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RESPONSES FROM MUCOSAL MECHANORECEPTORS IN THE SMALL INTESTINE OF THE CAT

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Tower (1933) recorded the discharge of impulses in the sympathetic rami of the frog and showed clearly that they contain afferent fibres from the intestine. In the cat, observations of this nature were made several years later by Gernandt & Zotterman (1946). They found that continuous or rhythmical spontaneous discharges occurred in intestinal afferent fibres running in the mesenteric and splanchnic nerves, and that local pinching and the passing of peristaltic waves stimulated the receptors of these fibres. Further they, and later Brown & Gray (1948), also observed that acetylcholine aroused impulses in some of these intestinal fibres. Subsequently Bein & Meier published records which suggested that there were distension-sensitive receptors in the cat's intestine (Meier & Bein, 1950; Bein & Meier, 1951). Unfortunately, Bein & Meier did not attach much importance to this significant finding as they were primarily interested in the effects of drugs on the autonomic system. Very recently Iggo (1957*a*) has added valuable information concerning intestinal receptors of this type innervated by vagal afferent fibres.

On the other hand, it is known that there are certain intestinal vagal afferent fibres in which impulses appear on local squeezing but not on distension of the intestine (Paintal, 1954*a*, *b*). However, apart from the response of these distension-insensitive receptors to certain chemical substances little is known about their normal excitation. The present investigation was undertaken to study this problem, and the endings concerned have been found to be mechanoreceptors associated with muscular elements in the mucosal layers of the small intestine.

METHODS

Experiments were carried out on cats anaesthetized with chloralose. Vagal afferent fibres were dissected according to previously described methods (Paintal, 1953). Distension of the stomach was carried out by a balloon inserted via the mouth. In all the experiments a catheter was

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inserted into the right atrium through the external jugular vein. In the earlier experiments a catheter was also inserted near the bifurcation of the abdominal aorta and pushed cranially so that its tip lay about 1–2·5 cm above the aortic opening of the diaphragm. Both these catheters were used for injecting chemical substances into the circulation.

The intra-intestinal pressure was recorded locally near the receptor whenever necessary. This was done by inserting into the intestinal lumen a glass tube which was connected by a narrow piece of polyethylene tubing to a mirror membrane manometer.

In order to perfuse the intestine with solutions of different chemical substances two openings were made in the intestine, one above and the other below the location of the receptor. Substances were usually introduced into the opening on the oral side of the receptor and allowed to flow out through the other.

In two cats changes in the villi following application of various solutions were observed by reflected light, using a loupe or dissecting microscope ($\times 6$ or $\times 10$). For this purpose a 5–10 cm length of the small intestine was simply slit along the antimesenteric border to expose the mucosa. Sometimes the external coats of longitudinal and circular muscle were first removed leaving the muscularis mucosae and the mucous membrane intact; the intestine was then slit along the antimesenteric side to expose the mucosa. The observations on the villi were made separately and not simultaneously with those on the intestinal receptors.

RESULTS

Observations have been gathered from a total of seventeen distension-insensitive intestinal mechanoreceptors. These constitute a homogenous group in that they possessed certain typical characteristics.

Since the procedures for isolating afferent fibres influence the type of fibres that come under observation, these procedures will be described briefly. The first seven receptors were isolated by using phenyl diguanide to stimulate these receptors. Since phenyl diguanide also stimulates distension-sensitive receptors in the stomach (Paintal, 1954*b*; Iggo, 1957*a*), efforts were directed at dissecting filaments which yielded a discharge of impulses following injection of about 175 μg phenyl diguanide into the aorta, but not following distension of the stomach. On obtaining such a filament, attempts were made to locate the ending in some portion of the small intestine. This was achieved in five of the seven receptors by observing a discharge of impulses on squeezing a localized portion of the small intestine (Fig. 5*A*). The fact that the other two were also located in the small intestine was confirmed by noting that they were stimulated in a characteristic manner following introduction of NaCl solution 30% (w/v) into the lumen of the intestine (see below).

Although other substances such as 5-hydroxytryptamine can also stimulate these receptors (Paintal, 1954*b*), phenyl diguanide has been the most useful for isolation of their afferent fibres because it yields reproducible effects without apparent damage to the preparation. Other substances found to excite these receptors on injection into the circulation are nicotine and potassium chloride (Fig. 1). Acetylcholine, 88 μg, had no effect on the receptor illustrated in Fig. 1. It should be noted that phenyl diguanide also consistently stimulates distension-sensitive intestinal receptors (Iggo, 1957*a*).

By the time the first seven receptors had been studied it became clear that they possessed an unimpressive but nevertheless characteristic type of spontaneous activity (Fig. 2), which is described below. This type of spontaneous activity was thereafter used as a means for detecting fibres of these receptors. On isolating a filament which showed such spontaneous activity, but which was unaffected by gastric distension, phenyl diguanide was injected into the right atrium. If a discharge of impulses appeared with characteristic latency (see Paintal, 1954*a*, *b*), attempts were then made to locate the receptor in the small intestine. The remaining ten fibres were isolated in this manner.

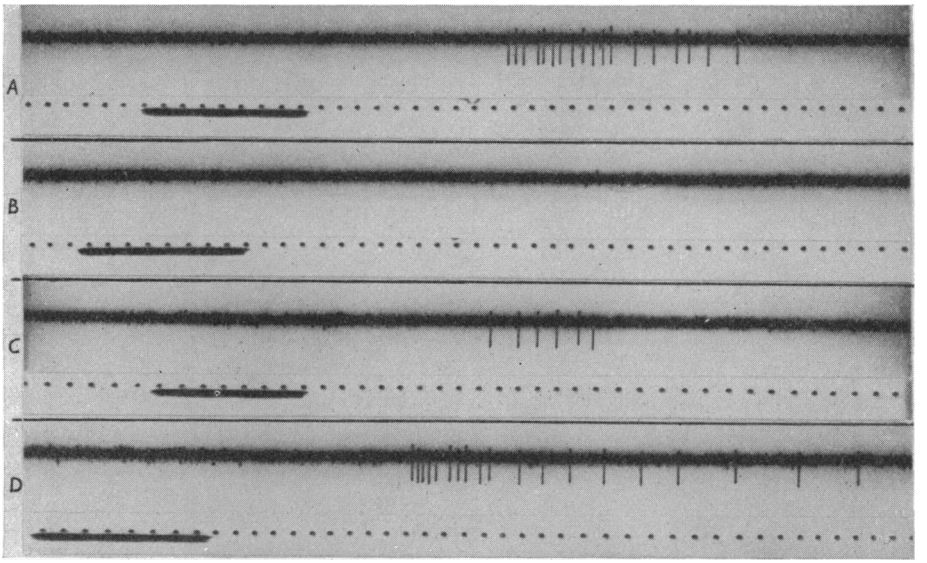

Fig. 1. Responses of a distension-insensitive mucosal receptor in the small intestine to intra-aortic injection of the following substances. *A*, phenyl diguanide 175 μg; *B*, ACh 88 μg; *C*, nicotine 175 μg; *D*, 1·75 ml. KCl (1·2%). From above downwards in each record: impulses in a fibre; time marker 0·1 sec; injection signal.

On locating a receptor, the region of the intestine concerned was marked appropriately, and at the end of the experiment its position in relation to the total length of the small intestine was determined. For this purpose the small intestine was excised from the pylorus to the ileocoecal junction and spread lengthwise on a flat surface. Since the length of the small intestine varied somewhat in different preparations, the position of the receptors has been expressed relative to the total length of the small intestine—the pylorus being regarded as 0% and the ileocoecal junction as 100%. Reckoned in this way the positions of the fifteen receptors were as follows: 5, 12, 17, 27, 35, 49, 50, 56, 58, 64, 65, 66, 75, 79 and 96%. These figures indicate that the intestinal

receptors are not selectively located in any particular region of the small intestine.

In a number of experiments transverse section of the intestine about 2–5 cm to the oral side of the receptor abolished its activity, thus showing that the afferent fibres concerned ran caudally for a short distance in the small intestine before reaching the receptor. However, in one case this procedure had no effect although removing the portion of the intestine containing the receptor abolished all activity.

TABLE 1. Some characteristics of cyclical spontaneous activity in nine intestinal mechanoreceptors

Serial no. of fibre	Duration of cyclical discharge (sec)	Peak frequency of discharge (impulses/sec)	Frequency of groups (groups/min)
3	1·7	15	3–4
6	2·0	20	<4
7	0·7–1·2	19–26	4–6
8	6·0	12	>2<10
9	9–14	18–25	2–4
11	6·0	10	4
13	5·5	8	3–4
14	6·0	7	6
17	3·0	15	5

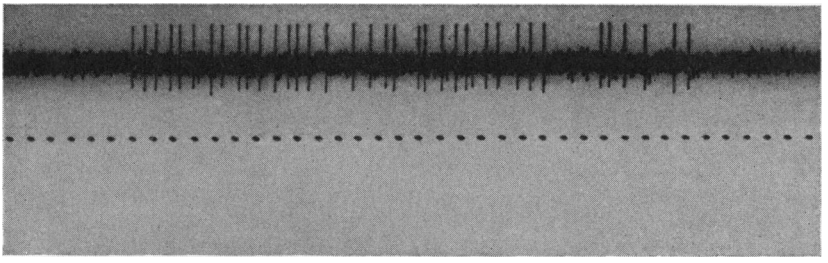

Fig. 2. A typical spontaneous discharge of impulses in an intestinal fibre. These discharges occurred 3·5 times/min. Time marker 0·1 sec.

Spontaneous activity

A significant feature of these intestinal receptors is the characteristic spontaneous activity that may be observed on careful inspection (Figs. 2–4). In thirteen fibres this consisted of groups of discharges of variable duration interspersed with periods of inactivity. Some of the characteristics of periodic activity in ten of these fibres are given in Table 1. The duration of the grouped discharges varied from 0·7 to 14 sec in different fibres. The groups appeared at a frequency of 2–6/min. The peak frequency of impulses varied from 7 to 26 impulses/sec. Between groups there were often no impulses. When the receptors were stimulated artificially, e.g. by 30% NaCl, the spontaneous

activity was superimposed on the discharge initiated by the artificial stimulus (Fig. 3).

The occurrence of peristaltic rushes was at times associated with considerably increased activity in these intestinal fibres. This is illustrated in Fig. 4, which is a graph of spontaneous activity that occurred in a fibre at a time when

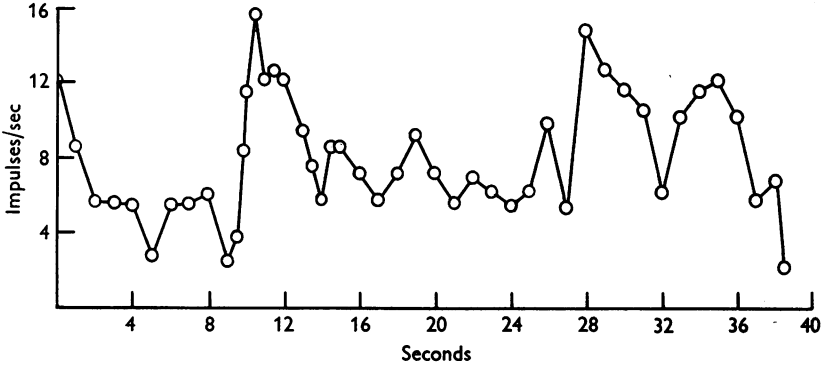

Fig. 3. Impulse activity in the fibre illustrated in Fig. 2 after introduction of 30% NaCl into the lumen of the small intestine. Note stimulation of receptor and that the bursts of spontaneous activity (e.g. between 10 and 13 sec) are superimposed on the general level of excitation.

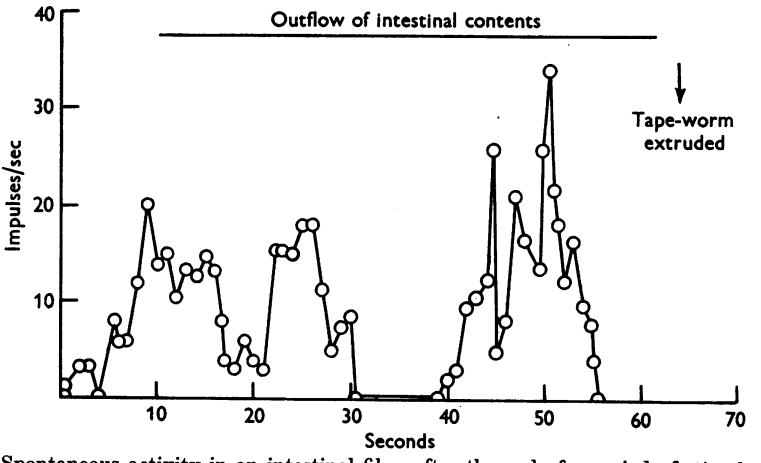

Fig. 4. Spontaneous activity in an intestinal fibre after the end of a period of stimulation by 30% NaCl. The intestine had been incised a short distance caudal to the receptor and the appearance of intestinal contents from this opening was observed. Note the appreciable increase in the frequency of impulses a short while before the tape-worm was extruded, ↓.

its receptor was being stimulated much more than normally some time after the introduction of 30% NaCl into the intestinal lumen. In this case an opening was made caudal to the location of the receptor, and it was observed that during the period of peristaltic rushes the activity in this receptor was enhanced considerably. These rushes were associated with the outflow of intestinal contents through the opening caudal to the receptor. Indeed, in

one record from which Fig. 4 has been plotted it was possible to correlate the discharge of impulses in this fibre with the appearance of the contents from the opening. This figure also shows the possible effect of the nature of the contents inasmuch as the passage of a tape-worm apparently produced an appreciably greater increase in the discharge of impulses than that produced by the viscid intestinal contents alone. In this fibre the spontaneous discharge of impulses disappeared when the peristaltic rushes ceased and the intestine seemed to be at a standstill. A little later in this experiment a second opening was made, this time on the oral side of the receptor; the peristaltic rushes now failed to arouse the receptor and it was noted that the contents flowed out of the new opening and were thus unable to flow past the receptor It would thus appear that the spontaneous activity of these receptors is in some way related to the passage of intestinal contents.

In three experiments the spontaneous activity was unchanged after local application of atropine which caused the intestine to be markedly atonic and free from contractions. Conversely, in many cases it was confirmed that strong local contractions of the intestine did not stimulate the receptors. It seems therefore that contraction of the external muscles of the intestines is not the primary factor in the normal excitation of these receptors.

Responses to mechanical stimuli

Squeezing localized portions of the intestine repeatedly as a rule stimulated fifteen of the receptors examined on each trial (Fig. 5*A*). Sometimes for no apparent reason they were not stimulated in spite of strong compressions, which, to be effective, had usually to be distributed over an area of about 3–4 cm^2. The latency between the application of pressure and the beginning of the discharge varied between 0·2 and 1·5 sec (average, 0·6 sec).

The discharge evoked by local compression usually had a duration less than or nearly equal to the duration of the stimulus. However, in five fibres the discharge outlasted the stimulus by several seconds. In three of these fibres, after the local pressure had stimulated the receptor in the usual manner, there was a short gap lasting about a second, after which the discharge started once again. This delayed discharge lasted about 1 sec in two of these fibres; in the third it lasted 14 sec (Fig. 6). In the remaining two fibres there was no gap separating the early from the late discharge but there was a continuous discharge lasting 9 and 14 sec respectively; the duration of the stimulus in these cases being not more than 1·8 sec. The discharge occurring during the period of compression may be attributed to a mechanical stimulation of the receptor. However, the delayed discharge must be attributed to an event aroused by the compression. This event could be the contraction of the smooth muscles locally, and, as will be shown below, the muscle concerned is most probably the muscularis mucosae.

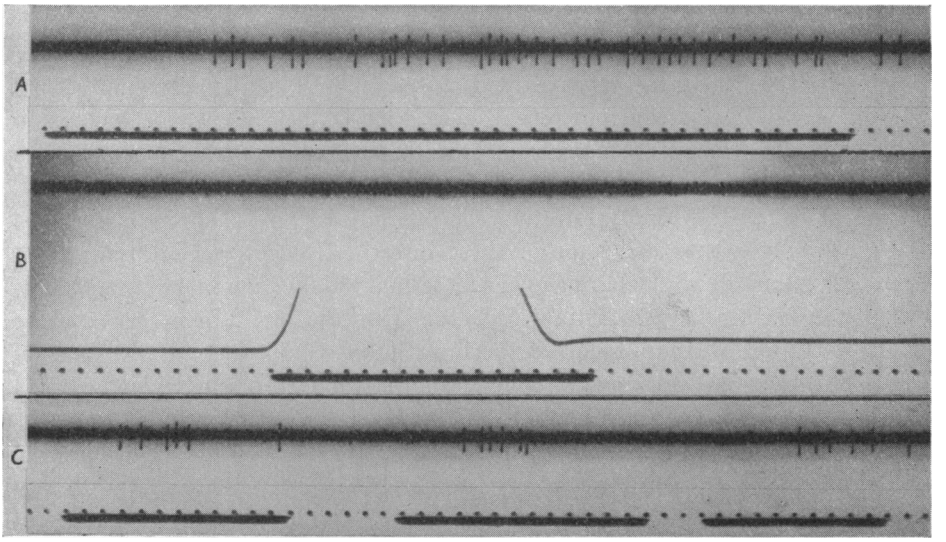

Fig. 5. Effects of mechanical stimuli on the same fibre illustrated in Fig. 1. *A*, the effects on the receptor of squeezing the intestine locally; *B*, distension of the intestine with 0·9% NaCl; *C*, stroking the mucosa locally with rubber tubing. The stimuli were applied at the signals shown in the lowest trace in each record. *B* also has a record of the intra-intestinal pressure. Time marker 0·1 sec.

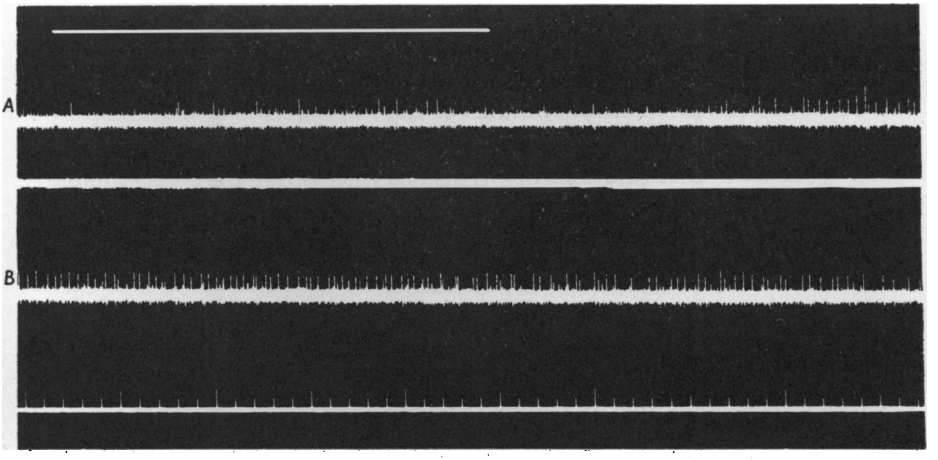

Fig. 6. Secondary stimulation of an intestinal receptor by local pressure applied at signal in *A*. The stimulus seems to have excited the receptor directly as shown by the few impulses which coincide with the signal. However, the secondary discharge which started about 1·3 sec after the end of the pressure in *A* is more intense and it continued for about 14 sec. *A* and *B* are continuous. Time marker 0·1 sec. (This record is different from others because it was recorded on film instead of sensitive photographic paper.)

In most of these receptors it was clear, from the negative effect of introducing 0·9% NaCl rapidly into the lumen locally, that a rise of intestinal pressure or distension of the intestine did not stimulate the receptors. Grossly distending the intestine repeatedly with 0·9% NaCl to pressures above 30–40 mm Hg did not affect four receptors at all (Fig. 5*B*). However, distension did yield a discharge of impulses in two fibres after a variable latency. This response could not be obtained repeatedly and the discharge, once produced, was unaffected by rapidly lowering the pressure to zero. This indicates that distension can stimulate some of these intestinal receptors, but this is not related intimately to stretching of the intestinal wall in a manner characteristic of distension-sensitive intestinal receptors (see Fig. 3 in Iggo, 1957*a*). As with local digital compression of the intestine it would seem that distension initiated an event, presumably contraction of smooth muscles, which in turn stimulated the receptors.

Five receptors were stimulated by stroking the mucous membrane with a solid object—a glass rod, or rubber tubing (Fig. 5*C*). Another receptor was stimulated by the manual propulsion of a sponge bolus. Three receptors could not be stimulated by the above stimuli applied to the mucosa.

In three experiments the receptors were stimulated by the passage of intestinal contents which were made to move past the receptor by massaging the intestine caudally. In another experiment injection of the intestinal contents with a syringe also gave rise to a discharge of impulses. However, in the latter case, there was a latency of 4 sec between the beginning of injection and the discharge of impulses. Since nearly all the contents had flowed past the receptor by 4 sec it seems the receptor must have been stimulated by a secondary event, once again probably the contractions of the muscularis mucosae. The fact that the mechanical stimulus of fluid motion *per se* had little to do with the excitation was evident from the observation that rapid introduction of 0·9% NaCl or other solutions or perfusions with these solutions stimulated these receptors only rarely.

The part played by local contractions of the external muscles in stimulating the receptors has to be considered. In this regard a short length of the intestine containing the receptor was painted with 10% ACh and 0·1% mecholyl in two experiments respectively so that this portion of the intestine underwent a strong and persistent contraction. In spite of this spastic state, the two receptors were but feebly stimulated. In one case 24 sec after the application of ACh the frequency of discharge was about 10 impulses/sec, and about 20 sec later the discharge stopped at a time when the contraction was still present. This response, which is shown in Fig. 7*B*, was not impressive when compared to the spontaneous discharge of impulses which occurred before the application of ACh (Fig. 7*B*). This experiment, and the second with mecholyl, do not indicate whether the effect of the drugs was direct or secondary to

contraction of muscular elements. However, they do show that contraction of the external muscles is not intimately related to the activation of these receptors, because they were often inactive at a time when the intestine was strongly contracted in the region of the receptors. It was confirmed that this silence was not due to depression of the excitability of the receptor, because its response to local pressure and mucosal irritation was not reduced. It was

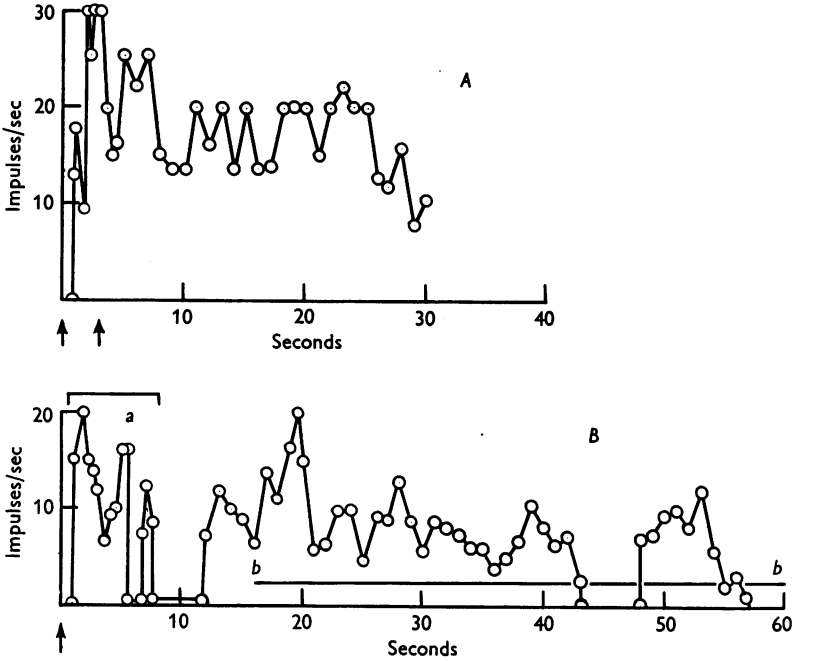

Fig. 7. Responses of an intestinal receptor to: *A*, intra-luminal introduction of 5 ml. 30% NaCl (between arrows); *B*, local application (at arrow) of 10% ACh. *a*, spontaneous activity; *b–b*, strong spasm of intestine. The loop of intestine was painted with atropine 2 mg/ml. so that it became quite atonic before introduction of NaCl.

also noted in other experiments that strong spontaneously occurring contractions at the site of the receptor did not stimulate the receptors.

Asphyxia or occlusion of the local blood supply to the intestine did not stimulate the receptors.

Fibre size. No conduction velocity measurements were made, but judging from the size and nature of impulses in these intestinal fibres as compared to other vagal afferent fibres whose conduction velocities are known (Paintal, 1953), these fibres are probably myelinated.

Effect of introduction of certain solutions into the lumen

While studying the first receptor in this investigation it was found accidentally that intraluminal introduction of a concentrated solution of NaCl

stimulated this receptor remarkably. Since this response was obtained consistently, 30% NaCl (w/v) was introduced into the lumen in subsequent experiments when required. The twelve receptors on which this was tried were all stimulated in a characteristic manner (Figs. 3, 7*A*, 8). The interval between the beginning of introduction of 30% NaCl and the beginning of stimulation

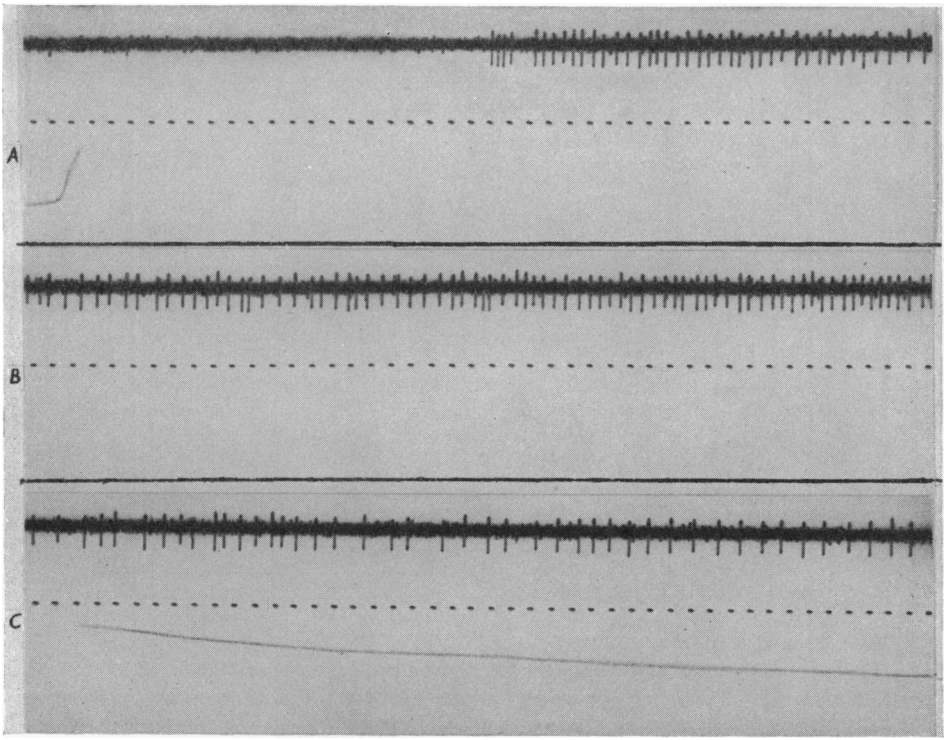

Fig. 8. Response in an intestinal fibre following introduction of 5 ml. 30% NaCl into the lumen, marked by the rise in intra-intestinal pressure recorded locally in *A*. From above downwards in each record: impulses in a fibre; time marker 0·1 sec; and in *A* and *C* record of intestinal pressure. Records *A* and *B* are continuous, but between *B* and *C* a piece of record of 8·5 sec duration has been omitted. Note that in *C* the fall of pressure accompanying the withdrawal of fluid did not influence the activity of the receptor.

varied between 2 and 8 sec in different fibres; the longer latencies could not be accounted for on the basis of slower rate of introduction of the fluid. A peak frequency of 16–30 impulses/sec in different fibres was soon attained and this fell to a steady level. In most fibres the stimulation persisted for over 30 sec, and in some it continued for over 1–2 min. Most often this stimulation was terminated by the introduction or perfusion of another solution, e.g. dis-

tilled water or 0·9% NaCl. Lower concentrations of NaCl, e.g. 5% (w/v), can also stimulate the receptors in a similar manner, as was shown in one fibre.

Local application of atropine (2 mg/ml. or 0·4 mg/ml.) had no influence on the effect of 30% NaCl on three receptors on which this was examined. Fig. 7*A* illustrates this quite clearly in one case. It is clear from this figure that the response produced by NaCl after atropine was appreciably greater than that following local application of ACh before atropinization. If it is assumed that the action of NaCl is secondary to contraction of smooth muscles, the above observations indicate that the receptor could not be located in the external muscles of the small intestine. On the other hand, if it is assumed that NaCl acts directly (chemical influence) the receptor cannot once again be expected to be located in the external muscles because of the mucosal barrier to substances introduced into the lumen. Besides, serosal application of 30% NaCl had no effect whatsoever. In either case, therefore, the evidence favours the location of the receptors in the mucosal layers of the intestine in association with the muscularis mucosae.

Six receptors were not appreciably affected by one or more of the following solutions: 20–30% sucrose (three receptors); 20% magnesium sulphate (three receptors); liquid paraffin (two receptors); 30% sodium sulphate (one receptor); bile (one receptor); 20% casein hydrolysate (one receptor); 20% calcium chloride (one receptor); 10% magnesium chloride (one receptor); and 2% barium chloride (one receptor). This indicates that the receptors are not stimulated by raised osmotic pressure of the intestinal contents and that they are not chemosensitive to any of the above substances. They also suggest strongly that the action of 30% NaCl is not consequent on some non-specific injurious action on the intestinal mucosa. The only chemical other than NaCl that stimulated the receptors somewhat was 20% KCl, but this stimulation was much weaker than the response following the introduction of 30% NaCl. In one instance introduction of 20% sucrose solution was followed by a discharge of impulses which lasted only 6 sec, but this could have been spontaneous activity in the receptor.

Introduction of solutions of phenyl diguanide (100 μg/ml.) into the lumen did not stimulate two receptors, although intra-aortic injections of 2 ml. of this solution stimulated both receptors. Similarly, introduction of 5-hydroxytryptamine into the lumen did not stimulate a third receptor and 5% ACh left a fourth unaffected.

The receptor illustrated in Fig. 8 was unaffected by dilute HCl or a strong solution of soda-lime, thereby showing that pH was not an important factor in the excitation of this receptor. This contrasts with the behaviour of certain gastric mucosal receptors found by Iggo to respond to changes in pH (Iggo, 1957*b*).

Observations on intestinal villi

Once it was apparent from the effect of 30% NaCl after local atropinization of the intestine (see above) that the receptors were probably located in the mucosal layers of the intestine, the next step was to determine whether NaCl acted directly on the receptors or whether it did so by causing the muscularis mucosae to contract. It is known that various mechanical and chemical stimuli can cause the muscularis mucosae to contract (Brücke, 1851; Exner, 1902; Gunn & Underhill, 1914; King, Arnold & Church, 1922; Wells & Johnson, 1934). If 30% NaCl acted indirectly it was predicted that it would influence the muscularis mucosae and the villi. Accordingly, the effect of pouring 30% NaCl on the mucosa was observed, and it was found that it caused a distinct change in the villi giving the appearance of granularization and blanching of the villi (due to contraction of smooth muscle in them) as described by Exner (1902). This action set in within 1–10 sec (cf. latency of response in receptors), and it lasted often for several minutes. It was most easily observed in cats with low systemic blood pressure. Since sucrose, magnesium sulphate, liquid paraffin and sodium sulphate did not stimulate the receptors as did NaCl, it was expected that these substances in a concentration of 20% would not have the same effect on the villi; this was found to be the case. Next, the effect of several other substances was observed in order to find a substance that would produce the response in the villi characteristic of 30% NaCl. 20% dextrose, 20% calcium chloride, and 2% barium chloride did not yield the typical response; 30% KCl did so but it produced a weaker response than 30% NaCl. The effect of the latter three substances in addition to some of those mentioned above, on the activity of more intestinal fibres, was therefore tried and, as predicted, KCl was the only substance that had any stimulating effect on the receptors.

The response of the villi to 30% NaCl was not altered by local application of atropine. This is in fact what would be expected if contraction of the muscularis mucosae stimulates the receptors, because stimulation of the receptors by NaCl persists after atropinization (see above).

It is conceivable that NaCl may have a direct (chemical influence) action, but the above evidence points heavily to the conclusion that 30% NaCl stimulates the receptors by first causing some contractile elements (muscularis mucosae) to contract, which event then stimulates the receptors.

DISCUSSION

The main conclusions that emerge from the results are that there are certain distension-insensitive mechanoreceptors innervated by the vagus which are distributed throughout the small intestine; that they are not connected with

the external layers of smooth muscle; but that they are located in the mucosal layers of the intestine and are stimulated by contractions of muscular elements therein. The possibility that they may be chemoreceptors responding to specific chemical changes in the intestinal contents has also to be considered. But this is unlikely because rhythmical discharges continue to occur spontaneously in spite of almost constant chemical composition of the intestinal contents, e.g. during presence of 0·9% NaCl.

The rhythmical nature of the spontaneous discharges agrees rather well with what is known about contractions of the villi and the muscularis mucosae (Gunn & Underhill, 1914; Hambleton, 1914; King *et al.* 1922; Verzar & Kokas, 1927; Kokas, 1930; Kokas & Ludány, 1933; Wells & Johnson, 1934; King & Robinson, 1945; King, Glass & Townsend, 1947). These contractions, although possibly influenced by their nervous connexions (King & Robinson, 1945), can nevertheless occur quite spontaneously in villi devoid of any nervous connexions (Wells & Johnson, 1934). The individual villi are known to contract quite irregularly and independently of their neighbours (Kokas & Ludány, 1933). Further, King *et al.* (1922) and King & Robinson (1945) observed two types of movements, movements of individual villi and movements of the mucosa as a whole, due presumably to contraction of a sheet of muscularis mucosae. The effect of 30% NaCl may be due to movement of the latter type.

Assuming that 30% NaCl acts indirectly, the persistent stimulation of the receptors by this substance suggests that it causes a tonic contraction of the muscular elements in the mucosa. Such a response has been reported by Verzar & Kokas (1927), Wells & Johnson (1934) and King & Robinson (1945) in the case of certain substances. It must be stressed that in observing the responses of the receptors to the introduction of various substances a straightforward stimulation of the type yielded by 30% NaCl was sought and no particular attention was paid to alterations in the rhythmicity of the cyclical discharges. The results of Verzar & Kokas (1927) are therefore only partially applicable, because they looked mainly at the rhythmical movements of the villi.

If the muscular elements of the mucosa are indeed a basic mechanism for the stimulation of the intestinal mechanoreceptors then the present results would lead one to expect that these elements can be caused to contract by a heterogeneous group of chemical and mechanical stimuli. This indeed appears to be the case from the work of earlier investigators who showed that the frequency and duration of the rhythmic contractions of the muscularis mucosae is influenced by the chemical and mechanical stimuli. This being so, it is suggested that the series of events leading to the initiation of activity in these intestinal receptors occurs as follows: various types of stimuli stimulate the muscularis mucosae either directly, or by a local enteric reflex initiated by some sensory mechanism in the epithelium. The muscularis mucosae then

contracts and this leads to the stimulation of the receptors. If the contraction is of a short duration, as that following local mechanical stimuli, e.g. solid contents of the intestine such as undigested food or tape-worms, a discharge lasting a few seconds results. If a prolonged tonic contraction occurs, a persistent discharge results. As far as the brain is concerned the receptors would be effectively signalling the passage or presence of certain types of intestinal contents. Contents altering the rhythmicity of the contractions would produce corresponding changes in the activity of the receptors. Since the tone of the muscularis mucosae is controlled by the sympathetic and vagal fibres (King *et al.* 1947), a delicate adjustment of the sensitivity of the receptor can conceivably be maintained. The receptors though basically mechanoreceptors would appear to be capable of responding to chemical stimuli by virtue of their connexion with the muscularis mucosae. In addition they can also respond directly to mechanical stimuli.

It would be expected that the receptors bear some precise geometrical relation to the muscularis mucosae. Ideally, one would expect them to lie in series with the contractile elements. This is not so as far as the longitudinal and circular layers of the muscularis mucosae are concerned because stretching the wall by introduction of solutions or pulling on the intestine in the long axis neither stimulates nor inhibits the receptors. The act of distension may, rather infrequently, fire off a discharge but as shown already this has nothing to do with the tension developed in the wall. The receptors may therefore lie in a plane which is unaffected by stretching the wall. One such plane is that of the villi, and it would not be surprising if these receptors are actually located in the villi because there is histological evidence that endings presumably sensory do exist in the villi (see Kuntz, 1953). There are logitudinally arranged muscle fibres in the villi (Brücke, 1851), responsible for shortening the villi, which could adequately serve as the contractile mechanism for the activation of the receptors. However, the receptors can as well be located elsewhere in the mucosa.

No experiments were carried out to determine the central effects of these receptors. The central effects of both types of intestinal receptors, the distension-sensitive (Iggo, 1957*a*) and the distension-insensitive mechanoreceptors (both innervated by the vagus), have yet to be established. In this connexion some possible lines of approach suggested by Whitteridge (1956) may be helpful.

SUMMARY

1. By recording impulses from certain vagal afferent fibres it has been determined that these fibres are connected to distension-insensitive mechanoreceptors which are located in the mucosa of the small intestine.

2. The receptors possess a characteristic spontaneous activity consisting of periodic trains of impulses which are not particularly altered by atropine.

3. These receptors yielded both primary responses and secondary responses (probably due to contraction of the muscularis mucosae) following various mechanical stimuli.

4. Local application of acetylcholine or mecholyl stimulated the receptors; the evidence showed that this was not due to contraction of the external muscles.

5. Intraluminal introduction of strong solutions of NaCl, but not of several other substances, stimulated the receptors greatly and also caused the villi to contract with a time course similar to its action on the receptors. This suggests that NaCl stimulated the receptors indirectly by causing the muscularis mucosae to contract.

6. The normal functions of the receptors appears to be to signal the presence or passage of certain intestinal contents which can excite the receptors either directly, or more commonly, indirectly through contraction of the muscularis mucosae.

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