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Effects of Serotonin 1A or 1B Receptor Agonists on Social Aggression in Male and Female Syrian Hamsters

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JOPPA, M. A., R. K. ROWE AND R. L. MEISEL. *Effects of serotonin 1A or 1B receptor agonists on social aggression in male and female Syrian hamsters.* PHARMACOL BIOCHEM BEHAV **58**(2) 349–353, 1997.—Numerous studies have demonstrated that activation of serotonin 5-HT_{1A} or 5-HT_{1B} receptor decreases aggression in male mammals. To determine whether female mammals also show decreased aggression in response to 5-HT_{1A} or 5-HT_{1B} activation, we assessed the effects of the serotonin receptor agonists 8-OH-DPAT (5-HT_{1A}) and CGS-12066A (5-HT_{1B}) on aggression in female Syrian hamsters. Female Syrian hamsters were tested for interfemale aggression 2 days before and 15 min after receiving intracerebroventricular infusions of 8-OH-DPAT (5, 10, 20 μg) or CGS-12066A (5, 10, 20 μg). Neither drug affected aggression as measured by the latency and frequency of attacks or uprights, although the highest dose of 8-OH-DPAT increased general activity. For male hamsters, intraventricular infusions of 10 μg of 8-OH-DPAT essentially eliminated aggression, whereas 5 μg of 8-OH-DPAT or 20 μg of CGS-12066A were without effect. Systemic treatment with 8-OH-DPAT (1 mg/kg body weight) did reduce aggression in females, although there was an attendant increase in symptoms of nonspecific serotonergic activity. There were no behavioral effects of systemic CGS-12066A (4 mg/kg body weight) on female hamsters. These results indicate that there may be sex differences in the neurochemical regulation of aggression and point to a need for more studies directed at this issue. © 1997 Elsevier Science Inc.

Serotonin agonists Aggression Activity 8-OH-DPAT CGS-12066A Sex differences

OFFENSIVE aggression, which forms an important component of social behaviors for females of many species (7), has been studied extensively in female Syrian hamsters (25). Although much less work has been conducted in rats and mice (3), the physiological regulation of offensive aggression seems to be common to females of all three rodent species. Surprisingly little is known about the neural regulation of aggression in females, despite the recognition that interfemale aggression is a legitimate class of aggression that is distinct from intermale aggression (5,8).

Studies of the neurochemical control of aggression in vertebrates, including humans, have focused on intermale aggression. These studies indicate that high levels of serotonergic activity are associated with low levels of aggression (6,9,13, 16–18,21–23,26,31). This serotonergic inhibition of aggression seems to be mediated through interactions with several serotonin (5-HT) receptor subtypes, although most research has focused on 5-HT_1 receptors (6). The 5-HT_{1A} receptor agonist, 8-hydroxy-2-(di-*n*-propylamino)tetralin (8-OH-DPAT), effectively inhibits aggression in both rats and mice (6,17,31). In addition, mixed 5-$HT_{1A/1B}$ receptor agonists inhibit aggression, with some indication that the actions of these drugs is via the 5-HT_{1B} receptor subtype (17). Clearer evidence for the involvement of 5-HT_{1B} receptors in mediating aggression comes from transgenic mouse studies in which mice lacking 5-HT_{1B} receptors are more aggressive than the wild-type mice (24).

Unfortunately, few studies to date have examined the question of neurotransmitter regulation of any type of aggression in female mammals. Because the contextual, hormonal and neuroanatomical bases of offensive aggression in males and females differ (3,5), it is not necessarily the case that males and females should share neurotransmitter pathways important for the regulation of aggression. Because serotonin activation is associated so consistently with a reduction of aggression in males, we tested the effects of intracranial treat-

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ment with 5-HT_{1A} (8-OH-DPAT) and 5-HT_{1B} receptor (CGS-12066A) agonists on interfemale aggression in Syrian hamsters.

MATERIALS AND METHODS

Subjects

The subjects in this study were adult female and male Syrian hamsters (Charles River Breeding Laboratories, Kingston, NY) about 60 days old at the time of delivery to the laboratory. Experimental females and males were housed individually in plastic cages (50.8 × 40.6 × 20.3 cm), and additional stimulus females and males were housed in groups of 4 per cage. Group housing reduces aggression in hamsters, thereby minimizing the likelihood that the stimulus animals would initiate attacks during aggression tests (15). All animals were housed in a colony room with controlled temperature (22°C) and lighting (lights out at 1:30–11:30 p.m.). Food and water were freely available except during behavioral testing.

Drugs

Both R(+)-8-hydroxy-2-(di-*n*-propylamino)tetralin hydrobromide (8-OH-DPAT) and 7-trifluoromethyl-4(4-methyl-1-piperazinyl)-pyrrolo[1,2-a]quinoxaline maleate (CGS-12066A) were obtained from Research Biochemicals International (Natick, MA). (CGS-12066A is also referred to in the literature as CGS-12066B. Our use of CGS-12066A is consistent with the nomenclature of Research Biochemicals International.) 8-OH-DPAT has over a 200-fold selectivity for the serotonin 5-HT_{1A} receptor compared with the 5-HT_{1B} receptor, whereas CGS-12066A has a 17-fold selectivity for the 5-HT_{1B} receptor over the 5-HT_{1A} receptor (19). For both intracerebroventricular and systemic injections, the drugs were dissolved in 45% 2-hydroxypropyl-β-cyclodextrin (Research Biochemicals International). The cyclodextrin vehicle was used for all control injections.

Procedures

Because ovarian hormones can inhibit aggression (15), about 10 days after arrival to the laboratory, all females (including stimulus females) were bilaterally ovariectomized while anesthetized with sodium pentobarbital (8.4 mg/100 g body weight, IP). Experimental males were not surgically altered and were tested with intact stimulus male hamsters. One week after ovariectomy (or an equivalent time period for the males), experimental females and males were given two aggression tests with the appropriate stimulus animals. For each test, the stimulus animal was placed in the home cage of the experimental animal. Experimental animals were given 5 min in which to attack, after which the test continued for 5 min. An attack was scored if the experimental female or male was roughly perpendicular to and the muzzle in contact with the stimulus animal, whether or not a bite actually occurred. The results of these tests were used only to equate levels of aggressiveness for females assigned to the two drug-treatment groups prior to stereotaxic surgery and to give males and females equivalent aggressive experiences.

The next week, experimental females and males were anesthetized and stereotaxically implanted (27) with bilateral stainless steel cannulae (21 gauge) aimed at the lateral ventricles. Butorphanol (0.2 mg/hamster, SC) was used for postsurgical analgesia. Following a 1-week recovery period, females were tested twice weekly for aggression for 4 weeks. Females received intraventricular infusions of the vehicle (1 μl/side) prior to the first weekly test (vehicle baseline tests) and infusions of the drug prior to the second test conducted 2 days later (drug tests). Ten minutes after the infusion, solitary activity of the experimental female was observed for 5 min. A stimulus female was then introduced into the cage. The aggression test lasted for 5 min after the first attack or for 5 min if no attacks were observed. Experimental females were always paired with a different stimulus female. Different groups of females were treated with 5, 10 and 20 μg/2 μl (1 μl/side) of 8-OH-DPAT ($n = 8$) or CGS-12066A ($n = 10$) over 3 successive weeks. Within each drug group, each female received all three doses of the drug, although the order of the drug doses differed among the females. The fourth week, females were injected intraperitoneally with the drug vehicle prior to the first test and injected intraperitoneally with either 8-OH-DPAT (1 mg/kg body weight) or CGS-12066A (4 mg/kg body weight) 10 min prior to the second test of the week.

All females responded aggressively. Attack latency, number of attacks and number of uprights (rearings directed toward and within one body length of the stimulus female) were recorded. In addition, a composite subjective behavioral assessment of side effects associated with nonspecific activation of the serotonin system (30) was made, with 1 point given each for the appearance of hypoactivity or hyperactivity, flat body posture, crouching, grimacing (lower lip retraction), hyperreactivity to touch or grooming (6 points maximum). All behavioral tests were videotaped, although only pretest locomotor activity was scored from the videotapes. For this activity measure, the video screen was divided into six equal sections, and the number of sections entered during the 5 min period prior to the aggression test was counted. For five of the vehicle pretests, two raters independently scored the number of attacks. Pearson product moment correlations showed the independent ratings to be highly correlated (mean $r = 0.91$, range = 0.78–0.98).

A single group of males was used to validate the effectiveness of these drugs in reducing aggression in male Syrian hamsters. Males were tested twice a week for 3 weeks as described for the females. The order of the drug treatments was 8-OH-DPAT (10 μg, $n = 10$), CGS-12066A (20 μg, $n = 6$) and 8-OH-DPAT (5 μg, $n = 5$). Attrition of males over the weeks of testing was due to some of the males losing their cannulae.

After the completion of the behavioral tests, the experimental animals were given an overdose of pentobarbital (about 15 mg/100 g body weight) and perfused intracardially with 4% buffered paraformaldehyde. The brains were frozen sectioned (50 μm), mounted on slides and stained with cresyl violet to verify cannulae placements. Histological analyses indicated that the drugs had access to the cerebral ventricles for all animals in this study.

RESULTS

Males

For the males, each drug pretest was compared individually with that week's posttest. The 10-μg dose of 8-OH-DPAT significantly increased attack latencies [$t(8) = 6.60$, $p < 0.001$] and significantly reduced attack frequency ($z = 6.67$, $p < 0.01$, Wilcoxan test) compared with the previous vehicle test. Neither the 5-μg dose of 8-OH-DPAT nor the 20-μg dose of CGS-12066A had any significant effect on attacks (Table 1). Neither dose of 8-OH-DPAT affected the frequency of uprights, although CGS-12066A significantly reduced uprights [$t(5) = 2.85$, $p < 0.04$; Table 1]. Infusion of 10 μg of 8-OH-

TABLE 1

EFFECTS (MEAN ± SEM) OF INTRAVENTRICULAR 8-OH-DPAT AND CGS-12066A ON AGGRESSIVE AND NON-AGRESSIVE BEHAVIORS OF MALES

	Dose of 8-OH-DPAT				Dose of CGS-12066A	
	Vehicle	5μg	Vehicle	10μg	Vehicle	20μg
Attack latency (sec)	53.4 ± 18.8	183.2 ± 71.5	53.1 ± 15.4	253.3 ± 31.4**	56.3 ± 16.0	87.0 ± 48.3
Attacks per 5 min	14.0 ± 2.0	10.6 ± 8.7	22.1 ± 5.1	1.6 ± 1.0***	18.0 ± 6.1	10.3 ± 3.5
Uprights per min	1.4 ± 0.4	1.0 ± 0.4	2.1 ± 0.4	1.6 ± 0.6	2.3 ± 0.3	1.6 ± 0.4*
Activity†	41.2 ± 4.7	58.8 ± 8.8	32.0 ± 6.3	86.6 ± 20.7**	35.8 ± 10.3	28.2 ± 6.9

†Number of grid crossings 5 min before introduction of stimulus male. *$p < 0.05$ versus the Vehicle test. **$p < 0.01$ versus the Vehicle test. ***$p < 0.001$ versus the Vehicle test.

DPAT significantly increased activity [$t(8) = 3.06$, $p < 0.02$] during the 5 min prior to the aggression test (Table 1). There were no significant effects on activity following administration of either 5 μg of 8-OH-DPAT or 20 μg of CGS-12066A. Side effects associated with serotonin activation were rarely observed (data not shown).

Females

8-OH-DPAT. For the intraventricular drug treatments, the mean of the vehicle pretests was compared with each dose of the drug (Table 2). Repeated measures analyses of variance indicated that there were no significant effects of any of the doses of 8-OH-DPAT on attack latency, attack frequency or frequency of uprights. Side effects associated with serotonin activation were rare (data not shown). In the 5-min period preceding the aggression tests, there was a significant effect of 8-OH-DPAT on general activity [$F(3,21) = 4.74$, $p = 0.01$]. Activity levels were significantly elevated following infusion of 20 μg of 8-OH-DPAT vs. 5 μg 8-OH-DPAT or the vehicle ($p < 0.05$, Newman-Keuls test). Activity levels following the 10-μg dose of 8-OH-DPAT were intermediate to and did not differ significantly from either of the other treatments.

Systemic injection of 1 mg/kg 8-OH-DPAT significantly increased attack latency [$t(7) = 2.47$, $p < 0.05$] and reduced the frequency of attacks [$t(7) = 3.80$, $p < 0.01$] and uprights [$t(7) = 4.26$, $p < 0.01$; Table 3]. There was also a significant increase in side effects following systemic 8-OH-DPAT treatment [$\chi^2(1) = 7.0$, $p < 0.01$, Friedman test]. There was no effect of systemic 8-OH-DPAT on activity.

CGS-12066A. None of the intraventricular doses of CGS-12066A had any significant effects on attack latency, attack frequency or frequency of uprights (Table 4). The CGS-12066A did not produce any of the symptoms of general serotonergic activation (data not shown), and there were no effects on activity (Table 4). Systemic treatment with CGS-12066A did not significantly affect any of these measures (Table 3).

DISCUSSION

The results of this study demonstrate that interfemale aggression is unaffected by intracerebroventricular treatment with 8-OH-DPAT, although systemic injection of 8-OH-DPAT effectively inhibited aggression. CGS-12066A administered either systemically or intracranially to female hamsters had no behavioral effects. These results suggest that neural activation of either 5-HT_{1A} or 5-HT_{1B} receptor has no effect on interfemale aggression in hamsters.

Previous studies of aggression in female rats have focused largely on maternal aggression. In female rats, maternal aggression is inhibited by treatment with the 5-HT_{1A} or the 5-HT_{1B} agonist (12,18), suggesting that aggression in females may be under serotonergic control. The intracranial doses of 8-OH-DPAT used in our study were without effect on interfemale aggression. Our findings do not necessarily disagree with those studies of maternal aggression because aggression is not a unitary construct (1,2), and each of the forms of aggression shown by female rodents (e.g., maternal aggression, interfemale aggression, competitive aggression) may be differentially regulated.

It seems unlikely that the inability of intracranial administration of either drug to affect aggression in female hamsters resulted from an insensitivity of hamsters to serotonin receptor agonists. First, a moderate intracranial dose of 8-OH-DPAT (10 μg) all but eliminated aggression in male hamsters,

TABLE 2

EFFECTS (MEAN ± SEM) OF INTRAVENTRICULAR 8-OH-DPAT ON AGGRESSIVE AND NON-AGGRESSIVE BEHAVIORS OF FEMALES

		Dose of 8-OH-DPAT		
	Vehicle†	5μg	10μg	20μg
Attack latency (sec)	87.4 ± 20.9	199.9 ± 46.1	142.1 ± 38.0	134.3 ± 29.2
Attacks per 5 min	10.2 ± 1.9	5.0 ± 2.2	9.3 ± 3.0	9.0 ± 2.3
Uprights per min	2.4 ± 0.3	1.7 ± 0.3	1.7 ± 0.5	1.1 ± 0.3
Activity‡	27.3 ± 3.0	25.0 ± 4.2	37.0 ± 5.7	45.8 ± 5.6*

†Average of 3 vehicle baseline tests. ‡Number of grid crossings 5 min before introduction of stimulus female. *$p < 0.05$ versus both the Vehicle and the 5 μg tests.

TABLE 3

EFFECTS (MEAN ± SEM) OF IP 8-OH-DPAT AND CGS-12066A ON AGGRESSIVE AND NON-AGGRESSIVE BEHAVIORS

	8-OH-DPAT		CGS-12066A	
	Vehicle	1 mg/kg	Vehicle	4 mg/kg
Attack latency (sec)	65.5 ± 16.8	180.0 ± 45.5*	57.3 ± 37.5	67.7 ± 26.5
Attacks per 5 min	13.0 ± 2.1	4.8 ± 1.9**	8.9 ± 1.9	7.8 ± 1.5
Uprights per min	1.8 ± 0.2	0.4 ± 0.3**	1.1 ± 0.2	1.0 ± 0.1
Activity†	39.6 ± 5.4	32.1 ± 4.8	75.3 ± 37.8	75.1 ± 28.6

†Number of grid crossings 5 min before introduction of stimulus female. *$p < 0.05$ versus the Vehicle test. **$p < 0.01$ versus the Vehicle test.

and both females and males in the present study showed increased activity following intracranial 8-OH-DPAT. Second, for hamsters as for other rodent species, 8-OH-DPAT has a variety of behavioral effects including inhibition of female sexual behavior (11), induction of hyperglycemia (4) and increased exploratory behavior (10). Furthermore, high systemic doses of 5-HT_1 agonists produce the "serotonin syndrome" in rats and mice, components of which were evident in the female hamsters given 1 mg/kg 8-OH-DPAT systemically.

The behaviors associated with the serotonin syndrome seem to be the result of activation of brainstem and/or spinal cord serotonin receptors (32). The absence of these behaviors following intraventricular infusions suggests that the distribution of the 8-OH-DPAT in this case was restricted to more rostral neural regions. Because we do not know where in the nervous system serotonergic drugs act to inhibit even intermale aggression, the drugs may not have reached the effective targets following intraventricular treatment. However, because the reduction in aggression following systemic 8-OH-DPAT was accompanied by a general debilitation, with all of the animals exhibiting at least a flattened body posture, this reduction in aggression may have been secondary to the debilitating effects of the drug. Nevertheless, in male rats, there are similar side effects of serotonergic activation, although the decreases in aggression can be obtained in animals not showing any side effects of the drugs (31).

Although there is some suggestion in the literature that 5-HT_{1B} receptor activation can affect aggression in males (17,24), we found little evidence for this in either the female or male hamsters given the CGS-12066A. Clearly, our use of only one drug and a limited range of doses does not permit making strong statements about the role of 5-HT_{1B} receptors in aggression, although it seems reasonable to conclude that this serotonin receptor subtype has a lesser role than the 5-HT_{1A} subtype on aggression in males.

One methodological consideration in this study concerns our focus on the intracerebroventricular application of the drugs. A limitation of this approach is that the drug may not have access to its potential site(s) of action. One reason for our choice of this route of administration was to minimize behavioral side effects that could interfere with the expression of aggression. Neverthelss, lower systemic doses of the drugs could have achieved that goal. More problematic in the use of systemic injections is the interpretation of sex differences in behavioral responsiveness. Within a restricted range of drug doses, there could be sex differences in absorption, peripheral metabolism and/or distribution of the drug to the nervous system that could lead to the impression that there were sex differences in the efficacy of the drugs. By delivering the drugs centrally, we hoped to minimize potential peripheral pharmacodynamic differences between the male and female hamsters.

Finally, it is clear that there are several other sex differences in the behavioral and physiological regulation of offensive aggression for several rodent species. Males are more likely to direct attacks toward other males, whereas females preferentially direct aggression toward other females (5). Gonadal hormones activate aggression in males and inhibit aggression in females (5,15). The neural sites of action of gonadal hormones on aggression also differ between males and females (5,14,20,27–29). Although 5-HT_{1A} receptor agonists are so clearly effective in inhibiting aggression in male rodents, we might expect, as indicated by the results of this study, that the neurochemical pathways mediating offensive aggression may also differ between males and females. Testing this possibility is a goal of future studies.

TABLE 4

EFFECTS (MEAN ± SEM) OF INTRAVENTRICULAR CGS-12066A ON AGGRESSIVE AND NON-AGGRESSIVE BEHAVIORS OF FEMALES

		Dose of CGS-12066A		
	Vehicle†	5 μg	10 μg	20 μg
Attack latency (sec)	77.8 ± 11.6	109.3 ± 31.4	117.7 ± 37.5	122.9 ± 33.7
Attacks per 5 min	8.3 ± 0.5	7.2 ± 1.6	3.9 ± 1.0	7.1 ± 1.8
Uprights per min	2.2 ± 0.2	2.4 ± 0.5	2.1 ± 0.4	1.7 ± 0.3
Activity‡	35.2 ± 6.5	27.9 ± 4.7	44.0 ± 13.3	31.1 ± 4.3

†Average of 3 vehicle baseline tests. ‡Number of grid crossings 5 min before introduction of stimulus female.

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