Elfazepam Stimulates Feed Intake in Sheep Fed Roughage and/or Concentrate Diets

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Abstract

Two experiments were carried out to analyze the effect of Elfazepam, a minor tranquilizer, on the eating and ruminating behaviour of sheep fed Sudan grass (*Sorghum sudanese* STAPF.) hay or pelleted concentrate (barley and wheat bran) (*ad libitum*) (Expt. I), and Alfalfa (*Medicago sativa* L.) hay (2% BW/day) (Expt. II). In Experiment I, 0, 0.05 and 0.10mg/kg BW of Elfazepam dissolved in ethyl alcohol were administered orally to 3 non-pregnant ewes twice a day during 7 days (roughage diet) along with 0.1mg/kg BW of Elfazepam (concentrate diet). In Experiment II, Elfazepam at the same level as in Experiment I was orally administered to 3 wethers for 2 weeks in a 3×3 latin square design. Elfazepam administration resulted in the increase of feed intake which lasted for 7 days when sheep were fed a concentrate diet, though the response to Elfazepam disappeared 5 days after the initiation of the administration in sheep fed the roughage diet alone (Expt. I). In sheep with restricted feed, Elfazepam increased the rate of eating and decreased the chromium (Cr) passage rate through the gut, although there were no differences in the rumination parameters (Expt. II). On the basis of these results, it is suggested that the action of Elfazepam on feed intake decreases when the ruminal retention time of ingesta is the factor limiting feed intake due to its suppressive effect on the passage through the digestive tract.

Introduction

In animal production, it is important to increase the feed intake by animals for raising their productivity. It is well known that in monogastric animals the blood glucose level plays an important role in the control of the eating behaviour. Ruminant animals, however, do not possess a mechanism of control of their feed intake by the blood glucose level.

Recently, some trials have been carried out to promote the feed intake in ruminants using chemicals (Baile *et al.*, 1976 ; Baile and McLaughlin, 1978, 1979 ; Seoane *et al.*, 1986, 1988), which display a stimulative effect on the central nervous system. One of these chemicals, Elfazepam, a minor tranquilizer of the benzodiazepine group, has been found to stimulate the feed intake in ruminant animals (Baile and McLaughlin, 1979).

The stimulative effect of benzodiazepine on feed intake is considered to involve the action of gamma-aminobutyric acid (GABA) in the central nervous system (Leeb-Lundberg *et al.*, 1981).

It has been suggested that 2 stages are involved in the regulation of the feed intake, i.e., feed intake in the rumen (physical regulation stage) and feed intake suppression when the energy supply exceeds the requirement (metabolic regulation stage) (Dulphy *et al.*, 1980). It is, therefore, likely that the factors regulating the feed intake in ruminants are different when the animals are given roughage alone and when they are fed a concentrate-based diet.

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In the present study, the stimulative effect of Elfazepam on feed intake was compared in sheep fed a concentrate-based diet and in sheep given roughage alone.

Materials and methods

Experiment I

Three non-pregnant ewes (about 45kg BW) were kept in metabolism cages throughout the experimental period in a room with controlled temperatures (25℃ ±3℃), the animals being fed at 6h intervals. Residual feed was collected prior to feeding, dried and weighed. Fresh water and salt lick containing minerals were always available.

In the roughage trial, the animals were given Sudan grass hay (*Sorghum sudanese* STAPF.) *ad libitum*. Three sheep were allotted to a 3×3 latin-square design to examine the effect of 3 levels of Elfazepam administration. After a preliminary period of 7 days, each sheep orally received 0, 0.05 and 0.10mg/kg BW of Elfazepam (Sumitomo Chemicals, Co. Osaka, Japan) dissolved in ethyl alcohol (200mg/l and 400mg/l) by drenching at 9 : 00 and 17 : 00h for 7 days. In the trial with the concentrate-based diet, the pelleted feed was given in the same manner as in the trial with roughage. After a preliminary period of 7 days, each sheep orally received ethyl alcohol for 5 days. Then, the animals received 0.1 mg/kg BW of Elfazepam twice a day for 7 days, as in the trial with roughage.

Experiment II

Three wethers (about 40kg BW) were kept in metabolism cages throughout the experimental period, and fed Alfalfa hay at a level of 1% of BW at 9 : 00 and 17 : 00h. Fresh water and salt lick containing minerals were always available.

Elfazepam at the same level as in Experiment I was orally administered to 3 wethers for 2 weeks in a 3×3 latin square design. Seven days after the initial administration, eating and rumination behaviour, apparent digestibility, and passage rate of Chromium (Cr) through the digestive tract were determined. At the beginning of each experimental period, a bolus composed of 8g of Cr_2O_3 and the same amount of flour was orally administered, and the feces were collected at 4h intervals for 3 days. Total amount of feces was collected for 7 days to measure the apparent digestibility of feed. Eating and ruminating behaviour was observed daily for the last 4 days according to the method of Harumoto and Kato (1979).

Chemical analysis

Nitrogen content in the diet and feces was analyzed by the Kjeldhal procedure, and ether extract, crude fiber and crude ash were analyzed by the method of A.O.A.C. (1980). Cr content in the feces was analyzed by spectrophotometry after ashing with a phosphate-potassium reagent (Morimoto, 1971).

Statistical analysis

Statistical differences were evaluated by the Student's t-test. In Experiment I, the differences of feed intake were evaluated between the vehicle and 2 doses of Elfazepam in the roughage trial and the differences were evaluated between feed intake during vehicle administration and feed intake on each day after the initiation of Elfazepam administration in the trial with the concentrate-based diet. In Experiment II, the differences in feed intake were evaluated between the vehicle and 2 doses of Elfazepam.

Results and discussion

Chemical composition (as % of DM) of Sudan grass and Alfalfa hay, and ingredient and chemical composition of the concentrate-based diet are shown in Table 1.

Table 1 Chemical composition of diets (% of dry matter)

	Sudan grass hay (*Sorghum sudanese* STAPF.)	Pelleted concentrate[z]	Alfalfa hay (*Medicago sativa* L.)
Crude protein	9.5	11.9	18.1
Ether extract	2.0	2.0	2.5
Crude fiber	29.5	7.6	26.1
Crude ash	11.3	9.5	9.3
Nitrogen-free extract	47.7	69.0	44.0

[z] Ingredient of pelleted concentrate (% of dry matter) ; barley, 39.5 ; wheat bran, 20.0 ; corn starch, 20.0 ; alfalfa hay, 20.0 ; calcium carbonate, 0.5.

In both Experiments I and II, during the Elfazepam administration, the sheep did not show an abnormal behaviour, such as hypnolepsy. It has been reported that Elfazepam elicits a hunger-like response in ruminants without inducing tranquilization (Baile and McLaughlin, 1979).

Table 2 Effect of Elfazepam administration on feed intake (g/kg body weight) in sheep offered roughage alone

(Experiment I)

	Days after the initiation of Elfazepam administration						
	1	2	3	4	5	6	7
0 mg[z]	29.0±1.9	26.8±3.2	28.3±1.9	26.8±3.5	27.1±4.2	28.1±2.6	27.1±2.9
0.05 mg[z]	27.3±6.0	29.0±2.8	30.6±2.5	33.6±2.3*	26.7±5.4	28.3±5.7	25.7±2.4
0.1 mg[z]	31.5±3.4	33.8±2.6*	34.5±3.3*	29.9±4.1	27.6±7.4	28.4±2.0	28.6±4.7

[z] Sheep which received orally the vehicle (0 mg), 0.05 and 0.1 mg/kg body weight of Elfazepam twice a day.
Note : Mean±SD for 3 sheep.
* : Significantly different from the value of vehicle administration.

As shown in Table 2, the feed intake was significantly ($p<0.05$) higher in sheep to which a larger dose of Elfazepam had been administered than in sheep which received ethyl alcohol alone on the second and third days of the treatment. Feed intake was also significantly ($p<0.05$) higher in sheep which received the lower dose than in those to which the vehicle was administered on the fourth day of the treatment. However, the stimulative effect did not last and the feed intake was not affected by both doses of Elfazepam 5 days after the initiation of the treatment.

In the trial with the concentrate-based diet, since one sheep showed anorexia during the preliminary period, this animal was omitted in the trial. As shown in Table 3, the feed intake increased after the administration of Elfazepam in sheep which received the concentrate-based diet. Although the feed intake fluctuated daily, the average feed intake was 16% higher during the Elfazepam administration period than the average intake of feed during the control period.

The results of this experiment showed that Elfazepam indeed stimulated the feed intake in ruminants but that the action of Elfazepam was largely affected by the kind of feeds. The increase in the feed intake induced by Elfazepam lasted for 7 days in the animals fed the

Table 3 Effect of Elfazepam administration on feed intake (g/kg body weight) in sheep offered the concentrate-based diet

(Experiment I)

Control period[Z]	Days after the initiation of Elfazepam administration[Y]						
	1	2	3	4	5	6	7
25.4±3.6[X]	27.5±7.4	30.0±4.9	27.0±5.8	29.8±7.2	31.9±4.3*	26.9±6.9	31.8±3.5*

[Z] Sheep which received orally the vehicle for 5 days twice a day.
[Y] Sheep which received orally 0.1 mg/kg body weight of Elfazepam twice a day.
[X] Mean±SD for 2 sheep with 5 replications ; other values are means±SD for 2 sheep without replication.
Note : Significantly (* ; $p<0.05$) different from the value of control period.

concentrate-based diet, whereas the response to Elfazepam disappeared 5 days after the initiation of the treatment in the animals fed the roughage alone.

The reason why the response to Elfazepam did not persist in sheep offered the roughage alone is not clear.

It is possible that the accumulation of feed in the rumen limited the roughage intake (Dulphy *et al.*, 1980), or that Elfazepam suppressed the ruminal motility (Della-Fera *et al.*, 1977) and thus the passage rate of digesta decreased by Elfazepam as described later.

In the ruminants fed slowly digestive feed such as roughage, the reduction in the passage rate of the digesta may affect the stimulative action of Elfazepam on feed intake.

Table 4 Effect of Elfazepam administration on the digestibility of alfalfa hay by sheep

(Experiment II)

	Amount of Elfazepam administered[Z]		
	0	0.05	0.1
Organic matter	65.2±0.8	65.2±0.3	65.5±0.7
Crude protein	74.1±1.9	74.0±2.1	75.6±1.4
Ether extract	38.7±4.3	36.8±2.5	34.7±0.9
Crude fiber	36.1±1.4	36.9±1.2	38.6±1.0*
Nitrogen-free extract	72.2±0.3	71.7±1.5	71.6±0.4

[Z] Sheep which received orally the vehicle (0 mg), 0.05 and 0.1 mg/kg body weight of Elfazepam twice a day.
Note : Mean±SD for 3 sheep.
* : Significantly ($p<0.05$) different from the value of vehicle administration.

As shown in Table 4, the higher dose of Elfazepam increased the digestibility of crude fiber. This observation is consistent with the report of Krabill *et al.* (1978) which showed that the digestibility of neutral detergent fiber and acid detergent fiber was improved by Elfazepam administration in sheep. Elfazepam tended to increase the time spent on excretion of ingested Cr in a dose-dependent manner, and the retention of Cr was significantly ($p<0.05$) prolonged when higher doses of Elfazepam were administered compared to the vehicle administration (Table 5).

Della-Fera *et al.* (1977) indicated that Elfazepam reduced the ruminal contraction after feeding resulting in the prolongation of the ruminal retention time of digesta.

The results in this study appear to suggest that Elfazepam increases the crude fiber

Table 5 Effect of Elfazepam administration on Cr retention time in the digestive tract of sheep

(Experiment II)

Amount of Cr excretion (percentage to total excreted Cr)	Amount of Elfazepam administered[Z]		
	0	0.05	0.1
10	17.8±4.9[Y]	19.5±2.1	21.5±2.1
25	24.2±3.6	24.0±5.1	27.4±0.7
50	33.3±3.0	37.6±7.1	38.4±2.0*

[Z] Sheep received orally the vehicle (0 mg), 0.05 and 0.1 mg/kg body weight of Elfazepam twice a day.

[Y] Time (hours) spent in excretion of 10, 25, 50% of Gr was calculated by interpolation from Cr excretion measured at 4-hr intervals.

Note : Mean±SD for 3 sheep.

* : Significantly ($p<0.05$) different from the value of vehicle administration.

Table 6 Effect of Elfazepam administration on eating behavior in sheep

(Experiment II)

	Amount of Elfazepam administered[Z]		
	0	0.05	0.1
Time spent eating (min/day)	101±7	94±12	81±7*
Mean rate of eating (g DM/min)	4.0±0.3	4.3±0.7	5.0±0.3*
Number of chewings (number of movements/day)	8,760±1041	8,790±1496	9,504±1247

[Z] Sheep which received orally the vehicle (0 mg), 0.05 and 0.1 mg/kg body weight of Elfazepam twice a day.

Note : Mean±SD for 3 sheep.

* : Significantly ($p<0.05$) different from the value of vehicle administration.

digestibility by reducing the passage rate of digesta in the rumen, which is induced by the suppression of the rumen motility.

As shown in Table 6, the time spent eating was reduced by Elfazepam administration and there was a significant ($p<0.05$) difference in the effect between the control and the administration of a higher dose of Elfazepam. The eating rate (gDM/min) increased by the administration of Elfazepam in proportion to the reduction in the time spent eating. Chewing number during eating tended to increase with the increase of the dose of Elfazepam. Elfazepam is known to increase the daily feed intake in ruminants (McLaughlin *et al.*, 1976 ; Baile and McLaughlin, 1977), and furthermore, it has been also reported that the intravenous injection of Elfazepam stimulates eating in satiated sheep (Krabill *et al.*, 1978). In the present study, Elfazepam increased the rate of eating regardless of the prolongation of the retention time of digesta in the gut, suggesting that Elfazepam increased the rate of eating by suppressing satiety.

As indicated in Table 7, Elfazepam administration did not affect the rumination behav-

Table 7 Effect of Elfazepam administration on rumination in sheep
(Experiment II)

	Amount of Elfazepam administered[z]		
	0	0.05	0.1
Rumination time (min/day)	353±458	397±47	377±367
Boli (number of movements/day)	330±119	341±96	340±91
Rumination period (number of movements/day)	21.2±3.3	24.3±4.5	23.7±3.6
Remastication (number of movements/day)	16,610±2784	20,523±7105	18,545±4196

[z] Sheep which received orally the vehicle (0 mg), 0.05 and 0.1 mg/kg body weight of Elfazepam twice a day.
Note : Mean±SD for 3 sheep.

iour. According to Freer *et al.* (1962), there was a direct relationship between the reticulo-ruminal contraction during rest and the time spent ruminating in a day. Therefore it is suggested that Elfazepam may exert a suppressive effect on rumination due to the reduced rumen motility. However, the current study did not enable to determine why the Elfazepam administration did not affect the rumination behaviour.

Conclusion

Elfazepam appears to be effective in sheep fed a readily digested diet such as a concentrate-based diet, whose requirement exceeded the energy supply. Conversely, it is postulated that the action of Elfazepam on feed intake decreases when the retention time of digesta in the rumen is the factor limiting the feed intake due to its suppressive effect on the passage of digesta through the gut. It is also suggested that the administration of Elfazepam increases the crude fiber digestibility by reducing the passage rate of rumen digesta, which is induced by the suppression of the rumen motility. Elfazepam administration increased the rate of eating, although there was no difference in the ruminating behaviour.

References

1) Association of Official Agriculture Chemists (1980) : Official Method of Analysis. 13th ed. Association of Official Agricultural Chemists. Washington D. C.
2) Baile, C. A., McLaughlin, C. L. and Krabill, L. F. (1976) : Performance of cattle fed a feed intake stimulant. J. Anim. Sci., 43, 313-314.
3) Baile, C. A. and McLaughlin, C. L. (1977) : Feeding behavior of sheep following intravenous injection of imidazole benzodiazepines. Fed. Proc., 36, 460.
4) Baile, C. A. and McLaughlin, C. L. (1978) : Chemically stimulated feed intake in ruminants. Cereal Foods World, 23, 291.
5) Baile, C. A. and McLaughlin, C. L. (1979) : A review of the behavioral and physiological responses to Elfazepam, a chemical feed intake stimulant. J. Anim. Sci., 42, 1371-1395.
6) Della-Fera, M. A., McLaughlin, C. L., Weston, R. H., Bender, P. E., Baile, C. A. and Chalupa, W. V. (1977) : Rumen function during Elfazepam and O-aza-cannabinol elicited feeding in sheep. Fed. Proc., 36, 1141.
7) Dulphy, J. P., Bemond, B. and Theriez, M. (1980) : Ingestive behavior and related

activities in ruminants in digestive physiology and metabolism in ruminants. Edited by : Ruckebusch, Y. and Thivend, P. MTP Press, Lancaster, England. pp. 103-122.
8) Freer, M. C., Campling, R. C. and Balch, C. C. (1962) : Factors affecting the voluntary intake of food by cows. 4. The behavior and reticular motility of cows receiving diets of hay, oat straw and oat straw with urea. Br. J. Nutr., 16, 279-295.
9) Harumoto, T. and Kato, M., (1979) : Effect of different amounts of hay intake on the rumination behavior in sheep. Jpn. J. Zootech. Sci., 50, 155-160. (In Japanese).
10) Krabill, L. F., Wangsness, P. J. and Baile, C. A. (1978) : Effects of Elfazepam on digestibility and feeding behavior in sheep. J. Anim. Sci., 46, 1356-1359.
11) McLaughlin, C. L., Krabill, L. F., Scott, G. C. and Baile, C. A. (1976) : Chemical stimulants of feeding animals. Fed. Proc., 35, 579.
12) Morimoto, H. (ed.) (1971) : Dohbutsu-Eiyoh-Shiken-Hoh. Yokendoh Co., Tokyo. 393pp. (In Japanese).
13) Seoane, J. R., Dumont, F., Girard, C. L., Bedard, L. and Matte, J. J. (1986) : Effects of intraventicular injections of alpha-aminobutyric acid and related substances on feeding behavior in satiated sheep. Can. J. Physiol. Pharmacol., 62, 1296-1299.
14) Seoane, J. R., Vircher, J. and Christen, A. M. (1988) : Effects of sodium barbital administration on performance and ration digestibility of young ruminants. Can. J. Anim. Sci., 68, 1187-1194.

Discussion

Sasaki, M. (FAO) : What is the practical use of this sedative for livestock farmers? The increase in feed intake and improved digestibility of crude fiber do not necessarily imply that the feed efficiency will be enhanced or the growth rate increased.

Answer : If livestock farmers wish to use Elfazepam, a minor tranquilizer, for increasing the feed intake of their animals, for example in the case of heat stress, they should mix it with a small amount of concentrate diet (at the level of 0.05-0.1 mg/kg BW/DM). It appears that the increase of feed intake may be an important factor for improving the growth rate. This chemical should be used during a short period of time, 1 or 2 days only at a time.

Ku Vera, J. C. (Mexico) : One of the problems of the use of Elfazepam under tropical conditions is the increase in the rumen retention time, since tropical forages probably tend to show a long retention time (low fiber degradability).

Answer : On the basis of our results, it was obvious that the effect of Elfazepam on feed intake was largely affected by the kind of feeds. Therefore it can not be expected that the administration of the chemical will remarkably improve and/or stimulate the voluntary intake of low quality roughage by ruminants under tropical conditions. However the effect of Elfazepam on the rumen motility is not particularly strong. The chemical could be used to increase the feed intake under tropical conditions if it is administered for a short period of time and at short intervals.

Haryanto, B. (Indonesia) : Is the oral administration of Elfazepam more effective than if it is administered intra-venously?

Answer : The effect of Elfazepam on the increase of feed intake is similar whether the chemical is administered orally or intra-venously.