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VAGAL AFFERENT DISCHARGE FROM MECHANORECEPTORS IN DIFFERENT REGIONS OF THE FERRET STOMACH

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SUMMARY

1. The rate and volume of gastric filling was estimated in conscious ferrets by measuring the amount of milk they would drink after an overnight fast. The mean volume was 94·5 ± 7·5 ml. at a rate of 13·0 ± 0·74 ml./min. An intragastric infusion rate of 10 ml./min to a total of 50 ml. was selected as a standard distension stimulus.

2. Action potentials were recorded from single gastric afferent fibres in the cervical vagus. All but two of thirty-six afferent units were tonically active when the stomach was deflated.

3. Afferent fibres arising from receptors in the antrum showed modulation in phase with spontaneously occurring antral contractions. Afferent fibres from the corpus and fundus, however, discharged at irregular rates between 0·35 and 7·5 Hz with no correlation with the intragastric pressure rises associated with the antral contractions.

4. Inflation of the stomach with 50 ml. 0·9 % NaCl at a rate of 10 ml./min stimulated antral motility and the rhythmic afferent discharge from the antrum was enhanced Receptors in the corpus and fundus increased their rate of discharge with increasing gastric volumes. Receptors in the region between the antrum and the corpus had the property of both types so that they responded to both distension and contractions.

5. On distension with 0·9 % NaCl, fluid is distributed unevenly in the stomach. 80 % was accommodated in the corpus and fundus, the remainder of the fluid entering the antrum.

6. The tension was measured in strips of stomach wall taken from corpus and antrum. For equal increments of stretch the development of tension was greater in the antral than in corpus strips. This physical property together with neurally mediated receptive relaxation of the corpus is the reason for the fluid distribution described above.

7. It is concluded that the properties of the tension receptor are determined by their site in the stomach. Those in the body and fundus signal the degree of distension and those in the antrum signal information concerning the amplitude, rate and duration of antral contractions.

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INTRODUCTION

Receptors in the stomach which respond to both distension and contraction of the gastric musculature have been implicated in post-prandial satiety, in sensing the effectiveness of a contraction to expel contents and in a variety of reflexes (Leek, 1977). These mechanoreceptors are either non-adapting or very slowly adapting and initiate a spike discharge related to tension in the wall of the viscus and as they respond to passive distension and active contraction, they have been regarded as being located 'in series' with smooth muscle (Iggo, 1957; Mei, 1970; Davison & Clark, 1977). The studies of gastric tension receptors of non-ruminant animals (Paintal, 1954; Iggo, 1955, 1957), were performed under conditions in which naturally occurring propagated waves of contraction were rarely observed, indeed it seems likely that the stomachs of these animals were flaccid and in an atonic state. In these cases, distension was achieved by using rates of inflation which were likely to be well in excess of the physiological rates of filling. The resting stomach of the non-anaesthetized animal is rarely quiescent, and the stomach responds to a distension stimulus such as a meal by increased motor activity. Distension is the only natural stimulus known to increase gastric emptying by stimulating gastric peristalsis (Hunt & Macdonald, 1954). The stomach of the urethane anaesthetized ferret shows well developed naturally occurring gastric motility and responds to a distension stimulus by increased antral motility (Andrews, Grundy & Scratcherd, 1979). This preparation seemed to be an appropriate one on which to re-investigate the role of gastric mechanoreceptors using physiological rates of gastric distension.

METHODS

Measurement of gastric filling in conscious ferrets. Eleven ferrets which has been fasted overnight were allowed to drink milk at room temperature from a vertical cylinder. A tube was connected to the base of the cylinder through which the pressure of the column of milk was measured using a SEM 480 pressure transducer. The signal was displayed, after amplification, on a flat bed pen recorder, so that the rate and change in pressure of the column of milk was continuously recorded. The experiment was deemed to have ended when the animal stopped drinking for a period of 1 min. The volume of milk drunk was determined after direct calibration by either addition or removal of milk in small increments, by pipette.

Operative procedures. Experiments were performed on twenty-two ferrets (490–1700 g) fasted 12–18 hr, but having access to water, and anaesthetized by a single intraperitoneal injection of urethane (1·5 g/kg body wt.). A clear airway was maintained by intubating the trachea through the mouth. The stomach was intubated via the mouth and oesophagus and also from the duodenum through the pylorus. Inflation and deflation of the stomach was carried out through the oesophageal tube and intragastric pressure measured through the fluid filled pyloric tube attached to a pressure transducer (SEM 480). In some experiments the movements of the antral wall were recorded in the open abdomen by means of threads sewn to the serosa and attached to an optical wedge. The filling of the stomach was also observed directly in some animals and also recorded photographically in an open abdomen using an 8 mm movie camera (Bolex). The abdominal wall was opened just sufficiently wide for recording purposes and the viscera were kept warm with saline swabs between periods of recording. The rectal temperature was maintained between 38·5 and 39·5 °C on a homeostatic blanket. The right cervical vagus was exposed and contained in a paraffin pool. The nerve was carefully dissected away from the adjacent carotid artery and placed over a black perspex tray. Single afferent nerve fibres were teased from the nerve trunk as previously described by Paintal (1953) for the cat. The receptive fields of the different afferent units were located by probing the stomach with a blunt glass rod.

Neurophysiological recording. Action potentials were recorded on conventional neurophysiological equipment with neural activity and intragastric pressure displayed on a Medelec M-scope (Medelec Ltd). The integrated output of the spike discharge was fed from a Digitimer D130 to one channel of a flat bed pen recorder, with gastric pressure or antral movements recorded on the second channel (Bryans 28000).

The distribution of fluid in the stomach. The ferret stomachs were excised from the anaesthetized animal or left in situ and filled with either 30, 50 or 70 ml. Paraplast at 50 °C. When this material had hardened, the wall of the stomach was cut away and 1 cm segments were cut at right angles to the long axis of the stomach with a sharp knife. The volume of these 1 cm casts was then measured.

Length-tension studies. The relationship between the length and tension of strips (10 × 5 mm) of stomach, cut in the longitudinal and circular axes from antrum and body, was measured. The passive tension was recorded following 1·0 mm ramp stretches, with the strips immersed in a Ringer bicarbonate buffer at 37 °C and gassed with 95 % O_2 and 5 % CO_2.

TABLE 1. The volume and rate of drinking milk in 11 conscious ferrets

Parameter	Mean	S.E.	Range
Body weight (g) $n = 11$	784	60	500–1130
Rate of drinking (ml./min)	13	0·74	9·6–17·6
Volume drunk (ml.)	94·5	7·5	41–124

RESULTS

Measurement of gastric filling

The volume of milk drunk and the rate of drinking by eleven ferrets is illustrated in Table 1. Each experiment was repeated between 2 and 4 times on each animal on different days. In any one animal the volume drunk and the rate of drinking (gastric filling) were remarkably constant. The animals drank continuously and the rate of drinking was shown to be close to linear ($r = 0{\cdot}91$–$0{\cdot}99$) throughout the duration of feeding. The rate of drinking was shown to approximately equate to gastric filling. Fifteen minutes after the completion of drinking the animals were anaesthetized and more than 90 % of the milk was recovered from the stomach. In the experiments which follow it was decided to use a rate of gastric distension of 10 ml./min and a total volume of usually 50 ml., parameters which were well within the physiological range as observed above.

Gastric afferent fibre discharge

Thirty-six afferent fibres with receptors situated in the stomach wall were isolated from the cervical vagus. Conduction velocities were measured in twenty-four of these fibres. All were C-fibres and the mean conduction velocity was $0{\cdot}91 \pm 0{\cdot}21$ m/sec (Fig. 1).

All afferent fibres, with the exception of two were spontaneously active when the stomach was deflated. 'Spontaneous' motility was present in all animals and in those in which direct observation was possible, the motility was confined to the pyloric antrum.

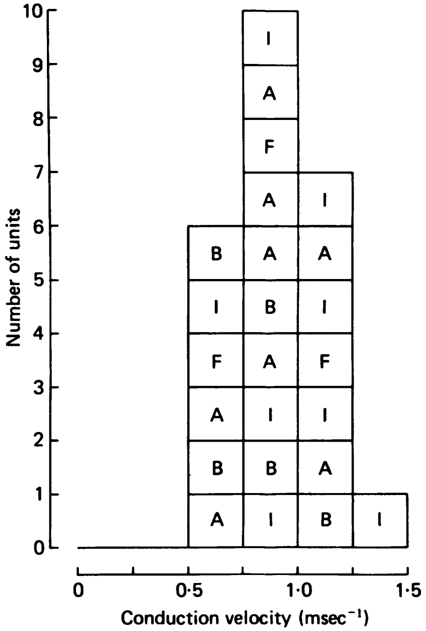

Fig. 1. Conduction velocities in twenty-four single afferent fibres from gastric mechanoreceptors. A, antrum. B, body of corpus. F, fundus. I, region of incisura angularis. The conduction velocities in the fibres were independent of the receptive field location.

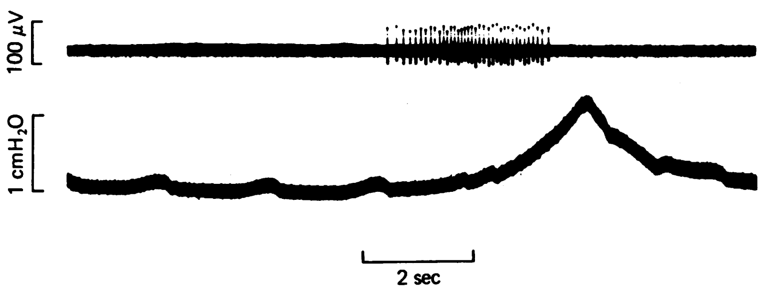

Fig. 2. Impulses in an afferent vagal fibre from a mechanoreceptor in the antrum. Upper trace, afferent nerve discharge; lower trace, intragastric pressure. As spontaneous waves of contraction pass over the receptive field, firing occurs in the afferent nerve. The three small transient waves on the intragastric pressure record were due to respiration.

Afferent discharge patterns in fibres with receptive fields located in the antrum

Eleven single afferent units had receptive fields located in the wall of the antrum. In the deflated state the afferent discharge showed modulation in phase with spontaneously occurring contractions with very little activity during the period between contractions (Fig. 2). The frequency of discharge during the contractions ranged from 0·36 to 32 Hz. Inflation of the stomach with 0·9 % NaCl at a rate of 10 ml./min caused an enhancement of antral motility (Andrews *et al.* 1979). This increased activity was associated with an increase in afferent discharge (Fig. 3) and was manifested as an increase in peak frequency or an increase in the duration of each burst which occurred with contraction, or an increase of both types of activity.

This discharge rate was correlated with motility; if there was no increase in motility there was no increase in afferent discharge. When afferent discharge was recorded during step inflation a volley of impulses was recorded during the dynamic phase. In an experiment in which step inflation was at a rate and volume well outside physiological conditions (50 ml. in 1 sec) not only was there a response in the dynamic phase but as the pressure in the stomach declined to a plataeu, so did the discharge rate which remained constant and unmodulated. This manoeuvre also inhibited antral evoked contractions, which probably accounted for the absense of modulation. Following deflation of the stomach the evoked contractions returned to their predistension amplitude as did the frequency of discharge of the afferent fibre. Large antral contractions evoked by electrical stimulation of the cut peripheral end of the left cervical vagus also caused an increase in afferent discharge association with contractions (Fig. 4).

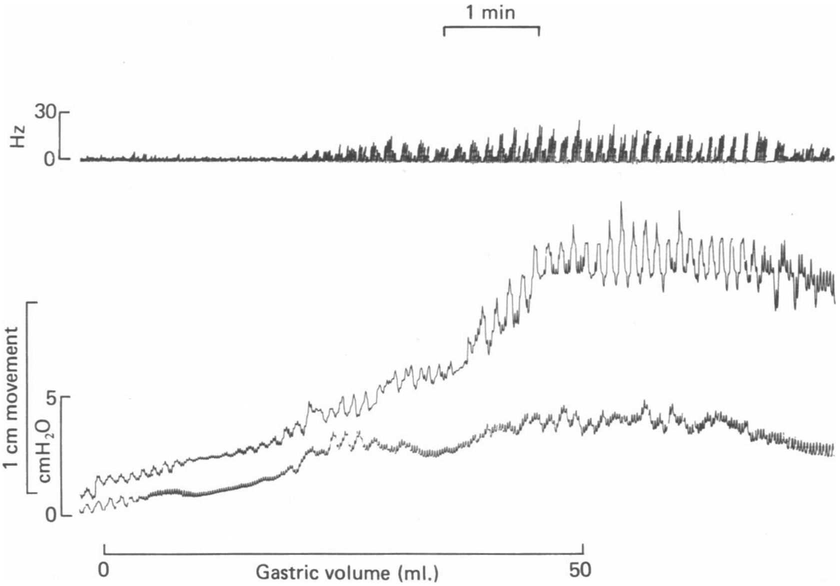

Fig. 3. Discharge in a single afferent nerve fibre from a mechanoreceptor located in the antrum. Upper trace, integrated response of the afferent discharge displayed as the total count during successive 1·25 sec intervals. Middle trace, antral wall movement as measured with a displacement optical wedge. The gradual upward slope of the trace is due to the displacement of the stomach as the organ adapts to filling. Lower trace, intragastric pressure. The bar marks the duration over which 50 ml of 0·9 % NaCl at 37 °C was infused into the stomach at a rate of 10 ml./min. Note the increase in antral contractions which occur as a consequence of distension and that the afferent discharge is correlated with antral wall movement (peristalsis).

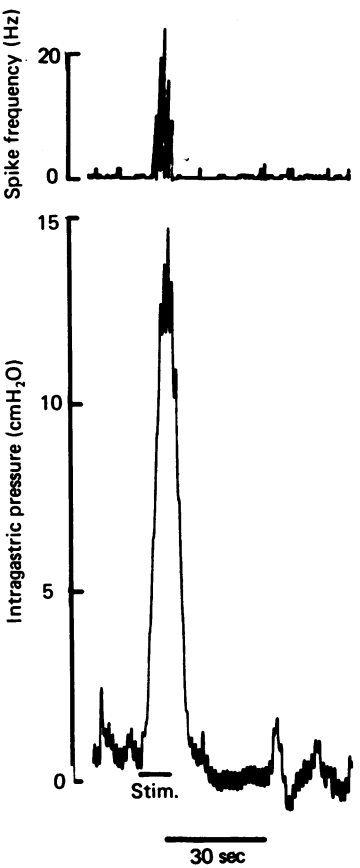

Fig. 4. Increase in afferent discharge associated with increased antral motility consequent upon stimulation of the peripheral cut end of the left cervical vagus nerve (10 Hz, 20 V, 0·5 m sec). Upper trace, integrated spike discharge during 1·25 sec periods. Lower trace, intragastric pressure.

Vagal afferent discharge patterns in fibres with receptive fields located in the body or fundus of the stomach

Fifteen single afferent fibres had receptive fields which were located in the corpus region or the fundus of the stomach. All but one of these units showed tonic activity, that is a continuous irregular discharge unrelated to intragastric pressure rises associated with antral contractions. In the deflated state the discharge frequency ranged from 0·35 to 7·7 Hz. Inflating the stomach at a rate of 10 ml./min resulted in an increase in afferent discharge with increasing volume, which was non-adapting or only slowly adapting (Fig. 5). The threshold of volume and intragastric pressure necessary to induce increased activity varied from 5 to 50 ml. and 0·5 to 6·0 cm H_2O respectively. The discharge frequency reached after 50 ml. inflations varied between 11·4 and 23 Hz.

Intragastric pressure rises associated with antral contractions had very little effect on these corpus afferents, but if the region of the receptive field was stimulated

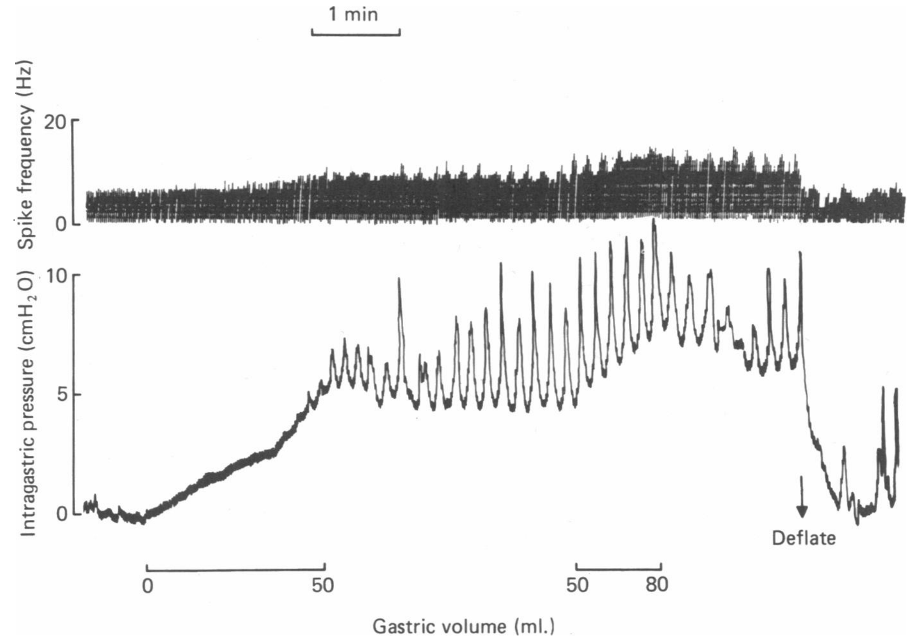

Fig. 5. The response of an afferent fibre from a mechanoreceptor situated in the corpus of the stomach to a slow gastric inflation (10 ml./min). Upper trace, integrated record of afferent discharge during 1·25 sec periods. Lower trace, intragastric pressure record. The horizontal bars represent the duration of gastric inflation with the gastric volume shown at the beginning and end of each period of inflation.

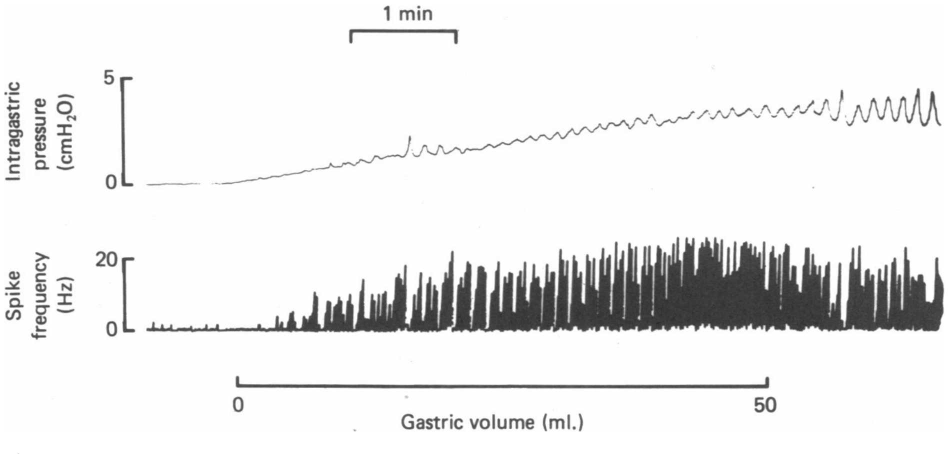

Fig. 6. The response of an afferent fibre from a receptor in the region of the incisura angularis to slow gastric inflation (10 ml./min). Upper trace, intragastric pressure. Lower trace, integrated record of afferent discharge during 1·25 sec periods.

electrically to cause a local contraction then an increased discharge was obtained so long as the contraction persisted. On deflation of the stomach, the frequency of firing in all the units returned to the pre-distension frequency. However, some units showed a transient period of reduced activity following deflation (Fig. 5).

Vagal afferent discharge patterns in fibres with receptive fields in the region of the incisura angularis

Ten afferent units were isolated which had receptive fields in the area between the pyloric antrum and the body of the stomach. The afferent discharge recorded from fibres with receptors in this region showed both modulation with gastric contractions and also responded to gastric inflation (Fig. 6).

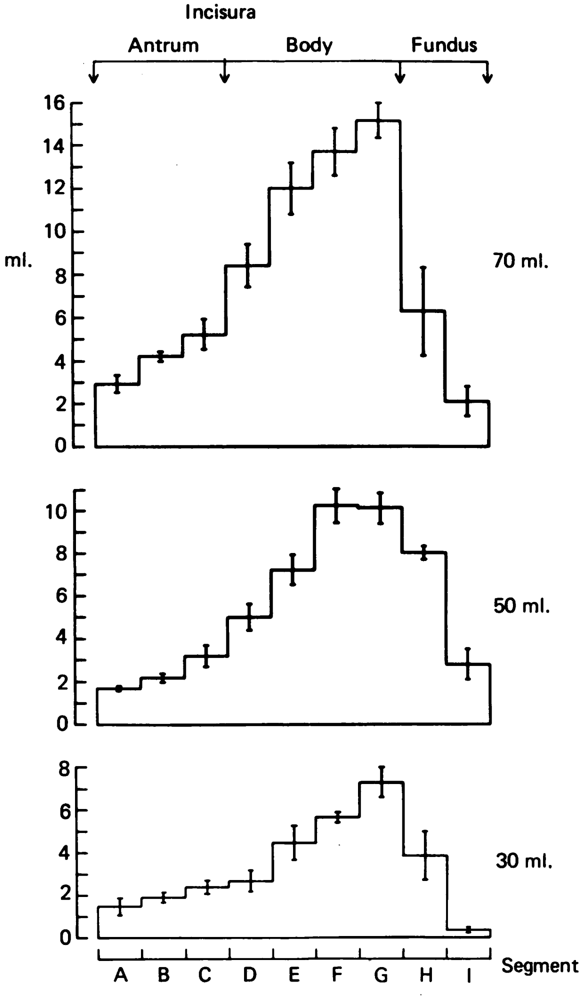

Fig. 7. The distribution of fluid in the different divisions of the stomach when inflated with 30, 50 and 70 ml. ($n = 4$ for each volume).

All but one of the units isolated demonstrated spontaneous firing, that is in the absence of gastric inflation. The frequency of firing was between 0·36 and 13·6 Hz, however the higher values were associated with contractile activity. When the stomach was inflated at 10 ml./min there was an increase in afferent discharge, both as a consequence of increased motility but also by the direct effect of distension (Fig. 6). Following deflation the afferent discharge returned to the pre-distension frequency.

The distribution of the distending fluid in the stomach

When the stomach was directly observed during inflation at 10 ml./min with 0·9 % NaCl, it was noticed that almost all the fluid was retained in the body and fundus with little passing into the antrum. This state of affairs was the same for the occluded and unoccluded pylorus. An attempt was made to quantify the distribution of the fluid by the Paraplast method, The calculated distribution of fluid volumes in the various segments with infusions of 30, 50 and 70 mls. is illustrated in Fig. 7. The body and fundus accommodate 80 % of the total fluid at all three levels of distension.

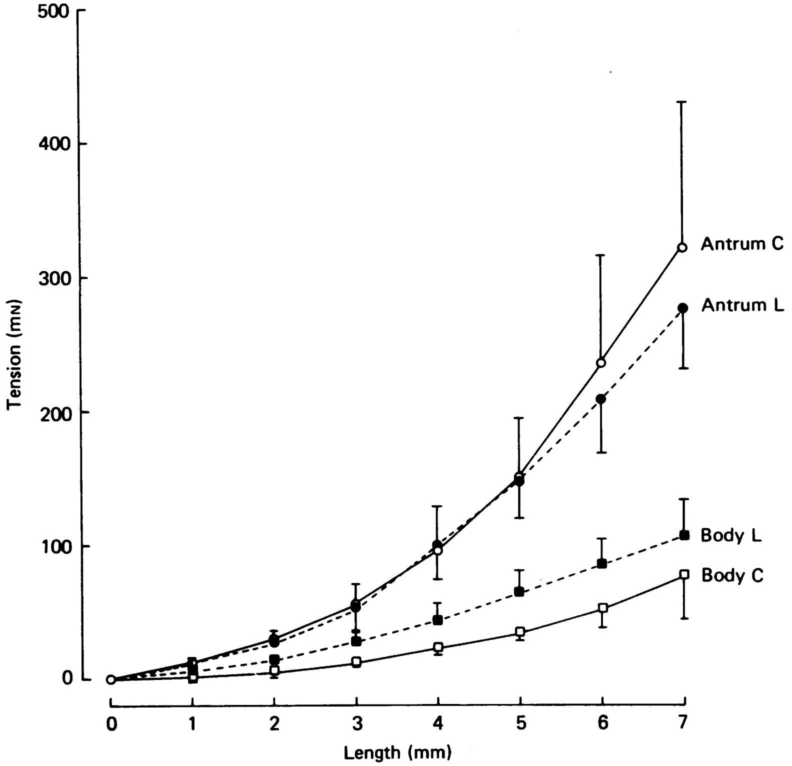

Fig. 8. The length tension relationship of strips of antral and body regions of the stomach wall. C strips cut parallel to the circular axis, L strips cut parallel with the longitudinal axis (n = 4).

The relationship between length and tension of the gastric smooth muscle.

The distribution of fluid observed above may be due in part to different physical properties of the antrum and body of the stomach. Length–tension curves were constructed for (10 × 5 mm) segments of the gastric wall cut in parallel with, and at right angles to, the longitudinal axis of the stomach from body and antral regions. The body was found to be more distensible than the antrum (Fig. 8.) and it may be that it is the different distensibility of the two regions which accounts not only for the distribution of fluid on distension but also the discharge characteristics of the mechanoreceptors.

DISCUSSION

The properties of the mechanoreceptors in this paper depended upon their site in the stomach. Those located in the corpus and fundus responded to distension whereas those of the antrum showed modulation with each contraction (Fig. 9). Not surprisingly those receptors located at the junction of the corpus and antrum exhibited properties common to both regions. However, the antral receptors were capable of responding to high levels of distension and receptors in the corpus responded to local contraction induced by direct electrical stimulation of the smooth muscle in the area of the receptor. Thus, all receptors were of the same functional type capable of responding to both passive stretch and active contraction and this in principle confirms the earlier work of Paintal (1954) and particularly Iggo (1955, 1957), that the mechanoreceptors were 'in series' with the smooth muscle elements. However, there were many differences between the results of this paper and those of Paintal (1954) and Iggo (1955, 1957). In their work almost all the fibres from all regions of the stomach responded in a similar way, they were non-adapting or slowly adapting; only one fibre was described which responded to spontaneous contraction of the pyloric antrum (Iggo, 1957). However, excitation of receptors could be brought about by

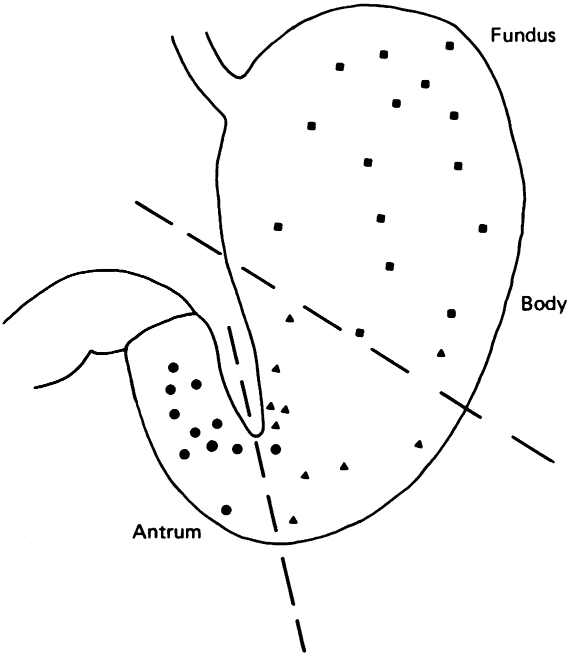

Fig. 9. The receptive fields of thirty-six mechanoreceptors in the stomach wall. ●, units responding mainly to gastric contractions; ■, units responding mainly to distension; ▲, units which respond both to distension and contractions.

direct stimulation of the smooth muscle in the receptive field of the fibre (Iggo, 1957; Davison & Clarke, 1977). Surprisingly both Paintal (1954) and Iggo (1957) were unable to elicit clear cut contractions of the abdominal viscera by faradic stimulation of the cervical vagi. These results are in marked contrast to those reported in this paper. The reason for these differences is not clear, there may have been a species difference between cat and ferret, but the most likely explanation is that both Paintal and Iggo were working with stomachs which were in an atonic state. This is suggested by the absence of spontaneous discharge in the afferent fibres, the absence of pyloric contractions which normally accompany gastric distension (Andrews *et al.* 1979) and the absence of contractile responses which usually accompany electrical excitation of the vagus nerves (Harper, Kidd & Scratcherd, 1959; Martinson & Muren, 1963). The explanation of Paintal (1973) to account for distension of the pyloric antrum 'that contraction of the stomach starting in the body and fundus would distend the pyloric antrum thereby stimulating the endings' is not tenable in the light of subsequent research. The consensus of opinion is that the corpus is a distensible food reservoir, whilst the antrum provides the motive force for stomach emptying (for reference see Cooke, 1975). The physical properties of the antrum and corpus, the distribution of the distending fluid and the pattern of discharge of the antral receptors described in this paper does not support Paintal's (1973) view. The distension of the stomach sets in motion antral contractions partly reflexly through the vagus nerves and partly through the intramural plexus (Andrews *et al.* 1979) and failure of such a procedure in man to release gastrin (Strunz & Grossman, 1978) does not support the view that under physiological conditions the receptors in the pyloric antrum discharge because of distension. Mei (1970) described five receptors situated in the cat pyloric antrum which discharged rhythmically and he presumed that they were synchronous with antral peristalsis. Similar results have been described for the dog by Takeshima (1971). However, in none of the previous studies was a stimulus used which could be described as physiological. Although the total volumes were likely to be representative of the volume of a meal, the rates of distension used were in excess of those normally encountered. Leek (1977) has pointed out that the rate of filling of a viscus may be a more important stimulus parameter than the degree of filling. We have attempted to mimic rates and volumes which, in the ferret are as near as possible to those normally encountered. Such rates and volume consistently produce smaller peak intragastric pressure and larger antral contractions than those produced by step inflation of the same volume. The threshold pressure which induced afferent discharge was 0·5 cm H_2O, slightly lower than those reported by Iggo (1957) and this raises the question of the significance of 'spontaneous' activity. The view that the normal function subserved by afferent fibres is to signal distension and that they constitute the peripheral mechanism for the immediate satiation of hunger and thirst (Paintal, 1954) is too simplistic a view.

Afferent fibres from the corpus could play a role in signalling the initial phase of post-prandial satiety, but they are also likely to serve as the afferent pathway for a number of vago-vagal reflexes (Davison & Grundy, 1978). These include the reflex excitation of antral motility (Andrews *et al*, 1979), gastric secretion (Grossman, 1962), pancreatic enzyme secretion (Blair, Brown, Harper & Scratcherd, 1966) and reflex corpus relaxation (Abrahamsson, 1973). However, the reason mechanoreceptors in the antrum send information centrally concerning each contraction, both spontaneous and evoked, and the need for such precise monitoring of contractile activity has yet to be elucidated.

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