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Subchronic Administration of Fluoxetine Impairs Estrous Behavior in Intact Female Rats

Josefa Vega Matuszczyk, Ph.D., Knut Larsson, Ph.D., and Elias Eriksson, Ph.D.

Treatment with serotonin reuptake inhibitors (SRIs) has been shown to cause reduced libido and anorgasmia in women. A large body of evidence suggests that serotonin may influence sexual behavior in estradiol + progesterone primed, gonadectomized female rats; however, the influence of selective SRIs on the estrous behavior of intact female rats has not been described previously. In the present study, the effect of 1 to 3 weeks of fluoxetine administration (10 mg/kg daily) on vaginal and behavioral estrus in intact female rats was studied; in addition, the effect of fluoxetine (same dose, 1–8 weeks) on copulatory behavior and on sexual motivation in hormone-primed gonadectomized rats was investigated. Subchronic administration of fluoxetine did not influence cyclicity as judged by the examination of vaginal smears but significantly reduced the percentage of rats displaying receptive behavior in the estrous phase. In addition, fluoxetine significantly reduced receptive behavior, including lordosis, in ovariectomized female rats primed with estradiol (6.25 μg/rat; −48 hr) plus progesterone (1.0 mg/rat, −4 hr); in contrast, sexual motivation—as reflected by the amount of time these rats elected to spend in the vicinity of a male rather than in the vicinity of a female or elsewhere—was little affected by the treatment. ***[Neuropsychopharmacology 19:492–498, 1998]*** *© 1998 American College of Neuropsychopharmacology. Published by Elsevier Science, Inc.*

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Treatment with serotonin reuptake inhibitors (SRIs) has been reported to reduce libido in both sexes, to cause anorgasmia in women (Monteiro et al. 1987; Herman et al. 1990; Zajecka et al. 1991; Balon 1995; Eriksson et al. 1995; Shen and Hsu 1995; Feiger et al. 1996; Sundblad et al. 1997) and to increase ejaculation latency in men (Hsu and Chen 1995; Waldinger et al. 1994; Kara et al. 1996). Particularly when the SRIs are used for prophylactic purposes in patients that have recovered from depression, and when they are used for psychiatric conditions not associated with a reduction in libido (such as panic disorder, obsessive compulsive disorder, and premenstrual dysphoria) (Eriksson and Humble 1990), sexual dysfunction is probably the most cumbersome of the SRI-associated side effects.

Given the fact that all serotonin reuptake inhibitors, despite marked differences in chemical structure, induce similar sexual side effects, it is likely that these effects are, indeed, attributable to inhibition of the serotonin transporter and to a subsequent increase in the synaptic concentrations of serotonin. However, the postsynaptic receptor subtype(s) mediating the effects of serotonin reuptake inhibitors on sexual behavior and the brain region in which these effects are exerted have yet to be clarified. Also, to what extent the reduction in libido and difficulty in achieving orgasm are causally related remains to be established.

Needless to say, the elucidation of the mechanisms underlying SRI-induced sexual side effects would be facilitated if these effects could be studied in animal ex-

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periments. Previous studies by us and others have shown that administration of an SRI to male rats does induce changes in sexual behavior similar to those observed in humans (Ahlenius et al. 1979; Yells et al. 1994; Yells et al. 1995; Taylor et al. 1996; Vega Matuszczyk et al. 1988); in contrast, there are, to our knowledge, no studies on the effect of subchronic administration of a selective SRI on sexual behavior in female rats.

Intact female rats in the estrous phase—as well as gonadectomized females primed with estradiol and progesterone—respond to male mounting with a characteristic dorsiflexion of the back that can be easily registered, so-called lordosis behavior. In addition, the female solicits male sexual activity by distinct presenting postures, such as darting, hopping, and ear wiggling (Beach 1976). Thus, examination of a female rat exposed to a sexually active male can easily assess her sexual receptivity. Sexual motivation is somewhat more difficult to investigate; however, tentatively, this aspect of sexual behavior may be reflected by the time spent by a female rat in the vicinity of a male rather than a female, or elsewhere (Meyerson et al. 1978; Vega Matuszczyk and Larsson 1993).

In the present study, the extent to which the sexual side effects induced by SRIs in women can be mirrored in animal experiments was addressed; to this end, we investigated the effect of subchronic administration of the selective SRI fluoxetine (Fuller et al. 1991) on various aspects of female sexual behavior. In the first experiment, the effects of 1 to 3 weeks of fluoxetine administration on sexual receptivity in the estrous phase of normally cycling animals was studied. In this experiment, the female was exposed to a sexually active male while penile insertion was prevented. In the second experiment, the effect of 1 to 6 weeks of fluoxetine treatment on sexual behavior in ovariectomized female rats rendered sexually responsive by treatment with estradiol plus progesterone was tested; in addition, as a tentative measure of sexual motivation, the time the female rat elected to spend in the vicinity of a male rat rather than in the vicinity of a female, or elsewhere, was assessed.

METHODS

Animals

Wistar rats (Mol:Wist; 60 days of age) were bought from Møllegaard Breeding Laboratories (Vejle, Denmark) and allowed an adaptation period of 2 weeks before the beginning of the experiments. The animals were maintained in groups of same sex, five per cage (Macrolon cage No. 4), under reversed light/dark conditions (lights on between 2200–1000) and with controlled temperature (22°C) and humidity (50–60%) conditions. Food and tap water were available ad libitum. The behavioral experiments were always started 2 hours after the onset of darkness.

Experiment 1: Effects of Fluoxetine on Vaginal and Behavioral Estrous

The first experiment investigated the effect of fluoxetine on the estrous cyclicity of intact female rats. To this end, 30 female rats were divided into two groups and tested daily for vaginal and behavioral estrous over an 8-week period.

Vaginal smears were obtained by placing a drop of saline in the vagina of the rat and then transferring the liquid to a slide. After drying, the smear was stained in Giemsa solution, dried, and inspected microscopically. Vaginal estrous was defined by the presence of large, squamous epithelial cells, nucleated epithelial cells, and leukocytes (Long and Evans 1922).

Behavioral receptivity of the female was determined by placing her with a male and registrating whether she displayed any signs of receptivity—such as lordotic behavior, hop/darting (= a short leap with the animal landing on all four paws followed by the assumption of a crouching posture) and ear wiggling (= a rapid lateral shaking of the head that produces the appearance of distinctive vibrations of the ears)—or not. The male rats were prevented from making penile insertions.

One week after the beginning of the experiment, treatment of the experimental group ($n = 15$) with fluoxetine (10 mg/kg, dissolved in saline, volume: 2 ml/kg) was initiated; controls ($n = 15$) were given the same volume of saline. The treatment continued (one injection per day) for 3 weeks. The daily registration of vaginal and behavioral cyclicity continued for another 3 weeks after the drug treatment had been stopped.

Experiment 2: Effects of Fluoxetine on Sexual Motivation and Female Sexual Behavior

The second experiment was aimed at studying the effect of treatment with fluoxetine on sexual motivation and on copulatory behavior in female rats. To this end, 29 adult female rats were ovariectomized under Brietal anaesthesia (5 mg/kg) by a ventral incision and allowed a resting period of 1 week. They were then tested for feminine sexual behavior and sexual motivation after priming with estradiol benzoate (EB, 6.25 μg/rat in 0.1 ml sesame oil, −48hr) and progesterone (P, 1.0 mg/rat in 0.1 ml sesame oil, −4 hr).

After the first behavioral tests, one group of animals was treated daily with fluoxetine 10 mg/kg (dissolved in saline, administration volume: 2 ml/kg), and the other group received daily injections of saline (same volume). Sexual behavior and sexual motivation were tested after 7, 14, 21, 28, 35, and 42 days of treatment. In

the last test, performed after 42 days of treatment, the amount of EB given was doubled (12.5 μg).

Sexual motivation was assessed by studying the time a female rat elected to spend in the vicinity of a sexually active male rather than in the vicinity of an estrous female or elsewhere. The testing apparatus was an open field arena (plexiglas, 100 × 50 cm) with two plastic boxes (25 × 15 cm) positioned on opposite sides of the arena; in these boxes, the stimuli (i.e., the male and female rat) were placed. The positions of the stimuli were changed randomly for each test. The partition between the stimuli and the experimental animal was a metal net allowing the animals to see, hear, and smell each other. Platforms (18 × 11 cm) in front of the stimulus compartments were balanced upon microswitches that were sensed by the controller to record the visits and the duration of each visit to each of the two stimuli. Testing was performed in a dark, silent room. Each experimental animal was placed in the arena, allowed to adapt for 5 min in the presence of the stimuli and, thereafter, tested for 15 min. After each test, the arena was cleaned with soapy water before another animal was introduced. Percentage of total time spent near the stimulus male, the female, or away from both stimuli were registered.

In all tests, the sexual behavior was studied immediately after the sexual motivation test. The experimental female was presented to a sexually active male in a circular yard (50 cm in diameter). The male was allowed to perform 10 mounts. A lordosis quotient was computed by dividing the number of lordosis (dorsiflexion of the back in response to a mount) with the total number of mounts and multiplying this ratio with 100. Besides lordosis, the amount of hop/darting and ear wiggling (see above) in response to male mounting was registered.

RESULTS

Experiment 1

Before drug treatment, all animals showed regular 4-day behavioral estrous cycles. Whereas a nonsignificant decrease in the percentage of animals showing behavioral estrous was observed as early as 1 week after the beginning of treatment with fluoxetine, the difference between fluoxetine-treated rats and controls achieved statistical significance during the 2nd and 3rd weeks of treatment and remained significantly decreased 1 week after the termination of drug administration (Figure 1). A full recovery of estrous behavior in the fluoxetine-treated group was observed 3 weeks later.

In both fluoxetine-treated animals and in controls, a regular vaginal cyclicity was observed throughout the treatment period (data not shown). Thus, 100% of both the fluoxetine-treated ($n = 8$) and the saline-treated ($n = 7$) females showed regular vaginal cyclicity.

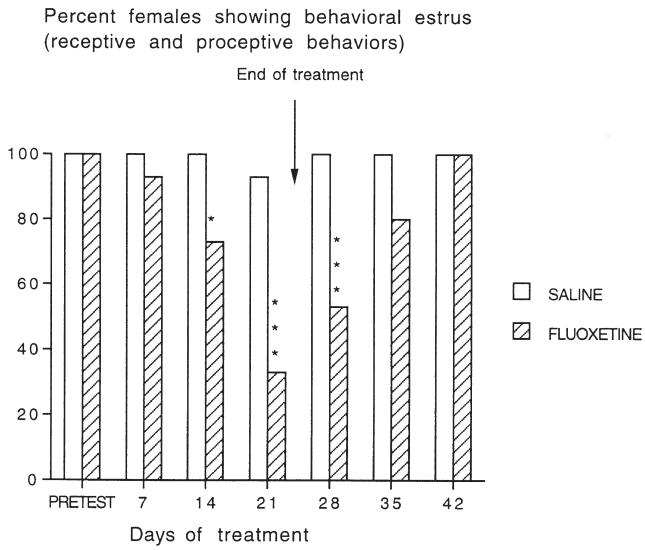

Figure 1. Percentage of females showing behavioral estrous before, during, and after treatment with fluoxetine ($n = 15$) or saline ($n = 15$). Shown is the percentage of animals displaying behavioral estrous at least once a week during the period indicated. * = $p < .05$; *** = $p < .01$ (chi^2 test).

Experiment 2

As shown in Figure 2, fluoxetine-treated females displayed significantly less proceptive behaviors (hop/darting and ear wiggling) than controls. These differences were statistically significant on treatment days 21 and 35. A significant difference between the two groups was observed also when the dose of EB was increased (day 42).

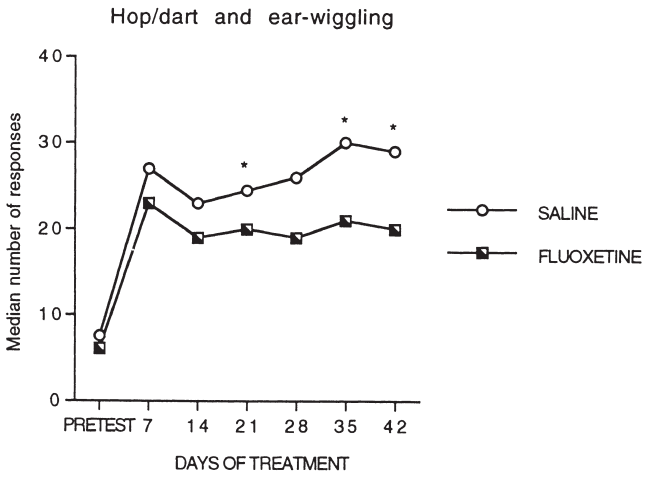

Figure 2. Number of proceptive behaviors (hop/darting and ear wiggling) displayed by ovariectomized female rats primed with estradiol benzoate and progesterone (see methods) before and during treatment with fluoxetine (10 mg/kg) or saline. * = $p < .05$ (Mann–Whitney U-test).

Fluoxetine-treated females showed significantly less lordosis behavior than controls on treatment days 21, 28, and 35 (Figure 3). However, on day 42, when the dose of EB had been increased, no group differences were observed with respect to lordotic behavior.

Both fluoxetine-treated animals and controls displayed a significant preference for the male in the sexual motivation tests (Figure 4). Fluoxetine-treated animals spent relatively less time near the male than did controls on day 7, but not during the subsequent tests.

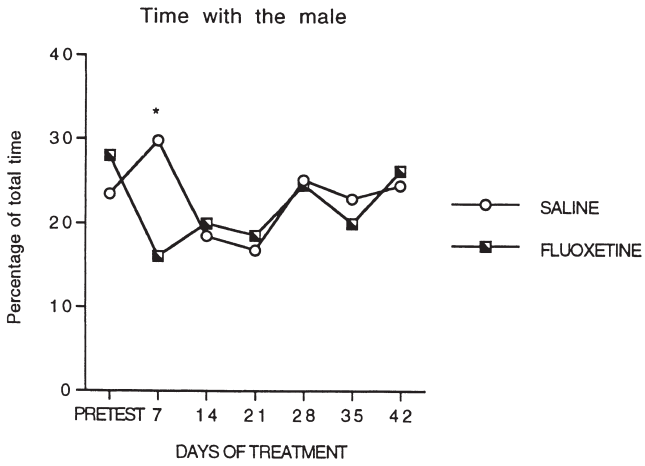

Figure 4. Median percentage of total test time spent in the vicinity of a male in the sexual motivation tests before and during treatment with fluoxetine or saline. * = $p < .05$ (Mann–Whitney U-test).

DISCUSSION

Many reports suggest that SRIs may cause anorgasmia and reduced libido in women. The purpose of this study was to investigate to what extent subchronic administration of a selective SRI (fluoxetine) influences sexual motivation, sexual receptivity, and sexual behavior in female rats.

The most dramatic effect of fluoxetine administration observed was a marked reduction in the percentage of normally cycling animals displaying behavioral estrous when exposed to sexually active male rats that were prevented from making intromission. Thus, after 3 weeks of treatment, only 5 of 15 of the fluoxetine-treated animals, but 14 of 15 of the controls, displayed signs of receptivity in the estrous phase. To our knowledge, this study is the first to show an effect of a selective SRI on estrous behavior in normally cycling rats; however, an inhibitory effect of a 5HT1A agonist (see below) on lordosis behavior in the estrous phase has previously been reported by Uphouse and co-workers (Uphouse et al. 1991, Uphouse et al. 1992; Uphouse and Caldarola-Pastuszka 1993).

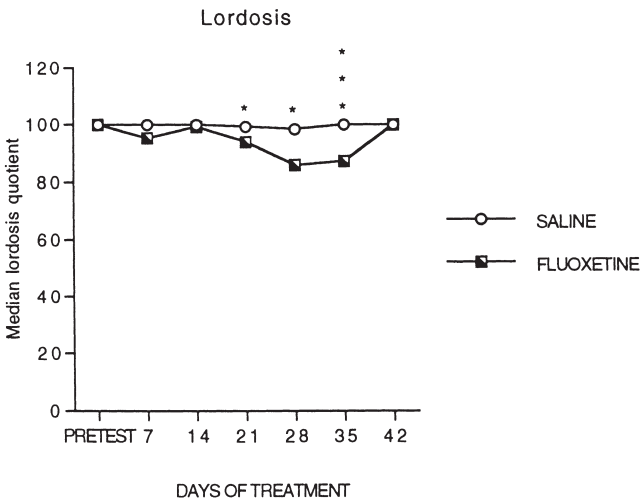

Figure 3. Median lordosis quotient displayed by ovariectomized female rats primed with estradiol benzoate and progesterone (see methods) before and during treatment with fluoxetine (10 mg/kg) or saline. * = $p < .05$; *** = $p < .001$ (Mann–Whitney U-test).

No measurement of pituitary or sexual hormones was undertaken; however, the observation that vaginal estrous was not influenced by fluoxetine suggests that the effect of the drug on behavioral estrous was not caused by interference with the hormonal cyclicity, but to an influence on brain areas involved in mediating the effects of sex steroids on behavior. In contrast, subchronic administration of the tricyclic antidepressant drug imipramine has previously been reported to disrupt both female rat vaginal cyclicity and estrous behavior (Maswood and Uphouse 1992). As with fluoxetine, imipramine inhibits serotonin reuptake; however, it also affects noradrenaline reuptake as well as muscarinic, histaminergic, alpha-adrenergic, and 5HT2-serotonergic receptors.

The concept that serotonin is a factor of importance for cycle-related changes in behavior lends support from a recent study showing that cycle-related differences in stress induced by swimming in rats is abolished by the administration of the strong (but nonselective) SRI clomipramine (Marvan et al. 1996). Moreover, many studies have shown that cycle-related irritability and depressed mood in women (premenstrual dysphoria, PMD) can be effectively reduced either by compounds disrupting the hormonal cyclicity (Muse et al. 1984) or by SRIs such as clomipramine (Sundblad et al. 1992), fluoxetine (Steiner et al. 1995), and paroxetine (Eriksson et al. 1995). The lack of effect of fluoxetine on vaginal cyclicity observed in the present study also is in line with clinical experience; thus, although SRIs profoundly influence cycle-related changes in mood in women with PMD, and often reduce libido, they are not

reported to exert any major influence on the regularity of the menstrual bleedings.

A negative effect of fluoxetine on sexual behavior was observed also in ovariectomized rats primed with EB+P. Fluoxetine, thus, induced a small but significant reduction in the lordosis quotient as well as in proceptive behavior; the former but not the latter effect could be overcome by an increase in the estradiol dose from 6.25 to 12.5 μg. Notably, also 6.25 μg of estradiol is a rather high dose. To what extent the effect of fluoxetine on sexual behavior is more pronounced in rats primed with a lower dose of estradiol is the topic of on-going studies in our laboratory.

The observation that a serotonin reuptake inhibitor reduced lordosis in ovariectomized rats primed with EB+P is well in line with previous studies, suggesting that serotonin exerts a predominantly inhibiting effect on this behavior. Thus, in early studies, Meyerson and coworkers showed that lordosis in hormonally primed rats is enhanced by serotonin-depleting agents such as reserpine, tetrabenazine, and p-chlorphenylalanine (PCPA), and counteracted by the serotonin precursor 5-hydroxytryptophan (5-HTP) (Meyerson 1964a,b; Meyerson and Lewander 1970; Meyerson et al. 1974). Further support for an inhibitory influence of serotonin on the lordosis response in rat has subsequently been obtained in studies using the serotonergic neurotoxin 5,7-DHT (Frankfurt et al. 1985), monoamine oxidase inhibitors (Luine and Paden 1982; Allen et al. 1993), the serotonin releaser fenfluramine (Everitt et al. 1974), or the combination of a serotonin precursor plus a selective SRI (Ahlenius et al. 1989). Also, studies in nonhuman primates support the concept that serotonin reduces sexual receptivity in females; thus, in rhesus monkeys, female sexual behavior was suppressed by the serotonin reuptake inhibitor clomipramine and stimulated by the serotonin synthesis inhibitor PCPA. Moreover, the latter effect was counteracted by the serotonin precursor 5-HTP (Gradwell et al. 1975; Everitt 1978).

Although the predominant influence of serotonin on lordosis behavior is inhibitory, all serotonin receptor subtypes do not counteract lordosis. Thus, whereas selective 5-HT1A agonists do inhibit lordosis in rat (Ahlenius et al. 1986; Uphouse et al. 1991), 5HT2 receptors apparently have the opposite effect (Hunter et al. 1985; Mendelson and Gorzalka 1985; Ahlenius et al. 1989). Of interest in this context is the observation that subchronic administration of fluoxetine (and other SRIs) to rat has been reported to downregulate the responsiveness of 5-HT2 receptors but not that of 5HT1A receptors (see, e.g., Maj and Moryl 1993).

Notably, both with respect to hop/darting and lordosis in the mating experiments, and with respect to spontaneous estrous behavior, the effects of fluoxetine increased by time; thus, after only 7 days of fluoxetine administration, no significant effects were observed. This observation underlines the necessity of subchronic drug administration when exploring the effect of SRIs on sexual function in rats.

With respect to sexual motivation, as reflected by the amount of time a sexually active rat elects to spend in the vicinity of a rat of the opposite sex (rather than in the vicinity of a rat of the same sex, or elsewhere), the effect of fluoxetine in female rats was weaker than that previously found in males (Vega Matuszczyk et al. 1998). A significant difference between fluoxetine-treated animals and controls was observed only after 7 days of treatment, but not in the subsequent testing. Thus, in the present experiments, a dissociation between performance and sexual motivation was observed. When interpreting the results in the motivation test, the fact that the rats were primed with a relatively high dose of estradiol (see above) should be taken into consideration; to what extend fluoxetine exerts a more profound effect on motivation in rats primed with lower doses of estradiol is presently being investigated.

The effect of fluoxetine on estrous behavior, on receptive behavior, and on lordosis was, hence, increased as a function of time; whereas, the effect on motivation was fast in onset and transient. Unfortunately, information regarding the onset of action and time course of SRI-induced sexual side effects in women is scarce. However, recent studies suggest that both reduced libido and anorgasmia may display a relatively short onset of action (⩽14 days) (Wikander et al. in press). To what extent these effects of SRIs in women are the subject of drug tolerance seems to be dependent on which of the difference SRIs is given, and/or on the dose (Monteiro et al. 1987; Sundblad et al. 1997; Wikander et al. in press).

In conclusion, subchronic administration of fluoxetine was shown to impair estrous behavior in normally cycling rats and to reduce receptive behavior in ovariectomized rats primed with EB+P. In contrast, the amount of time a female rat put in an open field arena elected to spend in the vicinity of a male rat (rather than in the vicinity of female, or elsewhere) was only marginally influenced. Further investigations of the effects of SRIs on estrous behavior and on receptive behavior in hormonally primed animals may lead to an increased understanding of the mechanisms underlying SRI-induced sexual side effects in women.

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