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ORIGINAL INVESTIGATION

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Chronic fluoxetine inhibits sexual behavior in the male rat: reversal with oxytocin

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Abstract *Rationale:* Selective serotonin reuptake inhibitors, used widely in the treatment of depression, progressively inhibit sexual orgasm in many patients and induce a transient inhibition of sexual desire. *Objectives:* We attempted to model the effects of these drugs in sexually experienced male rats during tests of copulation in bilevel chambers. These chambers allow the study of both appetitive and consummatory sexual responses of male rats. *Methods:* Males were treated daily with fluoxetine hydrochloride (0, 1, 5, or 10 mg/kg) and tested for sexual behavior with receptive females at 4-day intervals. Rats were treated with oxytocin (200 ng/kg) or saline after ejaculations had decreased. *Results:* Fluoxetine decreased ejaculatory responses of male rats in a dose- and time-dependent fashion, but left the copulatory efficiency of the males intact. In contrast, conditioned level changing, a measure of appetitive sexual excitement, was inhibited following acute and chronic treatment with 10 mg/kg, although tolerance may have developed to the effect of 5 mg/kg. Subsequent administration of oxytocin restored the ejaculatory response but not the measure of sexual excitement to baseline levels. *Conclusions:* The reversal by oxytocin of the fluoxetine-induced deficit in ejaculations is consistent with the hypothesis that serotonin suppresses ejaculatory mechanisms by interrupting the action of oxytocin, which normally accompanies sexual behavior. Co-administration of oxytocin may help to alleviate the predominant sexual side effect of serotonin reuptake blockers.

Key words Sexual behavior · Ejaculation · Male rat · Drug · Serotonin · Neuropeptide

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Introduction

Fluoxetine, a selective serotonin reuptake inhibitor (SSRI) in widespread clinical use, induces anorgasmia and loss of sexual desire in humans (Crenshaw and Goldberg 1996). Clinical reports indicate orgasm dysfunction in up to 75% of patients (Herman et al. 1990; Zajecka et al. 1991; Patterson 1993) and hypoactive sexual desire in 20–40% (Solyom et al. 1990; Jacobsen 1992; Modell et al. 1997). In fact, fluoxetine has been shown to be an effective means of increasing ejaculation latency in premature ejaculation (Kara et al. 1996; Lee et al. 1996) and of decreasing sexual desire in certain paraphilias (Kafka 1991; Kafka and Prentky 1992; Greenberg et al. 1996). Similar observations have been made regarding other SSRIs, including paroxetine, sertraline, and fluvoxamine (Waldinger et al. 1994, 1997; Zohar et al. 1994; Hsu and Shen 1995; Mendels et al. 1995; Ludovico et al. 1996; Model et al. 1997). Despite the reports of fluoxetine-induced loss of sexual desire and delay of ejaculation or orgasm, erectile dysfunction is not as frequently observed with SSRIs as it is with tricyclic antidepressants (Balon et al. 1993; Shiavi and Segraves 1995; Crenshaw and Goldberg 1996). Better understanding of the role of serotonin in this specific pattern of sexual dysfunction would help to refine our understanding of the neurochemical basis of normal sexual behavior and serve as a basis for research to reduce the sexual side effects of SSRI treatment.

Both acute and chronic effects of fluoxetine on the sexual behavior of male rats have been examined. High doses of fluoxetine (10 mg/kg and 20 mg/kg, i.p.) have been reported to increase the post-ejaculatory intervals of male rats during their first ejaculatory series, increase the intromission frequency and ejaculation latencies of males during their last ejaculatory series prior to sexual exhaustion, and decrease the copulatory efficiency during the last series (Yells et al. 1994). A lower dose of 5 mg/kg produced similar effects only during the final ejaculatory series. In contrast, 4 weeks of daily fluoxetine treatment to sexually naive males (0.75 mg/kg/day,

i.p.) produced a progressive decrease in the acquisition of normal sexual performance, as indicated from a composite of measures, including increased intromission latencies, decreased numbers of intromissions, and a reduced frequency of ejaculation (Taylor et al. 1996). Chronic fluoxetine treatment did not alter the relative time that the males spent near sexually receptive versus nonreceptive females, suggesting that sexual motivation was not affected by this treatment. Although Taylor et al. used a dose of fluoxetine within the lower range of therapeutic value for humans, both fluoxetine and its active metabolite, norfluoxetine, clear blood plasma many times more quickly in rats than in humans (Stark and Wong 1985; Caccia et al. 1990). This necessitates the use of higher doses in the rat. In addition, the use of sexually naive males in that study precluded an analysis of the effect of fluoxetine on normal baseline rates of sexual behavior.

The mechanism by which chronically elevated levels of serotonin exert an inhibitory effect on sexual desire, ejaculation, or orgasm remains unclear. In humans, some success has been reported in treating SSRI-induced sexual dysfunction with indirect dopamine agonists such as amantadine or D-amphetamine (Balogh et al. 1992; Gitlin 1995), the α_2 adrenergic antagonist yohimbine (Hollander and McCarley 1992), or the mixed 5-$HT_{2A/2C}$/α_2 adrenergic antagonist mianserin (Aizenberg et al. 1997). Chronically elevated serotonin levels also change certain neuroendocrine systems, some of which may be involved directly in sexual desire and orgasm. In particular, chronic fluoxetine treatment alters the sensitivity of oxytocin neurons to different serotonin receptor agonists (Li et al. 1993a, 1993b, 1996). With regard to human sexual behavior, plasma levels of oxytocin rise during sexual stimulation in both men and women (Carmichael et al. 1987, 1994; Murphy et al. 1987, 1990). Systemic administration of oxytocin to male and female rats facilitates copulatory behaviors (Fjellstrom et al. 1968; Argiolas et al. 1985, 1986; Arletti et al. 1985, 1990, 1992; Stoneham et al. 1985; Moody et al. 1994), whereas oxytocin antagonists disrupt it (Argiolas et al. 1987, 1989). Given the direct influence of oxytocin in sexual behavior, these observations suggest that SSRIs could induce sexual dysfunction by interfering with the endogenous release of oxytocin. Administration of oxytocin exogenously may therefore compensate for its loss and serve to maintain the normal expression of sexual behavior during ongoing fluoxetine treatment. We tested this hypothesis in the present experiments.

Materials and methods

Animals

Male Long-Evans rats (300–500 g) were obtained from Charles River Canada, Inc., St. Constant, Québec. They were housed in pairs in plastic cages (36×26×19 cm) in a colony room maintained on a reversed 12 h:12 h light/dark cycle (lights off at 0800 hours) at approximately 21°C. Food and water were continuously available. Sexually experienced female Long-Evans rats, obtained from the same breeder, were used as stimulus partners in the experiment. The females had been ovariectomized bilaterally under ketamine/xylazine anesthesia and subsequently rendered sexually receptive by subcutaneous injections of estradiol benzoate (10 µg in sesame oil) 48 h and progesterone (500 µg in sesame oil) 4 h before all tests of sexual behavior were performed. All animal housing, handling, injections, and testing procedures conformed to the guidelines of the Canadian Council on Animal Care.

Drugs

Fluoxetine hydrochloride was purchased from Sigma (St. Louis, Mo.) and dissolved in distilled water to obtain four concentrations: 10.0 mg/ml, 5.0 mg/ml, 1.0 mg/ml, and 0.0 mg/ml (vehicle control). All drug concentrations were prepared once a week and stored at 4°C. Daily injections were delivered i.p. at 1.0 ml/kg body weight to obtain final doses of 10.0 mg/kg, 5.0 mg/kg, 1.0 mg/kg, and control. Fluoxetine was injected daily between 1500 hours and 1700 hours, except on testing days, when the males received injections 60 min before behavioral observations began. Oxytocin (Bachem, Sacramento, Calif.) was dissolved in physiological saline at a concentration of 0.001 mg/ml and stored at –20°C. The solution was warmed to room temperature immediately before use. Oxytocin (200 ng/kg) was injected i.p. 60 min before each test at a concentration of 0.2 ml/kg, as in Arletti et al. (1985, 1992).

Behavioral screening

All tests of sexual behavior took place in bilevel chambers, as described previously (Pfaus et al. 1990). Male rats placed into bilevel chambers for a 5-min adaptation period prior to the presentation of a sexually receptive female develop conditioned level changing, a behavior that has been used as a measure of anticipatory sexual excitement in previous studies of opioid and dopaminergic regulation of sexual behavior (Pfaus and Phillips 1991; van Furth et al. 1994; van Furth and van Ree 1996). The 24 females used as copulatory partners in these experiments were given at least ten preliminary trials with sexually experienced males in the bilevel chambers to acquire the full range of sexual behaviors, including high rates of solicitation, pacing, other proceptive behaviors, and lordosis. The males were allowed 1 week to adapt to the animal care facility before preliminary testing began. Prior to sexual contact, males were acclimated to the bilevel chambers for five 30-min sessions over 10 days. After this, each male was placed into the bilevel chamber for 5 min prior to the introduction of a sexually receptive female. Both rats were allowed to copulate for 30 min before the test was terminated. Screening tests continued for a total of eight 30-min sessions at 4-day intervals to provide the males with requisite sexual experience. The final three tests served as injection baselines during which the vehicle was administered to each male 60 min before each test. All noncopulators were discarded.

Procedure

Males were assigned randomly to one of the four groups (n=8–10 per group) and were tested for sexual behavior at 4-day intervals for a total of 11 trials, with the first fluoxetine test commencing 4 days after the last baseline test. Males continued to receive daily fluoxetine treatment on each of the three days between trials. Each test session consisted of the introduction of the male into the bilevel test chamber followed 5 min later by the introduction of the female. The pair was permitted to copulate freely for 30 min. A video camera recorded each session for later scoring. Following the final fluoxetine-alone test, the males in the four groups continued to receive daily injections of fluoxetine (or vehicle). The next four trials consisted of oxytocin or the saline vehicle being admin-

istered to each male using an A–B–B–A design; thus, the fluoxetine groups received oxytocin treatment on trials 1 and 4, and saline on trials 2 and 3, whereas the control group received only the saline vehicle. Daily fluoxetine or vehicle treatment was maintained throughout all four trials.

Data analyses

A scorer, blind to the animals' group membership, coded the videotapes using a real-time, computerized event recorder (Cabilio 1996). Appetitive level changes were scored when the male moved completely from one level to another, as defined by Mendelson and Pfaus (1989). This resulted in two appetitive measures, the total number of level changes (LCs) and the latency to the first level change (LCL). Copulatory behaviors consisted of mounts, intromissions, and ejaculations, and were scored for each male during successive ejaculatory series, as defined by Sachs and Barfield (1976). Latencies were calculated to the first mount (ML), intromission (IL) and ejaculation (EL) of the first ejaculatory series. Numbers of mounts without intromission (NM) and mounts with intromission (NI) were calculated for each ejaculatory series, and the total number of ejaculations (NE) were calculated for the entire test. Three secondary measures were calculated from these primary measures: the post-ejaculatory interval (PEI) was calculated as the time from the first ejaculation to the next intromission. The intromission ratio (IR) was calculated as the number of intromissions divided by the total frequency of both mounts and intromissions (IR=NI/NM+NI). The interintromission interval (III) was calculated as the ejaculation latency divided by the number of mounts with intromission (EL/NI). All latency and frequency data from the first ejaculatory series were used in the present analysis.

To study the acute effects of fluoxetine, the mean of the three baseline trials was subtracted from the results of first trial. The resulting difference scores were analyzed using a one-way multivariate analysis of variance (MANOVA) with Wilks' lambda criterion and using dosage (control, 1 mg/kg, 5 mg/kg, and 10 mg/kg of fluoxetine) as the single between-subjects factor. Univariate ANOVAs and stepdown analysis permitted assessment of the individual dependent variables. The dependent variables were the four behavioral frequencies (LC, NM, NI, and NE), the four latency measures (LCL, ML, IL, EL), and the three secondary variables (PEI, IR, and III).

With chronic fluoxetine treatment, increasing numbers of animals failed to exhibit all behaviors, obviating the latency and interval measures. Therefore, the five dependent variables which reflect frequency measures were selected for analysis of chronic fluoxetine treatment. For the omnibus tests of dose, time, and their interaction, each of the dependent variables formed a 4(dosage) times 14(trial) ANOVA design, with trial as a repeated measure. Significance tests on the repeated measure (time and the dosage × time interaction) were subjected to Greenhouse–Geisser correction for violations of sphericity. All the significance tests on repeated factors which appear below reflect the reduced degrees of freedom. To examine the time course of changes within each dependent variable, the first three fluoxetine trials, the middle three trials, and the final three trials were each averaged to produce a single mean score for that period. As before, analyses were then conducted on the differences from baseline. For each significant omnibus ANOVA, post-hoc comparisons of the experimental groups to the control group were made using protected one-tailed *t*-tests; differences were considered significant at $P<0.05$ (Keppel and Zedek 1989). One-tailed tests were used to gain statistical power in circumstances where only one direction of effect, e.g., a decrease in ejaculation frequency, is tested.

Finally, the two oxytocin and the two non-oxytocin sessions were each collapsed into single means for each dependent variable. The mean of the final fluoxetine trials was then subtracted from that score to produce the gain scores caused by oxytocin co-treatment. The gain scores were then analyzed by one-way ANOVA to detect differences from the fluoxetine-only trials. For each significant ANOVA, post-hoc comparisons of the experimental groups to the control group were made using protected *t*-tests, one- or two-tailed, depending on the hypothesized direction of effect; differences were significant at $P<0.05$.

Results

Of the original 37 copulating males in the study, 4 did not survive long-term fluoxetine treatment and an additional 2 males died during co-treatment with oxytocin. Data from those animals were removed retroactively from the chronic fluoxetine data set.

Acute effects of fluoxetine

The types of male rat sexual behavior observed after acute administration of fluoxetine are shown in Table 1. The MANOVA on the difference from baseline scores indicated a significant main effect of dose, $F(33, 62.57)=1.62$, $P<0.05$. Univariate analyses on the difference scores showed that the multivariate effect was significantly related to changes in three of the dependent variables: LCL, NE, and PEI – Fs(3,31)=3.38, 3.41, and 3.78; Ps<0.04, 0.04, and 0.03, respectively. A trend toward significance was also found for LC, $F(3,31)=2.52$, $P<0.08$. Due to the known correlations between the various sexual behaviors in male rats (Pfaus et al. 1990), the effect of overlapping variance was eliminated by entering each of the dependent variables into a stepdown analysis. Variables were ordered a priori by the sequence in which they occur during copulatory bouts (e.g., level changes precede mounting, intromissions precede ejaculation, etc.). Stepdown analysis indicated that significant and independent contributions were made by two variables: LCL, $F(3,31)=3.40$, $P<0.04$, and PEI, $F(3,21)=6.53$, $P<0.004$. Although the NE remained the next strongest effect, it was no longer statistically significant, $F(3,26)=1.66$, n.s. Relative to the control group, males in the 10-mg/kg dose group exhibited a significant increase in LCL, $t(31)=4.69$, $P<0.02$, and a significant increase in the PEI, $t(31)=5.91$, $P<0.003$. Neither the 5-mg/kg nor the 1-mg/kg dose groups differed significantly from the control group on these measures.

Chronic effects of fluoxetine

Weight loss

The males showed a strong, dose-dependent decrease in body weight throughout fluoxetine treatment which reflected an inability to gain weight relative to the control group (Fig. 1). The weight loss appeared to occur throughout the first month of treatment, after which the males in the two higher dose groups appeared to gain weight at a slow rate. The ANOVA detected significant main effects of dose, $F(3,27)=5.02$, $P<0.008$; time, $F(3.71,100.23)=51.00$, $P<0.0001$; and their interaction, $F(11.14,100.23)=14.15$, $P<0.0001$. Follow-up analyses

Table 1 Male rat sexual behavior following acute administration of fluoxetine (*LCL* level change latency, *LC* number of level changes, *ML* mount latency, *NM* number of mounts, *IL* intromission latency, *NI* number of intromissions, *IR* intromission ratio, *EL* ejaculation latency, *NE* number of ejaculations, *III* interintromission interval, *PEI* postejaculatory interval). *LC, NM, NI,* and *NE* are expressed as mean frequency counts (±SEM). *LCL, ML, IL, EL, III,* and *PEI* are expressed as mean seconds (±SEM). IR is expressed as a mean ratio (±SEM). All behaviors were calculated for the first ejaculatory series. Univariate and stepdown Fs reflect difference scores from baseline performance

Behavior	Dose of fluoxetine				Univariate $F(3,31)$	Stepdown F
	Vehicle (n=9)	(1 mg/kg) (n=8)	(5 mg/kg) (n=10)	(10 mg/kg) (n=8)		
LCL	16.7 (3.43)	17.2 (5.08)	17.0 (3.60)	41.4 (12.9)†	3.38*	$F(3.31)=3.38$*
LC	10.2 (1.24)	8.38 (1.42)	5.60 (0.60)	5.63 (1.32)	2.52	$F(3,30)=1.47$
ML	5.89 (1.70)	7.25 (1.82)	6.50 (2.05)	9.00 (1.87)	0.62	$F(3,29)=0.87$
NM	11.1 (2.50)	5.25 (1.84)	6.70 (2.53)	4.00 (1.00)	0.75	$F(3.28)=0.76$
IL	20.9 (6.25)	16.5 (4.33)	14.1 (2.68)	12.9 (2.07)	1.61	$F(3,27)=0.84$
NI	10.1 (0.93)	9.38 (1.13)	8.20 (1.01)	5.88 (0.67)	1.43	$F(3,26)=0.98$
IR	0.508 (0.057)	0.718 (0.072)	0.669 (0.080)	0.638 (0.067)	1.88	$F(3,25)=1.15$
EL	234 (32.0)	196 (34.4)	180 (32.8)	145 (28.5)	1.67	$F(3,24)=0.23$
NE	2.89 (0.20)	3.38 (0.18)	3.30 (0.21)	2.63 (0.18)	3.41*	$F(3,23)=1.66$
III	24.2 (3.39)	20.0 (2.13)	22.8 (4.80)	23.2 (2.82)	1.06	$F(3,22)=0.21$
PEI	318 (13.2)	313 (16.5)	357 (33.7)	441 (33.1)***	3.78*	$F(3,21)=6.53$**

*P<0.05
**P<0.01
***P<0.05 from vehicle

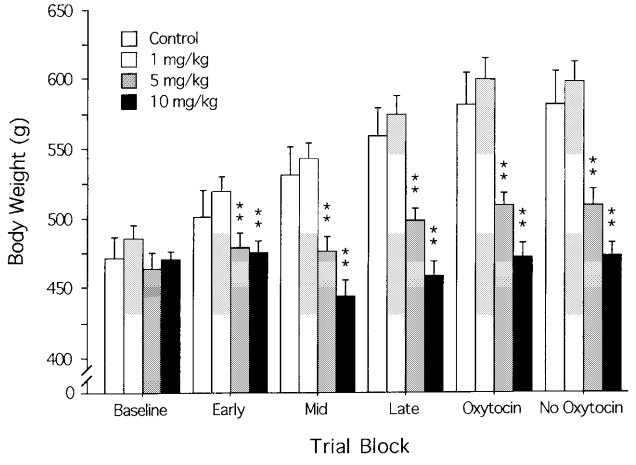

Fig. 1 Body weight of males in each dose group at baseline, as a function of chronic fluoxetine treatment, and following co-administration of oxytocin. Data are means±SEM. **P<0.01 from controls. Each animal's score represents the mean body weight on three consecutive test days during each phase of the experiment, except following oxytocin treatment, during which there are only two test days

indicated significant group differences during the early, mid-way, and late portions of the experiment, $F(3,27)=15.02$, 29.04, and 29.17, respectively; all Ps<0.0001. Relative to the control group, males in the 10-mg/kg and 5-mg/kg dose groups had significantly decreased body weight during each of the three time periods: 10-mg/kg group, $t(27)=$–9.88, –15.65, and –15.31, all Ps<0.0005 (one-tailed); 5-mg/kg group, $t(27)=$–7.23, –10.86, and –10.49, all Ps<0.0005. The weights of males in the 1-mg/kg dose group were not significantly different from those of the control group during any time period, $t(27)=1.74$, –0.68, and 0.18, n.s. (one-tailed).

Appetitive sexual excitement

A dose-dependent decrease in LC was apparent during the early phase of fluoxetine treatment (Fig. 2, top). However, some tolerance appeared to accrue to this effect with chronic treatment, especially at the 5-mg/kg dose. Analysis of LC detected significant main effects of dosage, $F(3,27)=7.72$, P<0.001, and the dose by time interaction, $F(23.17,208.51)=2.03$, P<0.005. Testing the effects of dose within each time phase revealed significant differences between groups during all three periods, Fs(3,27)=7.544, 24.04, and 6.125, Ps<0.0008, 0.0001, and 0.0026. The LCs of the 10-mg/kg group were decreased significantly from control levels during each time period, ts(27)=–9.322, –14.852, and –8.218, all Ps<0.0005 (one-tailed). The 5-mg/kg group showed a decrease relative to controls during the early phase, $t(27)=$–4.362, P<0.02 (one-tailed), but not during the midway or late phases, t s(27)=0.626 and –0.760, respectively, n.s. (one-tailed).

Ejaculation frequency

Despite the fact that all males copulated without any significant disruption of mounts or intromissions, the total number of ejaculations decreased in a dose- and time-dependent fashion. There was a significant dose times time interaction, $F(22.96,206.62)=1.68$, P<0.04, indicating that the different doses caused different changes over time. As shown in Fig. 2 (bottom), the groups differed only marginally during the early time phase, $F(3,27)=2.53$, P<0.08. However, significant differences were detected for the NE during both the mid- and late phases, Fs(3,27)=5.06 and 4.53, Ps<0.007 and 0.02, respectively. Relative to the control group during

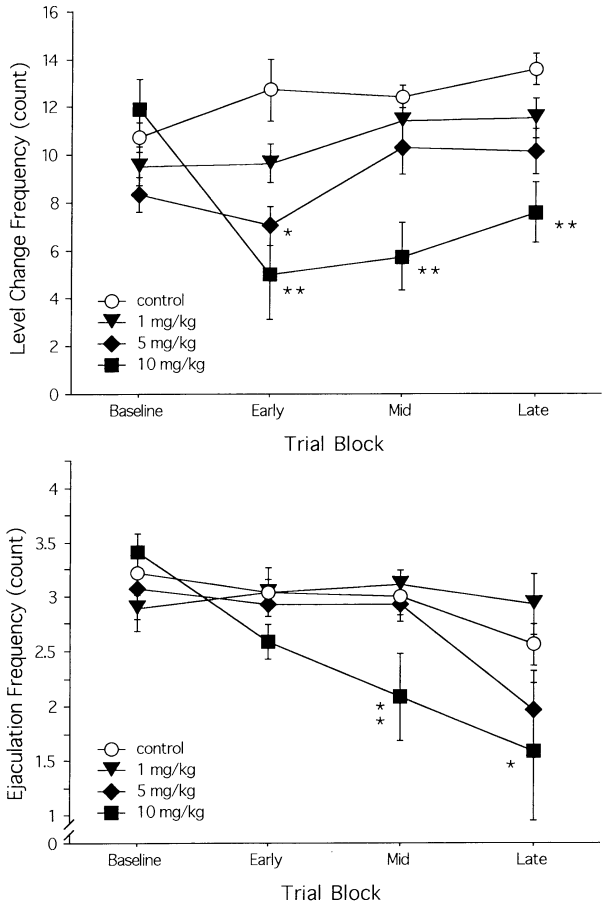

Fig. 2 Conditioned level changes (*top*) and ejaculation frequencies (*bottom*) at baseline and during chronic fluoxetine treatment. Data are means±SEM. Each animal's score represents the mean number of level changes exhibited before the introduction of the stimulus female on three consecutive trials, or the mean number of ejaculations exhibited on three consecutive trials. Analyses were conducted on differences from baseline scores. **P*<0.05, ***P*<0.01 from controls

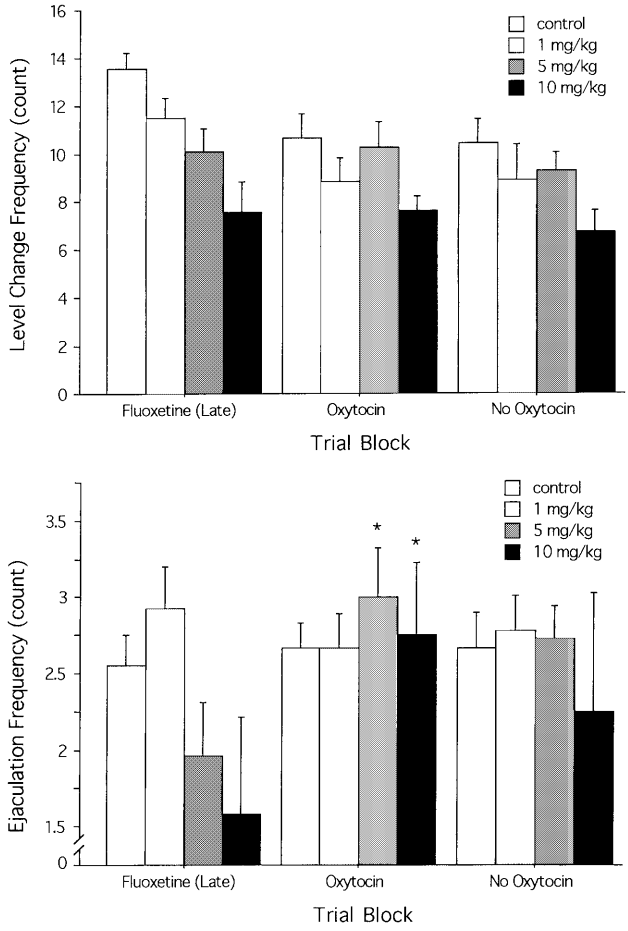

Fig. 3 Effect of oxytocin or vehicle on the number of conditioned level changes (*top*) or ejaculations (*bottom*) shown by male rats treated with chronic fluoxetine. Data are means±SEM. Late phase fluoxetine data from Fig. 2 are included for comparison. **P*<0.05 from late treatment with fluoxetine

these two testing phases, males in the 10-mg/kg group had significantly decreased NEs, $t(27)=-5.54$ and -4.21, Ps<0.005 and 0.03 (one-tailed). Although the 5-mg/kg group decreased from baseline relative to controls during the late phase, this effect was not statistically significant, $t(16)=2.04$, 1.92, P <0.04, (one-tailed).

Effects of co-treatment with oxytocin

Weight loss

The analysis of gain scores indicated that the fluoxetine-induced group differences in body weight did not change when oxytocin co-treatment was added to fluoxetine administration, $F(3, 27)=2.33$, n.s., or when oxytocin treatment was discontinued, $F(3, 27)=0.13$, n.s. As indicated in Fig. 1, the groups continued to differ by dose.

Appetitive sexual excitement

There were no significant differences in gain scores with oxytocin co-treatment on measures of LC, $F(3,27)=2.35$, n.s., or with its removal, $F(3,27)=0.29$, n.s. (Fig. 3, top). The overall group differences in LC persisted when oxytocin was added to the treatment, $F(3,27)=3.80$, P<0.03, and when it was removed, $F(3,27)=3.41$, P<0.04. Specifically, the 10-mg/kg group continued to show fewer level changes than the control group in both cases, ts(27)=2.25 and 2.52, Ps<0.03 and 0.02, respectively.

Ejaculation frequency

Oxytocin treatment produced a significant increase in the NE relative to controls (Fig. 3, bottom). Analysis of gain scores indicated a differential effect on groups, $F(3,27)=4.29$, P<0.02, with both the 10-mg/kg and 5-mg/kg groups significantly increasing relative to the late phase, $t(27)=4.31$ and 3.86, Ps<0.03 and 0.02, re-

spectively, (one-tailed). These dose groups no longer differed significantly from controls on NE after oxytocin co-treatment, $F(3,27)=1.14$, n.s. This improvement appeared long lived, as the removal of oxytocin was not associated with the return of any significant group difference in NE, $F(3,27)=1.14$, n.s., or in gain scores from the oxytocin treatments, $F(3, 27)=0.62$, n.s.

Discussion

Chronic administration of fluoxetine produced a dynamic decline in certain appetitive and consummatory aspects of sexual behavior in sexually active male rats. Doses of 5 mg/kg and 10 mg/kg, which are associated with acute antidepressant activity in animal models of depression (Muscat et al. 1992), decreased body weight, decreased appetitive sexual behavior, and decreased ejaculation frequency, but did not alter other copulatory behaviors significantly. The effects on ejaculation appeared to follow relatively linear dose- and time-response relationships, with the greatest effect observed at 10 mg/kg. Although fluoxetine produced a rapid decrease in the measure of appetitive excitement (level changing), tolerance appeared to accrue to the effects of the 5-mg/kg dose. Both of these effects on sexual behavior occurred without a significant decrease in the ability of males to gain intromission.

Oxytocin produced a long-lasting reversal of the decrease in ejaculation frequency produced by chronic fluoxetine treatment. This effect was specific to ejaculation, as no effect of oxytocin was observed on appetitive level changing. Previous studies have shown that chronic fluoxetine treatment decreases the affinity of serotonin receptor subtypes found on oxytocin-synthesizing neurons (Li et al. 1993a, b, 1996), which might alter patterns of oxytocin release. However, it is not known whether the ameliorative effect of oxytocin in the present experiment reflects an action at oxytocin receptors in the brain or in the periphery. Oxytocin receptors exist throughout the dorsal horn of the spinal cord and within the male reproductive tract (Reiter et al. 1994; Ivell et al. 1997; Tribollet et al. 1997). Thus, systemically administered oxytocin could induce ejaculation by stimulating either sympathetic outflow or smooth muscle cells of the reproductive tract directly. Indeed, oxytocin appears to be released in a pulsatile fashion from the posterior pituitary as males reach the threshold for ejaculation (Ivell et al. 1997), and oxytocin injections to the cartoid artery of male rats stimulate ejaculation (Stoneham et al. 1985). However, the ability of the dopamine agonist apomorphine to stimulate ejaculation in rats can be blocked by intracerebroventricular infusions of an oxytocin antagonist (Argiolas et al. 1989), suggesting that central actions of oxytocin may facilitate ejaculation.

Unfortunately, chronic administration of the 10 mg/kg dose into the later phase of testing was lethal for several rats. The LD_{50} (lethal dose for 50% of animals) following oral administration of acute fluoxetine to rats is 452 mg/kg (Stark and Wong 1985). However, we have subsequently found no mortality if daily doses of 10 mg/kg of fluoxetine are administered at the end, rather than the beginning of the dark circadian cycle (Wright and Pfaus, unpublished data). We have also found that 10 mg/kg of fluoxetine produces conditioned taste aversions (unpublished results), suggesting that the increased mortality may have been caused by starvation. Doses as low as 2 mg/kg have been shown to induce a conditioned taste aversion to a novel sucrose solution (Prendergast et al. 1996). Rats tend to eat the largest meal of the day at the beginning of the dark cycle, and prior treatment with fluoxetine may have induced an aversion in some rats to their normal diet. Nevertheless, sickness alone is not sufficient to explain the disruption of sexual behavior. First, this disruption was selective to appetitive sexual excitement and ejaculation; other aspects of copulation were not affected. Second, the ameliorative effect of oxytocin on ejaculation occurred quickly despite these animals continuing the chronic fluoxetine regimen.

The disruption of sexual activity and body weight produced by fluoxetine in rats is generally analogous to that reported in humans (Crenshaw and Goldberg 1996). The dose dependence is also reminiscent of its effects in humans, and lowering the dose or using drug holidays are used by some individuals to combat the sexual effects (Patterson 1993; Rothschild 1995). These results are also consistent with previous reports of the acute effect of fluoxetine on the sexual behavior of male rats (Yells et al. 1994; Taylor et al. 1996). Yells et al. reported a significant increase in the final ejaculation latency prior to sexual exhaustion following a single administration of 5, 10, or 20 mg/kg. This study also reported a significant increase in the PEIs of successive ejaculatory series following the two higher doses. Although the first exposure of our males to fluoxetine produced a dose-dependent increase in successive PEIs, we did not detect significant effects on the ejaculation latencies. It is possible that strain differences or differences in the amount of prior sexual experience could account for these minor discrepancies. Similarly, Taylor et al. (1996) reported increased intromission latencies, interintromission intervals, and decreased frequency of ejaculation following chronic administration of 0.75 mg/kg to sexually naive males. Although we did not observe any effect of 1 mg/kg fluoxetine on sexual behavior, the sexually naive males used in the Taylor study may have been more sensitive to the effects of fluoxetine than the sexually experienced males used in our study. Taylor et al. also reported no effect of chronic fluoxetine on measures of partner preference, which led to the conclusion that chronic fluoxetine affects copulatory behaviors but not sexual motivation.

A recent study of the effects of acute and chronic fluoxetine treatment (10 mg/kg/day for up to 3 weeks) on the sexual behavior of female rats reported significantly reduced lordosis quotients in both intact rats and ovariectomized rats primed with estradiol and progesterone, but no decrease in partner preference and no disruption

of estrous cyclicity in the intact rats (Matuszczyk et al. 1998). It would thus appear that different types of appetitive sexual behavior might be affected by fluoxetine in different ways.

In summary, our results suggest that chronic fluoxetine treatment inhibits ejaculation in male rats in part by altering normal oxytocin transmission. The rapid amelioration of this effect by a low dose of oxytocin may represent a useful approach to managing this side effect of fluoxetine or other SSRIs.

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