Effects of metoclopramide on gastrointestinal myoelectric activity in rats

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Ten healthy male Wistar rats, weighing 250-350 g, were anesthetized with ketamine hydrochloride (100 mg/kg, intramuscularly). Four pairs of bipolar stainless steel electrodes 3 mm apart were implanted on the serosal surface of the antrum at one, 10 and 20 cm distal to the pylorus. Five to ten days after operation, the gastrointestinal myoelectric activity of fasted rats after intramuscular injection of 2.5, six and 12 mg/kg MCP was recorded using an 8-channel EEG machine, and these values were quantitatively compared with the myoelectric activity after saline injection.

RESULTS: In fasted rats, 2.5 mg/kg MCP increased the amplitude of spike activity (407.0 ± 138.4 μV, vs 345 ± 163.4 μV, P < 0.05), while in small intestine (1 cm distal to the pylorus) only the amplitude of spike activity (407.0 ± 179.0 μV vs 345.0 ± 163.4 μV, P < 0.05) and the percentage of the slow wave-containing spike bursts was also quantified. The results were represented as mean ± SD and analyzed statistically by Student's t-test.

CONCLUSION: Different mechanisms may be involved in enhancing the myoelectric activity of the antrum and small intestine following MCP administration.

Key words: Metoclopramide; Stomach; Intestine; Myoelectric activity

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INTRODUCTION

Metoclopramide (MCP) improves gastroduodenal coordination[1], relieves postsurgical and diabetic gastroparesis[2,3], and increases the spike activity during migrating motor complexes (MMC) of small intestine without disrupting the fasting pattern in dogs[4]. While these studies suggest that MCP complicates pharmacological action, few have studied the effects of MCP on gastrointestinal myoelectric activity. It is important to compare how different doses impact MCP's effect on the myoelectric activity of the antrum and small intestine. Such studies might be useful both for investigating the side effects of MCP and for further understanding the mechanisms controlling gastrointestinal motility.

MATERIALS AND METHODS

Ten healthy male Wistar rats, weighing 250-350 g, were anesthetized with ketamine hydrochloride (100 mg/kg, intramuscularly). Four pairs of bipolar stainless steel electrodes (3 mm apart) were implanted onto the serosal surface of the gastrointestinal tract. The first pair was placed on the antrum 0.5 cm from the pylorus and the others on the small intestine at one, 10 and 20 cm distal to the pylorus. The free ends of the electrodes were moved subcutaneously to the back of the neck. Recordings began five to ten days after operation. Electric activity was registered with a 8-channel EEG machine (ND-82B, Shanghai) with a time constant of 0.1 s and a high cutoff frequency of 30 Hz.

In the first, second and third series of experiments, MCP (The Seventh Pharmaceutical Factory of Wuxi) doses were 2.5, six and 12 mg/kg. Each experiment lasted one week and the myoelectric activities were recorded every other day.

The frequency and amplitude of the slow wave and spike activity from the antrum and small intestine were recorded and analyzed 30min following MCP administration, and the number of slow wave-containing spike bursts was also quantified. The results were represented as mean ± SD and analyzed statistically by Student's t-test.
**Table 1** Effects of metoclopramide on myoelectric activity in the antrum of rats (x ± s)

| Groups    | Frequency (num/min) | Amplitude (V) | Spike activity |
|-----------|---------------------|---------------|----------------|
| Control   | 38.2 ± 1.4          | 172.0 ± 101.9 | 345.0 ± 163.4  |
| 2.5 mg/kg | 38.2 ± 1.6          | 173.0 ± 81.9  | 402.0 ± 138.4  |
| 6 mg/kg   | 38.0 ± 1.3          | 173.7 ± 110.1 | 407.3 ± 179.0  |
| 12 mg/kg  | 37.6 ± 1.1          | 179.0 ± 136.6 | 456.0 ± 145.4  |
| Control   | 37.3 ± 1.4          | 201.4 ± 100.1 | 335.8 ± 138.6  |
| 2.5 mg/kg | 36.9 ± 1.6          | 201.7 ± 113.3 | 383.6 ± 150.3  |
| 6 mg/kg   | 37.0 ± 1.2          | 210.7 ± 105.2 | 412.5 ± 158.6  |
| 12 mg/kg  | 37.2 ± 1.3          | 203.2 ± 103.8 | 452.6 ± 144.7  |
| Control   | 35.9 ± 1.1          | 152.3 ± 94.7  | 320.2 ± 93.1   |
| 2.5 mg/kg | 36.6 ± 1.2          | 149.1 ± 69.1  | 338.2 ± 162.7  |
| 6 mg/kg   | 36.2 ± 1.2          | 150.2 ± 50.2  | 356.4 ± 117.9  |
| 12 mg/kg  | 35.6 ± 1.4          | 152.9 ± 71.4  | 347.3 ± 159.6  |

Values represent mean ± SD (n = 8); *P < 0.05, **P < 0.01 vs control.

**Table 2** Effects of metoclopramide on myoelectric activity in the small intestine of rats (x ± s)

| Sit | Groups | Frequency (num/ min) | Amplitude (V) | Spike bursts (%) |
|-----|--------|----------------------|---------------|-----------------|
| 1 cm | Control | 38.2 ± 1.4          | 172.0 ± 101.9 | 345.0 ± 163.4  |
| 2.5 mg/kg | 38.2 ± 1.6          | 173.0 ± 81.9  | 402.0 ± 138.4  |
| 6 mg/kg   | 38.0 ± 1.3          | 173.7 ± 110.1 | 407.3 ± 179.0  |
| 12 mg/kg  | 37.6 ± 1.1          | 179.0 ± 136.6 | 456.0 ± 145.4  |
| Control   | 37.3 ± 1.4          | 201.4 ± 100.1 | 335.8 ± 138.6  |
| 2.5 mg/kg | 36.9 ± 1.6          | 201.7 ± 113.3 | 383.6 ± 150.3  |
| 6 mg/kg   | 37.0 ± 1.2          | 210.7 ± 105.2 | 412.5 ± 158.6  |
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| 12 mg/kg  | 35.6 ± 1.4          | 152.9 ± 71.4  | 347.3 ± 159.6  |

Values represent mean ± SD (n = 8); *P < 0.05, **P < 0.01, ***P < 0.001 vs control.

**DISCUSSION**

Gastrointestinal myoelectric activities are divided into slow wave and spike activity (fast wave). Slow wave pace and direct gastric contraction. Thus, the alteration of slow wave would influence the mechanical contraction[15]. The spike activity can improve gastrointestinal motility[16]. The gastrointestinal myoelectric activity is a sensitivity index of gastrointestinal motility.

In this study, we find that MCP enhances gastrointestinal myoelectric activity, which is consistent with results reported by previous investigations[16]. Our results, however, also show significant differences in drug responses between the antrum and small intestine. Firstly, the drug only increased the spike activity in the small intestine, while both the slow wave and the spike activity in the antrum increased. Secondly, MCP’s effect on the myoelectric activity of the small intestine was not dose-dependent, as reported by 6 Wingate, et al[15] and 7 Achem-Karam, et al[16] in dogs. Nevertheless, the minimal effective doses (or threshold dose) of this drug varied between the antrum and small intestine. For example, a dosage as small as 2.5 mg/kg increased myoelectric activity in only the small intestine, but did not have any effect on the antrum. Thirdly, the latency periods of this drug between the antrum and small intestine were remarkably different (i.e. 0.7 ± 0.18 min vs 2.50 ± 0.35 min, respectively). These results suggest that the biochemical control of motor activity is not consistent along the gastrointestinal tract. MCP, an analogue of procainamide[15,16], could directly act on the smooth muscle cholinergic M receptor, while also causing acetylcholine release from the postganglionic cholinergic nerve endings[17], as well as increased myoelectric activity in the antrum. However, this increased spiking activity in the small intestine may not be the result of direct action, as other mechanisms are also likely to be involved.

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