JOURNAL OF PHYSIOLOGY AND PHARMACOLOGY 2000, 51, 4, 833—846

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5-HT1A RECEPTOR AGONISTS BUSPIRONE AND GEPIRONE ATTENUATE APOMORPHINE-INDUCED AGGRESSIVE BEHAVIOUR IN ADULT MALE WISTAR RATS

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We have studied the effects of acute serotonin (5-HT) 5-HT1A receptor agonist buspirone (0.5, 1.0, 2.5 and 5.0 mg/kg, s.c.), gepirone (5.0 and 10 mg/kg, s.c.), and 8-OH-DPAT (0.1, 0.25, and 0.5 mg/kg, i.p.) treatment on the apomorphine-induced aggressive behaviour in adult male Wistar rats. Buspirone in doses of 2.5 and 5.0 mg/kg completely blocked, gepirone (10 mg/kg) significantly attenuated the aggressiveness, and 8-OH-DPAT abolished aggressive behaviour only in the lowest dose used (0.1 mg/kg) which effect disappeared in higher doses. The antiaggressive effect of buspirone (2.5 mg/kg) and gepirone (10 mg/kg) was not reversed by a 5-HT1A receptor antagonist WAY 100635 (0.3 mg/kg). All 5-HT1A receptor agonists tested dose-dependently decreased the exploratory behaviour of experimentally naive rats, while buspirone (2.5 mg/kg) and gepirone (10 mg/kg) had only a weak effect on the locomotor activity and stereotyped behaviour in the apomorphine-pre-sensitised rats. In conclusion, our experiments demonstrate the 5-HT1A receptors may be involved in the mediation of the apomorphine-induced aggressive behaviour in adult male Wistar rats. However, the prominent antiaggressive effect of buspirone, and to a lesser extent — gepirone, seems to be mediated by some other mechanisms, evidently via the dopamine D2 receptors.

Key words: *buspirone, gepirone 8-OH-DPAT, apomorphine, aggressive behaviour, rat.*

INTRODUCTION

Psychotic aggressive behaviour is a serious medical and social problem (1). Today, there is a large arsenal of psychotropic drugs available that may abolish aggressive behaviour. However, most of them are non-specifically sedative and display many adverse effects limiting their use (2).

During the last two decades the search for novel antiaggressive drugs has been focused on the compounds acting at the serotonin- (5-HT)-ergic

neurotransmission (3, 4). Since late eighties, the selective serotonin reuptake inhibitors (SSRIs) are widely in use as antidepressive and antipanic drugs (5—8). First attempts have been done to introduce those compounds also as antiaggressive drugs, but with controversial results. It seems, that the SSRIs are more effective in patients with borderline disorders than in acute psychotics (9, 10). Since the 5-HT is an endogenous ligand for all subtypes of 5-HT receptors (recently identified at least 14 types), the SSRIs induce activation of all 5-HT receptor subtypes. The 5-HT receptor subtype selective ligands might be superior in this regard, because it has been found that distinct 5-HT receptors mediate different components of emotional, motivational, and cognitive behaviour (for a review, see 11). Although the 5-HT receptor subtype-selective compounds are promising psychotropic drugs, today only buspirone is clinically used as an antiaggressive drug (12).

However, the search of novel antiaggressive drugs is complicated because there exists only a limited number of animal models of aggressive behaviour (13). It should be born in mind that the human aggressive behaviour is not a disease in the strict term, but rather a symptom or a syndrome of psychiatric disorders. Therefore, the animal models widely used, for example the isolation-induced aggressive behaviour model in mice, do not reflect properly the human *psychotic* aggressiveness (14). The apomorphine- (an unselective dopamine D_1, D_2 receptor agonist) induced aggressive behaviour is effectively antagonised by neuroleptics, D_2 receptor blockers, morphine, NMDA receptor antagonists and intensified by dopaminergic agonists and drugs that potentiate catecholaminergic neurotransmission (15—24). These drugs have similar effects on human psychosis thereby confirming the general validity of the apomorphine-induced aggressive behaviour paradigm in male rats as a model of psychotic behaviour.

In our previous experiments, we have found that fluoxetine and citalopram, the SSRIs, do not have any major antiaggressive effect in this test, although some statistically insignificant tendencies were found (25). However, L-tryptophan challenge manifested the antiaggressive effect of fluoxetine (26). We proposed that it might be due to the subsequent 5-HT receptor activation but not due to the 5-HT transporter blockade *per se* (25). We have also found that the 5-HT3 receptor antagonsts modulate (but not primarily mediate) the apomorphine-induced aggressive behaviour in male rats (27), while the 5-HT2A/2C receptor antagonists do not have a gross effect (28).

The objective of the present study was to compare the possible antiaggressive effects of the 5-HT1A receptor partial agonists buspirone and gepirone and the 5-HT1A receptor full agonist 8-OH-DPAT [(±)-8-hydroxy-di-N-propyl-aminotetralin HBr] in the apomorphine-induced aggressive behaviour test. Because the apomorphine-induced aggressive behaviour test is time-consuming, the same animals were used repeatedly as

reported in our previous works (25—31). The experiments were performed in three separate sets, while in order to minimise the possible strain effect, all animals were ordered from the same breeder (Kuopio National Animal Centre). The doses tested were chosen on the basis of our preliminary experiments (buspirone, gepirone, and WAY 100635) or reference experiments (8-OH-DPAT) (32—33). Repeated apomorphine treatment is known to induce hyperlocomotions and stereotyped behaviour, therefore we studied also some effects of the 5-HT1A receptor ligands on the behaviour of apomorphine-pre-sensitised and non-sensitised rats in the open-field and locomotor activity tests.

In an our previous work we reported that the 5-HT1A receptor partial agonist buspirone may abolish the aggressiveness (25). In order to elucidate whether the expected antiagressive effect of buspirone is mediated by the 5-HT1A receptors, we applied also a combined buspirone plus 5-HT1A receptor antagonist WAY 100635 treatment.

The apomorphine-induced aggressive behaviour experiments were performed as single-factor experiments (factor: drug treatment) without a repeated vehicle *versus* a repeated apomorphine treatment control.

MATERIALS AND METHODS

Ethics

The apomorphine-induced aggressiveness test was approved by The Ethics Committee of the University of Tartu for the pharmacological studies of the monoaminergic neurotransmission.

Animals

Adult male Wistar rats weighing 350—420 g were obtained from Kuopio National Animal Centre, Kuopio, Finland. They were housed one per cage under standard laboratory conditions; water and food were available *ad libitum*. The animal room had controlled temperature (20°C ± 2°C) and light/dark cycle (lights on from 8.00 a.m. to 8.00 p.m.).

General procedure of the apomorphine-induced aggressive behaviour test

The apomorphine-induced aggressiveness study was performed as reported in our earlier experiments (12, 14, 25—31). The standard polycarbonate, semitransparent cages were placed into the stainless steel racks. The animals were housed singly and on the next day, the apomorphine treatment was started. After an injection, the animals were either tested for aggressiveness as described below or returned to the home cage. The same animal pairs were used throughout the study, while the animal pairs were always picked from the neighbouring cages and subjected to the same drug treatment. The apomorphine treatment lasted for 12 days during which the aggressiveness was scored four times (on the first, fourth, eighth, and 12th day), thereafter the elucidation of the effect of drugs was started.

Apomorphine-induced aggressive behaviour test

Aggressive behaviour was measured in specially designed cages [transparent plastic sidewalls (35 × 35 × 55 cm, length × width × height) and stainless steel floor, covered with sawdust]. Immediately after apomorphine 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 behaviour. The animals were observed for 15 min and the rating of aggressive behaviour was scored in the 0—3 point scale:

0 — no aggressive manifestations;
1 — intermittent mild aggressive posture or attack with other 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 behaviour, the test was immediately terminated to avoid injuries.

Open-field test

The open-field consists of a wooden grey painted quadrate arena 1 × 1 m with 40 cm side walls. The surface of the floor was divided into sixteen squares of equal size.

For the test, the animal was placed into one of the central squares and observed during four minutes for (1) horizontal (number of line crossing on the floor) and (2) vertical activity (number of rearings).

Locomotor activity test

The locomotor activity test was performed in an apparatus similar to this used for the open-field test, while the same criteria were followed as described above. The test lasted for 15 minutes, the horizontal and vertical activity was counted during the five-minutes periods.

Measurement of stereotyped behaviour

At the end of the five-minutes periods of the locomotor activity test (total duration — 15 minutes), the stereotyped behaviour of animals was scored on using the scoring system of Voikar *et al.* (34):

0 — no signs of stereotyped behaviour;
1 — discontinuous sniffing and locomotor activity;
2 — continuous sniffing and small head movements, periodic locomotor activity;
3 — continuous sniffing, discontinuous biting or chewing, brief periods of locomotor activity;
4 — continuous gnawing, biting, and licking, no locomotor activity.

Drugs

The following drugs were used (doses in parenthesis): apomorphine hydrochloride, from Reakhim, Krasnoyarsk, Russian Federation; 8-OH-DPAT hydrobromide and WAY 100635 maleate from RBI Chemicals, Natick, MA, USA; and buspirone hydrochloride and gepirone

hydrochloride, from Bristol-Myers-Squibb, London, UK. Buspirone (0.5, 1.0, 2.5, and 5 mg/kg), gepirone (5.0 and 10 mg/kg), 8-OH-DPAT [(±)-8- hydroxy-di-N-propyl-aminotetralin HBr] (0.1, 0.25, and 0.5 mg/kg), and WAY 100635 N-[2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl]--N-2-pyridinyl-cyclohexanecarboxamide maleate (0.1, 0.3, and 1.0 mg/kg) were dissolved in distilled water. Apomorphine (1.0 mg/kg) was dissolved in distilled water containing 0.01% L-ascorbic acid and stored as a stock solution at +4°C. All drugs were injected 30 min before apomorphine. Apomorphine, buspirone and gepirone were injected s.c., 8-OH-DPAT and WAY 100635 were injected i.p. In the case of the co-administration of two drugs, both of them were administered 30 min before apomorphine on the opposite parts of abdomen.

Statistics

For statistical analysis, the data from apomorphine-induced or open-field experiments were subjected to one-way analysis of variance (ANOVA) followed by Scheffe test.

The data from the locomotor activity and stereotyped behaviour were subjected to the repeated measures ANOVA (data from the time points of 5, 10, and 15 minutes). Whenever a treatment effect or treatment × time point interaction was found, the data were further analysed by one-way ANOVA followed by Scheffe test.

P values < 0.05 were always considered statistically significant. All data are expressed as means ± SEM.

RESULTS

Development of apomorphine-induced aggressive behaviour

The repeated apomorphine treatment induced a gradual development of aggressive behaviour as evidenced by the increased intensity of aggressiveness and the shortened latency before the first attack toward the opponent (*Fig. 1*).

Effect of buspirone, gepirone, and 8-OH-DPAT on apomorphine-induced aggressive behaviour

The 8-OH-DPAT experiment was repeated twice, because in the first test no obvious effect of 8-OH-DPAT treatment was found. Since the results were matching, in the subsequent statistical analysis the data from those experiments were summarised. Thus, the ANOVA showed a significant treatment effect on the latency before the first aggressive posture [$F(3,86) = 7.1$, $p < 0.01$], but not on the intensity of aggressiveness [$F(3,86) = 2.4$, $p = 0.07$]. On the latency, Scheffe test demonstrated a significant effect of the dose 0.1 mg/kg as compared with the vehicle group (*Table 1*).

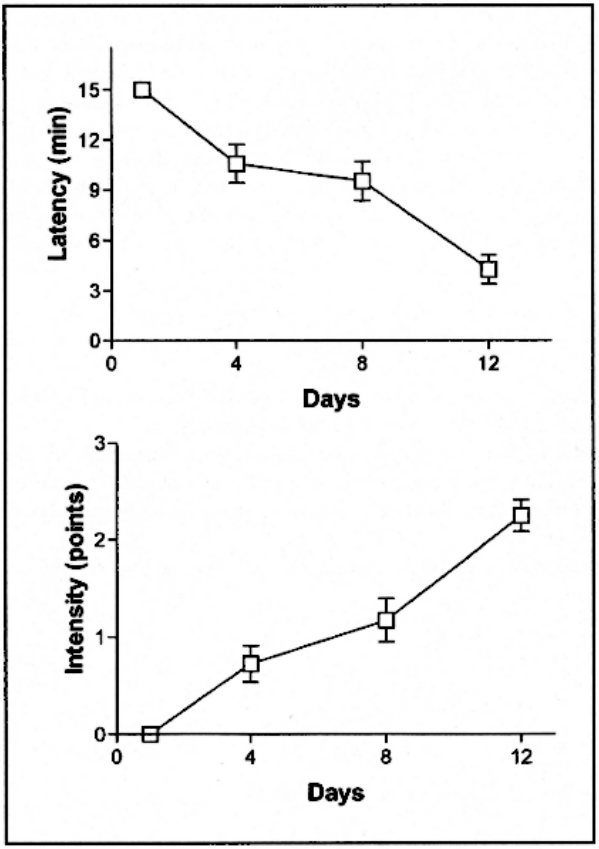

Fig. 1. A typical example of the development of aggressiveness in adult male Wistar rats (n = 30) during twelve consecutive days: time of latency before first aggressive posture (upper panel) and intensity of aggressive postures (lower panel). These curves express typical patterns of the development of apomorphine--induced aggressiveness in adult male Wistar rats, while this treatment schedule was repeated three times using different groups of animals with similar results. Data are given as means ± SEM.

The effect of acute buspirone treatment on the apomorphine-induced aggressive behaviour was studied in two separate experiments. In the both cases, the effects of buspirone were compared with their own control group. In the buspirone 0.5 and 1.0 mg/kg treatment experiment, the ANOVA failed to reveal any statistically significant treatment effect, but in the intensity parameter, it was quite close to the significance level ($p = 0.055$). In the buspirone 2.5 and 5.0 mg/kg treatment experiment, the ANOVA showed a significant treatment effect both on the intensity of aggressiveness [$F(2,21) = 107.3$, $p < 0.001$] and on the latency before the first aggressive posture [$F(2,21) = 162.7$, $p < 0.001$]. Scheffe test demonstrated a significant effect of buspirone doses of 2.5 and 5.0 mg/kg as compared with the corresponding vehicle group (*Table 1*).

In the gepirone treatment test, the ANOVA showed a significant treatment effect both on the intensity of aggressiveness [$F(2,21) = 8.5$, $p < 0.01$] and on the latency before the first aggressive posture [$F(2,21) = 6.1$, $p < 0.01$]. Both on

the latency and intensity parameters, Scheffe test demonstrated a significant effect of gepirone dose of 10 mg/kg as compared with the corresponding vehicle group (*Table 1*).

Table 1. Effect of 5-HT1A receptor ligands on apomorphine-induced aggressive behaviour in rats.

Drug	Dose mg/kg	Intensity of aggressiveness (points)	Latency (minutes)
8-OH-DPAT (summarised data)			
n = 44	0	2.41 ± 0.08	2.31 ± 0.25
n = 16	0.1	2.06 ± 0.17	5.12 ± 1.20 **
n = 16	0.25	2.50 ± 0.13	1.50 ± 0.13
n = 14	0.5	2.57 ± 0.14	2.43 ± 0.38
Buspirone Experiment I:			
n = 4	0	2.25 ± 0.25	6.00 ± 1.16
n = 4	0.5	1.75 ± 0.25	12.04 ± 1.18
n = 4	1.0	1.00 ± 0.41	9.10 ± 2.88
Experiment II:			
n = 12	0	2.75 ± 0.13	3.42 ± 0.48
n = 6	2.5	0.00 ± 0.00 ***	15.00 ± 0.00 ***
n = 6	5.0	0.00 ± 0.00 ***	15.00 ± 0.00 ***
Gepirone			
n = 12	0	2.58 ± 0.15	4.25 ± 0.63
n = 6	5.0	2.00 ± 0.36	6.33 ± 0.66
n = 6	10.0	1.50 ± 0.24 **	8.33 ± 0.81 **

** $p < 0.01$, *** $p < 0.001$ as compared with the corresponding vehicle group (Scheffe test).
n — number of animals per group.

In the combined buspirone 2.5 mg/kg plus WAY 100635 0.3 mg/kg or gepirone 10 mg/kg and WAY 100635 0.3 mg/kg experiment, the one-way ANOVA showed a significant treatment effect on the intensity of aggressiveness [$F(3,12) = 19.6$, $p < 0.001$] and on the latency [$F(3,12) = 20.7$, $p < 0.001$]. Scheffe test demonstrated a significant difference between the vehicle-treated and buspirone plus WAY 100635-treated or vehicle-treated and gepirone plus WAY 100635-treated animals. A strong tendency toward a statistical significance between the vehicle-treated and WAY 100635-treated animals was found as well ($p = 0.095$ for the intensity of aggressiveness and $p = 0.064$ for the latency), (*Table 2*).

Table 2. Effect of combined 5-HT1A receptor ligand treatment on apomorphine-induced aggressive behaviour in rats.

Drug	Intensity of aggressiveness (points)	Latency (minutes)
Vehicle, n = 4	2.50 ± 0.28	3.54 ± 0.52
WAY 100635 0.3 mg/kg, n = 4	1.50 ± 0.29	8.53 ± 2.06
Buspirone 2.5 mg/kg + WAY 100635 0.3 mg/kg, n = 4	0.00 ± 0.00 ***	15.00 ± 0.00 ***
Gepirone 10.0 mg/kg + WAY 100635 0.3 mg/kg, n = 4	0.50 ± 0.28 ***	13.50 ± 0.86 ***

*** $p < 0.001$ as compared with the corresponding vehicle group (Scheffe test), n — number of animals per group.

Table 3. Effect of 5-HT1A receptor ligands on rat exploratory behaviour in open field test.

Drug/number of animals per group	Dose mg/kg	Line crossings	Rearings
8-OH-DPAT			
n = 12	0	36.58 ± 5.30	9.66 ± 2.13
n = 6	0.1	19.83 ± 5.15 *	1.50 ± 0.56 **
n = 10	0.5	1.20 ± 0.39 ***	0.00 ± 0.00 ***
Buspirone			
n = 5	0	54.40 ± 5.79	16.80 ± 2.45
n = 5	0.5	69.60 ± 3.91	14.00 ± 2.00
n = 6	1.0	47.50 ± 7.85	7.17 ± 1.45 **
n = 6	2.5	15.83 ± 5.06 **	1.17 ± 0.83 ***
n = 6	5.0	6.67 ± 2.04 ***	0.00 ± 0.00 ***
Gepirone			
n = 6	0	60.83 ± 8.79	19.50 ± 2.75
n = 6	5.0	15.33 ± 5.55 **	0.00 ± 0.00 ***
n = 5	10.0	3.40 ± 1.47 ***	0.00 ± 0.00 ***
WAY 100635			
n = 10	0	45.50 ± 7.25	13.10 ± 3.31
n = 6	0.1	44.67 ± 5.97	11.67 ± 2.74
n = 10	0.3	48.70 ± 5.42	22.90 ± 3.80
n = 10	1.0	36.90 ± 5.22	17.80 ± 2.18

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ as compared with the corresponding vehicle group (Scheffe test), n — number of animals per group.

Effect of acute buspirone, gepirone, 8-OH-DPAT, and WAY 100635 treatment on exploratory behaviour in non-sensitised, experimentally naive rats in open field test

One-way ANOVA demonstrated a significant treatment effect of all 5-HT1A receptor agonists studied: (1) 8-OH-DPAT — [$F(2,25) = 18.8$, $p < 0.001$] for the number of line crossings and [$F(2,25) = 12.0$, $p < 0.001$] for the number of rearings; (2) buspirone — [$F(4,23) = 24.3$, $p < 0.001$] for the number of line crossings and [$F(4,23) = 24.7$, $p < 0.001$] for the number of rearings; (3) gepirone — [$F(2,14) = 22.3$, $p < 0.001$] for the number of line crossings and [$F(2,14) = 45.4$, $p < 0.001$] for the number of rearings. Acute WAY 100635 treatment was ineffective (*Table 3*).

Effect of buspirone and gepirone on locomotor activity and stereotyped behaviour of apomorphine-pre-sensitised aggressive rats

On the number of line crossings, the repeated measures ANOVA failed to show any statistically significant effect.

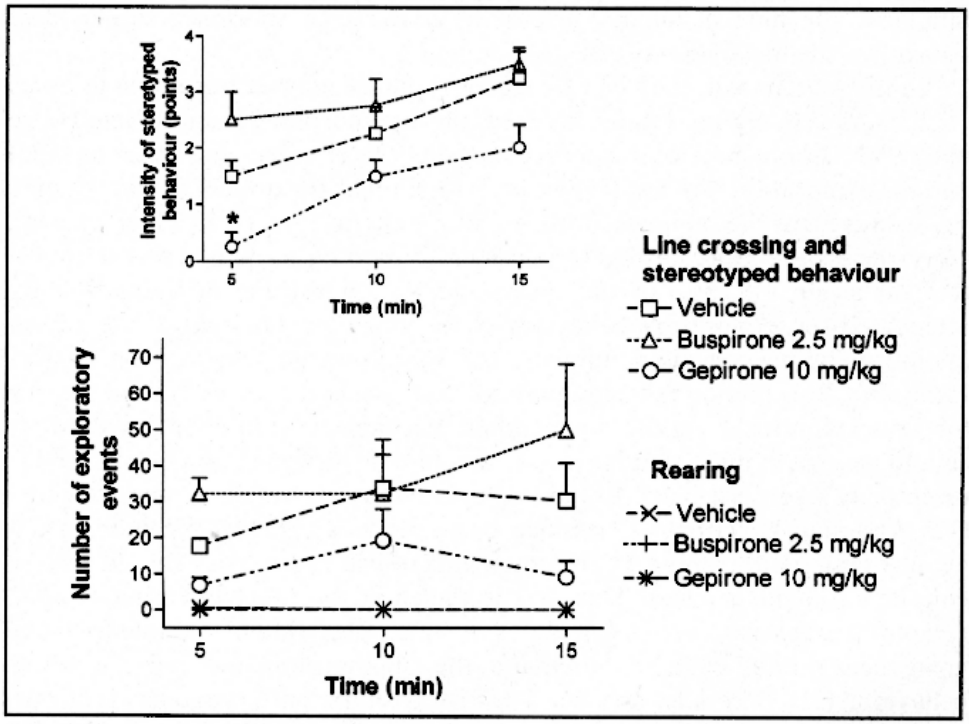

Fig. 2. Effect of buspirone and gepirone treatment on the locomotor activity and stereotyped behaviour in the apomorphine-pre-sensitised adult male Wistar rats (n per group = 4). Data are given as means ± SEM. * $p < 0.05$ as compared with the buspirone group (Scheffe test).

On the number of rearings, repeated measures ANOVA failed to find any variation at all, because during the test periods of 5—10 minutes and 10—15 minutes no rearings were observed.

On the score of the stereotyped behaviour, the repeated measures ANOVA showed a statistically significant treatment effect [$F(2,9) = 5.58$, $p < 0.05$] and time effect [$F(2,18) = 38.37$, $p < 0.001$], while there was no treatment × time interaction. When further analysed using the one-way ANOVA (factor: treatment), the only statistically significant effect was found during the period 0—5 minutes [$F(2,9) = 9.63$, $p < 0.01$]. Surprisingly, Scheffe test showed a difference between the buspirone and gepirone groups, but not between the vehicle and buspirone or gepirone groups (*Fig. 2*).

DISCUSSION

In our study, the repeated administration of apomorphine gradually induced aggressive behaviour. The first signs of aggressive behaviour were observed on the fourth day of the apomorphine administration (14, 25—31). Similarly, the time of latency before the first attack shortened day-by-day, indicating the reliability of the test design.

In the present test, the 5-HT1A receptor partial agonist buspirone in doses of 2.5 and 5.0 mg/kg totally blocked the apomorphine-induced aggressive behaviour. In our previous experiments using the elevated zero-maze test (35) and the exploration box test (36) we have found that the dose of 5.0 mg/kg may be sedative in the animals used in our experiments (WIST:Kuo strain). Nevertheless, we expected that the dose of 2.5 mg/kg should not be sedative in this rat strain (35, 36). In the open field test, buspirone dose-dependently attenuated the exploratory behaviour of the experimentally naive rats, but in apomorphine-pre-sensitised animals, the buspirone dose of 2.5 mg/kg was ineffective. This finding indicates, indeed, that beside the robust antilocomotor (or antiexploratory) action, some other mechanism should be involved. It should be kept in mind that buspirone was initially designed as a dopamine D2 receptor blocker, but failed to have a high affinity to the dopamine receptors (37). Although buspirone is classified primarily as a 5-HT1A receptor partial agonist (38), its dopamine D2 receptor antagonistic properties should still be considered in this context. This idea is evidenced by two facts. First, the D2 receptor anatgonists even in low doses in which they are not capable to evoke gross behavioural changes, attenuate the apomorphine-induced aggressive behaviour (21). Secondly, another 5-HT1A receptor partial agonist gepirone, which shares with buspirone its 5-HT1A agonistic but not considerable D2 blocking properties, was considerably less active in the present study. The maximal dose of gepirone (10 mg/kg) used in our study is sufficient to have

a maximal intrinsic activity for the 5-HT1A receptors. With this regard, our study is in good agreement with the neurophysiological experiments of Piercey *et al.* (39), where it was found that buspirone binds to the dopamine D2 receptors with a considerably higher affinity as compared with gepirone or 8-OH-DPAT. Furthermore, it has been reported that the partial agonists of 5-HT1A receptors act predominantly at the presynaptic and/or autoreceptors. It can not be excluded that the effect of the lowest dose of 8-OH-DPAT used in our study (0.1 mg/kg) is associated with the presynaptic/autoreceptors of the 5-HT1A type. Although out of the framework of our study, it can be speculated that the 5-HT1A presynaptic and/or autoreceptors mediate the aggressive behaviour in this test, while the postsynaptic 5-HT1A receptors seem do not have a major role in this phenomenon. The latter idea is also evidenced by the fact that higher doses of 8-OH-DPAT were completely ineffective. At the same time, it should also be born in mind that the apomorphine dose of 1.0 mg/kg s.c., once daily is sufficiently high to cause disregulation in both presynaptic and postsynaptic dopamine D2 receptors. Taking into consideration the functional integrity of the mammalian CNS, it is probable, but not proved that the disregulation of the dopamine D2 receptors as a consequence of the apomorphine treatment might have some impact on the 5-HT1A receptors in the apomorphine-aggressive rats. In our recent work we found that the post-mortem 5-HT and its major metabolite 5-HIAA (5-hydroxyindolacetic acid) contents in apomorphine-aggressive animals were not changed as compared with the non-aggressive or experimentally naive animals (40), thereby indicating that such link between the dopaminergic and serotoninergic neurotransmission could exist on the receptors level.

Involvement of the 5-HT receptors in the mediation of aggressive behaviour has also been reported earlier, while the special emphasis has been put on the serotonin 5-HT1A and 5-HT1B receptors. Sanchez and co-workers have found that the 5-HT1A receptors are involved in the neurobiology of isolation-induced aggressiveness in male mice (41, 42). Later, it has been reported that 5-HT1A receptor expression in forebrain regions of aggressive house mice is enhanced (43). Enhanced aggressiveness has been found in animals lacking 5-HT1B receptors (44), while *vice versa*, aggressiveness can be attenuated by the 5-HT1B receptor agonists (45). Nevertheless, from the methodological point of view it should be emphasised that the social behaviour (including inter-male aggressive postures) in rodents consists of several components like defence, avoidance, social interaction, exploration *etc.* (46, 47). In the apomorphine-induced aggressive behaviour paradigm the "physiological" components of social interaction of animals are suppressed and the animals display strongly disturbed, chaotic, and frantic behavioural elements. Therefore, the results of our present study should be considered only in the context of "psychotic" aggressiveness.

In conclusion, our experiments demonstrate the involvement of the 5-HT1A receptors in the neurobiology of apomorphine-induced aggressive behaviour. Summarising the present data, it might be proposed that the partial agonists of 5-HT1A receptors (buspirone and gepirone) reveal more pronounced antiaggressive properties in the apomorphine-induced aggressive-behaviour test as compared with the full agonist 8-OH-DPAT. This effect is evidently associated with the presynaptic and/or autoreceptors, but only further experiments may bring final clarity of this issue. Since the antiaggressive effect of buspirone and gepirone was not blocked by the 5-HT1A antagonist WAY 100635, some other mechanisms, evidently via the dopamine D2 receptors, are also involved in the action of buspirone and gepirone.

Acknowledgement: This study was supported by a post-doctoral scholarship from The Ministry of Education of The Republic of Estonia (to VM, contract No TARFR0808) and by a grant from the Estonian Science Foundation (to LA, grant No 3379).

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Received: March 15, 2000
Accepted: October 18, 2000

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