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Motor effects of short-chain fatty acids and lactate in the gastrointestinal tract

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Short-chain fatty acids (SCFA) affect local and remote motility of the gastrointestinal tract by mechanisms that are not completely understood. In the large intestine where they are produced, they inhibit peristaltic activity and may stimulate tonic activity. When present in the terminal ileum as a result of reflux of colon contents, they elicit propulsive contractions. These local motor effects could involve a neuro-hormonal sensory mechanism located in the mucosa of the terminal ileum and proximal colon. Finally, through a humoral pathway probably involving polypeptide YY release, ileal and colonic SCFA modify upper motility by inducing relaxation of the proximal stomach and lower oesophageal sphincter and reducing gastric emptying. One characteristic feature of the SCFA effects is the dose-dependency of the gastrointestinal motor responses. Indeed, the effects occur only below or above a threshold of SCFA concentration in lumen contents. One putative physiological role of the motor effects of SCFA might be to maintain the physico-chemical balance of the lumen environment in the terminal ileum and proximal colon. Another role might be to co-regulate motility of the upper intestine. The clinical relevance of these effects is unclear. However, some recent findings suggest that excessive SCFA concentrations might induce adverse effects on gastrointestinal and colonic motility and sensitivity in certain diseases such as inflammatory bowel disease and gastro-oesophageal reflux disease.

Short-chain fatty acids: Gastrointestinal motor responses: Lactate: Polypeptide YY

While the effects of short-chain fatty acids (SCFA) on the intestinal epithelium have been, and still are, widely investigated all over the world, less is known about the other physiological effects of SCFA. Nevertheless, SCFA, the main end products of colonic fermentation, have functions other than those associated with intestinal mucosal integrity. Furthermore, the effects of SCFA are not limited to the large intestine, where they are present at high levels; they extend to the upper intestinal sites.

Motility and sensitivity to distension, which are pivotal in gut functioning, health and well-being, are modulated by colonic fermentation, especially by SCFA. The present brief review summarizes both the local and remote effects of SCFA on gastrointestinal and colonic motility, focusing on mechanisms. In addition, some putative consequences of these effects for the health and well-being of the intestine are suggested.

Short-chain fatty acids and colon motility

Colonic motor activity is characterised by two main types of contractions. One type is tonic contractions that can decrease the organ volume; the other is peristaltic contractions, propagated over long or short distances and associated with anterograde and retrograde movements of contents. Transit rate depends on the pattern of occurrence of these contractions. SCFA could evoke tonic contractions and inhibit peristaltic activity, which would result in an overall increase in the fluid flow through the large intestine and a reduction in colonic transit time. However, the colonic motor effect of SCFA is related to their concentration in the lumen and seems to occur only when the concentration is dramatically elevated. In addition, SCFA effects might also differ between species, and there is no evidence that SCFA influence colon motility in man.

A possible direct influence of SCFA on intestinal motility in single-stomached animals was first suggested by Yajima (1985), who recorded a tonic contraction of rat colonic muscle strips in response to propionate, butyrate or valerate *in vitro*. The dose-dependent contractile 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. The hypothesis that SCFA may be one of the lumen stimuli

Abbreviations: LES, lower oesophageal sphincter; PYY, polypeptide YY; SCFA, short-chain fatty acids.
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regulating colonic motility was further elucidated using *in vitro* and *in vivo* animal models. When infused into an empty isolated rat colon *in vitro* SCFA decreased the contractile peristaltic activity (Squires *et al*. 1992). Similar motor inhibition was observed *in vivo* in rats infused with SCFA directly into the proximal colon (Cherbut *et al*. 1998), while depression of SCFA by antibiotics induced an increase in the motor index (Cherbut *et al*. 1991). These results thus indicate that SCFA exert an inhibitory influence on the peristaltic contractile activity of the large intestine in rats.

However, these effects appear to depend on the lumen concentration of SCFA and occur only above a physiological threshold. Indeed, infusion of SCFA at either low concentration (10 mM) in the empty colon, or physiological concentration (100 mM) in the rat colon had no effect on colonic motility and transit time. In contrast, infusion at high concentration (100 mM in the empty colon and 500 mM in the normal colon) markedly decreased the motor index. It is noteworthy that infusion of 100 mM-SCFA in the colon of normally-fed rats did not change the concentration of SCFA in the contents (75 (SE 12) mmol/kg), whereas the 500 mM solution doubled it (150 (SE 13) mmol/kg), suggesting that high lumen concentrations of SCFA are required to stimulate a change in motility (Fig. 1). It is also possible that the motor effect of SCFA may depend on the nature of the individual SCFA. Yajima (1985) reported that acetate and lactate had no contractile effect on colonic muscle strips

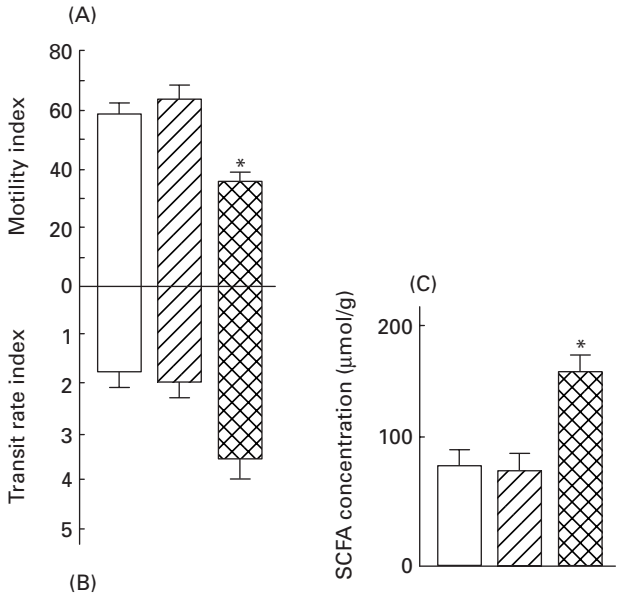

Fig. 1. Concentration-dependent motor response of the large intestine to infusion of short-chain fatty acids (SCFA) in rats. Normally-fed rats were infused with solutions of saline (9 g NaCl/l; ▭), 100 mM-SCFA at 0·4 mmol/h (▨) and 500 mM-SCFA at 2 mmol/h (⋈) and motility index (A), transit rate index (B) and SCFA concentrations (C) were determined. Values are means with their standard errors represented by vertical bars. The mean values for overall motility index of the colon, transit rate index through the large intestine and SCFA concentration in colon contents of rats infused with 500 mM-SCFA were significantly different from those of rats infused with saline: $*P < 0{\cdot}05$. Infusion of 100 mM-SCFA did not change the SCFA concentration and had no effect on colon motility. (Adapted from Cherbut *et al*. 1998.)

in vitro, even at high doses, whereas propionate, butyrate and valerate evoked a similar response. However, Squires *et al*. (1992) found no significant difference between the effects of individual SCFA and that of the mixture. *In vivo* only propionate and butyrate affected the rat colonic motility, acetate having no effect (Cherbut *et al*. 1998).

The motor effect of SCFA might differ between species. Indeed, infusion of a 100 mM-SCFA solution did not modify the colonic capacitance and transit in two healthy human subjects (Kamath *et al*. 1990). Similarly, there was no change in the colonic motility of healthy human subjects receiving an infusion of a SCFA mixture in the proximal colon for 3 h (Gorbatchef *et al*. 1998) at a concentration of 200 mM and infusion rate of 50 mmol SCFA/h into the lumen. Even if this dose was sufficient to elevate SCFA concentration in the contents, it is possible that it was insufficient to activate a putative sensory mechanism to SCFA in the human proximal colon.

Short-chain fatty acids and colon sensitivity to distension

In addition to altered intestinal motility, increased visceral sensitivity is an extremely common disorder that is associated with impairment in intestinal well-being and overall quality of life. Visceral sensitivity is also considered to be the most important therapeutic target in patients with irritable bowel syndrome. While the involvement of gas overload in abdominal discomfort is still considered, the possible effects of SCFA remain undetermined. A preliminary study showed that colo-rectal enemas of SCFA did not improve the increased sensitivity to distension in 2,4,6-trinitrobenzenesulfonate-induced colitis in rats (Tarrerias *et al*. 2002). Moreover, rectal administration of butyrate greatly decreased the volume of distension inducing pain in normal rats, and worsened hypersensitivity in rats with colitis. This effect was abolished when butyrate was delivered with propionate and acetate. Although these findings are unconfirmed, they may suggest that increasing the butyrate concentration in the colon might have adverse effects on gastrointestinal well-being.

Short-chain fatty acids and ileal motility

Physiologically, SCFA are at low concentration in the ileum. However, the level of ileal SCFA may increase in some physiological and clinical conditions such as ileal reflux of colonic contents, bacterial overgrowth etc. Several studies have investigated the direct effect of SCFA on the ileal motility in rats (Yajima, 1984), dogs (Kamath *et al*. 1987), pigs (Cuche & Malbert, 1998) and healthy human subjects (Kamath *et al*. 1988; Coffin *et al*. 1997). All studies have demonstrated that SCFA, present in the terminal ileum as a result of an intraluminal infusion or of colo-ileal reflux, stimulate peristaltic contractions and increase tonic activity (Fig. 2), which may elicit an 'emptying response'.

Short-chain fatty acids and the ileo-colonic brake

It is well established that nutrients in the human proximal and distal small intestinal lumen participate in regulating gastric motility and emptying, a phenomenon known as the

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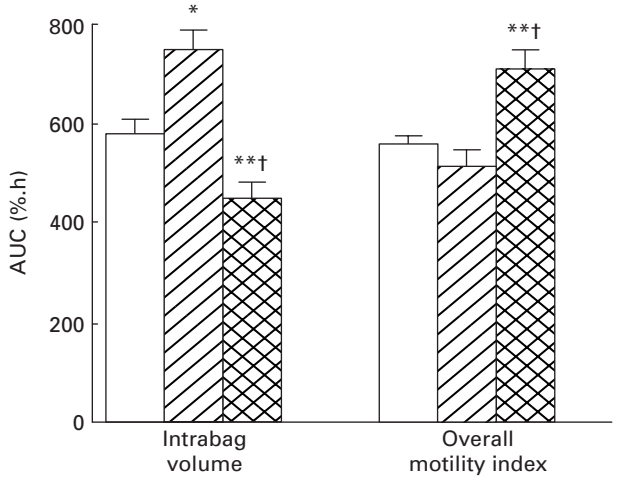

Fig. 2. Areas under curves (AUC) of intrabag volume and overall motility index during 1 h infusion of saline (9 g NaCl/l; ▭), lipids (▨) and short-chain fatty acids (⧓) in the terminal ileum of healthy human subjects. Values are means with their standard errors represented by vertical bars. Mean values were significantly different from those for saline: ** $P < 0{\cdot}01$. Mean values were significantly different from those for lipids: † $P < 0{\cdot}05$. (Adapted from Coffin *et al*. 1997.)

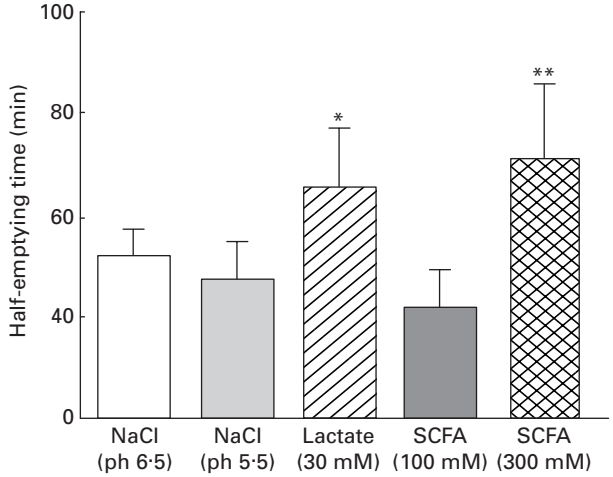

Fig. 3. Half-emptying times of the stomach for healthy human subjects infused with saline (9 g NaCl/l; at pH 6·5 (□) and 5·5 (▭)), short-chain fatty acids (SCFA; 100 (▩) and 300 mM(⧓)) or lactate (▤) into the proximal colon. Values are means with their standard errors represented by vertical bars. Mean values were significantly different from those for subjects infused with saline: * $P < 0{\cdot}05$, ** $P < 0{\cdot}01$. For SCFA the increase in gastric emptying time was dose dependent, and lactate had a similar delaying effect. Gastric emptying was not influenced by saline pH.

'intestinal brake'. More recently, it has been shown that the proximal large intestine can also affect the upper gut motility. Furthermore, SCFA could be responsible for this 'colonic brake'. A decrease in gastric tone was observed after intracolonic administration of lactose, and the effect was reproduced in the same volunteers by infusion of SCFA into the proximal colon (Ropert *et al*. 1996). Lactate displayed a similar effect to SCFA (V Bicheler, unpublished results). The gastric response to SCFA depended on the dose and was induced only by highly concentrated solutions (Fig. 3). Gastroparesia was also triggered by SCFA infused in the distal ileum in pigs (Cuche & Malbert, 1999).

In addition to their effect on gastric motility, colonic SCFA affect lower oesophageal sphincter (LES) activity. They enhanced the postprandial fall in LES pressure and increased the number of transient LES relaxations and the number of gastro-oesophageal reflux episodes associated with the LES relaxations in healthy human subjects (Piche *et al*. 2000). Accordingly, oral administration of fructo-oligosaccharides increased the rate of transient LES relaxations as well as the number of reflux episodes and oesophageal acid exposure in patients with gastro-oesophageal reflux disease (Piche *et al*. 2002).

Mechanisms of the intestinal motor action of short-chain fatty acids

Surprisingly, although mechanisms for the remote action of SCFA on gastrointestinal motility have been elucidated, those of their local effects are incompletely understood. Colonic and ileal SCFA inhibit gastric motility by an endocrine mechanism probably involving polypeptide YY (PYY) secretion. Using innervated and denervated ileal loops, Cuche *et al*. (2000) demonstrated that, in conscious pigs, extrinsic ileal innervation was not necessary for ileal SCFA to inhibit gastric motility. In addition, the authors observed that PYY but not glucagon-like peptide 1 was released in the bloodstream during SCFA ileal infusion, suggesting that this peptide may be responsible for gastric motility inhibition. In healthy human subjects the postprandial elevation of blood PYY was enhanced by SCFA infusion into the proximal colon, whereas a similar infusion of saline or lactate had no effect. Systemic levels of oxyntomodulin-like immunoreactivity (OLI) and glucagon-like peptide 1 were unchanged in these experiments. Moreover, a relaxation of the proximal stomach and a delay in gastric emptying were observed in response to intravenous PYY administered at doses mimicking blood concentrations induced by SCFA colonic infusion (Bicheler *et al*. 1999). These results strongly suggest that PYY release is involved in the ileo-colonic brake triggered by SCFA.

A similar mechanism could be responsible for the local motor effects of SCFA in the rat colon. Indeed, infusing SCFA into the rat colon increased the blood concentration of PYY, and administration of exogenous PYY reproduced the motor effect of SCFA (Cherbut *et al*. 1998). Furthermore, immunoneutralization of circulating PYY with a PYY antiserum abolished the motor effect of SCFA (Fig. 4). In addition to this humoral pathway, activation of vagal afferents sensitive to SCFA may be involved. When procaine, an agent that blocks neural conduction, was administered locally, the motor effect of SCFA in the rat colon was abolished (Cherbut *et al*. 1998). A similar finding was reported *in vitro* (Yajima, 1985) as well as *in vivo* in the dog ileum (Kamath *et al*. 1988), and vagal mechanosensitive units inhibited by SCFA have been identified in the ileal mucosa of pigs (Cuche *et al*. 2001). SCFA might interact with the vagal units by means of two putative mechanisms. SCFA induced contractions in the isolated ileal

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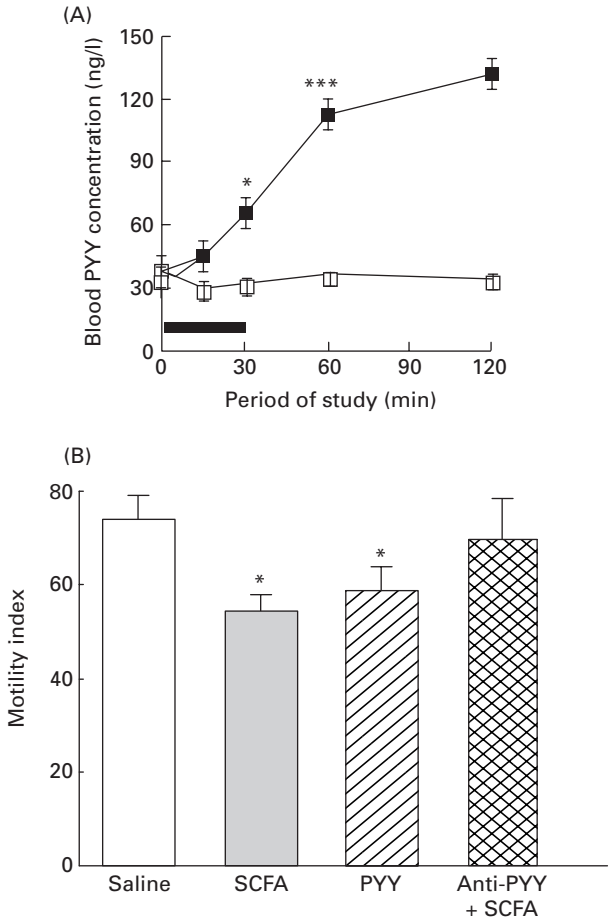

Fig. 4. Involvement of polypeptide YY (PYY) release in the motor effects of short-chain fatty acids (SCFA) in the rat large intestine. Values are means with their standard errors represented by vertical bars. (A) Blood PYY concentrations for rats infused with saline (9 g NaCl/l; ▭) or SCFA (▬). (——), Period of infusion. Mean values were significantly different from those for saline infusion: $*P < 0{\cdot}05$, $***P < 0{\cdot}001$. (B) Overall motility index in rats receiving intravenous saline (▭), SCFA (▤), PYY (▨) or anti-PYY + SCFA (▬). Mean values were significantly different from those for saline infusion: $*P < 0{\cdot}05$. Intravenous PYY mimicked the SCFA-induced decrease in overall motility index, whereas intravenous antiserum of PYY abolished the motor effect of SCFA. (Adapted from Cherbut *et al.* 1998.)

muscle cell by means of an acid-sensitive Ca-dependent mechanism (Cherbut *et al*. 1996) that could also occur at the terminal ending of vagal afferents. Similarly, the large PYY response induced by SCFA might also activate vagal afferents.

Putative physiological and clinical importance of the short-chain fatty acids motor activity in the intestine

The local effects of SCFA on motor activity of the distal gut (ileum and colon) could result in maintenance of physico-chemical balance in the lumen environment. In the ileum SCFA are considered the chemical signal whereby the ileum can 'sense' the presence of colon contents in the lumen as a result of an ileal reflux. Such a reflux has been described in pigs (Cuche & Malbert, 1998), but whether it occurs physiologically or only in pathological situations in man is unknown. In the large intestine SCFA may exert an inhibitory control of peristaltic activity. However, this effect would occur only below or above thresholds of SCFA concentration in the colon contents. In this way a large decrease in SCFA concentration, for instance during antibiotic therapy, could stimulate the contractile activity of the colon in order to increase the mixing and turnover rate of contents, thus enhancing bacteria activity, as suggested *in vitro* (El Oufir *et al*. 2000). Conversely, if there is a dramatic increase in SCFA in the colon contents, they might depress motility and increase fluid flow in an attempt to attenuate fermentation. In most cases these physiological effects are normal events that have no deleterious consequences. Nevertheless, it cannot be excluded that, in certain pathological situations such as inflammatory bowel disease or irritable bowel syndrome, a large increase in SCFA production in the large intestine might induce adverse motor and sensitive effects.

Through the remote effects of SCFA, colonic fermentation may contribute to the regulation of upper gut motility, including gastric and LES relaxation, reduction in gastric emptying rate and possibly lower interdigestive acid output and suppression of short-term food intake. These outcomes are possible because under normal conditions the amount of carbohydrates escaping digestion and absorption in the small intestine may exceed 10 g after a normal meal, and bacterial fermentation of these carbohydrates will induce approximately 50 mmol SCFA, which is close to the experimental doses inducing delayed gastric emptying and a fall in LES pressure. Moreover, it can be calculated that a much higher quantity of SCFA would be produced as a result of lactose malabsorption in lactase-deficient patients after consumption of about 1 litre cows' milk. However, the role of these motor effects in disturbances observed in these patients cannot be ascertained. Similarly, it is unclear whether increased LES dysfunction induced by consumption of fermentable carbohydrates in gastro-oesophageal reflux disease is related to the motor effects of SCFA.

In conclusion, it should be stressed that the intestinal motor effects of SCFA depend on the SCFA concentration in the lumen contents, and that these effects seem to occur only below or above a certain threshold. This situation may indicate that not all fermentable carbohydrates would have the same effects, and the effects would depend on their fermentation patterns and the ingested dose. While excessive amounts of rapidly-fermented sugars might induce undesirable motor and sensitive effects, more-steadily-fermented fibre might contribute to the regulation of gastrointestinal motility in a beneficial way.

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