



Review Article

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Androgens and human Behavior

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Abstract

Despite decades of research on the effect of androgens on human behavior, many questions remain. The interaction between androgens and behavior is complex. This review article defines androgens, and describes their physiology, receptors and mechanisms of action and summarized their effects on cognitive function, sexual behavior, aggression and depression in men and women.

Keywords: Androgen, human behavior, aggression and depression.

Introduction

An androgen, or male sex hormone, is defined as a substance capable of developing and maintaining masculine characteristics in reproductive tissues (notably the genital tract, secondary sexual characteristics, and fertility) and contributing to the anabolic status of somatic tissues. Testosterone is the principal androgen in the circulation of mature male mammals. Testosterone is one of the major sex hormones produced by the body, occurring in both men and women. In men, it is mainly produced by the Leydig cells of the testes, whereas the ovaries and placenta produce it in women. The adrenal cortex also secretes it in both sexes¹.

Testosterone includes a characteristic four-ring C18 steroid structure and is synthesized by an enzymatic sequence of steps from cholesterol². Leydig cell secretion creates a high local

concentration of testosterone in the testis as well as a steep downhill concentration gradient into the bloodstream, maintaining circulating testosterone levels that exert characteristic androgenic effects on distant androgen-sensitive target tissues^{3:4}.

Synthesis:

The cholesterol is predominantly formed by de novo synthesis from acetate, although preformed cholesterol either from intracellular cholesterol ester stores or extracellular supply from circulating low-density lipoproteins also contributes^{2:2}.

Testosterone biosynthesis involves two multifunctional cytochrome P-450 complexes involving hydroxylations and side-chain scissions

(cholesterol side-chain cleavage [CYP11A1, P450c11 or P450scc, which produces C20 and C22 hydroxylation and C20,22 lyase activity] and 17-hydroxylase/17,20 lyase [which hydroxylates the C17 and then excises two carbons (20 and 21) converting a 21- to a 19-carbon structure]) together with 3 and 17 -hydroxysteroid dehydrogenases and isomerase⁵. The highly tissue-selective regulation of the 17,20 lyase activity (active in gonads but inactive in adrenals) independently of 17-hydroxylase activity (active in all steroidogenic tissues) is a key branch-point in steroidogenic pathways. Both activities reside in a single, multifunctional protein with the directionality of pathway flux determined by enzyme cofactors, notably electron supply from NADPH via the P450 oxidoreductase (POR), a membrane-bound flavoprotein serving diverse roles as a reductase and cytochrome *b5*⁶.

In addition, some extragonadal biosynthesis of testosterone and dihydrotestosterone from circulating weak adrenal androgen precursor DHEA within specific tissues has been described⁷; however, the net contribution of adrenal androgens to circulating testosterone in men is minor,^{8;9} although it makes a much larger proportional contribution to circulating testosterone in women.^{10;11}

Testicular testosterone secretion is principally governed by luteinizing hormone (LH) through its regulation of the rate-limiting conversion of cholesterol to pregnenolone within Leydig cell mitochondria by the cytochrome P-450 cholesterol side-chain cleavage enzyme (CYP11A1) complex located on the inner mitochondrial membrane. Cholesterol supply to mitochondrial steroidogenic enzymes is governed by proteins including sterol carrier protein 2.¹² This facilitates cytoplasmic transfer of cholesterol to mitochondria together with steroidogenic acute regulatory protein¹³ and peripheral benzodiazepine receptor,¹⁴ which govern cholesterol transport across the mitochondrial membrane. All subsequent enzymatic steps are located in the Leydig cell endoplasmic reticulum. The high testicular production rate of testosterone creates both high local concentrations (up to 1 µg/g tissue, ~100 times higher than blood

concentrations) and rapid turnover (200 times per day) of intratesticular testosterone¹⁵.

Secretion

Testosterone is secreted at adult levels during three epochs of male life: transiently during the first trimester of intrauterine life (coinciding with masculine genital tract differentiation), during early neonatal life as the perinatal androgen surge (with still undefined physiologic significance), and continually after puberty to maintain virilization. The dramatic somatic changes of male puberty are the consequence of striking increases in testicular secretion of testosterone, rising ~thirtyfold over levels that prevail in prepubertal children and in women or castrate men originating from extratesticular sources. After middle age, there are gradual decreases in circulating testosterone as well as increases in gonadotrophin and sex hormone-binding globulin (SHBG) levels^{16;17} with these trends being absent until late old age among men who remain in excellent health^{18;19} but exaggerated by the coexistence of chronic illness^{17;20-22} as well as temporal trends including increasing prevalence of obesity^{23;24}. These age-related changes from the accumulation of chronic disease states are functionally attributable to impaired hypothalamic regulation of testicular function²⁵⁻²⁷, as well as Leydig cell attrition^{27;28} and dysfunction²⁹ and atherosclerosis of testicular vessels³⁰. As a result, the aging hypothalamic-pituitary-testicular axis exhibits reactive changes to concomitant systemic disorders as well as multilevel functional defects that, in concert, lead to reduced circulating testosterone levels during male aging.³¹

Metabolism

After testicular secretion, a small proportion of testosterone undergoes activation to two bioactive metabolites, that is, estradiol and DHT, whereas the bulk of secreted testosterone undergoes inactivation by hepatic phase I and phase II metabolism to inactive oxidized and conjugated metabolites for urinary and/or biliary excretion³².

Action and androgen receptor

Androgen action involves prereceptor, receptor, and postreceptor mechanisms that are centered on

the binding of testosterone (or an analogue) to the AR. Testosterone undergoes prereceptor activation by conversion to potent bioactive metabolites, DHT, and estradiol. The steroidogenic enzyme 5 α -reductase has two isozymes, types 1 and 2, which form a local androgen amplification mechanism converting testosterone to the most potent natural androgen, DHT³³.

The other form of prereceptor androgen activation is conversion of testosterone to estradiol by the enzyme aromatase³⁴, which diversifies androgen action by facilitating effects mediated via ERs.³⁵ Consequently, whereas DHT may be considered a pure androgen because its bioactivity is solely mediated via AR, testosterone has a wider spectrum of action that includes diversification by aromatization and ER-mediated effects. These prereceptor mechanisms provide testosterone with a versatile and subtle range of regulatory mechanism before receptor-mediated effects depending on the balance between direct AR mediated versus indirect actions and/or ER-mediated mechanisms. Probably as a result, tissues vary in their androgenic thresholds and dose-response characteristics to testosterone and its bioactive metabolites³.

The human AR is specified by a single X chromosome encoded gene located at Xq11-12 that specifies a protein of 919 amino acids, a classic member of the large nuclear receptor superfamily¹⁸³ that includes receptors for the 5 mammalian steroid classes (androgen, estrogen, progesterone, glucocorticoid, mineralocorticoid) as well as for thyroid hormones, retinoic acid, and vitamin D, as well as numerous orphan receptors where the ligand was originally not identified.³⁶ AR expression is not confined to reproductive tissues and it is ubiquitously expressed, although levels of expression and androgen sensitivity of nonreproductive tissues vary³.

Androgens and behavior

The concept that androgens influence behavior can be traced back over 2,000 years to Aristotle, who observed that castration of immature male birds prevented the development of characteristic male singing and sexual behavior. In 1889 Dr. Charles Brown-Sequard a pioneer French

endocrinologist and neurophysiologist, described the salutary effects on his health (e.g., energy, muscular strength, stamina, mental agility—all the functions depending on the power of action of the nervous centers") of self-injections of extracts of crushed animal testicles³⁷. Following the footsteps of Brown Sequard, Viennese physiologist Eugen Steinach (1861-1944) studied the rejuvenating effects of vasoligation in older animals. In 1920 Steinach concluded that unilateral vasoligation of the ductus deferens produced an increased hormonal production after cessation of the secretory output of the gonads^{38;38}

Efforts to identify the active testicular substance (which Brown-Sequard mistakenly believed to be seminal fluid) led in 1931 to the isolation of the weak androgen androsterone. As androsterone was clearly not the main active component of testicular extracts, the search continued. A second androgen, dehydroepiandrosterone, was also isolated from urine in 1934 and testosterone, the prototypical androgen, was finally isolated from testes and characterized in 1935³⁸.

Since the early 1970s psychoendocrinological research on sexual dimorphic behavior has focused on testosterone, quantitatively the most potent androgen in males which is also present in females at approximately one-tenth of the male serum concentration³⁹. Gender related differences (sexual dimorphisms) in the structure of the brain include the size of brain nuclei, the number of neurons contained in the nuclei, the patterns of connections between neurons and different brain regions (i.e. synaptic development), and axonal and dendritic branching patterns. While CNS sexual dimorphisms have been far more extensively demonstrated in animals, they have also been identified in humans. These dimorphisms include differences in brain structure, physiology (e.g., functional organization for language and other cognitive processes is more asymmetric (lateralized) in men, and cerebral blood flow is greater in women, and behavior (e.g., cognitive test performance in humans is reported to differ, with females showing greater articulatory and fine motor skills, verbal fluency and verbal memory⁴⁰ and males showing greater spatial ability⁴¹, excel

in mathematical problem solving, map reading and targeted motor skills⁴⁰.

Cognition:

It is generally accepted that among many other sources of variance which contribute to the sex differences in cognition, sex hormones, especially androgens, play a critical role in sex-typical cognitive functioning as well as in inter individual differences within the sexes^{1;39}.

In the brain, testosterone can be metabolized to dihydrotestosterone and bind to androgen receptors, or it can be converted to oestradiol by the enzyme aromatase. Both aromatase and androgen receptors are found in key regions in the brain involved in memory and learning, including the hippocampus and amygdala⁴². Testosterone has been shown to increase concentrations of nerve growth factor (NGF) in the hippocampus and upregulate NGF receptors in the forebrain⁴³. Androgens can prevent N-methyl-D-aspartate receptor excitotoxicity in hippocampal neurons and promote fibre outgrowth and sprouting, which may help neurons recover after injury^{44;45}. Neuroprotective effects against oxidative stress⁴⁶ and apoptosis⁴⁷ could also help protect the brain against accelerated age-related cognitive decline.

Testosterone may protect the brain against the development of Alzheimer's disease AD by inhibiting two hallmarks of AD pathology: β -amyloid found in senile plaques and hyperphosphorylated tau found in neurofibrillary tangles. Testosterone has been shown to reduce β -amyloid secretion in rat cortical neurons by altering the processing of the amyloid precursor protein⁴⁸. In hippocampal neurons grown in culture, testosterone can reduce β -amyloid-induced neurotoxicity⁴⁹. In addition, testosterone has been shown to inhibit the hyperphosphorylation of tau in animal models⁵⁰. Despite these observations, the biological effects of testosterone on the brain are far from fully understood. Further insight on the effects of testosterone substitution on neurological activity in different regions of the brain may be provided by advances in imaging techniques. For example, Zitzmann and colleagues⁵¹ used 18F-deoxyglucose deoxyglucose positron emission

tomography to study cerebral glucose metabolism during a standardized mental rotation task in six hypogonadal men. Each patient performed the test before and during treatment with testosterone substitution. During testosterone substitution four patients exhibited improved visuospatial performance, which corresponded with enhanced cerebral glucose metabolism during the test⁵¹. Using single photon emission computed tomography, Azad and colleagues⁵² showed that cerebral perfusion was increased in the midbrain and the superior frontal gyrus after 3–5 weeks testosterone substitution in seven men with hypogonadism. After 12–14 weeks, increased perfusion was still observed in the midbrain as well as the midcingulate gyrus. Lastly, Park and colleagues⁵³ used blood oxygenation level dependent (BOLD) functional magnetic resonance imaging to demonstrate differences in regional brain activation among 12 eugonadal sexually potent men and 2 hypogonadal impotent men in response to visual erotic stimulation. Activation of cerebral cortices in the two men with hypogonadism was low but was partially restored following testosterone substitution. Whether similar techniques could be used to assess differences in brain activity during cognitive tasks remains to be studied. These and other approaches could help to further establish the effects of testosterone on the brain in relation to cognitive ability⁵⁴.

Cognitive symptoms of andropause are frequently reported in clinical practice. A large cross-sectional study of 302 older men found that 36% of patients who identified themselves as experiencing andropause on a standardized questionnaire survey reported memory loss as a symptom⁵⁵. Numerous investigators have examined the effect of androgen substitution and withdrawal upon various study populations. A double-blind study conducted by Janowsky et al⁵⁶ demonstrated that trans-dermal testosterone enhanced spatial cognition of healthy men aged 60–75 years when testosterone levels were raised to those commonly found in young men for a 3-month period. Endogenous production of estradiol was decreased in men receiving testosterone supplementation, and estradiol levels were found to be inversely correlated to performance on tests of spatial cognitive skills⁵⁶.

Cherrier et al. recently reported a 6-week randomized, double blind, placebo controlled study of healthy older men aged 50–80 years in which 100 mg of testosterone enanthate improved both spatial and verbal memory⁵⁷. Another small randomized, double-blind study of healthy volunteers aged 61–75 years demonstrated improved working memory following testosterone enanthate 150 mg/week. Better performance on tasks involving frontal lobe mediated working memory was related to a higher testosterone to estrogen ratio⁵⁸. It is important to note that subjects in these studies were healthy volunteers who did not have Alzheimer's disease and may be in the transition into andropause.

Recently, the existence of an optimal testosterone level that activates in a curvilinear fashion for different verbal and spatial cognitive functions was supported in a small 8-week randomized, controlled trial. Supra-physiological levels of testosterone (200 mg testosterone enanthate/week), reduced visuospatial ability and improved verbal fluency in 30 healthy young men aged 19–45 years⁵⁹. This is consistent with the hypothesis first proposed by Janowsky that high levels of testosterone may be aromatized to estradiol within the brain⁵⁶.

The hypothesis that gonadal replacement therapy might prevent or delay Alzheimers disease (AD) in postandropausal men has recently been supported by a study of the effect of gonadal hormone withdrawal on plasma levels of amyloid-B peptide (AB), the main neurotoxic component of cerebral amyloid found in AD. Six men receiving flutamide (250 mg, three times daily) and leuprorelin acetate (22.5 mg, weekly for 12 weeks) were found to have nearly a twofold increase in AB which paralleled a rapid decrease in plasma testosterone and 17 Bestradiol, and remained elevated over a 6-month period while gonadal hormones remained at low detectable levels⁶⁰.

Dihydroepiandrosterone (DHEA) is an adrenal steroid hormone that decreases with aging and is commonly used as an anti aging nutritional supplement. Clinical studies of the effects of DHEA and its sulfate DHEAS on cognition have produced conflicting results. Fifty-two

community dwelling AD patients (mean age 76 years) were compared to a control group of age and gender-matched healthy elderly men and women on a test of everyday memory. No differences were seen between the AD patients and controls in DHEA-S levels. However, AD patients with higher levels of DHEA-S scored better than those with lower levels⁶¹.

Ross and his colleagues (2003) investigated the effects of androgen replacement therapy in Turner syndrome (TS) girls on cognitive function (TS represents a unique, sex hormone deficient model, in which to study the biological effects of androgen replacement on cognition in female because TS girls have gonadal dysgenesis and absent ovarian androgen and estrogen production). A total of 64 TS girls were randomized to receive oxandrolone or placebo for 2 years. They conclude that oxandrolone treatment for 2 years improves working memory in adolescent girls with TS⁶².

Although it is reasonable to conclude from pertinent studies that androgens may play a role in cognitive functioning throughout life, from the prenatal period till old age, any causal model will have to recognize the reciprocal effects that environment and androgen have on each other¹.

Sexual behavior:

Early behavioral endocrinology studies in normal human males were focused predominantly on the interaction between androgens and sexual activity^{25;63}. It has long been recognized that androgens play a critical role in human male sexual behavior, although it can be profoundly influenced by intrapsychic, social, somatic and cultural factors. It is quite obvious that the general pattern of age-dependent rise and decline of androgen levels¹ in men corresponds to average levels of male sexual activity throughout the life-cycle. Before puberty, boys do not engage in sexual activity outside the context of play. After puberty, when the testes begin to secrete androgens, sex drive and the motivation to seek sexual contact become powerful and are overtly expressed. When blood levels of testosterone, especially free testosterone, diminish as men age,

this mirrors their usually declining sexual interest, arousability and potency.¹

The physiological range of testosterone lies between 3 and 12 ng/ml, which is higher than necessary to maintain normal sexual functions. Testosterone levels found to be critical for sexual functions in males lie below or around 3 ng/ml, and they show a clear intersubject variation¹.

Besides evidence from non-human primates and clinical case reports on effects of castration in human males, studies of hypogonadal men on androgen-replacement therapy provide convincing evidence of the essential role of androgens in some aspects of male sexual behavior. In patients with induced or spontaneous hypogonadism, both pathological withdrawal and reintroduction of exogenous androgens affected the frequency of sexual interest, sexual arousal and desire, spontaneous nocturnal or morning erections, ejaculation, sexual activities with and without a partner, and orgasms³⁹. When supraphysiological doses of testosterone, used as potential hormonal male contraceptive agents, were administered to healthy volunteers, this resulted in a significant increase in psychosexual stimulation or arousal during testosterone substitution. But there was no change in sexual activity or spontaneous erections. In eugonadal men, external administration of high doses of testosterone was said to increase sexual awareness and arousal ability, but this is not reflected in any general modification of sexual activity⁶⁴. McNicholas et al 2003 reported that testosterone levels decrease with aging and that the decrease in testosterone below levels considered physiological eugonadal for young mature men has a deleterious effect on sexual characteristics and sexual behavior while restoring testosterone levels ameliorates these deleterious effects⁶⁵.

Less obvious and difficult to infer from everyday observation is the role of testosterone in female sexual behavior. Physiological testosterone levels in women, which are one-tenth of those in the normal male and to which males are unresponsive, were, for a long time, thought to be irrelevant. Thus, the idea that androgens could have enhancing effects on female sexual desire and arousal received little attention until

testosterone was used to treat oophorectomized women¹.

A variety of models have been employed to test the relationship between testosterone and sexuality in women. Because plasma testosterone levels peak around the time of ovulation, one investigational strategy has involved monitoring changes in several aspects of sexual behavior at different points during the menstrual cycle. But as plasma levels of estradiol also reach their highest point at the ovulatory phase, this research design makes it difficult to prove that testosterone alone induces the increase in sexual behavior during the mid-cycle portion of the menstrual cycle observed in some studies¹. But several well-controlled correlational studies measuring endogenous concentrations of testosterone in women found evidence of an androgenic enhancement of sexual behavior. Sexual gratification, as well as frequency of intercourse, were positively related to testosterone level⁶⁴. The most powerful design for the study of the specificity of testosterone influence involves hormone replacement therapy in women who are oophorectomized. Some studies have shown – without contradictory evidence that administration of testosterone, either alone or in addition to an estrogen-replacement regimen, is more effective than estrogens alone or a placebo³⁹.

Aggression:

Does testosterone have the same aggression-related behavioral effects in humans as it appears to have in nonhuman animals? This question continues to generate substantial controversy in the literature⁶⁶.

Aggression is usually positively correlated with testosterone but the relation is not simple, many more factors are involved in aggressive behavior. The relation between mood and androgens is less clear, results of studies have not been consistent⁴⁰. Animal studies generally indicate that the presence of androgens in early life is important in establishing a biological readiness for future aggressive behavior. Castration leads to a decrease of aggression in animals⁶⁷.

High testosterone levels in male prisoners have been linked to having a history of rape, murder and armed robbery, and relatively lower levels to a history of theft and drug abuse⁶⁸. A similar pattern was observed in a study of female prison inmates⁶⁹. However, the causality in these studies remains unclear: the higher levels of aggression might well have caused the higher testosterone levels, leaving open the question of whether testosterone is a causal factor driving this behavior⁶⁶.

In humans, testosterone cannot illicit violence, it can only alter the probability that aggression is shown in a particular situation under a specific combination of external and internal cues³⁹.

When sexual offenders receive anti-androgenic gestagen, a clearly hypogonadal state is achieved and sexual activity decreases and, with it, criminal potential. The rate of re-offence is much higher in delinquents not receiving, or discharged from medication. In violent sexual offenders, testosterone serves as a catalyst to initiate the expression of aberrant desires already present, and withdrawal of androgens can inhibit delinquency⁶⁴.

Dabbs and Hargrove (1997) found salivary testosterone to be linked to both violent crime and aggressive dominant behavior in females prison inmates⁷⁰. Cotrufo and his colleagues (2000) observed a positive correlation between testosterone and aggressiveness in women with bulimia nervosa⁷¹.

Study of Von der Pahlen et al 2002 confirmed the earlier observations of an association between testosterone and aggression in women and suggested that testosterone is an important contributor to female criminal behavior in particular but they also emphasize both social and the significance of other hormones⁷². In women, the level of plasma testosterone varies depending on the phase of the menstrual cycle, with increasing levels at ovulation and luteal phase. The relationship between testosterone and

aggressive behavior may, therefore, differ across the menstrual cycle^{70:71}.

Aggressive behavior which was not a punishable offence also showed significant correlation with androgens in men and women. During experimentally controlled alcohol intake, aggressively predisposed students were more dominant in a discussion and had higher free testosterone levels than non-aggressively predisposed students. In male hockey players the pre-play testosterone levels correlated positively with reactive aggression during the tournament. Male and female patients in a clinic for nervous diseases showed more destructive aggression with higher levels of testosterone³⁹.

Anabolic steroids are synthetic derivatives of testosterone modified to enhance the anabolic rather than the androgenic actions of the hormone. The anabolic effects are considered to be those promoting protein synthesis and muscle growth. There are numerous side effects of anabolic steroids, including hypertension, atherosclerosis, blood clotting, jaundice, hepatic carcinoma, psychiatric and behavioral effects. Anabolic steroids were added to the international Olympic Committee's list of banned substances in 1975. One large study in the USA demonstrated that 25% of abusers of anabolic steroids exhibited some form of mood disorders varying from mania, bipolar disorder to major depression. A survey of violence between male anabolic steroid abusers and their female partners revealed a significant increase in severe hostility and aggression compared to steroid free males and their partners. Anabolic-androgenic steroid (AAS) abuse in men and women, controlled AAS substitution in sportsmen, testosterone replacement therapy for hypogonadal adolescent or adult males, in surgically menopausal females and in female-to-male transsexuals and exogenous testosterone as a potential hormonal male contraceptive can result in increased irritability and aggressiveness, but not necessarily³⁹. Members of body-building studios using steroids engaged in confidential interviews about their steroid use. One-third of the individuals were reported to be manic or near manic. Most symptoms subsided when anabolic steroid use was discontinued³⁹.

Depression:

Rohr 2002 mentioned that high androgen levels cause aggressive behavior in men and women and as a consequence may cause depression⁷³. In hypogonadal men whose often lethargic or depressive mood significantly improved under testosterone therapy⁶⁴. Studies exploring the relationship between gonadal function and depressive episodes showed that testosterone secretion as well as mean levels were decreased significantly in patients⁷⁴. In cross sectional study of 85% men, bioavailable testosterone levels were inversely associated with depression⁷⁵.

Women suffer more often from depression than males, indicating that hormones might be involved in the etiology of this disease. Low as well as high testosterone levels are related to depression⁷³.

After menopause, especially after bilateral oophorectomy, androgens are significantly reduced in blood and this would influence the well being of the woman. In women, both low and elevated androgen levels seem to be associated with depressive mood in adolescent girls, adult females, and in women with premenstrual dysphoria. On the other hand, women with abnormally low androgen levels after oophorectomy reported significantly less depression and anxiety during testosterone substitution reaching normal female serum concentrations³⁹.

In a large group of perimenopausal women, those with still relatively high endogenous dehydroepiandrosterone sulphate (DHEA-S) levels felt less dysphoric and had a higher degree of emotional wellbeing in comparison with women with low DHEA-S concentrations. These findings point to a negative effect of hormonal changes from low to high levels (e.g. puberty, premenstrual dysphoria) or withdrawal from normal androgen levels (postpartum, perimenopause, castration)³⁹.

Conclusive remarks

In- spite that androgens effect on human behavior has been the focus of intensive research for

decades, the exact mechanism by which testosterone has these effects remain elusive.

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