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Antiemetic Drugs Attenuate Food Aversions in Sheep

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ABSTRACT: Ruminants learn to avoid many foods that contain toxins by associating the flavor of the foods with aversive postingestive feedback. We hypothesized the emetic system is a cause of aversive feedback, and three experiments were conducted to determine whether antiemetic drugs (diphenhydramine, metoclopramide, dexamethasone) would attenuate food aversions caused by the toxicant lithium chloride (LiCl). Lambs were assigned to one of four treatments: antiemetics plus LiCl (A+L), antiemetics alone (A), LiCl alone (L), or neither antiemetics nor LiCl (C). The LiCl was administered immediately after sheep ate oats, wheat, and milo in Exp. 1, 2, and 3, respectively. The antiemetics were given 1 h before and at the time LiCl was administered to sheep. Lambs that received antiemetics (A and A+L) consistently ate more grain than lambs that did not receive the drugs (C and L) (Exp. 1, P < .08; Exp. 2, P < .05; Exp. 3, P < .08), and there was no interaction between antiemetics and LiCl. Thus, the results of all three experiments were consistent with the hypothesis that antiemetic drugs attenuate food aversions caused by the toxicant LiCl because sheep receiving antiemetic drugs (Group A+L) ate more grain than sheep not receiving the drugs (Group L). In addition, we suggest aversive postingestive feedback limited intake of grain because sheep receiving antiemetic drugs (Group A) ate somewhat more grain than sheep not receiving the drugs (Group C).

Key Words: Intake, Toxins, Emetics, Learning, Sheep, Malaise


Introduction

Ruminants have physiological mechanisms to counter toxins (McArthur et al., 1991), and if the capacity of these detoxification systems is exceeded, animals become ill and may die. This does not occur often because through behavioral mechanisms animals reduce intake of foods containing toxins (Provenza, 1994). Our objective was to better understand the physiological basis for behavioral responses of ruminants to the presence of toxins in food. We hypothesized ruminants decrease intake of foods containing toxins (behavioral response) as a result of increasing levels of internal malaise (physiological cause), which could be caused by various mechanisms including stimulation of the emetic system (Grant, 1987). Based on what is known about nonruminants (Seynaeve et al., 1991; Mitchelson, 1992), we supposed the emetic system is a likely candidate for the cause of malaise in ruminants. We further hypothesized if stimulation of the emetic system causes food aversions, antiemetic drugs should attenuate malaise and increase intake of food.

Materials and Methods

In all experiments, sheep were offered a specific food for 15 min, and immediately after its ingestion, they were gavaged with the toxicant LiCl. This procedure reduces intake of that specific food by sheep on subsequent days, and the result is referred to as a conditioned food aversion (Provenza et al., 1992). When LiCl is administered directly into the rumen, the effects of LiCl on the acquisition of a food aversion occur primarily within 60 min (Provenza et al., 1993). In essence, LiCl was used to induce a malaise that may be similar to the malaise caused by excessive ingestion of many compounds (Provenza, 1994).
Antiemetic drugs were given 1 h before and at the time LiCl was given to sheep to determine whether antiemetics counteracted the direct effects of the toxicant and thus attenuated development of a food aversion. Three drugs were used: diphenhydramine hydrochloride, metoclopramide monohydrochloride, and crystalline dexamethasone. These drugs are frequently used in mixture to attenuate nausea-induced food aversions and emesis in humans undergoing chemotherapy, because their combined effect exceeds that of any one antiemetic (Harris and Cantwell, 1986; Italian Group for Antiemetic Research, 1992). Diphenhydramine is an antihistamine, and antihistamines antagonize in varying degrees most of the pharmacological effects of histamine at the H1 receptor site (Olin, 1992). Metoclopramide is a procainamide derivative with peripheral and central dopamine antagonist activity (Plumb, 1991; Olin, 1992); it also blocks activity at serotonin (5-HT3) receptors (Miner et al., 1987). Dexamethasone is a steroid antiemetic (Olin, 1992). Neurochemical studies of the area postrema and the chemoreceptor trigger zone in the emetic system have demonstrated the presence of receptors or binding sites for histamine, dopamine, serotonin, norepinephrine, cholecystokinin, enkephalins, and acetylcholine (Seynaeve et al., 1991; Mitchelson, 1992).

Twenty-four orphaned lambs (Finn-Targhee-Columbia-Polypaycrossbreds) were reared at the Green Canyon Ecology Center in Logan, UT, until they were approximately 3 mo of age. On June 29, 1992, lambs were moved from a large pen into individual pens, and fed as follows from June 29 until July 14: rolled barley from 0800 until 0815 and alfalfa pellets in ad libitum amounts from 0830 until 1700. Lambs were without food from 1700 until 0800 the next day. Lambs had access to trace mineral blocks and water ad libitum. The same lambs were used in all of the following experiments.

**Experiment 1**

Lambs (21 kg BW) were randomly assigned to one of four treatments: 1) antiemetics plus LiCl (A+L), 2) antiemetics alone (A), 3) LiCl alone (L), or 4) neither antiemetics nor LiCl (C). Doses for the antiemetics were diphenhydramine (1.19 mg/kg BW), metoclopramide (.95 mg/kg BW), and dexamethasone (.19 mg/kg BW). Dosages of antiemetics were at the lower range commonly recommended for humans (Harris and Cantwell, 1986; M. Boardman, personal communication), because their possible beneficial or detrimental effects on lambs were unknown. The dose of LiCl (200 mg/kg BW) used causes sheep to acquire strong aversions to novel foods, but has never produced overt signs of toxicity in sheep (Provenza et al., 1993), even at dosages of 300 to 500 mg/kg BW (duToit et al., 1991).

On July 14, all lambs were offered 600 g of oat grain, a food lambs had not previously eaten (i.e., a novel food), from 0800 until 0815. On July 15, each lamb in A+L and A received an antiemetic tablet with a balling gun at approximately 0700; the balling gun was placed in the mouths of lambs in L and C. One hour later, lambs were offered 600 g of oats for 15 min; average intake was 155 g. Immediately after eating oats, each lamb in A+L received by gavage 100 mL of a solution containing a dissolved antiemetic pill and 200 mg/kg BW of LiCl; each lamb in A and L received the same solution minus either LiCl or antiemetics, respectively. Lambs in C received 100 mL of water. Seventy minutes later, lambs were fed alfalfa pellets. The effects of antiemetics and LiCl were tested for the next 5 d, July 16 to 20, by offering lambs 700 g of oats from 0800 until 0815. The amount of food ingested was determined as the difference between what was offered and what was left.

The analysis of variance in this and the following experiments was a factorial design with antiemetics and LiCl as the main effects. When data were collected on the same animals for more than 1 d, a repeated measures analysis was used (Winer, 1971). Six lambs were nested within each treatment. The intake of oats on the day treatments were imposed was used as a covariate in the analysis. In this and all other experiments we considered $P < .10$ to be significant.

**Experiment 2**

The first experiment was modified in three ways to provide a somewhat different test of the hypothesis that antiemetics attenuate food aversions caused by LiCl. First, a food was used that lambs had previously ingested because animals acquire less aversion to a familiar than to a novel food (Revusky and Bedarf, 1967; Burritt and Provenza, 1989, 1991). Second, a lower dose of LiCl was used (150 mg/kg BW). Finally, the dose of the antiemetics was increased (diphenhydramine, 2.19 mg/kg BW; metoclopramide, 1.75 mg/kg BW; dexamethasone, .35 mg/kg BW; lambs averaged 29 kg). Lambs were assigned to treatments, such that lambs that received LiCl in Exp. 1 were equally distributed in all treatments in Exp. 2.

From July 24 to 28, lambs were offered 600 g of wheat grain from 0800 until 0815. On July 29 at 0700, each lamb in A+L and A received by gavage the antiemetics in 200 mL of water; lambs in L and C received 200 mL of water by gavage. One hour later, lambs were fed wheat for 15 min; intake averaged 518 g. After eating the wheat, each lamb in A+L received by gavage 200 mL of a solution containing the antiemetics and LiCl; each lamb in A and L received the same solution minus either LiCl or antiemetics, respectively; lambs in C received 200 mL of water. Ninety minutes later, all lambs were given alfalfa pellets; uneaten pellets were removed at 1700. The effects of the antiemetics and LiCl on the food aversion were determined by measuring intake of wheat from 0800 until 0815 for 5 d.
Experiment 3

Experiment 3 was conducted to assess the effects of the antiemetics on appetite. If the antiemetic drugs caused a general increase in appetite, the effect should be apparent not only in the intake of the test food (grain), but in the intake of the basal diet (alfalfa pellets) as well, because it was also eaten during the time that the antiemetics were expected to have their effects.

From August 26 through September 7, lambs (37 kg BW) were offered 800 g of milo from 0800 until 0815; the lambs had ingested milo several times during the summer. On September 8 at 0700, lambs received either antiemetics (A+L and A) or water (L and C) as described for Exp. 2. One hour later, lambs were fed milo for 15 min; average intake was 678 g. After eating milo, lambs received antiemetic drugs and LiCl as described for Exp. 2; lambs that received LiCl in Exp. 1 and 2 were distributed among treatments. Ninety minutes later, lambs were given alfalfa pellets until 1700. Intake of alfalfa pellets and milo was measured on the day the treatments were imposed and on the following day.

Results

Experiment 1

There was an interaction between antiemetic drugs and day (P = .079; Figure 1). Lambs that received the antiemetic drugs ate more oats than lambs that did not receive the drugs (A+L vs L and A vs C, respectively), particularly on d 3 to 5 of testing. There was also an interaction between LiCl and day (P = .038; Figure 1). Lambs that received LiCl (A+L and L) gradually increased intake of oats during d 1 to 4 of testing and then decreased intake on d 5, whereas lambs that did not receive LiCl (A and C) maintained a considerably higher level of intake throughout testing. Lambs in treatment A generally increased intake from d 1 to 5, whereas intake of oats by lambs in treatment C did not change during testing. There was no interaction between antiemetics, LiCl, and day (P > .10).

Experiment 2

Both the LiCl and the antiemetics affected the intake of wheat on the 1st d of testing (Figure 2). Lambs that received LiCl (A+L and L) consumed less wheat than lambs that did not receive LiCl (A and C) (230 vs 439 g; P = .009), and lambs that received antiemetics (A+L and A) ingested more wheat than lambs that did not receive antiemetics (L and C) (413 vs 256 g; P = .034). There was no interaction between LiCl and antiemetics (P = .194), nor did day and antiemetics interact (P = .256). Lambs that received LiCl increased intake of wheat on each day during testing (interaction P = .046), a result that reflected the gradual attenuation of the aversion as they ingested wheat and received no LiCl.

![Figure 1](https://example.com/figure1.png)

**Figure 1.** Average intake [SEM = 49] of oat grain during 5 d of testing by lambs that received antiemetic drugs plus LiCl (A+L), LiCl alone (L), antiemetic drugs alone (A), or neither antiemetics nor LiCl (C). The covariate, which was the intake of oat on the day the treatments were imposed, was not significant (P > .10).

![Figure 2](https://example.com/figure2.png)

**Figure 2.** Average intake [SEM = 72] of wheat grain in Exp. 2 by lambs in treatments A+L [antiemetic drugs plus LiCl], L [LiCl only], A [antiemetic drugs only], and C [neither antiemetic drugs nor LiCl]. The means were adjusted for a covariate [P = .040], which was the intake of wheat on the day before the treatments were imposed.
Figure 3. Average intake of milo (SEM = 48) in Exp. 3 by lambs in treatments A+L [antiemetic drugs plus LiCl], L [LiCl only], A [antiemetic drugs only], and C [neither antiemetic drugs nor LiCl]. The means were adjusted for a covariate (P < .001), which was the intake of milo on the day the treatments were imposed.

**Discussion**

**Effects of Antiemetic Drugs on Lithium Chloride-Induced Food Aversions**

Antiemetic drugs attenuated LiCl-induced food aversions in sheep, which is consistent with the hypothesis that the emetic system caused malaise and reduced food intake in sheep. The effects varied with doses of antiemetics and LiCl and with familiarity of the food. A high dose of LiCl diminished the effects of low doses of antiemetics on intake of a novel food (oats in Exp. 1). The effects of the antiemetics on intake were more pronounced when a lower dose of LiCl and higher doses of antiemetics were used with a food lambs had eaten for 5 d (wheat in Exp. 2) and with a food lambs had eaten throughout the summer (milo in Exp. 3).

The results of Aldrich et al. (1993) are consistent with the hypothesis that antiemetic drugs attenuate toxin-induced food aversions. They showed that when sheep ate tall fescue containing the endophytic fungus *Acremonium coenophialum*, which produces ergopeptide alkaloids (primarily ergovaline), intake was lower than for sheep that ate endophyte-free fescue. Intake of endophyte-infected fescue increased by 24% when sheep received doses of metoclopramide (20 mg·kg·BW⁻¹·d⁻¹ by ruminal cannulas), whereas intake of endophyte-free fescue by sheep was not affected by metoclopramide. Consequently, their findings are consistent with other evidence that metoclopramide is an effective antiemetic for ergot alkaloids, and that antiemetic drugs like metoclopramide increase intake of foods that cause aversive postingestive feedback because they attenuate food aversions (Mitchelson, 1992).

The emetic system has been studied extensively in nonruminants. This system, which is highly sensitive to low doses of most toxins (Davis et al., 1986), involves complex interactions between adjacent areas in the brain stem (Seynaeve et al., 1991; Mitchelson, 1992). It can be stimulated by toxins in the cardiovascular system and cerebrospinal fluid (Borison and Wang, 1953), and through visceral afferents (i.e., neurons that carry sensory information to the brain), primarily vagal afferents, and to a lesser extent, splanchnic afferents (Borison, 1986; Davis et al., 1986; Grahame-Smith, 1986; Kosten and Contreras, 1989). Efferent impulses (i.e., neurons that provide motor input to innervated structures) from the emetic system to effector organs travel through the hypoglossal, glossopharyngeal, and trigeminal nerves (innervating the buccal cavity and pharynx), through the vagal nerve (innervating the pharynx, and respiratory and gastrointestinal tracts), from the respiratory center to the phrenic and intercostal nerves, and through some sympathetic efferents in the gastrointestinal tract (Seynaeve et al., 1991). Thus, upon ingesting a food containing a toxin, afferent impulses to the central nervous system cause malaise, which in turn causes the animal to decrease intake of the food, whereas efferent impulses from the central nervous system to the gastrointestinal tract cause a decrease in gut motility and a decrease in the rate of absorption of the toxin (Stricker and Verbalis, 1990), both of which can attenuate impending toxicosis.

**Effects of Antiemetic Drugs on Intake of Grain**

A major portion of the effect of the antiemetics occurred because they attenuated the LiCl-induced food aversion in Group A+L compared with Group L. For instance, the difference in intake of grain between
lams in Groups A+L and L was 248 g in Exp. 2 and 118 g in Exp. 3, whereas the difference in intake between lambs in Groups A and C was only 65 g in Exp. 2 and 69 g in Exp. 3 (Figures 2 and 3). Accordingly, we anticipated, but did not find, an interaction between LiCl and antiemetics, which should have occurred because lambs in Groups A+L, A, and C ate similar amounts of grain, and they ate more grain than lambs in Group L. The interaction was diminished, and the main effect of antiemetic was significant, because lambs in A consistently ate somewhat more grain than lambs in C.

There are at least two explanations for the greater intake of grain by lambs in Group A than that by lambs in Group C. First, dexamethasone and(or) metoclopramide may stimulate appetite that in turn could have caused lambs in Group A to eat more grain than lambs in Group C. Lambs injected subcutaneously with dexamethasone trimethylacetate began to eat more pellets than did control lambs 7 d after the drug was administered, and the effect persisted for 7 d (Adams and Sanders, 1992). In the same experiment, lambs that received dexamethasone sodium phosphate increased intake within 24 h. Moreover, metoclopramide stimulates motility of the upper gastrointestinal tract in humans (Olin, 1992) and could conceivably cause an increase in intake in ruminants by increasing rate of passage (Aldrich et al., 1993). Alternatively, malaise from overingesting grain may have caused lambs in Group C to ingest less wheat than lambs in Group A. Sheep, beef cattle, and dairy cattle decrease intake of diets high in grain (Britton and Stock, 1987; Grovum, 1988; Ortega-Reyes et al., 1992), perhaps because an excess of organic acids or volatile fatty acids like propionate causes malaise (Provenza, 1994). According to this hypothesis, the antiemetic drugs caused a decrease in internal malaise and a resultant increase in intake of grain by lambs in Group A.

The data from this and other studies are consistent with the latter hypothesis. If the increase in intake of grain occurred because the antiemetics stimulated appetite, lambs in Group A should have eaten more grain on the 1st d of testing than on the day the treatments were imposed. In Exp. 2, lambs in both Groups A and C ate less (P = .054) wheat on the 1st d of testing (465 g) than on the day the treatments were imposed (562 g), and lambs in Group C ate even less grain than lambs in Group A (Figure 2). Nor do the data from Exp. 3 support the hypothesis that an increase in appetite was the reason for greater intake of grain by lambs in Group A than by those in Group C. During testing, lambs in Group A ate no more of the basal ration (alfalfa pellets) than lambs in Group C, but lambs in A ate more grain than lambs in C (Figure 3). Likewise, the antiemetic metoclopramide caused an increase in intake only when sheep ate endophyte-infected fescue (Aldrich et al., 1993). Thus, we suggest the lack of an interaction between LiCl and antiemetics was caused by the small, but meaningful, decrease in intake by lambs in Group C compared with those in Group A, perhaps as a result of grain-induced malaise.

Finally, the results raise questions concerning how malaise, antiemetic drugs, and LiCl may have interacted to affect intake of oats by lambs in Exp. 1 (Figure 1). Lambs in C ate only an average of 349 g of oats daily during testing, which is unusual because lambs normally increase intake of novel grains from less than 50 to more than 600 g during a 5-d period, and they can eat from 600 to 800 g of grain (e.g., Figure 3) in the time allowed for testing (Provenza et al., unpublished data). We hypothesize that lambs in C experienced malaise as a result of over-ingesting oats on the 1st d oats were offered, which caused them to limit their intake of oats during testing. Lambs in A ate more oats than lambs in C because the antiemetics attenuated the malaise caused by the oats. Lambs given LiCl (A+L and L) decreased intake of oats on d 5, after eating a moderate amount of oats on d 4, for the same reason. Malaise from ingesting grain on d 4, in combination with their previous experience with LiCl on the day treatments were imposed, caused them to limit their intake of oats on d 5. Lambs in A+L were affected less during testing than lambs in L because of the effects of the antiemetic drugs on the day treatments were imposed.

Implications

The results obtained are consistent with the hypothesis that stimulation of the emetic system by the toxicant LiCl and by excess ingestion of grain caused internal malaise because sheep receiving antiemetic drugs ate more grain than sheep not receiving the drugs. Nonetheless, it would be unwise to recommend the use of antiemetic drugs to increase intake of foods that contain toxins or of grains because the purpose of the emetic system is to prevent overingestion of substances that may potentially harm animals. Conversely, some therapeutic drugs evidently cause food aversions and administration of antiemetic drugs in combination with such drugs could attenuate drug-induced food aversions. Further research is required to determine the feasibility of such a practice.

Literature Cited


