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8-OH-DPAT Suppresses Vomiting in the Cat Elicited by Motion, Cisplatin or Xylazine[1,2]

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LUCOT, J. B. AND G. H. CRAMPTON. *8-OH-DPAT suppresses vomiting in the cat elicited by motion, cisplatin or xylazine.* PHARMACOL BIOCHEM BEHAV **33**(3) 627–631, 1989.—Vomiting was suppressed in cats pretreated with 8-OH-DPAT and then challenged with an emetic stimulus; motion, xylazine or cisplatin. The antiemetic effect is likely due to stimulation of postsynaptic serotonin-1A receptors. The most parsimonious explanation is that it acts at a convergent structure, presumably at or near the vomiting center. If so, 8-OH-DPAT may block emesis elicited by virtually any other stimulus. A supplementary experiment revealed that lorazepam suppressed motion sickness at a dose that produced ataxia, but did not suppress xylazine-induced emesis. These results do not support the possibility that the antiemetic effects of 8-OH-DPAT were the result of anxiolytic activity.

Cat Cisplatin Emesis Lorazepam Motion sickness Serotonin Vomiting Xylazine 8-OH-DPAT

BUSPIRONE is effective in blocking motion sickness, xylazine-induced vomiting (20) and cisplatin-induced vomiting (21) in the cat. The most parsimonious explanation for the generality of its antiemetic effects is that it acts on a common convergent structure, possibly the ill-defined vomiting center (6,40), because these stimuli elicit vomiting through more than one neural pathway. Specifically, area postrema ablations eliminate emesis elicited by xylazine (8) and cisplatin (23), but not motion (5). It has also been argued that cisplatin elicits emesis by stimulating peripheral sites (30). Further, yohimbine blocks xylazine-induced emesis but not motion sickness (19), scopolamine blocks motion sickness but not xylazine-induced emesis (unpublished observations) and serotonin-3 antagonists prevent cisplatin-induced emesis but not xylazine-induced emesis or motion sickness (22).

The broad spectrum of antiemetic effects exhibited by buspirone is novel, which suggests that a new mechanism for the suppression of emesis may be involved. Buspirone is an anxiolytic agent that is a partial agonist at serotonin-1A (5-HT_{1A}) receptors (1,32). At higher doses, it is a weak dopamine antagonist, with some selectivity for presynaptic receptors (25). The latter is a possible mechanism of action since sulpiride, which can block presynaptic dopamine receptors (18,33), has been reported to prevent motion sickness in the squirrel monkey (28). However, it is not clear that the presynaptic component of sulpiride's action led to the antiemetic effect. The action of buspirone at 5-HT_{1A} receptors seems the more likely mechanism, but it is necessary to directly test this interpretation.

This paper reports experiments designed to test if 5-HT_{1A} receptor stimulation leads to suppression of emesis.

1) The drug 8-hydroxy-2-(di-n-propylamine)tetralin (8-OH-DPAT) was tested for antiemetic effects. It is reported to be a selective agonist at 5-HT_{1A} receptors (27). It has a structure appreciably different from that of buspirone, which is an azaspirodecanedione. Unlike buspirone (3), no significant active metabolites have been reported for 8-OH-DPAT. This drug also has an anxiolytic effect (13). The emetic challenges are provocative motion, xylazine and cisplatin.

2) Possible nonspecific actions resulting from some component of an anxiolytic effect are evaluated using lorazepam followed by motion and xylazine challenges. Diazepam has been reported to decrease nausea induced in humans by vestibular stimulation (24), while high doses of lorazepam decrease emesis induced by cancer chemotherapy (4). The pharmacologically related barbiturates decrease motion sickness in the dog (31).

METHOD

Subjects

A total of 58 cats were housed in the University Laboratory

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Animal Resources facility. Normal free-fall righting and vestibulo-ocular reflexes were displayed by all animals selected for the motion sickness and xylazine trials. Female cats were used exclusively in these groups because they tolerate long-term experiments better than males. All cats had free access to food and water until the time of testing.

Twenty-four female cats were selected for the motion sickness tests on the basis of their susceptibility to motion sickness as determined by their responses to five screening motion challenges. On the five screening tests, six cats vomited five times, three vomited four times, five vomited three times, six vomited twice and four vomited once.

Another ten female cats assigned to the xylazine challenge group were not susceptible to motion sickness. A dose-response curve for xylazine was determined and the minimum dose of xylazine that elicited emesis in all of these cats was 0.66 mg/kg.

Twenty-four male and female cats were assigned to the cisplatin group. A few of the females were tested and found to be nonsusceptible to motion sickness; males were not so tested. There were four males and six females in the control group, three males and five females in the group receiving the low dose and two males and four females in the group receiving the high dose. Six of the control animals were historical controls whose data have been reported elsewhere (20).

Emetic Challenges

Motion stimulus. The motion stimulus was provided by a motor-driven device that resembled an amusement-park Ferris wheel. The cats rode in clear plastic boxes suspended from two 0.445 m arms that rotated about the central horizontal axis at 0.28 Hz (17 rpm) (10). Motion tests lasted for 30 min of rotation followed by one min of observation at rest. The dependent variable was retching, though it was followed shortly by vomiting in all cases. In addition, a motion sickness rating scale was used (36). Saline control tests were conducted before and after every determination of a dose-response curve. In all screening, vehicle and drug tests, the motion challenges were separated by at least two weeks to prevent habituation to the motion stimulus.

Twenty of the cats were used to determine the dose-response curve for 8-OH-DPAT. Of the cats receiving lorazepam before motion testing, all but four were in the 8-OH-DPAT experiment. The two doses of lorazepam were tested 20 months apart, with only four cats being in both tests. Therefore, the data resulting from each dose are treated as if from testing in separate groups.

Xylazine. Xylazine was administered SC and the cats monitored for thirty minutes or for fifteen minutes after the last emetic event, whichever occurred later. Saline alone was tested between determinations of dose-response curves to evaluate conditioned responses. Further, the emetic efficacy of xylazine was confirmed before and after each dose-response curve by administering saline before xylazine. Tests with this group were conducted at weekly intervals. Potential antiemetic drugs were tested in the xylazine challenge group before being administered to the motion group.

Cisplatin. Jugular catheters were implanted under sterile conditions and ketamine and pentobarbital anesthesia. Antibiotics were administered after the surgery. The catheters were implanted in the jugular, threaded under the skin and externalized at the nape of the neck. Catheter patency was maintained by withdrawing blood, flushing with 50 U/ml heparin and filling with 1000 U/ml heparin. This was done immediately after surgery and every other day thereafter. The heparin was withdrawn just prior to the infusion of cisplatin. Experiments were conducted 72–96 hr after implantation.

Both experimental and control groups received IV infusions of cisplatin over a period of 4–5 min. The challenge dose of 7.5 mg/kg has been established as the most reliable for eliciting emesis in the cat (23). The number and latency of emetic events were observed for six hours after the infusion. At the end of the observation period, the cats were euthanized by intravenous administration of T-61® (Hoechst, Somerville, NJ).

Drugs

Xylazine HCl (Bayvet, Shawnee, KS) was dissolved in sterile saline to an injection volume of 0.066 ml/kg. 8-OH-DPAT (Research Biochemicals Inc., Wayland, MA) was dissolved in sterile saline to an injection volume of 0.1 ml/kg. The order of doses in the xylazine group was 0.01, 0.04, 0.16 and 0.64 mg/kg. The order of doses in the motion group was 0.01, 0.02, 0.04 and 0.028 mg/kg. In the motion and xylazine tests, 8-OH-DPAT was administered SC 15 min before the emetic challenge. The dose of 0.16 mg/kg was initially chosen for the cisplatin study because it produced acute changes in behavior and effects on xylazine-induced emesis that were roughly equivalent to that of 4.0 mg/kg of buspirone (19). 8-OH-DPAT was administered SC immediately before cisplatin infusion. Lorazepam (Sigma Chemical Co., St. Louis, MO) was suspended in sterile saline with one drop of Tween-80 per five ml by sonication in hot water. The pH was adjusted to 7.0 with sodium hydroxide. The injection volume was 0.5 ml/kg. Lorazepam was administered SC 30 min before motion or xylazine challenges. Drugs were freshly prepared just before administration. Doses are expressed in terms of the base.

Statistics

Dose-response curves were analyzed by Cochran's Q-test to establish significant effects (7). Paired comparisons, as for pre- and postdrug vehicle tests, were made using McNemar's test (23). Tests for line parallelism, relative potency and ED50 were based on least squares regression in a program for pharmacological statistics (34). Motion sickness scores without values for retching/vomiting were analyzed using Friedman's ANOVA (35). Data from experiments with each dose of 8-OH-DPAT administered before cisplatin were compared with data from experiments with cisplatin alone. Analyses performed were the Fisher-Yates test (14) and Wilcoxon's test using the number of emetic events. Analysis of the latency to the first emetic event was performed using a procedure for parametric right-censored data that computes a log-likelihood function based on the log of the latency to emesis (12).

RESULTS

Motion Challenge

8-OH-DPAT produced a dose-dependent decrease in the incidence of motion sickness ($p<0.01$, Fig. 1). There was no change in the susceptibility of the animals during the course of the experiment as shown by the pre- and postdrug vehicle tests, on which 13 and 14 exhibited motion-induced emesis, respectively. The ED50 was 0.022 mg/kg. The line of best fit (dose-response curve expressed in log dose of the number of moles) as determined by least squares regression was not different from parallel to the line describing the buspirone dose-response curve (20), $t(4) = 2.03$, $p>0.05$. Construction of parallel lines and subsequent analysis of the resulting ED50 values revealed that 8-OH-DPAT was 10 times more potent than buspirone on a mg basis.

The motion sickness rating scale scores (36) were analyzed without the points normally assigned for retch/vomits. The remaining symptom scores reflect the sum of arbitrarily assigned values for the symptoms of salivation, panting, urination and

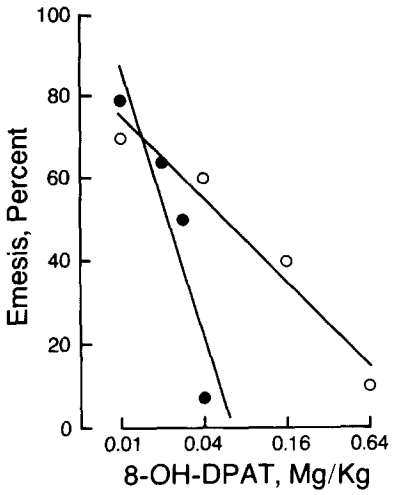

FIG. 1. Effects of 8-OH-DPAT on emesis elicited by motion or xylazine. 8-OH-DPAT was administered SC 15 min before presentation of the emetic stimuli. Motion testing lasted for 30 min followed by one min of observation at rest (solid circles). The xylazine challenge was 0.66 mg/kg SC, followed by observation for 30 min or for 15 min after the last emetic episode, whichever occurred later (open circles). Data are presented as the percent displaying emesis following 8-OH-DPAT compared to control. The control incidence of emesis was fourteen of twenty for the motion group, observed following administration of saline after determination of the dose-response curve. All ten cats in the xylazine group vomited in response to the challenge dose alone both before and after determination of the dose-response curve. The dose of 8-OH-DPAT is on a log scale.

defecation (Table 1). 8-OH-DPAT produced a significant decrease in scores, $\chi^2(5) = 15.18$, $p<0.01$. This analysis demonstrated that 8-OH-DPAT decreased the symptoms associated with motion sickness in addition to suppressing emesis.

Lorazepam also suppressed motion sickness (Table 2). The dose of 0.1 mg/kg produced drowsiness and ataxia. The dose of 0.2 mg/kg produced restlessness and prominent ataxia. At the latter dose, some cats repeatedly lurched forward, striking their face on the end of the test box.

Xylazine Challenge

8-OH-DPAT produced a dose-dependent decrease in xylazine-induced emesis ($p<0.01$; Fig. 1). The ED50 was 0.056 mg/kg. There was no change in the efficacy of xylazine, with all ten cats vomiting to xylazine alone both before and after determination of the 8-OH-DPAT dose-response curve. The dose-response curves for the effects of 8-OH-DPAT on motion sickness and xylazine-induced emesis were not different from parallel, $t(4) = 2.60$, $p>0.05$. When compared to the effects of buspirone on xylazine-induced emesis (20), 8-OH-DPAT was roughly 16 times more potent on a mg basis. However, this is only approximate, as only one dose of buspirone was tested in xylazine-treated cats. The dose of 0.64 mg/kg produces strong defensive behavior similar to that reported for buspirone. However, unlike buspirone, the effect was not evident on the following day.

Lorazepam failed to alter xylazine-induced vomiting. All ten cats vomited in response to xylazine despite pretreatment with the doses of 0.1 and 0.4 mg/kg, which produced gross behavioral disruption.

Cisplatin Challenge

The four cats tested as controls responded similarly to historical controls. Accordingly, these subjects were pooled. 8-OH-DPAT produced a decrease in cisplatin-induced emesis (Table 3). The dose of 0.16 mg/kg produced an increased latency to the first emetic event that was marginal compared to the control data, $\chi^2(1) = 2.563$, $p<0.0547$, failed to significantly alter the number of emetic events and did not significantly alter the number of cats vomiting ($p = 0.170$). The dose of 0.64 mg/kg significantly decreased the number of events ($p<0.05$) and significantly altered

TABLE 1

THE EFFECTS OF 8-OH-DPAT ON A MOTION SICKNESS RATING SCALE

Treatment	Mean Score	Median Friedman Rank
Presaline	5.4	5
8-OH-DPAT,		
0.01 mg/kg	4.2	3.75
0.02 mg/kg	3.5	3
0.028 mg/kg	3.3	3
0.04 mg/kg	1.4	2
Postsaline	4.4	4

The scale described by Suri *et al.* (36) was modified by omitting scores for retch/vomits. Data represent the mean of the remaining scores across cats and the median ranking in the Friedman ANOVA.

TABLE 2

THE EFFECTS OF LORAZEPAM ON MOTION SICKNESS

Vehicle	0.1 mg/kg	0.2 mg/kg	Vehicle
8	5	—	8
7	—	0	8

The doses were determined in separate groups of cats. Data are presented as the number vomiting of 10 tested.

TABLE 3

THE EFFECTS OF 8-OH-DPAT ON EMESIS INDUCED BY CISPLATIN

Control Lat.*/No.†	0.16 mg/kg Lat./No.	0.64 mg/kg Lat./No.
47.85/9	61.35/12	49.15/1
51.81/6	100.55/6	285.97/1
71.78/6	102.67/5	360/0
72.75/1	171.83/3	360/0
87.65/3	360/0	360/0
95.62/6	360/0	360/0
96.90/4	360/0	
171.58/2	360/0	
360/0		
360/0		

*Latency to the first emetic event in minutes. Data ordered by latency. Three hundred and sixty denotes a test with no emesis.

†Number of emetic events.

8-OH-DPAT was administered SC immediately before infusion of 7.5 mg/kg of cisplatin. Cats were observed for six hr.

the latency to the first event, $\chi^2(1) = 3.94$, $p < 0.025$, and produced a marginal decrease in the number of cats vomiting ($p = 0.084$). When compared to the effects of buspirone on cisplatin-induced emesis (21), 8-OH-DPAT was roughly four times more potent.

DISCUSSION

8-OH-DPAT prevented emesis elicited by motion, xylazine and cisplatin. It also suppressed symptoms associated with the development of motion sickness. Because each stimulus appears to use different neural pathways (see Introduction), 8-OH-DPAT presumably acts at some point of convergence of these pathways. This point of convergence could be the brainstem region that organizes the emetic reflex (6,40), through details of the anatomical site have been questioned (29). The antiemetic effect may result from an action directly on the neural site which organizes emesis or on an inhibitory pathway to the neural site. Consequently, 8-OH-DPAT may be effective as a general antiemetic drug, perhaps offering suppression of radiation-induced emesis and chronic vomiting as well.

The results from the 8-OH-DPAT studies show that the effects of buspirone on 5-HT_{1A} receptors are adequate to explain its antiemetic effects. This conclusion is based on the observation that 8-OH-DPAT is a selective agonist at 5-HT_{1A} receptors, with minimal affinity for other known receptors (27). 8-OH-DPAT has been reported to reverse the response to agonists at $alpha_2$ adrenoceptors with an IC_{50} of 250 nM (11). This is weak compared to binding of 8-OH-DPAT at 5-HT_{1A} receptors, which has a K_i of 1.2 nM (16). Buspirone has an active metabolite that blocks $alpha_2$ adrenoceptors (3). However, this mechanism is unlikely to be relevant to the antiemetic effect of either drug, as the $alpha_2$ adrenoceptor antagonist yohimbine is ineffective in preventing motion sickness at doses up to 0.25 mg/kg (19).

Although blockade of 5-HT_3 receptors has been reported to prevent cisplatin-induced emesis in the ferret (9,30), it is unlikely this is relevant to the present experiment. There is no evidence that either buspirone or 8-OH-DPAT act at these sites. Further, the 5-HT_3 antagonist ICS 205–930 prevents cisplatin-induced emesis in the cat but does not prevent either motion sickness or xylazine-induced emesis in this species (22).

The possibility that the anxiolytic effects of 8-OH-DPAT and buspirone are responsible for their antiemetic effects was tested by examining the response to lorazepam. While 0.2 mg/kg of lorazepam was able to prevent motion sickness, 0.4 mg/kg did not alter xylazine-induced emesis. The relative effectiveness of lorazepam in reversing the emesis elicited by these two stimuli differed from that of 8-OH-DPAT, which decreased xylazine-induced emesis at doses that decreased motion sickness. This discrepancy suggests a different mechanism of action for the two drugs. Further, the dose of lorazepam that suppressed motion sickness also produced ataxia. Benzodiazepines produce ataxia in cats at doses above those considered to be anxiolytic in this species (37). Thus, an anxiolytic effect of lorazepam is not adequate to explain its suppression of motion sickness. The possibility that antiemetic effects result from an anxiolytic action is not supported.

Doses of benzodiazepines that suppress the firing of 5-HT neurons in cats produce ataxia (37). The dose of lorazepam that suppressed motion sickness also produced ataxia (present study). One conclusion from the above is that the suppression of 5-HT turnover produced by the presynaptic action of 8-OH-DPAT (2,17) and buspirone (38,39) leads to suppression of emesis. This is unlikely, because it leads to the prediction that 0.4 mg/kg of lorazepam should decrease xylazine-induced emesis. Further, responses produced by suppression of 5-HT turnover would presumably be mimicked by blockade of postsynaptic 5-HT receptors. The nonspecific 5-HT antagonist metergoline (15) does not decrease motion sickness in cats (unpublished results). If decreasing 5-HT turnover cannot account for antiemetic effects, then it is likely that the antiemetic actions of 8-OH-DPAT result from stimulation of postsynaptic receptors. This possibility requires further study.

8-OH-DPAT did not appear to be as effective in preventing cisplatin-induced emesis as in preventing xylazine-induced emesis or motion sickness. While 8-OH-DPAT was 10 times more potent than buspirone at preventing motion sickness and roughly 16 times more potent than buspirone at preventing xylazine-induced emesis, it was only four times more potent at preventing cisplatin-induced emesis. It is not evident why such a discrepancy exists. Buspirone may have some action in addition to its effects on 5-HT_{1A} receptors which contributes to its antiemetic effects on the other emetic syndromes. One possibility is its action on presynaptic dopamine receptors (25). An alternative is inaccurate estimation of the relative potencies on the tests with xylazine and cisplatin, as only one dose of buspirone was tested with these stimuli.

In summary, we find 8-OH-DPAT, like buspirone, prevents emesis elicited by motion, xylazine and ciplatin. The antiemetic effect is probably due to stimulation of postsynaptic 5-HT_{1A} receptors. Because parsimony suggests that it acts at or near the vomiting center, it is possible that these drugs may block emesis elicited by other stimuli.

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