Ephedrine-Activated Physiological Sexual Arousal in Women

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**Background:** The present investigation was designed to provide the first empirical examination of the effects of ephedrine sulfate, an \( \alpha \)- and \( \beta \)-adrenergic agonist, on subjective and physiological sexual arousal in women. The purpose was to help elucidate the effects of increased peripheral adrenergic activity on sexual response in women.

**Methods:** Twenty sexually functional women participated in 2 experimental conditions in which subjective (self-report) and physiological (vaginal photoplethysmography) sexual responses to erotic stimuli were measured following administration of either ephedrine sulfate (50 mg) or placebo in a randomized, double-blind, cross-over protocol.

**Results:** Ephedrine significantly \( (P<.01) \) increased vaginal pulse amplitude responses to the erotic films and had no significant \( (P>.10) \) effect on subjective ratings of sexual arousal.

**Conclusions:** Ephedrine can significantly facilitate the initial stages of physiological sexual arousal in women. These findings have implications for deriving new pharmacological approaches to the management of sexual dysfunction in women.

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**Biochemical and physiological evidence indicates that** the sympathetic nervous system (SNS) is actively involved in the normal control of female sexual response. Diffuse SNS discharge occurs during the later stages of sexual arousal \(^1\) with marked increases in heart and blood pressure occurring during orgasm. \(^2\) Increases in the plasma noradrenaline (NA) level, a sensitive index of SNS activity, have also been shown to accompany increases in sexual arousal during intercourse, and to decline rapidly following orgasm. \(^3\) If SNS activation is integral to the normal sexual response, then it follows that disturbances in this autonomic system might lead to disturbances in sexual function. Moreover, impaired sexual responding may be effectively alleviated with appropriate pharmacological manipulation of peripheral adrenergic activity, although at present this is more hypothesis than reality.

Few studies have examined the effects of peripherally acting adrenergic agonists and antagonists on sexual function in women. Riley and Riley \(^4\) compared the effects on the pressor response to sexual arousal induced by masturbation of single oral doses of propranolol (80 mg) and labetalol (100 mg), 2 adrenergic antagonists, with placebo control. Labetalol, but not propranolol, significantly decreased the increase in blood pressure that occurred at orgasm, and significantly decreased subjective reports of vaginal lubrication. \(^4\) Because the dose of propranolol used had greater \( \beta \)-blocking activity than labetalol, the authors attributed the sexually suppressant effects of labetalol to decreased \( \alpha \)-adrenergic activity. In a follow-up, double-blind study \(^5\) that compared the effects of 2 doses of labetalol (100 and 300 mg) with placebo, these authors reported a dose-related inhibition of the orgasmic-pressure response; the higher the dose of labetalol the greater the time to reach orgasm. In contrast to subjective reports of decreased vaginal lubrication with labetalol in their earlier study, these authors found no significant effect of labetalol on genital secretions when measured gravimetrically and no significant differences in subjective measures of arousal, sensation of orgasm, or satisfaction between the labetalol and placebo conditions. \(^5\) Using a double-blind, placebo-controlled de-
SUBJECTS AND METHODS

SUBJECTS

Twenty sexually functional women (mean age, 25.80 years; age range, 19-44 years) participated in 2 experimental conditions, ephedrine and placebo. The subjects were recruited via advertisements in the university student newspaper. Because of reported ethnic differences in sexual activity, subject background information was recorded. Ethnic background of the subjects was: non-Hispanic white (n = 16), Southeast Asian (n = 3), and African (n = 1). All subjects were currently involved in sexual relationships; 3 subjects were married. Initial telephone screening inclusion criteria were aged 18 to 45 years, no use of any medications other than birth control pills for at least 6 months, no history of treatment for depression or sexual dysfunction, no medical condition that may put the subject at risk when exercising, no history of high or low blood pressure, and current involvement in a heterosexual relationship.

To screen for absence of sexual dysfunction, profile descriptions of all subjects were obtained via the Derogatis Sexual Functioning Inventory (DSFI) and the Orgasmic Functioning Questionnaire (C.M.M., S. Jung, BA, L. Hansen, MA, and B. B. Gorzalka, PhD, unpublished data, 1993). All subjects employed in the study scored greater than or equal to the 30th percentile (ie, within 2 SDs of the normative mean) on the Sexual Functioning Index (mean, 57.35; range, 3-69) and the Drive subscale (mean, 55.55; range, 38-72). The Brief Symptom Inventory 10 subtest of the DSFI was used to screen for absence of general psychopathologic characteristics. All subjects scored greater than or equal to the 30th percentile on the total Brief Symptom Inventory scale (mean, 46.35; range, 32-62). Data from the Experience subtest of the DSFI was used to ensure that all subjects were within the normative range of sexual experience. All subjects scored at or above the 30th percentile on the Experience subtest (mean, 32.15; range, 30-63). As in previous studies of this nature, data from the Orgasmic Functioning Questionnaire were used to screen for absence of orgasmic dysfunction. All subjects were able to achieve orgasm by some means (eg, intercourse, oral sex, masturbation) at least 50% of their sexual experiences (mean percent, 81).

DESIGN AND PROCEDURE

The study consisted of 2 counterbalanced experimental conditions, ephedrine and placebo. The experimental conditions were scheduled at approximately 1-week intervals and excluded times during which the subjects were menstruating. Phase of the menstrual cycle was not controlled for, given that sexual arousability to erotic stimuli is only minimally, if at all, influenced by the menstrual cycle. Subjects were scheduled at approximately the same time during both conditions (ie, morning, afternoon, or evening) to control for potential daily circadian fluctuations. All subjects were asked to abstain from caffeine and alcohol and to refrain from engaging in any strenuous physical activity for 24 hours prior to each experimental condition. Because the rate of drug absorption may be influenced by food in the stomach, subjects were also asked to refrain from eating for 4 hours prior to the experimental conditions.

During the experimental conditions, subjects were given either a placebo or ephedrine sulfate (50 mg) capsule using a double-blind protocol. Both capsules were taken orally with 250 mL of water. Subjects' heart rates and systolic and diastolic blood pressures were monitored using an oscilometric electronic digital blood pressure and pulse monitor (model 02-707, Graham-Field, New York, NY) prior to the administration of drug or placebo and at 15 and 30 minutes after drug ingestion. The half-hour waiting period following the administration of drug or placebo was used to ensure that ephedrine had been absorbed. Following the half-hour waiting period, subjects were instructed on how to insert the photoplethysmograph and were asked to remain as still as possible throughout the condition to minimize potential movement artifacts. When the subject notified the experimenter, via an intercom system, that she had finished inserting the photoplethysmograph, a 10-minute baseline adaptation recording was taken to allow the photoplethysmograph time to adapt to each subject's body temperature. Following the adaptation period, subjects viewed 1 of 2 9-minute videotaped sequences that consisted of a 1-minute display of the word "relax" followed by a 3-minute neutral travelogue film and then a 5-minute erotic film. The sequences differed only in the content of the neutral and erotic films. In both sequences, the erotic films depicted a heterosexual couple engaging in foreplay, intercourse, and oral sex. The films were previously shown to reliably elicit physiological and subjective sexual arousal in women (C.M.M., unpublished data, 1994). Immediately following the erotic film, subjects were asked to fill out the subjective rating scale. The time from the ingestion of ephedrine or placebo to the onset of the erotic film

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sign, Meston and associates found that clonidine, an antihypertensive medication that blocks sympathetic outflow, inhibited vaginal pulse amplitude (VPA) and vaginal blood volume responses to an erotic film. Under conditions of heightened nervous system arousal, subjective reports of sexual arousal were also significantly decreased with clonidine. Although the authors provided evidence to suggest that the decreases in sexual arousal were likely because of suppressed SNS activity, the interpretation of their findings is confounded by the fact that clonidine also acts centrally as an α2-adrenergic agonist.

To date, the only study that has examined the effects of adrenergic agonists on sexual function in women found that intravenously administered doses (5 mg) of midrodrine, a selective α-adrenergic agonist, had no significant effect on subjective reports of time to reach orgasm. The present investigation was designed to provide the first empirical examination of the effects of increased adrenergic activity on sexual arousal in women measured both subjectively and physiologically. Twenty sexually functional women participated in 2 counterbalanced conditions in which they received either placebo or ephedrine sulfate (50 mg), an α- and β-adrenergic agonist, 45 minutes prior to viewing an erotic film. Sexual responses to the erotic film were measured subjectively using a self-report questionnaire and physiologically using vaginal
was approximately 45 minutes (half-hour waiting period, 10-minute baseline, 1-minute photoplethysmograph insertion, 1-minute display of the word relax, 3-minute neutral film). All subjects were paid $35 for their participation. The study design and consent forms were approved by the Human Subjects Review Committee at the University of Washington in Seattle.

DATA SAMPLING AND REDUCTION

Physiological Measurements

A vaginal photoplethysmograph was used to measure VPA responses. The VPA was sampled at a rate of 60 samples per second throughout the entire 180 seconds of neutral film and 300 seconds of erotic film, bandpass filtered (0.5-30 Hz), and recorded on a personal computer (Power Macintosh 6100/60, Apple, Cupertino, Calif) using the software program AcqKnowledge III, version 3.2 (BIOPAC Systems, Inc, Santa Barbara, Calif) and a data acquisition unit (model MP100WS, BIOPAC Systems, Inc) for analog/digital conversion. In accordance with previous studies of this nature, artifacts caused by movement or contractions of the pelvic muscles were deleted using the computer software program after visual inspection of the data. The VPA scores were then computed for both the neutral and erotic films by averaging across the middle 1 minute of the neutral or erotic film stimulus. For correlational analyses, difference scores were computed for each experimental condition by subtracting the average VPA score during the neutral film from the average VPA score during the erotic film.

Heart rates and systolic and diastolic blood pressures were measured using an oscillographic electronic digital blood pressure and pulse monitor prior to administration of the drug and at 15 and 30 minutes following the ingestion of ephedrine or placebo. Heart rates during the film presentations were extracted from the VPA signal and averaged across the middle 1 minute of neutral and erotic films. Difference scores in heart rate and systolic and diastolic blood pressures were computed by subtracting the baseline (before the administration of the drug measure) from each of the measures taken after the administration of the drug. These scores yielded 4 heart rate, 2 diastolic blood pressure, and 2 systolic blood pressure measures after ingestion of the drug or placebo for each subject per experimental condition.

RESULTS

ANALYSES OF VAGINAL PULSE AMPLITUDE

The condition (ephedrine vs placebo) × film (neutral vs erotic) ANOVA revealed a significant effect of the erotic films on VPA scores ($F[1, 19] = 26.46, P < .001$), a significant effect of ephedrine on VPA scores ($F[1, 19] = 4.69, P = .04$), and a significant interaction between condition and film ($F[1, 19] = 9.29, P < .01$). There was a significant increase in VPA scores with ephedrine administration during the erotic films ($t[19] = 2.97, P < .01$). This increase occurred in 17 of 20 subjects. There was no significant difference in VPA scores between ephedrine and placebo conditions during the neutral films ($t[19] = -0.45, P = .66$). Significant increases in VPA responses to the erotic films were noted in both the ephedrine ($t[19] = -4.94, P < .001$) and placebo ($t[19] = -4.47, P < .001$) conditions, which indicate that the experimental stimuli were effective in eliciting sexual arousal. Mean VPA raw scores (±SD) during the ephedrine and placebo conditions are presented in the Figure.
The condition (ephedrine vs placebo) × time (4 time blocks following the administration of ephedrine or placebo) ANOVA revealed a significant effect of time on heart rate scores (F[3, 57] = 15.97, P < .001), and a significant interaction between condition and time (F[3, 57] = 3.96, P < .05). No significant differences in heart rate were noted at either 15 (t[19] = −0.70, P = .49) or 30 (t[19] = 0.22, P = .83) minutes after the ingestion of drug or placebo, but significant increases in heart rate scores with ephedrine administration were found during both the neutral (approximately 45 minutes after the ingestion of drug or placebo) (t[19] = 2.08, P = .05) and erotic (approximately 45 minutes after ingestion of drug or placebo) (t[19] = 2.41, P < .03) film presentations. These findings are consistent with previous research that indicates ephedrine may increase or decrease peripheral vascular resistance. In addition, these findings suggest that, as intended, the cardiovascular consequences of ephedrine were in effect during the measurement of sexual arousal. No significant differences in heart rate were found during either the placebo (t[19] = 0.28, P = .78) or ephedrine (t[19] = −1.25, P = .23) condition. Mean heart rates (± SD) during the placebo neutral film, placebo erotic film, ephedrine neutral film, and ephedrine erotic film, were 62.6 (± 8.2), 62.8 (± 8.6), 68.9 (± 8.9), and 70.2 (± 11.6), respectively.

ANALYSES OF BLOOD PRESSURE

There were no significant effects of condition or time, and no significant interaction between condition and time for either systolic or diastolic blood pressure scores.

ANALYSES OF SUBJECTIVE MEASURES

Results indicated a significant increase in subjective ratings of heart rate during the ephedrine condition (t[19] = −3.46, P = .003). There were no significant effects of ephedrine on subjective measures of physical sexual arousal (t[19] = 1.15, P = .27), mental sexual arousal (t[19] = 0.00, P = 1.00), positive affect (t[19] = 0.64, P = .53), negative affect (t[19] = −0.20, P = .84), or anxiety (t[19] = −0.37, P = .72). Mean (± SD) subjective ratings are presented in the Table.

ANALYSES OF THE RELATIONSHIP BETWEEN PHYSIOLOGICAL AND SUBJECTIVE RESPONSES

There was a significant correlation between VPA difference scores and subjective ratings of mental sexual arousal (r[20] = .53, P < .02) and a trend toward a significant correlation between VPA difference scores and subjective ratings of physical sexual arousal (r[20] = .41, P < .08) during the ephedrine condition. There were no significant correlations between VPA difference scores and subjective ratings of mental sexual arousal (r[20] = 0.23, P = .33) or physical sexual arousal (r[20] = 0.14, P = .56) during the placebo condition.

COMMENT

The present investigation examined the effects of ephedrine, an α- and β-adrenergic agonist, on self-report and photoplethysmograph indices of sexual arousal in women. The results revealed ephedrine significantly increased VPA responses to an erotic film. The facilitation of physiological sexual arousal by ephedrine is consistent with recent research that has shown increased SNS activity, induced via intense acute exercise, enhances photoplethysmographic (VPA and vaginal blood volume) measures of sexual arousal in women and clonidine, a drug that blocks peripheral sympathetic outflow, decreases VPA and vaginal blood volume responses. The present findings are also consistent with studies conducted in the female rat that show that peripheral administration of epinephrine facilitates sexual behavior, and that drugs such as naphazoline and guanethidine that selectively block peripheral adrenergic activity suppress sexual responding.

Interestingly, ephedrine increased physiological sexual responses only during presentation of the erotic film. When subjects viewed a nonsexual travel film, there were no significant differences in VPA responses be-
between the ephedrine and placebo conditions. This suggests that ephedrine did not simply facilitate physiological responses through a general increase in peripheral resistance but, rather, acted in some way that selectively “prepared” the body for genital response. Precisely what this “physiological preparedness” might involve is highly speculative given it is unknown whether vaginal vasodilation occurs in the arteries, arterioles, capillaries, venules, or veins.

Ephedrine had no significant influence on subjective measures of sexual arousal. This finding is consistent with previous research that has generally found a desynchrony between subjective and physiological components of the sexual response in women. Possible explanations for this desynchrony in women include response biases associated with self-report measures of sexual responding and a rather indirect (ie, small changes in vasocongestion) feedback system between physiological and cognitive sexual processes in women. It should be noted that, although subjective reports of sexual arousal did not significantly increase with ephedrine administration, there was a significant correlation between subjective mental sexual arousal and VPA responses apparent in the ephedrine, but not in the placebo, condition. This finding is consistent with the notion that when physiological sexual responses are increased in women, they are more likely to be subjectively perceived. Like subjective measures of sexual arousal, subjective measures of positive affect, negative affect, and anxiety also did not differ between ephedrine and placebo conditions. This suggests that the increases in physiological sexual arousal noted with the administration of ephedrine are not likely attributable to changes in cognitive factors, such as mood, that may have potentially been altered with the administration of ephedrine.

Given the present study examined the effects of ephedrine on sexual responding only among relatively young, healthy women, the current results may be limited in their generalizability to clinical cases of women with sexual dysfunction. It may be the case that ephedrine increases physiological sexual responding in sexually functional women by providing a “boost” to already increasing levels of sexual arousal. Whether ephedrine might also provide an initial “jump start” for women who have difficulty becoming sexually aroused needs further investigation.

When asked during the debriefing session, subjects in the present study reported no adverse side effects with the use of ephedrine. It should be noted, however, that at higher doses ephedrine has been reported to cause a variety of negative effects (eg, anxiety, restlessness, insomnia, dizziness, headache, hypertension). Such adverse reactions are most likely to occur in patients with hypertension, hyperthyroidism, diabetes, or cardiovascular disease. The results of the present investigation provide the first empirical suggestion of a facilitatory influence of increased peripheral adrenergic activity on physiological sexual arousal in women. Before suggestions for treatment are warranted, future studies are needed to examine whether these effects hold true for women with impaired sexual functioning.

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