Studies on the physiological basis of appetite depression in nematode infection in sheep

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ABSTRACT

A major factor in the reduction of growth in parasitized lambs is the depression in food intake by a mechanism not yet understood.

Investigation of the pattern of eating has shown that parasitized lambs have a lower (35%) cumulative intake, especially within the first hour of feeding, which return to a control level on drenching. The importance of two factors which may moderate intake depression, the activity of the ventromedial hypothalamus (VMH) and elevated cholecystokinin (CCK), were investigated.

Four animals with intake depression (approximately 40% $P<0.05$) as a result of continuous infection with 4000 *T.colubriformis* per day for 12 weeks together with 4 control animals received, in a replicated latin square design 0, 1, 2 and 4 ml *i.v.* of a compound (brotizolam) used to block the satiety effect at the VMH. Intake increased ($P<0.05$) within the first hour of feeding of both parasitized and control animals (approximately 2.6 and 1.9 times, respectively). Four similarly infected and 4 control lambs were given varying doses of a potent antagonist of peripheral CCK action without effect on food intake. These results suggest that depression of food intake in parasitized lambs appears to involve central satiety signals and not peripheral CCK.

Keywords Parasites, Intake, Mederantil, Loxiglumide

INTRODUCTION

A reduction in feed intake is one of the major factors causing poor performance of animals exposed to parasites at pasture (Sykes, 1983). The control of feed intake is complex, involving both peripheral and central nervous system factors (Morley, 1980), but little is known of the mechanism by which parasites induce a depression in food intake. Some evidence exists that gastrointestinal hormone changes associated with the pathophysiology of the parasite are involved, in particular cholecystokinin (CCK) associated with *Trichostrongylus colubriformis* (Symons and Hennessy, 1981) and gastrin associated with *Ostertagia ostertagi* (Fox, *et al* 1989).

An investigation to identify the pathways by which a parasite residing in the small intestine influences the hypothalamus and thereby intake was initiated. Two studies are reported here, both using the principle of antagonising a particular pathway to examine peripheral CCK receptors and the satiety action of the VMH through the diazepam receptor. The role of these pathways was elucidated by monitoring eating patterns.

MATERIALS AND METHODS

Sixteen female sheep (Coopworth x Dorset Down) were weaned at seven weeks of age (liveweight 17±1.5kg) and drenched with ivermectin 200mg/kg (Ivomec®). Animals were raised on 'safe pasture', and suppression drenched with fenbenadazole 25mg/kg (Panacur®) at fortnightly intervals to minimise acquisition of parasite infection. At approximately 25kg liveweight, 8 animals were randomly allocated to parasite infection and 8 to control group. Animals were then housed indoors in individual pens and fed a complete pelleted diet.

The infected animals were dosed *per os* three times per week with 9333 infective *Trichostrongylus colubriformis* larvae (4000/head/day) for 12 weeks. In the first four weeks, control animals were pair fed with infected animals to minimise liveweight differences between groups. In the initial two weeks of the trial a pattern of short term intake was established for each animal, by recording intake following a two hour fast, at 10,20,30,40,50,60,75,90,105 and 120 minutes post feeding, then hourly for 8 hours and finally 22 hours

post feeding. Following the onset of intake depression (minimum 30%) in the infected group, the 16 animals were randomly assigned to Mederantil (4 infected, 4 control) or groups (4 infected, 4 control).

Mederantil™ (Boehringer Ingleheim NZ) is a member of the benzodiazepine family and operates at the satiety centre of the hypothalamus (the VMH) to produce an orexigenic action in several species (Baile and McLaughlin, 1979). Loxiglumide (CR1505:Rotta Laboratory Italy), a pentanoic acid derivative has been shown effective in both *in vivo* and *in vitro* trials as a potent competitive antagonist of peripheral CCK.

Both experiments were run in a replicated 4 x 4 Latin square design, with treatments being applied on alternate days, to minimise any carry-over effects of the treatments. Mederantil was administered in doses of 0, 1, 2 or 4ml by intravenous injection immediately prior to feeding. Similarly, Loxiglumide was administered by intravenous injection immediately prior to feeding, in 5ml of saline at 0,5,10 or 20mg/kgW. Short term intake was recorded on both treatment and rest days.

At the completion of the trial all animals were drenched with ivermectin (200mg/Kg). Daily feed intakes were then recorded in all animals until intakes were restored in both infected groups.

Statistical analysis was carried out on data using the GENSTAT statistical package. Analysis of variance was carried out on cumulative feed intake at 1 hour and 22 hours.

RESULTS

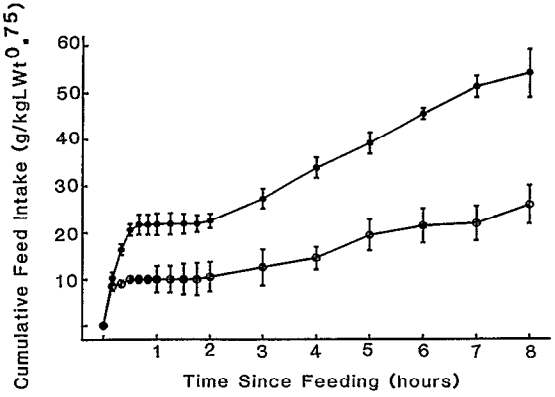

FIG 1 Cumulative feed intake (g/kgW$^{0.75}$) for infected o——o and controls animals •——•

A pattern of short term intake was established for all animals prior to the onset of parasite infection. This pattern was very similar to that of control animals (Figure 1). Continuous larval dosing produced significant daily intake depression. Mean overall values were 56 and 80g/W$^{0.75}$/day ($P<0.05$) for infected and control animals, respectively.

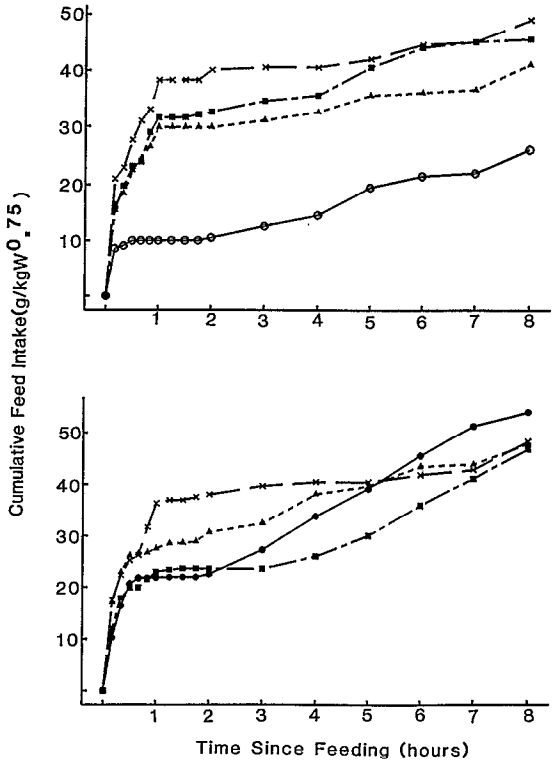

FIG 2a (Top) Cumulative feed intake (g/kgW0.75) for infected lambs at 0ml (o), 1ml (▲), 2ml (■), and 4ml (x) of Mederantil (max SEM = 2.8).

2b (Bottom) Cumulative feed intake (g/kgW0.75) for infected lambs at 0ml (●), 1ml (▲), 2ml (■), and 4ml (x) of Mederantil (max SEM = 3.6).

The intake depression produced changes in the short term intake pattern of infected animals (Figure 1.). Meal frequency appeared similar but the consumption at each meal was reduced significantly such that cumulative feed intake at various time intervals was lower

(e.g. at 60 minutes 10 vs 20g/kgW$^{0.75}$ P<0.05).

Each of the three levels of Mederantil produced a significant increase in initial feed intake in infected animals immediately post injection. In the control group, only 1ml and 4ml of Mederantil produced significant increases in initial intake. There was no clear dose dependent response in intake to the mederantil in either group of sheep. (Figures 2a and 2b). The response was much greater in infected animals than in control animals 2.9 vs 1.6 times increase respectively (Table 1). Mederantil did not alter total daily intake.

TABLE 1 Mean feed intake (g/kgW$^{0.75}$) at 1 hour and 22 hours for animals on Mederantil treatment.

	Mederantil				
	0ml	1ml	2ml	4ml	S.E.M.
Infected					
1 hour	10^a	29^b	31^b	38^c	2.8
22hr	56^d	61^d	59^d	54^d	2.6
Control					
1 hour	20^e	25^f	21^e	34^g	1.6
22hr	78^h	76^h	74^h	72^h	2.4

Differences in alphabetical superscript indicates significant differences (p<0.05).

TABLE 2 Mean feed intake (g/kgW$^{0.75}$) at 1 hour and 22 hours for animals on Loxiglumide treatment.

	Loxiglumide (per kgW)				
	0mg	5mg	10mg	20mg	S.E.M.
Infected					
1 hour	12^a	15^a	11^a	16^a	2.6
22 hr	62^b	64^b	68^b	63^b	5.9
Control					
1 hour	19^c	12^a	17^a	17^a	3.0
22 hr	77^d	80^d	83^d	84^d	3.5

Differences in alphabetical superscript indicates significant differences (p<0.05).

In the Loxiglumide experiment cumulative feed intakes were 19 vs 12 g/W$^{0.75}$day at 1 hour and 77 vs 62g/W$^{0.75}$/d at 22 hours for control and infected groups respectively. There was no effect of Loxiglumide on cumulative intake at 1 hour or 22 hours nor was there any effect of dose rate (Table 2).

DISCUSSION

In both trials, parasite infection produced a characteristic depression in daily feed intake, similar to that found by Steel *et al.*, (1980). This intake depression manifests itself in changes in meal intake. The most interesting observation was that pattern of eating (initiation and cessation of meals) was not markedly altered by parasitised animals, but that rate of intake expressed as cumulative food intake was significantly depressed under parasitism. This may be indicative of opioid involvement (Baile *et al.*, 1987). The recovery of daily intake and restoration of intake rate following anthelmintic suggests the pathway causing the depression is temporary and/or reversible.

The significant increase in intake over 1 hour as a result of Mederantil in both infected and control animals was similar to those of Della-Fera, Naylor and Baile (1978) in debilitated horses using Elfazepam and U31576 (other benzodiazepines). The non-significant response of control animals to 2ml Mederantil may be an isolated observation or due to moderate ataxia which was evident on several occasions.

The benzodiazepines have been demonstrated to elicit feeding in rats when injected into the VMH (a recognised satiety centre) but not when injected into the lateral hypothalamus(feeding centre) indicating a role in satiety suppression (Anderson-Baker 1978). Our results indicate this mechanism works in both infected and control sheep as it does in other species.

The response to Mederantil was greater (2.9 vs 1.6 times) in infected animals compared to control animals. This is in agreement with the findings of Fanneau de la Horie and Vaugon(1986) who found cattle with a variety of gastro-intestinal disorders responded more than healthy animals. Our results suggest a primary role of the satiety centre VMH and that the activity of the VMH may be greater in parasitised animals. The lesser response by the control animals may also be attributed to these animals being closer to

maximum potential physical rate of consumption. Thus in removing satiety blockage other factors limited the intake response. All animals were fed once daily and the eating response to Mederantil was of short duration suggesting intake limitation due to rumen fill was unlikely under these conditions.

Mederantil did not significantly change the 24hr intake in control or infected animals. Fanneau de la Horie and Vaugon(1986) found similar results and concluded this was due to the very short half life (0.3hr) of the drug. Other workers, Baile and McLaughlin (1978) and Breier (1985) did find an increase in daily intake but in both instances treatment was administered when animals were satiated whereas in this trial animals had been fasted for two hours at the time of treatment.

The nature of the benzodiazepine family means we are unable to exclude the potential analgesic role of Mederantil nor the suppression of any psychological influences which had been inhibiting eating (Baile and McLaughlin, 1979).

Antagonism of the action of peripheral CCK action through the use of Loxiglumide did not affect either short term (over 1 hour) or daily (24hr) intake. Loxiglumide has been shown to be a potent inhibitor of peripheral CCK in a number of species (Setnikar *et al.*, 1987). CCK acts peripherally to control the rate of outflow of digesta from the stomach and contraction of the gall bladder. Its peripheral action may also involve stimulating the vagal nerve. CCK may also cross the blood-brain barrier (Dockray, 1987). It is thought the central receptors in the brain are different to the peripheral receptors (Morley, 1982).

These results demonstrate that peripheral action of CCK is unlikely to be responsible for the depression in food intake observed in parasitised animals but the role of CCK in the brain remains to be elucidated. It is possible that the dose rate of Loxiglumide was insufficient, based as it was on rat and human data, or that a rapid clearance of the single injection occurred. Further work is necessary to clarify these findings.

These studies aim to identify the pathways involved in the depression of intake observed under subclinical parasitism. The practical long-term objective of this work is to identify pharmacological or immunological techniques which might be utilised in conjunction with current control measures to improve the liveweight gain of parasitised animals. It is the extended time required for parasitised animals to reach slaughter weight that imposes management constraints on the farm.

It was concluded that parasitism results in reduced rate of consumption, an effect which may be overcome in the short term by blocking the satiety action of the VMH. Peripheral CCK antagonists are not effective in changing short term intake in either control or infected animals.

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