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CONTRACTILE EFFECT OF SHORT-CHAIN FATTY ACIDS ON THE ISOLATED COLON OF THE RAT

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SUMMARY

1. The contractile effect of short-chain fatty acids on proximal, middle and distal segments of the rat colon was studied *in vitro*. A single contraction of the longitudinal muscle of the everted preparation of the middle and distal but not the proximal colon was induced by mucosal application of propionate, butyrate or valerate.

2. Sigmoid dose–responses were observed between contraction and log dose of propionate, butyrate and valerate. The threshold concentration of short-chain fatty acids was between 0·02 and 0·04 mM. A maximal contraction was induced with 0·1 mM-propionate, butyrate and valerate. While acetate (up to 10 mM) and lactate (up to 30 mM) had no contractile effect at all.

3. Serosal application of short-chain fatty acids was without effect, while the contractile response with up to 10 mM-propionate was abolished in both the middle and distal colon by scraping away the mucosa.

4. Cumulative addition of short-chain fatty acids to the organ bath (without wash-out of the first dose) caused adaptation of the contractile response; thus, the effect of propionate (1 mM) was abolished by prior addition of acetate (10 mM) or lactate (30 mM) or propionate (1 mM) or butyrate (1 mM) or valerate (1 mM).

5. The contractile effect of propionate was also inhibited by atropine (1 μM), procaine (0·4 mM) and tetrodotoxin (3 μM); was unaffected by hexamethonium (0·1 mM) and enhanced by eserine (10 nM).

6. The results suggest that short-chain fatty acids, which are normal constituents of the colon, have the ability to stimulate colonic contractions, probably via an enteric reflex involving local sensory and cholinergic nerves.

INTRODUCTION

The motility of the colon is influenced by local physical or chemical stimuli in the lumen (Christensen, 1981; Wienbeck & Erckenbrecht, 1981). The effects of physical factors, such as distension, or the volume of luminal contents, on colonic motility have been extensively studied (Bayliss & Starling, 1900; Costa & Furness, 1976; Fioramonti & Bueno, 1980). On the other hand, the effects of luminal chemical stimuli on colonic motility are still unclear (Costa & Furness, 1982).

In most mammals, the colon functions as a chamber of continuous microbial

fermentation. Short-chain fatty acids such as acetic, propionic, butyric and valeric acid, are the major products of this fermentation (Wrong, Edmonds & Chadwick, 1981), and constitute the major anions in the colon (Wrong *et al.* 1981). We previously reported preliminary results that short-chain fatty acids stimulate the motility of the everted segments of the rat colon (Yokokura, Yajima & Hashimoto, 1977), and we therefore proposed that short-chain fatty acids may act as a luminal chemical stimuli for the colonic motility.

In the present study I have further examined the effect of short-chain fatty acids on colonic motility *in vitro* in three anatomically defined segments (proximal, middle and distal) of the rat colon. Such division of the colon was essential, because the mammalian colon shows marked regional variation in structure and function (Snipes, Clauss, Weber & Hörnicke, 1982; Engelhardt & Rechkemmer, 1983).

METHODS

Animals

Male Sprague–Dawley rats (250–300 g) were used. They were fed a pelleted diet (Type MF, Oriental Yeast Co., Tokyo, Japan) *ad libitum* with free access to the water, and were starved overnight before each experiment.

Anatomical division of the colon

The colon was arbitrarily divided into three segments in this study, namely the proximal, middle and distal colon. The middle colon was defined as the segment between the entrances of the right and left branches of the middle colic artery; the proximal colon as the segment orad to the middle colon, and the distal colon as the segment aborad to the middle colon, terminating at the border between the peritoneal cavity and the pelvic cavity.

Experiments

Rats were stunned by a blow on the head and bled. The colon was quickly removed, the luminal contents were gently squeezed out and the colon was placed in modified Krebs solution (pH 7·3) of the following composition (mM): NaCl, 123·5; KCl, 4·7; $CaCl_2$, 2·5; $MgSO_4$, 1·2; KH_2PO_4, 1·2; $NaHCO_3$, 20; glucose, 11·1, which was bubbled with a gas mixture of 95% O_2 and 5% CO_2.

Five experimental preparations were used. (a) Everted preparations were used to determine the effects on colonic motility of short-chain fatty acids applied from the luminal side. Each colonic segment was everted and cut to approximately 2 cm long and was vertically mounted with both ends open to the mucosal solution (10 ml Krebs solution). For the mucosal application of local anaesthetics, the aboral end of the everted segment was ligated with the open oral end placed above the meniscus of the bath just before the application of short-chain fatty acids. (b) Uneverted preparations were used to determine the effect of short-chain fatty acids from the serosal side. After both ends of the segment were ligated, each colonic segment (approximately 2 cm) was mounted vertically. (c) Mucosa-scraped preparations: the mucosa of the middle and distal colon were scraped with a surgical blade (4–5 times) and mounted vertically. Each preparation was checked histologically for the removal of the mucosa. (d) Strip preparations: to determine the effect of atropine, eserine, tetrodotoxin and hexamethonium on the contractile response to propionate, segments of the middle and distal colon were opened and halved longitudinally to form a strip preparation and mounted vertically. (e) Longitudinal muscle preparations: strips of the longitudinal muscle of the distal colon were prepared from a sheet of the tissue turned mucosa down using fine forceps.

In all experiments the tissues were kept in the modified Krebs solution at 32 °C, continuously bubbled with a mixture of 95% O_2 and 5% CO_2. A longitudinal tension of 2 g was initially applied to all preparations to aid relaxation. During experiments the preparations were kept at a resting load of approximately 1 g. The longitudinal mechanical activity was recorded isometrically with

a force transducer (TB-611T, Nihon Kohden) and a polygraph (RM-6000, Nihon Kohden). The tissues were left to equilibrate for 20 min before application of the short-chain fatty acids and 15–20 min intervals allowed between each application.

Data analysis

Results are expressed as mean ± S.E. of the mean. The mean results were compared by Student's *t* test for paired variates (Table 1). A difference resulting in P value less than 0·05 was considered significant.

Drugs

Sodium acetate, sodium propionate, sodium butyrate and sodium valerate were obtained from Kanto Kagaku Co., Ltd. (Tokyo). Acetylcholine chloride (ACh), atropine sulphate, eserine sulphate, 1,1-dimethyl-4-phenylpiperazinium iodide (DMPP), hexamethonium bromide, 5-hydroxytryptamine hydrochloride (5-HT) and sodium lactate were obtained from Sigma Chemical Co. (St. Louis, MO, U.S.A.). Procaine hydrochloride and tetrodotoxin (TTX) were obtained from Sankyo Seiyaku Co. (Tokyo). Bradykinin and substance P were obtained from Peptide Institute, Inc. (Osaka).

RESULTS

Spontaneous activity of the rat everted colon

The everted preparations of the three colonic segments exhibited less spontaneous contractions than the uneverted preparations. The proximal segments showed regular phasic contractions, and the distal segments showed small regular phasic and less regular tonic contractions. The spontaneous contractions seldom occurred in the middle segments (Fig. 1).

Effect of short-chain fatty acids on the everted preparations

Mucosal application of propionate, butyrate and valerate evoked a tonic contraction of the middle and distal colon, but not of the proximal colon (Fig. 1). The contraction occurred within 10 s after the addition of the acids to the bath. In contrast to the effect of ACh, the contraction was not sustained but faded rapidly, to reach the base line in about 1 min (Fig. 1). The effects of propionate, butyrate and valerate were dose dependent over a narrow range of concentrations in the middle and distal colon (Fig. 2). The threshold concentration of these acids was between 0·02 and 0·04 mM. The maximum response was attained by approximately 0·1 mM of these acids. On the other hand, acetate (up to 10 mM) had no effect at all on the contraction of the colonic segments (Fig. 2*A*).

Effect of short-chain fatty acids on the uneverted preparations

To discover the effects of acetate, propionate, butyrate and valerate (up to 10 mM) applied from the serosal side on the contractile response of the three colonic segments, uneverted preparations were used ($n = 4$, for each). Fig. 3 shows a typical trace obtained with propionate in the three segments.

The uneverted proximal segment exhibited rhythmic spontaneous phasic contractions (Fig. 3*A*). The serosal application of ACh elicited a tonic contraction, but short-chain fatty acids did not affect the rhythmic contraction of the proximal colon (Fig. 3*A*). The uneverted middle colon showed spontaneous tonic contractions that had a mean frequency of 0·66 ± 0·08 contractions per minute ($n = 4$). Short-chain

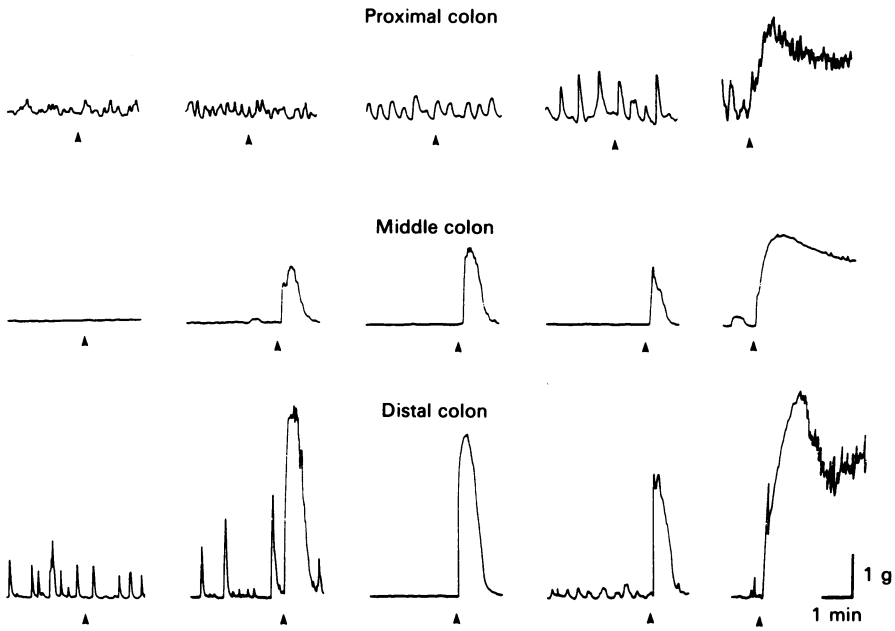

Fig. 1. The effects of short-chain fatty acids and ACh on the contraction of the three everted colonic segments *in vitro*. The drug concentrations indicated refer to the final molarity in the organ bath.

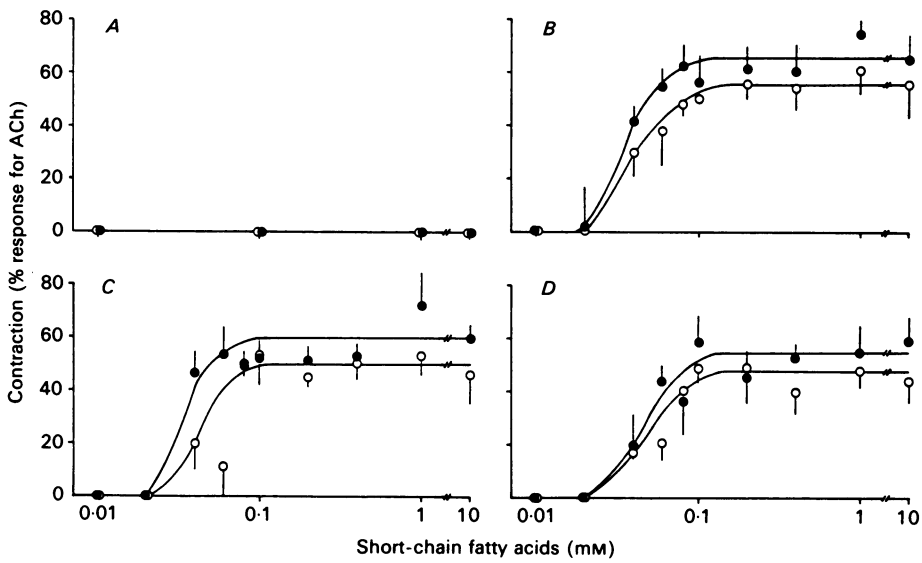

Fig. 2. The dose–response of colonic contraction to short-chain fatty acids. The everted preparations of the middle (○) or distal (●) colon were used. The results were expressed as the percentage of the contraction elicited by ACh (10 μM). *A*, acetate; *B*, propionate; *C*, butyrate and *D*, valerate. Values are mean ± S.E. of the mean ($n = 5$ or 6).

fatty acids were added to the bath immediately after the decline of a spontaneous tonic contraction. Over a period of a few minutes after the serosal addition of short-chain fatty acids hardly any contractions were seen in the middle colon, although ACh instantaneously elicited a tonic contraction (Fig. 3*B*). The uneverted distal colon showed spontaneous phasic contractions the amplitude and frequency of which were less regular. The serosal application of short-chain fatty acids slightly decreased the resting tone of the muscle and the spontaneous phasic activity, but

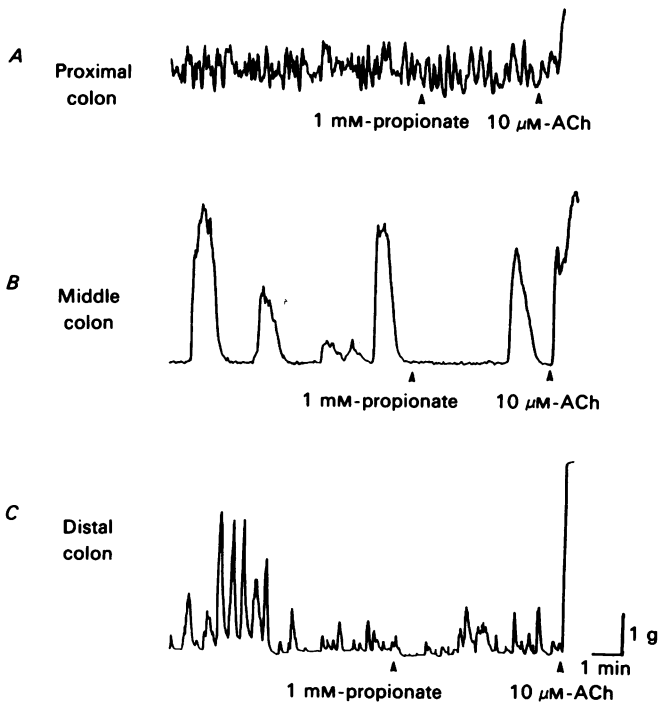

Fig. 3. The effects of propionate and ACh on the contraction of the uneverted preparation from the three colonic segments.

did not cause any contractions exceeding the spontaneous ones, while ACh elicited a strong tonic contraction (Fig. 3*C*). From the above observations, it can be concluded that short-chain fatty acids from the serosal side had no contractile effect in the three colonic segments.

Effect of propionate on the scraped-mucosa and longitudinal muscle preparations

The scraped-mucosa preparations of the middle and distal colon exhibited a contractile response to ACh but not to propionate (up to 10 mM; $n = 6$ for each segment). Fig. 4*A* shows a typical result obtained with the middle colon. The longitudinal muscle preparations from the distal colon exhibited the response to DMPP but not to propionate ($n = 4$) (Fig. 4*B*).

Effect of atropine, eserine, procaine or TTX on propionate-induced contraction in the middle and distal colon

Atropine (1 μM) and TTX (3 μM), and to a lesser extent procaine, inhibited the contractile responses to propionate (1 mM) in the middle and distal colon, while eserine (10 nM) enhanced the contractile effects (Table 1). Hexamethonium (0·1 mM)

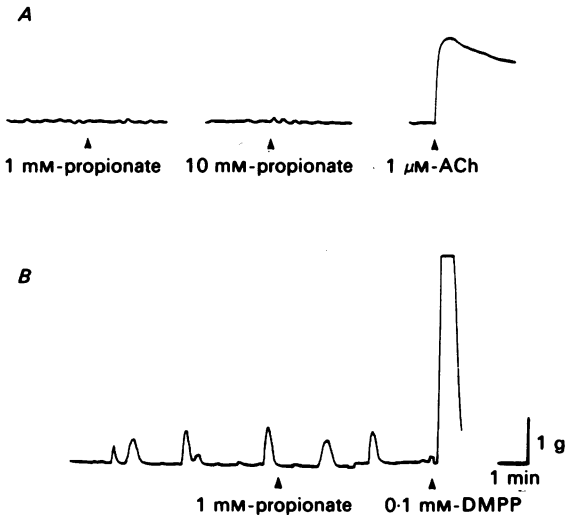

Fig. 4. The effect of propionate on the contraction of the scraped-mucosa preparations of the middle colon (*A*) and on that of the longitudinal muscle preparations of the distal colon (*B*).

TABLE 1. Effects of pharmacological drugs on the contractile response of the middle and distal colon to propionate (1 mM)

	Contraction (*g* of tension)					
	Middle colon			Distal colon		
Drugs	In absence of drug	In presence of drug	*P*	In absence of drug	In presence of drug	*P*
1 μM-atropine	1·38±0·15	0	< 0·01	2·46±0·29	0	< 0·01
10 nM-eserine	1·36±0·22	2·01±0·23	< 0·05	2·35±0·24	2·71±0·24	< 0·05
0·4 mM-procaine	1·81±0·33	0·13±0·07	< 0·01	2·55±0·33	0	< 0·01
3 μM-TTX	2·15±0·14	0	< 0·01	2·89±0·51	0	< 0·01
0·1 mM-hexamethonium	1·83±0·28	2·03±0·34	< 0·05	2·50±0·30	2·57±0·33	N.S.

Values are mean±S.E. of mean (n = 6 for each).

had no inhibitory effect on propionate-induced contraction (Table 1). Figs. 5 and 6 show typical effects of atropine, eserine, procaine, TTX and hexamethonium in the middle colon.

To examine the effects of propionate from the mucosal side a local anaesthetic, procaine, was applied to the mucosal side of everted preparations. The mucosal

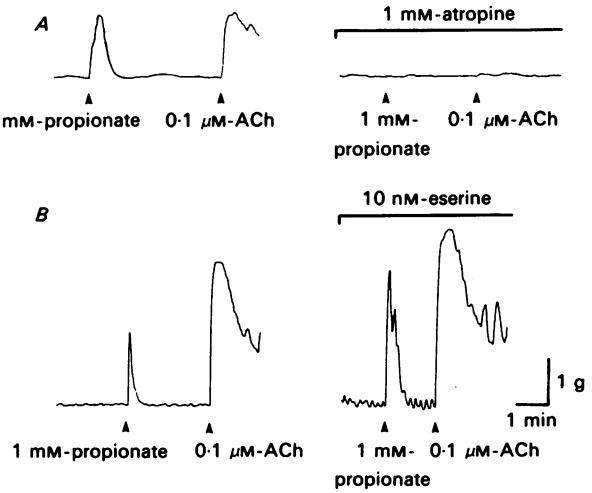

Fig. 5. The effect of atropine and eserine on the contractile response to propionate in the strip preparations of middle colon before (left panel) and after (right panel) the addition of these agents. Both agents were applied 2 min before the addition of propionate. *A*, atropine; *B*, eserine.

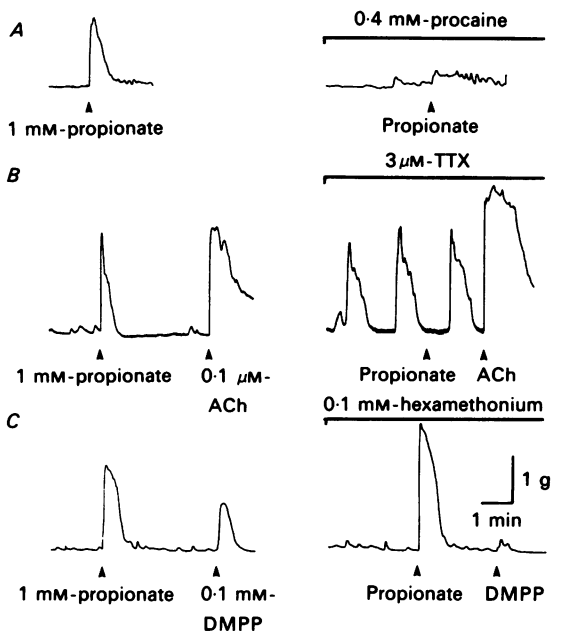

Fig. 6. The effect of procaine, TTX and hexamethonium on the contractile response to propionate, ACh and DMPP in the middle colon before (left panel) and after (right panel) the addition of these blocking agents. The blocking agents were applied 3 min before the addition of propionate. *A*, procaine added only to the mucosal side of the everted preparations; *B*, TTX and *C*, hexamethonium given to the strip preparations.

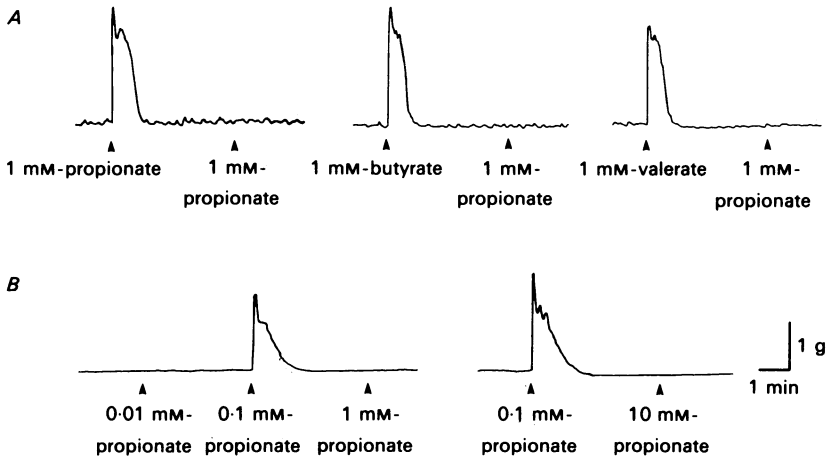

Fig. 7. The self- and cross-adaptation produced by the cumulative addition of propionate, butyrate or valerate. The everted preparations from the middle colon were used. The same or a different acid was cumulatively applied after an interval of about 4 min. *A*, the effect of equal concentrations of the same or a different acid; *B*, the effect of different concentration of the same acid.

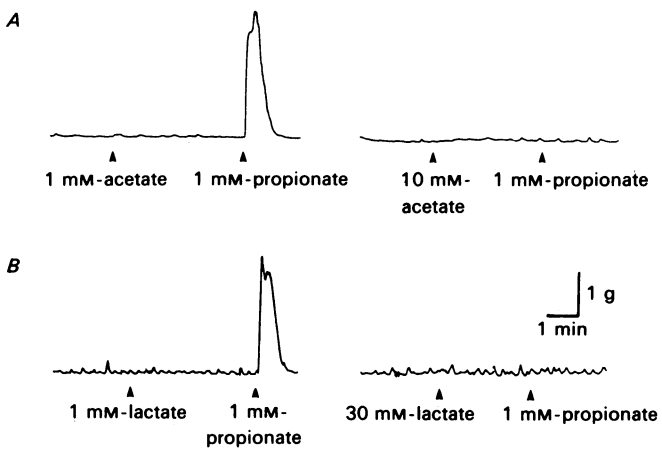

Fig. 8. The cross-adaptation produced between *A*, acetate or *B*, lactate and propionate. The everted preparations from the middle colon were used. The acid was cumulatively applied at about 4 min intervals.

application of procaine (0·4 mM) markedly reduced the propionate-induced contraction (Fig. 6*A*).

Strip preparations facing the bathing medium both at the mucosal and serosal side, were also used to examine the effects of atropine, eserine, TTX and hexamethonium on propionate-induced contraction. The strip preparations exhibited a contractile response to short-chain fatty acids just as the everted preparation did.

TTX itself brought about rhythmic contractions with a mean frequency of $0{\cdot}48 \pm 0{\cdot}03$ contractions per minute ($n = 6$) (Fig. 6*B*). Propionate or ACh was added

to the bath in the presence of TTX immediately after a spontaneous contraction declined to the resting tone. ACh retained its effect in the presence of TTX. However, the contractile responses to propionate did not appear even after 45–120 s (which was equal to the duration of the resting tone between the two rhythmic contractions) of application (Fig. 6*B*). It can be concluded, therefore, that TTX inhibited the contractile effect of propionate without inhibiting the contractile effect of ACh.

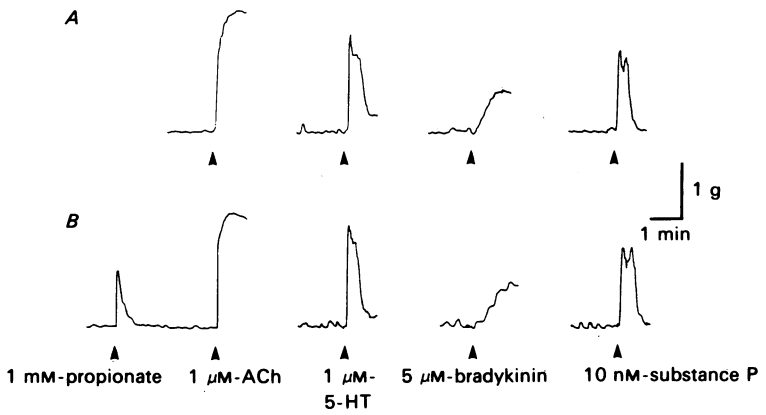

Fig. 9. Effect of pre-treatment with propionate on contractile response to ACh, 5-HT, bradykinin and substance P. The strip preparations from the middle colon were used. *A*, response before addition of propionate (as control); *B*, response 3 min after addition of propionate. The response to each substance was made by using the different preparations.

Hexamethonium inhibited the contractile effect of DMPP but not that of propionate (Fig. 6*C*).

Self- and cross-adaptation of the contractile response produced by short-chain fatty acids

The colonic contractions produced by propionate, butyrate or valerate were reproduced if the organ bath was washed with buffer every time. Then, the recovery time after washing was of necessity more than 5 min. However, the cumulative addition of propionate, butyrate or valerate did not produce any further contraction. Such adaptation to short-chain fatty acids occurred between the same acid (self-adaptation: e.g. propionate followed by propionate) or between different acids (cross-adaptation: e.g. butyrate followed by propionate). Fig. 7*A* shows typical traces of the self- and cross-adaptations ($n = 5$, for each).

Pre-treatment with propionate at 0·01 mM, being below the minimum effective concentration (0·02 mM), did not inhibit the contractile effect of subsequent propionate (0·1 mM) (Fig. 7*B*). However, once the adapted state was set by propionate (0·1 mM), further propionate did not produce any further contraction ($n = 5$) (Fig. 7*B*).

Pre-treatment with acetate at 10 mM resulted in cross-adaptation for 1 mM-propionate ($n = 5$), although 1 mM-acetate was not effective in this regard (Fig. 8*A*).

Similarly lactate (up to 30 mM) did not stimulate any colonic contraction, but pre-treatment with lactate (30 mM) resulted in cross-adaptation for 0·1 mM-propionate ($n = 4$) (Fig. 8*B*).

The rat colon also exhibited a contractile response to 5-HT (1 μM), bradykinin (5 μM) and substance P (10 nM) (Fig. 9*A*). Pre-treatment with propionate (1 mM) scarcely influenced the contractile effects of ACh, 5-HT, bradykinin and substance P ($n = 4$) (Fig. 9*B*).

DISCUSSION

The contractile response of the colon to mucosal application of short-chain fatty acids such as propionate, butyrate and valerate, observed in the present study, was evidently not due to a direct action of short-chain fatty acids on the muscle. Contractions were not induced by serosal application of short-chain fatty acids or by direct application of short-chain fatty acids to longitudinal muscle strips. Rather the contractions appeared to be mediated through release of ACh, probably via stimulation of cholinergic nerves, since they were inhibited by atropine, enhanced by eserine and abolished with TTX.

The short-chain fatty acids evidently do not stimulate cholinergic motor neurones or nerve endings directly, since the nerve–muscle preparations obtained after scraping off the musoca, and the longitudinal muscle strips were not stimulated by short-chain fatty acids. This requirement for an intact mucosa, and the inhibition of the response by mucosally applied procaine suggests the presence of a sensory mechanism for short-chain fatty acids near the epithelium. Short-chain fatty acid-sensitive receptors have previously been postulated to be present in nerve plexus of the sheep liver (Anil & Forbes, 1980); in the renal brush border where the monocarboxylate carrier has a receptor site with high affinity for propionate, butyrate, valerate and caproate (Nord, Wright, Kippen & Wright, 1983), and in the sheep reticulorumen where there is evidence both for vagally innervated receptors (Leek & Harding, 1975) and more recently for receptors within the enteric nervous system (Gregory, 1984). With single-fibre recording of vagal afferent neural activity, Leek & Harding (1975) used the latent period of the response (12–50 s) and the published diffusion coefficients to estimate the position of the receptor at about 150 μm from the epithelial surface. In the present study the short latency (< 10 s) suggests that receptors for short-chain fatty acids may exist somewhere in or just beneath the epithelium in the rat colon.

Further, indirect evidence that receptors for short-chain fatty acids are involved in the contractile response of the rat colon is the reversible self- and cross-adaptations elicited by propionate, butyrate and valerate, and the apparent antagonism exerted by acetate and lactate. Such adaptation must occur at an early step of the mechanism for short-chain fatty acids, and not in the final motor response to ACh since there was no cross-adaptation between short-chain fatty acids and ACh.

It seems possible that the motor response to mucosal short-chain fatty acids observed in the present study could be mediated by an enteric reflex (Costa & Furness, 1982), but the lack of influence of hexamethonium suggests that if this is so it involves non-cholinergic ganglionic transmission. An alternative mechanism can also be hypothesized, involving enteroceptor cells (Leek, 1972; Fujita & Kobayashi, 1978).

Mucosal application of local anaesthetics is reported to block release of chemical messengers from endocrine cells (Shapiro & Woodward, 1965; Matuo & Seki, 1978) and this might explain the inhibitory effect of procaine seen in the present study. If chemical messenger(s) are released from enteroceptor cells by short-chain fatty acids they could have a paracrine action to stimulate cholinergic motor neurones. Further studies will be necessary to clarify the mechanism.

In the present study it was observed that there was regional variation in the contractile response to short-chain fatty acids. The middle and the distal colon showed similar response to short-chain fatty acids, while the proximal colon completely lacked any contractile response. At the present time we do not know whether such regional variation is due to differences in mucosal sensitivity to short-chain fatty acids (Yajima, Kojima, Tohyama & Mutai, 1983) or to the regional heterogeneity of the structural and histological nature of the colon (Snipes *et al.* 1982; Engelhardt & Rechkemmer, 1983).

Other workers have previously demonstrated that chemical stimuli to the lumen of the colon can stimulate colonic motility. Thus, Hukuhara & Miyake (1959) showed that dilute HCl, mustard paste and NaCl crystals elicit colonic contractions in dogs; Hukuhara, Nakayama & Namba (1961) demonstrated that 0·01 M-HCl increases the rate of movement of fluid through isolated segment of dog colon; high luminal concentrations of deoxycholic acid cause an increase in the force of contraction of the circular muscle of the rabbit colon (Snape, Shiff & Cohen, 1980); and laxatives increase the occurrence of mass peristalsis in humans (Ritchie, 1971). However, these substances are generally absent or at least in very low concentrations in the normal large bowel under physiological conditions. In contrast the short-chain fatty acids such as propionate, butyrate or valerate are usually present in the colonic contents (Wrong *et al.* 1981). We measured circadian fluctuation of luminal short-chain fatty acids in three colonic segments of rat (T. Yajima and T. Sakata, unpublished observations). Mean concentrations of acetate, propionate, butyrate and valerate in the rat colon were approximately 76, 13, 26 and 2 mM, respectively. The dose of short-chain fatty acids and the pH in the present study were well within the physiological range. It is concluded that the short-chain fatty acid content of the colon is likely to be one of the physiological luminal stimuli regulating colonic motility.

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