Effects of ergotamine and ergovaline on the electromyographic activity of smooth muscle of the reticulum and rumen of sheep

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Objective—To investigate the effects of IV administration of ergotamine and ergovaline and intraruminal administration of ergotamine on electromyographic (EMG) activity of reticuloruminal smooth muscle in conscious sheep.

Animals—3 sheep with indwelling electrodes in the musculature of the reticulum and rumen.

Procedure—In a crossover design study, reticuloruminal motility before and after IV administration of ergotamine (5, 10, 20, and 40 nmol/kg) or ergovaline (2.5, 5, and 10 nmol/kg) was evaluated; EMG effects were compared with those of corresponding control treatments (IV administration of saline [0.9% NaCl] solution or acetone, respectively) in sheep. Ergotamine (800 nmol/kg) or water was also administered intraruminally and their effects compared.

Results—After IV administration of ergopeptides, vagally dependent cyclical A and B sequences of contraction of the reticuloruminen were immediately inhibited, preceding increases in baseline EMG activity (tonus). The return of cyclical contractions was associated with an increase in contraction amplitude. The effects were dose dependent; administration of 40 nmol of ergotamine/kg resulted in responses that continued for 3 to 4 hours. The effects of intraruminal administration of ergotamine were variable; after 8 hours, EMG activity was increased from baseline for < 2 hours in 1 sheep, 10 hours in another, and > 15 hours in the third.

Conclusions and Clinical Relevance—In sheep, the effects of ergotamine and ergovaline on reticuloruminal motility after IV administration and the duration of responses following intraruminal administration suggest that disruption of digestion may occur in animals grazing endophyte-infected pasture that has a high ergopeptide content. (Am J Vet Res 2006;67:707–714)

Members of the grass family Gramineae may contain toxins produced by or in response to symbiotic fungi (endophytes); ingestion of pasture containing these toxins is associated with several toxicoses in grazing livestock.1 Among the toxins produced in

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Abbreviations

EMG Electromyography

endophyte-infected grasses are the lolitremes, which include indole-diterpenoid tremorgens that cause perennial ryegrass staggers and the vasoactive ergot alkaloids that cause the syndromes associated with fescue and ergot toxicoses in ruminant and laboratory animal species.2 In New Zealand, ryegrass, which is the dominant pasture species, is usually infected with Neotyphodium lolii, and the production of peramine has provided resistance in ryegrass against insect attack, thereby facilitating the grass’s persistence in pasture.3 However, despite the beneficial effect of resistance against insect attack conferred by peramine, other chemicals produced by N lolii affect livestock; ryegrass staggers is a well-known syndrome in ruminants in New Zealand, and animals grazing endophyte-infected ryegrass develop syndromes identical to fescue toxicosis involving hyperthermia, inappetence, and reduced milk production. The ergopeptide ergovaline has been implicated in these responses.4,5 As a consequence, we have investigated the pathophysiologic effects of these 2 groups of mycotoxins in conscious sheep; in previous studies,6,7 we determined that the mycotoxic tremorgens paxilline and lolitrem B have marked excitatory effects on the EMG activity of skeletal muscle of conscious sheep and both excitatory and inhibitory effects on the EMG activity of gastrointestinal smooth muscle. In another investigation8 in conscious sheep, the effects of ergovaline on blood pressure, heart rate, respiration rate, and body temperature were assessed and compared with the effects of ergotamine. Compared with values recorded after administration of control treatments, both ergopeptides increased blood pressure, respiration rate, and body temperature; effects of ergovaline were more pronounced than those of ergotamine.

Ergovaline, ergotamine, and related ergot toxins act on several types of receptors, including adrenergic, dopaminergic, and serotonergic receptors,9,10 and thereby have the potential to markedly affect reticuloruminal function.11,12 The effects of ergotamine and its activation of various receptors have been widely studied.4 In contrast, ergovaline isolate has only recently become available, and studies of its effects are few.6,10,15 There is a paucity of information on the physiologic effects of ergovaline. The purpose of the study reported here was to investigate the effects of IV administration of ergotamine and ergovaline and the intraruminal administration of ergotamine on EMG activity of smooth muscle of the reticulum and rumen in con-
scious sheep. It was our intention to extend our observations on tremorgens and reticuloruminal motility. Because insufficient quantities of ergovaline are available for studies involving oral administration of the ergopeptide in ruminants, the effects of IV administration of both ergovaline and ergotamine were compared. Experiments were also undertaken that involved intraruminal administration of ergotamine to sheep to mimic its ingestion by ruminants on pasture. The intake of ergotamine via parenteral and oral routes is known to result in vasoactive effects.

Materials and Methods

The experiments performed in this study were approved by The University of Waikato Animal Ethics Committee and the Ruakura Research Centre Animal Ethics Committee.

Ergopeptides—Ergotamine hemitarrate was dissolved in 2 mL of saline (0.9% NaCl) solution, and ergovaline was dissolved in 2 mL of acetone (because ergovaline is not soluble in aqueous solutions). The doses of ergotamine administered IV were 5, 10, 20, and 40 nmol/kg, and the doses of ergovaline administered IV were 2.5, 5, and 10 nmol/kg. According to the suppliers, the purity of the ergotamine hemitarrate was > 97%, whereas that of ergovaline was 90% to 95%. Doses of the ergopeptides were determined on the basis of ergotamine administered IV in conscious cattle, which was calculated from their feed intake and the concentration of ergovaline in grass. The highest doses of the ergopeptides were based on those administered IV previously in conscious sheep that produced increases in diastolic blood pressure of approximately 50 mm Hg, compared with control treatment values. The amount of ergovaline available was limited, and because of the relatively large body weight of the sheep used in the study and ethical concerns regarding the toxicity of ergovaline, the number of animals used in these experiments was restricted to 3.

Animals—Three castrated male Romney × Dorset cross-bred sheep were included in the study; the sheep were 1 to 2 years old and weighed 30 to 32.5 kg. They were maintained indoors in pens on a daily diet of 1,200 g of dried chaffed lucerne hay and 100 g of concentrate pellets each. The feed was analyzed for lolitrem B and ergovaline content; lolitrem B was not detected, and ergovaline was present at 60 ppb (ie, at a substantially lower amount than the threshold levels associated with clinical signs in cattle [300 to 400 ppb]).

Preparation—The gastric EMG used as an index of motility of the reticulorumens was based on the method of Ruckebusch. In each sheep, anesthesia was induced by use of thiopentone sodium and maintained with halothane; a set of 3 stainless steel electrode wires was sutured into the smooth musculature of the reticulum and the cranial aspect of the dorsal sac of the rumen. The electrodes were exteriorized via the upper abdominal wall and secured in a plug on the sheep’s back. Such preparations were maintained and tested for at least 1 month before experiments. All electrodes were connected to battery-operated preamplifiers. To facilitate the long-term recording of the gastric EMG, the EMGs were integrated by use of an integrator with a time constant of 2 seconds and recorded on a chart recorder running at a chart speed of 5 mm/min. In addition, the outputs of the integrators were captured on disc by use of a computer program that provided total integrated volts under the trace over any time period and allowed expansion and contraction of the trace over time. Recordings corresponding to A and B sequences of contraction of the reticulum and rumen were obtained via this method (Figure 1). Contractions were counted by hand from the chart recordings and were assessed as real contractions based on our experience of recording A and B sequences of contraction of the reticulum and cranial aspect of the dorsal sac of the rumen obtained via several techniques, including partial exteriorizations involving strings and levers writing on smoked drums; partial exteriorizations with strain gauges, and open-tipped catheters or balloons. A contraction of the reticulum was defined as a diphasic (triphasic during ruminination) increase in amplitude of at least 60% of full-scale deflection of the pen on the chart that was of at least 5 seconds’ duration. The amplitude of the contraction varied among sheep according to the strength of the signal. The strength of the signal was less from the rumen (for A sequences, at least 30% of full-scale deflection of the pen on the chart) than the reticulum, and B sequences of contraction of the rumen were defined as an increase in amplitude of at least 10% of full-scale deflection of the pen on the chart that was of at least 3 seconds’ duration. The B sequences of contraction of the dorsal sac were distinguished from A sequences by their smaller amplitude and their lack of correlation with contractions of the reticulum. The minimum intercontraction interval to detect separate contractions at the chart speed of 5 mm/min was 6 seconds.

A sequence of contractions of the reticulorumens was clearly identified under most circumstances, including in association with a raised baseline trace, because of the high amplitude of reticulum contractions and their diphasic or triphasic nature. This was not the case (especially with B sequences of contraction for the rumen, and at times, increases in what we termed tonus (ie, an increase in baseline activity with superimposed phasic activity) did not allow B sequences to be distinguished from the baseline trace (eg, during the later stages of 24-hour experiments, following intraruminal administration of ergotamine, or when fasting was prolonged).

An increase in baseline activity with superimposed phasic activity (ie, tonus) was a characteristic EMG feature following administration of the ergopeptides. This was evaluated visually and was defined as an increase above the range of baseline activity of at least 100% that was maintained for at least 5 minutes; moderate tonus was defined as an increase of 20% to 50% of the maximum amplitude of the A sequence of contraction, and marked tonus was defined as an increase of > 50% of the maximum amplitude of the A sequence of contraction.

Jaw movements were recorded with the aid of a balloon that was attached beneath the jaw and connected to a pressure transducer; this allowed inactivity and rumination to be distinguished and correlated with reticuloruminal motility.

At least 24 hours prior to each experiment, each sheep had an indwelling IV catheter inserted into a jugular vein. At the start of each experiment at 8 AM, 2 sheep were brought from their holding pens into the recording room and placed in metabolism crates (a procedure to which they had become habituated over a 3-week period before experiments commenced). They did not have access to food or water during the short-term experiments involving IV administration of ergopeptides, but were offered water periodically during the 24-hour experiments involving intraruminal administration of ergotamine. Sheep were able to stand or lie down during the experiments; during the 24-hour recording periods, reticuloruminal motility and jaw movements were monitored continuously in all sheep.

Clinical observations—The effects of the ergopeptides on respiration in all animals were closely observed, as this parameter was a sensitive indicator of an animal’s well-being in response to ergopeptide administration in a previous study. Respiration was visually observed continuously for any changes in rate and depth that were associated with the
IV infusions; after intraruminal administration, respiration was monitored during the first 8 hours and thereafter at 6-hour intervals for the remainder of the study. Temperatures of the sheep’s extremities (lower portions of the limbs) were monitored by touch for several days after administration of the ergopeptides. At the times that respiration and temperature were monitored, a visual assessment for any skeletal muscle tremoring was also made.

**Experimental procedure**—Prior to each administration of ergopeptide, a recording was collected for at least 30 minutes followed by an additional 30-minute recording immediately prior to the administration of the control treatment (saline solution or acetone) and immediately prior to the administration of the ergopeptide in the same volume of control solution. Separate controlled experiments were conducted on different days in which 2 consecutive administrations of 2 mL of control solution were administered 30 minutes apart to allow comparisons with ergopeptide administration. The 2 mL of infusate was introduced slowly over a period of 2 minutes into the jugular catheter; the catheter was flushed with 2 mL of saline solution containing heparin. Recordings were continued for 7.5 hours after IV administration of the ergopeptides. On separate days, each sheep received saline solution or acetone (control treatments) first and each ergopeptide in a semirandomized block design. The interval between doses of ergopeptide was 1 day for the smallest doses and varied from 2 to 14 days between the other doses. Experiments were also conducted in which ergotamine (at a dose of 400 nmol/kg in 1 sheep and 800 nmol/kg in each of 3 sheep) was administered intraruminally via an esophageal tube; EMG recordings were made continuously over 23 hours, and findings were compared with similar experiments performed on separate days involving doses of water as a control treatment. A 1-hour control period of recording preceded the esophageal intubation of the sheep, after which ergotamine dissolved in 200 mL of water was introduced and washed down the esophageal tube with 200 mL of water or 400 mL of water alone. This procedure was completed within 2 minutes.

Sheep were returned to their pens after the 24-hour recordings and given access to freshly provided food. For sheep that had increased baseline tonus after 23 hours, animals were returned to the recording room where 30-minute recordings were made 32, 48, and 72 hours after the intraruminal administration of ergotamine in an attempt to determine when tonus was no longer present.

**Data analysis**—The effects of the administered substances on EMG activity of smooth muscle of the reticulum and rumen were monitored for each sheep from the chart recordings. Effects on the baseline activity and the amplitude of the integrated EMG of the reticulum and rumen were assessed. Cyclical contractions of the reticulum and rumen (represented by their A and B sequences) were analyzed according to their frequency at 15-minute intervals after IV administration of the ergopeptides and at 1-hour intervals after intraruminal administration of ergotamine. Quantitative data regarding the frequency of A and B sequences of contraction...
were normalized for each animal by expressing frequency over 15-minute periods as a percentage of the mean value of the first two 15-minute periods. The significance of the difference in frequency of A and B sequences of contraction of the reticulorumen for each ergopeptide, compared with findings during the corresponding period of its control treatment, was assessed by use of an ANOVA involving mixed-model residual maximum likelihood and treating individual sheep as random effects. The differences between individual means were tested by use of standard multiple comparison procedures. A value of \( P < 0.05 \) was considered significant.

**Results**

Effects of IV administration of ergotamine and ergovaline on reticulorumen motility in sheep—Before IV administration of the ergopeptides, motility of the reticulum and rumen recorded as integrated EMGs involved cyclical contractions of the reticulum and rumen (A sequences) and of the rumen alone (B sequences) at a frequency of approximately 1/min (Figure 1). There was no increase in baseline activity of the reticulum or rumen in sheep that received the saline solution or acetone control treatments.

**Ergotamine**—In sheep, IV administration of ergotamine caused an immediate decrease in the frequency of the cyclical A and B sequences of contraction of the reticulum and rumen, compared with that recorded before its administration (Figure 2). This was followed by an increase in baseline activity (tonus) of both the reticulum and rumen, which persisted in all 3 sheep for at least 4 to 5 hours after receiving the highest dose of 40 nmol/kg. At times, cyclical contractions of greater amplitude were superimposed on the baseline tonus from an early stage. One sheep was more sensitive to ergotamine than the others, in that tonus of the reticulum and rumen was more pronounced and persisted for longer periods (as long as 8 hours) and that in the rumen, cyclical contractions were not detected for 7 hours. The administration of the lowest dose of 5 nmol of ergotamine/kg resulted in a slowing in frequency of A and B sequences of contraction for approximately 1 hour in all sheep, but no increases in baseline tonus were detected as they were after administration of all other doses. The decrease in the frequency of A and B sequences of contraction with 5, 10, 20, and 40 nmol of ergotamine/kg was more prolonged with the higher doses administered (Figure 3). An increase in the frequency of B sequences of contraction occurred in the 2- to 4-hour period after administration of 10 nmol of ergotamine/kg.

**Ergovaline**—In sheep, IV administration of ergovaline produced similar responses to those of ergotamine in that there was an immediate decrease in the frequency of cyclical reticulum and rumen contractions (compared with that recorded before its administration), followed by increases in baseline tonus, and an increased amplitude of reticulum contractions once they were restored (Figure 2). The highest dose of ergovaline resulted in the greatest and most prolonged decrease in the frequency of A and B sequences, which lasted for approximately 2 hours (Figure 4). There was a significant increase in the frequency of B sequences in the 2- to 4-hour period after 5 nmol of ergovaline/kg.

![Figure 3](image-url) — Mean ± SEM frequencies of A sequences of contraction of the reticulum (A) and B sequences of contraction of the rumen (B) in 3 sheep in response to IV administration of saline solution (first arrow; squares) and ergotamine (second arrow) at doses of 5 nmol/kg (closed circles), 10 nmol/kg (open circles), 20 nmol/kg (triangles), and 40 nmol/kg (diamonds). Data are displayed at 15-minute intervals; values are expressed as a ratio of that activity averaged over the first two 15-minute periods before saline solution was administered (considered as 100%). *Value significantly \( P < 0.05 \) different from that of the saline control treatment at this time point.
ings after administration of control treatment (water). The only marked effect was an increase in tonus of the reticulum, the first signs of which appeared after 6 hours and became moderate in degree by 10 hours after intraruminal administration. The tonus of the reticulum persisted at a moderate degree at 24 hours and was decreased but still present at 32 hours. At 48 hours after intraruminal administration of ergotamine, the EMG recording of the reticulum was apparently normal and no tonus was detected in the rumen. Subsequent food intake and characteristics of feces excreted were considered normal.

Because of the slight effects detected after intraruminal administration of 400 nmol of ergotamine/kg, the intraruminal dose was doubled to 800 nmol/kg and evaluated in all 3 sheep. After the control and ergotamine treatments, the frequencies of A and B sequences of contraction were recorded continuously and are presented for clarity at 1-hour intervals (Figure 5; Table 1). Responses to intraruminal ergotamine varied among the 3 sheep. In the sheep that was most sensitive to the effects of ergotamine following IV administration, increased tonus of both reticulum and rumen occurred from 8 hours to approximately 24 hours (Figure 5); when this sheep was reexamined for short periods after 24 hours, tonus was still present in the reticulum at reduced levels at 32 and 48 hours and was not detectable at 72 hours. Increased tonus in the rumen did not allow the detection of B sequences of contraction at some assessment times, especially in the aforementioned sheep but also in the other 2, negating hourly totals for some periods. The sheep that was most affected left a considerable amount of food in its feed bin during the 24- to 48-hour period, food that normally would have been consumed. Thereafter, food intake in this sheep was normal. Feces produced were of normal consistency.

In another sheep, increased tonus of the reticulum and rumen was detected at 8 hours, with reductions in the amplitude of rumen contractions. These effects were no longer detectable by 18 hours. During the 24- to 48-hour period, all food provided to this sheep was eaten, but feces produced were moist, compared with their normal character. In the remaining sheep, the least effects of treatments were detected; after 9 hours, the rumen had increased tonus for 2 hours. No subsequent effects on food intake or fecal characteristics were apparent.

Clinical observations—The effects of the ergopeptides on character and rate of respiration in all sheep were closely monitored because these variables were a sensitive indicator of the sheep’s well-being in response to ergopeptides in a previous study. One of the 3 sheep had a marked response in respiration (slow rate and deep breaths, as previously reported) and motility of the reticulum and rumen after the highest IV dose of ergotamine, and this, together with the stronger potency of ergovaline, led to the maximum dose of ergovaline being halved for the remaining experiments. Generally, the sheep started to ruminate between 3.5 to 5 hours after receiving...
ergotamine IV and 2 to 2.5 hours after receiving ergovaline IV at the highest doses and within 10 to 60 minutes of receiving water or ergotamine intraruminally. Sheep continued to ruminate with long bouts of rumination (30 to 45 minutes’ duration) over the 2- to 5-hour period after IV administration of the ergopeptides. This pattern was similar to that detected during the control experiments.

Following the experiments, the sheep were returned to their pens, where they immediately ate freshly provided food. Temperatures of their extremities were monitored by touch for several days and found not to change. Skeletal muscle tremors were not induced by either IV or intraruminal administration of the ergopeptides.

Discussion

The results of the present study have indicated that the ergopeptides ergotamine and ergovaline have profound and similar effects on motility of the reticulum and rumen of sheep. The effects detected were both excitatory and inhibitory: excitatory with regard to the baseline EMG activity of the reticulum and rumen and the amplitude of A sequences of contraction of the reticulum and inhibitory with regard to the frequency of A and B sequences of contraction of the reticulorumen.

The mechanisms whereby ergotamine and ergovaline affected the reticulorumen are probably varied given the variety of receptors (including adrenergic, dopaminergic, and serotoninergic receptors) on which the ergopeptides are known to act.\(^1\) Peripherally, the excitatory effects on the reticulorumen musculature could be a result of adrenoceptor stimulation because adrenaline (which does not cross the blood-brain barrier) has been shown to cause contraction of the reticulorumen musculature both in vivo\(^2\) and in vivo.\(^3\) The increase in amplitude of reticulum contractions may be due to \(\alpha_1\)-adrenoceptor activity because \(\alpha_1\)-adrenoceptor agonists are claimed to sensitize reticulorumen tension receptors, thereby increasing excitation of reflex-stimulated cyclical contractions of the reticulorumen.\(^4\) Peripheral excitatory effects may also be a result of stimulation of serotonergic receptors because serotonin increases tone of reticulum and rumen muscle in vitro\(^5\) and in conscious animals.\(^6\) The inhibitory effects of the ergopeptides on reticulorumen motility could also involve a variety of adrenergic receptors.\(^7\) Inhibition is also possible via dopaminergic receptors; dopamine has been shown to inhibit cyclical contractions of the reticulorumen.\(^8\) Indirectly, peripheral excitatory effects on serotonergic receptors that result in increased intrinsic activity and tone could reflexively inhibit cyclical contractions.\(^9\)

Systemic administration of serotonin has been shown to activate vagal mucosal afferent fibers from the upper portions of the gastrointestinal tract,\(^10\) and evidence has been provided that 5-hydroxytryptamine

### Table 1

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*Contractions could not be counted because of increased baseline EMG activity (tonus). NA = Not available.*
motility in sheep. The question arises as to whether ergopeptides had profound effects on reticuloruminal blockers are warranted. Additional experiments involving pharmacologic ulorumen to ergopeptides awaits determination, and and pathways involved in these responses of the retic- AJVR, Vol 67, No. 4, April 2006 713 on this.11,18 Direct stimulation of serotonergic receptors ity and the influence of the abomasum and duodenum nants given the reflex nature of reticuloruminal motil- This pathway may be of particular importance in rumi- For the effects on reticuloruminal motility that we detected in the present study. In addition, there are several central serotonergic receptors that influence motility of the reticulum and rumen differentially, and some of these mediate inhibitory effects.33 The possibility also exists that inhibitory effects may have developed from a direct excitatory effect on epithelial receptors in the reticulum; the consequent vagal afferent activity of those receptors could inhibit the frequency of contractions.32,34 A better elucidation of the receptors and pathways involved in these responses of the reticulorumen to ergopeptides awaits determination, and additional experiments involving pharmacologic blockers are warranted.

Pharmacologically, IV administration of the ergopeptides had profound effects on reticuloruminal motility in sheep. The question arises as to whether such effects might be detected in sheep after consump- tion of herbage containing high amounts of endophytes under natural grazing conditions. To investigate this, ergotamine was administered intraruminally as single doses (estimated to be equivalent to 3 mg and 6 mg of ergovaline) to sheep in the present study. With respect to the initial dose used, it was calculated from ergovaline concentrations in ryegrass,31 which indicated that sheep could ingest as much as 2 to 3 mg/d. Effects on reticuloruminal motility characteristic of those detected after IV administration of ergotamine (eg, increased tonus) were obtained after administration via the intraruminal route, but were not clearly apparent until at least 6 hours after administration of ergotamine. The duration of tonus was as long as 48 hours in some instances. Excitatory effects are consistent with a suggested increased motility responsible for increased fluid outflow from the reticulorumen of sheep fed ergovaline.38 The latency in response suggests that either there is minimal absorption from the reticulorumen, or that which is absorbed is quickly removed via first-pass metabolism in the liver. Hill et al19 studied the movement of ergot alkaloids across ovine reticuloruminal and omasal tissue in vitro and determined that the transport of ergotamine is relatively slow. Oral administration of ergotamine may result in undetectable systemic concentrations presumably because of extensive first-pass metabolism,3 but in another study18 in humans involving radiolabeled ergot alkaloids, the highest plasma concentrations were detected 2 hours after oral administration; dihydroergovaline was absorbed poorly, compared with ergotamine. Presumably, the greater latency for detectable effects on reticuloruminal motility in sheep was a consequence of the delayed passage of ergotamine from the reticulorumen to the intestines, where it is absorbed.38 Delayed passage through the reticulorumen and consequent continual prolonged delivery to the intestines probably also account for the longevity of the responses to ergotamine administered intraruminally, compared with responses to ergotamine administered IV.

The syndromes associated with animals consuming herbage with high ergot alkaloid content include effects on the cardiovascular system, character and rate of respiration, and body temperature. In a previous study9 in sheep, we determined that ergotamine and ergovaline had effects on all these variables that were consistent with those syndromes. In the present study, we extended our investigations to examine the effects of IV and intraruminal administration of these ergopeptides on reticuloruminal motility in sheep and suggest that our data indicate that ingestion of endophyte-infected grasses with high ergopeptide content has the potential to affect reticuloruminal motility and impair digestion. Previous studies have revealed that endophyte-infected ryegrass and fescue pastures that contain ergopeptides or tremorgens are associated with reduced weight gains,39 clinical signs of diarrhea (dag- giness),38 or effects on feed digestibility40 in herbivores. In addition, the situation may become exacerbated with possible interactions of the ergopeptides with other mycotoxins in ryegrass, such as patxilline.
and lolitrem B, which have also been shown to have profound effects on reticuloruminal motility in sheep.\textsuperscript{7}

\textbf{References}


