Pharmacology Biochemistry and Behavior, Vol. 66, No. 2, pp. 337–342, 2000

0091-3057/00/$–see front matter

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PII S0091-3057(00)00191-X

Multiple Ejaculations and Chronic Fluoxetine: Effects on Male Rat Copulatory Behavior

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Received 16 April 1999; Revised 11 October 1999; Accepted 28 October 1999

WIESELER FRANK, J. L., S. E. HENDRICKS AND C. H. OLSON. *Multiple ejaculations and chronic fluoxetine: effects on male rat copulatory behavior.* PHARMACOL BIOCHEM BEHAV **66**(2) 337–342, 2000.—Male rats were treated with fluoxetine (FLX) or vehicle daily for 14 days and copulatory behavior tested on day 15. Rats were either mated to three ejaculations or to sexual exhaustion. Both standard measures and the mount bout analysis were used to evaluate the effects of the chronic FLX on male rat copulatory behavior. Only 56.25% of the animals treated with FLX achieved three ejaculations. FLX inhibited the consumatory aspect of male sexual behavior, especially the ability to achieve three ejaculations, but there was no effect on the propensity of the male to pursue the female. These differences were observed for the first three ejaculations. Analysis of the last three ejaculations in those animals that mated to exhaustion did not reveal an effect of FLX. The behavioral pattern of FLX-treated animals during the first three ejaculations resembled that observed during the last three ejaculatory series in the vehicle-treated animals that mated to exhaustion. The results are discussed in terms of the serotonergic effects on male rat sexual behavior. © 2000 Elsevier Science Inc.

Sexual behavior Fluoxetine Serotonin Ejaculation

FLUOXETINE (FLX) is a selective serotonergic reuptake inhibitor (SSRI) commonly used as an antidepressant, and less frequently as an anxiolytic. Patients treated with FLX have reported various types of sexual dysfunction [for a review, see (16)]. In men, the most commonly reported problem is delayed ejaculation or an inability to ejaculate, and some report reduced libido (3,6,13–15,23,25).

In male rats, acute administration of FLX results in an inhibition of sexual behavior evidenced by prolonged ejaculation latency and/or by increased number of mounts and/or intromissions exhibited prior to ejaculation (4,35–37). Yells et al. (36) used the mount bout analysis as an additional assessment of the effects of FLX on male rat sexual behavior. The mount bout begins when the male rat orients towards the female and ends when he loses interest. Within the mount bout interval, the amount of time the animal spends orienting towards and pursuing the female, and genital grooming is measured and analyzed. The mount bout analysis includes not only those measures recorded during the mount bout interval, but also the time the male spends away from the female (31). Acute administration of FLX increased the intermount bout intervals and time outs. Additionally, genital groooming was increased in FLX treated rats (36).

The antidepressant effects of FLX are typically realized after 2–4 weeks of treatment. Thus, the effects of chronic administration of the drug is of interest from both theoretical and practical perspectives. Taylor et al. (32) investigated the effects of chronic administration of FLX (0.75 mg/kg; 28 days) on social behavior and copulation. They reported that FLX had no effect on the propensity of the male rat to be near the female rat; however, the copulatory pattern was altered in that FLX-treated rats exhibited longer latencies to intromission and reduced ejaculation frequencies. Vega Matuszcyk et al. (34) reported that subchronic administration of FLX (10 mg/kg; 13 and 28 days) inhibited the copulatory pattern by increasing latency to ejaculation and increasing the frequency of mounts. Further, they reported that the FLX reduced the apparent motivation of the male rat to pursue an estrous female based on the amount of time the male spent near the female rat. Taken together, these two studies are consistent with the patient data in that sexual behavior was inhibited; however the effects on the apparent motivation of male rat to pursue the female are inconclusive.

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The purpose of the current study was to address the questions of how chronic administration of FLX affects male rat copulatory behavior, and if the male rat is a suitable model for the effects of SSRIs and similar drugs on human male sexual behavior.

METHOD

Animals

Male and female Sprague–Dawley rats, 70–100 days old, were housed three per stainless-steel wire mesh cage (45 × 25 × 20 cm). Female rats were ovariectomized under sodium pentobarbital (IP; 50 mg/kg) and used as stimulus animals for sexual screening and testing. Standard laboratory conditions were maintained on a reverse light cycle (lights on 2300–1100 h), and ambient temperature maintained at 23°C. Standard laboratory diet and tap water were available ad lib.

Copulatory Screening and Experimental Testing

Male rats were screened for sexual activity prior to experimental testing. For screening male rats were placed in glass aquaria (31 × 33 × 76 cm) with corncob bedding and allowed a 10 min adaptation period. An ovariectomized female rat induced into estrus was then introduced into the aquarium. Estrus was induced via IM injections of 10 μg estradiol benzoate 48 h and 500 μg progesterone 5 h, per rat, prior to testing; hormones were dissolved in vegetable oil. Only those females demonstrating high levels of proceptive and receptive behaviors were used in testing. Screening tests lasted for 30 min or until the first intromission after an ejaculation. Males were included in the study if they ejaculated in each of the three weekly screening tests. Screening and testing were conducted under red lighting during the dark portion of the light:dark cycle.

Behavior Testing

Male rats were randomly assigned to either the drug group or a control group, and then further assigned to one of two behavioral conditions: three ejaculations, or sexual exhaustion. Behavior was recorded using The Observer 3.0 computer package (28). Standard measures of the male copulatory pattern included frequency and latency of mounts, intromissions, and ejaculations, and the post ejaculatory interval (PEI). PEI duration was determined as the time from ejaculation to the first intromission following that ejaculation. The measures considered within the mount bout analysis were the duration of the mount bout and intermount bout interval, time spent autogrooming, time spent away from the female, and mount and intromission frequency per mount bout (31). Sexual exhaustion was defined as 30 min with no mating.

Drug Treatment

Fluoxetine HCl (Eli Lilly Co., Indianapolis, IN) was dissolved in distilled water. Animals received IP injections of either distilled water (control group) or 10 mg/kg fluoxetine (drug group) daily for 14 days. Behavioral testing took place on day 15.

Statistical Analysis

Cochran's Q statistic was used to evaluate the percentage of animals ejaculating three times between treatment groups. The chi-square statistic was used to test the difference between drug and water treatment and the frequency of ejaculation in those that mated to exhaustion.

A two-way repeated-measures analysis of variance was used to evaluate the differences between groups across ejaculatory series for each of the behavioral measures. These measures were analyzed across the first three ejaculatory series of animals that exhibited at least three ejaculations. Behavior was then analyzed across the first ejaculatory series and last three ejaculatory series in those animals allowed to mate to sexual exhaustion. Within these analyses, drug treatment (FLX vs. control) was treated as a between-subjects variable, and each sequential ejaculatory series was treated as a within-subjects variable. When appropriate, post hoc analyses were carried out using the Tukey's Honestly Significant Difference test.

RESULTS

Of the 16 animals treated with FLX, 25% ($n = 4$) did not ejaculate and 56.25% ($n = 9$) ejaculated three times, compared to 100% of the 16 control animals ejaculating three times (Table 1). The difference between FLX treatment and control was significant, $Q = 7.00$, $p < 0.01$.

Animals That Exhibited Three Ejaculations

Further analyses were conducted on those rats that exhibited at least three ejaculations. The FLX by ejaculatory sequence interaction for mounts per ejaculation approached a significant level, $F(2, 46) = 3.161$, $p = 0.052$ (Fig. 1). Although the statistic did not reach a significant level, the pattern of data prompted further analysis. Simple effects analysis showed that FLX increased the frequency of mounts in the third ejaculatory series compared to control. The main effect for ejaculatory sequence on the frequency of mounts was significant, $F(2, 46) = 5.771$, $p < 0.01$. Post hoc analysis showed that the frequency of mounts without intromission increased with each ejaculation (data not shown).

There was a significant FLX by ejaculatory sequence interaction for the frequency of mounts with intromission per ejaculation, $F(2, 26) = 3.792$, $p < 0.05$ (Fig. 1), and on latency to ejaculation, $F(2, 46) = 4.144$, $p < 0.05$ (Fig. 1). Simple effects analysis showed that FLX increased the frequency of mounts with intromissions relative to control in the first and third ejaculatory sequences and latency to ejaculation in the third ejaculatory sequence.

There were significant main effects for ejaculatory sequence on the frequency of mount bouts per ejaculation, $F(2, 46) = 22.222$, $p < 0.001$; on the duration of mount bouts, $F(2, 46) = 26.698$, $p < 0.001$; on the duration of grooming, $F(2, 46) = 26.369$, $p < 0.0001$. In the first ejaculatory sequence, the number of mount bouts was the highest followed by the second ejaculatory sequence having the fewest and the third having slightly more (ns) than the second. The mount bout duration

TABLE 1

PERCENTAGE OF ANIMALS ACHIEVING 1, 2, OR 3 EJACULATIONS AFTER CHRONIC TREATMENT WITH FLUOXETINE OR VEHICLE CONTROL

	Ejaculation		
	1	2	3
Fluoxetine	75%	75%	56.25*
Vehicle	100%	100%	100%

*$p < 0.05$, compared to vehicle control.

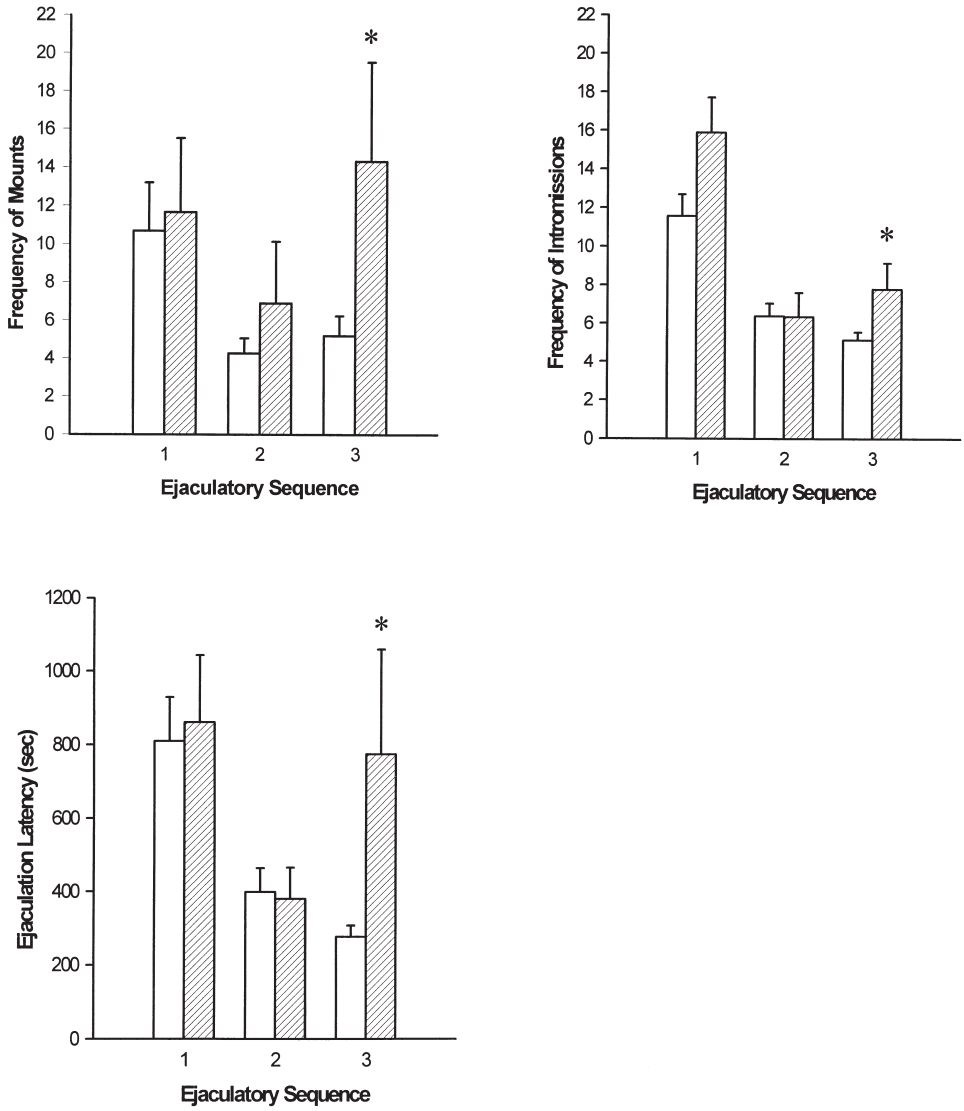

FIG. 1. Mean ± SEM (FLX condition, $n = 9$; vehicle control, $n = 16$) among the first three ejaculatory sequences for mount frequency per ejaculation, intromission frequency per ejaculation, and ejaculation latency. The open bars reflect the behavior of the control group and the shaded bars reflect the behavior of the group administered FLX. The symbols above the bars reflect differences between FLX and control groups within the ejaculatory sequence; $*p < 0.05$.

increased significantly with each ejaculation, and the duration of grooming followed the same pattern.

FLX significantly, $F(1, 25) = 5.082$, $p < 0.05$ (Fig. 2) reduced the PEI across ejaculations compared to control group. The main effect for ejaculatory sequence on PEI was significant, $F(1, 25) = 118.892$, $p < 0.001$. PEI duration increased after the second ejaculation when compared to the first. The score of one of the FLX animals was found to be an outlier (greater than 2 standard deviations from the mean) within the group and was excluded from the analysis.

Animals Mated to Sexual Exhaustion

The second set of analyses was conducted across the first ejaculatory series and last three ejaculatory series for those animals allowed to mate to sexual exhaustion. A total of 16 animals were tested to sexual exhaustion, FLX ($n = 8$) and vehicle control ($n = 8$). Of the eight in FLX group, two did not achieve three ejaculations. The chi-square analysis was used to evaluate the difference in ejaculation frequency, and did not reveal a significant difference between the groups.

The main effect for ejaculatory sequence on mount bout duration was significant, $F(3, 36) = 39.339$, $p < 0.001$. The last three ejaculatory sequences showed a progressive increase in mount bout duration with each ejaculation. The last three ejaculatory sequences showed shorter groom time duration as whole than the first ejaculatory sequence, $F(3, 36) = 5.224$, $p < 0.005$. The main effect for ejaculatory sequence on PEI was significant, $F(2, 22) = 17.250$, $p < 0.001$. The duration of PEI increased with each subsequent ejaculation. The main effect

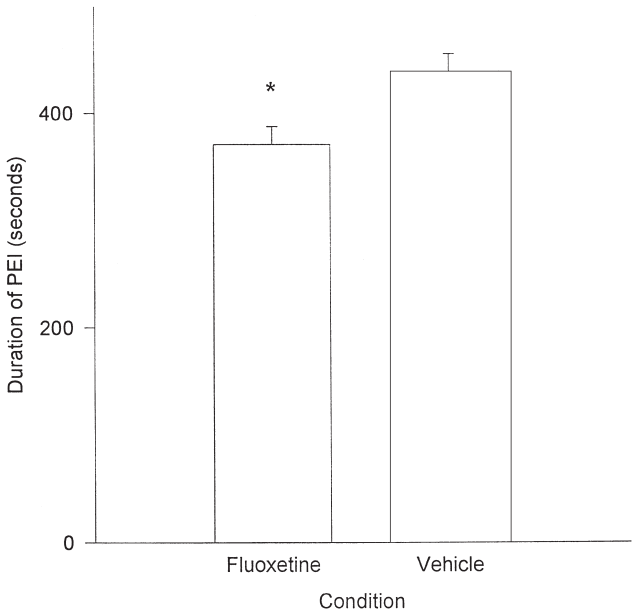

FIG. 2. Effect of chronic FLX on PEI across the first two ejaculatory series (mean ± SEM). Chronic FLX resulted in reduced PEI (fluoxetine treatment, $n = 9$; vehicle control, $n = 16$); $p < 0.05$.

for FLX on PEI approached significance, $F(1, 11) = 4.109$, $p = 0.07$. The mean of the FLX group was less than the mean calculated for the control group.

DISCUSSION

The present study provides further evidence for the inhibitory effects of chronic FLX treatment on male rat sexual behavior, and provides a more thorough analysis of the male rat copulatory pattern across ejaculatory series than is typically provided. The most notable finding from this study is that, of the animals treated with FLX, almost half did not achieve three ejaculations. The effects of FLX on the other parameters of the copulatory pattern were evident when the behavior was analyzed for those rats achieving three ejaculations. Fewer differences between FLX and the vehicle control group were observed among the behavioral parameters when the last three ejaculations were analyzed. It must be kept in mind that when considering these data, the animals presumably most affected by the FLX were those that did not achieve three ejaculations and were excluded from these analyses.

Consistent with previous findings of both acute and chronic treatment studies, there was no difference between FLX and control groups with respect to exhibiting one ejaculation (34,37). In addition, only 56.25% of the animals in the current study achieved three ejaculations. Even if the male rats did not achieve three ejaculations, they still pursued the female and attempted to mount, with many of them achieving up to two ejaculations. Taylor et al. (32) also reported a difference between chronic FLX-treated animals and control animals with respect to frequency of ejaculation. Animals treated with FLX ejaculated less often compared to vehicle control animals.

In the present study, chronic FLX treatment increased the frequency of mounts without intromission, mounts with intromission and latency to ejaculation in the third ejaculatory series. This is consistent with results from studies evaluating acute administration of FLX. This pattern of increasing mounts, with and without intromission, and increasing ejaculation latency is also similar to the pattern observed during the last three ejaculatory series prior to sexual exhaustion in untreated animals (2). When an animal is mated to sexual exhaustion, the sexual pattern is characterized by progressively fewer mounts, with and without intromission, and shorter latencies to ejaculation across the first three to four ejaculations. This pattern changes during the last three to four ejaculations preceding sexual exhaustion, and is characterized by an increased frequency of mounts, with and without intromission, and latency to ejaculation.

In FLX-treated animals, the increase in mounts without intromissions may be the result of a drug-induced inability to complete an intromission. FLX may be altering the sensory information received, directly or indirectly, with each attempted mount. The role of sensory input received through mounts has been shown to be critical in the male's ability to achieve intromission (1,7,31). The increase in intromission frequency in the the third ejaculatory series in the FLX group compared to control may be the result of increased interintromission intervals caused by altered sensory stimulation. Animals treated with FLX, including those that did not achieve three ejaculations, appeared to struggle to complete an intromission. When they did complete an intromission, the intervals between mounts with intromissions were longer than in those animals treated with vehicle control. It has been shown that longer interintromission intervals inforced by limiting the male's access to take estrous females increases intromission frequency prior to ejaculation and prolongs ejaculation latency (5,11,12). It is also possible that FLX is contributing to these effects directly.

An additional difference between the previous reports with acute administration of FLX and the results of the current study with chronic administration of FLX is the effect on the PEI. Yells et al. (36) reported prolonged PEI after acute administration with 10 and 20 mg/kg in the first ejaculatory sequence, and with 5, 10, and 20 mg/kg of FLX in the last ejaculatory sequence of sexually exhausted animals. Other studies have reported results consistent with Yells et al. (36) or no change in PEI (37). Our results revealed a shortened PEI in response to chronic FLX treatments when compared to vehicle control data. This finding has not been reported before.

Acute administration of FLX has been found to affect male copulatory motivation as measured by mount bout analysis. Yells et al. (36) observed increased mounts per mount bout and increased mount bouts per ejaculation. As discussed in the introduction, the effects of chronic administration on the motivation of the male rat to pursue the female is not clear. Taylor et al. (32) found no effect on male rat motivation after 28 days at 0.75 mg/kg. This dose, though it affected copulatory behavior, it did not affect motivation. Vega Matuszczyck et al. (34) found that 10 mg/kg for 13 days and 28 days significantly affected the amount of time the male spent in the vicinity of the female rat. In the current study with 10 mg/kg for 14 days, we did not observe an effect of chronic FLX on the mount bout parameters. In other words, our analyses did not reveal any differences between the FLX and vehicle control conditions with respect to the male pursuing the female as measured by the mount bout analysis. Differences between our study and that presented by Vega Matuszczyck et al. may be attributed to the differences in methodology. In our study, each rat was tested once, whereas Vega Matuszczyck et al. tested animals at

7- or 3-day intervals during treatment. The reduction in time spent with the estrous female that they observed may reflect a learned association of an inability to ejaculate with the environment or the female. Also, the amount of time the male spent with the female decreased across tests further suggesting that the more the male experienced not ejaculating with the female, the lower the motivation to pursue the female rat.

One proposed explanation for the effects of FLX is through an inhibition of the dopaminergic system in the nucleus accumbens (2). Nakamura (26) found that tissue concentrations of the dopamine metabolite, DOPAC, decreased in the nucleus accumbens after acute administration of FLX. Chronic treatment with FLX for 14 or more days also results in a significant decrease of dopamine concentrations in the nucleus accumbens (9). Taken together, these studies suggest that the administration of FLX may inhibit dopaminergic activity in the nucleus accumbens. Increased dopaminergic activity in the nucleus accumbens, via localized administration of DA agents or microdialysis analyses in the nucleus accumbens, has been associated with increased male rat sexual behavior, and specifically sexual motivation [for a review, see (29)] (30).

An alternative to the 5-HT–DA interaction hypothesis for the effects of FLX on male sexual behavior is that FLX inhibits descending brain stem spinal pathways. It has been proposed that serotonin affects sexual behavior via a tonic descending inhibitory pathway of the spinal cord (19,20,35). The nucleus paragigantocellularis (PGi) in the ventrolateral medulla has been proposed to be the source of the serotonergic influence (19,35). The target of the PGi projections has been shown to be in the lumbosacral spinal cord in the area of the spinal nucleus of bulbocavernosus (22). Furthermore, 5-HT_1 and 5-HT_2 receptors have been found in the lumbosacral area of the spinal cord (8,24). Chronic administration of FLX has been found to reduce concentrations of whole brain 5-HT (10,33) and alter the sensitivity and the density of 5-HT receptor subtypes in discrete brain regions, and may be having the same effect in the spinal cord (17,18,27). Marson and McKenna (21) administered 5-HT intrathecally at the upper lumbar level of the spinal cord and inhibited penile erections, ejaculation, and rhythmic contractions of the perineal muscles. Yells et al. (37) found that when the PGi is lesioned, male rat sexual behavior is facilitated and FLX does not further affect sexual behavior.

The current results suggest that the consumatory aspects of male sexual behavior, and not the appetitive aspects, are inhibited by chronic FLX treatment. As described above, our results evaluating the standard measures of those that did achieve at least three ejaculations were consistent with the pattern observed in animals receiving acute FLX. The mount bout analysis revealed no differences when FLX-treated animals were compared to control animals, whereas previous studies evaluating acute FLX did show differences in the mount bout parameters. An evaluation of the dose response relationship would further clarify these effects of chronic FLX on male copulatory behavior. As discussed above, we are suggesting that the effects of chronic FLX on male rat copulation may reflect altered 5-HT concentrations and receptors in the lumbosacral area of the spinal cord. This may also explain in part the sexual behavior pattern observed with sexual exhaustion. Though chronic FLX also affects the dopamine activity, the 5-HT/DA interaction does not appear to be the dominant mechanism affecting male sexual behavior in chronically treated animals. The inhibitory effects of FLX observed in this study are consistent with the theory that the FLX is acting via a descending serotonergic pathway to its target of the lumbosacral spinal cord in the area of the spinal nucleus of bulbocavernosus, and involves an inhibition of erectile function rather than an inhibition of motivation to pursue the female.

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