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## The cyclic motor activity of the ovine gut: its reset at a faster rhythm

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*Summary.* In adult sheep, the frequency of the migrating motor complexes (MMC) was increased by the duodenal administration of methysergide, but not affected by other 5-$HT_1$ or 5-$HT_2$ antagonists. This reset of the MMC pattern at a faster rhythm suggests a selective action on the enteric neuronal serotoninergic mechanism modulating the pacing of the gut cyclic motor activity.

Recordings of the motor events of the small intestine throughout 24 h indicate that a cyclic activity, the migrating motor or myoelectric complex (MMC), recurs at intervals of 90–120 min during the interdigestive state in dogs[1] or regardless of feeding in ruminants[2]. The existence of an intrinsic mechanism for initiation of the MMC pattern has been located at the duodenal bulb level in sheep[3]. The persistence of MMCs after combined vagotomy and splanchnicectomy, which abolishes the cyclic activity of the stomach (reticulum), indicates the major role of the enteric nervous system[4]. A great variety of substances including serotonin (5-hydroxytryptamine; 5-HT)[5] or substance P[6] have been suggested as enteric neurotransmitters, but none of them are able to increase the daily number of MMCs. Likewise, motilin, pancreatic polypeptide, somatostatin and morphine, which induce premature MMC-like phases of activity, may be considered as triggering agents rather than initiators of the MMC pattern[7]. This report presents the first evidence in both intact and vagotomized sheep of a resetting at a different rhythm of the enteric biological clock, which generates the MMC pattern, by the local administration of 5-HT antagonists.

*Materials and methods.* 6 ewes, 4 years old and weighing 48–50 kg, were maintained continuously in large cages and prepared for long-term electromyographical and mechanical recording of gastroduodenal motility by serosal implantation of nichrome wires (120 µm in diameter) and fixation of force strain gauges on the duodenum at 3 cm and 23 cm beyond the pylorus and on the proximal jejunum at 1 m from the pylorus[8]. The connecting wires, 2 m in length, were exteriorized in the right flank. In addition, 2 silastic catheters (2 mm in ext. dia.) leading into the lumen of the proximal duodenum and jejunum were inserted and anchored at 3 and 100 cm from the pylorus. An electroencephalograph (Reega VIII, Alvar) set at a paper speed of 30 cm/h was used to register over a period of 3 months the electrical activity of the duodenum and its mechanical activity via a Wheatstone bridge[8].

The animals, fed twice daily (9:00 and 17:00), received through the catheters, within 3 h following the morning meal, either 5-$HT_1$ or 5-$HT_2$ antagonists dissolved in a constant volume (5 ml) of distilled water or propylene glycol 20% w/v. The order of treatment (water or propylene glycol; methysergide maleate – courtesy of Sandoz, Basle: 50, 100 and 200 µg/kg; xylamidine tosylate – courtesy of Wellcome, Beckenham: 1 mg/kg and cyproheptadine HCl: 1 mg/kg) was randomized and the timing of injections was normalized by making them at a moment that was a fixed percentage (about 50%) of the previous duration of the MMC in progress. Ketanserin (R 41468) and R 50970 (courtesy of Janssen, Beerse) were used as antag-

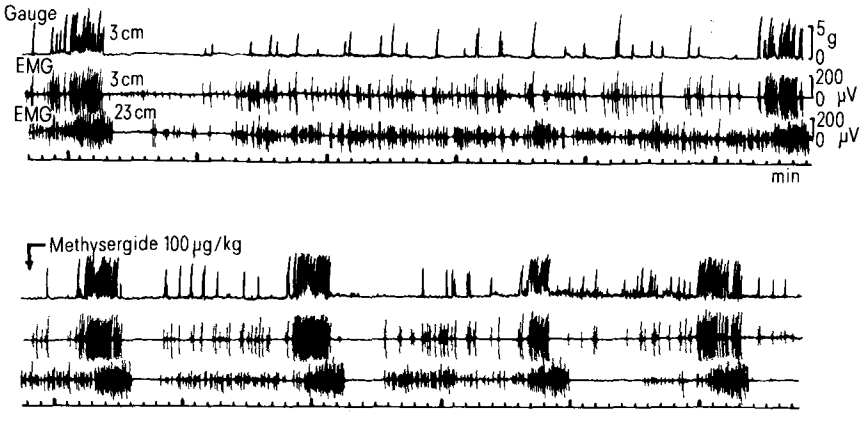


Figure 1. In an intact sheep, electrical (EMG) and mechanical (strain gauge) activity of the duodenal bulb, at 3 cm from the pylorus, showing isolated and in-series contractions lasting about 3 min repeated at 60-min intervals, and propagated to the duodenum, at 23 cm from the pylorus within approximately 1 min. The in-series contractions of the duodenal bulb corresponded to the phases III of the MMC pattern on the proximal duodenum. The intraduodenal administration of methysergide at the dosage of 100 µg/kg reduced for several hours the interval between the in-series contractions of the phases III of the MMC pattern to less than 15 min.

onists of 5-$HT_2$ receptors[9] at the dosage of 0.5 mg/kg. The effects of identical dosages of 5-HT (5 µg/kg) were compared for the intravenous and enteric routes of administration. The effects of methysergide administered in the proximal duodenum at different dosages (50, 100 and 200 µg) were compared with those occurring when R 41468 (0.5 mg/kg) was given 10 min previously. In addition, the effects of methysergide (100 and 200 µg/kg) were tested in 3 sheep which underwent a surgical section of the vagus and splanchnic nerves[4].

The MMC duration was evaluated by measuring the intervals between the periods of maximal activity also known as activity fronts or phases III of the MMC which correspond to the in-series contractions on the duodenal bulb[3]. Statistical differences were evaluated with a paired t-test.

*Results.* The duration of MMCs recorded on the duodenum, 98.6 min (n = 2 352 in 6 animals) in the intact sheep, was shortened (76.6 min, n = 160 in 3 animals) in sheep which underwent surgical extrinsic nerve section (table). In the intact sheep, the i.v. injection of 5-HT (5 µg/kg), inactive by the other route, elicited for 2–6 min a phase III-like activity which was not followed by changes in the MMC duration.

The intrajejunal administration of 5-HT antagonists, except for methysergide (200 µg/kg), did not modify the MMC duration. At this high dosage, methysergide caused 2–4 MMCs of shorter duration (about 50 min) to occur. In contrast, their effects after intraduodenal administration were pronounced (table). Methysergide (50, 100 and 200 µg/kg) elicited a dose-related increase in the MMC frequency lasting from 5–24 h depending upon the dosage (fig. 1). Cyproheptadine and xylamidine lengthened the MMC's duration (table). The control pattern remained unchanged after the administration of 5-$HT_2$ antagonists, ketanserin and R 50970, but their previous administration in the proximal duodenum potentiated the effects of methysergide given by the same route (fig. 2).

In the sheep after removal of the extrinsic nerve supply, duration of the MMCs was further shortened by the duodenal administration of methysergide (100 and 200 µg/kg) (table).

*Discussion.* The cyclic phenomena of the MMCs have characteristics of an activity initiated by an enteric biological clock, modulated by hormonal and neural factors. The period of the enteric clock mechanism can be altered by several agents such as morphine, motilin or somatostatin, which act as triggering factors of phase III, or 5-HT which elicits a premature phase III-like activity. These agents influence transiently the cycle duration in a manner more all-or-none than dose-related.

The striking feature of this study is the long duration of the more frequent MMCs elicited by local administration of methysergide, even after extrinsic denervation. These results support the idea of an interference with the local enteric nervous system of methysergide which has mixed 5-$HT_1$ – 5-$HT_2$ antagonistic[9] and also agonistic properties[10]. However, the action of methysergide on the enteric clock is obviously different from that obtained with the other 5-$HT_1$ – 5-$HT_2$ antagonists, cyproheptadine and xylamidine. The existence of several types of 5-$HT_1$ excitatory and inhibitory receptors in the enteric nervous system, e.g. one methysergide-insensitive but activated by other antagonists[11], may be a part of the explanation. Cyproheptadine and xylamidine might act on neural receptors of types different from those of methysergide.

Ketanserin, a highly potent specific 5-$HT_2$ antagonist with no effect per se, is able to enhance the effects of methysergide, a poor antagonist, on 5-$HT_2$ receptors. The non-fixation of methysergide on sites already occupied by ketanserin[9] might be the reason for the increased effect of methysergide under ketanserin.

The generation of the MMC patern may thus be mediated by a serotoninergic neural mechanism in which methysergide should act as a potent initiating factor, by blockade of 5-$HT_1$ inhibitory receptors. A strong hindrance in gastrointestinal motility is caused by a partial 5-HT depletion by neurotoxins[12]. In the adult sheep, methysergide raises the MMC frequency to values approaching the faster rhythm recorded in young animals[13]. These findings are consistent with the possible existence in the adult animal of a brake-like mechanism, involving 5-HT interneurones, to hamper the initiation of the MMC on the cranial part of the duodenum.

Changes induced by 5-HT antagonists in the duodenal MMC duration in intact sheep (control) and after extrinsic denervation (vagotomy)

| Drugs (number of experiments) | Dosages (intraduodenal route) | MMC duration (min) mean ± SD | Duration of changes (range in min) |
|---|---|---|---|
| Control (n = 2352) | – | 98.6 ± 9.3[a] | – |
| Methysergide (n = 24) | 50 µg/kg | 40.7 ± 6.1[b] | 300– 480 |
| | 100 µg/kg | 30.9 ± 8.4[b] | 600– 720 |
| | 200 µg/kg | 20.8 ± 9.7[c] | 1200–1440 |
| Cyproheptadine (n = 4) | 1 mg/kg | 150.0 ± 25.8[d] | 300– 500 |
| Xylamidine (n = 4) | 1 mg/kg | 125.0 ± 19.1[d] | 240– 300 |
| Ketanserin (n = 4) | 0.5 mg/kg | 101.5 ± 6.3[a] | – |
| R 50970 (n = 4) | 0.5 mg/kg | 98.9 ± 10.2[a] | – |
| Vagotomy (n = 160) | – | 76.1 ± 6.1[e] | – |
| Methysergide (n = 8) | 100 µg/kg | 21.1 ± 8.1[c] | 410– 710 |
| | 200 µg/kg | 15.6 ± 6.1[c] | 800–1650 |

[a,b,c,d,e] mean not sharing a common superscript differ at $p < 0.01$.

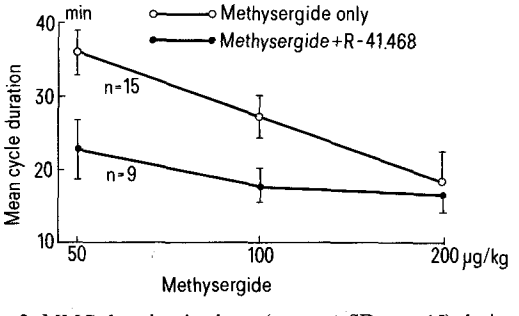


Figure 2. MMC duration in sheep (mean ± SD; n = 15) during a period of 6 h following the intraduodenal administration of methysergide at the dosage of 50, 100 and 200 µg/kg (o) and following the administration of methysergide and ketanserin (0.5 mg/kg 10 min previously; n = 9 ). The mean cycle duration was 98.6 min in control animals receiving saline.

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