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Blockade of Lithium Chloride-Induced Conditioned Place Aversion as a Test for Antiemetic Agents: Comparison of Metoclopramide With Combined Extracts of *Zingiber officinale* and *Ginkgo biloba*

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RISCH, C., R. U. HASENÖHRL, C. M. MATTERN, R. HÄCKER AND J. P. HUSTON. *Blockade of lithium chloride-induced conditioned place aversion as a test for antiemetic agents: Comparison of metoclopramide with combined extracts of* Zingiber officinale *and* Ginkgo biloba. PHARMACOL BIOCHEM BEHAV **52**(2) 321-327, 1995.—The present study tests the hypothesis that the blockade of lithium chloride-induced conditioned place aversion might be a suitable model to assess antiemetic properties of drugs, especially in species that do not vomit, like rats. The effects of the known antiemetic compound metoclopramide were compared with those of zingicomb®, a combination preparation of extracts of *Ginkgo biloba* and *Zingiber officinale*, also presumed to have antiemetic properties. Place conditioning was performed using a conventional three-compartment test procedure. On three successive conditioning trials, rats received an intraperitoneal (IP) injection of lithium chloride (125 mg/kg) and were placed into the compartment that they had preferred over three baseline trials. During the test, rats treated with lithium chloride (LiCl) spent less time in the treatment compartment, indicative of a conditioned place aversion (CPA). In the first experiment, metoclopramide (MCP) was administered intragastrically (IG) in doses of 2 or 10 mg/kg 60 min prior to LiCl injection. The pretreatment with 10 mg/kg MCP blocked the LiCl-produced CPA, whereas injections of 2 mg/kg had no effect. In the second experiment, zingicomb was administered IG in a dose range of 10-100 mg/kg 60 min prior to LiCl injection. The pretreatment with 50 and 100 mg/kg zingicomb attenuated the LiCl-produced CPA, whereas a dosage of 10 mg/kg had no effect. These findings suggest that LiCl-induced CPA is a viable procedure with which to assess the antiemetic properties of metoclopramide. Furthermore, the data confirm the hypothesis that the phytopharmacon zingicomb might have antiemetic properties that are comparable to those of metoclopramide.

Lithium chloride Conditioned place aversion Metoclopramide *Ginkgo biloba* Ginger Emesis Rat

NAUSEA and vomiting occur in a wide variety of disorders and as a side effect of many drugs, radiation, and anesthesia (9,32,33,42). The pharmacological treatment of emesis focuses on certain subclasses of receptors and functional systems known to be involved in gastrointestinal distress and vomiting. Here, antagonists at the dopamine D_2 or serotonin 5-HT_3 receptor, like metoclopramide, domperidone, or ondansetron, have acquired therapeutical significance [e.g., (1,23)]. Besides chemically defined drugs, there are phytopharmaca with known antiemetic properties, such as powdered rhizomes or extracts of *Zingiber officinale*. Ginger extracts are potent antagonists at the 5-HT_3 receptor (47) and have been found to

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attenuate emesis and vomiting in humans (5,14,34) and in *Suncus murinus* (48). Ginkgo extracts are indirect serotonin antagonists by inhibition of thrombocyte aggregation (22,25) and can diminish the humoral stimulation of brain stem regions involved in the induction of emesis by decreasing the permeability of the blood–brain barrier for vasopressin, histamine, and TRH (13,20). In a recent series of studies, the compound zingicomb®, a combination of ginger and ginkgo extracts, has been found to reduce cytotoxic drug-induced vomiting in ferrets (Mühle and Masleniy, unpublished results) and chemotherapy-produced emesis in humans (Mattern and Kasjanenko, unpublished results).

Research on emesis and antiemetics has been limited because the traditional animal models used have been dogs, cats, and ferrets, which vomit in response to emetic stimuli (15,27). Recently, emesis-related behaviors, such as pica, (30,31,43), and conditioned taste aversion (11) have been examined in species that do not vomit, like rats and mice. We propose that the conditioned place preference (CPP) paradigm might be an alternative method for the research on emesis and antiemetics. Place conditioning is generally used to assess reinforcing and aversive properties of drugs [(8,40) for review]. Using this paradigm, administration of the drug is paired with a distinctive environment, and a subsequent increase or decrease in time spent in that environment during a preference test is taken as evidence of the drug's reinforcing or aversive effects, respectively. Several stimuli that provoke gastrointestinal distress, emesis, and vomiting in humans produce a conditioned place aversion in rats, like ionizing radiation (17), apomorphine (3), or lithium chloride [e.g., (35,36,41)]. These findings suggest that place conditioning is sensitive to toxin-induced illness responses related to emesis, and that the CPP paradigm could be a procedure for measuring emetic as well as antiemetic properties of drugs, especially in species that do not vomit.

In the present experiments, we provide evidence that place conditioning is a suitable model to assess antiemetic drug effects. To validate the model, the antiemetic compound metoclopramide (12) was tested against lithium chloride (LiCl)-induced place aversion. Based on the assumption that LiCl induces an emesis-related illness response in rats, it was proposed that the "classical" antiemetic should block or at least attenuate LiCl-induced place aversion. Furthermore, we gauged the effects of zingicomb®, a combination of standardized extracts of *Zingiber officinale* and *Ginkgo biloba*, on LiCl-induced place aversion. On the basis of its pharmacodynamic profile and its beneficial effects on drug-induced emesis and vomiting in humans and animals (see above), zingicomb was hypothesized to have effects on LiCl-induced place aversion similar to those observed for metoclopramide.

METHOD

Animals

The experiments were performed on 96 male Wistar rats (TVA, Heinrich-Heine-University Düsseldorf), weighing 250–350 g at the beginning of the experiments. Rats were housed in groups of six to eight per cage under a 12L : 12D cycle, with food and water continuously available. The animals were handled daily for 1 week before the beginning of the experiments. Rats were weighed before and after behavioral testing. All testing was conducted during the rats' daylight period between 0800 and 1700 h.

Experimental Apparatus

The three-compartment box used for place conditioning has been described in detail previously [e.g., (26,37)]. Briefly, the box consisted of two compartments of equal size (30 × 23 × 35 cm), differing in color (black, white) and floor texture (rough, fine wire mesh) separated by a small gray alley (30 × 10 × 35 cm) with a transparent Plexiglas floor. From the center alley the rat could enter either of the two compartments through guillotine doors. The testing device was set up in a sound-protected experimental chamber with dim overhead lighting (40 W). Masking noise (68 dB) was provided by a noise generator. The behavior of the animals throughout the experiments was recorded by a video system and the position of the rat was defined by the position of its front paws. After each trial the apparatus was swept out with water containing 0.1% acetic acid. All behavioral recordings were carried out with the observer being unaware of the treatment of the rat.

Drugs and Injection Procedure

Standardized extracts of rhizomes of *Zingiber officinale* (ginger CO_2 extracts), folia *Ginkgo biloba,* comparable to EGb 761 (ginkgo) and their combination zingicomb® (ZC: a mixture of 50% ginger + 20% ginkgo + 30% water), as well as metoclopramide hydrochloride (MCP), were supplied by Mattern et Partner (Starnberg, Germany). The drugs were dissolved and diluted to the desired concentrations with water and were administered intragastrically (IG) via a gastric tube. Lithium chloride (LiCl; Sigma, Germany) was dissolved in physiological saline and was given intraperitoneally (IP) in a dosage of 125 mg/kg. This dosage had been found to be effective in producing a reliable place aversion in a pilot study using the three-compartment place preference procedure described above. The drugs were freshly prepared before each treatment trial. All injections were given in a volume of 2 ml/kg body weight. The same volume was used for injecting the diluent vehicles: VEH (water) and SAL (physiological saline).

Conditioning Protocol

Behavioral testing, carried out over 7 consecutive days, consisted of three baseline trials (days 1–3), three treatment trials (days 4–6), and a test trial (day 7). The video system was used to record the time spent in the black and white compartments and the number of entries made into both compartments during baseline and test trials. An animal was considered to be in a compartment when its head and forepaws were inside it. During each of the three baseline trials, after placing the rats into the center alley, the animals were allowed to explore the testing apparatus with both guillotine doors opened for 15 min per trial. After the third baseline trial the preference for one of the two compartments was calculated by taking the mean time spent in the compartments over the three baseline trials. The compartment in which the rat spent less time was called *nonpreferred* and the other one was considered *preferred.* Then the rats were assigned randomly to the treatment groups. Treatment trials consisted of three 60-min sessions. During a typical session, the rats were pretreated IG with MCP, ZC, or VEH 60 min before being injected IP with LiCl or SAL. Immediately thereafter, the rat was placed into its *preferred* compartment for 60 min. The guillotine doors were closed to prevent entry into the other compartments. During the test trial, on day 7, the animals were placed into the center alley and were allowed to explore the test box for 15 min with both guillotine doors opened. Behavior was registered as during the baseline trials.

Treatment Schedule

Experiment 1. The effects of two doses (2.5 and 10 mg/kg) of the antiemetic compound MCP on LiCl-induced place aversion were assessed to validate the procedure. Rats were assigned randomly to the following treatment groups: 2.5 mg/kg MCP + LiCl (n = 8), 10 mg/kg MCP + LiCl (n = 8), VEH + LiCl (n = 7), and VEH + SAL (n = 6).

Experiment 2. The effects of ZC against LiCl-induced place aversion were gauged. Different doses of ZC were used in combination with LiCl to construct a dose–response curve. Rats were assigned randomly to the following treatment groups: 10 mg/kg ZC + LiCl (n = 13), 50 mg/kg ZC + LiCl (n = 13), 100 mg/kg ZC + LiCl (n = 18), 100 mg/kg ZC + SAL (n = 7), VEH + LiCl (n = 9), and VEH + SAL (n = 7).

Data Collection and Analysis

Data given represent means ± SEM values. During baseline and test trials, the time spent in the black and white compartments was recorded. As a measure of gross locomotor activity, the total number of entries into the compartments, the number of entries into the treatment compartment as well as the time spent per entry in the treatment compartment, were recorded. To investigate possible time-dependent influences of the treatment, the time spent in the treatment compartment during the test trial was divided post hoc into three time blocks of 5 min (min 0–5, min 6–10, min 11–15). The Mann–Whitney U-test (two-tailed) was used to test for between-group differences; the Wilcoxon rank-sum test was used to compare the time spent in the compartments on the third baseline trial with the respective test values.

RESULTS

Baseline Trials

Over the 3 days of baseline trials the rats developed a preference for either the black or the white compartment. Only 6 out of 96 animals spent more time in the white than in the black compartment. The amount of time spent in the preferred compartment during baseline ranged from 298.7 ± 8.0 s in Exp. 1 to 314.1 ± 7.2 s in Exp. 2 (means ± SEM). On day 3 (BL3; pretreatment), the groups did not differ in the amount of time spent in the treatment compartment, number of entries into the compartments, number of entries into the treatment compartment, and time spent after each entry in the treatment compartment (corresponding p-values > 0.10, data not shown).

Experiment 1: Effects of MCP on LiCl-Induced Place Aversion

Rats treated with VEH in combination with LiCl spent significantly less time in the drug-paired compartment compared to VEH + SAL-injected controls (VEH + LiCl vs. VEH + SAL, p = 0.012) (Fig. 1, Table 1). This effect was most pronounced during the last 5 min of the test period (VEH + LiCl vs. VEH + SAL: min 0–5, p = 0.134; min 6–10, p = 0.100; min 11–15, p = 0.018, data not shown). Metoclopramide (10 mg/kg), when given prior to LiCl injections, blocked the conditioned place aversion induced by LiCl (10 mg/kg MCP + LiCl vs. VEH + LiCl, p = 0.007); the dose of 2.5 mg/kg MCP did not significantly influence the LiCl-induced place aversion (2.5 mg/kg MCP + LiCl vs. VEH + LiCl, p = 0.272). Rats treated with MCP in combination with LiCl did not differ from vehicle controls in the amount of time spent in the treatment compartment (2.5 mg/kg MCP + LiCl vs. VEH + SAL, p = 0.107; 10 mg/kg MCP + LiCl vs. VEH + SAL, p = 0.651). The analysis of entry data re-

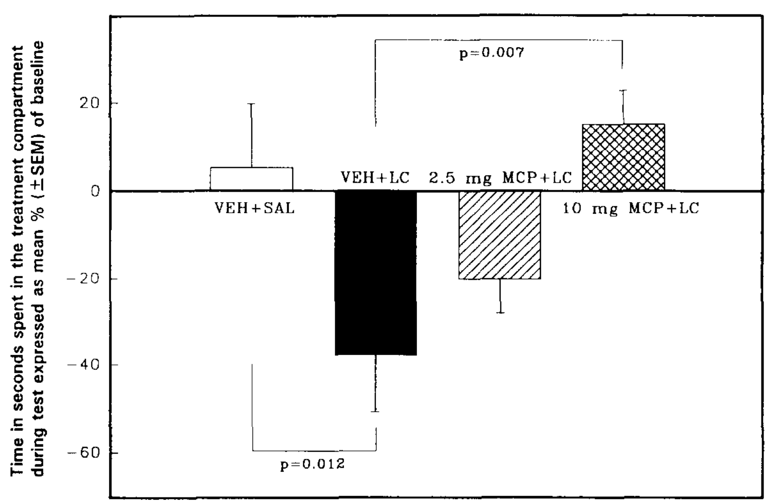

FIG. 1. Experiment 1: effects of metoclopramide. Time spent in the treatment compartment on the day of testing for each treatment group expressed as percent of corresponding baseline values (mean ± SEM). Rats were administered intragastrically with metoclopramide (MCP; 2.5 or 10 mg/kg) or VEH (2 ml/kg) 60 min before being IP injected with 125 mg/kg LiCl or SAL (2 ml/kg). Immediately after treatment, the rats were placed into their treatment compartment for 60 min on 3 consecutive days. Mann–Whitney U-tests (two-tailed) performed on raw data were used to test for between-group differences.

TABLE 1

TIME SPENT IN THE TREATMENT COMPARTMENT (TC), NUMBER OF ENTRIES INTO THE COMPARTMENTS, NUMBER OF ENTRIES INTO THE TREATMENT COMPARTMENT, AND TIME IN SECONDS SPENT AFTER EACH ENTRY INTO THE TC DURING TEST TRIAL IN EXPERIMENTS 1 AND 2

Treatment	Time in TC	Entries	Entries in TC	Time/Entry in TC
Exp. 1: Effects of metoclopramide				
VEH + SAL	313.0 ± 27.2*	50.5 ± 6.3	13.2 ± 1.5	25.6 ± 4.2
VEH + LiCl	179.2 ± 30.9	40.9 ± 6.4	11.4 ± 1.6	16.1 ± 2.2
2.5 mg MCP + LiCl	232.7 ± 30.7	51.6 ± 5.4	13.6 ± 1.3	17.4 ± 1.9
10 mg MCP + LiCl	332.5 ± 14.9*	54.3 ± 5.6	14.3 ± 1.4	24.7 ± 2.1*
Exp. 2: Effects of zingicomb®				
VEH + SAL	268.4 ± 8.7*	48.1 ± 5.7	12.1 ± 1.5	24.6 ± 3.5
VEH + LiCl	229.1 ± 43.6	42.0 ± 5.1	11.0 ± 1.4	23.0 ± 4.9
10 mg ZC + LiCl	256.3 ± 46.2	42.7 ± 6.5	10.6 ± 1.7	27.0 ± 4.7
50 mg ZC + LiCl	293.9 ± 21.4*	41.4 ± 3.6	10.6 ± 0.9	29.8 ± 3.1
100 mg ZC + LiCl	276.2 ± 19.0*	56.9 ± 4.2*	14.1 ± 1.1	20.3 ± 1.3
100 mg ZC + SAL	238.1 ± 37.2	44.3 ± 5.9	12.0 ± 1.6	21.4 ± 4.0

Values are means ± SEM. LiCl = lithium chloride, MCP = metoclopramide, ZC = zingicomb®. *Different from corresponding VEH + LiCl treated controls, $p < 0.05$ (Mann-Whitney U-test: two-tailed).

vealed that there were no treatment-related differences in the number of entries into the compartments and the number of entries into the treatment compartment during the test (corresponding p-values > 0.10) (Table 1). Rats injected with VEH in combination with LiCl spent less time after each entry into the treatment compartment, compared to animals treated with 10 mg/kg MCP + LiCl and vehicle controls (VEH + LiCl vs. 10 mg/kg MCP + LiCl, $p = 0.024$; VEH + LiCl vs. VEH + SAL, $p = 0.074$) (Table 1).

Experiment 2: Effects of Zingicomb on LiCl-Induced Place Aversion

Like in Exp. 1, the administration of LiCl induced a reduction in the time spent in the treatment compartment during the test (VEH + LiCl vs. VEH + SAL, $p = 0.034$) (Fig. 2, Table 1). Again, this reduction in time was most pronounced at the end of the test session (VEH + LiCl vs. VEH + SAL: min 0–5, $p = 0.597$; min 6–10, $p = 0.397$; min 11–15, $p = 0.044$; data not shown). Injections of both 50 and 100 mg/kg zingicomb, given prior to LiCl injection, blocked the conditioned place aversion induced by LiCl (50 mg/kg ZC + LiCl vs. VEH + LiCl, $p = 0.033$; 100 mg/kg ZC + LiCl vs. VEH + LiCl, $p = 0.048$); the dose of 10 mg/kg ZC did not influence the LiCl-induced decrease in time spent in the treatment compartment (10 mg/kg ZC + LiCl vs. VEH + LiCl, $p = 0.593$). There were no differences in the time spent in the treatment compartment between animals treated with ZC in combination with LiCl and VEH-treated controls (10 mg/kg ZC + LiCl vs. VEH + SAL, $p = 0.303$; 50 mg/kg ZC + LiCl vs. VEH + SAL, $p = 0.476$; 100 mg/kg ZC + LiCl vs. VEH + SAL, $p = 0.832$). The pretreatment with ZC (100 mg/kg) without LiCl had no effect on the amount of time spent in the treatment compartment (100 mg/kg ZC + SAL vs. VEH + SAL, $p = 0.443$). Furthermore, rats injected with 100 mg/kg zingicomb in combination with LiCl spent more time in the previously *nonpreferred* compartment ($p = 0.004$; data not shown) and were more active compared to rats that were treated with vehicle + LiCl (Table 1; 100 mg/kg ZC + LiCl vs. VEH + LiCl: number of entries, $p = 0.033$; number of entries into the treatment compartment, $p = 0.070$). The time spent per entry into the treatment compartment did not differ between groups (Table 1).

DISCUSSION

The most important finding of the present study was that the antiemetic drug MCP as well as the antiemetic phytopharmacon ZC given IG can block the conditioned place aversion produced by systemically administered LiCl. In line with the outcome of recent studies using biased and unbiased place conditioning procedures (10,38,41), the systemic injection of LiCl resulted in a decrease in time spent in the compartment that had previously been paired with the drug, indicative of an aversive action of the compound. Rats treated with MCP in combination with LiCl did not differ from vehicle-treated controls in time spent in the treatment compartment and in the parameters of activity. Thus, the MCP blockade of LiCl-induced place aversion cannot be interpreted in terms of a change in locomotor activity, which can interfere with the expression of place aversion. These findings confirm our hypothesis that LiCl-induced place aversion might be a valuable tool for investigating emetic as well as antiemetic properties of drugs, because place aversion was produced by LiCl, a drug with a high emetic potential in humans [(45) for review], and was prevented by MCP, an agent with known antiemetic properties in humans and animals (12,15,19).

Prior treatment with the antiemetic phytopharmacon ZC also blocked LiCl-produced CPA. This effect was dose dependent and evident after the injection of 50 and 100 mg/kg, but not 10 mg/kg, of the compound. The data demonstrate that ZC on its own neither influenced the preference behavior nor the entry parameters during the testing period. These results argue against the possibility that ZC might have attenuated LiCl-produced CPA as a result of having reinforcing or other associative or nonassociative effects. These findings are engaging in the light of recent experiments showing that the compound can attenuate cytotoxic drug-induced vomiting in ferrets (Mühle and Masleniy, unpublished results) and che-

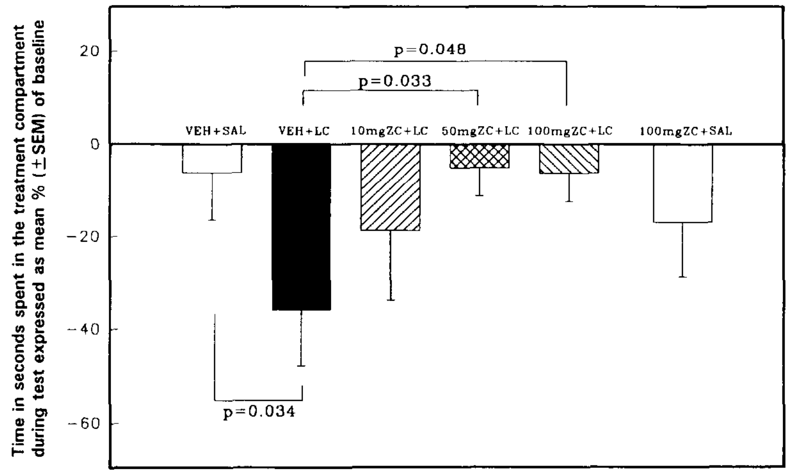

FIG. 2. Experiment 2: effects of zingicomb®. Time spent in the treatment compartment on the day of testing for each treatment group expressed as percent of corresponding baseline values (mean ± SEM). Rats were administered intragastrically with zingicomb® (ZC; 10, 50, or 100 mg/kg) or VEH (2 ml/kg) 60 min before being IP injected with 125 mg/kg LiCl or SAL (2 ml/kg). Immediately after treatment, the rats were placed into their treatment compartment for 60 min on 3 consecutive days. Mann-Whitney *U*-tests (two-tailed) performed on raw data were used to test for between-group differences.

motherapy-produced emesis in humans (Mattern and Kasjanenko, unpublished results). They also substantiate that the phytopharmacon might have antiemetic effects comparable to those of MCP.

Although rats do not vomit, they have the same brain stem nuclei, motor systems, and neurochemical mechanisms necessary for emesis as vomiting species (4,27). The pharmacological mechanisms that might account for the effects of MCP and ZC on LiCl-produced place aversion have yet to be determined. The effects of MCP might be related to its D_2 and 5-HT_3 antagonistic properties (32,33). Ginger extracts are potent antagonists at the 5-HT_3 receptor (47) and ginkgo extracts are indirect serotonin antagonists by preventing the aggregation of thrombocytes (22,25), and they can reduce the humoral stimulation of brain stem regions involved in the induction of emesis by decreasing the permeability of the blood–brain barrier (13,20). Systemic administration of LiCl was found to increase serotonin and dopamine levels in several brain regions (18,46) and in plasma (21,44). An anatomical substrate, possibly related to the antiemetic effects of MCP and *Zingiber officinale*, is the area postrema, which is the site of a chemoreceptor trigger zone mediating nausea and emesis (6,7). The density of D_2 and 5-HT_3 receptors in the area postrema is high (1,2), and lesions of this region eliminate aversive reactions to LiCl in rats (29,39) and inhibit apomorphine-induced emesis in the ferret (28). Furthermore, application of 5-HT_3 receptor antagonists in the area postrema attenuates emesis induced by cytotoxic agents (24). Thus, it is possible that the blockade of D_2 and 5-HT_3 receptors in this region is critical for the MCP- and ZC-induced blockade of LiCl-produced conditioned place aversion. However, a direct peripheral action of MCP and ZC also could be responsible for the effects on LiCl-produced place aversion.

Alternative interpretations of the MCP and ZC-produced attenuation of the LiCl conditioned place aversion other than in terms of pharmacological antagonism should also be taken into account. Rats treated with 100 mg/kg ZC in combination with LiCl displayed an apparent increase in time spent in the previously nonpreferred compartment during the test trial, suggesting that the compound could have anxiolytic effects. This suggestion was confirmed recently by showing that ZC is active in the elevated plus-maze test of anxiety (Huston and Hasenöhrl, unpublished data). Thus, it is possible that anxiolytic effects of the compound may have served to decrease the CPA induced by LiCl. Another possibility is that MCP and ZC attenuated LiCl-produced CPA by producing state-dependent learning, that is, by interfering with the expression of LiCl place aversion, rather than with its acquisition during conditioning. To control for state dependency, a treatment group injected with MCP or ZC before both conditioning and test trials would have been required. However, MCP produces acute stereotyped behavior and hypomotility (16), which can interfere with the preference behavior when given pretest. When injected before the conditioning trials, as in the present study, MCP did not influence locomotor activity during the test for CPA.

For the research on emesis and the screening of antiemetic compounds, dogs, cats, and ferrets have mostly been used. Monkeys may be a primate model, but they do not respond to apomorphine, a typical emetic in humans (27). In the present study we showed that a conditioned place aversion can be produced by the same pharmacological stimuli as emesis and vomiting in humans and that MCP, known to block emetic-induced vomiting in humans, blocks emetic-induced place aversion in rats. These findings suggest that LiCl-induced place aversion could be an emesis-related behavior in rats like pica (30,31,43) or conditioned taste aversion (11). Certain aspects of the place conditioning procedure may be advantageous for the investigation of emetic and/or antiemetic properties of pharmacological stimuli. A variety of drugs known to produce gastrointestinal distress, emesis, and vomiting in humans produce a conditioned place aversion, suggesting that the procedure is a valid animal model for emesis and nausea.

Taken together, the present results show that LiCl-induced CPA can be blocked by metoclopramide, suggesting that this paradigm may serve as a procedure with which to gauge the antiemetic properties of drugs. Furthermore, the data provide evidence that the phytopharmacon ZC has antiemetic properties that are comparable to those of MCP.

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