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Zaprinast, a Phosphodiesterase 5 Inhibitor, Overcomes Sexual Dysfunction Produced by Fluoxetine, a Selective Serotonin Reuptake Inhibitor in Hamsters

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A high incidence of sexual dysfunction among women is reported in the clinical literature. Little experimental investigation has been initiated on the ability of phosphodiesterase (PDE) inhibitors to overcome deficits in sexual functioning because of selective serotonin reuptake inhibitors (SSRIs). The effects of fluoxetine, an SSRI, and zaprinast, a PDE-5 inhibitor, on the lateral displacement response (used as a measure of sensitivity to reproductively relevant stimuli) of hamsters in behavioral estrus were investigated. In Experiment 1, hamsters that were maximally sensitive to reproductively relevant stimuli because they were at the peak of behavioral estrus were administered fluoxetine (10 mg/kg, i.p.); they had significantly decreased lateral displacement responses compared to vehicle-administered hamsters. In Experiment 2, hamsters that were relatively less sensitive to sexual stimuli because they were at the termination of behavioral estrus were administered zaprinast (3 mg/kg; i.p.); they had significantly enhanced lateral displacement responses compared to responses seen following vehicle administration. In Experiment 3, fluoxetine-induced deficits in the lateral displacement of hamsters at the peak of behavioral estrus were overcome by the coadministration of zaprinast. These data confirm previous findings that sexual dysfunction can be induced by SSRIs and extend the current knowledge to suggest that administration of a PDE-5 inhibitor can override SSRI-induced deficits in sexual functioning.
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INTRODUCTION

In many cases, women may experience sexual dysfunction as a result of drug treatment for depression. Selective serotonin reuptake inhibitors (SSRIs) can produce anorgasmia and a reduction in libido in women (Ayd, 1995; Balon, 1995; Feiger *et al*, 1996; Laumann *et al*, 1999; Terao, 2001). Notably, SSRIs are used for the treatment of various other disorders, such as anxiety, premenstrual dysphoric disorder, pain syndromes, impulse control disorders, and personality disorders, many of which are more common among women than men (Hensley and Nurnberg, 2002). Adverse side effects of drugs may reduce medication compliance. Therefore, an important area for further investigation is the effects and possible treatment of SSRIs on the sexual function of women.

Although the sexual side effects of SSRIs observed in people have been demonstrated to occur in rodents, studies using animal models to investigate these effects are sparse (Vega Matuszczyk *et al*, 1998). Notably, the majority of studies using animal models to investigate the effects of SSRIs to disrupt sexual functioning have utilized male rodents (Ahlenius *et al*, 1979; Taylor *et al*, 1996; Yells *et al*, 1995; Yells *et al*, 1994). One study assessed the effects of a SSRI on the sexual receptivity and behavior of female rats. Intact female rats administered fluoxetine (10 mg/kg) had reduced lordosis behavior compared to vehicle-administered control females (Matuszczyk *et al*, 1998).

There are ample data in the literature to support the idea that serotonin can robustly influence sexual behavior. As early as the 1960s, it was hypothesized that serotonin inhibited sexual receptivity, and more recent evidence supports this idea (Mendelson, 1992; Meyerson, 1964a, b). For example, in female rats, treatments that increase serotonin activity decrease lordosis responses (Allen *et al*, 1993; Luine and Paden, 1982). These data are consistent with the multitude of reports in the clinical literature that SSRIs induce sexual dysfunction. SSRIs block the function of the presynaptic transporter for serotonin reuptake, but do not appear to block any of the postsynaptic serotonin receptors. This blockade of the presynaptic transporter would thus result in increased serotonin activity, which could explain the negative sexual side effects associated with SSRI treatment.

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There is evidence to suggest that inhibitors of phosphodiesterase 5 (PDE-5), such as sildenafil and zaprinast, can significantly improve SSRI-induced sexual dysfunction in women (Fava *et al*, 1998; Rosen *et al*, 1999). Women taking SSRIs who received 50 or 100 mg of sildenafil self-report improved sexual function (Ashton, 1999; Schaller and Behar, 1999; Shen *et al*, 1999). However, there have been no controlled experimental studies utilizing animal models of sexual dysfunction to confirm that PDE inhibitors can overcome SSRI-induced decrements in sexual functioning.

Sildenafil and zaprinast are selective inhibitors of GMP-specific PDE-5, which is the predominant PDE isoenzyme metabolizing cGMP in the smooth muscle cells of the corpus canvernosum. As cGMP levels are improved, there is increased vasodilation and dilation of the sinusoids in the corpus cavernosum, allowing for increased blood flow, which results in enhanced erections in men. While the majority of the investigations of the actions of PDE inhibitors have focused on erectile dysfunction in men, it is presumed that increased blood flow to the vaginal area of women would also result in enhanced sexual functioning.

The present studies investigated the effects of a SSRI, fluoxetine, and/or a PDE-5 inhibitor, zaprinast, to influence sexual sensitivity of female hamsters at the peak and termination of behavioral estrus using lateral displacement. Lateral displacement is a sensitive measure of the sensitivity of female hamsters to sexually relevant stimuli. The ovulation of naturally cycling female hamsters occurs every 4 days in coordination with behavioral estrus. Behavioral estrus is characterized by female hamsters' display of lordosis in response to sexually relevant stimuli. Female hamsters are unique in that they maintain the lordosis posture, elevation of the head and tail, and dorsoflection of the back, for minutes at a time. Hamsters in behavioral estrus assume the lordosis posture in the presence of sexually relevant stimuli. They then make pelvic adjustments in response to stimulus behavior such as sniffing and licking the perineal region prior to initiating a mount and during mounting when males engage in preinsertion thrusting (Noble, 1979a, b; Ostrowski *et al*, 1979, 1981). Dogs (Hart, 1970), cats (Diakow, 1971), and rats (Kow & Pfaff, 1973–1974) show similar patterns of pelvic adjustments. In hamsters, because of their tonic maintenance of the lordosis posture, these pelvic adjustments are observable and can be measured with a high degree of inter-observer reliability. The pelvic adjustments, referred to as lateral displacement, depend upon the stimulation applied to the perineum and fluctuate with behavioral estrus. Lateral displacement facilitates insertion by the male during mating (Noble, 1979a, b, 1980): anesthetizing the perineum of female hamsters eliminates lateral displacement, and disrupts copulatory behavior of male hamsters (Noble, 1979a, b, 1980).

We hypothesize that increasing serotonin activity, by administration of the SSRI fluoxetine, to hamsters that are maximally sensitive to sexual stimuli (at the peak of behavioral estrus) will decrease sexual responsivity, as measured by lateral displacement. Further, it is expected that increasing cGMP levels, with the PDE-5 inhibitor zaprinast, will enhance lateral displacement of hamsters that show less responsivity to sexual stimuli as they near the termination of behavioral estrus. Finally, it is predicted that zaprinast administered to hamsters with maximal sexual sensitivity (peak of behavioral estrus) will override deficits in lateral displacement caused by fluoxetine.

METHODS

These methods were preapproved by the Institutional Animal Care and Use Committee at SUNY, Albany.

Animals and Housing

A total of 16 sexually inexperienced female hamsters (*Mesocricetus auratus*) were obtained from Charles River Laboratories (Kingston, NY) at ~60 days of age or 100–125 g of body weight.

Hamsters were group housed, four to a cage, in solid bottom, plastic cages ($38 \times 33 \times 17\,cm^3$) in a temperature- ($22^{\circ}C$) and humidity-controlled (60%) hamster *vivarium* at SUNY, Albany. Hamsters were on a reversed light dark cycle (light:dark 14:10, lights off at 08:00). Chow and water were available *ad libitium* in the home cages.

Determination of Behavioral Estrus

Daily screening was performed of all hamsters between 0700 and 0800 h to determine those that were in behavioral estrus. Hamsters were placed in an arena with a male who was allowed to investigate the female. If the female exhibited lordosis in response to the stimulus male and/or manual palpation by the experimenter, the female was considered in behavioral estrus and tested in one condition on that day. We have previously demonstrated that hamsters identified as being in behavioral estrus in this fashion show maximal sexual behavior between 0900 and 1100 h and that responses are significantly reduced later in the day (between 1500 and 1700 h; Frye and Rhodes, 2002). Hamsters were tested once per cycle (ie no more than once a week) with counterbalancing between test times (ie peak and termination of behavioral estrus) to control for order effects. Behavioral estrus, rather than examination of vaginal epithelium, was used as an indicator of hormonal status of hamsters in order to reduce vaginocervical stimulation that occurs when collecting vaginal cytology of hamsters, which has been shown to alter lateral displacement responses (Noble, 1979).

Drugs

Fluoxetine was obtained from Sigma Chemical Co. (St Louis, MO). The fluoxetine regimen was based on previous reports that demonstrated effects of the drug on aggressive behavior of hamsters (Ferris *et al*, 1997) and sexual responses of rats (Matuszczyk *et al*, 1998; Muck-Seler *et al*, 1996; Page *et al*, 1999; Vega Matuszczyk *et al*, 1998). Fluoxetine was administered in a saline vehicle, in a dosage of 10 mg/kg (i.p.), 60 min prior to behavioral testing.

Zaprinast was obtained from Sigma Chemical Co. (St Louis, MO). The zaprinast regimen was based on previous reports that the drug increased sexual responses of mice (Pare and Kerchner, 2000). Zaprinast was administered in a vehicle of 25% DMSO in saline (v/v), in a dosage of 3 mg/kg (i.p.), 20 min prior to behavioral testing.

Behavioral Testing — Lateral displacement

The coordination of copulatory interactions in hamsters depends on a cluster of responses to tactile stimuli of the female's perineal region. The lateral displacement methodology has been developed to measure a female hamster's responses to tactile stimulation that mimics that made by the male during a mating sequence (Noble, 1979a, b). The response of female hamsters to tactile stimulation from the male facilitates penile insertion (Noble, 1980) and has been demonstrated, like other reproductively relevant behaviors, to fluctuate across the estrous cycle. The measure of lateral displacement was used as a more robust measure of a female's sensitivity to tactile stimuli (compared to lordosis) as more traditional measures, such as lordosis, have been demonstrated to occur in situations where mating is unlikely (ie among females that are pregnant or that have just been mated), while the lateral displacement response is severely depressed or absent during these times (Wise, 1974).

The lateral displacement methodology was as previously described (Frye and Rhodes, 2002; Noble, 1979a, b; Ostrowski *et al*, 1981). The female was briefly exposed to a stimulus male until she assumed lordosis. The male was then removed from the test chamber and the experimenter maintained the lordosis posture of the female with manual flank stimulation. A calibrated set of von Frey aesthesiometric probes was manually applied by the experimenter to the perineum in descending order of force. These probes are calibrated in 11 log-unit steps ranging from 0.69 to 75.9 g of pressure (Ostrowski *et al*, 1979). The probes were applied in a pulsatile manner (until the female's lateral movement stopped), similar to male-typical stimuli (ie preinsertion thrusting), to the right and left inner zones ($\pm$ 2 mm from the ano-vaginal midline) and the right and left outer zones ($\pm$ 7 mm from the ano-vaginal midline). The inner zone of the perineum is typically more sensitive to tactile stimulation than the outer zone and hence generally responds to a lower threshold of stimulation (Frye and Rhodes, 2002). The movement (in mm) of the female's perineum in response to stimulation was measured by a ruler positioned along her feet. We have previously demonstrated that total lateral displacement scores decrease as a function of the force of the probes applied to the inner and outer zone of the perineum (Frye and Rhodes, 2002). Scores of lateral displacement for the inner and outer perineum were summed to yield a total lateral displacement score. It has previously been demonstrated that there are no test decay effects with repeated testing in this behavioral assay (Frye and Rhodes, 2002). Notably, there were no overt changes in appearance of the perineum as a function of repeated testing, behavioral estrus, or drug treatment.

Procedure

Experiment 1: Does fluoxetine reduce lateral displacement of hamsters at the peak of behavioral estrus? Hamsters that were maximally receptive, at the peak of behavioral estrus (between 0900 and 1100 h) were administered fluoxetine (10 mg/kg, i.p.) or vehicle (saline) and tested for effects on lateral displacement 60 min later. Each hamster was tested in both the fluoxetine and vehicle conditions; the order of initial drug *vs* vehicle administration was randomized and counterbalanced to prevent order effects.

Experiment 2: Does zaprinast enhance lateral displacement of hamsters late in behavioral estrus? Hamsters later in behavioral estrus (1500–1700 h) were administered zaprinast (3 mg/kg, i.p.) or vehicle (25% DMSO in 0.9% saline) and tested for effects on lateral displacement 20 min later. Each hamster was tested in both the zaprinast and vehicle conditions; the order of drug *vs* vehicle administration was randomized and counterbalanced to prevent order effects.

Experiment 3: Can zaprinast overcome fluoxetine's inhibitory effects on lateral displacement of hamsters at the peak of behavioral estrus? Hamsters that were maximally receptive at the peak of behavioral estrus (between 0900 and 1100 h) were administered fluoxetine (10 mg/kg, i.p.) or vehicle (saline), followed 40 min later by zaprinast or vehicle (25% DMSO in 0.9% saline). Hamsters were tested for lateral displacement 20 min after zaprinast administration. Each hamster was tested in each of the four drug regimens: vehicle (saline)+vehicle (DMSO); Fluox (fluoxetine+vehicle (DMSO)); Zap (vehicle (saline)+zaprinast); Fluox and Zap (fluoxetine+zaprinast). The conditions under which hamsters were tested were randomized and counterbalanced to prevent order effects.

Statistical Analyses

One-way analyses of variance (ANOVAs) were utilized to examine effects of drug treatment on lateral displacement. Factors revealed as significant in the overall ANOVAs were confirmed with least-squares means *post hoc* tests to ascertain group differences. The alpha level for statistical significance was $P \leqslant 0.05$.

RESULTS

Experiment 1: Fluoxetine decreases lateral displacement of hamsters at the peak of behavioral estrus

Fluoxetine administration to hamsters at the peak of behavioral estrus significantly diminished lateral displacement responses compared to vehicle administration. Total lateral displacement responses for the more sensitive inner ($F(1,15) = 32.47$, $P < 0.01$) and the less sensitive outer ($F(1,15) = 30.09$, $P < 0.01$) zones were significantly decreased by fluoxetine *vs* vehicle administration (see Figure 1).

Experiment 2: Zaprinast enhances lateral displacement of hamsters late in behavioral estrus

Zaprinast administration to hamsters late in behavioral estrus significantly enhanced lateral displacement responses compared to vehicle administration. Total lateral displacement responses for both the inner ($F(1,15) = 27.38$, $P < 0.01$) and the outer ($F(1,15) = 18.61$, $P < 0.01$) zones were significantly increased by zaprinast compared to vehicle administration (see Figure 2).

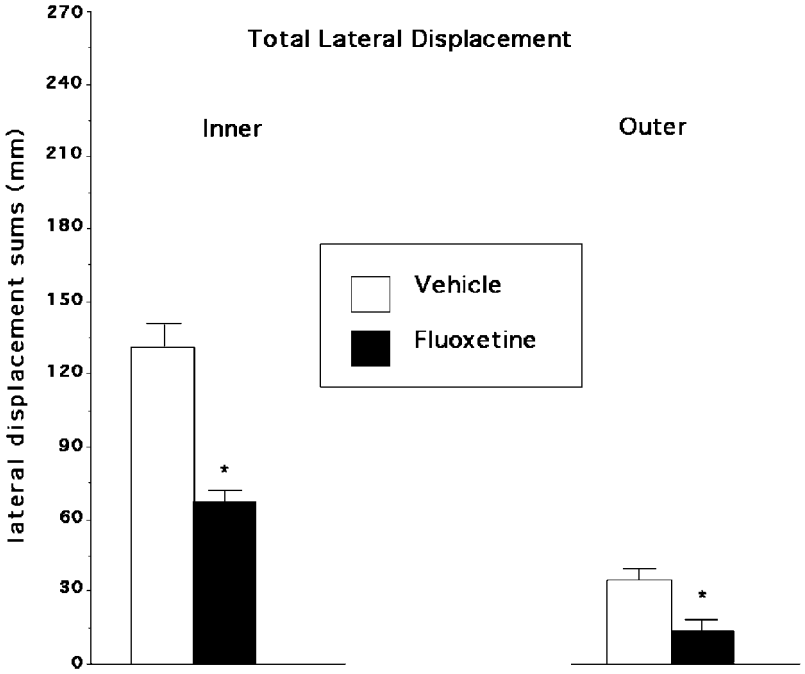

Figure 1 Total lateral displacement of hamsters that received vehicle (open bar; $n=16$) or fluoxetine (dotted bar; $n=16$). *indicates a significant difference ($P<0.05$) compared to vehicle.

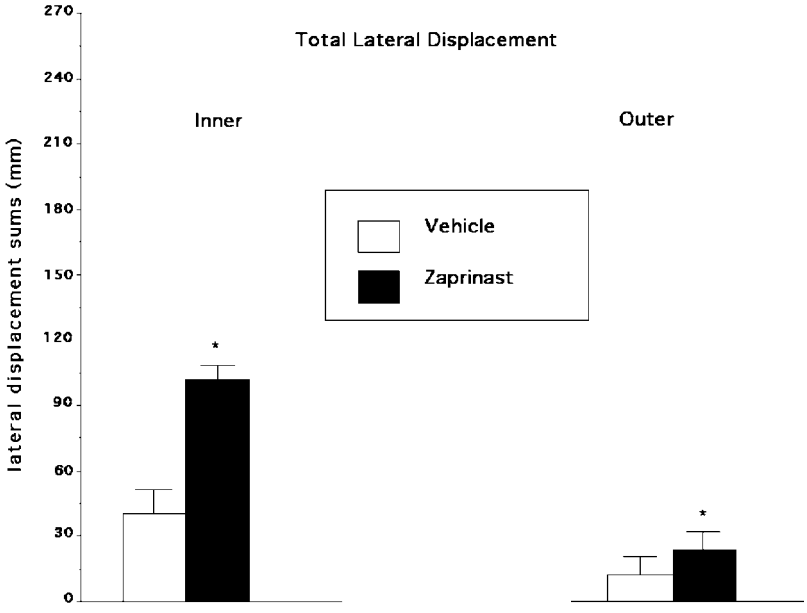

Figure 2 Total lateral displacement of hamsters that received vehicle (open bar; $n=16$) or zaprinast (diagonally striped bar; $n=16$). *indicates a significant difference ($P<0.05$) compared to vehicle.

Experiment 3: Zaprinast attenuates fluoxetine's inhibitory effects on lateral displacement of hamsters at the peak of behavioral estrus

Zaprinast administration to hamsters that had previously received fluoxetine early in behavioral estrus significantly increased total inner and outer lateral displacement responses compared to those produced by fluoxetine combined with later administration of vehicle. Total lateral displacement responses for both the inner ($F(3,15)=22.89$, $P<0.01$) and the outer ($F(3,15)=29.31$, $P<0.01$) zones were significantly different across groups (see Figure 3). Consistent with the results from Experiment 1, fluoxetine administration decreased total inner and outer scores of hamsters when administered early in behavioral estrus compared to vehicle administration. Zaprinast, when administered early in behavioral estrus, did not further increase total inner and outer scores, above that seen with vehicle administration. However, when fluoxetine administration was followed by zaprinast, total lateral displacement scores for both the inner and outer zones were no longer

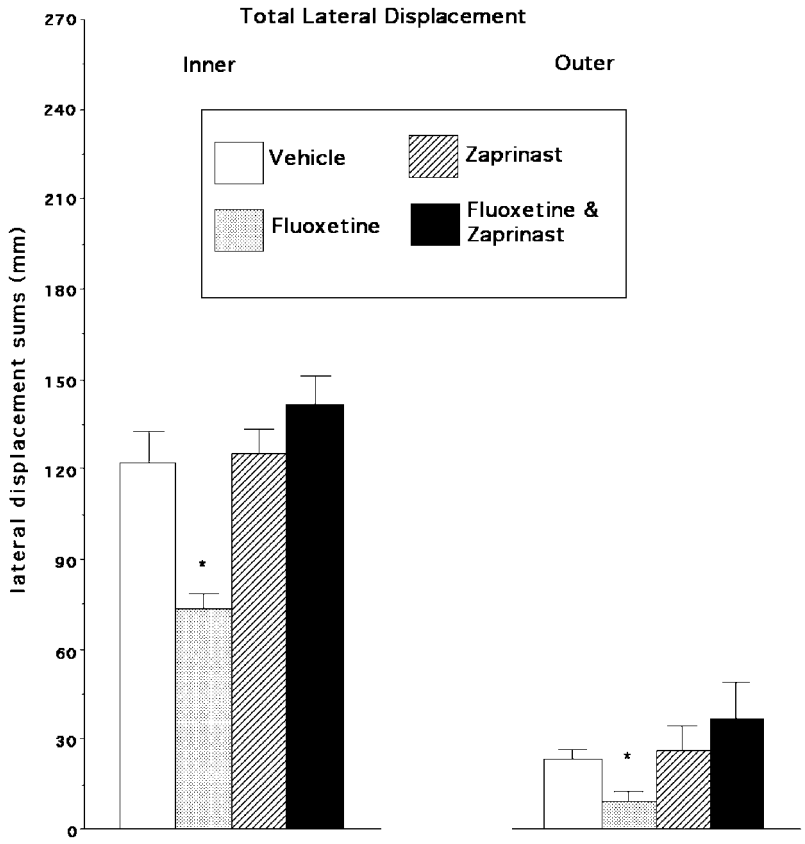

Figure 3 Total lateral displacement of hamsters that received vehicle/vehicle (open bar; $n = 16$), fluoxetine/vehicle (dotted bar; $n = 16$), vehicle/zaprinast (diagonally striped bar), or fluoxetine/zaprinast (horizontally striped bar). *indicates a significant difference ($P < 0.05$) compared to all other groups.

reduced. Instead, the total lateral displacement scores were reinstated to high levels that were comparable to those seen following only vehicle administration to hamsters at the peak of behavioral estrus.

DISCUSSION

The present results supported our hypothesis that administration of fluoxetine or zaprinast alone, or coadministration of fluoxetine and zaprinast, would alter the lateral displacement response of hamsters that are differentially sensitive to sexually relevant stimuli (because of testing at different time points in behavioral estrus). Fluoxetine administration significantly lowered total lateral displacement compared to that seen following vehicle administration to hamsters that were maximally sensitive to sexual stimuli (Experiment 1). Zaprinast significantly increased total lateral displacement scores compared to that seen following vehicle administration to hamsters that were less sensitive to sexual stimuli (Experiment 2). Deficits in lateral displacement produced by fluoxetine administration to hamsters, maximally sensitive at the peak of behavioral estrus, were overcome by coadministration of zaprinast, but not vehicle (Experiment 3). Together, these data indicate that fluoxetine can decrease the sexual response of hamsters that, because of cyclic fluctuations, show greater lateral displacement responses. Zaprinast can enhance the endogenous reductions in lateral displacement scores seen of hamsters late in behavioral estrus. Most importantly, zaprinast could override deficits in lateral displacement produced by fluoxetine administration to hamsters at the peak of behavioral estrus.

Our results confirm that SSRIs produce sexual dysfunction and extend the current literature to demonstrate that PDE inhibitors can overcome these effects. Previous research has demonstrated that SSRIs can induce sexual dysfunction in male rodents (Ahlenius *et al*, 1979; Taylor *et al*, 1996; Yells *et al*, 1995; Yells *et al*, 1994); however, few studies have investigated the effects of SSRIs on the sexual function of female rodents (Matuszczyk *et al*, 1998). As well, PDE inhibitors can facilitate sexual behavior of female rats. Ovariectomized, estrogen-treated rats administered a subthreshold dose of progesterone and a PDE inhibitor (1-methyl, 3-isobutylxanthine or theophylline) had enhanced lordosis responses compared to rats treated with estrogen and a subthreshold dose of progesterone alone (Beyer and Canchola, 1981). The present studies demonstrate novel findings using this animal model of female sexual response that the SSRI fluoxetine can induce sexual dysfunction and that sexual behavior of female hamsters can be facilitated with the administration of the PDE-5 inhibitor zaprinast. Further, the present data indicate that sexual dysfunction induced by fluoxetine can be ameliorated with the coadministration of zaprinast in the lateral displacement model.

Although the exact mechanism of SSRI's therapeutic effects on depression are not known, fluoxetine does have

effects on the serotonin system. It is well known that the serotonin system is important in the modulation of female sexual response. Activation of 5-HT_{1A} receptors generally inhibits lordosis of rats (Fernandez-Guasti *et al*, 1987; Gonzalez *et al*, 1997; Hebert *et al*, 1995). Long-term treatment with SSRIs enhances serotonin neurotransmission, and it is hypothesized that stimulation of 5-HT_{1A} receptors is associated with the antidepressant and anxiolytic effects of these drugs (Uphouse, 2000). Hence, it is possible that SSRI-induced sexual dysfunction is partly because of activation of $5HT_{1A}$ receptors. A better understanding of the neural substrates for female sexual behavior can be attained by examining the effects of antidepressant drugs on sexual responses using this model of lateral displacement. Such an approach may elucidate important neural substrates contributing to sexual dysfunction in women.

The data presented here are exciting as they suggest that zaprinast, a PDE-5 inhibitor, can attenuate deficits in sexual responses of female hamsters induced by fluoxetine, an SSRI. However, we must be cautious in our interpretation of the data. First, the model utilized in the present studies is a model of sexual response and sexual sensitivity, not one of sexual desire or motivation. Although it should be noted that people experiencing depression might initially experience a loss of sexual desire or motivation, treatment with SSRIs generally overcomes this ahedonia. However, the deficits in sexual response or sensitivity induced by SSRI treatment often negate the positive effects of SSRIs on sexual desire or motivation. The model utilized addresses this issue by examining the effects of a PDE-5 inhibitor to overcome deficits in sexual response caused specifically by SSRI administration. Second, generalizing data from a rodent model to humans is always difficult, but in this case even more so as hamsters are not representative of other rodents. For example, hamsters metabolize many drugs in a different manner than do other rodents (Brodie, 1964). In the present experiments, this criticism does not seem to apply as the drug dosages used were analogous to dosages used in previous studies with rats.

The neurochemical basis of the ability of PDE inhibitors to overcome deficits in sexual functioning induced by SSRIs is not yet fully understood. There is some evidence to suggest that PDE inhibitors may alter serotonin levels (Freitag *et al*, 1998). However, the exact interactions between PDE inhibitors and SSRIs that give rise to these effects are unknown. One hypothesis is that SSRIs may alter steroid metabolism enzymes (Griffin and Mellon, 1999) that are important for the formation of progestins, which are integral for the facilitation of sexual responses (Frye, 2001). It is possible that PDE inhibitors may also target these steroid metabolism enzymes; however, this is a subject of ongoing investigation in our laboratory.

In conclusion, the negative impact of SSRIs on sexual function is a major clinical problem, and the possibility to counteract such effects by PDE inhibitors is hence of considerable importance. To our knowledge, this is the first report that PDE inhibitors may antagonize negative effects of SSRIs on sexual responses of animals. This is important for two reasons. First, it encourages further clinical research regarding the possibility of PDE inhibitors to ameliorate SSRI-induced sexual dysfunction in women. Second, it provides a model by which these kinds of drug interactions can be investigated in animals.

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