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Effects of Tegaserod on Ileal Peristalsis of Guinea Pig In Vitro

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Abstract. The mechanisms of prokinetic action of tegaserod in the gastrointestinal tract has not been studied in detail. The aim of this study was to investigate the effect of tegaserod on peristaltic reflexes and propagating peristaltic waves in guinea pig ileum. A partitioned organ bath divided into three chambers was used to investigate the effect of tegaserod on peristaltic reflexes. A sensory stimulus was applied to the intermediate chamber, and changes in the circular muscle tension were monitored in a peripheral chamber. Another peristaltic bath was used to investigate the effect of tegaserod on peristaltic waves induced by intraluminal perfusion. Guinea pig ileum exhibited contractions in the circular muscle both orally and anally in response to mucosal stroking. Tegaserod (10^{-8} – 10^{-6} M) did not influence the maximal amplitude and the area under the curve of contraction both orally and anally to a mucosal stimulus. Intraluminal perfusion of fluid containing tegaserod (10^{-8} – 10^{-6} M) significantly increased the number of peristaltic waves in a concentration-dependent manner (P<0.05). Also, tegaserod (10^{-8} – 10^{-6} M) significantly increased the area under the curve of peristaltic waves (P<0.05). It is concluded that tegaserod has prokinetic action on guinea pig ileum by increasing the number of the circular muscle contractions during peristalsis.

Keywords: tegaserod, peristalsis, Ileum (guinea pig), prokinetic action

Introduction

Recently, there has been increasing evidence indicating that serotonin (5-HT) has an influence on the secretory, motor, and sensory function in the gastrointestinal (GI) tract (1 – 4). These varied effects can occur because there are a number of different 5-HT-receptor subtypes within the body. At present, there are seven major classes of receptor subtypes (5). Among these receptor subtypes, the 5-HT_4 receptor is known to mediate peristaltic reflexes in humans (6).

Endogenous serotonin released from the enterochromaffin cells in response to chemical or mechanical stimuli activates the 5-HT_4 receptors on intrinsic primary afferent neurons (6). These neurons release transmitters such as calcitonin gene-related peptide (CGRP), activating interneurons which in turn stimulate exitatory neurons on the orad side of the mucosal stimulus and stimulate inhibitory neurons on the caudad side. This results in the peristaltic reflexes with contraction above and relaxation below the site of origination of the stimulus. The exitatory neurons mediate their effects through acetylcholine (ACh) and substance P. The transmitters for the inhibitory arm of the reflex are vasoactive intestinal peptide (VIP), pituitary adenylate cyclase activating peptide (PACAP), and nitric oxide (NO).

Tegaserod is an amino guanidine-indole with selective and partial 5-HT_4-receptor agonist activity (7, 8). Both preclinical and clinical investigations have shown that tegaserod can stimulate motility throughout the GI tract. In a model using isolated guinea pig colon segments, intraluminal perfusion of tegaserod caused a concentration-dependent increase in the velocity of propulsion of synthetic fecal pellets (9). Studies of Nguyen et al. (10) using tegaserod in dogs showed acceleration in colonic transit, although the effects on upper GI transit were more variable. Also, tegaserod accelerated GI transit in both healthy male subjects and patients with constipation-predominant irritable bowel syndrome (11, 12).

The mechanisms of prokinetic action of tegaserod in the GI tract were suggested by Grider et al. (6) They

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demonstrated that addition of tegaserod in guinea pig and rat colon caused a concentration-dependent contraction of circular muscle in the oral side of the mucosal stimulus and relaxation of the circular muscle in the anal side. However, the ascending excitatory and descending inhibitory reflexes are simple standing reflexes evocable by localized distension or other stimuli in the intestine. In contrast, peristalsis is a co-ordinated series of movements involving both longitudinal and circular muscle layers and resulting in propagated waves of contraction. Therefore, it is necessary to examine the effects of tegaserod not only on the ascending and descending reflex, but also on the propagating peristaltic waves, for confirming the mechanisms of prokinetic action of tegaserod on the GI tract. In the present study, we investigated the effect of tegaserod on peristaltic reflexes and propagating peristaltic waves in guinea pig ileum.

Materials and Methods

Preparation of tissues

Male guinea pigs weighing 250 g were killed by a blow to the occipital region of the head and severing the carotid arteries. A 15-cm segment of distal ileum was removed and the lumen flushed clean with Krebs-Henseleit (K-H) solution (pH 7.4, 118 mM NaCl, 4.8 mM KCl, 2.5 mM $CaCl_2$, 1.2 mM KH_2PO_4, 1.5 mM $MgSO_4$, 25 mM $NaHCO_3$, 11 mM glucose). Then the preparation was set up immediately as described below and allowed to equilibrate for at least 60 min before experiments started. The experimental procedures were conducted in accordance with the guidelines of the University of Yonsei Animal Care and Use Committees.

Procedure for the peristaltic reflexes experiments

To pharmacologically isolate certain regions of the ileum, the partitioned organ bath technique was used (Fig. 1A) (13, 14). This technique allows the selective addition of drugs to specific neural components active during orally and anally directed reflexes. The organ was divided into three chambers by two plastic partitions sealed with vacuum grease. It contained K-H solution, which was maintained at 37°C and saturated with 95% O_2 and 5% CO_2 at each chamber.

The preparation was threaded through a greased hole in two partitions. The portions of the preparation in the peripheral (orad and caudad) chambers were secured with pins placed at intervals through the attached mesentery. Then the portion in the intermediate chamber was cut open along the mesenteric border and pinned mucosal side up to the base of the chamber for the mucosal stimulation. A sensory stimulus was applied to the opened mucosa by stroking five times with a fine brush and repeated three times at intervals of 5 min. The mechanical activity of the circular muscle was monitored using small clips mounted orad and caudad 1-cm-apart from the opened stimulating region. These were attached via the serosal surface to the underlying circular muscle of the ileum and connected via thread to independent tension transducers (BIOPAC TSD 105; BIOPAC Systems, Inc., Santa Barbara, CA, USA). Circular muscle activity was quantified by means of a computerized integration procedure (BIOPAC MP 100, BIOPAC Systems, Inc.). Initial resting tension was routinely set to 1 g.

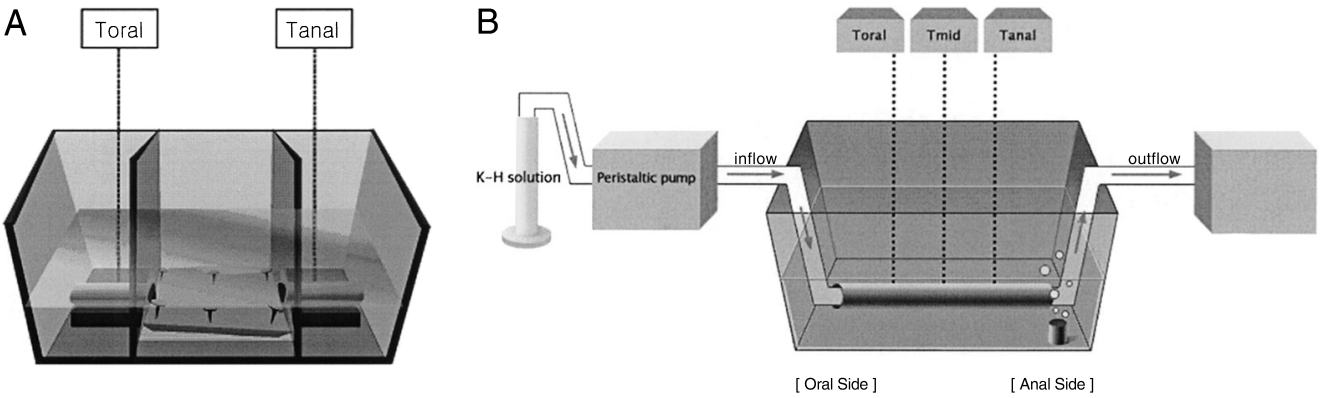

Fig. 1. Peristaltic apparatus. A: The partitioned organ bath used to elicit peristaltic reflexes. A segment of the ileum was mounted in the three-chambered organ bath, so that the tissue spanned three regions. A sensory stimulus was applied to the intermediate chamber, and changes of the circular muscle tension were monitored in the peripheral chambers by use of tension transducers. Five strokes with a fine brush were used to evoke peristaltic reflexes. B: The peristaltic bath used to evoke propagating peristaltic waves. Intraluminal perfusion at a rate of 0.4 ml/min by use of peristaltic pump was used for induction of propagated peristaltic waves. Changes of the circular muscle tension were monitored by use of tension transducers, which are arranged at intervals of 2.5 cm.

Drugs including tegaserod, tetrodotoxin (TTX), and the selective 5-HT_4-receptor antagonist GR113808 were applied to the intermediate chamber. Each drug was allowed to equilibrate for 20 min before further reflex responses were elicited. The effects of drugs on the mechanical activity of the circular muscle were assessed by comparing the mean of three responses before and after applications of drugs. The maximal amplitude and the area under the curve of the oral and anal contraction to a mucosal stimulus were obtained for the evaluation of the effects of drugs on peristaltic reflexes.

Procedure for the peristaltic waves experiments

Propagated peristaltic waves were induced according to a modification of the method of Waterman et al. (15), the apparatus used being illustrated in Fig. 1B. The preparation was cannulated in the oral and anal ends and secured horizontally in the peristaltic bath containing K-H solution. K-H solution was maintained at 37°C and saturated with 95% O_2 and 5% CO_2. Oral and anal ends of the preparation were cannulated to the inflow and outflow tubes, respectively. After the oral and anal ends had been tied securely to the respective tube, K-H solution was pumped (0.4 mL/min) into the lumen of the preparation by use of the peristaltic pump (Masterflex 7523-30 with cartridge 3519-85; Cole-Palmer, Chicago, IL, USA) to induce peristalsis. The mechanical activity of the circular muscle in the fixed guinea pig ileum was monitored using three small clips arranged at intervals of 2.5 cm. These were connected to independent tension transducers. Initial tension was routinely set to 1 g.

After perfusion of control solution for periods of 30 min, 10^{-8}, 10^{-7}, and 10^{-6} M tegaserod were applied to the bathing solution and the perfusion fluid at intervals of 30 min without washing. TTX, atropine, or GR113808 was added to the bathing solution and perfusion fluid containing tegaserod, and the mechanical activity of circular muscle evoked by intraluminal perfusion was monitored during 30 min before and after administration of any test compound. To evaluate the effects of drugs on peristaltic waves, the number and the area under the curve of peristaltic waves evoked for periods of the latter 10 min were compared.

Drugs

The drugs used in this study were tegaserod (Novartis Pharma AG, Basel, Switzerland); TTX and atropine (Sigma Chemical Co., St. Louis, MO, USA); and GR113808 (Tocris Cookson Inc., Ellisville, MO, USA).

Data analyses

Results were expressed as percentage of control levels. Statistical analysis of results was performed with repeated measures ANOVA or the Mann-Whitney *U* test. When repeated measures ANOVA revealed a significant difference, the significance of individual differences was determined with a Tukey multiple comparisons test. Differences were considered significant if $P<0.05$. Values are means ± S.E.M. of n experiments, where n represents the number of ileal segments.

Results

Peristaltic reflexes evoked by mucosal stroking

In response to brush stroking the mucosa (5 strokes) in the intermediate chamber, guinea pig ileum exhibited contractions in the circular muscle layers, both orally and anally to a stimulus in 22 out of 24 trials (n = 8) (Fig. 2A). It was presumed that each contractile response is composed of about 1 – 3 units of contraction. In the remaining two trials, the oral and anal contractions were faint or within the level of the recording noise. The anal relaxation of the circular muscle to a stimulus was not recorded.

Effects of tegaserod on peristaltic reflexes

Addition of 10^{-8}, 10^{-7}, 10^{-6}, and 10^{-5} M tegaserod to the intermediate chamber did not change the pattern of peristaltic reflexes, contractions both orally and anally to a mucosal stimulus (Fig. 2A). The maximal amplitude of the oral contractions were 109.15 ± 4.06%, 110.27 ± 6.67%, 107.60 ± 7.66%, and 78.54 ± 5.59%, respectively; and those of the anal contractions were 112.48 ± 6.86%, 112.04 ± 7.22%, 99.99 ± 7.90%, 80.28 ± 11.28%, respectively, in the presence of 10^{-8}, 10^{-7}, 10^{-6}, and 10^{-5} M tegaserod. There was no significant effect of tegaserod on the maximal amplitude of the oral and anal contractions to a mucosal stimulus (Fig. 2B). The area under the curve of the oral contractions to a mucosal stimulus were 115.51 ± 6.72%, 120.64 ± 8.20%, 109.64 ± 14.62%, and 47.19 ± 6.32% of the control, respectively; and those of the anal contractions were 117.57 ± 11.75%, 114.09 ± 12.20%, 90.15 ± 16.71%, and 43.77 ± 5.60% of the control, respectively, in the presence of 10^{-8}, 10^{-7}, 10^{-6}, and 10^{-5} M tegaserod. Tegaserod at 10^{-5} M significantly decreased the area under the curve of both oral and anal contractions to a mucosal stimulus ($P<0.05$) (Fig. 2C).

TTX or GR113808 was applied to the intermediate chamber containing 10^{-7} M tegaserod. Addition of 10^{-6} M TTX abolished both oral and anal contractions to a mucosal stimulus (n = 1) (Fig. 3A), suggesting tegaserod acts on the enteric nervous system, but not

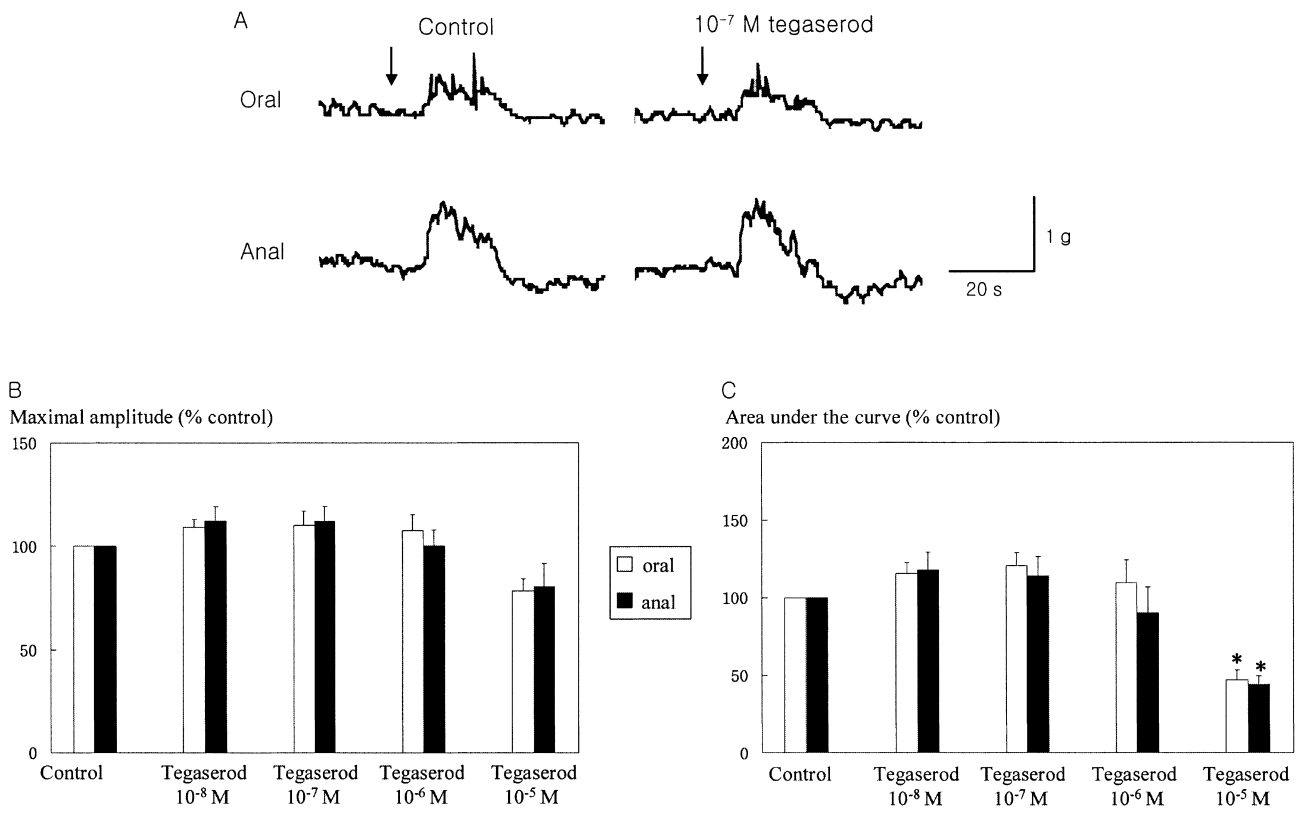

Fig. 2. Effects of tegaserod on peristaltic reflexes elicited by a mucosal stimulus. A: Mechanical recordings of the circular muscle activity elicited by a mucosal stimulus before and after addition of tegaserod. Guinea pig ileum exhibited contraction in the circular muscle both orally and anally to a stimulus. Anal relaxation was not recorded. The recordings show that addition of 10^{-7} M tegaserod to the intermediate chamber has no effect on the mechanical activity of the circular muscle. Arrows indicate the beginning of the mucosal stimulation. B and C: Tegaserod ($10^{-8} - 10^{-5}$ M) had no effect on the maximal amplitude of both oral and anal contraction. Higher concentration of tegaserod (10^{-5} M) significantly decreased the area under the curve of both oral and anal contraction. Data are expressed as percentage of control levels. Values are means ± S.E.M. of 8 experiments. *P<0.05, compared with control levels.

on smooth muscle cells. GR113808 at 10^{-6} M had no effect on the maximal amplitude and the area under the curve of both oral and anal contractions to a mucosal stimulus (n = 5) (Fig. 3: B and C).

Peristaltic waves evoked by intraluminal perfusion

Guinea pig ileum normally exhibited propagated peristaltic waves when K-H solution was pumped (0.4 mL/min) into the lumen by use of the peristaltic pump. Most of all peristaltic contractions were developed in groups, and groups of 2 – 11 contractions alternated with latency periods (Fig. 4A).

Effects of tegaserod on peristaltic waves

Addition of tegaserod induced concentration-dependent increase in the numbers of peristaltic waves (180.51 ± 26.97% at 10^{-8} M, P<0.05; 201.38 ± 27.34% at 10^{-7} M, P<0.05; 230.52 ± 32.47% at 10^{-6} M, P<0.05) (Fig. 4B). The area under the curve of peristaltic waves measured by mid tension transducer were 169.66 ± 23.37% (P<0.05), 151.36 ± 18.82% (P<0.05), and 164.55 ± 22.88% (P<0.05) of the control, respectively, in the presence of 10^{-8}, 10^{-7}, and 10^{-6} M tegaserod (Fig. 4C). Tegaserod did not increase the amplitude of peristaltic waves as seen in Fig. 4A. The results obtained by the oral and anal tension transducer were similar with that obtained by the mid tension transducer (data not seen). Addition of tegaserod had no effect on the resting tone of the circular muscle (94.85 ± 3.56% at 10^{-8} M, 96.49 ± 2.78% at 10^{-7} M, 93.77 ± 2.96% at 10^{-6} M).

Addition of 10^{-6} M TTX to the bathing solution and perfusion fluid in the 10^{-7} M tegaserod-treated preparation abolished peristaltic waves (Fig. 5A). Addition of 10^{-6} M atropine induced faint contractile activity, suggesting that the contractile responses of the circular muscle are mainly generated by the release of Ach from excitatory motor neurons (Fig. 5A). By addition of 10^{-6} M GR113808, the number and the area under the curve of peristaltic waves were 67.58 ± 7.58% (P<0.05)

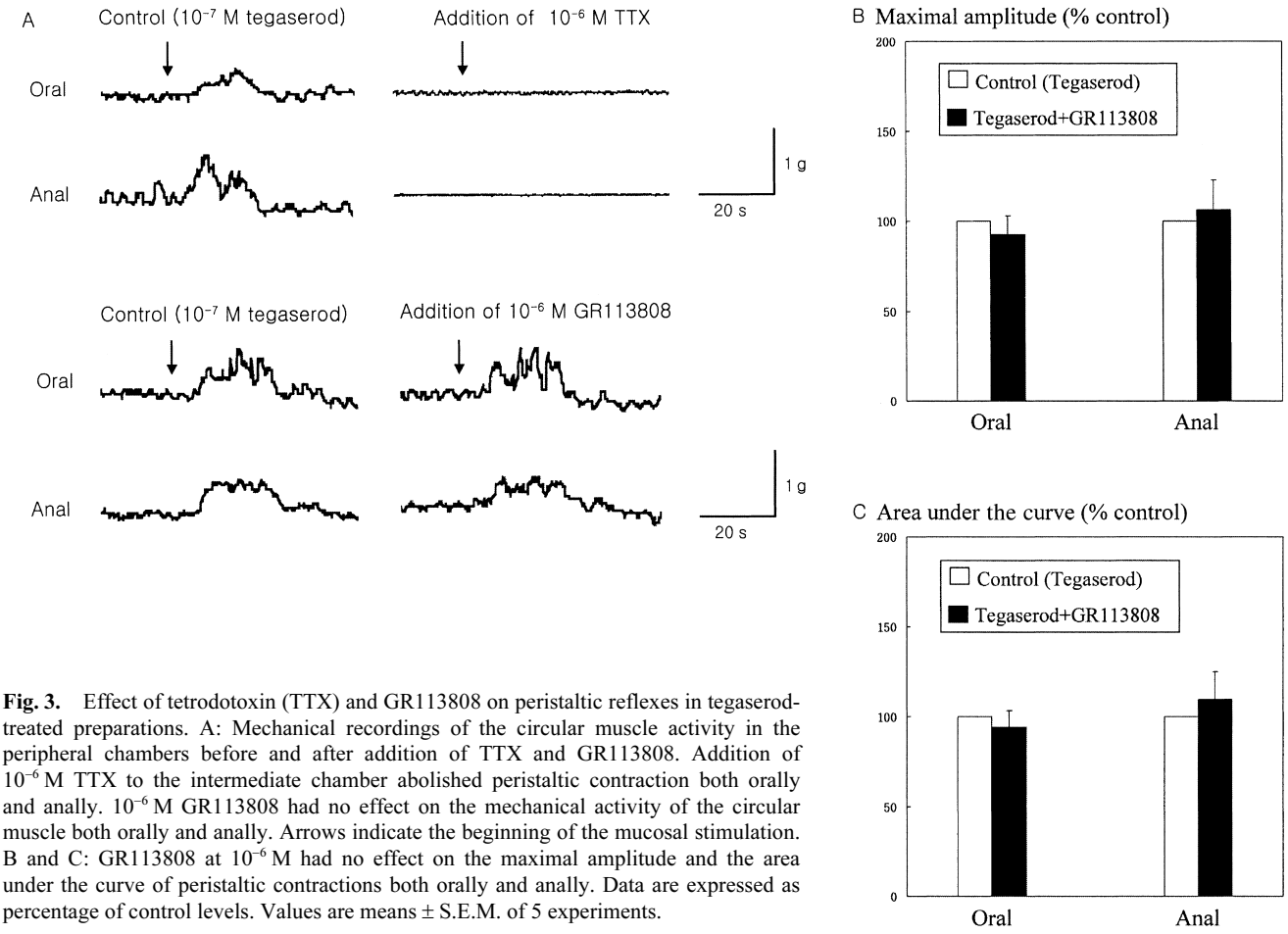

Fig. 3. Effect of tetrodotoxin (TTX) and GR113808 on peristaltic reflexes in tegaserod-treated preparations. A: Mechanical recordings of the circular muscle activity in the peripheral chambers before and after addition of TTX and GR113808. Addition of 10^{-6} M TTX to the intermediate chamber abolished peristaltic contraction both orally and anally. 10^{-6} M GR113808 had no effect on the mechanical activity of the circular muscle both orally and anally. Arrows indicate the beginning of the mucosal stimulation. B and C: GR113808 at 10^{-6} M had no effect on the maximal amplitude and the area under the curve of peristaltic contractions both orally and anally. Data are expressed as percentage of control levels. Values are means ± S.E.M. of 5 experiments.

and 71.82 ± 8.21% (P<0.05) of the control, respectively (n = 5) (Fig. 5B).

Discussion

This study shows that tegaserod, a selective 5-HT_4-receptor agonist, stimulates peristalsis in guinea pig ileum by increasing the number of circular muscle contractions. The types of stimulated sensory neurons may be different between the two sets of our experiments. In the peristaltic reflex experiments, stimulation of the mucosal sensory neurons by brush stroking might elicit peristaltic reflexes. On the other hand, in the peristaltic wave experiments, stimulation of the mechanoreceptors by distension of the bowel might evoke propagating peristaltic waves. However, the results derived from both experiments do not seem to have a different meaning, since both types of sensory neuron converge onto the same population of motoneurons in the circular muscle (16). The fact that tegaserod increases the area under the curve of peristaltic waves is a result of an increase in the number of contractions by addition of tegaserod, because tegaserod had no effect on the amplitude of peristaltic waves induced by intraluminal perfusion. In the peristaltic reflex experiments, tegaserod did not increase the maximal amplitude and the area under the curve of both oral and anal contractions to a stimulus. The discreptancy between our two sets of experiments for the effect of tegaserod on the area under the curve is thought to be reasonable, because in the peristaltic reflexes experiments, the area under the curve of about 1 – 3 contraction(s) induced by a mucosal stimulus orally and anally was measured, while in the peristaltic wave experiments, the area under the curve of multiple propagating peristaltic waves induced by intraluminal perfusion was measured. Therefore, the results of this study suggest that tegaserod (10^{-8} – 10^{-6} M) exerts a prokinetic effect on the circular muscle of guinea pig ileum by increasing the number of peristaltic waves, but has no effect on the mechanical activity of an individual peristaltic wave.

The present finding that tegaserod had no effect on the maximal amplitude of the circular muscle contractions induced by a mucosal stimulus both orally and

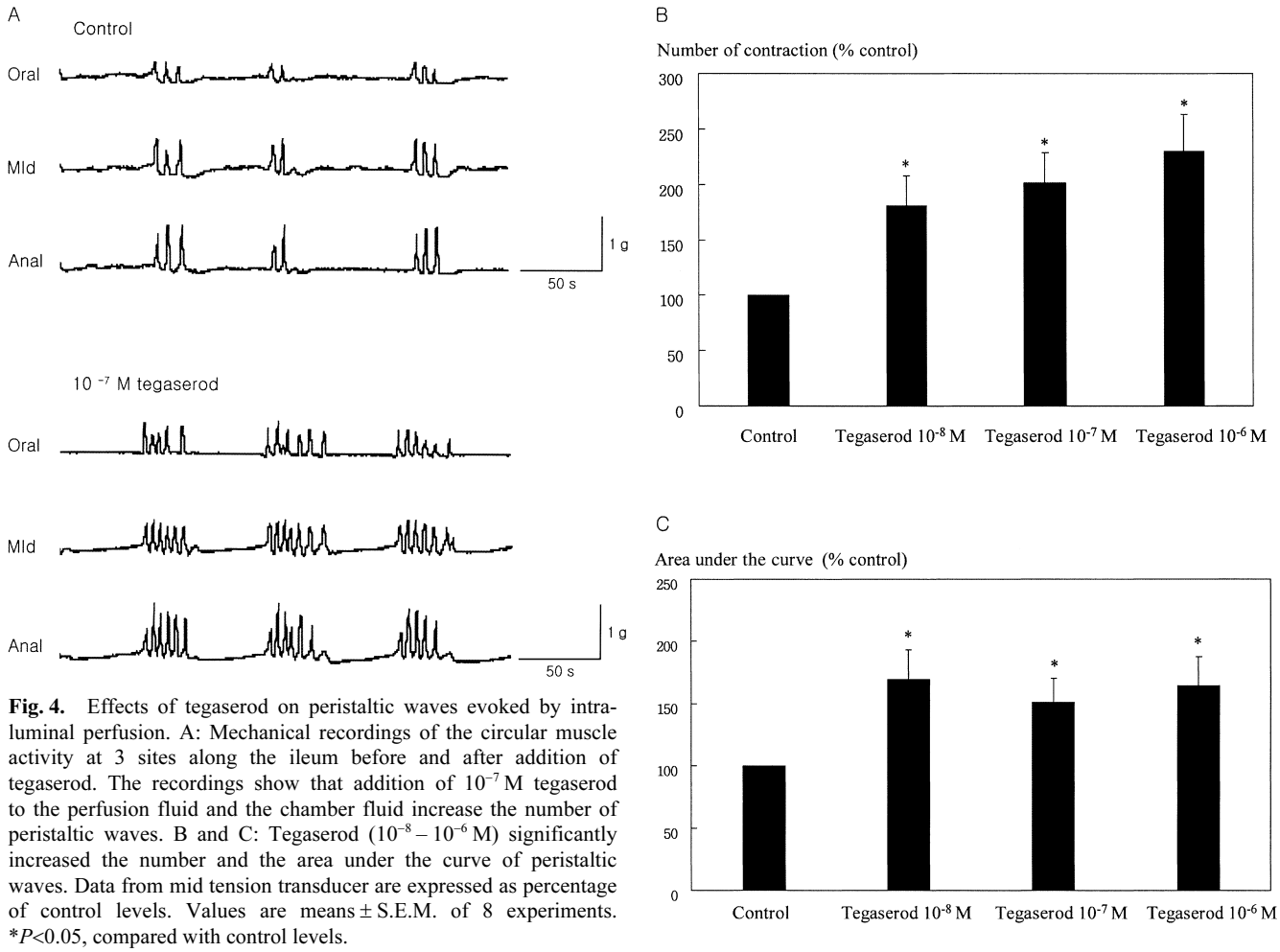

Fig. 4. Effects of tegaserod on peristaltic waves evoked by intraluminal perfusion. A: Mechanical recordings of the circular muscle activity at 3 sites along the ileum before and after addition of tegaserod. The recordings show that addition of 10^{-7} M tegaserod to the perfusion fluid and the chamber fluid increase the number of peristaltic waves. B and C: Tegaserod ($10^{-8} - 10^{-6}$ M) significantly increased the number and the area under the curve of peristaltic waves. Data from mid tension transducer are expressed as percentage of control levels. Values are means ± S.E.M. of 8 experiments. *P<0.05, compared with control levels.

anally differs from the previous study of Grider et al. (6) In their study, it was found that addition of tegaserod in guinea pig and rat colon caused concentration-dependent changes of the circular muscle tension in the oral and anal side of a mucosal stimulus. Several possibilities should be considered. First, the region of bowel used in the two studies was different from each other. In the guinea pig, it was known that there are the differences in the classes of interneurons between the colon and the small intestine (17, 18). Second, it is possible that desensitization of the 5-HT_4 receptors occurred in our experiments, since we preincubated tegaserod for a relatively prolonged period. While the guinea pig 5-HT_4 receptors have been less well characterized, the presence of the rapidly desensitizing isoform has been demonstrated in the GI tract (19).

In this study, brush stroking the mucosa (5 strokes) elicited contractions of the circular muscle both above (ascending excitation) and below (descending excitation) the site of stimulation. The anal relaxation of the circular muscle to a stimulus was not recorded. Generally, it has been known that peristalsis in the small and large intestine consists of activation of ascending excitatory and descending inhibitory reflex pathways that produce an oral contraction and anal relaxation of circular muscle layer behind and in front of a bolus (20, 21). In the guinea pig ileum, both oral contraction and anal relaxation have been identified repeatedly in electrophysiological studies of reflexes evoked by distension and mechanical or chemical stimulation of the mucosa (22 – 25). However, in addition to ascending excitatory and descending inhibitory pathways, there is evidence for descending excitatory pathways (22). Moreover, in agreement with our results, recent studies of Spencer et al. (14, 26) have demonstrated that local physiological stimulation of guinea pig ileum elicited a contraction both orally and anally to a stimulus, which occurs synchronously in both the circular muscle and longitudinal muscle layers. They confirmed that the inhibitory response (relaxation) did not occur regardless of the distances anal to a stimulus or the level of resting tone applied to the muscles (26). We did not investigate

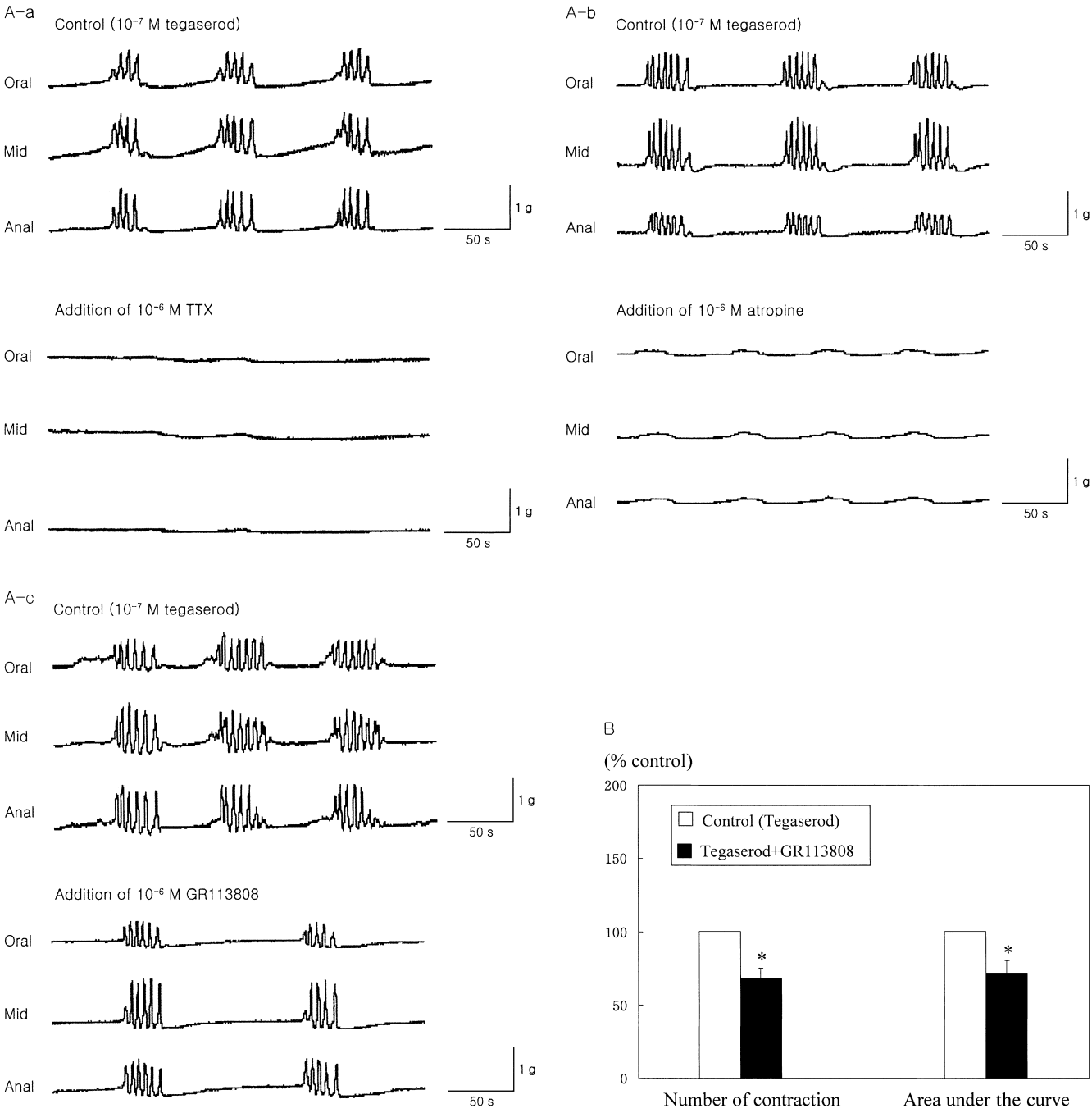

Fig. 5. Effects of TTX, atropine, and GR113808 on peristaltic waves in tegaserod-treated preparations. A: Mechanical recordings of the circular muscle activity before and after addition of TTX (a), atropine (b), and GR113808 (c). TTX at 10^{-6} M abolished peristaltic waves. Addition of 10^{-6} M atropine induced faint contractile activity. GR113808 at 10^{-6} M decreased the number of peristaltic waves. B: GR113808 at 10^{-6} M significantly decreased the number and the area under the curve of peristaltic waves. Data from mid tension transducer are expressed as percentage of control levels. Values are means ± S.E.M. of 5 experiments. *P<0.05, compared with control levels.

furthermore why anal relaxation did not occur, since the investigation is beyond the aims of this study. Further studies are needed to elucidate why the results are different between electrophysiological studies (22 – 25) and the studies of Spencer et al. (14, 26) in which the smooth muscle activity was evaluated by use of a tension transducer as in this study.

As expected, addition of TTX (10^{-6} M) in the 10^{-7} M tegaserod-treated preparation abolished propagated peristaltic waves elicited by intraluminal perfusion and

both oral and anal contractions to a mucosal stimulus by brush stroking, suggesting that tegaserod acts on the enteric nervous system, but not on smooth muscle cells. Although the selective 5-HT_4-receptor antagonist GR113808 had no effect on the maximal amplitude and the area under the curve of the oral and anal contractions to a mucosal stimulus in the tegaserod-treated preparation, it significantly decreased the number and the area under the curve of peristaltic waves. Together with the results that tegaserod increases the number of peristaltic contractions but not the amplitude, these results suggest that the 5-HT_4 receptors are mainly involved in the modulation of the frequency of peristaltic contraction but not the contractility of circular muscle during peristalsis in the guinea pig ileum.

Higher concentration of tegaserod (10^{-5} M) significantly decreased the area under the curve of both oral and anal contractions to a mucosal stimulus in this study. Similarly, an in vitro study of Jin et al. (9) showed that higher concentration of tegaserod did not elicit an increase in velocity of fecal pellet propulsion in guinea pig colon. A possibility is that there may be the desensitization of 5-HT_4 receptors located on the sensory neurons in the presence of higher concentration of tegaserod. This hypothesis can be derived from the study of Grider et al. (27). They demonstrated that the ability of tegaserod to cause desensitization is dependent on the concentration of, and time of exposure to, tegaserod in rat colon. Jin et al. (9) postulated that at higher concentrations of tegaserod, an increase in the velocity of propulsion was offset by the direct relaxant effect of tegaserod on the smooth muscle. The fact that higher concentrations of tegaserod have a direct relaxant effect on the smooth muscle could be another explanation for the result of this study, since muscle tone is important not only for initiation but also for maintenance of peristalsis (28).

Although tegaserod increased the number of circular muscle contractions during peristalsis in our study, the mechanism is still unclear. An in vitro study of Costall et al. (29) may explain the action mechanism of tegaserod in the GI tract. In their study, addition of 5-HT ($10^{-7} - 10^{-6}$ M) to guinea pig ileum caused a decrease in the threshold pressure required to trigger peristaltic reflexes; and in the 5-HT-treated preparations, the magnitude of the reduction of the threshold was decreased by addition of the selective 5-HT_4-receptor antagonist SDZ 205 – 557. These results imply that stimulation of the 5-HT_4 receptor decreases the threshold pressure required to trigger peristaltic reflexes. Accordingly, stimulation of the 5-HT_4 receptor by tegaserod may decrease the threshold and consequently, decrease the intervals between peristaltic waves. Further studies are needed to investigate how tegaserod increases the number of circular muscle contractions during peristalsis.

In conclusion, it is suggested that tegaserod exerts prokinetic action on the guinea pig ileum by increasing the number of circular muscle contractions during peristalsis, although it has no effect on the mechanical activity of an individual peristaltic wave.

Acknowledgments

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