Combined Blockade of 5-HT$_3$- and 5-HT$_4$-Serotonin Receptors Inhibits Colonic Functions in Conscious Rats and Mice

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ABSTRACT
We have already reported that 5-hydroxytryptamine 3 (5-HT$_3$) receptor antagonists failed to modify 5-HT-accelerated colonic transit in conscious rats, but the 5-HT$_3$ and 5-HT$_4$ receptor dual antagonist FK1052 prevented the enhancement. In this study, the inhibitory effect on the stimulated colonic transit was not also observed with 5-HT$_4$ receptor antagonists (SDZ205-557 and SB204070) in freely moving rats with chronic cannulas implanted into the proximal colon. In contrast, combined antagonism by simultaneous administration of ondansetron and the 5-HT$_4$ receptor antagonist exerted a drastic inhibitory effect on the propulsive motility. Furthermore, we examined the effect of 5-HT receptor antagonists on 5-HT-induced fluid secretion in mice. Although none of these selective 5-HT receptor antagonists (YM060 and ondansetron as 5-HT$_3$ receptor antagonist, SB204070 as 5-HT$_4$ receptor antagonist) by itself produced a great inhibition of the 5-HT-induced diarrhea, the combination of a 5-HT$_3$ receptor antagonist and a 5-HT$_4$ receptor antagonist markedly reduced the diarrhea. These data suggest that 5-HT-accelerated colonic motility and 5-HT-evoked fluid secretion are mediated by both 5-HT$_3$ and 5-HT$_4$ receptors and that the pathways activated by these receptors may collaborate.

Gershon et al. (1965) showed that 5-HT might be a neurotransmitter of the enteric nervous system. 5-HT is secreted from enterochromaffin cells of the epithelium in response to a variety of luminal stimuli, which activate the neuronal circuit within the gastrointestinal wall (Bulbring and Lin, 1958; Bulbring and Crema, 1959a,b). 5-HT has many different types of actions on the gut and, in particular, has been proposed to play a critical role in the mediation of the peristaltic reflex and in electrolyte transport by acting at 5-HT receptors in the enteric nervous system (Gershon et al., 1994; Cooke and Reddix, 1994).

Electrophysiological studies on GI motility have revealed the presence of at least three excitatory subtypes of 5-HT receptor (5-HT$_1P$, 5-HT$_3$ and 5-HT$_4$) on myenteric neurons of the guinea pig intestine (Mawe et al., 1986; Wade et al., 1994; Craig and Clarke, 1990; Pan and Galligan, 1994), but it is not yet clear which subtypes are of physiological significance in GI motility. The mediation of a slow excitatory response has been associated only with the 5-HT$_1P$ receptor (Mawe et al., 1986), which mediates the peristaltic reflex and in electrolyte transport by acting at 5-HT receptors in the enteric nervous system (Gershon et al., 1994; Cooke and Reddix, 1994).

In terms of electrolyte transport, 5-HT is a strong secretagogue in the gut and produces an increase in $I_{sc}$, indicative of chloride secretion by stimulation of some 5-HT receptor subtypes. For example, it has been shown that the $I_{sc}$ response to 5-HT in guinea pig ileum consists of two components, one sensitive to TTX and mediated by 5-HT$_3$ receptors and the other insensitive to TTX and mediated in part by 5-HT$_4$ receptors (Scott et al., 1992), and that in guinea pig distal colon, the $I_{sc}$ is mediated by neural 5-HT$_3$ receptors (Cooke et al., 1991). On the other hand, in tissues such as rat colon (Bunce et al., 1991), human jejunum (Kellum et al., 1994) and ileum (Borman and Burleigh, 1993) 5-HT seems to induce an increase in the $I_{sc}$ by stimulating non-neural 5-HT$_4$ receptors. Thus there are many reports of in vitro studies showing an involvement of 5-HT$_3$ and 5-HT$_4$ receptors in secretory response to 5-HT, but are few in vivo studies.

Many questions about enteric 5-HT receptors remain to be answered. These questions have only recently begun to be addressed, because an experimental approach using selective 5-HT$_3$ receptor antagonists and selective 5-HT$_4$ receptor antagonists has enabled us to investigate the role of 5-HT receptors in gastrointestinal function.

The purpose of this study was to determine, in animal

ABBRVIATIONS: 5-HT, 5-hydroxytryptamine; TTX, tetrodotoxin; 5-HTP-DP, 5-hydroxytryptophyl-5-hydroxytryptophan amide; $I_{sc}$, short-circuit current; ENS, enteric nervous system.
models in vivo, whether 5-HT$_3$ and/or 5-HT$_4$ receptors are involved in colonic function and, if so, whether there are additive, synergistic or nullifying effects of activating or inhibiting these subtypes of enteric 5-HT receptor.

**Materials and Methods**

**Animals.** Male Sprague-Dawley rats (211–331 g; Charles River Japan, Hino, Japan) and male ddY strain mice (29–37 g; Japan SLC, Hamamatsu, Japan) were used in these studies. Before experiments, animals were housed under standard controlled environmental conditions, with 12-hr light/dark cycles. Animals were allowed at least 1 week to acclimate to the environment before the experiments were performed. The animals were allowed food and water ad libitum while housed. Mice, but not rats were deprived of food overnight before the experiment but were allowed free access to water.

**5-HT-accelerated transit in rat colon.** After rats were anesthetized with pentobarbital (50 mg/kg i.p.), a chronic indwelling polyethylene cannula (I.D., 0.58 mm; O.D., 0.97 mm; PE-50, Becton, Dickinson and Co., Parsippany, NJ) was implanted into the proximal colon about 1.5 cm from the ileocecal junction. The cannula was led s.c. to the interscapular region of the animal’s neck. The abdominal incision was closed with a suture. Rats were individually housed and allowed to recover from surgery for 5 days. The experiments were performed in conscious and freely moving rats. 5-HT (1 mg/kg) or normal saline was administered s.c. 20 min before gentle infusion of carmine red (0.3 ml; 3 g carmine red and 5 g arabic gum in 50 ml of 0.5% methylcellulose) as a nonabsorbable marker into the proximal colon through the implanted cannula. Ondansetron was administered p.o. and SB204070 or SDZ205-557 was injected s.c. 30 min before 5-HT administration. Twenty minutes after the injection of 5-HT (or saline in controls), the animals were sacrificed, and the entire colon was carefully and quickly removed. The length of colon marked by carmine red was measured and expressed as percent of total length of colon.

**5-HT-induced diarrhea in mice.** The experiments were carried out as previously reported (Kadowaki et al., 1993). Evaluation of diarrhea was made 15 min after the i.p. administration of 5-HT (0.32 mg/kg). Diarrhea was defined as wet and unformed stools and was scored as present or absent for each animal. The occurrence of diarrhea was noted, and the incidence of diarrhea (number of mice with diarrhea/total number of mice tested) was calculated as a percentage. 5-HT (0.32 mg/kg i.p.) caused diarrhea in 80% to 100% of the fasted mice within 15 min. Ondansetron and YM060 were administered p.o. and SB204070 was injected s.c. 30 min before 5-HT administration.

**Statistics.** Values for the experiments in rats represent mean ± S.E.M. Group data were compared by analysis of variance (ANOVA) followed by Dunnnett’s Multiple Range test. Chi-square analysis was used in mice to compare the incidence of diarrhea and to determine the statistical significance of differences between the groups. Probability values < .05 were considered statistically significant.

**Drugs.** Ondansetron, YM060, SDZ205-557 and SB204070 were synthesized by Fujisawa Pharmaceutical Co., Ltd., Osaka, Japan. 5-HT creatinine sulfate was purchased from E. Merck (Darmstadt, Germany). Ondansetron, YM060 and SB204070 were dissolved in distilled water. SDZ205-557 was initially dissolved in equivalent 0.1 N HCl and was then diluted in physiological saline. 5-HT was dissolved in saline. The drugs were administered at a volume of 2.0 ml/kg in rat and 5.0 ml/kg in mouse.

**Results**

**Effect of 5-HT$_4$ receptor antagonist on 5-HT-accelerated colonic transit in rats.** The submaximal effective dose (1 mg/kg) of 5-HT was used to examine the effects of the test drugs on 5-HT-accelerated colonic transit in rats, as reported previously (Kadowaki et al., 1993). 5-HT (1 mg/kg s.c.) accelerated the colonic transit of carmine red about 30% above the basal rate with vehicle alone (fig. 1). Two 5-HT$_4$ receptor antagonists, SDZ205-557 (0.05 mg/kg s.c.; fig. 1) and SB204070 (0.1 mg/kg; fig. 2), had no effect on 5-HT-accelerated colonic transit in conscious rats at moderately high concentrations. When the dose of SDZ205-557 was increased to 10.0 mg/kg, a significant inhibition (66%) was obtained (fig. 1), but at this concentration, SDZ205-557 may have other, nonspecific effects. It is notable that the more potent and selective 5-HT$_4$ receptor antagonist, SB204070, had no effect on the colonic transit.

**Effect of the combination of ondansetron and 5-HT$_4$ receptor antagonist on 5-HT-accelerated colonic transit in rats.** The inhibition of colonic transit that was observed after the administration of a high dose of SDZ205-557 (see the account above and Fig.) agreed with previous observations of the effects of FK1052 (Kadowaki et al., 1993). However, these drugs have activities at both 5-HT$_3$ and 5-HT$_4$ receptors. We therefore tested the hypothesis that both 5-HT$_3$ and 5-HT$_4$ receptors participate in the 5-HT-induced acceleration of colonic motility by employing the selective 5-HT$_3$ receptor antagonist ondansetron (3.2 mg/kg p.o.) and the selective 5-HT$_4$ receptor antagonist SDZ205-557 (3.2 mg/kg s.c.) individually and in combination. Alone, neither ondansetron nor SDZ205-557 affected 5-HT-stimulated colonic transit, but when administered together, the drugs inhibited the stimulated transit by 88% (fig. 3). Furthermore, simultaneous administration of ondansetron (3.2 mg/kg p.o.) and the more potent and selective 5-HT$_4$ receptor antagonist

![Figure 1](https://jpet.aspetjournals.org/doi/fig/10.1124/jpet.1997.285.8.1)
SB204070 (0.1–1.0 mg/kg, s.c.) also had a strong inhibitory effect (0.1 mg/kg, 112% inhibition; 1.0 mg/kg, 90% inhibition; fig. 4).

**Table 1.**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Colonic Transit (%)</th>
<th>p-value</th>
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</thead>
<tbody>
<tr>
<td>Normal</td>
<td>80</td>
<td></td>
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<tr>
<td>5-HT (1 mg/kg)</td>
<td>60</td>
<td></td>
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<tr>
<td>SB204070 (0.1 mg/kg)</td>
<td>40</td>
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Fig. 2. The 5-HT₄ antagonist SB204070 does not alter 5-HT-accelerated colonic transit in conscious rats. Test drug or distilled water as a control and a normal was administered 30 min before 5-HT injection (1 mg/kg s.c.). The normal group was given saline instead of 5-HT. The distance traveled by the nonabsorbable marker carmine red in the 20 min after 5-HT injection was measured. The ratio of the length of the colon marked by carmine red to the total length of the colon was recorded, and the data are expressed as the mean value ± S.E.M. for 14 to 18 animals. **P < .01 compared with the 5-HT-treated control group.

Fig. 3. The combined administration of ondansetron (3.2 mg/kg p.o.) and SDZ205-557 (3.2 mg/kg s.c.) abolishes 5-HT-accelerated colonic transit in conscious rats. Test drugs or vehicle as a control and a normal were administered 30 min before 5-HT (1 mg/kg s.c.) injection. The normal group was given saline instead of 5-HT. The distance traveled by the nonabsorbable marker carmine red in the 20 min after 5-HT injection was measured. The ratio of the length of the colon marked by carmine red to the total length of the colon was recorded, and the data are expressed as the mean value ± S.E.M. for 19 to 22 animals. *P < .05 and **P < .01 compared with the 5-HT-treated control group.

Fig. 4. The combined administration of ondansetron (3.2 mg/kg p.o.) and SB204070 (0.1 or 1.0 mg/kg s.c.) abolishes the 5-HT-induced acceleration of colonic transit in conscious rats. Test drugs or distilled water as a control and a normal were administered 30 min before 5-HT (1 mg/kg s.c.) injection. The normal group was given saline instead of 5-HT. The distance traveled by the nonabsorbable marker carmine red in the 20 min after 5-HT injection was measured. The ratio of the length of the colon marked by carmine red to the total length of the colon was recorded, and the data are expressed as the mean value ± S.E.M. for 14 to 26 animals. **P < .01 compared with the 5-HT-treated control group. †P < .05 and ††P < .01 compared with the combined group.

SB204070 (0.1–1.0 mg/kg, s.c.) also had a strong inhibitory effect (0.1 mg/kg, 112% inhibition; 1.0 mg/kg, 90% inhibition; fig. 4).

**Effect of 5-HT₄ receptor antagonist on 5-HT-induced diarrhea in mice.** The submaximal effective dose (0.32 mg/kg) of 5-HT was used to examine the effects of the test drugs on 5-HT-evoked diarrhea in mice, as reported previously...
The i.p. administration of 5-HT (0.32 mg/kg) induced diarrhea in more than 80% of fasted mice. Effects of the 5-HT<sub>4</sub> receptor antagonists SDZ205-557 and SB204070 on 5-HT-induced diarrhea were tested. At low concentrations, neither SDZ205-557 (≤ 3.2 mg/kg s.c.; fig. 5) nor SB204070 (≤ 0.32 mg/kg s.c.; fig. 6) had an inhibitory effect on 5-HT-induced diarrhea. A reduction in the incidence of 5-HT-induced diarrhea was observed when a higher dose of SDZ205-557 (10 mg/kg s.c.; 33% decrease; fig. 5) or SB204070 (1.0 mg/kg s.c.; 38% decrease; fig. 6) was used.

**Effect of the combination of 5-HT<sub>3</sub> receptor antagonist and 5-HT<sub>4</sub> receptor antagonist on 5-HT-induced diarrhea in mice.** The observation that the combined antagonistic effects of 5-HT<sub>3</sub> and 5-HT<sub>4</sub> receptors were necessary to inhibit 5-HT-induced diarrhea prompted us to examine the role of these two 5-HT receptors in 5-HT-stimulated fluid secretion. First, the effect of the combined administration of ondansetron (3.2 mg/kg p.o.) and SB204070 (1.0 mg/kg s.c.) on 5-HT-evoked diarrhea was examined, because the same treatment almost completely abolished 5-HT-accelerated colonic transit in rats (fig. 4). A decrease in 5-HT-induced diarrhea was observed when either ondansetron (36% inhibition) or SB204070 (25% inhibition) was administered alone (fig. 7). The combined administration of ondansetron and SB204070 appeared to be additive, inhibiting 5-HT-induced diarrhea by 60% (fig. 7). However, in contrast to the colonic transit study, the combination of selective 5-HT<sub>3</sub> and 5-HT<sub>4</sub> receptor antagonists did not abolish the 5-HT-induced effect. To determine further the effects of combining 5-HT<sub>3</sub> and 5-HT<sub>4</sub> receptor antagonism, we tested the combination of a more potent 5-HT<sub>3</sub> receptor antagonist, YM060 (0.032–0.32 mg/kg p.o.), and SB204070 (0.001–0.1 mg/kg s.c.). The administration of YM060 alone at 0.032 mg/kg was maximally effective at reducing the incidence of diarrhea (50% inhibition, fig. 8). The combined administration of SB204070 (0.01–0.1 mg/kg s.c.), which by itself had no effect, with YM060 resulted in a marked decrease in the incidence of 5-HT-induced diarrhea; complete inhibition of the 5-HT response was obtained when YM060 at 0.32 mg/kg p.o. was combined with SB204070 at 0.1 mg/kg s.c. (fig. 8).
Discussion

In the present in vivo study, we have demonstrated that 5-HT accelerates colonic transit in rats and evokes diarrhea in mice through the activation of both 5-HT$_3$ and 5-HT$_4$ receptors. Both of these subtypes of 5-HT receptor have been located in the ENS (Craig and Clarke, 1990; Kilbinger and Wolf, 1992), and our observations therefore suggest that neural pathways involving both receptors mediate the actions of 5-HT in colonic motility and/or secretion.

Physiological studies have revealed that 5-HT is an important signaling molecule in the initiation of the peristaltic reflex (Bulbring and Lin, 1958; Bulbring and Crema, 1959a and b; Wade et al., 1996) and in the stimulation of secretory processes in the gut (Cooke and Reddix, 1994). Both 5-HT$_3$ and 5-HT$_4$ receptors mediate excitatory responses in enteric neurons (Wade et al., 1994; Pan and Galligan, 1994).

The 5-HT$_3$ receptor is a ligand-gated cation-conducting channel (Derakh et al., 1989) that mediates a transient excitatory response to 5-HT (Vanner and Surprenant, 1990; Wade et al., 1994). This receptor has been reported to regulate an ascending excitatory reflex that can be elicited by mucosal stimulation in the small intestine (Neya et al., 1993; Yuan et al., 1994). The observation that administration of either 5-HT or the selective 5-HT$_3$ agonist 2-methyl-5-HT enhances the colonic transit in conscious rats lends support to the idea that 5-HT$_3$ receptors mediate the stimulation of GI motility; however, the discovery that neither ondansetron (pK$_i$ = 8.9 for 5-HT$_3$ receptor, Akuzawa et al., 1995; pK$_i$ = 5.2 for 5-HT$_4$ receptor; Miyata et al., 1995) nor granisetron (pK$_i$ = 9.5 for 5-HT$_3$ receptor, Akuzawa et al., 1995; pK$_i$ = 5.6 for 5-HT$_4$ receptor, Miyata et al., 1995), two potent and selective 5-HT$_3$ receptor antagonists, was effective in blocking 5-HT-stimulated colonic transit indicates that other pathways besides those containing 5-HT$_3$ receptors must exist (Kadowaki et al., 1993). These findings are consistent with other evidence that 5-HT$_3$ receptor-selective ligands, 2-methyl-5-HT, tropisetron (in the 5-HT$_3$-selective concentration range, $10^{-9}$ to $10^{-7}$ M) and granisetron, do not affect peristaltic responses (Buchheit and Buhl, 1991; Wade et al., 1996). Likewise, peristaltic contractions evoked in the isolated guinea pig ileum by the application of exogenous 5-HT are not blocked by a low concentration of tropisetron, nor are they inhibited by granisetron (Buchheit and Buhl, 1991) or ondansetron (Craig and Clarke, 1991).

Intracellular electrophysiological studies have revealed that 5-HT$_4$ receptors presynaptically facilitate nicotinic synaptic transmission in the myenteric plexus of guinea pig ileum (Pan and Galligan, 1994). 5-HT$_4$ receptor agonists have been reported to produce contractile responses in the guinea pig ascending and distal colon (Eglen et al., 1991; Kadowaki et al., 1992; Wardle and Sanger, 1993) and to accelerate colonic transit in conscious rats (Kadowaki et al., 1993). Furthermore, 5-HT-stimulated peristaltic reflexes in the guinea pig ileum are antagonized by the 5-HT$_4$ receptor antagonist SDZ205-557 (Costall et al., 1993). These data are consistent with the idea that 5-HT$_4$ receptors are, like 5-HT$_3$ receptors, involved in the enteric neural circuitry that is responsible for mediating the peristaltic reflex. In the present study, we tested the hypothesis that 5-HT$_4$ receptors are involved in enteric motor functions in the colon by using the selective 5-HT$_4$ receptor antagonists SDZ205-557 (pA$_2$ = 7.8 for 5-HT$_4$ receptor, Wardle and Sanger, 1993; pK$_i$ = 6.9 for 5-HT$_4$ receptor, Eglen et al., 1991) and SB204070 (pA$_2$ = 10.7–11.1 for 5-HT$_4$ receptor; pK$_i$ = 6.4–6.8 for 5-HT$_4$ receptor; Wardle et al., 1994). Banner et al. (1993) reported that SDZ205-557 at a dose of 5 mg/kg produced the maximum inhibition of 5-HTP (10 mg/kg s.c.)-induced fecal pellet output in mice and that SB204070 inhibited the 5-HTP responses at doses of 0.0003 to 1 mg/kg. Therefore, the doses 1 to 10 mg/kg of SDZ205-557 and 0.01 to 3.2 mg/kg of SB204070 were employed in the present study.

Neither SB204070 (0.01–1 mg/kg s.c.) nor SDZ205-557 (at doses up to 3.2 mg/kg s.c.) had an effect on 5-HT-induced colonic transit. However, at a high dose (10 mg/kg s.c.), SDZ205-557 reduced the 5-HT-stimulated colonic transit by 66%, an action that is likely to be due to the simultaneous antagonism of both 5-HT$_3$ and 5-HT$_4$ receptors, because neither the 5-HT$_4$ receptor antagonist ondansetron nor the more potent and selective 5-HT$_4$ receptor antagonist SB204070 significantly inhibited the 5-HT-stimulated transit. This interpretation is supported by recent studies in which a high dose (10 µmol/kg) of SDZ205-557 inhibited 5-HT$_4$ receptor-mediated bradycardia response (Franks et al., 1995); furthermore, the selectivity of SDZ205-557 for 5-HT$_3$ and 5-HT$_4$ receptors has been demonstrated to be similar in rat, but not guinea pig (Eglen et al., 1993). Thus the high dose of SDZ205-557 that we employed probably affects both 5-HT$_3$ and 5-HT$_4$ receptors in rats. In our own study, FK1052, another 5-HT$_4$ dual antagonist, greatly inhibited 5-HT-stimulated transit; however, when the drugs were given simultaneously, they slowed transit in a synergistic manner. Moreover, a similar result was obtained with ondansetron and SB204070.
These results are consistent with the idea that the effector pathways activated by 5-HT₃ and 5-HT₄ receptors interact in a cooperative manner to regulate colonic transit. 5-HT₃ receptors are located at cell bodies (Derkach et al., 1989; Wade et al., 1994), and 5-HT₄ receptors may be located at nerve endings of cholinergic interneurons because stimulation of 5-HT₄ receptors enhances nicotinic fast excitation postjunctional potentials in enteric neurons (Pan and Galligan, 1994). In addition, it has been shown that stimulation of both 5-HT₃ and 5-HT₄ receptors mediates a release of ACh in the guinea pig myenteric plexus (Kilbinger and Wolfe, 1992). These data suggest that 5-HT can stimulate colonic transit through the activation of either presynaptic 5-HT₄ receptors or postsynaptic 5-HT₃ receptors. The failure of selective antagonism of either 5-HT₃ or 5-HT₄ receptors to inhibit 5-HT-mediated responses might suggest that the receptors are not arranged in series in the enteric microcircuit(s) critical to the response of the organ to exogenous 5-HT.

5-HT increases Iₑ in several species, such as rat (Bunce et al., 1991), guinea pig (Scott et al., 1992), pig (Hansen et al., 1994) and human (Borman and Burleigh, 1993; Kellum et al., 1994). Hypersecretion induced by cholera toxin (Beubler and Horina, 1990) and the diarrhea in patients with carcinoid syndrome (Gustafsen et al., 1986; Anderson et al., 1987; Platt et al., 1992) were partly reduced by 5-HT receptor antagonists. These findings strongly indicate that 5-HT is a potent secretagogue in the gut. In the present study, the administration of 5-HT (0.32 mg/kg i.p.) to mice caused diarrhea in the gut. In the present study, the administration of 5-HT (0.32 mg/kg i.p.) to mice caused diarrhea in the gut. In the present study, the administration of 5-HT (0.32 mg/kg i.p.) to mice caused diarrhea in the gut. In the present study, the administration of 5-HT (0.32 mg/kg i.p.) to mice caused diarrhea in the gut. In the present study, the administration of 5-HT (0.32 mg/kg i.p.) to mice caused diarrhea in the gut. In the present study, the administration of 5-HT (0.32 mg/kg i.p.) to mice caused diarrhea in the gut. In the present study, the administration of 5-HT (0.32 mg/kg i.p.) to mice caused diarrhea in the gut. In the present study, the administration of 5-HT (0.32 mg/kg i.p.) to mice caused diarrhea in the gut. In the present study, the administration of 5-HT (0.32 mg/kg i.p.) to mice caused diarrhea in the gut. In the present study, the administration of 5-HT (0.32 mg/kg i.p.) to mice caused diarrhea in the gut. In the present study, the administration of 5-HT (0.32 mg/kg i.p.) to mice caused diarrhea in the gut. In the present study, the administration of 5-HT (0.32 mg/kg i.p.) to mice caused diarrhea in the gut. In the present study, the administration of 5-HT (0.32 mg/kg i.p.) to mice caused diarrhea in the gut. In the present study, the administration of 5-HT (0.32 mg/kg i.p.) to mice caused diarrhea in the gut.
has mixed 5-HT3 and 5-HT4 antagonist properties may be a more effective agent in the treatment of functional colonic disorders (e.g., irritable bowel syndrome) than one that acts as a highly selective blocker of either receptor alone.

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References


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