Effect of previous locoweed (*Astragalus* and *Oxytropis* species) intoxication on conditioned taste aversions in horses and sheep[1]

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ABSTRACT: Locoweed species (*Astragalus* and *Oxytropis* spp.) are a serious toxic plant problem for grazing livestock. Horses and sheep have been conditioned to avoid eating locoweed using the aversive agent LiCl. The objective of this study was to determine if previous locoweed intoxication affects food aversion learning in horses and sheep. Horses and sheep were divided into 3 treatment groups: control (not fed locoweed and not averted to a novel feed); locoweed-novel feed averted (fed locoweed and averted to a novel feed); and averted (not fed locoweed and averted to a novel feed). Animals in the locoweed-novel feed averted groups were fed locoweed during 2 periods of 21 and 14 d, respectively, with each feeding period followed by a 14-d recovery period. Animals were averted to a novel test feed at the end of the first locoweed-feeding period, and periodically evaluated for the strength and persistence of the aversion. During the first recovery period, locoweed-novel feed averted horses ate less (9.5% of amount offered) of the test feed than did control horses (99.8%) and did not generally differ from averted horses (0%). During recovery period 2, locoweed-novel feed averted horses (4.3%) differed ($P = 0.001$) in consumption (% of offered) of the test feed from controls (100%) and the averted group (0%). Locoweed-novel feed averted sheep differed ($P = 0.001$) from controls (14.4 vs. 99.5%, respectively, during recovery period 1), whereas locoweed-novel feed averted sheep did not differ ($P > 0.50$) from averted sheep (0.6%). During the second recovery period, control sheep (100%) differed ($P < 0.05$) from averted (0%) and locoweed-novel feed averted (12.2%) groups. Two intoxicated sheep (locoweed-novel feed averted) partially extinguished the aversion during the first recovery period, but an additional dose of LiCl restored the aversion. Two of 3 intoxicated horses had strong aversions that persisted without extinction; 1 horse in the locoweed-novel feed averted group had a weaker aversion. These findings suggest that horses and sheep previously intoxicated by locoweeds can form strong and persistent aversions to a novel feed, but in some animals, those aversions may not be as strong as in animals that were never intoxicated.

Key words: horse, locoweed, sheep, taste aversion, toxic plant

J. Anim. Sci. 2007. 85:1836–1841
doi:10.2527/jas.2007-0046

INTRODUCTION

Astragalus and *Oxytropis* species that contain the indolizidine alkaloid swainsonine (locoweeds) are a serious toxic plant problem for grazing livestock worldwide. Swainsonine inhibits lysosomal α-mannosidase and mannosidase II (Dorling et al., 1980). Inhibition of these enzymes results in oligosaccharide accumulation in lysosomes with characteristic vacuolated cells (Stegelmeier et al., 1995b). Clinically, locoweeds cause depression, proprioceptive deficits, intention tremors, nervousness, emaciation, and death (James et al., 1970). Locoweeds are palatable to horses (Marsh, 1909; Pfister et al., 2003), cattle (Ralphs et al., 1987), and sheep (Marsh, 1909). Horses are particularly susceptible to locoweed intoxication (Pfister et al., 2003).

Averting livestock to toxic plants to reduce losses has been a research topic for many years (Ralphs and Provenza, 1999). Sheep (Pfister and Price, 1996), horses (Pfister et al., 2002), and cattle (Ralphs et al., 1997) have been averted to locoweed. Oral gavage using LiCl is the preferred method of conditioning aversions in livestock (Ralphs and Provenza, 1999). Unlike other livestock species, gastric gavage in horses involves nasogastric intubation, thus requiring veterinary assistance. Even so, averting horses to locoweed may be feasible and cost effective (Torell et al., 2000) because of the relatively high economic and emotional value of individual horses, and the relatively small numbers

[1]We thank Kermit Price, Rex Probst, Al Macilius, Ed Knoppel, and Danny Hansen for technical assistance and animal care and handling.
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Received January 18, 2007.
Accepted April 11, 2007.

of grazing horses on affected ranches compared with grazing sheep and cattle.

The effect of previous locoweed consumption on conditioning taste aversions in horses or sheep is not known. The neurological effects of locoweed intoxication (Stegelmeier et al., 1995b) may negatively influence formation and persistence of aversions in animals.

Thus, the objective of this study was to determine if previous locoweed intoxication affects food aversion learning in horses and sheep.

MATERIALS AND METHODS

All research was conducted at the Poisonous Plant Research Laboratory, Logan, UT. Animals were cared for by experienced handlers under veterinary supervision. The procedures were approved by the Utah State University Institutional Animal Care and Use Committee.

Plant Material

A 50:50 (vol/vol) mixture of 2 locoweeds was used in the study. *Astragalus lentiginosus var. diphysis* was collected during spring, 1998 near St. Johns, AZ (34° 24′N 109° 13′W). *Oxytropis sericea* was collected in spring, 2000 near Capulin, NM (36° 43′N 104° 1.5′W). Voucher specimens were deposited at the Utah State University Herbarium (#23739 and 226461). All collections were air-dried, ground to pass a 2-mm screen, sealed in plastic bags, and stored at 10°C. Long-term storage has no effect on the concentration of swainsonine (R. J. Molyneux, USDA-ARS, Albany, CA, personal communication). Locoweed pellets (15% by weight) were commercially made by mixing ground locoweed with barley (19.5%), ground corn (21%), soybean meal (9%), wheat bran (16%), ground alfalfa (15%), molasses (2.5%), dicalcium phosphate (1%), and trace mineral salt (1%), as-fed basis. Locoweed pellets were analyzed for swainsonine using reversed phase HPLC (Hewlett-Packard Model 1100, Palo Alto, CA) coupled to atmospheric pressure, chemical ionization, tandem mass spectrometer (Thermo Finnigan LCQ, San Jose, CA; Gardner et al., 2001). The limit of detection was 0.0005% of the dry weight, and the limit of quantification was 0.001% for this analysis.

Animals and Treatments

Horses and sheep were divided into 3 treatment groups (n = 3 for each group and species): control (not fed locoweed and not averted to a novel feed); locoweed-novel feed averted (fed locoweed and averted to a novel feed); and averted (not fed locoweed and averted to a novel feed). Horses (mixed breed; BW = 405 ± 20 kg) and sheep (Suffolk × Polypay wethers; BW = 49 ± 4 kg) were housed in a heated barn at 9°C in individual pens, with water and trace mineral salt available at all times. Animals had no previous exposure to locoweeds.

Locoweed Period 1

Locoweed-novel feed averted treatment subjects were initially fed locoweed pellets for 21 d. Grazing livestock are often exposed to locoweed for several weeks (Pfister et al., 2003). Horses were fed locoweed pellets to achieve a swainsonine dose of 1 mg/kg of BW, whereas sheep in this treatment were fed locoweed pellets at a swainsonine dose of 2 mg/kg of BW. Previous work has indicated that horses are more sensitive to swainsonine than are sheep or cattle (Pfister et al. 2003; B. L. Stegelmeier, unpublished data). Horses were offered locoweed pellets plus alfalfa hay; the total ration was fed at 1.5% of BW daily. Sheep were offered locoweed pellets plus alfalfa pellets for a ration equal to 2% of BW daily, as-fed basis. Locoweed pellets were fed at 0800 each morning; after the locoweed pellets were consumed (typically < 30 min) alfalfa hay was fed. During the first few days of the study, a few animals did not eat all of the locoweed pellets, but within 3 d all animals ate all the locoweed pellets each day throughout the remainder of the study. Control and averted groups were given only 100% alfalfa pellets (sheep) or alfalfa hay (horses).

Serum was collected on d 0, 7, 14, and 21 via jugular venipuncture from control and locoweed-novel feed averted animals and analyzed for swainsonine concentration as an index of intoxication (Stegelmeier et al., 1995a). Briefly, 50 μL of serum was incubated with 40 μL of 0.25 *M* sodium acetate, 10 μL of 10 m*M* 4-methylumbelliferyl-D-mannopyraniside and 0.08 U of jack bean α-mannosidase. This assay measured the amount of swainsonine indirectly by determining the inhibition of jack bean α-mannosidase photometrically at 350 nm. The assay has a lower detection limit of 30 ng/mL.

On d 19 and 20, all animals were exposed to milo (*Sorghum bicolor,* common name grain sorghum; 20 g for sheep; 50 g for horses), a novel but palatable grain, for 5 min each day at 0700 after an overnight fast. All animals initially ate some novel feed. On d 21, each animal was offered grain sorghum (100 g for sheep; 250 g for horses) for 5 min at 0700 after an overnight fast, and animals in the locoweed-novel feed averted and averted groups were immediately dosed with LiCl at 190 mg/kg of BW (Pfister et al., 2002). The LiCl was mixed with tap water (1 L for sheep and 3 L for horses) and given by oral gavage in sheep and nasogastric gavage in horses. Controls were dosed with tap water only.

Recovery and Testing Period 1

After locoweed period 1, the subjects were given a 14-d recovery period with no locoweed (recovery 1). Horses were fed alfalfa hay at 1.5% of BW daily, and sheep were given alfalfa pellets at 2% of BW daily. During the 14-d recovery period all animals were tested for the strength and persistence of the aversion on d 1, 3, 7, and 14 by offering grain sorghum (100 g for sheep; 250 g for horses) for 5 min at 0700 after an overnight fast.

Locoweed Period 2

At the end of the 14-d recovery period, the locoweed-novel feed averted group was fed locoweed pellets again for 14 d (locoweed period 2). Locoweed pellets were fed at the levels previously given for the locoweed period 1, at 0800 each day. The remainder of the animals' diet was alfalfa, as previously noted. No serum was collected during this period because locoweed-treated horses were behaviorally erratic, and serum collection was disruptive.

Recovery and Testing Period 2

A second recovery period of 14 d was given to all the animals at the end of the second locoweed feeding period. On the first day of this recovery period, all subjects were again offered grain sorghum (100 g for sheep; 250 g for horses) for 5 min at 0700 after an overnight fast. On test d 1 of recovery period 2, averted animals (locoweed-novel feed averted or averted groups) that ate any amount of grain sorghum were dosed with LiCl at 190 mg/kg of BW (a second LiCl dose, if necessary), and all animals were tested again on d 3, 7, and 14 of this second recovery period. No LiCl was dosed on d 3, 7, or 14 even if animals ate some grain sorghum.

Statistical Analysis

Intake of the novel feed (grain sorghum) was analyzed using the MIXED procedure (SAS Inst. Inc., Cary, NC). Swainsonine in serum was analyzed using a similar mixed procedure. Horses and sheep were examined separately. Subjects were a random factor, with the model including treatments, animals nested within treatments, with repeated measurements over time. The variance-covariance structure was examined, and the best fit models used the compound symmetry option. Each period was analyzed separately; means for each species and each recovery period were compared at $\alpha = 0.05$ using the PDMIX800 macro procedure in SAS.

RESULTS

Horses

Swainsonine concentration in locoweed-novel feed averted horse serum varied from 128 to 195 ng/mL during the first 21-d feeding period (Figure 1). Control animals (horses or sheep) had no swainsonine in their sera.

Horses and sheep in the averted group ate essentially none of the grain sorghum during the test studies, and control sheep and horses ate essentially all (>98%) of the grain sorghum during the test sessions (Table 1). Overall, there was a treatment effect ($P = 0.001$) for horses in recovery period 1. Locoweed-novel feed averted horses ate less (9.5 ± 5.4%) of the test feed than did control horses (99.8 ± 0.3%) and did not differ from averted horses, which ate none (Table 1). During all tests during recovery periods 1 and 2, the same horse in the locoweed-novel feed averted treatment accounted for >90% of the consumption of the test feed. The average consumption for the locoweed-novel feed averted horses was 6 to 14% of the grain sorghum during 4 test sessions in recovery period 1 (Table 1). There was a treatment effect ($P = 0.001$) for horses during recovery period 2, with locoweed-novel feed averted horses (4.3 ± 5.7%) differing in consumption of the test feed from the controls (100%) and the averted group (0%). During recovery period 2, locoweed-novel feed averted horses ate 6 to 10% of the test feed on test d 1 and 3, but consumption of the test feed declined to essentially 0 on d 7 and 14.

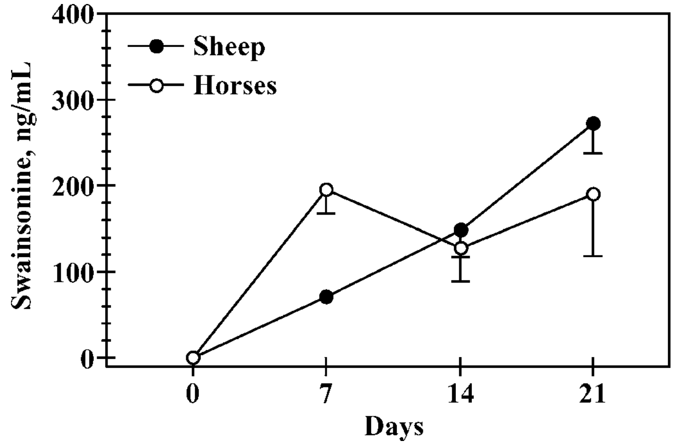

Figure 1. Serum swainsonine concentration (ng/mL ± SE) in treated sheep and horses when given 15% locoweed pellets for 21 d. Horses and sheep were fed locoweed pellets to achieve a daily swainsonine dose of 1 or 2 mg/kg of BW, respectively. Control animals had no swainsonine in their sera.

Sheep

Swainsonine concentration in locoweed-novel feed averted sheep serum peaked at 272 ng/mL on d 21 (Figure 1). Sheep in the locoweed-novel feed averted treatment ate increasing amounts of the grain sorghum during the 4 test sessions during recovery period 1, eventually consuming over 36% on test d 14 (Table 1). There was a treatment effect ($P < 0.001$) for sheep during recovery period 1; locoweed-novel feed averted sheep differed from controls (14.4 ± 8.4% vs. 99.5 ± 0.4%, respectively), whereas locoweed-novel feed averted sheep did not differ from averted sheep (0.6 ± 0.3%). During recovery period 2, 2 of 3 locoweed-novel feed averted sheep ate some grain sorghum on test d 1 of this recovery period; these animals were dosed with LiCl; on subsequent test days, 1 sheep from this group ate small amounts of the test feed. There was a treatment effect ($P < 0.001$); control sheep (100%) were greater ($P < 0.05$) than averted (0%) and locoweed-novel feed averted (12.2 ± 8.3%) groups (Table 1).

Table 1. Consumption (% of offered) of grain sorghum during 5-min testing periods[1]

Period/test day	Treatment[2] Control	Novel feed averted	Locoweed-novel feed averted	SEM[3]	P-value[4]
Horses					
Recovery period 1					
d 1	100.0[a]	0.0[b]	6.5[b,x]	—	
d 3	100.0[a]	0.0[b]	11.3[b,xy]	—	
d 7	100.0[a]	0.0[b]	13.9[b,y]	—	
d 14	99.1[a]	0.0[b]	6.1[b,x]	—	
				4.4	0.001
Recovery period 2					
d 1	100.0[a]	0.0[b]	6.1[b,x]	—	
d 3	100.0[a]	0.0[b]	10.1[c,x]	—	
d 7	100.0[a]	0.0[b]	0.9[b,y]	—	
d 14	100.0[a]	0.0[b]	0.1[b,y]	—	
				2.3	0.001
Sheep					
Recovery period 1					
d 1	100.0[a]	0.0[b]	0.0[b,x]	—	
d 3	99.3[a]	0.0[b]	2.8[b,x]	—	
d 7	100.0[a]	0.0[b]	18.3[b,x]	—	
d 14	98.3[a]	2.3[b]	36.4[b,y]	—	
				9.1	0.001
Recovery period 2					
d 1	100.0[a]	0.0[b]	45.8[c,x]	—	
d 3	100.0[a]	0.0[b]	0.2[b,y]	—	
d 7	100.0[a]	0.0[b]	2.8[b,y]	—	
d 14	100.0[a]	0.0[b]	0.2[b,y]	—	
				3.9	0.001

[a–c]Row means for horses or sheep between treatments within a recovery period and test day without a common superscript letter differ ($P < 0.05$).

[x,y]Column means for horses or sheep within a recovery period without a common superscript letter differ ($P < 0.05$).

[1]All tests were conducted during recovery periods 1 and 2 (14 d each period), while animals recovered from previous locoweed feeding of 21 and 14 d, respectively.

[2]The treatments were: control = not fed locoweed and not averted to a novel feed; novel feed averted = not fed locoweed and averted to a novel feed; and locoweed-novel feed averted = fed locoweed and averted to a novel feed. There were 3 subjects of each species in each treatment. Milo was initially a novel feed, and initial consumption by the locoweed-novel feed averted and novel feed averted animals was paired with LiCl dosed at 190 mg/kg of BW.

[3]Pooled SEM.

[4]P-value for a treatment effect; there were no day effects or day × treatment interactions.

DISCUSSION

The primary objective of the study was to determine if previous intoxication from locoweed would interfere with acquisition or persistence of conditioned taste aversion learning in horses and sheep. Two horses were visibly intoxicated at the end of the 21-d initial locoweed feeding period (trembling; easily startled), whereas none of the sheep showed overt signs of intoxication. There is no definitive test or biomarker to determine locoweed intoxication, but previous studies have shown pathological lesions in all animals (rodents and livestock) exposed to swainsonine doses >1.0 mg/kg of BW for more than 2 wk (Stegelmeier et al., 1995b, 1998; B. L. Stegelmeier, unpublished data for horses), sometimes with no aberrant behavioral signs. Locoweed induces many lesions in the brain (Van Kampen and James, 1972; Stegelmeier et al., 1995b), which may affect food aversion learning (Mediavilla et al., 1998) and aversion extinction (Berman et al., 2003; Delamater, 2004). Conditioned taste aversions are formed in the brain (Borison, 1989; Kesner et al., 1992), and various brain lesions may disrupt taste aversion learning (Curtis et al., 1994; Yamamoto et al., 1995; Touzani and Sclafani, 2002). This study suggests that the neurological effects of locoweed intoxication have only a modest, if any, influence on formation and persistence of aversions in domestic livestock.

The LiCl-based aversive conditioning was strong and persistent as indicated by the lack of consumption of the test feed by the averted animals. Generally averted animals, both sheep and horses, ate none of the test feed, with 1 exception. One averted sheep ate a small amount of grain sorghum on d 14 during the first recovery period. The lack of extinction in averted animals is notable for several reasons. First, averted animals were exposed 8 times to the test feed without additional reinforcement, yet the aversion persisted. Typically, extinction to aversions will occur more rapidly as the number of pairings between the flavor and positive (or lack of negative) consequences increases (Kyriazakis et al., 1998; Berman et al., 2003). Second, the lack of extinction over both of the 14-d recovery periods indicates that the initial aversion was quite strong. A weak aversion would be expected to extinguish more easily (Bures et al., 1998). Finally, the grain sorghum was a very palatable food, and aversions to preferred tastes such as saccharin tend to extinguish faster than aversions to less palatable flavors (Berman et al., 2003). Preferred flavors are often associated with nutritious foods, and positive feedback may enhance extinction. As expected, control animals ate virtually all of the test feed, indicating that gavage alone had no negative impact on subject animals.

Results from this study suggest that previously intoxicated horses and sheep can form strong aversions to novel feeds, but in some animals at least, those aversions may not be as persistent as in normal animals. The ultimate response for taste aversion in livestock is for averted horses and sheep (locoweed-novel feed averted and averted treatments) to reject all of the test feed during all subsequent tests. Partial aversions occur when animals substantially reduce intake of a referent feed (rats, Massei and Cowan, 2002; horses, Houpt et al., 1990; Zahorik et al., 1990; cattle, Ralphs and Stegelmeier, 1998; sheep, Egber et al., 1998; Kyriazakis et al., 1998), but do not completely abstain from eating. Such aversions typically diminish over time when the taste of the test feed is not paired with adverse gastrointestinal feedback (Kraemer and Spear, 1992; Kyriazakis et al., 1998). On most test days (7 out of 8 d for horses and sheep), there were no statistical differences in consumption of the test feed between locoweed-novel feed averted and averted animals even when the locoweed-novel feed averted group ate small amounts of the novel feed. Nonetheless, even limited consumption by the locoweed-novel feed averted group suggests that the aversion was not complete and indicates that the aversion might diminish with repeated exposure (Ralphs and Provenza, 1999). Previous work with cattle has shown that extinction of conditioned feed aversions often begins with consumption of small and seemingly unimportant (statistically insignificant) amounts of the test feed (Ralphs and Provenza, 1999; Pfister, 2000).

Partial extinction by previously intoxicated horses and sheep might be due in part to the severity of the no-choice test procedure. Rats given a no-choice test had greater extinction compared with a 2-choice test (Mikulka and Klein, 1977; Nolan et al., 1997). We used a no-choice test because these tests are well suited to examine subtle changes in aversive conditioning and extinction, whereas 2-choice tests are best used to test for weak aversions (Smith et al., 2004).

Studies of extinction of taste aversions in rodents indicate that extinction does not abolish the original associative trace; rather the extinction process generates new learning that is context specific (Bouton, 2002; Berman et al., 2003; Delamater, 2004). Extinction can be expected to result in behavioral instability (Bouton, 2002) as displayed by 2 subjects (1 horse, 1 sheep) in this study. Most consumption of the test feed was by 1 horse (>94% over all tests) and 1 sheep (>80% over all tests) in the locoweed-novel feed averted treatment.

Unlike earlier work with horses (Pfister et al., 2002), no second dose of LiCl in averted horses was required to condition avoidance of the palatable food. In previous studies we have conducted with horses (Pfister et al., 2002), 1 averted horse required multiple doses of LiCl to form an aversion. One sheep and 1 horse in the locoweed-novel feed averted treatment groups did not avert completely after 2 doses of LiCl. It appears that some animals, normal or previously intoxicated, will require multiple doses of LiCl or a stronger initial dose in order to form strong and persistent aversions. It is not unusual for some individual animals in aversion studies to require more than 1 dose of the emetic in order to condition a strong aversion (cattle: Ralphs and Provenza, 1999; sheep: Burritt and Provenza, 1989).

Swainsonine concentration in horse sera increased rapidly within the first 7 d after exposure, even more rapidly than in sheep receiving twice the swainsonine dose in feed. Swainsonine is not, however, a reliable biomarker of intoxication because serum concentrations decline rapidly when animals are removed from the plant (Stegelmeier et al., 1995a). Additionally, some horses were overtly intoxicated at the end of the first locoweed feeding period, as noted by several experienced observers, and sheep were not. It may be easier, however, to note adverse behavioral changes in horses compared with sheep because of their large stature, excitability, and sometimes extreme reactions to stress. Even so, these results indicate that horses are more sensitive to locoweed poisoning than are other domestic livestock (Marsh, 1909; James and Van Kampen, 1971; Pfister et al., 2003).

Locoweed poisoning in horses and sheep is a serious problem on some rangelands worldwide. Aversive conditioning using the emetic drug LiCl may provide a partial solution if averted horses and sheep are conditioned to avoid the toxic plants. This study indicates that previously intoxicated horses and sheep can be successfully averted to a palatable novel feed while recovering from locoweed poisoning. Locoweed is typically less palatable than the grain sorghum used in this study. Therefore, these results suggest that previously intoxicated animals can be averted successfully to locoweed as a management tool to reduce losses.

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