Physiology & Behavior, Vol. 67, No. 3, pp. 315–320, 1999

0031-9384/99/ $–see front matter

ELSEVIER

PII S0031-9384(98)00298-4

Behavioral Effects of Acute and Chronic Fluoxetine in Wistar–Kyoto Rats

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Received 3 August 1998; Accepted 14 October 1998

GRIEBEL, G., C. COHEN, G. PERRAULT AND D. J. SANGER. *Behavioral effects of acute and chronic fluoxetine in Wistar–Kyoto rats.* PHYSIOL BEHAV **67**(3) 315–320, 1999.—It has been previously reported that Wistar–Kyoto (WKY) rats may be useful in the study of the biological mechanisms involved in stress-related disorders. In the present study, WKY were treated acutely or chronically (one daily i.p. injection for 22–24 days) with the selective 5-HT reuptake inhibitor and clinically effective antidepressant and anxiolytic fluoxetine (5 and 20 mg/kg) and exposed to the forced swimming test (FST) and to the elevated plus-maze (EPM) at different times postinjection (30, 60, min or 24 h). In the FST, WKY failed to respond to fluoxetine, regardless of treatment. In the EPM, acute fluoxetine (20 mg/kg) produced anxiolytic-like effects when animals were tested 24 h, but not 30 min after drug administration. Positive effects in the EPM were evident on both conventional (open-arm activity) and ethological (risk assessment) measures in the absence of effect on activity measures (total and closed-arm entries). No evidence for anxiolytic-like activity was observed following chronic fluoxetine. These results indicate that WKY rats are resistant to fluoxetine treatment in the FST, while their behavior may be modified in the EPM when animals received a single fluoxetine challenge 24 h before testing. Overall, these findings provided little evidence that WKY rats may represent a valid model of stress-related disorders. © 1999 Elsevier Science Inc.

Acute treatment Anxiety Chronic treatment Depression Elevated plus-maze Fluoxetine Forced swimming test Wistar–Kyoto rats

WISTAR–KYOTO (WKY) rats were developed initially to serve as a control strain to Spontaneously Hypertensive Rats (SHR), which were selectively bred for the tendency to develop arterial hypertension (17). Unlike SHR, WKY maintain normal blood pressure. Together, these animals represent one of the most widely accepted pairs of strains for the study of hypertension. In addition to differences in blood pressure, WKY and SHR rats were found to show neurophysiological and behavioral differences. For example, SHR rats display a greater increase in plasma levels of catecholamines following exposure to a variety of stressors (electric shock, cold exposure, immobilization) than WKY rats (11,16,23). Studies that investigated behavioral differences between the two strains showed that WKY rats displayed lower exploratory activity when exposed to novelty than SHR rats. WKY rats, compared to their hypertensive counterparts, showed both reduced locomotor activity in the elevated plus-maze (EPM) and/or the open-field tests and greater reactions to aversive environments (fewer entries into the central area of the open-field and fewer visits to the open arms of the EPM) (7,10,28). Moreover, compared to SHR, WKY rats showed increased startle responses and immobility reactions following audiogenic stimulation (10,30). Furthermore, WKY rats have been reported to display high levels of immobility in the forced swimming test (FST) and to be more suceptible to stress-induced ulcers than SHR rats (13,19,20). Direct comparisons between WKY, SHR, and other strains of rats have revealed that WKY, but not SHR, display a high tendency to adopt passive strategies in anxiety models (open-field, EPM, social interaction, and light/dark tests) or in the FST, compared to several inbred (Fisher 344, Lewis, Brown Norway, Wistar Furth) and/or outbred (Sprague–Dawley, Wistar) strains (8,13, 14,18,25). Together, these findings led to the suggestion that WKY rats may represent a genetic model of depression and/or anxiety-related disorders (18,20,26). However, several recent studies with the antidepressants imipramine and desipramine have indicated that WKY rats are resistant to acute and repeated treatments with these drugs in the FST (13,14).

To further examine the idea that WKY rats may provide a valid model of stress- related disorders, the present study investigated the effects of short- and long-term schedules of administration of the 5-HT reuptake inhibitor fluoxetine on the

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behavior of WKY rats in the FST and EPM. Fluoxetine has been successfully used in the clinical management of several anxiety disorders, including social phobia, panic, obsessive–compulsive and posttraumatic stress disorders [e.g. (4,5,31)]. In addition, large-scale clinical trials showed fluoxetine to be as effective as tricyclics in the treatment of depression [for review, see (29)]. The FST is a test that measures the ability of antidepressants to reduce the occurrence of behavioral immobility after exposure to swimming stress (24). It is one of the most commonly used tests for antidepressant activity, and is sensitive to all major classes of antidepressant drugs (3). The EPM is one of the most popular animal tests for research on the behavioral pharmacology of anxiety (21). In this test, rodents of most strains show a pattern of behavior characterized by open-arm avoidance, a tendency that is generally suppressed by anxiolytics [for review, see (27)].

MATERIALS AND METHODS

Animals

Male Wistar–Kyoto rats weighing 180–280 g at time of testing were used. All animals were housed in groups of five and maintained under standard laboratory conditions with free access to food and water. They were kept on a 12:12-h light:dark cycle with light onset at 0700 h. Animals were bred and provided by Charles River (Saint-Aubin-les-Elbeuf, France).

Forced Swimming Test

Rats were placed in individual glass cylinders (39 cm high, 20 cm diameter) containing 18 cm of water maintained at 25°C. Two swimming sessions were conducted, between 0830 and 1530 h: an initial 15-min pretest followed 24 h later by a 5-min test. Following both swimming sessions, the rats were removed from the cylinders, dried with papel towels, and placed under a 60-W bulb for 15 min before being returned to their home cage. The total duration of immobility was measured during the 5-min test. The animal was judged to be immobile whenever it remained floating passively in the water.

Elevated Plus-Maze

All parts of the apparatus were made of dark polyvinylplastic with a black rubber floor. It consisted of a maze elevated to a height of 50 cm with two open (50 × 10 cm) and two enclosed arms (50 × 10 × 50 cm), arranged so that the arms of the same type were opposite each other, connected by an open central area (10 × 10 cm). To prevent rats falling off, a rim of Plexiglas (0.5 cm high) surrounded the perimeter of the open arms. The illumination in the experimental room consisted of one red neon tube fixed on the ceiling so that experiments were performed under dim light conditions. At the beginning of the experiment, rats were placed in the center of the maze, facing one of the enclosed arms, and observed for 4 min. The apparatus was equipped with infrared beams and sensors capable of measuring

TABLE 1
SCHEDULE OF INJECTIONS FOR EACH CONDITION

Days 1–21	Day 22		Day 23			Day 24		
Daily Injection	Test	Injection After Test	Injection 1 h Before Test	Test	Injection After Test	Injection 30 min Before Test	Test	Groups
Vehicle	FST1	Vehicle	Vehicle	FST2	Vehicle	Vehicle	EPM	1. Vehicle: FST + EPM
						Fluoxetine (5 or 20 mg/kg)	EPM	2. Fluoxetine (5): EPM/ Acute (30 min)
								3. Fluoxetine (20): EPM/ Acute (30 min)
			Fluoxetine (5 or 20 mg/kg)	FST2	Vehicle	Vehicle	EPM	4. Fluoxetine (5): FST/ Acute (1 h) + EPM/ Acute (24 h)
								5. Fluoxetine (20): FST/ Acute (1 h)+ EPM/ Acute (24 h)
	FST1	Fluoxetine (5 or 20 mg/kg)	Vehicle	FST2				6. Fluoxetine (5): FST/ Acute (24 h)
								7. Fluoxetine (20): FST/ Acute (24 h)
Fluoxetine (5 or 20 mg/kg)	FST1	Fluoxetine (5 or 20 mg/kg)	Vehicle	FST2	Fluoxetine (5 or 20 mg/kg)	Vehicle	EPM	8. Fluoxetine (5): FST/ Chronic (24 h) + EPM/ Chronic (24 h)
								9. Fluoxetine (20): FST/ Chronic (24 h) + EPM/ Chronic (24 h)
			Fluoxetine (5 or 20 mg/kg)	FST2	Vehicle	Fluoxetine (5 or 20 mg/kg)	EPM	10. Fluoxetine (5): FST/ Chronic (1 h) + EPM/ Chronic (30 min)
								11. Fluoxetine (20): FST/ Chronic (1 h) + EPM/ Chronic (30 min)

FST1: forced swimming test (first session); FST2; forced swimming test (second session); EPM; elevated plus-maze testing.

time spent in open arms, number of open-arm entries, and number of closed-arm entries (defined as entry of all four limbs into an arm of the maze). In addition, rats were observed via videolink by an observer located in an adjacent room. This permitted the recording of more ethologically orientated measures: (a) attempt: attempt at entry into open arms followed by avoidance responses; (b) head dipping: protruding the head over the ledge of an open arm and down towards the floor (this response can occur while the animal's body is in the closed arms, central square, or on open arms). The results were expressed as mean ratio of time spent in open arms to total time spent in both open and closed arms, mean total number of entries in both open and closed arms, mean total number of closed-arm entries, mean total number of attempts, and mean total number of head dips. Testing was performed between 0830 and 1300 h.

Drugs

Fluoxetine (synthesized by the chemistry department, Synthélabo Recherche) was prepared as suspensions in physiological saline containing one or two drops of Tween 80. Rats were randomly assigned to treatment with fluoxetine (5 or 20 mg/kg, $n = 8$–10), or saline ($n = 50$) for 21 days administered intraperitoneally once daily. They were exposed to the first swimming session on Day 22, the second swimming session on Day 23, and the elevated plus-maze test on Day 24. Animals were tested either 30 min (EPM), 1 h (FST), or 24 h (EPM, FST) after the last drug administration. Schedules of injections and testing are given in Table 1.

Statistics

Data were analyzed by a one-way analysis of variance (ANOVA). Subsequent comparisons between treatment groups and control were carried out using Dunnett's *t*-test.

RESULTS

Forced Swimming Test

The effects of acute and chronic treatment with fluoxetine on immobility time in the FST test are shown in Table 2. Neither acute (5 and 20 mg/kg) nor chronic (5 mg/kg) treatment with fluoxetine decreased immobility time. Rats chronically injected with fluoxetine 20 mg/kg were not able to swim for the entire 15-min session on Day 22, so that their performance was not included in the statistical analysis. Although the reason for this is unclear, it is worth mentioning that rats from this group showed dramatic weight loss, suggesting that it may have disrupted their behavior in the FST.

Elevated Plus-Maze

The effects of acute and chronic treatment with fluoxetine in rats exposed to the EPM are shown in Fig. 1 and in Table 3. ANOVA revealed a significant main effect for all behavioral measures: percentage of time spent in open arms, $F(8, 57) = 2.89$, $p < 0.05$; number of head dippings, $F(8, 57) = 7.02$, $p < 0.001$; number of attempts, $F(8, 57) = 6.27$, $p < 0.001$; total number of arm entries, $F(8, 57) = 3.25$, $p < 0.01$; and number of closed arm entries, $F(8, 57) = 2.56$, $p < 0.05$. Post hoc analysis showed that rats treated chronically with saline and injected with 20 mg/kg of fluoxetine 24 h before testing spent significantly more time in open arms, displayed more head dippings, and made fewer attemps at entry into open arms followed by avoidance responses than vehicle-treated rats. The other treatments failed to modify significantly the spatio-temporal measure and head dippings. In contrast, animals treated with fluoxetine at 20 mg/kg, regardless of treatment regimen or injection latency, showed significantly less attempt responses. All animals treated chronically with 20 mg/kg of fluoxetine made significantly fewer entries in both open and closed arms than other groups.

DISCUSSION

The present results showed that neither acute nor chronic fluoxetine challenge modified the behavior of WKY rats in the FST. These findings are consistent with previous reports indicating that WKY are poorly responsive to the antidepressants imipramine and desipramine in this test (13,14). For example, these authors showed that desipramine had antiimmobility effects in WKY rats at a much higher dose (i.e., 25 mg/kg) than that producing positive effects in Sprague–Dawley or Brown–Norway rats (i.e., 5 mg/kg). Moreover, the magnitude of the antiimmobility effects with WKY rats at 25 mg/kg was smaller than that observed with the two other strains at this

TABLE 2

EFFECTS OF ACUTE OR CHRONIC (ONE DAILY INJECTION FOR 22–23 DAYS) TREATMENT WITH FLUOXETINE ON IMMOBILITY TIME IN THE FORCED SWIMMING TEST ON DAY 23

	Fluoxetine (mg/kg)	Immobility time (sec)
Vehicle	0	240 ± 9
Acute (1 h)	5	231 ± 13
	20	233 ± 16
Acute (24 h)	5	242 ± 14
	20	251 ± 11
Chronic (1 h)	5	224 ± 8
	20	—
Chronic (24 h)	5	235 ± 11
	20	—

Animals were tested either 1 h or 24 h after drug administration. Data represent mean ± SEM (n = 4–5 per group, except for rats treated chronically with saline where $n = 10$).

TABLE 3

EFFECTS OF ACUTE OR CHRONIC (ONE DAILY INJECTION FOR 23–24 DAYS) TREATMENT WITH FLUOXETINE ON LOCOMOTOR INDICES IN THE ELEVATED PLUS-MAZE TEST

	Fluoxetine (mg/kg)	Total Arm Entries	Closed Arm Entries
Vehicle	0	5.8 ± 0.5	5.4 ± 0.5
Acute (30 min)	5	3.4 ± 1.7	3.2 ± 1.5
	20	2.8 ± 1.3	2.8 ± 1.3
Acute (24 h)	5	6.6 ± 1.0	4.8 ± 0.6
	20	5.3 ± 0.8	3.3 ± 1.0
Chronic (30 min)	5	5.8 ± 0.5	5.8 ± 0.5
	20	2.0 ± 0.6*	1.8 ± 0.5*
Chronic (24 h)	5	5.6 ± 0.7	5.0 ± 0.6
	20	2.0 ± 0.7*	1.8 ± 0.9*

Animals were tested either 30 min or 24 h after drug administration. Data represent mean ± SEM (n = 4–5 per group, except for rats treated acutely with fluoxetine (24 h) and saline where $n = 10$).

*$p < 0.05$ (Dunnett's *t*-test).

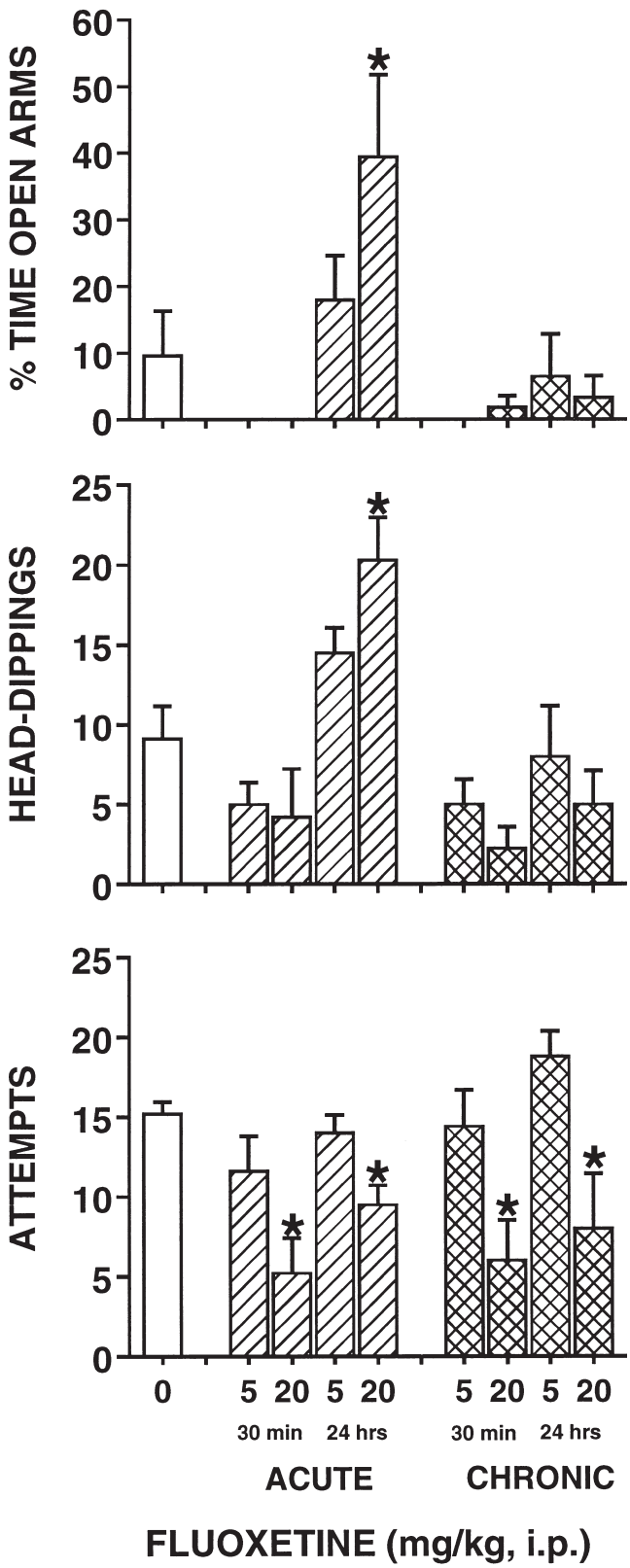

FIG. 1. Effects of acute or chronic (one daily injection for 23–24 days) treatment with fluoxetine on anxiety indices in the elevated plus-maze test. Animals were tested either 30 min or 24 h after drug administration. Data represent mean ± SEM (n = 4–5 per group, except for rats treated acutely with fluoxetine (24 h) and saline, where n = 10). *$p < 0.05$ (Dunnett's t-test).

dose. Taken together with these latter findings, the present results further strengthen the idea that this strain may be resistant to antidepressant treatment.

In the EPM, all animals showed low levels of exploration regardless of the treatment they had received. This is consistent with previous findings showing that WKY rats adopt passive strategies in anxiety models compared to other rat strains (8,13,14,18,25). A single injection of 20 mg/kg of fluoxetine produced anxiolytic-like effects in WKY rats when animals were tested 24 h after the administration of the drug. Thus, on the traditional spatio-temporal indice of anxiety, fluoxetine increased the time spent by animals in the open arms of the maze. Furthermore, on the more ethologically derived measures of anxiety, this treatment increased head dippings over the ledge of the open arms and reduced attempts at entry into open arms followed by avoidance responses. These latter findings indicate that WKY rats treated acutely with 20 mg/kg of fluoxetine 24 h before testing showed a reduced reluctance to leave relatively safe areas of the maze (decreased attempts) and an enhanced tendency to actively explore the potentially dangerous open arms (increased head dipping), a behavioral pattern that strengthens the conclusion of an anxiolytic-like action based upon the traditional index of anxiety. Traditionally, among the basic parameters scored in plus-maze studies, closed-arm entries and, to a lesser extent, total arm entries, are often considered as indices of general activity (15). The present findings that positive effects were observed in the absence of modification of either activity measure indicates that the anxiolytic-like effects of 20 mg/kg fluoxetine given acutely 24 h prior testing have not been contaminated by behavioral impairment.

No evidence for anxiolytic-like activity was observed after fluoxetine was administered on a chronic basis or acutely, 30 min prior to testing. It is, however, worth mentioning that all animals challenged with a dose of fluoxetine 30 min before experiments spent very little time in the open arms, with no animal exploring the more aversive parts of the apparatus, suggesting an anxiogenic-like activity. This effect failed to reach statistical significance because baseline levels of time spent in open arms were too low to be further decreased (less than 10% of total time). Similar findings have been reported with Wistar rats in the EPM after single dosing of fluoxetine 30 min prior exposure to the test (9,12,22). Taken together, these results indicate that time between fluoxetine challenge and testing appears to be of crucial importance when investigating the anxiolytic-like effects of fluoxetine in the EPM. Whether or not these findings may be extended to other strains of rats remains to be established. However, a recent study with fluoxetine (8 mg/kg) in Wistar rats showed that an injection-test interval of 17 or 40 h had no influence on the behavior of animals exposed to two conflict tests (2).

The underlying mechanims for these observed effects of fluoxetine remain to be established, because no study has so far investigated neurochemical changes following acute or chronic treatment with fluoxetine in WKY rats. Studies using outbred (i.e., Sprague–Dawley or CD-COBS) rats have demonstrated that acute administration of fluoxetine (10–20 mg/kg) rapidly (within 20 min) increases extracellular concentrations of 5-HT (e.g., raphe nuclei, striatum, frontal cortex). The increase in 5-HT levels is, however, balanced by concurrent

inhibition of the activity of 5-HT neurons through stimulation of 5-HT_{1A} autoreceptors. Similarly, extracellular concentrations of 5-HT were reported to be increased following protracted treatment with fluoxetine (8 to 21 days). Moreover, the feedback inhibition of the activity of 5-HT neurons in the raphe nuclei was successively reduced and after 14 days administration the firing rate has returned to baseline values (1).However, the rise in 5-HT content was still evident 24 h after the last fluoxetine administration, although such an effect is not present 24 h after a single injection. Assuming that similar neurochemical changes occur in WKY rats after fluoxetine administration, the rapid increase in 5-HT concentration after acute fluoxetine challenge might underlie the anxiogenic-like activity. Further, according to the 5-HT hypothesis of anxiety suggesting that a reduction of the function of brain 5-HT pathways may lead to an anxiolytic-like effect, whereas increased activity of ascending 5-HT pathways usually results in an anxiogenic-like action (6), it can be proposed that the anxiolytic-like effects observed 24 h after a single administration of fluoxetine might be associated with a reduction of 5-HT levels probably secondary to the stimulation of 5-HT_{1A} autoreceptors.

In summary, the present experiments showed that in WKY rats, acute treatment with fluoxetine failed to produce antidepressant-like effects in the FST, whereas a single injection of the compound produced anxiolytic-like effects in the EPM when animals were tested 24 h but not 30 min after the administration of the drug. Because significant clinical improvement of depressed and anxious patients requires prolonged administration of fluoxetine, it might have been expected that chronic fluoxetine counteract immobility and/or hypoactivity in a passive strain such as WKY. However, this was not the case. The reasons for the lack of sensitivity of WKY rats to fluoxetine remain to be determined, but may include several factors such as procedures, housing conditions, level of illumination, scoring technique, or timing of administration during the light/dark phase of the day, as it is known that for most of experimental and clinical drugs their activity varies, depending on the time of administration. Alternatively, these results confirm that WKY rats are insensitive to antidepressants in the FST and indicate that they are only poorly responsive to fluoxetine challenge in the EPM. It is possible that the mechanisms controlling the behavior of WKY rats in the FST and the EPM are dissociated from those controlling emotional-oriented responses, thus questioning the idea that WKY rats may provide a valid model of stress-related disorders.

ACKNOWLEDGEMENTS

The expert technical assistance of Stéphanie Hamon, Christine Chantelauze. and Anne-Marie Poisson is greatly appreciated.

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