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BRIEF ARTICLE

Effects of 5-HT2B, 5-HT3 and 5-HT4 receptor antagonists on gastrointestinal motor activity in dogs

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Abstract

AIM: To study the effects of 5-hydroxytryptamine (5-HT) receptor antagonists on normal colonic motor activity in conscious dogs.

METHODS: Colonic motor activity was recorded using a strain gauge force transducer in 5 dogs before and after 5-HT2B, 5-HT3 and 5-HT4 receptor antagonist administration. The force transducers were implanted on the serosal surfaces of the gastric antrum, terminal ileum, ileocecal sphincter and colon. Test materials or vehicle alone was administered as an intravenous bolus injection during a quiescent period of the whole colon in the interdigestive state. The effects of these receptor antagonists on normal gastrointestinal motor activity were analyzed.

RESULTS: 5-HT2B, 5-HT3 and 5-HT4 receptor antagonists had no contractile effect on the fasting canine terminal ileum. The 5-HT3 and 5-HT4 receptor antagonists inhibited phase Ⅲ of the interdigestive motor complex of the antrum and significantly inhibited colonic motor activity. In the proximal colon, the inhibitory effect was dose dependent. Dose dependency, however, was not observed in the distal colon. The 5-HT2B receptor antagonist had no contractile effect on normal colonic motor activity.

CONCLUSION: The 5-HT3 and 5-HT4 receptor antagonists inhibited normal colonic motor activity. The 5-HT2B receptor antagonist had no contractile effect on normal colonic motor activity.

Key words: 5-hydroxytryptamine receptor antagonist; Colonic motility; Irritable bowel syndrome

Core tip: Previous studies have investigated the effects of 5-hydroxytryptamine (5-HT) receptor antagonists on abnormal colonic motor activity, following either the administration of 5-HT or stress induction. This study is the first to investigate the effects of 5-HT receptor antagonists on normal colonic motor activity in dogs. 5-HT3 and 5-HT4 receptor antagonists inhibited normal colonic motor activity. A 5-HT2B receptor antagonist had no contractile effect on normal colonic motor activity. 5-HT3 and 5-HT4 receptor antagonists may also be used as premedications for colonoscopy. A 5-HT2B receptor antagonist may be used for the treatment of diarrhea-predominant irritable bowel syndrome without the side effect of constipation.

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INTRODUCTION

Over 95% of the 5-hydroxytryptamine (5-HT) in the body is found in the gastrointestinal tract; 90% of the gastrointestinal 5-HT is contained within enterochromaffin cells[1,2], and the remaining 10% is contained within the enteric neurons[3,4]. Seven major types and multiple subtypes of 5-HT receptors have been identified. 5-HT receptors that are known to affect gut motor functions are those belonging to the 5-HT1, 2, 3, 4 and 7 subtypes[5]. 5-HT has a variety of actions; it can cause smooth-muscle contraction (*via* cholinergic nerve stimulation) or relaxation (*via* stimulation of inhibitory nitric oxide-releasing neurons)[6]. Mucosal release of 5-HT stimulates both intrinsic sensory neurons (most likely *via* 5-HT4 receptors) and extrinsic sensory neurons (*via* 5-HT3 receptors); these actions modulate sensation[7]. Previous studies have shown that 5-HT3 and 5-HT4 receptor agonists stimulate gastrointestinal motility[8-12]. However, the effects of these antagonists are unknown.

Irritable bowel syndrome (IBS) is a common gastrointestinal disorder associated with altered motility, secretion and visceral sensation[5]. Stress is known to strongly contribute to the pathogenesis of IBS[13]. Data have shown that systemic administration of 5-HT3 receptor antagonists abolishes the abnormal contractions and visceral sensations induced by stress[14-16], leading to the use of 5-HT3 receptor antagonists in the treatment of diarrhea-predominant IBS. However, the effects of 5-HT3 receptor antagonists on normal colonic motor activity are controversial. Previous studies have shown that 5-HT3 antagonists have no effect on colonic motor activity during the interdigestive state in dogs and humans[17-19]. By contrast, the migrating motor complex in the murine small and large bowel is abolished by 5-HT3 antagonist activity[20]. Ondansetron, a 5-HT3 receptor antagonist, has been shown to delay colonic transit time in healthy subjects[21-23] and tends to slow left-sided colonic transit in patients with diarrhea-predominant IBS[24]. The effect of 5-HT3 receptor antagonists on normal colonic motor activity is still unknown. However, these studies suggest that 5-HT3 receptor antagonists may have an inhibitory effect on colonic motor activity.

5-HT2B receptors are expressed by the smooth muscle of the adult human gut[25], but their functions are unclear. It is known that 5-HT2B receptor antagonists inhibit visceral hypersensitivity[26]. These data suggest that 5-HT2B receptor antagonists also have a potential therapeutic role in the treatment of IBS. The effects of 5-HT2B receptor antagonists on normal colonic motor activity *in vivo* remain unknown.

5-HT4 receptors are distributed along the gut, where they may play a role in mediating smooth muscle tone, peristaltic reflex and mucosal secretion. In healthy humans, 5-HT4 receptor agonists have been demonstrated to stimulate both whole gut transit and colonic transit. Clinically, 5-HT4 receptor agonists are used for patients suffering from gastro-esophageal reflux disease, dyspepsia or constipation-predominant IBS[5,27,28]. As with the 5-HT3 receptors, the effects of 5-HT4 receptors are complex. 5-HT4 receptors mediate both the relaxation and contraction of circular smooth muscle[28-31]. The effect of 5-HT4 receptor antagonists on normal colonic motor activity remains unknown.

This study aimed to determine the effects of 5-HT2B, 5-HT3 and 5-HT4 receptor antagonists on normal colonic motor activity in conscious dogs.

MATERIALS AND METHODS

Preparation of animals

Experiments were completed in 5 healthy conscious dogs of both sexes, each weighing 8-11 kg. The procedures were approved by the Review Committee on Animal Use of Gunma University, Maebashi, Japan. Overnight-fasted dogs were anesthetized by a single intravenous injection of thiopental sodium (Ravonal; Tanabe Pharmaceutical, Osaka, Japan) at a dose of 20 mg/kg. General anesthesia was maintained by endotracheal inhalation of halothane (Fluothane; Takeda Chemical Industries, Osaka, Japan) and oxygen. A Silastic tube (Silastic 602-205; Dow Corning, Midland, MI) was inserted into the superior vena cava through a branch of the right internal jugular vein (jugular tube). The abdominal cavity was opened, and eight force transducers[32] were implanted on the serosal surfaces of the gastric antrum, terminal ileum (5 and 15 cm proximal to ileocecal sphincter) (I1/I2), ileocecal sphincter (ICS) and colon (C1-C4); C1 was placed 5 cm distal to the ICS, and C4 was placed 5 cm proximal to the peritoneal reflection. C2 and C3 were placed at equal distances between C1 and C4 (Figure 1). The ICS was identified by inspection and palpation. Wires from each force transducer were tunneled subcutaneously to the dorsum and connected to an eight-channel telemeter (GTS-800; Star Medical, Tokyo, Japan); gastrointestinal and colonic contractile activities were thereby continuously recorded on a computer (Adif1412.dill; Star Medical).

After the operation, the dogs were housed in individual experimental cages. They were fasted for 2 d after this procedure and maintained by intravenous infusion of Lactec G (Otsuka Pharmaceutical, Tokyo, Japan) at a daily volume of 500 mL. Cefmetazole (1 g) was administered intravenously, once preoperatively and once on postoperative day 1. The dogs were allowed to recover for $\geqslant$ 10 d. They were fed normal dog food (20 g/kg; Funabashi Farm, Funabashi, Japan) once daily and pro-

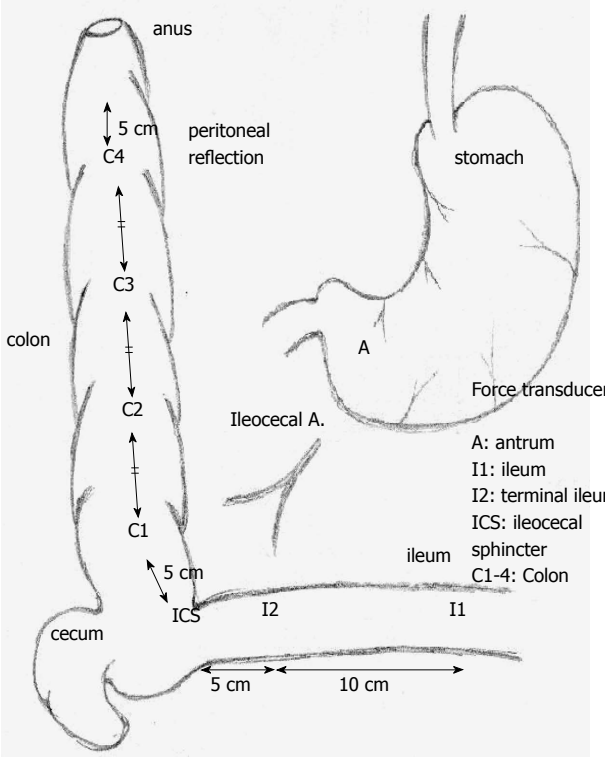

Figure 1 Scheme of the dog model and the locations of the force transducers implanted in the canine gastrointestinal tract. Force transducers were implanted in the colon on the serosal surfaces of the gastric antrum (A), terminal ileum [5 and 15 cm proximal to ileocecal sphincter (ICS); I1-I2], ICS and colon (C1-C4); C1 was placed 5 cm distal to the ICS and C4 5 cm proximal to the peritoneal reflection. C2 and C3 were implanted equidistantly between C1 and C4.

vided water ad libitum.

After all experiments were completed, the dogs were sacrificed by an overdose of potassium chloride. Specimens of ICS were then fixed in 10% formalin and stained with hematoxylin and eosin. Proper placement of the transducers was confirmed.

Drugs

Ondansetron, a 5-HT3 receptor antagonist, was purchased from Sigma Japan (Tokyo). GR113808, a selective 5-HT4 receptor antagonist[33], was purchased from Wako Pure Chemical Co. (Osaka, Japan). RQ-00310941, a novel, potent, and selective 5-HT2B receptor antagonist[34], was synthesized by RaQualia Pharma Inc. (Aichi Japan). Ondansetron was dissolved in distilled water, GR113808 was dissolved in DMSO, and RQ-00310941 was dissolved in acid DMSO.

Experimental protocol and recording of contractile activity

The dogs were fasted overnight before each experiment. After the interdigestive motor complex[35] had been recorded at the antrum, ≥ 2-h of contractile activity was recorded. Test material or vehicle (5 mL of 154 mmol/L NaCl solution) alone was then administered as an intravenous bolus injection during a quiescent state of the whole colon in the interdigestive state. The experiments were performed with the following treatment doses: ondansetron (0.01, 0.03, 0.10 and 0.30 mg/kg), GR 113808 (0.1 and 0.3 mg/kg), and RQ-00310941 (1, 3 and 10 mg/kg). Contractile activities were recorded for ≥ 2-h after administration. All experiments were carried out in a random order, and the test material was given once per day.

Data analysis

The recorded mechanical activities were analyzed using software for analysis of gastrointestinal motility (8STAR, Star Medical Co., Ltd). The analysis of colonic contractile activity (from ICS to C4) was performed for 1 h both before and after administration. The mean motility index (MI) and average MI of colonic contractile activity were recorded at each site. The MI was defined as the integrated area between baseline (zero level) and the contractile wave expressed in motor units. This parameter was expressed as the inhibition ratio: the ratio of contractile activity before and after drug administration.

Statistical analysis

Student's *t* test was used for statistical analysis. The results are expressed as the mean ± SD. $P < 0.05$ was considered statistically significant.

RESULTS

Effects of 5-HT2B, 5-HT3 and 5-HT4 receptor antagonists on gastric and terminal ileum motility

5-HT2B, 5-HT3 and 5-HT4 receptor antagonists had no contractile effect on the fasted canine terminal ileum (I1, I2) during the observation period (Figures 2-5). In contrast, the 5-HT3 and 5-HT4 receptor antagonists both significantly inhibited phase Ⅲ of the interdigestive motor complex of the antrum (Figures 4 and 5).

Effects of 5-HT2B, 5-HT3 and 5-HT4 receptor antagonists on normal colonic motor activity

The 5-HT2B receptor antagonist had no contractile effect on normal colonic motor activity (Figure 3). However, both the 5-HT3 and 5-HT4 receptor antagonists inhibited colonic motor activity (Figures 4 and 5). At 0.3 mg/kg, the 5-HT3 receptor antagonist significantly inhibited whole colonic motor activity (ICS - C4) (72% ± 9% *vs* -11% ± 6%, 70% ± 10% *vs* 6% ± 10%, 65% ± 15% *vs* 1% ± 11%, 61% ± 7% *vs* 5% ± 9% and 68% ± 7% *vs* -10% ± 3%, respectively; Figure 4). In the proximal colon, the inhibitory effects of the 5-HT3 and 5-HT4 receptor antagonists were dose dependent. However, no dose-dependent response was observed in the distal colon. Upon administration of the 5-HT4 receptor antagonist, colonic migrating motor complexes (CMMCs) corresponding to phase Ⅲ of the migrating motor complex at the ileum were sometimes observed (Figure 5, see arrow). The motor complex independent of phase Ⅲ of the migrating motor complex tended to be inhibited (Figure 5). These inhibited effects were observed for at least 1 h.

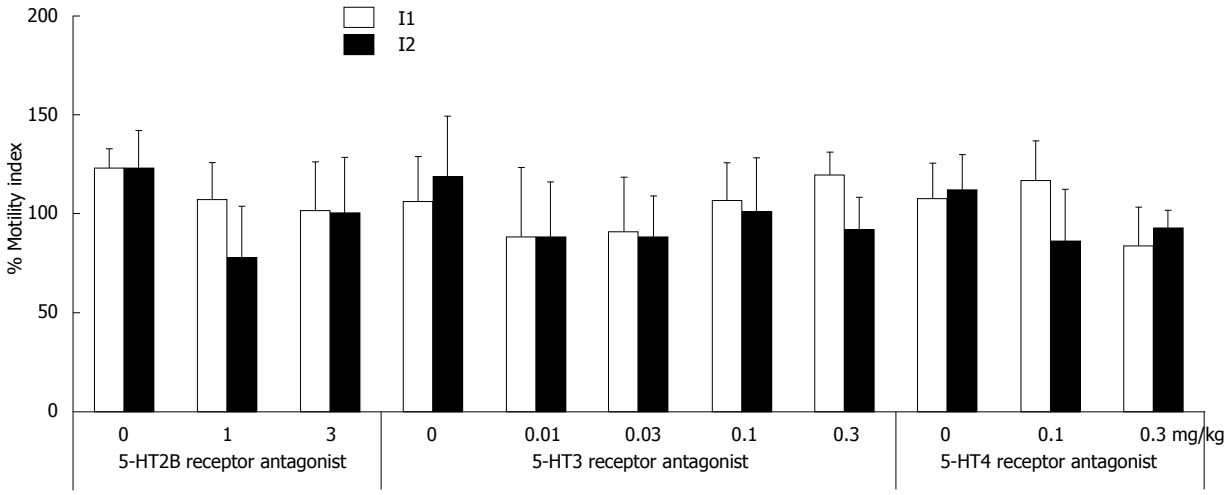

Figure 2 Inhibition ratio based on comparing the drug effects to before 5-hydroxytryptamine receptor antagonist administration in the terminal ileum (I1-I2). A systematic change was not observed. Values are mean ± SE. 5-HT: 5-hydroxytryptamine; I1:Ileum; I2: Terminal ileum.

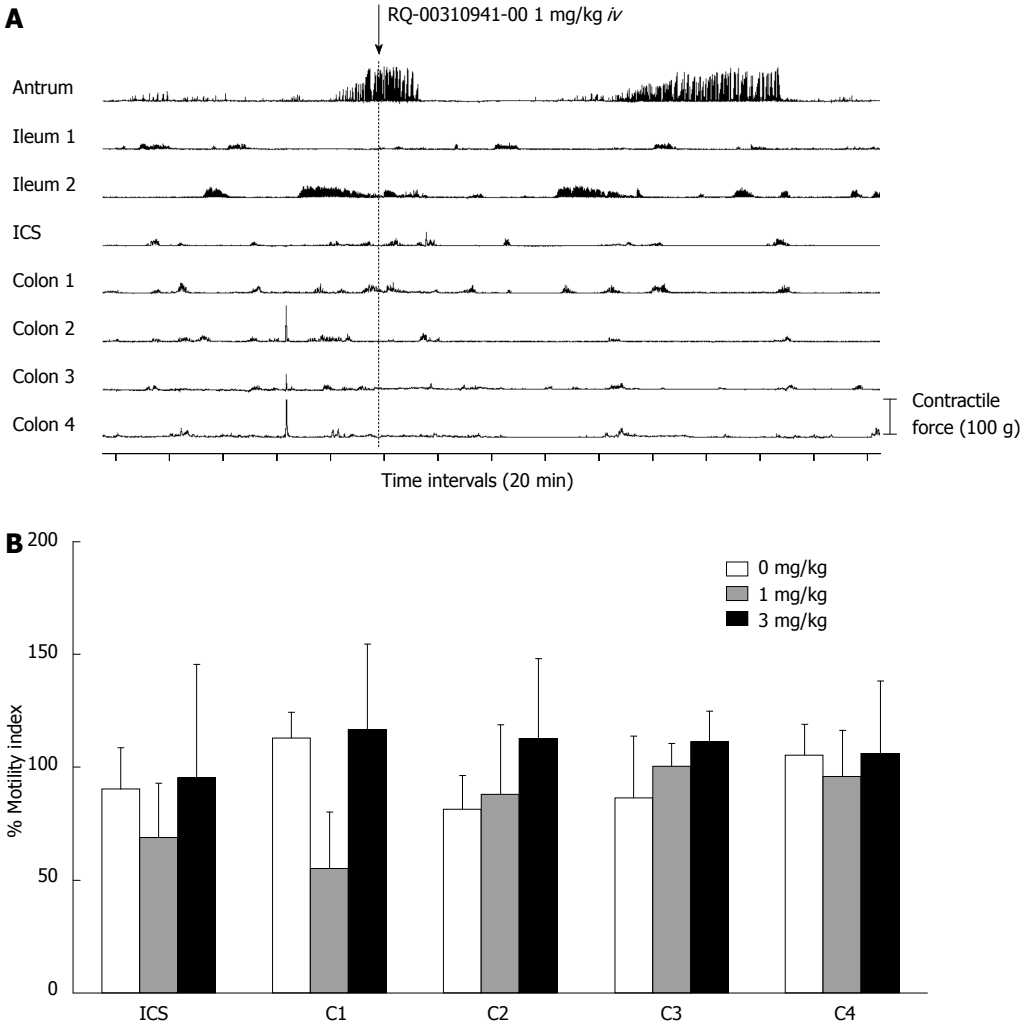

Figure 3 5-hydroxytryptamine 2B receptor antagonists on normal colonic motor activity. A: Typical effect of the 5-hydroxytryptamine (5-HT) 2B receptor antagonist. The 5-HT2B receptor antagonist had no contractile effect on the whole intestine; B: The inhibition ratio compared with before 5-HT2B receptor antagonist administration. A systematic change was not observed. Values are mean ± SE. ICS: Ileocecal sphincter; C1-4: Colon 1-4.

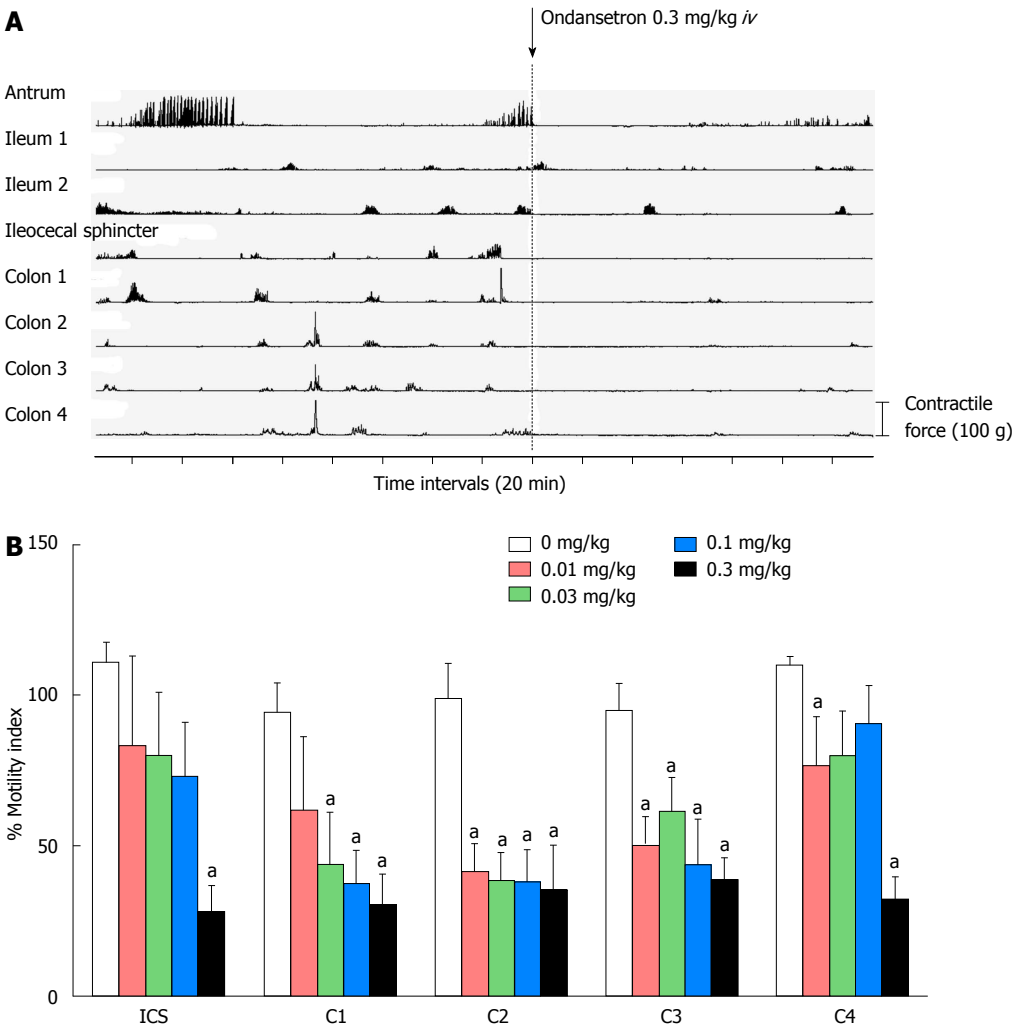

Figure 4 5-hydroxytryptamine 3 receptor antagonists on normal colonic motor activity. A: Typical effect of the 5-hydroxytryptamine (5-HT) 3 receptor antagonist. The 5-HT3 receptor antagonist inhibited phase Ⅲ of the interdigestive motor complex at the antrum and whole colonic motor activity; B: The inhibition ratio compared with before 5-HT3 receptor antagonist administration. The inhibitory effect of the 5-HT3 receptor antagonist was dose dependent in the proximal colon (ICS-C2). At a dose of 0.3 mg/kg, whole colonic motor activity was inhibited significantly. Values are mean ± SE. $^{a}P < 0.05$ *vs* control (0 mg/kg). ICS: Ileocecal sphincter; C1-4: Colon 1-4.

DISCUSSION

Previous studies have investigated the effects of 5-HT receptor antagonists on abnormal colonic motor activity, following either the administration of 5-HT or the induction of stress[14,26,31,36,37]. This study is the first to investigate the effects of 5-HT receptor antagonists on normal colonic motor activity in dogs using a force transducer.

In this study, 5-HT3 and 5-HT4 receptor antagonists inhibited normal colonic motor activity. In contrast, a 5-HT2B receptor antagonist had no contractile effect on normal colonic motor activity. The 5-HT3 receptor antagonist inhibited phase Ⅲ of the interdigestive motor complex of the antrum. None of the three 5-HT receptor antagonists had contractile effects on the fasted dog terminal ileum.

The effects of 5-HT3 receptor antagonists on colonic motor activity are controversial. In the present study, the 5-HT3 receptor antagonist inhibited normal colonic motor activity. However, Yoshida *et al*[17] reported that ondansetron (GR38032F) had no contractile effect on normal colonic motor activity in the interdigestive state in dogs. In their study, the 5-HT3 receptor antagonist was administered at a high dose of 1 mg/kg. It is possible that a higher dose of the 5-HT3 receptor antagonist may paradoxically have no contractile effect on normal colonic motor activity.

Because we administered the 5-HT3 receptor antagonist systemically, we were unable to determine its mechanism of action. We did observe, however, that the inhibitory effects were exerted in the extrinsic denervation region[38] (data not shown), suggesting that it acted locally.

How colonic contractions are generated is unclear. It is known that the pacemaker of colonic contractions lies within the colon wall itself because contractions can occur in an isolated colon. The pacemaker itself, however, has not been characterized. Heredia *et al*[39] showed that the initiation of colonic contractions requires serotonin. Dickson *et al*[40] demonstrated that 5-HT initially excites

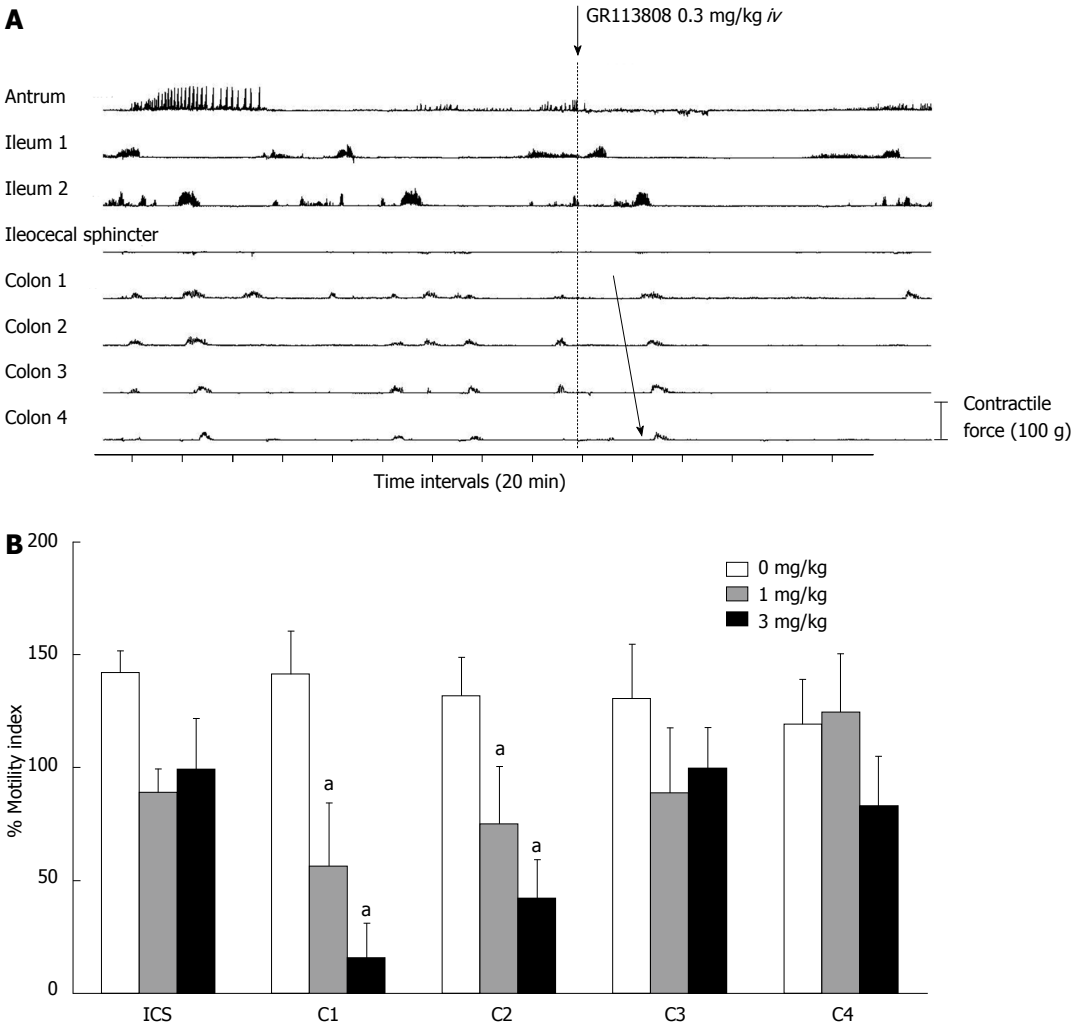

Figure 5 5-hydroxytryptamine 4 receptor antagonists on normal colonic motor activity. A: Typical effect of the 5-hydroxytryptamine (5-HT) 4 receptor antagonist. The 5-HT4 receptor antagonist inhibited phase Ⅲ of the interdigestive motor complex at the antrum and whole colonic motor activity, CMMCs corresponding to phase Ⅲ of the migrating motor complex at the ileum were sometimes observed (see arrow); B: The inhibition ratio compared with before 5-HT4 receptor antagonist administration. The inhibitory effect of the 5-HT4 receptor antagonist was dose dependent in the proximal colon (C1-C2). Values are mean ± SE. $^{a}P < 0.05$ *vs* control (0 mg/kg). ICS: Ileocecal sphincter; C1-4: Colon 1-4.

5-HT3 receptors on the mucosal endings of Dogiel type Ⅱ/AH neurons and that this is coincidental with colonic contractions. It is possible that the inhibitory effects of 5-HT3 receptor antagonists demonstrated in this study may act at this site. Bharucha *et al*[41] showed that a 5-HT4 receptor antagonist (SB-207266) tended to delay colonic transit. Consistent with this, in our study, the 5-HT4 receptor antagonist inhibited colonic motor activity. Studies have shown that receptors on contractile nerves may be more sensitive to receptor antagonism than those on relaxation nerves[22-25]. We hypothesize that the 5-HT4 receptor antagonist inhibitory effect on colonic contractile nerves may be a mechanism that results in the delay of colonic transit.

Glucagon and scopolamine butylbromide are commonly used as antispasmodic premedications for colonoscopy. In addition, 5-HT3 and 5-HT4 receptor antagonists may also be used as premedications for colonoscopy. In this study, we used ondansetron as the 5-HT3 receptor antagonist. Ondansetron has no effect on visceral sensations[28]. Visceral hypersensitivity has been proposed as a mechanism of IBS, and Kim *et al*[42] have reported that the degree of pain perception during colonoscopy is higher in IBS patients than in non-IBS patients. Alosetron, which can abolish visceral sensations[14], may be used as a premedication for colonoscopy without pain. However, whether alosetron is effective in controlling colonic motor activity has not been conclusively determined.

In a study by Ohashi-Doi *et al*[26], a 5-HT2B receptor antagonist inhibited visceral hypersensitivity and reduced restraint stress-induced defecation It is therefore logical to hypothesize that a 5-HT2B receptor antagonist may have therapeutic potential for the treatment of non-constipation IBS. Bassil *et al*[43] have previously shown that high-dose (10 and 30 mg/kg) 5-HT2B antagonists inhibit colonic motility and defecation in normal mice. The present study did not confirm their findings, as the 5-HT2B receptor antagonist had no contractile effect on normal colonic motor activity. However, we only evaluated doses up to 3 mg/kg. By contrast, our previous study showed

that RQ-00310941 at 3 mg/kg *p.o.* inhibited restraint stress-induced defecation in TNBS-treated rats[34]. In that preliminary study, rats were administered 3 mg/kg TNBS orally, but the plasma concentration of RQ-00310941 was greater than that in the dogs in the current study, which were also administered 3 mg/kg *iv* (data not shown). We therefore speculate that RQ-00310941 can inhibit restraint stress-induced defecation at higher doses.

In the proximal colon, the inhibitory effects of 5-HT3 and 5-HT4 antagonists were dose dependent. However, this inhibition was dose independent in the distal colon. Nagakura *et al*[36] also showed that the effect of a 5-HT4 receptor agonist on colonic motor activity in the proximal colon was stronger than that in the distal colon. A different distribution of 5-HT receptors in the distal colon compared with the proximal colon may explain this effect. These confounding effects may also be based on a differential sensitivity to drugs in the proximal and distal colon[44,45]. Further studies are needed to clarify this result. In conclusion, 5-HT3 and 5-HT4 receptor antagonists inhibited phase Ⅲ of the interdigestive motor complex at the antrum and colonic motor activity. The 5-HT2B receptor antagonist had no contractile effect on normal colonic motor activity.

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COMMENTS

Background

Most of the body's 5-hydroxytryptamine (5-HT) is found in the intestinal tract, where it helps regulate intestinal motor activity. The 5-HT receptors that are known to affect gut motor functions are those belonging to the 5-HT1, 2, 3, 4 and 7 subtypes.

Research frontiers

Irritable bowel syndrome (IBS) is a common gastrointestinal disorder associated with altered motility, secretion and visceral sensation. Recently, 5-HT was identified as the cause of IBS.

Innovations and breakthroughs

Previous studies have investigated the effects of 5-HT receptor antagonists on abnormal colonic motor activity, following either the administration of 5-HT or the induction of stress. This study is the first to investigate the effects of 5-HT receptor antagonists on normal colonic motor activity in dogs.

Applications

The study results suggest that 5-HT3 and 5-HT4 receptor antagonists may also be used as premedications for colonoscopy. 5-HT2B receptor antagonists may be used for the treatment of diarrhea-predominant IBS without the side effect of constipation.

Terminology

Motility index (MI): MI was defined as the integrated area between baseline (zero level) and the contractile wave expressed in motor units. MI is an index used when analyzing gastrointestinal motility. 5-HT: Over 95% of the 5-HT in the body is found in the gastrointestinal tract; 90% of the gastrointestinal 5-HT is found within enterochromaffin cells. 5-HT receptors are known to affect gut motor functions.

Peer review

This is a good descriptive study in which the authors analyze the effects of 5-HT3, 5-HT4 and 5-HT2B receptor antagonists on normal gastrointestinal motility. 5-HT3 and 5-HT4 receptor antagonists inhibited colonic motor activity. The 5-HT2B receptor antagonist had no contractile effect on normal colonic motor activity.

REFERENCES

1 **Gershon MD**. Review article: serotonin receptors and transporters -- roles in normal and abnormal gastrointestinal motility. *Aliment Pharmacol Ther* 2004; **20** Suppl 7: 3-14 [PMID: 15521849]
2 **Gershon MD**, Tack J. The serotonin signaling system: from basic understanding to drug development for functional GI disorders. *Gastroenterology* 2007; **132**: 397-414 [PMID: 17241888 DOI: 10.1053/j.gastro.2006.11.002]
3 **Gershon MD**. 5-HT (serotonin) physiology and related drugs. *Curr Opin Gastroenterol* 2000; **16**: 113-120 [PMID: 17024028 DOI: 10.1097/00001574-200003000-00004]
4 **Wade PR**, Tamir H, Kirchgessner AL, Gershon MD. Analysis of the role of 5-HT in the enteric nervous system using anti-idiotopic antibodies to 5-HT receptors. *Am J Physiol* 1994; **266**: G403-G416 [PMID: 8166280]
5 **Sikander A**, Rana SV, Prasad KK. Role of serotonin in gastrointestinal motility and irritable bowel syndrome. *Clin Chim Acta* 2009; **403**: 47-55 [PMID: 19361459 DOI: 10.1016/j.cca.2009.01.028]
6 **Kim DY**, Camilleri M. Serotonin: a mediator of the brain-gut connection. *Am J Gastroenterol* 2000; **95**: 2698-2709 [PMID: 11051338]
7 **Gershon MD**. Review article: roles played by 5-hydroxytryptamine in the physiology of the bowel. *Aliment Pharmacol Ther* 1999; **13** Suppl 2: 15-30 [PMID: 10429737 DOI: 10.1046/j.1365-2036.1999.00002.x-i2]
8 **Coleman NS**, Marciani L, Blackshaw E, Wright J, Parker M, Yano T, Yamazaki S, Chan PQ, Wilde K, Gowland PA, Perkins AC, Spiller RC. Effect of a novel 5-HT3 receptor agonist MKC-733 on upper gastrointestinal motility in humans. *Aliment Pharmacol Ther* 2003; **18**: 1039-1048 [PMID: 14616171 DOI: 10.1046/j.1365-2036.2003.01797.x]
9 **Inui A**, Yoshikawa T, Nagai R, Yoshida N, Ito T. Effects of mosapride citrate, a 5-HT4 receptor agonist, on colonic motility in conscious guinea pigs. *Jpn J Pharmacol* 2002; **90**: 313-320 [PMID: 12501007 DOI: 10.1254/jjp.90.313]
10 **Jin JG**, Foxx-Orenstein AE, Grider JR. Propulsion in guinea pig colon induced by 5-hydroxytryptamine (HT) via 5-HT4 and 5-HT3 receptors. *J Pharmacol Exp Ther* 1999; **288**: 93-97 [PMID: 9862758]
11 **Nagakura Y**, Ito H, Kamato T, Nishida A, Miyata K. Effect of a selective 5-HT3 receptor agonist on gastric motility in fasted and fed dogs. *Eur J Pharmacol* 1997; **327**: 189-193 [PMID: 9200559 DOI: 10.1016/S0014-2999(97)89660-4]
12 **Prins NH**, Akkermans LM, Lefebvre RA, Schuurkes JA. 5-HT(4) receptors on cholinergic nerves involved in contractility of canine and human large intestine longitudinal muscle. *Br J Pharmacol* 2000; **131**: 927-932 [PMID: 11053213 DOI: 10.1038/sj.bjp.0703615]
13 **Chang L**. The role of stress on physiologic responses and clinical symptoms in irritable bowel syndrome. *Gastroenterology* 2011; **140**: 761-765 [PMID: 21256129 DOI: 10.1053/j.gastro.2011.01.032]
14 **Hirata T**, Keto Y, Nakata M, Takeuchi A, Funatsu T, Akuzawa S, Sasamata M, Miyata K. Effects of serotonin 5-HT3 receptor antagonists on stress-induced colonic hyperalgesia and diarrhoea in rats: a comparative study with opioid receptor agonists, a muscarinic receptor antagonist and a synthetic polymer. *Neurogastroenterol Motil* 2008; **20**: 557-565 [PMID: 18221252 DOI: 10.1111/j.1365-2982.2007.01069.x]
15 **Nakade Y**, Fukuda H, Iwa M, Tsukamoto K, Yanagi H, Yamamura T, Mantyh C, Pappas TN, Takahashi T. Restraint stress stimulates colonic motility via central corticotropin-releasing factor and peripheral 5-HT3 receptors in con-

scious rats. *Am J Physiol Gastrointest Liver Physiol* 2007; **292**: G1037-G1044 [PMID: 17158256 DOI: 10.1152/ajpgi.00419.2006]
16 **Miyata K**, Ito H, Fukudo S. Involvement of the 5-HT3 receptor in CRH-induce defecation in rats. *Am J Physiol* 1998; **274**: G827-G831 [PMID: 9612262]
17 **Yoshida N**, Mizumoto A, Iwanaga Y, Itoh Z. Effects of 5-hydroxytryptamine 3 receptor antagonists on gastrointestinal motor activity in conscious dogs. *J Pharmacol Exp Ther* 1991; **256**: 272-278 [PMID: 1846418]
18 **Hayashi K**, Shibata C, Nagao M, Sato M, Kakyo M, Kinouchi M, Saijo F, Miura K, Ogawa H, Sasaki I. Intracolonic capsaicin stimulates colonic motility and defecation in conscious dogs. *Surgery* 2010; **147**: 789-797 [PMID: 20079916 DOI: 10.1016/j.surg.2009.11.019]
19 **von der Ohe MR**, Hanson RB, Camilleri M. Serotonergic mediation of postprandial colonic tonic and phasic responses in humans. *Gut* 1994; **35**: 536-541 [PMID: 8174993 DOI: 10.1136/gut.35.4.536]
20 **Bush TG**, Spencer NJ, Watters N, Sanders KM, Smith TK. Effects of alosetron on spontaneous migrating motor complexes in murine small and large bowel in vitro. *Am J Physiol Gastrointest Liver Physiol* 2001; **281**: G974-G983 [PMID: 11557518]
21 **Talley NJ**, Phillips SF, Haddad A, Miller LJ, Twomey C, Zinsmeister AR, MacCarty RL, Ciociola A. GR 38032F (ondansetron), a selective 5HT3 receptor antagonist, slows colonic transit in healthy man. *Dig Dis Sci* 1990; **35**: 477-480 [PMID: 2138532 DOI: 10.1007/BF01536922]
22 **Talley NJ**, Phillips SF, Haddad A, Miller LJ, Twomey C, Zinsmeister AR, Ciociola A. Effect of selective 5HT3 antagonist (GR 38032F) on small intestinal transit and release of gastrointestinal peptides. *Dig Dis Sci* 1989; **34**: 1511-1515 [PMID: 2529108 DOI: 10.1007/BF01537102]
23 **Gore S**, Gilmore IT, Haigh CG, Brownless SM, Stockdale H, Morris AI. Colonic transit in man is slowed by ondansetron (GR38032F), a selective 5-hydroxytryptamine receptor (type 3) antagonist. *Aliment Pharmacol Ther* 1990; **4**: 139-144 [PMID: 2151757 DOI: 10.1111/j.1365-2036.1990.tb00458.x]
24 **Steadman CJ**, Talley NJ, Phillips SF, Zinsmeister AR. Selective 5-hydroxytryptamine type 3 receptor antagonism with ondansetron as treatment for diarrhea-predominant irritable bowel syndrome: a pilot study. *Mayo Clin Proc* 1992; **67**: 732-738 [PMID: 1434911 DOI: 10.1016/S0025-6196(12)60797-6]
25 **Borman RA**, Tilford NS, Harmer DW, Day N, Ellis ES, Sheldrick RL, Carey J, Coleman RA, Baxter GS. 5-HT(2B) receptors play a key role in mediating the excitatory effects of 5-HT in human colon in vitro. *Br J Pharmacol* 2002; **135**: 1144-1151 [PMID: 11877320]
26 **Ohashi-Doi K**, Himaki D, Nagao K, Kawai M, Gale JD, Furness JB, Kurebayashi Y. A selective, high affinity 5-HT 2B receptor antagonist inhibits visceral hypersensitivity in rats. *Neurogastroenterol Motil* 2010; **22**: e69-e76 [PMID: 19740115 DOI: 10.1111/j.1365-2982.2009.01395.x]
27 **Spiller R**. Serotonin and GI clinical disorders. *Neuropharmacology* 2008; **55**: 1072-1080 [PMID: 18687345 DOI: 10.1016/j.neuropharm.2008.07.016]
28 **Talley NJ**. Serotoninergic neuroenteric modulators. *Lancet* 2001; **358**: 2061-2068 [PMID: 11755632 DOI: 10.1016/S0140-6736(01)07103-3]
29 **Prins NH**, Van Haselen JF, Lefebvre RA, Briejer MR, Akkermans LM, Schuurkes JA. Pharmacological characterization of 5-HT4 receptors mediating relaxation of canine isolated rectum circular smooth muscle. *Br J Pharmacol* 1999; **127**: 1431-1437 [PMID: 10455293 DOI: 10.1038/sj.bjp.0702665]
30 **McLean PG**, Coupar IM, Molenaar P. A comparative study of functional 5-HT4 receptors in human colon, rat oesophagus and rat ileum. *Br J Pharmacol* 1995; **115**: 47-56 [PMID: 7647983 DOI: 10.1111/j.1476-5381.1995.tb16318.x]
31 **Tam FS**, Hillier K, Bunce KT, Grossman C. Differences in response to 5-HT4 receptor agonists and antagonists of the 5-HT4-like receptor in human colon circular smooth muscle. *Br J Pharmacol* 1995; **115**: 172-176 [PMID: 7647972 DOI: 10.1111/j.1476-5381.1995.tb16335.x]
32 **Itoh Z**, Honda R, Takeuchi S, Aizawa I, Takayanagi R. An extraluminal force transducer for recording contractile activity of the gastrointestinal smooth muscle in the conscious dogs: its construction and implantation. *Gastroenterol Jpn* 1977; **12**: 275-283 [PMID: 590700]
33 **Gale JD**, Grossman CJ, Whitehead JW, Oxford AW, Bunce KT, Humphrey PP. GR113808: a novel, selective antagonist with high affinity at the 5-HT4 receptor. *Br J Pharmacol* 1994; **111**: 332-338 [PMID: 8012715]
34 **Takahashi N**, Inagaki K, Taniguchi K, Sakaguchi Y, Kawamura K. The novel 5-HT2B receptor antagonist, RQ-00310941, attenuates visceral hypersensitivity and abnormal defecation in rat models. *Gastroenterology* 2011; **140**: S-607 [DOI: 10.1016/S0016-5085(11)62513-4]
35 **Itoh Z**, Takeuchi S, Aizawa I, Takayanagi R. Characteristic motor activity of the gastrointestinal tract in fasted conscious dogs measured by implanted force transducers. *Am J Dig Dis* 1978; **23**: 229-238 [PMID: 665611 DOI: 10.1007/BF01072323]
36 **Nagakura Y**, Kamato T, Nishida A, Ito H, Yamano M, Miyata K. Characterization of 5-hydroxytryptamine (5-HT) receptor subtypes influencing colonic motility in conscious dogs. *Naunyn Schmiedebergs Arch Pharmacol* 1996; **353**: 489-498 [PMID: 8740141 DOI: 10.1007/BF00169167]
37 **Ataka K**, Kuge T, Fujino K, Takahashi T, Fujimiya M. Wood creosote prevents CRF-induced motility via 5-HT3 receptors in proximal and 5-HT4 receptors in distal colon in rats. *Auton Neurosci* 2007; **133**: 136-145 [PMID: 17182287 DOI: 10.1016/j.autneu.2006.11.002]
38 **Morita H**, Mochiki E, Ogawa A, Yanai M, Toyomasu Y, Tabe Y, Ohno T, Tsutsumi S, Asao T, Kuwano H. Effects of denervation at ileocecal junction and ileocecal resection in dogs. *Neurogastroenterol Motil* 2012; **24**: 86-93, e14 [PMID: 22082338 DOI: 10.1111/j.1365-2982.2011.01810.x]
39 **Heredia DJ**, Dickson EJ, Bayguinov PO, Hennig GW, Smith TK. Localized release of serotonin (5-hydroxytryptamine) by a fecal pellet regulates migrating motor complexes in murine colon. *Gastroenterology* 2009; **136**: 1328-1338 [PMID: 19138686 DOI: 10.1053/j.gastro.2008.12.010]
40 **Dickson EJ**, Heredia DJ, Smith TK. Critical role of 5-HT1A, 5-HT3, and 5-HT7 receptor subtypes in the initiation, generation, and propagation of the murine colonic migrating motor complex. *Am J Physiol Gastrointest Liver Physiol* 2010; **299**: G144-G157 [PMID: 20413719 DOI: 10.1152/ajpgi.00496.2009]
41 **Bharucha AE**, Camilleri M, Haydock S, Ferber I, Burton D, Cooper S, Tompson D, Fitzpatrick K, Higgins R, Zinsmeister AR. Effects of a serotonin 5-HT(4) receptor antagonist SB-207266 on gastrointestinal motor and sensory function in humans. *Gut* 2000; **47**: 667-674 [PMID: 11034583 DOI: 10.1136/gut.47.5.667]
42 **Kim ES**, Cheon JH, Park JJ, Moon CM, Hong SP, Kim TI, Kim WH. Colonoscopy as an adjunctive method for the diagnosis of irritable bowel syndrome: focus on pain perception. *J Gastroenterol Hepatol* 2010; **25**: 1232-1238 [PMID: 20594249 DOI: 10.1111/j.1440-1746.2010.06338.x]
43 **Bassil AK**, Taylor CM, Bolton VJ, Gray KM, Brown JD, Cutler L, Summerfield SG, Bruton G, Winchester WJ, Lee K, Sanger GJ. Inhibition of colonic motility and defecation by RS-127445 suggests an involvement of the 5-HT2B receptor in rodent large bowel physiology. *Br J Pharmacol* 2009; **158**: 252-258 [PMID: 19371340 DOI: 10.1111/j.1476-5381.2009.00155.x]
44 **Briejer MR**, Prins NH, Schuurkes JA. Effects of the entero-

kinetic prucalopride (R093877) on colonic motility in fasted dogs. *Neurogastroenterol Motil* 2001; **13**: 465-472 [PMID: 11696108 DOI: 10.1046/j.1365-2982.2001.00280.x]

45 **Hata F**, Kataoka T, Takeuchi T, Yagasaki O, Yamano N. Differences in control of descending inhibition in the proximal and distal regions of rat colon. *Br J Pharmacol* 1990; **101**: 1011-1015 [PMID: 2085703 DOI: 10.1111/j.1476-5381.1990.tb14198.x]

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