 4	25 ± 3	41 ± 8	41 ± 10	59 ± 13	37 ± 3	41 ± 8
Latencies secs to finding platform in Morris Water maze	61 ± 4	74 ± 8	61 ± 7	71 ± 7	62 ± 6	63 ± 5	59 ± 7	65 ± 5
No. of entries to light side in light/dark transition task	1	1	2	1	4	3	3	2

to its 5 α -reduced metabolite, DHT, via systemic finasteride significantly decreased prostate weight and sexual behavior of male rats. In addition, in this study, there was a trend for finasteride to reduce cognitive performance in the water maze task (see Table 2). Importantly, the effects described here in this study show that manipulations of androgens with finasteride altered steroid levels and behavior well after finasteride from administration was cleared by the body. This study supports and extends previous work on androgen metabolism for trophic effects, as measured by prostate mass and behavioral effects in this study. For example, GDX of young male rats decreased prostate weight as has been demonstrated previously [64, 69]; herein, this phenomenon occurred concurrent with lower levels of DHT and T in plasma and brain, and unchanged or increased E₂ levels. This lower androgen to E₂ ratio that was observed here in male rats is similar to that observed among aged men. Concomitant with these changes

in androgen levels, there were robust effects of GDX to decrease reproductive functions, including sexual responding and prostate weight. Others have reported that prostate weight [64, 69] and sexual behavior [44, 70, 71] were reduced with GDX. Brain circuitry for this effect likely involves the hypothalamus and midbrain, which mediate reward, motivation, and sexual behavior of rodents [72, 73]. In our study, we observed reduced androgen formation in the midbrain and hypothalamus, areas related to sexual function, following GDX. Moreover, reductions in androgens following GDX were also observed in the hippocampus and cortex, regions that are considered to be critical for cognitive and anxiety-like behavior [45, 74, 75], and sensitive to androgens for these functions [43, 76–83]. Together, these effects suggest a role of androgens for growth in body and neural plasticity, and that these effects can persist longer than the time for which the androgen manipulations occur.

Table 2 Overlapping symptoms of post-finasteride syndrome (PFS) and traumatic brain injury (TBI)

Demasculinization	Feminization
Steroid levels	
□ Androgens	⊗ Estrogens
Variable levels of progestins	Variable levels of pituitary/adrenal steroids
Physical effects	
□ Testes size	⊗ Breast tissue
□ Sexual motivation and/or performance (PFS) absent (TBI)	⊗ Need for affiliation, due to isolation
Cognitive behavior	
□ Spatial performance	⊗ Verbal
Social/emotional behavior	
⊗ Impulsivity	⊗ Depression, anxiety, erratic behavior, suicidality

Through competitive binding, finasteride is a potent inhibitor of type II 5 α -R (mean inhibitory concentration, or IC₅₀, of 69 nM). Finasteride has also been shown to be similarly potent in binding to the type III isoenzyme of 5 α -R (IC₅₀ 17.4 vs. 14.3 nM for 5 α -R type II) when tested in a HEK-293 in vitro cell preparation [84]. The type II isoenzyme of 5 α -R predominates in the clinical targets for MPB and BPH, the hair follicles and prostate, respectively, and is also expressed in the liver, seminal vesicle, and epididymis [67, 85]. Approximately one-third of circulating levels of DHT are due to the actions of the type I isoenzymes, with the rest from the actions of the other isoenzymes [67, 85, 86]. Based on preferential binding and the tissue-specific expression of 5 α -R type II, finasteride was initially considered to have little potential for adverse actions in other tissues, beyond the hair follicles and prostate. Importantly, there are differential expression patterns of 5 α -R isoenzymes in different tissues, and developmental periods [67, 68]. Finasteride binds both types II and III, which are expressed in the brain opening the door to these other neural effects.

We will focus here on these expression pattern differences in human tissues and developmental periods to explain the clinical usage of finasteride. For example, in adult humans, 5 α -R type III is ubiquitously expressed, but types I and II show different patterns of expression in the brain, genital and nongenital skin, prostate, internal and external male genitalia, liver, kidneys, and pancreas [68, 85, 87–91]. Human type I isoenzyme of 5 α -R is found mainly in high levels in sebaceous glands of the scalp and the majority of skin tissue as well as the brain, liver, and muscles [85, 92] and low levels in the prostate (NB: levels may increase in prostate cancer cells [93]). Like types I and III, human type II isoenzyme of 5 α -R is primarily expressed in the hair follicles, epididymis, and prostate [85], and can be expressed in various structures of the brain (but the data on this are more limited than for these other well-characterized tissues) [68, 88, 94].

A recent study, however, in rats demonstrates regional patterns of 5 α -R type II expression [95]. Specifically, 5 α -R type II was expressed in the olfactory bulb, cortical regions including olfactory bulb, corticolimbic regions (prefrontal and somatosensory cortex, hippocampus, amygdala), thalamus, and cerebellum [95]. This expression pattern seemed to be limited to neurons; moreover, there was 5 α -R type II expression in GABA cells in the striatum, hippocampus, and cortex [95]. Given that these isoenzymes have distinct expression patterns, they represent distinct therapeutic targets as well as adverse side effects from their exposure to finasteride [86, 96].

The role of 5 α -R for brain function is also supported by looking at studies in mice that are genetic knockouts. 5 α -R knockout mice are a valuable research tool in which the expression of the type I 5 α -R gene is perturbed. This results in deficiencies in its protein product, the 5 α -R enzyme throughout life [97, 98]. Effects of reducing this enzyme can be robust. For example, female mice that are

deficient in 5 α -R have smaller litter sizes (2–3 pups compared to 8 in wild-type controls); this greater rate of fetal death is due to higher E₂ concentrations producing toxicity because of failure to metabolize androgens via the 5 α -R pathway [98]. In adults, we have observed additional evidence of brain trauma with knockout of this enzyme [11, 16] as well as increased anxiety [99–101] and aggression [12], poorer spatial cognition [102], and reduced sexual responding [103]. These mice also show different patterns of alcohol consumption [104], similar to what is observed with finasteride administration to mice [105]. In addition to the behavioral and phenotypic effects of 5 α -R type II deficiency already discussed, there is further evidence of the role of 5 α -R for brain function and behavior of people. One such example has been reported recently [106]. In this pilot study, depressed patients and those that were not diagnosed with a psychiatric disorder were compared for 5 α -R type I messenger RNA expression in the brain. Results showed that individuals with depression showed a more than 50% reduction in 5 α -R messenger RNA in prefrontal cortex Brodmann's area 9 (but not in the cerebellum [106]). In a follow-up experiment, levels of neurosteroids in this same region of the brain were reduced in depressed non-treated patients; depressed patients treated with antidepressants had increased neurosteroid levels [106]. These data show that altering 5 α -R gene expression can have robust effects on brain function and point to differences in steroid levels.

Finasteride's Effect on Neurosteroid Production A recent paper has investigated the effects of 5 mg of finasteride (Proscar) that is used for BPH on neurosteroid levels [107]. In this report, older men (57–79 years old) were administered placebo or finasteride for 12 months and plasma levels of androstenedione, T, DHT, DHT sulfate, 3 α -diol glucuronide, and androsterone glucuronide were measured in serum by radioimmunoassay. As expected, there were no differences in the placebo control group; however, there were reductions in many of the steroids assessed even 1 month after finasteride treatment was initiated that generally persisted. For example, DHT, DHT sulfate, and 3 α -diol glucuronide decreased by more than 70% among the users of finasteride in the first month of treatment compared to baseline levels; this occurred concomitantly with higher levels of T and androstenedione approximately 18% and 35%, respectively. These data show altering steroid metabolism with finasteride can have actions beyond those at 5 α -R alone.

We know that neurosteroids play a significant role for protection of the brain following insult, cognition, and anxiety and depression [108–111]. Synthesis of neurosteroids requires 5 α -R. As such, finasteride alters neurosteroid levels and can have robust effects clearly related to the adverse effects of finasteride that have been reported in men in the short term

and long term following cessation of its use. For example, dysregulation of neurosteroid synthesis and androgen deficiency is associated with mood disorders, such as depression [54, 112]. Of clinical relevance is consideration of long-term effects of androgen manipulations that extend beyond the treatment period.

Neuroendocrine Effects of Prefrontal Synthesis

In cases of PFS, there appear to be long-term consequences of changing androgen milieu that may be independent of specific levels of androgen concentrations at a particular time. For example, reports indicate long-term changes in these behaviors as well as neuroactive steroid levels of men [51, 52, 54]. In the report by Melcangi and colleagues [52], three men who had taken finasteride for MPB and reported physical and psychological symptoms at assessment, which persisted after cessation of finasteride (e.g., stiffness, cramps, and tremors in muscles, chronic fatigue, and symptoms of anxiety and depression), had neurosteroid levels measured in cerebrospinal fluid (CSF) and plasma. Levels of these steroids in tissues were compared in these three patients to five control subjects who were around the same age, but had not taken finasteride. Levels of neurosteroids in CSF and plasma were measured with liquid chromatography–tandem mass spectrometry (LC/MS). In addition to some differences between finasteride patients, there were greater effects for some steroids when assessing across the finasteride treatment group and the control group. Among the finasteride group, compared to the control group, there were lower levels of several neurosteroids in CSF: 3 α ,5 α -THP, isopregnanolone, and DHT; there were also higher levels of T and E₂ in CSF. There were lower plasma levels of dihydroprogesterone, but higher levels of 3 α -diol and E₂, of former, symptomatic users of finasteride compared to healthy controls.

A follow-up study from this group [51] demonstrated a similar pattern. In this study, former users of finasteride ($n = 7$) that were showing physical and psychological adverse effects much like the previously described Melcangi and colleagues study were compared to age-matched, healthy men (control group, $n = 12$). In this study, LC/MS was used to measure levels of several steroids in CSF and plasma: T, DHT, 3 α -diol, 3 β -diol, E₂, pregnenolone, progesterone, dihydroprogesterone, 3 α ,5 α -THP, isopregnanolone, and dehydroepiandrosterone (DHEA).

Results showed that former users of finasteride had higher levels of pregnenolone in CSF and plasma compared to controls and no differences in DHEA. Progesterone was reduced in CSF, but not altered in plasma, of former finasteride users compared to controls. Progesterone's metabolites (dihydroprogesterone, 3 α ,5 α -THP, isopregnanolone) were reduced in CSF and plasma of former finasteride users. Testosterone and 3 α -diol were increased in CSF and plasma among former finasteride users with

concomitant reduction in CSF levels of DHT (with no change in plasma levels of DHT). The other androstane neurosteroids, 3 β -diol and E₂, were not detected or not changed in CSF, respectively, or were increased in plasma of former finasteride users compared to controls. Overall, this complex pattern of change in these neurosteroids shows that finasteride can have enduring effects on many different neurosteroids, even after it is no longer being used as treatment. That some steroids were increased and others decreased supports a general dysregulation of these steroids as measured in CSF and plasma. These steroid levels were not assessed in isolation among these former users of finasteride. Indeed, there were persistent physical and psychological effects among these men, coincident with this dysregulation in neuroendocrine function.

In sum, finasteride acting at 5 α -R interferes with many downstream or alternative pathways for production of steroids; reducing one pathway increases activity of other enzymes to increase or decrease neurosteroids that have many effects. Perhaps most importantly, these actions of finasteride via 5 α -R are not limited to current treatment, but can have lasting effects on patients long after they have discontinued finasteride.

Neurosteroids and Receptor Targets

Decades of work by many laboratories show that neuro(active)steroids have rapid effects, including those on neuronal excitability and synaptic function [113–121]. These rapid effects are understood to involve direct or indirect modulation of ion-gated or other metabotropic neurotransmitter receptors, rather than traditional actions via cognate nuclear steroid hormone receptors; these actions are referred to as novel or non-traditional actions of steroids. Indeed, these findings about neurosteroids have changed many of these aforementioned concepts regarding the possible sources, mechanisms, and effects of steroids. In brief, unlike circulating hormones, neurosteroids are produced in the brain and can have actions locally at neurotransmitter receptors. This means that they can change the function of neuronal circuitry locally and rapidly. Our research and other research published in the scientific community demonstrate many receptor targets for neurosteroids, including GABA, dopamine, and sigma receptors. As such, finasteride exposure that results in changes to neurosteroid levels also effects GABA, dopamine, sigma, and ER β receptors, as well as a number of other substrates which are beyond the scope of this report. We propose further that these (de)masculinization and (de)feminization steroid pathways can be re-organized in adult males, such as naturally occurs with aging or purposely with finasteride administration or when certain insults occur to the brain as with mild traumatic brain injury (mTBI). In males, steroid hormones have robust effects on many tissues even in very low concentrations. Testosterone is the most abundant androgen in circulation. It is produced by testicular Leydig cells following

sequential signaling by gonadotropin-releasing hormone (GnRH) from the hypothalamus and luteinizing hormone from the anterior pituitary; yet, only 3% is free with the other 97% being bound to proteins, such as albumen and sex-hormone binding globulin. Testosterone that is bound is not able to diffuse across cell membrane to have actions at its primary target, ARs. Despite a small percentage of T being free in circulation, those physiological levels have actions at many tissue targets with clear functions. During early fetal development, T is important for promoting Wolffian duct development into the internal male genitalia, as well as other organizing effects on the brain. Many of the effects of T occur following its metabolism to DHT via 5 α -R within target cells, such as those of the hair follicles, prostate, and brain. Likewise, DHT has important effects during fetal development to promote differentiation and growth of the male external genitalia and the prostate gland. Our research and other's research have shown that natural changes in steroids or induced changes can have a profound effect on behavior and phenotype and that part of this mechanism involves changes in neurosteroids [122•, 123•, 124••, 125, 126, 127••].

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- Of importance
- Of major importance

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