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Androgens' Effects across the Lifespan in Men and Animal Models

Cheryl A. Frye, Jennifer K. Torgersen, Vincent F. Lembo and Kelly Drew

Abstract

The clinical literature and recent studies in our laboratory using rodent models demonstrate that there are individual differences in androgens' pleiotropic effects across the lifespan that need to be better understood. The question to address that challenges the field is that levels of androgens (current and/or prior) may not drive differing responses to androgens. The clinical example of Post-finasteride Syndrome, in which side-effects persist long after treatment is discontinued, supports investigations of this novel question relating to long-term effects of androgen manipulations, independent of existing levels of androgens.

Keywords: steroids, neurosteroids, testosterone, 3 α -Androstanediol, post-finasteride syndrome, traumatic brain injury

1. Introduction

Androgens have well-known trophic actions on the reproductive, nervous, skeletal, and cardiovascular systems throughout the lifespan. A focus in behavioral neuro-endocrinology has been on understanding dose-dependency, brain targets, cellular mechanisms of testosterone (T) and its metabolites for reproduction through androgen receptors. Research has challenged the existing paradigm about androgen action,

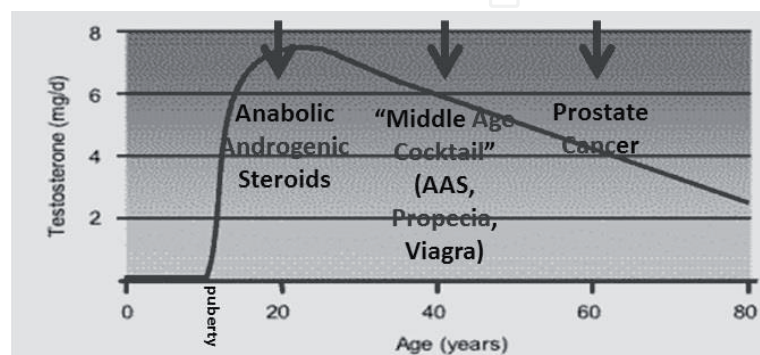
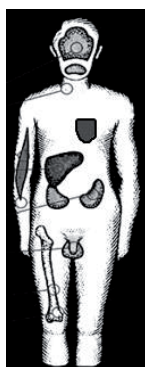


Figure 1.

Androgens target brain, heart, muscle, liver, kidneys, adrenals, testes, penis, bones (left) and (right) changes in androgens across the lifespan with a decade by decade decline naturally or by points indicated by arrows with pharmacological interventions or disease [1].

as well as taking a novel approach to understand how these trophic actions in the brain occur in relation to growth in the body (reproductive organs). Given androgens' pervasive trophic effects from early development throughout adulthood, unique studies are discussed that impact our understanding of androgens' actions (**Figure 1**).

2. Actions of androgens

2.1 Disparate effects and mechanisms of androgens may be meaningful

Androgens have profound effects on physiological and psychological function. This is apparent throughout the lifespan and with normal development as well as in pathological situations. In early development, androgens lay the framework for sex differences in reproductive tissues and brain circuitry and behavior. At puberty, typical diurnal secretion of androgens in males is initiated. The main circulating androgen is T, which can be aromatized into estradiol and 5α -reduced to dihydrotestosterone (DHT). DHT is further converted to 5α -androstane, 3α , 17β -diol (3α -diol) by 3α -hydroxysteroid dehydrogenase. These different androgens have varied effects and mechanisms that will be discussed throughout this paper (**Figure 2**).

2.2 Patterns of androgens and effects in men

Men experience a decade-by-decade decline in androgens, with marked androgen deficiency typically observed in the 6th–8th decade of life [1]. This shift in balance of androgens and estrogens can contribute to some of the adverse physiological effects observed in aging, such as reduced muscle mass, osteoporosis, and gynecomastia, as well as increase risk of prostate pathologies. The brain is also adversely affected by these changes as evidenced by memory impairments, reduced libido, and an increased risk for depression among some men. As such, many older men turn to androgen-based therapies to ameliorate these symptoms. However, androgen-based therapies may increase risk for unwanted proliferation in the prostate, as well as other physical and psychological side effects. Moreover, men are often reported to use androgen replacement therapies even in their 4th decade or earlier, suggesting that some men may be particularly sensitive to even modest androgen decline, or trophic effects of synthetic androgens (e.g. anabolic steroids).

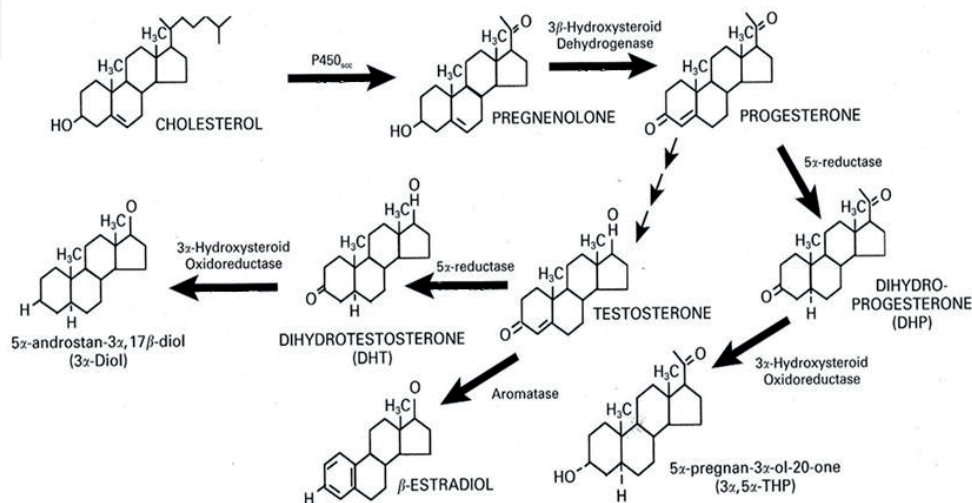


Figure 2.

Metabolism- depicts T metabolism via aromatase to estradiol and 5α -reductase and 3α -hydroxysteroid oxidoreductase to dihydrotestosterone and 3α -diol.

A serious concern is that such treatments have potential to increase risk for prostate pathologies and other unwanted effects for brain function.

2.3 Disparate effects and mechanisms of androgens may be meaningful

Some men use treatments, such as finasteride, a 5 α -reductase inhibitor, to manipulate trophic effects of androgens (e.g. alopecia, benign prostatic hyperplasia) and to reduce side effects of synthetic androgens. There can be long-term effects of such treatment. Finasteride use has been linked to sexual dysfunctions and mental side effects, including depression, even months after its use is discontinued (“Post-finasteride Syndrome”) [2–4]. The individual differences in response to androgens, as well as their manipulations, are not understood but will be discussed herein. Foci will be on androgen receptor-independent effects and mechanisms (estrogen receptor β - ER β ; brain derived neurotrophic factor- BDNF) of 5 α -reductase manipulations and the T metabolite (3 α -diol) for driving trophic effects in the brain that may be parsed from such effects in peripheral targets (prostate) (**Figure 3**).

2.4 Novel targets of androgens and why they may be meaningful

Individual differences in responses to androgens may be attributed in part to current and past exposure to androgens and/or their manipulation, and subsequent actions at ER β and BDNF. To address this challenging question of individual differences in responses to androgens, a unique strain and species comparison approach has been utilized. Rat and mouse models with different androgen load, androgen replacement, and 5 α -reductase inhibition have been utilized. Social/reproductive, cognitive, and affective behavior, androgen levels, and indices of growth (BDNF, prostate weight) has been measured to model age- and androgen manipulation-related changes in physical and psychological function. One-rate limiting step to elucidating better treatment options for androgen-related pathologies is to have animal models that mimic the human condition and can be used to systematically address question about persistent effects of androgens in the brain and peripheral targets. These studies address questions of clinical importance with substantial depth and breadth for human health, given the pervasive nature of androgens' lifelong effects throughout the body.

2.5 The normative role of androgens for physiological and psychological processes

Androgens have well-known growth-enhancing effects to regulate development and functional aspects of the reproductive, central nervous system, skeletal, and cardiovascular systems throughout the lifespan (thru the lifespan that include patterns of androgen secretion. Supported by early investigations in the field [5], the capacity of androgens that are secreted from the testes during early pre- or peri-natal development may “organize” the central nervous system, including the

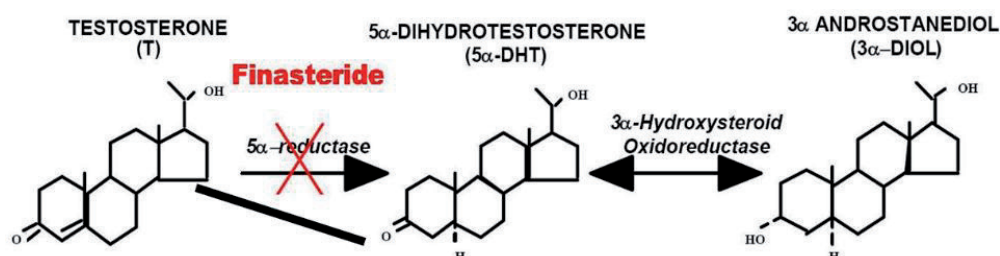


Figure 3.
Mechanism of action of finasteride.

neural control of post-pubertal patterns of androgen release, as well as sensitivity of specific brain structures to androgens in adulthood for behaviors. From birth until sexual maturation, androgen levels are typically low. At puberty, androgen levels increase and remain high until midlife when androgen levels begin to decline. Many of the targets of androgens have been highlighted by changes in the tissues' functions with decline in androgens. Among people, 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. **Figure 4** displays the data from Handelsman et al. 1995 and show the decline in these hormones with age [6]. This decline is 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 at this time. For example, decline in bioactive androgens in men with aging is associated with diminished libido, fatigue, decreased muscle mass, osteoporosis, depression, and/or cognitive dysfunctions. Given the aging population and robust effect that androgens have on physiological and psychological function, there is now great interest in the role of androgen-based therapies to obviate some of these symptoms. Moreover, there are younger populations that are using synthetic androgens, such as illicit anabolic androgenic steroids (AAS), with or without other drugs to alter steroid metabolism (finasteride). A serious concern that limits the use of steroid-based treatments in men is their potential to increase risk for prostate pathologies as well as psychological effects (**Figure 5**).

2.6 Typical approach to understanding the normative effects of androgens – sex differences, seasonal and correlational effects

In behavioral neuroendocrinology, to determine the role of a hormone for a behavioral process, an approach is to assess endogenous changes in hormones,

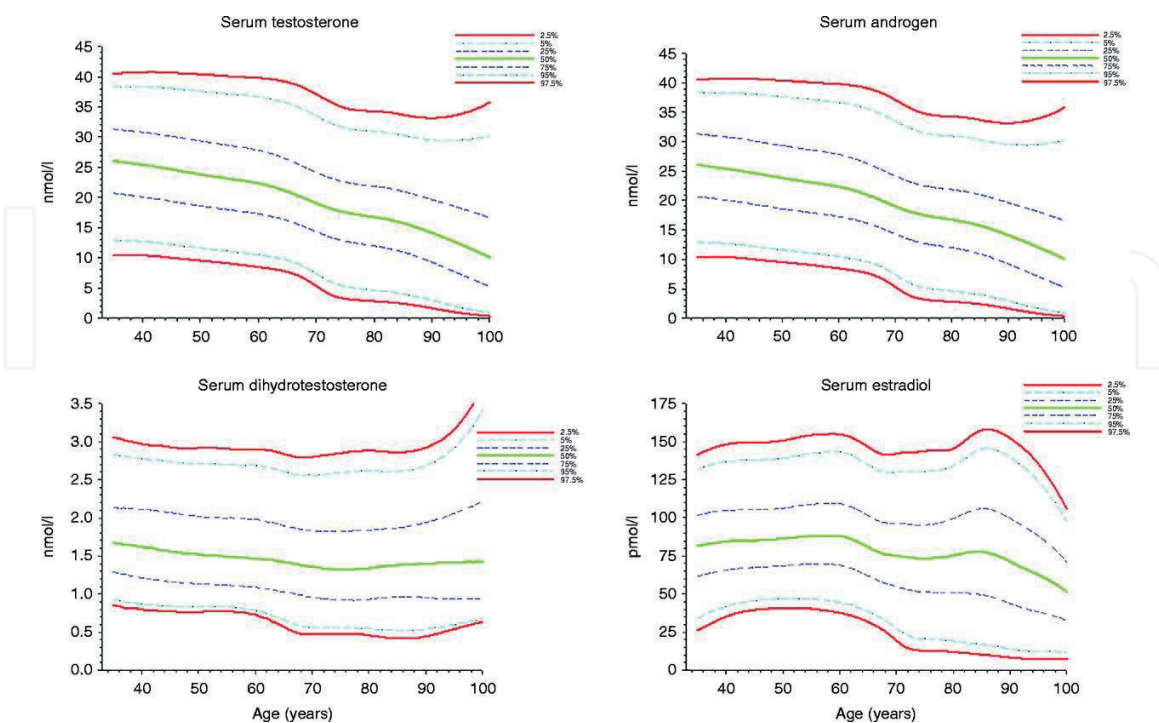
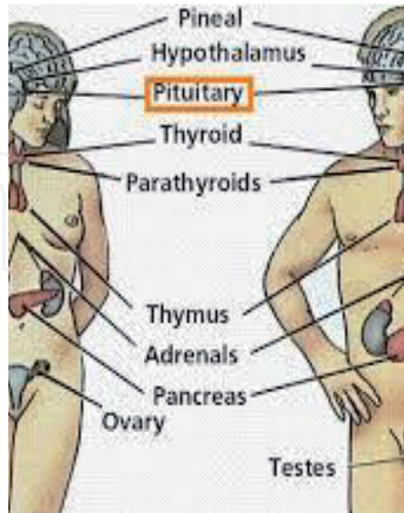


Figure 4.

Plot of smoothed age-specific population centiles (97.5, 95, 75, 50, 25, 5, and 2.5%) for serum testosterone (nmol/l; upper left), DHT (nmol/l; lower left), androgen (nmol/l; right top), and E_2 (pmol/l; right lower) in 10897 samples from men aged over 35 years from population-based studies in three Australian cities (Adelaide, Perth, and Sydney) using LC-MS steroid measurements from a single lab with data analyses using GAMLSS modeling. A full color version of this figure is available at <http://dx.doi.org/10.1530/EJE-15-0380>.

Physical:

- Decreased body hair
- Decreased muscle strength and mass
- Development of breast tissue
- Hot flashes, sweats
- Sleep disturbances and fatigue
- Osteoporosis/ height loss



Symptoms of Testosterone Deficiency Among Men

Cardiometabolic:

- Increased body mass and abdominal obesity
- Metabolic syndrome
- Insulin resistance and type 2 diabetes

Sexual:

- Delayed puberty
- Hypogonadism (small testes)
- Decreased frequency of sexual thoughts and desire, and sexual activity
- Decreased or absent morning/nighttime erections
- Erectile Dysfunction and/or infertility

Psychological:

- Changes in mood
- Greater lability
- Anger, irritability, sadness, depression
- Overall sense of poor well-being and health
- Poor cognitive function
- Reduced concentration, spacial performance, and verbal memory

Figure 5.

Summary of effects of loss of androgens among men <https://www.guidelinesinpractice.co.uk/mens-health/testosterone-deficiency-treat-men-who-have-bothersome-symptoms/454121.article> Signs and symptoms.

extirpation of the hormone (i.e. surgical removal of the gonads), and replacement back of a 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 from: 1) 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). One example of this type of investigation would be assessments of reproductively relevant behavior, such as aggression, among a seasonal breeder, such as a deer. Male, but not female, deer begin to grow antlers (which have utility for aggressive responding in this species) during mating season post-puberty. Aggressive behavior among male deer coincides with peak levels of androgens and is reduced during non-breeding season associated with androgens levels at nadir.

2.7 Typical approach to understanding the normative effects of androgens

To begin to assess the causative role of the hormone in this behavior, the second and third approaches of extirpation and replacement are utilized; extirpation should remove the hormone and result in abolishment of the behavior and then replacement back of this hormone should reinstate the behavior. A classic example of this approach is the Berthold experiment. Although this experiment predates basic knowledge that hormones existed, it had been known for centuries in agriculture that there are clear behavioral differences in male animals when their testes were removed. Dr. Berthold is credited with completing the first systematic study (1849) of extirpation and replacement of the testes (which we now know are a main source of circulating androgens) to investigate secondary sex characteristics and reproductive behaviors of roosters. Roosters were castrated and reductions in appetitive and consummatory aspects of mating, as well as secondary sex characteristics, were abolished. This was reversed when roosters were implanted with testes. Dr. Berthold hypothesized that these changes in behavior and phenotype were due to a substance in the testes (rather than actions via nerves in the body, which was the prevailing notion at the time).

In summary, although these methods to understand effects of hormonal variations, extirpation, and replacement have a long history and have clearly contributed to our understanding of the relationship between hormones and a hormone-mediated behavior, there is also individual differences in the responses of individuals that need to be better understood. The relationship between a behavior and hormone levels may not be linear, and this relationship may be mediated by individual experience (i.e. current/prior androgen exposure), a response first noted over 60 years ago [7].

2.8 Typical approach to understanding the normative effects of androgens

Actions of T metabolites may account for some of T's functional effects. T, the primary androgen secreted from the testes, travels in circulation to the brain (as well as many other target organs) and then can be metabolized by enzymes to other neuroactive metabolites. T can be aromatized into estradiol (E₂) and 5 α -reduced to DHT (Figure 6). DHT is metabolized to 5 α -androstane,3 α ,17 β -diol (3 α -diol). A consideration in understanding the effects of androgens is novel sources of androgens beyond metabolism. The traditional idea is that neuroactive metabolites such as 3 α -diol are formed following secretion of T from the testes, which is then converted by 5 α -reductase and 3 α -HSD in androgen sensitive targets, such as the brain.

2.9 The brain is an endocrine organ and can produce androgens

These enzymes as well as others are critical for *de novo* production of androgens in the brain (termed "neurosteroidogenesis") from precursors, such as cholesterol, pregnanolone, and progesterone. The biosynthetic pathway for neurosteroid production involves many recognized factors, including the 18kDA translocator protein (see Figure 7): TSPO, a.k.a. peripheral-type benzodiazepine receptor), the steroidogenic acute regulatory (StAR) protein, cytochrome P450-dependent C27 side chain cleavage enzymes (P450_{scc}), 3 β -hydroxysteroid dehydrogenase (3 β -HSD),

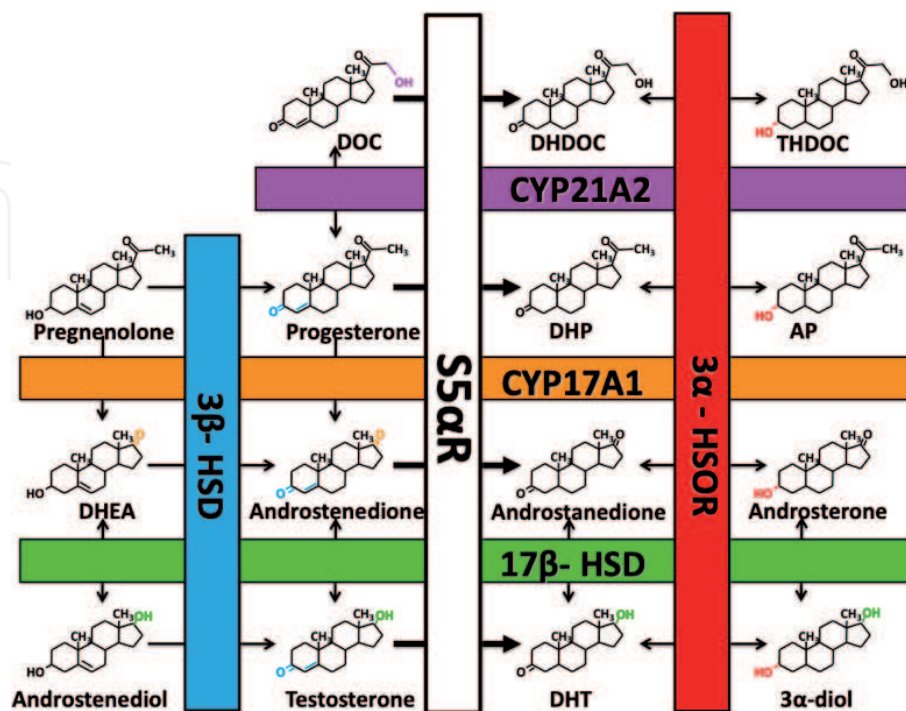


Figure 6. Metabolic pathways for formation of testosterone and its metabolites in the brain, figure provided by and modified from colleague Marco Bortelatto.

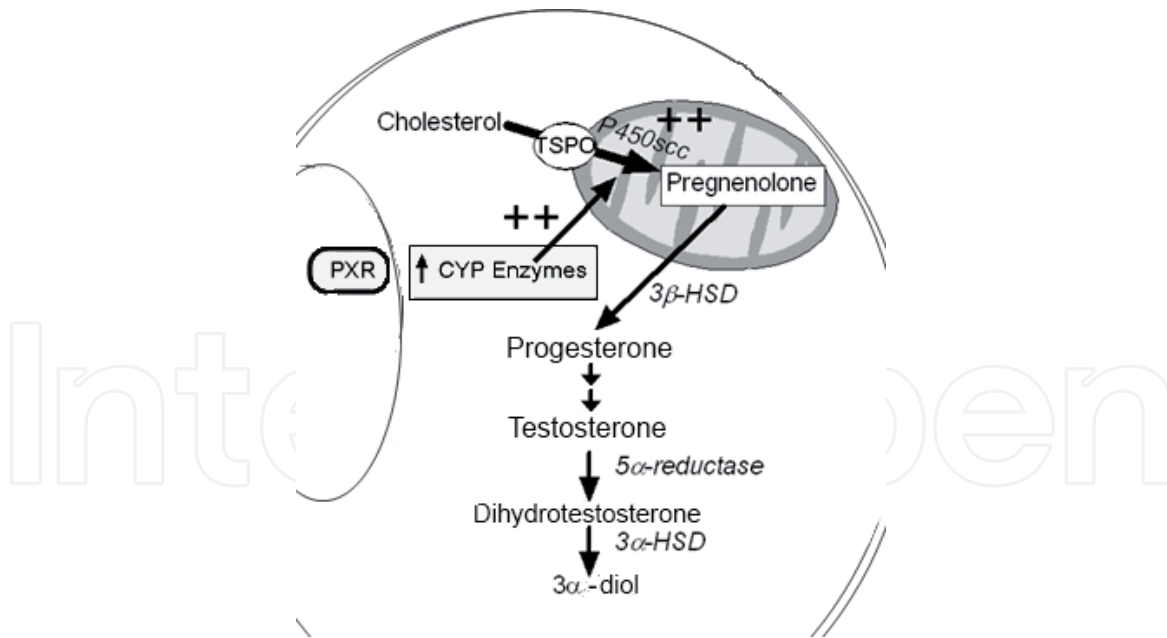


Figure 7.
 Neurosteroidogenesis- formation of 3 α -diol from cholesterol.

5 α -reductase, and 3 α -HSD. TSPO and StAR have actions to transport cholesterol (a requisite precursor for all steroids) into the mitochondria. In the mitochondria, cholesterol is oxidized by P450_{scc} to form pregnanolone, which is then metabolized by 3 β -HSD to progesterone. Progesterone can then be metabolized to form T. A pathway to form 3 α -diol from T involves sequential actions of 5 α -reductase (an irreversible action that forms DHT) and then 3 α -hydroxysteroid 3 α -HSD. Most recently, we have been investigating the pregnane xenobiotic receptor (PXR) as a novel target for neurosteroid production [8].

2.10 ER β and GABA_A receptors as targets for androgens in brain

Here we focus on two novel targets of androgens for trophic effects, estrogen receptor beta (ER β) and GABA_A receptors. Androgen metabolites act at a variety of targets to influence psychological (affective, cognitive) and physiological processes (prostate). High physiological androgens are associated with improved affective and cognitive performance; castration (gonadectomy- GDX) increases anxiety-like behavior, and detriments in their cognitive abilities and effects can be reversed with administration of T [9–14]. These studies using the typical approach assessed these effects in young male rodents (with comparable lifetime exposure to

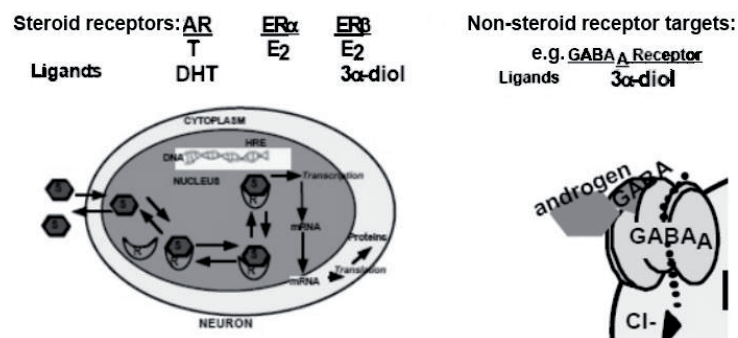


Figure 8.
 Receptor targets of androgens.

androgens). Aged male rodents do not have improved cognitive or affective performance when administered T, compared to their younger counterparts; this effect was associated with a reduced capacity for producing 3α -diol [14]. 3α -diol may be similarly effective, if not more so, than administration of T alone for decreasing anxiety behavior of GDH rats [12, 13]. Blocking formation of 3α -diol through administration of indomethacin can reverse these beneficial effects of androgens on affect and cognition [12, 13, 15]. An important consideration in understanding the role androgens is their different mechanisms of action. See **Figure 8**.

2.11 The brain has multiple targets for androgens

3α -diol has novel mechanisms of action. T and DHT bind to androgen receptors (ARs), and some of the proliferative effects of androgens on the prostate may be through this mechanism. However, it seems that non-AR mechanisms of other T metabolites may be important for cognitive and/or affective behavior. 3α -diol has actions via $ER\beta$ and $GABA_A$ receptors [16–20] (**Figure 8**). E_2 readily binds to cognate $ER\alpha$ and $ER\beta$, and can enhance benign prostatic hyperplasia and adenocarcinoma, likely via actions at $ER\alpha$, not $ER\beta$, but this is not completely understood. Indeed, androgens' and estrogens' (anti)proliferative effects may depend in part upon tissue type and actions at ERs subtypes, $ER\alpha$ and $ER\beta$, which are differentially distributed across the body and brain. In the prostate, $ER\beta$ is highly expressed in epithelial cells. Although $ER\alpha$ is localized in the stroma, $ER\alpha$ also has been found in premalignant and malignant epithelium of the prostate. In the brain, $ER\beta$ expression predominates in hippocampus and cortex, regions involved in cognition and affect. $ER\beta$ knockout mice have prostate hyperplasia in aging, suggesting a potential inhibitory role of $ER\beta$ for prostate growth [21, 22]. However, the stress reducing, cognitive and affective behavior enhancing effects likely occur through actions at $ER\beta$ as male mice or rats have greater responses to androgens that have actions at $ER\beta$ and $ER\beta$ knockout mice show reductions in these cognitive and affective responses [17]. Mice with the *tfm* mutation, rendering ARs non-functional, respond better than do wildtype mice to administration of 3α -diol for anti-depressive behavior in the forced swim test (**Figure 9**). Thus, trophic effects of androgens in the brain and body may be dissociable and involve different targets beyond the traditional target of androgens, the ARs.

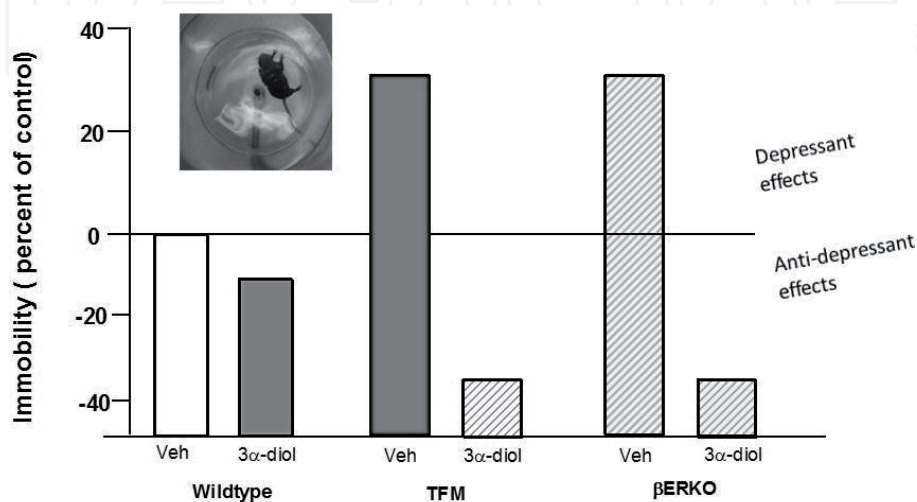


Figure 9. *Tfm* and $ER\beta$ knockout mice show more depressive-like behavior than do wildtype mice, an effect that can be reversed by administration of 3α -diol in the forced swim.

2.12 BDNF as another novel mechanism for individual differences in responses to androgens

In addition to mechanisms of androgens in the brain and body through ER β , the proposed project will investigate brain-derived neurotrophic factor (BDNF) as a target for these trophic actions. BDNF is a neurotrophin that is abundantly expressed in many central nervous system regions, most notably in regions of interest in the proposed studies for their involvement in cognitive, affective, and reproductive function (prefrontal cortex, hippocampus, and hypothalamus). BDNF is considered a marker of brain plasticity owing to its role in synaptic reorganization, neurogenesis, and dendritic branching and spine formation as well as cognitive and affective processes. Moreover, there is growing evidence for the role of gonadal hormones for regulating BDNF, namely, estradiol [23]. Less is known about the role of androgens for BDNF, but there is some evidence for sex differences, regimen, and region/cell-specific effects of androgens for BDNF. For instance, it has been argued that T produces tonic suppression of BDNF levels in mossy fibers of the hippocampus among adult male rats (but the opposite occurs with estradiol among female rats [24]). Indeed, among male rats that do not show GDX-induced decrements in cognitive performance, there is increased BDNF in mossy fibers of the hippocampus [25]. Enriched environment increases testosterone and BDNF levels in the grossly-dissected hippocampus of female, more so than male rats, compared to rats living under typical lab conditions [26]. However, among male mice, GDX decreased levels of BDNF in pyramidal neurons in the CA1 area, an effect prevented by T replacement [27]. Physiological dosing of T produced antidepressant effects that were mitigated when the BDNF target, extracellular signal-regulated kinase 2, is blocked [28]. We propose that some effects of T for BDNF may be related to its metabolite, 3 α -diol. We have found that hippocampus levels of BDNF are reduced among mice with knockout of ER β , coincident with lower 3 α -diol levels (**Figure 8**). These findings indicate the role of androgens for BDNF is not linear, and there are gender, regimen, and target-specific effects (**Figure 10**).

2.13 Differential responses to androgens

Variations in the levels of T and its metabolites, may influence affect and/or cognition in men. Men who have higher endogenous levels of T have a lower incidence of depression [29]. Conversely, young hypogonadal men, with low endogenous T and DHT levels, are more likely to be diagnosed with an anxiety or depressive disorder, and exhibit decreased performance in cognitive tasks [30, 31].

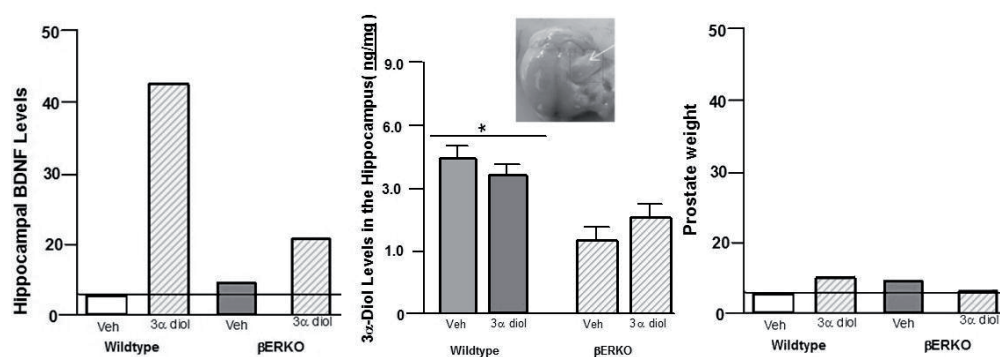


Figure 10. 3 α -diol administration increases BDNF levels, but not prostate weight, among wildtype mice, irrespective of 3 α -diol levels in the hippocampus. Among ER β knockout mice, 3 α -diol levels are lower and there is reduced BDNF in the hippocampus (but no change in prostate weight).

Treatment for these men includes T replacement, which can increase positive, and decrease negative, mood, while improving cognition [32]. However, a different pattern is apparent with use of androgens, such as AAS, among some eugonadal men. AAS are the synthetic variants of T. They are abused by growing numbers of individuals in this country ranging from adolescents, seeking to improve their appearance, to professional athletes attempting to elevate their performance. The costs associated with AAS abuse are substantial. For the individual, AAS abuse is associated with many adverse physical and behavioral consequences. There can be dramatic cognitive and mood changes that are observed among some users of AAS (“roid rage”) and other serious, permanent side effects: kidney and liver damage, liver cancer, heart disease, and hypertension, suppression of T production, testicular atrophy, and gynecomastia. In adolescent males, AAS abuse can hasten the onset of adulthood, promote early baldness, limit stature, and cause premature growth plate closing. Together, these data suggest that there are individual differences in response to androgens that may be related to current hormonal state and/or age.

2.14 Aging and androgens

In aged men, there is a decade-by- decade decline in levels of androgens and an increase in bioavailable estrogens, with marked androgen deficiency most typically observed in the 6th–8th, even 9th, decade of life [33]. However, this shift in balance of androgens and estrogens can contribute to some of the adverse physiological effects observed in aging (termed “andropause”), such as reduced muscle mass, osteoporosis, and gynecomastia, as well as increase risk of prostate pathologies (from benign prostate hyperplasia to prostate carcinoma). The brain is also adversely affected by these changes and there are increased memory impairments, reduced libido/sex drive, and an increased risk for depression. As such, many men turn to androgen-based therapies to replace back androgens to ameliorate these symptoms. Clinical studies have demonstrated that administration of T to some aged men reinstates their affective and cognitive performance [34–36]. Despite the notion that marked androgen deficiency is most common after 60 years of age among men, men are often reported to use androgen replacement therapies even in their 4th decade, suggesting that some men may be particularly sensitive to decline or age-related changes in androgens, but this is not clear.

2.15 Prostate health and androgens

T and its metabolites have trophic effects on the prostate in addition to other reproductive structures of males from early development. Among older men, decline in androgens, and an increase in estrogens, may underlie risk for prostate proliferation. Indeed, treatments for prostate cancer include those that alter androgen levels (releasing hormone or metabolism inhibitors) [37] and/or actions (androgen receptor antagonists). DHT binds with a higher affinity than does T to ARS [36], and DHT is highly active in prostate, where it may cause proliferation [38]. Because of this, 5 α -reductase inhibitors have been used as a treatment for BPH and prostate cancer [39–41]. As prostate cancer progresses, carcinomas can become steroid-insensitive and metastasize, leaving no effective treatments. Moreover, there can be side effects of such androgen manipulations. For instance, men have a slightly decreased sex drive with finasteride, which can be reversed upon treatment cessation [42], among most individuals. There is a clinical situation where there is a prolonged response to such androgen manipulations, even when the therapy has ceased, that is informing present studies (below).

2.16 Post-finasteride syndrome

The 5 α -reductase inhibitor, finasteride, whose mechanism of action can be seen in **Figure 11**, is approved for treatment of benign prostate hyperplasia and male pattern baldness (androgenic alopecia). It also has off-label use among men using AAS to decrease side effects of AAS or block detection of AAS with drug tests. Effects of finasteride treatment to persistently reduce levels of DHT and 3 α -diol glucuronidate have been reported among older men assessed over a years (~75 reduction from baseline; [43]. Benefits of finasteride for benign prostate hyperplasia and alopecia generally occur after chronic administration (6+ months) and subside when the treatment is discontinued [44, 45]. However, a more recent report suggests that there are individual differences in response to finasteride for alopecia. In this study, men were treated with finasteride and hair growth assessed over 10 years. Men that had the greatest increase in hair growth were those who had started treatment over 30 years of age, suggesting those that had experienced longer decline in hair growth were most responsive to the treatment. Additionally, subjects that had the greatest amount of hair growth in the first year were those same subjects who had the greatest overall hair growth over the period of the study [46]. Together, these

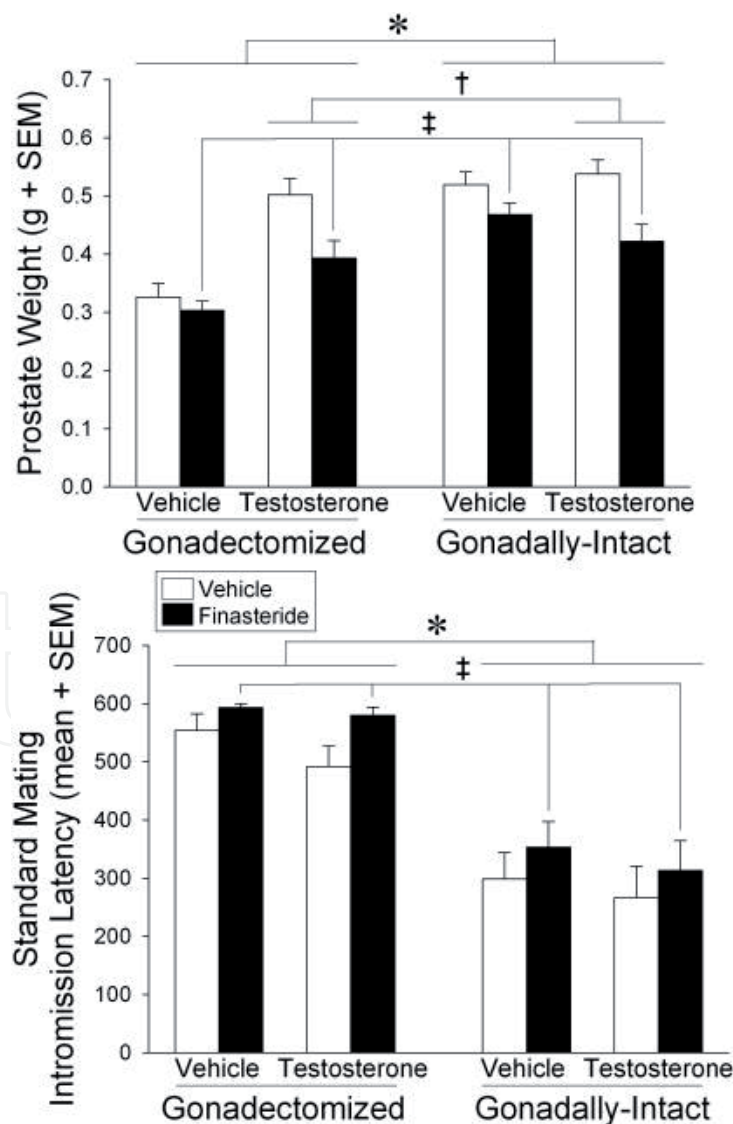


Figure 11. Prostate weight (top) and the latency to intromit in standard mating paradigm (bottom) among gonadectomized (GDX) or gonadally-intact male rats implanted with vehicle, testosterone, and/or finasteride. * indicates main effect of gonadal condition; † indicates main effect of T condition; ‡ indicates main effect of inhibitor condition, $p < 0.05$.

results suggest that there are individual differences in response to manipulation of 5 α -reductase by finasteride. Additionally, there is evidence of individual differences in response to finasteride when considering side effects of this treatment.

The known side effects of finasteride include sexual dysfunction (e.g. loss of libido, impotence, ejaculatory or erectile dysfunction), gynecomastia, changes in cognition, and affect (including depression, which was added to the product package insert by Merck in 2010). Of particular interest is that there are side effects after finasteride is discontinued. For example, there are reports of persistent sexual dysfunction following discontinuation of finasteride [4, 46–48]. Additionally, former users of finasteride report sexual dysfunction and have high scores on the Beck Depression Inventory more than 3 months after cessation of finasteride use [2, 3]. In this study, 75% of men (61 total in the study) showing persistent sexual dysfunction following finasteride discontinuation had symptoms of depression (assessed by Beck Depression Inventory) over 3 months later. It is assumed in these individuals that endogenous androgen levels have normalized, so the question remains regarding potential mechanisms of these long-term changes in behavioral responses. A recent publication has shown that there seems to be a reduced capacity for neuroactive steroid production (as measured in cerebrospinal fluid or plasma) of individuals with side effects following discontinuation of finasteride for alopecia [49]. Studies in patients at risk for prostate cancer prescribed finasteride demonstrate increased testosterone and decreased DHT and 3 α -diol glucuronide (mainly produced in the liver) in circulation [43], in addition to differences in cholesterol profile [49]. Whether levels coincide with symptoms is not understood. We have collected pilot data in support of this idea in male rats. In this study, male rats were GDX or gonadally-intact and were administered T or vehicle chronically in conjunction with finasteride or vehicle. Rats that were GDX, compared to intact rats, had lower circulating T and DHT levels, smaller prostates and longer latencies to initiate sexual contacts with a female (as to be expected). T-replacement increased plasma T and prostate mass. Similar to GDX, finasteride decreased prostate weight and inhibited sexual behavior (**Figure 11**). A preliminary finding in this study was that the finasteride treatment had variable effects to reduce the 5 α -reduced metabolite, DHT, and that the levels determined do not seem to coincide with the behavioral patterns observed. As such, the present proposal is informed by the clinical literature and preliminary results in our laboratory using an animal model. Thus, of clinical relevance is consideration of long-term effects of androgen manipulations that extend beyond the treatment period. We propose, such as with post-finasteride syndrome, that there may be long-term consequences of changing androgen milieu that may be independent of specific levels of androgens at a particular time.

One factor that seems to be linking the individual differences in responses to androgens is related to different current and/or prior exposure to androgens, rather than linear effects of androgen levels for the response; additionally, effects of androgens may be via novel targets, ER β , BDNF or GABA_A activity. Studies will be challenging the current notion in field of behavioral neuroendocrinology that behavioral effects are not just due to the levels at the time the behaviors are assessed, but that there can be persistent effects beyond this. Testing this hypothesis is also a challenge to pharmacology in that effects/side effects should subside when the drug is discontinued. Proposed work is a challenge to the insular nature of science in that assessments of androgens will not only be in the brain/behavior, but also an investigation of brain effects in context of body (e.g. prostate growth/sex behavior). Overall, to address this question about long-term consequences of changing androgen milieu that may be independent of specific levels of androgen concentrations at a particular time and novel cellular targets for these effects, is a transformative approach to the problem that must be taken.

Recently, the chemist who began making Viagra has appeared in daytime TV shows such as Dr. Oz and Dr. Phil. He has made a great deal of money for himself and his company, so much so that he feels guilty because Viagra is based on L-Arginine, which increases blood flow to all cells of the body. This was effective for ED and could be used by most people except those with risk for hypertension, heart attack, and stroke, and is readily available at low to no cost in pharmacies groceries stores. The investigator knew this, he only needed to figure out how to more specifically increase the blood flow and also had to increase not just consummatory (bigger and longer erections) aspects of behavior, but motivational (increase sex drive, sexual confidence, energy) which L-arginine itself did not do. Through my extensive pharmacological training and knowledge of naturopathic medicine, I suggest the use of Boron rather than L-Arginine so that blood flow would be more directed to the penis rather than the whole body, preventing potential side effects of heart attack, stroke, etc. Orchic could be added because it has a beneficial effect on mood patterns to reduce stress and promote relaxation. Saw palmetto is well known Asia to enhance energy, strength and stamina. Nettle extract is a known aphrodisiac that can also help boost testosterone levels. Biopterin is used to more rapidly enter target sites and boost energy, stamina, and sexual motivation. My colleague gave up most of the formula that increases testosterone and nitric oxide production in the penis and results in improved libido, sexual motivation, sexual confidence, and sexual performance. Within days there were multiple substances on the market, most of which were a supplement similar to this. It is unclear what the long-term consequences are going to be of this supplement, however it may well be a solution to using finasteride for hair growth and it may help those with post finasteride syndrome as part of their recovery on sexual side effects and anhedonia. Like all good cooks, who occasionally have memory lapses, I did not include a key naturopathic ingredient in our original formula. We do however hope to have our product patented out and on the market soon, aimed at the target audiences indicated above and hitting targets that are not just based upon ED or consummatory aspects of finasteride syndrome but also will have beneficial aspects of drive and motivation (regulated by dopamine) and impulse control regulated by the inputs on the A8, A9, A10 dopamine cell bodies (GABA, GLUTAMATE), and other drive desire aspects to socialize (oxytocin) [50].

Author details

Cheryl A. Frye^{1,2,3*}, Jennifer K. Torgersen¹, Vincent F. Lembo² and Kelly Drew³


1 The State University of New York at Albany, Psychology, Biology, Neuroscience and Life Science Programs, Albany, NY, USA

2 Comprehensive Neuropsychological Services, Albany, NY, USA

3 Alaska INBRE / University of Alaska, Fairbanks, Alaska

*Address all correspondence to: cafrye@albany.edu

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