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EFFECTS OF INTESTINAL SECRETAGOGUES AND DISTENSION ON SMALL BOWEL MYOELECTRIC ACTIVITY IN FASTED AND FED CONSCIOUS DOGS

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SUMMARY

1. Defined jejunal segments were perfused with solutions of bile salts and of ricinoleic acid during fasting and after feeding in two groups of conscious dogs, one with the segment in continuity, and the other with a Thiry-Vella loop. Myoelectric activity was recorded from chronically implanted electrodes on the jejunal segment and also from the proximal and distal *in situ* bowel.

2. The results in both groups were identical. During fasting, migrating complexes were present in the segment, but were replaced by intermittent spike activity during chenodeoxycholate without and with ricinoleic acid perfusion. After food, when migrating complexes were replaced by intermittent spike activity, none of the solutions produced any consistent effect.

3. In fasted animals, low levels of distension (15 mmHg) interrupted the migrating complexes in the segment and induced intermittent spike activity which was similar to that seen with the secretagogues. The migrating complexes in the main bowel continued during distension. In fed animals, spike activity increased in the segment during distension at 25 mmHg and decreased in the main bowel. In both groups, distension of the segment to pressures between 37·5 and 50 mmHg abolished spike activity both in the distended segment and the main bowel in fasted and fed states, and, in fasted dogs, migrating complexes were also abolished.

4. These results demonstrate that the inhibitory intestino-intestinal reflex is mediated through extrinsic nerves and does not require an intact myenteric plexus, whereas the altered myoelectric activity induced by secretagogues is a local effect and does not spread to adjacent bowel through either intrinsic or extrinsic neural pathways. It seems likely that the local motor effect of secretagogues is a result of net secretion, producing distension to pressures below the threshold required to activate the intestino-intestinal reflex.

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INTRODUCTION

The relative importance of secretion and motility with respect to the diarrhoea induced by secretagogues, such as ricinoleic acid or bile acids, is unknown. Data in the literature is conflicting and incomplete. Ricinoleic acid, the active principle of the cathartic castor oil, inhibits absorption and/or evokes intestinal secretion (Ammon, Thomas & Phillips, 1974) by producing surface epithelial injury and increased mucosal permeability (Cline, Lorenzsonn, Benz, Bass & Olsen, 1976). When administered orally, it was observed to inhibit motility in the gastric antrum and ileum (Stewart, Gaginella, Olsen & Bass, 1975; Stewart & Bass, 1976*a*). Under other experimental conditions it induced unique migrating spike bursts of greater than 2·5 sec duration (MAPC's) or a distinctive pattern of groups of migrating spike bursts (Mathias, Martin, Burns, Carlson & Shields, 1978; Atchison, Stewart & Bass, 1978). Conjugated dihydroxy bile salts are also known to inhibit absorption or induce secretion of water and electrolytes, but motility effects have not been studied (Teem & Phillips, 1972), although earlier *in vitro* studies suggest that they inhibit motor activity (Sparrow & Simmonds, 1975).

We wanted to determine whether these secretagogues do affect motility, and if so whether the effects were only local, or whether adjacent segments of intestine were affected by reflexes mediated through intrinsic or extrinsic neural networks. The latter effect might be mediated via the intestino-intestinal reflex, which can be demonstrated by inhibition of motility in the main segment of bowel when a Thiry-Vella segment is distended (Chang & Hsu, 1942; Youmans, Karstens & Aumann, 1942). We therefore studied spike burst activity modified by two conjugated bile salts, ricinoleic acid, and distension in defined jejunal segments of conscious dogs, before and after a meal.

METHODS

Intact jejunal segment studies

Three dogs, each weighing about 20 kg, were operated upon under pentobarbitone anaesthesia for placement of electrodes and cannulae. Bipolar electrodes were made of silver wires separated by 1 cm and protruding 1 mm from wing-shaped acrylic buttons. The proximal electrode was sutured to the jejunal serosa 27 cm distal to the ligament of Treitz (Fig. 1). The proximal inlet cannula was fixed in the lumen 6 cm beyond that or 33 cm from the ligament of Treitz. The distal outlet cannula was placed 30 cm beyond the inlet cannula and a segmental electrode was placed midway between the cannulae. Insulated wires leading from the electrodes were tunnelled through the lateral abdominal wall and subcutaneous tissue of the thorax to terminate in an external multi-way electrical connector in the skin at the dorsum of the neck.

The dogs were trained to stand quietly in slings for the experiments which began after an 18 hr period without food. Cables from the electrode connectors led to a Beckman Dynograph R recorder equipped with 9853A universal AC couplers and myoelectric activity was recorded continuously throughout the experiment. The output from the amplifiers also led to an analogue spike burst detector which counted the individual spikes from all spike bursts over 5 min time intervals during the experiment. A Foley catheter, inserted through the inlet cannula and directed aborally, served as the conduit for the perfusing solutions (Fig. 1). The balloon was inflated slightly throughout the experiment to prevent intestinal contents from the proximal bowel from entering the perfused segment and to ensure that the perfusate entered the segment. When distension was required a 20 cm long balloon was inserted into the segment and inflated to the desired pressure. The pressure was monitored throughout the experiment through the use of a Y connector attached to a rubber

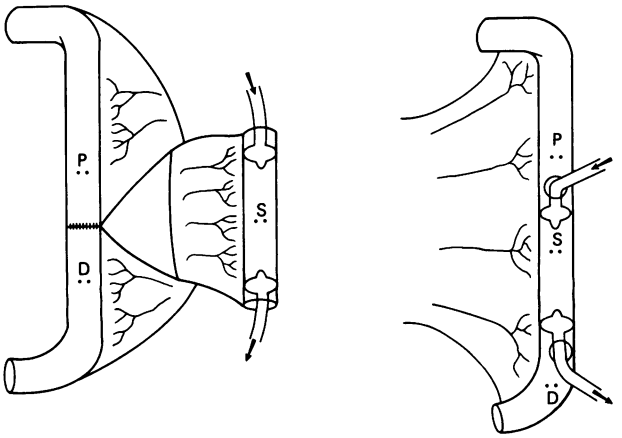

Fig. 1. Diagram of experimental models. On the left is the 30 cm long Thiry-Vella loop. Foley catheters served as conduits; the electrodes (dots) are identified as P for proximal, S for segmental, and D for distal electrodes. On the right is the 30 cm long intact jejunal segment with access to the segment for perfusion and drainage or distension via stainless-steel cannulae.

TABLE 1. Protocol of experiments in intact jejunal segment or Thiry-Vella segment

	Time after beginning experiment (hr)	Perfusion experiments composition of perfusate	Distension experiments pressure (mmHg)
Fasting	0–3	—	—
Experiments	3–6	Test solution	15 or 37·5
Fed	0–1	—	—
Experiments	1–2	154 mM-NaCl	25
	2–3	Test solution	50
	3–4	154 mM-NaCl	25
	4–5	Test solution	—
	5–6	—	—

Test solutions (in âqueous 154 mM-NaCl):
1 10 mM-cholate*
2 10 mM-chenodeoxycholate*
3 10 mM-chenodeoxycholate* + 5 mM-ricinoleic acid
4 154 mM-NaCl control

* Cholate and chenodeoxycholate refer to Na salts of the respective glycine- or taurine-conjugated bile acids.

bulb and a manometer. The fasting experiments lasted 6 hr with no perfusion for the first 3 hr period and perfusion of one of the test solutions at 1 ml./min or balloon distension at 15·0 or 37·5 mmHg was continued through the second 3 hr period (Table 1). The test solutions are listed in Table 1. Concentrations of chenodeoxycholic acid and ricinoleic acid were chosen which are known to cause secretion and inhibition of absorption of water and electrolytes.

One can (480 g) of meat dogfood was fed to the dog 15 min before the feeding experiments began. The semi-fluid digesta drained from the proximal cannula because of the occluding Foley catheter and were collected in a large container throughout the experiment. At 60 min intervals, the recording was interrupted for 20 min and the digesta re-fed into the distal cannula via a straight rubber catheter directed aborally. This procedure was necessary to insure that a fed myoelectric pattern

would continue throughout the 6 hr study. The hourly sequence of perfusion at 1 ml./min was as follows: no perfusion, 154 mM-NaCl, test solution, 154 mM-NaCl, test solution and no perfusion. The test solutions are listed in Table 1.

In the distension experiments following food, 15–20 mmHg pressure regularly stimulated motility in the segment but had no observable effect upon the adjacent bowel segments. A pressure of 25 mmHg seemed to be the threshold for inducing inhibition in the main bowel and was chosen as the initial pressure for the distension experiments. The protocol for the distension experiments is outlined in Table 1.

Thiry-Vella loop studies

Three dogs, each weighing about 30 kg, were operated upon under pentobarbitone anaesthesia. The proximal division of the bowel was 33 cm distal to the ligament of Treitz and the second division was 30 cm distal to the first (Fig. 1). The Thiry-Vella loop was completed by fashioning appropriate stomata in the anterior abdominal wall and anastomosing the main bowel end to end. Monopolar electrodes, constructed of silver wires embedded in acrylic, were sutured 6 cm proximal and 6 cm distal to the anastomosis and to the midpoint of the loop. Insulated wires led from the electrodes to a stainless-steel cannula fitted with a multi-terminal plug connector sutured in the antero-lateral abdominal wall.

The dogs were trained to stand in slings for the experiments. Before each study, food was removed for 18–24 hr. During each 6 hr study, myoelectric activity was recorded continuously on C120 $\frac{1}{8}$″ magnetic tape cassettes (TDK) using a Medilog 4-24 cassette tape recorder (Oxford Medical Systems, Abingdon, England). The Thiry-Vella loop was perfused in a manner similar to that described for the perfused intact segment studies. Fasting and feeding studies followed the protocol for the intact jejunal segment studies (Table 1). Foley catheters were used to infuse and collect the perfusate. Distension was established by occluding the distal catheter and injecting sufficient saline into the proximal catheter to achieve the desired pressure. The pressure was monitored throughout the experiment by a Y connector, manometer and rubber bulb. In the feeding studies, the animals were given 480 g canned meat dogfood 15 min before the beginning of the experiment. No digesta from the proximal bowel were collected or re-infused.

Data analysis

(i) *Fasting studies.* In the intact jejunal segment studies, the number of spikes cumulated over 5 min intervals was expressed graphically. In the Thiry-Vella segment studies, the recorded spike activity was analysed during rapid replay through the use of band-pass filters and Schmitt triggers (Wingate, Barnett, Green & Armstrong-James, 1977) which allowed the number of spikes occurring in consecutive 1 min periods at each electrode to be recorded graphically. In both groups, the number and time of occurrence of activity fronts at each recording site during the first 3 hr of the study was compared to the number and time of occurrence of fronts during the second 3 hr period of perfusion or distension using the two-tailed sine test.

(ii) *Feeding studies.* In the intact jejunal segment studies, the number of spikes cumulated over 5 min intervals for each electrode was expressed graphically and summed over hourly intervals for the duration of the experiment. In the Thiry-Vella loop studies, the recorded myoelectrical activity was analysed and graphed during rapid replay as described for the fasting studies above. Using a planimeter, the areas under the curves were determined for each hour interval of the study since the area was proportional to the total spike activity. The first hour after feeding with no perfusion was considered to be base line activity. The spike activity in subsequent hours was expressed as a percentage above or below the base line activity in order to compensate for variations between recordings and to allow comparisons between the two methods of analysis. Spike activity during each 1 hr period was compared to the base line spike activity in the first hour using the paired t test.

RESULTS

In none of the studies described below could we detect any consistent differences in the results obtained with the continuity of the bowel intact when compared with those in dogs having a Thiry-Vella loop. Therefore, the results are discussed together.

(*a*) *Fasting studies*

Perfusion of the jejunal segments with saline or cholate produced little or no change with myoelectric activity in the segment itself. We detected activity fronts in the segments during cholate perfusion in five of six experiments and the pattern of spike activity resembled that seen during saline perfusion. In one animal, cholate stimulated

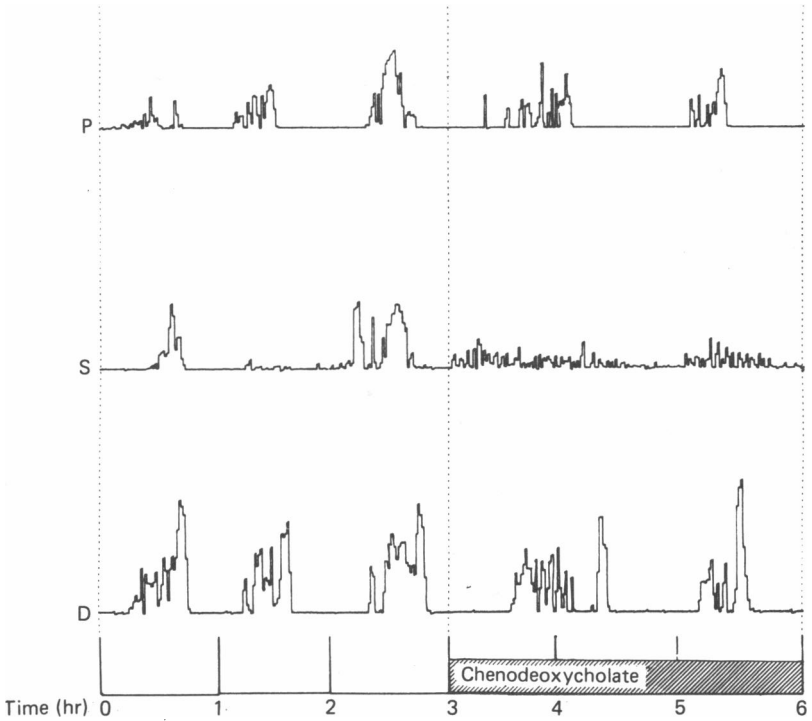

Fig. 2. The effect of chenodeoxycholate on fasting spike activity. Spike activity displayed as continuous histograms (spikes/min) for the proximal (P), segmental (S), and distal (D) electrodes. Migrating complexes are identified as cyclically recurring sequences of absent spike activity, irregular spike activity and intense spike activity (phase III); in this example, the three phases of the sequence are most clearly seen at D. For the 3 hr without perfusion, complexes are seen in all electrodes. During the 3 hr when segment is perfused with chenodeoxycholate, migrating complexes in the segment are replaced by intermittent spike activity similar to that seen after feeding, but continue in the main bowel proximal and distal to the segment.

intermittent low-grade spiking activity within the segment. In the bowel proximal and distal to the perfused segments, no effect of perfusion with saline or cholate was seen in any experiment; migratory myoelectric complexes continued both proximal and distal to the segment without interruption during the 3 hr period of perfusion and there was no significant difference in the occurrence of activity fronts between periods with and without perfusion.

Perfusion of chenodeoxycholate alone (Fig. 2) or chenodeoxycholate with ricinoleic acid consistently interrupted the migratory myoelectric complex in the perfused

segments and produced a pattern resembling that seen after feeding ($P < 0{\cdot}05$). However, no change in myoelectric activity occurred in the intestine proximal or distal to the perfused segments. As with cholate perfusion there was no difference in the occurrence of activity fronts in the main bowel during the perfusion of either of these test solutions when compared to the control period.

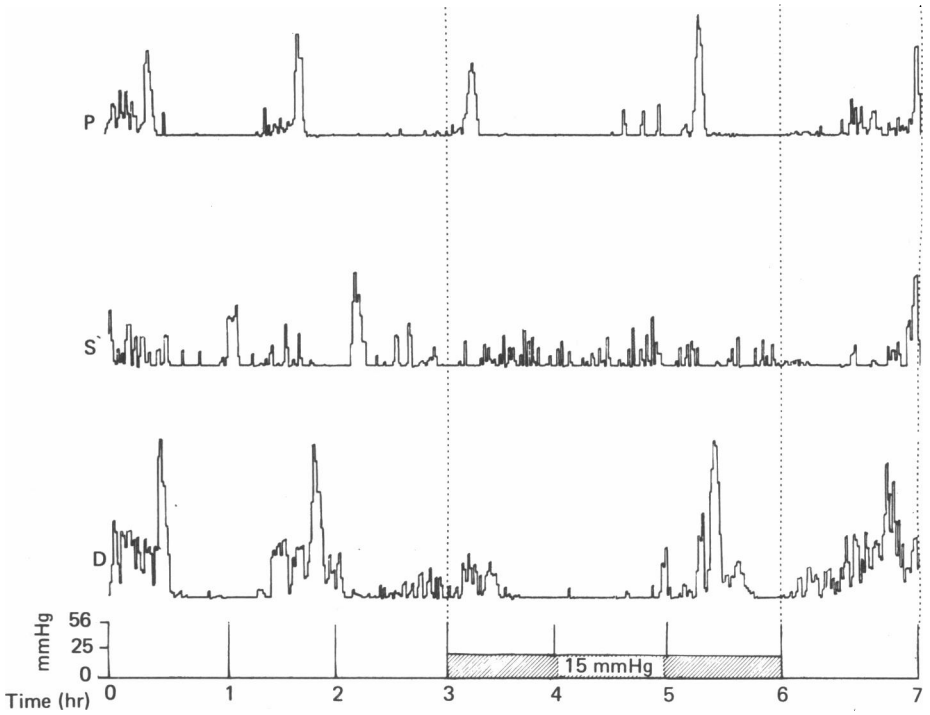

Fig. 3. The effect of low distension pressure on fasting spike activity. Histograms of spike activity as in Fig. 2. Complexes occur in all electrodes during the 3 hr before distension. When the segment is distended to 15 mmHg, the spike activity in the segment becomes intermittent and resembles that seen after feeding or during perfusion with chenodeoxycholate without or with ricinoleic acid. Activity fronts in the main bowel are not affected by this low level of distension. In this study, recording continued for an hour after distension was relieved and complexes returned at all three electrodes.

Distension of the segment at 15 mmHg interrupted the activity fronts in the segment and produced intermittent spike activity similar to that seen with perfusion of chenodeoxycholate without or with ricinoleic acid (Fig. 3). No effect on the myoelectric pattern of the main bowel could be detected. Activity fronts migrated from the proximal to the distal electrodes in all experiments.

Distension of the segments at 37·5 mmHg produced distortion of slow waves and disorganization of their progression. Spike activity in the distended segments was almost completely inhibited (Fig. 4). The effect on the main bowel was marked; activity fronts and essentially all spike burst activity were inhibited in all experiments.

The results of all fasting experiments are summarized in Fig. 5 except that results

with 154 mM-NaCl perfusion are omitted since activity fronts were not interrupted with the control solution.

(*b*) *Feeding studies*

After feeding, spike activity was intermittent in both the segment and main bowel. Perfusion of saline, cholate (Fig. 6) or chenodeoxycholate, or ricinoleic acid with chenodeoxycholate produced no detectable change in spike activity in the

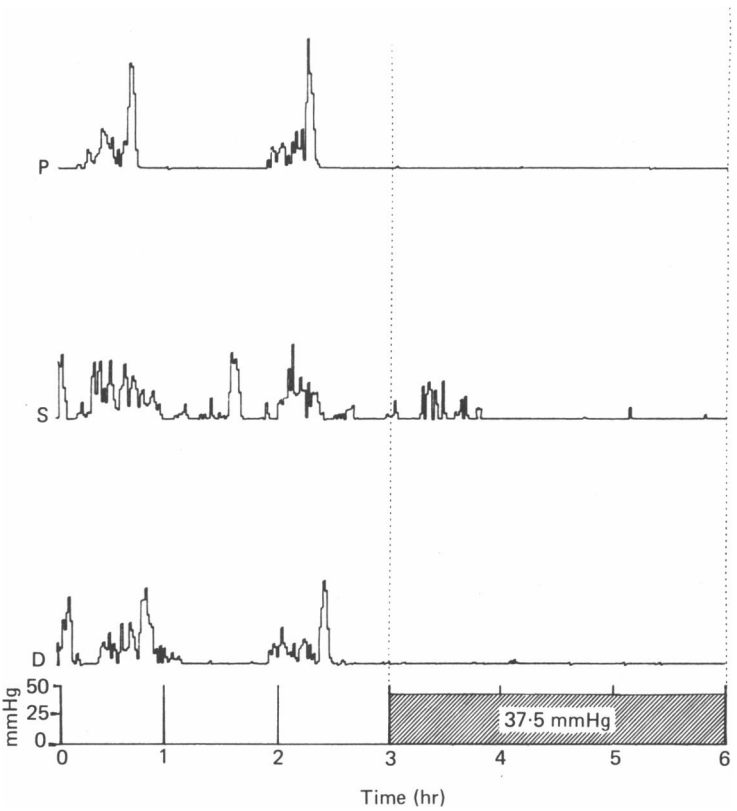

Fig. 4. The effect of high distension pressure on fasting spike activity. Fasting spike activity for 3 hr before distension shows migrating complexes in all electrodes. In this study, there was some initial intermittent spike activity in the segment at a distending pressure of 37·5 mmHg, but thereafter spiking was absent in both the segment and in the main bowel during the entire period of distension.

perfused segment or in the segments proximal or distal to the segment with one exception. In one dog, ricinoleic acid with chenodeoxycholate caused a marked increase in segmental spike burst activity during perfusion (Fig. 7). In this animal outflow of the perfusate was reduced in comparison to that seen in the other animals with this combination. Before this animal was killed, a radiological study with dilute barium sulphate infused into the loop revealed one stricture in the mid-portion of the segment and another at the exit of the segment from the abdominal wall. These strictures produced a partial obstruction to flow and resulted in distension of the loop

during perfusion. However, even with this stimulus, the secretagogues produced no inhibition of motility in the main bowel proximal or distal to the segment.

Distension of the intact jejunal segments and the Thiry-Vella segments, however, produced inhibition of motility in the adjacent segments of bowel (Fig. 8). With 25 mmHg distending pressure, the response in the segment and main bowel was

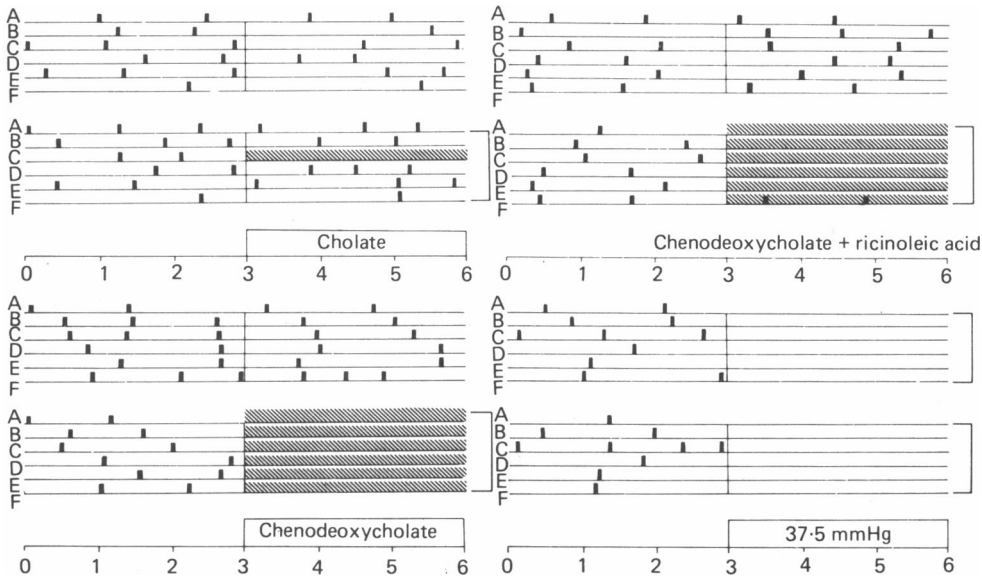

Fig. 5. Summary of the pattern of spike activity recorded in the proximal bowel and the jejunal segment during a 3 hr control period followed by perfusion of the segment for 3 hr with 10 mM-cholate, 10 mM-chenodeoxycholate (CDC), 10 mM-chenodeoxycholate plus 5 mM-ricinoleic acid, or distension at a pressure of 27·5 mmHg. The results for the distal bowel are not shown since they are essentially identical to those seen with the proximal electrode. Within each pair of groups, each horizontal line represents one experiment and in each group, the top line under the proximal electrode (upper group) is from the same experiment as the top line under the segmental electrode (lower group). Subsequent experimental pairs follow in sequence. Vertical bars indicate timing of migrating complexes and diagonal shaded areas represent intermittent spike activity similar to that seen with feeding. The brackets indicate that the occurrence of complexes during the 3 hr experimental period is statistically less, than during the 3 hr control period ($P < 0{\cdot}05$: sign test). ■, activity fronts; ▧, 'fed' activity.

variable; in some studies, the segment demonstrated increased spiking activity while in others, it was inhibited and both the proximal and distal segments exhibited variable degrees of inhibition. With 50 mmHg, inhibition of motility was immediate and complete in both the distended segment and in the segments proximal and distal segments. Spike activity returned within minutes after the distension was released. In five of six distension experiments the dog vomited; in two instances the vomiting occurred during the first period of distension at 25 mmHg; in three instances it occurred early during the 50 mmHg distending pressure period.

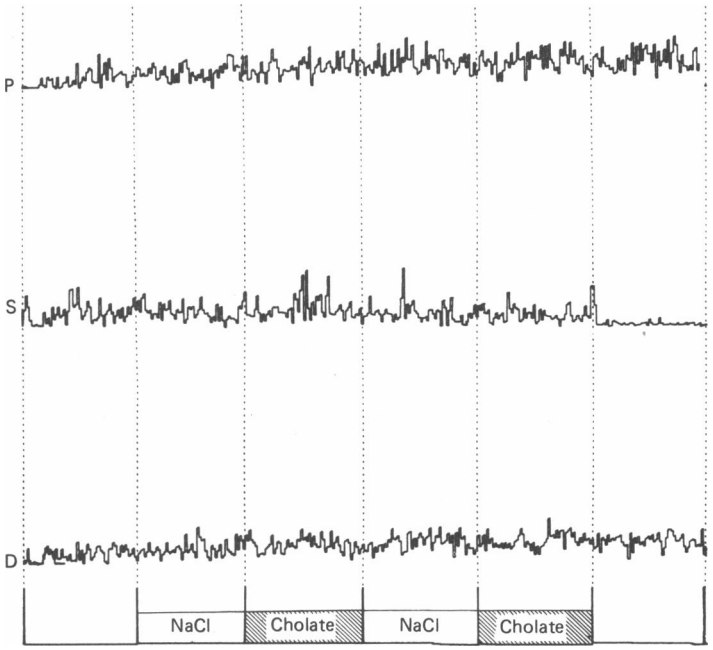

Fig. 6. Spike activity after food in response to 10 mM-cholate. There is no change in spike activity during perfusion with 10 mM-cholate in any of the three electrodes.

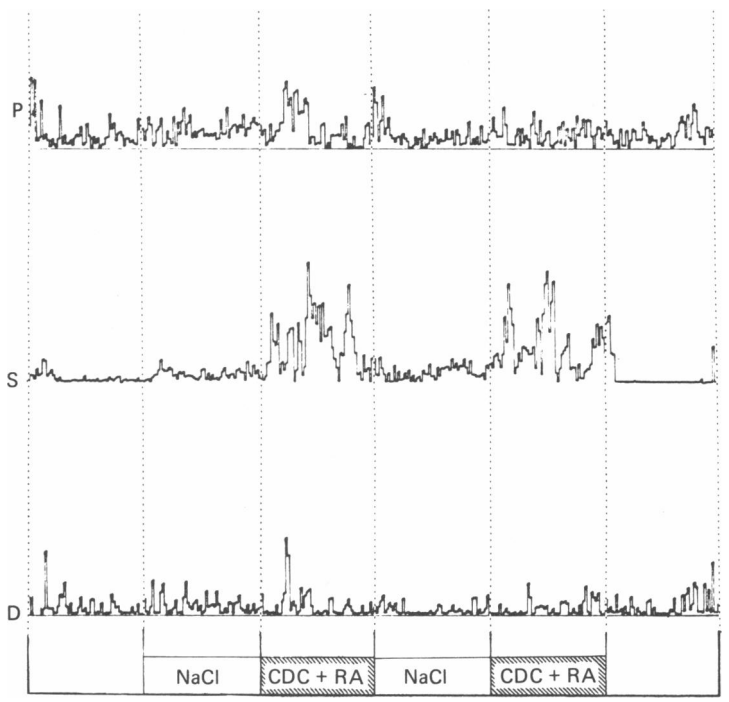

Fig. 7. Spike activity after food in response to 10 mM-chenodeoxycholate (CDC) with 5 mM-ricinoleic acid (RA). During perfusion with this combination in this study, there was a striking increase in spike activity in the electrode on the segment. Subsequently, it was discovered that in this dog, partial obstruction existed to outflow of the perfusate; even so, there was no change in spike activity in the proximal or distal electrodes in the main bowel.

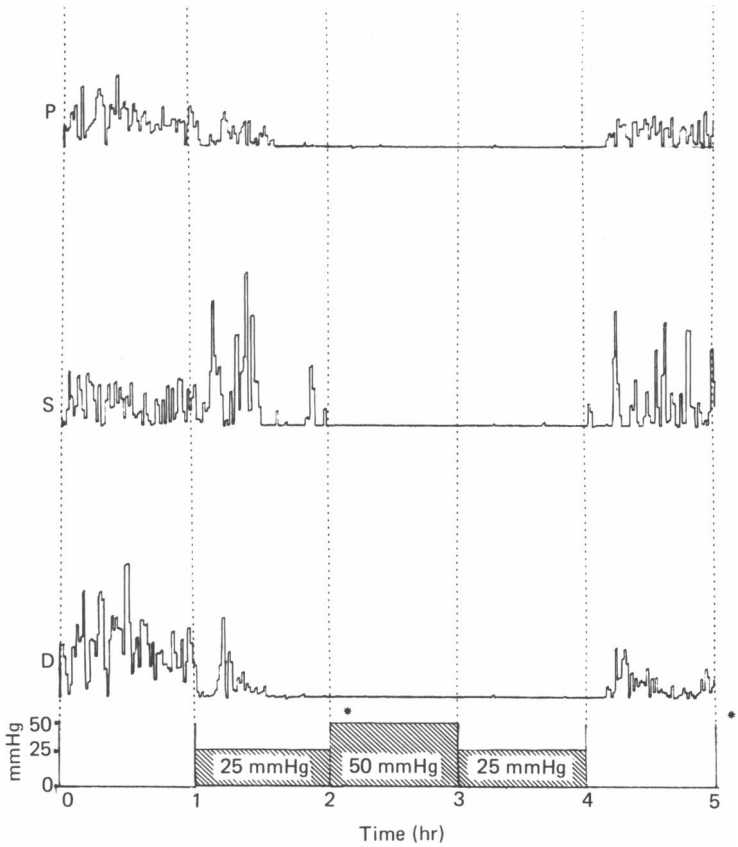

Fig. 8. Spike activity after food in response to two levels of distension. During distension pressures of 25 mmHg, there was initially a marked increase in spike activity in the segment followed by inhibition. This pressure also produced inhibition of spike activity in the bowel proximal and distal to the segment. At a pressure of 50 mmHg, spike activity was completely inhibited in all three electrodes. In this example, inhibition persisted during the second period of distension at 25 mmHg. Spike activity returned in all three electrodes with release of the distension.

DISCUSSION

The control of the cyclically recurring migrating myoelectric complex remains an enigma. The normal pattern seems to be regulated by some mechanism extrinsic to the intestinal wall. Whether the mechanism is neural or hormonal is unknown. Initially, in a Thiry-Vella loop model, it was thought that activity fronts systematically migrated from the main bowel proximal to the loop, to the loop itself, and then back to the main bowel distal to the loop (Carlson, Bedi & Code, 1972). This sequence implied a tight, probably neural, regulatory mechanism. However, subsequent studies demonstrated that matters were more complex and that with time, the isolated segment becomes more autonomous (Bueno, Praddaude & Ruckebusch, 1979; Ormsbee, Telford & Mason, 1979; Pearce & Wingate, 1980). Our study confirms

that local factors may override or modulate the external mechanisms which form the complex.

Chenodeoxycholate alone or with ricinoleic acid stimulated contractile activity within the perfused segment but induced no reflex inhibition of motility in adjacent segments. This was similar to the motility effects seen with distension of the segment at low pressure (15 mmHg). It was also similar to the reported effects of the perfusion of isotonic or hypertonic glucose solutions in other studies in the canine Thiry-Vella loop model (Eeckhout, de Wever, Vantrappen & Janssens, 1980; Pearce & Wingate, 1980). These solutions changed the myoelectric activity of the loop from an 'interdigestive' to a 'digestive' pattern but as in our studies, did not interfere with the migratory myoelectric complex during fasting or with the intermittent spike activity in the main portion of the small bowel after feeding. Chenodeoxycholate alone or with ricinoleic acid and also hypertonic glucose solutions all induce intestinal secretion. The increase in spike activity with these dissimilar agents may be induced by non-specific mechanical factors due to increased volume within the lumen of the bowel. In an earlier study of jejunal perfusion of glycine-conjugated bile acids in humans, experimental subjects experienced moderately severe non-specific abdominal distress, malaise, vomiting and diarrhoea (Wingate, Hyams & Phillips, 1974). It was observed that this effect was related to incomplete recovery of the perfusate, and calculation revealed that the secretogenic bile salts generate significant volumes of fluid which may have distended the lumen of the intestine. Our data demonstrate that low levels of distension locally stimulate contractile activity. We did not see any of the long migrating spike bursts as described by Mathias *et al.* (1978) or the groups of migratory spike bursts as described by Atchison *et al.* (1978). Our data suggest that the major effect of these secretagogues on the small bowel is that they induce a larger intraluminal volume and local mechanical stimulation of motility rather than a specific direct motility effect to produce catharsis. There is no evidence that they stimulate a local chemoreceptor which is capable of initiating the intestino-intestinal inhibitory reflex. The effect of sodium ricinoleate on the colon may be entirely different. In that organ it appears to produce a dose-related excitation of ectopic pacemakers (Christensen & Freeman, 1972).

The study reconfirms the activation of the intestino-intestinal reflex by distension in intact conscious animals. Low distending pressure (15 mmHg) interrupted the migrating myoelectric complex in the distended segment of fasting animals and produced intermittent spike activity, but no effect on adjacent sequents of jejunum was detected. Intermediate pressure distension (25 mmHg) caused variable local stimulation and variable inhibition of motility in adjacent segments of bowel in fed animals. Higher distension pressures (37·5–50 mmHg) produced inhibition of spike activity in both the distended as well as adjacent segments. There appears to be no difference in the activity of this reflex whether the bowel is intact or whether the reflex is mediated exclusively through the extrinsic reflex arc as in the Thiry-Vella loop. It is capable of total inhibition of the migratory myoelectric complex as well as the pattern of intermittent spike burst activity seen after feeding. It is very likely that this reflex only plays a role in pathologic conditions such as bowel obstruction since pressures of this magnitude are unlikely to occur under physiological conditions.

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