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# Abomasal Function Following Injections of Elfazepam and 9-Aza-Cannabinol

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KEIM, D. A., C. A. BAILE, J. R. BOLTON, P. J. WANGSNESS AND M. A. DELLA FERA. *Abomasal function following injections of elfazepam and 9-aza-cannabinol.* PHARMAC. BIOCHEM. BEHAV. **10**(1) 63–70, 1979.—The feed intake stimulants elfazepam (E), a benzodiazepine, and 9-aza-cannabinol (9-AC) decrease rumen contractions and abomasal acid content in sheep and E increases rumen fluid volume, digestibility and overall nutrient availability. E has been hypothesized to decrease the propulsive activity of the entire GI tract. To further examine the effects of E and 9-AC on gastric function, 4 ewes were prepared with abomasal cannulas and 3 silver/silver chloride monopolar electrodes alternated with 2 strain gauges on the distal one-third of the abomasal serosa. Electromyographical (slow waves and action potentials) and contractile (rates and forces) activities and abomasal pH were measured. Treatments of 8 and 16 mg E had no effect on slow wave frequency, action potential rate, contraction rate, or contraction force. Abomasal content pH was decreased with 8 mg E. Treatments of 125 and 250 μg 9-AC depressed action potential and contraction rates and contraction force but had no effect on slow wave frequency or pH.

Elfazepam  9-Aza-cannabinol  Abomasum  Slow waves  Action potentials  Contractions  pH

BENZODIAZEPINES and cannabinols can influence central nervous system (CNS) autonomic control of the gastrointestinal (GI) tract of both monogastrics and ruminants. Benzodiazepines reduce pressor and intestinal motility responses to hypothalamic stimulation [30] and reduce unstimulated (versus pentagastrin-stimulated) gastric secretion and volume of gastric juice in the monogastric stomach [11] and acid concentration, volume, and total acid secreted in the abomasum [33,34]. Benzodiazepines in sheep also decrease rumen contraction rate and fluid dilution rate resulting in increased rumen fluid volume [18] and ration nutrient availability [24,35]. Little is known about cannabinol effects on the monogastric GI tract; however, in ruminants, cannabinols severely decrease rumen contraction rate [17] and abomasal acid concentration, volume, and total acid secreted [33,34].

Elfazepam (7-chloro-1-[2-ethyl sulfonyl)ethyl]-5-(2-fluorophenyl)-1,3-dihydro-2-H-1,4 benzodiazepin-2-one) (E), a benzodiazepine, has been shown to increase feed intake in sheep [3, 5, 6, 7, 17, 18, 24, 33, 34], cattle [5, 21, 32], horses [19], and puppies [20], and increase the overall digestible nutrient supply from roughage rations in sheep [24,35] since the digestibility of the rations was not depressed when intake was increased [24]. Increased digestible nutrient supply could occur with decreased ruminal outflow which would allow greater time for digestive processes to occur. E injected IV did, in fact, decrease rumen contraction rate of sheep 35% but only when the sheep were not permitted to eat [5,18]. It has been speculated that elfazepam acting through the CNS, causes a general depression in GI propulsive activity.

A more potent inhibitor of rumen motility than E, 9-aza-cannabinol (10-hydroxy-β-(3-methyl-2-octyl)-5'5-dimethyl-5 H[1] benzopyranol[3,4-d] pyridine, HCl) (9-AC),decreased ruminal contraction rate of sheep for 15 to 120 min whether or not feed was available [17]. Similar to elfazepam, 9-AC increased feed intake in sheep [8, 9, 18], cattle [8], and rats (C. A. Baile and C. L. McLaughlin, unpublished data); however, a similar response was obtained using a smaller quantity of 9-AC than E.

To determine, then, if the depressant effects of elfazepam and 9-aza-cannabinol occur distal to the rumen, abomasal electromyographic (slow-waves and action potential bouts) and contractile (rate and force) activities and pH were measured in sheep injected IV with E and 9-AC.

## METHOD

Four crossbred ewes weighing approximately 40 kg were chronically implanted with three silver/silver chloride monopolar electrodes to measure abomasal electromyographical activity; the electrodes were alternated with two strain gauges (supplied by R. B. Products, Madison, WI) (for specific construction, see [10]) to record abomasal wall mechanical activity (Fig. 1). The electrodes were constructed as previously described by Bolton *et al.* [12], with the lead wires from the electrodes and strain gauges soldered into a miniature 9-pin plug and sealed into a stainless steel modified Thomas cannula. Each sheep was prepared with an abomasal cannula consisting of a piece of Silastic silicone rubber tubing 1.59 cm o.d. and 9.52 mm i.d. cut to a 15.2 cm length. A 7.62 cm o.d. flange of Medical Adhesive Silicone

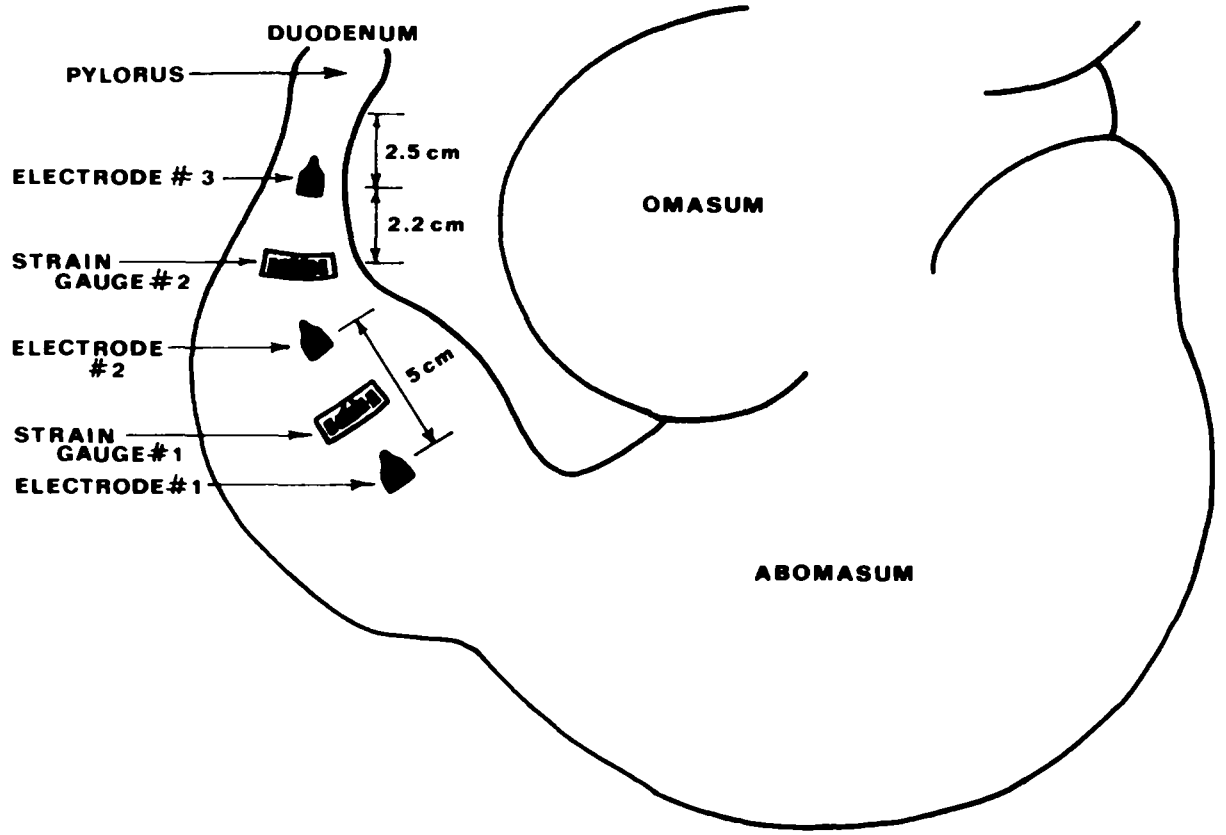


FIG. 1. Surgical placement of electrodes and strain gauges on the abomasum.

was formed at one end of the tube. The cannula was placed in the mid one-third of the abomasum and plugged with a rubber stopper which could be removed to obtain samples by simply allowing the abomasal contents to flow out.

An anesthesia mixture of oxygen and Halothane was used to maintain the sheep during the surgery. Using aseptic technique, a 10.2 cm paracostalceliotomy was made parallel and 2 cm caudal to the thirteenth rib. Electrode 3 was sutured 2.5 to 3 cm proximal to the pylorus and midway between the lesser and greater curvatures of the abomasum. The other electrodes and strain gauges were transversely placed alternately and proximally in a longitudinal line (Fig. 1). The strain gauges were sutured with the abomasum slightly stretched to keep each gauge taut and cause distortion of the gauge upon muscular contraction. A paralumbar incision was made midway between the last rib and the wing of the ileum. The stainless steel cannula was passed intraabdominally, was exteriorized through a stab incision 5 cm cranial to the paralumbar incision and was fastened to the peritoneum. Midway on the greater curvature an incision was made in the center of a purse string suture, the abomasal cannula was inserted, and the suture was tightened. A proxoplast mesh was sutured onto the abomasal serosa around the cannula. The cannula was then exteriorized through a stab incision in the eleventh intercostal space at the level of the costachondral junction.

The sheep were placed in individual crates and housed in a room with constant light and temperature. They were fed ad lib a pelleted diet composed of 47.0% alfalfa, 44.5% ground shelled corn, 8.0% molasses, and 0.5% trace mineral salt.

Recordings were made on a Honeywell 1508 Visicorder by connecting the 9-pin plug to a connector box strapped on the back of the sheep. The strain gauges were connected directly to Accudata 105 gauges in the recorder, then to Accudata 109 DC amplifiers with high frequency cutoffs of 100 hertz. The electrodes were connected to Accudata 108 AC amplifiers with low frequency cutoffs of 1 hertz and no high frequency cutoffs. Recordings were made on Kodak Linagraph direct print paper moving at 5 cm per min.

Two series of experiments were performed on each sheep. Treatments in each series were assigned randomly and consisted of 4 ml injections via an indwelling jugular catheter. One series included: carrier (1 ml ethanol, 3 ml propylene glycol), 8 and 16 mg E with feed present, and 8 and 16 mg E with feed absent. The second series included: carrier (2 ml ethanol, 2 ml water), 125 and 250 $\mu$g 9-AC with feed present, and 125 and 250 $\mu$g 9-AC with feed withheld.

Feed and water were available ad lib except for feed-withheld treatments, where feed was absent for 60 min after injection. One hour prior to injection the sheep were given fresh feed. Intakes were measured at −5, +15, +30, +60, +90 and +120 min. For feed-withheld treatments, intakes were measured at −5, +75, +90 and +120 min.

Abomasal content samples (15 ml) were collected from the abomasal cannula and the pH was measured at various intervals with an Orion Ionanalyzer Specific Ion Meter.

Recordings were begun 15 min prior to injection and were continued for 120 min after injection. The slow wave frequency was measured in cycles per minute. Bursts of action potentials (AP) (hereafter simply called action potentials) and contractions were measured as rates (AP/min, contrac-

tions/min). Action potentials were counted if the deflection of the recording pen was greater than the largest recorded slow wave encountered for each sheep (approximately 5 mV). The force of contractions was measured by the height of the peaks recorded from the strain gauges which were calibrated before insertion into the sheep. The frequencies of slow waves, action potentials, and contractions were averaged in 5 min intervals from −15 to +30 min to expose any rapidly occurring changes, and in 10 min intervals thereafter. Additional 5 min intervals were measured from +60 to +90 min for feed-withheld treatments. When no changes were apparent, various intervals of 15, 30 and 60 min were tabulated for ease of presentation.

The means were subjected to two-way analysis of variance, Duncan's multiple range test, and paired *t*-tests. Correlation coefficients were also computed.

## RESULTS

Electrode 3 was chosen for recording since this electrode, located most distally on the abomasum, enabled the best identification of slow waves. Because of the close proximity to electrode 3, strain gauge 2 was chosen for recording mechanical contractile activity.

### *Pretreatment period*

Pretreatment period parameters were not different between E and 9-AC series indicating no significant time effect on these parameters. The mean (n=40) slow wave frequency for the pretreatment periods for both series was 6.5 ± 0.1 cycles/min ($\bar{x}$ ± SEM), within the range (6 to 7) reported in sheep [29]. The mean action potential rate was 4.0 ± 0.4 action potentials/min; there was no difference (ANOVA) between successive days of pretreatment periods. The mean contraction rate was 3.6 ± 0.4 contractions/min and was highly correlated with the action potential rate (r=.86; n=10; $p<0.01$), indicative of the relationship between strain gauge 2 and electrode 3. The average contraction force was 75.59 ± 4.33×10$^{-3}$ Newtons/contraction. Action potential rate was not correlated with slow wave frequency (r=.25; n=10; NS), or contraction force (r=.41; n=10; NS) (the number of action potential bursts/min vs force/contraction/min) during this period. The mean pH of abomasal contents sampled immediately before treatment was 3.3 ± 0.1.

### *Elfazepam Effects*

The quantity of feed consumed during the first 60 min after administration of elfazepam was small and variable; therefore, an analysis of variance was applied to the data with feed present versus feed withheld. No significant difference was found, and the data were combined within treatment doses.

During the entire 120 min treatment period, the abomasal action potential rate was highly correlated with the contraction rate (r=.97; n=5; $p<0.05$). Treatments of 8 and 16 mg

TABLE 1

ABOMASAL PARAMETERS MEASURED BEFORE AND AFTER ELFAZEPAM (E) TREATMENT*

| Parameter / Time Period | Treatment: Carrier | 8 mg E | 16mg E |
|---|---|---|---|
| Slow Waves/Min | | | |
| −15 to 0 min | 6.6 ± 0.1 | 6.5 ± 0.1 | 6.4 ± 0.2 |
| 0 to 15 min | 6.4 ± 0.2 | 6.2 ± 0.1 | 6.2 ± 0.2 |
| 15 to 30 min | 6.4 ± 0.2 | 6.3 ± 0.2 | 6.2 ± 0.2 |
| 30 to 120 min | 6.6 ± 0.1 | 6.6 ± 0.1 | 6.5 ± 0.1 |
| Action Potentials/Min | | | |
| −15 to 0 min | 3.8 ± 1.2 | 4.6 ± 0.8 | 5.0 ± 0.5 |
| 0 to 15 min | 3.1 ± 1.1 | 2.0 ± 0.5 | 2.5 ± 0.8 |
| 15 to 30 min | 2.6 ± 0.8 | 3.8 ± 0.6 | 3.0 ± 0.3 |
| 30 to 120 min | 3.7 ± 0.3 | 5.2 ± 0.2 | 4.0 ± 0.2 |
| Contractions/Min | | | |
| −15 to 0 min | 3.1 ± 1.4 | 4.4 ± 0.8 | 4.7 ± 0.6 |
| 0 to 15 min | 2.7 ± 1.2 | 1.7 ± 0.5 | 2.3 ± 0.8 |
| 15 to 30 min | 2.6 ± 1.3 | 3.4 ± 0.8 | 2.8 ± 0.4 |
| 30 to 120 min | 3.4 ± 0.3 | 4.9 ± 0.2 | 3.8 ± 0.2 |
| Newtons × 10 $^{3}$/Contraction | | | |
| −15 to 0 min | 77.69 ± 29.21 | 67.91 ± 19.95 | 62.03 ± 6.88 |
| 0 to 15 min | 88.12 ± 26.95 | 46.60 ± 11.62 | 50.85 ± 2.20 |
| 15 to 30 min | 80.74 ± 5.52 | 53.90 ± 12.13 | 53.57 ± 5.02 |
| 30 to 120 min | 101.26 ± 9.74 | 101.67 ± 6.78 | 83.31 ± 4.95 |
| pH | | | |
| −15 to 0 min | 3.5 ± 0.5 | 3.4 ± 0.6 | 3.4 ± 0.5 |
| 0 to 15 min | 3.6 ± 0.3 | 3.1 ± 0.4 | 3.4 ± 0.4 |
| 15 to 30 min | 3.5 ± 0.7 | 3.4 ± 0.5 | 3.3 ± 0.4 |
| 30 to 120 min | 3.4 ± 0.3 | 3.5 ± 0.1 | 3.5 ± 0.1 |

*Data expressed as mean (n=4) ± SEM.

elfazepam had no effect on slow wave frequency, abomasal action potential rate, contraction rate or contraction force (Table 1).

Treatments of 8 mg E decreased abomasal pH compared to the carrier during the first 15 min after injection. This effect was masked by the absolute mean values computed for this period, but proved significant when mean pH changes (Δ) were computed subtracting mean pH values during the 15-min postinjection period from the 15-min pretreatment period (−0.3 ± 0.1 with 8 mg E versus +0.3 ± 0.2 with carrier, $p<0.05$). The pH changes (Δ) with E were no longer different from the carrier during 15 to 30 min (0.3 ± 0.2 with 8 mg E versus −0.2 ± 0.4 with carrier). Side effects occasionally noted for the length of the treatment period with E included ataxia, excessive salivation, drowsiness, and hyperventilation.

*9-Aza-Cannabinol Effects*

As in the elfazepam series, the quantity of feed consumed during the first 60 min after injection of 9-aza-cannabinol or the carrier was small and variable. An analysis of variance was applied to the data and no difference was found between parameters measured in this series with feed present and those with feed withheld; therefore, the data were combined within each dose.

Abomasal action potential and contractile rates were depressed within 1 to 3 min after injection of 9-AC (Fig. 2). The action potential rate during the 120 min treatment period was highly correlated with both the contraction rate (r=.98; n=5; $p<0.01$) and the contraction force (r=.97; n=5; $p<0.01$); however, the contraction force was not depressed by the chemical before the 15 to 30 min interval (Table 3). During the 15-min postinjection period, treatments of 125 and 250 μg 9-AC compared to the carrier severely depressed action potential and contraction rates ($p<0.05$) shown by changes (Δ) in these parameters from the pretreatment period to the 15-min post-treatment period (Tables 2 and 3). This effect was not apparent when the absolute means for these parameters were analyzed, probably due to the wide variability between animals. The effect of 9-AC on these parameters continued through the 15 to 30 min period since the changes measured in these parameters during this period were small, thus indicating no further depression (Table 3). Also during this period, the contraction force was decreased ($p<0.05$) (Table 3) because the few contractions that did occur were quite weak. During the 30 to 90 min interval, treatments of 250 μg 9-AC continued to suppress action potential and contraction rates and contraction force severely enough to reflect the decrease in the absolute mean values ($p<0.05$) (Table 2). By 90 to 120 min, these parameters were recovering from the 250 μg 9-AC treatments and were not different from the carrier (Table 2).

Abomasal slow wave frequency and pH were not affected by treatments of 125 or 250 μg 9-AC (Tables 2 and 3). The 125 μg dose of the chemical did, however, increase water intake during the 90 to 120 min period (621 ± 56 ml vs 0 ml for carrier) ($p<0.05$). Side effects with 9-AC were similar to those with E and included ataxia, drowsiness, and an overall depressed attitude, all of which, when present, lasted for the length of the treatment period.

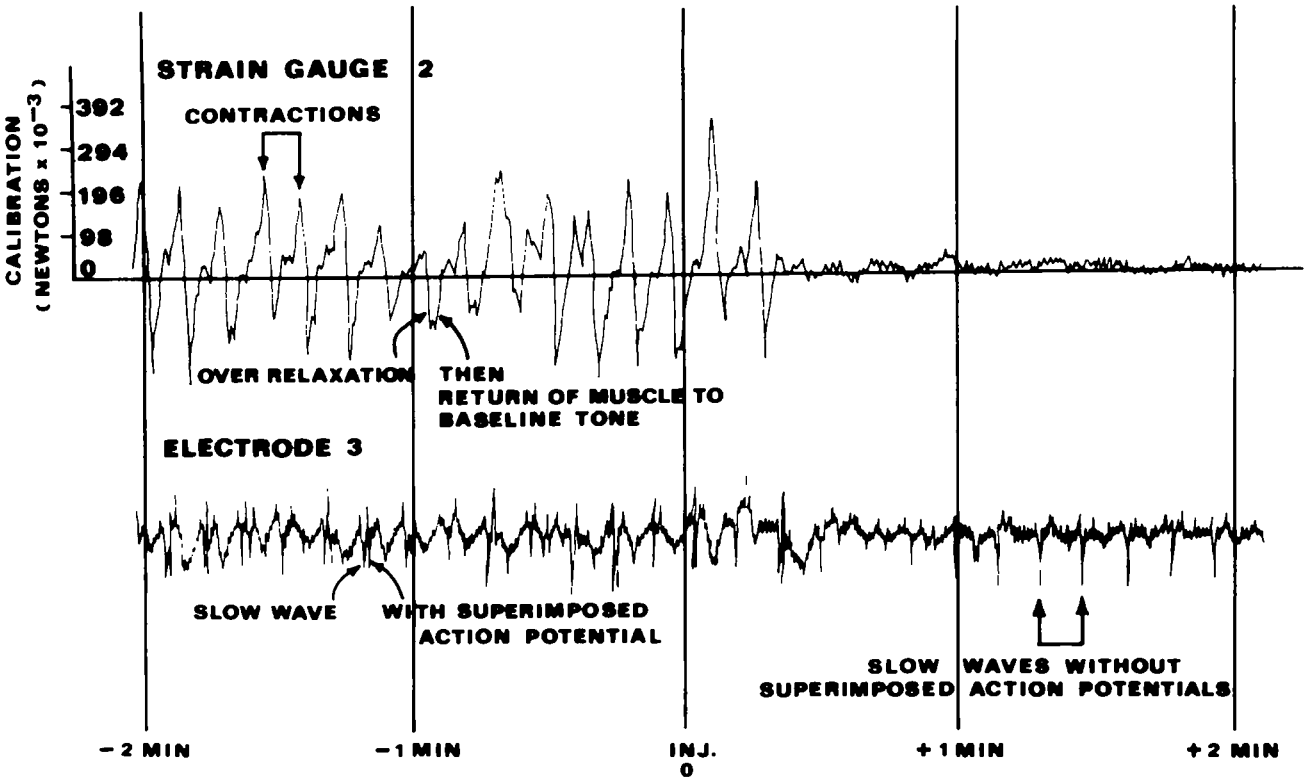


FIG. 2. Copy of a section of recording from sheep 4 before and following injection of 250 μg 9-aza-cannabinol (9-AC).

TABLE 2

ABOMASAL PARAMETERS MEASURED BEFORE AND AFTER 9-AZA-CANNABINOL (9-AC) TREATMENT*

| Parameter Time Period | Treatment Carrier | 125 μg 9-AC | 250 μg 9-AC |
|---|---|---|---|
| Slow Waves/Min | | | |
| -15 to 0 min | 6.4 ± 0.1 | 6.6 ± 0.2 | 6.6 ± 0.1 |
| 0 to 30 min | 6.3 ± 0.1 | 6.6 ± 0.2 | 6.6 ± 0.1 |
| 30 to 90 min | 6.6 ± 0.1 | 6.6 ± 0.1 | 6.4 ± 0.1 |
| 90 to 120 min | 6.5 ± 0.2 | 6.8 ± 0.1 | 6.6 ± 0.2 |
| Action Potentials/Min | | | |
| -15 to 0 min | 2.2 ± 0.6 | 4.3 ± 0.9 | 4.0 ± 0.9 |
| 0 to 30 min | 2.2 ± 0.9 | 0.8 ± 0.7 | 0.5 ± 0.4 |
| 30 to 90 min | 4.6 ± 0.8[b] | 3.2 ± 1.1[ab] | 0.4 ± 0.2[a] |
| 90 to 120 min | 4.2 ± 1.3 | 4.8 ± 1.3 | 2.0 ± 1.0 |
| Contractions/Min | | | |
| -15 to 0 min | 2.2 ± 0.5 | 3.8 ± 1.2 | 3.4 ± 1.0 |
| 0 to 30 min | 1.8 ± 0.9 | 0.6 ± 0.4 | 0.0 ± 0.0 |
| 30 to 90 min | 4.5 ± 0.8[b] | 3.0 ± 1.2[ab] | 0.3 ± 0.2[a] |
| 90 to 120 min | 4.2 ± 1.3 | 4.6 ± 1.4 | 1.8 ± 1.0 |
| Newtons × $10^{-3}$/Contraction | | | |
| -15 to 0 min | 77.76 ± 20.66 | 93.24 ± 30.52 | 74.87 ± 21.22 |
| 0 to 30 min | 49.07 ± 21.08 | 23.28 ± 11.20 | 7.24 ± 7.24 |
| 30 to 90 min | 98.69 ± 25.09[b] | 74.63 ± 22.57[ab] | 25.78 ± 13.33[a] |
| 90 to 120 min | 106.04 ± 8.33 | 110.64 ± 33.63 | 56.25 ± 23.52 |
| pH | | | |
| -15 to 0 min | 3.2 ± 0.7 | 3.1 ± 0.4 | 3.4 ± 0.6 |
| 0 to 30 min | 2.7 ± 0.2 | 2.2 ± 0.1 | 2.6 ± 0.4 |
| 30 to 90 min | 2.7 ± 0.1 | 2.8 ± 0.2 | 2.9 ± 0.2 |
| 90 to 120 min | 2.8 ± 0.1 | 3.1 ± 0.4 | 3.0 ± 0.2 |

*Data expressed as mean (n=4) ± SEM.
[ab]Means with different superscripts are different, ANOVA, $p<0.05$.

## DISCUSSION

Slow waves consist of cyclic depolarization and repolarization fluctuations of 5 to 15 mV of the smooth-muscle membrane potentials [1,13] and occur regardless of the presence or absence of contractions [37]. Action potentials, usually associated with contractile activity of the muscle [14] normally occur during the positive phase of the slow wave; therefore, the frequency of action potentials and contractions is dependent upon the slow wave frequency [16,38].

As previously reported in sheep [12] action potentials were superimposed on the last portion of the slow waves, and never occurred without the presence of a slow wave. The slow wave frequency and action potential rate were not highly correlated during this study possibly because bouts of action potentials often occurred sporadically with variable periods of time between bouts while slow waves occurred at regular time intervals.

The contraction rates were highly correlated with the action potential rates throughout this study. The choice of electrodes may have biased the correlations since the recording electrode was most distal on the abomasum and probably recorded action potentials of greatest amplitude that would normally be associated with abomasal contractions [12]. Also, infrequently, the most distal electrode records action potentials that are not associated with more proximal contractile activity and active abomasal emptying (Bolton, personal communication).

It is possible that elfazepam has a slight depressing effect on ruminant GI tract motility though the results of this study do not support this speculation. The previous report of decreased rumen contraction rate with elfazepam states this effect occurred only when the sheep were not permitted to eat [5,18]. Therefore, the depressing effect of elfazepam may be partially overriden by normal GI motility associated with feeding. A slight depression in ruminal outflow, however, could explain the increased nutrient digestibility and availability previously reported by allowing greater time for ruminal digestive processes. A decreased ruminal outflow, in turn, would decrease abomasal outflow since the inflow to the abomasum of predigested food from the forestomach is integrated with the flow of material from the abomasum [2]. Other animal studies have shown that diazepam, another benzodiazepine, reduced central autonomic effects such as the pressor and intestinal motility responses to hypothalamic stimulation in the cat [30]. The decreased ruminal motility previously reported and unaltered slow wave frequency in

TABLE 3

CHANGES (Δ) IN ABOMASAL PARAMETERS MEASURED AFTER 9-AZA-CANNABINOL (9-AC) TREATMENT *

| Parameter Change Time Period | Treatment Carrier | 125 μg 9-AC | 250 μg 9-AC |
|---|---|---|---|
| Δ Slow Waves/Min | | | |
| −15 to 0 min vs 0 to 15 min | −0.2 ± 0.3 | −0.4 ± 0.1 | −0.3 ± 0.1 |
| 0 to 15 min vs 15 to 30 min | 0.0 ± 0.0 | 0.0 ± 0.0 | 0.0 ± 0.0 |
| Δ Action Potentials/Min | | | |
| −15 to 0 min vs 0 to 15 min | −0.6 ± 0.8[a] | −3.7 ± 1.0[b] | −3.4 ± 1.0[b] |
| 0 to 15 min vs 15 to 30 min | 0.3 ± 0.2 | 0.1 ± 0.1 | 0.2 ± 0.1 |
| Δ Contractions/Min | | | |
| −15 to 0 min vs 0 to 15 min | −1.0 ± 0.6[a] | −3.5 ± 1.1[b] | −3.3 ± 1.0[b] |
| 0 to 15 min vs 15 to 30 min | 0.3 ± 0.2 | 0.1 ± 0.1 | 0.0 ± 0.0 |
| Δ Newtons $\times 10^{-3}$/Contraction | | | |
| −15 to 0 min vs 0 to 15 min | −38.79 ± 5.54 | −66.81 ± 29.26 | −58.14 ± 11.24 |
| 0 to 15 min vs 15 to 30 min | 5.05 ± 3.04 | −1.57 ± 3.08 | −3.68 ± 4.12 |
| Δ pH | | | |
| −15 to 0 min vs 0 to 15 min | −0.4 ± 0.2 | −0.9 ± 0.4 | −0.5 ± 0.1 |
| 0 to 15 min vs 15 to 30 min | 0.0 ± 0.3 | 0.0 ± 0.1 | −0.1 ± 0.2 |

*Data expressed as mean (n=4) ± SEM.
[ab]Means with different superscripts are different, ANOVA, $p<0.05$.

this study could be accounted for if elfazepam affects CNS autonomic function, specifically sympathetic function [16].

Diazepam has also been shown to influence autonomic function causing reduced unstimulated gastric secretion and volume of gastric juice [11]. As previously reported, elfazepam also decreased abomasal acid concentration, volume, and total acid secreted in sheep prepared with Pavlov abomasal pouches [33,34]. The reason for the decrease in abomasal content pH which occurred with the lower 8 mg dose of elfazepam in this study is not clear.

Benzodiazepines have been shown to override the inhibitors of feeding associated with apparent metabolic products, gastric distention, protein deficiency anorexia, heat stress, amphetamine-induced anorexia [6] and pathologically associated anorexia [19]. These chemicals have been shown to elicit feeding in many species [5, 19, 28] apparently by their activity on the CNS [19]. Elfazepam failed to affect feed intake when injected either into the anterior hypothalamus of sheep or into the lateral hypothalamus of rats; when elfazepam was injected into the anterior preoptic area, sheep doubled their average intake. The lack of feeding with E in this study was probably due to disruption of the feeding patterns of the sheep with abomasal content sampling. Nevertheless, it is probable that the benzodiazepines, including elfazepam, affect the hypothalamus since much integration of the many signals important in the regulation of feeding and energy balance probably takes place there [4].

The depressant effects of 9-AC on abomasal motility were expected since treatments of 250 μg 9-AC were previously shown to decrease ruminal contraction rate for 15 to 120 min whether or not feed was available [17]. The chemical, then, may affect the propulsion of digesta in the rumen in a similar but more severe manner than elfazepam. The abomasal motility may be initially depressed since the effect of 9-AC was almost immediate. Decreased abomasal motility, then, could cause a decrease in the outflow of digesta from the abomasum to the duodenum, and a compensatory decrease in outflow from the forestomachs to the abomasum; hence the longer time period before decreased activity is observed in the rumen.

Cannabinols probably elicit their effects in some discrete area of the CNS. Since cannabis has been found to be an effective analgesic with impressive anticonvulsant and muscle-relaxing properties in humans [25], action through

the autonomic nerve supply may account for the rapidly depressed abomasal activity, previously reported depressed ruminal activity in sheep, and may also explain why 9-AC had no effect on the abomasal slow wave frequency during the entire treatment period. Though feed intake in this study was not affected by 9-AC, cannabinols may also directly stimulate the lateral hypothalamus to elicit feeding, unlike the benzodiazepines which might suppress the inhibitory action of the ventromedial hypothalamus, resulting in increased lateral hypothalamic activity and consequent feeding.

Treatments of 9-AC had no effect on abomasal content pH. Severely decreased acid concentration, volume and total acid secreted have been reported with 9-AC treatments in sheep prepared with Pavlov abomasal pouches, 9-AC being a more potent inhibitor of abomasal acid secretion than elfazepam [33,34]. A change in pH may not have been apparent due to the dilution of abomasal secretions with digesta.

Another effect of 9-AC was increased water intake during the 90 to 120 min period with the lower dose of 125 $\mu$g. It has been reported that 250 $\mu$g 9-AC decreased drinking bar presses 90% and time spent drinking 91% in sheep [9]. Previous reports also showed that $\Delta^9$-THC decreased water intake at high doses [15, 22, 27, 31], but increased water intake at low doses [23,36]. The lower dose of 9-AC may have shown this phenomenon while the higher dose was not as effective.

The other side effects with 9-AC were previously reported to some extent in humans [26] and were expected for a compound with possible anticonvulsant and muscle-relaxing properties.

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