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Effects of Antiemetics on the Acquisition and Recall of Radiation- and Lithium Chloride-Induced Conditioned Taste Aversions[1]

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RABIN, B. M. AND W. A. HUNT. *Effects of antiemetics on the acquisition and recall of radiation- and lithium chloride-induced conditioned taste aversions.* PHARMACOL BIOCHEM BEHAV 18(4) 629–635, 1983.—A series of experiments were run to evaluate the effect of antiemetics on the acquisition and recall of a conditioned taste aversion induced by exposure to ionizing radiation or by injection of lithium chloride. Groups of male rats were exposed to 100 rad gamma radiation or 3 mEq/kg lithium chloride following consumption of a 10% sucrose solution. They were then injected with saline or with one of three antiemetics (prochlorperazine, trimethobenzamide, or cyclizine) at dose levels that have been reported to be effective in attenuating a previously acquired lithium chloride-induced taste aversion. The pretreatments with antiemetics had no effect on the acquisition or recall of either the lithium chloride- or radiation-induced taste aversion. The data suggest that antiemetics do not disrupt lithium chloride-induced taste aversions as previously reported, nor do they effect radiation-induced taste aversion learning.

Conditioned taste aversion Ionizing radiation Lithium chloride Antiemetic

WHEN a rat is exposed to a novel tasting solution, such as saccharin or sucrose, which is paired with injection of lithium chloride (LiCl) or with exposure to ionizing radiation, the animal will avoid further ingestion of that solution at a later time. This avoidance behavior, called a conditioned taste aversion (CTA), is acquired in a single trial [9,18]. Because treatment with antiemetics has been reported to attenuate a previously acquired LiCl-induced CTA, Coil *et al.* [7] have proposed that a drug-induced illness related to emesis is a factor leading to taste aversion learning following LiCl injection.

Rabin *et al.* [16] have shown that lesions of the area postrema of rats can disrupt the acquisition of a CTA following exposure to radiation as well as following injection of LiCl. Since area postrema lesions do not disrupt the acquisition of a CTA following injection of amphetamine [2,17], the common disruption of LiCl- and radiation-induced taste aversions by these lesions would suggest that these two unconditioned stimuli must share some common mechanism by which they can lead to CTA learning. Since antiemetics can attenuate a previously acquired CTA [7] and since lesions of the area postrema, the chemoreceptive trigger zone for emesis [5], disrupt the emesis produced by a variety of treatments including radiation [3, 4, 6] in addition to attenuating a CTA, it seems reasonable to expect that antiemetics should be capable of attenuating a CTA produced by exposure to radiation, as well as to injection of LiCl. Therefore, the experiments described in this report were initially designed to analyze the effects of pretreatment with antiemetics on the acquisition of a radiation-induced conditioned taste aversion.

GENERAL METHOD

Subjects

The subjects were male Sprague-Dawley rats weighing 325–375 g at the start of the experiment. The rats were maintained in individual cages in a room with a 12:12 light:dark cycle. Food and water were continually available except as required by the experimental protocol.

Drugs and Treatments

The antiemetics used in the various experiments were prochlorperazine, trimethobenzamide and cyclizine administered as an intraperitoneal injection. Injections of isotonic saline were used as a control.

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For taste aversions produced by exposure to ionizing radiation, the rats were placed in a plastic restraining tube and individually exposed to 100 rad whole body gamma radiation at a rate of 40 rad/min using a cobalt-60 source. Dose measurements were made with a 3.3 cc Victoreen ionization chamber and with thermoluminescent detectors (LiF TLD 100s). Sham irradiated rats were placed in the restraining tube, but were not exposed to the cobalt source. LiCl-induced aversions were produced by administering a single intraperitoneal injection of lithium chloride at a dose of 3 mEq/kg.

Taste Aversion Training

Two sets of procedures were used to establish conditioned taste aversions. The first procedure utilized a two-bottle preference test to evaluate the effects of antiemetics on the acquisition of a CTA [15,16]. All animals were adapted to a 23.5 hr water deprivation schedule for 10 days, during which water was available for 30 min a day during the early light part of the diurnal cycle. Because taste aversions can be produced by a variety of drugs, including those which animals will self-administer [10], all subjects were injected on the fourth and seventh days of the adaptation period with the appropriate antiemetic or saline to reduce the possibility that the antiemetic injection alone could produce a taste aversion.

On the conditioning day (day 11), the rats were presented with two calibrated drinking tubes, one containing tap water and the other containing a 10% sucrose solution. Intake of each solution was recorded. Animals which did not show a greater intake of the sucrose solution than of water on the conditioning day were eliminated from the study. Immediately after the drinking period, all subjects were given the antiemetic or saline injection. Within 15–30 min following injection, all rats were exposed to one of the following as an unconditioned stimulus: irradiation or sham irradiation procedures and LiCl or saline injections. On the test day, 24 hr later, the rats were again presented with the two calibrated drinking tubes containing tap water and 10% sucrose solution for 30 min and intake of each recorded. The data from the experiments using this two-bottle procedure are given as preference score: sucrose intake divided by water intake plus sucrose intake. A preference score greater than 0.50 indicates a preference for the sucrose solution.

The second procedure involved the use of a single-bottle test and represented a partial replication and extension of the experiments of Coil *et al.* [7] on the effects of antiemetics on the recall of a previously acquired LiCl- or radiation-induced CTA. The subjects were adapted to a water deprivation schedule in which water was available for 15 min a day during the early light phase of a 12:12 light:dark cycle. Since this experiment involved a replication of the experiments of Coil *et al.* [7], the subjects were not preexposed to the antiemetics during the adaptation period. Following adaptation, the rats were given access to a calibrated drinking tube containing 10% sucrose solution, instead of tap water, for their 15 min drinking period on days 1, 4, and 7. Water was available on the other days. On day 4 (conditioning day) the drinking period was followed by irradiation or by injection of LiCl. Day 7 was the test day, with the rats being given the appropriate antiemetic or saline injection 30 min prior to the drinking period test for sucrose intake.

EXPERIMENT 1

As indicated above, the reported effect that antiemetics can attenuate a previously acquired CTA [7] and the common involvement of the emetic trigger zone in both radiation- and LiCl-induced taste aversions [16] suggests that antiemetics would have a similar attenuating effect on a radiation-induced CTA. The present experiment was designed to provide a direct test of the hypothesis that a radiation-induced illness possibly related to emesis plays a role in the acquisition of a CTA following exposure to ionizing radiation. The antiemetic doses used in this experiment were the only doses reported to be effective by Coil *et al.* [7] in attenuating a previously acquired LiCl-induced CTA.

Methods

Fifty-six male rats were divided into 8 equal groups and adapted to the two-bottle preference procedure described above. Immediately after the conclusion of the drinking period on the conditioning day, 14 rats were injected with prochlorperazine (0.1 mg/kg, IP), trimethobenzamide (5.0 mg/kg, IP), cyclizine (4.0 mg/kg, IP), or an equal volume injection of isotonic saline. Within 15–30 min following injection, half the rats receiving each drug were exposed to ionizing radiation and the other half to the sham irradiation procedures.

Results and Discussion

The results are summarized in Fig. 1. For statistical analysis the preference scores were transformed using the arcsin transformation [19] and subjected to a 3-way analysis of variance with one repeated factor. If treatment with the antiemetic drugs were effective in attenuating the acquisition of the radiation-induced CTA, then for the irradiated animals the test day sucrose preference for the three groups receiving antiemetics should be significantly higher than the preference score of the saline injected controls. This should be reflected as a significant 3-way interaction in the analysis of variance. Although this interaction was marginally significant, $F(3,42)=2.735$, $p=0.55$, the pattern was not as predicted. The irradiated animals showed a significant reduction in test day sucrose preference compared to both conditioning day preference, $F(1,42)=79.389$, $p<0.001$, and to sham irradiated controls, $F(1,42)=59.948$, $p<0.001$. That the antiemetic injections had no effect on sucrose preference is indicated by the fact that the main effect for drugs, $F(3,42)=0.514$, $p>0.10$, as well as the radiation × drug, $F(3,42)=0.413$, $p>0.10$, and the day × drug, $F(1,42)=1.692$, $p>0.10$, interactions were all nonsignificant. These data also indicate that the antiemetic injection did not produce a CTA by itself and that preexposure to the antiemetics during the adaptation period did not produce a generalized disruption of taste aversion learning.

The results of this experiment do not support the hypothesis, drived from the experiments of Coil *et al.* [7], that pretreatment with these antiemetics can block a physiological change related to emesis which may play a role in the acquisition of a radiation-induced CTA. As such, these results are consistent with preliminary data discussed by Levy *et al.* [13] but are not consistent with an hypothesis derived from the experiments of Coil *et al.* [7]. These differences in results could be due to several factors. First, they could result from differences in stimulus characteristics between LiCl and irradiation: the time course of action of the unconditioned stimuli may not be the same [1,18]. Second, the mechanism of action of LiCl and radiation may be different: an antiemetic sensitive physiological change may not play a role in a

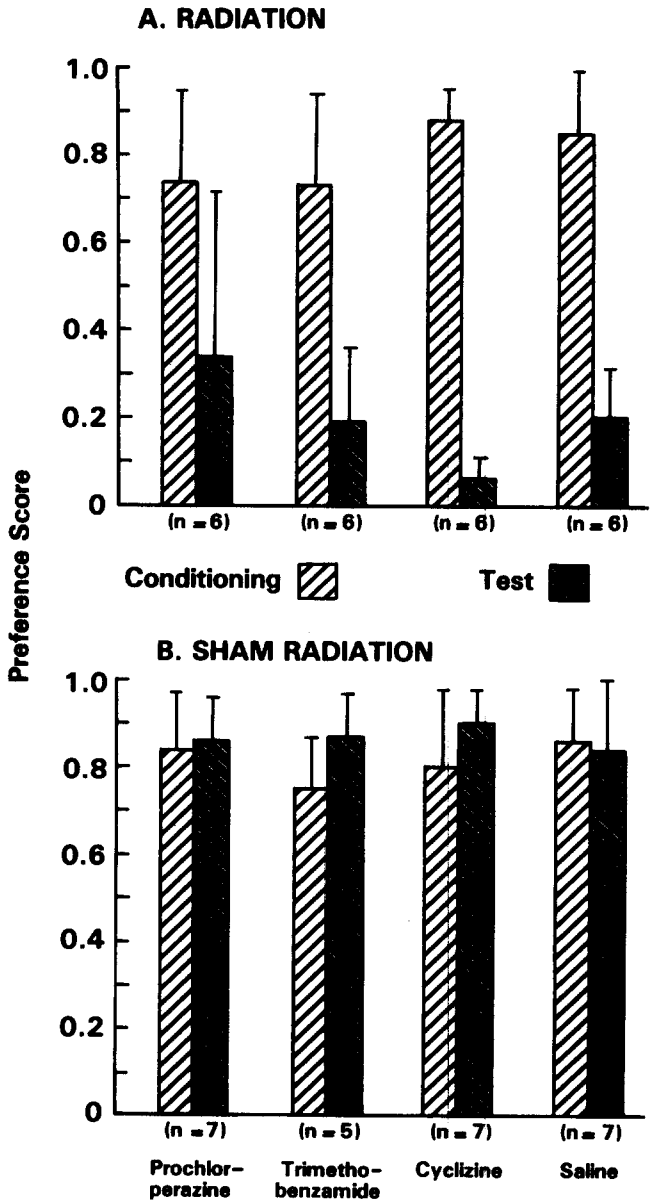

FIG. 1. Effects of antiemetic pretreatment on acquisition of a radiation-induced conditioned taste aversion. Sucrose preference scores of animals treated with antiemetics or saline prior to exposure to ionizing radiation (A) or sham irradiation (B) procedures. Variance bars indicate the standard deviation. Initial sample size was 7 rats per group.

radiation-induced CTA. And third, the differences may result from the fact that the present experiment looked at acquisition, whereas Coil *et al.* [7] looked at the effects of antiemetic treatment on the recall of a previously acquired CTA. The remaining experiments of this series were designed to test these three hypotheses.

EXPERIMENT 2

Unlike LiCl, which seems to affect the organism within a restricted period of time following an intraperitoneal injection, the time course of the radiation-induced changes which lead to CTA learning seem to be more extended over time [1,18]. As a result, it may be that the single antiemetic injection was not effective over a long enough period of time to block the effects of irradiation. The present experiment was designed to evaluate the hypothesis that the failure to obtain an attenuation of a radiation-induced CTA by antiemetic pretreatment in the first experiment may have resulted from a too limited time course of action of the antiemetic relative to the time course of action of the radiation.

Methods

The procedures were identical to those of the preceding experiment with the following exceptions. Thirty-two rats were divided into 4 equal groups; three of the groups receiving an antiemetic treatment while the fourth group received injections of isotonic saline. All of the rats were exposed to radiation. Fifteen min prior to irradiation, all rats were given the appropriate injection. Three hr after the first injection, all were given a second antiemetic or saline injection, as appropriate.

Results and Discussion

The results are summarized in Fig. 2. A two-way analysis of variance using arcsin transformed preference scores showed that there was a significant reduction in test day sucrose preference compared to conditioning day preference, $F(1,24)=203.52$, $p<0.001$, and that this decrease did not differ significantly across the groups given the antiemetic injections as opposed to a saline injection, $F(3,24)=0.53$, $p>0.10$. These results indicate that repeated doses of the various antiemetics did not attenuate the acquisition of a radiation-induced CTA and that there were no differences between the antiemetic and saline injections. Therefore, it seems unlikely that a radiation-induced physiological change related to emesis which can be attenuated by the specific antiemetics tested can function as the proximal unconditioned stimulus leading to the acquisition of a radiation-induced CTA.

EXPERIMENT 3

This experiment was designed to examine whether the failure of antiemetic pretreatment to attenuate the acquisition of a radiation-induced CTA was unique to the use of the radiation unconditioned stimulus or whether a similar result would also be observed with the acquisition of an LiCl-induced CTA.

Methods

The subjects were 30 rats divided into 3 equal groups. The taste aversion was produced using the preference test procedure and a single injection of LiCl (3 mEq/kg). Fifteen min prior to LiCl injection, one group of rats was given an injection of prochlorperazine (0.1 mg/kg, IP) and a second group of rats was given an equivalent injection of isotonic saline. The third group of rats was given an injection of prochlorperazine but no LiCl to control for potential aversive effects resulting from the prochlorperazine injection.

Results and Discussion

The results are summarized in Fig. 3. A two-way analysis

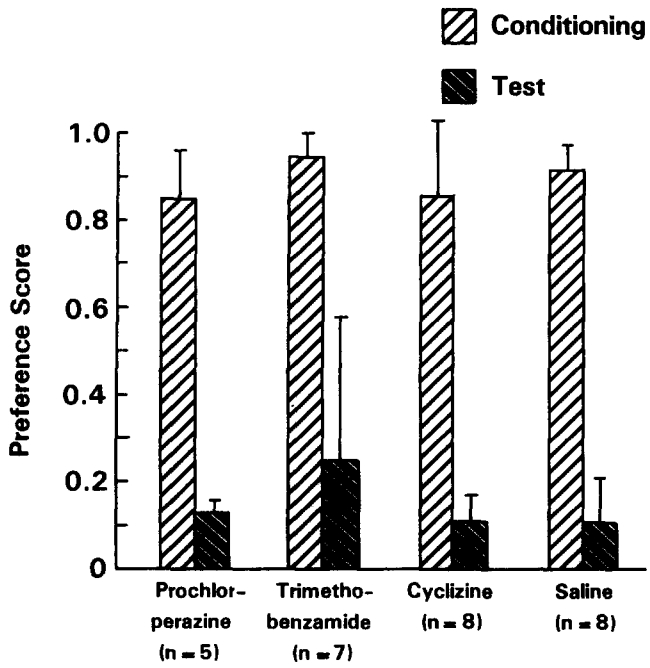

FIG. 2. Sucrose preference scores of animals given an initial antiemetic or saline injection prior to irradiation and a second treatment 3 hr after the initial injection. Variance bars indicate the standard deviation. Initial sample size was 8 rats per group.

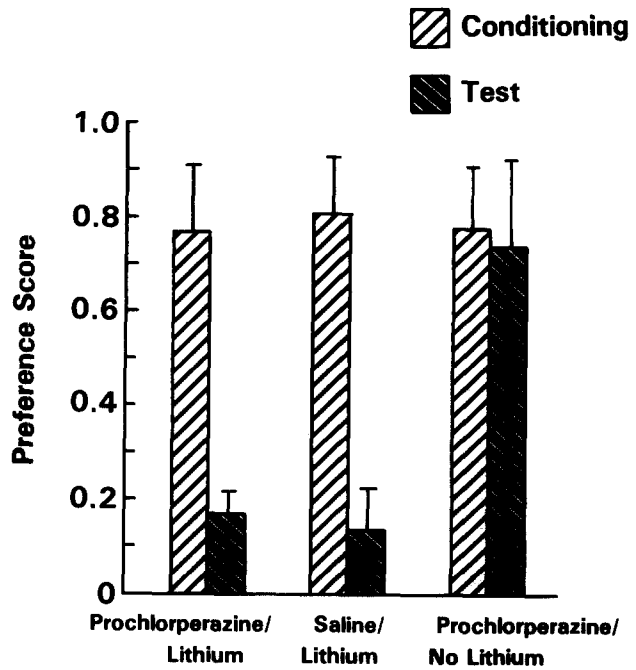

FIG. 3. Effects of prochlorperazine on the acquisition of a LiCl-induced CTA. Sucrose preference scores of animals pretreated with prochlorperazine prior to injection of LiCl. Variance bars indicate the standard deviation. Sample size was 10 rats per group.

of variance, using arcsin transformed data, indicated that the comparisons between LiCl and no LiCl groups, $F(2,27)=20.56$, $p<0.001$, and between conditioning and test days, $F(1,27)=117.49$, $p<0.001$, were both highly significant, as was the drug × day interaction, $F(2,27)=26.31$, $p<0.001$. To determine which of the comparisons were producing the significant differences, a series of orthogonal comparisons were run using the Scheffe correction [12] to control familywise Type I error. These comparisons indicated that there were no significant differences in test day sucrose preference between the prochlorperazine- and saline-treated animals, $F(1,27)=0.874$, $p>0.10$. Comparison of the test day preference of the LiCl-injected groups with the group not given LiCl indicated that this latter group of animals showed a significantly greater sucrose preference than the LiCl injected animals, $F(1,27)=97.64$, $p<0.01$. These results indicate that LiCl is similar to radiation as an unconditioned stimulus in that pretreatment with this dose of prochlorperazine is not effective in attenuating the acquisition of a CTA produced by either unconditioned stimulus.

EXPERIMENT 4

The results of the preceding series of experiments are not consistent with the hypothesis derived from the experiments of Coil *et al.* [7] that an antiemetic sensitive physiological change functions as the proximate unconditioned stimulus leading to the acquisition of a CTA. However, since their experiment looked at the effects of antiemetics on the recall of a previously acquired CTA, it might still be argued that an antiemetic sensitive physiological change plays a role in the recall of a CTA even though it might not be involved in the initial acquisition of the aversion. The present experiment was designed to examine this possibility by looking at the effects of antiemetics on the recall of previously acquired LiCl- and radiation-induced taste aversions using procedures similar to those utilized by Coil *et al.* [7] using a single bottle test.

Methods

The subjects were 140 rats, half receiving an LiCl injection on the conditioning day and half receiving irradiation. Within each condition the rats were divided into 7 equal groups and given test day injections of saline, prochlorperazine (0.05, 0.1, 0.2 mg/kg, IP) or trimethobenzamide (2.5, 5.0, 10.0 mg/kg, IP). Within the group exposed to radiation, 1 rat receiving 2.5 mg/kg and 2 receiving 5.0 mg/kg trimethobenzamide were eliminated from the experiment because they did not show sucrose intake on the conditioning day. The taste aversion training procedures were the single-bottle test procedures detailed in the general methods.

Results and Discussion

The results are summarized in Fig. 4, which presents absolute sucrose intake, rather than a preference score, because of the use of the single-bottle test. The data for the irradiated animals and those injected with LiCl were analyzed separately using two-way analyses of variance. For the irradiated animals, comparisons of the conditioning/test day intakes were highly significant, $F(1,60)=331.06$, $p<0.001$, indicating that irradiation had produced a CTA. Given the significant main effect for drugs, $F(6,60)=7.40$, $p<0.001$, and the significant day × drug interaction, $F(6,60)=3.92$, $p<0.01$, indicating that the different injections had different effects on the CTA response to irradiation, comparison of the individual test day intakes of the drug-

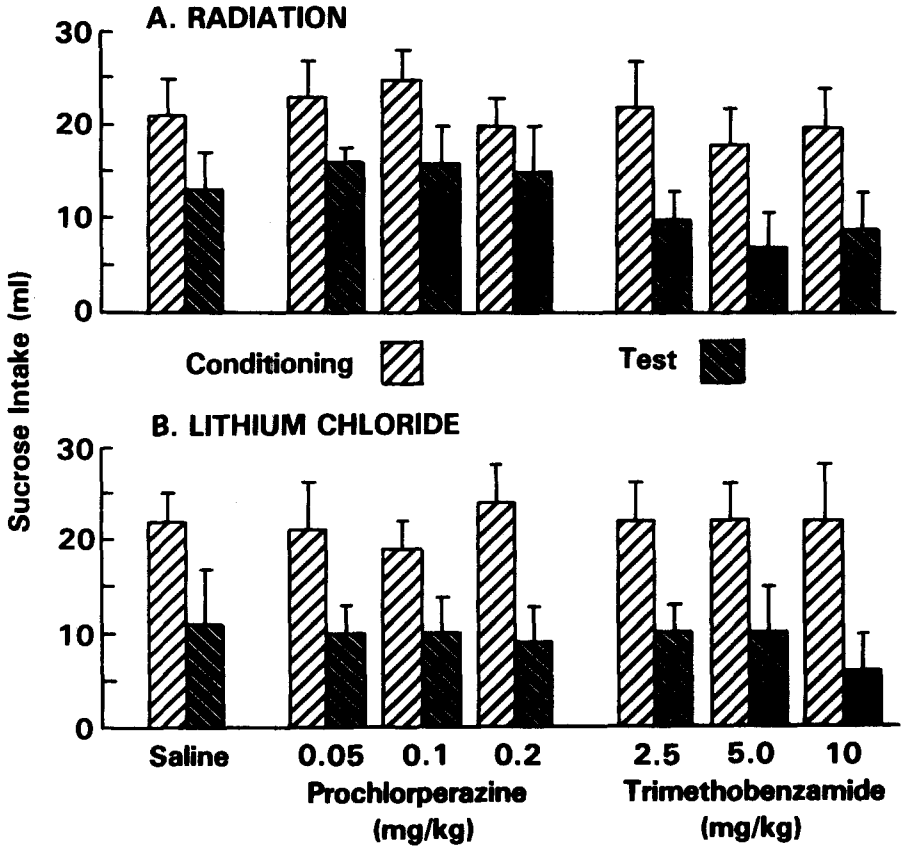

FIG. 4. Effects of antiemetic treatment on the recall of a previously acquired radiation- and LiCl-induced CTA. Sucrose intake of animals given antiemetic injection on the test day following exposure to ionizing radiation (A) or LiCl (B) on the conditioning day. Variance bars indicate the standard deviation. Initial sample size was 10 rats per group.

injected rats with the intake of the saline-injected rats was run using the Dunnett Test [12] for comparisons between a control and several experimental groups. This analysis indicated that the only drug-injected group of animals that showed an intake significantly different from that of the saline-injected controls was the one receiving 5.0 mg/kg trimethobenzamide, and that this intake was less than that of the controls. None of the other comparisons were significant. These results, therefore, indicate that the specific antiemetic treatment did not attenuate the recall of a previously acquired CTA following exposure to radiation.

For the animals injected with LiCl, the only component of the analysis of variance that was significant was the main effect for day (conditioning/test), $F(1,63)=364.73$, $p<0.001$, indicating that the test day sucrose intake was significantly less than the conditioning day intake. Neither the main effect for drug, $F(6,63)=0.88$, $p>0.10$, nor the day × drug interaction, $F(6,63)=2.00$, $p>0.05$, was significant, indicating that there were no differences between the various antiemetic injections and the saline control. These data, therefore, provide no support for the hypothesis that these antiemetics can attenuate an LiCl-induced CTA.

GENERAL DISCUSSION

These experiments were designed to test two hypotheses: first that an antiemetic sensitive physiological change possibly related to emesis serves as the immediate unconditioned stimulus leading to the acquisition of a radiation-induced CTA; and second, that this unconditioned stimulus is common to both radiation and LiCl. The results, however, provided no clear support for either hypothesis.

Since lesions of the area postrema, the chemoreceptive trigger zone for emesis [5], disrupt the acquisition of both radiation- and LiCl-induced taste aversions [16,17], it would seem to be a reasonable inference that some treatment-induced physiological change related to emesis serves to mediate the acquisition of the CTA. If we can assume that the various antiemetics used in these experiments are effective, as would be suggested by the findings of Wyant [20] showing the attenuation of emesis in dogs, and if nausea and/or emesis are involved in mediating the behavior, then these drugs should have been effective in attenuating a CTA following irradiation or injection of LiCl. Therefore, the failure to obtain an effect of antiemetic treatment on the acquisition of the CTA might suggest that a physiological change possibly related to emesis does not play a role in CTA learning produced by irradiation or by LiCl. Alternatively, it may be that the antiemetic drugs in the doses used here are simply not effective in preventing nausea and/or emesis. The available data do not permit a comparative evaluation of these two alternative hypotheses.

Although it might be argued that antiemetic doses larger than the ones used here might have been effective in disrupt-

ing CTA acquisition, it should be noted that the tested doses have been reported to be clinically effective doses [20] and the most effective in attenuating a previously acquired LiCl-induced CTA [7]. Also, Levy *et al.* [13], working with much larger doses of trimethobenzamide failed to find an effect on the acquisition of a radiation-induced CTA. Similar contradictory results have been reported by Gadusek and Kalat [8] and by Goudie *et al.* [11] who found no effect of higher doses of scopolamine on the recall of a previously acquired LiCl-induced CTA. Since Coil *et al.* [7] reported that antiemetic doses greater than those used here were ineffective in attenuating the recall of a previously acquired LiCl-induced CTA, there is no reason to expect that the use of larger antiemetic doses in the present experiment would have been any more effective in attenuating the radiation- or LiCl-induced taste aversions.

Alternatively, it might be argued that the failure to observe an antiemetic-induced attenuation of CTA learning resulted from the fact that the unconditioned stimuli produced strong aversions which masked the effects of the drugs. This interpretation would not be consistent, however, with the results of Experiment 4 in which the unconditioned stimuli did not produce extreme taste aversions, but in which there was still no attenuation of the CTA by the antiemetic treatment. Also, in a recent report, Goudie *et al.* [11] looked at the effect of scopolamine on weak taste aversions produced by morphine and LiCl. Scopolamine was not effective in producing an attenuation of the taste aversion produced by either unconditioned stimulus. It therefore seems unlikely that the failure of the present experiments to find an effect of antiemetics on CTA acquisition could have been dependent upon the initial strength of the aversion.

Given the failure to obtain an effect of antiemetic pretreatment on the acquisition of either a radiation- or LiCl-induced CTA, it is not surprising that the antiemetics had no effect on the recall of a previously acquired aversion. Logically, it is difficult to understand how a conditioned nausea can be a factor in the recall of a behavior if an unconditioned nausea is not involved, at least at some level, in the original acquisition of the behavior. It is, however, not clear why the present experiment failed to replicate the findings of the original experiments. Although the procedures used in Experiment 4 were similar to those of Coil *et al.* [7], there were some differences. First, we used an intraperitoneal injection of LiCl, as opposed to intragastric administration. This difference does not appear to be critical because other research has indicated that the route of administration is not a critical factor in LiCl-induced CTA learning [14]. We also ran an additional set of rats using intragastric administration of LiCl and found no differences in the lack of effectiveness of this antiemetic treatment. A second difference is that we measured actual intake as opposed to using drinkometers. It may be that the drinkometer measurment was more sensitive to extraneous factors which can influence responding, such as a possible state-dependent learning effect resulting from the use of different drug states on the conditioning day than on the testing day [15], than the more direct measure of intake.

Overall, the results of the present experiment are consistent with previous research in showing that conventional antiemetics have no effect on the acquisition or recall of either radiation- or LiCl-induced taste aversions [8, 11, 12]. These results also further indicate that there are not differential effects of these antiemetic treatments on the acquisition of a CTA produced by either unconditioned stimulus. Therefore, the present results would be consistent with the hypothesis that there is a common mechanism underlying the acquisition of taste aversions produced by exposure to ionizing radiation and by injection of LiCl.

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