MODULATION OF RETICULO-RUMINAL MOTILITY IN GOATS AND SHEEP BY OPIOID MECHANISMS

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Normorphine and naloxone were administered via selective routes in sheep and goats. The results with normorphine indicate the presence of both (1) a central action depressing frequency and amplitude and, (2) a peripheral action — probably on the intramural plexus — depressing only the amplitude of the cyclical reticulo-ruminal contractions.

Key words: Sheep, goat, normorphine, naloxone, forestomach motility

In ruminants, cyclical reticulo-ruminal motility is a critical part of the digestive process. It facilitates microbial break-down of feed in the forestomachs by mixing the digesta and it prevents accumulation of gas by initiating eructation. Opioids are known to inhibit cyclial forestomach motility in different species (Ruckebusch 1983). Recently, opiate antagonists have been shown to stimulate the frequency of the extrinsic ruminal contractions in conscious goats, indicating an inhibitory role for endogenous opioids in the control of cyclical reticulo-ruminal motility (Maas 1982). In the present study, the effects of normorphine were recorded after administration via selective routes: intracerebroventricular, the carotid artery, the aortic arch, the jugular vein, the left gastric artery and the celiac artery. Additionally, the effects of opioids and spasmogenic agents upon isolated longitudinal reticular strips (sheep) and circular ruminal strips (goat) were determined in vitro.

Twelve dwarf goats, female and castrated males, were used; they weighed between 21.5 and 35.5 kg (mean ± SE: 26.3 ± 1.2). These animals were kept in stables and fed a diet of hay and pelleted concentrate (Van Miert et al. 1983a). Water was provided ad libitum. Each goat had a permanent cannulation of the third cerebral ventricle (Van Miert et al. 1983b). The extrinsic ruminal contractions were monitored by a technique previously described (Maas 1982). Also, nine adult Blackface and Suffolk sheep were used; their weight varied between 36 and 80 kg. They were kept in a pasture near the laboratory. Prior to an experiment an animal was taken indoors at 0900 h and anesthesia was induced with a 4% halothane-oxygen mixture employing a face mask. After endotracheal intubation, a level of anesthesia was maintained with a controlled mixture of 1–4% halothane-oxygen. The left common carotid artery was brought into a skin loop and a ruminal fistula was made by the technique described by Leek (1976). This fistula allowed placing of balloons in both rumen and reticulum. To record gastric motility, the balloons were inflated with 100 mL air and connected via polythene tubing to pressure transducers and a pen-recorder. At least 6 mo elapsed following this treatment before the animals were used. Additionally, in four of these sheep the celiac artery was cannulated chronically. The cannulae were exteriorized via small paravertebral laparotomy on the left side. These sheep were allowed to recover 14 days before experiments commenced. The cannulations of the carotid artery, the aortic arch, the left gastric artery and the jugular vein were performed using techniques previously described (Maas and Van Miert 1982; Maas and Leek 1984). The in vitro experiments were done with ruminal tissue from goats killed at the local slaughterhouse and with tissue isolated from the reticulum during the preparatory surgery in sheep. Details of the method have been given previously (Maas et al. 1982).

In sheep ($n = 4$), normorphine (> 20 $\mu g \cdot kg^{-1}$, carotid artery) depressed both frequency and amplitude of cyclical contractions of reticulum and rumen. Low doses (20 $\mu g \cdot kg^{-1}$) induced a minor effect if administered via the jugular vein and were ineffective via the celiac artery. A tenfold higher dose via the celiac artery was needed to evoke a depression of the amplitude of the reticulo-ruminal contractions; the drug (0.2–1 $mg \cdot kg^{-1}$) did not, however, affect the frequency of these contractions. These doses (200 $\mu g \cdot kg^{-1}$), when administered via the carotid artery or via the jugular vein, induced prolonged depressions of both frequency and amplitude of the reticulo-ruminal contractions. The fre-

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quency was most effectively diminished by the administration of the drug via the carotid artery. The actions of normorphine could be prevented or abolished by the injection of naloxone (100 $\mu g \cdot kg^{-1}$) via the corresponding routes. To assess whether the depression of the amplitude of the reticular contractions by normorphine via the carotid artery or jugular vein could result from the interaction with receptors within the reticulo-ruminal wall, normorphine (100 $\mu g \cdot kg^{-1}$) was injected via the carotid arteries during infusion of naloxone (1 $\mu g \cdot kg^{-1} \cdot min^{-1}$) via the celiac artery. This dose of naloxone, which antagonized normorphine (100 $\mu g \cdot kg^{-1}$) administered via the celiac artery, did not modify the response to normorphine given via the carotid arteries.

In goats ($n = 4$), the intracerebroventricular (ICV) injection of normorphine (17.5 $\mu g \cdot kg^{-1}$) caused a longer-lasting inhibition of the extrinsic ruminal contractions than i.v. infusion of a 30-times-higher dose. Moreover, ICV administered naltrexone ($\geq$ 1.9 $\mu g \cdot kg^{-1}$) partly antagonized or ($\geq$ 14.1 $\mu g \cdot kg^{-1}$) completely prevented the inhibitory response to i.v. normorphine (17 $\mu g \cdot kg^{-1} \cdot min^{-1}$ during 30 min (Table 1)).

In the in vitro experiments, opioids failed to modulate the smooth muscle tension of the longitudinal reticular strips (sheep) or circular ruminal strips isolated from goats, whereas spasmogenic agents such as substance P increased the tone of the strips dose-dependently (Maas and Leek 1984; Maas et al. 1982; Veenendaal et al. 1982). Furthermore, opioids did not alter the contractile responses to acetylcholine or substance P.

The present results with conscious sheep and goats indicate the presence of both (1) a central opioid action depressing frequency and amplitude, and (2) a peripheral opioid action depressing only the amplitude of the extrinsic reticulo-ruminal contractions. Opioids did not alter the resting discharge of afferent tension units (Maas and Leek 1984) and similarly failed to modulate smooth muscle tone of reticular and ruminal strips in vitro, suggesting that opioids act peripherally on the intramural neuronal plexus, possibly by diminishing the output of the excitatory transmittor.A more detailed analysis would be necessary to confirm this hypothesis.

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LEEK, B. F. 1976. A simple and effective ruminal cannulation technique for sheep. J. Physiol. (Lond.) **263**: 233–234 P.

MAAS, C. L. 1982. Opiate antagonists stimulate ruminal motility of conscious goats. Eur. J. Pharmacol. **77**: 71–74.

MAAS, C. L. and LEEK, B. F. 1984. Central and local actions of opioids upon reticulo-ruminal motility in sheep. Vet. Res. Commun. (submitted).

Table 1. Antagonism by intracerebroventricularly administered naltrexone of the inhibitory effect of normorphine on cyclical ruminal motility in conscious goats

Pretreatment					
ICV dose (μg naltrexone per animal)	Time interval† (min)	Normorphine (17 $\mu g \cdot kg^{-1} \cdot min^{-1}$ during 30 min i.v.)	Relative inhibition of cyclical motility		n
			Frequency‡	Amplitude‡	
Placebo	–	–	−0.2 ± 2.7%	2.8 ± 1.2%	4
Placebo	30	+	100 ± 4.6%	100 ± 13.0%	4
50 (1.9 $\mu g \cdot kg^{-1}$)	30	+	41.0 ± 18.4%*	32.2 ± 25.3%	4
100 (3.7 $\mu g \cdot kg^{-1}$)	30	+	8.0 ± 15.8%*	22.0 ± 4.5%*	4
200 (7.2 $\mu g \cdot kg^{-1}$)	60	+	18.0 ± 15.4%*	60.0 ± 10.8%	4
400 (14.1 $\mu g \cdot kg^{-1}$)	60	+	1.5 ± 5.5%*	−19.3 ± 8.4%*	3
800 (28.7 $\mu g \cdot kg^{-1}$)	60	+	−13.7 ± 7.0%*	−7.5 ± 16.1%*	4

†Time elapsed between pretreatment and starting the infusion of normorphine.
‡Calculated as the cumulative depression in min. % over the two 15-min periods of infusion of normorphine and expressed as mean ± SEM; asterisks indicate significant differences between naltrexone and placebo results in the presence of normorphine.

MASS, C. L. and VAN MIERT, A. S. J. P. A. M. 1982. Loperamide inhibits cyclical forestomach motility via an opioid-pathway. Colloq. l'INRA **8**: 169–172.

MASS, C. L., VAN DUIN, C. T. M. and VAN MIERT, A. S. J. P. A. M. 1982. Modification by domperidone of dopamine- and apomorphine-induced inhibition of extrinsic ruminal contractions in goats. J. Vet. Pharmacol. Therap. **5**: 191–194.

VAN MIERT, A. S. J. P. A. M., VAN DUIN, C. T. M., VERHEIJDEN, J. H. M. and SCHOTMAN, A. J. H. 1983a. Staphylococcal enterotoxin B and *E. coli* endotoxin: Comparative observations in goats on fever and associated clinical hematologic and blood biochemical changes after i.v. and intramammary administration. Am. J. Vet. Res. **44**: 955–963.

VAN MIERT, A. S. J. P. A. M., VAN DUIN, C. T. M. and WOUTERSEN- VAN NIJNANTEN, F. M. A. 1983b. Effect of intracerebroventricular injection of PGE_2 and 5-HT on body temperature, heart rate and rumen motility of conscious goats. Eur. J. Pharmacol. **92**: 143–146.

RUCKEBUSCH, Y. 1983. Pharmacology of reticulo-ruminal motor function. J. Vet. Pharmacol. Therap. **6**: 245–272.

VEENENDAAL. G. H., WOUTERSEN-VAN NIJNANTEN, F. M. A. and VAN MIERT, A. S. J. P. A. M. 1982. Responses of goat ruminal musculature to substance P in vitro and in vivo. Vet. Res. Commun. **5**: 363–367.