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Effect of a Single Dose of Levodopa on Sexual Response in Men and Women

Stephanie Both*[1,2], Walter Everaerd[1], Ellen Laan[1] and Louis Gooren[3]

[1]Department of Clinical Psychology, Faculty of Social and Behavioral Sciences, University of Amsterdam, Amsterdam, The Netherlands; [2]Department of Psychosomatic Gynecology and Sexology, Academic Hospital, Leiden University, Amsterdam, The Netherlands; [3]Department of Internal Medicine, Academic Hospital, Free University, Amsterdam, The Netherlands

From animal research, there is ample evidence for a facilitating effect of dopamine on sexual behavior. In humans, little experimental research has been conducted on the inter-relation between dopamine and sexual response, even less so in women than in men. We investigated the effect of levodopa (100 mg) on sexual response in men and women following a double-blind, placebo-controlled crossover design. Genital and subjective sexual responses were measured as well as somatic motor system activity by means of Achilles tendon (T) reflex modulation. Genital and subjective sexual arousal were not affected by levodopa. However, the drug increased T reflex magnitude in response to sexual stimulation in men, but not in women. These results support the view that dopamine is involved in the energetic aspects of appetitive sexual behavior in men. The observed gender difference in the effect of levodopa is discussed in the perspective of possible dopamine–steroid interaction.
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INTRODUCTION

There is extensive evidence from animal studies for the involvement of dopamine systems in the activation of responses to stimuli with incentive-motivational properties (Kalivas and Nakamura, 1999; Robbins and Everitt, 1999). Dopamine systems seem to be involved in reward signaling and in the initiation of behavioral responses to obtain a rewarding stimulus (Kalivas and Nakamura, 1999; Phillips *et al*, 2003; Schultz, 2001). Dopamine is a major neurotransmitter in the motive circuit, involved in the translation of reward perception to behavioral output. The nucleus accumbens, part of the motive circuit, is described as the integration site for the limbic system and the motor system, where emotion is translated to action (LeDoux, 2001; Mogenson *et al*, 1980; Salamone and Correa, 2002). Dopamine release from the ventral tegmental area to the nucleus accumbens results, via facilitation of the pathway to the pallidum, in amplified activation of motor regions in the cortex and the brainstem (LeDoux, 2001). Thus, dopamine seems to be involved in the psychomotor activation in response to incentive stimuli.

So far, experimental studies in rodents showed that dopamine seems to be to a larger degree involved in anticipatory than in consummatory motivational responses. Depletion of dopamine in the nucleus accumbens does not impair consummatory behavior but it may reduce incentive-motivational responses (Robbins and Everitt, 1999). Berridge and Robinson (1998) showed that dopamine is not involved in the hedonic pleasure of reinforcers (the affective component or 'liking') but mediates the instigation of goal-directed behavior and the attraction to an incentive stimulus ('wanting'). Going one step further, Salamone and Correa (2002) state that dopamine depletion does not reduce appetite for, or attraction to, incentives, but influences mainly the instigation of instrumental behavior. They distinguish two components of wanting, the appetite to consume and the activation to obtain incentive stimuli. They underline that motivation has both a valence and an activational aspect. The valence aspect refers to the fact that behavior is directed toward or away from particular stimuli, and activation refers to the energetic aspect of motivated behavior, the vigor or persistence. In the view of Berridge and Robinson, and Salamone and Correa, dopamine is involved in the energetic aspects of motivated behavior.

Regarding sexual motivation, there is extensive evidence from studies in rats for a facilitating influence of dopamine (for review, see Melis and Argiolas, 1995). In line with research on the role of dopamine in reward processes in

*Correspondence: S Both, Department of Clinical Psychology, Faculty of Social and Behavioral Sciences, University of Amsterdam, Roetersstraat 15, 1018 WB Amsterdam, The Netherlands. Tel: +31 20 525 6799, Fax: +31 20 639 1369, E-mail: s.both@uva.nl
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general, the discrimination of anticipatory from consummatory sexual behavior showed that dopamine seems to be to a larger degree involved in the appetitive components of sexual behavior. In humans, effects of dopamine on sexual motivation were suggested by the observation of increased sexual desire or activity, and even hypersexuality, in Parkinson patients treated with the dopamine agonists apomorphine or levodopa (Crenshaw and Goldberg, 1996; Everaerd and Laan, 2000; Meston and Frohlich, 2000). It should be noted that these sexual side effects are observed in only a very small number of patients, and mostly in males, and that the responses of Parkinson patients may not reflect the responses of healthy men and women. The sexual side effects do, however, point to an enhancing effect of dopamine on sexual response, which is in line with evidence from studies in animals. In addition, there is evidence for a positive effect of bupropion, which is primarily a dopamine uptake inhibitor, on sexual functioning in women (Crenshaw and Goldberg, 1996; Segraves *et al*, 2004), and for a facilitating effect of apomorphine, a dopamine agonist, on sexual functioning in women with female sexual desire and arousal problems (Russell, 2002), and on erection in healthy men and in men with erectile dysfunction (Lal *et al*, 1984; Padma-Nathan *et al*, 1999). The latter resulted in the use of apomorphine in the treatment for erectile dysfunction (Giuliano and Allard, 2001; Heaton, 2000).

Most research on the effect of dopamine on sexual behavior in animals as well as in humans concentrated on males. The findings in female rats are conflicting with some studies reporting a facilitating effect of dopamine on lordosis responses and other studies reporting an inhibitory effect (Melis and Argiolas, 1995). As far as we know, reports about psychophysiological studies on the effect of dopamine on sexual response in women are lacking.

Taken together, research on the role of dopamine in motivation suggests that dopamine influences appetitive responses to incentive stimuli including sexual stimuli. Following incentive motivation models, sexual motivation is an emerging property, the outcome of the processing of sexual stimuli (Bindra, 1974; Singer and Toates, 1987). Hence, sexual motivation may be best investigated by studying the process of action generation. This process can be studied through the monitoring of responses within various response systems involved in general motivated behavior and specific sexual behavior. The few laboratory studies on dopaminergic effects on sexual response in men concentrated on genital responses. Appetitive behavior, however, includes both autonomic responses that prepare the animal for efficient interaction with the goal and locomotor responses to approach the goal (Robbins and Everitt, 1999). To study the effect of dopamine on the generation of sexual appetitive behavior, it may be advantageous to measure sex-specific changes in autonomic motor system activity as well as approach behavior reflected in activity in the somatic motor system. Measuring somatic motor system activity can be expected to offer a sensitive measure to investigate the effects of a psychomotor stimulant drug like dopamine on the instigation of appetitive behavior. Therefore, in the present study, in addition to genital response we investigated somatic motor system activity in response to sexual stimuli.

Somatic motor activity can be measured by monitoring Achilles tendon (T) reflexes. T reflexes are not sensitive to the valence of an affective state but are augmented in states of action and are modified by differences in arousal (Bonnet *et al*, 1995; Brunia and Boelhouwer, 1988). T reflexes can be elicited by a hammertap at the heel tendon. The hammer tap results in a reflexive electromyographic (EMG) response in the soleus muscle of the lower leg. When circumstances are held equal, taps of a constant force lead to reflex amplitudes of constant size. Supraspinal excitatory or inhibitory influences on the motoneuron pool or other elements of the reflex arc are reflected in an increase or decrease in reflex amplitude. Thus, changes in reflex amplitude are a peripheral manifestation of supraspinal processes influencing spinal excitability (Brunia and van Boxtel, 2000). Previously, we have found that T reflexes as well as genital responses and subjective action tendencies were augmented by sexual stimuli indicating the value of T reflex modulation in research on appetitive sexual responses (Both *et al*, 2003, in press).

In the present study, we investigated the effect of a single dose of levodopa (100 mg) on T reflex magnitude, genital response, emotional experience, and subjective action tendencies in response to central sexual stimulation, namely erotic fantasy and erotic film. As is customary, levodopa was administered in combination with the decarboxylase inhibitor carbidopa (25 mg) to prevent levodopa from metabolizing to dopamine outside the brain. Participants visited the laboratory two times, receiving at one visit placebo and at the other visit levodopa, following a double-blind, crossover protocol. At 50 min after drug administration, when increased dopamine levels were expected (Sagar and Smyth, 2000), subjects were asked to fantasize erotically for 2 min, which was followed by 6 min exposure to erotic film. Both erotic fantasy and erotic film were used to allow for the investigation of dopaminergic effects on sexual stimuli varying in intensity and source. Erotic fantasizing as well as erotic film elicits genital and subjective sexual arousal, but erotic film yields higher levels of arousal than fantasy (eg Laan *et al*, 1993).

Following incentive salience theory (Berridge and Robinson, 1998) and Salamone and Correa's suggestion that dopamine influences the activational aspects of motivation, levodopa was expected to affect the instigation of action, and therefore to result in stronger T reflex magnitudes in response to sexual stimulation compared to placebo. Second, based on the evidence for dopaminergic influences on penile response in men, levodopa was expected to facilitate genital response. Third, levodopa was expected to facilitate feelings of sexual arousal and lust, and to enhance subjective approach tendencies in response to sexual stimulation.

METHOD

Participants

Participants were 47 psychology students (19 men and 28 women) who received course credit for their participation. The study was conducted in accordance with the declaration of Helsinki and approved by the Human Subjects Ethical Review Board at the Free University Medical Hospital. To

Test schedule

1. Screening (medical, psychiatric) and consent form
2. Test session 1 (levodopa or placebo)
3. Day after test session 1: questionnaire sexual behavior during the 24 hours following session 1
4. Test session 2 (levodopa or placebo) (at least 3 days after test session 1)
5. Day after test session 2: questionnaire sexual behavior during the 24 hours following session 2

Test session

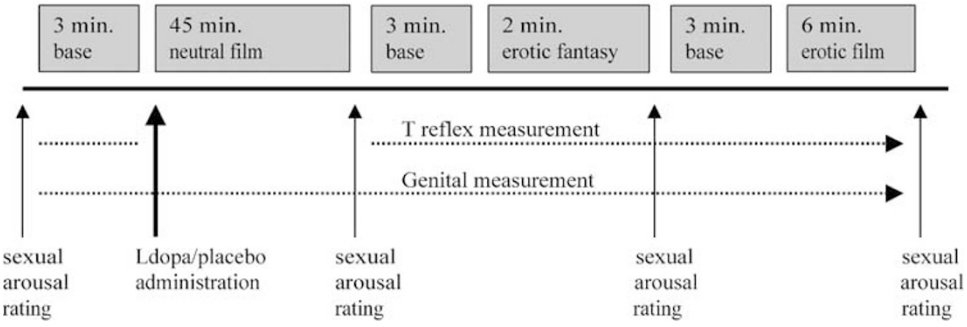

Figure 1 Test schedule and a schematic representation of the test sessions.

help subjects make an informed decision about whether to participate in this experiment, they were informed about the experimental procedure, the medication used, and the genital and T reflex measurements. Confidentiality, anonymity, and the opportunity to withdraw from the experiment without penalty were assured to all subjects. Subjects read and signed an informed consent form prior to study participation. The decision to participate was followed by a screening interview. Inclusion criteria were: ages 18–45; no use of medications contra-indicated in combination with levodopa; no use of medications that could interfere with sexual response; no history of major mental illness; and no severe medical illness. Smokers were not excluded but self-reported smoking status was recorded.

Mean age of both men and women was 22 (men: range = 20–29 years, SD = 2.3; women: range = 18–37 years, SD = 4.1). All subjects had a heterosexual orientation. In the male subjects, nine men (47%) had a steady partner. All men experienced coitus and practiced masturbation. None of them experienced sexual abuse. In the female subjects, 19 women (68%) had a steady partner. All women experienced sex with a partner and practiced masturbation, 27 women (96%) had experienced coitus. Three women (10.7%) experienced sexual abuse once in their lives. All subjects had seen erotic films prior to participation, and all subjects but one man and one woman were familiar with erotic fantasy.

Design

We used a 2 (drug) × 2 (stimulus) × 2 (drug-order) × 2 (gender) factor design, with drug and stimulus as within-subjects variables, and drug-order and gender as between-subjects variables. Men and women were randomly assigned to drug-order groups. Figure 1 shows the test schedule and a schematic representation of the test sessions.

Materials and Response Measurement

Stimuli. In the erotic fantasy condition, subjects received the following instruction: 'Fantasize about a sexually arousing situation for 2 min and try to become as sexually aroused as you possibly can'. The erotic film was a 6-min heterosexual videotape, depicting petting, cunnilingus, and intercourse. The scene originated from a film directed and produced by Candida Royalle. Films produced by Candida Royalle are aimed at women, and are more female-initiated and female-centered than conventional erotic movies. The film had previously been demonstrated to elicit physiological and subjective sexual arousal in men and women (Both *et al*, in press). Following drug administration, during the 45-min waiting period after which optimal plasma levels of levodopa were expected, participants viewed a neutral film about Tibet. Previously, the neutral film had been shown not to enhance T reflexes or genital response (Both *et al*, in press).

Physiological recordings. The procedure for T reflex measurement was carried out in accordance with standard methods for evoking T reflexes (Desmedt, 1973). To measure reflex activity (EMG), surface electrodes (Ag/AgCl electrodes, 2 cm^2 contact area, 3 cm apart) were placed upon the soleus muscle, along the longitudinal axis of the calf, the proximal electrode of the pair 2 cm distal to the insertion of the gastrocnemius muscle on the Achilles tendon. Reflexes were elicited at a constant rate of 1 every 5 s during baselines, erotic fantasy, and film presentation, resulting in 36 reflexes during the 3-min baseline periods, 24 reflexes during erotic fantasy, and 72 reflexes during the film presentation period.

In women, genital response was measured using a vaginal photoplethysmograph assessing vaginal pulse

amplitude (VPA) (Laan *et al*, 1995). The VPA signal was sampled at 100 Hz with a Keithley KPCI3107 A/D converter, running on a Windows2000 PC system. Depth of the probe and orientation of the light-emitting diode were controlled by a device (a 9×2 cm plate) attached to the photoplethysmograph. Subjects were instructed to insert the photoplethysmograph such that the plate touched their labia.

Genital response in men was measured by a mechanical penile strain gauge assessing penile circumference changes (Barlow *et al*, 1970; Janssen *et al*, 1994). Changes in electrical output caused by expansion of the strain gauge were recorded by a continuous DC signal. Calibration was accomplished using a 26-step plastic cone with steps ranging from 85 to 160 mm circumference. The strain gauge was positioned two-thirds of the way down the shaft of the penis toward the base. The experimenter checked for proper placement of the device. Both the vaginal photoplethysmograph and the penile strain gauge were sterilized in a solution of Cidex-activated glutaraldehyde between uses (Geer, 1980).

To provide evidence of drug 'bioactivity', in line with studies on dopamine-induced changes in pre-pulse startle inhibition (eg Swerdlow *et al*, 2002), heart rate and blood pressure were monitored. Heart rate and blood pressure were measured by an inflatable cuff (Finapress BP monitor), which was applied around the middle finger of the nondominant hand.

Genital response, heart rate, and blood pressure were recorded continuously, and T reflexes were elicited during baselines, erotic fantasy, and erotic film presentation.

Subjective measurements. Prior to drug administration, and following the neutral film, erotic fantasizing, and erotic film presentation, data of subjective sexual arousal and emotional experience were collected. Subjects were asked to assess on a 7-point scale: (a) overall sexual arousal; (b) strongest feeling of sexual arousal; and (c) strongest genital sensations. The scale extremes were *not sexually aroused at all* and *very strongly sexually aroused* for items (a) and (b), and *no sensations in my genitals* and *orgasm* for item (c). The answer categories for men and women were slightly different: genital sensations were described for men as erection and for women as vaginal lubrication.

Emotional experience was measured by a questionnaire consisting of 21 emotions (including sexual emotions). Subjects were asked to indicate on a 7-point scale (with *not at all* and *very strong* as extremes) to what extent they had experienced these emotions while erotic fantasizing and during viewing of the film excerpts. In an earlier study, factor analysis had indicated that the 21 emotions could be divided into four factors: seven emotions reflecting lust (Cronbach's $\alpha = 0.82$), four emotions relating to anger (Cronbach's $\alpha = 0.85$), eight emotions relating to threat (Cronbach's $\alpha = 0.71$), and two emotions reflecting tension (Cronbach's $\alpha = 0.79$; Laan *et al*, 1995).

The Action Tendency Questionnaire (ATQ) measured subjective action tendencies. This questionnaire, which assesses the tendency to execute overt behavior without necessarily doing so (Frijda *et al*, 1989), was administered after erotic fantasizing and after the erotic film presentation. Subjects were asked to assess on 5-point Likert scales (with *does not apply to me* and *strongly applies to me* as extremes) the degree to which 25 statements were applicable to them. The statements varied from statements indicating approach tendencies (eg 'I wanted to approach, to make contact') to statements indicating avoidance (eg 'I wanted to have nothing to do with something or someone, to be bothered by it as little as possible, to stay away'). Formerly, factor analysis revealed that the questionnaire could be divided into four subscales: approach (Cronbach's $\alpha = 0.87$), avoidance (Cronbach's $\alpha = 0.75$), protection (Cronbach's $\alpha = 0.81$), and attention (Cronbach's $\alpha = 0.76$; Laan and Everaerd, 1995).

The questionnaires were presented on a TV monitor and answered by pressing buttons corresponding with the answer categories. The answers were stored in a Windows2000 PC system.

Sexual behavior. To explore the effects of levodopa on actual sexual activity, a questionnaire assessing the frequency of sexual activity (alone or with a partner and with or without coitus) during the 24 h after each laboratory visit was administered. The subjects were asked to return the day after each laboratory visit to complete this questionnaire. The nature of the questionnaire was not disclosed beforehand. The questionnaire consisted of 10 items. The first seven items on sexual desire asked how often during the 24 h after the laboratory visit the subject had: (a) had sexual thoughts; (b) felt erotically aroused; (c) searched for sexual incentives; (d) felt sexually attracted to someone; (e) had sexual fantasies or daydreams; (f) experienced feelings of sexual arousal; (g) experienced feelings of sexual desire. The next three items on sexual activity asked how often during the 24 h following the laboratory visit the subject had: (a) masturbated; (b) had sexual intercourse; (c) had sexual contact without intercourse.

Procedure

Subjects were asked to abstain from drugs for 24 h, alcohol for 8 h, and food for 1.5 h prior to the laboratory visits. Female subjects were scheduled for the visits on days they were not menstruating. A trained experimenter of the same sex tested each subject individually. On arrival at the laboratory, alcohol and drug use, and food intake prior to the visit were checked. Since it is advised not to use levodopa during pregnancy, for female subjects a pregnancy test was conducted. The subjects also answered questions about smoking habits, and completed a questionnaire about sexual experience and sexual problems. Following explanation of the details of the experimental procedure, the experimenter attached the electrodes. Then the experimenter determined the intensity of mechanical stimulation necessary to elicit reflexes. The intensity was adjusted to obtain, at rest, a reflex EMG with an amplitude between 25 and 50% of the estimated maximum T reflex. The experimenter then left the room and the subject inserted the vaginal probe or attached the penile strain gauge. The subjects were allowed to cover the lower part of their body again after placement of the transducer. When the subjects signaled (using a one-way intercom system) that the transducers had been placed, the experimenter attached

the Finapress cuff. The participants were instructed to keep their arm at the armrest of the chair, and to keep movement of their hand to a minimum to avoid artifacts in the measurement. After the experimenter left the room, the recordings started (see Figure 1). During the baseline periods, subjects listened to quiet music. After the first baseline, the experimenter entered the room to give the, identically looking, placebo or levodopa capsule, which subjects took orally with a glass of water. Time from levodopa/placebo ingestion to the onset of the erotic fantasy period was approximately 50 min, the period in which optimal plasma levels of levodopa were expected (Sagar and Smyth, 2000). The 2-min erotic fantasy period was followed by a 2-min return-to-baseline and a 3-min baseline period. To facilitate return-to-baseline, subjects were asked to count aloud backwards from 100 during the last minute of the return-to-baseline period. At the end of the experiment, an exit interview was held. Subjects were asked about their reactions to the experimental procedure, the use of the genital device, the T reflex measurement, and the experience of drug side effects. Finally, the appointment was made to complete the questionnaire about sexual behavior the next day.

Data Reduction, Scoring, and Analysis

The raw EMG data were loaded into a Windows program. The mean T reflex amplitude elicited during the baseline periods (X) and during each erotic stimulation period (Y) was calculated. A percentage of baseline score (percentage of baseline $= Y/X \times 100$) was calculated for the erotic fantasy period and the erotic film period, using the preceding baselines. In addition, a percentage of baseline score was calculated for baseline 2 (the baseline following the neutral film), using the baseline preceding drug administration as reference.

The raw genital data were loaded into a Windows program allowing visual inspection of the signal. Artifacts in the VPA channel are caused by movements of the lower part of the body or by voluntary or involuntary contractions of the pelvic muscles. A two-pass algorithm for automatic artifact removal developed at our department was used to analyze the VPA data. Also, artifacts in the strain gauge data were removed following visual inspection. Thereafter, the data were scored as millimeter circumference based on pre-session calibration of the strain gauge. Then, VPA, as well as penile circumference, was averaged for the neutral film, erotic fantasy, and erotic film periods. For genital responses during neutral film, erotic fantasy, and erotic film, statistical analyses were performed with absolute deviation from preceding baseline as the dependent variable.

For heart rate and blood pressure, the mean responses during the baseline period preceding drug administration and the mean responses during the baseline period following the neutral film period were calculated. Statistical analysis was performed with absolute deviation from baseline preceding drug administration as the dependent variables.

For emotional experience, the items belonging to each of the described factors were averaged, thus creating a lust, anger, threat, and tension score. For action tendency ratings, only the approach and avoidance factors were used for further analysis. The approach items and the avoidance items were averaged, thus creating a mean approach and a mean avoidance score.

For frequency of sexual activity during the 24 h after participation, a sexual desire and a sexual activity score were calculated. The first score was calculated by adding up the scores on the items about sexual desire, and the second score was calculated by adding up the scores on the items about sexual activity.

Within-subjects and between-subjects effects were tested with repeated measures univariate and multivariate analysis of variance procedures (General Linear Model in SPSS), using a significance level of 0.05. T reflex magnitude was submitted to a 2 (drug) $\times$ 2 (stimulus) $\times$ 2 (drug-order) $\times$ 2 (gender) repeated measures ANOVA, with drug and stimulus as within-subjects variables and drug-order and gender as between-subjects factors. Since changes in vaginal vascular responses are not comparable to changes in penile responding (Geer and Janssen, 2000), genital responses were analyzed separately for men and women, and were submitted to 2 (drug) $\times$ 2 (stimulus) $\times$ 2 (drug-order) repeated measures ANOVAs. Heart rate and blood pressure were submitted to a 2 (drug) $\times$ 2 (drug-order) $\times$ 2 (gender) repeated measures MANOVA. Subjective sexual arousal, emotional experience, and action tendencies were also submitted to 2 (drug) $\times$ 2 (stimulus) $\times$ 2 (drug-order) $\times$ 2 (gender) repeated measures MANOVAs. Following significant F ratios for dependent measures, univariate analyses were performed to test for specific effects.

RESULTS

General Observations

Responses at exit interviews indicated that the subjects felt comfortable during the experiment despite the genital and T reflex measurements. Although levodopa is known to induce nausea, spasms, or drowsiness, only a small number of participants reported side effects of the drug. Three men reported side effects after levodopa administration, namely lightheadedness, restlessness, and headache, and unprovoked penile erection during the neutral film. These side effects were indicated as a little or moderately bothersome. In the female subjects, none of the subjects reported side effects after levodopa administration; however, three women were uncertain and reported drowsiness, coldness, and urge to urinate. Of these three women, two indicated the possible effects as not bothersome and one woman as moderately bothersome. Following placebo administration, two male subjects reported side effects, namely dizziness and nausea, which were indicated as a little and strongly bothersome. Two men were uncertain about their experience of side effects following placebo and reported drowsiness and lack of concentration. None of the women reported side effects following placebo administration, although two women were uncertain and experienced nausea and stomach cramps.

There were no significant effects of drug, drug-order, or gender on sexual arousal and emotional experience prior to drug intake; therefore, raw post-test scores were used for the statistical analysis. There was no difference between drug-order groups on the baselines of T reflex amplitude and genital response prior to drug intake.

Evidence for Drug Bioactivity: Heart Rate and Blood Pressure

First it was determined whether heart rate and blood pressure data provided evidence for the expected bioactivity of levodopa 45 min following drug administration. For two male participants, data of heart rate and blood pressure were missing due to technical problems. Inspection of the data revealed a slight decrease of heart rate and a slight increase of systolic and diastolic blood pressure during the 45-min neutral film. The drug × drug-order × gender repeated measures MANOVA of change scores (baseline preceding drug intake minus baseline following the neutral film) revealed a significant effect of drug, $F(3.39) = 4.9$, $p < 0.01$, and an interaction of drug and drug-order, $F(3,39) = 4.1$, $p < 0.05$. There was no effect of gender and no interaction with gender. Univariate tests showed an effect of levodopa on heart rate $F(1,41) = 14.2$, $p < 0.01$, but not on systolic and diastolic blood pressure. Change in heart rate in the placebo condition was –2.8 ($\pm$4.4) beats per minute, and in the levodopa condition −0.5 ($\pm$4.4) beats per minute. Changes in systolic and diastolic blood pressure in the placebo condition were respectively 9.8 ($\pm$11.3) and 6.8 ($\pm$6.5) mmHg, and in the levodopa condition respectively 8.3 ($\pm$9.1) and 6.0 ($\pm$7.8) mmHg. The decrease in heart rate was smaller following levodopa administration than following placebo administration, providing evidence for bioactivity of levodopa. The univariate test of the interaction of drug and drug-order was significant for heart rate, $F(1,41) = 6.04$, $p < 0.05$; inspection of the data revealed a larger decrease in heart rate during the second visit than during the first visit, indicating an effect of visit.

T Reflex Magnitude and Genital Responses

T reflex magnitude. Figure 2 shows mean T reflex magnitude during baseline 2, erotic fantasy, and erotic film following placebo and levodopa administration, for men and women. Results of the drug × stimulus × drug-order × gender repeated measures ANOVA revealed that erotic fantasy and erotic film yielded differential levels of T reflex magnitude. As expected, reflex magnitudes were higher during erotic film than during erotic fantasy, $F(1,43) = 22.73$, $p < 0.001$. There was no main effect of gender and no interaction of stimulus and gender.

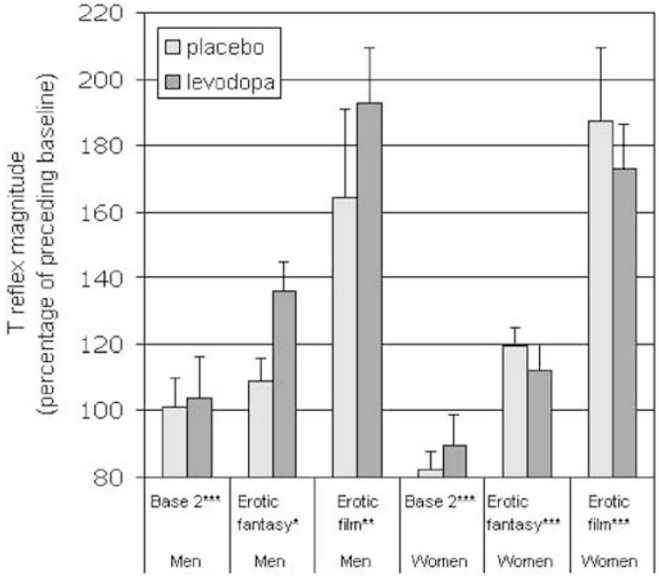

Figure 2 Mean T reflex magnitude (and SEM) during baseline 2, erotic fantasy, and erotic film, following placebo and levodopa administration, for men and women (*$p = 0.05$, **$p = 0.1$, ***NS).

Since levodopa was expected to increase T reflex magnitude in response to sexual stimuli but not during rest, an analysis of reflex magnitude during the baseline following the neutral film (at that time, optimal levels of dopamine were expected) was performed. Due to technical problems, for one female participant reflex data of the baseline that preceded drug intake were missing. Therefore, data of 46 participants were available for the analysis. The drug × drug-order × gender repeated measures ANOVA revealed no effect of drug, $F(1,42) = 7.79$, $p = 0.38$, indicating that T reflex amplitudes during rest were not affected by levodopa. There were also no effects of drug-order or gender, and no interaction effects on T reflex magnitude during rest.

There was an effect of drug during sexual stimulation, $F(1,43) = 6.34$, $p < 0.05$, indicating that, as expected, T reflex magnitude in response to the sexual stimuli was higher following levodopa administration. There was no main effect of drug-order, no interaction of drug with stimulus, and no interaction of drug with drug-order. However, there was a significant interaction of drug and gender, $F(1,43) = 6.57$, $p < 0.05$, indicating that the male participants showed stronger T reflexes following drug administration while reflex magnitude in the female participants was unaffected by drug.

Additional analyses of T reflex magnitudes were performed for men and women separately. This revealed a significant facilitating effect of drug in men, $F(1,17) = 6.67$, $p < 0.05$, but no effect of drug in women. Separate analysis of T reflex magnitude in response to erotic fantasy and erotic film in men revealed a significant effect of drug on T reflex magnitude during erotic fantasy, $F(1,17) = 4.71$, $p = 0.05$, but a nonsignificant effect of drug on reflex magnitude during erotic film, $F(1,17) = 2.81$, $p = 0.1$. In women, there was no significant effect of drug for reflex magnitude during erotic fantasy ($p = 0.31$), or reflex magnitude during erotic film ($p = 0.5$).

Genital responses. For the female participants, VPA data for one woman were missing due to technical problems. Figure 3 shows genital responses for men (Figure 3a) and women (Figure 3b) during the neutral film, erotic fantasy, and erotic film following placebo and levodopa administration. In men, a main effect of stimulus, $F(1,17) = 14.70$, $p = 0.001$, showed that, as expected, genital responses during erotic film were stronger than during erotic fantasy. Although erectile responses were stronger during erotic fantasy than during the neutral film, this difference did not reach statistical significance. There were no effects of drug on penile circumference change during the neutral film. Also, the drug × stimulus × drug-order repeated measures ANOVA revealed no main effect of drug, nor an interaction of drug with stimulus or drug-order. Thus, levodopa did not facilitate penile responses during erotic fantasy and erotic film.

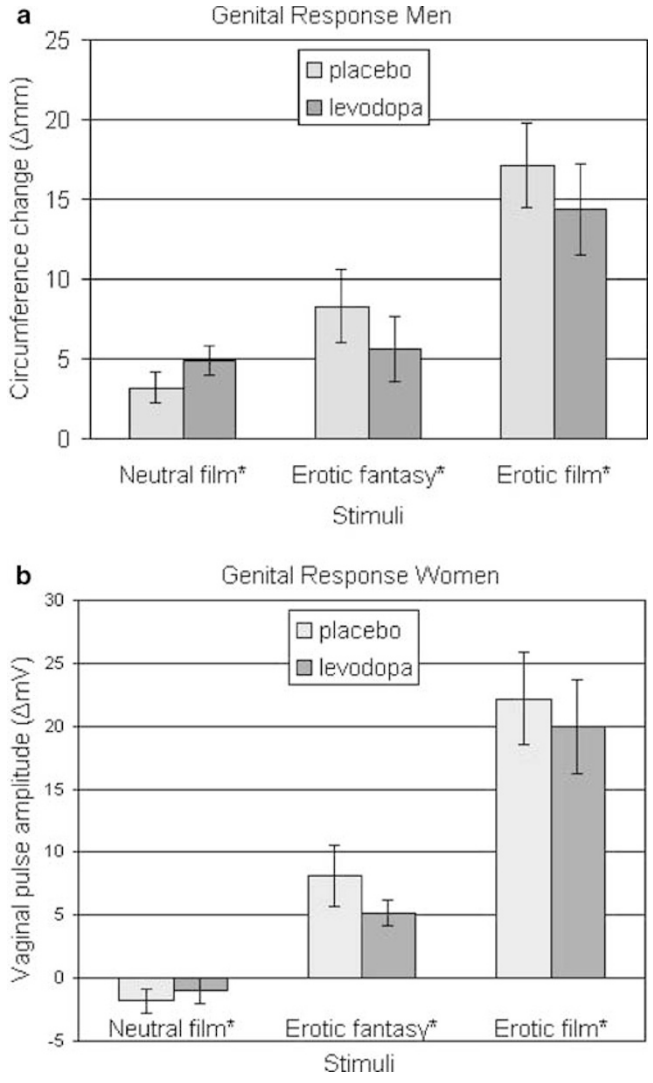

Figure 3 Mean genital response (and SEM) during the neutral film, erotic fantasy, and erotic film, following placebo and levodopa administration, for men (a) and women (b) (*NS).

In women, as expected, VPA increase was stronger during erotic film than during erotic fantasy, $F(1,25) = 28.84$, $p < 0.001$, and VPA was higher during erotic fantasy than during the neutral film, $F(1,25) = 124.23$, $p < 0.001$. There was no main effect of drug nor any interactions of drug with drug-order or stimulus on VPA during the neutral film or during erotic stimulation.

Subjective Sexual Arousal, Emotional Experience, Action Tendencies, and Sexual Behavior

Subjective sexual arousal. Mean ratings of subjective sexual arousal are shown in Table 1. The drug × stimulus × drug-order × gender repeated measures MANOVA for subjective feelings of sexual arousal showed a significant effect of stimulus, multivariate $F(3,41) = 8.95$, $p < 0.001$. As expected, erotic film elicited stronger feelings of sexual arousal than erotic fantasy. There was no main effect of drug; thus, levodopa did not increase feelings of sexual arousal in response to the erotic stimuli. There was a significant interaction between drug and drug-order, multivariate $F(3,41) = 4.89$, $p < 0.01$. In both order groups, participants reported the strongest feelings of sexual arousal during the first visit, indicating a main effect of visit. In addition, univariate analysis revealed a main effect of gender for strongest feelings of sexual arousal, $F(1,43) = 7.04$, $p < 0.05$, and for strongest genital sensations, $F(1.43) = 5.49$, $p < 0.05$, showing that the male participants reported stronger feelings of sexual arousal than the females.

Emotional experience. There was a main effect of stimulus on emotional experience, multivariate $F(4,40) = 3.97$, $p < 0.01$. Univariate tests showed an effect of stimulus on feelings of lust, $F(1,43) = 10.8$, $p < 0.005$, showing that feelings of lust were stronger in response to erotic film than to erotic fantasy. As expected, there was no effect of stimulus on feelings of anger, threat, or tension. There was no effect of gender and no interaction of stimulus and gender. There was also no main effect of drug or drug-order on emotional experience. However, there was an interaction between drug and drug-order, multivariate $F(4,40) = 2.54$, $p = 0.05$. The univariate tests of the interaction of drug and drug-order revealed an effect on feelings of lust, $F(1,43) = 5.74$, $p < 0.05$, indicating that, in line with feelings of sexual arousal, feelings of lust were strongest during the first laboratory visit.

Subjective action tendencies. There was no main effect of stimulus on subjective action tendencies; erotic fantasy and erotic film evoked comparable ratings of approach and avoidance tendencies. There was an interaction approaching significance of stimulus and gender, multivariate $F(2,42) = 2.75$, $p < 0.1$. The univariate tests revealed no interaction of stimulus and gender for the approach ratings, although an interaction for avoidance tendencies was reported, $F(1,43) = 4.57$, $p < 0.05$. In response to the erotic film, the men reported less avoidance tendencies than the women. There was no main effect of drug or drug-order on action tendencies. There was an interaction of drug and drug-order, multivariate $F(2,42) = 10.09$, $p < 0.001$, and an interaction of drug and stimulus, multivariate $F(2,42) = 3.46$, $p < 0.05$. The univariate tests showed that drug × drug-order significantly affected approach tendencies, $F(1,43) = 20.45$, $p < 0.001$. In line with feelings of sexual arousal and feelings of lust, approach tendencies in response to the sexual stimuli were strongest during the first visit. Drug and stimulus interacted significantly for approach tendencies, $F(1,43) = 6.94$, $p < 0.05$; in response to erotic fantasy approach ratings were highest following placebo administration, while in response to erotic film ratings were highest following levodopa intake.

Sexual behavior. Since one male subject did not show up to complete the questionnaire regarding postexperimental sexual desire, activity data of 46 participants were available for statistical analysis. Mean sexual desire sum score for men was 27.6 (±27.2) in the placebo condition and 23.3 (±29.4) in the levodopa condition; for women, these scores were respectively 14.9 (±20.9) and 8.5 (±8.0). The drug × drug-order × gender repeated measures ANOVA for sexual desire during the 24 h after the laboratory visits showed no effect of drug or drug-order, and no interaction of drug and

Table 1 Mean (SD) Subjective Ratings of Sexual Arousal in Response to Erotic Fantasy and Erotic Film, Following Placebo and Levodopa Administration, for Men and Women

	Placebo		Levodopa		*p*-Value	
Sexual arousal ratings	**Erotic fantasy**	**Erotic film**	**Erotic fantasy**	**Erotic film**	**Stimulus effect**	**Drug effect**
Overall sexual arousal[a]						
Men	3.0 (1.4)	4.1 (1.1)	2.6 (1.1)	3.8 (1.2)		
Women	2.9 (1.4)	3.8 (1.5)	2.9 (1.2)	3.4 (1.5)		
Total	2.9 (1.4)	3.9 (1.3)	2.8 (1.2)	3.6 (1.4)	0.000	NS
Strongest sexual arousal[a]						
Men	3.2 (1.5)	4.7 (1.2)	2.9 (1.5)	4.7 (1.4)		
Women	2.7 (1.6)	3.5 (1.6)	2.5 (1.6)	3.4 (1.7)		
Total	2.9 (1.6)	4.0 (1.6)	2.6 (1.6)	3.9 (1.7)	0.000	NS
Strongest genital sensations[b]						
Men	3.6 (1.7)	4.5 (1.4)	3.4 (1.6)	4.8 (1.2)		
Women	2.8 (1.5)	3.8 (1.7)	2.9 (2.1)	3.5 (1.7)		
Total	3.2 (1.7)	4.1 (1.6)	3.1 (1.9)	4.0 (1.6)	0.000	NS

Statistical significance of stimulus and drug comparison is reported for the total groups only.
[a]Item response format of 1 (*not sexually aroused at all*) to 7 (*very strongly sexually aroused*).
[b]Item response format of 1 (*no sensations in my genitals*) to 7 (*orgasm*).

drug-order. There was an effect of gender, $F(1,42) = 7.62$, $p < 0.05$; the male subjects had higher postexperimental sexual desire scores. Mean sexual activity sum score for men was 1.2 (± 1.1) in the placebo condition and 1.0 (± 1.2) in the levodopa condition; for women, these scores were, respectively, 1.0 (± 1.6) and 0.6 (± 0.9). For sexual activity, no effect of drug and no other effects were found.

Additional Analyses

Use of hormonal contraceptives. There is evidence for reduced bioavailability of androgens as a result of the use of hormonal contraceptives (Casson *et al*, 1997; Carlstrom *et al*, 2002). To explore a possible influence of testosterone levels on the effect of levodopa on T reflex magnitudes and VPA, women using hormonal contraceptives ($N = 20$) were compared to women not using hormonal contraceptives ($N = 8$). A 2 (drug) $\times$ 2 (stimulus) $\times$ 2 (hormonal contraceptives use) repeated measures ANOVA for T reflex magnitude revealed no main effect of group and no interaction of drug and group. A similar analysis was performed for VPA, and no effects were found. Due to the small sample size, analyses investigating the influence of menstrual cycle phase were not performed.

Smoking. There is evidence from research on rats that nicotine affects dopaminergic function (eg Ferrari *et al*, 2001; Trauth *et al*, 2001), and in humans smoking has been related to greater dopamine activity in the basal ganglia (Salokangas *et al*, 2000). To investigate smoking as a possible mediating variable in the effect of levodopa on somatic motor activity, smokers and nonsmokers were compared on T reflex magnitude during sexual stimulation. Regular tobacco use was reported by 46% of the male participants and 40% of the female participants. There was no significant difference in the percentage of smokers between men and women, indicating that the gender difference in the effect of levodopa on T reflex magnitude during sexual stimulation cannot be attributed to differences in smoking habits. A 2 (drug) $\times$ 2 (stimulus) $\times$ 2 (gender) $\times$ 2 (smoking) repeated measures ANOVA for T reflex magnitude revealed an interaction of drug and smoking, $F(1,43) = 4.2$, $p < 0.05$. The smokers showed the strongest effect of levodopa (smokers: placebo erotic fantasy 106.6 ± 23.3, placebo erotic film 123.6 ± 30.5, levodopa erotic fantasy 118.9 ± 43.8, levodopa erotic film 170.3 ± 89.3; nonsmokers: placebo erotic fantasy 118.8 ± 32.0, placebo erotic film 154.5 ± 52.1, levodopa erotic fantasy 123.1 ± 40.8, levodopa erotic film 159.8 ± 61.3). To explore whether the observed effect of levodopa on T reflex magnitude during sexual stimulation in men appeared only in the male smokers, a separate 2 (drug) $\times$ 2 (stimulus) $\times$ 2 (smoking) repeated measures ANOVA for the male participants was performed. A main effect of drug was found, $F(1,17) = 9.9$, $p < 0.01$, and an interaction of drug and smoking approaching significance was revealed, $F(1,17) = 3.6$, $p = 0.08$. The effect of levodopa on T reflex magnitude in response to sexual stimulation in men was stronger in the smokers (male smokers: placebo erotic fantasy 96.1 ± 21.1, placebo erotic film 115.5 ± 32.8, levodopa erotic fantasy 133.1 ± 61.1, levodopa erotic film 203.8 ± 130.4), but not absent in the nonsmokers (male nonsmokers: placebo erotic fantasy 114.7 ± 31.1, placebo erotic film 151.1 ± 54.1, levodopa erotic fantasy 137.2 ± 51.5, levodopa erotic film 159.8 ± 73.5).

In addition, a 2 (drug) $\times$ 2 (gender) $\times$ 2 (smoking) repeated measures ANOVA for T reflex magnitude during the baseline following the neutral film was performed. This revealed a main effect of smoking, $F(1,42) = 4.1$, $p = 0.05$; smokers showed stronger T reflex magnitudes during rest, but no interaction of drug and smoking.

DISCUSSION

The present study shows that a single dose of levodopa facilitates T reflex magnitude in response to erotic stimulation in men but not in women. In accordance with evidence from studies in male rats, an increased level of dopamine resulted in stronger instigation of action in response to sexual incentives in human males. The absence of an effect of levodopa on T reflex magnitude in women is in line with the conflicting reports about the effects of dopamine on sexual motivation in female rats and warrants further study. The fact that levodopa increased male T reflex magnitude during sexual stimulation shows that dopamine is involved in the energetic aspects of motivated behavior in males (Berridge, 1996; Salamone and Correa, 2002), and that T reflex modulation offers a sensitive measure for dopaminergic effects on the generation of sexual appetitive behavior in humans. However, the single administration of levodopa did not facilitate genital responses, and did not result in enhanced feelings of sexual arousal or subjective approach tendencies.

The observed pattern of the effect of the drug on heart rate offered evidence for the expected 'bioactivity' of levodopa. The single dose of 100 mg levodopa/25 mg carbidopa resulted in significantly stronger cardiac activity than placebo. The timing of bioactivity of the drug in the present study is in line with reports about the pharmacokinetics of levodopa (Sagar and Smyth, 2000), and with studies on the effects of single dose of levodopa on sensorimotor processes (Hasbroucq *et al*, 2003; Rihet *et al*, 2002). Taken together, it may be safely concluded that levodopa was pharmacologically active during the testing of sexual responding.

The data regarding T reflexes, genital responses, subjective sexual arousal, and emotional experience show that both erotic fantasy and erotic film evoked a sexually aroused state, and that erotic film elicited, as expected, a higher level of sexual arousal than erotic fantasy. In addition, the participants reported subjective approach tendencies in response to the erotic stimulation. It can be concluded that the experimental stimuli were effective in eliciting sexual arousal in both the male and the female participants, thereby offering the opportunity to investigate the effect of levodopa on sexual response in men and women.

One may argue that the data obtained in the present study show a facilitatory effect of levodopa on general motor function as opposed to an effect on sexual motivation. However, the facilitating effect of levodopa on T reflex magnitude was observed only during sexual stimulation and not during rest, which indicates that the enhancing effect of levodopa concerned responses to the sexual incentive stimuli. In addition, one may question whether the effect of levodopa on T reflex magnitude reflects a dopaminergic effect on nonspecific arousal rather than an effect on motivational activity. However, it can be argued that arousal is always associated with motivational activation. Psychologically relevant somatic activity may range from undifferentiated activation to emotion-specific activation patterns (Cacioppo *et al*, 2000; Bradley, 2000). In this view, general somatic arousal signifies activity in motivational systems. In line with this view, Salamone and Correa (2002) state that a broader consideration of motivational functions leads one to recognize the overlap between aspects of motor function and aspects of motivation. The behavioral activation produced by motivational stimuli is related to both motor and motivational functions.

Another issue is whether the observed facilitating effect of levodopa on T reflex magnitude in men should be considered as based on enhancement of general incentive motivation processes or as specific for sexual incentive conditions. Research on the role of dopamine in motivation focused mainly on appetitive motivation; however, dopamine appeared to be not only involved in processes of appetitive conditions but also in aversive conditions (Ikemoto and Panksepp, 1999; Salamone and Correa, 2002). Several studies in rats showed effects of nucleus accumbens dopamine levels on avoidance responses, indicating that nucleus accumbens dopamine is not only involved in approach responses to rewards but also in avoidance responses elicited by aversive stimuli (Ikemoto and Panksepp, 1999). In the present study, we focused on sexual incentive conditions; however, future studies may include various rewarding as well as aversive stimuli to investigate dopaminergic influences on appetitive and aversive motivation in humans.

Smokers showed heightened motor system reactivity to the dopamine challenge during erotic stimulation compared to nonsmokers. The results regarding the effect of smoking in the male participants, however, showed that the facilitating effect of levodopa did not appear only in the male smokers. Thus, smoking mediated the effect of dopamine on somatic motor preparation in response to erotic incentives. In addition, smokers showed stronger T reflex magnitudes during rest, indicating increased sensitivity of the somatic motor system in smokers. These findings are in line with evidence for changes in dopaminergic systems and reward processing as a result of tobacco use (eg Martin-Sölch *et al*, 2001; Rose *et al*, 2003; Salokangas *et al*, 2000), and with evidence for increased locomotor activity after changes in the mesolimbic dopamine system by nicotine administration in rats (eg Ferrari *et al*, 2001). The observed differences between smokers and nonsmokers in the present study underline the importance to record smoking status in studies on the effect of dopamine on appetitive responses in humans. Secondly, they provide support for the validity of T reflex modulation as a measure for changes in dopaminergic systems and reward processing in humans.

Levodopa did not facilitate genital responses. Thus, while prosexual effects are reported in Parkinson patients treated with apomorphine or levodopa, and single sublingual (SL) administration of apomorphine does facilitate erection (Giuliano and Allard, 2001; Heaton, 2000), in the present study a single oral dose of 100 mg levodopa did not result in increased genital response. To date, the only direct support for an effect of dopamine on penile response in men comes from studies using apomorphine (SL), which is known as a powerful, fast-acting D_1/D_2 dopamine receptor agonist (Giuliano and Allard, 2001). The absence of an enhancing effect of levodopa on penile response in our study may be due to the low and single dosage we used. Possibly higher dosage or continuous treatment with levodopa will have an effect. However, the different findings in our study and the

apomorphine (SL) studies may also be related to dissimilar actions of the drugs on dopamine receptor subtypes, or on the brain structures involved in the various components of sexual response. Penile responses are supposed to be triggered by dopamine through action on oxytocinergic neurons in the paraventricular nucleus of the hypothalamus, and possibly on the pro-erectile sacral parasympathetic nucleus within the spinal cord (Giuliano and Allard, 2001). Experimental studies using dopaminergic drugs that are known to act on specific dopamine receptor subtypes, and brain imaging techniques, may provide insight into the exact involvement of dopamine in sexual motivation and genital arousal in humans.

It is remarkable that in women levodopa did not affect motor preparation in response to sexual stimulation. The sexual stimuli used in the present study were effective in eliciting genital and subjective sexual response in men and women, and there were no significant differences between the male and female participants in the evidence for the bioactivity of levodopa, indicating that these factors cannot explain the observed gender difference in the effect of levodopa on T reflexes. However, the observed mediating effect of smoking underlines that more specific data regarding smoking habits, like the amount of tobacco use, and also regarding for example caffeine consumption, which also may affect the dopaminergic system, are needed to rule out the possibility that such factors account for the observed gender difference in the effect of dopamine on T reflex change. However, as noted before, studies on dopaminergic effects on sexual motivation in female rats revealed conflicting results, which are often attributed to possible interactions of dopamine with the hormonal treatments that are used to induce estrus in female rats. Since there is evidence for steroid–dopamine interactions (eg Balthazart *et al*, 2002; Becker, 1999; Giuliano and Allard, 2001; Hull *et al*, 1999), the gender difference in the effect of levodopa in the present study might be due to differences in sex steroid levels in the brain. Becker (1999) provided evidence for an enhancing effect of estrogen and progesterone on dopamine release and dopamine-mediated behaviors in female rats. Possibly, also in women, steroid levels modulate the effect of dopamine on sexual response. To explore a possible influence of testosterone levels on the effect of levodopa on physiological responses, we compared women using hormonal contraceptives to women not using hormonal contraceptives. This comparison showed no influence of hormonal contraceptives on the effect of levodopa. However, it should be noted that the group not using hormonal contraceptives included only eight women. To gain insight into the interaction of dopamine and sex steroids, in future studies sex steroid levels should be included as a variable. However, a complicating factor is that the gender difference in the effect of levodopa may not only be due to differences in steroid levels but also due to differences in those levels at different locations in the brain.

Emotional feelings and subjectively experienced tendencies for approach behavior were not affected by levodopa. The conscious awareness of a motivational state may be dissociable from the underlying motivational processes (Berridge, 1996; LeDoux, 2001). For example, discordance of genital response and subjective sexual arousal is observed in studies on sexual response in women. However, the agreement of physiological sexual arousal and subjective report seems to increase as a function of the strength of the physiological response (Laan and Everaerd, 1995). In the present study, the enhanced somatic motor activity, induced by the single and low dose of levodopa, may have been not strong enough to be experienced subjectively.

To conclude, our study showed that dopamine facilitates somatic motor responses in response to sexual stimuli in men but not in women. To reveal the cause of this gender dimorphic effect of dopamine, future studies may focus on the interaction between steroid and dopamine levels. More continuous use of levodopa or dose–response assessment may show whether higher levels of dopamine will affect genital responses and subjective feelings of sexual arousal. T reflex modulation showed to be sensitive to changes in reward processing due to dopaminergic influences. Disorders in appetitive motivation, like substance addiction, are supposed to be related to dysregulation or sensitization of the mesolimbic dopaminergic system (Robinson and Berridge, 2001; Verheul *et al*, 1999). T reflex modulation may offer a sensitive tool to investigate reward signaling and the instigation of action tendencies in disorders in appetitive motivation, for example in substance addiction and hyper- and hypoactive sexual desire disorder.

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