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A New Look at the 5α-Reductase Inhibitor Finasteride

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ABSTRACT

Finasteride is the first 5α-reductase inhibitor that received clinical approval for the treatment of human benign prostatic hyperplasia (BPH) and androgenetic alopecia (male pattern hair loss). These clinical applications are based on the ability of finasteride to inhibit the Type II isoform of the 5α-reductase enzyme, which is the predominant form in human prostate and hair follicles, and the concomitant reduction of testosterone to dihydrotestosterone (DHT). In addition to catalyzing the rate-limiting step in the reduction of testosterone, both isoforms of the 5α-reductase enzyme are responsible for the reduction of progesterone and deoxycorticosterone to dihydroprogesterone (DHP) and dihydrodeoxycorticosterone (DHDOC), respectively. Recent preclinical data indicate that the subsequent 3α-reduction of DHT, DHP and DHDOC produces steroid metabolites with rapid non-genomic effects on brain function and behavior, primarily via an enhancement of γ-aminobutyric acid (GABA)ergic inhibitory neurotransmission. Consistent with their ability to enhance the action of GABA at $GABA_A$ receptors, these steroid derivatives (termed neuroactive steroids) possess anticonvulsant, antidepressant and anxiolytic effects in addition to altering aspects of sexual- and alcohol-related behaviors. Thus, finasteride, which inhibits both isoforms of 5α-reductase in rodents, has been used as a tool to manipulate neuroactive steroid levels and determine the impact on behavior. Results of some preclinical studies and clinical observations with finasteride are described in this review article. The data suggest that endogenous neuroactive steroid levels may be inversely re-

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lated to symptoms of premenstrual and postpartum dysphoric disorder, catamenial epilepsy, depression, and alcohol withdrawal.

INTRODUCTION

Rapid membrane effects of steroid hormones provide a mechanism by which steroids can influence brain function and behavior in addition to their classic genomic actions. The pioneering studies of Hans Seyle first described the neuroactive properties of several steroidal compounds (128). The time course for action of the steroidal compounds was consistent with the idea that steroid metabolism produced the neuroactive compound(s). After the initial demonstration that the synthetic steroid alphaxalone potentiated GABA-gated chloride currents (67), strong evidence indicated that steroid metabolites have rapid membrane actions via an interaction with ligand-gated ion channels (8,13,93,102,123). Based on this evidence and consensus in the field, the term "neuroactive steroids" refers to the rapid membrane actions of steroids and their derivatives.

The progesterone metabolite allopregnanolone (3α,5α-THP or tetrahydroprogesterone) is the most potent endogenous positive modulator of $GABA_A$ receptors yet identified. Fluctuations in endogenous levels *in vivo* occur within the range of concentrations that potentiate GABAergic inhibition *in vitro* (8), and clinical and animal research show that these fluctuations can contribute to diverse disorders such as premenstrual and postpartum dysphoric disorder (37), catamenial epilepsy (68), depression (148), and alcohol withdrawal (118). The inverse relationship between endogenous 3α,5α-THP levels and anxiety, depression and seizure susceptibility is consistent with 3α,5α-THP's pharmacological profile, since exogenous administration produces anxiolytic, anticonvulsant and antidepressant effects (53,72).

Generally speaking, the two-step metabolism of testosterone, progesterone and deoxycorticosterone yields neuroactive compounds through the actions of the enzymes 5α-reductase and 3α-hydroxysteroid dehydrogenase (20,94). The 5α-reduction of testosterone, progesterone and deoxycorticosterone (to produce DHT, DHP, and DHDOC, respectively) is unidirectional. In contrast, the 3α-reduction of DHT, DHP, and DHDOC (to produce androstanediol, 3α,5α-THP and tetrahydrodeoxycorticosterone or 5α-THDOC, respectively) is a reversible reaction. Hence, use of a 5α-reductase inhibitor can be considered a blockade of the rate-limiting step to the two-step production of neuroactive steroid metabolites (see Fig. 1). Since androstanediol, 3α,5α-THP and 5α-THDOC all have higher potency at $GABA_A$ receptors than at androgen, progesterone or corticosteroid receptors, respectively, it is possible that inhibition of 5α-reductase would have consequences on central nervous system (CNS) inhibitory tone and resultant behavioral processes.

The 4-azasteroid finasteride [17β-(N-t-butyl)carbamoyl-4-aza-5α-androst-1-en-3-one] was the first 5α-reductase inhibitor to be clinically approved for use in men for the treatment of BPH in 1992 and for the treatment of androgenetic alopecia in 1997. These clinical applications of finasteride are based on its ability to prevent the conversion of testosterone to DHT. As described above, finasteride also should prevent the conversion of progesterone to DHP and of deoxycorticosterone to DHDOC, providing the possibility of additional research applications for the use of finasteride. This review will begin with a brief discussion of the current clinical uses of finasteride and will summarize what is cur-

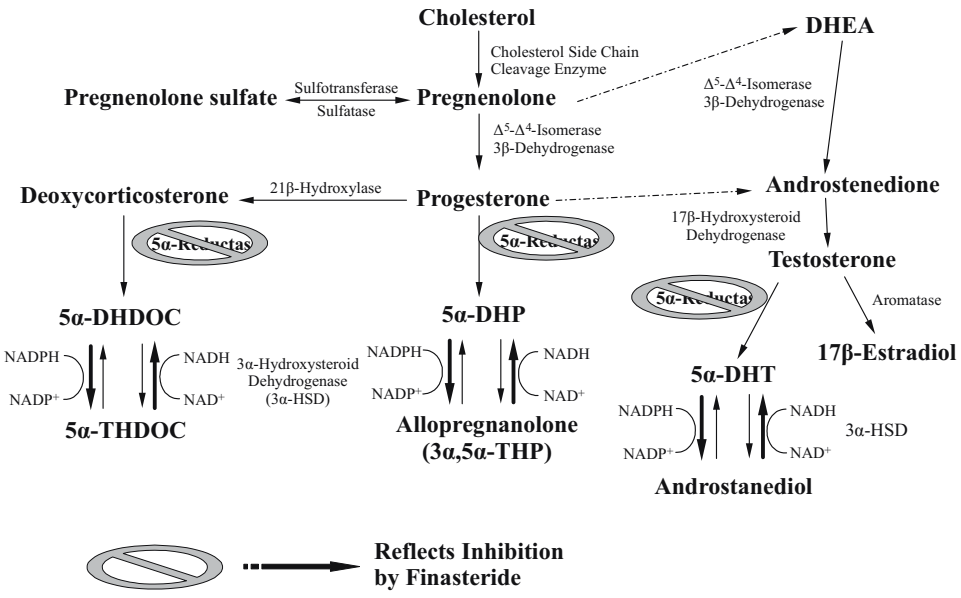

Fig. 1. Biosynthesis of the GABAergic neuroactive steroids 3α,5α-THP, 5α-THDOC and androstanediol and the point in the pathway where finasteride exerts its inhibitory effect. The broken lines indicate that 17-OH pregnenolone and 17-OH progesterone are omitted from the diagram in the formation of DHEA from pregnenolone and formation of androstenedione from progesterone, respectively. DHEA, dehydroepiandrosterone.

rently known regarding the pharmacokinetics and potency of finasteride to inhibit the 5α-reductase enzymes in rodents and humans. The primary purpose of the present review will be to survey recent preclinical and clinical data that are consistent with the notion that finasteride may alter brain function and behavior via its ability to inhibit the formation of GABAergic neuroactive steroids.

PHARMACODYNAMICS AND PHARMACOKINETICS

5α-Reductase Isozyme Sensitivity to Finasteride: Species Differences

Two distinct 5α-reductase isozymes, Type I and II, are found across mammalian species, including rodents (mice and rats) and primates (monkeys and humans). Each of these isozymes is differentially expressed in tissues and during distinct developmental stages, and thus may represent separate therapeutic targets. While 5α-reductase can influence progesterone, corticosteroid and androgen metabolism, the current therapeutic role for finasteride in humans involves blocking the conversion of testosterone into DHT, the major androgen metabolite. However, potential therapeutic options also are being explored with inhibition of progesterone metabolism in the CNS, described below.

In humans, Type I 5α-reductase is found primarily in the sebaceous glands of most regions of skin including scalp, and in liver, muscle, and brain (31,140), with low levels also present in prostate that may increase in prostate cancer (142). Type I 5α-reductase is responsible for approximately one-third of circulating DHT (58). The Type II 5α-reductase isozyme is found in prostate, seminal vesicle, epididymis, and hair follicles as well as in liver (140), and is responsible for the remaining two-thirds of circulating DHT. Because of this profile of tissue specific expression and the specificity of finasteride inhibition in humans, few adverse reactions are observed in other organ systems. Finasteride has no affinity for the androgen receptor and exhibits no known androgenic, anti-androgenic, estrogenic, anti-estrogenic, or progesterone-like activity (136).

The mechanism of action of finasteride in humans is based on its preferential inhibition of the Type II isozyme (2). *In vitro* binding studies that examined finasteride's ability to inhibit either isozyme of 5α-reductase documented a 100-fold selectivity for the human Type II over the Type I isozyme (78). Based on the tissue-specific expression of Type II 5α-reductase in humans, currently approved clinical uses for finasteride target the diminution of DHT levels and the concomitant decrease in activity of DHT at the androgen receptor in the prostate and the scalp of men.

In contrast to the selective inhibition of the Type II isozyme by finasteride in humans, both isozymes of the 5α-reductase enzyme in the rodent demonstrate comparable inhibition following finasteride exposure (5,139). Even though the human and rat Type I isozymes share approximately 60% amino acid sequence homology and exhibit similar steroid substrate specificities, human vs. rat sensitivity to finasteride differs by approximately 100-fold (3). A subsequent report utilizing a chimeric 5α-reductase cDNA approach determined that disparity within a 4 amino acid sequence on exon 1 conferred either resistance or sensitivity to finasteride at the Type I isozyme in humans and rats, respectively (139).

The rodent 5α-reductase isozymes also differ in the mechanism by which finasteride inhibits their enzymatic activity. Finasteride acts as a classical competitive inhibitor of the rat Type I enzyme and time-dependently dissociates from this isozyme, whereas it binds and irreversibly modifies rat Type II 5α-reductase following the formation of a high affinity complex (5,135). This mechanistic difference in finasteride binding between rat isozymes results in a 10-fold difference in K_i values (i.e., 10 vs. 1 nM finasteride for type I and type II, respectively; 5). Little is known regarding the recovery of the 5α-reductase enzymes and the subsequent restoration of 5α-reduced steroid metabolite levels following the cessation of finasteride treatment in rodents. Based on the competitive vs. irreversible inhibition of the two 5α-reductase enzymes, it is feasible that the rat Type I enzyme would recover more quickly than the Type II enzyme. This difference may have important implications in the rodent, given that Type I is predominantly localized in the CNS and Type II 5α-reductase is largely in the periphery (135).

Onset and Duration of Finasteride's Effects in Humans and in Rodents

In humans, pharmacokinetic data for 5α-reductase inhibitors are limited and generally reflect the results following a bolus administration of the drug (66). Finasteride pharmaco-

kinetics has been most extensively characterized following oral doses of either 1 or 5 mg/day in men, corresponding to treatment formulations for male pattern baldness (Propecia) and BPH (Proscar), respectively. A single 5 mg dose was found to produce peak plasma concentrations of 35–40 ng/mL (approximately 94 nM) finasteride within 2–6 h (62,65,100,132). When the pharmacokinetics of finasteride was examined after single and multiple administration of the drug over an increasing dose range (5–100 mg), the relationship between peak plasma concentration and dose of finasteride was linear (100). The relationship between finasteride dose and peak concentration did not change following multiple administration over 7 days, suggesting that no accumulation of finasteride occurred. The terminal half-life of finasteride in circulation, independent of dose, ranged from 4.7–7.1 h (61).

Inhibition of Type II 5α-reductase blocks the peripheral conversion of testosterone to DHT, resulting in significant decreases in serum and tissue DHT concentrations. Treatment with finasteride produces a rapid reduction in serum DHT concentration from 60 to 80% (18,116,117), which demonstrates the contribution of the human Type I enzyme to serum DHT levels. However, finasteride decreases prostatic DHT concentrations (where the Type II enzyme predominates) by as much as 90% (55,92). Multiple daily doses for 1–2 weeks led to a similar 65–80% suppression of serum DHT (62), suggesting that tolerance did not develop to a chronic finasteride regimen in men. It has been reported that DHT concentrations recover within 2-weeks following the cessation of finasteride treatment in men (133), a finding that would be consistent with the slow turnover for the human Type I and Type II enzyme complexes (96).

Another point to consider with regard to the relative efficacy of a specific finasteride dose and resultant concentration in plasma and tissue is that the IC_{50} for finasteride in prostate and scalp homogenates was reported to be 5.9 and 310 nM, respectively (98). With this in mind, it was estimated that a concentration of 94 nM finasteride would inhibit prostate homogenate 5α-reductase by 85%, but would inhibit scalp homogenate 5α-reductase by 25% (66). Results from clinical studies that measured DHT reduction in prostatic tissue (92) and scalp skin (28) are consistent with these estimates. By extrapolation, in order to achieve a level of inhibition in scalp that was comparable to that in the prostate, the concentration of finasteride in plasma would have to be 1 μM (66), which would be obtained following a 50 mg dose of finasteride (100).

In rodents, systemic finasteride doses comparable to oral doses taken by human subjects have typically been administered, with doses ranging from 25–150 mg/kg (approximately 0.625–3.75 mg per 25 g mouse or 6.25–37.5 mg per 250 g rat). Although finasteride concentrations following injection in rodents have not been reported to date, behavioral manifestations of this 5α-reductase inhibitor in rats have been documented following as little as a 4-h pretreatment time (151). Medial basal hypothalamic and ovarian 5α-reductase enzymatic activity were found to be reduced by 45 and 80%, respectively, in pregnant rats receiving 50 mg/kg finasteride for 7 days (86). Measurement of the steroid metabolites 3α,5α-THP and 5α-THDOC in estrus female rats at 2-h post-treatment with a single application of 25 mg/kg finasteride revealed equivalent suppression of both metabolites by 75% in the cerebral cortex and by 65% in plasma (24). A slightly reduced efficacy for finasteride was noted when it was administered over 7 days; 46 and 42% suppression of these steroid metabolites within the cerebral cortex and plasma, respectively (24). Preliminary findings from our laboratory have demonstrated that administration of a

50 mg/kg dose of finasteride to mice suppressed plasma and brain 3α,5α-THP concentrations by 66 and 80%, respectively, at a 24-h post-injection time point (35). As noted above, the recovery of 5α-reduced steroid concentrations and 5α-reductase enzymatic activity following cessation of finasteride treatment in rodents has not yet been studied.

THERAPEUTIC APPLICATIONS

Clinical Uses of Finasteride

A 5-mg dose of finasteride is approved for treatment of symptomatic BPH (88), which reduces prostate volume by 19–27% (see 4,61,116). Finasteride has been shown to be most effective in men with enlarged prostates and the most severe symptoms (91). Finasteride is also approved for the treatment of male-pattern hair loss (androgenetic alopecia) and vertex baldness, and is generally prescribed at a lower dose of 1 mg (77,87).

In postmenopausal women with androgenetic alopecia, finasteride treatment has not been generally effective (101), although its efficacy in women remains controversial (146). Also, finasteride is contraindicated in pregnant or potentially pregnant women because it has been linked to abnormalities of the reproductive tissues in a male fetus (for example, see 122). Nevertheless, there have been several studies published on the efficacy of daily or intermittent doses of finasteride ranging from 2.5–5 mg for the treatment of hirsutism in women, defined as the development of terminal hair growth in a male pattern (e.g., 89,97,116,124,137).

Future Therapeutic Options

Preliminary clinical findings suggest that finasteride may have some efficacy for the prevention of prostate cancer in men. In The Prostate Cancer Prevention Trial, investigational use of finasteride as a chemopreventative agent showed that patients administered a dose of 5 mg per day (as is commonly prescribed for BPH) were 25% less likely to have developed prostate cancer at the end of the 7-year trial, when compared to subjects taking placebo (141). However, concerns have been raised, since the results indicated that finasteride might increase the risk of higher-grade disease in those that went on to develop prostate cancer (141). Debate continues as to the risk/benefit ratio and the potential public health impact (81,154). In females, treatment of acne and facial hirsutism observed in polycystic ovary syndrome could be potential indications for finasteride, although a selective 5α-reductase Type I inhibitor might be more effective (21), and finasteride was not as beneficial as alternative anti-androgen therapies (19).

Finasteride crosses the blood-brain barrier, and thus can be used to inhibit 5α-reductase activity in the CNS (85). Given this finding, there has been speculation that finasteride might be useful to inhibit progesterone metabolism, and the concomitant synthesis of neuroactive steroids in the brain. Thus, the remainder of the review will focus on recent preclinical and clinical data that are consistent with the notion that finasteride alters brain function and behavior via its ability to inhibit the formation of GABAergic neuroactive steroids, with particular emphasis on 3α,5α-THP.

POTENTIAL IMPACT ON BRAIN FUNCTION AND BEHAVIOR

Depression

This section will highlight preclinical research involving animal models of anxiety and depression and clinical investigations with findings relevant to depression.

Preclinical studies on anxiety- and depression-related behaviors

Numerous studies have documented that systemic administration of 3α,5α-THP produces anxiolytic (53,75,111,155) and antidepressant effects (79). Co-administration of a 5α-reductase inhibitor (different than finasteride) with progesterone blocked its anxiolytic effect, providing evidence that the anxiolytic effect of progesterone was due to its metabolism to 3α,5α-THP (12). Likewise, a similar strategy demonstrated that the anxiolytic effect of testosterone was mediated by its 5α-reduced metabolites (30). Microinjection studies have targeted the amygdala and hippocampus, brain regions thought to be relevant in anxiety and depression. Bilateral infusion of 3α,5α-THP into the dorsal hippocampus (11) or amygdala (14) produced anxiolytic effects, and intracerebroventricular administration of 3α,5α-THP generated antidepressant effects (72). In contrast, both systemic and intrahippocampal administration of finasteride increased depression- and anxiety-like behaviors in rats (50,51). A subsequent study determined that finasteride increased depression- and anxiety-like behaviors in rats when administered into the amygdala (152). Therefore, bi-directional manipulation of endogenous 3α,5α-THP levels in the amygdala and hippocampus (↑ with exogenous 3α,5α-THP or progesterone, ↓ endogenous synthesis with finasteride) produced opposite effects in animal models of anxiety and depression. These findings suggest that 3α,5α-THP levels may be inversely related to mood states.

Animal models of postpartum dysphoric disorder document that withdrawal from high levels of progesterone increased anxiety and seizure susceptibility concomitant with a reduction in $GABA_A$ receptor function, and that blocking progesterone metabolism (and consequently, 3α,5α-THP formation) reduced these symptoms of "progesterone withdrawal" (129,130). The results from a recent mouse model of premenstrual dysphoric disorder indicated that 3 daily injections of finasteride significantly decreased hippocampal 3α,5α-THP levels. This reduction in 3α,5α-THP levels was associated with a decrease in sensitivity to the anxiolytic effect of pregnanolone (3α,5β-THP), the 5β-isomer of 3α,5α-THP that also is a positive modulator of $GABA_A$ receptors with slightly less potency than 3α,5α-THP (131). While the array of symptoms and hormonal correlations reported for premenstrual dysphoric disorder in females suggest a diverse etiology, it has been suggested that the extent or rate of change in 3α,5α-THP levels might be more important than the absolute levels of this neuroactive steroid with regard to its contribution to dysphoric symptoms (39,131).

An inverse relationship between endogenous 3α,5α-THP levels and symptoms of anxiety and/or depression was reported in cohorts of male subjects with depression (148) or in the early phase of alcoholic withdrawal (118). Treatment with drugs that restored

3α,5α-THP levels to those found in control subjects significantly reduced the symptoms of anxiety and depression in both the depressed and alcoholic subjects (119,120,134). Specifically, drugs clinically employed for the treatment of depression, such as the selective serotonin reuptake inhibitors fluoxetine and paroxetine (63) and the atypical, third-generation antidepressant mirtazepine (127), were found to increase 3α,5α-THP levels, albeit via different effects on the 3α-hydroxysteroid dehydrogenase enzyme. Whereas fluoxetine and paroxetine favor the enzymatic reduction of DHP (to form 3α,5α-THP), mirtazepine inhibits the oxidation of 3α,5α-THP (to form DHP). In summary, preclinical studies with finasteride and other drugs that alter 3α,5α-THP biosynthesis support a role for endogenous 3α,5α-THP in maintaining normal GABAergic brain function, and suggest that alterations in endogenous 3α,5α-THP levels could contribute to symptoms of anxiety and depression (84).

Clinical findings of finasteride-induced depression

As reviewed above, there is ample evidence in rodents to suggest that finasteride could act as a depression- or anxiety-inducing agent in humans. This hypothesis is consistent with the finding that testosterone deprivation in prostate cancer patients was associated with an increased rate of depression (105). However, it should be noted that the cases of depression were connected to histories of depression that predated androgen deprivation. Thus, it may be that a history of depression in the male might be a risk factor for a depressive reaction to treatments for prostate cancer.

Nonetheless, the most direct evidence that finasteride may produce depressive effects in humans is a collection of case reports in which 19 (5 females and 12 males) of 23 patients that were treated with finasteride for androgenetic alopecia developed mood complaints, including depression (1). Some of the patients also presented comorbid anxiety-like symptoms, but depression was described as the dominant psychological complaint. After suspension of finasteride treatment, all patients recovered from depression in approximately 11 days. Two patients who agreed to recommence finasteride treatment relapsed into a depressed state, but both patients recovered after a second termination of finasteride therapy.

In a small study in which finasteride was used to treat hirsutism (22), fewer finasteride-treated participants reported depression as a side effect than participants taking placebo. Although a recent review concluded that finasteride was well tolerated for hirsutism (145), we are unaware of any other published reports of women taking finasteride that include depression as a measure following treatment. Thus, despite emerging preclinical evidence that finasteride might have psychoactive effects, available data suggest that finasteride may not have negative psychological effects in women.

A subsequent study of quality of life (but not depression explicitly) in men taking finasteride also failed to provide evidence that finasteride detracted from life quality. In a double-blind, placebo-controlled study there was little or no difference between placebo and finasteride groups in ratings of general health and life satisfaction (57). Although life satisfaction can be influenced by factors aside from depression, it was apparent that quality of life did not diminish. Since BPH symptoms did improve, it is possible that depression did not emerge following finasteride treatment or that the severity of depression was offset by the improvement in BPH symptoms.

Finally, a more recent study of association between different treatments for BPH and rates of antidepressant prescription showed that, while finasteride was associated with depression, the association was better predicted by the presence of BPH (23). These data suggest that the depression in finasteride-treated patients was due to the disorder (i.e., BPH) rather than finasteride treatment *per se*.

Seizure Susceptibility

Preclinically, finasteride has proven a useful tool in elucidating the role of neuroactive steroids in seizure activity. While the exact mechanism through which neuroactive steroids reduce seizure severity is not clear, the anticonvulsant action of these steroid metabolites is consistent with their ability to rapidly enhance GABAergic neurotransmission (see **Introduction**). Although both progesterone and 3α,5α-THP are reported to be positive modulators of $GABA_A$ receptors (54,90,102), the potency of 3α,5α-THP is 500 times higher than that of progesterone (90), and evidence gathered in animal models using finasteride has suggested that it is 3α,5α-THP, rather than progesterone, that most likely modulates seizure severity (82). Likewise, swim stress odeozycorticosteroner (DOC) increased 5α-THDOC levels and had anticonvulsant properties (114). The following section summarizes the studies conducted using finasteride to examine the role of neurosteroids in seizure activity.

Animal models of epileptic and absence seizures

Results in two different seizure models are consistent with an inverse relationship between endogenous 3α,5α-THP levels and seizure susceptibility in female rats. Mimicking the hormonal phase of proestrus/estrus (with high progesterone administration) in ovariectomized (OVX) rats was associated with increased brain 3α,5α-THP levels and decreased number of partial seizures following perforant pathway stimulation, when compared with low hormonal phases (46). Administration of finasteride reversed the anticonvulsant effects of hormonally simulated estrus, suggesting that metabolism of progesterone to 3α,5α-THP contributed to the anticonvulsant effects of estrus. A separate study measured sensitivity to kainic acid-induced seizures in female rats during various stages of the estrous cycle as well as during and following pseudopregnancy and pregnancy (41). Notably, mean duration of tonic-clonic seizures was significantly negatively correlated with brain 3α,5α-THP levels ($r = –0.92$). Finasteride treatment significantly decreased brain 3α,5α-THP levels and increasing seizure susceptibility (41).

In male mice, finasteride reduced the anticonvulsant effects of progesterone and fluoxetine, both of which increase 3α,5α-THP levels (discussed above), measured by susceptibility to pentylenetetrazol (PTZ)-induced convulsions (82,147). Finasteride also blocked the anticonvulsant effect of progesterone in progesterone receptor knockout and wildtype mice, measured by susceptibility to PTZ-induced and amygdala-kindled seizures (110). Collectively, these findings demonstrated that the anticonvulsant effect of progesterone was not mediated via action at the progesterone receptor and that it required metabolism of progesterone.

In contrast, finasteride had the opposite effect on seizure susceptibility in the WAG/Rij rat, a model of absence epilepsy (149). That is, when the number of spike wave discharges

(SWD), a measure of absence seizure activity, was measured following administration of progesterone, this model exhibited a significant dose-dependent increase in SWD. With co-administration of finasteride this effect was blocked, again suggesting that 3α,5α-THP mediated the observed increases in SWD.

With regard to testosterone metabolism, proconvulsant and anticonvulsant properties have been observed, depending on whether testosterone was aromatized or reduced, respectively (109). Specifically, blocking the aromatization of testosterone to 17β-estradiol by letrazole eliminated the proconvulsant effects of testosterone, which were most probably mediated by estradiol (109). In contrast, finasteride blocked the anticonvulsant activity of testosterone, which could be mediated via its 5α-reduced metabolite, 3α-androstanediol (e.g., 44). Alternatively, two additional testosterone metabolites with GABAergic properties (androsterone and the 5b-epimer etiocholanolone) were found to possess anticonvulsant properties in various mouse seizure models (76). As these testosterone metabolites are produced via further reduction by 17β-hydroxysteroid dehydrogenase (after sequential actions by 5α-reductase and 3α-hydroxysteroid dehydrogenase), one can surmise that finasteride would decrease levels of androsterone and etiocholanolone. Notably, androsterone and etiocholanolone are the major excreted metabolites of testosterone (15, 126), and long term antiepileptic drug therapy was found to decrease urinary excretion of both metabolites (e.g., 15). Thus, it was suggested that a reduction in GABAergic testosterone metabolites in men with epilepsy could contribute to increased seizure susceptibility (76).

Catamenial epilepsy

Catamenial epilepsy refers to the clustering of seizure activity at specific times during the menstrual cycle. Specifically, Newmark and Penry (99) identified the three days prior to the start of menstruation and the four days after its onset as the time during which a significant increase in epileptic seizure activity was most often present in women with catamenial epilepsy, although other patterns have been described (69). These clusters coincided with a decrease in progesterone levels, which was thought to contribute to the increased incidence of the epileptic seizures (reviewed in 108). Consistent with this notion, seizure incidence in epileptic women was most directly and inversely correlated with 3α,5α-THP, rather than progesterone, levels (121).

A rat model of catamenial epilepsy supports this assertion. Administration of finasteride to pseudopregnant female rats, which have high progesterone levels, produced a significant increase in sensitivity to PTZ-induced convulsions when compared to controls (112,113). Earlier work also determined that administering finasteride to a pseudopregnant rat increased seizure susceptibility and decreased sensitivity to benzodiazepines, measured behaviorally and electrophysiologically (129,130). Similar findings were obtained when progesterone withdrawal was induced by OVX (which also would decrease progesterone and ALLO levels; 130), suggesting that some of the symptoms of progesterone withdrawal were due to the concomitant drop in endogenous 3α,5α-THP levels.

Furthermore, a recent case study described a woman suffering from catamenial epilepsy that had responded well to progesterone treatment (68). A recurrence in the number and severity of epileptic seizures led to the discovery that she was receiving finasteride as a treatment for male pattern baldness. Upon cessation of finasteride treatment, her epi-

lepsy was once again managed with progesterone, a finding that lends support to the assertion that a reduction in the levels of progesterone metabolites may contribute to catamenial epilepsy.

Stress-induced modulation of seizure susceptibility

Another consideration is whether conditions of acute or chronic stress could alter levels of GABAergic neuroactive steroids and impact seizure susceptibility (107). While early work demonstrated that ambient temperature swim stress significantly increased brain 3α,5α-THP and 5α-THDOC levels (106), it was recently determined that swim stress produced an anticonvulsant effect in rats (114) and mice (103). Notably, finasteride blocked the swim stress-induced increase in 5α-THDOC levels as well as the anticonvulsant effect of swim stress, measured by PTZ seizure threshold (114). Subsequent studies determined that administration of DOC (precursor to 5α-THDOC, see **Introduction**) produced a dose-dependent increase in 5α-THDOC levels concomitant with an anticonvulsant effect in several different seizure models in mice. Finasteride completely blocked the anticonvulsant effect of DOC administration and markedly reduced the increase in 5α-THDOC obtained after administration of the precursor (114). Collectively, these observations suggest that the conversion of DOC to its $GABA_A$ receptor active metabolite is another pathway through which neuroactive steroids can influence seizure activity and highlight a potential physiological role for 5α-THDOC in stress-sensitive conditions (107).

Sexual Behavior

Sex behavior in female rats engages proceptive and receptive behaviors. Proceptive behaviors involve the solicitation of sexual activity (e.g., hopping, darting, ear wiggling, and pacing), whereas receptive behaviors ensure that mating is successful (e.g., lordosis; 42). Early work documented that proceptive behaviors were controlled by progesterone, while the expression of receptive behaviors was amplified by a combination of estrogen and progesterone (56). For example, OVX and adrenalectomized females do not display proceptive or receptive behaviors when in the presence of a male. However, more recent research indicates that progesterone metabolites (such as 3α,5α-THP) also play an important role in the expression of these sex behaviors, and that treatment with finasteride can have a profound effect on some aspects of sexual behavior. Thus, this section will summarize findings regarding finasteride's effects on sexual behavior in animal models and describe the limited data available in humans.

Systemic finasteride and lordosis behavior

The typical measure of sexual activity in female rodents is lordosis behavior, in which the female rodent assumes a position of sexual receptivity with the back arched and the tail deflected (32). This position allows for the male rodent to successfully mount and mate with the female. Initiation of this sexual activity in rodents requires the initial release of estrogen, followed by release of progestins, into the CNS. While estrogens and progestins primarily are released by ovarian or adrenal tissue, they can be synthesized *de novo* in the brain. These steroids modulate sexual receptivity in rodents mainly through actions at classic intracellular steroid receptors, but these genomic effects can work in concert with

non-genomic effects to modulate aspects of sexual behavior (40). For example, evidence suggests that 3α,5α-THP can influence sexual behavior, presumably via its interaction at $GABA_A$ receptors.

Lordosis is often quantified with the lordosis quotient (LQ), which is the percentage of contacts with a male that elicit the lordosis posture. Rodents that have undergone OVX surgery will have a LQ close to zero, and those treated with estrogen alone following OVX also will have a very low LQ. In contrast, OVX rodents treated with estrogen plus an appropriate dose of progesterone will have a LQ close to 60%. Recent work determined that this increased LQ was attenuated by systemic administration of finasteride, but not to the level observed following treatment with estrogen alone (48). The authors concluded that lordosis required both progesterone and its reduced metabolites for full expression of the behavior.

Brain regional effects of finasteride on lordosis behavior

The full expression of lordosis behavior requires progesterone action in the ventromedial hypothalamus (VMH) and the ventral tegmental area (VTA; 43). Notably, progesterone's actions in the VMH require intracellular progesterone receptors (i.e., genomic mechanism), while progesterone's actions in the VTA are rapid (within 1–5 min) and do not require intracellular progesterone receptors (i.e., non-genomic mechanism) (40). The effects of progesterone in the VTA are most likely non-genomic for several reasons. First, progesterone receptor antagonists administered into the VTA had little effect on lordosis. Second, intra-VTA 3α,5α-THP was the most effective progestin at activating lordosis despite its lack of potency at progesterone receptors (47). Third, when progesterone was complexed to a macromolecule so that it could not penetrate the membrane, the progesterone complex altered lordosis behavior, consistent with an action in the VTA via a membrane bound receptor (such as $GABA_A$ receptors). Finally, intra-VTA infusions of finasteride produced a reliable reduction in LQs, whereas infusions into adjacent midbrain sites did not (49), suggesting that the metabolism of progesterone to 3α,5α-THP in the VTA was important for receptive behaviors in rodents.

Finasteride and proceptive behaviors

Proceptive behaviors such as ear wiggling, hopping, darting, partner preference and pacing are controlled by progesterone levels. Although large doses of estrogen will induce low levels of these behaviors, progesterone produces dose-dependent increases (138). However, doses of 3α,5α-THP will increase some proceptive behaviors (notably ear wiggling and darting) to levels indistinguishable from those observed in progesterone-treated animals. In addition, female rats treated with estrogen, progesterone and finasteride have low levels of proceptive behaviors that are similar to those of females treated with estrogen alone (42). Lateral displacement, a proceptive behavior unique to hamsters in which the female moves the perineum in response to sexual contact with a male, also is increased with progesterone or 3α,5α-THP administration and is attenuated with progesterone and finasteride co-administration (45). This evidence is consistent with the involvement of progesterone metabolites in the proceptive sexual behavior exhibited by rodents.

Finasteride and human sex behaviors

Evaluating the effects of finasteride on human behaviors is undeniably more difficult than assessing its effects in animals. Finasteride is often prescribed to individuals in an attempt to correct hormone disorders (such as hirsutism in women) or to men with an enlarged prostate gland, both of which can alter sexual function independent of finasteride administration. With that in mind, there are some long-term studies that examined the effects of finasteride on sexual function. In a six month trial of men administered a high dose (5 mg/day) of finasteride for BPH, a slight increase in ejaculatory dysfunction was reported (156). Data from large, placebo-controlled trials of finasteride for BPH treatment indicated that the highest reported side effects of finasteride were impotence and decreased libido (e.g., 4,61,116). However, it should be noted that these side effects were reported to be mild, to occur in a small percentage of patients (~5%), and to improve as finasteride treatment continued. In a one year trial of women with hirsutism being administered a low dose (2.5 mg/day) of finasteride, only one of 29 women reported any side effects on sexual function (7). While these studies report that finasteride was very effective at treating symptoms of the disease, the mechanism by which finasteride could alter aspects of sexual behavior in humans is not presently known.

Alcohol-Related Behaviors

Alcohol is a drug that interacts with many neurotransmitter systems, but its ability to potentiate $GABA_A$ receptor function is believed to underlie some of its behavioral effects (see 27,64). Based on 3α,5α-THP's potent positive modulation of $GABA_A$ receptors (e.g., 8), many researchers have focused on the interaction between 3α,5α-THP and alcohol-related behaviors and have used finasteride as a pharmacological tool to examine this interaction. This section will summarize relevant preclinical and clinical data on the use of finasteride to modulate alcohol-related behaviors.

Acute effects of alcohol

An acute injection of alcohol (ethanol) in doses ranging from 1.0 to 4.0 g/kg significantly increased cortical 3α,5α-THP levels to pharmacologically active concentrations at 40 to 80 min following injection in male and female rats (6,95,151) as well as in male C57BL/6J (36) and DBA/2J mice (52). Consumption of intoxicating doses of ethanol also significantly increased brain 3α,5α-THP levels in male C57BL/6J mice (36) as well as in male and female adolescent humans (143,144). These data suggest that an ethanol-induced increase in endogenous 3α,5α-THP levels may potentiate or prolong certain behavioral effects of ethanol via its action at $GABA_A$ receptors.

Consistent with this notion, pharmacological manipulation of endogenous 3α,5α-THP levels modulated some behavioral and physiological effects of ethanol. Progesterone administration (5 mg/kg i.p. for 5 days) increased cortical content of 3α,5α-THP in male rats and potentiated the biphasic effect of varying doses of alcohol on dopamine content (i.e., shifted the inverted U-shaped dose response curve to the left; 29). Co-administration of finasteride prevented the effect of progesterone on cortical levels of 3α,5α-THP and on modulation of dopamine content by ethanol. Separate studies determined that pretreatment with finasteride reduced the ethanol-induced increase in cortical 3α,5α-THP levels and the

anticonvulsant effect of an acute ethanol injection (151). Finasteride pretreatment also antagonized the antidepressant-like effect of ethanol in the forced swim test procedure (72) and the anxiolytic effect of ethanol in an elevated plus maze test (73). A clinical study in humans found that finasteride pretreatment (2 daily 100 mg capsules) prior to the consumption of 3 alcoholic drinks (0.8 g/kg in men and 0.7 g/kg in women; doses chosen to ensure a measurable subjective effect with adjustment for sex differences in alcohol pharmacokinetics) decreased several subjective effects of alcohol (104), further supporting observations from rodent models. Notably, finasteride was particularly effective in individuals that were homozygous for the common A-allele variant of the *GABRA2* gene that encodes the $GABA_A$ receptor α_2 subunit. The fact that finasteride pretreatment also decreased ethanol self-administration in C57BL/6J mice (38) suggests that manipulation of endogenous 3α,5α-THP levels may modulate the initiation, maintenance and termination of ethanol consumption episodes.

In contrast to the above findings, finasteride pretreatment did not alter ethanol-induced ataxia (80) or conditioned place preference (52), suggesting that finasteride may primarily affect alcohol-related behaviors or physiological responses with a strong GABAergic component. This suggestion is consistent with a recent *in vitro* study in which finasteride was found to block the secondary, indirect effect of ethanol on GABAergic inhibition, which appeared to be mediated by neuroactive steroid biosynthesis rather than the initial direct effect of ethanol on $GABA_A$ receptor activity (125).

Effects of chronic alcohol exposure and withdrawal

Recent findings indicate that chronic alcohol administration alters 3α,5α-THP concentration in rodents and in human alcoholic patients. Hippocampal 3α,5α-THP levels were significantly reduced in rats after withdrawal from a chronic intermittent ethanol procedure, a time point associated with increased anxiety and seizure susceptibility during withdrawal (16,17). Studies from our laboratory determined that chronic ethanol vapor exposure and subsequent withdrawal produced a persistent and significant decrease in plasma 3α,5α-THP levels in two mouse genotypes that exhibit severe withdrawal (i.e., Withdrawal Seizure-Prone selected line and DBA/2J inbred strain; 34). Interestingly, an inverse relationship between both 3α,5α-THP and 5α-THDOC plasma levels and symptoms of alcohol withdrawal was demonstrated in small cohorts of alcoholic patients (118,119). A decrease in neuroactive steroid levels was correlated with an increase in subjective ratings of anxiety and depression during the early withdrawal phase (i.e., days 4–5), when compared with control subjects. Use of psychotherapy or pharmacological agents to restore 3α,5α-THP levels was associated with decreased subjective ratings of anxiety and depression in the acutely withdrawn alcoholic subjects and increased psychosomatic stability of the patients (70,71,119). Therefore, results in rodents and humans are suggestive of a relationship between endogenous GABAergic neuroactive steroid levels and behavioral changes in excitability during ethanol withdrawal.

Our laboratory has used finasteride to pharmacologically manipulate 3α,5α-THP levels in two models of ethanol dependence and withdrawal, yielding mixed results. In a chronic ethanol administration procedure, physical dependence was induced by exposure to 72 h of ethanol vapor, with mice receiving a total of 4 injections of a 50 mg/kg dose of finasteride (one 24 h prior to, and each day of the exposure to 72 h EtOH vapor or air; 35,60).

The first study was conducted in the C57BL/6J and DBA/2J inbred strains that differ markedly in chronic alcohol withdrawal severity, as indexed by handling-induced convulsions (HICs), a sensitive measure of CNS excitability (DBA/2J ≫ C57BL/6J; 25,26). In general, treatment with finasteride produced a significant decrease in chronic ethanol withdrawal severity in DBA/2J vs. C57BL/6J mice (35). Treatment with finasteride significantly reduced HICs in female DBA/2J mice, while producing a nonselective suppressive effect on HICs in male mice of both strains. That is, treatment with finasteride produced a decrease in both the air- and ethanol-exposed male mice. In contrast, finasteride treatment did not alter withdrawal severity in female C57BL/6J mice. The second set of studies were conducted in male Withdrawal Seizure-Prone (WSP) and Withdrawal Seizure-Resistant (WSR) lines of mice, which have been selectively bred to exhibit negligible (WSR) or severe (WSP) HICs during chronic ethanol withdrawal (83). Finasteride pretreatment reduced ethanol withdrawal severity, measured by HICs and anxiety-related behavior, but only in the WSP selected line (60). However, a surprising finding from all the chronic ethanol studies was that finasteride treatment significantly decreased blood ethanol concentration upon the initiation of withdrawal, suggesting that finasteride might decrease withdrawal severity via an indirect effect on ethanol pharmacokinetics (35,60).

Another model of ethanol dependence examined withdrawal following a single, acute injection of a sedative dose (4 g/kg) of ethanol. In this acute ethanol withdrawal model, the initial ethanol-induced sedation is followed by rebound hyperexcitability as the ethanol is metabolized (approximately 4–8 h post-injection). Since the terminal elimination half-life of finasteride in the circulation in humans is 4.7 to 7.1 h (132), we presumed that the use of an acute ethanol withdrawal procedure would allow the clearance of finasteride prior to ethanol injection, reducing or eliminating this potential interaction with ethanol metabolism. Using this model, results from our laboratory suggest that pretreatment with finasteride decreased acute withdrawal severity, measured by HICs, in male C57BL/6J and DBA/2J mice (59). In contrast, finasteride increased acute withdrawal severity in female mice of both inbred strains. With this acute ethanol procedure, pretreatment with finasteride did not alter blood ethanol concentration, nor did it alter plasma corticosterone or 17β-estradiol levels in a manner that could explain the sex difference in finasteride's effect on acute ethanol withdrawal severity (59). Overall, finasteride pretreatment produced comparable effects in the acute and chronic ethanol withdrawal models in male mice, whereas it produced opposite effects in the female mice. While further studies are necessary to characterize finasteride's effects on the development of physical dependence in male and female mice, the clinical studies described above suggest that manipulation of neuroactive steroid levels and their metabolism may represent a fruitful avenue for the development of adjuvant therapies in the treatment of multiple aspects of alcoholism.

CONCLUSIONS

Current clinical applications of finasteride are based on its ability to inhibit the conversion of testosterone to DHT. While the therapeutic efficacy for the treatment of BPH and androgenetic alopecia in men has been well documented, its utility for prevention of

prostate cancer in men or its efficacy for the treatment of hirsutism in women remains controversial. Additionally, the ability of finasteride to inhibit the enzyme 5α-reductase is not selective for testosterone as a substrate. Rather, finasteride inhibits the metabolism of testosterone, progesterone and deoxycorticosterone (Fig. 1). Hence, the formation of GABAergic neuroactive steroids is likely impacted by finasteride. Based on the preclinical data summarized in this review, finasteride may also be useful as a research tool to examine the role of GABAergic neuroactive steroids in brain function and behavior.

Animal research has yielded a promising body of evidence that supports a role for finasteride as a depressogenic drug, while clinical research has yielded mixed results. Whether this is a reflection of the innate differences between species in the selectivity of finasteride for the Type I vs. Type II isoforms of 5α-reductase or the experimental procedures used to assess depressive-like symptoms in the different species remains to be determined. Another consideration is that neuroactive steroid effects may be more pronounced in experimental animals than in humans, a finding that is not unique to 3α,5α-THP. For example, administration of the neuroactive steroid dehydroepiandrosterone (DHEA) exhibited a consistent memory-enhancing effect in several animal models (see 153), but yielded contradictory results in clinical studies (e.g., 74,150). While this review has focused on effects of finasteride on 3α,5α-THP biosynthesis, neuroactive steroids that are negative modulators of $GABA_A$ receptors also may be influenced (e.g., DHEA and pregnenolone sulfate; see Fig. 1). With this in mind, it was recently suggested that a change in the balance of fluctuating steroids and their neuroactive derivatives, in conjunction with an alteration in brain sensitivity to neuroactive steroids, may contribute to symptoms of depression in "susceptible" individuals (10). Nonetheless, the inhibition of 5α-reductase has proven to be a useful strategy for dissecting the relative contributions of progesterone and its neuroactive derivative 3α,5α-THP to the increased excitability and dysphoric symptoms that are observed in animal models of premenstrual and postpartum dysphoric disorder.

Likewise, finasteride has been used to discern the contribution of 3α,5α-THP to aspects of sexual behavior in female rodents that are predominantly mediated by progesterone. The ability of finasteride to robustly inhibit rodent female sexual behavior differs from data in clinical trials, which have reported that sexual side effects occurred in a small proportion of males and females treated with finasteride (typically ≤5%). As the putative mechanism by which finasteride might affect human sexual behavior is not presently known, it is difficult to generalize the results from the preclinical studies to the clinical data.

A great deal of our understanding of the role of neurosteroids in seizure mechanisms has been garnered using finasteride. This 5α-reductase inhibitor has enabled researchers to better pinpoint contributors to seizure sensitivity. Currently, the focus has begun to shift toward understanding the brain circuitry involved in complex behaviors such as seizures. At the present time, one brain region under scrutiny is the hippocampus, as recent findings suggest that it may be an integral structure in the circuitry mediating the anticonvulsant effects of 3α,5α-THP. In OVX rats, the administration of progesterone was anticonvulsant in the PTZ seizure threshold paradigm, and as expected, systemic injection of finasteride blocked this effect (115). Interestingly, progesterone increased hippocampal levels of 3α,5α-THP, and this effect was reversed with finasteride. Infusion of finasteride directly into the hippocampus of OVX rats after systemic injection of progesterone also blocked

the anticonvulsant effect of progesterone as well as the effect on hippocampal 3α,5α-THP levels, thereby suggesting that the hippocampus was an important target for the anticonvulsant effects of 3α,5α-THP. Data from our laboratory have also demonstrated that bi-directional manipulation of 3α,5α-THP levels in the hippocampus produced effects on seizure susceptibility in male mice that were consistent with alterations in GABAergic inhibition (↑ with exogenous 3α,5α-THP or progesterone, ↓ endogenous synthesis with finasteride). Bilateral infusion of 3α,5α-THP was anticonvulsant, whereas bilateral infusion of finasteride was proconvulsant, as measured by sensitivity to PTZ-induced convulsions (33). These findings identify an intriguing and novel use for finasteride in the quest to decipher the role of neurosteroids in seizure activity.

Another consideration is that stress can increase levels of endogenous neuroactive steroids that are both positive and negative modulators of $GABA_A$ receptors (107). Since stress has been reported to exert both anticonvulsant and proconvulsant effects on seizure susceptibility in epileptic patients, it has been suggested that the extent of seizure susceptibility during stress might represent a balance between anticonvulsant (e.g., neuroactive steroids) and proconvulsant (e.g., glucocorticoid and corticotrophin releasing hormone) steroid levels (107). Consequently, enzyme inhibitors (such as finasteride) can be used to delineate enzymatic conversions in the neuroactive steroid biosynthetic pathway that are altered during stress, providing important mechanistic information on conditions altered by stress (e.g., epilepsy and depression).

Work in animal models indicates that chronic ethanol exposure significantly decreased expression and activity of 5α-reductase, consistent with the decrease in endogenous 3α,5α-THP levels. However, it is not known whether a similar effect of chronic alcohol exposure on the 5α-reductase enzyme is responsible for the decrease in endogenous 3α,5α-THP levels reported in alcoholic patients. Gene mapping studies in mice indicate that the region of chromosome 13 where the murine gene for 5α-reductase Type I (*Srd5a1*) has been mapped was found to affect chronic ethanol withdrawal severity (25). Additional studies provide a hint for an epistatic interaction between genes for $GABA_A$ receptor subunits and *Srd5a1* (9). While the evidence is indirect, the gene mapping studies suggest that the *Srd5a1* gene may affect chronic ethanol withdrawal severity perhaps through a modifying effect on the activity or expression of certain $GABA_A$ receptor subunit genes on chromosome 11 (discussed in ref. 34). More specific studies manipulating these genes and/or studying their expression and downstream effects will be necessary to further establish their roles.

The pharmacological manipulation of 5α-reduced steroids, including 3α,5α-THP, has provided important insights into the role of GABAergic neurosteroids in alcohol-related behaviors and may elucidate the underlying mechanisms involved in ethanol dependence and withdrawal. Since treatment with finasteride influenced some, but not all alcohol-related behaviors, further studies are needed to characterize this effect. Similarly, since treatment with finasteride differentially affected male and female mice, pharmacological interventions may need to account for differences in endogenous/physiological hormonal fluctuations. Thus, although a promising intervention, additional studies are needed to characterize the use of finasteride as a pharmacological tool in the treatment of alcohol abuse.

In conclusion, finasteride has been very useful as a research tool in preclinical studies to examine the relationship between changes in GABAergic neuroactive steroid levels and anxiety-related behaviors, symptoms of depression, seizure susceptibility, aspects of sexual behavior, and certain alcohol-related behaviors. The preclinical data are very consistent with the inverse relationship between GABAergic neuroactive steroids and symptoms of premenstrual and postpartum dysphoric disorder, depression, catamenial epilepsy and alcohol withdrawal that has been reported in humans. The fact that finasteride does not appear to produce anxiety, depression, increased seizure susceptibility, sexual side effects or precipitate alcohol withdrawal in a large proportion of patients bodes well for its continued clinical application for the treatment of BPH and androgenetic alopecia. Nonetheless, side effects have been reported with finasteride in a small percentage of patients, suggesting that caution might be warranted regarding the use of finasteride in susceptible populations.

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