Pharmacology Biochemistry & Behavior, Vol. 37, pp. 283–287. © Pergamon Press plc, 1990. Printed in the U.S.A. 0091-3057/90 $3.00 + .00

Effects of Serotonin Antagonists on Motion Sickness and Its Suppression by 8-OH-DPAT in Cats

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Received 18 December 1989

LUCOT, J. B. *Effects of serotonin antagonists on motion sickness and its suppression by 8-OH-DPAT in cats*. PHARMACOL BIOCHEM BEHAV **37**(2) 283–287, 1990.—This investigation evaluated the antagonist properties of (−)propranolol, (+)propranolol, metergoline and BMY 7378 on the known effect of 8-OH-DPAT (DPAT) to decrease motion sickness in cats. (−)Propranolol produced a greater decrease in the antiemetic effect of DPAT than did (+)propranolol. Although metergoline produced a decrease in the antiemetic effect of DPAT, the decrease could not be clearly attributed to interactions with 5-HT_{1A} receptors because metergoline alone slightly enhanced motion sickness. Depletion of 5-HT with PCPA produced a weaker, nonsignificant enhancement of motion sickness, while mesulergine had no effect. As neither nonspecific 5-HT receptor blockade with metergoline nor depletion of 5-HT mimicked the antiemetic effect of DPAT, it was concluded that DPAT acts on postsynaptic 5-HT_{1A} receptors to prevent emesis. BMY 7378 alone decreased the incidence of motion sickness. A dose just below this agonist range did not decrease the effects of DPAT.

BMY 7378 Cat Emesis Mesulergine Metergoline PCPA Postsynaptic receptors Propranolol Serotonin receptors

THE role of 5-HT_1 and 5-HT_2 receptors in emetic mechanisms is far less well characterized than is the role of 5-HT_3 receptors. In the dog, the 5-HT_1 and 5-HT_2 agonist LSD (16) suppressed emesis elicited by apomorphine, morphine and hydergine but not that elicited by emetine, ouabain or protoveratrine (11). Both the nonspecific antagonist methysergide and the 5-HT_{1C} and 5-HT_2 antagonist 1-(1-naphthyl)piperazine (1-NP) (16) blocked emesis elicited by apomorphine and orally administered copper sulfate but not that elicited by CCK-8 (18). Cinanserin, which differs from 1-NP in having a lower affinity for 5-HT_{1C} receptors (16), was ineffective. The authors presented an argument for involvement of 5-HT_2 receptors in the emetic central pattern generator.

In the cat, hallucinogenic 5-HT_2 agonists were not reported to elicit emesis (28,35), although 5-HT_2 antagonists have not been tested as antiemetics. Elevation of 5-HT levels with 5-HTP elicited emesis, an action blocked by inhibition of catecholamine synthesis (6). This paper cited unpublished results that the cat is more susceptible to 5-HTP-induced emesis that the dog. RU 24969 also elicited emesis in cats via a 5-HT_1 receptor subtype, possibly the 5-HT_{1D} (22).

The serotonin-1A (5-HT_{1A}) agonists buspirone and 8-OH-DPAT (DPAT) suppress motion sickness and emesis elicited by other stimuli in cats (23,24). The present experiments test the conclusion that 5-HT_{1A} receptors are the relevant sites of action by blocking the antiemetic effect of DPAT with suitable antagonists. One such antagonist is (−)propranolol, which binds to the 5-HT_{1A} receptor. The possibility that antagonistic effects of (−)propranolol are due to nonspecific effects can be evaluated by testing (+)propranolol, which binds with roughly 25 times less affinity at the 5-HT_{1A} receptor (25) and 180 times less affinity at the beta adrenoceptor (26). BMY 7378 also binds selectively to the 5-HT_{1A} receptor, and has been reported to act as an antagonist (8,37), although on some measures it acts as a partial agonist (20, 29, 31).

Additional experiments address the issue of whether the relevant 5-HT_{1A} receptors are located postsynaptically or on the 5-HT-containing cell bodies (presynaptic). Metergoline, a potent antagonist of 5-HT_2 receptors and 5-HT_1 receptor subtypes (16), was administered alone before motion testing. Such a nonspecific blockade of postsynaptic receptors should mimic the effects of decreased 5-HT neuronal firing. In a separate study, 5-HT stores were depleted with the synthesis inhibitor, p-chlorophenylalanine (PCPA) (17). If the antiemetic effect of DPAT results from stimulation of presynaptic 5-HT_{1A} receptors, then each of these treatments should decrease motion sickness.

For completeness, 5-HT_{1C} and 5-HT_2 receptors were blocked with mesulergine (16) to determine if these receptor subtypes are involved in motion sickness.

METHOD

Subjects

Twenty-six cats were housed in the University Laboratory Animal Resources facility. All were tested to assure the presence of normal free-fall righting and vestibulo-ocular reflexes. Female cats were used exclusively because they tolerate long-term exper-

iments better than males. All vomited on at least two of five biweekly screening tests and were considered susceptible to motion sickness. There were 11 cats in the first experiment. Ten of these were in the second experiment and 6 were in the fourth experiment; 5 cats were in all three experiments. In the third experiment, only 3 of the cats were in the other experiments, and one animal was substituted for another between tests with PCPA and with mesulergine. The cats had free access to food and water until the time of testing.

Procedure

The motorized motion testing device was modelled after a Ferris wheel. The cats rode alone in two clear plastic boxes suspended from the ends of a 0.89 m beam that rotated about a horizontal axle at 0.28 Hz (17 rpm) (10). Motion tests lasted for 30 min followed by one min of observation at rest. The latency to the first retch was measured, although emesis always followed retching. Control tests with drug vehicle preceded and followed each dose-response curve. All tests were separated by two weeks to prevent the development of habituation to the motion stimulus.

In the first experiment, a dose-response curve for DPAT vs. motion sickness was determined in eleven susceptible cats. Then 1.0 mg/kg of (−)propranolol was tested by injecting it before administration of saline or the doses of 0.02, 0.028 and 0.04 mg/kg of DPAT. Motion testing began 15 min after the second injection. In a third series, 1.0 mg/kg of (+)propranolol or 1.0 mg/kg of metergoline were administered before saline or the doses of 0.02 and 0.04 mg/kg of DPAT.

The results from the first experiment suggested that metergoline may increase rather than decrease the incidence of motion sickness. This possibility was evaluated in the second experiment by determining a dose-response curve for metergoline alone before motion testing in 14 cats. An alternative approach was used in the third experiment, in which the effects of depletion of 5-HT by PCPA on motion sickness were evaluated in ten cats. The dose of 150 mg/kg of PCPA was administered on three consecutive days before motion testing. In addition, the possibility that blockade of 5-HT_{1C} and 5-HT_2 receptors alters motion sickness was evaluated using the antagonist, mesulergine.

The fourth experiment evaluated BMY 7378 in 9 cats. It was previously found that the dose of 0.4 mg/kg decreased the number of cats vomiting in response to 0.66 mg/kg of xylazine from 10 to 8 (unpublished observations). Therefore, a limited dose-response curve for BMY 7378 alone before motion testing was determined to establish the maximum dose that was devoid of agonist effects on this test. This dose was then administered before DPAT plus motion testing.

Drugs

DPAT HBr (Research Biochemicals Inc, Natick, MA) was dissolved in sterile saline to an injection volume of 0.1 ml/kg and was administered 15 min before motion testing. The isomers of propranolol (Wyeth Laboratories Inc., Philadelphia, PA) were suspended in sterile saline and a few drops of Tween 80 to an injection volume of 0.5 ml/kg and were administered 30 min before the second injection (saline or DPAT). Doses of DPAT and propranolol were calculated as the base. BMY 7378 (Bristol-Myers Inc., Wallingford, CT) was dissolved in sterile saline with a small quantity of 0.1 N NaOH added to an injection volume of 0.1 ml/kg and was administered just before administration of DPAT or 5 min before motion testing. Metergoline (Farmitalia, Milano, Italy) was suspended in saline with a few drops of Tween 80 to an injection volume of 0.2 ml/kg. Metergoline was administered 3 hr before the second injection (DPAT or saline), as it has a long latency to onset and a long duration of action (4,13). PCPA methyl ester HCl (Sigma, St. Louis, MO) was dissolved in minimal 0.1 N NaOH, the pH adjusted to 6.2 with 1 N NaOH and made to an injection volume of 0.5 ml/kg with sterile saline. Doses were administered 72, 48 and 24 hr before motion testing. Mesulergine (Sandoz, E. Hanover, NJ) was suspended in 0.025 N HCl with a few drops of Tween 80 and injected in a volume of 0.2 ml/kg 30 min before motion testing. Doses of BMY 7378, metergoline, mesulergine and PCPA are expressed in weight of compound as received from the manufacturer. All drugs were freshly prepared before experiments and were administered SC.

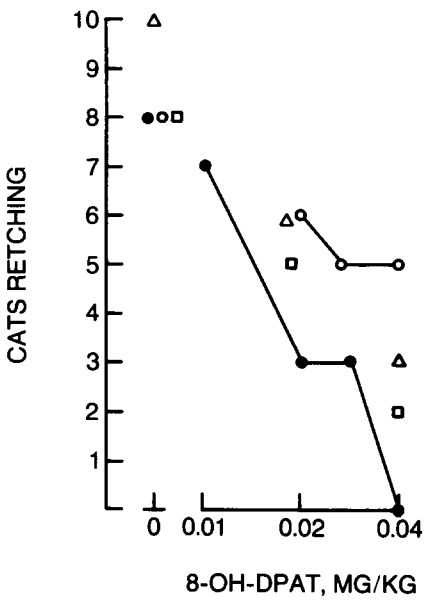

FIG. 1. Effects of metergoline and the isomers of propranolol on the suppression of motion sickness by DPAT. Motion testing lasted for 30 min followed by one min of observation at rest. DPAT was administered SC 15 min before motion testing in 11 cats (solid circles). (−)Propranolol (1.0 mg/kg) (open circles) or 1.0 mg/kg of (+)propranolol (open squares) was administered SC 30 min before saline or DPAT. Metergoline (1.0 mg/kg) (open triangles) was administered SC 3 hr before saline or DPAT. The dose of DPAT is plotted on a log scale.

Statistics

Dose-response curves were analyzed by Cochran's Q-test to evaluate overall significant effects (9). Tests for line parallelism, relative potency and the '2 and 2' assay were from a program for pharmacological statistics (32). Analyses of the latency to the first retch were performed using a procedure for right-censored data (27). All tests had an alpha of 0.05.

RESULTS

DPAT suppressed motion sickness (Fig. 1). The dose of 1.0 mg/kg of either isomer of propranolol alone had no effect on the incidence of motion sickness. (−)Propranolol produced a 2.6-fold shift in the DPAT dose-response curve; the two curves were not significantly different from parallel. (+)Propranolol had a weaker effect, producing only a 1.6-fold shift in the dose-response curve. The results from the administration of metergoline before DPAT were confounded, and therefore rendered uninterpretable, by the

TABLE 1

EFFECTS OF METERGOLINE ON MOTION SICKNESS

Pretreatment	No. Retching	Latency
saline	9	12.53
0.1 mg/kg metergoline	10	10.84
0.3 mg/kg metergoline	11	7.48
1.0 mg/kg metergoline	11	6.07
3.0 mg/kg metergoline	13	5.22*
saline	9	19.73

Metergoline was administered SC 3 hr before motion testing in 14 susceptible cats. Measures are the number of cats retching and the estimated latency to the first retch based on the two-parameter Weibull distribution which includes the censored data. The data set exceeded the parameters of the tables, precluding determination of the 90% confidence interval. *$p<0.05$ vs. both saline tests.

increase in the incidence in motion sickness when given without DPAT.

The results from further motion tests with metergoline alone are shown in Table 1. Whereas the dose of 3.0 mg/kg produced a significant decrease in the latency to the first retch, the Cochran Q test was not significant, $Q(5)=7.67$, $p>0.05$. In contrast, the decrease in the latency to the first retch following treatment with PCPA did not achieve significance (Table 2). Several of the cats that received PCPA developed lesions at the site of the injection, sometimes after some delay. The lesions were permitted to heal before the next experiment. Administration of mesulergine had no effect on motion sickness (Table 2).

BMY 7378 produced a dose-dependent decrease in the incidence of motion sickness (Fig. 2). Higher doses were not tested because the goal was to determine the maximum dose that was devoid of agonist-like effects. The dose of 0.02 mg/kg was selected for administration before DPAT. It was evident that this dose of BMY 7378 did not alter the dose-response curve for DPAT.

DISCUSSION

Three conclusions are drawn from the results. First, DPAT

TABLE 2

EFFCTS OF PCPA ON MOTION SICKNESS

Pretreat	No. Retching	Latency (90%)
saline	7	20.13 (5.23–38.45)
PCPA	8	9.37 (2.53–19.87)
saline	7	17.08 (2.49–43.02)
saline	5	28.95 (5.42–60.01)
mesulergine	6	21.44 (3.34–48.13)
saline	7	18.08 (3.01–39.52)

PCPA (150 mg/kg) was administered SC 72, 48 and 24 hr before motion testing in 10 susceptible cats. The latency measure is followed by the 90% confidence interval. One cat was substituted for another before testing with mesulergine. Six weeks elapsed between experiments. The rest is the same as Table 1.

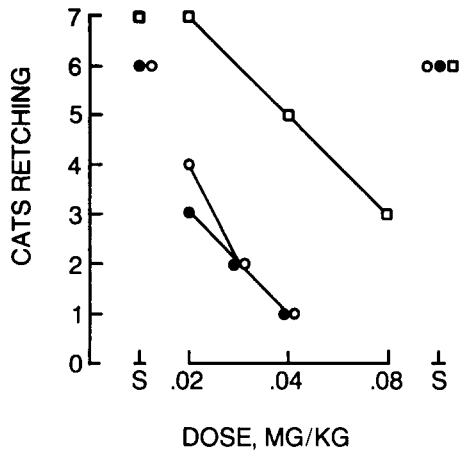

FIG. 2. Effects of BMY 7378 alone and before DPAT on motion sickness. BMY 7378 was administered SC 5 min before motion testing (open squares) in nine cats. The dose of 0.02 mg/kg of BMY 7378 was administered just before administration of DPAT (open circles). DPAT alone was also tested (solid circles). The doses of DPAT and BMY 7378 are on a log scale.

suppresses motion sickness by stimulating 5-HT_{1A} receptors. Second, the 5-HT_{1A} receptors involved in the suppression of motion sickness are located postsynaptically. Third, BMY 7378 possesses agonist effects in this paradigm.

The conclusion that DPAT suppresses motion sickness by stimulating 5-HT_{1A} receptors is drawn from the results with the isomers of propranolol. The (−) isomer produced a more pronounced attenuation of the response to DPAT than was produced by the (+) isomer. While some response was obtained with the (+) isomer, it is important to remember that the selectivity between the isomers for 5-HT receptors is relative and not absolute (25). The possibility that propranolol shifted the DPAT dose-response curve to higher doses as a result of displacing DPAT from beta adrenoceptors is unlikely because DPAT does not activate NE receptors at doses 40 times its ED_{50} at activating 5-HT receptors (2).

The conclusion that the relevant 5-HT_{1A} receptors are located postsynaptically is based on the results from the metergoline and PCPA experiments. If the antiemetic effect of DPAT results from stimulation of presynaptic receptors, then the effect arises from an absence of serotonergic stimulation at postsynaptic sites. An absence of postsynaptic stimulation was induced by depletion of 5-HT stores with PCPA and by blocking 5-HT_1 and 5-HT_2 receptors with metergoline (16) [5-HT_3 receptors are not involved in motion sickness (21)]. As neither PCPA nor metergoline decreased motion sickness, a presynaptic site of action for DPAT can be ruled out. It is not likely that the doses of metergoline selected were subthreshold for antiemetic effects, as the doses in the present study included those reported to block the effects of LSD in the cat (15). Neither is it likely that PCPA was ineffective at the doses used, since 75 mg/kg × 4 days produced 52–75% depletions in cats (33), while 150 mg/kg × 5 days produced an 86% depletion in cats (34). Thus, the present results support our previous conclusion that the relevant 5-HT_{1A} receptors are located postsynaptically (24).

This conclusion is indirectly supported by the results with propranolol. Propranolol has been reported to not block the presynaptic 5-HT_{1A} receptor in vivo, as evidenced by its inability to reverse the suppressant effect of DPAT on dorsal raphe cell firing (1,5) or on release of 5-HT in the hippocampus (30). These

negative results with propranolol in vivo are in contrast to its ability to block presynaptic 5-HT_{1A} receptors in vitro as well as postsynaptic 5-HT_{1A} receptors in vivo (29). The ability of propranolol to shift the DPAT dose-response curve to higher doses in the present study is consistent with an action of DPAT on postsynaptic 5-HT_{1A} receptors.

The increase in the incidence of motion sickness following metergoline was a weak effect. The mechanism underlying the slight decrease in the latency to retching is not clear. Doses of 1 to 10 mg/kg of metergoline have been reported to induce a nondose-dependent, low incidence of emesis in marmosets, although administration of saline also occasionally induced emesis (7). One possible explanation for the present results is that serotonin exerts a tonic inhibition of motion sickness. Indeed, a high dose of methysergide elicited emesis in cats (22). However, the emetic effect of methysergide was slightly reduced, not enhanced, by pretreatment with metergoline. Blockade of postsynaptic 5-HT_{1A} receptors with (−)propranolol and blockade of 5-HT_{1C} and 5-HT_2 receptors with mesulergine had no effect on motion sickness in this study. Thus, 5-HT would have to be acting on several receptor subtypes simultaneously to tonically inhibit motion sickness. However, depletion of 5-HT with PCPA produced a slight, nonsignificant decrease in the latency to retching in this study. A study using a more severe dose regimen of PCPA in cats, producing 91% depletions of 5-HT, did not report emesis (12). Further, depletion of 5-HT in ferrets with PCPA prevented emesis elicited by cisplatin (3). Thus, it is unlikely that 5-HT exerts a tonic inhibition of emesis, though it may play a modulatory role.

Another possible explanation is that nonserotonergic mechanisms are involved. High doses of metergoline produce other effects, such as blockade of $alpha_1$ and dopamine receptors (19), while the doses of PCPA used were adequate to decrease catecholamines as well as 5-HT (17). Although blockade of dopamine receptors does not increase the incidence of motion sickness (unpublished observations), blockade of alpha receptors has been reported to produce a slight facilitation in the development of malaise in human subjects exposed to provocative motion (36).

The conclusion that BMY 7378 has 5-HT_{1A} agonist-like effects is based on its ability to decrease the incidence of motion sickness. Other evidence for agonist effects has been reported, such as its ability to produce interoceptive cues similar to those of DPAT in rat (20) and pigeon (31). In the present study, the combination of a subthreshold dose of BMY 7378 with DPAT did not produce additional antiemetic effects. These negative results are consistent with the typical interaction between a low dose of a partial agonist with doses of a full agonist (14). This dose of BMY 7378 was also too low to reverse the antiemetic effect of DPAT. It is possible that higher doses of BMY 7378 may attenuate the antiemetic effect of DPAT, consistent with the effects of a partial agonist. However, there were not enough susceptible cats available to adequately evaluate the effects of higher doses of BMY 7378 on this response to DPAT.

ACKNOWLEDGEMENTS

This work supported by cooperative agreement NCC2-229 between NASA-Ames Research Center and Wright State University. I give thanks to Farmitalia, Wyeth, Sandoz and Bristol-Myers for the gifts of drugs and to Jennifer S. Kulinski, David L. Kirkhart, Stephanie A. Lake, Colleen M. Kennedy, David E. Spanier and Andrea M. Feldmann for their excellent technical assistance.

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