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Effects of Mosapride Citrate, a 5-HT_4–Receptor Agonist, on Gastric Distension–Induced Visceromotor Response in Conscious Rats

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Abstract. Mosapride citrate (mosapride), a prokinetic agent with 5-HT_4–receptor agonistic activity, is known to enhance gastric emptying and alleviate symptoms in patients with functional dyspepsia (FD). As hyperalgesia and delayed gastric emptying play an important role in the pathogenesis of FD, we used in this study balloon gastric distension to enable abdominal muscle contractions and characterized the visceromotor response (VMR) to such distension in conscious rats. We also investigated the effects of mosapride on gastric distension–induced VMR in the same model. Mosapride (3 – 10 mg/kg, p.o.) dose-dependently inhibited gastric distension–induced VMR in rats. However, itopride even at 100 mg/kg failed to inhibit gastric distension–induced VMR in rats. Additionally, a major metabolite M1 of mosapride, which possesses 5-HT_3–receptor antagonistic activity, inhibited gastric distension–induced VMR. The inhibitory effect of mosapride on gastric distension–induced visceral pain was partially, but significantly inhibited by SB-207266, a selective 5-HT_4–receptor antagonist. This study shows that mosapride inhibits gastric distension–induced VMR in conscious rats. The inhibitory effect of mosapride is mediated via activation of 5-HT_4 receptors and blockage of 5-HT_3 receptors by a mosapride metabolite. This finding indicates that mosapride may be useful in alleviating FD-associated gastrointestinal symptoms via increase in pain threshold.

Keywords: mosapride citrate, 5-HT_4–receptor agonist, gastric distension, visceral pain, functional dyspepsia

Introduction

Functional dyspepsia (FD) is a clinical syndrome defined by chronic or recurrent upper abdominal symptoms without identifiable cause by conventional diagnostic means. These symptoms are often related to feeding and include epigastric pain, bloating, fullness, epigastric burning, nausea, and vomiting (1). In general, delayed gastric emptying, visceral hypersensitivity to gastric distension and impaired accommodation of a meal, as well as various psychosocial factors are considered important pathophysiological events underlying the symptoms of FD (1, 2). Recently, the Rome III committee proposed the development of evidence-based nomenclature and classification for FD symptoms. According to Rome III criteria, patients with FD are now categorized as those having postprandial-distress syndrome (PDS or meal-related FD, characterized by unexplained postprandial fullness or early satiation) and those with epigastric pain syndrome (EPS or meal-unrelated FD, characterized by unexplained epigastric pain or epigastric burning) (1, 3).

Drug treatment for patients with FD includes acid suppression with either histamine H_2–blockers or proton-pump inhibitors, agents that eradicate *H. pylori*, antidepressants, and prokinetics (4 – 6).

Mosapride citrate (mosapride), a prokinetic agent with 5-HT_4–receptor agonistic activity, is commercially available in several Asian countries (7). Mosapride stimulates gastric motility and gastric emptying in animals and hu-

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man (7, 8) and has been shown to enhance colonic motility and rectorectal and rectoanal reflexes in guinea pigs (9, 11). In clinical trials, mosapride was effective and well tolerated in the treatment of gastrointestinal symptoms associated with chronic gastritis, gastro-esophageal reflux disease, or FD (7, 12). Recently, in an open label trial involving about 1000 patients with FD, treatment with mosapride for 2 weeks has proved to be more effective than teprenone, a standard gastroprotective agent available in Japan, in improving symptoms of gastric stasis (PDS) and gastric pain (EPS) (7, 13). Based on these findings, it is believed that mosapride not only enhances delayed gastric emptying, but also improves visceral pain. Actually, it has been reported that certain 5-HT_4 agonists reduce visceral pain induced by colorectal distension in experimental animals and humans (14, 15). However, it is not clear whether 5-HT_4 agonists can suppress visceral pain induced by gastric distension in experimental animals. Although visceromotor response (VMR) to colorectal distension has been studied by many investigators (14 – 16), there are limited animal models that allow objective measurement of gastric sensation. The aim of the present study was therefore to develop a visceral pain model to gastric distension that enables abdominal muscle contractions using force transducers and to characterize VMR to such gastric distension in conscious rats. In addition, the effects of mosapride on gastric distension–induced VMR were investigated in the same model.

Material and Methods

Animals

Male Wistar rats (Nihon SLC, Inc., Shizuoka) weighing between 280 and 350 g at the time of the experiments were used in this study. They were housed, with free access to food and water, in an animal room kept at 23 ± 2°C under a 12-h light-dark cycle. Food, but not water, was withheld for 16 h before surgery. All experiments in this study were approved by the Internal Committee for Use of Experimental Animals at Dainippon Sumitomo Pharmaceutical Co., Ltd.

Surgical procedure

Animals were randomly allocated to treatment groups and anesthetized with intraperitoneal sodium pentobarbital (50 mg/kg). A flexible latex balloon catheter was surgically placed into the stomach though a small incision at the forestomach. A force transducer (F-08IS; StarMedical, Tokyo) was then sutured to the abdominal external oblique muscle as previously reported (14, 16) to measure the number of abdominal contractions as an indicator of visceral pain sensation.

The balloon catheter is one-unit composed of a polyethylene tube (5 Fr; AtomMedical, Tokyo) with a flexible latex balloon (20-mm-long, 10-mm in diameter, MB-50; Star Medical). The tubing for air inflation of the gastric balloon and the lead wires of the force transducer were tunneled subcutaneously and externalized at the back of the head. After the operation, a jacket protector (PJ-R15, Star Medical) was placed on the rat to protect the tubing and lead wires. Measurement was performed at least 4 days after the surgical operation.

Measurement of abdominal muscle contractions

Visceral pain was assessed by measuring abdominal muscle contractions during gastric distension in conscious rats. The amplitude and duration of abdominal muscle contractions, which were detected by the force transducer, were recorded using a recording system (AP-630G; Nihon Kohden Kohgyo, Tokyo), and the area under the curve (AUC) of the recorded data was calculated using an in-house system controlled by a personal computer (PC-9821 Bp; NEC, Inc., Tokyo). Abdominal muscle contractions were expressed as a muscle contraction index (MCI) equivalent to the AUC (g × min).

Experimental protocol

Conscious rats were acclimated to a testing cage for 2 to 3 h after 16 h–long fasting. Gastric distension was first performed by slow air-infusion into the balloon (1 ml/min) to monitor inflation volume that produces gastric distension–induced abdominal muscle contractions. After examining VMR and pain behavior, the inflated balloon was immediately deflated. One hour after the first (1st) balloon distension, a second (2nd) balloon distension was performed. To confirm reproducibility of gastric distension–induced response in each rat, the 2nd balloon distension was performed with the same air volume as that which induced muscle contractions. At 15 min after the end the 2nd balloon distension, a test-drug or vehicle was administered orally or subcutaneously to each rat. Baseline MCI was determined at the 2nd balloon distension, and the effect of the test-drug on abdominal muscle contractions was evaluated 1 and 2 h later. The experimental procedure was repeated 4 times on average at an interval of 7 days.

Hot plate test (somatic pain)

This test was carried out to determine rats latency of response to hot plate stimulus (17). In each rat, reaction time, which corresponds to the time elapsed between contact with the hot plate (model 7280; Ugo Basile, Milan, Italy) at 50.0 ± 1.0°C and jumping or paw licking in response to pain, was measured in seconds. Measurements were taken at baseline and 60 and 120 min after

test-drug oral administration. Rats with baseline latencies of more than 20 s were excluded from the study.

Drugs

Mosapride; itopride hydrochloride (itopride); M1, a major metabolite of mosapride (*N*-des-4-fluorobenzyl mosapride); granisetron hydrochloride (granisetron); and SB-207266, a selective 5-HT_4–receptor antagonist, were synthesized at our laboratories. Mosapride, itopride, and morphine hydrochloride (morphine; Takeda Pharmaceutical Co., Ltd., Osaka) were suspended in 0.5% tragacanth solution (Wako Pure Chemical Industries, Ltd., Osaka) for oral administration, and SB-207266 and metabolite M1 were dissolved in saline for subcutaneous injection. The doses of the test-drugs used in the present study were based on the results of previous reports (18 – 20).

Statistical analyses

Statistical analyses were performed using the SAS System (Release 8.2; SAS Institute Inc., Canny, NC, USA). Results were analyzed using the paired or unpaired *t*-test. A value of $P < 0.05$ was considered statistically significant.

Results

Effects of intragastric balloon distension on VMR

For intragastric balloon distension, air was continuously infused into the balloon at a rate of 1 ml/min. When balloon volume reached 3 to 5 ml (pressure of approximately 20 – 50 mmHg), the rats began to exhibit abnormal behavior indicative of some sort of pain sensation, including constant movement, teeth grinding, and wood chips chewing. When the balloon volume reached 8 to 12 ml (approximately 60 – 100 mmHg), the rats stared to exhibit pain behaviour such as writhing.

MCI values, which represent abdominal muscle contractions, were measured while the balloon volume was increased from 1 ml up to 12 ml. Mean MCI values in the non-distension and distension groups were 4.46 ± 0.59 and 9.30 ± 0.99 ($P = 0.026$), respectively, indicating a positive correlation between the magnitude of gastric distention and the intensity of abdominal muscle contractions associated with pain sensation.

Effects of test-drugs on VMR to balloon gastric distention

In the vehicle group, mean MCI values at baseline, 1 h post-dose, and 2 h post-dose were 8.30 ± 0.68, 7.20 ± 0.91, and 8.05 ± 1.38, respectively, indicating that the vehicle had almost no effect on VMR at 1 or 2 h after administration (Fig. 1). On the other hand, mosapride (1 mg/kg, p.o.) tended to inhibit VMR induced by gastric distention (Fig. 1A). In the animals treated with mosapride at 3 mg/kg, p.o., MCI values at baseline, 1 h post-dose, and 2 h post-dose were 8.31 ± 0.81, 5.32 ± 1.18 ($P = 0.0069$), and 5.52 ± 1.00 ($P = 0.0244$), respectively, indicating that mosapride significantly inhibited VMR at 3 mg/kg (Fig. 1A). The corresponding MCI values in the mosapride (10 mg/kg) group were 8.77 ± 1.09, 3.36 ± 0.91 ($P = 0.0011$), and 4.45 ± 1.30 ($P = 0.0466$), indicating more potent inhibition of VMR at 10 mg/kg (Fig. 1A). The inhibitory effect of mosapride on VMR was not only dose-dependent but also sustained for up to 2 h after administration. Figure 2 shows a typical tracing of the inhibitory effect of mosapride at 10 mg/kg on VMR.

Oral administration of itopride (30 or 100 mg/kg) did not inhibit VMR induced by gastric distention (Fig. 1B). However, morphine at 10 mg/kg, p.o. decreased MCI by 66.5% ($P = 0.004$) and strongly inhibited VMR at 1 h after administration, although no inhibitory effect on VMR was observed at 2 h after administration (Fig. 1B).

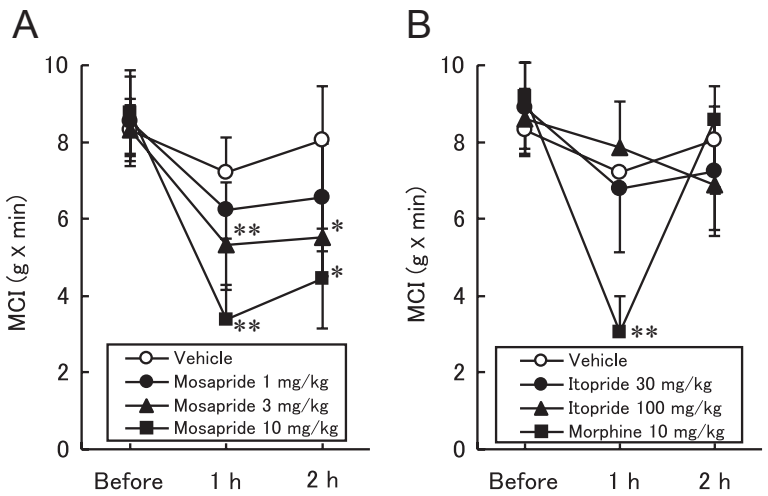

Fig. 1. Effects of mosapride (A), itopride, and morphine (B) on gastric distension–induced abdominal muscle contractions in conscious rats. A: Vehicle (opened circles); mosapride at 1 (closed circles), 3 (closed triangles), and 10 (closed squares) mg/kg, p.o. B: Vehicle (opened circles); itopride at 30 (closed circles) and 100 (closed triangles) mg/kg, p.o.; morphine at 10 mg/kg, p.o. (closed squares). At 15 min after the 2nd balloon distension, a test drug or vehicle was administered orally to each rat. Baseline MCI (muscle contraction index) was determined at the 2nd balloon distension, and the effect of each test drug on MCI was evaluated 1 and 2 h later. Each point represents the mean ± S.E.M. of 7 – 8 rats. *$P < 0.05$ and **$P < 0.01$, compared to the pre-value (paired *t*-test).

A major metabolite of M1 at 1 mg/kg, s.c. produced a significant inhibitory effect on VMR at 1 h post-dose (Fig. 3A). Granisetron at 1 mg/kg, p.o. also significantly inhibited VMR at 2 h post-dose (Fig. 3B).

Antagonistic effect of SB-207266, a 5-HT$_4$–receptor antagonist, on the inhibitory effect of mosapride on VMR

SB-207266, given alone at 0.3 mg/kg, s.c. exerted little effect on VMR induced by gastric distention. However, mosapride, given alone at 10 mg/kg, p.o. inhibited VMR by 61.3% at 1 h post-dose. When the rats were pretreated with SB-207266 (0.3 mg/kg, s.c.) before administration of mosapride, the inhibitory effect of mosapride on VMR was significantly inhibited. The antagonistic effect of SB-207266 did not completely eliminate the effect of mosapride (Fig. 4).

Effects of mosapride in a hot plate test

Rats were placed on a hot plate maintained at 50°C, and the latency to nociceptive response, identified as licking of the hind paw, was measured before and after oral administration of mosapride. As shown in Fig. 5, oral administration of mosapride at 10 mg/kg did not affect rats latency to the nociceptive response 1 or 2 h after dosing, indicating that mosapride has no inhibitory effect on somatic pain induced by thermal stimulation. In contrast, morphine administered orally to the rats at 10 mg/kg significantly prolonged rats latency to nociceptive response 1 and 2 h after dosing.

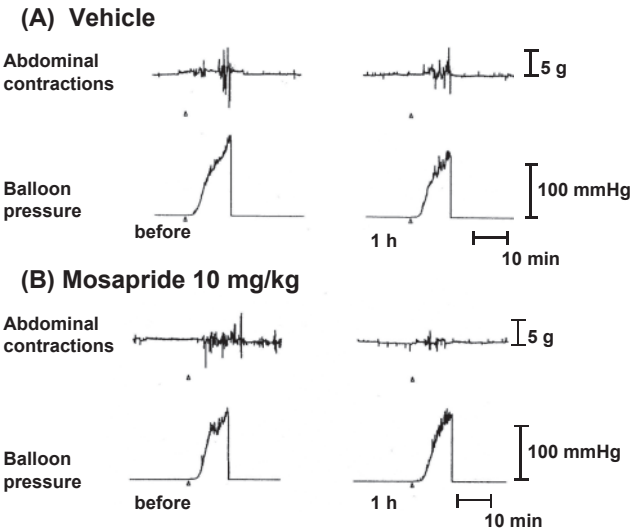

Fig. 2. Representative tracing of the effect of vehicle (A) or mosapride at 10 mg/kg, p.o. (B) on gastric distension (1 ml/min)-induced abdominal muscle contractions.

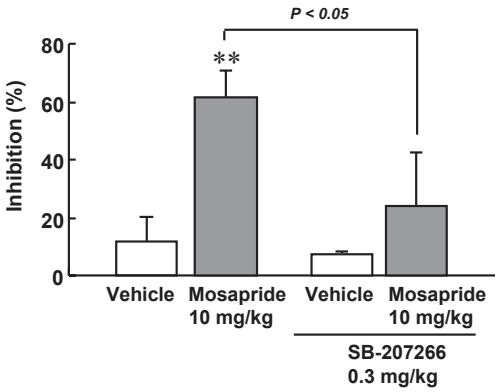

Fig. 4. Antagonistic effect of SB-207266 on mosapride-induced suppression of visceromotor response in conscious rats. Mosapride was administered orally to each rat 15 min after the 2nd balloon distension. SB-207266, a selective 5-HT$_4$–receptor antagonist was subcutaneously administered to each rat 1 min before administration of mosapride. Each bar represents the mean ± S.E.M. of 5 – 7 rats. $^{**}P < 0.01$, compared to the vehicle-treated group (unpaired *t*-test).

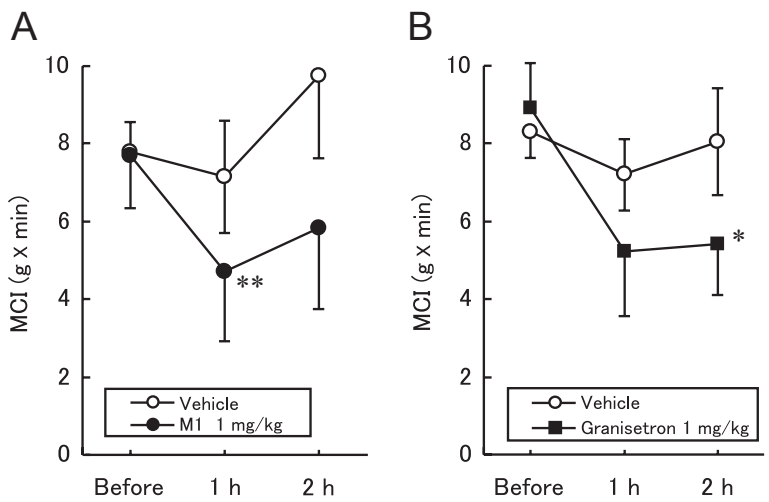

Fig. 3. Effects of mosapride metabolite M1 (A) and granisetron (B) on gastric distension–induced abdominal muscle contractions in conscious rats. A: Vehicle (opened circles) and metabolite M1 at 1 mg/kg, s.c. (closed circles). B: Vehicle (opened circles) and granisetron at 1 mg/kg, p.o. (closed squares). At 15 min after the 2nd balloon distension, a test drug or vehicle was administered to each rat. Baseline MCI (muscle contraction index) was determined at the 2nd balloon distension, and the effect of each test drug on MCI was evaluated 1 and 2 h later. Each point represents the mean ± S.E.M. of 7 – 8 rats. $^{*}P < 0.05$ and $^{**}P < 0.01$, compared to the pre-value (paired *t*-test).

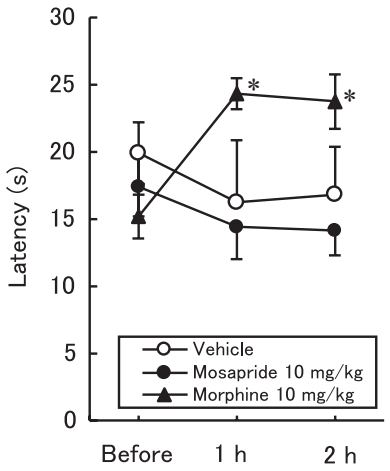

Fig. 5. Effects of mosapride and morphine on latency to nociceptive response in the hot plate test in conscious rats. Vehicle (opened circles), mosapride at 10 mg/kg, p.o. (closed circles), and morphine at 10 mg/kg, p.o. (closed triangles). In each rat, the reaction time, which corresponds to the time elapsed between contact with the hot plate and jumping or paw licking in response to pain, was measured in seconds. Measurements were taken at baseline and at 1 and 2 h after test-drug oral administration. Each point represents the mean ± S.E.M. of 5 rats. *$P < 0.05$, compared to the pre-value (paired *t*-test).

Discussion

Visceral pain is considered as one of the important pathophysiologic factors in FD and may partially result from sensitization of primary afferent fibers innervating the GI tract (21). In patients with FD, visceral pain to graded gastric distension appears to correlate with postprandial pain (2, 22). The present study demonstrates that VMR to gastric distension can be detected by monitoring abdominal muscle contractions using force transducers in free moving rats. To objectively quantify this sequence of pain-associated behavior, a force transducer was sutured to the abdominal external oblique muscle for continuous monitoring of abdominal muscle contractions. In a pilot study, the transducer could detect contractions of the abdominal external oblique muscle at an amplitude larger than that for detection of acromiotrapezius muscle contractions under similar intragastric balloon distension stimuli. In contrast, Ozaki et al. (23) have suggested that the acromiotrapezius muscle, unlike the abdominal external oblique muscle, produces vigorous electromyographic responses that increase with increasing intensity of gastric distension. The difference between the results of the present study and those of the study by Ozaki et al. (23) may be due to physiological and methodological differences (muscle contraction vs. electromyographic response), although the exact reason for this discrepancy is still not clear. In the present study, abdominal muscle contractions and pain-associated behavior intensified with increasing balloon volume, and MCI value peaked when writhing was noted. These findings indicate a positive correlation between the magnitude of gastric distention and the intensity of abdominal muscle contractions associated with pain behavior. Abdominal muscle contractions in response to balloon gastric distention were therefore regarded as an indicator of visceral pain.These results provide strong evidence that VMR to gastric distension can be used to study the sensation of visceral pain in the stomach. It is usual practice to use a barostat system to ensure constant gastric distension pressure (24). However, in the present study, slow air-infusion into an intragastric latex balloon was used to determine the volume and corresponding pressure that produce VMR. Due to the limitations of this conventional method, we examined the correlation between distension pressure and MCI, as recently reported (25).

The novel finding of the present study was that mosapride (3 – 10 mg/kg, p.o.) dose-dependently inhibited visceral pain induced by balloon gastric distension in rats. This result is in accordance with clinical findings showing that mosapride improves symptom of gastric pain in patients with FD, although the properties of pain between the two species might be different (7, 13). Further studies using rats with hyperalgesia are necessary to confirm the significance of our finding. Morphine at 10 mg/kg, p.o. also exhibited a strong inhibitory effect on visceral pain induced by balloon gastric distension in rats. However, unlike morphine, mosapride at 10 mg/kg failed to inhibit somatic pain induced by thermal stimulation in the hot plate test. These results suggest that mosapride selectively inhibits visceral pain induced by balloon gastric distension, whereas morphine inhibits both visceral and somatic pain as previously reported (17, 26).

Itopride, the other prokinetic agent used in this study, is reported to exert its prokinetic effect by way of antidopaminerigic and antiacetylcholinestarse actions and is often prescribed for patients with FD in Japan (5). In this study, itopride at 30 – 100 mg/kg (effective dose to enhance gastric emptying) did not inhibit visceral pain induced by balloon gastric distension in rats. Based on these findings, it is believed that mosapride would improve the symptom of gastric pain in patients with FD with an efficacy superior to that of itopride.

To elucidate the mechanism of action of mosapride, we investigated the effect of pretreatment with SB-207266, a selective 5-HT_4–receptor antagonist, on mosapride-induced analgesic action. We found that the inhibitory effect of mosapride on gastric distension–induced visceral pain was significantly, but not completely, reversed by pretreatment with SB-207266 at the dose of

0.3 mg/kg, s.c., which is potent enough to antagonize 5-HT_4 receptors (20). These findings suggest that another mechanism, different from that involving the 5-HT_4–receptor subtype, may be, at least in part, responsible for mosapride inhibition of visceral pain in rats.

In both animals and human, mosapride is well absorbed through the intestinal tract wall and is biotransformed in the body into several metabolites (27, 28). Among these metabolites, M1, identified as *N*-des-4-fluorobenzyl mosapride, is a major one. An interesting finding from a previous study is that metabolite M1 possesses potent 5-HT_3–receptor antagonistic activity. Namely, metabolite M1 dose-relatedly inhibited cisplatin-induced emesis in ferrets, which has been reported to be mediated though activation of 5-HT_3 receptors (29). Moreover, it has been reported that M1 metabolite of mosapride inhibits 5-HT_3–receptor binding in rat brain synaptic membrane with a potency 5 times less than that of ondansetron, a selective 5-HT_3–receptor antagonist (29). Furthermore, it is known that alosetron, a selective 5-HT_3–receptor antagonist, is effective in diarrhea-predominant irritable bowel syndrome patients with abdominal pain and bowel discomfort. Finally, a number of 5-HT_3–receptor antagonists have been reported to inhibit VMR to noxious intestinal distension in animals (15, 26). Thus, it is believed that 5-HT_3 receptors are involved in nociceptive visceral pain. To confirm this hypothesis, we examined in the present study whether metabolite M1 contributes to the inhibitory effect of mosapride on abdominal muscle contractions induced by balloon gastric distention. In our model, metabolite M1 at 1 mg/kg, s.c. inhibited visceral pain induced by balloon gastric distension in rats. It is reported that the maximal plasma concentration of metabolite M1 following oral administration of mosapride is 2 – 3 times higher than that of mosapride in rats, indicating that the dose of M1 used in this study is potent enough to block 5-HT_3 receptors (27). Granisetron, a selective 5-HT_3–receptor antagonist, also inhibited visceral pain induced by balloon gastric distension in rats. From these findings, it is suggested that the anti-visceral pain response produced by mosapride might be mediated via both 5-HT_4–receptor activation and 5-HT_3–receptor antagonistic activity, which arises from the major mosapride metabolite M1. However, further pharmacological studies are needed to clearly elucidate the analgesic action of mosapride.

In conclusion, we have shown in this study that mosapride, a 5-HT_4–receptor agonist, inhibits the VMR response to balloon gastric distension in conscious rats. In addition, we have shown that mosapride analgesic action is specifically effective against visceral pain, but not somatic pain. We hypothesize that the inhibitory effect of mosapride on gastric distension–induced visceral pain is mediated via activation of 5-HT_4 receptors and blockage of 5-HT_3 receptors by mosapride's major metabolite. These findings suggest that mosapride may be useful in alleviating FD gastrointestinal symptoms via increase in pain threshold.

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