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Leading article

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ROLES OF SHORT-CHAIN FATTY ACIDS RECEPTORS, GPR41 AND GPR43 ON COLONIC FUNCTIONS

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Short chain fatty acids (SCFAs) are the major anions in the large intestine. They are produced by a bacterial fermentation of dietary fiber. SCFAs are known to have a variety of physiological and pathphysiological effects on intestine. However, the mechanisms by which intraluminal SCFAs are sensed are not known. In 2003, two orphan G protein coupled receptors (GPRs), GPR41 and GPR43, have been cloned and demonstrated to be receptors for SCFAs. Thus, we had attempted to make antibodies raised against GPR43 and GPR41 to elucidate the roles of SCFAs on colonic functions. We have also evaluated the effects of SCFAs on colonic motility to define the physiological roles on luminal SCFAs. In rat and human colon, GPR43 protein was detected by Western blot analysis in extracts of whole wall and separated mucosa, but not in muscle plus submucosa extract. By immunohistochemistry, GPR43 immunoreactivity was localized with enteroendocrine cells expressing peptide YY, whereas 5-HT immunoreactive enteroendocrine cells were not immunoreactive for GPR43. GPR41 immunoreactivity was also found in human colon. In functional studies, propionate and butyrate concentration-dependently (10 μM - 10 mM) induced phasic and tonic contractions in rat colonic circular muscle. The propionate-induced phasic contraction was attenuated by atropine, tetrodotoxin and the 5-HT_4 receptor antagonists SB204070. However, acetate did not induce phasic or tonic contractions. Propionate-induced responses were not observed in mucosal free preparations. The present results suggest that the SCFA-induced physiological effects on colonic functions might be attributable to the activation of SCFA receptors on epithelial cells in the colon.

Key words: *short chain fatty acids, G-protein coupled receptor, colon, motility, enteroendocrine cell*

INTRODUCTION

Short-chain fatty acids (SCFAs) are the major anions, present at about 100 mM, in the lumen of the non-ruminant mammalian large intestine. They are produced by bacterial fermentation of undigested carbohydrate from ingested dietary fiber. They are 2-carbon to 5-carbon weak acids, including acetate (C2), propionate (C3), butyrate (C4), and valerate (C5). The ratio of SCFA concentrations in the colonic lumen is about 60% acetate, 25% propionate, and 15% butyrate. Luminal SCFAs are not only absorbed as nutrients across the intestinal epithelium, but also influence various functions of the gastrointestinal tract (1). For example, SCFAs influence colonic blood flow (18), fluid/electrolyte uptake (19), colonic motility(2 - 7), ion transport (6) and inhibit transit in regions more proximal to their luminal application (8). The SCFAs-induced colonic motility is reported to disappear in mucosal free preparations (3). Therefore the effects of SCFA in the intestinal lumen are considered to be induced via the activation of specific receptors and/or via absorption in epithelial cells, but the mechanisms by which intraluminal SCFAs are sensed are not known. In 2003, two different groups, Brown et al. and Le Poul et al., simultaneously reported that the SCFA receptors were identified from orphan G-protein coupled receptors, specifically GPR41 and GPR43 (9, 10). They also reported that both receptors are coupled with G_q and $G_{i/o}$, and their activation induces an increase in intracellular Ca^{2+} concentration and a decrease in intracellular cyclic adenosine monophosphate (cAMP). GPR41 mainly initiates its signaling through coupling with the $G_{i/o}$ and GPR43 is mainly coupled with Gq-proteins(9, 10). The potency orders of each SCFA for GPR41 is propionate >butyrate>>acetate, whereas GPR43 is equally sensitive to each SCFA. Acetate is more selective for GPR43 than GPR41 and propionate is the most potent and efficacious ligand for GPR41. These distinction allow for functional discrimination between GPR41 and GPR43. Since SCFAs are at highest concentrations in the colon, it is reasonable that receptors might reside in this location, for recognition of passing ingesta content and indirect monitoring of bacterial flora populations by their metabolic by-products.

In this paper we will summarize the present knowledge on the roles of SCFAs receptors in the large intestine. We also discuss the local effects of SCFA on colonic motility based on our recent studies.

EXPRESSION AND LOCALIZATION OF SCFA RECEPTORS, GPR41 AND GPR43 IN THE GASTROINTESTINAL TRACT

RT-PCR and Western blot analysis

Messenger RNA for GPR43 was detected in extracts of whole wall and separated mucosa from the rat distal ileum and colon (*Fig. 1A*) (12).

By western blot, GPR43 protein was detected in the mucosa and whole wall, but not in muscle plus submucosal layers, both from the rat distal ileum and colon (*Fig. 1B*) (12).

In the human ascending colon, mRNA for GPR43 was also detected in extracts of whole wall and GPR43 protein was detected in extracts of whole wall and in the separated mucosa but not in extracts of submucosa and muscle layer (32).

These results indicate that GPR43 is expressed by cells in the mucosa, but not by enteric neurons or smooth muscle.

For the expression of GPR41 in human colon, our preliminary result showed that expression pattern of GPR41 was similar to that of GPR43 (34). The expression of GPR41 mRNA in mucosa, muscle and whole wall were clear but faint smear band was observed in submucosa. GPR41 protein was also detected in human colon. The protein was higher expressed in colonic mucosa than submucosa or muscle.

Immunohistochemistry

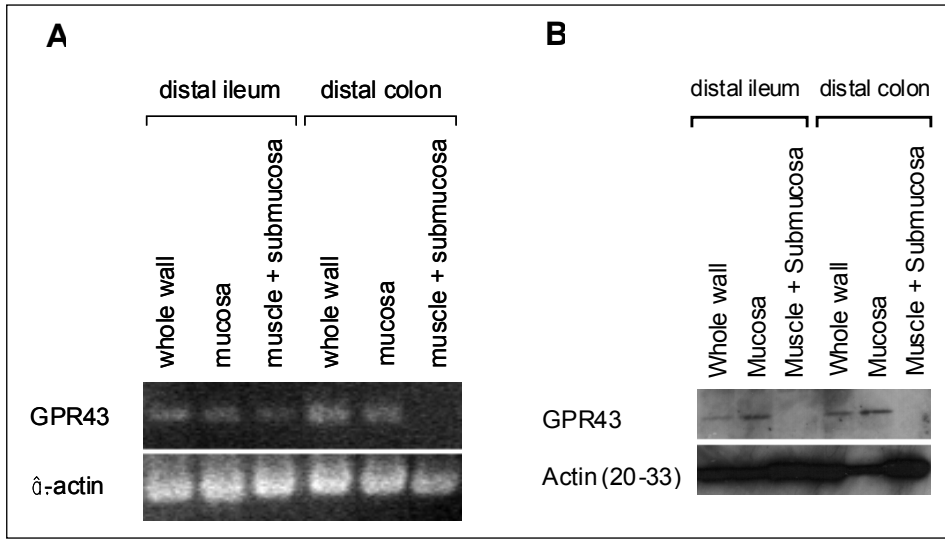

Fig. 1. nalysis of expression of GPR43 mRNA and protein in the rat distal ileum and colon by RT-PCR. (A) All samples in the distal ileum expressed GPR43 mRNA, but no expression was detected in the combined external muscle plus submucosal layers in the distal colon. RT-PCR for β-actin message was used as a control. (B) GPR43-immunoreactive protein was most abundant in the mucosa but was undetectable in the muscle plus submucosal layers. The same volumes of extracted protein s were separated by SDS-PAGE. Western blots probed with anti-actin (20-33) antibody were used as a control. (Adapted from Karaki *et al*. 2006).

To identify the cellular distribution of GPR41 and GPR43 protein in rat and human colon, an immunohistochemical staining was performed by using anti-GPR41 or anti-GPR43 antiserum.

Immunoreactivity for GPR43 occurred at a low level in all enterocytes within the epithelium of the mucosa in the rat distal ileum and colon (12). Immunoreaction also occurred in a population of enteroendocrine cells and in small cells in the lamina propria in rat intestine. GPR43-immunoreactive (IR) cells in the epithelium had the morphology of enteroendocrine cells. Immunoreactivity for GPR43 in human ascending colon showed similar pattern to those of rat intestine (32). GPR43-IR enteroendocrine cells in the rat intestine were open-type enteroendocrine cells, which extended their cell bodies to the luminal surface and often had processes that extended from their bases and ran beneath adjacent epithelial cells but such is not the case in human ascending colon (*Fig. 2*).

GPR41-immunoreactivities in human colon were observed in the crypt, and they were open type enteroendocrine cells, with thin cell bodies that extended to the lumen surface (34).

Previous physiological studies reported that SCFAs caused 5-HT and PYY release (7, 11). Thus, we performed double-staining for GPR43 and 5-HT, and GPR43 and PYY. No GPR43-IR enteroendocrine cells exhibited 5-HT immunoreactivity, whereas GPR43 immunoreactivity was colocalized with 5-HT immunoreactivity in small round cells of the lamina propria in the rat distal ileum

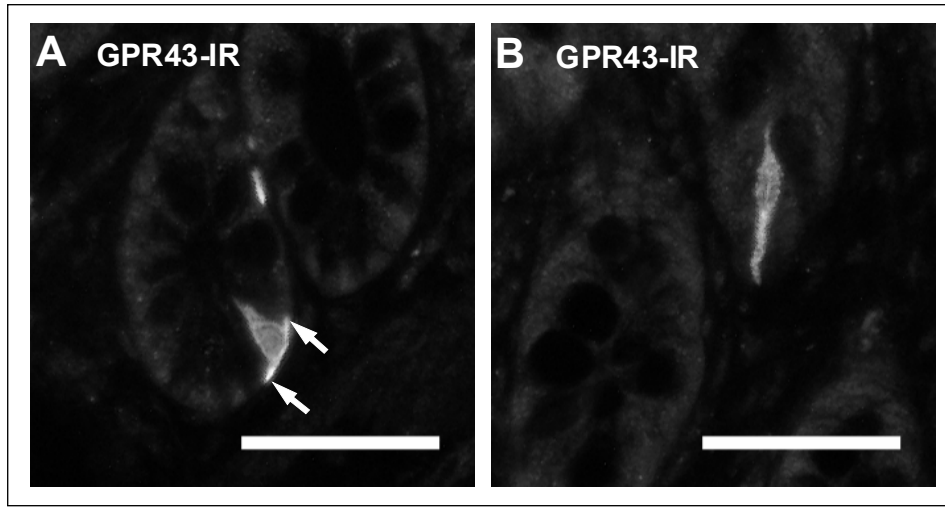

Fig. 2. Morphology of GPR43-IR enteroendocrine cells in the rat colon. Two typical GPR43-IR enteroendocrine cells are shown in the epithelium. (A) GPR43-IR enteroendocrine cell at the base of a colonic crypt. Processes are seen at the base of the cell (*arrows*). (B) Immunoreactive cell that extends across the epithelium (open-type enteroendocrine cell). *Bar* = 50 μm. (Adapted from Karaki *et al*. 2006).

and colon (12). They were mucosal mast cells. There is complete co-localization of immunoreactivity for GPR43 and PYY in enteroendocrine cells in the distal ileum and colon, i.e. all GPR43-IR cells are PYY-IR and vice-versa.

We have also performed double-staining for GPR41 and 5-HT and GPR41 and PYY. GPR-IR enteroendocrine cells in human colon were also colocalized with PYY similar to that of GPR43 (34).

Immunoreactivity for GPR43 and GPR41 in rat and human colon is observed in PYY-IR enteroendocrine cells in the mucosal epithelium and in mast cells of the lamina propria of the distal ileum and colon (12, 32, 34). These data are consistent with previous physiological and pharmacological studies and suggest that SCFA directly affects 5-HT and PYY release by cells containing these mediators, and that this occurs via the GPR43 receptor type.

Role of SCFA receptors in the intestine

SCFAs have been reported to induce enhancement of colonic motility via the release of 5-HT (3, 7). These are two possible sources of 5-HT: enteroendocrine cells that are numerous throughout the gastrointestinal tract (13) and 5-HT-containing mast cells that occur in mucosal lamina propria of the rat intestine (14). However previous our study has shown that GPR43 immunoreactivity does not occur in 5-HT-IR enteroendocrine cells, whereas 5-HT-IR mast cells of the lamina propria co-express GPR43 (12). Therefore, the GPR43-IR lamina proprial cells might be the sources of 5-HT that is released by SCFA.

Fats, including SCFAs, induce an inhibition of upper gastrointestinal motility, the so-called ileal and colonic brakes, *via* PYY release into the blood circulation (15, 16). Therefore, the majority of PYY-containing enteroendocrine cells probably express GPR43 as a SCFA receptor, and SCFAs might stimulate PYY-containing enteroendocrine cells directly, *via* GPR43, to release PYY. This is supported by the following observation that acetate, which is selective for GPR43, is reported to cause an increase in the release of PYY (17). Our study clearly showed that processes extended from the basal parts of the PYY/GPR43 endocrine cells to the bases of adjacent epithelial cells (12). Thus, the results suggest that PYY has a local paracinre role, in addition to it hormonal role.

SCFAs are produced by bacterial fermentation of the carbohydrates of dietary fiber in the large intestinal lumen. Therefore, the presence of SCFAs in the lumen reflects the activity of the luminal bacterial flora and SCFA receptors possibly monitor the bacteria for host defense. Indeed, two types of putative SCFA receptor, GPR41 and GPR43, have been reported to be expressed by cells of the immune defense system, including polymorphonuclear cells (GPR41 and GPR43), monocytes (GPR43), and dendritic cells (GPR41) (10). Our previous study indicates that the mucosal mast cells also express GPR43 (12). Polymorphonuclear cells, monocytes (macrophages in the tissue), and dendritic cells are the phagocytes for non-selective antigens involved in the innate immune

system. The evidence seems to support a hypothesis that one of the roles of SCFA receptors in the intestinal mucosa is the luminal surveillance of bacterial flora, but further study is necessary to clarify the roles of SCFA-receptor-mediated host defense mechanisms in the intestine. GPR43 and GPR41 immunoreactivities have also been found in the enterocytes of the mucosa. Thus, absorptive/secretory cells probably detect the presence of SCFAs in the lumen through GPR43.

MOTOR EFFECTS OF SHORT-CHAIN FATTY ACIDS IN THE GASTROINTESTINAL TRACT

A possible direct influence of SCFA on intestinal motility in monogastric animals was first suggested by Yajima (5), who recorded a tonic contraction of rat colonic muscle strips in response to propionate, butyrate or valerate *in vitro*. The

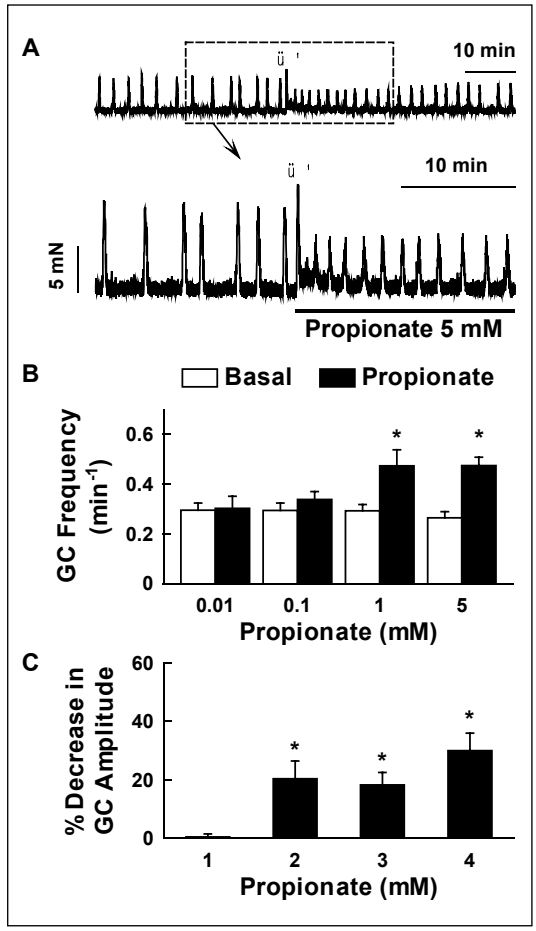

Fig. 3. (A) Representative trace showing the effects of 5 mM propionate on spontaneous giant contractions (GCs) in circular muscle strip of the rat distal colon with the mucosa attached. A part of the upper trace is enlarged below. Immediately after the addition of propionate (*arrowheads*), a contraction with large amplitude was observed. After this propionate-induced contraction, the frequency of GCs was increased and the mean amplitude was decreased. (B) An addition of 1 mM or 5 mM propionate significantly increased the frequency of GCs. (C) An addition of 0.1 - 5 mM propionate significantly decreased the mean amplitude of GCs. Values are expressed as mean ± SEM, n = 4-5. *$P <$ 0.05 by a paired Student's t-test. (Adapted from Mitsui *et al*. 2005).

dose-dependent contratile effect occurred only when SCFA were applied on the mucosal side and disappeared when the mucosa was removed, suggesting the presence of sensory mechanisms near the epithelium. Therefore, the hypothesis that SCFA may be one of the lumen stimuli regulating colonic motility was further studied using *in vitro* animal models.

Circular muscle

When recorded mechanically, *in vitro* and *in vivo* colonic motor activity in most species, including mice and rats, is characterized by two distinct types of contraction : (1) rhythmic phasic contractions, and (2) spontaneous contractions, which are also termed giant contractions (GCs) by Gonzalez and Sarna (20-22). GC shows the contractions with low frequency and high amplitude (*Fig. 3A*); the other is characterized by low amplitude contractions (rhythmic phasic contractions) (3). Some spontaneous circular muscle contractions in the rat colon propagate aborally and may play a role in the propulsion of luminal contents (23, 24). Therefore, the regulation of these GCs in the circular muscle layers seems to be important.

We have shown that propionate increases the frequency and decreases the mean amplitude of spontaneous GCs as shown in *Fig. 3*. However, acetate and butyrate had no such effects. The propionate induced increase in the frequency of GCs was blocked by the muscarinic acetylcholine receptor antagonist, atropine. In contrast, the nicotinic receptor antagonist, hexamethonium, augmented the response. Therefore, the propionate-induced increase in the frequency of GCs seems to be mediated by cholinergic motor neurons. This result also suggests that propionate may activate an inhibitory neural pathway mediated by nicotinic ganglionic transmission in addition to the activation of an excitatory neural pathway. The propionate-induced decrease in the mean amplitude of GCs was prevented by the cyclooxygenese inhibitor piroxicam (4). GCs of colonic circular muscle layer are thought to enhance the propulsion of luminal contents because at least part of these contractions propagates in an anal direction as mentioned above (23 - 26). Thus the stimulatory effect of propionate on the frequency of GCs seems to be important for the propulsion of feces in the colon. Propionate could not cause an increase in the frequency of GCs in preparation without the mucosa. Thus, luminal propionate probably causes a release of some sensory mediator in the mucosa to induce an increase in the frequency of GCs. Furthermore, our results suggest that propionate may be sensed by the SCFA receptors located on the mucosal epithelial cells.

Longitudinal muscle

In comparison with circular muscle, the contribution of longitudinal smooth muscle to colonic function has been less well studied. However, GCs are observed not only in circular muscle layer, but also in longitudinal muscle layer of the colon (27). Powell and Bywater have suggested that GCs in circular and

longitudinal muscle layers synchronously occur in the isolated mouse colon (27). During peristalsis, it has also been suggested that oral contraction of the longitudinal muscle tends to pull the intestine over the rear of a pellet, the simultaneous contraction of both muscle layers ensuring that contraction of the longitudinal muscle also contributes to propulsion by providing a vector of force along the intestine (28, 33). Therefore, it is important to know how SCFA affect longitudinal spontaneous contraction.

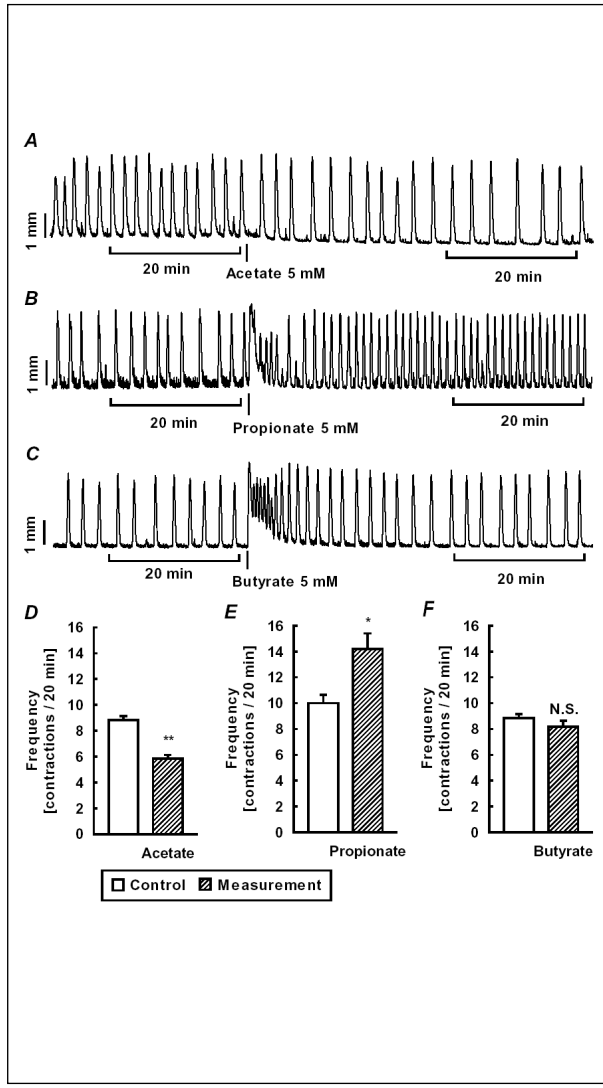

Fig. 4. Effects of individual SCFAs on the frequency of spontaneous contractions of the longitudinal muscle in rat distal colon. (A) Representative trace showing that acetate (5 mM) decreased the frequency of spontaneous contractions of the longitudinal muscle without a transient contraction immediately after its addition. (B) Representative trace showing that propionate (5 mM) increased the frequency of spontaneous contractions of the longitudinal muscle with a transient contraction immediately after its addition. (C) Representative trace showing that butyrate (5 mM) caused a transient contraction. (D) Acetate (5 mM) significantly decreased the frequency of spontaneous contractions of the longitudinal muscle. Values are means ± SEM, $n = 6$. $^{**}P < 0.01$, significantly different from control. (E) Propionate (5 mM) significantly increased the frequency of spontaneous contractions of the longitudinal muscle. Values are means ± SEM, $n = 5$. $^{*}P < 0.05$, significantly different from control. (F) Butyrate (5 mM) did not influence the frequency of spontaneous contractions of the longitudinal muscle. Values are means ± SEM, $n = 6$. (Adapted from Ono *et al*. 2004).

The exogenous addition of SCFAs (>5 mM) decreases the frequency of GC of longitudinal muscle in rat diatal colon (*Fig. 4 A &D*) (2). The result suggests that GC of the longitudinal muscle in rat distal colon is decreased by SCFAs in the intestinal lumen. Among individual SCFAs, only acetate decreases the frequency of spontaneous contractions in longitudinal strips of the rat distal colon. Thus it is suggested that acetate appears to be a substantial stimulus of SCFA-induced inhibitory response in rat distal colon. In contrast to acetate, propionate increases the frequency of GC of the longitudinal muscle similar to that of circular muscle (*Fig. 4 B & E*). However, butyrate had no such effect (*Fig. 4 C & F*). Only acetate induced the inhibitory response decreasing the frequency of GCs of the longitudinal muscle. Since propionate coexists with acetate in SCFAs, the effect of propionate, in the presence of acetate, on the frequency of GCs of the longitudinal muscle was also examined. Acetate (5 mM) significantly blocked the propionate-induced an increase in the frequency of GCs of the longitudinal muscle (2). Therefore, it appears that SCFAs under physiological conditions usually induce a decrease in the frequency of GCs of the longitudinal muscle in rat distal colon.

It has been known that the enteric nervous system influences intestinal motor activity (26). Therefore, whether acetate-induced inhibitory response was mediated by the enteric nervous system was tested by use of several neural blockades. Tetrodotoxin and combination of hexamethonium and 5-HT3 receptor antagonist, granisetron abolished acetate-induced inhibitory response (2). Thus, acetate-induced inhibitory response is considered to be mediated by nicotinc and 5-HT3 receptors.

Mechanism of SCFA-induced muscle activities

In our previous studies, we found out that SCFA also affected the basal muscle contractility in rat distal colon (*Fig. 3B, Fig. 4 B&C*) (2 - 4). Therefore, we investigated the effects of SCFAs on basal muscle contractility of the rat distal colon. Propionate and butyrate, but no acetate, concentration-dependently (10 μM - 10 mM) induced rapid, large amplitude phasic contractions followed by tonic contraction in strips of the circular muscle in rat distal colon (*Fig. 3B*) (3). However, acetate itself had no effect on muscle activity. The propionate-induced phasic and tonic contractions are not observed in the mucosal-free preparations (3). The results suggest that propionate does not directly act on circular muscle. The propionate-induced phasic contraction was attenuated by atropine, tetrodotoxin and 5-HT4 antagonist SB204070 (3). Therefore, the phasic contractions seem to depend on the integrity of the mucosa, cholinergic motor neurons and 5-HT4 receptors. These results also suggests that propionate acts on receptors in the mucosa causing the release of 5-HT from the cells containing 5-HT. 5-HT acts through 5-HT4 receptors on the endings of intrinsic primary afferent neurons that in turn activate cholinergic motor neurons that contract the circular muscle. On the other hand, the tonic contraction was attenuated by the

non-selective COX inhibitor, piroxicam or the COX-1 inhibitor, SC-560 (3). So propionate probably induces release of COX products to cause the tonic contraction. As atropine and TTX had no effect on the tonic contraction, this is probably due to a direct action of prostagalndins on the circular muscle.

CONCLUSION

We have briefly reviewed the role of SCFA receptors and the SCFA-induced colonic motility based on our recent studies and others. SCFA receptors, GPR41 and GPR43 are located in mucosal enteroendocrine cells expressing PYY. Thus, GPR41 and GPR43 are important molecular devices to monitor the chemical composition in colonic lumen. For the local function of SCFAs and SCFA receptors, it should be stressed that individual SCFAs have different mode of actions on the colonic smooth muscles. These different effects may be due to the different contributions of GPR41 or GPR43 on the control of intestinal muscle activity. For the remote effects of GPR41 or GPR43 on the whole body energy balance, GPR41 and/or GPR43 may be contributed to release the gastrointestinal regulatory peptides related to feeding control. However, further study needs to define the precise functions of GPR41 and GPR43 on both local intestinal and whole body effects of SCFA.

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