Androgens, Brain, and Behavior

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Objective: This article defines androgens (and anabolic steroids), describes their mechanisms of action, and summarizes their behavioral effects and relevance in animals and humans. Method: A MEDLINE-derived review of the literature on androgens and behavior was performed; pivotal earlier publications were also obtained and included in the review. Results: In animals, the effects of androgens on brain structure and function are well-established and profound, with behavioral implications extending far beyond reproduction. Androgens play a prominent role in the organization or programming of brain circuits, which are subsequently activated by gonadal steroids. In humans, roles for androgens have been described, albeit inconsistently, in the regulation of sexuality, aggression, cognition, emotion, and personality. The relevance of androgens for psychiatry is further suggested by gender-related differences in pharmacokinetics/pharmacodynamics and in the prevalence, course, and treatment response characteristics of several psychiatric disorders. Direct psychoactive effects of exogenously administered androgens have been described for many years, most recently in reports of the psychotoxic effects of anabolic steroids. Conclusions: Data from both animals and humans suggest that the biological and behavioral responses to androgens are context-dependent.

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In 1889 Dr. Charles Brown-Séquard 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 testicles (1). Subsequently, it was shown that in animals, the active ingredients in these extracts, androgens, organize the brain during critical periods of development and activate a variety of reproductive and nonreproductive behaviors. Roles for androgens in the regulation of human sexuality, aggression, cognition, and emotion have been frequently described, but consistently observed only under restricted conditions. In addition, several observations suggest the potential importance to psychiatrists of knowledge of the effects and mechanisms of action of androgens. First, there are gender-related differences in the prevalence, course, and treatment response characteristics of several neuropsychiatric disorders. For example, women show a greater prevalence of depression and a lesser prevalence of learning disorders (2–4), a later onset of schizophrenia (5), and an enhanced response to thyroid augmentation of antidepressant treatment (6). Second, gender-related differences in pharmacokinetics and pharmacodynamics influence drug metabolism and may underlie differences observed in the optimal dose and adverse effects of psychotropic medications (7). Third, androgens have been used to treat de novo mood disorders (8) and those occurring in the context of the perimenopause (9) and in patients with AIDS (10). Fourth, certain androgens, the anabolic steroids, have direct behavioral effects and have been reported both to cause mood disorders and to be effective in their treatment (8, 11). Fifth, abnormal levels or secretory patterns of androgens have been seen, albeit inconsistently, in depression (12, 13), schizophrenia (14), posttraumatic stress disorder (15), and anorexia (16). Finally, a major role for androgens has been postulated in the pathophysiology of Tourette's syndrome (17) and obsessive-compulsive disorder (18). This article summarizes current knowledge of the androgens, particularly as they relate to CNS function and behavior.

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HISTORY OF BEHAVIORAL EFFECTS OF ANDROGENS

The concept that androgens influence behavior can be traced back over 2,000 years to Aristotle, who observed in his biological treatise *Historia Animalium*

that castration of immature male birds prevented the development of characteristic male singing and sexual behavior (19). The masculinizing effects of testicular secretions were also noted by the second-century Greek physician Arataeus of Cappadocia, who said, "For it is the semen, when possessed by vitality, which makes us to be men, well braced in limbs, hairy, well voiced, spirited, strong to think and to act, as the characteristics of men prove. For when the semen is not possessed of its vitality, persons become shriveled, have a sharp tone of voice, lose their hair and their beard and become effeminate, as the characteristics of eunuchs prove" (20). The notion, dating back to Arataeus and Aristotle, that symptoms of old age accompany testicular degeneration stimulated multiple attempts by the organotherapists of the nineteenth century to reverse the symptoms of aging by administering or stimulating testicular secretions (21, 22). In addition to the subcutaneous administration of extracts from ground-up guinea pig and dog testes performed by Dr. Brown-Séquard, highly touted revitalizing surgical procedures were performed, including ligation of the vas deferens (the Steinach procedure) and transplantation into humans of numerous species of animal testes (22). It is noteworthy that Freud himself underwent the Steinach procedure in November of 1923 in hopes of both assisting his immune system's fight against cancer and enhancing his capacity for enjoyment of work and sexual activity (23). Even Brown-Séquard's concoction was marketed as (the modestly named) "sequarine—the medicine of the future," with claims for the successful treatment of everything from diabetes to dyspepsia (24). Efforts to identify the active testicular substance (which Brown-Séquard mistakenly believed to be seminal fluid) led in 1931 to the isolation of the weak androgen androsterone (25). 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 (26), and testosterone, the prototypical androgen, was finally isolated from testes (27) and characterized (28, 29) in 1935 (for reviews, see references 30 and 31).

WHAT ARE ANDROGENS AND HOW DO THEY ACT?

Androgens are steroid hormones that have two different effects: androgenic effects, i.e., differentiation, growth, and development of the male reproductive tract; and anabolic effects, the stimulation of linear body growth and somatic growth. During early development, androgens masculinize the internal and external genitalia and the brain, while after puberty, the masculinizing effects consist of maturation of the external genitalia and accessory sexual organs; stimulation of the beard and axillary and pubic hair; temporal hair recession and balding; enlargement of the larynx and thickening of the vocal cords; and facilitation of libido and sexual potency (32). Structurally, androgens are members of the larger family of steroid hormones, derivatives of cholesterol that contain a basic skeleton of four fused carbon rings. Relatively few enzymatic steps performed by a small group of enzymes result in the generation of all steroid hormones (figure 1). Thus, the way in which a steroid is metabolized determines the nature of the steroid signal and the degree to which it is amplified. As shown in figure 2, this point is critical to understanding the means by which androgens exert their effects.

Most, but not all, of the effects of testosterone and other androgens are mediated through the androgen receptor, an approximately 919-amino-acid protein (33), which is widely but selectively distributed throughout the brain. Once androgen binds the androgen receptor, structural changes occur in the receptor that facilitate its binding to complementary regions of DNA in the cell nucleus. The receptor binding activates transcription of the gene or genes, producing messenger RNA transcripts that encode a wide array of enzymatic, structural and receptor proteins (34). Recent studies suggest that androgens, like other steroids, may also influence cellular activity in a nongenomic fashion (i.e., not requiring protein synthesis) by acting directly at the cell membrane or by modulating the activity of other membrane receptors or second messenger systems (35). Through both nongenomic and receptor-mediated genomic mechanisms, androgens in animals appear to regulate the actions of a wide range of neurotransmitters and neuropeptides (table 1).

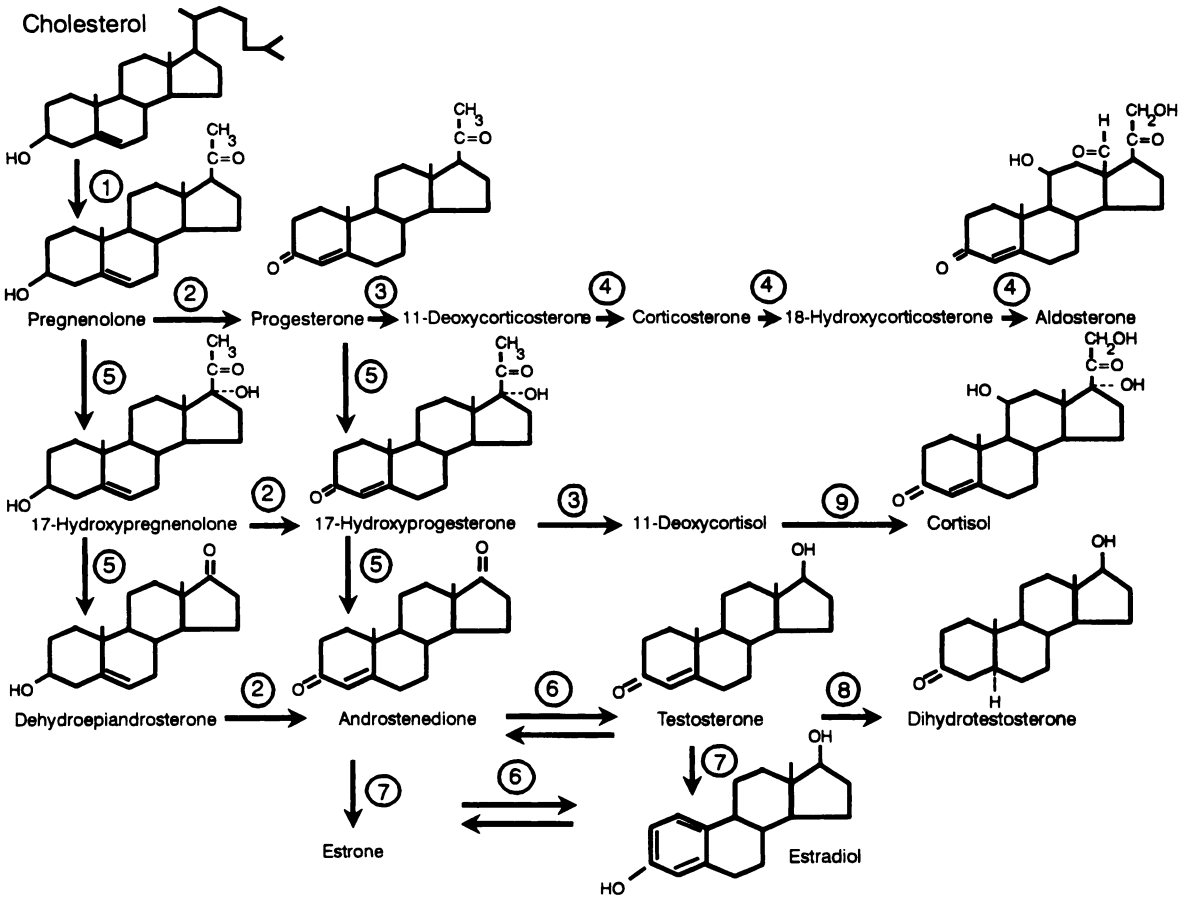
EFFECTS OF ANDROGENS ON THE BRAIN

Androgens and estrogens acting through their respective receptors are responsible for most of the observed differences between males and females in brain structure and function. Gender-related differences (sexual dimorphisms) in the structure of the brain include the size of brain nuclei, the number of neurons contained in these nuclei, the patterns of connections between neurons and different brain regions (i.e., synaptic development), and axonal and dendritic branching patterns (48). The dramatic effects of gonadal steroids on brain structure and function are consistent with the regulatory interactions that they demonstrate with brain growth factors (49, 50) and probably underlie gender-related differences in the response to brain injury (51, 52).

Gender-related differences in neuroregulation take the form of sexual dimorphisms in the regional concentration of neuropeptides and neurotransmitters (53) as well as differences in brain physiology (e.g., growth hormone response to α-adrenergic stimulation is greater in male rats [54]). A variety of behavioral dimorphisms have also been identified: female rats show increased behavioral response to serotonin agonists (55, 56), and the capacity to sing tends to be limited to the males of a number of species (57, 58).

These and other sexual dimorphisms represent the product of two types of actions of gonadal steroids: temporary or activational effects and permanent or organizational effects. Activational effects are acute, tem-

FIGURE 1. Synthetic Pathways for Steroid Hormones[a]



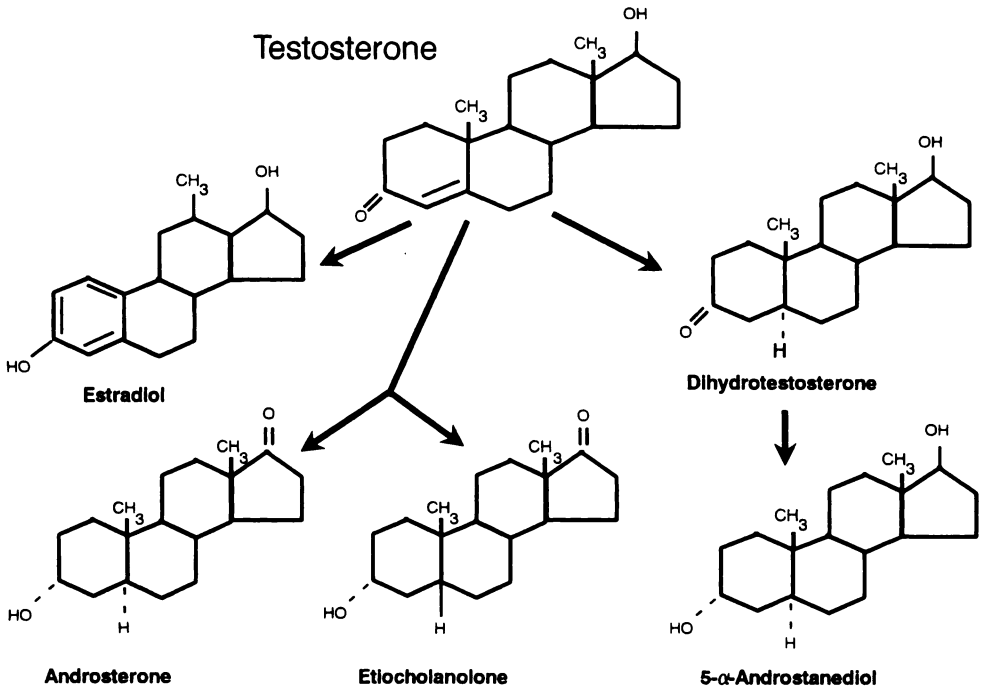
[a]Circled numbers identify synthetic enzymes: 1=cytochrome P450 (CYP) 11A (cholesterol desmolase); 2=3β-hydroxysteroid dehydrogenase; 3=CYP21 (21-hydroxylase); 4=CYP11B2 (11β-hydroxylase, 18-hydroxylase, 18-oxidase); 5=CYP17 (17α-hydroxylase, 17,20-lyase); 6=17β-hydroxysteroid dehydrogenase (or oxidoreductase); 7=aromatase; 8=5α-reductase; 9=CYP11B1 (11β-hydroxylase).

porary actions of hormones. Some sexual dimorphisms simply reflect these acute actions of the predominant gonadal steroid (androgen versus estrogen) that is present and can be eliminated by castration or manipulation of hormone levels (59, 60). Organizational effects refer to the ability of gonadal steroids, when acting on the brain during brief developmental windows, to *permanently* alter the structure or functional potential of the brain (61). For example, if a female rat is exposed to testosterone perinatally, the size of the sexually dimorphic nucleus of the hypothalamic preoptic area will thereafter approximate that in the male, three to five times larger than that usually seen in the female (62, 63). Further, perinatal exposure to androgen will eliminate the capacity of the adult female rat to express cyclic gonadotropin secretion (required for normal postpubertal ovarian function [64]). A remarkable example of the ability of gonadal steroids to create a context that shapes development was recently described by Piferrer et al. (65). Exposure of an all-female stock of chinook salmon to an inhibitor of aromatase (the enzyme that converts testosterone to estradiol) for only 2 hours during an early developmental stage created salmon with normal testes; i.e., the salmon were phenotypically male but genetically female.

In some instances, the organizational effect takes the form of an altered behavioral response when the animal is reexposed to gonadal steroids after puberty (66). In such cases, it is a context-dependent behavioral predisposition that is organized by perinatal gonadal steroids. For example, a female rat that is briefly exposed to androgens during the first postnatal week will display male mating behaviors if reexposed to androgens after puberty (66). Gonadal steroid levels, then, can influence, through acute or prior exposure, the behavioral repertoire of animals.

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 (67), physiology (e.g., functional organization for language [68] and other cognitive processes [69, 70] is more asymmetric [lateralized] in men, and cerebral blood flow is greater in women [71]), and behavior (e.g., cognitive test performance in humans is reported to differ, with females showing greater articula-

FIGURE 2. Metabolism of Testosterone[a]



[a]Testosterone may be reduced (cleavage of a double bond/addition of electrons) by 5α-reductase to dihydrotestosterone, which has a much higher binding affinity for the androgen receptor than testosterone and is required for the masculinizing effects on reproductive tract tissues such as the prostate and seminal vesicles. Testosterone may itself act at the androgen receptor, or it may be converted to other weaker androgens such as androsterone. Testosterone may also be aromatized (i.e., the A-ring is converted to a benzene ring) to produce estradiol, which then acts at the estrogen receptor to mediate the effects of androgens.

tory and fine motor skills and males showing greater spatial ability [72–74]). Thus, in humans as in animals, there is evidence suggesting the ability of gonadal steroids to influence CNS structure and function.

BEHAVIORAL EFFECTS OF ANDROGENS IN ANIMALS

As might be inferred from the myriad effects of androgens on the brain, a wide variety of behaviors in animals are androgen-dependent. The behaviors influenced by androgens are deduced from observations of both sexually dimorphic behaviors and the consequences of hormone manipulation studies, which use castration, hormone replacement, or blockers of steroid synthetic enzymes or receptors.

The most compelling argument can be made for a role of androgens in sexual behavior, aggression, and, to some extent, social rank. Apart from the organizational actions of androgen (mentioned above), which influence the development of neural circuitry to support male sexual behavior, androgens are necessary to activate or maintain sexual behavior in male rats; postpubertal castration eliminates or interferes with expression of male sexual behavior, and androgen replacement restores it (66, 75).

In most species, androgens appear to exert a significant influence on the degree and form of aggressive behavior (66, 76, 77). In general, males tend to be more aggressive than females, may display different motor patterns during their agonistic encounters (e.g., stallions use front feet and mares use hind feet), and engage as youths in more rough-and-tumble play and chasing (76, 77). In many animals, aggression increases during breeding (particularly in seasonal breeders) and with the associated increased testosterone secretion (76, 78).

The effects of androgen on aggression again reflect both organizational and activational influences. In rodents, male aggressive behavior appears to be organized similarly to sexual behavior: males castrated within 6 days postnatally display little intermale aggression when treated with testosterone as adults, but neonatal androgen replacement restores normal adult aggressive behavior (66). Neonatal treatment of female mice with androgens produces increased aggressive behavior in oophorectomized (ovaries removed) adults treated with androgens, an effect not seen in the absence of neonatal androgenization (79, 80). In adult animals, androgen administration increases (activates) social aggression in male but not female rats, although some female ungulates (cows, mares, ewes, goats) display androgen-related increases in aggression as well as masculinization of the form of aggression (81). Of particular interest is the rise in social rank following androgen treatment, which in female ungulates is less related to changes in aggression than to a simple refusal to submit to the threats or attacks of hierarchically superior animals (76, 78, 82).

Androgens may directly or indirectly regulate a variety of other behaviors in a species-dependent fashion. In the adult canary, song learning and behavior is androgen-dependent, and administration of testosterone to females both increases the size of the brain song control nuclei and leads to production of male-like song (83). Androgens regulate feeding behavior and food intake in birds and rats, perhaps through interactions between androgens and central opiates (84, 85). Social recognition in adult male rats is modulated by androgen-dependent vasopressin-containing neurons; i.e., the regulatory effects of vasopressin are eliminated by castration and restored by testosterone replacement (86).

Studies of the behavioral effects of androgens in animals yield several conclusions. First, androgens may, in a species-dependent fashion, influence behavior through organizational or activational effects produced by different metabolites, estradiol (87) or dihydrotestosterone (88–90). Second, as one expands the range of species considered beyond rodents to nonprimate mammals, the relation between androgens and behavior becomes increasingly complex; in some instances, the animal's past experience is associated with more of the variance than the hormonal status (66, 76). Third, the results of studies of androgens and behavior are even more contradictory, and the effects of past experience and social factors more prominent, when the study subjects are primates (76, 91).

TABLE 1. Neuroregulatory Effects of Testosterone Replacement in Castrated Male Rodents

System	Action	Site
Serotonin	↓ 5-HT_2 binding after imipramine (36)	Cortex (frontal)
	↑ [^{3}H]quipazine binding (5-HT_3) (37)	Amygdala (lateral, basal-lateral)
	↑ Imipramine binding (transporter)	Cortex, hypothalamus
	↓ Imipramine binding (transporter) (38)	Hippocampus
	↓ 5-HIAA (39)	Hypothalamus, striatum
Dopamine	↓ Dopamine release (amphetamine-induced) (40)	Mesolimbic tract
	↑ Tyrosine hydroxylase (41)	Amygdala (anteromedial)
	↓ Dihydroxyphenylacetic acid, HVA (39)	Brain stem
Acetylcholine	↑ Choline acetyltransferase (42)	Hypothalamus (medial preoptic area)
Norepinephrine	↑ MAO (42)	Hypothalamus (medial preoptic area)
GABA	↑ GABA turnover (43)	Hypothalamus
Vasopressin	↑ Vasopressin mRNA (44)	Bed nucleus of stria terminalis
Oxytocin	↑ [^{3}H]oxytocin binding (45)	Hypothalamus (ventromedial nucleus, preoptic area)
Neurokinin	↑ Neurokinin A (46)	Hypothalamus
Cholecystokinin	↑ Preprocholecystokinin mRNA (47)	Amygdala, bed nucleus of stria terminalis

BEHAVIORAL EFFECTS OF ANDROGENS IN HUMANS

In contrast to the wealth of data suggesting the critical role of androgens in a variety of behaviors in lower animals, relatively little is known about the behavioral effects of androgens in humans. In general, three types of studies have been performed: group comparison studies, in which groups are selected for the presence or absence of a particular characteristic (e.g., aggression); correlational studies that examine the degree of association between measures of androgens and selected behaviors; and treatment or experimental studies, in which the behavioral consequences of manipulations of androgen levels are observed (91).

In the human male, certain components of sexual function are clearly androgen-dependent. Sexual desire, sexual thoughts, intensity of sexual feelings, and sexual activity are diminished in hypogonadal males and restored with testosterone treatment (92–95). Similarly, testosterone increases the frequency, duration, and magnitude of spontaneous and nocturnal erections, all of which are impaired in hypogonadal men (96). However, erections in response to erotic stimuli do not appear to be androgen-dependent (93, 94). In addition, androgen dependence, for all practical purposes, takes the form of a threshold level, below which libido (sexual interest and arousal) and sexual function are impaired and above which they are not, with no correlation between either the ideational or erectile components of sexual function and testosterone levels in the normal range (97–100). Thus, disturbances of libido and erectile function in men with normal gonadal function are not remedied by increasing androgen levels, and in young men, increasing testosterone does not increase self-reports of sexual interest or spontaneous erections (97, 99). In women, both a positive correlation (101) and the absence of a correlation (102) between testosterone levels and sexual interest and behavior have been observed. Similarly, androgen replacement therapy increases libido in women who are androgen-deficient (e.g., after surgical menopause) (103, 104) but does not affect sexual arousal or behavior in naturally menopausal women (105). In humans, then, androgens play an important role in sexual function but are not its sole determinant.

A role of androgens in aggression has been inferred from studies in which samples were selected on the basis of violent behavior. In comparison with prisoners convicted of nonviolent crimes, male prisoners with histories of violent crime during adolescence (106) or chronic violent behavior (107) had higher testosterone levels. Similarly, higher testosterone levels were seen in female neuropsychiatric patients with histories of violence and in prisoners with histories of unprovoked violence than in control subjects (108, 109). Further, in a recent study of alcoholic, violent criminals, Virkkunen et al. (110) observed that a high free testosterone level in the CSF was the best biological discriminator of violent offenders from nonviolent, noncriminal control subjects. In contrast, a number of studies did not find higher plasma testosterone levels in violent criminals

than in nonviolent criminals (111, 112), including the study by Kreuz and Rose (106) (mentioned above) that did find higher testosterone levels in prisoners with a *history* of adolescent violence. While these inconsistencies apply to groups of violent and "less-violent" sex offenders (113, 114), as well as to normal subjects selected for aggression on the basis of psychometric measures (115, 116), it is worth noting that studies do not suggest group differences in the opposite direction, i.e., violence associated with lower testosterone levels.

Correlative studies of androgens and aggression, like the group studies, are characterized primarily by their inconsistency. Some show a positive association between androgen levels and measures of aggressive behavior, particularly in adolescence (117–123). Others, using similar measures, show no correlation (106, 115, 124–126). Particularly troubling is the relative paucity of significant correlations reported, given the array of measures of (or proxies for) aggression that have been used (e.g., hostility, impulsivity, irritability, antisocial behavior, self-reported or observed aggression) even within a single study. As reviewed by Archer (91), these studies are difficult to summarize because of wide variations in subject characteristics, sample sizes, hormonal measures (e.g., total versus free levels, plasma versus CSF), and aggression measures used.

Finally, studies in which testosterone was administered to hypogonadal men (127–129) or men with normal gonadal function (97, 130) did not report increased aggression with treatment. Most of these studies sampled mood rather than aggression and described either no change (100, 128, 130, 131) or improvement (127, 129, 132–134) following testosterone treatment. (In addition, Burris et al. [95] reported a significant *decrease* in anger during testosterone treatment in hypogonadal men, who were significantly more angry at baseline than control subjects.)

The relation between androgen levels and depression has been examined in several studies, presumably consequent to reported activating effects of androgens as well as to beliefs (recently challenged by Nofzinger et al. [135]) about the prevalence of sexual dysfunction in depression. The absence of differences in plasma testosterone levels in depressed men compared with control subjects (136–139) is seen as frequently as lower levels of testosterone in depressed men (140–143). A negative correlation between testosterone levels and severity of depression was observed in several studies (139, 140, 144), although, again, not without exception (145). As reviewed by Danziger and Blank (11) and Bahrke et al. (8), there is an extensive literature containing studies and case reports of the successful treatment of depressed and climacteric/involutional men with androgens. This literature dates back to a study by Schmitz in 1937 (146), 2 years after the isolation of testosterone. Approximately four times as many positive as negative reports exist that describe the efficacy of testosterone in depression (primarily involutional) and anabolic steroids (described below) in a mixture of psychiatric diagnoses (8). While the majority of these reports represent uncontrolled studies, and a reporting bias would favor the publication of positive rather than negative studies, it is of interest that earlier reports of the mood-enhancing effects of the androgen dehydroepiandrosterone (147, 148) have recently been supported in a double-blind, placebo-controlled trial (149). Finally, roles have been postulated for androgens in the pathophysiology of other neuropsychiatric disorders. For example, Peterson et al. (17) suggested that androgens influence the symptom expression, course, and dimorphic prevalence of Tourette's syndrome and described attempts to treat the disorder with antiandrogens. Future investigations of the sexual dimorphisms and effects of androgens in humans may identify physiologically and pathophysiologically relevant brain regions as well as mechanisms underlying differences in disease acquisition and expression.

ANABOLIC-ANDROGENIC STEROIDS

Interest in the effects of androgens on mood and behavior has been considerably stimulated by the epidemic of anabolic steroid use and the numerous reports of adverse behavioral consequences of this abuse. Anabolic steroids are modified forms of testosterone that possess relatively more anabolic (anticatabolic, growth-promoting, nitrogen-retaining) than androgenic (masculinizing) activity. All androgens and modified androgens possess both androgenic and anabolic effects and consequently are part of a group of steroids called anabolic-androgenic steroids (150). The structural changes represented by the dozens of synthetic anabolic-androgenic steroids primarily influence absorption (oral or parenteral), metabolism, and affinity for the androgen receptor. Differential effects among members of this group may then reflect differences in the net potency (concentration, duration of action, and receptor affinity) of the individual steroids and their metabolites at the androgen receptor, although alternative mechanisms of action (e.g., direct enzymatic inhibition) have been postulated (34).

Reports of major psychiatric symptoms and syndromes (aggression, psychosis, mania, hypomania, and depression) associated with anabolic-androgenic steroids have replaced the earlier reports of their therapeutic efficacy in psychiatric disorders. These psychotoxic effects (as well as the relative absence of adverse reactions reported in association with the treatment of medical disorders such as anemia and hypogonadism) may reflect the enormous amounts (six to 100 times the therapeutic doses) and combinations of steroids used by body builders and athletes. In a recent study, Pope and Katz (151) identified manic, hypomanic, or depressive syndromes (by retrospective self-reports), diagnosed according to the Structured Clinical Interview for DSM-III-R, in 23% of 88 steroid users for the period of their steroid use, compared with 10% of this group for the period when they were not taking steroids and 6% of 68 nonusers. Several of the steroid users reported psychotic or violent symptoms during steroid use. Similar serious psychiatric symptoms (e.g., aggression, hostility, anger, irritability, and anxiety) have been reported in some recent studies (152–155) but not

all (8), most of which were naturalistic and compared groups of users with nonusers or performed comparisons of retrospective accounts. The methodologic limitations of these studies (e.g., retrospective design, subject selection bias, inadequate subject characterization, inability to control for co-administration of other psychoactive agents, lack of placebo control) have been reviewed elsewhere (8, 151, 156).

In a prospective study, Hannan et al. (157) observed significant treatment-related increases in scores on the hostility and resentment/aggression subscales of the MMPI after 6 weeks of treatment with testosterone or the anabolic steroid nandrolone. Consistent with these findings, we demonstrated significant and sometimes marked mood and behavioral changes during administration of anabolic-androgenic steroids in the only placebo-controlled, prospective study of the effects of anabolic-androgenic steroids in normal volunteers (156). During the high-dose condition (240 mg/day of methyltestosterone), we observed significant albeit subtle increases in a variety of "negative mood" symptoms, including irritability, mood swings, violent feelings, anger, and hostility, as well as in some "positive mood" symptoms, such as euphoria, increased energy, and sexual arousal. Significant increases in ratings of cognitive symptoms (distractibility, forgetfulness, and confusion) were also obtained. Profound "psychoactive effects" (mania requiring seclusion) were seen in one of the 20 subjects, representing a 5% incidence, even under the conservative conditions (short-term, relatively low-dose administration) of this trial. This study confirmed earlier naturalistic studies and case reports suggesting both the activating and adverse mood and behavioral effects of anabolic-androgenic steroids. It is noteworthy, however, that the response to anabolic steroids across members of our subject group was highly variable, ranging from negligible to dramatic. It appears, therefore, that anabolic-androgenic steroids can exert mood and behavioral effects, but the effects across individuals are far from uniform. Are these individual differences responsible for the inconsistency in the literature regarding the behavioral effects of androgens/anabolic-androgenic steroids, and if so, how are they best to be understood?

ANDROGENS AND BEHAVIOR: CONTEXT OF THE INDIVIDUAL

Apart from methodological confounding factors already addressed (e.g., differences in measures used across studies), a number of factors may modulate the relation between androgens and behavior, resulting in considerable interindividual differences and differences across studies. First, differences in metabolism will yield different steroid metabolic profiles and behaviors that represent the sum of individual steroid effects. For example, appetite in a male rat is suppressed by castration and restored by exogenous testosterone; however, replacement with larger, pharmacologic doses of testosterone will again suppress appetite because of the increased production of estrogen through aromatization (158). Second, a variety of factors such as age (159) and circadian rhythm (160) can modulate androgen levels. Testosterone levels are decreased by physical and emotional stress (161–164) and, in fact, are modulated by the very aggressive encounters that frequently constitute the study outcome measures (91, 165, 166). Third, past experience, environment, social interactions, and social rank to some degree determine the effects of androgens on behavior. For example, a prepubertal mouse that is castrated before its first aggressive encounter will show greatly attenuated aggressive responses; however, once the mouse experiences aggressive encounters, the aggressive response is maintained despite castration (167–171). Further, the androgen-dependent aggressive response in rats is increased by prior exposure to activating events (e.g., cohabitation or competition) (172). In studies across a variety of species, social rank influences the endocrine and behavioral responses to various stimuli. The dominant olive baboon will respond to a stressor by increasing testosterone levels, whereas a submissive baboon will respond with decreased testosterone (173). Rejeski et al. (174) observed that anabolic steroids increased dominant behavior and basal heart rate in the dominant cynomolgus monkey but increased submissive behavior and lowered basal heart rate in the submissive monkey. In men, as well, prior success in competition (175), dominant social interactions (176), and perception of victory (177) have been reported to alter testosterone but not cortisol response to competition. Thus, one can have a very different behavioral or biochemical response profile as a function of the meaning of an event and past experience with it, social rank, or context. These different biochemical and behavioral patterns were exactly what we observed following administration of anabolic-androgenic steroids. For example, subjects manifesting cognitive dysfunction during administration of high doses of anabolic-androgenic steroids showed significant elevation of plasma cortisol and dehydroepiandrosterone and CSF adrenocorticotropic hormone (ACTH) levels as well as less of a decrease in reproductive axis hormones than subjects showing no cognitive effects of anabolic-androgenic steroids (178). The response to anabolic-androgenic steroids, then, may be context-dependent, with the context determined by a person's past history, expectations, environment, and biological substrate. To that extent, it is unlikely that there exists a simple causal relation between androgens and behavior.

Behavior is multiply encoded, and prior experience can override the influence on behavior of manipulations of testosterone (78, 91, 168, 179). Nonetheless, data overwhelmingly demonstrate that androgens are major modulators of brain biochemistry and behavior. They regulate and interact with growth factors, neurotransmitters, neuropeptides, neuroactive steroids, and neuronal second messengers to influence neuronal differentiation, growth, survival, activation, and synapse formation. They both regulate vital behaviors (e.g., sex, aggression) and are, in turn, regulated by those behaviors. They create a context that determines the behavioral effects of at least several neuropeptides, and their behavioral actions often appear to be determined by

context. Despite a confusing and intricate web of interactions, we are at present uniquely poised to isolate and define the behavioral effects of specific androgen metabolites by using the array of enzyme inhibitors and receptor agonists and antagonists at our disposal. By so doing, we may begin to understand how androgens and related steroids create behavioral capacities rather than cause behavior. Studies with androgens highlight a critical caveat in behavioral research: the differential response across individuals to ostensibly the same stimulus cannot be understood without properly characterizing the context (biochemical, environmental, and historical) of the individuals studied.

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