ELSEVIER

European Journal of Pharmacology 321 (1997) 53–57

ejp

Short communication

Gastrointestinal motor activity in conscious ferrets

Yukinori Nagakura *, Kin-ya Sohda, Hiroyuki Ito, Keiji Miyata

Neuroscience Research, Pharmacological Laboratories, Institute for Drug Discovery Research, Yamanouchi Pharmaceutical Co. Ltd., 21 Miyukigaoka, Tsukuba, Ibaraki 305, Japan

Received 12 November 1996; revised 20 December 1996; accepted 24 December 1996

Abstract

Gastrointestinal motility was measured with force transducers in conscious ferrets. The gastrointestinal motility pattern in both the interdigestive and digestive states was similar to that reported for humans. The activity front, phase III contractions of the migrating motor complex, occurred cyclically in the antrum and migrated to the duodenum and ileum in the interdigestive state, and relatively low-amplitude contractions were sustained in the antrum, duodenum and ileum in the digestive state. Colonic motility was characterized by basal relatively low-amplitude contractions and a single high-amplitude contraction preceding defecation. Cisapride (0.3–3 mg/kg s.c.) enhanced antral and colonic motility. This ferret model will help the investigation and evaluation of drug effects on gastrointestinal motility in humans.

Keywords: Gastrointestinal motility; Migrating motor complex; Force transducer; Cisapride; (Ferret)

1. Introduction

The gastrointestinal motility pattern in humans can mainly be divided into the interdigestive and digestive states. The interdigestive state is characterized by the cyclical occurrence of the activity front, phase III contractions of the migrating motor complex which occurs in the stomach and migrates through the small intestine. The digestive state is characterized by sustained contractions with relatively low amplitude in the gastric antrum and small intestine (Itoh and Sekiguchi, 1984; Kerlin and Phillips, 1982; Sarna et al., 1991). On the other hand, spontaneous colonic motility in humans is represented by basal relatively low-amplitude contractions and a single high-amplitude contraction preceding defecation (Narducci et al., 1987).

The anatomical and physiological characteristics of the gut of ferrets have been reported to show good similarity to those of the human gut (Mackay and Andrews, 1983). This animal is therefore commonly used in studies on the pathophysiology of the gastrointestinal tract in humans. Although the stomach of ferrets was reported to show a cyclical motility pattern which was similar to the migrating motor complex in the interdigestive state (Grundy, 1990), such a cyclical motility pattern was not evident in the rat stomach (Garrick et al., 1986). This suggests that the ferret model is more appropriate than the rat model for the study of human gastrointestinal motility. At present, however, the gastrointestinal motility pattern throughout the gut of this animal in the conscious state is not known precisely.

In the present study, gastrointestinal motility from the gastric antrum to the colon of conscious ferrets was investigated by means of chronically implanted force transducers. After confirming that stable measurement was possible, we examined the effect of a clinically used drug in this model. Gastrointestinal prokinetic benzamides, which exert a gastrointestinal prokinetic effect by facilitating cholinergic neurotransmission in the gut, are currently widely used to treat gastrointestinal motility disorders such as gastroesophageal reflux and gastroparesis. Nowadays, the most widely applied gastrointestinal prokinetic benzamide is cisapride, and thus data on the effect of this agent on gastrointestinal motor activity in humans have been accumulating (Briejer et al., 1995; Wiseman and Faulds, 1994). Therefore, we chose this agent for testing in the ferret model. The experiments were designed to assess whether spontaneous gastrointestinal motility and its response to cisapride in conscious ferrets are similar to those in humans.

* Corresponding author. Tel.: (81-298) 52-5111; Fax: (81-298) 52-2965.

0014-2999/97/$17.00
PII S0014-2999(97)00005-8

2. Materials and methods

All experiments were performed in compliance with the regulations of the Animal Ethical Committee of Yamanouchi Pharmaceutical.

Four male ferrets (Marshall Farms, North Rose, NY, USA) weighing 1.3–1.4 kg were used. They were given a standard laboratory carnivore diet and allowed free access to water. The animals were fasted for 18 h before surgery with free access to water. Under halothane (Fluothane, Takeda, Osaka, Japan) anesthesia, strain gauge force transducers, 8 mm wide and 5 mm long (F-08IS, Star Medical, Tokyo, Japan), were sutured to the gastric antrum (3 cm proximal to the pyloric ring), duodenum (3 cm distal to the pyloric ring), ileum (20 cm distal to the pyloric ring) and colon (6 cm proximal to the anus) to measure circular muscle contractions. The free end of the transducers was brought subcutaneously to a skin incision made between the scapulae and protected with a jacket (PJ-F3, Star Medical). The surgical operation was performed with reference to the literature on the anatomy of the ferret (An and Evans, 1988). The animals were allowed to recover for at least 8 days after surgery before the commencement of experiments.

The ferrets were fasted for 18 h with free access to water before all experiments. Each animal was used for experiments at an interval of 3 days or more. During the experiments, each animal was placed without constraint in an observation box (40 cm wide × 40 cm long × 40 cm height). The free end of the force transducers was connected to a gastrointestinal motility measuring system (ESC-820A; Star Medical) via a connecting cable suspended from the ceiling. On each experimental day, the animals were habituated to this recording procedure for at least 1 h before the start of measurement of gastrointestinal motor activity. The analog signals of gastrointestinal motor activity, stored in the measuring system, were digitized at a sampling frequency of 10 Hz by an analog-to-digital converter (ESC-1012; Star Medical) and analyzed by a computer system (ESC-820C; Star Medical). Gastrointestinal motility was quantified by determining a motility index which was calculated by the computer system. The motility index was equivalent to the integrated area surrounded by the contractile wave and baseline, i.e., the product of the amplitude (voltage) and the time in minutes during a certain fixed period.

The measurement of gastrointestinal motility in the interdigestive state was started in the morning (9:00–10:00 h) in each ferret. After three cycles of the migrating motor complex in the interdigestive state had been measured, carnivore food (Boiled Chicken Meal, 20 g/kg body weight; Excel Foods Lab., Tokyo, Japan) was given to switch gastrointestinal motility from the interdigestive to the digestive state.

The duration of the migrating motor complex, comprising the contractile phase and quiescent phase (phase I), was visually determined in the antrum, duodenum and ileum. Although the contractile phase in the antrum seemed a single state, phase III of the migrating motor complex, that in the duodenum and ileum, could be further divided into phase II (a period of irregular contractions with relatively low amplitude) and phase III (a period of regular intense contractions). Therefore, the duration of phase II and phase III was determined separately in the duodenum and ileum. The average of three migrating motor complex cycles in each ferret was calculated. The duration of the digestive period was also visually determined, as was the time interval (min) between the meal and the first appearance of the activity front after the meal. The activity front in the antrum was identified as at least 5 consecutive intense antral contractions that migrated down to the duodenum and ileum and were followed by a period of quiescence, and that in the duodenum and ileum was identified as the occurrence of a group of regular high-amplitude duodenal (or ileal) contractions which were followed by a period of quiescence.

Colonic motility was compared between the interdigestive and digestive states. The motility indexes at the colon for the 2-h period before and after feeding were determined and compared.

The evaluation of cisapride was performed in the digestive state. Cisapride was extracted and purified from Acenalin Tab. (Janssen-Kyowa, Tokyo, Japan), dissolved in 1% lactic acid and subcutaneously administered 90–120 min after feeding in a volume of 1 ml/kg. The motility index for the 2-h period after cisapride or vehicle administration was determined at each recording site. Evaluation of the drug was conducted with paired control (vehicle treatment) and drug treatment observations for each ferret. Doses of cisapride are in terms of the free base. Each animal received vehicle or only one dose of cisapride per day. The order of doses in each ferret was randomized.

All results are presented as the means ± S.E.M. Statistical analysis of data was performed with the Wilcoxon signed rank test or Friedman test. Probability values of < 0.05 were considered significant.

3. Results

One week after surgery, a contractile wave with stable baseline could be observed at each recording site in each animal. This contractile wave was not affected by body movements of the animals, and thus substantially reflected gastrointestinal motor activity. Stable measurement was possible for at least 2 months after surgery in each animal.

The activity front, phase III contractions of the migrating motor complex, occurred cyclically in the antrum, and migrated distally to the duodenum and ileum but not to the colon. The contractile phase in the antrum seemed a single state, phase III. The mean duration of the entire cycle, contractile phase and quiescent phase (phase I) of the

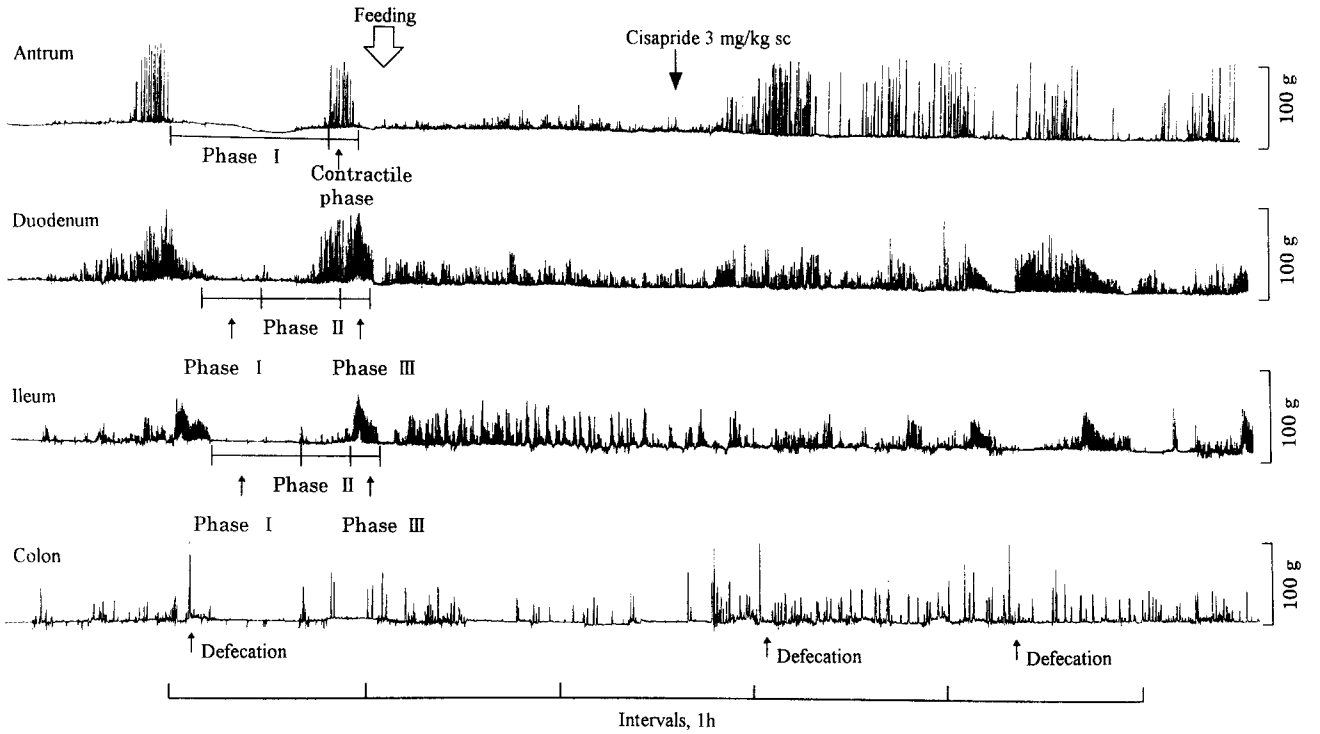

Fig. 1. A typical chart showing the spontaneous gastrointestinal (gastric antral, duodenal, ileal and colonic) motility in the interdigestive and digestive states in a conscious ferret, and the effect of cisapride on gastrointestinal motility in the digestive state. The periods of contractile and quiescent phase (phase I) of the antral, duodenal and ileal migrating motor complex were visually determined and indicated below each contractile wave. Carnivore food (20 g/kg body weight) was given at the point indicated by an open arrow to switch gastrointestinal motility from the interdigestive to the digestive state. A single colonic high-amplitude contraction preceded defecation which is indicated by arrows. Cisapride (3 mg/kg s.c.) was administered at the point indicated by an arrow.

migrating motor complex in the antrum was 56 ± 5, 14 ± 2 and 41 ± 4 min, respectively ($n = 4$). The contractile phase in the duodenum and ileum could be further divided into phase II (a period of irregular contractions with relatively low amplitude) and phase III (a period of regular intense contractions). The mean duration of the entire cycle, phase II, phase III and quiescent phase (phase I) in the duodenum was 57 ± 6, 14 ± 2, 11 ± 2 and 30 ± 2 min, respectively ($n = 4$), and in the ileum it was 54 ± 4, 14 ± 1, 9 ± 1 and 33 ± 4 min, respectively ($n = 4$).

The migrating motor complex pattern was disrupted by feeding, and irregular contractions with relatively low amplitude were sustained in the antrum, duodenum and ileum for at least 3.5 h after feeding. The mean duration of the digestive period in the antrum, duodenum and ileum was 340 ± 43, 296 ± 66 and 291 ± 60 min, respectively ($n = 4$).

The contractile activity of the colon was independent of that at other recording sites, with relatively low-amplitude contractions occurring sporadically and irregularly in the colon in both the interdigestive and digestive states. Defecation was always preceded by a single colonic high-amplitude contraction. The motility index for the 2-h period before feeding was 161.7 ± 29.6 g × min and that after

Table 1
Effect of cisapride on gastric antral, duodenal, ileal and colonic motility in the digestive state in conscious ferrets

Dose of cisapride	Motility index for 2-h period after cisapride administration (g × min)			
(mg/kg s.c.)	Gastric antrum	Duodenum	Ileum	Colon
1% lactic acid	210.1 ± 42.9	210.4 ± 49.6	289.6 ± 41.1	155.8 ± 28.4
0.3	243.4 ± 15.4	158.9 ± 39.9	343.5 ± 27.8	281.4 ± 77.3
1	503.1 ± 95.8	186.5 ± 50.5	288.3 ± 71.7	441.9 ± 49.0
3	506.0 ± 59.1 [a]	213.2 ± 58.2	291.4 ± 82.0	579.2 ± 31.6 [b]

Cisapride was administrated 90–120 min after feeding. The motility index for the 2-h period after cisapride administration was determined. The motility index is equivalent to the integrated area between the contractile wave and baseline. Each value represents the mean ± S.E.M. for four ferrets. Statistical analysis was performed with the Friedman test. [a] Significant dose effect, $P < 0.05$ for antrum column, [b] $P < 0.01$ for colon column.

feeding was 132.8 ± 15.5 g × min ($n = 4$). There was no significant difference between the two motility indexes (Wilcoxon signed rank test).

Cisapride given in the digestive state at 0.3–3 mg/kg s.c. stimulated antral and colonic motility in a dose-dependent manner, but the stimulatory effect on duodenal and ileal motility was weak, even at 3 mg/kg s.c. (Fig. 1 and Table 1). The Friedman test indicated a significant increase of antral motility ($Q = 9.6$, $P < 0.05$) and colonic motility ($Q = 12$, $P < 0.01$). No significant difference was found among four groups of data for duodenal motility ($Q = 3.9$) and ileal motility ($Q = 0.9$).

4. Discussion

We measured gastrointestinal motility from the gastric antrum to the colon in conscious ferrets during both the interdigestive and digestive states. The pattern of interdigestive upper gastrointestinal motility observed in the present study was consistent with the migrating motor complex reported for humans (Kerlin and Phillips, 1982) and dogs (Sarna, 1985). The duration of the entire migrating motor complex cycle in the stomach was reported to be about 120 min in humans and 105 min in dogs (Itoh and Sekiguchi, 1984), whereas that in ferrets was somewhat shorter, being about 56 min. This short duration was also seen by Grundy (1990), who investigated the motility of the gastric antrum in conscious ferrets and reported that the interval of the migrating motor complex was about 44 min. The contractile phase in the stomach in humans and dogs has been further divided into sub-states, phases II–IV (Itoh and Sekiguchi, 1984). However, these sub-states could not clearly be identified in the ferret stomach. Although this difference may be due to species differences between ferrets and humans, it remains possible that the short duration of the contractile phase in the ferret stomach made the visual discrimination of these sub-states difficult. Further precise study, especially the recording of myoelectrical activity in the ferret stomach, may elucidate whether or not the ferret stomach has sub-states (phases II–IV). On the other hand, the contractile phase in the duodenum and ileum could further be divided into phase II and phase III, as with humans and dogs (Itoh and Sekiguchi, 1984; Kerlin and Phillips, 1982). The pattern of digestive upper gastrointestinal motility observed in the present study was consistent with those reported for humans and dogs (Itoh and Sekiguchi, 1984; Kerlin and Phillips, 1982; Sarna et al., 1991). The duration of the digestive period in ferrets (about 340 min) was similar to those in humans (Kerlin and Phillips, 1982; Thompson et al., 1980) and dogs (Itoh and Sekiguchi, 1984). The duration of the digestive period in the duodenum and ileum was shorter than that in the antrum in the present study, in accord with the result of Itoh and Sekiguchi (1984) who reported that the duration of the digestive period was 278 min in the stomach and 203 min in the duodenum in humans. Furthermore, the colonic motility pattern observed in the present study was also very similar to those reported for humans (Narducci et al., 1987) and dogs (Karaus and Sarna, 1987). In view of these observations, spontaneous gastrointestinal motility from the antrum to the colon in conscious ferrets is, in spite of a few differences, similar to those in humans and dogs.

Cisapride is currently widely used in the treatment of gastrointestinal motility disturbances. This agent has been reported to stimulate motor activity throughout the gut in healthy humans and dogs (Wiseman and Faulds, 1994; Yoshida et al., 1991). In the present study, cisapride clearly and dose dependently stimulated antral and colonic motility in accord with the results in humans and dogs. In contrast, the stimulatory effect of this compound on duodenal and ileal motility was weak. Stacher et al. (1989) reported that cisapride stimulated jejunal motility after a 1000-kJ but not a 4200-kJ meal in healthy humans, suggesting that this agent produces no further stimulation when small intestine motility is already near-maximally enhanced by a high-energy meal. Such a meal energy-dependent effect of cisapride may explain the weak stimulatory effect on small intestinal motility in the present study. Although the cause of the weak effect on ferret small intestinal motility remains to be elucidated, the response of gastrointestinal motility to cisapride in ferrets is roughly similar to that reported for humans and dogs.

The gut of the ferret has been shown to have anatomical and physiological similarities to that of humans. For example, the distribution of the vagus nerves to the stomach is closely similar in ferrets and in humans. The ferret is a basal secretor of acid and proteolytic enzymes in the interdigestive state as in humans, and the distribution of food in the ferret stomach after a meal is similar to that in humans (Mackay and Andrews, 1983). Garrick et al. (1986) reported that the cyclical motility pattern could not be observed in the rat stomach despite cyclical occurrences of the migrating motor complex in the small intestine. In contrast, phase III contractions occurred cyclically in the ferret stomach as shown in the previous (Grundy, 1990) and present study. The results of the present study additionally show that the spontaneous motility throughout the gut and its response to cisapride in ferrets are similar to those in humans. Ferrets do not move so violently as to disturb the connecting cable suspended from the ceiling during observation, and therefore no restriction of movement is needed. In addition, ferrets are smaller than dogs, which have most commonly been used in studies on gastrointestinal motility, so that experiments with ferrets can be performed in a smaller space and with smaller quantities of compounds than with dogs. The ferret model is therefore a useful alternative to the dog model, and will help in the investigation and evaluation of drug effects on gastrointestinal motility in humans.

In conclusion, we measured gastrointestinal motility

from the gastric antrum to the colon in conscious ferrets. This ferret model is suitable for studies of gastrointestinal motility in humans.

Acknowledgements

The authors wish to thank Drs. Toshiyasu Mase and Shinji Usuda for their critical review of the manuscript and helpful discussions.

References

An, N.Q. and H.E. Evans, 1988, Anatomy of the ferret, in: Biology and diseases of the ferret, eds. G. Games and D.V.M. Fox (Lea & Febiger, Philadelphia, PA) p. 14.

Briejer, M.R., L.M.A. Akkermans and J.A.J. Schuurkes, 1995, Gastrointestinal prokinetic benzamides: the pharmacology underlying stimulation of motility, Pharmacol. Rev. 47, 631.

Garrick, T., S. Buack and P. Bass, 1986, Gastric motility is a major factor in cold restraint-induced lesion formation in rats, Am. J. Physiol. 250, G191.

Grundy, D., 1990, The effect of surgical anaesthesia on antral motility in the ferret, Exp. Physiol. 75, 701.

Itoh, Z. and T. Sekiguchi, 1984, Interdigestive motor activity in health and disease, in: Basic Science in Gastroenterology, Physiology of the Gut, eds. J.M. Polak, S.R. Bloom, N.A. Wright and A.G. Butler (Page Bros, London) p. 121.

Karaus, M. and S.K. Sarna, 1987, Giant migrating contractions during defecation in the dog colon, Gastroenterology 92, 925.

Kerlin, P. and S. Phillips, 1982, Variability of motility of the ileum and jejunum in healthy humans, Gastroenterology 82, 694.

Mackay, T.W. and P.L.R. Andrews, 1983, A comparative study of the vagal innervation of the stomach in man and the ferret, J. Anat. 136, 449.

Narducci, F., G. Bassotti, M. Gaburri and A. Morelli, 1987, Twenty four hour manometric recording of colonic motor activity in healthy man, Gut 28, 17.

Sarna, S.K., 1985, Cyclic motor activity; migrating motor complex, Gastroenterology 89, 894.

Sarna, S.K., K.H. Soergel, T.R. Koch, J.E. Stone, C.M. Wood, R.P. Pyan, R.C. Arndorfer, J.H. Cavanaugh, H.N. Nellans and M.B. Lee, 1991, Gastrointestinal motor effects of erythromycin in humans, Gastroenterology 101, 1488.

Stacher, G., G. Gaupmann, H. Steinringer, J.G. Stacher, M.G. Steiner and T.A. Abatzi, 1989, Effects of cisapride on postcibal jejunal motor activity, Dig. Dis. Sci. 34, 1405.

Thompson, D.G., D.L. Wingate, L. Archer, M.J. Benson, W.J. Green and R.J. Hardy, 1980, Normal patterns of human upper small bowel motor activity recorded by prolonged radiotelemetry, Gut 21, 500.

Wiseman, L.R. and D. Faulds, 1994, Cisapride; an updated review of its pharmacology and therapeutic efficacy as a prokinetic agent in gastrointestinal motility disorders, Drugs 47, 116.

Yoshida, N., T. Ito, T. Karasawa and Z. Itoh, 1991, AS-4370, a new gastrokinetic agent, enhances upper gastrointestinal motor activity in conscious dogs, J. Pharmacol. Exp. Ther. 257, 781.