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# Effects of Short-Chain Fatty Acids on Gastrointestinal Motility

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Besides their action on gut morphology and function, short-chain fatty acids (SCFAs), produced by bacterial fermentation of carbohydrates in the colon, influence gastrointestinal motility. As they are not present in the stomach and proximal small intestine, SCFAs do not directly affect motility of these segments. However, caecal infusion of SCFAs as well as colonic fermentation of lactulose induce a relaxation of the proximal stomach in humans, indicating that SCFAs can affect motility at a distance from their site of production. Moreover, this suggests that SCFAs may be involved in the so-called 'ileocolonic brake', i.e. the inhibition of gastric emptying by nutrients reaching the ileo-colonic junction. In the terminal ileum, where their concentration may increase following a colo-ileal reflux, SCFAs stimulate contractions and shorten ileal emptying, which may protect ileal mucosa against the potentially harmful effects of the reflux of colonic contents. Although SCFAs are produced and concentrated in the colon, their action on motility of this organ is not clearly understood and may depend on concentration, molecular structure of the acids, responsiveness of the colonic segments and animal species. The mechanisms of action of SCFAs on gastrointestinal motility are not completely elucidated. They may involve systemic humoral and neural pathways as well as local reflexes and myogenic responses.

**Key words:** Colon; motility; short-chain fatty acid; small intestine; stomach

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Short-chain fatty acids (SCFAs) are the main end products of colonic bacterial fermentation of unabsorbed starch and non-starch polysaccharides (i.e. dietary fibres) and the major organic anions present in the colonic content. The term SCFAs refers to a group of C<sub>2</sub>–C<sub>6</sub> monocarboxylic acids, but of these compounds only acetic, propionic and n-butyric acids are produced in significant amounts by the fermentation of carbohydrates in the human colon; the branched-chain (i.e. isobutyric and isovaleric) acids result from the degradation of proteins. The pivotal importance of SCFAs has been known for many years in some animal species, especially ruminants, where they represent most of the energy supply, but only recently has their role in the maintenance of human intestinal 'mucosal health' and their implication in the pathophysiology of several diseases been recognized (1, 2). Whereas excellent reviews on their actions on GI morphology and function have been previously published (1, 2), there is little information on the effects of SCFAs on gastrointestinal motility. These are briefly discussed in this review.

## EFFECTS OF SCFAS ON GASTRIC MOTILITY

When administered at fairly high concentrations (60 to 80 mmol/L) with a meal, acetic acid delays gastric emptying through the activation of duodenal receptors and inhibitory vagal reflexes. However, in physiological conditions, SCFAs do not accumulate in the stomach and duodenum at concentrations sufficient to directly influence gastric emptying.

On the contrary, using an electronic barostat to measure gastric tone in healthy volunteers, we recently showed (3) that colonic fermentation of lactulose as well as colonic infusion of a mixture of SCFAs in the caecum resulted in a marked and dose-dependent relaxation of the proximal stomach (Fig. 1). Therefore, SCFAs may be one of the mediators involved in the so-called 'ileo-colonic brake', i.e. the inhibition of gastric emptying by the presence of nutrients in the distal ileum and proximal colon. Whether this effect is mediated through a neural pathway or by hormonal effects is still unknown. Although in animal experiments (4) SCFAs have been shown to release several intestinal peptides, especially peptide YY (PYY), in humans we failed to detect any specific effect of SCFA colonic infusions on PYY and enteroglucagon-related peptides (oxyntomodulin and glucagon-like peptide-1 plasma levels) (3). The role of SCFAs and colonic fermentation as a regulator of upper GI motility is likely because under normal conditions physiological malabsorption of nutrients occurs, especially of resistant starch. Moreover, since the same inhibitory effects on gastric tone were reproduced by colonic infusion of 20 g lactose, it is conceivable that some of the symptoms observed in lactase deficiency may be related to the fermentation of this malabsorbed disaccharide into SCFAs which, in turn, could affect gastric motility.

## EFFECTS OF SCFAS ON SMALL INTESTINAL MOTILITY

In the human gut, SCFAs are found in high concentrations

Table I. Studies of the effects of SCFAs on colonic motility (15–19)

References	Species	Models	Results	Interpretation
Yajima (15)	Rat	In vitro (segments of proximal middle and distal colon in organ bath)	(1) Mucosal application induced contraction but serosal applications were without effect (2) Maximal response at 0.1 mM for propionate, valerate, butyrate (acetate without effect) (3) Contractile effect abolished by atropine and TTX	Enteric reflex involving local sensory neurons
Squires et al. (16)	Rat	In vitro (isolated colon mounted in vitro. Luminal infusion of acetate, butyrate, propionate and mixture)	(1) Dose-dependent reduction of colonic activity (maximal at 100 mM) (2) Na salts of SCFAs or acidified Krebs solution without effect	SCFAs inhibit smooth muscle activity
Flourié et al. (17)	Dog	In vivo (isolated colonic loop) Infusion of a mixture of SCFAs: 71 mM acetate, 26 mM propionate, 11 mM butyrate	No effect of SCFAs on periodicity of cycles of motility	Colon is less sensitive than ileum to SCFAs
Cherbut et al. (18)	Rat	In vivo (colonic motility and transit time after antibiotics and infusion of SCFAs into the caecum)	(1) No effect on caecocolonic transit time despite dramatic reduction of SCFAs in feces (2) Increased motility index (3) Cyclic motility pattern replaced by continuous activity (4) Stimulation of myoelectrical activity by SCFAs followed by inhibition	SCFAs may regulate colonic motility. Interaction with the pharmacological effects of antibiotics and modifications of colonic contents
Kamath et al. (19)	Human	In vivo (measure of colonic Capacitance and transit by scintigraphy). Caecal infusion of a mixture of SCFAs (100 mM)	No significant effect of SCFAs	

only in the large bowel. However, following colo-ileal reflux their concentration may increase locally in the distal ileum. In pathological conditions, increased concentrations of SCFAs have been reported in both the jejunum and ileum of patients with small-bowel bacterial overgrowth (5). It is therefore of biological relevance to examine the action of SCFAs on small-bowel motility. Because regional differences in responsiveness to SCFAs may contribute to explain some conflicting results in the literature (for review see 6), it seems appropriate to examine separately studies dealing with proximal and distal intestinal motility.

#### Proximal small-bowel motility

There is now quite a large body of knowledge suggesting that SCFAs do not affect the motility of the upper small intestine. For instance, we did not detect, by manometric recording performed in both fasting and postprandial states, any significant change after either bolus injection or continuous infusion of a mixture of SCFAs into the duodenum of healthy subjects (7). Moreover, in contrast to studies performed in rats, which showed that SCFAs may shorten stomach-to-caecum transit time (8), we did not observed any significant variation of *oro-caecal transit time*—measured by hydrogen breath test—after duodenal infusion of SCFAs in humans. The different routes of administration (ileal versus jejunal) as well as different species may account for the

resulting differences in transit time. SCFAs are also unable to modify jejunal contractions of anaesthetized rats (9). Finally, in humans as in dogs (10), the motility of the proximal small bowel does not appear to respond to SCFAs, whether administered distally in the ileum (10) or proximally as in our studies (7).

#### Effects on ileal motility

It has now been established beyond doubt that, at least in some conditions, SCFAs can stimulate *ileal motility in the fasting and early postprandial phases*. For instance, in humans and in dogs, ileal infusion of SCFAs is followed by many bursts of contractions which rapidly migrate aborally (11–14). Similarly, in rats, intravenous administration of SCFAs was able to elicit ileal contractions (9). With regard to their action on ileal motility, the potency of the different SCFAs seems to be inversely related to the length of their chain (8). Hence, acetic acid is more potent than propionic acid, while butyric acid is the less effective one. The magnitude of the effect of SCFAs on ileal motility is also concentration-dependent, the maximal stimulation occurring at levels close to those found in the colon. Similarly, there is a trend toward a greater effect of SCFAs at pH 7.0 than at pH 3.8, which suggests that they are probably more efficient when dissociated than in their protonated form (8, 11).

In summary, SCFAs are able to specifically stimulate the

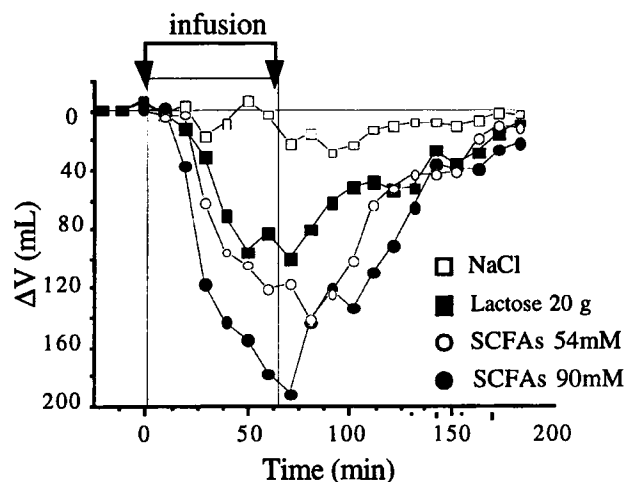


Fig. 1. Average effects on barostat bag volumes ( $\Delta V$ , mL; mean in 7 healthy subjects) of the colonic infusion (3 mL/min during 60 min) of the following solutions: 0.15 mol/L NaCl ( $\square$ ), 20 g/180 mL lactose ( $\blacksquare$ ), 54 mmol/180 mL SCFAs ( $\circ$ ), and 90 mmol/180 mL SCFAs ( $\bullet$ ). Barostat bag volume increased during the intracolonic infusions of SCFAs and lactose. Saline had no significant effect on bag volume. The peak increase in bag volume was greater ( $p < 0.01$ ) and occurred earlier ( $p < 0.05$ ) during SCFA infusion (90 mmol) than during lactose or SCFA infusion (54 mmol). (Reproduced from *Gastroenterology* with the permission of the Editor).

ileum of dog and man, thus resulting in a motility pattern responsible for emptying of the distal small bowel. Direct evidence of this *clearance function* has been provided by Fich et al. (10) by elegant scintigraphic studies showing that ileal emptying was significantly accelerated by SCFAs, whereas simultaneous recording of intraluminal pressures exhibited phasic burst activity. Although protection of the ileal mucosa against the potentially harmful effects of the reflux of colonic contents may be an important function of SCFAs-induced ileal motility, the exact mechanisms of this action are not completely elucidated. Whether SCFAs are able to act locally on smooth muscle and/or to trigger on chemoreceptors or release intestinal neuropeptides should be further investigated.

## EFFECTS OF SCFAS ON COLONIC MOTILITY

The effects of different SCFAs on colonic motility have been studied in various conditions (15–19), namely in *in vitro* and *in vivo* models, at various concentrations and in different animal species (Table I). Overall, SCFAs seem to have little (if any) effect on transit time itself. The effects on colonic motility are probably far more complex than in the ileum. At low concentrations, SCFAs may have a contractile effect through an enteric cholinergic reflex. In contrast, when they are at high concentrations and in their non-dissociated forms, they may rather exert an inhibitory influence on colonic motility. Other parameters, e.g. different responsiveness of proximal versus distal colon or characteristics of the molecule itself, may also influence the resultant effect of SCFAs. Taken

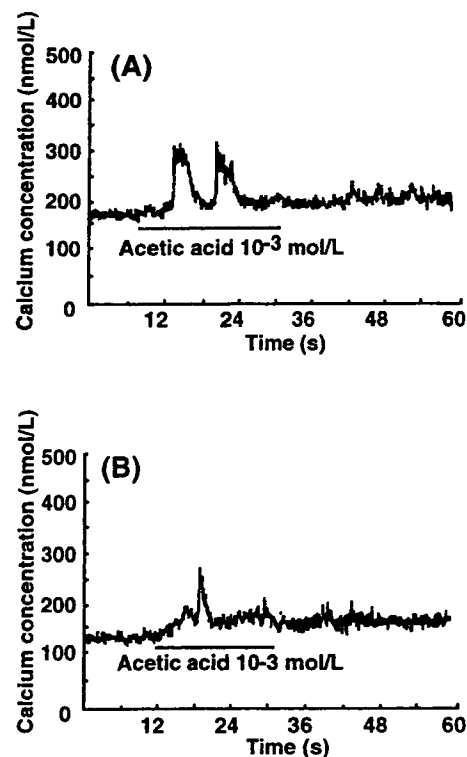


Fig. 2. Representative tracing showing the effect of acetic acid ( $10^{-3}$  mol/L) applied to isolated ileal smooth muscle cells on intracellular calcium concentration. The bathing solution did not contain (A) or contained (B) D 600 (10  $\mu$ mol/L) to inhibit calcium entry through voltage-dependent calcium channels. (Reproduced from *Gut* with the permission of the Editor).

together, these results suggest that SCFAs may also participate in adaptation of the colon to its contents, which in turn depends on diet and microflora.

## NEW INSIGHTS ON THE MECHANISMS OF ACTION OF SCFAS ON SMOOTH INTESTINAL MUSCLE

The mechanisms of action of SCFAs on gastrointestinal motility are not completely elucidated. It is now established that SCFAs can influence motility of gut segments (e.g. gastric tone) distant from their organ of production (i.e. the colon). This type of effect strongly suggests humoral or neural pathways. The role of glucagon-like peptides and PYY has already been discussed, though controversial results have been published in various species and models (4, 20).

SCFAs may also influence motility by local reflexes which do not require systemic control and which are not abolished by either adrenergic or cholinergic blockade. However, it is not defined whether SCFAs act through the enteric plexus or directly on the intestinal smooth muscle cells.

In that context, we recently investigated the effect of individual SCFAs on isolated rat terminal ileal segments and isolated smooth muscle cells (21). SCFAs (as well as exogenous acids like tartaric or citric acids) induced

concentration-dependent contractions of ileal strips. The effect was not different among the individual SCFAs, whereas sodium salts were without effect. The contractions elicited were not blocked by tetrodotoxin, atropine or hexamethonium, showing that it was not mediated through a cholinergic pathway. Moreover, removal of the mucosa or addition of procaine to the bath did not change the SCFA-induced contractions. In contrast, the calcium-channel antagonist verapamil completely abolished the response. In addition, application of SCFAs to isolated ileal myocytes increased intracellular calcium concentration, an effect which was inhibited by D 600 (a blocker of voltage-dependent calcium channels) (Fig. 2). In conclusion, these results strongly suggest that the contractile response stimulated by SCFAs in the rat jejunal ileum results from an acid-sensitive calcium-dependent myogenic mechanism. This effect of SCFAs on smooth muscle may differ from that operating in other tissues, e.g. colonic arteries (which are dilated by SCFAs (22)) or uterine muscle cells.

Finally, the effects of SCFAs on the smooth cells deserve further evaluation in more chronic conditions of administration. Indeed, some effects of chronically enriched dietary fibre regimens may be the result of a trophic action on the cytoskeleton and the extracellular matrix of the smooth muscle cells, as suggested by preliminary experiments from our laboratory (23).

## CONCLUSIONS AND PERSPECTIVES

SCFAs which are produced in the colon by bacterial fermentation of carbohydrates can influence the motility of the gut in different ways and by different mechanisms, acting either locally or at a distance, modulating physiological functions such as the ileocolonic brake or the protection against colo-ileal reflux. The motor response of the colon is probably complex. It may be speculated that regulation of colonic motility by SCFAs could contribute to the adaptation of this metabolic organ to its contents, the balance between the production of fermentation products and the requirements or tolerance of the body to these compounds being maintained. In that connection, evidence from our group has recently shown that drugs which affect transit time (namely cisapride and loperamide) are capable of inducing dramatic changes in the production and concentration of SCFAs (24). These variations may be of pathophysiological relevance to colonic disorders and especially to colorectal cancer.

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