

# Role of CCK in anti-exploratory action of paroxetine, 5-HT reuptake inhibitor

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## Abstract

The administration of paroxetine (0.5–8 mg/kg), a selective 5-HT reuptake inhibitor, induced a dose-dependent reduction of exploratory activity of rats in the motility test. In the elevated plus-maze paroxetine was less effective, only 8 mg/kg of paroxetine decreased the exploratory behaviour of rats. The doses of paroxetine (2–8 mg/kg) reducing the exploratory activity in the motility test increased the density of CCK receptors in the frontal cortex, but not in the hippocampus. The treatment of rats with the CCK<sub>B</sub> receptor antagonist LY288,513 (0.01–1 mg/kg) did not change the exploratory activity. However, the reduction of exploratory activity induced by the low dose of paroxetine (2 mg/kg), but not by the higher dose (8 mg/kg), was dose-dependently reversed by the administration of LY288,513. Moreover, LY288,513 did not affect the anti-exploratory action of paroxetine (8 mg/kg) in the elevated plus-maze. Diazepam at doses (0.5–1.0 mg/kg) not suppressing the locomotor activity did not change the anti-exploratory action of paroxetine in the motility test. It is likely that the anti-exploratory action of a low dose of paroxetine (2 mg/kg) is not related to the increase in anxiety, but rather to the reduction of exploratory drive. Evidence exists that this effect of paroxetine is mediated via the activation of CCK-ergic transmission.

Received 7 September 1998; Reviewed 9 November 1998; Revised 1 December 1998; Accepted 6 December 1998

**Key words:** 5-HT, cholecystokinin, motility test, elevated plus-maze, rat.

## Introduction

There is a growing body of evidence that cholecystokinin (CCK) and 5-hydroxytryptamine (5-HT) interact in the regulation of behaviour. The administration of cholecystokinin tetrapeptide (CCK-4), an agonist of CCK<sub>B</sub> (brain subtype, CCK<sub>2</sub>) receptors, induces an anxiogenic-like action in the elevated plus-maze, and this behavioural action of CCK agonist is accompanied by the increased release of 5-HT in the cerebral cortex (Rex et al., 1994). On the other hand, CCK<sub>B</sub> receptor antagonist L365,260 causes the opposite effect and antagonizes the behavioural and neurochemical action of CCK-4 (Rex et al., 1994). Peripherally administered CCK-8 reduces the food intake and elevates the levels of 5-HT in the hypothalamus (Voigt et al., 1998). The stimulation of somatodendritic 5-HT autoreceptors by 5-HT<sub>1A</sub> receptor agonist 8-OH-DPAT reverses CCK-8 induced satiety and CCK-4 caused anxiety (Poeschla et al., 1992; Rex et al., 1997). However, it should be noted that the anxiogenic-like action of CCK

is mediated via the CCK<sub>B</sub> receptor subtype, whereas CCK<sub>A</sub> (peripheral subtype, CCK<sub>1</sub>) receptors are responsible for CCK-induced satiety (Shlik et al., 1997). The application of CCK-4 to the brain membranes increases the density of 5-hydroxytryptamine 5-HT<sub>2</sub> receptors in the frontal cortex (Agnati et al., 1983). Therefore, it is not surprising that the 5-HT<sub>2</sub> receptor antagonist deramciclane antagonizes the anxiogenic-like action of caerulein, an unselective CCK<sub>A</sub>/CCK<sub>B</sub> receptor agonist (Gacsalyi et al., 1997).

However most experiments have studied a role of 5-HT in the action of CCK receptor agonists and antagonists, whereas very little attention is paid to the opposite interaction. Nevertheless, it has been shown that 5-HT can increase the release of CCK in the cerebral cortex and nucleus accumbens (Raiteri et al., 1993). The acute administration of alaproclate, the 5-HT reuptake inhibitor, significantly elevates the levels of CCK in the cingulate cortex and periaqueductal grey (Rosén et al., 1995). Moreover, the exposure of rats to the novel aversive environment clearly increases the release of 5-HT in the frontal cortex and hippocampus (File et al., 1993; Rex et al., 1994). The administration of fluoxetine, the 5-HT reuptake inhibitor, dose-dependently reduces the exploratory behaviour of rats in the elevated plus-maze

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(Handley and McBlane, 1993). Handley and McBlane (1993) have considered the anti-exploratory action of fluoxetine as the anxiogenic-like action. Den Boer and Westenberg (1996) have shown in the clinical studies that the acute administration of 5-HT reuptake inhibitors may increase anxiety in patients suffering from anxiety disorders. Therefore, the aim of present experiments was to clarify a possible role of CCK in the anxiogenic-like action of drugs increasing 5-HT-ergic transmission. For that purpose a selective 5-HT reuptake inhibitor paroxetine was chosen. The behavioural effects of paroxetine were analysed in the motility box and elevated plus-maze. These two behavioural tests were selected to distinguish whether paroxetine-induced inhibition of exploratory behaviour is due to the increase in anxiety or the reduction of exploratory drive. Moreover, the action of paroxetine was studied on the parameters of CCK binding in the frontal cortex and hippocampus. Also the influence of CCK<sub>B</sub> antagonist LY288,513 and diazepam, a benzodiazepine anxiolytic drug, on the behavioural effects of paroxetine was examined.

## 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  $20 \pm 2$  °C in a 12-h light/dark cycle (light on at 07:00 hours). Tap water and food pellets were available ad libitum. All animal procedures were approved by 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 at least 2 wk before the beginning of experiment.

### Materials

Paroxetine, a selective 5-HT reuptake inhibitor, was provided by SmithKline Beecham (UK). LY288,513 [*trans*-*N*-(4-bromophenyl)-3-oxo-4,5-diphenyl-1-pyrazolidinecarboxamide], an antagonist of CCK<sub>B</sub> receptor, was kindly donated by Eli Lilly & Co. (USA). Paroxetine was dissolved in saline, whereas LY288,513 and diazepam (Sigma, USA) were suspended in 1% Tween-80 (Ferak, Germany) solution in saline. [Propionyl-<sup>3</sup>H]propionylated-CCK-8-sulphated (<sup>3</sup>H]pCCK-8) was obtained from Amersham Radiochemicals (UK). The other chemicals for radioligand-binding studies (caerulein, Hepes (*N*-[2-hydroxyethyl]piperazine-*N'*-[2-ethane-sulphonic acid]), NaCl, MgCl<sub>2</sub>, KCl and EDTA (ethylenediamine-tetraacetic acid)) were purchased from Sigma (USA).

### Behavioural testing

The animals were brought into the experimental room 1 h before the experiment. The rats were new to handling and were not adapted to the experimental situation. Each rat was used only once. All experiments were carried out between 14:00 and 19:00 hours. Paroxetine, diazepam and LY288,513 were given 30 min before the beginning of studies.

### Motility test

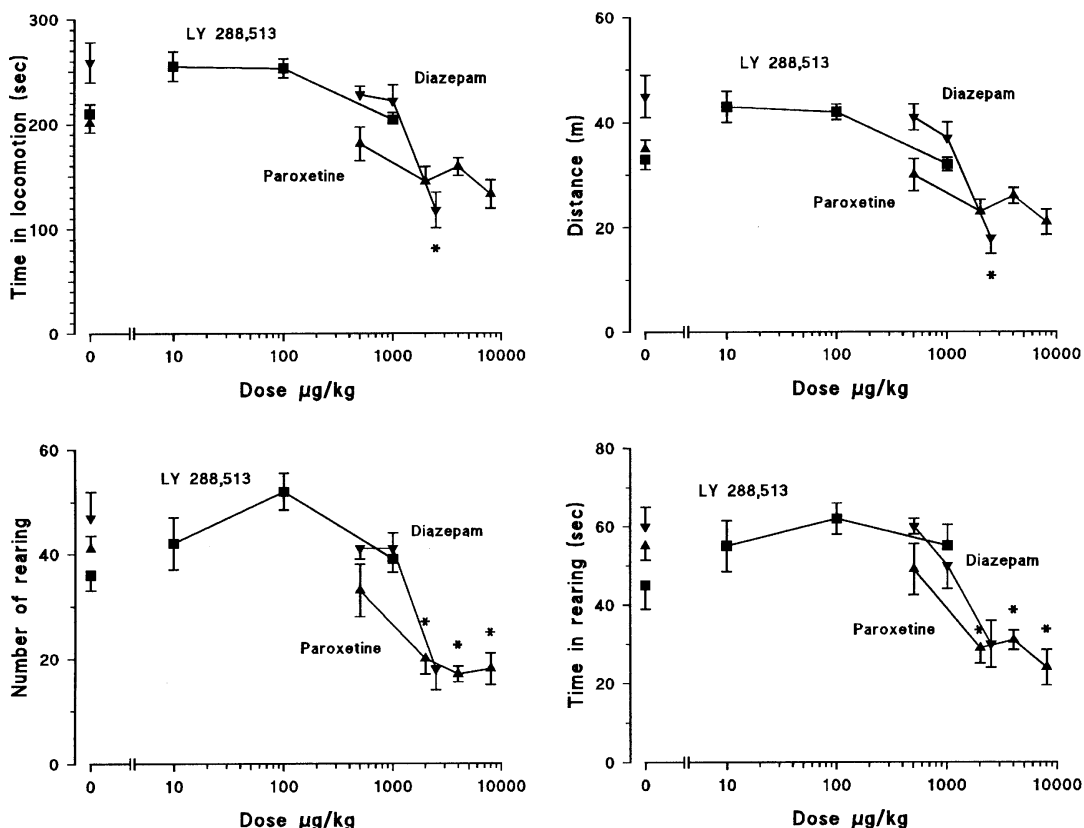
Exploratory activity of rats was measured by means of photoelectric motility boxes (448 × 448 × 450 mm) connected to a computer (TSE Technical & Scientific Equipment GmbH, Germany). Animals, new to the test situation were placed singly into the apparatus. Time in exploration (s), distance of exploration (in metres), number and duration of rearing were registered in 5-min intervals during the 15-min observation period.

### Elevated plus-maze

The method initially suggested by Handley and Mithani (1984) for the measurement of exploratory activity was employed in rats with some modifications (Pellow et al., 1985). 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). The maze was elevated to the height of 50 cm, and placed in a lit room. During a 5 min observation session the following measures were taken by an observer: (1) time spent in exploring of open part (central square and open arms) of plus-maze; (2) time spent in open arm; (3) number of closed and open arm entries; (4) number of line crossings in open part; and (5) ratio between open and total arm entries. At the beginning of experiment an animal was placed into the centre of plus-maze, facing towards a closed arm. An arm entry was counted only when all four limbs of the rat were within a given arm.

### [<sup>3</sup>H]pCCK-8 binding assay

The animals were decapitated 30 min after the injection of various doses of paroxetine (0.5–16 mg/kg i.p.). After decapitation the brains were quickly dissected on ice. The binding studies were performed in the frontal cortex (also containing the anterior cingulate and frontoparietal cortex) and hippocampus. These brain structures were selected according to previous studies since the most prominent neurochemical changes due to the reduced exploratory behaviour have been found in these brain



**Figure 1.** The effect of paroxetine (0.5–8 mg/kg), diazepam (0.5–2.5 mg/kg) and LY288,513 (0.01–1 mg/kg) on the exploratory activity of rat in the motility box. \*  $p < 0.05$  compared to saline (paroxetine) or vehicle-treated (LY288,513, diazepam) rats, Tukey HSD test after the significant one-way ANOVA). Vehicle for LY288,513 and diazepam was 1% Tween-80 solution in saline.

regions (File et al., 1993; Harro et al., 1995; Köks et al., 1997; Rex et al., 1994). Brain tissues were homogenized in 20 volumes of ice-cold 50 mM Tris-HCl (pH 7.4 at 4 °C) using a Potter-S glass-Teflon homogenizer (1000 rpm, 12 passes). The membranes were washed twice in the same buffer by centrifugation (48 000 g for 20 min) and resuspension. After the last centrifugation, the crude brain membranes were homogenized in Hepes buffer (10 mM Hepes; 130 mM NaCl; 5 mM KCl; 1 mM MgCl<sub>2</sub>; 1 mM EDTA; pH 6.5 adjusted with 1 N NaOH) containing bovine serum albumin (0.5 mg/ml). The parameters of CCK receptors were determined in the presence of 0.05–2.4 nM [<sup>3</sup>H]pCCK-8 (specific activity 79 Ci/mmol) at 23 °C in a total incubation volume of 0.5 ml. Caerulein (100 nM) was added to determine the nonspecific binding. The incubation was terminated after 120 min by the rapid filtration over Whatman GF/B filters presoaked with the bovine serum albumin (0.5 mg/ml). The filters were washed with 3 × 3 ml of ice-cold Hepes buffer. In the separate study paroxetine (0.01–1 mM) was added to the incubation medium to reveal the direct interaction of paroxetine with CCK-binding sites in the cerebral cor-

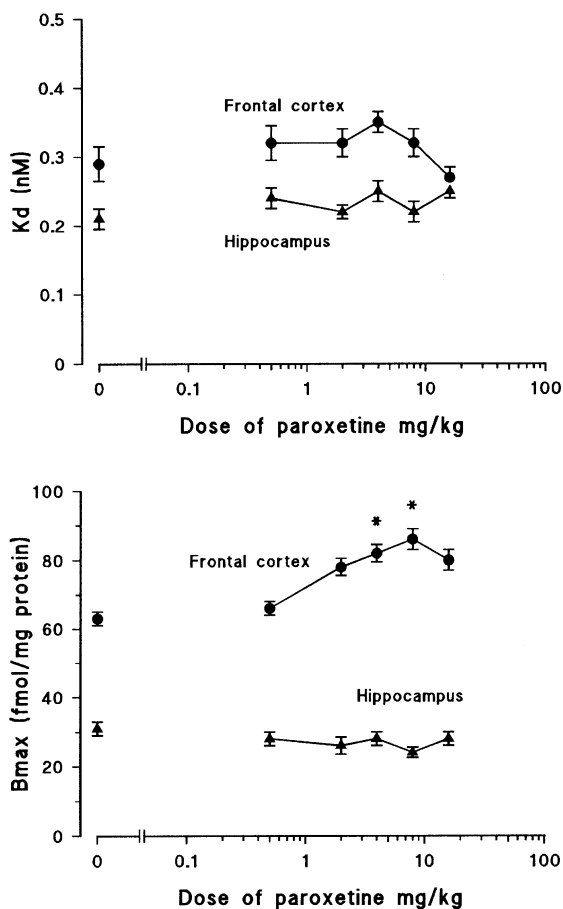
tex. The protein content was measured according to a dye-binding assay (Bradford, 1976). Saturation curves were analysed using nonlinear least squares regression (Leatherbarrow, 1987).

### Statistics

Results are expressed as mean values  $\pm$  s.e.m. The behavioural studies were analysed using one-way analysis of variance (ANOVA). Post hoc comparisons between individual groups were performed by means of Tukey HSD test using the Statistica for Windows software. The data of radioligand-binding experiments were assessed by means of Student's *t* test.

### Results

The administration of paroxetine (0.5, 2, 4, 8 mg/kg) induced a dose-dependent reduction of exploratory activity of rats in the motility test (Figure 1). Paroxetine significantly reduced the frequency of rearing ( $F_{4,51} = 3.50$ ,  $p < 0.05$ ) and time spent in rearing ( $F_{4,51} = 3.02$ ,



**Figure 2.** The effect of paroxetine (0.5–16 mg/kg) on the parameters of CCK binding in the frontal cortex and hippocampus.  $K_d$ , dissociation constant in nM;  $B_{max}$ , the apparent number of binding sites in fmol/mg protein. \*  $p < 0.05$  (compared to saline-treated rats, Student's  $t$  test).

$p < 0.05$ ). Paroxetine also tended to inhibit the other parameters of exploratory activity in the motility test. However, these changes were not statistically significant. The same doses of paroxetine tended to elevate the density of CCK-binding sites in the frontal cortex (also including the cingulate and frontoparietal cortex), but not in the hippocampus (Figure 2). The addition of paroxetine (0.01–1 mM) to the brain membranes did not modify CCK binding in the cerebral cortex (data not shown). Differently from the motility test, only 8 mg/kg of paroxetine inhibited the exploratory behaviour of rats in the elevated plus-maze. Paroxetine decreased time spent in open part ( $F_{5,43} = 2.63$ ,  $p < 0.05$ ), number of line crossings ( $F_{5,43} = 2.97$ ,  $p < 0.05$ ) and closed arm entries ( $F_{5,43} = 3.18$ ,  $p < 0.05$ ) (Table 1).

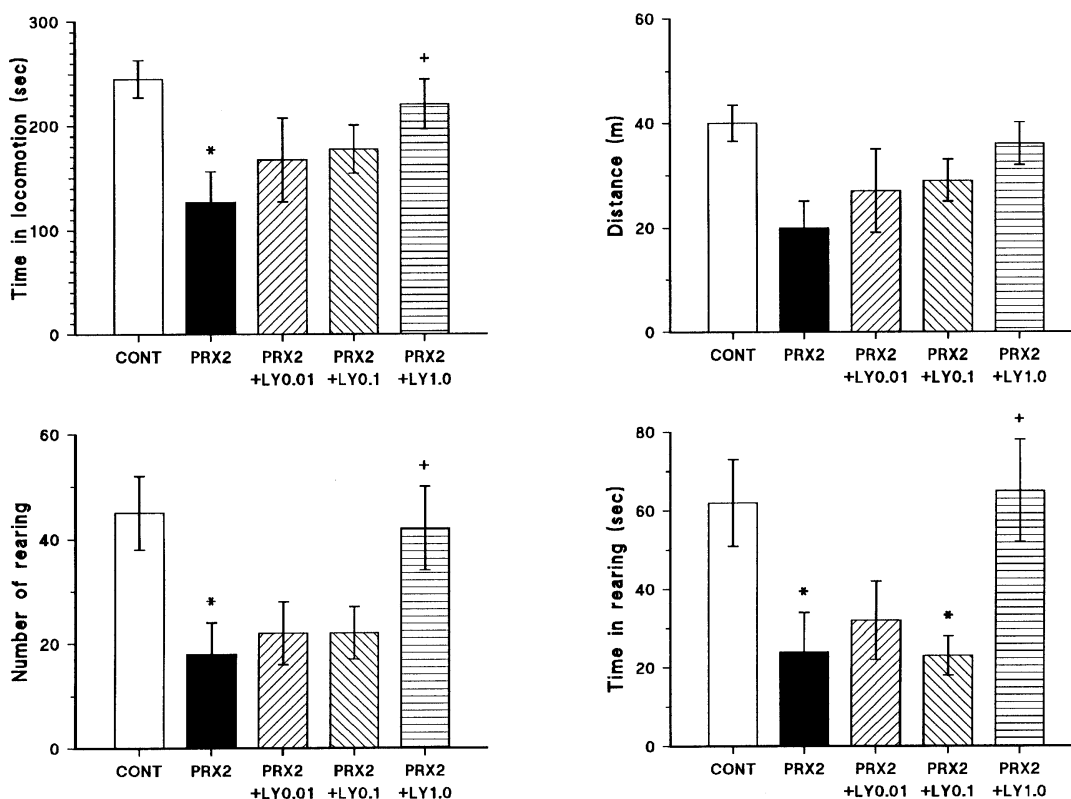
LY288,513 (0.01–1 mg/kg), a CCK<sub>B</sub> receptor antagonist, did not affect the behaviour of rats in the motility test (Figure 1). Nevertheless, the pretreatment of rats with LY288,513 dose-dependently antagonized the anti-exploratory action of paroxetine (2 mg/kg; time in locomotion  $F_{4,35} = 2.8$ ,  $p < 0.05$ ; frequency of rearing  $F_{4,35} = 3.83$ ,  $p < 0.05$ ; time in rearing  $F_{4,35} = 4.13$ ,  $p < 0.01$ ) (Figure 3). The combination of CCK<sub>B</sub> receptor antagonist with the higher dose of paroxetine (8 mg/kg) did not reverse the behavioural suppression induced by 5-HT reuptake inhibitor (Figure 4). In addition, LY288,513 (0.01–1 mg/kg) did not antagonize the anti-exploratory action of paroxetine (8 mg/kg) in the elevated plus-maze (data not shown).

The administration of the benzodiazepine agonist diazepam (0.5–2.5 mg/kg) also suppressed the exploratory activity of rats at the highest dose (2.5 mg/kg) (Figure 1, time spent in exploration  $F_{3,32} = 3.33$ ,  $p < 0.05$ ; the exploration distance  $F_{3,32} = 2.97$ ,  $p < 0.05$ ).

**Table 1.** The effect of paroxetine (0.5–16 mg/kg) on the exploratory activity of rats in the elevated plus-maze

Treatment	Time in open part (s)	No. of line crossings	No. of open arm entries	Time in open arm (s)	No. of closed arm entries	Ratio open:total arm entries
Saline	124 ± 13	24 ± 2.7	1.6 ± 0.5	18 ± 6	6.0 ± 0.5	18 ± 5
Paroxetine (0.5 mg/kg)	114 ± 18	21 ± 3.8	1.4 ± 0.3	21 ± 5	5.1 ± 0.9	19 ± 4
Paroxetine (2 mg/kg)	131 ± 17	25 ± 5.5	1.3 ± 0.6	19 ± 9	6.0 ± 1.2	10 ± 4
Paroxetine (4 mg/kg)	114 ± 15	19 ± 3.9	1.3 ± 0.7	13 ± 8	4.4 ± 0.7	12 ± 7
Paroxetine (8 mg/kg)	66 ± 16*	8 ± 1.9*	0.3 ± 0.3	4 ± 3	1.9 ± 0.4*	6 ± 4
Paroxetine (16 mg/kg)	85 ± 13	14 ± 4	0.5 ± 0.4	18 ± 13	4.0 ± 1.2	7 ± 5

\*  $p < 0.05$  (Tukey HSD test after the significant one-way ANOVA, compared to saline-treated rats).



**Figure 3.** The effect of LY288,513 (0.01–1 mg/kg) on the anti-exploratory action of paroxetine (2 mg/kg). \*  $p < 0.05$  (compared to saline + vehicle-treated rats); +,  $p < 0.05$  (compared to paroxetine-treated rats, Tukey HSD test after the significant one-way ANOVA). CONT, saline + vehicle-treated rats; PRX2, paroxetine 2 mg/kg; LY, LY288,513.

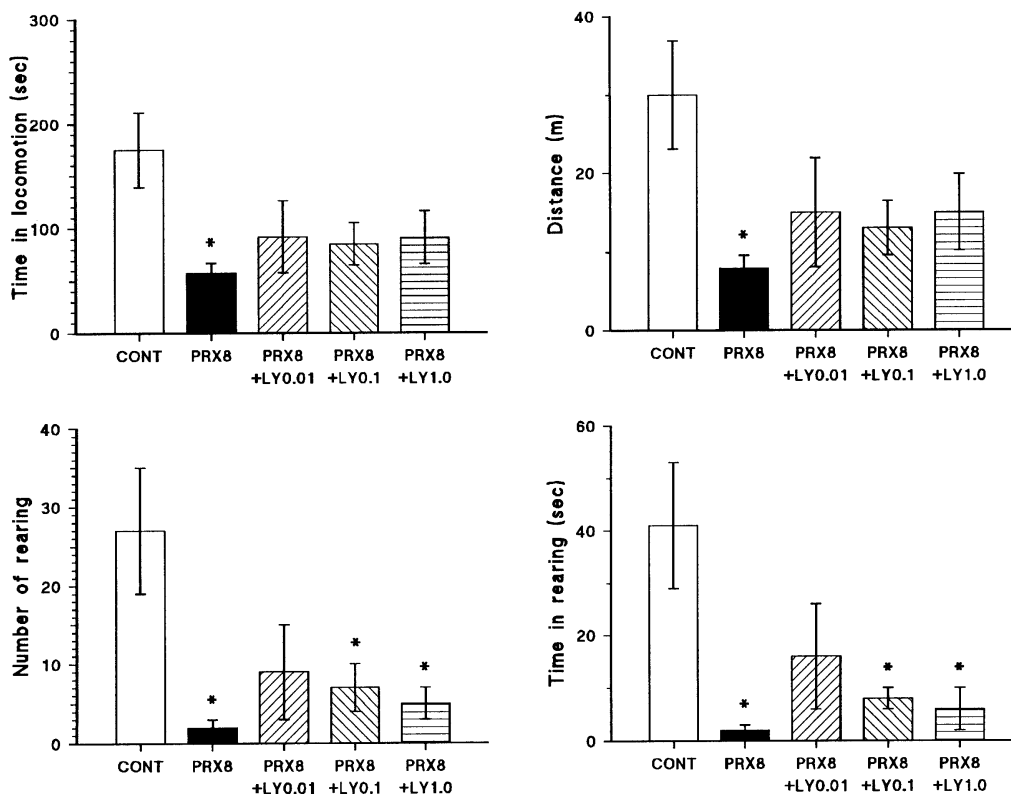
However, the combination of diazepam at doses not suppressing exploratory behaviour (0.5–1.0 mg/kg) with paroxetine (2 mg/kg) did not modify the anti-exploratory action of 5-HT reuptake inhibitor (Figure 5).

## Discussion

The administration of paroxetine, a selective inhibitor of 5-HT reuptake, induced a significant suppression of exploratory activity of rats in the motility test. Already 2 mg/kg of paroxetine inhibited the frequency of rearing and time spent in rearing. However, the selectivity of paroxetine in inhibition of rearing depends on the basal exploratory activity of control animals. In the experiments where the activity of rats was higher, this dose of paroxetine also reduced the other parameters of exploratory behaviour, namely time spent in exploration and distance of exploration. Nevertheless, the frequency of rearing and time spent in rearing are the most sensitive parameters in revealing the anti-exploratory action of paroxetine in the motility test. Moreover, paroxetine was apparently less potent in the reduction of exploratory activity of rats in the elevated plus-maze. Only 8 mg/kg of paroxetine decreased the exploratory behaviour of

animals. The anti-exploratory action of paroxetine in the elevated plus-maze was accompanied by the decreased number of closed arm entries, reflecting the suppression of locomotor activity. The existing experimental data support the role of 5-HT in the regulation of anxiety. Handley and McBlane (1993) have shown that the administration of fluoxetine, the 5-HT reuptake inhibitor, induces the anxiogenic-like action in the rat elevated plus-maze. The administration of paroxetine produced an anxiogenic-like profile in the rat two-compartment exploration test (Sanchez and Meier, 1997). The exposure of rats to the aversive environment clearly increases the release of 5-HT in the frontal cortex and hippocampus (File et al., 1993; Rex et al., 1994). Nevertheless, the present behavioural study is in disagreement with the data since the anti-exploratory action of paroxetine is related to the decrease of exploratory drive rather than to the increase in anxiety.

Rosén et al. (1995) have shown that 5-HT reuptake inhibitor alaproclate increases the levels of CCK in the cingulate cortex and periaqueductal grey. The direct application of 5-HT to the neurons of cerebral cortex and nucleus accumbens evoked the release of CCK (Raiteri et al., 1993). In the present study paroxetine elevated the

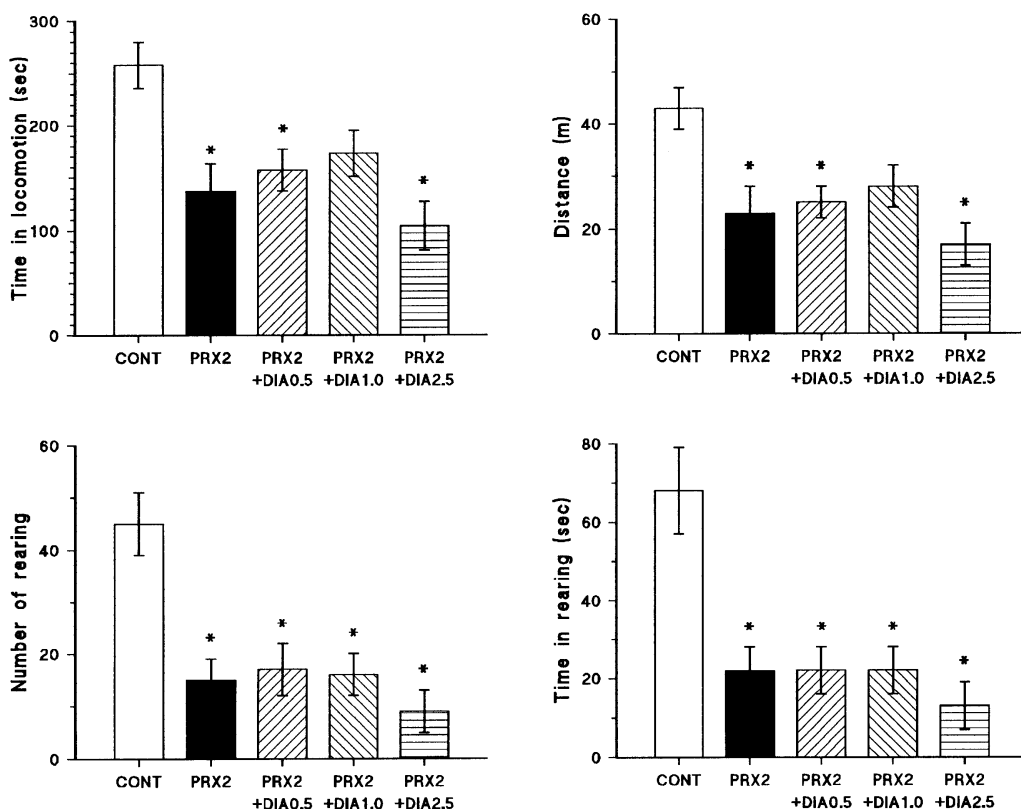


**Figure 4.** The effect of LY288,513 (0.01–1 mg/kg) on the anti-exploratory action of paroxetine (8 mg/kg). \* $p < 0.05$  (compared to saline + vehicle-treated rats, Tukey HSD test after the significant one-way ANOVA). CONT, saline + vehicle-treated rats; PRX8, paroxetine 8 mg/kg; LY, LY288,513.

number of CCK-binding sites in the frontal cortex, but not in the hippocampus. The stressful manipulations in rats are shown to increase the density of CCK receptors and mRNA levels of preproCCK in the frontal cortex (Harro et al., 1995; Pratt and Brett, 1995). The social isolation of rats for 7 d induced an anxiogenic-like action and elevated the number of CCK receptors in the frontal cortex, but not in the hippocampus (Vasar et al., 1993). Therefore, it is not surprising that the pretreatment of rats with the CCK<sub>B</sub> receptor antagonist LY288,513 dose-dependently reversed the anti-exploratory action of paroxetine (2 mg/kg). This is in line with the study of Matto et al. (1996) showing the ability of the CCK<sub>B</sub> receptor antagonist L365,260 to antagonize the anti-exploratory effect of the 5-HT reuptake inhibitor citalopram in the elevated plus-maze. The data support the hypothesis that the administration of 5-HT reuptake inhibitors increases CCK-mediated neurotransmission in the brain. The antagonism of LY288,513 against paroxetine seems to be a specific since the CCK<sub>B</sub> receptor antagonist does not increase the exploratory activity per se. Nevertheless, LY288,513 did not block the effect of the higher dose of paroxetine (8 mg/kg) showing a difference in the action of two doses of 5-HT reuptake inhibitor. This discrepancy

could be explained by the fact that paroxetine at higher doses induces a more pronounced increase in the concentration of 5-HT in the synaptic cleft, masking a possible interaction of a drug with CCK. Differing from the present study, Harro et al. (1997) did not find changes in the density of CCK receptors or in the content of CCK-related peptides after long-term treatment with various antidepressant drugs, including 5-HT reuptake inhibitors. However, they analysed the action of long-term administration of antidepressant drugs, whereas the effect of acute treatment was not examined.

In conclusion, the selective serotonin reuptake inhibitor paroxetine induces a clear anti-exploratory effect in the motility boxes. However, the above-described behavioural studies do not reflect the increase in anxiety after the acute treatment with paroxetine. This statement is supported by the findings that paroxetine did not cause the anxiogenic-like action in the elevated plus-maze and that diazepam, a potent anxiolytic drug, did not antagonize the anti-exploratory action of paroxetine in the motility test. Therefore, it is likely that paroxetine reduces the exploratory drive in rats. This effect of paroxetine seems to be mediated via the increase in CCK-ergic neurotransmission.



**Figure 5.** The effect of diazepam (0.5–2.5 mg/kg) on the anti-exploratory action of paroxetine (2 mg/kg). \*  $p < 0.05$  (compared to saline + vehicle-treated rats, Tukey HSD test after the significant one-way ANOVA). CONT, saline + vehicle-treated rats; PRX2, paroxetine 2 mg/kg; DIA, diazepam.

### Acknowledgements

Paroxetine and LY288,513 were kindly provided by SmithKline Beecham, and Eli Lilly & Co., respectively. This study was also supported by grant no. 1409 from the Estonian Science Foundation.

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