Pharmacology Biochemistry and Behavior, Vol. 59, No. 3, pp. 747–752, 1998

0091-3057/98 $19.00 + .00

ELSEVIER

PII S0091-3057(97)00468-1

Apomorphine-Induced Aggressiveness and [^{3}H]Citalopram Binding After Antidepressant Treatment in Rats

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Received 29 May 1997; Revised 23 August; Accepted 23 August 1997

MATTO, V., L. ALLIKMETS AND T. SKREBUHHOVA. *Apomorphine-induced aggressiveness and [^{3}H]citalopram binding after antidepressant treatment in rats.* PHARMACOL BIOCHEM BEHAV **59**(3) 747–752, 1998.—The effects of acute and repeated administration of antidepressive drugs on apomorphine-induced aggressive behavior and [^{3}H]citalopram binding were studied. In acute behavioral experiments with apomorphine pretreated (1.0 mg/kg, once daily) animals, desipramine (10 mg/kg) and clomipramine (10 mg/kg) enhanced, buspirone (2.5 and 5.0 mg/kg) completely blocked, but fluoxetine, amitriptyline, imipramine (10 mg/kg), and citalopram (10 and 20 mg/kg) had no effect on the intensity of aggressive behavior. Repeated concomitant apomorphine (1.0 mg/kg) and citalopram (10 mg/kg) administration reduced the affinity (K_d) of the 5-HT transporter binding sites in three brain regions. This finding was confirmed by an additional experiment as the effect of citalopram treatment. Repeated apomorphine (1.0 mg/kg) or apomorphine (1.0 mg/kg) plus desipramine (10 mg/kg) treatment had no unidirectional effect on K_d, the maximal number of apparent binding sties (B_{max}) was unchanged in all experiments. Our study indicates that the 5-HT reuptake blockade has no major influence on the apomorphine-induced aggressive behavior, but the 5-HT_{1A} receptor subtype may be involved in the mediation of the aggressive behavior in this paradigm.
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Apomorphine SSRIs Aggressive behavior [^{3}H]Citalopram binding Rat

SEROTONIN (5-hydroxytryptamine, 5-HT) has been found to play an important role in the mediation of aggressive behavior (18,19). The effects of several drugs acting at serotonin receptors or serotonin reuptake have been investigated in animal models of aggressive behavior. Thus, the 5-HT_{1A} receptor agonists have been found to elicite antiaggressive effects in some paradigms of aggressive behavior (28). The selective serotonin reuptake inhibitors (SSRIs) are widely in use as antidepressive and antipanic drugs (9,30,32). The clinical effectiveness of SSRIs on aggressive behavior is not well established yet, but in some recent clinical studies it has been reported that chronic SSRI administration may be effective in aggressive patients with borderline disorders (8) or in hostile depressed outpatients (7). In preclinical studies, it has been found that sertraline, fluoxetine, femoxetine, and fluvoxamine (SSRIs) elicited weak antiaggressive effect on isolation-induced aggression in mice (29). On the other hand, in the same study, Sanchez and Hyttel (29) found that SSRIs citalopram and paroxetine were ineffective. Citalopram, the most selective 5-HT reuptake inhibitor available today (11), has been reported to be as effective as other SSRIs or tricyclic antidepressants in the clinical practice (6) and, therefore, it has been widely used as a reference drug of SSRIs in the preclinical experiments (11).

Repeated treatment with small doses of an unselective dopamine receptor agonist apomorphine (0.5–2.0 mg/kg, SC, once or twice daily), has been found to induce aggressive behavior in rodents (1,13–15,20,24–26,33), which is effectively antagonized by neuroleptics, D_2 receptor blockers, morphine, NMDA receptor antagonists, and intensified by dopaminergic agonists (1,14,15,24). The apomorphine-induced aggressive behavior has been proposed to be an equivalent to human pathology of aggressive behavior or schizophrenia (14,15) and the apomorphine-induced aggressiveness test may be classified as a "pathological" method of aggressive behavior in rats (16). In a recent study, Rowlett and collaborators (27) found

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that after repeated apomorphine treatment the basal dopamine synthesis is enhanced, but the role of the serotoninergic neurotransmission in this paradigm remains unclear. Therefore, our study was addressed to clarify whether citalopram, other antidepressants, or buspirone (5-HT_{1A} receptor agonist) have antiaggressive effects on apomorphine-induced aggressiveness paradigm in rats. In our experiments, two different treatment schedules were used: 1) we investigated the effect of acute antidepressant treatment on aggressiveness in apomorphine pretreated, sensitized animals; and 2) we investigated the effects of concomitant administration of apomorphine and desipramine or citalopram treatment on rat aggressive behavior.

In addition, our study was addressed to measure the binding characteristics of the 5-HT transporter binding sites after repeated apomorphine administration. On rat brain membranes, [^{3}H]citalopram binds to the 5-HT transporter site in a saturable high affinity and a single binding site manner (5,21–23). In our study, we measured the number of the maximal apparent binding sites (B_{max}, fmol/mg protein) and the affinity of the binding sites (K_d, nM) in four rat brain regions (frontal cortices, hippocampi, hypothalami, and striatums) after 2 weeks of administration of apomorphine or apomorphine and desipramine or citalopram challenge. For comparison, the binding characteristics of the 5-HT transporter binding site after 2-week antidepressant treatment were studied.

METHODS

Animals

Male Wistar rats (from Gridnex Breeding Center, Riga, Latvia) weighing 300–400 g were used in all experiments. The animals were housed separately (one per cage) under standard laboratory conditions except in the repeated antidepressant administration test when the animals were grouped five per cage; water and food were available ad lib. The animal room had controlled temperature (20 ± 2°C) and light/dark cycle (light on from 0800 to 2000 h).

Drugs and Drug Administration

In the behavioral experiments, the following drugs were used: citalopram, donated by Lundbeck, Denmark; desipramine, imipramine, amitriptyline, clomipramine, and fluoxetine, from Sigma, St. Louis, MO; buspirone, donated by Bristol-Myers Company, UK; and apomorphine, in the form of a commercially available substance for clinical use. Desipramine, imipramine, amitriptyline, clomipramine, fluoxetine, citalopram (all as hydrochloride salt), buspirone, and apo-morphine were dissolved in distilled water. Fluoxetine was adjusted with distilled water up to volume 2 ml/kg, all other drugs 1 ml/kg body weight.

Behavioral Experiments

The measurement of aggressive behavior was performed in specially designed cages [transparent plastic side walls (35 × 35 × 55 cm, length × width × height) and stainless steel floor, covered with sawdust]. Immediately after apomorphine (1.0 mg/kg, SC) injection, the animals were put pairwise to the test cage and observed for 1) the time of the latency (the time before the first attack or the first aggressive posture); and 2) the intensity of aggressive behavior. The animals were observed for 15–20 min, and the rating of aggressive behavior was scored on the 0–3-point scale [modified from (2)]: 0, no aggressive manifestations; 1, intermittent mild aggressive posture or attack with another rat, no vocalizations; 2, intermittent intensive upright aggressive posture or attack or boxing with other rat, vocalizations, but no biting or continuous fighting; 3, continuous fighting or attempts to bite the opponent rat, loud vocalizations. In the case of the development of the highest score of aggressive behavior, the test was cancelled to avoid injuries.

In the experiments of the acute antidepressant treatment, desipramine (10 mg/kg), imipramine (10 mg/kg), amitriptyline (10 mg/kg), clomipramine (10 mg/kg), fluoxetine (10 mg/kg), citalopram (10 and 20 mg/kg), or buspirone (2.5 and 5.0 mg/kg) were injected intraperitoneally 30 min before the test. Apomorphine pretreatment lasted 2 weeks (1.0 mg/kg, SC, once daily); on the test day apomorphine was injected immediately before the behavioral test.

In the experiments of the acute antidepressant treatment, the same apomorphine-pretreated animals were used for no more than five independent experiments. The interval between the independent experiments was not less than 3 days during which the apomorphine treatment was continued. The apomorphine-pretreated animals were randomly divided to apomorphine plus vehicle-treated and apomorphine plus drug-treated group, but always the same animal pairs were used. The apomorphine pretreatment was considered appropriate for the acute antidepressant treatment experiment when the score of the aggressive postures of the apomorphine plus vehicle-treated (control) group was higher than 1.5. In the repeated apomorphine plus antidepressant treatment experiments, desipramine (10 mg/kg) and citalopram (10 mg/kg) were injected IP and apomorphine (1.0 mg/kg SC) once daily for 14 days.

In the repeated antidepressant treatment experiment, vehicle, desipramine (10 mg/kg), fluoxetine (10 mg/kg), and citalopram (10 mg/kg) were injected once daily for 2 weeks (no behavioral experiments were performed).

[^{3}H]citalopram Binding Experiments

In the radioligand binding experiments, the following chemicals were used: [^{3}H]citalopram (85 Ci/mmol) from NEN, Netherlands; fluoxetine, Tris HCI from Sigma, St. Louis, MO; all other chemicals were of analytical grade from local commercial sources.

Rats were moved from the animal department to the laboratory, decapitated, and the brains were quickly dissected on ice. All this procedure took no more than 5 min. The brain samples were stored in polypropylene tubes at −82°C until assayed. The binding studies were performed as described previously [(23), slightly modified]. In brief, the brain samples were homogenized using a glass-teflon homogenizer (Braun Melsungen AG, 10 strokes, 1000 rpm) in buffer (mM): 150 NaCl, 20 EDTA, 50 Tris HCl, pH 7.4 20°C. The homogenate was centrifuged at 30,000 × *g* for 15 min. The buffer was discarded, the pellet was rehomogenized in buffer (mM): 5 Tris HCl, 5 EDTA, pH 7.4 20°C, the membrane homogenate was lysed at 4°C for 30 min, and centrifuged (15 min, 30,000 × *g*). The buffer was discarded, the pellet was rehomogenized in incubation buffer (mM): 120 NaCl, 5 KCl, 50 Tris HCl, pH 7.4 20°C and centrifuged for 15 min, 30,000 × *g*. The latter procedure was repeated three times. The final pellet was resuspended in the incubation buffer using Kinematica Polytron homogenizer, setting 5, 5 s. The binding was performed on standard 96-hole microplates at room temperature in a total volume of 350 μl. [^{3}H]citalopram was used in concentrations from 0.1 to 4.0 nM; 1 μM fluoxetine was used as a displacer and all probes were measured in duplicate. The incubation

TABLE 1

THE EFFECT OF ACUTE ANTIDEPRESSANT TREATMENT ON APOMORPHINE-INDUCED AGGRESSIVE BEHAVIOR IN RATS

Drug	Scoring of Aggressive APO + VEH	Postures (Points) APO + DRUG	Time of Latency (min) APO + VEH	APO + DRUG
Desipramine 10 mg/kg	1.75 ± 0.49	3.00 ± 0.00*	11.75 ± 3.20	3.50 ± 0.33*
Fluoxetine 10 mg/kg	3.00 ± 0.00	2.50 ± 0.19	10.00 ± 3.89	9.87 ± 0.61
Citalopram 10 mg/kg	2.93 ± 0.07	2.19 ± 0.27	3.50 ± 0.42	7.25 ± 1.33
Imipramine 10 mg/kg	2.72 ± 2.25	2.25 ± 0.41	2.85 ± 0.46	6.37 ± 2.02
Amitriptyline 10 mg/kg	1.58 ± 0.43	1.25 ± 0.39	11.00 ± 2.73	12.08 ± 2.43
Clomipramine 10 mg/kg	1.75 ± 0.39	2.25 ± 0.33*	8.16 ± 2.53	6.00 ± 1.99
Citalopram 20 mg/kg	2.85 ± 0.14	2.62 ± 0.37	1.57 ± 0.57	4.00 ± 2.29
Buspirone 5.0 mg/kg	1.83 ± 0.60	0.00 ± 0.00*	2.00 ± 0.00	15.00 ± 0.00†
Buspirone 2.5 mg/kg	2.83 ± 0.16	0.00 ± 0.00†	3.33 ± 0.76	15.00 ± 0.00†

*$p < 0.05$; †$p < 0.01$ APO + DRUG group vs. APO + VEH group. All values are data obtained (mean ± SEM) from experiments that were analyzed by Mann–Whitney *U*-test. APO—apomorphine, VEH—vehicle.

(90 min) was terminated with rapid filtration through the 48-channel Brandell cell harvester (Whatman GF/B glass-fiber filters). The filters were washed five times with a 0.5-ml incubation buffer and dried. The dried filters were left overnight in a Wallac High Safe III scintillation cocktail and assayed in Wallac β-scintillation counter.

Protein concentration was measured by the classic Lowry method.

Statistics

For statistical analysis of the results from behavioral experiments. Kruskal–Wallis one-way analysis of variance (ANOVA) followed by Mann–Whitney *U*-test was used. The data obtained from biochemical experiments were subjected to one-way ANOVA, and when appropriate, for post hoc data comparison, Fischer's LSD test was used. The probability levels $p < 0.05$ were always considered statistically significant.

RESULTS

The Effect of Acute Antidepressant or Buspirone Treatment on Apomorphine-Induced Aggressive Behavior

After acute drug treatment, the Mann–Whitney *U*-test revealed a significant drug treatment effect on scoring of aggressive postures after 10 mg/kg desipramine (Mann–Whitney $U = 48$; $p < 0.05$), 10 mg/kg clomipramine (Mann–Whitney $U = 42$; $p < 0.05$), 2.5 (Mann–Whitney U = 36; $p < 0.01$) and 5.0 (Mann–Whitney $U = 30$; $p < 0.05$) mg/kg buspirone treatment, but failed to reveal a significant effect after 10 mg/kg citalopram, fluoxetine, imipramine, amitriptyline, or 20 mg/kg citalopram treatment. At the time of latency, ANOVA revealed a significant effect after 10 mg/kg desipramine (Mann–Whitney $U = 9.5$; $p < 0.05$), 2.5 (Mann–Whitney $U = 0.0$; $p < 0.01$) and 5.0 (Mann–Whitney $U = 0.0$; $p < 0.01$) mg/kg buspirone treatment; but failed to reveal any effect in other experiments (Table 1).

The Effect of Repeated Apomorphine or Concomitant Apomorphine and Antidepressant Treatment on Rat Aggressive Behavior

The animals were tested on the 1st, 3rd, 5th, 8th, and 14th day of the treatment. Similar to the previous study, on the first day of the experiment, desipramine enhanced apomorphine-induced aggression in animals ($H(2) = 12.21$, $p < 0.01$ for the score of aggressive postures; $H(2) = 8.94$, $p < 0.05$ for the latency, Kruskal–Wallis test), there was no difference between the apomorphine plus vehicle and apomorphine plus citalopram group. On the third ($H(2) = 7.33$, $p < 0.05$ for the score of aggressive postures; $H(2) = 6.21$, $p < 0.05$ for the latency, Kruskal–Wallis test), and fifth ($H(2) = 6.21$, $p < 0.05$ for the score of aggressive postures; $H(2) = 6.09$ $p < 0.05$ for the latency, Kruskal–Wallis test) day, a similar effect was found. On the third and fifth day, citalopram challenge tended also to enhance the apomorphine-induced aggressiveness, but this effect was not statistically significant. On the 8th and 14th day, between the test groups no differences were found either in the intensity of the aggressive postures or in the time of latency parameter (Figs. 1 and 2).

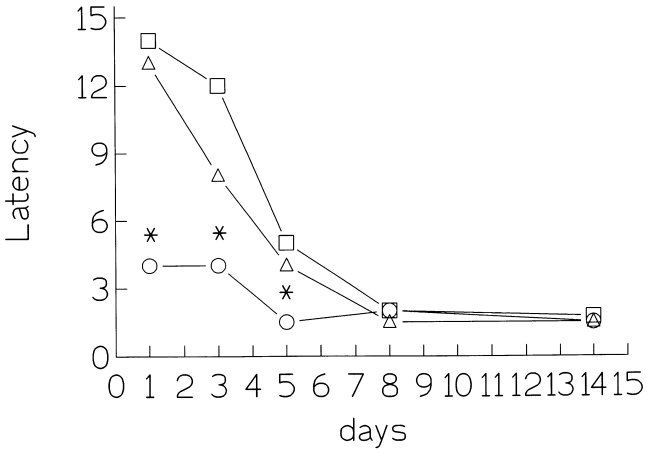

FIG. 1. The effect of repeated apomorphine, apomorphine plus desipramine, or apomorphine plus citalopram treatment on the intensity of aggressive postures. Squares, apomorphine group; triangles, apomorphine + citalopram group; circles apomorphine + desipramine group. *$p < 0.05$ apomorphine + desipramine group vs. apomorphine group (Kruskal–Wallis one-way ANOVA followed by Mann–Whitney *U*-test).

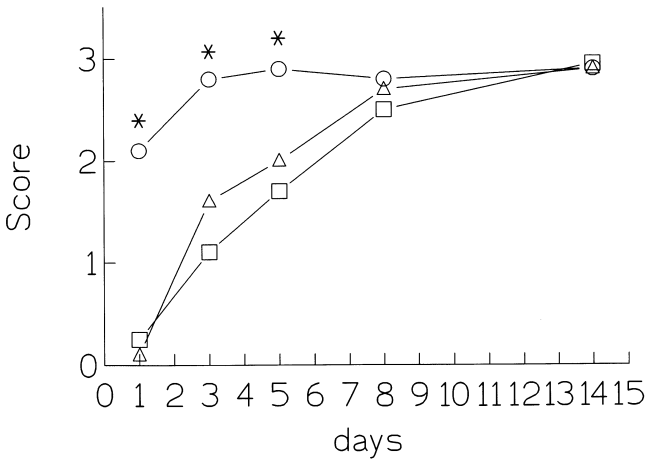

FIG. 2. The effect of repeated apomorphine, apomorphine plus desipramine, or apomorphine plus citalopram treatment on the time of latency. Squares, apomorphine group; triangles, apomorphine + citalopram group; circles apomorphine + desipramine group. *$p < 0.05$ apomorphine + desipramine group vs. apomorphine group (Kruskal–Wallis one-way ANOVA followed by Mann–Whitney *U*-test).

[³H]Citalopram Binding in Rat Brain Membranes After Repeated Apomorphine or Concomitant Apomorphine and Antidepressant Administration

The repeated administration of apomorphine or apomorphine and antidepressant challenge had a significant effect on the affinity (K_d) of the 5-HT transporter binding sites in frontal cortex, $F(3, 16) = 3.403$, $p < 0.05$, striatum, $F(3, 12) = 7.254$, $p < 0.01$, and hypothalamus, $F(3, 12) = 4.197$, $p < 0.05$. The affinity of the 5-HT transporter binding sites in hippocampus and the maximal number of apparent binding sites (B_{max}) in all brain regions tested were unchanged (Table 2).

[³H]Citalopram Binding After Repeated Antidepressant Administration in Rat Frontal Cortex

The repeated administration of antidepressants had a significant effect on the affinity (K_d) of the 5-HT transporter binding sites in frontal cortex, $F(3, 16) = 3.817$, $p < 0.05$, but failed to have a significant effect on the maximal number of apparent binding sites (B_{max}, Table 3).

DISCUSSION

In our study, the repeated administration of moderate doses of apomorphine gradually induced aggressive behavior. Likewise, in the experiments of Lang et al. 1995, the first signs of aggressive behavior were observed during the first 3 days of the apomorphine administration, whereas from eighth day of the experiment all animals tested became aggressive. Furthermore, although the time of latency parameter in our experiments is quite variable, our results are in good agreement with previous studies (1,13–15).

The acute experiments of the present study indicates that the 5-HT_{1A} receptor agonist buspirone blocks the apomorphine-induced aggressive behavior at both doses (2.5 and 5.0 mg/kg) tested. This result is in line with the previous report of Sanchez et al., 1993, in which isolation of male mice was used as aggression inducing stimulus. Recently, it has been reported that 5-HT_{1A} receptor expression in forebrain regions of aggressive house mice is enhanced (17). Thus, our study provides further support that the 5-HT_{1A} receptors may be involved in the mediation of the aggressive behavior in rodents. Furthermore, the social behavior in rodents consists of several elements like defense, avoidance, social interaction, exploration etc. (10,31). In our studies, we measured only two elements of aggressive behavior (the intensity of aggressive postures and the time of latency), and those were completely blocked by buspirone. Although not specially measured in our study, the buspirone doses used had only weak effects on the rat exploratory activity in the home cage. This finding excludes the explanation of the inhibition of the aggressive behavior as a simple sedative effect of the drug.

In a previous study, in which a similar experimental protocol was used, it has been demonstrated that desipramine may enhance apomorphine-induced aggressive behavior (12). In our study, both desipramine and clomipramine increased the intensity of the aggressive postures, and desipramine reduced the time of latency. This finding further confirms that our study design is appropriate for the measurement of the effects of pro- or antiaggressive drugs. In the acute antidepressant treatment experiments, citalopram, amitriptyline, imipramine, and

TABLE 2

THE BIOCHEMICAL CHARACTERISTICS OF THE 5-HT TRANSPORTER BINDING SITES AFTER REPEATED APOMORPHINE OR APOMORPHINE PLUS ANTIDEPRESSANT TREATMENT

		APO + CIT	APO + DES	APO	VEH
Frontal cortex	B_{max}	379 ± 23	365 ± 37	364 ± 21	301 ± 22
	K_d	0.680 ± 0.079*	0.591 ± 0.064	0.631 ± 0.064*	0.420 ± 0.029
Hippocampus	B_{max}	193 ± 35	160 ± 32	154 ± 27	207 ± 45
	K_d	0.458 ± 0.044	0.431 ± 0.068	0.493 ± 0.106	0.472 ± 0.094
Hypothalamus	B_{max}	349 ± 52	383 ± 19	315 ± 15	289 ± 47
	K_d	0.581 ± 0.053*	0.600 ± 0.119*	0.360 ± 0.044	0.344 ± 0.013
Striatum	B_{max}	250 ± 82	249 ± 24	213 ± 31	227 ± 20
	K_d	0.637 ± 0.036*	0.286 ± 0.034	0.435 ± 0.075	0.411 ± 0.060

*$p < 0.05$ VEH groups vs. APO, APO + DES, or APO + CIT group. All values are data obtained (mean ± SEM) from biochemical experiments that were analyzed by one-way ANOVA followed by Fisher's LSD test. APO—apomorphine, CIT—citalopram, DES—desipramine, VEH—vehicle.

TABLE 3

THE BIOCHEMICAL CHARACTERISTICS OF THE 5-HT TRANSPORTER BINDING SITES IN THE RAT FRONTAL CORTEX AFTER REPEATED ANTIDEPRESSANT TREATMENT

		CIT	FLX	DES	VEH
Frontal cortex	B_{max}	287 ± 24	302 ± 19	335 ± 27	315 ± 31
	K_d	0.704 ± 0.061*	0.537 ± 0.039	0.462 ± 0.040	0.439 ± 0.045

*$p < 0.05$ VEH group vs. CIT group. All values are data obtained (mean ± SEM) from biochemical experiments that were analyzed by one-way ANOVA followed by Fischer's LSD test. CIT—citalopram, FLX—fluoxetine, DES—desipramine, VEH—vehicle.

fluoxetine were without any effect, although fluoxetine tended to have a weak (statistically not significant) antiaggressive effect. Thus, these results provide evidence that after acute administration the SSRIs and the unselective monoamine reuptake inhibitors are ineffective or have only weak antiaggressive effect in rodents, but the drugs that primerly block the noradrenaline reuptake may even intensify the aggressive behavior. Further, in our preliminary experiments we have found that 3 weeks antidepressant pretreatment does not presensitise the animals to the single apomorphine injection (unpublished), which was the particular reason to investigate the effect of concomitant antidepressant and apomorphine treatment on the aggressive behavior. Our experiments confirm that the repeated concomitant citalopram and apomorphine treatment did not influence the development or the intensity of the aggressive behavior, although on the third and fifth day weak statistically not significant tendencies to potentiate the aggressive behavior were found. Further, this findings have been confirmed with the results from the biochemical experiments. Thus, neither repeated apomorphine treatment alone nor the antidepressant challenge had a clear, unidirectional influence on the binding characteristics of the 5-HT transporter binding sites. Citalopram challenge reduced the affinity of the 5-HT transporter binding sites in the frontal cortex, striatum, and hypothalamus but not in hippocampus (the latter structure had a twice lower B_{max} value) in comparison to the vehicle group; however, in the frontal cortex, there was no difference found in the K_d values between the apomorphine and the apomorphine plus citalopram group. The experiments with repeated antidepressant administration demonstrate that these changes could be explained rather as the effect of citalopram but not apomorphine treatment. Failure to demonstrate any changes in B_{max} values may be explained due to the relative short time of antidepressant administration. It should be emphasised, however, that the control animals used in our study had a somewhat lower maximal number of the apparent binding sites than in some reference experiments (5,22,23). Furthermore, it could be expected that the separate housing of the animals might also influence the binding characteristics of the 5-HT transporter binding sites. Until recently, the effect of this variable was not well characterized. In the apomorphine experiments, the animals were kept separately. In the control experiment of the repeated antidepressant administration (the animals were from the same stock), the animals were housed five per cage, but the K_d and B_{max} values of the control group were matching. This finding rather indicates that the housing conditions have no effect on [^{3}H]citalopram binding.

Apomorphine or apomorphine plus desipramine treatment also reduced the affinity of the 5-HT transporter binding site in two different brain regions. This finding is difficult to explain in the frame of our study. At the same time, apomorphine plus desipramine treatment tended to increase the K_d value in the frontal cortex but to reduce it in the striatum. Although this effect just failed to reach the significance level, these bidirectional changes indicate that the effect of apomorphine on the 5-HT transporter binding site is rather nonspecific. Previously, it has been shown that chronic antidepressant drug treatment attenuates motor suppressant effects of apomorphine without changing dopamine binding site characteristics (3).

Furthermore, there are reports that withdrawal from prolonged citalopram treatment may lead to the subsensitivity to the apomorphine-induced hypomotility (4) and the 5-HT_{1C} and 5-HT_2 receptors may also be the targets for the drugs that modulate the function of the dopaminergic neurotransmission (34). These findings indicate that a link between dopaminergic and serotoninergic neurotransmission exists. On the other hand, the protocols of these studies (4,34) were principally different and, therefore, no direct comparison is feasible. It can be speculated that apomorphine treatment per se has no major effect on [^{3}H]citalopram binding. The changes of the 5-HT transporter binding site characteristics found may be a secondary response to the changes in the dopaminergic neurotransmission. However, further experiments are needed to study whether and which variables influence the dopaminergic-serotoninergic interactions.

In conclusion, our experiments confirm that the apomorphine-induced aggressive behavior may be mediated through the 5-HT_{1A} receptor subtype, but the acute or repeated 5-HT reuptake blockade has no major influence on apomorphine-induced aggressiveness in rodents either on the behavioral or on the neurochemical level.

ACKNOWLEDGEMENTS

This study was supported by the Estonian Science Foundation (Grant No. 07, to L. A.) and by a scholarship from the "Ants ja Maria Silvere ning Sigfried Panti Mälestustipendium Tartu Ülikoolis" Foundation (to V. M.). Citalopram was a generous gift from H. Lundbeck, Copenhagen, Denmark.

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