

# Time Course of Effects of Testosterone Administration on Sexual Arousal in Women

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**Background:** The assumption that testosterone is involved in human female sexual functioning is mainly based on results of studies of women with hypogonadotropic hypogonadism. This study sought to determine the effect of testosterone administration on physiological and subjective sexual arousal in sexually functional women.

**Methods:** In a double-masked, randomly assigned, placebo-controlled crossover design, we examined whether administration of a single dose of testosterone to sexually functional women increases vaginal and subjective sexual arousal when they are exposed to erotic visual stimuli. To search for a time lag in the effect of testosterone therapy, we exposed 8 healthy women to 6 erotic film excerpts depicting intercourse. The first and second excerpts were shown immediately before and 15 minutes after, respectively, intake of placebo or testosterone; the last 4 excerpts were then shown at 1½-hour intervals.

**Results:** Sublingual intake of testosterone caused a sharp increase in plasma testosterone levels within 15 minutes; these levels declined to baseline values within 90 minutes. Three to 4½ hours after reaching peak testosterone level, we found a statistically significant increase in genital responsiveness ( $P = .04$ ). Furthermore, on the day of testosterone treatment, there also was a strong and statistically significant association between the increase in genital arousal and subjective reports of “genital sensations” ( $P = .02$ ) and “sexual lust” ( $P = .01$ ) after 4½ hours.

**Conclusions:** There is a time lag in the effect of sublingually administered testosterone on genital arousal in women. In addition, a consecutive increase in vaginal arousal might cause higher genital sensations and sexual lust.

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**I**N MANY mammalian species, female sex steroids are necessary for the expression of female sexual behavior. Consequently, the capacity for copulation in these animals is limited to the period of ovulation.<sup>1,2</sup> Higher primates—such as humans—have sexual intercourse outside the periovulatory period, and it has been suggested<sup>3</sup> that testosterone is involved in their female sexual behavior. The disappearance of testosterone after ovariectomy and adrenalectomy is accompanied by a complete loss of libido,<sup>4,5</sup> whereas substitution of this steroid maintains sexual desire and fantasies after surgical menopause.<sup>6</sup>

*See also pages  
133, 141, and 155*

An important aspect of sexual functioning is physiological sexual responding. Measured as an increase in vaginal vasocongestion elicited by sexual stimuli, this responding is considered to be preparatory for copulatory behavior.<sup>7</sup> In women

with hypogonadotropic hypogonadism (ie, individuals with hypothalamic amenorrhea), Tuiten et al<sup>7</sup> recently found that substitution with testosterone undecanoate, 40 mg/d orally for 8 weeks, enhanced vaginal responsiveness. The effect of testosterone therapy on genital arousal was not found in a parallel experiment conducted with a different group of patients with hypogonadotropic hypogonadism (ie, women with panhypopituitarism) (E. Laan, PhD, A.T., H.K., W. Everaerd, PhD, unpublished data, 1994). In both studies, there were no effects of testosterone use on several indices of subjective sexual functioning. The discrepancy in the effect of testosterone on physiological responding between the groups might be due to a design difference in the studies. In both studies, participants received testosterone each morning, but underwent physiological testing in the first experiment during the afternoon and in the second experiment during the morning. Thus, the different outcomes in physiological responding could be caused by a time-dependent effect of testosterone on vaginal arousal.

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## PARTICIPANTS AND METHODS

### PARTICIPANTS

Participants were recruited among students taking a scientific course at Utrecht University, Utrecht, the Netherlands. Potential participants completed a general questionnaire concerning personal details (including an extensive self-report on sexual functioning) and were interviewed by a research psychologist (A.T.). Eight healthy premenopausal white women, with backgrounds ranging from single students to married mothers, participated in the study (mean  $\pm$  SD age, 27.9  $\pm$  10.1 years). These women were medication-free and had no history or signs or symptoms of psychiatric illness. The 4 nonusers of oral contraceptives had regular menstrual cycles. There were no signs or symptoms of impending menopause or pituitary or endocrine diseases.

Results of the inquiry related to sexual functioning revealed the following: All the women were heterosexual and had had intercourse during the past year (from several times a year to several times a week), 5 of them within a steady relationship and 3 with multiple partners. All participants reported experiencing—more than once—sexual arousal, masturbation, and orgasm during the past year. Watching a hardcore videotape was a new experience for 3 women, and the other 5 had seen such a film once or twice.

### PROCEDURE

The procedure was explained in detail, and participants were instructed to not use any medications, psychoactive drugs, or alcohol on the days of experimentation. They were guaranteed privacy, anonymity, and confidentiality; were told that they could withdraw from the study at any time; gave informed consent; and received payment for participation. The protocol was approved by the Medical Ethics Committee of the University Hospital Utrecht.

We used a double-masked, randomly assigned, placebo-controlled crossover design. All participants were tested within 10 days of the end of their period of menstruation. Experimental days (testosterone and placebo) were separated by 5 days. Participants underwent 6 consecutive experimental trials during each day of drug manipulation: the first trial occurred immediately before and the second trial occurred 15 minutes after intake of testosterone or placebo; the other 4 trials were then conducted at 1½-hour intervals. Before both the intake of the substances and the experimental sessions described in the following paragraph were carried out, venous blood samples were taken (time = -¼ hours).

Immediately afterward, all women were exposed first to a 5-minute neutral videotape, and then to a 5-minute hardcore videotape. During this exposure, psychophysiological and subjective evaluation of sexual functioning was conducted (see the “Measures” subsection). Participants then took 0.5 mg of testosterone undecanoate (or placebo) sublingually, with cyclodextrines as carrier.<sup>10</sup> Venous blood samples were taken 15 minutes (time = 0 hours) and 105 minutes (time = 1½ hours) later, immediately followed by the same experimental trials (exposure to film excerpts and measurement of physiological and subjective sexual functioning). Without blood sampling, participants also underwent these trials 195 minutes (time = 3 hours), 315 minutes (time = 4½ hours), and 375 minutes (time = 6 hours) after intake of testosterone or placebo.

We used 6 different neutral and erotic film excerpts. The neutral excerpts were selected from a nonerotic popular movie (*JFK*). The 6 erotic excerpts depicted heterosexual vaginal intercourse, and were expected to evoke comparable levels of sexual arousal. On the different treatment days (testosterone and placebo), we used the same film excerpts in the same order.

### MEASURES

Plasma samples were analyzed for levels of total testosterone<sup>11</sup> and sex hormone-binding globulin. Levels of sex

Testosterone induces behavioral changes via altered central neurophysiological functioning of particular neuronal pathways.<sup>8</sup> These central changes increase reactivity of the sympathetic nervous system. Higher sympathetic nervous system activity is involved in the regulation of female sexual responses.<sup>9</sup> Conclusions about the involvement of testosterone in human female sexual functioning are almost exclusively based on the effects of long-term testosterone treatment of patients with hypogonadism. It has recently been shown<sup>9</sup> that intake of ephedrine sulfate, which enhances sympathetic reactivity, causes increased vaginal responsiveness within 20 minutes in sexually functional women but does not affect their subjective sexual arousal. Effects of testosterone therapy on sexual functioning can be expected to be more delayed than those of ephedrine therapy, but they have to occur much faster than the several weeks or months that are usually taken in treatment studies. In the present study, we investigated whether administration of a single dose of testosterone to sexually functional women affects physiological and subjective indices of sexual responsiveness over time.

## RESULTS

### PHYSIOLOGICAL DATA

Within 15 minutes of testosterone intake, there was a 10-fold or more increase in total testosterone levels, and a subsequent return to baseline levels occurred within 90 minutes (**Figure 1**, top). Between and on test days, there were no changes in sex hormone-binding globulin levels (data not shown).

The first part of our statistical procedure for the genital arousal data revealed no significant effects of order of drug intake ( $P = .44$ ) or use of oral contraceptives ( $P = .56$ ) for the difference between contrasts of both treatments. The Wilcoxon exact test revealed a significant effect for the linear contrasts between the placebo (mean  $\pm$  SEM,  $-0.02 \pm 0.06$ ) and testosterone (mean  $\pm$  SEM,  $0.35 \pm 0.09$ ) treatment conditions ( $P = .04$ ). This result demonstrates a difference in effect of testosterone compared with placebo treatment on the alteration of VPA over time (**Figure 1**, bottom). Subsequently, Wilcoxon exact tests

hormone-binding globulin were determined by immunoradiometric assay (SHBG IRMA; Orion Diagnostica, Espoo, Finland). Testosterone was extracted from plasma samples with diethyl ether and measured using a competitive radioimmunoassay using [ $1\alpha,2\alpha$ - $^{3H}$ (N)]-testosterone (DuPont NEN, Dordrecht, the Netherlands), antiserum 3290 (John Pratt, PhD, Department of Nuclear Medicine, University Hospital, Groningen, the Netherlands), and dextran-coated charcoal to separate the free and bound fractions. The interassay coefficient of variation was 8.8% at a testosterone level of 0.75 nmol/L (22 ng/dL), and 9.4% at a level of 2.55 nmol/L (73 ng/dL). Reference values for women were 0.5 to 2.0 nmol/L (14-58 ng/dL).<sup>12</sup>

A vaginal photoplethysmograph was used to measure vaginal pulse amplitude (VPA) (the AC component of the signal), which is a reliable index for genital vasocongestion.<sup>13</sup> Changes in the amplitude of the signal reflect changes in vaginal vasocongestion. The plethysmography system consisted of a photoelectric transducer, vaginal photoplethysmograph (Geer Gauge; Behavioral Technology Inc, Salt Lake City, Utah), and multipurpose bridge amplifier developed by the Biomedical Engineering Department of the University Hospital Utrecht, the Netherlands. The bandpass-filtered (0.5-30.0 Hz) VPA was sampled at 20 Hz and was recorded continuously during the experimental sessions. A filtering algorithm based on moving average computations was used to separate low-frequency blood volume changes from the VPA component. The algorithm intrinsically corrected for changes in pulse rate (heartbeat). Artifacts caused by contractions of the pelvic muscles or movements of the body were readily visible<sup>14</sup>; after visual inspection of the data, these artifacts were manually deleted. Subsequently, peak-to-trough amplitude was calculated for each pulse and averaged over 5 minutes, which resulted in 1 data point for each baseline trial (VPA:BA) and 1 data point for each erotic trial (VPA:ET). Because of differences in vascular density of the vaginal wall between and within participants, absolute values could not be used.

Therefore, we calculated the relative increase (percentage) in vasocongestion during the erotic condition compared with the neutral condition (ie, [(VPA:ET-VPA:BA)/VPA:BA]  $\times$  100).

Self-report ratings of sexual functioning were collected after each trial. Based on earlier research, subjective experiences related to "bodily arousal," "genital sensations," and "sexual lust" were assessed using 5 (0-100 mm, from "not at all" to "extremely") visual analog scales. The Cronbach  $\alpha$  for these scales were .81 for bodily arousal, .83 for sexual lust, and .84 for genital arousal. Mean values of these variables at each time were calculated.

## STATISTICAL ANALYSES

To test the assumed relations in this small sample of women, nonparametric tests were used. Because our main interest concerns a difference in the effect of drug treatment on genital arousal over time, for each individual and during each drug treatment condition for 6 points, the linear, quadratic, and cubic contrasts for the physiological data were calculated. To control for the possible effects of "order of drug intake" and "use of oral contraceptives," we used a Mann-Whitney test for the difference between the contrasts of both treatments, with order of drug intake and use of oral contraceptives, respectively, as between-participant factors. Based on the results of these comparisons, the same contrasts were used to compare the effects of the drugs. We applied the Wilcoxon signed rank test on the contrasts of both treatment conditions and on the differences between the testosterone and placebo treatment conditions over different times related to genital arousal and indices of subjective sexual functioning. In the testosterone treatment condition, Spearman rank correlation coefficients were calculated for the shift in genital arousal and subjective sexual functioning between different times. The  $\alpha$  level of significance was set at  $P = .05$  using 2-tailed levels of significance.

were carried out for the difference in genital response between the placebo and testosterone treatment conditions over the shifts between 0 and 3 hours and 0 and 4½ hours. These analyses revealed the same significant effects for both shifts ( $P = .04$ ) and demonstrated a time course effect of testosterone treatment on genital arousal of about 3 to 4½ hours.

## SUBJECTIVE SEXUAL FUNCTIONING

To investigate the possible parallel effect of testosterone treatment on indices of subjective sexual functioning (**Figure 2**), we performed a Wilcoxon exact test on the differences in subjective reports between the placebo and testosterone treatment conditions over the shift between 0 and 4½ hours. Experience related to bodily arousal revealed no significant effects ( $P = .64$ ). Although close, the Wilcoxon exact tests were not significant for genital sensations or sexual lust ( $P = .06$  for both).

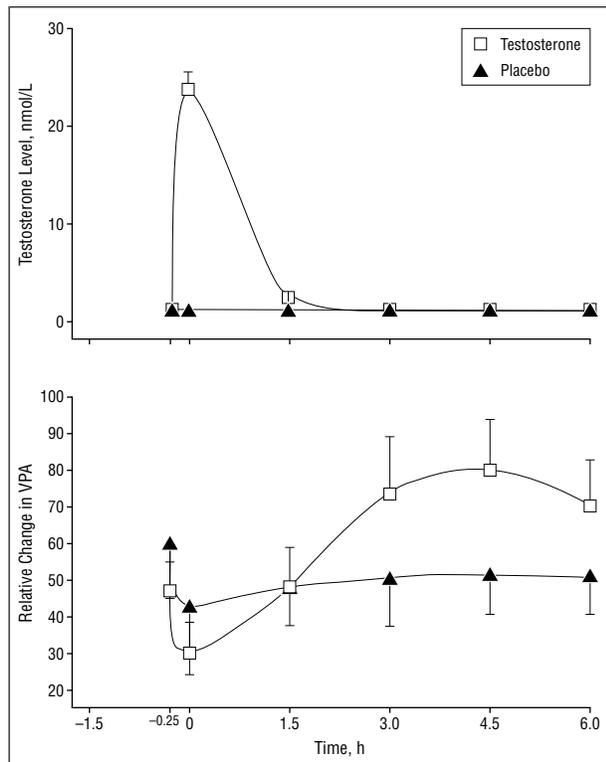
Analyses of the relation in alterations of genital arousal and genital sensations and sexual lust between

0 and 4½ hours revealed, in the testosterone treatment condition, correlation coefficients (Spearman  $\rho$ ) of  $\rho = 0.80$  ( $P = .02$ ) and  $\rho = 0.83$  ( $P = .01$ ), respectively (**Figure 3**). Thus, changes in genital sensations and sexual lust in the testosterone treatment condition show a parallel pattern to the physiological variable.

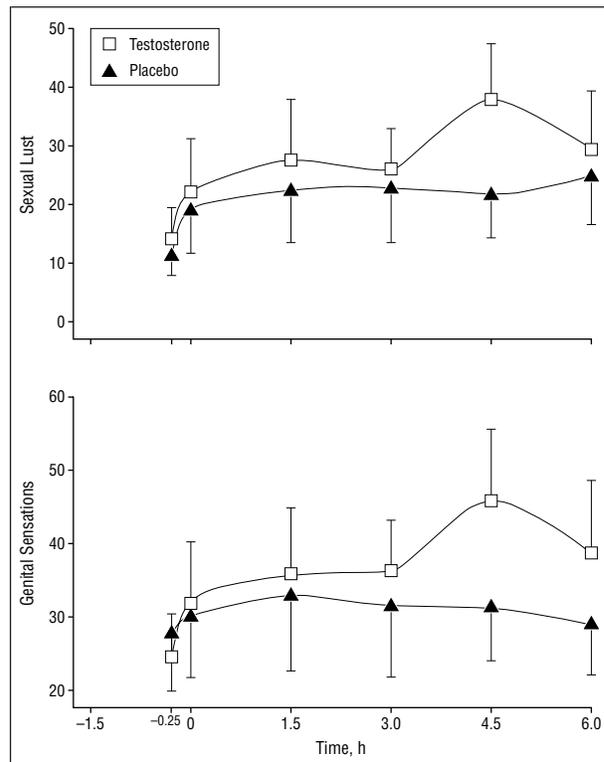
## COMMENT

Our results corroborate the hypothesis that testosterone treatment increases vaginal responsiveness in a time-dependent fashion. In addition, in the testosterone treatment condition, we also found a strong association between an increase in genital arousal and the occurrence of genital sensation and sexual lust.

A delayed effect of testosterone on physiological sexual responding might be explained by the involvement of brain mechanisms that regulate (human) female sexual behavior. To develop animal models for sexual behavior, scientists focused on the relation between neurophysiological brain mechanisms and several indices of sexual behavior. As a result, a steroid-responsive neural



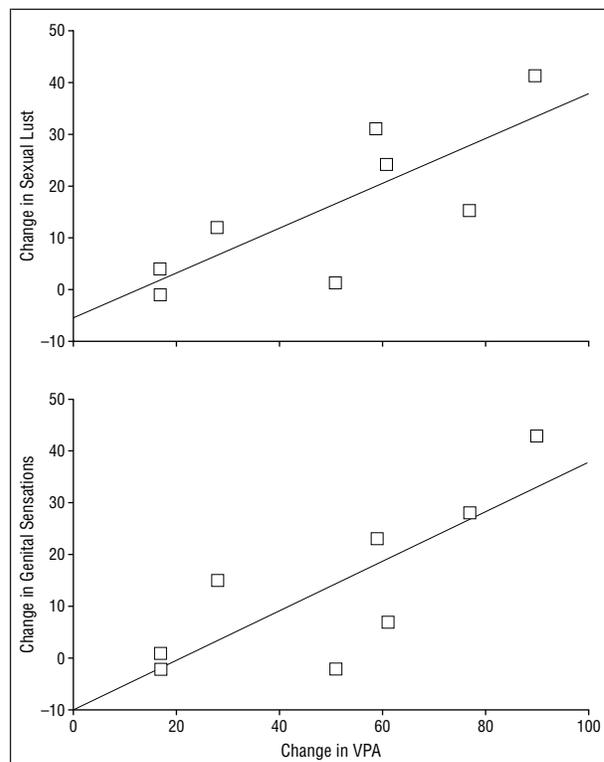
**Figure 1.** Top, Average levels of total testosterone at different times during placebo and testosterone undecanoate treatment ( $N = 8$ ). To convert testosterone from nanomoles per liter to nanograms per deciliter, divide nanomoles per liter by 0.0347. Bottom, Average relative increases in vaginal pulse amplitude (VPA) induced by erotic film excerpts viewed at 6 consecutive times during placebo and testosterone treatment ( $N = 8$ ). Error bars indicate SEM.



**Figure 2.** Mean scores of experiences on sexual lust (top) and genital sensations (bottom) after exposure to erotic film excerpts at 6 consecutive times during testosterone and placebo treatment ( $N = 8$ ). Error bars indicate SEM.

network<sup>15</sup> was postulated, consisting of a highly interconnected group of sex hormone receptor-containing neurons in the brain. This network is not a closed circuit, but serves reproductive aims by functioning as an integrating and activating center for external sensory cues, hormonal processes, and reproductive behavior. This is partly accomplished by selective filtering of sensory input and amplification of signals that may facilitate sexual behavior. Steroid hormones cause neurophysiological alterations in the brain.<sup>8</sup> The time it takes these changes to occur ranges from several hours to several days. In animal experiments, Ohkura et al<sup>16</sup> demonstrated that ovarian hormones change neuronal processing of sexual cues, activating large parts of the steroid-responsive network. Testosterone seems to be involved in the steroid-responsive network regulation of the sexual behavior of female higher primates that have intercourse outside the periovulatory phase.<sup>3</sup> Moreover, the present data suggest that the increased readiness and activity of the steroid-responsive network induced by testosterone on sexual responding in women takes about 3 to 4½ hours.

That testosterone treatment in our study seemed to affect subjective indices of sexual functioning is at odds with the previously described<sup>7</sup> absence of such an effect in patients with hypogonadism and with the frequently occurring discordance between physiological and subjective sexual arousal in sexually functional women. The change in subjective sexual functioning could, how-



**Figure 3.** Correlation (Spearman  $\rho$ ) of the changes between 0 and 4½ hours in vaginal pulse amplitude (VPA) and the experience of sexual lust (top) and genital sensation (bottom) during testosterone undecanoate treatment ( $N = 8$ ).

ever, be caused by a change in neurophysiological processes induced by testosterone in a delayed manner, as measured in the present design. Alternatively, the increase in genital sensations and sexual lust might have resulted from the perception of consecutive increases in physiological sexual arousal. The chance of perceiving physiological sexual arousal enhances when these levels themselves become higher, which may lead to an increase in subjective sexual excitement.<sup>9</sup> In this respect, there was a remarkable difference in the effect of ephedrine administration in the study by Meston and Heiman<sup>9</sup>; subjective sexual arousal was not enhanced. This difference might indicate that affecting peripheral processes related to sexual responding at only a single time is not sufficient for altering subjective sexual experiences. Laan et al<sup>14</sup> demonstrated that conditions that produce more pronounced changes in genital arousal over trials lead to a closer connection between genital and subjective sexual arousal. This observation is in agreement with the present results, which demonstrate that the increase in vaginal arousal in consecutive trials in the testosterone treatment condition resulted in increases in genital sensations and sexual lust.

The fact that our study was performed in a small sample might limit the generalizability of the results. To replicate and extend our findings, we are preparing experiments in clinical and nonclinical populations.

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### Correction

**Error in Figure Legend.** In the article titled "Time Course of Effects of Testosterone Administration on Sexual Arousal in Women" (*Arch Gen Psychiatry*. 2000;57:149-153), the word *undecanoate* was mistakenly added to the legends for Figure 1 and Figure 3, as well as in the fifth paragraph of the "Participants and Methods" section. The ARCHIVES regrets the error.