

Effects of the Selective Serotonin Reuptake Inhibitor Fluoxetine on Social Behaviors in Male and Female Prairie Voles (*Microtus ochrogaster*)

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The selective serotonin reuptake inhibitor fluoxetine modifies social behavior in a number of species, including humans. Because the neural substrates for social behavior in prairie voles are sexually dimorphic, we tested whether the effects of fluoxetine on these behaviors differ by sex. Parental and pair-bonded voles were chronically treated with fluoxetine or saline and subsequently tested for parental responsiveness. Fluoxetine-treated animals displayed a longer latency to exhibit parental responsiveness than did saline-treated controls ($p < 0.02$), but they did not differ in other aspects of parental care. There were no sex differences in the effects of fluoxetine on parental behavior. After completion of the tests for parental behavior, the subjects were tested for aggressive behavior using the resident-intruder paradigm. Fluoxetine-treated males displayed less aggressive behavior than their saline-treated counterparts ($p < 0.02$). Although we did not find any effects of fluoxetine on aggressive behavior in females, no significant interaction was found between sex and treatment. Fluoxetine did not alter nonsocial behaviors. The findings suggest that serotonin influences social behavior in prairie voles. © 1997 Academic Press

Prairie voles (*Microtus ochrogaster*) are a monogamous species of microtine rodents. Males and females of this species participate equally in the care of offspring (Hartung and Dewsbury, 1979; Gruder-Adams and Getz,

1985; Oliveras and Novak, 1986), form stable pair bonds (Getz and Hoffmann, 1986), and become extremely aggressive toward conspecifics after forming a pair bond (Getz, Carter, and Gavish, 1981). Little is known about the neural substrates of social behavior in voles. Limbic vasopressin innervation has, however, been implicated in the control of these behaviors in prairie voles. Cohabitation alters vasopressin immunoreactivity and vasopressin mRNA expression in limbic brain structures, suggesting a stimulation of the vasopressin system (Bamshad, Novak, and De Vries, 1993, 1994; Wang, Smith, Major, and De Vries, 1994a). In fact, pharmacological studies support a role for vasopressin in parental and aggressive behavior (Wang, Ferris, and De Vries, 1994; Winslow, Hastings, Carter, Harbaugh, and Insel, 1993). Because the changes in the limbic vasopressin innervation are observed in males but not in females, the neural substrates underlying social behavior appear to be sexually dimorphic (Bamshad *et al.*, 1993, 1994; Wang *et al.*, 1994a).

The present study investigated the effects of the selective serotonin reuptake inhibitor, fluoxetine, on the social behavior of voles. Serotonin is likely to be involved in the control of social behavior in voles due to its putative role in the modulation of various social behaviors in other mammals. Specifically, changes in the serotonin system are correlated with mating (Mas, Fumero, and Gonzalez-Mora, 1995a, Mas, Fumero, Fernandez-Vera, and Gonzalez-Mora, 1995b), agonistic displays (Amstislavskaya and Kudryavtseva, 1995), and aggressive behavior (Virkkunen, Goldman, Niel-

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sen, and Linnoila, 1995). We tested whether chronic fluoxetine treatment affects parental and aggressive behavior differently in male and female voles because the neural substrates of social behavior appear to be sexually dimorphic in this species (Bamshad *et al.*, 1993,1994; Wang *et al.*, 1994a; Insel and Hulihan, 1995).

METHODS

Subjects

The animals used in this study were taken from a colony of prairie voles established in 1996 at the University of Massachusetts, Amherst, from breeding stock kindly provided by Dr. Betty McGuire (Smith College, Northampton, MA) and Dr. Zuoxin Wang (Emory University, Atlanta, GA). The breeding stock originated from offspring of wild-caught animals from Urbana, Illinois. All voles were maintained on a 14 h light/10 h dark cycle at 21°C and housed in 10-gallon plexiglass tanks supplied with pine chips and shavings and a covering of hay. Water, dried corn, sunflower seeds, and rabbit chow were provided *ad libitum*.

Treatment

The subjects were randomly selected from established breeding pairs who had been successfully and predictably breeding for at least three successive litters. Twelve breeding pairs between the ages of 4 and 7 months were divided into four treatment groups (three pairs per group). In the first treatment group, both parents received daily fluoxetine injections (6 mg/kg in 0.9% saline, ip); in the second and third groups, either the father or the mother received fluoxetine while the other parent received saline; in the fourth group, both parents received saline. Injections began on the fifth day after the birth of a litter, were given 4 h after the lights went on, and continued daily for 8 weeks. On the fifth day after the birth of the subsequent litter, approximately 3 weeks after the onset of treatment, each individual was tested for parental responsiveness in the home cage with pups born to experimental subjects. During these tests, the mate and offspring were removed from the cage, as was the hay covering. Two to three stimulus pups were placed in the center of the home cage, and the animal's behavior was videotaped for 10 min. Stimulus pups consisted of a random mix of 5-day-old pups born to saline-treated and fluoxetine-

treated females. Every animal was tested with a combination of its own and novel pups.

After the completion of the parental behavior tests, individual animals were tested for aggressive behavior using the resident-intruder paradigm (Miczek, 1979). During these tests, the mate and offspring were removed from the cage, as was the hay covering. All subjects served as resident and intruder once during the experiment. The order in which these roles were taken was counterbalanced across trials, as was the combination of the subjects' treatment and sex. Because the births of the litters born to our experimental breeding pairs were not synchronized, there was a variable lag between the parental and the aggressive behavior tests. At the time of the aggressive behavior tests, subjects had been receiving treatment for a minimum of 4 weeks and a maximum of 8 weeks, and pairs were at different stages of breeding.

Behavioral Assessment

Noldus Observer software (Wageningen, The Netherlands) was used to score the behavioral profiles of our subjects. Parental behavior was analyzed as previously described by McGuire and Novak (1984). The following interactions between subjects and pups were assessed: approaching, sniffing, grooming, nonventral contact (including all forms of contact except huddling), huddling, and retrieving. In addition, the following nonsocial behaviors were assessed: self-grooming, exploring, escaping (i.e., climbing along the sides of the cage), and inactivity. Parental behavior was defined as the composite of grooming, nonventral contact, huddling, and retrieving. Latency to parental behavior was correspondingly defined as the latency to exhibit any one of these behaviors.

Aggressive behavior was analyzed using the parameters described by Blanchard, Blanchard, Takahashi, and Kelley, (1977). The following interactions between residents and intruders were assessed: approaching, sniffing, side-by-side contact, escaping (i.e., aggressor avoidance), chasing, rearing, boxing, biting, and "rolling fight." The rolling fight is characterized by the two opponents clasp each other with their forepaws and rolling together while attempting to bite (Siegel, 1985). In addition, the following nonsocial behaviors were assessed: exploring, self-grooming, and inactivity. Aggressive behavior was defined as the composite of chasing, biting, and rolling fights. Latency to aggressive behavior was correspondingly defined as the latency to exhibit any one of these behaviors. Upright postures

including boxing and rearing, and escaping were collectively classified as defensive behavior.

The data were analyzed using a two-way ANOVA to determine the effects of sex and treatment on parental and aggressive behavior. The aggressive behavior data were also analyzed using a *t* test to determine the effects of treatment in each sex separately.

Neurochemical Assessment of Serotonin Turnover

At the completion of the experiment, a random sample of the subjects was euthanized by carbon dioxide asphyxiation. Their brains were then rapidly extracted and frozen. Serotonin and the serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA) concentrations were determined by HPLC by Celeste Capers and Dr. Ed Caliguri at Wellesley College (Wellesley, MA) as described by Mefford, Caliguri, Grady, Capella, Durkin, and Chevalier (1986). Concentrations, expressed as pmoles per milligram of wet tissue, were 16.4 ± 3.5 vs 13.1 ± 2.9 for serotonin and 48.2 ± 11.2 vs 11.2 ± 9.2 for 5-HIAA in the hypothalamus of saline- vs fluoxetine-treated animals, and 9.7 ± 1.4 vs 9.4 ± 1.3 for serotonin and 18.8 ± 4.0 vs 8.3 ± 3.7 for 5-HIAA in the frontal cortex of saline- vs fluoxetine-treated animals. These measurements confirmed that fluoxetine treatment significantly decreased serotonin turnover in the hypothalamus as measured by the ratio of the concentrations of 5-HIAA over serotonin by approximately 70% (3.6 ± 0.7 vs 1.0 ± 0.6 ; $F = 7.49$; $df = 1, 10$; $P < 0.03$, two-way ANOVA) and tended to decrease serotonin turnover in the frontal cortex by approximately 40% (1.6 ± 0.2 vs 1.0 ± 0.2 ; $F = 4.05$; $df = 1, 10$; $P = 0.069$, two-way ANOVA). This effect of fluoxetine has been described by several studies assessing fluoxetine's effects on serotonin metabolism (Fuller, Perry, and Molloy, 1974; Caccia, Fracasso, Garattini, Guiso, and Sarati, 1992; Frankfurt, Mc Kittrick, and Luine, 1994).

RESULTS

Parental Behavior

There were no behavioral differences associated with the treatment of the subject's mate. Therefore, the treatment of the mate was not considered a factor in further analyses. Fluoxetine did not significantly influence the length or percentage of time spent engaging in specific aspects of parental behavior (such as grooming or huddling) or the total time spent displaying parental behavior (Fig. 1). However, the latency to exhibit parental responsiveness was significantly longer in fluoxetine-treated voles than in saline-treated voles ($F = 7.56$; $df = 1, 20$; $P < 0.02$; two-way ANOVA; Fig. 1). Males spent more time self-grooming than females ($F = 5.52$; $df = 1, 20$; $P < 0.03$, two-way ANOVA). Exploratory behavior, escape behavior, and inactivity were unaffected by treatment or sex.

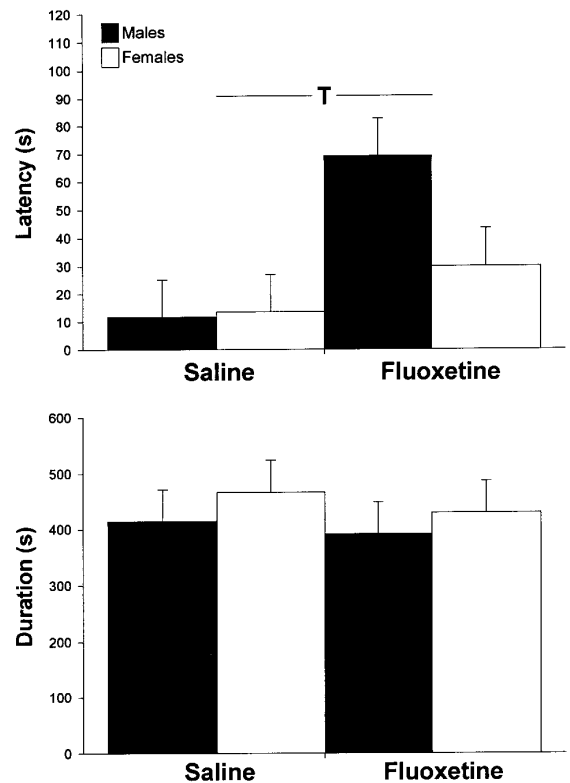


FIG. 1. Latency to parental behavior (top) and duration of parental behavior (bottom) of male and female voles treated with saline or fluoxetine ($n = 6$ for each group). Bars represent mean latency (\pm SEM) or mean duration (\pm SEM), in seconds, per 10-min testing period. T represents an overall treatment effect ($P < 0.05$).

ling) or the total time spent displaying parental behavior (Fig. 1). However, the latency to exhibit parental responsiveness was significantly longer in fluoxetine-treated voles than in saline-treated voles ($F = 7.56$; $df = 1, 20$; $P < 0.02$; two-way ANOVA; Fig. 1). Males spent more time self-grooming than females ($F = 5.52$; $df = 1, 20$; $P < 0.03$, two-way ANOVA). Exploratory behavior, escape behavior, and inactivity were unaffected by treatment or sex.

Aggressive Behavior

There were no behavioral differences associated with the treatment of the subject's mate. Therefore, the treatment of the mate was not considered a factor in further analyses. There were no behavioral differences associated with the sex or treatment of the subject's opponent. Therefore, sex and treatment of the opponent were not considered factors in further analyses. In females, flu-

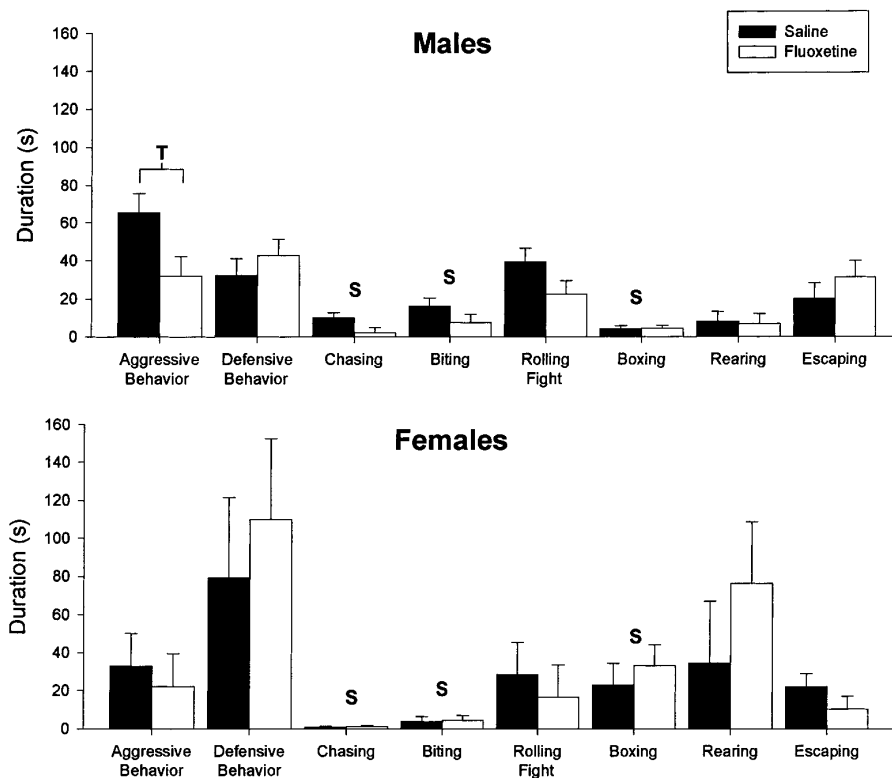


FIG. 2. Duration of aggressive behaviors of intruder voles treated with saline or fluoxetine ($n = 6$ for both groups of males and females). Bars represent mean duration (\pm SEM), in seconds, per 10-min testing period. T represents significant treatment effects ($P < 0.05$, t test). S represents significant sex effects ($P < 0.05$, two-way ANOVA).

oxetine did not significantly influence the latency, length, or percentage of time spent engaging in specific aspects of aggressive behavior (such as chasing or biting) or the total time spent displaying aggressive behavior. In males, however, fluoxetine decreased the levels of aggressive behavior in intruders ($F = 5.24$; $df = 1, 10$; $P < 0.05$, t test; Fig. 2) and residents ($F = 8.19$; $df = 1, 9$; $P < 0.02$, t test; Fig. 3). In resident males, fluoxetine tended to increase defensive behavior ($F = 4.71$; $df = 1, 20$; $P = 0.058$, two-way ANOVA; Fig. 3). A two-way ANOVA revealed no treatment or sex effects on total duration of aggressive or defensive behavior. However, it did reveal sex differences in specific types of aggressive and defensive behaviors. Intruder females tended to spend significantly more time displaying defensive behavior than their male counterparts ($F = 3.51$; $df = 1, 20$; $P = 0.076$, two-way ANOVA; Fig. 2). This difference reflected females' tendency to spend more time boxing ($F = 5.70$; $df = 1, 20$; $P < 0.03$, two-way ANOVA; Fig. 2) and rearing ($F = 4.22$; $df = 1, 20$; $P = 0.053$, two-way ANOVA; Fig. 2) than males. Conversely, intruder males

spent significantly more time biting ($F = 4.43$; $df = 1, 20$; $P < 0.05$, two-way ANOVA; Fig. 2) and chasing ($F = 7.30$; $df = 1, 20$; $P < 0.02$, two-way ANOVA; Fig. 2) than did their female counterparts. Resident females spent significantly more time rearing than their male counterparts ($F = 4.84$; $df = 1, 20$; $P < 0.05$, two-way ANOVA; Fig. 3). In resident voles, there was a significant interaction between treatment and sex ($F = 8.3$; $df = 1, 20$; $P < 0.01$, two-way ANOVA; Fig. 3). In resident males, fluoxetine tended to increase defensive behavior, whereas in resident females, fluoxetine tended to decrease defensive behavior. Exploratory behavior, self-grooming, and inactivity were unaffected by treatment or sex.

DISCUSSION

Fluoxetine treatment significantly delayed the latency to exhibit parental behavior in pair-bonded and parental voles of both sexes, but it did not affect the

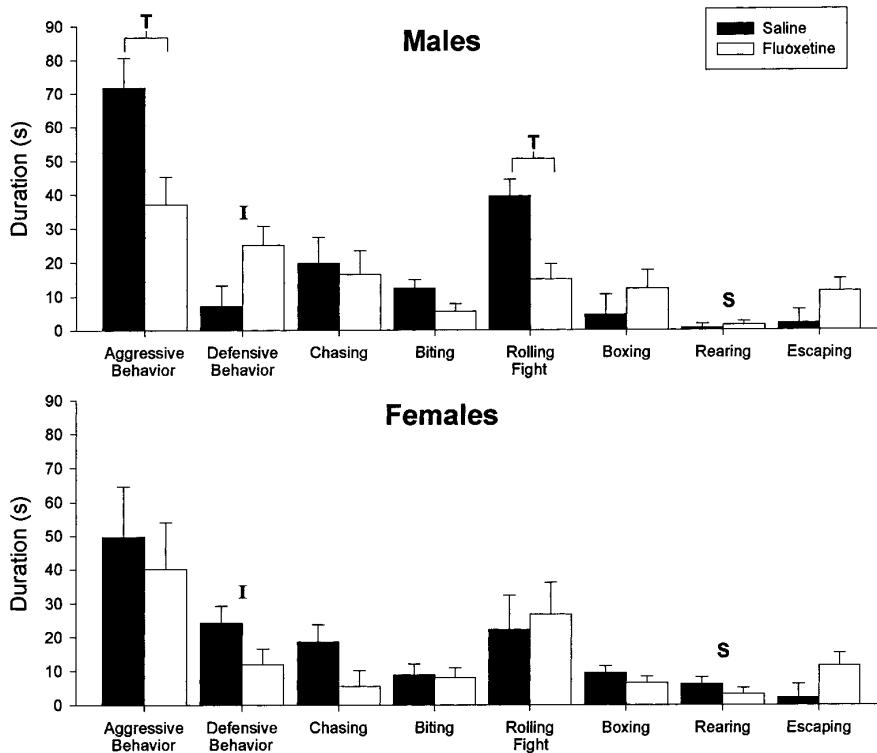


FIG. 3. Duration of aggressive behaviors of resident voles treated with saline or fluoxetine ($n = 6$ for both groups of males and females). Bars represent mean duration (\pm SEM), in seconds, per 10-min testing period. T represents significant treatment effects ($P < 0.05$, t test). S represents significant sex effects and I represents significant interactions ($P < 0.05$, two-way ANOVA).

duration or apparent quality of the behavior. Fluoxetine also reduced aggressive behavior in males, but it did not affect aggressive behavior in females. Comparisons of aggressive and defensive behavior in males and females revealed sex differences in aggressive and defensive strategies. Other behaviors such as locomotor behavior and exploratory behavior were unaffected by treatment and did not show sexual dimorphism. The findings suggest that aggressive behavior is regulated differently in males and females and may indicate that fluoxetine can interfere with only the aggressive strategies used by males.

Although fluoxetine did not alter the overall quality of parental care in voles, a higher dosage of fluoxetine may have rendered different results. This is the first experiment evaluating the effects of fluoxetine on social behavior in voles. We administered a moderate dose of fluoxetine that impaired sex behavior in rats (Cantor, Binik, and Pfaus, 1996). On the other hand, the lack of a dramatic serotonin-mediated effect on parental behavior is not unprecedented. The serotonin receptor ag-

onists 8-OH-DPAT (8-hydroxy-2-(di-*n*-propylamino)tetralin) and DOI (1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane) do not alter overall parental quality (De Almeida and Lucion, 1994). However, in that study the different aspects of parental behavior were collapsed into one behavioral measure, "pup care"; our experiments, therefore, cannot be directly compared.

Fluoxetine did not differentially affect parental behavior in male and female prairie voles despite the sexual dimorphism of the neural substrates of parental behavior (Bamshad *et al.*, 1993, 1994; Wang and De Vries, 1993; Wang *et al.*, 1994a,b). Studies addressing the neurochemical and behavioral effects of fluoxetine have demonstrated that fluoxetine inhibits vasopressin-mediated aggressive behavior (Ferris and Delville, 1994; Delville, Mansour, and Ferris, 1996), reduces hypothalamic vasopressin secretion *in vivo* (Ferris, 1996) and *in vitro* (Altemus, Cizza, and Gold, 1992), and reduces vasopressin levels in the cerebrospinal fluid of humans (De Bellis, Gold, Gera- cioti, Listwak, and Kling, 1993). Therefore, fluoxetine

may alter social behavior in voles via an interaction with vasopressin system. If fluoxetine influences parental behavior by interacting with vasopressin innervation, then one would predict sexually dimorphic effects on parental behavior, given the sexually dimorphic nature of the vasopressin innervation (De Vries, Buijs, and Swaab, 1981; Van Leeuwen, Caffè, and De Vries, 1985). Fluoxetine delayed parental behavior, but there were no significant sex differences in this effect. Fluoxetine appeared to delay parental behavior more in males than in females, but there was no significant interaction between sex and treatment. However, sexually dimorphic effects of fluoxetine resulting from fluoxetine interacting with the vasopressin system may be complicated because the prime target of fluoxetine, the serotonin system, is itself sexually dimorphic (Fischette, Biegón, and McEwen, 1983; Becu de Villalobos, Lux, Lacau de Mengido, and Libertun, 1984; Carlsson, Svensson, Eriksson, and Carlsson, 1985; Carlsson and Carlsson, 1988). Fluoxetine may therefore have sex-specific effects on serotonin innervation that mask potential differences in effects on parental behavior caused by the sexual dimorphism of the vasopressin system. Furthermore, fluoxetine alters not only vasopressin, but a variety of other systems (Fuller and Snoddy, 1990; Van de Kar, Rittenhouse, Li, and Levy, 1996; Saydoff, Rittenhouse, Van de Kar, and Brownfield, 1991) including systems involved in control of maternal behavior. These results may therefore reflect the convergent behavioral manifestations of fluoxetine-mediated effects on various neural systems.

Although fluoxetine did not affect the overall parental responsiveness of parentally experienced voles, it may affect parental behavior in parentally inexperienced voles. In rats, gonadal hormones induce maternal behavior, but are not necessary to maintain the behavior once pups are born (Rosenblatt and Siegel, 1981). The same may apply for prairie voles. Castration of parentally inexperienced male voles completely abolishes parental responsiveness (Wang and De Vries, 1993), whereas castration of parentally experienced male voles does not (unpublished data from our laboratory). Fluoxetine's inability to significantly alter overall parental behavior may therefore indicate that fluoxetine treatment must precede the onset of parental care in order to interfere with its quality.

In contrast to fluoxetine's effects on parental behavior, fluoxetine significantly altered aggressive behavior in male voles. Fluoxetine inhibited aggressive behavior in resident and intruder males. These inhibi-

tory effects on aggressive behavior in male voles corroborate fluoxetine's established role as an antiaggressive agent in rats, mice, hamsters, monkeys, and humans (Fuller, 1996; Ferris, 1996; Raleigh, Brammer, McGuire, and Yuwiler, 1985; Coccaro, Astil, Herbert, and Schut, 1990).

The absence of a fluoxetine-mediated effect on female aggressive behavior conflicts with research showing that serotonin receptor agonists inhibit rat maternal aggression (De Almeida and Lucion, 1994) and mouse territorial aggression (Haug, Wallian, and Brain, 1990). Serotonin's role in female aggression, nonetheless, remains uncertain; in this experiment, the variable hormonal conditions of the females may have contributed to high variability in monoamine levels and baseline aggressive behavior (Rastegar, Ciesielski, Simler, Messripour, and Mandel, 1993; Hood, 1984). However, sexual dimorphism in the neural substrates of aggressive behavior may make the female less susceptible to the antiaggressive effects of fluoxetine. In fact, treatment of lactating female rats with a serotonin synthesis inhibitor decreases, rather than increases, maternal aggression, as does treatment with serotonin antagonists (Ieni and Thurmond, 1985). Moreover, central serotonergic activity is inversely correlated with measures of aggression in men, but not in women (Cleare and Bond, 1997). These data suggest that the involvement of serotonin in aggressive behavior differs between males and females.

The neural bases for the behavioral effects of fluoxetine are poorly understood. While it is clear that potentiation of the serotonin system is important, downstream neurochemical effects of the drug have not been identified. Perhaps more importantly, relatively nothing is known about how fluoxetine affects behaviors that are regulated differently in males and females. Our study demonstrates a link between serotonin and social behavior in prairie voles. Identification of the systems that are affected by fluoxetine may be pivotal in elucidating how this drug affects social behavior.

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