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Does experience with sagebrush *in utero* and early in life influence use of sagebrush by sheep?

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ABSTRACT

Learning from mother begins early in the developmental process and can have lifelong effects when it comes to foraging behavior. Pregnancy is not just an incubation period but a starting point for animal well-being and disease later in life. A better understanding of the effects that early exposure to unpalatable feeds impinges on their use later in life may help create management plans that utilize grazing animals to their full potential as landscape manipulators. Thus, the objective of this research was to explore how experience *in utero* and early in life with sagebrush (*Artemesia tridentata spp. tridentata*) -a terpenoid-containing shrub- affected intake of and preference for sagebrush by sheep later in life. Eighty pregnant ewes (8 weeks of gestation) were divided into two groups, one group was exposed to sagebrush in their pens (25 to 30 Kg of freshly cut sagebrush was offered during 2-3 times a week), whereas the other group did not receive such exposure. Subsequently, lambs with their mothers were separated into four groups according to prior and subsequent exposure to sagebrush: 1) no exposure, 2) exposure *in utero*, 3) exposure *in utero* and for the first 2 mo. of life, and 4) exposure for the first 2 mo of life. At approximately 8 weeks of age, all lambs were weaned and four months later they were tested for their ability to ingest sagebrush. No differences regarding intake of sagebrush were detected among groups of lambs when they had choices between *ad libitum* amounts of alfalfa pellets and sagebrush ($P > 0.10$). When the amounts of alfalfa pellets in the choice test were restricted to 50% of *ad libitum* intake, lambs in the group that only had *in utero* experience with sagebrush (Group 2) showed the lowest intakes of sagebrush ($P < 0.05$). This suggests that *in utero* exposure to sagebrush decreased sagebrush preference and/or the ability of lambs to ingest this shrub. Sagebrush intake also increased across testing ($P < 0.05$), suggesting that exposure to sagebrush during testing had a more pronounced effect on sagebrush intake than *in utero* or early

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life experiences with the shrub. In conclusion, prior experience with sagebrush under the conditions of the present study did not reveal an enhancement in sagebrush use later in life by sheep; on the contrary, *in utero* experiences with the shrub appeared to have reduced the ability of lambs to ingest sagebrush. Results from this study also suggest that exposing young lambs for several days to sagebrush while restricting the availability of high-quality forage is a viable option that may enhance utilization of sagebrush.

Keywords: Learning, Diet selection, Early-life programming, Preference, Landscape manipulation

Introduction

Sagebrush steppe is one of the largest eco-regions in North America, covering millions of hectares of rangeland in the western United States (West 1993). Over the past 30-40 years, forage production on sagebrush steppe has dramatically declined from approximately 900 Kg of grass and forbs per hectare to less than 100 Kg per hectare due to decadent stands of sagebrush which outcompete essential understory species (Winward 1991). In addition to primary production, plant diversity generally declined during the same period of time as woody species, such as sagebrush and juniper, came to dominate the landscape. Several factors have led to this decline including overgrazing by livestock in the 1930's-1950's as well as fire suppression policies all of which favor decadent stands of sagebrush (Striby et al 1987). This decline in production and diversity adversely affects sagebrush-steppe ecosystems (Bryant et al., 1991). Nutrient cycling, plant production, and herbivore nutrition are negatively impacted because sagebrush - although abundant and nutritious – contains high concentrations of terpenes (6 to 23% in the plant, including artemiseole, eucalyptol, p-cymene, 1,8-cineole, camphor, santolina epoxides, methyl santolinate; Shipley et al., 2006). This large and diverse class of plant secondary compounds are organic molecules biosynthetically derived from units of isoprene, which are toxic to soil and rumen microbes, and to herbivores (Estell, 2010; Ulappa et al., 2014).

To reverse the negative trends on production and biodiversity, management strategies must (1) rejuvenate sagebrush stands and (2) favor a mixture of plant species in the understory. Through proper management, the same animals that helped reduce biodiversity and primary production in sagebrush steppe ecosystems can become one of the most economical ways to rejuvenate sagebrush steppe. Fall grazing by sheep or cattle with the appropriate supplements increases plant diversity in sagebrush steppe ecosystems (Dziba et al., 2007, Petersen et al.,

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2014). While use of sagebrush by livestock is constrained by the presence of terpenes (Forbey et al., 2013), supplemental macronutrients (e.g., highly digestible carbohydrates, protein) facilitate detoxification of terpenoids, thus mitigating their negative impact and enabling substantial increases in intake of sagebrush (Villalba et al., 2002).

Another approach to increase intake of sagebrush by herbivores is to utilize locally-adapted animals which have experience consuming sagebrush early in their lives (Petersen et al., 2014). Experiences *in utero* and early in life have life-long influences on livestock by causing neurological, morphological, and physiological changes that influence foraging behavior (Distel et al., 1994; 1996; Distel and Villalba, 2018). By interacting with the genome during growth and development, social and biophysical environments influence gene expression and behavioral responses in mammals (Robinson and Barron, 2017; Grissom et al., 2017; Ye et al., 2018). Learning from mother begins early in the developmental process and can have lifelong effects when it comes to foraging preferences. For instance, dietary exposure of pregnant ewes to a NaCl-containing shrub (*Atriplex nummularia*; saltbrush) caused physiological (e.g., renin activity) and behavioral adaptations in their offspring that improved their ability to cope with high-salt diets, allowing animals to even gain weight when grazing saltbush as adults (Chadwick et al., 2009a,b). Thus, a better understanding of developmental processes, which take place *in utero* and the effects they have throughout life may help us create management plans that use grazing animals to their full potential as landscape manipulators.

Using *in utero* and early-life programming as a management tool, is a relatively new concept, but offers a faster approach than genetic selection to respond to environmental contingencies in the short-term and potentially increase the herbivores' ability to consume unpalatable forages. This effect can reduce the competitive ability of toxin-containing plants in the community and allow for greater primary production and diversity. However, information regarding herbivores' exposure to plant toxins and their subsequent physiological and behavioral responses is limited (Welch et al., 2012). Moreover, no information is available on early life experiences to toxin-containing shrubs, such as sagebrush, and their subsequent influence on feeding behavior by herbivores. Thus, the objective of this research was to explore how experience *in utero* and early in life with sagebrush affected intake of and preference for sagebrush by sheep later in life. We hypothesized that the fetus is a dynamic and active creature that responds and adapts to the environmental conditions experienced inside its mothers' body and such experiences, as well as experiences early in life help individuals prepare for the conditions in the outside world (Gluckman et al., 2005). Thus, we predicted that sheep exposed early in life to sagebrush (*in utero* and after birth) would consume more of sagebrush and display greater preferences than individuals lacking such experience.

Materials and Methods

Conditioning

Multiparous mature ewes (Rambouillet x Columbia x Finn) were held in two separate pens at the Utah State University/ARS research site in Richmond, UT (41.9194° N, 111.8103° W). All procedures were carried out in accordance with the Utah State University Animal Care and Use Committee (IACUC 1389). Throughout the study, ewes and their lambs had *ad libitum* access to water and trace mineral salt blocks.

In late October 2008, four mature rams were selected based on breeding soundness evaluation exams and two rams were placed in each pen. Rams were painted with an oil-based brisket paint to monitor breeding/cover rates. Immediately following the addition of rams to each of the two pens, all animals in one pen (N=40) were given access to freshly cut 25 to 30 Kg of sagebrush, 2-

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3 times a week after they had been fed their complete basal diet of alfalfa pellets in *ad libitum* amounts and barley grain (400 g/head/day). Assuming that intake capacity of the ewes was 2 Kg per day (NRC, 1985), animals consumed between 0.2 (10% of their diet) and 0.3 Kg (15% of their diet) of sagebrush per day. Sagebrush (*Artemesia tridentata* spp. *tridentata*) was cut from surrounding foothills and placed in holding pens during mid-morning and re-assessed the next morning to confirm intake by ewes. Animals in the other pen were not offered sagebrush. Thus, pens only varied in exposure to sagebrush. At approximately 8 weeks of gestation, all ewes were ultrasounded to confirm pregnancy and eighty pregnant ewes (40 exposed to sagebrush; 40 without exposure to sagebrush) continued to receive their respective sagebrush exposure.

In January 2009, due to bad weather conditions, animals were moved to the Green Canyon Ecology Center, Utah State University, Logan, UT (41°45'58.5"N 111°47'14.2"W). In April, 2009 ewes began to lamb. At birth, lambs were identified by ear tags, vaccinated, males were castrated and tails docked in all lambs. Ewes and their lambs were placed in individual pens for 3 days following parturition. On day 4, lambs with their mothers were separated into four groups according to prior and subsequent exposure to sagebrush: 1) no exposure, 2) exposure *in utero*, 3) exposure *in utero* and for the first 2 mo of life, and 4) exposure for the first 2 mo of life.

Ewes and their lambs in Groups 3 and 4 were fed their basal diet of alfalfa hay and barley daily along with 25 to 30 Kg of freshly cut sagebrush 3 to 4 days a week from April to the end of June. Groups 1 and 2 were kept in a paddock free of sagebrush and fed only alfalfa hay and barley. Both groups were offered the same amount of ration. As animals were group-fed, individual intakes were not recorded. At approximately 8 weeks of age, all lambs were weaned. Lambs from all 4 groups were then placed on a common orchardgrass pasture until feeding trials began in October 2009.

Throughout the trial, the amount of alfalfa pellets fed to all lambs was variable across feeding periods while the amount of sagebrush offered to lambs in all 4 groups was presented in *ad libitum* amounts from 0800 to 1700 daily for 32 days. All sagebrush was collected daily and ground up (3-4 cm particle size) using a bark shredder. Excess sagebrush was sealed, frozen and used the following day.

Testing

Lambs from all groups were moved to individual adjacent pens, measuring 2.4×3.6 m, located outdoors under a protective roof. Lambs, regardless of exposure group, were randomly distributed and assigned to individual pens. There were 16, 17, 21, and 19 lambs in the groups 1) no exposure, 2) exposure *in utero*, 3) exposure *in utero* and for the first 2 mo of life, and 4) exposure for the first 2 mo of life, respectively.

In an attempt to mimic a scenario typical of what sheep would experience in rangelands with variable availability of high-quality understory alternatives, all lambs were then offered alfalfa pellets in *ad libitum* amounts as well as *ad libitum* amounts of freshly ground sagebrush for the first 5 days of the trial, from 0800 to 1700. After these 5 days, average individual intake of alfalfa pellets was calculated and for the subsequent 10 days, the amount of alfalfa pellets offered was decreased to 75% of the individual average intake per animal. During the following period, the amount of alfalfa pellets was decreased to 50% of the initial intake for 7 days. The amount of alfalfa pellets was then increased to 75% of initial intake again and this amount was fed for another 4 days. Pellets were then offered in *ad libitum* amounts for 5 days. Every day at 1700 the refused sagebrush and pellets were weighed and intake calculated and recorded. At day 32 all animals were weighed.

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Statistical Analyses

Sagebrush and alfalfa intake were analyzed as a split-plot design with lambs (random factor) nested within group. Group (1-no exposure, 2- exposure *in utero*, 3-exposure *in utero* and for the first 2 mo of life, and 4- exposure for the first 2 mo of life) was the between-animal factor and day was the repeated measure in the analysis (fixed factors). Final lamb weight was a covariate in the analysis to account for differences in BW across groups. All analyses were computed using a mixed-effects model (SAS Inst., Inc. Cary, NC; Version 9.1 for Windows). The variance-covariance structure used was the variance components, which yielded the lowest Bayesian information criterion. The model diagnostics included testing for a normal distribution of the error residuals and homogeneity of variance. Means were analyzed using pairwise differences of least squares means.

Results

Body weights

Lambs had similar body weights by the end of the trial: no exposure 44 kg (SEM = 1.7); exposure *in utero* 45 kg (SEM = 1); exposure *in utero* and for the first 2 mo of life 44 kg (SEM = 1); and exposure for the first 2 mo. of life 43 kg (SEM = 1.4) kg.

When lambs' body weight was used as a covariate in the analyses, no significant effects were observed of the covariate with group (alfalfa intake: group x weight $P = 0.27$; sagebrush intake: group x weight $P = 0.14$), suggesting that body weight was similar across groups and that it didn't bias food intake.

Alfalfa intake

No differences in alfalfa intake were detected among groups of lambs (Group effect; P = 0.24; group x day; P= 0.99): no exposure 1377 g (SEM = 30); exposure *in utero* 1405 g (SEM = 26), exposure *in utero* and for the first 2 mo of life 1384 g (SEM = 22); and exposure for the first 2 mo of life 1362 g (SEM = 23). A day effect (P < 0.0001) was detected due to the different amounts of alfalfa fed to the lambs during the different feeding periods.

Sagebrush intake

No differences regarding intake of sagebrush were detected among groups when animals had *ad libitum* access to alfalfa pellets (Figure 1; P > 0.10). However, a group x day interaction was observed (P = 0.003). When alfalfa pellets were offered at 50% of *ad libitum* intake; lambs in the group that had only *in utero* experience with sagebrush showed the lowest intakes of sagebrush (days 17-20; P < 0.05; Figure 1). In addition, intake of sagebrush during the second restriction of alfalfa pellets to 75% of *ad libitum* intake (days 23 to 26) was much greater by all groups of lambs than intake of sagebrush during the first restriction of alfalfa pellets to 75% of *ad libitum* intake (P< 0.05; days 6 to 15; Figures 1 and 2).

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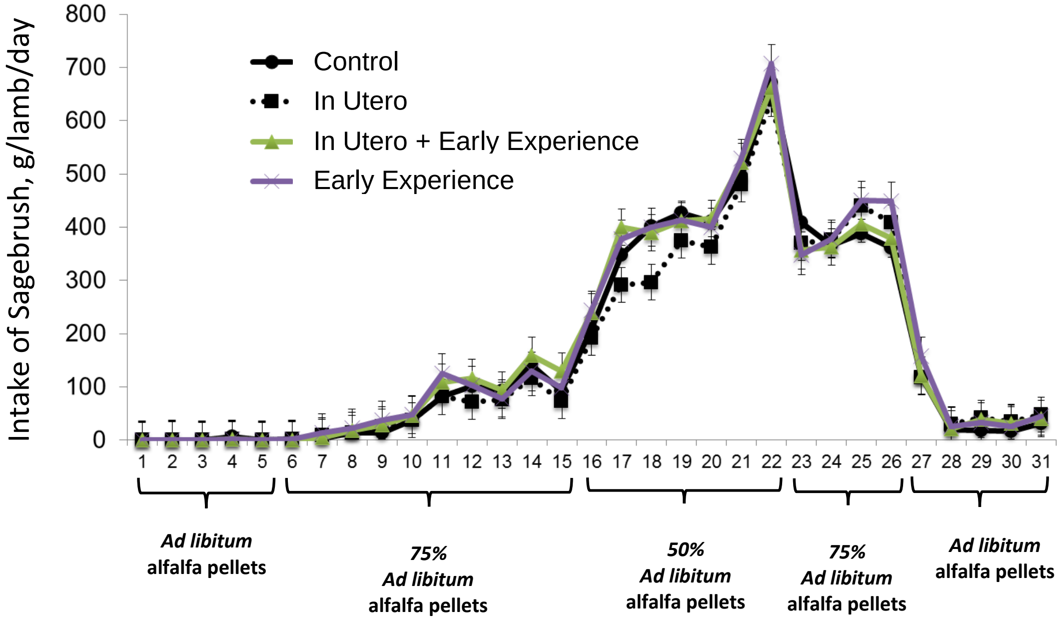

Fig. 1. Daily intake of sagebrush by four groups of lambs with different degrees of sagebrush exposure early in life. 1) no early exposure (Control), 2) exposure *in utero*, 3) exposure *in utero* and for the first 2 mo of life, and 4) exposure for the first 2 mo of life. Throughout the trial, the amount of alfalfa pellets fed to all lambs was variable across feeding periods (*ad libitum*; 75% of *ad libitum* and 50% of *ad libitum*) while the amount of sagebrush offered to lambs in all 4 groups and for all periods was presented in *ad libitum* amounts from 0800 to 1700 daily for 32 days.

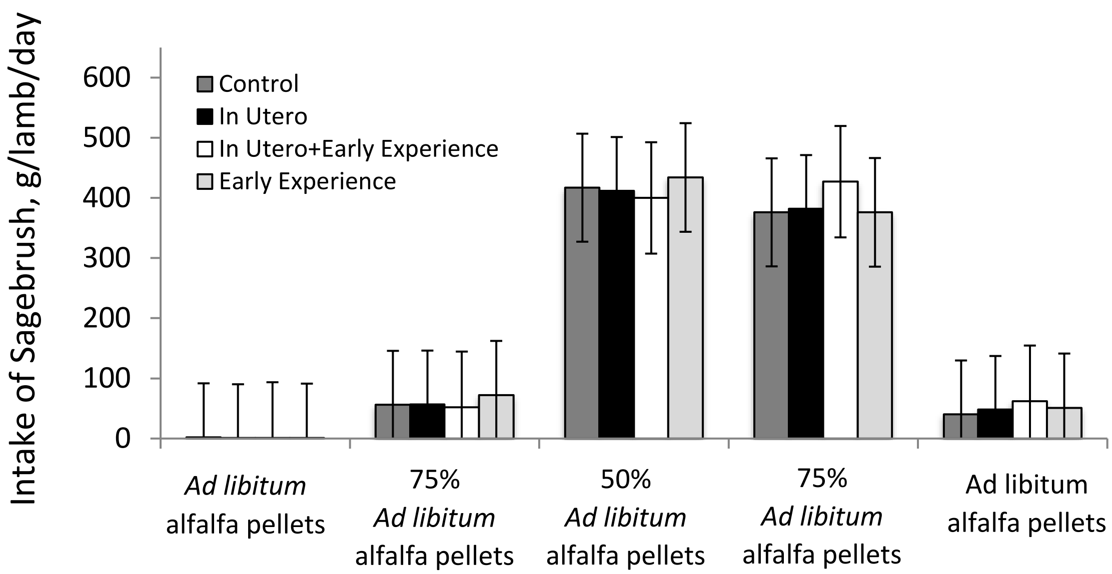

Fig. 2. Total average intake of sagebrush offered *ad libitum* by four groups of lambs with different degrees of sagebrush exposure early in life. 1) no early exposure (Control), 2) exposure *in utero*, 3) exposure *in utero* and for the first 2 mo of life, and 4) exposure for the first 2 mo of life. Intake was measured during different stages of pellet availability 1) *Ad libitum* pellets, 2) 75% *ad libitum*, 3) 50% *ad libitum*, 5) 75% *ad libitum*, and 6) *Ad libitum*.

Discussion

Early exposure to sagebrush (*in utero* and for the first 2 months of life) did not increase intake of sagebrush by lambs later in life. In fact, lambs exposed to sagebrush *in utero* showed the lowest intake of sagebrush (i.e., days 17-20) when availability of alfalfa pellets was restricted to 75% of *ad libitum* intake. This suggests that *in utero* exposure to sagebrush may have decreased sagebrush preference and/or the ability of lambs to consume sagebrush when they were forced to consume the shrub due to a restriction in the amount of alfalfa pellets available. Nevertheless, this reduction was transient and small relative to the differences observed in sagebrush intake by all groups across testing.

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Sheep exposed early in life to a low-quality feed (mature oat hay), later ate less of this feed than sheep that did not experience oat hay early in life (Catanese et al., 2010). Options that are commonly rated as 'good' can be perceived as 'less good' when experienced along with higher-quality alternatives (Flaherty and Sepanak, 1978). Consistent with this, sheep exposed early in life to an unpalatable feed 'devalue' this feed due to continuous comparisons against alternatives of greater quality (Catanese et al., 2011). On the other hand, heifers exposed to straw in utero ate more straw than non-exposed counterparts (Wiedmeier et al. 2002). It is possible that greater digestible dry matter intake – provided through associative effects triggered by supplementation - is important for pregnant cows and their offspring exposed to fibrous dormant low-quality forages, and thus this beneficial effect may enhance –instead on inhibit – preference for these forages by the offspring later in life (Wiedmeier et al., 2012).

Lambs exposed *in utero* to terpenes and other flavors from sagebrush may have "devalued" this feed when contrasted with ingestion of alfalfa pellets, a feed of much greater quality.

Alternatively, exposure *in utero* to terpenes in sagebrush may have reduced, instead of enhanced, the ability of lambs to detoxify terpenes in sagebrush. Studies *in vivo* as well as *in vitro* have shown that toxins are capable of changing the epigenetic pattern in certain cell types, leading to aberrant gene expression profiles in cells and tissues leading to disease (Rodenhiser and Mann, 2006; Smirnova et al., 2012; Kieffer and Medici, 2017).

The lack of positive responses of lambs to sagebrush intake as a function of experience could be due to the fact that exposure to sagebrush was not high enough to cause a permanent change in the animals' ability to ingest sagebrush. Greater exposure to sagebrush during conditioning (e.g., greater amounts of sagebrush consumed by ewes and lambs) might have enhanced the acceptability of this shrub by lambs later in life. Strong exposure effects have been identified in mammals such that the more frequently a particular food had been tasted, the better it is liked. Thus, the mere exposure effect may play a role in the acquisition and maintenance of food preferences (Pliner, 1982). This idea is supported by results found during testing in this study: Lambs forced to eat sagebrush due to restriction of alfalfa pellets (75% of intake capacity) consumed more sagebrush during the second exposure to that level of restriction than during the first exposure. Ruminants are typically neophobic when offered novel foods but they increase intake of the novel food as they become familiar with such food after a few days of exposure (Burritt and Provenza, 1989; Provenza, 1995). Thus, it appears that exposure to sagebrush during testing and for only a few days had a more pronounced effect on sagebrush intake than *in utero* or early in life experiences with the shrub. Nevertheless, an enhancement in sagebrush intake was observed only when the amounts of alfalfa pellets offered were restricted; intake of the shrub was negligible when *ad libitum* amounts of alfalfa were present either at the beginning or at the end of the study. Protein supplementation through the provision of alfalfa increased intake of sagebrush by cows (Petersen, 2014) and other terpene-containing plants such as juniper (Campbell et al., 207). Nevertheless, alfalfa provision in this study did not seem to have enhanced sagebrush intake by lambs. The greater availability of alfalfa during choice tests discouraged animals from consuming a lower-quality (and defended) shrub. Similarly, Shaw et al. (2006) observed that when animal density was low and there was high availability of preferred herbs, sheep that were previously conditioned to eat sagebrush due to understory restriction showed similar and very low preference for the shrub as sheep that had only experience with grazing high-quality herbs in the sagebrush understory (Control). However, when the animal density increased and there was a lower probability of encountering the

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preferred herbs, conditioned animals displayed a greater selection of sagebrush than animals in the Control group.

Lambs in all groups gradually increased intake of sagebrush during the first two weeks of testing. Notably, they ate significantly more sagebrush during the second 75% *ad libitum* trial than during the first 75% *ad libitum* trial, which suggests that detoxification systems in the liver and microbiome were adapting to sagebrush. In addition, while lambs' intake of sagebrush declined markedly during the last 100% *ad libitum* trial, they still ate more sagebrush in that trial than in the first 100% *ad libitum* trial. In support of the hypothesis that lambs adapt to sagebrush, prior exposure to a phenolic-rich resin extracted from *Larrea tridentata* altered the diversity and population structure of the gut microbiome in woodrats (*Neotoma bryanti and N. lepida*), which facilitated an increase in the abundance of genes that metabolize toxic compounds (Kohl and Dearing, 2012; Kohl et al., 2014). Additionally, herbivores increase the production enzymes in their tissues that detoxify plant toxins (i.e., cytochrome P450s) as a function of their previous exposure to these chemicals (Li et al., 2002; Delgoda and Westlak, 2004).

The decline in intake during the second transition of 75% *ad libitum* to 100% *ad libitum* trial may have been due to a transient aversion to sagebrush linked with the need to detoxify and eliminate terpenes from the animals' bodies. When terpenes are slowly infused into the rumen or the bloodstream as sheep eat a meal, sheep stop eating before the amount of infused terpenes reaches a toxic level (Dziba et al., 2006). They resume eating only after concentration of terpenes in the body decline. Terpenes thus affect satiation (processes that bring a meal to an end) and satiety (processes that inhibit eating between meals). Lambs reduce meal size (reach satiation sooner) and increase intervals between meals (longer satiety) as the amount of terpenes in their diets increase (Dziba and Provenza, 2007). Similar responses have been observed with cattle eating larkspur (Pfister et al., 1997). These physiological responses cause transient aversions that can last from hours to days (Provenza, 1996). In addition to the aforementioned physiological effects influenced by exposure, research suggests that teaching by mothers represent a powerful and positive influence after birth, which can influence dietary preferences and this mechanism may lead to improvements in sagebrush intake across generations (Petersen et al., 2014).

In summary, early exposure to sagebrush (*in utero* and for the first 2 months of life) did not increase intake of sagebrush by lambs later in life. Exposure to sagebrush during testing had a stronger impact on sagebrush intake than *in utero* and after birth experiences. However, such effect was only evident when the amounts of a high-quality alternative alfalfa were restricted. When alfalfa was available *ad libitum*, lambs displayed negligible intake of sagebrush regardless of their previous level of sagebrush exposure. Thus, exposing young lambs for several days to sagebrush while restricting the availability of high-quality forage is a viable option that may enhance utilization of sagebrush by sheep. In that regard, we note that providing supplemental nutrients markedly increases intake of sagebrush by enhancing detoxification processes (Villalba et al. 2002; Dziba et al., 2007).

Ethical Statement

No ethical issue.

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Conflict of interest statement

There is no conflict of interest for this work.

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