Pharmacology Biochemistry & Behavior, Vol. 11, pp. 51–56. Printed in the U.S.A.

Feeding and Depression of Abomasal Secretion in Sheep Elicited by Elfazepam and 9-Aza-cannabinol

G. W. VAN DEN BROEK, J. ROBERTSON, D. A. KEIM AND C. A. BAILE

New Bolton Center, Department of Clinical Studies, University of Pennsylvania School of Veterinary Medicine, Kennett Square PA 19348

Received 1 December 1978

VAN DEN BROEK, G. W., J. ROBERTSON, D. A. KEIM AND C. A. BAILE. *Feeding and depression of abomasal secretion in sheep elicited by elfazepam and 9-aza-cannabinol.* PHARMAC. BIOCHEM. BEHAV. 11(1) 51–56, 1979.—Elfazepam (7-chloro-1-[2-(ethylsulfonyl)ethyl]-5-(2-fluorophenyl)-1,3-dihydro-2*H*-1,4benzodiazepin-2-one) and-9-aza-cannabinol (10-hydroxy-β-(3-methyl-2-octyl)-5′,5-dimethyl-5H-1 benzopyranol 3,4-d pyridine, HCl) were administered IV to study their effects on feed intake and acid secretion in abomasal Pavlov pouches in sheep. Elfazepam and 9-aza-cannabinol increased 3-fold 3 hr postinjection feed intake and decreased abomasal acid secretion compared to saline and DMSO (dimethyl sulfoxide) control treatments. At doses which elicit feeding, 9-aza-cannabinol was a much more potent inhibitor of acid secretion than elfazepam. These results are consistent with the theory of localized hypothalamic nuclei which have roles in the control of both feed intake and gastric acid secretion. However, in contrast to feeding associated with normal hunger, the benzodiazepine and cannabinol stimulated feeding is associated with decreased gastric acid secretion.

Abomasal acid secretion Chemical feed intake stimulants Elfazepam 9-Aza-cannabinol Sheep

SEVERAL studies have demonstrated the dual control by hypothalamic nuclei on feed intake and gastric acid secretion and motility in the rat. Bilateral lateral hypothalamic (LH) lesions produced acute reductions in food intake and body weight, decreased gastric acid secretion [28], and increased intestinal transit rate [29]. Bilateral ventromedial hypothalamic (VMH) lesions produced hyperphagia and obesity, increased gastric acid secretion [30] and decreased intestinal transit rate [29].

Elfazepam (E) (7-chloro-1-[2-ethylsulfonyl)ethyl]-5-(2-fluorophenyl)-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one) and 9-aza-cannabinol (9-AC) (10-hydroxy-β-(3-methyl-2-octyl)-5′,5-dimethyl-5H-1 benzopyranol 3,4-d pyridine, HCl) have been reported to stimulate feed intake in sheep [5,12], cattle [5,24] and rats [24]. Both chemicals depressed rumen contraction rate [11] and 9-AC also reduced abomasal motility [21]. In sheep, E decreased the rate of rumen emptying [12] and increased the digestibility of several rations [16, 22, 34], perhaps by some central nervous system-elicited inhibition of gastrointestinal motility and rate of digesta passage.

The present study describes the effect of these two chemical feed intake stimulants on abomasal acid secretion in sheep.

METHOD

The innervated Pavlov abomasal pouch was prepared by the following procedure which is similar to a previously described procedure [32]. Sheep were immobilized with sodium pentobarbital, intubated and maintained on halothane anesthesia during surgery. With the animal in left lateral recumbency, a 15 cm incision was made parallel and 5 cm caudal to the last right costal arch starting 5 cm lateral to the xyphoid process. The omasum and abomasum were exteriorized and a window cut in the greater omentum to expose the greater curvature of the abomasum. A 6 to 8 cm incision was made longitudinally along the greater curvature midway between the omaso-abomasal and pyloric orifices, exposing the abomasal fundic region with its large, acid-secreting mucosal folds. Digesta were removed with suction, the pouch area isolated by clamping the abomasum proximal and distal to the incision, the abomasum washed with sterile saline and packed off with sterile towels. The mucosal surface was exposed by everting the abomasal wall. A fine, shallow circular incision was made through the mucosal and submucosal layers, thus delineating the internal border of the pouch. Three successive, interrupted suture lines (00-chromic gut, Ethicon Corp., Somerville, NJ) were sewn to close the mucosa-submucosa of the main body of the abomasum, the underlying connective tissue-muscle layer and the mucosa-submucosa of the internal border of the pouch, respectively. The abomasal incision along the greater curvature was closed and a Silastic® cannula (3 mm ID, 6 mm OD, Dow Corning Corp., Midland, MI) was sewn into the closure. A nylon mesh was sutured over the incision to reinforce the abomasal wall and prevent the cannula from pulling out. The cannula was exteriorized through a separate

TABLE 1

EFFECT OF ELFAZEPAM AND 9-AZA-CANNABINOL ON FEED INTAKE (g)*

Period Postinjection	Saline	DMSO	Elfazepam ad lib	Elfazepam restrict	9-aza-cannabinol
A. Feed available 0–3 hr postinjection					
0–1 hr	80.0^{x}†	66.7^{x}	303.3^{y}	83.3^{x}	272.0^{y}
	±20.8	±14.5	± 6.7	± 6.8	± 21.7
1–2 hr	46.6	36.7	56.7	38.3	50.0
	±13.3	± 6.7	±15.0	± 3.3	± 14.5
2–3 hr	40.0	50.0	56.7	38.3	56.7
	±23.1	± 5.7	±15.0	± 3.3	± 14.5
0–3 hr	166.7^{x}	153.3^{x}	416.7^{y}	160.0^{x}	378.3^{y}
	±14.5	±24.0	±23.6	±15.3	± 24.0
B. Feed available 1–3 hr postinjection					
0–1 hr	-	-	-	-	-
1–2 hr	110.0^{x}	106.7^{x}	467.0^{y}	103.3^{x}	353.3^{y}
	±45.8	± 6.7	±56.1	±14.5	± 79.7
2–3 hr	40.0	23.3	13.3	36.7	63.3
	±15.3	±12.0	±13.3	± 6.7	± 31.8
0–3 hr	150.0^{x}	130.0^{x}	480.0^{y}	140.0^{x}	416.7^{y}
	±32.1	±17.3	±43.6	±20.8	±104.8

*Mean ±SEM of 3 sheep

†Means within a row having different superscripts are significantly different, ($p<0.01$).

stab wound, the nylon mesh sutured to the ventral abdominal wall and the abdominal incision closed. Sheep were placed on 5-day, post-operative antibiotic treatment and one month elapsed before any animal was used experimentally.

The three sheep used were housed in individual metabolism crates in a closed room free from outside noise. Water and a complete, pelleted feed were available ad lib. Fresh feed was given at 7:30 a.m., at which time collection of abomasal pouch secretions began. Chemicals were injected at about 9:00 a.m. and feed intake was recorded hourly thereafter. Animals were trained to stand in their stalls for the entire collection period.

Order of injection of chemicals was assigned using a randomized block design. The chemicals were: saline, dimethyl sulfoxide (DMSO), DMSO + 5.5 μg/kg body weight 9-AC, and DMSO + 0.35 mg/kg body weight E. A total volume of 1 ml was injected into the jugular vein. DMSO was used as the carrier substance because the chemicals are insoluble in aqueous solution and ethanol markedly reduced abomasal acid secretion. Feed was available ad lib and was present 0 to 3 hr postinjection or was withheld for 1 hr postinjection. An additional E treatment, with feeding restricted to control level intake (average of intakes after saline and DMSO injections), was added on the final day of both treatment series.

Serial collections of abomasal acid secretion were made for 15-min periods in test tubes attached to the abomasal cannula. The volumes of secretions were determined at the time of collection. Aliquots were titrated to pH 7.2 against 0.01 N NaOH in an Auto-Burette (Radiometer, Copenhagen, Denmark), and acidity expressed as meq H^+/liter. Total acid secreted (acidity × volume) is expressed as meq H^+/15 min. The data were subjected to analysis of variance and significant differences among means determined by Duncan's multiple range test [13].

RESULTS

Compared to saline and DMSO treatments, 9-AC and E stimulated feed intake in satiated sheep (Table 1). Both chemicals caused intense feeding activity when feed was first available: either at the time of the injection or 1 hr postinjection. 9-AC and E increased feed intake the first hour feed was available ($p<0.01$) but not during subsequent hours. For the total 3-hr postinjection period, 9-AC and E increased feed intake compared to saline and DMSO treatments ($p<0.01$). Total 3-hr feed intakes for all treatments were not affected by withholding feed 1 hr postinjection.

Although attempts were made to create a standardized abomasal pouch (50 cc), volume of unstimulated pouch secretions differed among sheep. Average preinjection values for the three sheep were: volume, 7.26 ml/15min; acidity, 72.8 meq H^+/liter; and total acid secreted 0.551 meq H^+/15 min. Acidity and total acid secreted for a particular sheep were variable on different days despite a regular feeding schedule. As a result, data herein are expressed not as an absolute amount of acid secreted, but as a percentage of preinjection level of acid output. The validity of the use of ratios (eg., preinjection value/postinjection value) in analysis of variance has been recently discussed [1]. Our preinjection vs postinjection ratios meet the statistical criteria presented in this publication [1], thus validating the use of analysis of variance in the evaluation of our data.

Preinjection acid secretion was typically constant for each sheep on a particular day and preinjection measurements of acid output were based on a minimum of six 15-min

TABLE 2

EFFECT OF ELFAZEPAM AND 9-AZA-CANNABINOL ON ACIDITY (meq H^+/ liter) OF ABOMASAL POUCH SECRETIONS*

Period Postinjection	% of Preinjection Value Saline	DMSO	Elfazepam ad lib	Elfazepam restrict	9-aza-cannabinol
A. Feed available 0–3 hr postinjection					
0–1 hr	101.5^{cy}† ± 3.3	90.3^{bcy} ±10.1	66.6^{bxy} ±11.2	67.8^{bxy} ± 7.1	37.3^{ax} ± 8.1
1–2 hr	92.5^{by} ± 9.3	75.4^{bxy} ±28.3	59.1^{bxy} ±22.8	75.8^{bxy} ±12.3	10.0^{ax} ± 8.2
2–3 hr	85.1^{b} ±13.0	84.0^{b} ± 9.6	61.0^{ab} ±20.1	55.4^{ab} ±16.6	35.9^{a} ±25.9
0–3 hr	93.0^{by} ± 9.3	83.2^{by} ±14.1	62.2^{bxy} ±17.0	66.3^{bxy} ±11.5	27.3^{ax} ± 8.8
B. Feed available 1–3 hr postinjection					
0–1 hr	92.5^{by} ± 6.9	71.6^{aby} ±21.8	62.5^{axy} ± 4.9	55.0^{axy} ± 9.5	35.8^{ax} ±14.4
1–2 hr	79.4^{bc} ±39.1	85.1^{c} ± 4.8	73.4^{bc} ± 5.1	56.1^{b} ± 5.7	17.4^{a} ±17.4
2–3 hr	85.8^{b} ±20.0	91.3^{b} ± 2.8	69.4^{b} ±26.7	66.7^{ab} ±17.5	26.1^{a} ±10.6
0–3 hr	85.7^{cz} ±15.7	82.7^{cz} ± 7.7	68.5^{byz} ± 9.1	59.2^{by} ± 6.2	26.4^{ax} ± 8.6

*Mean ±SEM of 3 sheep

†Means within a row having different superscripts are significantly different (x,y,z, $p<0.01$; a,b,c, $p<0.05$).

serial collections. Acid output, expressed either as acidity (meq H^+/liter, Table 2) or total acid content (meq H^+/15 min, Table 3) tended to decrease after control treatments (saline or DMSO), thus postinjection levels were generally less than 100% of preinjection values. Acid output tended to be lower after DMSO than saline injections, although none of the hourly means between the two treatments were significantly different ($p>0.05$).

9-AC inhibited all measured parameters of abomasal acid secretion (Tables 2, 3, 4). Expressed as a percentage of preinjection values, 9-AC reduced acidity (meq H^+/liter, Table 2) and total acid secreted (meq H^+/15 min, Table 3) compared to saline and DMSO treatments. The reduction in acid secretion occurred during each 1-hr period and the total 3-hr postinjection period. The greatest inhibition of acid secretion occurred 0.5 to 2.0 hr postinjection with a step-like decrease during the first hour. The volume of abomasal secretions was also reduced by 9-AC, but to a lesser extent than hydrogen ion secretion (Table 4). The presence or absence of feed 1 hr postinjection had no effect on 9-AC inhibition of acidity (Table 2A vs 2B), total acid secreted (Table 3A vs 3B), or volume (Table 4A vs 4B) during the postinjection period.

Elfazepam also reduced all measured parameters of abomasal acid secretion but to a lesser extent than 9-AC. Compared to saline and DMSO treatments, E reduced total 3-hr acidity (meq H^+/liter, Table 2), although the effect was statistically significant only when feed was withheld the first hour postinjection ($p<0.05$, Table 2B). There were similar 3-hr decreases in acidity when feed was available 0–3 hr postinjection; however the results were not statistically significant due to the large standard error during this particular trial. The presence or absence of feed 1 hr postinjection (Table 2A vs 2B) or ad lib vs restricted levels of feed intake had no effect on reductions of abomasal acidity after E treatment. Three-hr postinjection levels of acidity for the four treatments ranged between 59 and 69% of preinjection values and did not significantly differ.

E reduced total acid secreted (meq H^+/15 min, Table 3) for 3-hr postinjection, but again a significant reduction was observed only when feed was withheld 1 hr postinjection ($p<0.05$, Table 3B). Comparing the two E treatments, total acid secreted was significantly lower when intake was restricted (140 g) than when intake was ad lib (480 g). Total 3-hr postinjection acid contents were 40.7% and 56.8% of preinjection levels, respectively. Acid contents were similar during the first postinjection hour when feeding was not permitted; during the second and third hours, acid contents were 42.5% and 40.5% for the restricted treatment, and 5.9% and 65.1% for the ad lib treatment. E also reduced 3-hr volume of abomasal secretion when feed was available 1 to 3 hr postinjection ($p<0.05$, Table 4B).

DISCUSSION

In sheep, the level of abomasal acid secretion is determined by the rate of digesta flow through the abomasum, abomasal pH and concentration of VFA [3, 4, 18, 19, 26].

TABLE 3

EFFECT OF ELFAZEPAM AND 9-AZA-CANNABINOL ON TOTAL ACID CONTENT (meq H^+/15 min) OF ABOMASAL POUCH SECRETIONS*

Period Postinjection	% of preinjection value Saline	DMSO	Elfazepam ad lib	Elfazepam restrict	9-aza-cannabinol
A. Feed available 0–3 hr postinjection					
0–1 hr	101.0^{bz}† ± 0.8	76.7^{byz} ±23.4	45.7^{axy} ± 7.1	45.3^{axy} ± 8.2	21.5^{ax} ± 4.2
1–2 hr	82.2^{by} ± 4.5	61.7^{bxy} ±35.1	47.3^{abxy} ±22.4	55.3^{bxy} ±15.0	4.2^{ax} ± 2.8
2–3 hr	69.8^{b} ± 5.0	67.7^{b} ± 7.6	48.4^{ab} ±21.1	34.2^{ab} ±15.3	25.5^{a} ±22.4
0–3 hr	84.3^{cy} ±14.1	68.7^{bcy} ±17.0	49.0^{bxy} ±16.8	45.0^{abxy} ±12.3	17.1^{ax} ± 5.9
B. Feed available 1–3 hr postinjection					
0–1 hr	83.8^{c} ±12.7	65.6^{bc} ±28.3	39.5^{ab} ± 8.8	39.1^{ab} ± 8.2	18.6^{a} ± 3.8
1–2 hr	67.6^{b} ±36.2	77.8^{b} ±16.4	65.9^{b} ± 9.9	42.5^{ab} ± 2.1	8.8^{a} ±10.9
2–3 hr	73.6^{b} ±11.5	77.0^{b} ± 5.0	65.1^{b} ±29.8	40.5^{ab} ±11.1	17.6^{a} ± 7.1
0–3 hr	74.6^{dz} ± 6.4	73.4^{dz} ± 9.7	56.8^{cyz} ±10.4	40.7^{by} ± 5.3	15.0^{ax} ± 1.7

*Mean ±SEM of 3 sheep.

†Means within a row having different superscripts are significantly different (x,y,z, $p<0.01$; a,b,c,d, $p<0.05$).

Meal feeding of fasted sheep caused an increased ruminoreticulum contraction rate, increased digesta flow through the abomasum and increased abomasal acid secretion presumably mediated by abomasal mechanical and chemical receptors and vagus nerve reflexes. Maximal response of acid secretion to meal feeding was observed within two hours.

A rise in abomasal acid secretion did not occur following saline or DMSO treatments because of the low level of postinjection feed intake (<80 g/hr) and high preinjection acid output (over 1/2 maximum), due to the satiated condition of the sheep. Sheep fed ad lib secreted acid at a constant rate and experienced only minor increases in acid secretion following meal feeding.

Despite stimulating feed consumption in satiated sheep, 9-AC totally abolished the expected increase in abomasal acid secretion. Voluntary meal sizes (400 to 500 g) in this experiment were comparable to meals in other studies where meal feeding fasted sheep elicited a 2- to 4-fold increase in acid output [3,19]. Preinjection acidity and acid output were well below maximum rates established by meal feeding 12-hr fasted sheep (unpublished data), so that a rise in acid output was possible. Nine-AC inhibited the potential rise in acid production and actually caused an 80 to 90% reduction in total acid secreted. The time of ingestion of a large quantity of feed (272 g during the first hour vs 352 g the second hour, Table 1A vs 1B) had no effect on the development of maximum inhibition of acid secretion suggesting that large meals and different temporal patterns of feeding do not moderate 9-AC inhibition of acid secretion.

In agreement with previous studies [5, 11, 16], E increased feed intake in satiated sheep. Feed intakes were similar following E and 9-AC treatment, although the dose of E per unit body weight was 60 times greater than the dose of 9-AC on a weight and molar basis. Nine-AC is a more potent stimulator of feeding than E, although the reason for the difference is unknown. E blocked the expected rise in acid output and caused a 44 to 60% decrease in total acid secreted, somewhat less than the 80 to 90% inhibition caused by 9-AC ($p<0.05$). In addition, ad lib feed intake partially overcame the E inhibition of acid secretion associated with restricted intake. In contrast to 9-AC, E inhibition of acid secretion appears to be moderated by the level of feed intake.

The lateral and ventromedial hypothalamic nuclei are known to have roles in the control of feeding. In the rat, an association between central nervous system (CNS)-elicited feed intake and gastric acid secretion has been demonstrated by manipulation of specific hypothalamic nuclei. Bilateral electrical destruction of the ventromedial hypothalamic nuclei caused hyperphagia and increased gastric acid secretion [30], while bilateral lesions in the lateral hypothalamic nuclei resulted in weight loss and decreased gastric acid secretion [28]. Electrical stimulation of the ventromedial and lateral hypothalamic nuclei resulted in decreased and increased acid

TABLE 4

EFFECT OF ELFAZEPAM AND 9-AZA-CANNABINOL ON VOLUME (ml) OF ABOMASAL POUCH SECRETIONS*

Period postinjection	% of preinjection value Saline	DMSO	Elfazepam ad lib	Elfazepam restrict	9-aza-cannabinol
A. Feed available 0–3 hr postinjection					
0–1 hr	100.1^{by}† ± 3.4	81.8^{bxy} ± 5.9	67.3^{abxy} ± 9.9	64.5^{abxy} ± 4.4	59.1^{ax} ±10.6
1–2 hr	86.9^{b} ± 7.7	74.8^{ab} ±12.2	62.9^{ab} ±21.2	70.1^{ab} ± 8.7	43.9^{a} ± 4.2
2–3 hr	80.5 ± 5.8	79.5 ± 3.3	66.6 ±11.1	54.9 ± 8.6	58.5 ±14.7
0–3 hr	89.6^{by} ± 4.6	78.8^{bxy} ± 5.0	66.0^{abxy} ±14.1	63.1^{abxy} ± 6.2	53.7^{ax} ± 8.5
B. Feed available 1–3 hr postinjection					
0–1 hr	90.2^{b} ± 3.8	88.8^{b} ±12.3	56.3^{ab} ± 9.0	69.1^{ab} ±11.5	43.6^{a} ± 7.2
1–2 hr	82.5^{by} ± 4.3	91.1^{by} ± 8.3	84.0^{by} ± 7.7	78.1^{by} ± 7.7	39.1^{ax} ± 8.3
2–3 hr	84.3 ± 4.5	84.3 ± 5.9	74.3 ±17.7	60.6 ± 3.0	64.1 ±10.8
0–3 hr	85.9^{cy} ± 0.9	87.8^{cy} ± 8.3	71.2^{by} ± 5.3	69.4^{by} ± 5.8	48.5^{ax} ± 4.2

*Means ±SEM of 3 sheep.

†Means within a row having different superscripts are significantly different (x,y, $p<0.01$; a,b,c, $p<0.05$).

secretion, respectively [27]. Lateral hypothalamic chemoreceptors, responsive to a lack of metabolizable glucose, stimulated vagus nerve mediated gastric acid secretion [10]. Thus, stimulation of the lateral hypothalamic feeding center is associated with gastric acid hypersecretion; stimulation of ventromedial hypothalamic satiety center with gastric acid hyposecretion.

Although no such detailed information exists for sheep, a presumably CNS-mediated increase in abomasal acid secretion occurred when fasted sheep were teased with feed but were not allowed to eat [25]. As in the rat, sheep possess a cephalic mechanism for the initiation of gastric (abomasal) acid secretion during ingestion of a meal. In contrast to the rat where insulin induces feeding and gastric acid hypersecretion, acid secretion was reduced in sheep [18]. The effect of hypothalamic lesions and stimulation of abomasal acid secretion has not been examined in sheep, and thus, hypothalamic-controlled acid secretion may respond in a different manner than in the rat.

In our experiments, chemicals which caused intense feeding reduced abomasal acid secretion in sheep, while hypothalamic-mediated hyperphagia was associated with gastric acid hypersecretion in rats. We propose that E and 9-AC may inhibit abomasal acid secretion via a primary effect in the CNS which is mediated by visceral autonomic nerves such as the vagus. Both the benzodiazepines (E) and cannabinoids (9-AC) act primarily in the CNS and not via peripheral receptors [17].

The benzodiazepines may represent a class of chemicals which stimulate food intake while depressing gastric acid secretion. The association between feeding and gastric acid secretion controlled by hypothalamic nuclei has been described. E injected into the anterior pre-optic area and diazepam injected into the ventromedial hypothalamus increased feed intake in sheep [11] and rats [2], respectively, demonstrating a direct effect on specific hypothalamic nuclei. Increased food intake was reported in rats injected peripherally with diazepam [20] and chlordiazepoxide [33]. Diazepam reduced non-stimulated gastric acid secretion [7, 9, 31] and occasionally stimulated appetite [17] in humans. Although E and other benzodiazepines appear to affect food intake by acting directly on hypothalamic nuclei, their effect on gastric acid secretion may be due to a cumulative action on other CNS as well as hypothalamic centers.

The location and specific effect of cannabinoids on feeding is less clear. Although the action of naturally-occurring and synthetic cannabinoids occurs primarily in the CNS, some peripheral effects have been described [8]. Nine-AC reduced food intake when injected into the LH of rats suggesting a direct effect on hypothalamic nuclei [2]. When administered peripherally, Δ^9-tetrahydrocannabinol increased food intake in humans and generally decreased intake in rats [8,15]. Differences in the feeding response to cannabinoids may be due to the species studied and route of administration and chemical composition of the cannabinoid used.

The inhibition of abomasal acid secretion may be part of an overall inhibition of forestomach motility and secretion.

Changes in gastrointestinal transit time after electrolytic lesioning of the ventromedial and lateral hypothalamic nuclei have been recently described in the rat [29]. Bilateral destruction of the ventromedial hypothalamus increased gastric retention and decreased intestinal transit rate; destruction of the LH produced opposite effects. Nine-AC inhibited rumen contraction rate 40% [6,11] and abomasal smooth muscle action potentials and propulsive contractions 90% [21] whether or not feed was available. When feed was withheld, E decreased rumen contraction rate 35% and rumen dilution rate approximately 15% in sheep on restricted intake [11]. Diazepam also slowed the rate of digesta movement through the GI tract in cattle [14]. E has been shown to maintain or increase digestibility of several rations despite increasing intake [16]. Both chemicals appear to produce a general depression in the propulsive and secretory activity of the ovine stomach, which may account for the increase in nutrient digestibility associated with this CNS-elicited reduction in the rate of digesta passage.

ACKNOWLEDGMENTS

This research was supported in part by grants-in-aid from the Cooperative State Research Service of the USDA (616-15-154), Biomedical Support Grant 5 S07 RR5464, and the Fund for the Study of Feeding Behavior, Department of Clinical Studies, School of Veterinary Medicine, University of Pennsylvania.

REFERENCES

1. Anderson, D. E. and R. Lydic. On the effect of using ratios in the analysis of variance. *Biobehav. Res.* **1:** 225–229, 1977.
2. Anderson-Baker, W. D., C. L. McLaughlin and C. A. Baile. Hypothalamic injections of barbiturates, benzodiazepines and cannabinols and food intake in rats. *Fedn. Proc.* **38:** 157, 1979.
3. Ash, R. W. Acid secretion by the abomasum and its relation to the flow of food material in the sheep. *J. Physiol.* **156:** 93–111, 1961.
4. Ash, R. W. Stimuli influencing the secretion of acid by the abomasum of sheep. *J. Physiol.* **157:** 185–207, 1961.
5. Baile, C. A. and C. L. McLaughlin. Chemically stimulated feed intake in ruminants. In: *Proc. First Symp. Vet. Pharmac. Therapeutics*, edited by C. R. Short. 1978, pp. 399–426.
6. Baile, C. A., C. L. McLaughlin, M. A. Della Fera. D. A. Keim, J. L. Ferrer and P. E. Bender. Responses of sheep to 9-aza-cannabinol. *Physiologist* **20:** 4, 1977.
7. Bennett, P. N., P. Davies, G. M. Frigo, W. M. T. Weerasingle and J. E. Lennard-Jones. Effect of diazepam on unstimulated and on stimulated gastric secretion. *Scand. J. Gastroent.* **10:** 101–103, 1975.
8. Bhargova, H. N. Potential therapeutic application of naturally occurring and synthetic cannabinoids. In: *General Pharmacol.* **9:** 195–213, Pergamon Press, Ltd., 1978.
9. Birnbaum, D., F. Karnell and M. Tefera. The effect of diazepam on human gastric secretions. *Gut* **12:** 616–618, 1971.
10. Colin-Jones, D. G. and R. L. Himsworth. The location of the chemoreceptors controlling gastric acid secretion during hypoglycemia. *J. Physiol.* **206:** 397–409, 1970.
11. Della Fera, M. A., W. D. Anderson and C. A. Baile. Intracerebral injections of elfazepam and feeding in sheep and rats. *Physiologist* **2:** 21, 1977.
12. Della Fera, M. A., C. L. McLaughlin, R. H. Weston, P. E. Bender, C. A. Baile and W. V. Chalupa. Rumen function during elfazepam and 9-aza-cannabinol elicited feeding in sheep. *Fedn. Proc.* **36:** 1141, 1977.
13. Duncan, D. B. Multiple range and F tests. *Biometrics* **11:** 1–42, 1955.
14. Dyer, I. A., E. J. Bris, J. D. Clark and J. A. Templeton. Diazepam and body weight gain. *J. Anim. Sci.* **23:** 874, 1964.
15. Gluck, J. P. and D. P. Ferraro. Effects of Δ^9-THC on food and water intake of deprivation experienced rats. *Behav. Biol.* **11:** 395–401, 1974.
16. Gonzalez, S. S., S. D. Farlin and C. A. Baile. Effect of elfazepam on apparent digestibility, intake and gain in sheep. *Abstr. 69th Ann. Mtg. Am. Soc. Anim. Sci.*, p. 236, 1977.
17. Goodman, L. S. and A. Gilman. *The Pharmacological Basis of Therapeutics*. 5th ed. New York: Macmillan Publ. Co., 1975.
18. Hill, K. J. Continuous gastric secretion in the ruminant. *Q. Jl. exp. Physiol.* **40:** 32–39, 1955.
19. Hill, K. J. Abomasal secretion in the sheep. *J. Physiol.* **154:** 115–132, 1960.
20. Johnson, D. N. Effect of diazepam on food consumption in rats. *Psychopharmacology* **56:** 111–112, 1978.
21. 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:** 63–70, 1979.
22. Krabill, L. F., P. J. Wangsness and C. A. Baile. Effects of elfazepam on digestibility and feeding behavior in sheep. *J. Anim. Sci.* **46:** 1356–1359, 1978.
23. McLaughlin, C. L., C. A. Baile and P. E. Bender. Cannabinols and feeding in sheep. *Psychopharmacology* (in press).
24. McLaughlin, C. L., L. F. Krabill, G. C. Scott and C. A. Baile. Chemical stimulants of feeding animals. *Fedn. Proc.* **35:** 579, 1976.
25. McLeay, L. M. and D. A. Titchen. Abomasal secretory responses to teasing with food and feeding in the sheep. *J. Physiol.* **206:** 605–623, 1970.
26. McLeay, L. M. and D. A. Titchen. Gastric, antral and fundic pouch secretion in sheep. *J. Physiol.* **248:** 595–612, 1975.
27. Misher, A. and F. P. Brooks. Electrical stimulation of hypothalamus and gastric secretion in the albino rat. *J. Physiol.* **211:** 403–406, 1966.
28. Opsahl, C. A. and T. L. Powley. Body weight and gastric acid secretion in rats with subdiaphragmatic vagotomy and lateral hypothalamic lesions. *J. comp. physiol. Psych.* **91:** 1284–1290, 1977.
29. Ralph, T. L. and P. E. Sawchenko. Differential effects of lateral and ventromedial hypothalamic lesions on gastrointestinal transit time in the rat. *Brain Res. Bull.* **3:** 11–14, 1978.
30. Ridley, P. T. and F. P. Brooks. Alterations in gastric secretion following hypothalamic lesions producing hyperphagia. *J. Physiol.* **209:** 319–329, 1965.
31. Roberts, D. M. and T. B. N. Oldrey. The effect of diazepam on pentagastrin-stimulated and nocturnal (sleeping) gastric secretion in man. *Am. J. Gastroent.* **61:** 386–389, 1974.
32. Thomas, J. E. A simplified procedure for preparing an improved Pavlov pouch. *PSEBM* **50:** 58–61, 1942.
33. Tye, N. C., D. J. Nicholas and M. J. Morgan. Chlordiazepoxide and preference for free food in rats. *Physiol. Behav.* **3:** 1149–1151, 1975.
34. Weston, R. H. and D. E. Morgan. Neural depressants and the voluntary consumption and digestion of roughage diets. *Proc. Nutr. Soc. Aust.*, 1978, in press.