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BRIEF COMMUNICATION

Effects of Selective Serotonergic Agonists on Aggressive Behavior in Rats

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MUEHLENKAMP, F., A. LUCION AND W. H. VOGEL. *Effects of selective serotonergic agonists on aggressive behavior in rats.* PHARMACOL BIOCHEM BEHAV **50**(4) 671-674, 1995. – The effects of the relatively specific serotonergic agonists 8-OH-DPAT (5-HT_{1A}), TFMPP (5-HT_{1B}), and DOB (5-HT_2) were studied on defensive aggressive behavior in rats using the water competition test. 8-OH-DPAT (up to 0.25 mg/kg) and TFMPP (up to 1 mg/kg) were found to be ineffective, whereas DOB (up to 0.4 mg/kg) significantly reduced aggressive behavior in this test as well as in the offensive aggression test of the resident-intruder model. These results, combined with those from other studies, suggest that stimulation of 5-HT_{1A}, 5-HT_{1B}, and 5-HT_2 receptors reduces offensive aggression, whereas defensive aggression is only decreased by 5-HT_2 stimulation.

Aggression Dominance Water consumption Rats Serotonin Serotonergic agonists

AGGRESSIVE and/or dominant behavior of animals can be controlled or influenced by a variety of chemicals acting upon different systems in the brain. Among these systems, the serotonergic system has been linked to aggressive and/or dominant behaviors in animals. It is believed that stimulation of this system seems to reduces and suppress aggressive/dominant behaviors (6,13,15,18-21,25). More recently, serotonin receptors have been divided into subtypes (14,22,24) such as 5-HT_{1A} receptors [8-OH-DPAT or 8-hydroxy-2-(di-*n*-propylamino) tetralin as a relative specific agonist] (4,10), 5-HT_{1B} receptors [TFMPP or 1-(3 trifluoromethylphenyl piperazine) as a relative specific agonist] (9,11), and 5-HT_2 receptors (DOB or dimethoxy-4 bromoamphetamine as a relatively selective agonist) (12,24). However, it is now recognized that these agents are not as selective as originally thought, and that some overlap in receptor specificity occurs (5,8,14,24).

To determine which of these different serotonergic subreceptors is most closely linked to aggressive/dominant behaviors, we tested rats for defensive aggression and dominance in a competitive water test situation before and after an administration of saline, DOB, TFMPP, and 8-OH-DPAT. In case a specific chemical would produce a positive result in the water competition test, this chemical would then be reevaluated in the isolation-induced resident-intruder aggression model, which measures offensive aggression.

METHODS

Animals

Animals employed were male Sprague-Dawley rats obtained from Charles River Laboratories (Wilmington, MA), which weighed between 250 and 400 g. They were kept in light-dark (12 L : 12 D), temperature (ca. 22°C), and humidity (ca. 55%) -controlled rooms.

Agents

8-OH-DPAT and DOB were obtained from Sigma Chemical Company (St Louis, MO) and TFMPP from Research Biochemical International (Natick, MA). Solutions were pre-

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TABLE 1

MEAN DURATION OF WATER CONSUMPTION OF ONE RAT IN A PAIR

Substance	Test 1	Test 2	Average 1	Test 3	Test 4	Average 2	Difference
None	115 ± 14	144 ± 14	130 ± 8	147 ± 12	131 ± 12	140 ± 11	10 ± 6
Saline	102 ± 8	99 ± 6	100 ± 6	118 ± 8	126 ± 5	126 ± 5*	22 ± 6
8-OH-DPAT (0.25 mg/kg, SC)	72 ± 1	90 ± 7	83 ± 8	88 ± 1	100 ± 14	94 ± 1	11 ± 7
TFMPP (1 mg/kg, IP)	130 ± 8	144 ± 13	137 ± 10	146 ± 9	153 ± 8	150 ± 8	13 ± 1
DOB (0.4 mg/kg, IP)	105 ± 10	99 ± 1	102 ± 10	95 ± 7	57 ± 7	76 ± 6*	−26 ± 9

Values represent the means ± SEM of duration of water consumption (in seconds) for a 5-min period. Values of the same rat in a pair were recorded on four occasions. Average 1 results from tests 1 and 2, and average 2 from tests 3 and 4, and difference is average 2 − average 1. Saline or the test substances were injected 15 min before tests 3 and 4, except 8-OH-DPAT, which was given 30 min before the test. *$p < 0.05$, comparing average 1 and average 2.

pared freshly each day. The doses chosen were the highest doses that had been shown in other studies to be behaviorally effective without producing gross abnormal behavior interfering with competitive behaviors or total water intake, which is crucial for our tests of aggressive/dominant behavior.

Tests

The water competition test (1,23) was performed in the home cage. Animals of equal weight were paired and housed in one cage. After 6 days, the animals were deprived of water for 23 h. Then, one water bottle was introduced with a shielded spout so that only one animal of a pair could drink at a time. Time (in seconds) and frequency of spout possession and water consumption were recorded in numbers with a special computer program for 5 min. Animals were then allowed another 55 min of water consumption. This test was repeated on 3 subsequent days; saline or drug treatment occurred on days 3 and 4. The animal with the longest duration of water consumption and frequency of spout possession was considered to be the more aggressive and/or dominant animal (23).

The isolation-induced resident-intruder aggression test (2,3,7,20) was conducted by introducing a small rat (about 250 g) into the cage of a large rat (about 450 g) that had been housed in isolation in this cage for at least 4 weeks. After the introduction of the smaller animal into the cage, time until the first attack (in seconds), number of attacks, and duration of each attack (in seconds) were recorded for the next 15 min by a blind observer.

Statistical Analysis

Statistical analyses used were the paired and unpaired *t*-tests for comparisons of means of absolute values, as well as means of differences of absolute value of the two rats.

RESULTS

Table 1 shows the effects of the different agents on water consumption (absolute values in seconds) of one rat in a pair, averaged for 10 pairs. In untreated rats, water consumption of the test animals did not change significantly over the four different test days, indicating that a stable relationship of water consumption and aggressive behavior had been established in each pair. Similar relationships were obtained when frequency of water spout possession was used. However, measurements of duration proved to be a more stable measure, and only values for duration are shown. An injection of saline before tests three and four slightly but significantly increased water consumption and aggressive behavior.

Administration of the 5-HT_{1A} agonist 8-OH-DPAT or the 5-HT_{1B} agonist TFMPP before tests three and four had no effects on water consumption or aggressive behavior of the test animal; averages 1 and 2 were not statistically different in each case. However, administration of the 5-HT_2 agonist DOB reduced the relationship between water consumption and aggressive behavior, with a significant difference between averages 1 and 2. Furthermore, the difference between both averages became negative. Similar results were obtained with these compounds when the frequency of water spout possession was calculated and evaluated.

Again, similar conclusions were obtained when the individual differences in the duration in water consumption between the rats of one pair (difference between the competing rats in each pair) were calculated and compared. No significant changes in these differences were observed after an injection of saline, 8-OH-DPAT, and TFMPP, whereas the difference decreased significantly after the administration of DOB ($p < 0.01$). Similar results were also obtained when the frequency or frequency differences of water spout possession were compared. No frequency effects were found for saline, 8-OH-DPAT, or TFMPP, but DOB caused a significant reduction in frequency of water consumption ($p < 0.01$).

To determine whether DOB would also affect aggressive behavior in a test for offensive aggression, we tested DOB in the isolation-induced resident-intruder aggression model.

TABLE 2

MEAN LATENCY UNTIL FIRST ATTACK, FREQUENCY OF ATTACKS, AND DURATION OF ATTACKS IN THE RESIDENT-INTRUDER MODEL

	Open Arms		
	Latency (s)	Frequency (no.)	Duration (s)
Saline	300 ± 33	3.8 ± 0.7	19 ± 3
DOB	392 ± 34*	2.6 ± 0.4*	10 ± 2*

Values represent means ± SEM of 10 rats. The resident was injected with saline or DOB (0.4 mg/kg IP) 15 min before the test. *$p < 0.05$, comparing the saline-injected with the DOB-injected animals.

DOB significantly increased the time until the first attack, reduced the frequency of attacks, and decreased the duration of each attack (Table 2).

DISCUSSION

Housing of two animals of equal weight in one cage for 6 days seemed to be sufficient to establish a firm social relationship between the animals in each pair, in that each animal consistently drank about the same amount with about the same frequency over time, as shown in the first experiment with untreated animals. During the water competition, animals competed by pushing and shoving continuously for possession of the water spout, but did not display overt aggressive features such as biting. We found the measurement of duration of water consumption to be a more stable measure of an individual animal than frequency of spout possession. By definition, we considered the animal with the higher duration and frequency of water consumption to be the more aggressive and dominant animal.

Injection of one animal with saline resulted in a slight but statistically significant increase in water consumption. This might be a coincidence, or it might be caused by the stress of injection. We believe the first to be the case, as other experiments using saline or vehicle injections did not reveal any effects, and because a comparison of the differences of duration of water consumption between the two rats in a pair showed no effect of the saline injection. No effects were seen when 8-OH-DPAT or TFMPP was injected. However, DOB injection reduced duration and frequency of water consumption in terms of both absolute values and differences of each measure between the animals in a pair. Thus, DOB clearly reduces water consumption and aggressive or dominant behavior. Because DOB showed a clear reduction in defensive/aggressive behavior, we tested this chemical in the isolation-induced resident-intruder aggression model, which tests for offensive aggression. Again, DOB caused a significant reduction in the aggressive behavior of the resident.

Before conclusions can be reached it has to be established that confounding variables did not influence water consumption or the isolation-induced resident-intruder aggression test. For instance, a test substance could produce abnormal behavior, reduce thirst, or decrease motor coordination, all of which could affect aggressive behavior during water competition or resident-intruder interactions. We do not believe that such confounding factors contributed to our results. First, after the injection of the test substances, the animals behaved and looked quite "normal" (as compared to naive animals) to an observer who was unaware of the drug treatment. Second, it has already been shown that 8-OH-DPAT and TFMPP do not interfere with water consumption at the doses employed in this study (3,4,16,17). However, it was not known whether DOB would show an effect on water consumption. Thus, we deprived animals of water for 23 h and determined fluid intake 15 min after DOB injection (0.4 mg/kg, IP). We found no effect on water consumption (20.4 ± 1.1 ml/20 min for control rats vs. 19.5 + 0.9 ml/20 min for DOB rats). Third, the effect of all three test substances at the doses studied on the motor coordination of five rats, each on a rotating rod, did not differ from that of a saline injection; animals fell from the rod at about the same speed: saline − 12.4 + 2.1 rotations, 8-OH-DPAT 14.1 + 3.2 rotations, DOB − 12.8 + 2.6 rotations, TFMPP − 13.7 + 2.8 rotations (Miller, unpublished observation). Doses higher than the highest one reported in this study started to interfere with these tests (e.g., our test dose of 0.4 mg/kg of DOB had no effect on total fluid consumption, whereas 0.8 mg/kg reduced this measure by half), and were not used in our aggression studies. Thus, this evidence seems to rule out confounding variables in the interpretation of the aggression tests at the doses reported.

A comparison of our results with those published in the literature show the following: The 5-HT_{1A} agonist 8-OH-DPAT was found to show antiaggressive actions in isolation-induced aggression (20,25), maternal aggression (19), resident-intruder aggression (19), and muricidal aggression (15). All of these tests measure offensive aggression. In our test of defensive aggression, 8-OH-DPAT was without effect at the highest dose testable. The 5-HT_{1B} or 5-HT_{1C} agonist TFMPP reduced resident-intruder or maternal aggression (19). Again, these tests measure offensive aggression. The water competition measures defensive behavior. In the later test, we found TFMPP to be without effect at the highest dose testable. To the best of our knowledge, the 5-HT_2 agonist DOB and aggressive behavior had not previously been studied. We found this compound to reduce both offensive (resident-intruder) and defensive (water competition) aggression up to the highest dose testable. These results seem to suggest that stimulation of 5-HT_{1A}, 5-HT_{1B}, and 5-HT_2 receptors reduces offensive aggression, whereas defensive aggression is only affected by stimulation of 5-HT_2 receptors.

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