Pergamon

Pharmacology Biochemistry and Behavior, Vol. 49, No. 1, pp. 121-127, 1994

0091-3057/94 $6.00 + .00

0091-3057(94)E0101-M

Fluoxetine-Induced Inhibition of Male Rat Copulatory Behavior: Modification by Lesions of the Nucleus Paragigantocellularis

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Received 14 June 1993

YELLS, D. P., M. A. PRENDERGAST, S. E. HENDRICKS AND M. NAKAMURA. *Fluoxetine-induced inhibition of male rat copulatory behavior: Modification by lesions of the nucleus paragigantocellularis.* PHARMACOL BIOCHEM BEHAV **49**(1) 121-127, 1994. – In Experiment 1, the 5-HT uptake blocker fluoxetine (FLX; 20 mg/kg) reduced the proportion of sexually experienced male rats displaying ejaculations. Among those animals that did ejaculate there was an increase in intromission frequency (IF), ejaculation latency (EL), and postejaculatory interval (PEI) and a reduction in copulatory efficiency (CE) during the final copulatory sequence prior to sexual exhaustion. In Experiment 2, we found similar inhibitory effects of FLX as well as facilitating effects of lesions of the nucleus paragigantocellularis (PGi) on male rat copulatory behavior. Males with PGi lesions displayed more ejaculations and a longer latency to sexual exhaustion compared to intact animals. When FLX was given to rats with PGi lesions, it did not influence the proportion of rats ejaculating nor did it alter IF, EL, or PEI during the final copulatory series prior to exhaustion. These findings suggest that the inhibitory influences of FLX on male rat copulatory behavior are mediated in part by the interaction of FLX with neurons originating in the PGi.

Paragigantocellularis Fluoxetine Serotonin Sexual behavior Sexual exhaustion

EVIDENCE is accumulating that the nucleus paragigantocellularis in the ventrolateral medulla is a source of descending inhibitory influence on male rat copulatory behavior. Sexually naive male rats with PGi lesions are more likely to copulate to ejaculation during a 30-min exposure to an estrous female and display reductions in intromission frequency (IF) and increases in copulatory efficiency (CE) (49). Sexually experienced male rats with PGi lesions demonstrate increases in CE (23) and prolonged latency and increased number of ejaculations prior to sexual exhaustion (49). The above findings suggest that ablation of the PGi may decrease supraspinal inhibition of mating behavior in male rats.

There exists converging evidence that the PGi-mediated inhibition of copulatory mechanisms may be serotonergic in nature. Cell bodies in the PGi display 5-HT immunoreactivity (25) and project to the lumbar spinal cord where 5-HT receptors and presumptive terminals have been identified using both autoradiographic (11,32) and immunoreactive (25) techniques. Intrathecal injections of 5-HT abolish the urethrogenital reflex in spinally transected male rats (25). Finally, effects of PGi lesions on male rat copulatory behavior are similar to those reported following other manipulations that reduce 5-HT activity (1,14,21,24,30,31,33,39,41-44).

Fluoxetine (FLX) is a selective 5-HT uptake inhibitor (45). Administration of FLX inhibits both in copula (5) and ex copula (37, 38) copulatory behavior in male rats. Additionally, there are clinical reports that FLX has adverse effects on sexual behavior in humans (4,16,20,22,29,34,50). However, the neural substrate(s) involved in the effects of FLX on male sexual behavior remain(s) unknown.

The present study further examined the effects of FLX on sexual behavior in male rats using several doses and employing

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an exhaustion paradigm. Additionally, we evaluated whether the inhibitory effects of FLX on male rat copulatory behavior are due to neurons originating in the PGi by examining the effects of FLX on sexual behavior in intact animals compared to animals with PGi lesions. If FLX exerts its inhibitory effects on male rat sexual behavior by blocking the uptake of 5-HT released from the PGi, male rats with PGi lesions should be resistant to such effects.

METHOD

Animals

Male and female Sprague-Dawley rats,90–120 days old at the beginning of the experiments, were housed two to three per stainless steel wire mesh cage (18 × 35 × 25 cm) with a reversed light : dark cycle (lights on 1100–2100 h) and constant temperature (23°C). Standard laboratory diet and tap water were freely available.

Copulatory Screening

Each male rat to be screened was placed in an 80 liter glass aquarium with corn cob bedding on the floor. Following a 10 min acclimation period, an ovariectomized female lure was introduced. Females were brought to estrus using previously reported procedures (49). Each screening test lasted for 30 min or until the first intromission following ejaculation. All males used in the subsequent studies were observed to ejaculate in at least four consecutive weekly screening tests. These screening tests and all subsequent copulatory testing were conducted under red lighting during the dark portion of the light cycle.

EXPERIMENT 1

Drug Treatment

Fluoxetine hydrochloride was dissolved in 0.9% saline. Forty-five minutes before testing, animals received IP injections of saline alone or 5, 10, or 20 mg/kg FLX. All males were exposed to each treatment condition in a counterbalanced design. There was a minimum of 9 days between injections.

Definitive Copulatory Testing

Sexually experienced male rats were placed in the aquaria as described above for a 10-min acclimation period prior to the introduction of a female lure. Female lures were evaluated with nonexperimental sexually experienced males prior to data collection. Only those females displaying high levels of both proceptive and receptive behaviors were used. Experimental males were allowed to mate until sexual exhaustion (6), i.e., 30 min without a mount or intromission. Data were collected as described previously (49).

Statistical Analysis

Cochran's Q statistic for related samples was used to evaluate differences among treatment groups in the proportion of animals displaying ejaculations. Data from animals that failed to ejaculate in any test were excluded from subsequent analyses. Analyses of variance (ANOVAs) were applied to number of ejaculations and latency to exhaustion. To examine the effects of FLX on male rats as they became sexually exhausted, ANOVAs were applied to data from the first ejaculatory sequence and to data from the final complete ejaculatory series prior to sexual exhaustion. Where appropriate, overall tests were followed by Scheffe's test for multiple comparisons. Because of reported intercorrelations (10,36,40) among the various measures of male rat copulatory behavior used in the present experiment, we accepted as significant only those analyses with $p < 0.01$.

Results

Table 1 shows the effects of FLX on percentage of rats ejaculating and on number of ejaculations and latency to exhaustion for those rats that did ejaculate. There was a significant reduction in the proportion of animals copulating to ejaculation in the 20 mg/kg group ($Q = 18, p < 0.001$) compared to all other groups. There was a significant drug effect on the number of ejaculations prior to exhaustion, $F(3, 27) = 7.99, p < 0.005$, with both the 10 and 20 mg/kg groups displaying fewer ejaculations than the 0 or 5 mg/kg groups. There were no effects on latency to exhaustion.

Figure 1 shows the effects of FLX on intromission frequency (IF), ejaculation latency (EL), copulatory efficiency (CE), and postejaculatory interval (PEI) for the first and final copulatory series for those animals that ejaculated. Analysis of the first ejaculatory series revealed a significant drug effect on PEI, $F(3, 27) = 6.81, p < 0.005$, with the two high dosage groups showing an increased PEI compared to the control group. There were no drug effects on the other measures during the first copulatory series.

Analysis of the final ejaculatory series revealed significant effects on IF, $F(3, 27) = 44.62, p < 0.001$, EL, $F(3, 27) = 11.56, p < 0.001$, PEI, $F(3, 27) = 4.97, p < 0.01$, and CE, $F(3, 27) = 9.91, p < 0.001$. IF, EL, and PEI were increased and CE was reduced for the animals receiving FLX at any dosage.

EXPERIMENT 2

Method

Stereotaxic surgery. Sexually experienced male rats were anesthetized with sodium pentobarbital (50 mg/kg, IP).

TABLE 1

EFFECTS OF VARIOUS DOSES OF FLUOXETINE ON MALE RAT COPULATORY BEHAVIOR

Dosage (mg/kg)	0 (n = 16)	5 (n = 16)	10 (n = 16)	20 (n = 16)
Percent ejaculating	100	100	100	62.5†
Mean number of ejaculations*	5.7	5.8	4.6‡	4.3‡
Mean latency to exhaustion (min)*	107.2	119.4	106.9	100.9

*Includes only those animals that ejaculated.
†$p < 0.001$, ‡$p < 0.005$.

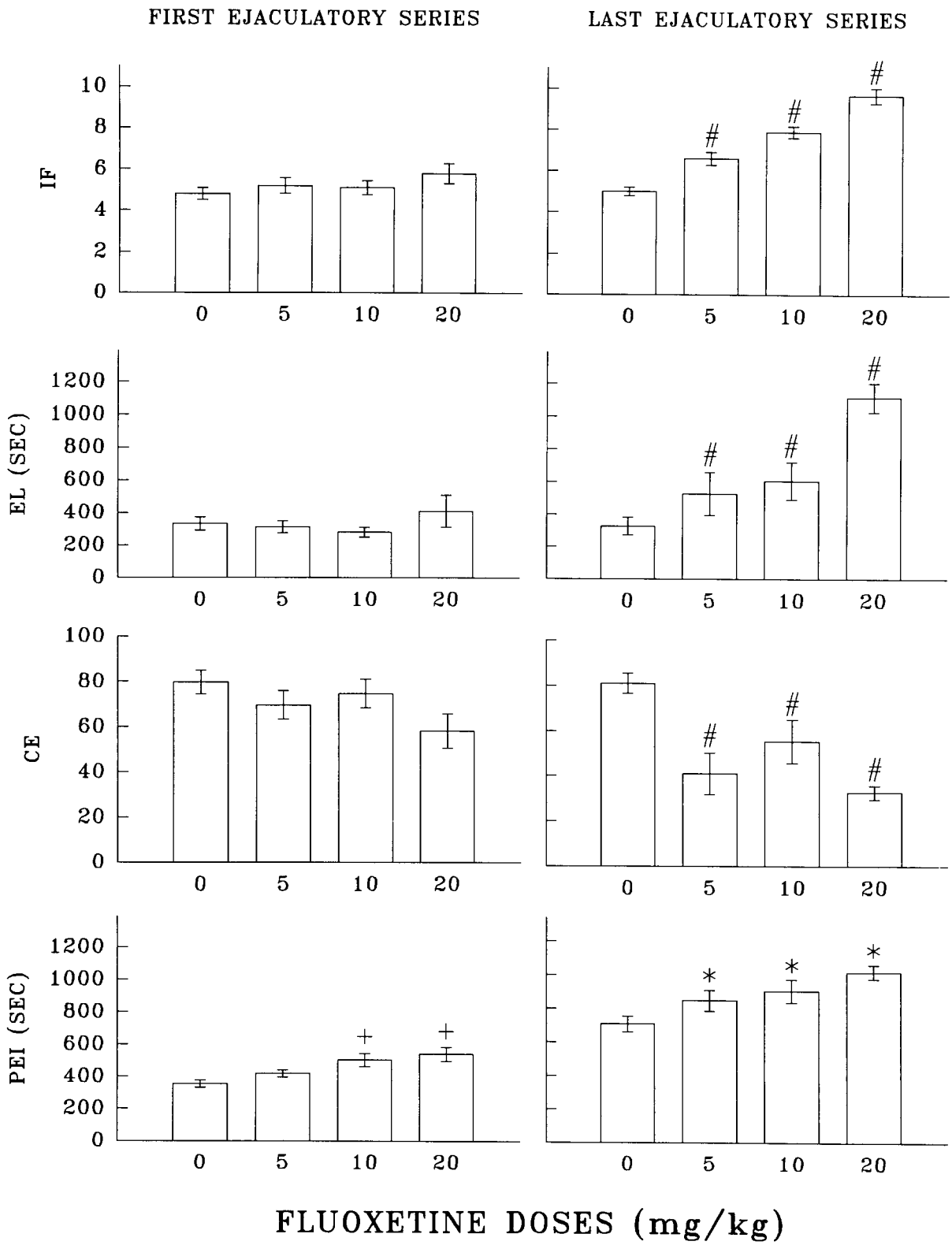

FIG. 1. Means and SEMs for intromission frequency (IF), ejaculation latency (EL), copulatory efficiency (CE), and postejaculatory interval (PEI) for the first and final ejaculatory series in Experiment 1. $n = 10$ for all groups. $^{*}p < 0.01$, $^{+}p < 0.005$, $^{\#}p < 0.001$.

Heads were shaved and the animals placed in a stereotaxic frame. A single midline incision was made and the scalp retracted. Based on atlas coordinates (35) and previous work in our laboratory (49), burr holes were drilled at 3.0 mm caudal to the interaural line and 1.6 mm lateral of midline. The electrode tip (1.0 mm diameter) was lowered to a position 0.9 mm below the interaural line. Bilateral radiofrequency lesions were produced by maintaining a current of 10 mA through a 1.0 mm diameter electrode for a period of 60 s. The tip temperature was 51°C. For sham surgery, no current was applied. The scalp was closed using wound clips.

Behavioral testing. Two weeks following surgery, all animals were again screened for sexual behavior. All animals displayed the full range of male rat copulatory behavior. The following week, animals received IP injections of either saline or FLX (20 mg/kg) dissolved in saline. Forty-five minutes following injections, the rats were tested for copulatory behavior and allowed to mate until sexual exhaustion (6). Data were collected as in Experiment 1.

Histology. Following behavioral testing, males were reanesthetized with IP injections of sodium pentobarbital (100 mg/kg) and perfused transcardially with 100 ml of phosphate buffered saline following by 100 ml of 10% formalin. Brains were removed and postfixed in phosphate buffered sucrose at 4°C for 48 h. Alternate 30 μ sections were taken from a freezing microtome and stained for Nissl substance. Lesion placement was verified by light microscopy and comparison with an atlas (35). Typical lesions were 0.5 mm in diameter and located 1.5 mm lateral of midline between the rostroventrolateral reticular nucleus and the inferior olive medial nucleus. In no case was the entire PGi destroyed. Data from animals with identifiable damage to other structures were not included in our analysis.

Statistical analysis. A chi-square test was used to evaluate group differences in the proportion of rats copulating to ejaculation. Among those rats that did copulate to ejaculation, ANOVAs were used to examine differences in the various measures of male rat copulatory behavior for the first and final copulatory series. Again, we accepted as significant only those analyses with $p < 0.01$.

Results

Table 2 shows the effects of FLX and PGi lesions on percentage of rats ejaculating and on number of ejaculations and latency to sexual exhaustion for those animals that did ejaculate. There was a significant reduction in the proportion of rats copulating to ejaculation in the intact group that received FLX compared to all other groups, $\chi^2(3) = 13.71, p < 0.01$. Among those animals that did achieve ejaculation, there were significant main effects for both drug, $F(1, 24) = 49.78, p < 0.001$, and lesion, $F(1, 24) = 53.61, p < 0.001$, on number of ejaculations to sexual exhaustion. There were also main effects for both drug, $F(1, 24) = 10.33, p < 0.005$, and lesion, $F(1, 24) = 71.96, p < 0.001$, on latency to sexual exhaustion. In all cases, the saline-treated animals were superior to the FLX-treated animals and the lesioned animals were superior to the intact animals. There were no significant interactions between drug and lesion for number of ejaculations or latency to sexual exhaustion.

Figure 2 shows the effects of FLX and PGi lesions on IF, EL, CE, and PEI for the first and final copulatory series for those animals that did ejaculate. In analyzing the first and final copulatory sequences, the animals that did not achieve ejaculation were not considered. For the first series, there were significant lesion effects on EL, $F(1, 24) = 8.90, p < 0.01$, IF, $F(1, 24) = 53.53, p < 0.001$, PEI, $F(1, 24) = 22.69, p < 0.001$, and CE, $F(1, 24) = 31.58, p < 0.001$. There were also significant drug effects on IF, $F(1, 24) = 8.18, p < 0.01$, and EL, $F(1, 24) = 18.08, p < 0.01$. In all cases, animals with PGi lesions were superior to sham animals and saline-treated animals were superior to FLX-treated animals.

For the final ejaculatory series, there were significant lesion effects on EL, $F(1, 24) = 133.84, p < 0.001$, IF, $F(1, 24 = 126.15, p < 0.001$, PEI, $F(1, 24) = 165.47, p < 0.001$, and CE, $F(1, 24) = 33.04, p < 0.001$. There were also significant drug effects on EL, $F(1, 24) = 36.54, p < 0.001$, IF, $F(1, 24) = 11.07, p < 0.005$, PEI, $F(1, 24) = 17.31, p < 0.001$, and CE, $F(1, 24) = 8.18, p < 0.01$. In all cases, lesioned animals were superior to sham animals and saline-treated animals were superior to FLX-treated animals.

There were significant drug by lesion interactions for the final ejaculatory sequence for IF, $F(1, 24) = 10.04, p < 0.01$, EL, $F(1, 24) = 8.27, p < 0.01$, and PEI, $F(1, 24) = 13.04, p < 0.001$. Simple effects analysis revealed that fluoxetine treatment increased all measures in the intact but not the lesioned animals.

GENERAL DISCUSSION

The results of Experiment 1 are consistent with previous reports (3,12,15,48) that increases in 5-HT inhibit copulatory behavior in male rats. More specifically, we found that treatment with the 5-HT uptake blocker FLX resulted in a dose-dependent inhibition of male rat sexual behavior. Rats receiving 20 mg/kg were much less likely to copulate to ejaculation compared to animals receiving lower doses, and among those rats that did achieve ejaculation there was a reduction in the

TABLE 2

EFFECTS OF FLUOXETINE (20 mg/kg) AND LESIONS OF THE NUCLEUS PARAGIGANTOCELLULARIS ON MALE RAT COPULATORY BEHAVIOR

Surgery: / Drug:	Sham Saline	Lesion Saline	Sham FLX	Lesion FLX
Number	8	8	8	8
Percent ejaculating	100	100	50†	100
Mean number of ejaculations*	5.00	8.33	2.83	5.83
Mean latency to exhaustion (min)*	146.5	205.7	114.0	186.6

*Includes only those animals that ejaculated.
†$p < 0.01$.

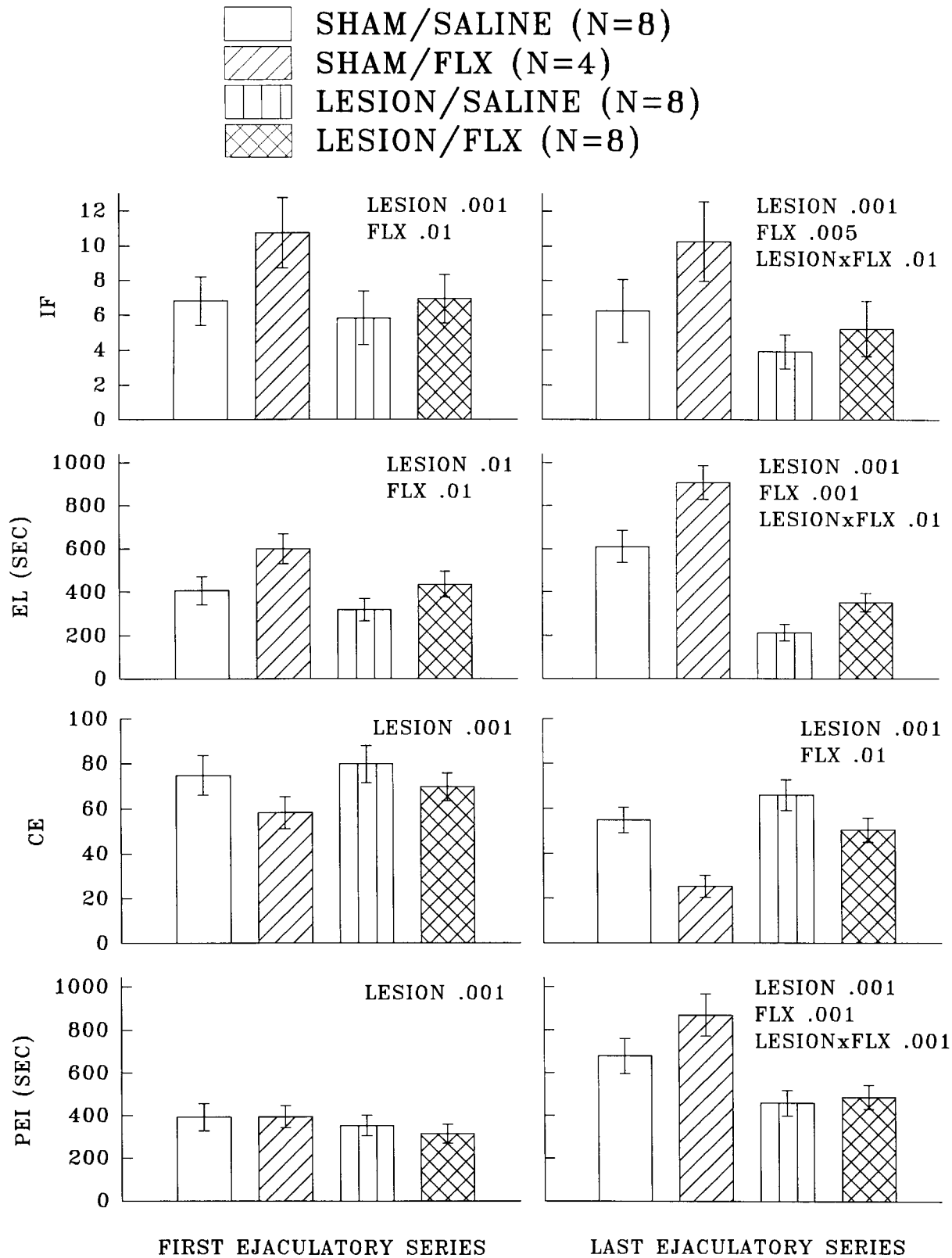

FIG. 2. Means and SEMs for intromission frequency (IF), ejaculation latency (EL), copulatory efficiency (CE), and postejaculatory interval (PEI) for the first and final ejaculatory series in Experiment 2. For each plot, the legend indicates significant effects along with levels of significance (LESION = main effect for lesion, FLX = main effect for fluoxetine, LESION × FLX = lesion by fluoxetine interaction).

number of ejaculations preceding sexual exhaustion. In a previous study (5) it was reported that the same dose of FLX reduced the rate of mounting and intromitting in castrated, steroid-treated males. However, effects on ejaculation were not reported. There are other reports (37,38) that FLX does inhibit ex copula ejaculation induced by treatment with *p*-chloroamphetamine. Thus, our findings are also in agreement with previous studies suggesting an inhibition of male rat copulatory behavior following treatment with FLX.

The effects of FLX on the rats that did achieve ejaculation became more pronounced as they approached sexual exhaustion. The only significant effect for the first copulatory series was an increase in PEI for the two highest dosage groups. However, for the final series there was an increase in PEI as well as an increase in EL and IF and a reduction in CE for the highest dosage groups. This may reflect an increase in 5-HT synthesis and release as a result of repeated copulation. It has been reported that sexual behavior increases 5-HT activity in the preoptic area (28) and the ventral and dorsal striatum (2). Additionally, sexually exhausted rats show high levels of 5-HT in the MPOA (18). Thus, the effects of a 5-HT uptake blocker such as FLX could be expected to be more pronounced in animals that have ejaculated repeatedly and, as a result, have higher levels of 5-HT.

In Experiment 2, we replicated the results of Experiment 1 regarding the inhibitory effects of FLX on male rat copulatory behavior. FLX-treated animals were less likely to copulate to ejaculation than saline-treated animals. Among those animals receiving FLX that did achieve ejaculation, there was a reduction in the number of ejaculations and latency to sexual exhaustion compared to animals receiving saline. Additionally, inhibitory effects of FLX in intact animals on IF, EL, CE, and PEI became evident during the final copulatory sequence.

In Experiment 2 we also replicated previous work in our laboratory (49) indicating that lesions of the PGi facilitate copulatory behavior in male rats. Animals with PGi lesions displayed more ejaculations and a longer latency to sexual exhaustion compared to intact controls. These results are consistent with reports that PGi lesions release a urethrogenital reflex in male rats (25,26) and that PGi lesions enhance ex copula penile reflexes (27).

The analysis of the first copulatory sequence in Experiment 2 revealed some unexpected effects for both the drug and lesion treatments. FLX treatment significantly increased IF and EL and had no effect on PEI or CE. This was not the case in Experiment 1, although group differences were in the same direction. Also, PGi lesions significantly reduced IF, EL, PEI, and increased CE. Previously (49), we found no such effects for the first ejaculatory series in sexually experienced males but did find such effects in sexually naive male rats. Increases in CE for sexually experienced male rats following PGi lesions have previously been reported (23).

The interaction between lesion and drug treatment for IF, EL, and PEI for the final copulatory series is consistent with our previous interpretation (49) of the effects of PGi lesions. We suggested that the facilitating effects of such lesions are most likely to occur in animals in which mating capacity has been compromised. Previous studies (7,9,19) have demonstrated that rats approaching sexual exhaustion show deficits in copulatory behavior (increased IF, EL, and PEI). In Experiment 1, these deficits were more apparent in animals that received FLX. Thus, during the final copulatory series in Experiment 2, rats that had received FLX would have had an extremely compromised capacity to copulate. The fact that PGi lesions prevented the deleterious effects of FLX on IF, EL, and PEI in rats as they become sexually exhausted further supports our previous contention that effects of such lesions on male rat copulatory behavior are most apparent in rats with compromised capacity to copulate.

The effects of PGi lesions on sexual behavior in male rats are similar to those observed following manipulations that reduce 5-HT activity. Destruction of the midbrain raphe nuclei reduces IF, EL, and PEI in male rats (30). Application of 5-HT into the raphe nuclei, which presumably stimulates inhibitory autoreceptors and reduces 5-HT release, lowers IF and EL in male rats (17). The 5-HT synthesis inhibitor *p*-chlorophenylalanine reduces EL and PEI in male rats (1,41). The 5-HT neurotoxin 5,7-dihydroxytryptamine can stimulate sexual behavior in intact and castrated male rats (21,39,43). We interpret our results as supporting the hypothesis that facilitating effects of PGi lesions on male rat copulatory behavior are at least partially due to a reduction in 5-HT.

In conclusion, we found in both experiments that FLX inhibits copulatory behavior in intact male rats and that such inhibition becomes more pronounced as the rats approach sexual exhaustion. We also found that lesions of the PGi facilitate male rat copulatory behavior and that such facilitation becomes more pronounced as sexual exhaustion approaches. Finally, some of the deficits in sexual behavior following treatment with FLX are eliminated in rats with PGi lesions, indicating that at least some of the effects of FLX on male rat copulatory behavior may be due to neurons originating in the PGi.

ACKNOWLEDGEMENTS

The authors thank Stephen Paige, Scott Balogh, Delores McArthur-Campbell, and Denis Fitzpatrick for their assistance in preparing this manuscript.

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