Short-chain fatty acids stimulate colonic transit via intraluminal 5-HT release in rats

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Fukumoto, Satoshi, Makoto Tatewaki, Tadanori Yamada, Mineko Fujimiya, Chris Mantyh, Miranda Voss, Steve Eubanks, Mary Harris, Theodore N. Pappas, and Toku Takahashi. Short-chain fatty acids stimulate colonic transit via intraluminal 5-HT release in rats. Am J Physiol Regul Integr Comp Physiol 284: R1269–R1276, 2003; 10.1152/ajpregu.00442.2002.—We studied whether physiological concentration of short-chain fatty acids (SCFAs) affects colonic transit and colonic motility in conscious rats. Intraluminal administration of SCFAs (100–200 mM) into the proximal colon significantly accelerated colonic transit. The stimulatory effect of SCFAs on colonic transit was abolished by perivagal capsaicin treatment, atropine, hexamethonium, and vagotomy, but not by guanethidine. The stimulatory effect of SCFAs on colonic transit was also abolished by intraluminal pretreatment with lidocaine and a 5-hydroxytryptamine (HT)3 receptor antagonist. Intraluminal administration of SCFAs provoked contractions at the proximal colon, which migrated to the mid- and distal colon. SCFAs caused a significant increase in the luminal concentration of 5-HT of the vascularly isolated and luminally perfused rat colon ex vivo. It is suggested that the release of 5-HT from enterochromaffin cells in response to SCFAs stimulates 5-HT3 receptors located on the vagal sensory fibers. The sensory information is transferred to the vagal efferent and stimulates the release of acetylcholine from the colonic myenteric plexus, resulting in muscle contraction.

5-hydroxytryptamine3 receptor; migrating contractions; vago-vagal reflex

FERMENTATION is an important function of the large bowel, in which anaerobic bacteria break down undigested carbohydrates to short-chain (C2–C6) fatty acids (SCFAs). SCFAs (mainly acetate, propionate, and butyrate) are produced in nearly constant molar ratio of 65:20:15. The luminal colonic concentration of SCFAs has been shown to be 60–130 mmol/l in humans (5, 6).

SCFAs are of major importance in understanding the physiological function of dietary fiber and its possible role in preventing colonic neoplasia. SCFA production and absorption is closely related to the nourishment of the colonic mucosa and sodium/water absorption. An increased production of SCFAs in the colon may be beneficial because SCFAs, especially butyrate, provide energy to colonocytes and inhibit tumor growth (25).

Because it is believed that most fermentation occurs in the proximal colon, the stimuli for proximal colonic motility may control the exposure of the distal colon to SCFAs. Therefore, the action of SCFAs themselves on colonic motility is of interest. If SCFAs slow proximal colonic motility, the exposure of the distal colon to SCFAs would be reduced. In contrast, if SCFAs promote colonic propulsion, then fermentation products would be spread further around the colon.

The effects of SCFAs on colonic motility still remain unclear, and previous studies have provided contradictory results. In vitro experiments have demonstrated that mucosal application of SCFAs (0.02–0.1 mM) caused contractions of the longitudinal muscle in the everted preparation of the rat colon. As the contractile effect of SCFAs was inhibited by atropine, procaine, and TTX, SCFAs may stimulate colonic contractions via an enteric reflex involving local sensory and cholinergic nerves (33). In contrast, others demonstrated that SCFAs (10–100 mM) inhibit smooth muscle contractility in the rat colon (27).

The in vivo effects of SCFAs on colonic motility have also been controversial. It has been shown that luminal administration of SCFAs (10 mM) stimulates colonic motility with increased peristaltic propulsion in anesthetized rats (34). Conversely, a study using conscious rats demonstrated that intracolonic infusion of SCFAs (2 mmol/h) accelerated colonic transit and reduced colonic motility by decreasing the nonpropulsive activity. Intraluminal procaine infusion suppressed the SCFA effect, suggesting an involvement of local neural mechanism (5). It seems that the action of SCFAs on colonic motility in vivo and in vitro differs and also depends on anesthetic agents and concentration of SCFAs administered.

Accumulated evidence suggests that serotonin [5-hydroxytryptamine (5-HT)] plays an important role in regulating colonic motility. There are significantly fewer 5-HT-immunoreactive cells in patients with...
chronic slow-transit constipation (7). Colonic transit is accelerated by 5-HT in conscious rats (13, 16); this effect is inhibited by a selective 5-HT3 receptor antagonist (13). A selective 5-HT3 receptor antagonist also slowed colonic transit in healthy men (30). Patients with carcinoid tumors arising from enterochromaffin (EC) cells exhibit predominant diarrhea and accelerated colonic transit (32). Improvements in diarrhea and colonic transit have been achieved using a 5-HT3 receptor antagonist in patients with carcinoid diarrhea (26). These observations suggest that 5-HT regulates colonic transit and motility via 5-HT3 receptors. However, the mechanism of the stimulatory effect of 5-HT on colonic transit and motility still remains unclear.

Recent studies support the idea that 5-HT released by mucosal stimulation may initiate a peristaltic reflex by interacting with 5-HT receptors located on the subepithelial sensory neurons. The facilitatory effect of mucosally applied 5-HT is mediated via a 5-HT3 receptor located on the mucosal side, not the serosal side (31). The presence of fecal pellets triggers the release of 5-HT, which acts via both 5-HT3 and 5-HT4 receptors to regulate propulsive activity by activating intramural sensory neurons that release calcitonin gene-related peptide in the guinea pig colon (15).

Cornstarch has been shown to be digested almost completely in the small intestine, whereas potato starch shows substantial resistance to α-amylase. Consumption of potato starch by rats leads to increased large bowel fermentation and production of SCFAs (22). It has been shown that cecal concentrations of SCFAs increase from 62 mmol/kg of cecal content to 163 mmol/kg of cecal content after the ingestion of potato starch diet (19). A much higher increase of SCFAs has been shown by Morita et al. (24), who demonstrated a fivefold increase of cecal SCFAs after a high-amyllose diet.

To investigate whether an increase of SCFA concentration in the proximal colon affects colonic transit and motility, we administered various concentrations of SCFAs into the proximal colon. Our present study demonstrates that the intraluminal administration of SCFAs (100–200 mM) into the proximal colon significantly accelerates colonic transit and provokes migrating colonic contractions. The stimulatory effects of SCFAs on colonic transit were abolished by perivagal capsaicin treatment, atropine, and vagotomy. Intraluminal pretreatment with lidocaine and a 5-HT3 receptor antagonist also abolished the stimulatory effects of SCFAs. It is suggested, therefore, that released 5-HT from EC cells in response to SCFAs stimulates 5-HT3 receptors in the colonic mucosa. We propose that the sensory information is transferred to the vagal efferent and stimulates the release of ACh from the colonic myenteric plexus, resulting in muscle contractions. Our new findings may contribute to understanding of the physiological role of SCFAs and mucosal 5-HT3 receptors mediating colonic transit.

MATERIALS AND METHODS

Surgical procedures. Male Sprague-Dawley rats (250–300 g) were obtained from Charles River Laboratories (Raleigh, NC). The animal experiments were carried out in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals and approved by the Institutional Animal Care and Use Committee of Duke University.

Rats were anesthetized with pentobarbital sodium (45 mg/kg ip). For the intraluminal administration of SCFAs and 5-HT, an indwelling Silastic cannula was inserted into the cecum and positioned to enter the proximal colon. To investigate whether spontaneous colonic motility was affected by SCFAs, four strain-gage transducers were sutured on the serosal surface of the proximal, mid-, and distal colon to monitor the circular muscle contraction, as previously reported (24). The wires to transducers were run under the skin to an opening made in the back of the neck. The abdominal wall was closed, and rats were allowed to recover for 7 days.

Fecal pellet output. After an overnight fast, saline (0.5 ml), SCFAs (30–200 mM, 0.5 ml), and 5-HT (10−7–10−5 M, 0.5 ml) were administered into the proximal colon through the cannula. The fecal pellet output was counted after saline, SCFA, and 5-HT administration for 90 min, as previously described (23). The molar ratio acetic acid:propionic acid:butyric acid of SCFAs was 65:20:15. The physiological concentration of SCFAs in the cecal content is reported as 62 mmol/kg in rats (19).

Colonic transit. After an overnight fast, a nonabsorbable radioactive marker (0.5 μCi, Na251CrO4 in 0.2 ml saline) was instilled into the proximal colon through the cannula. Saline (0.5 ml) or SCFAs (30, 100, and 200 mM, 0.5 ml) was administered with 51Cr, simultaneously.

After 90 min, rats were euthanized by CO2 inhalation. The entire colon was surgically removed and divided into 10 equal segments. Each segment was placed into a vial, and the radioactivity was counted by a gamma counter for 1 min. The geometric center (GC) of the distribution of 51Cr within the colon is the center of gravity for the distribution of radiochromium, and it was calculated using the following equation, as previously described (24):

\[
\text{GC} = \frac{\sum (\text{fraction of } 51\text{Cr per segment} \times \text{segment number})}{\text{segment number}}
\]

To investigate whether cholinergic muscarinic receptor is involved in the mechanism of SCFA-induced colonic transit and motility, atropine (50 μg/kg ip) was injected 30 min before the SCFA administration. To investigate whether cholinergic nicotinic receptor is involved in the mechanism of SCFA-induced colonic transit, hexamethonium (20 mg/kg ip) was injected. To investigate whether the adrenergic receptor is involved in the mechanism of SCFA-induced colonic transit and motility, guanethidine (5 mg/kg ip), was injected. To investigate whether mucosal sensory neurons are involved in the mechanism of SCFA-induced colonic transit, lidocaine (2%, 2 ml) was administered into the proximal colon through the cannula 20 min before SCFA administration.

To investigate whether 5-HT3 receptors located on the colonic mucosa might mediate SCFA-induced colonic transit, a 5-HT3 receptor antagonist (alosetron, 10−5 M, 0.5 ml) was administered 20 min before SCFA administration.

To investigate whether the vagus nerve is involved in mediating SCFA-induced colonic transit, trunval vagotomy was performed by cutting the vagal trunks around the abdominal esophagus, as previously reported (29).
Colonic motility. After an overnight fast, the wires from the transducers were connected to the recording system. The area under the curve of the colonic motility recording was calculated using a computer-assisted system (Power Lab/8SP; ADInstruments, Castle Hill, Australia), as a motility index, as previously reported (28). The motility index was evaluated before and after the intraluminal administration of saline (0.5 ml) or SCFAs (100 mM, 0.5 ml) in each rat.

Perivagal capsaicin treatment. Capsaicin is known to destroy primary afferent neurons (C-fibers). To investigate whether capsaicin-sensitive vagal afferents are involved in SCFA-induced colonic transit, rats were treated with perivagal capsaicin. Capsaicin (10 mg) was sonicated with 0.1 ml Tween 80 for 10 min and made up to 1 ml with olive oil and mixed thoroughly. After ketamine and xylazine anesthesia, both cervical vagal trunks were exposed, as previously described (29). A small piece of gauze soaked in capsaicin was placed around the nerve trunk for 30 min. The surrounding area was covered with gauze, which was frequently replaced to minimize the spread of capsaicin to surrounding tissues. Additional capsaicin was applied perivagally every 5 min. The maximum amount of capsaicin applied was 4 mg (1 mg/rat). The area was thoroughly rinsed with olive oil followed by saline and dried with sterile swabs, and the neck incision was closed. Experiments were performed 10–14 days after the perineural capsaicin treatment. Vehicle-treated rats served as controls. SCFA-induced colonic transit was compared between capsaicin-treated rats and vehicle-treated rats.

p-Chlorophenylalanine treatment. p-Chlorophenylalanine (PCPA) inhibits tryptophan hydroxylase, the enzyme acting at the rate-limiting step of 5-HT synthesis. Depletion of 5-HT stores in the brain, intestinal tissue, and blood has been shown after PCPA treatment (17). To investigate whether endogenous 5-HT affects colonic transit induced by SCFAs, rats were treated with PCPA before the colonic transit study. PCPA (500 mg/kg) suspended in 2 ml gum arabic solution was administered intraperitoneally on two consecutive days, as previously described (20, 35). Control rats received only gum arabic solution. After an overnight fast, the wires from the transducers were connected to the recording system. The area under the curve of the colonic motility recording was calculated using a computer-assisted system (Power Lab/8SP; ADInstruments, Castle Hill, Australia), as a motility index, as previously reported (28). The motility index was measured, as previously reported (9). To investigate whether intrinsic neurons were involved in mediating SCFA-induced 5-HT release, TTX (10^{-6} M) was continuously infused 10 min before, during, and after SCFA administration into the artery.

Materials. Atropine, ascorbic acid, acetic acid, BSA, butyric acid, desipramine, dextran, guanethidine, gum arabic, lidocaine, hexamethonium, hydrochloric acid, propionic acid, PCPA, 5,7-DHT, and 5-HT were obtained from Sigma Chemical (St. Louis, MO). Capsaicin was obtained from Tocris (Ballwin, MO). TTX was obtained from Sankyo (Tokyo, Japan). Alosetron was a gift from Glaxo SmithKline (Research Triangle Park, NC).

Statistical analysis. The results are expressed as means ± SE. Statistical analysis was performed by Student’s t-test, paired t-test, or ANOVA with Bonferroni correction. P values of <0.05 were considered significant.

RESULTS

Effects of SCFAs and 5-HT on fecal pellet output. Administration of SCFAs (100 mM, 0.5 ml) into the proximal colon significantly increased fecal pellet output compared with rats receiving saline injection. Intraluminal administration of 5-HT (10^{-6}–10^{-5} M, 0.5 ml) into the proximal colon also significantly increased fecal pellet output (Fig. 1A).

Effects of SCFAs and 5-HT on colonic transit. The GC in rats treated with intraluminal administration of saline (0.5 ml) was 5.18 ± 0.43 (n = 6). Intraluminal administration of SCFAs (100–200 mM, 0.5 ml) significantly accelerated colonic transit compared with saline-injected controls (Fig. 1B). Although the acidity of SCFAs (200 mM) is pH 2.84, intraluminal administration of HCl (pH 2.84) had no significant effects on colonic transit (Fig. 1B). A SCFA preparation (100 mM) with pH adjusted to 7.0 also significantly accelerated colonic transit (GC 7.51 ± 0.76, n = 5).

Colonic transit was not significantly delayed in rats treated with atropine, hexamethonium, and vagotomy. Intraluminal administration of SCFAs (100 mM) had no stimulatory effects on colonic transit in rats treated with atropine, hexamethonium, and vagotomy. Intraluminal administration of lidocaine also abolished superior mesenteric artery. All vessels apart from those leading into the proximal colon were cut between double ligatures. The stomach, jejunum, ileum, pancreas, and spleen were removed. The vascular perfuse consisted of Krebs solution containing 3% dextran (mol wt 40,000), 0.2% BSA, and 5 mM glucose. The perfusate was saturated with 95% O_{2}-5% CO_{2} gas to maintain pH of 7.4. The perfusate and the preparation were kept at 37 °C throughout the experiment using a thermostatically controlled heating apparatus. The perfusion flow rate was maintained at 3 ml/min (18).

SCFAs (50–200 mM) were perfused into the lumen for 9 min. The vascular and luminal perfusate was collected every 3 min before, during, and after SCFA administration.

Vascular effluents from ex vivo perfused rat colon were filtrated with Ultrafree-MC (30,000 NMWL, Millipore) by centrifuging for 30 min at 10,000 rpm at 4 °C. Luminal effluents were filtrated manually with a 0.22-μm-pore disk filter (Millex-GV, Millipore). One-hundred-microliter aliquots of filtrates were injected into HPLC, and the 5-HT content was measured, as previously reported (9). To investigate whether intrinsic neurons were involved in mediating SCFA-induced 5-HT release, TTX (10^{-6} M) was continuously infused 10 min before, during, and after SCFA administration into the artery.
the stimulatory effects of SCFAs (100 mM) (Fig. 2A). In contrast, the stimulatory effects of SCFAs (100 mM) were not affected in rats treated with guanethidine (GC 9.07 \pm 1.55, n = 3).

Although perivagal vehicle treatment did not alter the stimulatory effects of SCFAs (100 mM) on colonic transit, perivagal capsaicin treatment abolished SCFA-induced acceleration of colonic transit (Fig. 2B).

Similar to SCFAs, intraluminal administration of 5-HT (10^{-5} M, 0.5 ml) significantly accelerated colonic transit. The stimulatory effect of 5-HT was abolished by the intraluminal administration of a 5-HT_{3} antagonist, alosetron (10^{-5} M, 0.5 ml) (Fig. 3A). Intraluminal administration of alosetron (10^{-5} M, 0.5 ml) also abolished the stimulatory effects of SCFAs (100 mM) on colonic transit (Fig. 3B).

Intraluminal administration of alosetron (10^{-5} M, 0.5 ml) itself had no significant effects on colonic transit.

The stimulatory effects of SCFAs (100 mM) on colonic transit were not observed in rats treated with PCPA (GC 4.81 \pm 0.63, n = 4). In contrast, 5,7-DHT treatment did not affect colonic transit induced by SCFAs (100 mM) (GC 7.40 \pm 0.93, n = 4), compared with that of vehicle (ascorbic acid plus desipramine)-treated rats (GC 7.21 \pm 1.09, n = 4).

**Effects on SCFAs and 5-HT on colonic motility.**

Colonic motility was recorded for over 3 h in conscious rats before and after the intraluminal administration of SCFAs (100 mM, 0.5 ml) or saline (0.5 ml). Intraluminal administration of SCFAs (100 mM) significantly increased the fecal pellet output compared with saline-injected rats. Administration of SCFAs (100 and 200 mM) also significantly accelerated colonic transit. In contrast, intraluminal administration of HCl (pH 2.8) did not affect colonic transit (n = 4–7, *P < 0.01 by ANOVA).

**Fig. 2.** A: effects of atropine, hexamethonium, vagotomy, and lidocaine on colonic transit stimulated by SCFAs (100 mM) The stimulatory effects of SCFAs on colonic transit were abolished by atropine, hexamethonium, vagotomy, and lidocaine (n = 4–5, **P < 0.05 by ANOVA). B: effects of perivagal treatment of capsaicin and vehicle on colonic transit stimulated by SCFAs (100 mM). Perivagal capsaicin treatment abolished the stimulatory effects of SCFAs on colonic transit (n = 4, *P < 0.05 by Student’s t-test). NS, nonsignificant.

Motility index was calculated by a computer-assisted system, as previously described (28). Calculated motility index was increased to 150–200% of basal in the entire colon by SCFAs (Fig. 5). In contrast, intraluminal administration of saline or HCl (pH 2.8) had no significant effects on colonic motility (data not shown).
Increased motility index in response to SCFAs (100 mM) was significantly reduced by atropine, hexamethonium, and intraluminal administration of lidocaine (Table 1). Intraluminal administration of alosetron (10⁻⁵ M) also significantly reduced the stimulatory effects of SCFAs on colonic motility (Table 1 and Fig. 6).

**Luminal release of 5-HT in response to SCFA administration ex vivo.** The concentration of 5-HT in the luminal perfusate and vascular perfusate was 3.2 ± 0.3 and 2.2 ± 0.2 ng/ml (n = 9) in the basal state, respectively. Intraluminal perfusion of SCFAs (50–200 mM) for 9 min significantly increased the concentration of 5-HT of the luminal perfusate in a dose-dependent manner (Fig. 7A). In contrast, a very small 5-HT increment was observed in response to SCFAs in the vascular perfusate (Fig. 7B). Integrated release of 5-HT in response to SCFAs (200 mM) was 353 ± 7 ng/21 min (n = 3). Integrated release of 5-HT in response to SCFAs (200 mM) was not significantly altered by the pretreatment of TTX (304 ± 12 ng/21 min, n = 3).

**DISCUSSION**

Whether intraluminal administration of SCFAs stimulates (4, 34) or inhibits (5) colonic motility has been controversial. It has been shown that luminal administration of SCFAs stimulates colonic motility with an increased peristaltic propulsion in anesthetized rats (34), while others demonstrated that intracolonic infusion of SCFAs accelerated colonic transit by reducing the nonpropulsive activity (5).

Our study demonstrated that administration of SCFAs (100 mM) into the proximal colon significantly increased the colonic motility in conscious rats. The
high-amplitude contractions induced by SCFAs in the proximal colon migrated to the mid- and distal colon, suggesting that SCFAs promote the propulsive movement.

We have also demonstrated that intraluminal administration of SCFAs (100–200 mM) accelerated colonic transit in conscious rats. The stimulatory effects of SCFAs (100 mM) on colonic transit were abolished by perivagal capsaicin treatment, atropine, hexamethonium, and vagotomy, suggesting the mediation of vagal afferent and cholinergic pathway. We also demonstrated that the stimulatory effect of SCFAs on colonic transit was abolished by intraluminal pretreatment with lidocaine. This suggests that the stimulatory effects of SCFAs are mediated via mucosal sensory neurons.

Whereas the systemic administration of 5-HT has been shown to accelerate colonic transit in rats (13), the effects of intraluminal application of 5-HT were previously unknown. In our study, intraluminal administration of 5-HT into the proximal colon significantly increased the fecal pellet output and accelerated colonic transit.

5-HT₃ antagonists have been shown to delay colonic transit in humans (30), suggesting that 5-HT₃ receptor mediates colonic transit. It has been suggested that 5-HT₃ receptors are located on the cholinergic neurons of the myenteric plexus (23) as well as sensory neurons of the intestinal mucosa (11, 12).

The stimulatory effects of 5-HT and SCFAs on both colonic transit and colonic motility were abolished by the intraluminal application of a selective 5-HT₃ receptor antagonist, alosetron. This suggests that the stimulatory effects of SCFAs on colonic transit and motility are mediated via 5-HT₃ receptors located on the colonic mucosa.

In the present study, HCl at a similar pH with SCFAs (pH 2.84) had no stimulatory effects on colonic transit. This is different from the effect in the more proximal gut where HCl (150 mM) activates vagal afferent pathways in the mucosa via 5-HT₃ receptors (14).

It has recently been shown that fibers immunoreactive for 5-HT₃ receptors in the duodenal mucosa are markedly reduced by subdiaphragmatic vagotomy or chemical denervation of vagal afferents (12). This suggests that 5-HT₃ receptors are located on the nerve terminals of vagal afferents in the duodenal mucosa. In the crypts and villus of the rat duodenal mucosa, vagal terminal branches come in close contact with the lamina propria. Thus nerve endings may well be the targets for the 5-HT₃ released from EC cells (1). Exogenous 5-HT and alosetron applied to the lumen would act after diffusion across the mucosal epithelium to the 5-HT nerve terminals.

Our ex vivo model demonstrated that luminal administration of SCFAs increased the luminal concentration of 5-HT, while there was a negligible 5-HT release into the vascular lumen. The physiological sig-

Table 1. Effects of atropine, hexamethonium, intraluminal lidocaine, and alosetron on SCFA-induced colonic motility of the proximal colon

<table>
<thead>
<tr>
<th>SCFAs + saline</th>
<th>156.94 ± 15%</th>
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<tbody>
<tr>
<td>SCFAs + atropine</td>
<td>112.1 ± 4.0% *</td>
</tr>
<tr>
<td>SCFAs + hexamethonium</td>
<td>88.7 ± 3.5% *</td>
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<tr>
<td>SCFAs + lidocaine</td>
<td>111.5 ± 0.7% *</td>
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<tr>
<td>SCFAs + alosetron</td>
<td>105.5 ± 2.7% *</td>
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Values are means ± SE; n = 3. Motility index was calculated for 20 min after short-chain fatty acid (SCFA) administration. Increased motility index induced by SCFAs (100 mM) was significantly reduced by atropine, hexamethonium, lidocaine, and alosetron (*P < 0.05 by ANOVA).
nificance of luminal release of 5-HT from EC cells still remains unclear. It still remains unknown whether luminally released 5-HT acts on vagal afferent terminals of the lamina propria after diffusion across the mucosa, or 5-HT released into the lamina propria from EC cells acts on vagal afferent terminals. In the former case, 5-HT in the lumen would have functional significance. In the latter case, 5-HT in the lumen would be overspill and have no functional significance. Further study is needed to clarify the physiological role of luminally released 5-HT in the proximal colon.

Because TTX did not significantly affect SCFA-induced 5-HT release, the stimulatory effects of SCFAs are suggested to be independent of intrinsic neurons. It has previously been shown that 5-HT is released from the EC cells into the intestinal lumen (9, 21). Using a vascularly isolated and luminally perfused rat duodenum, we have previously shown that the elevated intraluminal pressure stimulates release of 5-HT into the duodenal lumen. In contrast, the elevated intraluminal pressure did not alter the vascular release of 5-HT. TTX had no effect on the pressure-stimulated luminal 5-HT release (9).

It has been shown that pancreatic enzyme secretion is stimulated by intraduodenal administration of hypertonic solutions. Intraduodenal administration of hypertonic solution stimulates the release of 5-HT from mucosal EC cells of the duodenum and evokes pancreatic enzyme secretion via 5-HT3 receptors. Perivagal capsaicin treatment abolishes the pancreatic enzyme secretion induced by intraduodenal administration of hypertonic solutions (21). Intraluminal perfusion of 5-HT increased vagal afferent discharges in the same nodose neurons that were activated by luminal stimuli (35). The neuronal responses to luminal osmolality at the nodose are dependent on the release of endogenous 5-HT from the mucosal EC cells, which acts on the 5-HT3 receptors on vagal afferent fibers (35).

PCPA depletes 5-HT stores in the brain, intestinal tissue, and blood (17). On the other hand, 5,7-DHT destroys 5-HT-containing neurons without affecting 5-HT-containing mucosal cells (20, 21). Our present
study showed that PCPA treatment abolished the stimulatory effect on colonic transit. These results suggest that 5-HT released from EC cells, but not from the myenteric plexus, is involved in mediating the stimulatory effects of SCFAs on colonic transit.

It generally accepted that 5-HT stimulates intrinsic nerve fibers via 5-HT1P and 5-HT4 receptors (8), while 5-HT stimulates extrinsic nerve fibers via 5-HT3 receptors (3, 10). Our data showed that SCFA-induced colonic motility is mediated via extrinsic neural reflex (vagovagal reflex) and that mucosal 5-HT3 receptors are involved in SCFA-induced colonic motility.

We conclude that 5-HT is released from EC cells in response to SCFAs and stimulates 5-HT3 receptors located on the vagal afferent fibers. The sensory information is transferred to the vagal efferent and stimulates the release of Ach from the colonic myenteric plexus, resulting in muscle contractions.

REFERENCES