ELSEVIER

Pharmacology, Biochemistry and Behavior 70 (2001) 95–103

PHARMACOLOGY BIOCHEMISTRY AND BEHAVIOR

www.elsevier.com/locate/pharmbiochembeh

Effect of the serotonin agonist 8-OH-DPAT on the sensorimotor system of the rat

Hilde Demeulemeester[a,*], Hilde Feys[b], Isabelle Goris[b], Iris Zwaenepoel[b], Willy De Weerdt[b], Paul De Sutter[a], Jan Gybels[a], Christiaan Plets[a], Bart Nuttin[a]

[a]*Laboratory of Experimental Neurosurgery and Neuroanatomy, Department of Neuroscience and Psychiatry, K.U. Leuven, Provisorium 1, Minderbroedersstraat 17, 3000 Leuven, Belgium*

[b]*Department of Rehabilitation Sciences, Faculty of Physical Education and Physiotherapy, K.U. Leuven, Tervuursevest 101, 3000 Leuven, Belgium*

Received 22 June 2000; received in revised form 9 May 2001; accepted 10 May 2001

Abstract

8-Hydroxy-2-(di-*n*-propylamino)-tetralin hydrobromide (8-OH-DPAT, 2 mg/kg) is used to induce perseverative behavior in rats in a T-maze as a model for obsessive–compulsive disorder (OCD). Using the open-field test, radiant heat test, and the test with von Frey filaments, we examined whether alterations in sensorimotor functioning could contribute to the perseverative tendencies in this model by measuring differences in left versus right hind paw reactions after 8-OH-DPAT administration (2 mg/kg, sc). Also, the effect of repeated 8-OH-DPAT administration on sensorimotor functioning was tested every third day. 8-OH-DPAT administration induced a significantly decreased sensorimotor performance in the open-field test, an increased threshold for noxious thermal stimulation (increased withdrawal latency, WL, and decreased elevation time, ET) in the radiant heat test, and a decreased nociceptive threshold for mechanical stimulation in the test with von Frey filaments. All changes in sensorimotor functioning were similar for left and right hind paws suggesting that, these changes as measured with the tests in the present study, are not likely to contribute to the perseverative behavior of rats in a T-maze. Further, repeated administration of 8-OH-DPAT had no effect in the radiant heat test and the test with the Frey filaments, but produced a tolerance effect in the open-field test.

Keywords: 8-OH-DPAT; Sensorimotor; Open-field test; Radiant heat test; von Frey filaments; Rats; Obsessive–compulsive disorder

1. Introduction

8-Hydroxy-2-(di-*n*-propylamino)-tetralin hydrobromide (8-OH-DPAT) is a highly selective serotonin agonist that binds to the serotonin 1A (5-HT1A) receptor subfamily (Middlemiss and Fozard, 1983). The highest affinity of 8-OH-DPAT for the 5-HT1A receptors was found in the hippocampus, the cerebral cortex and the striatum, and the raphe nuclei in both the rat and human brain (Hall et al., 1985; Hoyer et al., 1986; Marazziti et al., 1994). A number of studies indicated a role for the 5-HT1A receptor in anxiety (Engel et al., 1984; File and Gonzalez, 1996; Stanhope and Dourish, 1996) and depression (Cervo and Samanin, 1987). Also, 5-HT1A receptor agonists have been used in the study of a possible animal model for some symptoms of obsessive–compulsive disorder (OCD) (Yadin et al., 1991). In this model, spontaneous alternation behavior (SAB) in a T-maze was altered after treatment with the selective 5-HT1A receptor agonist 8-OH-DPAT resulting in perseverative tendencies, i.e., the rat explored one arm of the T-maze significantly more than the other. This feature can to some extent be compared with the repetitive motor behavior as seen in OCD patients. Furthermore, it was shown that chronic treatment with a selective serotonin uptake blocker protected animals from the deficits induced by the challenging 8-OH-DPAT (Yadin et al., 1991).

In a number of studies, it has been shown that 8-OH-DPAT administration elicits several behaviors associated with the serotonin syndrome including flat back posture, forepaw treading, lower lip retraction, and hyperlocomotion (Blanchard et al., 1993, 1997; Grahame-Smith, 1971a,b; Hillegaart et al., 1989; Jacobs, 1976). The use of 8-OH-DPAT also affects body temperature (Goodwin and Green, 1985; Johansson-Wallsten and Meyerson, 1994; Scott et al.,

* Corresponding author. Fax: +32-16-33-78-55.
E-mail address: hilde.demeulemeester@med.kuleuven.ac.be (H. Demeulemeester).

0091-3057/01/$ – see front matter
PII: S0091-3057(01)00576-7

1994; Thielen et al., 1996), feeding (Blanchard et al., 1993, 1997; Dourish et al., 1985; Hartley and Fletcher, 1994), glucose utilization (Grasby et al., 1992), sexual behavior (Agmo et al., 1989; Fernandez-Guasti and Escalante, 1991; Mos et al., 1991), and the cardiovascular system (Gradin and Persson, 1993; Hassessian et al., 1993) in rats. Moreover, repeated 8-OH-DPAT administration revealed in some studies tolerance effects (Evenden et al., 1995; Kennett et al., 1987; Larsson et al., 1990; Renyi et al., 1992), whereas in other studies no tolerance was observed at all (Cervo and Samanin, 1987; Giral et al., 1988), or even sensitization effects appeared (Evenden, 1992). Consequently, it is clear that in addition to face and predictive validity (see above), all these alterations have to be taken into account when interpreting the effects of 8-OH-DPAT administration in animal models for psychiatric disorders.

Decreased alternation behavior in the T-maze after 8-OH-DPAT administration has been reported as a possible animal model for OCD (Yadin et al., 1991), though the finding that 8-OH-DPAT affects SAB in the T-maze has not been replicated. Consequently, the first issue addressed in the present study was to reexamine the effect of 8-OH-DPAT administration on alternation behavior of rats in the T-maze. The second and the main goal was to investigate whether impairment of the sensorimotor system and more specifically left/right differences in sensorimotor function could contribute to the changes in SAB. A number of studies report on neural left/right asymmetries, which might be related to dopaminergic function (Belcheva et al., 1994; Glick et al., 1994; Heidbreder et al., 1999; Schwarting et al., 1991; Sullivan et al., 1998). In addition, serotonergic afferents from midbrain raphe nuclei have been shown to influence dopaminergic activity in the nucleus accumbens (De Deurwaerdere et al., 1996, 1998) and both neurotransmitter systems have been implicated in OCD (McDougle et al., 2000). Moreover, 8-OH-DPAT was shown to decrease striatal and increase prefrontal extracellular dopamine levels (Rasmusson et al., 1994). The integrity of dopaminergic function in the nucleus accumbens was also reported to be important on SAB (Taghzouti et al., 1985). Before exploring possible asymmetrical effects in the mechanisms underlying decreased SAB of rats in a T-maze, we first had to exclude that the perseveration was not simply the result of asymmetries in sensorimotor functioning and more specifically in left/right differences of hind paw function. This was investigated using the following tests: the open-field test, the radiant heat test, and the test with the von Frey filaments. Since the present study is designed to further explore the validity of a possible animal model for OCD, in all the tests performed, the amount of agonist (2 mg/kg) was identical to that used in the original study (Yadin et al., 1991). In future studies, we want to compare in the model, the effect of single versus repeated injection of 8-OH-DPAT administration. Therefore, in the present report, the effect of 8-OH-DPAT administration on sensorimotor functioning with regard to left/right differences was examined every third day.

2. Method

2.1. Subjects

Male Wistar rats (weight between 250 and 350 g at the start of the experiment) were housed in groups of three under a 12-h light/dark cycle, and they had free access to water and food.

Experiments on animals were carried out in accord with protocols approved by the Animal Care and the Ethics Committee of the K.U. Leuven (Leuven, Belgium) and in accord with the ethical guidelines of the International Association for the Study of Pain (IASP, 1983).

2.2. Drugs

Five minutes before testing, the 5-HT1A receptor agonist 8-OH-DPAT 2 mg/kg (Sigma H-8520) in saline (0.9%) or vehicle (0.9% saline) was administered subcutaneously on the back of the animals near the midline.

2.3. Behavioral tests

2.3.1. T-maze (Yadin et al., 1991)

Rats were placed in the start box of the T-maze and were allowed to run to either of the side arms in maximally 90 s where a reward was present (food pellet). After consuming this reward, they were removed from the T-maze and again introduced into the start box (intertrial interval <20 s). This sequence was repeated seven times. Alternation behavior was expressed as the percentage of side choice alternation in the seven trials performed on each test day.

2.3.2. Open-field test (Tarlov score, Gale et al., 1985)

The open-field test was used to assess hind limb deficits during locomotion. Each test day, the rat was observed for spontaneous activity in an open field for 5 min. Special attention was given to weight bearing and locomotion. The hind limbs were observed individually and coded according to the following scores:

Scores for weight bearing and spontaneous activity in the hind limbs of rats

0	no movement in hind limb; no weight bearing
1	barely perceptible movement of hind limb; no weight bearing
2	frequent and/or vigorous movement in hind limb but no weight bearing
3	can support weight on hind limb; may take one or two steps
4	walks with only mild deficit
5	normal walking

2.3.3. Radiant heat test (Hargreaves et al., 1988)

To assess nociceptive responses to thermal stimuli, the rats were placed in a transparent cage ($29 \times 29 \times 30$ cm^3) with a glass floor. To prevent stress-induced analgesia, the rats were placed in the new environment for at least 15 min before testing. Subsequently, a radiant heat source was placed under the glass floor underneath one of the hind paws. The heat source consisted of a high-intensity lamp projecting through an opening in the top of a movable box (5×10 mm^2). Two measures were recorded: the withdrawal latency (WL) and the elevation time (ET). WL was defined as the time between activating the heat source and the withdrawal of the hind paw, whereas ET was defined as the time between the elevation and replacement of the hind paw. If the rat failed to react within 15 s, the lamp was switched off to prevent the sole of the hind paw from being burnt. Testing left and right was randomly performed and 5 min elapsed between successive tests ($n=6$). To prevent local heating of the floor, which could affect the next test results, the rat had to move between the tests to a different spot on the plate.

2.3.4. Test with von Frey filaments

The test with the von Frey filaments (Kupers and Gybels, 1993) was used to assess the response of the rat to a mechanical stimulus. Each single nylon filament was defined by a value (1 = 1.4 g; 2 = 3.4 g; 3 = 7 g; 4 = 14 g; 5 = 25 g; 6 = 55 g; $7 \geq 55$ g) obtained by pushing the filament perpendicularly onto a balance until it started to bend. For the behavioral testing, the rats were placed in a plastic cage ($18 \times 26 \times 27$ cm^3) with a grid floor. After a habituation period of 15 min, the filaments (starting with filament 1) were pushed successively against the plantar surface of the hind paw until it just bent. Left and right hind paw were tested ($n=6$) at random with each filament and with a 5-min pause between the successive tests. The nociceptive threshold was determined as the filament for which the rat reacted three out of six times.

2.4. Design

In the T-maze, the rats were administered with vehicle during the first four test days and a single dose of 8-OH-DPAT on test day 5.

Rats were randomly assigned to groups submitted to the open-field test, radiant heat test, and the test with the von Frey filaments. In each of these groups, rats were again randomly assigned to a control (vehicle) and experimental (8-OH-DPAT) group. The observer was blind to treatment allocation. However, this blinding was not absolute since animals that received agonist displayed a different behavior as compared to those that received vehicle. Testing was carried out every third day for a total of eight test days. Baseline values were achieved by giving vehicle in both control and experimental animals on test days 1–4. Subsequently, in the next four test days (5–8), the experimental group received the selective serotonin 5-HT1A receptor agonist 8-OH-DPAT, whereas in the control group, administration of vehicle was continued.

2.5. Statistics

2.5.1. T-maze

The baseline performance (based on the mean of the four test days) was compared with the behavior after a single dose of 8-OH-DPAT by means of the Wilcoxon signed rank test.

2.5.2. Sensorimotor testing

Several statistical procedures were used to test for differences over repeated test days or to test for left/right differences. The statistical tests used were depending on the type of measure.

2.5.2.1. Open-field test. To determine the effect of 8-OH-DPAT administration on the motor performance of the experimental rats in the open-field test, a Cochran Q was used.

2.5.2.2. Radiant heat test. To account for the habituation of the rat to the stimulus, the first two test results of each session were omitted from the data set. A repeated measures ANOVA on two factors (time and side) was used to compare the means of both the WL and ET of left and right hind paw from test days 1–8 of the control group and from test days 1–4 of the experimental group. To compare the measurements of the first four and of the last four test days between the experimental group and the control group, a two-way repeated measures ANOVA was used. The repeated measures ANOVA on the last four measurements in the experimental group was employed to examine the effect of repeated 8-OH-DPAT administration.

2.5.2.3. Test with the von Frey filaments. The Friedman test was used to assess differences in baseline values of the eight test days in the control group and of the first four test days in the experimental group. In the two groups, the sum of scores of the first four test days was compared by the unpaired Student's t test. This test was also employed to assess the effect of 8-OH-DPAT treatment on the behavior of the experimental rats, by comparing the sum of scores of the last four test days of the control group with the last four test days of the experimental group. The paired Student's t test was used to assess differences in reactions between the left and right hind paw. In order to evaluate the effect of repeated 8-OH-DPAT administration, a

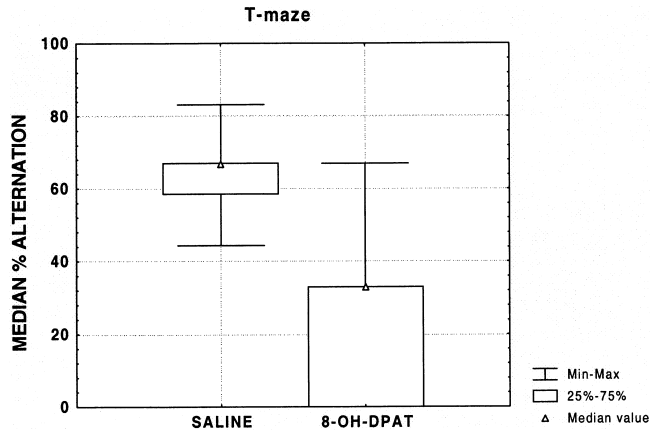


Fig. 1. Box and whisker plot expressing median, quartiles, and range of percentage SAB in animals that received vehicle (saline, test days 1–4) and a single dose of 8-OH-DPAT (2 mg/kg, sc, test day 5). In 8-OH-DPAT group, minimum value coincides with 25% quartile.

Friedman test was employed on the last four test days in the experimental group.

3. Results

In all rats that received 8-OH-DPAT, a typical behavior including lower lip retraction, flat back posture, and increased forward locomotion was observed.

3.1. T-maze

Rats ($n=10$) had a median alternation behavior in the T-maze of 67% during the baseline period (based on four test days), whereas administration of a single dose of 8-OH-DPAT on test day 5 showed a significantly ($P=.027$) impaired alternation behavior (median 33%) (Fig. 1).

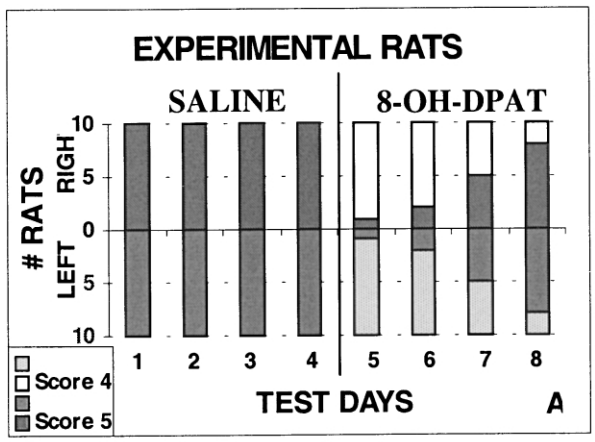
3.2. Open-field test (Tarlov score)

In the experimental group of rats ($n=10$), no left/right differences were observed and all rats obtained a score of 5 on the first four test days (Fig. 2A). In the first test day using 8-OH-DPAT administration, all but one rat obtained a score of 4. Rats typically displayed abduction and exorotation of the hind paws and walked with mild deficit. On test day 8, 8 out of 10 rats obtained a score of 5 for both hind paws. Hind paws were again placed under the abdomen and animals exhibited normal motor performance. The Cochran Q test revealed a significant time effect ($P<.001$). Rats that received vehicle ($n=10$) were all given a score of 5 on all test days for left and right hind paw (Fig. 2B).

3.3. Radiant heat test

3.3.1. Withdrawal latency

Fig. 3A and B show the means of the WL from the left and right hind paw for both the experimental ($n=10$) and control group ($n=10$) of rats on the eight test days. A significant time effect over the measurements of test days



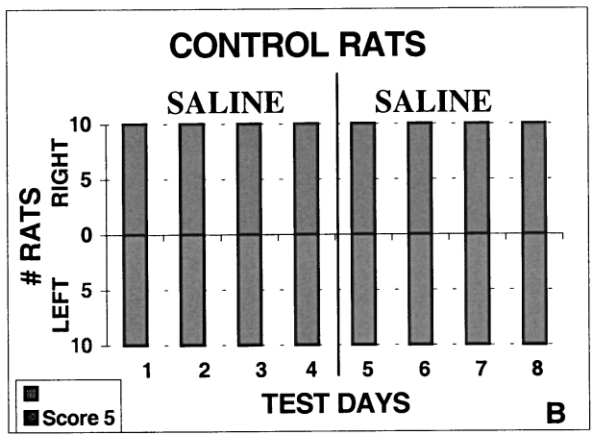


Fig. 2. Tarlov score for left and right hind paw in the group of experimental (A) and control animals (B). Since no rats had score of 1, 2, or 3, only scores 4 and 5 (A) and score 5 (B) are indicated. Number of rats with a score of 5 or 4 following administration of vehicle (saline) on test days 1–4 (experimental group) and on test days 1–8 (control group) or 8-OH-DPAT (2 mg/kg, sc) on test days 5–8 (experimental group).

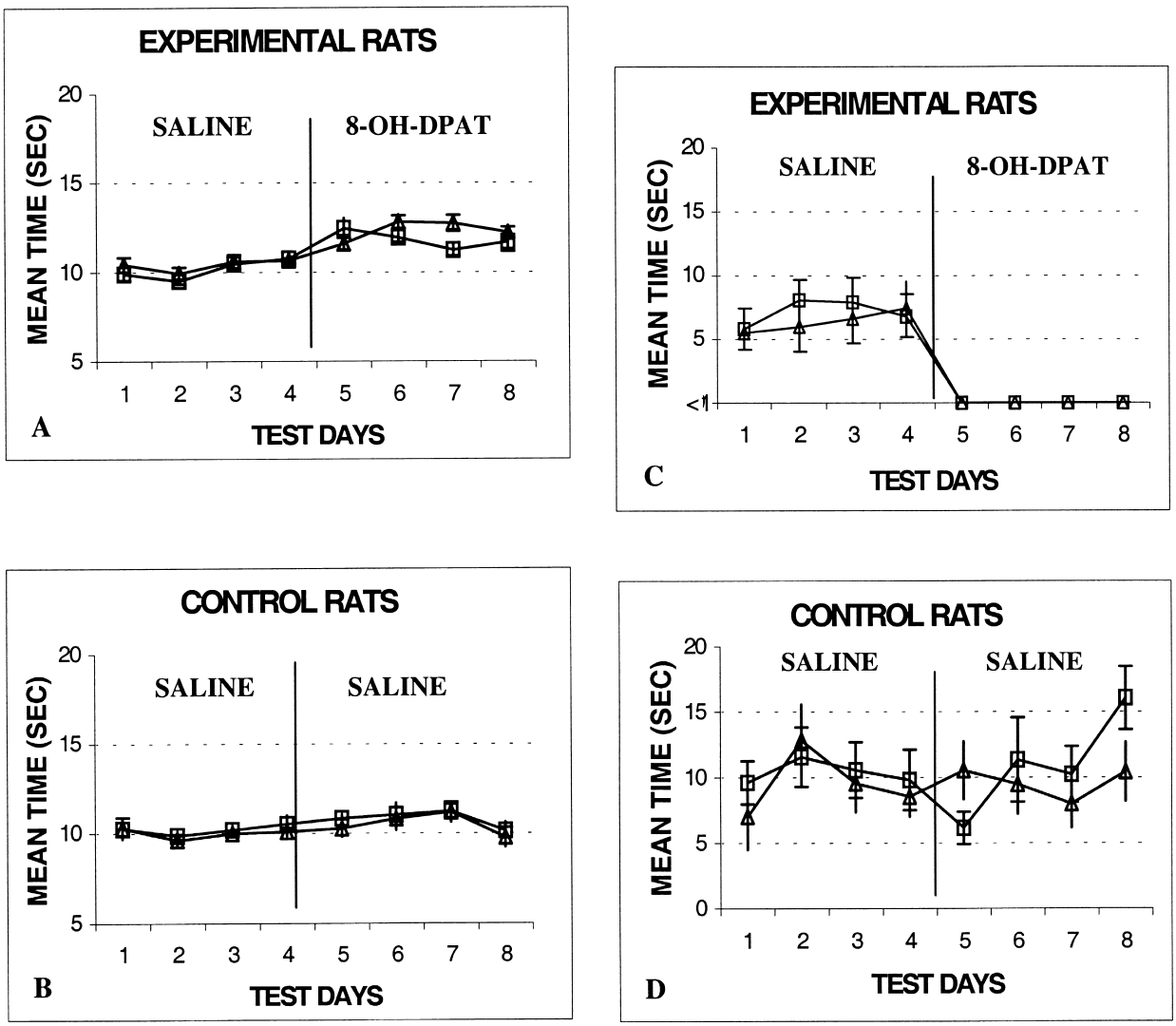
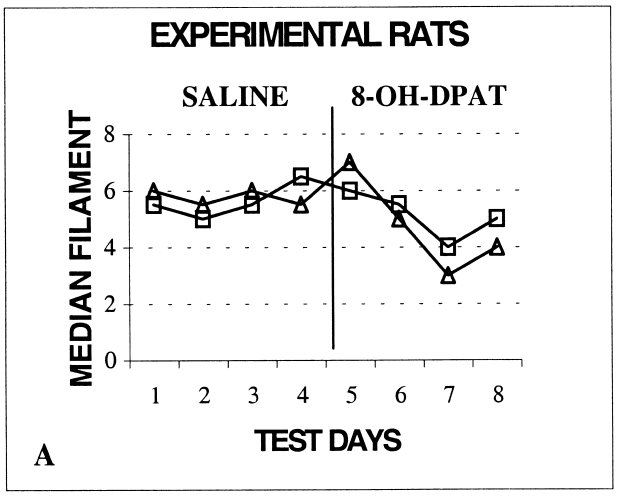


Fig. 3. Radiant heat test [WL (A and B) and ET (C and D)] for the group of experimental (A and C) and control animals (B and D). Mean ± S.E.M. WL and ET for the left (△) and right (□) hind paw following administration of vehicle (saline) on test days 1–4 (experimental group) and on test days 1–8 (control group) or 8-OH-DPAT (2 mg/kg, sc) on test days 5–8 (experimental group).

1–4 in the experimental group [$F(3,53)$, $P=.03$] and test days 1–8 in the control group [$F(14,49)$, $P=.02$] was noticed. Fig. 3A and B show a slight initial decrease in WL followed by an increase later on, which was similar for left and right hind paw (no significant interaction between side and time). Comparing the means of WL of the first four test days between the experimental and control group revealed no significant main and interaction effects. This indicates that no significant differences were found between the baseline measures in both groups for left and right hind paw. Comparison of the last four measurements between the experimental and control group indicated that the rats in the experimental group had significantly higher WLs than those in the control group [$F(14,52)$, $P=.001$] and this for both left and right hind paw. The repeated measures ANOVA on the last four measurements in the experimental group revealed no significant time effect.

3.3.2. Elevation time

The means of ET on the eight test days for the experimental and control group are demonstrated in Fig. 3C and D. No significant time effects for the left and right hind paw were found during the first four test days in the experimental group and during the eight test days in the control group. Comparison between the baseline values of the two groups of rats revealed no group differences for both left and right hind paw. There was however a highly significant group effect for the last four measurements [$F(50,33)$, $P=.0001$]. All experimental animals had an ET of <1 s (Fig. 3C), which means that the paw was replaced



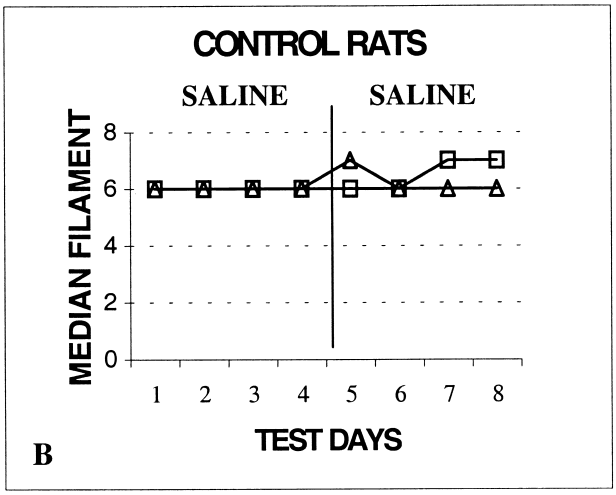


Fig. 4. von Frey hairs test for the group of experimental (A) and control animals (B) for the left (△) and right (□) hind paw separately. Median nociceptive threshold scores following administration of vehicle (saline) on test days 1–4 (experimental group) and on test days 1–8 (control group) or 8-OH-DPAT (2 mg/kg, sc) on test days 5–8 (experimental group).

immediately after withdrawal. However, the ET of the control group ranged between 6 and 15 s (Fig. 3D). Again, no significant differences between left and right side were found.

3.3.3. von Frey filaments

The median nociceptive threshold for left and right hind paws on the eight test days are shown in Fig. 4A and B for, respectively, the experimental ($n=10$) and control rats ($n=10$). The Friedman test revealed no significant differences between the medians of the experimental group for the first four test days and between the medians of the control group for the eight test days and this for both left and right hind paw. Also, no significant differences were found between the sum of scores of the experimental versus the control group for the first four test days. However, a significant difference was observed between the sum of scores of the two test groups over the last four test days for both the left ($t=2.9$, $P=.01$) and right ($t=3.3$, $P=.005$) hind paw. No significant left/right differences between the sum of scores neither for the experimental group nor for the control group over the first and last four test days were found. Finally, the Friedman test revealed no significant differences in the experimental group over the four last test days.

4. Discussion

The present study was designed to provide clues to what extent impairment of the sensorimotor system by 8-OH-DPAT administration might influence SAB in an animal model that mimics a feature of OCD. In this model, after 8-OH-DPAT administration rats preferentially visit one arm of the T-maze more frequently than the other arm, therefore special interest was given to sensorimotor behavior of the left and right hind paws separately. In this aspect, this study is unique since no other study has ever looked for this kind of asymmetries in sensorimotor functioning after 8-OH-DPAT treatment. Also, we examined the effects of repeated drug administration on sensorimotor function with emphasis on possible left/right differences. In the present study, we were aware that the dose of the drug used was rather high, especially since behavioral effects of 8-OH-DPAT administration were reported with very low doses. However, in the animal model for OCD as described by Yadin et al. (1991), perseveration in the T-maze was established using 8-OH-DPAT at a dose of 2 mg/kg. The goal of our study was to examine the effect of this amount of drug on SAB and on sensorimotor performance with emphasis on left/right asymmetries rather than producing a dose–response curve. We here report that 8-OH-DPAT administration has an effect on SAB and on sensorimotor functioning that appeared symmetrically in both hind paws.

Our results confirmed the findings that administration of 8-OH-DPAT (2 mg/kg) severely impairs SAB of rats in the T-maze (Yadin et al., 1991). This reduced alternation behavior is manifested as perseverative behaviors, which can be seen as repetitive motor patterns or as compulsive checking behavior in humans. However, the main goal of this study was to investigate whether impairment of the sensorimotor system and more specifically whether left/right differences in sensorimotor function, could account for these changes in SAB. To measure the effect of 8-OH-DPAT administration on sensorimotor function, the open-field test, the radiant heat test, and the test with the von Frey filaments were used. In the open-field test, rats exhibited flat back posture and they also displayed abduction and exorotation of the hind paws and walked with mild deficit. On the last test day, all but two animals exhibited normal motor performance, i.e., hind paws were again placed under the abdomen. Although the open-field test was initially designed to assess severe motor deficits in models of spinal cord injury, inclusion of

the open-field test in the present study was of particular interest to observe the animal's behavior in terms of differences in left versus right hind paw performance after 8-OH-DPAT administration. Possible impairment of motor performance after agonist administration of one body side could be easily detected in this test and in the present study we could demonstrate that although mild impairment was observed, scores were equal for both sides. Further, as a result of 8-OH-DPAT administration rats displayed an enhanced forward locomotion, and this increased locomotor activity has also been reported in other studies (Blanchard et al., 1993; Hillegaart et al., 1989; Tricklebank et al., 1984). The radiant heat test revealed a significant increase in WL and simultaneously a decrease in ET for both hind paws after 8-OH-DPAT administration. It is worthwhile mentioning that the heating of the hind paws in the control and experimental group did not occur under the same conditions. In the control group, the rats exhibited a normal contact with the sole of the hind paw on the glass surface. After 8-OH-DPAT administration, rats in the experimental group exhibited an almost complete plantar contact with the glass floor and therefore were expected to be even more heat sensitive. But instead of a decrease, an increased WL was observed after 8-OH-DPAT administration. Also a significant decrease in ET was found after 8-OH-DPAT treatment. After withdrawal of the hind paw, the rats almost immediately replaced their hind paw onto the surface of the glass plate. An antinociceptive effect was also observed after activation of the spinal 5-HT1A receptor in the increasing temperature hot-plate test (Mjellem et al., 1992). Similarly, a significant dose-dependent increase in tail-flick latencies in the rat has also been reported (Murphy et al., 1992) indicating a decrease in nociceptive sensitivity to noxious thermal stimuli. The tail is considered as being the most important thermoregulatory organ of the rat and changes in the blood flow or temperature of the skin may alter the effect of cutaneous heat stimulation and consequently tail-flick latencies. Similarly, an important role of the ambient temperature and skin temperature in the formalin test has been shown (Hole and Tjolsen, 1993). Although, intraspinal application of 8-OH-DPAT results in a dose-dependent antinociception in the radiant heat paw withdrawal test (Lin et al., 1996), a finding that is in line with the results of the present study, we have to take into consideration the effect of 8-OH-DPAT-induced hypothermia, which may interfere with our test results. This effect should be controlled in future studies.

In the test with the von Frey filaments, an increased sensitivity to mechanical stimulation of both hind paws after 8-OH-DPAT administration was observed. While in the control group, a minor but not significant adaptation to the test stimulus was observed, the opposite occurred in the experimental group, in particular during the last three test days. Increased sensitivity to mechanical stimulation after 8-OH-DPAT administration was also reported in studies (Murphy and Zemlan, 1990; Murphy et al., 1992) that determined the nociceptive sensitivity in the receptive field area of three spinal withdrawal reflexes (ventroflexion, dorsiflexion, and lateral flexion reflex) after noxious mechanical stimulation. The opposite results of the two tests (radiant heat test resulting in a decreased nociception and test with von Frey filaments resulting in an increased nociception) might reflect activation of different peripheral sensory receptors rather than activation of a spinal motor component (Murphy et al., 1992). In both tests, a motor response is elicited, which in the radiant heat test might be inhibited and in the test with the von Frey filaments might be facilitated. Although, considering the results of the radiant heat test, an effect of the drug-induced hypothermia may not be excluded.

In the literature, behavioral asymmetries have been well documented in the rat brain and have been related to neural left/right asymmetries in dopaminergic function (Belcheva et al., 1994; Glick et al., 1994; Heidbreder et al., 1999; Schwarting et al., 1991; Sullivan et al., 1998). Also, a serotonergic imbalance in the left anterior cingulate and pyriform cortices following repeated intermittent administration of cocaine has been reported (Heidbreder et al., 1999). In addition, it was shown that serotonergic neurons projecting from midbrain raphe nuclei exert an effect on dopamine activity in the nucleus accumbens of rats (De Deurwaerdere et al., 1996, 1998) and that 8-OH-DPAT administration significantly decrease extracellular dopamine in the striatum (Rasmusson et al., 1994). Given the interactions between the two neurotransmitter systems and the fact that they play a role in OCD (McDougle et al., 2000), it may be argued that left/right asymmetries in dopaminergic function may be relevant in the mechanisms underlying decreased SAB of rats in a T-maze. However, before exploring this hypothesis, it should first be ruled out that perseveration is not simply the result of asymmetries in sensorimotor functioning due to agonist administration. This was investigated in the present study emphasising left/right differences for sensorimotor performance and so far, no studies have looked for this kind of differences in sensorimotor functioning. In all tests performed in the present study, changes in sensorimotor functioning were demonstrated after 8-OH-DPAT administration but in none of the tests, significant left versus right hind paw differences in sensorimotor performance could be detected. Still further research is needed to investigate whether decreased SAB reflects perseveration rather than other behavioral parameters than those examined in the present study. Also, future studies have to determine the possible role of 8-OH-DPAT in the limbic–motor circuit of rats and how it may influence the dopamine system and its involvement in the generation of repetitive motor patterns.

As was already reported (Yadin et al., 1991), we also present evidence that single 8-OH-DPAT administration alter SAB of rats in the T-maze. Sensitization or tolerance effects has been reported that can occur after repeated administration of 8-OH-DPAT (Evenden, 1992; Evenden et al., 1995; Kennett et al., 1987; Renyi et al., 1992). The

present results did not show an effect of repeated 8-OH-DPAT administration on sensorimotor performance in the radiant heat test and the test with the von Frey filaments. However, in the open-field test, a significant tolerance effect was observed. Rats initially displayed hind limb abduction and exorotation but on the last test day, all but two animals displayed normal motor functioning. The rationale to study the effect of repeated 8-OH-DPAT injections on sensorimotor function with regard to left/right differences is based on the question whether in the context of another study, repeated administration of 8-OH-DPAT can be used when studying the effect on SAB of rats in a T-maze. More conclusive evidence can then be obtained by performing a correlational analysis of changes in the T-maze behavior and in the other tests by comparing the results obtained from the same animal, and by including other tests for the detection of left/right differences in sensorimotor functioning.

From the present experiments, it can be concluded that 8-OH-DPAT administration affects SAB in a T-maze and sensorimotor function in the rat. While impaired motor performance was established using the open-field test, an increased threshold for noxious thermal stimulation and a decreased nociceptive threshold for mechanical stimulation were observed. All test results were symmetrical indicating that changes in sensorimotor performance as observed in the present experiments and with the current tests performed, are not likely to contribute to the perseverative behavior of rats in a T-maze. Furthermore, repeated administration of 8-OH-DPAT produced a tolerance effect in the open-field test.

Acknowledgments

This work was supported by the FWO (Project No. G.0273.97.N) and by the Research Council (Project No. OT-98-31) of the K.U. Leuven.

References

Agmo A, Fernandez H, Picker Z. Naloxone inhibits the facilitatory effects of 8-OH-DPAT on male rat sexual behaviour. Eur J Pharmacol 1989; 166(1):115–6.

Belcheva I, Belcheva S, Petkov VV, Petkov VD. Asymmetry in behavioral responses to cholecystokinin microinjected into rat nucleus accumbens and amygdala. Neuropharmacology 1994;33(8):995–1002.

Blanchard RJ, Shepherd JK, Armstrong J, Tsuda SF, Blanchard DC. An ethopharmacological analysis of the behavioral effects of 8-OH-DPAT. Psychopharmacology 1993;112(1):55–63.

Blanchard RJ, Griebel G, Guardiola-Lemaitre B, Brush MM, Lee J, Blanchard DC. An ethopharmacological analysis of selective activation of 5-HT1A receptors: the mouse 5-HT1A syndrome. Pharmacol, Biochem Behav 1997;57(4):897–908.

Cervo L, Samanin R. Potential antidepressant properties of 8-hydroxy-2-(di-*n*-propylamino)tetralin, a selective serotonin1A receptor agonist. Eur J Pharmacol 1987;144(2):223–9.

De Deurwaerdere P, Bonhomme N, Lucas G, Le Moal M, Spampinato U. Serotonin enhances striatal dopamine outflow in vivo through dopamine uptake sites. J Neurochem 1996;66(1):210–5.

De Deurwaerdere P, Stinus L, Spampinato U. Opposite change of in vivo dopamine release in the rat nucleus accumbens and striatum that follows electrical stimulation of dorsal raphe nucleus: role of 5-HT3 receptors. J Neurosci 1998;18(16):6528–38.

Dourish CT, Hutson PH, Curzon G. Characteristics of feeding induced by the serotonin agonist 8-hydroxy-2-(di-*n*-propylamino) tetralin (8-OH-DPAT). Brain Res Bull 1985;15(4):377–84.

Engel JA, Hjorth S, Svensson K, Carlsson A, Liljequist S. Anticonflict effect of the putative serotonin receptor agonist 8-hydroxy-2-(di-*n*-propylamino)tetralin (8-OH-DPAT). Eur J Pharmacol 1984;105(3–4): 365–8.

Evenden JL. Effects of 8-hydroxy-2-(di-*n*-propylamino)tetralin (8-OH-DPAT) after repeated administration on a conditioned avoidance response (CAR) in the rat. Psychopharmacology 1992;109(1–2):134–44.

Evenden J, Ryan C, Palejko W. The effects of repeated treatment with 8-hydroxy-2-(di-*n*-propylamino) tetralin (8-OH-DPAT) on the lever press responding of the rat under FI and DRL schedules of food reinforcement. Psychopharmacology (Berlin) 1995;120(1):81–92.

Fernandez-Guasti A, Escalante A. Role of presynaptic serotonergic receptors on the mechanism of action of 5-HT1A and 5-HT1B agonists on masculine sexual behaviour: physiological and pharmacological implications. J Neural Transm: Gen Sect 1991;85(2):95–107.

File SE, Gonzalez LE. Anxiolytic effects in the plus-maze of 5-HT1A-receptor ligands in dorsal raphe and ventral hippocampus. Pharmacol Biochem Behav 1996;54(1):123–8.

Gale K, Kerasidis H, Wrathall JR. Spinal cord contusion in the rat: behavioral analysis of functional neurologic impairment. Exp Neurol 1985; 88(1):123–34.

Giral P, Martin P, Soubrie P, Simon P. Reversal of helpless behavior in rats by putative 5-HT1A agonists. Biol Psychiatry 1988;23(3):237–42.

Glick SD, Raucci J, Wang S, Keller RW, Carlson JN. Neurochemical predisposition to self-administer cocaine in rats: individual differences in dopamine and its metabolites. Brain Res 1994;653(1–2):148–54.

Goodwin GM, Green AR. A behavioural and biochemical study in mice and rats of putative selective agonists and antagonists for 5-HT1 and 5-HT2 receptors. Br J Pharmacol 1985;84(3):743–53.

Gradin K, Persson B. Cardiovascular effects of intrathecal administration of agents active at 5-hydroxytryptamine1-receptors in the rat: modulation by substance P and a substance P antagonist. J Neural Transm: Gen Sect 1993;93(3):225–34.

Grahame-Smith DG. Inhibitory effect of chlorpromazine on the syndrome of hyperactivity produced by L-tryptophan or 5-methoxy-*N*, *N*-dimethyltryptamine in rats treated with a monoamine oxidase inhibitor. Br J Pharmacol 1971a;43(4):856–64.

Grahame-Smith DG. Studies in vivo on the relationship between brain tryptophan, brain 5-HT synthesis and hyperactivity in rats treated with a monoamine oxidase inhibitor and L-tryptophan. J Neurochem 1971b; 18(6):1053–66.

Grasby PM, Sharp T, Allen T, Grahame-Smith DG. The putative 5-HT1A antagonist BMY 7378 blocks 8-OH-DPAT-induced changes in local cerebral glucose utilization in the conscious rat. Neuropharmacology 1992;31(6):547–51.

Hall MD, el Mestikawy S, Emerit MB, Pichat L, Hamon M, Gozlan H. [3H]8-hydroxy-2-(di-*n*-propylamino)tetralin binding to pre- and postsynaptic 5-hydroxytryptamine sites in various regions of the rat brain. J Neurochem 1985;44(6):1685–96.

Hargreaves K, Dubner R, Brown F, Flores C, Joris J. A new and sensitive method for measuring thermal nociception in cutaneous hyperalgesia. Pain 1988;32(1):77–88.

Hartley JE, Fletcher A. The effects of WAY-100135 and 8-hydroxy-2-(di-*n*-propylamino)tetralin on feeding in the rat. Eur J Pharmacol 1994; 252(3):329–32.

Hassessian H, Poulat P, Hamel E, Reader TA, Couture R. Spinal cord serotonin receptors in cardiovascular regulation and potentiation of the pressor response to intrathecal substance P after serotonin depletion. Can J Physiol Pharmacol 1993;71(7):453–64.

Heidbreder CA, Oertle T, Feldon J. Dopamine and serotonin imbalances

in the left anterior cingulate and pyriform cortices following the repeated intermittent administration of cocaine. Neuroscience 1999; 89(3):701–15.

Hillegaart V, Wadenberg ML, Ahlenius S. Effects of 8-OH-DPAT on motor activity in the rat. Pharmacol Biochem Behav 1989;32(3):797–800.

Hole K, Tjolsen A. The tail-flick and formalin tests in rodents: changes in skin temperature as a confounding factor. Pain 1993;53(3):247–54.

Hoyer D, Pazos A, Probst A, Palacios JM. Serotonin receptors in the human brain: I. Characterization and autoradiographic localization of 5-HT1A recognition sites. Apparent absence of 5-HT1B recognition sites. Brain Res 1986;376(1):85–96.

IASP. Committee for Research and Ethical Issues. Ethical standards for investigation of experimental pain in animals. Pain 1983;16:109–10.

Jacobs BL. An animal behavior model for studying central serotonergic synapses. Life Sci 1976;19(6):777–85.

Johansson-Wallsten CE, Meyerson BJ. The ontogeny of tolerance to the 5-HT1A agonist 8-OH-DPAT: a study in the rat. Neuropharmacology 1994;33(3–4):325–30.

Kennett GA, Marcou M, Dourish CT, Curzon G. Single administration of 5-HT1A agonists decreases 5-HT1A presynaptic, but not postsynaptic receptor-mediated responses: relationship to antidepressant-like action. Eur J Pharmacol 1987;138(1):53–60.

Kupers RC, Gybels JM. Electrical stimulation of the ventroposterolateral thalamic nucleus (VPL) reduces mechanical allodynia in a rat model of neuropathic pain. Neurosci Lett 1993;150(1):95–8.

Larsson LG, Renyi L, Ross SB, Svensson B, Angeby-Moller K. Different effects on the responses of functional pre- and postsynaptic 5-HT1A receptors by repeated treatment of rats with the 5-HT1A receptor agonist 8-OH-DPAT. Neuropharmacology 1990;29(2):86–91.

Lin Q, Peng YB, Willis WD. Antinociception and inhibition from the periaqueductal gray are mediated in part by spinal 5-hydroxytryptamine(1A) receptors. J Pharmacol Exp Ther 1996;276(3):958–67.

Marazziti D, Marracci S, Palego L, Rotondo A, Mazzanti C, Nardi I, et al. Localization and gene expression of serotonin 1A (5HT1A) receptors in human brain postmortem. Brain Res 1994;658(1–2):55–9.

McDougle CJ, Epperson CN, Pelton GH, Wasylink S, Price LH. A double-blind, placebo-controlled study of risperidone addition in serotonin reuptake inhibitor-refractory obsessive–compulsive disorder. Arch Gen Psychiatry 2000;57(8):794–801.

Middlemiss DN, Fozard JR. 8-Hydroxy-2-(di-*n*-propylamino)-tetralin discriminates between subtypes of the 5-HT1 recognition site. Eur J Pharmacol 1983;90(1):151–3.

Mjellem N, Lund A, Eide PK, Storkson R, Tjolsen A. The role of 5-HT1A and 5-HT1B receptors in spinal nociceptive transmission and in the modulation of NMDA induced behaviour. NeuroReport 1992; 3(12):1061–4.

Mos J, Van Logten J, Bloetjes K, Olivier B. The effects of idazoxan and 8-OH-DPAT on sexual behaviour and associated ultrasonic vocalizations in the rat. Neurosci Biobehav Rev 1991;15(4):505–15.

Murphy RM, Zemlan FP. Selective serotonin1A/1B agonists differentially affect spinal nociceptive reflexes. Neuropharmacology 1990;29(5): 463–8.

Murphy AZ, Murphy RM, Zemlan FP. Role of spinal serotonin1 receptor subtypes in thermally and mechanically elicited nociceptive reflexes. Psychopharmacology 1992;108(1–2):123–30.

Rasmusson AM, Goldstein LE, Deutch AY, Bunney BS, Roth RH. 5-HT1A agonist +/− 8-OH-DPAT modulates basal and stress-induced changes in medial prefrontal cortical dopamine. Synapse 1994; 18(3):218–24.

Renyi L, Moller KA, Ensler K, Evenden J. The non-competitive NMDA receptor antagonist (+)MK-801 counteracts the long-lasting attenuation of the hypothermic response induced by acute doses of 8-OH-DPAT in the rat. Neuropharmacology 1992;31(12):1265–8.

Schwarting RK, Steiner H, Huston JP. Asymmetries in thigmotactic scanning: evidence for a role of dopaminergic mechanisms. Psychopharmacology 1991;103(1):19–27.

Scott PA, Chou JM, Tang H, Frazer A. Differential induction of 5-HT1A-mediated responses in vivo by three chemically dissimilar 5-HT1A agonists. J Pharmacol Exp Ther 1994;270(1):198–208.

Stanhope KJ, Dourish CT. Effects of 5-HT1A receptor agonists, partial agonists and a silent antagonist on the performance of the conditioned emotional response test in the rat. Psychopharmacology (Berlin) 1996;128(3):293–303.

Sullivan RM, Talangbayan H, Einat H, Szechtman H. Effects of quinpirole on central dopamine systems in sensitized and non-sensitized rats. Neuroscience 1998;83(3):781–9.

Taghzouti K, Louilot A, Herman JP, Le Moal M, Simon H. Alternation behavior, spatial discrimination, and reversal disturbances following 6-hydroxydopamine lesions in the nucleus accumbens of the rat. Behav Neural Biol 1985;44(3):354–63.

Thielen RJ, Fangon NB, Frazer A. 4-(2′-Methoxyphenyl)-1-[2′-[*N*-(2″-pyridinyl)-*p*-iodobenzamido]ethyl] piperazine and 4-(2′-methoxyphenyl)-1-[2′-[*N*-(2″-pyridinyl)-*p*-fluorobenzamido]ethyl]piperazine, two new antagonists at pre- and postsynaptic serotonin-1A receptors. J Pharmacol Exp Ther 1996;277(2):661–70.

Tricklebank MD, Forler C, Fozard JR. The involvement of subtypes of the 5-HT1 receptor and of catecholaminergic systems in the behavioural response to 8-hydroxy-2-(di-*n*-propylamino)tetralin in the rat. Eur J Pharmacol 1984;106(2):271–82.

Yadin E, Friedman E, Bridger WH. Spontaneous alternation behavior: an animal model for obsessive–compulsive disorder? Pharmacol Biochem Behav 1991;40(2):311–5.