

Sexual effects of androgens in women: some theoretical considerations

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Objective: To consider explanations for the inconsistent evidence concerning behavioral effects of androgens in women. The following possible explanatory mechanisms are explored: [1] Women vary in their behavioral responsiveness to T. [2] Some reported effects of exogenous T may be induced by increasing bioavailable estrogen. [3] Sexual effects of T may be secondary to direct effects on mood. [4] The relationship between T and sexuality is readily obscured by psychological mechanisms. [5] Stress-induced increases in adrenal androgens may further confuse the picture. [6] Women who respond to T respond to levels that are ineffective in men. There is no evidence of a threshold in women above which further increases in T have no additional effect.

Conclusion(s): A theoretical model, involving desensitization of the central nervous system to T during early development in the male, is presented as a possible explanation for some of these relevant differences between men and women and for much of the conflicting evidence in the literature on women. (*Fertil Steril*® 2002; 77(Suppl 4):S55–9. ©2002 by American Society for Reproductive Medicine.)

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I was first confronted by the subject of this paper when I was involved in a treatment study of women with sexual problems in their relationships (1). In this study, the women and their partners received sex therapy and in addition half of the women received testosterone (T) therapy and the other half diazepam therapy on a randomized basis. The T group did significantly better than the diazepam group, which lead us to conclude that T has beneficial effects on women's sexuality. However, Mathews et al. (2) attempted to replicate this finding, using a placebo rather than diazepam in the design, and found no difference between T and placebo. In addition, Dow and Gallasher (3) did a further replication adding in a third group who received T treatment only. They also found no benefits from T.

Since those earlier experiences I have been struck by the inconsistencies and often contradictions in the now extensive literature on T and women's sexuality. In contrast, the evidence of the role of androgens in male sexuality, while much more modest in amount, is much more consistent, at least for adult men up to the age of 50 or so. Nevertheless, there are a fair number of studies suggesting that T does have a role in female sexuality, and I remain convinced that T is

important for women's sexuality. The question is, how does one reconcile the confusion?

This literature on T and women's sexuality, together with the literature on sexual effects in men, has been reviewed comprehensively elsewhere (4). In this paper, I will focus on a number of possible explanations for this confused picture and will conclude with an explanatory theoretical model of androgen effects.

POSSIBLE EXPLANATIONS FOR THE CONFUSION OVER THE ROLE OF T IN WOMEN'S SEXUALITY

Are Women Markedly Variable in Their Responsiveness to T?

Much of the confusion could be explained if we could show that in some women sexuality is markedly dependent on T, whereas in others it has little or no effect. Such variability could be genetically determined (see below for further discussion). Because this possibility has not been directly addressed in the research literature, we have only limited or indirect evidence to support it.

Negative effects on sexuality caused by an

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antiandrogen (cyproterone acetate) were reported in 60% of women who were in an ongoing sexual relationship at the time of administration of the drug (5). While 60% is a majority, there was a substantial minority apparently unaffected. Nathorst-Böös et al. (6), in a study of hormone replacement therapy in oophorectomized women, were unusual in reporting that the percentage of women in their sample who had experienced a sexual decline postoperatively was 50%. The other half had apparently not suffered any noticeable decline in their sexuality after the dramatic postoperative reduction in androgens.

Oral contraceptives (OCs) have adverse effects on sexual interest in a substantial minority of women (7), and this effect, together with adverse effects on mood, have been shown to be important, possibly the most important, reasons for discontinuation of OC use in the first 3 months (8). Although OCs predictably lower free T, we cannot be certain that these adverse OC effects result from the lowered free T; progestogens or other effects may be responsible. But free T reduction in those women for whom T levels are particularly important remains a plausible explanation until new data is reported.

More indirect evidence comes from a study of college students recalling their childhood and adolescent sexual experiences (9). Two samples of students were studied, one a recently collected representative sample of male and female students, the other an age-matched sample of college students studied in the original Kinsey survey (10, 11) of 50 years earlier. Although there was a substantial increase in the recent sample in the proportion of women who reported having even masturbated, there was in both samples a substantial proportion of those who had masturbated who started their masturbation before the age of puberty (i.e., menarche in females and first ejaculation in males). Eighty percent of the males in both studies started their masturbation within 2 years of either side of puberty onset. The onset of masturbation in the females was much more widely distributed, both pre- and postpuberty, and for those reporting prepubertal onset, the age of onset for the females was on average 2 years earlier than for the boys, a significant and almost identical difference in the two samples.

These data suggest a predominant organizing and activating effect of puberty in the boys, but a very different picture in the girls. The early-onset masturbators may have been responsive to the increased androgen levels around adrenarche, some of them responsive to the hormonal changes at puberty and some apparently unaffected by either time of hormonal change. A wide variation in responsiveness of sexual behavior of females to reproductive hormones would be consistent with these data.

To What Extent Are Observed Behavioral Effects of Exogenous Androgens Due to a Resulting Increase in Bioavailable Estrogen?

This is of particular relevance when considering evidence based on exogenous administration of both estrogens and

androgens. There are two aspects to consider: hormone binding and aromatization of T to E₂.

Exogenous estrogens, given alone, increase sex hormone-binding microscopy (SHBG). Because of the preferential binding of T over E₂, this results in a reduction of free T (the effect reported earlier with OC use). However, the increased SHBG also lowers the bioavailable estrogen (E). When exogenous T is also administered, the SHBG levels go down, and because of the preferential binding of T, the unbound, bioavailable E₂ increases, in addition to an increase in free T. To what extent are beneficial effects of adding the exogenous T due to increased free E or to increased free T?

In addition, T is an important source of E by aromatization; thus exogenous T will further increase bioavailable E. This effect, however, is dependent on the method of T administration. It has been recently shown that methyltestosterone, which is the most widely used androgen for oral administration, actually inhibits aromatase activity (12). With this androgen, therefore, increased bioavailability of E₂ is less likely to be an explanation.

There has been a tendency in the literature to link E effects to mood and T effects to sexuality (see further discussion on the relationship between mood and sexuality below). And strikingly there have been minimal attempts to study the effects of systematically varying the E level on sexuality. Only one such study was found in which two dosages of E administration were compared (13). The purpose of this study was to evaluate the effects of a synthetic progestogen and the extent to which adverse effects of the progestogen could be attenuated by increasing the E dose. The design involved four groups, two with progestogen and two with placebo, with one of each pair having a low E and the other a high E dosage. This resulted in two groups both taking placebo, but with different E dosages. The data on a measure of sexual interest over 12 months were shown graphically for these groups, and, given the error bars shown and the baseline levels for these two E only groups, it is difficult to escape the conclusion that there was a greater increase in sexual interest in the high E dose compared with the low E dose. This effect was not, however, considered in the paper because it was not central to the main purpose of the study.

Are the Beneficial Effects of T on Sexuality that Are Reported in the Literature Secondary to Direct Effects on Mood?

Not all studies of the behavioral/psychological effects of T replacement in women have reported the effects on mood, but those that have, consistently report a substantial improvement in mood and energy [e.g., (14–18)]. The relationship between mood and sexuality appears to be particularly strong in women. Whereas in men, negative mood is commonly associated with decreased sexual interest, the picture is less consistent than it is in women. Angst (19), reporting

on data from the longitudinal Zurich Cohort Study of men and women interviewed five times over a 15-year period between the ages of 20 and 35 years, found that when women were depressed, 35.3% reported a decreased sexual interest and 8.8% increased sexual interest. The figures for men were 25.7% and 23.3%, respectively.

In an earlier study on menstruating women (20), approximately one-third of the variance in sexual interest through the cycle could be attributed to variation in well-being. Cawood and Bancroft (21), in a study of 40- to 60-year-old women, found that measures of mood and energy were the best predictors of sexual well-being. In a recent national survey of women ages 20–65 years carried out by the Kinsey Institute, a measure of mood and energy was by far the most important predictor of sexual distress (22).

In spite of this strong association, only one study of the effects of hormone replacement was found that directly compared mood and sexual effects and it found high correlations, but this was an early study not involving androgens (23). Sherwin and her colleagues, who have been involved in several of the best studies of hormone replacement, have systematically reported the effects on mood and sexuality separately, usually in different journals [e.g., (15, 26)].

Direct Effects of Hormones on Sexual Behavior Appear to Be Easily Obscured by Coexisting Psychological Problems

Some of the clearest correlational evidence of the relevance of circulating T levels to sexual interest comes from studies of women without current sexual problems. Thus Bancroft et al. (24) compared women with sexual problems that they attributed to being on OCs with a group matched for age and OC who reported no sexual difficulties. A correlation between circulating T and sexual interest was found in the problematic but not the problematic group.

Along similar lines, Bancroft et al. (25) compared students on OCs with sexually active students using other methods of contraception. The OC users were shown to be more positive about their sexual relationships and about their own sexuality than the non-OC users, yet, in spite of the OC-induced reduction in free T, it was only the OC users who showed a correlation between circulating T and measures of sexual interest.

In the hormone replacement literature involving oophorectomized women, there is a striking contrast between the study of Sherwin et al. (26), in which women without sexual problems were evaluated immediately after oophorectomy, showing clear sexual benefits of T and virtually no placebo effect, and the study by Shifrin et al. (18), which involved oophorectomized women presenting with sexual problems, where there was a substantial placebo effect and the superiority of T over placebo was only demonstrated in the older patients in the sample. Other studies showing this contrast

between women with and without problematic sexuality include those of Tuiten et al. (27) and Riley and Riley (28).

Could the Increase in Adrenal Androgens that Accompanies Stress in Women Be Further Complicating the Picture?

In males, negative mood states, including depression and anxiety, are typically associated with suppression of testicular hormone production, which effectively counteracts the comparatively small increase in adrenal androgens that might also be associated. Hence, the limited evidence in men points to either unchanged or reduced T levels in states of negative mood. In women, by contrast, the adrenal proportion of androgen production is much greater, and a number of studies have reported increased T in negative mood states in women (29–31).

Given the strong association between mood and sexuality in women discussed earlier, this pattern could well serve to further confuse the evidence on the relationship between T and sexuality in women.

Is There a Threshold Effect for Androgens in Women?

In males, there is reasonable agreement that below a certain level of circulating T, signs and symptoms of T deficiency become apparent and are predictably reversed by raising the T level to above that threshold. The normal range above that threshold is very wide and it is not well understood to what extent some men have thresholds higher than the bottom of the assumed normal range. However, giving exogenous T to men with normal levels of T produces only subtle effects [see (4) for review], and the implication is that, provided T levels remain within a certain range, which may possibly vary across individuals, increasing T above that critical range will not have much behavioral effect, sexual or otherwise.

In women, we have no comparable evidence for a threshold. The laboratory values for “the normal range” are not well established, particularly at the lower end, because of inadequate assay sensitivity. Most studies that have found behavioral effects of exogenous T administration have resulted in T levels that are supraphysiological. So not only is there lack of a clear indicator of the lower threshold for women, below which signs of T deficiency will occur, there is also no clear evidence of an upper level above which increasing T will have little or no effect. It is, however, obvious that if T is important for behavioral effects in women, it normally achieves these effects at levels that would be totally ineffective in the male. Women, insofar as they are behaviorally responsive to T, are much more sensitive to its effects than are men.

Current interest in the concept of androgen or T deficiency in women is therefore confounded by this lack of evidence of clear threshold levels. To establish the existence of a deficiency state, it is necessary to show that the signs

and symptoms of such a state are eliminated by restoring the substance that is assumed to be deficient to normal physiological levels. At present, as much of the androgen replacement literature has reported on effects resulting from supra-physiological levels of T, where pharmacological rather than replacement effects of T may be involved, the deficiency concept must be regarded as uncertain.

The most likely common cause for marked T deficiency in women is oophorectomy. However, the only T replacement study of oophorectomized women that has relied on close to physiological replacement levels is that reported by Shifren et al. (18), and there the beneficial effects were partially obscured by a marked placebo effect. To show that the much more modest reductions in T levels that occur in late premenopausal women (32–34) are responsible for a deficiency state, it will be necessary to show reduction if not elimination of symptoms in such women by restoration of physiological and not supra-physiological levels of T. Such evidence is not yet available in the literature.

THE DESENSITIZATION HYPOTHESIS FOR TESTOSTERONE EFFECTS IN THE CENTRAL NERVOUS SYSTEM

The following is a theoretical attempt to explain some of the unanswered questions in relation to androgen effects on sexuality and mood raised in this paper.

1. The greater variability in the sensitivity to androgens in women could result from a greater genetic variability in women based on the fact that, in women, behavioral responsiveness to gonadal steroids is less crucial to reproduction than it is in men (34, 35, 37). However, the mechanism by which a genetically determined sensitivity might be expressed differently in women and in men requires explanation.
2. One of the consequences of the far greater levels of T in men is that they show masculinization, such as increased growth and muscle bulk, body hair growth, and voice change, which are dependent on the peripheral anabolic effects of T. It has been postulated that if males were as sensitive to the central nervous system (CNS) effects of T as females, then the behavioral effects of these masculinizing levels would be maladaptive. Hence, there is a need in the male to reduce responsiveness to androgen effects in the brain (38).
3. Exposure to substantially higher levels of T during fetal development and also during the first few weeks after birth could be responsible for desensitizing the CNS to T effects in the male, although as yet the precise mechanisms for such desensitization have not been established. A consequence of such desensitization in the male would be that genetically determined variations in CNS receptor responsiveness to T would be flattened out and allow much higher levels of T from puberty onward without hyperstimulation of CNS mechanisms.
4. With no such desensitization in females, the basic genetic variability would be more evident at much lower levels of T

and would be manifested as greater variability in behavioral responsiveness, demonstrated from early adolescent development onward.

5. Evidence from studies of women with congenital adrenal hyperplasia (CAH), particularly the salt-losing variety, which is associated with higher levels of T during fetal development, shows not only some degree of masculinization of behavior, but also low levels of sexual interest and activity associated with low fertility (39). Although in such cases there are a number of factors that could impair normal sexual development, this evidence is consistent with there being some degree of desensitization to the high fetal levels of T in these females, which fall and remain low after birth when the CAH is treated.
6. A key question that emerges from this hypothesis is whether such desensitization is restricted to early organizational effects of T exposure, or whether it could occur at any stage in the life cycle in the presence of supra-physiological levels of T. Evidence of tolerance to supra-physiological levels of T developing in women with repeated exposure has been reported in a number of hormone replacement therapy studies in the literature [e.g., (14, 40–42)]. This suggests that such desensitization might occur in women later in life also, at least to some extent. Another situation that might throw light on this question is the administration of T to female-to-male transgendered subjects.

While by no means simple, this theoretical model is open to testing in both animal and clinical studies.

CONCLUSIONS AND RECOMMENDATIONS FOR FURTHER RESEARCH

In general, our understanding of the effects of androgens on human sexuality is far from complete, particularly in the female. A number of key research issues will need attention if we are to progress, and several have been suggested in this paper. For women in particular, the idea that there are marked individual differences in the behavioral responsiveness to T deserves research consideration. In particular, what characteristics of a woman, from her earlier reproductive and developmental history, menstrual pattern, or behavioral reactions to pregnancy and lactation, might help to identify the “high T responder”? Given the age-related decline in T production, would the high T responder be more likely to show an age-related decline in sexual interest? Are the adverse effects of OCs on sexuality and mood due to their lowering of free T, and if so, are those women who succumb to such effects from the high T responder group? Do women become desensitized to the effects of supra-physiological levels of T, and if so, is this reversible? This has considerable implications for the long-term use of androgens in women.

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