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Effects of Vomitoxin (Deoxynivalenol) on Conditioned Saccharin Aversion and Food Consumption in Adult Rats[1]

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CLARK, D. E., P. J. WELLMAN, R. B. HARVEY AND M. S. LERMA. *Effects of vomitoxin (deoxynivalenol) on conditioned saccharin aversion and food consumption in adult rats.* PHARMACOL BIOCHEM BEHAV 27(2) 247–252, 1987.—Vomitoxin is a trichothecene mycotoxin that induces feed refusal. Experiment I evaluated the potential aversive action of vomitoxin in a conditioned taste aversion paradigm. Adult male rats were fed either a control chow diet or a diet adulterated with 640 ppm lithium chloride (positive control) or with 2, 4 or 8 ppm vomitoxin and given access to a 0.1% saccharin solution and tap water during three training days. The rats were then shifted to a plain chow diet during 5 extinction days. Vomitoxin (8 ppm) and the positive control diet induced marked taste aversion commencing on the first day of exposure. Rats fed the 4 and 8 ppm vomitoxin diets ate less food only on the first day of contaminated diet exposure. Experiment II evaluated the potential action of vomitoxin on food palatability. Adult male rats were fed a powdered commercial chow for 5 days and then offered, in a preference test, a choice of chow and either: the same chow or chow adulterated with either 0.25, 0.50, 1.0, 2.0, 4.0 or 8.0 ppm vomitoxin. Relative to the total food intakes and the choice ratios (control chow consumed/total chow consumed) of the chow-chow groups, adulteration with 8 ppm vomitoxin resulted in a significant reduction in overall food intake, but not in food choice ratio and this effect of vomitoxin on feed consumption was observed only on day 1 of exposure. Vomitoxin, at 4 and 8 ppm, does not alter food palatability but does induce conditioned saccharin aversion.

Conditioned taste aversion Feed refusal Taste preference Behavioral toxicology Vomitoxin Deoxynivalenol Trichothecene

VOMITOXIN (3,7,15-trihydroxy-12,13-epoxytrichothec-9-ene-8-one), commonly called deoxynivalenol, is a trichothecene mycotoxin produced primarily by the fungus *Fusarium graminearum* [15–17]. Vomitoxin has been found as a natural contaminant of grains, particularly corn and wheat, grown in many parts of the world [10–12, 22].

Vomitoxin produces emesis in swine, dogs, and ducklings [2,18] and feed refusal in swine and rats [2, 4, 23]. The agricultural and economic significance of vomitoxin stems from reduced feed consumption or refusal of contaminated feed by livestock with concomittant loss of body weight or reduced weight gain [9,10]. Moreover, vomitoxin contamination is relevant to the human condition. Consumption of *Fusarium*-infected rice by humans results in nausea, vomiting and drowsiness [19]. Similarly, symptoms of CNS involvement, including headaches, vertigo, chills, and visual disturbance, in addition to gastrointestinal effects, were reported in Siberians who consumed molded grain [16,17].

Refusal of feed may occur because the vomitoxin contamination induces aversive post-ingestional consequences or because the contaminant renders the feed unpalatable. The present study examined the etiology of the vomitoxin feed-refusal syndrome in a rat model by assessing the capacity of vomitoxin to induce conditioned taste aversion (Experiment I) and potential changes in palatability associated with vomitoxin contamination (Experiment II).

[1]Mention of a trade name, proprietary product, or specific equipment does not constitute a guarantee or warranty by the U.S. Department of Agriculture and does not imply its approval to the exclusion of other products that may be suitable.

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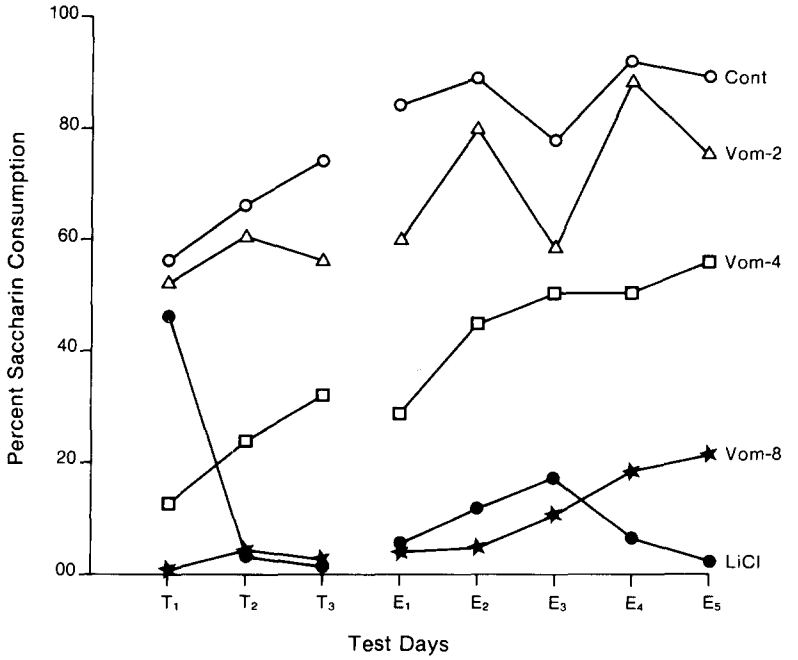

FIG. 1. Experiment I: Mean group saccharin consumption ratios (ml 0.1% saccharin consumed/total ml fluid consumed) during training (T) days 1–3 and extinction (E) days 1–5 for rats fed either a chow diet or a diet adulterated with 640 ppm lithium (as LiCl) or 2, 4, or 8 ppm vomitoxin during training (T) days 1–3.

METHOD

Animals

The animals were 89 (Experiment I=40, Experiment II=49), adult male Sprague-Dawley outbred albino rats (Timco, Inc., Houston, TX), weighing 171–216 g at the beginning of each experiment. The rats were individually housed in standard plastic cages (Lab Products, Bryan, TX) in a temperature-controlled room (23–25°C) under a 12/12 hr light/dark illumination schedule (lights on at 0800 hr). Food and water were available as described in the schedules below.

Diet Preparation

The chow diet provided the rats was prepared by mixing ground corn (either vomitoxin-free or naturally contaminated with 12.5 ppm vomitoxin) with a powdered concentrate (AIN-76A Purified Diet without carbohydrates, DYETS, Inc., Bethlehem, PA) to provide complete nutritionally balanced diets. Vomitoxin concentration in the contaminated corn was determined by electron capture gas chromatography and mass spectroscopy [12]. The control diet was prepared by mixing 1 kg batches of uncontaminated corn (65%) and the powdered concentrate (35%) using a large household mixer (Kitchen Aid K555 Mixer, Hobart Corp., Troy, OH) at approximately 150 rpm for 10 minutes. Vomitoxin diets were prepared by substituting appropriate quantities of 12.5 ppm vomitoxin corn for uncontaminated corn so that vomitoxin concentration in the test diets was either 8, 4, 2, 1, 0.5, or 0.25 ppm. In addition, a positive control diet was prepared identically to the control diet but with the addition of LiCl to yield a Li concentration of 640 ppm. Ten g of the positive control feed would provide a Li dose of 32 mg/kg for a 200 g rat. Lithium administered at 32 mg/kg will induce marked conditioned taste aversion in rats [6].

EXPERIMENT I

Procedure

Each of 40 rats was trained to eat a 10 g portion of control chow and to drink tap water in a test cage (separate from its home cage) during a 60 minute period on each of 7 consecutive (baseline) days. Tap water was available from calibrated drinking tubes (Wahmann). Water and food intakes for individual rats were recorded to the nearest 1 ml and 0.1 g, respectively. Food spillage was collected on paper placed under the wire floor of each test cage and the food intake values were corrected for spillage. Body weights were recorded to the nearest 1 g prior to each daily test session. Neither food nor water were available in the home cage between daily tests. After baseline food and water intake (averaged across days 5–7) were established, five groups (n=8 each) of comparable average group body weight, food intake and water intake were randomly assigned to each of the respective diet treatment conditions. During the acquisition or training phase (days 8–10), the rats were allowed access to water, to a 0.1% sodium saccharin solution and to either the control diet, the lithium diet, or a test diet containing either 2, 4, or 8 ppm vomitoxin. Bottle position was alternated across test days to prevent the formation of position preferences. During the extinction phase of the experiment (days 11–15), testing for food consumption and fluid selection continued as during the training phase except that the rats formerly fed the adulterated diets were shifted to the control chow diet.

Data Analyses

Separate analyses of variance (ANOVA) were computed for food intake (days 5–15), saccharin intake ratios (volume of saccharin solution consumed/total fluid consumed for

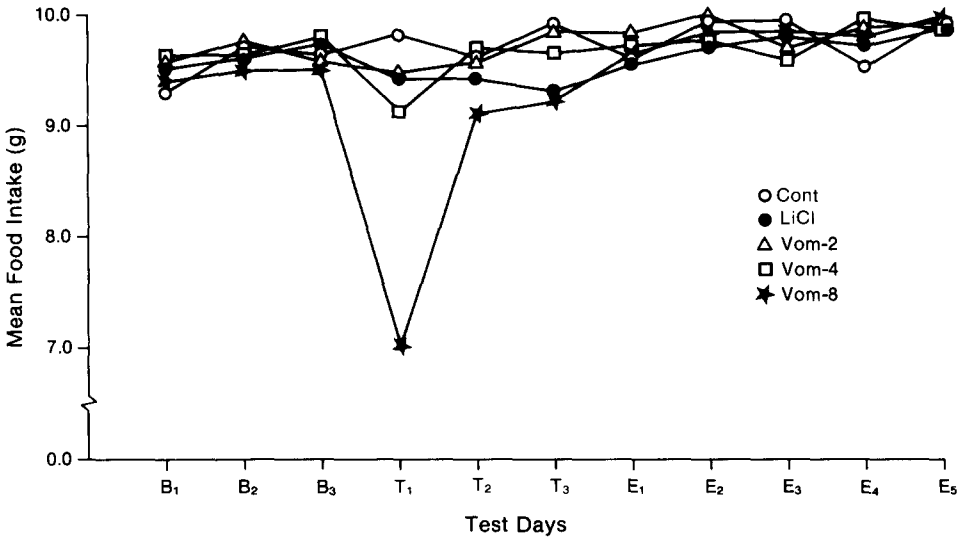

FIG. 2. Experiment II: Mean group food intake (grams) during final 3 baseline (B) days 1–3, training (T) days 1–3 and extinction (E) days 1–5 for rats fed control diet or vomitoxin adulterated diets during training (T) days 1–3.

days 8–15), total fluid intake (saccharin and water) (days 8–15), and body weight (days 5–15). Subsequent between- and within-group comparisons were performed using *a priori* two-tailed *t*-tests [5]. Difference probabilities less than 0.05 were deemed significant.

EXPERIMENT II

Procedure

A subsequent study, Experiment II, was designed to verify the transient feed refusal observed in Experiment I for rats fed either 4 or 8 ppm vomitoxin and to establish the level of vomitoxin adulteration that would result in feed refusal by rats. To accomplish this, the rats were allowed to choose between either control chow or vomitoxin-adulterated chow.

In Experiment II, 49 adult male Sprague-Dawley outbred rats were obtained, housed, and acclimatized as in Experiment I. The vomitoxin-adulterated diets and the control diet were prepared as described above. A commercial powdered chow diet (Teklad Rat and Mouse Diet, Harlan Sprague-Dawley, Inc., Winfield, IA) was used during the pre-test training period. In Experiment I, the rats were fed a control diet during the baseline phase and were then fed either the control diet or a vomitoxin adultered diet. Thus, the control rats continued to receive the same diet throughout the baseline and test phases whereas the vomitoxin rats may have experienced a shift in diet taste. To ensure that the reduced feed consumption observed in the 4 and 8 ppm vomitoxin groups in Experiment I was not an instance of neophobia (i.e., reduced feeding associated with the novel flavor of vomitoxin) [3], all rats were fed a commercial chow diet dissimilar in taste, color, and texture from the control chow diet during the baseline phase of this experiment. Thus, when the rats were shifted to the chow diet and adulterated chow diets, the control group also experienced a shift to a novel diet.

During the baseline period (days 1–5) of Experiment II, the rats were offered the commercial powdered chow during each of 5 daily 60 minute feeding periods. Food intake, water intake and body weight were recorded as in Experiment I. No saccharin flavor was made available in this experiment. Seven groups (n=7 each) of comparable average daily chow intake, water intake and body weight were formed using the data from days 3–5 of this baseline period. On days 6 and 7, each rat was offered a choice of two diets in a test cage. One was the control diet whereas the other diet was either the control diet, or one of the 6 vomitoxin-adulterated (8, 4, 2, 1, 0.5 or 0.25 ppm) diets.

During the test periods, two feeding dishes were positioned at opposite ends of each cage and were separated by cardboard retainers. One dish contained 80 g of control feed whereas the other contained 80 g of either control feed (control group) or one of the vomitoxin adulterated diets. To minimize position preference, the position of the diets, within each cage, was alternated both within each day and was counterbalanced across the two test days. After the 60 minute feeding period, the unconsumed feed and spillage was recovered and weighed to determine relative consumption of each diet.

Data Analyses

Separate ANOVAS were computed for total food consumption on each of the two test days and for food-choice ratios. For rats offered a choice between the control diet and a vomitoxin adulterated diet, the food choice ratio was calculated as g control feed consumed/total feed (control and contaminated) consumed. To control for spatial preferences, on Test Day 1, half of the rats in the control-control choice group had the feed positioned at the front of the cage arbitrarily designated as the control diet. For the remaining control rats, the designated control diet was positioned at the rear of the cage. The respective position designations were reversed on Day 2.

RESULTS

Experiment I

Fluid consumption. Figure 1 depicts the influence of dietary vomitoxin or lithium chloride on saccharin consump-

TABLE 1

EXPERIMENT II: EFFECT OF VOMITOXIN ON TOTAL FOOD INTAKE AND CHOICE RATIOS

Group[a]	Day 1		Day 2	
	Total Food Intake	Choice Ratio	Total Food Intake	Choice Ratio
Control	9.4 (0.5)[b]	0.37 (0.1)	10.1 (0.9)	0.60 (0.1)
0.25 Vom	9.1 (1.0)	0.42 (0.1)	10.3 (0.8)	0.61 (0.1)
0.50 Vom	10.0 (0.5)	0.37 (0.2)	11.3 (0.8)	0.53 (0.1)
1.0 Vom	10.4 (1.6)	0.40 (0.1)	10.2 (0.5)	0.58 (0.1)
2.0 Vom	8.8 (0.3)	0.41 (0.2)	9.9 (0.4)	0.46 (0.1)
4.0 Vom	8.6 (1.0)	0.54 (0.1)	11.0 (1.2)	0.63 (0.1)
8.0 Vom	7.4 (0.3)*	0.37 (0.1)	10.3 (0.4)	0.62 (0.1)

a: N=7 for each group. b: Mean ± S.E.M.
*$p<0.01$, comparison with control total food intake.

tion ratios during the 3 training days and the 5 extinction days. During training, control rats consumed an average of 67% of their total fluid intake as 0.1% saccharin. In contrast, dietary adulteration with lithium or the various levels of vomitoxin resulted in rejection of the saccharin flavor, as evidenced by saccharin consumption ratios smaller than those observed for the control chow rats. Analyses of variance revealed a significant effect of Group, $F(4,35)=13.4$, $p<0.0001$, and a significant interaction between the factors of Group and Day, $F(8,70)=5.5$, $p<0.0001$. Subsequent comparisons between saccharin consumption ratios, collapsed across the 3 training days, revealed no significant differences between the control group and the 2 ppm vomitoxin group or between the lithium group and the 8 ppm vomitoxin group. Rats fed the 4 ppm vomitoxin diet drank significantly less saccharin than did the control group ($p<0.001$) but consumed more saccharin solution than rats fed the 8 ppm vomitoxin diet ($p<0.05$). Both the lithium group and the 8 ppm vomitoxin group consumed significantly less saccharin than the control group ($p<0.001$ for each comparison). Rats fed the 4 and 8 ppm vomitoxin diets avoided the saccharin flavor on the first training trial, whereas the lithium group drank approximately normal levels of the saccharin solution on the first training trial but avoided the saccharin flavor on the second and subsequent trials. This suggests that the aversive action of vomitoxin is manifested within one hour of ingestion.

During the extinction period, the saccharin consumption ratios of the control and the 2 and 4 ppm vomitoxin groups gradually increased, whereas the saccharin consumption ratios of both the 8 ppm vomitoxin and the lithium groups did not. Analyses of variance revealed a significant effect of Group, $F(4,35)=25.9$, $p<0.0001$, and a significant interaction between the factors of Group and Day, $F(16,40)=1.9$, $p<0.02$. Within-group comparisons of changes in saccharin consumption ratios (extinction Day 1 less Day 5) revealed that the lithium and 8 ppm vomitoxin groups showed no significant change in saccharin consumption ratios whereas significant increases were observed in the 2 and 4 ppm vomitoxin groups ($p<0.03$ and 0.001), respectively.

Analyses of variance were computed for total fluid intake (water plus saccharin) during the training and the extinction phases of the experiment (not depicted). Although total fluid intake for all rats increased significantly over the course of the experiment, $F(7,245)=6.3$, $p<0.001$, there was no significant effect of the Group factor and the interaction between the factors of Group and Day was not statistically significant. Thus, although there were differential fluid consumption patterns across the training and extinction days (i.e., rats fed the lithium and vomitoxin diets drank less saccharin but more water), overall fluid intake was comparable between the groups.

Food consumption. The influence of lithium or vomitoxin adulteration on food consumption during training and extinction is depicted in Fig. 2. All groups consumed equivalent amounts (an average of 9.6 of the 10 g offered) of control chow during baseline days 1–3. Rats fed the control diet, the lithium diet, or the 2 ppm vomitoxin diet continued to consume baseline levels of diet during the training phase and the extinction. In contrast, rats fed the 4 and 8 ppm vomitoxin diet exhibited significant reductions in food consumption of 7% and 28% on the first training day (comparison between each adulterated group and the control chow group on day 1 of training: $p<0.05$ and 0.001, respectively). No other between-group differences on the first training day were statistically significant. The reduction in food consumption, however, was transient as the food intakes of the 4 and 8 ppm vomitoxin groups returned to control levels on the second and third days of training and remained there throughout the extinction phase.

Body weight. Mean group body weight of the diet groups (not depicted) were equivalent during baseline days 1–3 and remained so throughout the course of the experiment. The only significant effect noted in the analyses of body weight data was an effect of Day, $F(11,385)=71.9$, $p<0.0001$. The rats gained an average of 7.9 g over the 12 experimental days.

Experiment II

On Day 1, rats offered a choice of control diets consumed an average of 9.4 g whereas the rats offered a choice between either the control diet or one of the vomitoxin-adulterated diets exhibited average total food intakes ranging between 10.4 and 7.4 g (see Table 1). Analyses of variance of total food intakes on Day 1 revealed a significant main effect of vomitoxin dose, $F(6,43)=2.39$, $p<0.05$. This difference reflected the significant reduction in food intake

induced by the 8 ppm vomitoxin diet relative to the total intakes of the control group, $t(12)=3.1$, $p<0.01$. This effect of 8 ppm vomitoxin, as in Experiment I, was transient as analyses of total food intake on Day 2 revealed no significant between-group differences.

The rats exhibited consistent changes in food choice ratios on Days 1 and 2. On Day 1, the food choice ratios of all groups ranged between 0.37 and 0.54 whereas on Day 2, the ratios consistently increased and ranged between 0.46 and 0.63, suggesting a slight position preference. Yet, there were no significant differences between the groups in mean group food choice ratio on either day. Whereas the total food consumption of rats fed the 8 ppm vomitoxin diet was significantly suppressed on Day 1, the food choice ratio of this group was not significantly different from that of rats offered a choice of the control diets.

DISCUSSION

Experiment I demonstrated conditioned saccharin aversion associated with contamination of diet by vomitoxin. Rats fed diets adulterated with either 4 or 8 ppm vomitoxin exhibited avoidance of the saccharin flavor on the first of 3 training days, whereas rats fed a lithium-adulterated diet (positive control) exhibited aversion to the saccharin flavor only on the second training day and on each day thereafter. Moreover, the aversion to saccharin was potent as well as persistent. Rats fed the 8 ppm vomitoxin diet or the lithium diet on training days 1–3 showed but minimal increases in selection of the saccharin solution when fed a plain chow diet during the 5 extinction days. The avoidance of saccharin on the first day of exposure to vomitoxin may represent toxicant-induced neophobia in which rats that consume a toxic substance avoid a novel flavor while in an illness state. Domjan [3] has shown that rats treated with lithium (at dose levels greater than that used in the present study) 30 minutes prior to access to a saccharin solution exhibit reduced consumption of saccharin but not when treated with lithium 2 hours prior to access to saccharin. Informal observation of the rats suggested that the rats consumed the diet prior to consuming fluids. Although toxicant-enhanced neophobia may explain the rapid avoidance of saccharin (i.e., on the first training trial) associated with vomitoxin consumption, the persistent avoidance of saccharin on the 5 extinction days is not consistent with toxicant-enhanced neophobia in that this form of neophobia dissipates as the animals recover from the toxin. Sylvia [14] examined the pharmacokinetics of vomitoxin absorption and excretion in mice after a gastric load. Vomitoxin was rapidly absorbed from the gut and was rapidly excreted in urine (71% was found in urine within 12 hours of exposure). Sylvia's data suggest that the action of vomitoxin is rapid and that vomitoxin is rapidly excreted. Thus, the persistent reduction in saccharin consumption noted during the extinction phase of Experiment I in vomitoxin treated is unlikely to be the result of some chronic malaise state associated with vomitoxin ingestion. These data are consistent with an association between the novel taste of saccharin paired with a rapidly-induced aversive action of vomitoxin.

Experiment I also demonstrated that adulteration of a diet with vomitoxin at 4 or 8 ppm induced a transient reduction in food intake (day 1 of exposure only). This finding is consistent with other studies in which dietary contamination with vomitoxin at levels of 5–10 ppm had minimal impact of feeding in rats. Higher levels of vomitoxin (20–40 ppm) are required to induce feed refusal in rats and even these may be transient [8,21].

The results of Experiment II demonstrate that dietary contamination with 8 ppm vomitoxin results in a transient reduction of food intake on the first day of exposure, thus replicating the outcome of Experiment I. Moreover, at dose levels ranging between 0.25 and 8 ppm vomitoxin, no changes in diet preference were noted in a choice paradigm in which the rats could feed from a control diet or a diet contaminated with vomitoxin. These data suggest that dietary taste per se, as assessed in a diet choice procedure, is not altered by vomitoxin at levels lower than 8 ppm.

Comparisons of these data on taste aversion and diet preference in rats fed vomitoxin with the data from other species is complicated in several regards. Swine appear to be more sensitive to the taste of vomitoxin than rodents. Vesonder *et al.* [20] noted that 1.0 ppm vomitoxin in corn was rejected by pigs, whereas Forsyth *et al.* [4] observed that 3.6 ppm vomitoxin resulted in a 20% reduction of feeding in swine and 40 ppm vomitoxin reduced feeding by 90%. In contrast, rats fed 40 ppm vomitoxin exhibited a 54% reduction in intake of contaminated corn [21]. Mice offered 10, 20 and 40 ppm vomitoxin in drinking water exhibited reductions of water intake of 50, 57, and 70% [1]. Depending on the task and species, vomitoxin contamination has marked effects on food and water consumption in swine, mice and rats at levels approaching 40 ppm but a greater impact in swine and mice at lower levels. Yet, consideration of alterations of consumption of diets or fluids contaminated with mycotoxins such as vomitoxin should not be a sole criterion of toxicity (cf. [3]). Indeed, in the present study, vomitoxin at 8 ppm had only a transient effect on consumption of a diet yet this concentration produced a rapid and persistent conditioned saccharin aversion. Although rats may be less sensitive to the action of vomitoxin on feed consumption, the taste aversion paradigm in a rat model may offer a sensitive test of mycotoxicosis.

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