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VAGALLY MEDIATED GASTRIC MOTOR AND EMETIC REFLEXES EVOKED BY STIMULATION OF THE ANTRAL MUCOSA IN ANAESTHETIZED FERRETS

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SUMMARY

1. In the urethane-anaesthetized ferret chemical (NaCl, NaOH or HCl) or mechanical (stroking) stimulation of the gastric antral mucosa evoked a decrease in corpus pressure and inhibition of contractions in the presence of guanethidine, adrenalectomy and sectioned greater splanchnic nerves.

2. The fall in corpus pressure was present following administration of atropine but was abolished by vagotomy.

3. Preliminary evidence, using 100 mM-NaOH as the stimulus, is presented that the effects on corpus motility are due to simultaneous activation of the vagal efferents supplying the intramural non-adrenergic non-cholinergic inhibitory neurones and inhibition of those supplying the intramural cholinergic neurones.

4. The possible roles of this antro-corpus vago-vagal reflex in the regulation of gastric emptying and in the prodromal phase of vomiting are discussed.

INTRODUCTION

In many animals, including man, the majority of ingested food is accommodated in the gastric corpus and after partial digestion it is progressively squeezed into the antrum from where powerful peristaltic contractions propel it through the pyloric sphincter and into the duodenum (see Minami & McCallum, 1984, for review). Once initiated, emptying is thought to be regulated primarily through duodenal braking mechanisms elicited by stimuli in the chyme acting on receptors in the duodenum (Hunt, 1956). Stimulation of these receptors by acid, fats and hypertonic solutions slows emptying via vagal and splanchnic neural reflexes and the release of hormones. Gastric emptying is enhanced by gastric distension (Strunz & Grossman, 1978) but little attention has been paid to gastric-based stimuli which might slow emptying by reflexly modifying gastric motility. The stomach is supplied with a large number of vagal afferents with receptors in the muscle and the mucosa (Mei, 1983; Andrews 1986*a*). Activation of the tension receptors in the antral muscle produces a vago-vagal reflex relaxation of the gastric corpus and it has been suggested that this reflex prevents excessive distension of the antrum by controlling the delivery of food from the corpus (Abrahamsson, 1973). A number of neurophysiological studies of the

vagus have demonstrated that the mucosal receptors respond to stroking of the mucosa, topical application of acids (pH < 3) and/or alkali (pH > 10), some hypertonic solutions (e.g. M-NaCl) and some hypotonic solutions (e.g. tap water), depending on the species (Mei, 1983; Andrews, 1986*a*). In summarizing the function of these receptors Leek (1977) suggested that they might have 'an important role in optimizing gastric activity prior to intestinal digestion'. Very few studies have attempted to determine the influence on gastric motility of stimuli which would activate these receptors; therefore the aim of this study was to investigate whether stimuli applied to the antral mucosa could modify motility in the gastric corpus and hence provide a mechanism by which the stomach could influence its own rate of emptying. A preliminary account of part of this study has been presented to the Physiological Society (Andrews & Wood, 1984).

METHODS

Animals

Experiments were performed on twenty male or female ferrets weighing 500–1000 g. The number of animals used for each group of experiments is stated in the text. They were fed on a standard carnivore diet with free access to water but were deprived of food for 18 h before anaesthesia with urethane (1·5 g/kg in 154 mM-NaCl, I.P.).

Surgery

The trachea and right external jugular vein were cannulated. The jugular vein cannula was inserted so that its tip was within the thoracic cavity to allow measurement of intrathoracic pressure when required. Systemic arterial pressure was measured in most animals from a cannula in the right common carotid artery. The gastric corpus was intubated with a wide-bore tube via the mouth and oesophagus. The greater splanchnic nerves were sectioned in the abdomen. The stomach was divided into corpus and antral regions by two crushing ligatures (5 mm apart) placed around the stomach in the region of the incisura angularis. Particular care was taken in placing these ligatures to ensure that dorsal and ventral nerves of Latarjet supplying the gastric antrum were not damaged (Mackay & Andrews, 1983). Double ligatures were also tied on either side of the gastroduodenal junction to prevent reflux from the duodenum and to ensure that stimuli applied to the antral mucosa could not reach the duodenal mucosa. The antrum was opened into a sheet by cauterizing the muscle and mucosal layers along the greater curve and ligating blood vessels when required. The cut edges of the antrum were then secured to a frame adjusted to conform to the overall shape of the antral sheet. Great care was taken to minimize the tension on the antrum. In the majority of experiments a bead thermistor was rested on the antral mucosal surface to monitor the temperature. The antral mucosa was examined during the experiment using a binocular microscope (Nachet × 1·5–4 magnification) and fibre-optic illumination (Fort Lux 150 S). In some experiments the activity of antral musculature was monitored with a tension transducer orientated to preferentially record activity in the circular muscle layer. After preparing the antral sheet the abdominal wall was closed with sutures in such a way as to form a collar around the base of the antral sheet. A sheet of aluminium foil was placed over the closed mid-line abdominal incision and this in turn was covered with gauze which was changed periodically during the experiment.

The corpus was inflated with 20 ml 154 mM-NaCl and the pressure monitored (Bioscience 8138). The intracorpus pressure was displayed on a chart recorder (Gould 2400 and Bryans 28000) together with blood pressure, antral activity, heart rate (measured from the e.c.g. in some experiments) and antral mucosal temperature.

Rectal temperature was maintained at 39 °C by a homeothermic blanket and radiant heat. The antral mucosa was also maintained between 36–39 °C by radiant heat and intermittent superfusion with 154 mM-NaCl at 39 °C; at no time was the mucosal surface allowed to dry.

Antral mucosal stimulation

Mechanical stimuli were applied to the antral mucosa by stroking gently with a round-ended glass rod or a moistened cotton bud. Warmed solutions (39 °C) were applied to the mucosa either

by gently dropping them from a syringe or spraying them as an aerosol. The method of application had no effect on the nature of the response. The chemicals used were: NaOH (10, 50 and 100 mM), NaCl (38, 79, 154, 500, 750 mM, 1 M and 2 M), HCl (10, 50 and 100 mM), water, Tris base (0·5–2 M), $NaHCO_3$ (100 mM), L-tryptophan (1 and 5 mM). After application of a chemical or stroking, the mucosa was washed at least 5 times with warm 154 mM-NaCl. At least 15 min was allowed between applications and usually only two chemicals and mucosal stroking were tested in any one animal. Each substance was tested in at least three animals unless otherwise stated.

The antral mucosa was electrically stimulated via bipolar silver wires (1 mm diameter 5 mm separation) resting lightly on the mucosal surface.

Drugs and nerve lesions

During the course of the experiment all animals were given guanethidine (Ismelin, Roche 5 mg/kg I.V.) and in addition most had a combination of atropine (1 mg/kg I.V.) and bilateral cervical vagotomy. The greater splanchnic nerves were cut in all animals. In some experiments the adrenal glands were either removed or ligated and left *in situ*. The peripheral cut ends of the cervical vagi were stimulated as described previously (Andrews & Lawes, 1985) in the latter group to confirm the blockade of cholinergic muscarinic receptors.

Statistics

Results are expressed as the mean $\pm$ one standard error of the mean (n = numbers of animals) and significance tested where relevant using a paired sample t test.

RESULTS

Corpus motility

The level of the rhythmic contractile activity and prevailing intracorpus pressure showed a spectrum ranging from animals with a relatively low mean intracorpus pressure but large-amplitude contractions, to those with a higher mean pressure but low-amplitude high-frequency rhythmic contractions. Examples of these types of activity are shown in the Figures. The reasons for the variations in activity and the incidence with which each occurs are under investigation but care was taken to ensure that the antral stimuli were studied under a variety of levels of corpus activity.

The effect of antral stimulation on corpus motility

(*a*) *Mechanical stimulation*

Gentle stroking of the antral mucosa with a blunt glass rod or a moist cotton-wool bud produced a prompt onset (< 5 s) response of one of two types: (a) a fall in corpus pressure associated with an inhibition, or a decrease in the amplitude, of rhythmic contractions, (b) inhibition of rhythmic contractions with only a small change in intracorpus pressure. This latter type of response was most commonly observed in animals with a low corpus tone and a high level of spontaneous activity. Examples of each type of response are shown in Fig. 1*A* and *B*. In general, the inhibition of contractions was related to the duration of stroking (Fig. 1*A*), whereas the corpus tone tended to return slowly towards control levels during stimulation (Fig. 1*B*). When decreases in tone with associated reductions in the amplitude of rhythmic contractions were observed the corpus contractions showed no significant change in frequency either during or after stimulation of the antral mucosa.

The above responses were observed in the presence of guanethidine (5 mg/kg I.V.) in

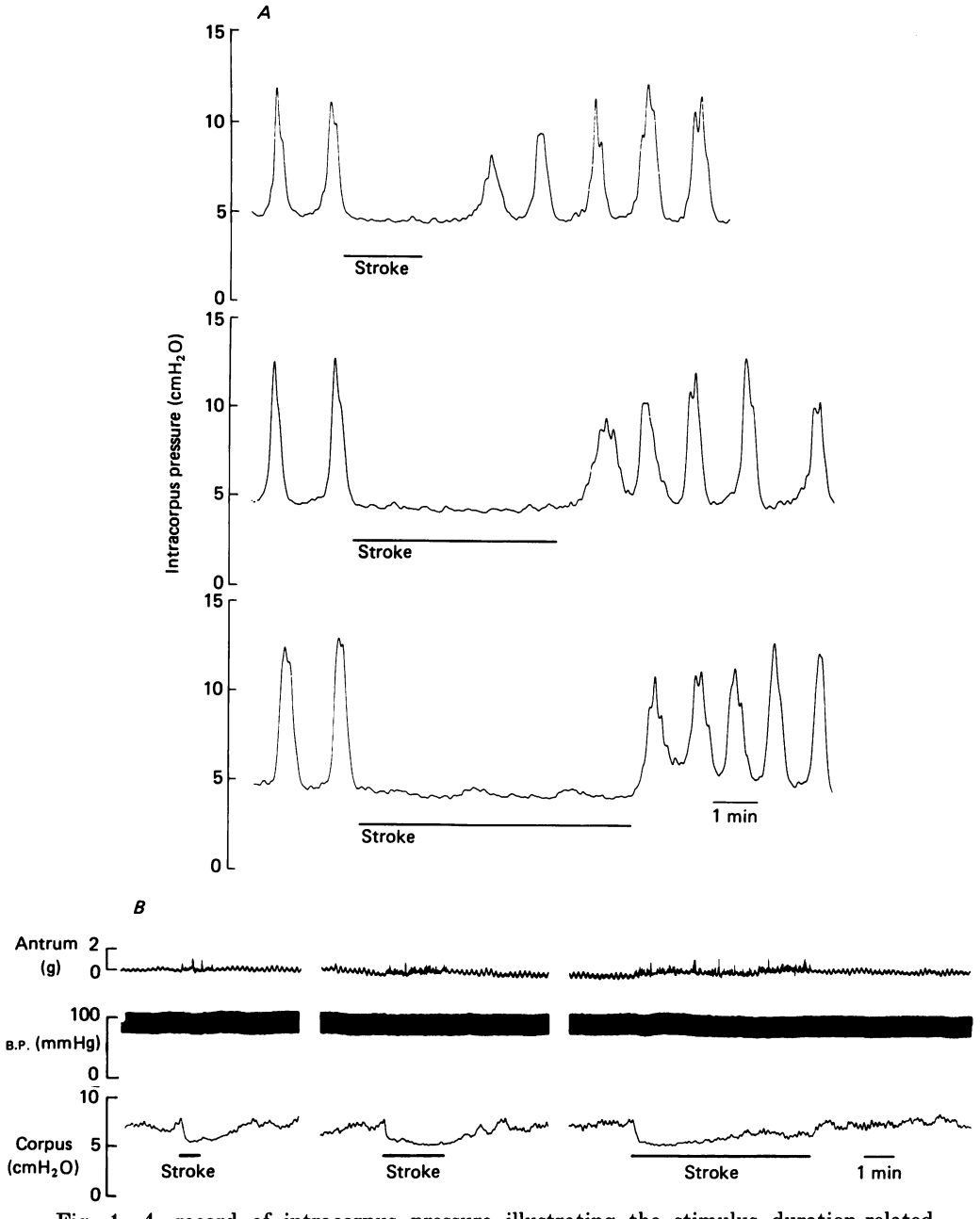

Fig. 1. *A*, record of intracorpus pressure illustrating the stimulus duration-related inhibition of ongoing contractions by gentle stroking of the antral mucosa in the presence of guanethidine and greater splanchnic nerve section. In animals with this type of spontaneous activity antral stimulation had little effect on the corpus tone. *B*, record of intracorpus pressure (lower panel) in an animal with a low level of rhythmic contractions, showing a stimulus duration-related fall in tone produced by gentle stroking of the antrum. Conditions as in *A*. This record also shows that stroking the antral mucosa produced only a small change in antral circular muscle tension (upper panel) and no change in blood pressure (middle panel).

addition to section of the greater splanchnic nerves. To assess whether a prevertebral sympathetic reflex was also involved, the corpus response to antral stroking was examined before and after guanethidine administration in animals with the greater splanchnic nerves cut. This showed that there was no significant difference in the pressure fall to the stimulus before or after treatment (control fall, $3{\cdot}9 \pm 0{\cdot}9$ cmH_2O; guanethidine treated, $4{\cdot}4 \pm 0{\cdot}9$ cmH_2O; $n = 5$) and indicates that a prevertebral adrenergic sympathetic reflex is not activated by antral mucosal stimulation.

In the above studies care was taken not to stretch the antral mucosa or muscle. Whilst the effects of antral muscle distension on corpus activity are known, those of stretching the mucosa are not, and therefore the opportunity was taken to study this. Stretching the mucosa in a circular orientation firmly enough to flatten the rugae caused an immediate fall in intracorpus pressure and/or a reduction in the amplitude of rhythmical contractions.

(*b*) *Hypertonic and hypotonic stimuli*

The following concentrations of NaCl were used to provide a range of stimuli: 154, 250, 500, 750, 1000 and 2000 mM. With a concentration of 500 mM-NaCl a small transient decrease in intracorpus pressure and/or an inhibition of ongoing rhythmical contractions was observed and this was maximal with a concentration of 750 mM-NaCl. The fall in corpus pressure always began within 5 s of the application of the NaCl to the antrum. The only consequence of increasing the concentration to 2000 mM-NaCl was to markedly prolong the recovery time (examples of the various types of response are shown in Fig. 2).

Isotonic NaCl was without effect and was used as a control stimulus in all future experiments. Lower concentrations of NaCl were either ineffective or produced weak transient falls in corpus pressure. Tap water was without significant effect in three animals but a clear fall in corpus pressure was observed in one animal.

(*c*) *Acidic and alkaline stimuli*

Both 50 and 100 mM-NaOH produced a rapid onset (< 5 s) profound fall in intracorpus pressure and/or inhibition of rhythmic contractions of the corpus (Fig. 3*A* and *B*). In animals in which only inhibition of contractions was observed the contractions usually began to return before the stimulus was removed. There was little difference between the response to the two concentrations but 10 mM-NaOH was without effect. Of all the stimuli used, 100 mM-NaOH produced the most profound and reproducible response and was therefore used as the representative stimulus for investigating the pathway for this reflex (see below). Sodium bicarbonate (100 mM) and Tris base (0·5–2 M) were without effect (Fig. 3*B*).

The effects of HCl (100 mM) were more variable than those of NaOH. Whilst it evoked a prompt (< 5 s) decrease in intracorpus pressure and an inhibition of rhythmic contractions, the magnitude of the response was variable and activity often returned before the stimulus was removed (Fig. 4). When the antral mucosa was washed *after* HCl application a period of elevated tone and enhanced contractions was often observed (five out of ten applications).

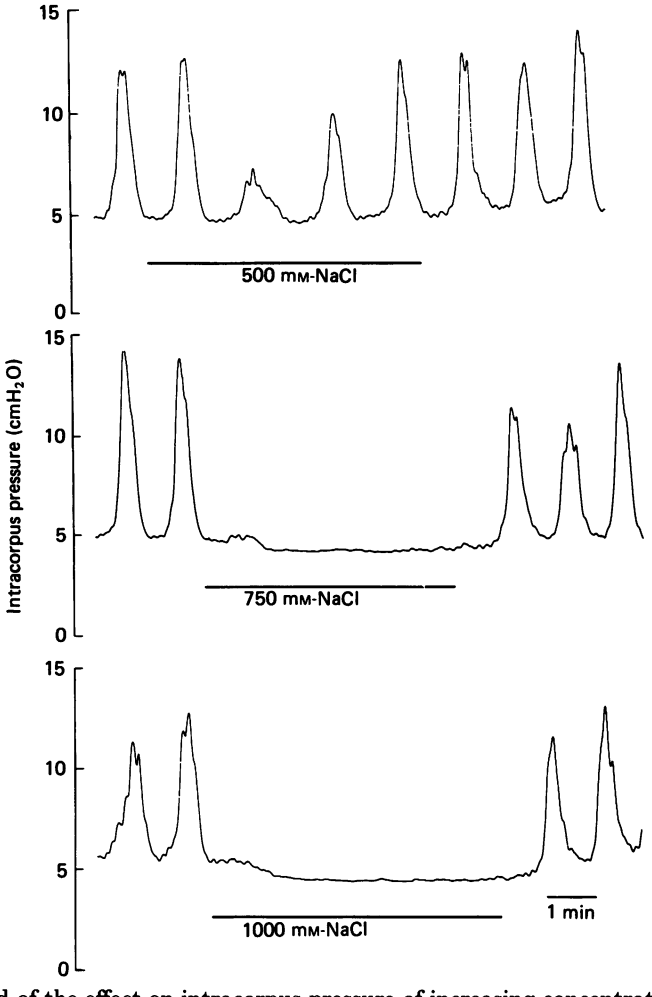

Fig. 2. Record of the effect on intracorpus pressure of increasing concentrations of NaCl applied to the antral mucosa in the presence of guanethidine and greater splanchnic nerve section. The major effect was inhibition of ongoing contractions although a small fall in tone occurred; and example of an animal with a more profound tone change is shown in Fig. 5.

(*d*) *Miscellaneous stimuli*

Several stimuli were not studied systematically but the results are reported briefly for completeness.

(i) *Thermal stimuli.* 154 mM-NaCl when applied to the mucosa at 37 °C was without effect, but at 45 °C it produced a decrease in the amplitude of rhythmic contractions in two out of two applications; the effect of 154 mM-NaCl at 26 °C was equivocal, in one application producing inhibition and in two applications an enhancement of corpus activity.

(ii) *Chemical stimuli.* L-tryptophan (1 and 5 mM) and sodium oleate (1 mM) when applied to the antrum were without effect on corpus activity.

(iii) *Electrical stimulation.* Stimulation of the antral mucosa (20–40 Hz, 10–30 s,

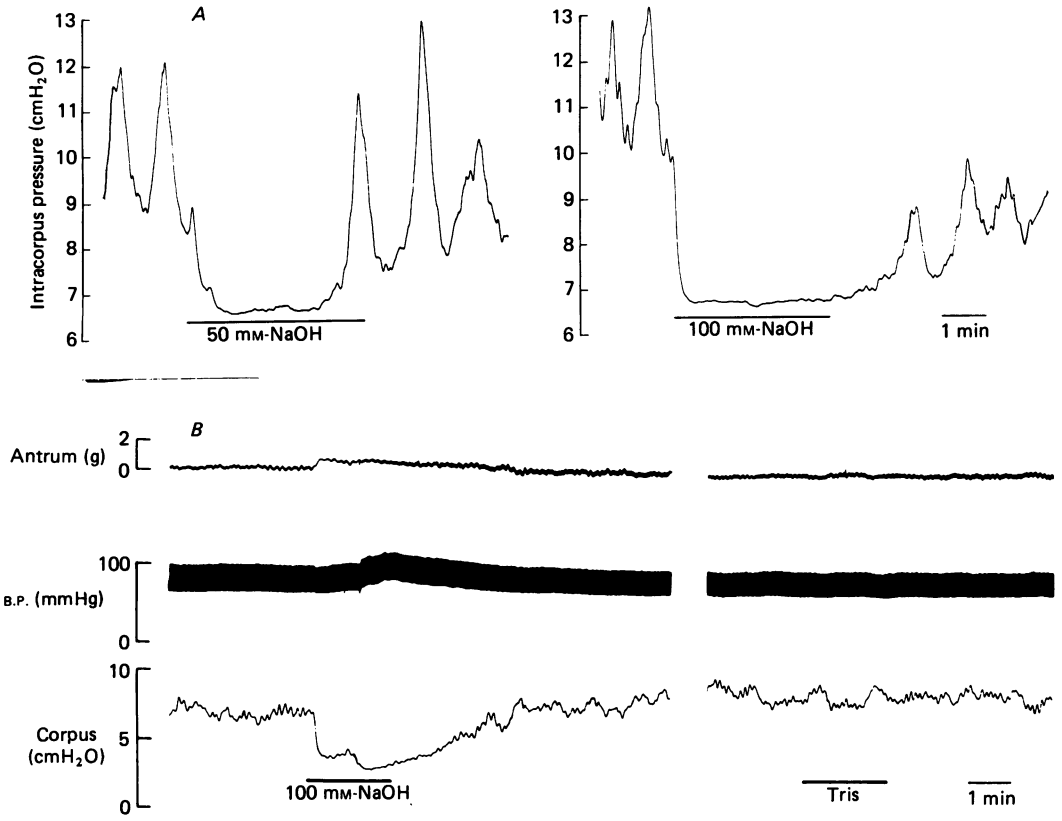

Fig. 3. *A*, record of the effect on intracorpus pressure of two concentrations of NaOH applied to the antral mucosa in the presence of guanethidine and greater splanchnic nerve section (see also Fig. 5). The corpus tone spontaneously increased between the two recordings. *B*, record of intracorpus pressure and blood pressure showing the small increase in blood pressure and the marked fall in corpus pressure produced by 100 mM-NaOH but not 0·5 M-Tris. Conditions as in Fig. 3*A*.

20 V, 0·5 ms) evoked an immediate fall in intracorpus pressure and inhibition of contractile activity; with the longer periods of stimulation the animals retched (see below).

The effects of antral stimulation on blood pressure

In the presence of guanethidine (5 mg/kg I.V.) and greater splanchnic nerve section the only stimulus which produced a consistent increase in blood pressure of > 5 mmHg was 100 mM-NaOH. This change in blood pressure was not observed in vagotomized animals. In no experiment was a consistent change in heart rate observed.

The effect of vagotomy and atropine on the corpus response to antral stimulation

The observation that antral stimulation produced an inhibition of corpus motility in the presence of greater splanchnic nerve section and guanethidine indicated that a sympathetic reflex was not involved and therefore the effect of vagotomy was investigated.

After section of the cervical or abdominal vagi antral stimulation by stroking, application of NaCl (1 M), HCl (100 mM) NaOH (100 mM) or electrical stimulation was without effect on corpus pressure or rhythmic contractions. In the presence of vagotomy rhythmic contractions were present in the corpus, although at a reduced amplitude, and the tone was elevated; thus any inhibitory effects of antral stimulation would have been apparent under these conditions.

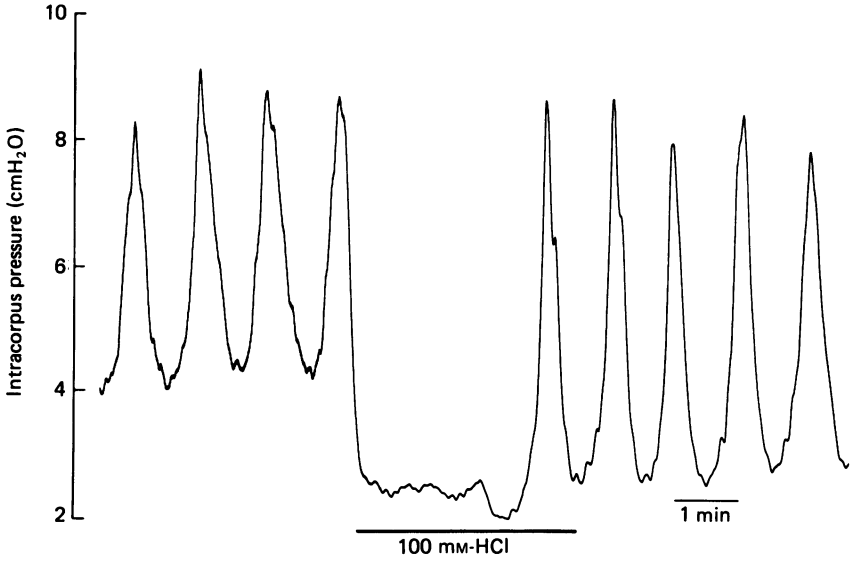

Fig. 4. Record of the effect on intracorpus pressure of HCl applied to the antral mucosa in the presence of guanethidine and greater splanchnic nerve section.

Because atropine (1 mg/kg I.V.) produced a reduction in the corpus tone and it has been demonstrated that the magnitude of inhibitory effects in the corpus is profoundly influenced by the prevailing pressure (Andrews & Lawes, 1985), the corpus tone was adjusted to match the pre-atropine levels so that a proper comparison of the corpus response to antral stimulation pre- and post-atropine could be made.

In the presence of atropine, NaCl (1 M), NaOH (100 mM) and stroking the antral mucosa all produced a prompt fall (< 5 s) in corpus pressure which returned slowly after removal of the stimulus (Fig. 5). The influence of atropine on the response was quantified using NaOH (100 mM) as the stimulus in the presence of greater splanchnic nerve section and guanethidine (5 mg/kg I.V.). This stimulus was used as it produced the most quantitatively consistent response prior to atropine although the reason for this is not clear. Under these conditions application of NaOH (100 mM) for 1 min to the antral mucosa produced a fall in corpus pressure of $3{\cdot}8 \pm 0{\cdot}5$ cm H_2O ($n = 5$ animals) and in the presence of atropine $2{\cdot}5 \pm 0{\cdot}5$ cmH_2O. The maximum fall in corpus pressure was reached within 60 s of application of the stimulus to the antrum. The most marked effect of atropine was on the time course of the response. Without atropine the corpus pressure returned to control levels 268 ± 30 s ($n = 5$

animals) after antral stimulation, whereas in the presence of atropine the return time was 740 ± 170 s ($n = 5$ animals, $P < 0{\cdot}05$). In the presence of atropine the rhythmic contractions of the corpus were markedly reduced in amplitude and therefore it was often difficult to determine whether contraction amplitude was influenced by antral stimulation. However, in some animals clear rhythmic contractions were present after atropine and in these animals NaOH (100 mM) applied to the antrum reduced the amplitude of the contractions.

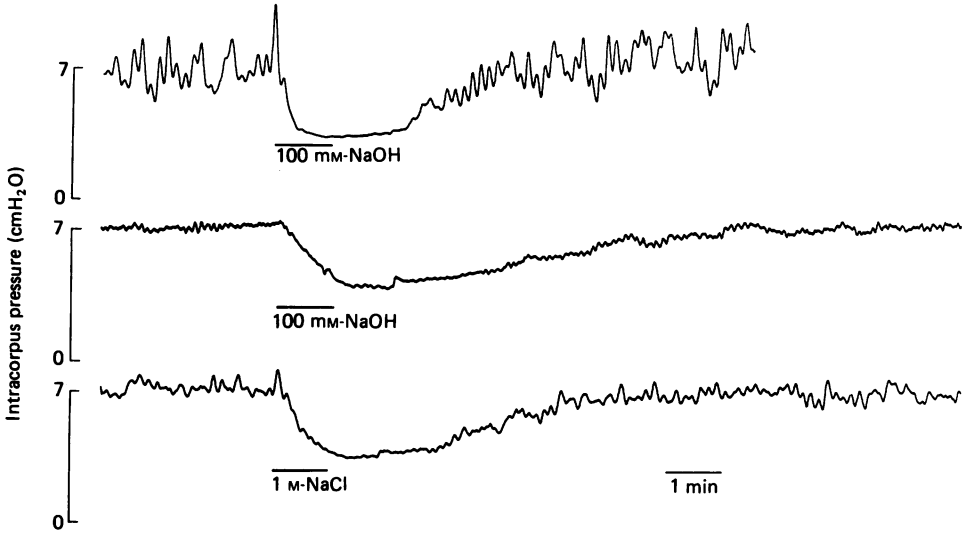

Fig. 5. Records of intracorpus pressure. The upper panel shows the response to NaOH applied to the antrum in the presence of guanethidine, greater splanchnic nerve section and adrenalectomy. The middle panel shows that, following administration of atropine (1 mg/kg I.V.), the response was still present but with a modified time course (middle panel). The lower panel illustrates that under these conditions 1 M-NaCl also produced a fall in corpus tone.

Emetic responses to antral mucosal stimulation

It was noted above that electrical stimulation of the antral mucosa produced a prompt fall in corpus pressure which was often followed by retching, visible as large negative oscillations in intrathoracic pressure or rapid positive excursions in the gastric pressure record (McCarthy & Borison, 1974). This response was observed in the presence of atropine (1 mg/kg I.V.) but not after cervical vagotomy. A similar response was observed in six animals after application of NaCl (1 M) to the antrum (Fig. 6*A* and *B*). Corpus pressure fell by $2{\cdot}7 \pm 0{\cdot}6$ cmH_2O, at which point retching began ($40 \pm 4{\cdot}5$ s ($n = 6$) after application of the stimulus to the antrum) and lasted 31 ± 6 s. After the burst of retching the corpus pressure returned to control levels over several minutes with a similar time course to that observed in animals which did not retch (e.g. Fig. 5, lower panel).

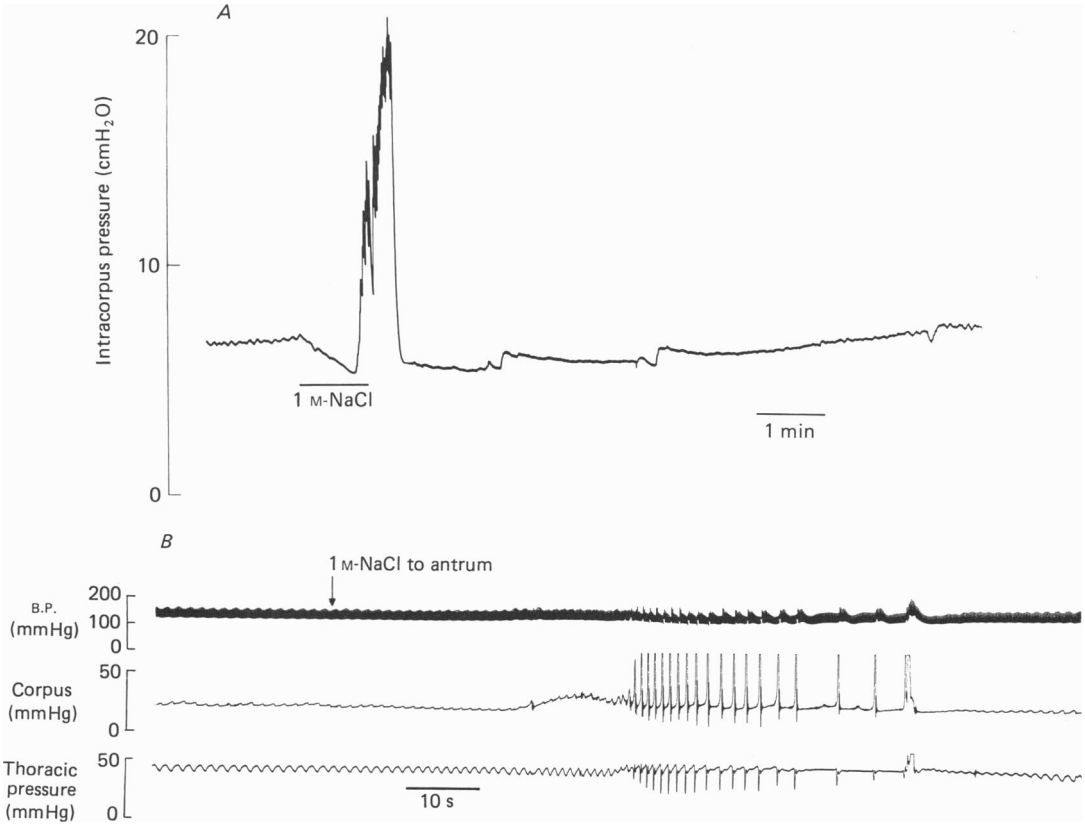

Figure 6. *A*, the effect of application of 1 M-NaCl to the antrum on intracorpus pressure in the presence of atropine, guanenthidine and greater splanchnic nerve section. Note the initial fall in pressure interrupted by the large increase in pressure when the animal retched, after which the pressure slowly returned (cf. time course of this return with that in Fig. 5). *B*, conditions as above except that the 1 M-NaCl was present from the point indicated to the end of the record and the recording was made at a fast paper speed. The 1 M-NaCl evoked a burst of retching (+ve intragastric and −ve intrathoracic pressure) concluding with a vomit (+ve intragastric and intrathoracic pressure). This record also illustrates the absence of effect of NaCl on blood pressure until retching intervened.

Effect of antral stimulation on the antrum

(*a*) *Appearance of the mucosa*

The antral mucosa was observed during application of the stimuli and intermittently throughout the experiment. After surgery the mucosa was pink in colour, covered with clear mucus and thrown into rugal folds which moved in a manner apparently unrelated to the contractions of the underlying muscle layer.

During stroking of the antral mucosa the motions of the rugae ceased, the mucosa flattened and there was a secretion of mucus. With NaOH (> 50 mM) and HCl (> 50 mM) the above changes were observed in the mucosa, but in addition the mucosa became bleached and with repeated applications of NaOH showed signs of haemorrhage. The mucous layer became cloudy, particularly with NaOH (100 mM).

In contrast, the mucosa became engorged and reddened when NaCl (> 750 mM) was applied.

If the mucosa was blotted during an experiment it was noted that it rapidly (< 1 min) became covered with a fresh layer of mucus and this indicates that the surgical procedure of preparing an antral mucosal sheet did not impair the secretory ability of this tissue.

(*b*) *Activity of the muscle*

In some experiments the activity of the circular muscle layer was monitored during application of stimuli to the mucosa. The antral muscle usually showed regular contractions in the absence of any overt stimuli and these contractions were observed to propagate over the antrum from the corpus towards the duodenum. Stroking the antral mucosa was without effect on antral muscle activity, as were HCl (100 mM), NaCl (154 mM) and all hypotonic stimuli. In contrast, NaCl (750 mM) and NaOH (50 mM) produced a transient inhibition of antral activity. With higher concentrations there was either an increase in the overall tone of the antral muscle or a burst of contractions. Neither the responses of the mucosa nor those of the muscle were studied in the presence of atropine or vagotomy and therefore no comment can be made concerning the mechanism of their production.

DISCUSSION

The present study has demonstrated that mechanical and chemical stimulation of the gastric antral mucosa can evoke a vagally mediated reflex reduction of corpus motility, apparently by simultaneous inhibition of cholinergic excitatory pathways and activation of non-adrenergic non-cholinergic inhibitory pathways. The afferent and efferent limbs of this reflex will be discussed separately and then its possible functional significance assessed.

Afferent limb

All the stimuli (stroking, NaCl, NaOH and HCl) effective in evoking reflex relaxation of the corpus have been shown in other species to activate vagal afferents with receptors in the gastrointestinal mucosa including the antro-pyloric region. (e.g. cat: Iggo, 1957; Paintal, 1957, 1973; Davison, 1972; Mei, 1983; rat: Clarke & Davison, 1978; sheep: Cottrell & Iggo, 1984*a*, *b*). Comparable electrophysiological studies have not been undertaken in the ferret and therefore we have only indirect evidence for an involvement of these afferents in the reflexly induced motility changes observed. Whilst the electrophysiological studies have revealed the wide range of stimuli to which these mucosal afferents are sensitive they have provided little indication as to their function. This study shows the potential that mucosal afferents have for influencing the vagal efferent control of gastric motility. Whilst it is most likely that the mucosal stimuli are activating *mucosal* afferents, recent studies by Cottrell & Iggo (1985*a*, *b*) have shown that mucosal stimulation may produce local reflex changes in the muscle underlying the mucosa and hence evoke a discharge in *muscle* mechanoreceptors. Such a mechanism cannot be excluded from the present study. Two other possible mechanisms could be involved. Firstly,

mucosal stimuli can produce changes in mucosal blood flow (as indicated by changes in mucosal colour in this study), which in turn could result in local hypoxia that may evoke afferent discharge. Secondly, luminal stimuli may evoke the release of a number of neuroactive substances (e.g. 5-hydroxytryptamine, histamine or gastrin) from mucosal cells and these could directly activate naked nerve endings terminating in the mucosa, submucosa or muscle (Mei, 1983; Paintal, 1973). This type of mechanism could contribute to the apparent polymodal nature of some of the vagal mucosal afferents.

Efferent limb

All the effects of antral stimulation on corpus motility were present in guanethidine-treated, adrenalectomized animals with the greater splanchnic nerves cut, indicating that a sympathetic reflex either via the spinal cord or the coeliac ganglion is unlikely to be involved. However, the corpus responses were modified by atropine and abolished by vagotomy. A comparison of the corpus response evoked by NaOH pre- and post-atropine administration showed that the relaxation was still present after atropine, but the time taken for the corpus pressure to return to pre-stimulus levels after washing the antrum was significantly prolonged. Taken together, these results indicate that during antral mucosal stimulation a vago-vagal reflex was evoked, leading to a reduction in size or abolition of corpus contractions and a prolonged reduction in tone. The efferent pathway appears to involve simultaneous inhibition of activity in the vagal efferents supplying the intramural cholinergic excitatory neurones and a stimulation of those driving the non-adrenergic non-cholinergic inhibitory neurones described in the ferret corpus (Andrews & Lawes, 1985). The main indication that this is the case comes from the demonstration that in the absence of a cholinergic drive (atropinized) the recovery time of the corpus pressure was prolonged. Without atropine not only did the pressure recover more quickly but contractions returned almost immediately after antral stimulation ceased. Thus in the presence of atropine the vagally driven non-adrenergic non-cholinergic inhibitory neurones act unopposed by the intramural cholinergic neurones.

The concept of a reciprocal organization of the vagal drive to the stomach was first suggested by Davison & Grundy (1978, 1980), based on recordings of vagal efferent activity in response to gastric distension in the rat. Studies in the dog and ferret have also demonstrated populations of vagal efferents with differential responses to the same gut stimulus (Andrews, Fussey & Scratcherd, 1980; Grundy, Salih & Scratcherd, 1981). It has also been suggested that a similar pattern of vagal efferent activity (decreased drive to intramural cholinergic neurones, increased drive to non-adrenergic non-cholinergic neurones) occurs following a meal, to maintain corpus pressure at a low level with small-amplitude contractions during the early part of gastric digestion (Andrews, 1986*b*). In view of the effects of mucosal stimulation it is possible that mucosal receptors could be involved in the generation of the adaptive response to feeding. Confirmation of this reciprocal driving of excitatory and inhibitory vagal efferents by mechanoreceptors and chemoreceptor inputs awaits electrophysiological studies and further quantitative investigations of this antro-corpus reflex pre- and post-atropine using a variety of mucosal stimuli.

Functional Significance

Gastric emptying

The potential that antral mucosal afferents have for reflexly influencing corpus motility has been demonstrated, and such a reflex could be involved in the control of emptying following a meal in addition to the previously demonstrated reflexes involving the antrum, pylorus and duodenum. For this antro-corpus reflex to be involved in the regulation of gastric emptying the stimuli used here must represent natural features of the gastric luminal environment and this aspect of the present study is discussed below.

(*a*) *Mechanical stimulation of the mucosa.* Removal of the antral mucosa in the dog has only a minor influence on the gastric emptying of liver cubes (Becker & Kelly, 1983), thus providing little support for an involvement of antral mucosal mechanoreceptors in the regulation of gastric emptying. However, it should be borne in mind that only relatively small particles of soft food were investigated. A more marked effect may be observed with larger more indigestible particles. As such particles tend to be retained until phase III of the migrating myoelectric complex occurs, it is possible that antral mucosal nerves could have a permissive role in cueing the migrating myoelectric complex. It is of interest that phase III of this complex was reduced in the dog by vagal blockade (Gleysteen, Sarna & Myrvik, 1985).

(*b*) *Chemical stimulation of the mucosa.* The major problem in assessing the functional role of the responses to chemical stimulation of the gastric mucosa has been relating the effective stimuli to the normal gastric environment. Whilst the gastric pH may be sufficiently acidic to activate the chemoreceptors described by Iggo (1957) which he proposed provided a degree of feed-back for the control of acid secretion, it is difficult to envisage a natural stimulus equivalent to 50 mM-NaOH, especially when $NaHCO_3$ (100 mM) and Tris base (0·5–2 M) were ineffective. Studies in the dog showed that chemical stimulation of the gastric mucosa with HCl or HNO_3 (pH 4–1) produced a pH related decrease in the gastric electrical control activity, as did NaOH or NH_4OH (pH 10–12·5) (Kuwahara, 1983*a*). These responses were predominantly mediated by the vagus nerves (Kuwahara, 1983*b*). Whilst NaOH (50–100 mM) does not appear to represent a physiological stimulus it is worth bearing in mind that it is the only alkaline stimulus shown to activate vagal gastric mucosal afferents, and as such serves to illustrate the potential that alkaline stimuli have for activating this antro-corpus reflex. Further studies using other alkaline stimuli are required. However, the lack of effect of Tris base and $NaHCO_3$ would suggest that hydroxyl ions are necessary for stimulation of the vagal mucosal afferents.

Hypertonic stimuli were also effective in evoking reflex inhibition of the corpus, and as the rate of gastric emptying for a liquid is related to its osmolarity (up to 1000 mosmol/l; Barker, Cochrane, Corbett, Hunt & Kemp Roberts, 1974) it is possible that this reflex could be involved in the control of liquid emptying in which the proximal stomach plays a predominant role (Minami & McCallum, 1984).

Vomiting

An interesting incidental observation was that 1 M-NaCl or electrical stimulation of the antrum evoked retching. Previous studies (Andrews, Bingham & Davis, 1985) in the anaesthetized ferret demonstrated that electrical stimulation of the cut central end of the ventral abdominal vagus evoked retching, and the present data suggest that some of the afferents involved probably originated in the antral mucosa. This study also supports the idea that vagal afferents play a key role in vomiting evoked by gastric stimulation (Davis, Harding, Leslie & Andrews, 1986). Studies in the conscious ferret (P. L. R. Andrews & C. J. Davis, unpublished observations) have shown that 1 M-NaCl given into the stomach is emetic and the response is in part dependent upon an intact abdominal vagus. Prior to vomiting the proximal stomach is quiescent and this phenomenon has been implicated in the genesis of the sensation of nausea (Willems & Lefebvre, 1986). The antro-corpus reflex described here could be involved in this stasis. In their study of gastric emptying in man Barker *et al.* (1974) reported that the higher concentrations of glucose and KCl used were nauseating when delivered directly into the stomach.

The above observations suggest the interesting possibility that the gastric mucosal receptors serve to monitor the chemical nature of the gastric contents, not with a view to regulating gastric function but to identify potentially harmful substances in the lumen. Once a harmful substance is detected, vagal afferents could evoke nausea to deter further ingestion, relax the corpus to help to confine the toxin to the stomach (Davis *et al.* 1986) and trigger vomiting to expel the confined gastric contents. It is also known that the antrum may have retroperistalsis prior to vomiting (Akwari, 1983), presumably to further confine the toxin in the stomach, and in this context it is of interest that Kuwahara (1983*a*) reported retroperistaltic discharges in the gastric electrical control activity with solutions of pH 12.

In conclusion, some of the antral stimuli evoking reflex relaxation of the gastric corpus can be reconciled with features of the luminal environment (e.g. acid or brushing the mucosa and could therefore play a role as indicators of the state of digestion and hence be involved in the regulation of emptying via this reflex. However, other effective stimuli (e.g. NaOH and 1M-NaCl) appear to represent potentially harmful substances and as such may evoke vomiting together with its prodromata.

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REFERENCES

ABRAHAMSSON, H. (1973). Vagal relaxation of the stomach induced from the gastric antrum. *Acta physiologica scandinavica* **89**, 406–414.

AKWARI, O. E. (1983). The gastrointestinal tract in chemotherapy induced emesis: a final common pathway. *Drugs* **25**, 18–34.

ANDREWS, P. L. R. (1986*a*). Vagal afferent innervation of the gastrointestinal tract. *Progress in Brain Research* **67**, 65–86.

ANDREWS, P. L. R. (1986*b*). The non-adrenergic, non-cholinergic innervation of the stomach. *Archives internationales de pharmacodynamie et de thérapie* **280**, 84–109.

ANDREWS, P. L. R., BINGHAM, S. & DAVIS, C. J. (1985). Retching evoked by stimulation of abdominal vagal afferents in the anaesthetized ferret. *Journal of Physiology* **358**, 103*P*.

ANDREWS, P. L. R., FUSSEY I. V. & SCRATCHERD, T. (1980). The spontaneous discharge in abdominal vagal efferents in the dog and ferret. *Pflügers Archiv* **387**, 55–60.

ANDREWS, P. L. R. & LAWES, I. N. C. (1985). Characteristics of the vagally driven non-adrenergic non-cholinergic inhibitory innervation of the ferret gastric corpus. *Journal of Physiology* **363**, 1–20.

ANDREWS, P. L. R. & WOOD, K. L. (1984). The effects of chemical and mechanical stimuli applied to the gastric antral mucosa in the anaesthetized ferret. *Journal of Physiology* **384**, 63*P*.

BARKER, G. R., COCHRANE, G. McL., CORBETT, G. A., HUNT, J. N. & KEMP ROBERTS, S. (1974). Actions of glucose and potassium chloride on osmoreceptors slowing gastric emptying. *Journal of Physiology* **237**, 183–186.

BECKER, J. M. & KELLY, K. A. (1983). Antral control of canine gastric emptying of solids. *American Journal of Physiology* **245**, G334–338.

CLARKE, G. D. & DAVISON, J. S. (1978). Mucosal receptors in the gastric antrum and small intestine of the rat with afferent fibres in the cervical vagus. *Journal of Physiology* **284**, 55–67.

COTTRELL, D. F. & IGGO, A. (1984*a*). Tension receptors with vagal afferent fibres in the proximal duodenum and pyloric sphincter of sheep. *Journal of Physiology* **354**, 457–475.

COTTRELL, D. F. & IGGO, A. (1984*b*). The response of duodenal tension receptors in sheep to pentagastrin, cholecystokinin and some other drugs. *Journal of Physiology* **354**, 497–522.

DAVIS, C. J., HARDING, R. K., LESLIE, R. A. & ANDREWS, P. L. R. (1986). The organization of vomiting as a protective reflex. In *Nausea and Vomiting: Mechanisms and Treatment*, ed. DAVIS, C. J., LAKE-BAKAAR, G. V & GRAHAME-SMITH, D. G., pp. 65–75. Berlin: Springer-Verlag.

DAVISON, J. S. (1972). Responses of single vagal afferent fibres to mechanical and chemical stimulation of gastric and duodenal mucosa in cats. *Quarterly Journal of Experimental Physiology* **57**, 405–416.

DAVISON, J. S. & GRUNDY, D. (1978). Modulation of single vagal efferent fibre discharge by gastrointestinal afferents in the rat. *Journal of Physiology* **284**, 69–82.

DAVISON, J. S. & GRUNDY, D. (1980). An electrophysiological investigation of vago-vagal reflexes. In *Gastrointestinal Motility*, ed. CHRISTENSEN, J. New York: Raven Press.

GLEYSTEEN, J. J., SARNA, S. L. & MYRVIK, A. L. (1985). Canine cyclic motor activity of stomach and small bowel: the vagus is not the governor. *Gastroenterology* **88**, 1926–1931.

GRUNDY, D., SALIH, A. A & SCRATCHERD, T. (1981). Modulation of vagal efferent discharge by mechanoreceptors in the stomach, duodenum and colon of the ferret. *Journal of Physiology* **319**, 43–52.

HUNT, J. N. (1956). Some properties of an alimentary osmoreceptor mechanism. *Journal of Physiology* **132**, 267–288.

IGGO, A. (1957). Gastric mucosal chemoreceptors with vagal afferents in the cat. *Quarterly Journal of Experimental Physiology* **42**, 389–409.

KUWAHARA, A. (1983*a*). Changes in gastric motility by chemical and mechanical stimulation in the dog. *Japanese Journal of Physiology* **33**, 29–40.

KUWAHARA, A. (1983*b*). Role of vagal and splanchnic nerves for gastric motility changes in response to stimulation of the canine gastric mucosa. *Japanese Journal of Physiology* **33**, 239–247.

LEEK, B. F. (1977). Abdominal and pelvic visceral receptors. *British Medical Bulletin* **33**, 163–168.

McCARTHY, L. E. & BORISON, H. L. (1974). Respiratory mechanics of vomiting in decerebrate cats. *American Journal of Physiology* **226**, 738–743.

MACKAY, T. W. & ANDREWS, P. L. R. (1983). A comparative study of the vagal innervation of the stomach in man and the ferret. *Journal of Anatomy* **136**, 449–481.

MEI, N. (1983). Sensory Structures in the viscera. In *Progress in Sensory Physiology* **4**, ed. OTTOSON, D., pp. 1–44. Berlin: Springer-Verlag.

MINAMI, H. & McCALLUM, R. W. (1984). The physiology and pathophysiology of gastric emptying in humans. *Gastroenterology* **86**, 1592–1610.

PAINTAL, A. S. (1957). Responses from mucosal mechanoreceptors in the small intestine of the cat. *Journal of Physiology* **139**, 353–368.

PAINTAL, A. S. (1973). Vagal sensory receptors and their reflex effect. *Physiological Reviews* **53**, 159–227.

STRUNZ, U. T. & GROSSMAN. M. I. (1978). Effect of intragastric pressure on gastric emptying and secretion. *American Journal of Physiology* **235**, 552–555.

WILLEMS, J. L. & LEFEBVRE, R. A. (1986). Peripheral nervous pathways involved in nausea and vomiting. In *Nausea and Vomiting: Mechanisms and Treatment*, ed. DAVIS, C. J., LAKE-BAKAAR, G. V. & GRAHAME-SMITH, D. G., pp. 56–64. Berlin: Springer-Verlag.