

Effects of motilin and ursodeoxycholic acid on gastrointestinal myoelectric activity of different origins in fasted rats

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Abstract

AIM: To investigate gastrointestinal migrating myoelectric complex (MMC) and the effects of porcine motilin and ursodeoxycholic acid (UDCA) on MMC of gastrointestinal tract of different origins in fasted rats.

METHODS: Three bipolar silver electrodes were chronically implanted on the antrum, duodenum and jejunum. Seven days later 24 experimental rats were divided into 2 groups. One group was injected with porcine motilin *via* sublingual vein at a dose of 20 µg/kg, the other group was perfused into stomach with UDCA. The gastrointestinal myoelectric activity was recorded 1 h before and 2 h after the test substance infusions into the rats.

RESULTS: In all fasted rats a typical pattern of MMC was observed. Among the totally 68 activity fronts recorded in fasted rats under control, 67% started in duodenum, and 33% in antrum. MMC cycle duration and duration of phase III of antral origin were longer than those of duodenal origin. Administration of 20 µg/kg porcine motilin induced a premature antral phase III of antral origin. But perfusion into stomach with UDCA resulted in shorter MMC cycle duration, longer duration of phase III of duodenal origin, which were followed with shorter cycle duration and duration of antral phase III.

CONCLUSION: In fasted rats, MMC could originate from antrum and duodenum respectively. The characteristics of MMC of different origins may contribute to the large variations within subjects. The mechanisms of different origins of phase III may be different. Porcine motilin and UDCA could affect MMC of different origins of the gastrointestinal tract in fasted state, respectively.

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INTRODUCTION

The migrating myoelectric complex (MMC) is a distinct pattern

of electromechanical activity observed in gastrointestinal tract during fasting. It is thought to serve a housekeeping role and sweep undigested residual through the digestive tract. Phase III of MMC originates at variable sites in the gut from the esophagus (especially from antrum and duodenum) to proximal ileum. Large variations in MMC characteristics were described both within subjects and between subjects. The reason for the large variation in MMC characteristics is unknown. However, regarding the supposed differences in mechanisms that regulate the phase III of MMC of antral or duodenal origins, different origin of phase III within subject could be a basis for the differences in MMC characteristics^[1,2].

Motilin, a 22 amino acid peptide secreted by endocrinocytes in the mucosa of the proximal small intestine, participates in controlling the pattern of smooth muscle contractions in the upper gastrointestinal tract. These bursts of motilin secretion are temporarily related to the onset of housekeeping contractions, which sweep the undigested material of stomach and small intestine^[3]. Previous studies showed that the enterohepatic circulation of bile acids and interdigestive motility must somehow be associated with each other. Phase III of MMC played an important role in the transport of bile acids from the proximal duodenum to the distal small intestine, where bile acids were absorbed for transport back to the liver.

The purpose of the present study was to investigate the gastrointestinal MMC characteristics with respect to the different origin of phase III in fasted rats. Furthermore, the effects of exogenous porcine motilin and UDCA on the interdigestive myoelectric activity were investigated and the relationship between the above two drugs and the MMCs of different origin in conscious rats were studied.

MATERIALS AND METHODS

Animal preparation

Twenty-four healthy Sprague-Dawley rats (15 male and 9 female) weighing 200-250 g were fed with a dry rat food, and tap water for drinking *ad libitum*. After fasted for one night, the rats were intraperitoneally anesthetized with sodium pentobarbital 30 mg/kg. The hair on the skull and abdomen was shaved. The surgery was done with sterile instruments, and under strict aseptic conditions. The abdominal musculature and peritoneum were opened through the linea alba. Three bipolar insulated silver electrodes made by Teflon-coated wire (0.5 mm in outer diameter, 20 cm in length) were implanted into the muscular layer of the bowel with a needle as a trocar. One millimeter of the wire was exposed near the implanted end, and the interval between pairs of electrodes should be 2.0-3.0 mm. The electrodes were placed on the gastric antrum at 5 mm proximal to the pylorus, on the duodenum and jejunum respectively at 1 cm and 15 cm distal to the pylorus. The bundled electrode wires were grasped by the clamp through a silastic tube (2.4 mm in diameter), which then passed through the subcutaneous tunnel from the abdominal incision to the back of the shoulder exit. During operation the intestine was kept moist with sterile 9 g/L NaCl solution, and 4 mL of this solution was applied intraperitoneally before closure of the abdomen to compensate for intraoperative fluid loss. The abdominal wall was closed in three layers with

running Vicryl 4-0 sutures. The rats were kept in a humidified incubator at 37 °C for 2 to 4 h after operation. Following this, they were individually housed with free access to water and food. Housing conditions were kept constant with temperature at 22 °C, humidity of 60% and a 12-h light/dark cycle. The rats were allowed to adjust to these conditions for 1 wk before experiment.

Motility recordings

Rats were fasted for 16 h with free access to water. The experiments were performed in conscious rats. The gastrointestinal myoelectric activity recordings were monitored by using an electrical swivel mechanism to a computerized, multichannel recorder (RM-6280C, Chengdu, China). Myoelectric activity was sampled at a rate of 1 kHz. The signals were amplified and bandpass filtered (frequencies above 0.3 Hz and below 100 Hz were cut off). The amplitudes of contractions were recorded in μV .

Experimental procedures

A randomized, placebo-controlled experiment was performed. The rats were coded and divided into 2 groups, 12 in each group. On each experimental day, at the beginning of the experiments, the gastrointestinal myoelectric activity was recorded for 1 h for each rat, and during this period at least 2 or 3 MMCs appeared. The substances were dissolved immediately before use in normal saline. In each group, 4 rats were placed as control that received placebo (vehicle), 0.2 mL saline containing 250 μg bovine serum albumin (BSA, Sigma). One group was injected with porcine motilin (Sigma) *via* sublingual vein at a dose of 20 $\mu\text{g}/\text{kg}$, and the other group was perfused into stomach with UDCA (Pharmaceutical Factory of Changzhou City) respectively. After the substances were used, the gastrointestinal myoelectric activity of the rats was continuously recorded at least for 2 h. After the conversion from analog to digital, the signals were stored on optical disk for later analysis.

Statistical analysis

All variables followed a normal distribution and are expressed as mean \pm SD unless otherwise stated. The presented means are unweighted means, *i.e.*, means of all subjects after first calculating the mean within each subject separately. The MMC characteristics such as MMC cycle duration, duration of phase III, mean amplitude and frequency of phase III were examined by using the ANOVA model, both before and after discrimination for antral or duodenal phase III origin effects. The homogeneity of variance for each variable, after being divided into antral and duodenal phase III origin effects, was tested and appeared equal. Within-subject and between-subject effects were analyzed by the ANOVA model. For the MMC cycle duration, the corresponding variance components between and within individuals were used to calculate the variance between individuals as a percentage of the total variance. To explain the importance of the factor preceding phase III origin in the total variance, the sum of squares of the factor preceding phase III origin was calculated as a percentage of the total sum of squares in the ANOVA model. The effects of unfamiliarity with gastrointestinal catheter studies on MMC cycle duration was examined using the ANOVA model. Student's *t* test was used to compare the different paired values before and after the test substances administration in the above 2 groups. Statistical significance was defined as two-tailed $P < 0.05$.

RESULTS

MMC characteristics of different origin

In all fasted rats typical pattern of MMCs were observed. The total number of MMC cycles recorded was 68. The mean MMC cycle duration was 746 \pm 140 s. In total, phase III cycles were

observed with 23 (33%) of antral origin and 45 (67%) of duodenal origin. Fifty-nine percent of the total variance in MMC cycle duration was explained by the within-subject variance. The duration and the amplitude of phase III were significantly different between subjects ($P < 0.05$; Table 1). The large variation in MMC cycle duration is visible in Figure 1. The MMC cycle duration following a phase III of antral origin was significantly longer than those of duodenal origin ($P < 0.05$; Table 2). When the factor preceding phase III origin was included in our model, this factor contributed significantly to the total variation in MMC cycle duration; 31% of the total sum of squares was explained by the factor preceding phase III in comparison to 36% explained by the between-subject variance. The duration of phase III for duodenum was significantly longer when it started in the antrum than in the duodenum ($P < 0.05$). The other characteristics of MMC for duodenum were not significantly different between the phase III of the above two origins.

Table 1 MMC characteristics in 24 normal rats

MMC characteristics	mean \pm SD
MMC cycle duration/s	746 \pm 140 ^a
Duration of phase III/s	214 \pm 53 ^a
Amplitude of phase III/ μV	287 \pm 23 ^a
Frequency of phase III/(bursts/min)	11.4 \pm 0.3

Values are shown for duodenum. ^a $P < 0.05$ vs between subjects.

Table 2 MMC characteristics of different origin of ongoing phase III ($n = 24$, mean \pm SD)

MMC characteristics	After phase III of antral origin	After phase III of duodenal origin
MMC cycle duration/s	901 \pm 74	667 \pm 91 ^a
Duration of phase III/s	271 \pm 30	186 \pm 35 ^a
Amplitude of phase III/ μV	292 \pm 17	284 \pm 25
Frequency of phase III/(bursts/min)	11.2 \pm 0.5	11.6 \pm 0.2

Values are shown for duodenum. ^a $P < 0.05$ vs antral.

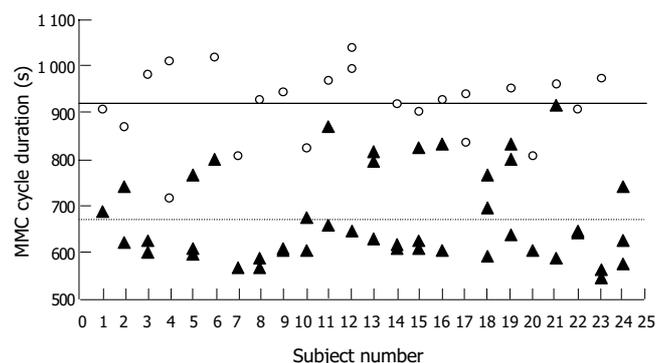


Figure 1 MMC cycle duration of all subjects following phase III. \circ , antral origin; \blacktriangle , duodenal origin; Solid line: antral mean MMC cycle duration (746.3); Dotted line: duodenal mean MMC cycle duration (667.0).

Effects of porcine motilin and UDCA

The effects of porcine motilin on the interdigestive gastrointestinal myoelectric activity were established within 1 to 2 min after the injection *via* sublingual vein at a dose of 20 $\mu\text{g}/\text{kg}$. A premature antral phase III which did not migrate caudad to the duodenum and jejunum was observed. And one injection only induced

one premature antral phase III. The characteristics of premature antral phase III were different significantly from those of normal antral phase III. The shorter duration and higher amplitude of premature antral phase III appeared (Figure 2). The effects of UDCA on the interdigestive gastrointestinal myoelectric activity were established within 3 to 4 min after the stomach was perfused of UDCA. The shorter MMC cycle duration, and the longer duration of phase III of duodenal origin, followed by the shorter cycle duration and duration of antral phase III were observed. There was no significant difference in the other parameters of MMC of antrum and duodenum before and after the treatment (Figure 3, Table 3). Furthermore, there was no significant difference in the MMC characteristics before and after placebo treatment in the above 2 experiments.

Table 3 Effects of UDCA on the interdigestive gastrointestinal myoelectric activity ($n = 8$, mean \pm SD)

MMC characteristics	Antrum		Duodenum	
	Before	After	Before	After
The number of MMC	7	11	11	21
MMC cycle duration/s	885 \pm 106	800 \pm 48 ^a	780 \pm 45	602 \pm 78 ^a
Duration of phase III/s	161 \pm 13	113 \pm 19 ^a	156 \pm 9	241 \pm 20 ^a
Amplitude of phase III/ μ V	297 \pm 11	284 \pm 20	288 \pm 22	285 \pm 19
Frequency of phase III/(bursts/min)	3.1 \pm 0.5	3.2 \pm 0.6	11.2 \pm 1.6	11.5 \pm 1.8

^a $P < 0.05$ vs before treatment.

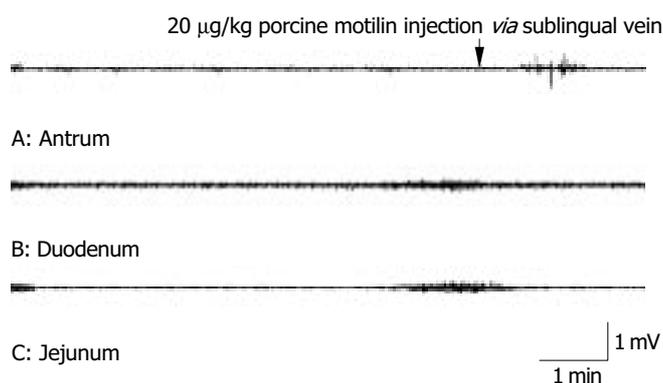


Figure 2 Effects of porcine motilin on the interdigestive gastrointestinal myoelectric activity in one case.

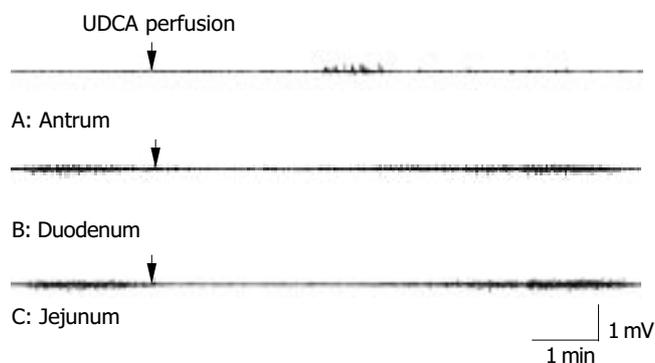


Figure 3 Effects of UDCA on the interdigestive gastrointestinal myoelectric activity in one case.

DISCUSSION

Gastrointestinal motility pattern could mainly be divided into the interdigestive and digestive states. The interdigestive state

is characterized by the cyclical occurrence of activity front, phase III contractions, which could occur in the antrum, duodenum and migrate to the small intestine. The digestive state is characterized by sustained contractions with different amplitude in the gastric antrum and small intestine. In our experiments, a typical pattern of MMC in interdigestive state was observed in all rats. The phases of the MMC can be distinguished: phase III, motor quiescence, phase III, a period of irregular contractile activity and phase III, a period of rhythmic contractions. The MMC pattern was disrupted by feeding, and irregular contractions with different amplitude were sustained in the antrum, duodenum and jejunum for at least 30 min after feeding. MMC was firstly described in the small intestine of fasting dogs and observed in the overall gastrointestinal tract of several species, including rats^[4-6]. In our study they have also been found in gastric antrum and small intestine. A method that could record the gastrointestinal myoelectrical activities in physiological conditions was established in our experiment. The model we have developed seemed to be suitable for studying the gastrointestinal myoelectric activities. The effects we obtained could be attributed to neither sedatives nor operative stress because of the method unable to record the gastrointestinal motility without the use of anesthesia. Furthermore, the surgical operations were well tolerated by the animals, especially by small animals. At present the method of stationary manometry was used in most of the experiments of this field^[7,8]. But it is not suitable for small animal experiments. Our method was simple, easy and successful. Few tissue was injured. Several pairs of electrodes could be implanted and work stably and repeatedly. The experimental techniques would be helpful for further studying the mechanisms of gastrointestinal motility.

A typical pattern of MMC was observed in all fasted rats. Among the totally 68 activity fronts recorded in them under control, 67% started in the duodenum, and 33% in the antrum. The MMC cycle duration and duration of phase III of antral origin were longer than those of duodenal origin. The MMCs were subject to large variations in its characteristics, both between subjects and within subjects. The reason for this wide variation is unknown. Our results contributed to a better understanding of this variation. Our study showed that MMC characteristics had close relationship with the origin of phase III. But Gregersen *et al.* described a positive correlation between the duration of phase III in the duodenum and the duration of the next MMC cycle^[9]. They could not attribute this to a difference in origin of phase III, most likely due to the limited number of observations within each subject. The percentages of antral and duodenal originated phase III observed within a subject would strongly affect the mean MMC cycle duration of this subject as well as the overall mean of a group of subjects^[10,11]. An explanation for the differences in MMC cycle duration and duration of phase III was that it might imply differences in the mechanism controlling interdigestive motility in antrum and small intestine. This may reflect functional differences existing in the hormonal mechanisms involved in the regulation of antral and duodenal phase III. It was thought that a difference might exist in the refractory period between the gastric antrum and small intestine, with a shorter refractory period in the duodenum compared with the antrum. Another possible reason may be the anatomic structure of rats. Because there is no gallbladder in rats, bile acids secreted to duodenum directly. In addition, our study could not explain why the density and the sensitivity of receptor in gastrointestinal tract changed^[12,13].

The mechanisms regulating MMC is not understood completely. Previous study showed that the area postrema of medulla oblongata, vagal innervation, enteric nervous system and gastrointestinal hormone could regulate the MMC. Among them motilin in plasma plays a very critical role in the initiation of MMC. Motilin is one of the gastrointestinal hormones. It

belongs to gut-brain peptide and distributes in the brain and gastrointestinal tract^[14-22]. Plasma levels of the motilin fluctuate in synchrony with the different phase of MMC. Motilin could stimulate the gastrointestinal motility of many animals, and there were species differences in its effects^[23]. After duodenectomy, no obvious phase III contractions were seen in the gastric antrum, but the contractile response of the stomach to exogenous motilin was similar to that of intact dogs^[24]. This experiment showed that endogenous motilin was released from duodenum. One research showed that the motilin could activate calcium current in human and canine jejunal circular smooth muscle. Furthermore, the density and sensitivity of motilin receptor of different parts of gastrointestinal tract were different. But recently the close relationship between motilin and MMC of antral but not duodenal origin was found^[25]. Porcine motilin could influence the MMC of antral origin in our experiment. Administration of 20 µg/kg porcine motilin could induce a premature antral phase III in rats. The characteristics of it were different significantly from those of normal antral phase III. But the results of our experiments were coincident with previous studies. Maybe the density and sensitivity of motilin receptor of antrum were higher than those of other parts of gastrointestinal tract^[12,13]. Some studies showed that duodenal pH governed interdigestive motility in humans. But neither duodenal acidification nor increases in motilin concentration were necessary to initiate MMC in man^[26]. Administration of a low dose of erythromycin induced an MMC that started from the gastric antrum, unaccompanied by a motilin peak. These findings showed that the activation of motilin receptor triggered the MMC.

Another important factor influencing MMC is enterohepatic cycle of bile acids. The enterohepatic cycle of bile acids had close relationship with MMC. The possible explanation was that the development of MMC of duodenal origin was not autonomous but dependent on the stimulation of bile acids to the local mucous of duodenum. Furthermore, duodenum, possibly by releasing endogenous motilin, might recruit and further augment the gastric response to initiation of the MMC of antral origin^[27-29]. So there are maybe two mechanisms for initiation of MMC in the stomach and duodenum. In our experiment perfusion into stomach of rats with UDCA could shorten the MMC cycle duration and elongate the duration of phase III of duodenal origin, which was followed by the contractions of antrum within a short time. We suggest that UDCA may drain into the duodenum influencing the MMC of duodenal origin and stimulate the release of endogenous motilin from the mucous of duodenum, because crushing the gallbladder of patient during operation could eject the bile acids and induce a higher level of plasma motilin. On the contrary, some researchers thought that bile acids in duodenum could not induce the release of motilin and affect the MMC^[30]. In the study of patients with gallstone, the motilin in plasma did not decrease obviously vs control group. But according to the above supposition, we could infer that the motilin in plasma should decrease obviously compared with control group because the motility of gallbladder decreased in most of the patients. The results obtained from this experiment did not coincident with those of previous experiments. Another research showed that the kinetics of duodenum did not change significantly after cholecystectomy. So these studies did not support the local stimulatory theory^[31,32]. But one study showed that the occurrence of MMC had close relationship with the increase of the plasma concentration of motilin and bile acids. Maybe it could explain the contradiction in this respect to some extent^[33]. But our study could not draw this conclusion.

Gastrointestinal motility disorder is common in clinical practice, and studying the mechanisms of it is very important to its diagnosis and therapy. Our study showed that the

mechanisms of different origin of phase III may be different and porcine motilin and UDCA could affect the MMC of different origin of the gastrointestinal tract in fasting state respectively. This may provide novel treatments for patients with disturbed gut motility.

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