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VAGAL INFLUENCES ON THE JEJUNAL 'MINUTE RHYTHM' IN THE ANAESTHETIZED FERRET

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SUMMARY

1. Spontaneous jejunal motility in the urethane-anaesthetized ferret shows a cyclical pattern of contraction bursts alternating with quiescent periods described as 'minute rhythm' in conscious animals.

2. Cooling the cervical vagi to below 4 °C or acute vagotomy abolished this pattern of motility.

3. On re-warming the vagi there was a return to cyclical motility after a latency which depended upon the contractile state at the time vagal conduction was restored.

4. Electrical vagal stimulation produced bursts of contractions at the same frequency as the spontaneous motility. Longer periods of stimulation gave rise to bursts of contractions interrupted by periods of relative quiescence, mimicking the spontaneous motility, despite the continuous stimulation.

5. Following atropinization all spontaneous motility was abolished, but electrical stimulation of the vagi revealed a non-cholinergic, non-adrenergic response whose characteristics differed from that of the cholinergic response.

6. It is concluded that the vagus plays a permissive role in regulating the jejunal 'minute rhythm' via a cholinergic pathway and that there is a second excitatory vagal pathway which innervates non-cholinergic post-ganglionic neurones whose functional significance and transmitter mechanism is unknown.

INTRODUCTION

Electrical recordings from the small intestinal muscle of the conscious fasted animal have revealed a pattern of motor activity referred to as the migrating myoelectric or migrating motor complex (m.m.c.) (Szurszewski, 1969) which is characterized by periods of intense contractile activity interrupted by periods of quiescence, the whole complex lasting between 1 and 2 h (see Vantrappen, 1982). Anaesthetized animals fail to show this pattern and although the reasons for this are not known they must, in some way, involve the removal of a controlling influence. Anaesthetization has thus been taken by some to represent a state which is not conducive to valid experimentation.

The importance of the vagal innervation in controlling intestinal motor function

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has frequently been questioned. First, the intrinsic plexus contains all the neural elements capable of co-ordinating and controlling peristaltic movements (Wood, 1981), and secondly, vagotomy has been reported to have remarkably little effect on spontaneous intestinal motility in both acute experiments (see Kewenter, 1965) and on the fasted pattern of intestinal motility in conscious animals (Weisbrodt, Copeland, Moore, Kearley & Johnson, 1975). Indeed, experiments on denervated or autotransplanted segments of intestine have led to the conclusion that m.m.c.s occur independently of the extrinsic nervous system (Aeberhard, Magnenant & Zimmermann, 1980; Itoh, Aizawa & Takeuchi, 1981). However, recent evidence from work on conscious dogs suggests some vagal involvement in controlling both the fed pattern of intestinal motility (Diamant, Hall, Mui & El-Sharkawy, 1980) and the phase II type activity of the m.m.c. (Hall, El-Sharkawy & Diamant, 1982).

Within this irregular phase (the phase II) of the m.m.c. of all species so far examined, spiking activity in the jejunum is grouped into bursts which recur at 0·5–2·5 min intervals (hence 'minute rhythm') (Fleckenstein & Øigaard, 1978; Fleckenstein, Bueno, Fioramonti, & Ruckebusch, 1982), and since significant flow of intestinal contents can occur during this phase (Bueno, Fioramonti & Ruckebusch, 1975) the 'minute rhythm' may be a major propulsive force within the intestines. Jejunal motility in the anaesthetized ferret shows a pattern of spontaneous motility very similar to the 'minute rhythm' recorded in the conscious animal and therefore provides a good preparation in which to study this type of motility. A preliminary account of this work has been published (Collman, Grundy & Scratcherd, 1982).

METHODS

The experiments were performed on male and female ferrets anaesthetized with a single intraperitoneal injection of urethane (1·5 g kg^{-1} body weight). They were fed on a standard carnivore diet with free access to water, but were deprived of food for 18 h before experimentation. A glass cannula was inserted into the trachea, and the right external jugular vein was cannulated for the administration of drugs, bicarbonate and further anaesthetic if required. In some experiments the right femoral artery was cannulated to enable arterial blood samples to be removed for blood gas and plasma bicarbonate estimations (Corning 178, pH/Blood Gas Analyser) and to monitor arterial blood pressure.

Motility in the upper small intestine (here designated jejunum from morphological considerations (Podder & Murgatroyd, 1976)) was recorded from a saline-filled cannula, attached to a pressure transducer (Elcomatic EM 760 system), inserted in an oral direction at a point 15 cm below the pylorus (the latter being ligated). The output from the pressure transducers was displayed on a flat-bed chart recorder (Bryans 2800).

Vagal influences on jejunal motility were investigated either by acute cervical vagotomy and subsequent stimulation of the peripheral end of the servered vagal trunks or by temporary interruption of the vagal supply by cooling the cervical vagi to below 4 °C (Linden, Mary & Weatherill, 1981). This reversible vagal blockade not only allows repeated observations to be made on individual animals but also allows observations to be made on the consequences of restoration of nervous conduction. Vagal cooling was accomplished by circulating a freezing mixture of alcohol and water through copper tubes positioned around the cervical vagi, the rate of flow through the tubes being adjusted to control the temperature of the nerves monitored by thermocouples. The nerves were cooled for a minimum of twice the duration of the contraction cycle interval. The temperature of the nerves was maintained at 37 °C between periods of cooling. Thin slivers of polystyrene were inserted between the nerves and underlying tissue to insulate against heat loss.

In three experiments the vagi were stimulated in the thorax after a right thoracotomy with resection of the lower ribs. After thoracotomy, the animals were artificially ventilated with room

air and expired agains a water resistance of 0·3 kPa. In these experiments, end-tidal CO_2 was monitored (EL 100 CO_2 analyser) and ventilation adjusted to give end tidal CO_2 values of 5–6%. Body temperature was maintained throughout by means of a Palmer Homeothermic blanket.

The animals were left for 30 min after completion of the surgery before any motility was recorded. Data on the spontaneous patterns of motility were obtained from a 10 min period prior to any experimental intervention. In the results peak pressure is taken as the maximum pressure generated above the base line while 'tone' refers to the amplitude of the base line above atmospheric pressure. All results are expressed as the mean (±S.E. of mean) with the number of animals in parentheses. A paired sample *t* test was used to assess statistical significance, with the control for each test being taken from the contraction burst immediately before the experimental procedure.

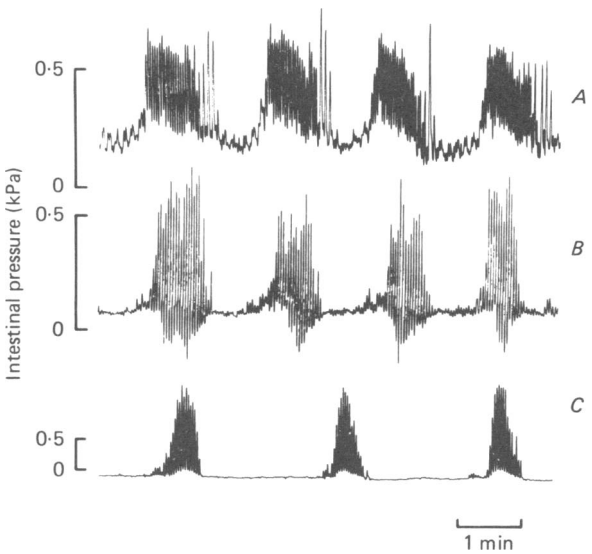

Fig. 1. Jejunal 'minute rhythm' recorded in three separate animals. Note the variations in the duration of the burst, the interburst interval and motility level during the relatively quiescent phase.

RESULTS

The anaesthetized ferret showed well-developed spontaneous jejunal motility. In eighteen out of twenty-one animals this motility was characterized by bursts of contractile activity interrupted by periods of relative inactivity (Fig. 1). These bursts of contractions had a mean duration of 52·6±2·9 s (n = 124 cycles in twenty-one animals) during which time there was a gradual increase in contraction amplitude up to a maximum of 0·9±0·05 kPa (range 0·2–2·4 kPa in 124 cycles); after this the amplitude gradually decreased to merge with the relatively inactive period (Fig. 1). The contraction frequency during these bursts was 29·4±0·15 min^{-1}. During the inactive periods, which on average had approximately the same duration as the bursts (50·1±3·9 s) the motility was greatly reduced and in many cases almost completely absent (Fig. 1 *B* and *C*). The motility that did occur during this quiescent phase was in general of a much slower wave form (7–10 min^{-1}) which occasionally had a 30 min^{-1} ripple superimposed (Fig. 1 *A*). The three animals which failed to show this cyclical

pattern of activity had either no motility (one animal) or a continuous type of motility. In the latter the contractions occurred at a similar frequency to that seen during the bursts in the other animals (i.e. approx. 30 min^{-1}).

Effect of reversible vagal blockade

An intact vagus was necessary for the cyclical pattern of jejunal motility described above. Cooling the cervical vagal trunks to below 4 °C produced complete abolition of cyclical jejunal motility and a small fall in tone (Fig. 2). In twenty-one experiments

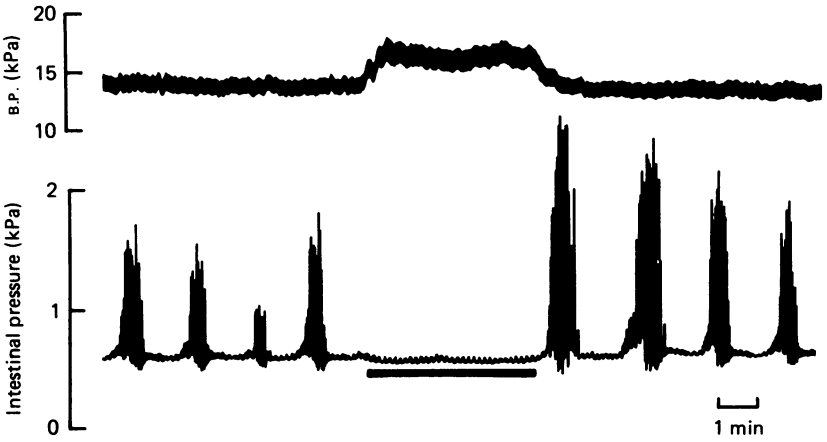

Fig. 2. The effect of cooling the vagus nerves to below 4 °C (indicated by bar) on jejunal motility (lower trace) and blood pressure (upper trace). Note that during the cooling period cyclical motility was abolished, but the slower, 7–10 min^{-1} contractions persisted. On re-warming cyclical motility returned, with a transient increase in amplitude.

peak contraction amplitude was reduced from $0{\cdot}93 \pm 0{\cdot}14$ kPa to $0{\cdot}12 \pm 0{\cdot}02$ kPa ($P < 0{\cdot}001$) by vagal cooling. The motility which persisted during vagal blockade was of low amplitude and generally occurred at a similar frequency to that seen during the quiescent phases between the bursts that were present prior to the cooling period (i.e. the 7–10 min^{-1} described above). On re-warming the nerves, motility returned to pre-control levels but after a highly variable latency, ranging from an almost immediate resumption on re-warming (2 s latency) to a delay of almost 5 min in one animal with long interburst intervals. Another feature of the motility which resumed following restoration of vagal conduction, seen in eleven cases, was a transient increase in contraction amplitude above the pre-cooling control level (Fig. 2), although taking the group as a whole this just failed to reach the 5% significance level.

During vagal cooling the mean blood pressure rose from $12{\cdot}76 \pm 1{\cdot}15$ kPa to $14{\cdot}73 \pm 1{\cdot}42$ kPa ($n = 7$) respectively (1 kPa is equivalent to 7·5 mmHg); however, these were not indirectly responsible (via changes in blood flow or activation of sympathetic reflexes) for the effects on jejunal motility, since the abolition of motility persisted after pre-treatment with phentolamine and propranolol (2 mg kg^{-1}) ($n = 9$) or section of the splanchnic nerves at the crus of the diaphragm ($n = 4$). These

procedures would prevent splanchnic inhibitory effects activated as a consequence of the removal of aortic arch baroreceptor afferents. Pre-treatment with the adrenergic blockers additionally prevented the blood pressure response to vagal cooling but not the abolition of jejunal motility.

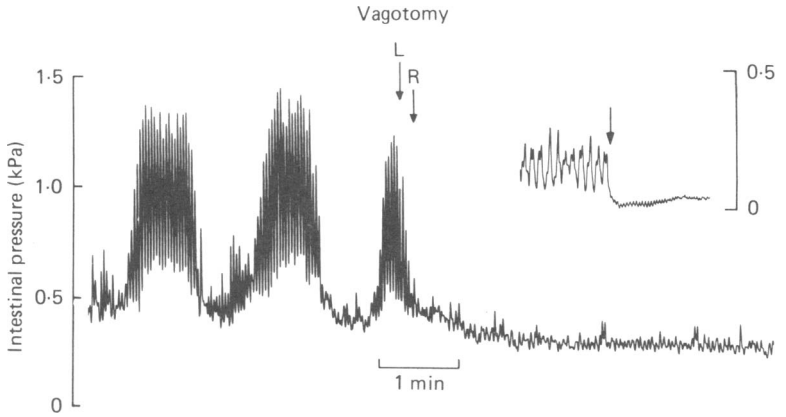

Fig. 3. Effect of acute cervical vagal section on jejunal 'minute rhythm'. Left vagal section (L) caused a reduction in amplitude whilst section of the remaining right vagal trunk (R) abolished the cyclical activity. Inset shows effect of atropine 1 mg kg^{-1} at arrow) on post-vagotomy motility in a different animal which showed prominent slow (10 min^{-1}) contractions. Same time scale as main record.

Changes in acid/base status as a result of the temporary removal of the lung inflation reflex were also discounted. In ten experiments the pH and bicarbonate concentration of arterial blood were measured before and during vagal blockade by cooling the cervical vagus. In three of these animals no bicarbonate was infused so that they become acidotic with an arterial pH before block of $7{\cdot}283 \pm 0{\cdot}025$ and a bicarbonate concentration of $16{\cdot}8 \pm 1{\cdot}3$ mM, and during blockade a pH of $7{\cdot}268 \pm 0{\cdot}042$ and bicarbonate concentration of $15{\cdot}7 \pm 0{\cdot}7$ mM. There was thus very little change, whereas the peak contraction amplitude fell from $0{\cdot}82 \pm 0{\cdot}36$ kPa to $0{\cdot}1 \pm 0{\cdot}04$ kPa during the blockade. In the seven other animals the acidotic state was prevented by the intravenous infusion of bicarbonate from the start of the experiment. In these animals the arterial pH and bicarbonate concentration before blockade were $7{\cdot}391 \pm 0{\cdot}017$ $21{\cdot}6 \pm 0{\cdot}8$ mM respectively, whereas the corresponding figures during blockade were $7{\cdot}381 \pm 0{\cdot}013$ and $21{\cdot}8 \pm 0{\cdot}6$ mM. During this time the contraction bursts were abolished (peak contraction amplitude decreased from $0{\cdot}79 \pm 0{\cdot}28$ kPa to $0{\cdot}04 \pm 0{\cdot}001$ kPa ($P < 0{\cdot}001$).

The effect of acute vagotomy and atropine

The cervical vagi were sectioned prior to electrical stimulation and in all cases this had the same effect as vagal cooling, namely a fall in tone and complete abolition of cyclical motility. This is illustrated in Fig. 3 in which the vagotomy was timed to occur during a burst of contractions; the burst was abruptly ended and no further cycles were seen. The only motility present after vagotomy was again of low

amplitude (peak contraction amplitude was $0{\cdot}09 \pm 0{\cdot}33$ kPa compared to $0{\cdot}54 \pm 0{\cdot}16$ kPa before vagotomy ($P < 0{\cdot}05$, $n = 10$)) and of the 7–10 min^{-1} type.

In the vagotomized preparation atropine (1 mg kg^{-1}) resulted in a further fall in tone of about 0·1 kPa and abolition of the remaining slower low amplitude contractions (Fig. 3 inset). In the vagally intact animal atropine caused a large fall in tone and abolition of all motility.

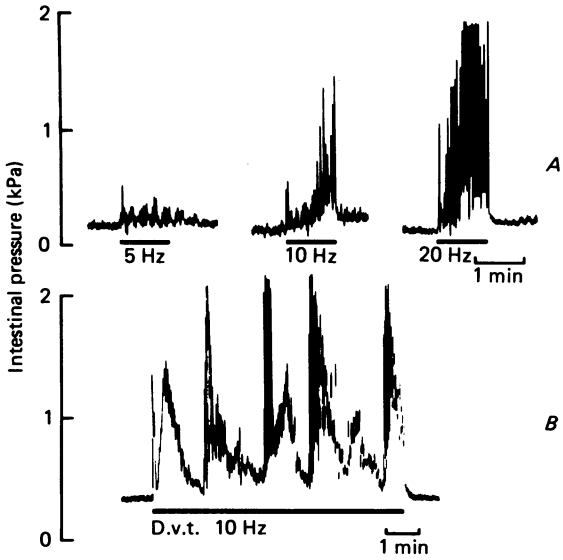

Fig. 4. *A*, electrical stimulation of the left cervical vagal trunk (20 V, 0·5 ms, for 1 min) at 5, 10 and 20 Hz. *B*, electrical stimulation of dorsal vagal trunk (d.v.t.) at 10 Hz. Bar indicates stimulation period.

Electrical vagal stimulation

Electrical stimulation of the peripheral end of the cervical vagi (20 V, 0·5 ms, 1–50 Hz for 1 min) elicited a contractile response from the jejunum which could be divided into several components. At stimulation frequencies above 5 Hz there was initially, after a latency of 2–4 s, a single contraction of 4–6 s duration followed by a burst of contractions at a similar frequency to those seen during the spontaneous bursts. Between these two contractile events there was a period of relative inactivity whose duration decreased as the frequency of stimulation increased (Fig. 4). On two occasions, however, there was no distinction between these two contractile events; instead the burst of contractions commenced after a latency normally associated with the initial spike. The amplitude of the contractions increased as the frequency of stimulation increased, up to a maximum response at approximately 20 Hz. At this frequency the first peak had an amplitude of $0{\cdot}39 \pm 0{\cdot}09$ kPa ($n = 8$) whilst the burst had a peak amplitude of $1{\cdot}04 \pm 0{\cdot}25$ kPa ($n = 10$). The contractions ceased abruptly on removal of the stimulus and were occasionally followed by periods of quiescence. Longer periods of stimulation were applied to the dorsal and ventral vagal trunks in the thorax (20 V, 0·5 ms, 5–20 Hz for > 5 min) and under these circumstances these elicited cyclical activity similar to that seen during the spontaneous bursts (Fig. 4*B*).

Thus the contractions did not persist throughout the period of stimulation but showed bursts of activity separated by periods of relative inactivity.

Vagal stimulation after atropine (0·1–5 mg kg^{-1}) failed to reveal any inhibitory innervation of the jejunum. It did, however, reveal an atropine-resistant contractile response, the characteristics of which were quite different from that seen in the absence of atropine. First, the latency of the response was much longer (16–30 s, mean

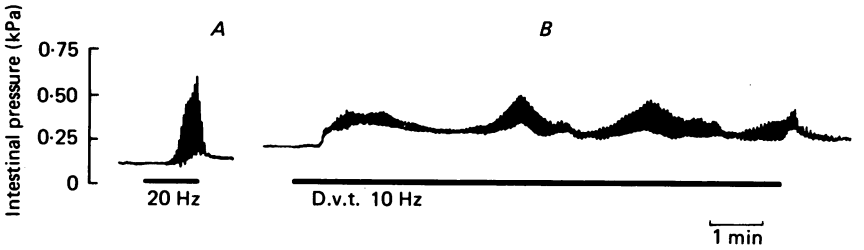

Fig. 5. *A*, stimulation of the left cervical vagal trunk following atropine (1 mg kg^{-1}) at 20 Hz for 1 min. *B*, longer period of stimulation applied to the dorsal vagal trunk (d.v.t.) at k10 Hz after pre-treatment with atropine (1 mg kg^{-1}). Bar denotes the period of stimulation.

24·3 ± 1·9, $n = 7$). Secondly, the amplitude of the contractions was lower after atropine (0·26 ± 0·06 kPa at 20 Hz compared to 1·11 ± 0·38 kPa at the same frequency before atropine); however, because one animal produced contractions which were much bigger than the rest, these differences failed to reach significance with the paired *t* test but were highly significant with the Mann–Whitney *U* test ($P < 0·01$). Thirdly, the threshold frequency of stimulation was higher (5 Hz produced no response after atropine), and finally, the response did not cease abruptly on removing the stimulus but persisted for several seconds (6–20 s) after removal of the stimulus (Fig. 5*A*). Stimulation of the thoracic vagal trunks for > 5 min in the presence of atropine still evoked cyclical activity (Fig. 5*B*).

The responses before and after atropinization were not abolished and in many cases were enhanced or elicited at lower stimulation frequencies by pre-treatment with phentolamine and propranolol (2 mg kg^{-1}).

DISCUSSION

The spontaneous pattern of motility generated by the jejunum of the anaesthetized ferret is similar to the 'minute rhythm' described by other workers in the conscious pig, cat, rabbit, dog and sheep (Fleckenstein *et al.* 1982) and in humans (Fleckenstein & Øigaard, 1978). This motility pattern in the ferret was characterized by cyclical contractile activity of 1·7 min duration and was, therefore, similar to the 0·5–2·5 min periodicity described by others. During these bursts of contractile activity the contractions occurred at the same frequency (approximately 30 min^{-1}) as the slow waves recorded from the conscious ferret (Bueno, Fioramonti & More, 1981), but unlike the conscious animal, no m.m.c. activity was recorded.

This pattern of motility was dependent upon an intact vagal supply. Thus,

following bilateral vagal section or after cooling the cervical vagi to below 4 °C, there was no cyclical activity in the jejunum. This is in contrast to acute experiments in other species in which vagal section had relatively little effect (see Kewenter, 1965) and thereby suggests considerable vagal tone in the present preparation. The significance of the slower (7–10 min^{-1}) contractions seen after vagotomy is not known since no electrical correlate of this type of activity has been described previously.

That the cyclical pattern of motility represents a physiological condition can be inferred from its similarity to the 'minute rhythm' seen during the phase II of the m.m.c. of conscious animals and also from the recent observation that only this component of the m.m.c. is susceptible to vagal blockade (Hall *et al.* 1982).

Removal of an excitatory vagal influence may possibly allow tonic sympathetic activity to go unchecked. However, in the present study, the inhibitory effect of vagal cooling was still present after either splanchnectomy or combined α- and β-adrenergic blockade, thereby ruling out an indirect effect via the sympathetics and suggesting the vagus has a controlling influence on jejunal 'minute rhythm'.

This vagal controlling influence may act either as a 'command signal' which initiates and maintains the periods of contraction or may have a more permissive role in providing the background conditions necessary for the bursts of contractions, which themselves are controlled and co-ordinated by the enteric nervous system. The present work supports the latter possibility since the contractions did not persist throughout long periods of electrical vagal stimulation but showed a pattern of cyclical activity similar to the spontaneous pattern of motility seen in vagally intact animals.

Thus the enteric plexuses would appear to determine the cyclical pattern of contractions. This conclusion might explain the variable latency for the return of contraction bursts following restoration of vagal conduction after a period of cooling. If vagal conduction returned during the quiet phase of a contraction cycle then a delay would be expected when the burst commenced, whilst if vagal conduction was restored at the time when a burst was possible then contractions should resume immediately. The transient increase in contraction amplitude following restoration of conduction might suggest that acetylcholine is involved in regulating the sensitivity of the jejunum and may possibly account for some of the discrepancies between the effectiveness of vagal cooling (Hall *et al.* 1982) and vagal section (Weisbrodt *et al.* 1975). With the latter, the long-term effects of vagotomy may be overcome by an increase in sensitivity to locally released acetylcholine.

The abolition of all spontaneous jejunal motility by atropine supports the view that the excitatory vagal input is cholinergic (see Costa & Furness, 1982). However, in the present study, not all the electrical vagally stimulated motility was abolished by atropine. There was a long latency response which persisted beyond the stimulation period which was resistant to atropinization (at doses up to 5 mg kg^{-1}). There may, therefore, be a group of non-cholinergic post-ganglionic neurones in the enteric plexuses which receive a vagal input and which, when activated, stimulate cyclical jejunal motility either directly or via the release of some hormonal substance. The latter is a possibility since the latency for the response approached the circulation time. There are, however, several alternative possibilities. First, the dose of atropine may have been insufficient to block the response to a build up of acetylcholine during

long periods of stimulation. This would seem unlikely since the dose of atropine was in excess of that required to block completely the gastric cholinergic response to vagal stimulation in the anaesthetized ferret (Andrews & Scratcherd, 1980) and also the matched jejunal response to close arterial injections of acetylcholine (P. I. Collman & D. Grundy, unpublished observation).

A second possibility arises, since the vagal inhibitory innervation of the gastrointestinal tract is often characterized by the presence of rebound contractions following removal of the electrical stimulation (Burnstock, Cocks, Paddle & Staszewska-Barczak, 1975). Occasionally the rebound contractions occur before the stimulus has ceased (Burnstock, 1979) or without prior relaxation (Campbell & Burnstock, 1968) and in this respect would appear as a long-latency increase in motility. This interpretation has been used to explain Bayliss & Starling's (1899) biphasic (inhibition followed by excitation) small intestinal response to electrical stimulation in the atropinized dog (Roman & Gonella, 1981). However, in the present study, inhibition was never seen in the jejunum, even though there was sufficient tone in the preparation, demonstrated by the prompt relaxation elicited by close arterial injection of acetylcholine in the presence of atropine (P. I. Collman & D. Grundy, unpublished observation). An explanation based on this phenomenon, therefore, also seems unlikely.

The presence of non-cholinergic excitatory nerves within the intrinsic nerve plexus has been shown by *in vitro* studies of small intestine in response to transmural stimulation (Ambache & Freeman, 1968; Bauer & Kuriyama, 1982; Takewaki & Ohashi, 1977) and transmural pressure (Tonini, Frigo, Leuchini, D'Angelo & Crema, 1981). The present work suggests that this non-cholinergic excitatory pathway may receive a vagal input and therefore presents the first evidence for such a pathway. The nature of the transmitter is unknown.

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