Psychopharmacology (2001) 153:365–372
DOI 10.1007/s002130000594

ORIGINAL INVESTIGATION

**Sulev Kõks · Sergei Beljajev · Indrek Koovit
Urho Abramov · Michel Bourin · Eero Vasar**

8-OH-DPAT, but not deramciclane, antagonizes the anxiogenic-like action of paroxetine in an elevated plus-maze

Received: 4 July 2000 / Accepted: 11 September 2000 / Published online: 13 December 2000

Abstract *Objective:* To investigate whether a 5-hydroxytryptamine (5-HT) reuptake inhibitor (paroxetine) has an anxiogenic-like effect and what possible pharmacological mechanism underlies that action. *Methods:* We used the rat elevated plus-maze paradigm followed by measurement of locomotor activity. Some of the rats were subjected to handling and adaptation to the experimental situation, while the rest were naive to the test situation. Paroxetine was administered as a single treatment and in combination with the 5-HT_{1A} receptor agonist (8-OH-DPAT) or 5-$HT_{2A/2C}$ receptor antagonist (deramciclane). *Results:* The administration of paroxetine induced an anxiogenic-like action in rats adapted to handling, but not in handling naive animals. Treatment with paroxetine (0.1–2 mg/kg) reduced the number of open arm visits and time spent in open arms, and the ratio between open and total arm entries in the elevated plus-maze. Paroxetine also decreased the number of line crossings and head-dips. Paroxetine caused the strongest anti-exploratory action at a dose of 0.5 mg/kg. Paroxetine did not suppress the locomotor activity of rats, showing that the described anti-exploratory effect was behaviourally specific to the plus-maze. Pretreatment with 8-OH-DPAT (0.05 mg/kg) completely reversed the anxiogenic-like action of paroxetine, whereas treatment with deramciclane (2 mg/kg) affected only the number of closed arm visits. Deramciclane (0.5–2 mg/kg) and 8-OH-DPAT (0.01–0.1 mg/kg) changed neither exploratory behaviour nor locomotor activity if given as single treatments to the habituated rats. *Conclusion:* The 5-HT reuptake inhibitor, paroxetine, at a low dose (0.5 mg/kg) induces an anxiogenic-like action in handling adapted rats. The effectiveness of 8-OH-DPAT against paroxetine probably supports a role of both pre- and postsynaptic 5-HT-ergic mechanisms in the anxiogenic-like action of paroxetine.

Keywords Handling adaptation · 5-Hydroxytryptamine · Paroxetine · 8-OH-DPAT · Deramciclane · Elevated plus-maze · Anxiety · Locomotor activity

S. Kõks (✉) · S. Beljajev · I. Koovit · U. Abramov · E. Vasar
Department of Physiology, University of Tartu, 19 Ravila Street, 50411 Tartu, Estonia
e-mail: Sulev.Koks@ut.ee
Tel.: 372-7-374335, Fax: 372-7-374332

M. Bourin
Laboratory of Pharmacology, University of Nantes, 1 rue Gaston-Veil, 44035 Nantes Cedex, France

Introduction

Activation of 5-hydroxytryptamine-(5-HT)-ergic neurotransmission has been reported to increase anxiety in laboratory animals (Iversen 1984; Handley and McBlane 1993; Handley et al. 1993). Thus, the exposure of rats to a novel aversive environment increases the release of 5-HT in the frontal cortex and hippocampus (File et al. 1993; Rex et al. 1994), while the administration of a 5-HT receptor agonist, *m*-chlorophenyl-piperazine (mCPP), induces anxiety both in humans and in animal models (Kennett et al. 1989; Pigott et al. 1993). Conversely, treatment with 5-HT_2 and 5-HT_3 receptor antagonists apparently reduces anxiety in rodents (Handley et al. 1993). Moreover, the administration of a 5-HT reuptake inhibitor fluoxetine dose-dependently increases anxiety of rats in an elevated plus-maze of anxiety (Handley and McBlane 1993). This is consistent with clinical studies where the acute administration of 5-HT reuptake inhibitors is reported to induce anxiety in patients suffering from anxiety disorders (Den Boer and Westenberg 1996). However, it is not clear whether the action of 5-HT reuptake inhibitors in animal models truly represents anxiogenesis, as in our previous study paroxetine, another 5-HT reuptake inhibitor, antagonized the exploratory behaviour of rats in the plus-maze but only at a dose which also suppressed their locomotor activity (Kõks et al. 1999).

In the present study, an attempt was made to clarify this issue. It has been shown that handling adaptation and acclimatization of animals to the experimental room increases the activity of anxiogenic compounds (Rodgers

et al. 1997). Therefore, before treatment with paroxetine, the rats were divided into two groups. One group of rats was subjected to handling for 3 consecutive days in the room where the experiment was to be carried out on day 4, whereas the other group of animals was naive to handling at the time of the experiment. The possible changes in anxiety were studied in the elevated plus-maze paradigm. Afterwards, the behaviour of rats was studied in locomotor activity boxes to exclude the possibility that any anti-exploratory effect seen might be due to the suppression of locomotor activity. After identifying a dose of paroxetine, which had anxiogenic-like effects in the model, studies of the pharmacological mechanism of action were conducted. Paroxetine was therefore co-administered with 8-hydroxy-2-(di-*n*-propylamino)tetralin (8-OH-DPAT), a 5-HT_{1A} receptor agonist (Fletcher et al. 1996), and deramciclane, a 5-$HT_{2A/2C}$ receptor antagonist (Gacsalyi et al. 1997), drugs affecting 5-HT-ergic neurotransmission in the brain.

Materials and methods

Animals

Male Wistar (Han/Kuo) rats (National Animal Centre, Kuopio, Finland) weighing 200–220 g were kept in the animal house at 20±2°C in 12-h light/dark cycle (light on at 0700 hours). Tap water and food pellets were available ad libitum. All animal procedures were approved by the University of Tartu Animal Care Committee in accordance with the European Communities Directive of 24 November 1986 (86/609/EEC). The animals were kept in the animal house for at least 2 weeks before the beginning of experiment.

Materials

Paroxetine, a selective 5-HT reuptake inhibitor, was provided by SmithKlineBeecham Pharmaceuticals (UK). Deramciclane fumarate was from Orion (Finland) and 8-OH-DPAT was obtained from RBI (USA). Paroxetine and 8-OH-DPAT were dissolved in saline. Deramciclane was suspended in 1% Tween-80 (Ferak, Germany) solution in saline. All experiments were conducted blind with respect to treatment.

Behavioural testing

In the first experiment, where the dose-response effect of paroxetine was studied, the rats were divided into two subgroups. One group of rats was subjected to handling for 3 consecutive days in the experimental room and the other group was handling naive. The handling habituation was performed each day between 1400 and 1600 hours. The animals were brought from the animal house into the experimental room where all conditions were similar to the experiment (lighting etc.). A person, performing the behavioural studies, took an animal out from the home cage by the hand and the imitation of IP injection was performed (with the poke of the syringe but without the injecting of solutions). After that the animal was put back into the home cage and 1 h later the procedure was repeated. The similar handling procedure was conducted on days 2 and 3. In the subsequent pharmacological studies, all the rats were handled for 3 days before exposure to the plus-maze experiment. On day 4, the animals were brought into experimental room 1 h before the experiment. Each rat was used only once. All experiments were carried out between 1400 hours and 1900 hours.

All drugs were given IP, the injection of deramciclane and 8-OH-DPAT being performed 35 min, and paroxetine 30 min pre-test. In studies where the interaction of paroxetine with deramciclane and 8-OH-DPAT was examined, the control animals received two vehicle injections, i.e. saline or 1% Tween in saline 35 min pre-test followed by saline 30 min pre-test.

Elevated plus-maze

The method initially suggested by Handley and Mithani (1984) for the measurement of exploratory behaviour was employed in rats with some modifications (Pellow et al. 1985). The elevated plus-maze was made from wood and painted green. The apparatus consisted of two opposite open arms (50×10 cm) without side walls and two enclosed arms (50×10×40 cm) with side walls and end wall, extending from a central square (10×10 cm). In the present study the protecting lips were not used on the open arms. In order to facilitate the counting of exploratory activity the open arms were divided by the lines into three equal parts. The maze was elevated to the height of 50 cm from the floor, and placed in a lit room (~750 lux). The behaviour of the animals was recorded on the videotape, which was afterwards analyzed by a person not involved in the performing of the experiment. During a 5-min observation session the following measures were taken by an observer: 1) number of head-dips; 2) number of line crossings on the open part; 3) time spent in exploring the open arms of plus-maze; 4) number of closed and open arm entries; 5) ratio between open and total arm entries. At the beginning of the test animals were placed onto the center of plus-maze, facing toward an open arm. An arm entry was counted only when all four limbs of the rat were within a given arm. The plus-maze was cleaned between the experiments by using of 5% alcohol solution.

Locomotor activity test

Immediately after the plus-maze exposure, the animals were placed singly into the photoelectric motility boxes connected to a computer (TSE Technical & Scientific Equipment GMBH, Germany). Each box consisted of a base frame (outer size: 56×56 cm, inner size: 48×48 cm) with two pairs of light barrier strips (transmitter and receiver), each equipped with 16 light barriers (located 35 mm from the bottom level of motility box). The distance between each light barrier was 28 mm. These light barrier strips were arranged at right angles to each other in the same plane and were used to determine the X and Y coordinates of the animal and thus its location during activity measurements. As the test animal normally interrupted several light barriers in each axis, an averaging procedure was used to define the actual coordinates of its location. The light barriers were scanned with a frequency of 10 Hz each. The light-barrier strips were connected to the control unit. By inserting a clear plastic box inside the base frame, the animal's movement was restricted to a square are of 448×448 mm. The height of this inner box was 450 mm. A transparent lid (made from the transparent material) was used to close the test boxes. The illumination level (~750 lux) was similar to that of in the plus-maze studies. After removing the rats from the boxes, the floor was cleaned using 5% alcohol solution. Time in exploration (s) and distance of exploration (m) were registered during the 5-min observation period.

Statistics

Results are expressed as mean values±SEM. The behavioural studies were analyzed using one-way analysis of variance (ANOVA). Post hoc comparisons between individual groups were performed by means of Newman-Keuls test using the Statistica for Windows software.

Results

The lowest dose of paroxetine (0.1 mg/kg) tended to reduce the exploratory behaviour of handling naive rats in the elevated plus-maze (Fig. 1). However, this action of paroxetine was not statistically significant. The treatment with paroxetine (0.1–2 mg/kg) did not change the locomotor activity of these rats either (not shown). In the habituated rats, the administration of paroxetine induced an anti-exploratory action in the plus-maze (Fig. 2). However, the effect of paroxetine was U-shaped with the strongest action at a dose 0.5 mg/kg. Paroxetine reduced the number of head-dips $F(3,56)=2.82$, $P<0.05$], line crossings [$F(3,56)=3.00$, $P<0.05$] and open arm visits [$F(3,56)=3.02$, $P<0.05$] (Fig. 2).

Time spent in open arms [$F(3,56)=2.96$, $P<0.05$] and ratio between open and total arm entires [$F(3,56)=2.85$, $P<0.05$] were also inhibited under the influence of paroxetine. It should be noted that paroxetine did not change the number of closed arm entries in this study. The administration of paroxetine did not modify the locomotor activity of rats in the motility boxes (Fig. 3). These data are in favour of an anxiogenic-like action of paroxetine in the plus-maze, since the 5-HT reuptake inhibitor reduces the "classical" (number of open arm entries, ratio of open and total arm entries), as well as the "ethological" measures (the number of head-dips) in the elevated plus-maze without changing the locomotor activity of rats. The administration of deramciclane (0.05–2 mg/kg) and 8-OH-DPAT (0.01–0.1 mg/kg) did not modify the exploratory behaviour of handling habituated rats in the plus-maze or their locomotor activity in the motility boxes (Fig. 3, Table 1). However, pretreatment of rats with the 5-HT_{1A} agonist 8-OH-DPAT (0.01–0.1 mg/kg) completely antagonized the anxiogenic-like action of paroxetine (0.5 mg/kg) [$F(4,45)=2.54$, $P<0.05$ (number of open arm entries), $F(4,45)=2.72$, $P<0.05$ (time in open arm), $F(4,45)=3.72$, $P<0.05$ (ratio between open and total arm entries), $F(4,45)=3.02$, $P<0.05$ (number of head-dips)] (Fig. 4) without changing the locomotor activity of animals (Fig. 3). It should be noted, however, that 8-OH-DPAT was effective only at one dose (0.05 mg/kg). By contrast from the other experiments, paroxetine reduced the number of closed arm entries in the study, where the interaction between paroxetine and deramciclane, a $5\text{-HT}_{2A/2C}$ receptor antagonist,

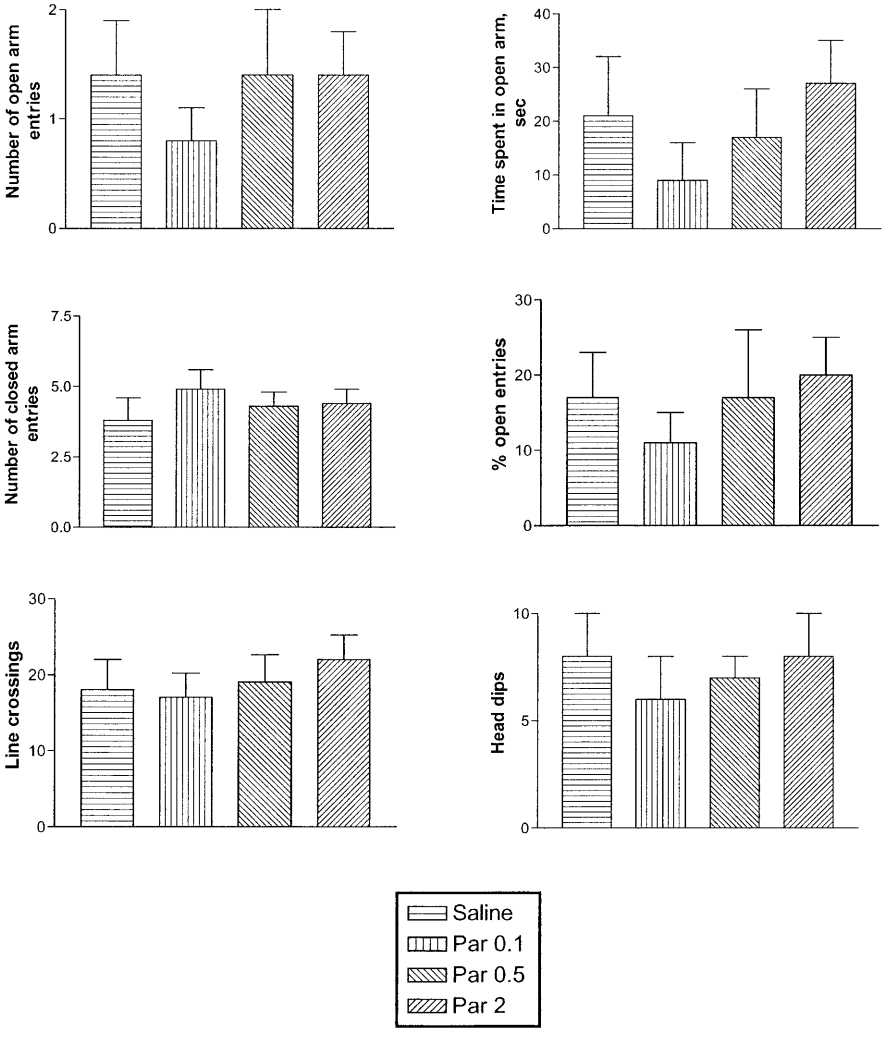

Fig. 1 Effect of paroxetine (0.1–2 mg/kg, 30 min before the test, IP) on the exploratory behaviour of handling naive rats in the elevated plus-maze (mean±SEM). The number of animals in each group was 12. *Par 0.1* paroxetine 0.1 mg/kg, *Par 0.5* paroxetine 0.5 mg/kg, *Par 2* paroxetine 2 mg/kg

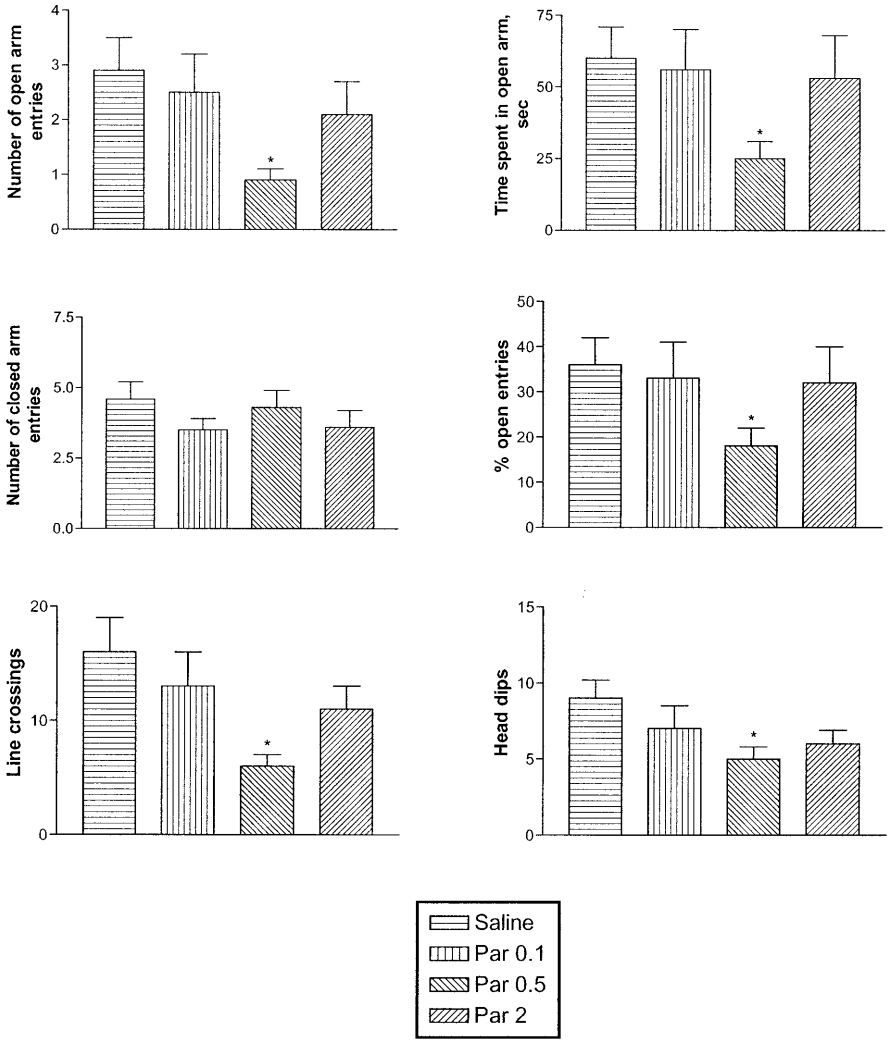

Fig. 2 Effect of paroxetine (0.1–2 mg/kg, 30 min before the test, IP) on the exploratory activity of handling habituated rats in the elevated plus-maze (mean±SEM). *P<0.05 (compared to saline-treated rats, Newman-Keuls test after significant one-way ANOVA), the number of animals in each group was 15. *Par 0.1* paroxetine 0.1 mg/kg, *Par 0.5* paroxetine 0.5 mg/kg, *Par 2* paroxetine 2 mg/kg

Table 1 Effect of 8-OH-DPAT and deramciclane on the exploratory activity of handling habituated rats in the elevated plus-maze (mean±SEM)

Treatment	Open arm entries	Time in open arm (s)	Closed arm entries	Open entries (%)	Line crossings	Head dips
Saline	2.9±0.8	61±15	6±2	33±7	18±4.2	12±2
8-OH-DPAT 0.01 mg/kg	1.9±0.8	50±14	5±2	28±9	13±4.3	8±3
8-OH-DPAT 0.05 mg/kg	2.0±0.7	45±18	6±2	25±6	13±2.9	8±2
8-OH-DPAT 0.1 mg/kg	3.8±0.7	71±12	6±2	39±4	21±3.4	10±3
Vehicle	2.5±1.0	36±14	6±2	29±6	17±5	11±2
Der 0.5 mg/kg	3.3±0.7	49±18	8±2	29±3	21±4	12±1
Der 1 mg/kg	2.4±0.7	41±2	7±1	26±7	15±2	10±2
Der 2 mg/kg	4.0±1.2	48±11	8±3	33±6	22±7	13±2

was analysed. However, paroxetine did not affect the locomotor activity in the motility boxes (Fig. 3). Pretreatment with deramciclane (0.5–2 mg/kg) only counteracted on one measure (closed arm entries) in the action of paroxetine [F(4,45)=3.90, P<0.05] (Fig. 5) and then only at the highest dose used (2 mg/kg). The combination of deramciclane with paroxetine (0.5 mg/kg) did not modify the locomotor activity of rats (Fig. 3).

Discussion

In the present study, the 5-HT reuptake inhibitor, paroxetine, induced an anxiogenic-like action in handling adapted, but not in the handling naive rats. Paroxetine reduced both the “classical” (number of open arm entries, ratio between open and total arm entries) and “ethological” (number of head-dips) measures of anxiety in the el-

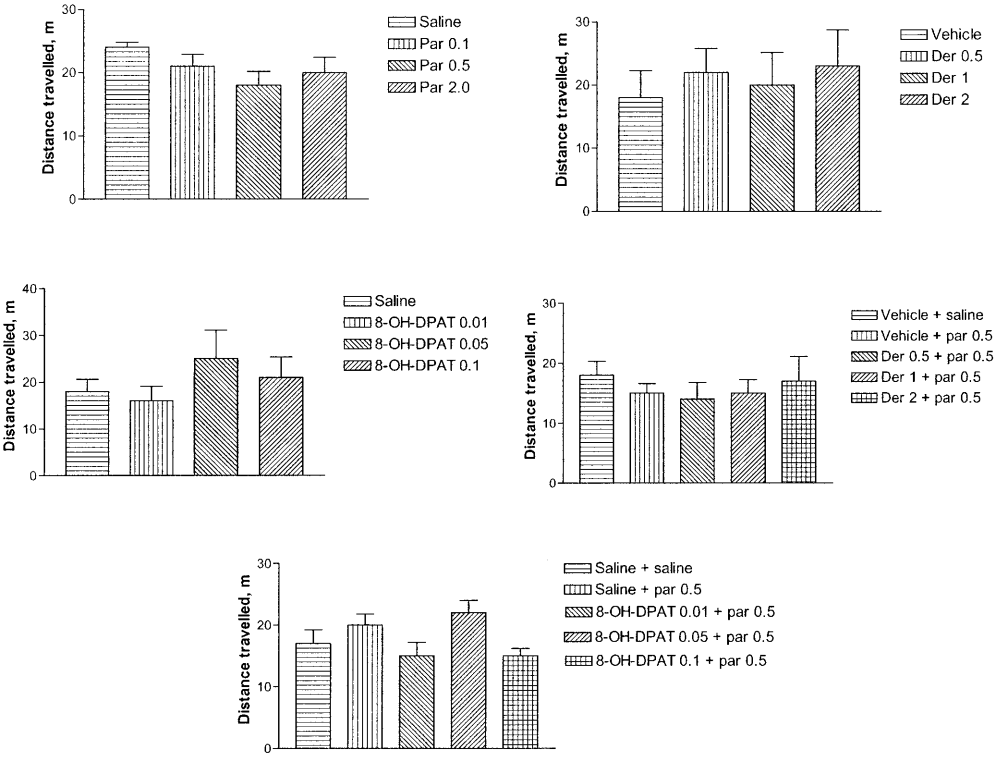

Fig. 3 Effects of paroxetine (0.1–2 mg/kg, 30 min before the test, IP), deramciclane (0.5–2 mg/kg, 35 min before the test, IP) and 8-OH-DPAT (0.01–0.1 mg/kg, 35 min before the test, IP) on the locomotor activity of handling habituated rats in the motility boxes (mean±SEM). The interaction of deramciclane (0.5–2 mg/kg, 35 min before the test, IP) with paroxetine (0.5 mg/kg, 30 min before the test, IP) and the interaction of 8-OH-DPAT (0.01–0.1 mg/kg, 35 min before the test, IP) with paroxetine (0.5 mg/kg, 30 min before the test, IP) in the motility boxes (mean±SEM). The number of animals in each group was 15. *Par 0.1* paroxetine 0.1 mg/kg, *Par 0.5* paroxetine 0.5 mg/kg, *Par 2* paroxetine 2 mg/kg, *Der 0.5* deramciclane 0.5 mg/kg, *Der 1* deramciclane 1 mg/kg, *Der 2* deramciclane 2 mg/kg, *8-OH-DPAT 0.01* 8-OH-DPAT 0.01 mg/kg, *8-OH-DPAT 0.05* 8-OH-DPAT 0.05 mg/kg, *8-OH-DPAT 0.1* 8-OH-DPAT 0.1 mg/kg

evated plus-maze. This is consistent with the findings of Rodgers et al. (1997) that pre-experimental adaptation increases the effect of anxiogenic drugs. It has been shown that the exposure of rats to a novel environment increases the release of 5-HT in the brain not seen in the familiar surrounding (File et al. 1993). Also, the exposure of rats to the elevated plus-maze increases the release of 5-HT in the ventral hippocampus and this effect is reversed by the anxiolytic treatments (Wright et al. 1992). Thus, one explanation for the difference between handled and non-handled animals in the present study is that an increased concentration of 5-HT in the synaptic cleft induced by the novel environment and exposure to the elevated plus-maze may have prevented any other effect due to paroxetine being observed.

It should be noted that the action of paroxetine was U-shaped and it was effective at a low dose (0.5 mg/kg). Sanchez and Meier (1997) have also established that paroxetine displayed an anxiogenic-like action only at low doses. The reason for this phenomenon is not clear, but may be related to the fact that the higher doses of paroxetine are inducing more pronounced increase of 5-HT release, probably stimulating other subsets of 5-HT receptors and hence masking the effect of lower concentrations of 5-HT. Indeed, the administration of paroxetine at a dose of 3 mg/kg induces anxiolytic-like action, suppressing ultrasound vocalization in rats, and this effect has been reversed by 5-HT_{2A} receptor antagonist MDL 100,907 (Schreiber et al. 1998). The possible involvement of different mechanisms in the action of paroxetine was also shown in our previous studies. The decrease of locomotor activity induced by a lower dose of paroxetine (2 mg/kg) was antagonized by the antagonist of CCK_2 receptors LY 288,513, whereas the effect of a higher dose of paroxetine remained unchanged after pretreatment with the CCK_2 receptor antagonist (Kõks et al. 1999). Nevertheless, it is noteworthy that the anti-exploratory action of paroxetine in the plus-maze was not due to a non-specific suppression of locomotor activity, since the administration of paroxetine did not modify the locomotor activity of rats.

The mechanism of the anxiogenic-like action of paroxetine was studied by means of two drugs influencing 5-HT-ergic neurotransmission – 8-OH-DPAT and deramciclane. 8-OH-DPAT, a 5-HT_{1A} receptor agonist, and deramciclane, a 5-$HT_{2A/2C}$ antagonist, have shown to possess anxiolytic-like properties in exploratory models of anxiety (Fletcher et al. 1993; File and Gonzalez 1996; File et al. 1996; Gacsalyi et al. 1997). Nevertheless, in the present study, neither drug elicited anxiolytic-like effects when given acutely to handling adapted rats. However, the pretreatment with 8-OH-DPAT completely reversed the anxiogenic-like action of paroxetine. 8-OH-DPAT displayed a bell-shaped action, since only one dose (0.05 mg/kg) of 5-HT_{1A} receptor agonist was effective against paroxetine. 5-HT_{1A} receptors are shown to be located both pre- and postsynaptically (Pompeiano et al. 1992; Kia et al. 1996). The site of antagonistic interaction between 8-OH-DPAT and paroxetine is not clear, but according to recent studies, this interaction is complex. One possible explanation is that 8-OH-DPAT inhibits the firing rate of raphe neurons via activation of autoreceptors

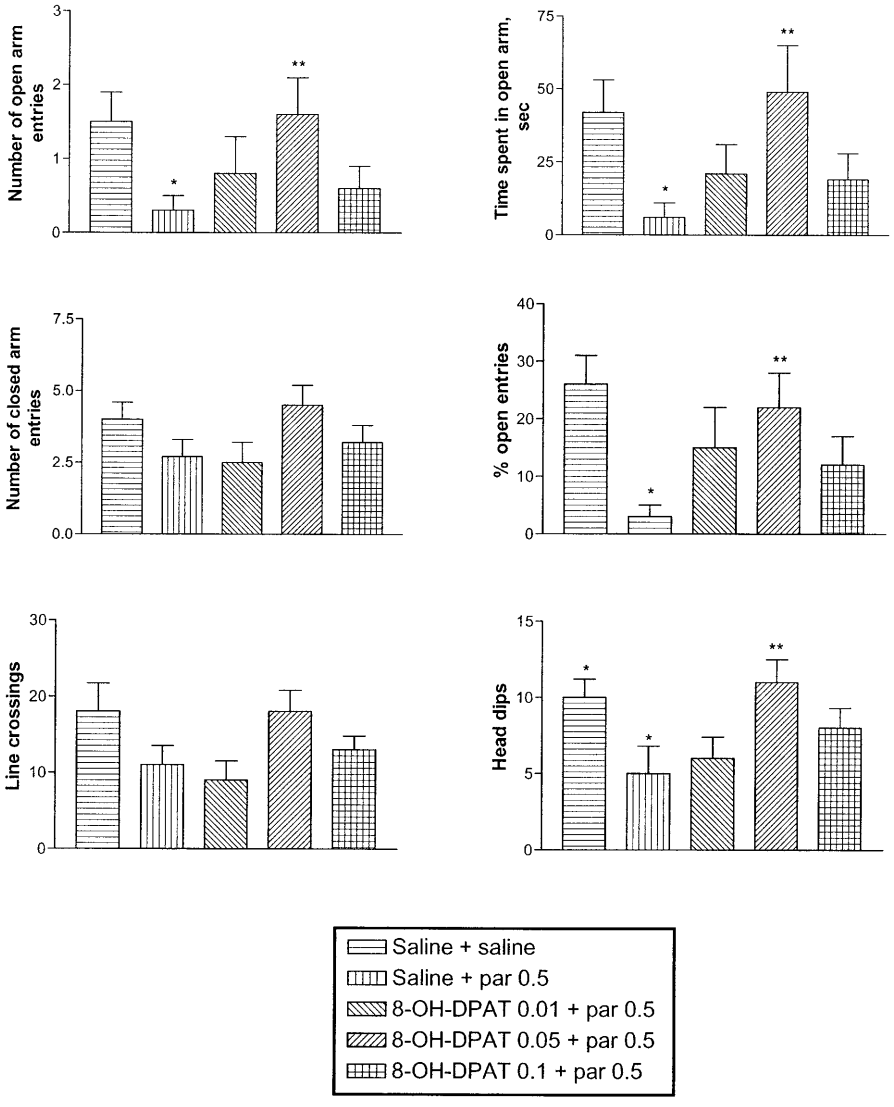

Fig. 4 Interaction of 8-OH-DPAT (0.01–0.1 mg/kg, 35 min before the test, IP) with paroxetine (0.5 mg/kg, 30 min before the test, IP) in the elevated plus-maze (mean±SEM). **P*<0.05 (compared to saline+saline-treated rats, Newman-Keuls test after significant one-way ANOVA); ***P*<0.05 (compared to saline+paroxetine-treated rats). The number of rats in each group was ten. *Par 0.5* paroxetine 0.5 mg/kg, *8-OH-DPAT 0.01* 8-OH-DPAT 0.01 mg/kg, *8-OH-DPAT 0.05* 8-OH-DPAT 0.05 mg/kg, *8-OH-DPAT 0.1* 8-OH-DPAT 0.1 mg/kg

(Hajos et al. 1995). This would reduce the release of 5-HT and therefore inhibits the action of paroxetine. On the other hand, it has been shown that the systemic administration of 8-OH-DPAT suppresses the firing of 5-HT-ergic raphe neurons via the stimulation of postsynaptic 5-HT_{1A} receptors located in the medial prefrontal cortex (Hajos et al. 1999). 8-OH-DPAT evoked excitation of medial prefrontal cortex neurons at doses (0.5–32 µg/kg) in the range of those inhibiting 5-HT cell firing. Accordingly, the lower doses of 8-OH-DPAT suppressed via the feedback loop the activity of 5-HT-ergic neurons and decreased the release of 5-HT. This could explain why 8-OH-DPAT potently reversed the anxiogenic-like action of paroxetine in the present study. At higher doses (32–512 µg/kg), 8-OH-DPAT inhibited the activity of neurons in the medial prefrontal cortex. The neuronal excitation and inhibition induced by 8-OH-DPAT were antagonized by WAY 100635, an antagonist of 5-HT_{1A} receptors (Hajos et al. 1999). The biphasic effect of 8-OH-DPAT on the activity of neurons in the medial prefrontal cortex could be a possible explanation for why the higher dose of 5-HT_{1A} receptor agonist (0.1 mg/kg) was ineffective against the anxiogenic-like action of paroxetine. In contrast to 8-OH-DPAT, deramciclane did not affect the action of paroxetine on the behavioural measures reflecting anxiety in the elevated plus-maze: number of open arm entries, number of head-dips and time spent on the open arm. The highest dose of deramciclane (2 mg/kg) antagonized the reduction of closed arm entries caused by paroxetine. The reduction of closed arm entries is believed to reflect the suppression of locomotor activity (Rodgers et al. 1997). However, paroxetine did not affect the locomotor activity in the motility boxes. Thus, it is unlikely that 5-$HT_{2A/2C}$ receptors exclusively mediate the anti-exploratory action of paroxetine, although it may contribute to the effects observed in the elevated plus-maze. The possible involvement of 5-HT_{2C} receptors in the anxiogenic-like effect of paroxetine cannot be exclud-

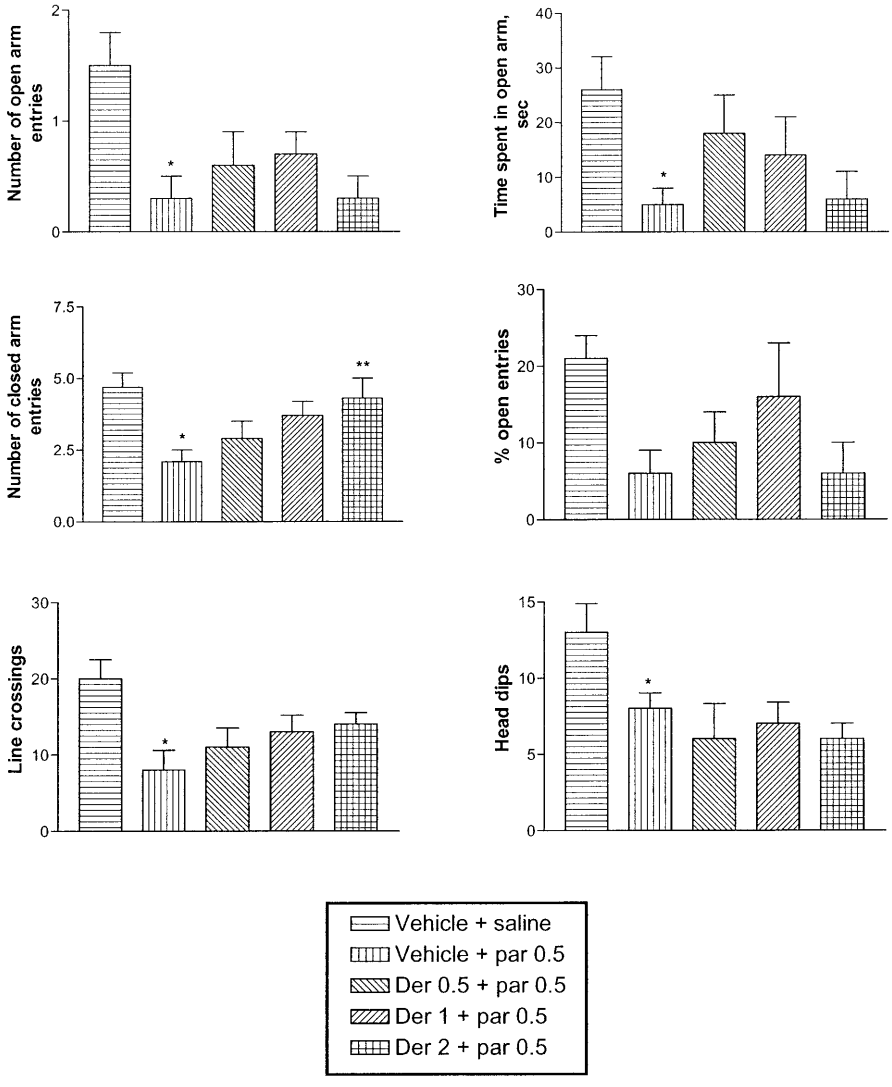

Fig. 5 Interaction of deramciclane (0.5–2 mg/kg, 35 min before the test, IP) with paroxetine (0.5 mg/kg, 30 min before the test, IP) in the elevated plus-maze (mean±SEM). **P*<0.05 (compared to vehicle+saline-treated rats, Newman-Keuls test after significant one-way ANOVA); ***P*<0.05 (compared to vehicle+paroxetine-treated rats). The number of rats in each group was 10. *Par 0.5* paroxetine 0.5 mg/kg, *Der 0.5* deramciclane 0.5 mg/kg, *Der 1* deramciclane 1 mg/kg, *Der 2* deramciclane 2 mg/kg. Vehicle for deramciclane was 1% Tween-80 in saline

ed. Recent findings with more selective 5-HT_{2C} antagonists (SB 200646A and SB 221284) showed reversal of the anxiogenic-like effect of paroxetine in the rat social interaction test (Bristow et al. 2000).

In conclusion, the present study has established that the pre-experimental adaptation of rats helps to reveal the anxiogenic-like action of the 5-HT reuptake inhibitor paroxetine. This is in good agreement with previous animal and clinical studies where the administration of 5-HT reuptake inhibitors induces anxiety both in laboratory animals and in patients with anxiety disorders (Handley and McBlane 1993; Den Boer and Westenberg 1996). The effectiveness of 8-OH-DPAT, an agonist of 5-HT_{1A} receptors, against paroxetine supports a role of both pre- and postsynaptic 5-HT-ergic mechanisms in the anxiogenic-like action of a 5-HT reuptake inhibitor.

Acknowledgements This study was supported by Grant ARFS 3922 from the Estonian Science Foundation.

References

Bristow LJ, O'Connor D, Watts R, Duxon MS, Hutson PH (2000) Evidence for accelerated desensitisation of 5-HT_{2C} receptors following combined treatment with fluoxetine and the 5-HT_{1A} receptor antagonist, WAY 100,635, in the rat. Neuropharmacology 39:1222–1236

den Boer JA, Westenberg HGM (1996) Involvement of serotonin receptor subtypes in panic disorder. In: Westenberg HGM, den Boer JA, Murphy DL (eds) Advances in the neurobiology of anxiety disorders. Wiley, Chichester, New York, pp 139–172

File SE, Gonzalez LE (1996) Anxiolytic effects in the plus-maze of 5-HT_{1A}-receptor ligands in dorsal raphe and ventral hippocampus. Pharmacol Biochem Behav 54:123–128

File SE, Zangrossi HJ, Andrews N (1993) Novel environment and cat odor change GABA and 5-HT release and uptake in the rat. Pharmacol Biochem Behav 45:931–934

File SE, Gonzalez LE, Andrews N (1996) Comparative study of pre- and postsynaptic 5-HT_{1A} receptor modulation of anxiety in two ethological animal tests. J Neurosci 16:4810–4815

Fletcher A, Cliffe IA, Dourish CT (1993) Silent 5-HT_{1A} receptor antagonists: utility as research tools and therapeutic agents. Trends Pharmacol Sci 14:441–448

Fletcher A, Forster EA, Bill DJ, Brown G, Cliffe IA, Hartley JE, Jones DE, McLenachan A, Stanhope KJ, Critch DJ, Childs KJ, Middlefell VC, Lanfumey L, Corradetti R, Laporte AM, Gozlan H, Hanon M, Dourish CT (1996) Electrophysiological, biochemical, neurohormonal and behavioural studies with WAY-100635, a potent, selective and silent 5-HT1A receptor antagonist. Behav Brain Res 73:337–353

Gacsalyi I, Schmid E, Gyertyan I, Vasar E, Lang A, Haapalinna A, Fekete M, Hietala J, Syvälahti E, Tuomainen P, Männistö PT (1997) Receptor binding profile and anxiolytic activity of deramciclane (EGIS-3886) in animal models. Drug Dev Res 40:123–132

Hajos M, Gartside SE, Sharp T (1995) Inhibition of median and dorsal raphe neurones following administration of the selective serotonin reuptake inhibitor paroxetine. Naunyn-Schmiedeberg's Arch Pharmacol 351:624–629

Hajos M, Hajos-Korcsok E, Sharp T (1999) Role of the medial prefrontal cortex in 5-HT_{1A} receptor-induced inhibition of 5-HT neuronal activity in the rat. Br J Pharmacol 126:1741–1750

Handley SL, McBlane JW (1993) 5-HT drugs in animal models of anxiety. Psychopharmacology 112:13–20

Handley SL, Mithani S (1984) Effects of alpha-adrenoceptor agonists and antagonists in a maze-exploration model of "fear"-motivated behaviour. Naunyn-Schmiedeberg's Arch Pharmacol 327:1–5

Handley SL, McBlane JW, Critchley MA, Njung'e K (1993) Multiple serotonin mechanisms in animal models of anxiety:environmental, emotional and cognitive factors. Behav Brain Res 58:203–210

Iversen SD (1984) 5-HT and anxiety. Neuropharmacology 23:1553–1560

Kennett GA, Whitton P, Shah K, Curzon G (1989) Anxiogenic-like effects of mCPP and TFMPP in animal models are opposed by 5-HT_{1C} receptor antagonists. Eur J Pharmacol 164:445–454

Kia HK, Brisorgueil MJ, Hamon M, Calas A, Verge D (1996) Ultrastructural localization of 5-hydroxytrypramine 1A receptors in the rat brain. J Neurosci Res 46:697–708

Kõks S, Bourin M, Võikar V, Soosaar A, Vasar E (1999) Role of CCK in anti-exploratory action of paroxetine, 5-HT reuptake inhibitor. Int J Neuropsychopharmacol 2:9–16

Pellow S, Chopin P, File SE, Briley M (1985) Validation of open:closed arm entries in an elevated plus-maze as a measure of anxiety in the rat. J Neurosci Meth 14:149–167

Pigott TA, Hill JL, Grady TA, L'Heureux F, Berstein S, Rubinstein CS, Murphy DL (1993) A comparison of the behavioural effects of oral versus intravenous mCPP administration in OCD patients and the effect of metergoline prior to i.v. mCPP. Biol Psychiatry 33:3–14

Pompeiano M, Palacios JM, Mengod G (1992) Distribution and localization of mRNA coding for 5-HT_{1A} receptor in the brain: correlation with receptor binding. J Neurosci 12:440–453

Rex A, Fink H, Marsden CA (1994) Effects of BOC-CCK-4 and L-365,260 on cortical 5-HT release in guinea-pigs on exposure to the elevated plus maze. Neuropharmacology 33:559–565

Rodgers RJ, Cao BJ, Dalvi A, Holmes A (1997) Animal models of anxiety: an ethological perspective. Braz J Med Biol Res 30:289–304

Sanchez C, Meier E (1997) Behavioral profiles of SSRIs in animal models of depression, anxiety and aggression. Are they all alike? Psychopharmacology 129:197–205

Schreiber R, Melon C, De Vry J (1998) The role of 5-HT receptor subtypes in the anxiolytic effects of selective serotonin reuptake inhibitors in the rat ultrasonic vocalization test. Psychopharmacology 135:383–391

Wright IK, Upton N, Marsden CA (1992) Effect of established and putative anxiolytics on extracellular 5-HT and 5-HIAA in the ventral hippocampus of rats during behaviour on the elevated X-maze. Psychopharmacology 109:338–346