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A METHOD OF LOCATING THE RECEPTORS OF VISCERAL AFFERENT FIBRES

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Afferent fibres yielding a discharge of impulses after an injection of phenyl diguanide have been described (Paintal, 1953*a*); these were thought to arise from receptors in the lungs, and later more suggestive evidence was obtained in support of this view (Mott & Paintal, 1953).

Till recently, attempts at determining the function of these receptors had failed because they were apparently inactive normally and were unaffected by any of the known procedures which affect the activity of thoracic visceral afferent fibres. With the aid of injections of phenyl diguanide into various vascular channels, however, direct evidence has been obtained to show that most of them are located in the wall of the stomach (Paintal, 1953*c*), a finding quite contrary to that expected. Since the method has many potentialities, it is described in detail in this paper.

METHODS

Adult cats, weighing 1.5-3.7 kg, were anaesthetized with chloralose (80 mg/kg). Afferent fibres with receptors stimulated by phenyl diguanide were isolated from the right cervical vagus as described earlier (Paintal, 1953*a*). Their action potentials were amplified with a differential resistance-coupled amplifier and recorded, along with the e.c.g. lead I, with a double-beam cathode-ray oscillograph and camera.

A plastic catheter, through which intra-atrial injections of phenyl diguanide were made, was inserted through the right external jugular vein. In two experiments a similar catheter was inserted into the left atrium through the left ventricle after opening the chest. In one experiment an intracarotid cannula, which consisted of a hollow needle, was inserted into the left common carotid as far as the innominate artery.

In the later experiments an aortic cannula, which consisted of a straight piece of glass tubing of 2 mm external diameter and 10.5 cm long was introduced into the aorta just before its bifurcation into the external iliac arteries and pushed centrally so that its tip lay just above the aortic opening of the diaphragm. All these catheters and cannulae were provided with taps and 'Record' fittings, through which injections were made with a syringe. By the use of leak-proof taps no

difficulty was encountered due to clotting, as the blood was prevented from flowing back into the cannulae. Their position was always ascertained post-mortem.

In the earlier experiments, the intrapleural pressure was recorded with a mirror membrane manometer; later this manometer was used to record the intragastric pressure with the aid of a balloon, inserted through the duodenum into the stomach.

RESULTS

Location of receptors sensitive to phenyl diguanide

In fibres with receptors sensitive to phenyl diguanide, a discharge of impulses was produced about 3–10 sec after injection of 100–200 μg of phenyl diguanide into the femoral vein. The maximum frequency of discharge attained varied from 10 to 20/sec. The injection-response time was not appreciably affected

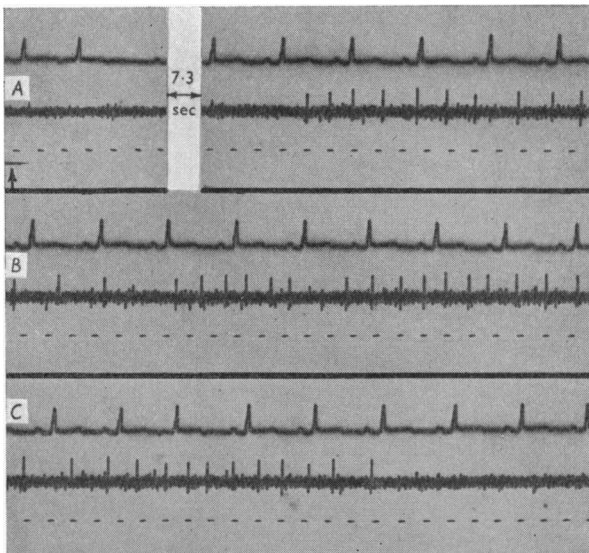


Fig. 1. Impulses in a vagal afferent fibre following injection of phenyl diguanide into the right atrium. Records B, C, and right side of A are continuous. From above downwards, e.c.g.; impulses in a vagal afferent fibre; time in $\frac{1}{10}$ sec. Phenyl diguanide, 200 μg injected at arrow in A.

when the injections were made directly into the right atrium (Fig. 1), although in some cases the intensity of the discharge was increased a little. From this it became apparent that the receptors concerned were not located in the right atrium, ventricle, pulmonary artery, or the more peripheral portions of the great veins. It might be thought that the likelihood of location in the heart or near it was small as there was no superimposed cardiac rhythm on the pattern of discharge (Figs. 1 and 3–5); but it is possible that chemoreceptors may be present in the right side of the heart in which case no cardiac rhythm

would be present, as has been shown by the records of impulses in chemoreceptor fibres (Landgren & Neil, 1951; Paintal, 1953*b*).

The next step was to determine whether these receptors were located in the lungs, particularly in the pulmonary vascular bed. To do this the chest was rapidly opened while the fibre was still on the recording electrodes and the left atrial catheter inserted. Injections of phenyl diguanide through this evoked a discharge of impulses with a shorter injection-response time and a greater frequency of discharge (Fig. 2). After observing the same type of response

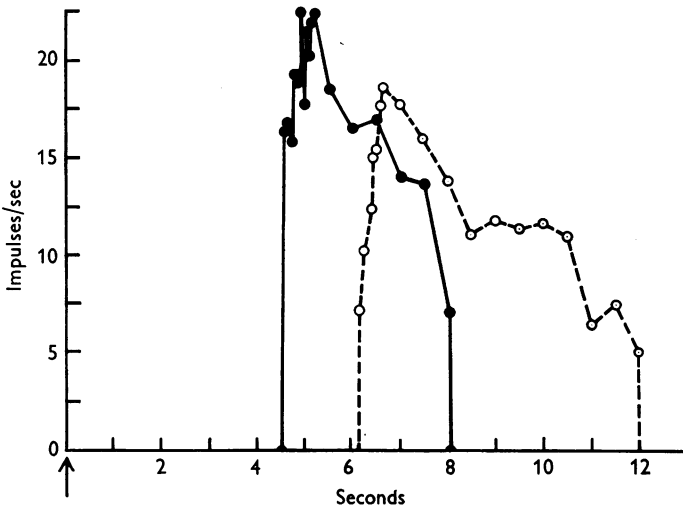


Fig. 2. Frequency of discharge in a single vagal afferent fibre after injections of 200 μ g phenyl diguanide into right (○ - - ○) and left (●—●) atria at arrow. The injection response time is reduced and the frequency of discharge is increased when the drug is injected into the left atrium.

again in another experiment, it was concluded that the receptors were definitely not located in the pulmonary circulation, though it was possible that they might be in other parts of the lung connected with the bronchial circulation.

To exclude the aortic bodies as the possible region where the receptors might be located, in a subsequent experiment injections were made through the carotid cannula. The evoked response was in all respects similar to that produced by left intra-atrial injections.

It was now clear that the receptors concerned were situated in viscera somewhere downstream with respect to the aorta. Proof of this was easily obtained. With a strand carrying impulses from a phenyl diguanide sensitive receptor on the recording electrodes, the aortic cannula was inserted into the abdominal aorta, so that the tip was upstream from the coeliac artery. Intra-

aortic injections of phenyl diguanide now yielded a discharge of impulses with an injection-response time of only 1.3–1.5 sec and a much higher frequency of discharge (Fig. 3). It was, therefore, certain that the receptors were situated in one of the abdominal viscera and definitely not in the lungs or the heart.

Finally, by digital compression, stretching, or distension of the viscera, such as the stomach, gall bladder, large and small intestines, and the peritoneum,

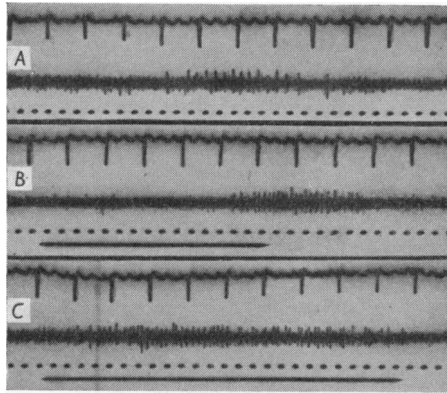


Fig. 3. Impulses in a gastric afferent fibre. *A* and *B* show responses to intravenous (200 μg) and intra-aortic (130 μg) injections of phenyl diguanide respectively. In *A*, the response occurred 10 sec after injection. *C* shows the discharge produced by digital compression of a small area of the cardiac end of the stomach. From above downwards, e.c.g.; impulses in a fibre; time in $\frac{1}{16}$ sec. The signals in *B* and *C* (lowest trace) represent the duration of injection and digital compression respectively.

it was confirmed that of the first seven receptors encountered, six were located with certainty in the wall of the stomach and one in the intestines. Of the gastric ones, all were localized satisfactorily by digital compression (Fig. 3) in different parts of the stomach, the localization in each case being within 1–4 cm^2 . These responded by a slowly adapting discharge to a maintained distension of the stomach from which it became clear that they were slowly adapting stretch receptors (Paintal, 1953*c*). In later studies on gastric stretch receptors (to be published), one more fibre from a receptor sensitive to phenyl diguanide was located within an area of 1 cm^2 at the attachment of the peritoneum to the jejunum. This failed to respond to distension of intestines with a balloon but readily responded to light pressure. Fig. 4 shows the response of this receptor to digital pressure which suggests that it might have been a Pacinian corpuscle (Gray & Malcolm, 1950).

To prove that the impulses were being recorded from fibres connected with

receptors in the abdominal viscera, the vagi were sectioned below the diaphragm in one experiment. This abolished all responses from the fibres (Fig. 5).

The situation of the receptors had now been clearly established.

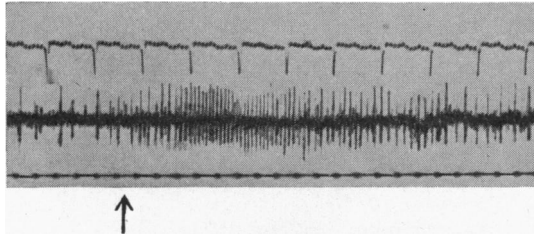


Fig. 4. Impulses in an afferent fibre from the small intestines. From above downwards, e.c.g.; impulses in a fibre; time in $\frac{1}{10}$ sec. At arrow light digital pressure was applied at the attachment of the peritoneum to the jejunum.

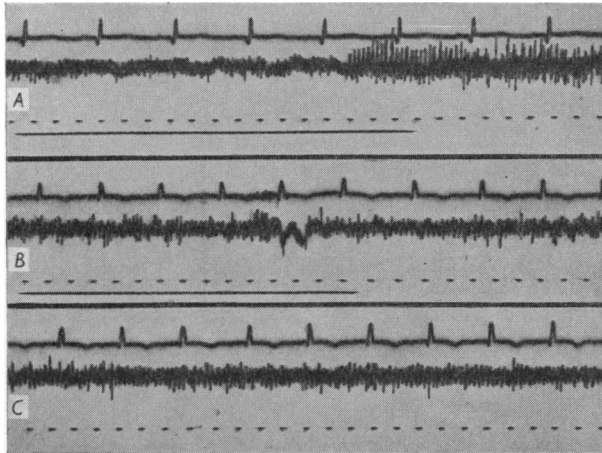


Fig. 5. Impulses in gastric afferent fibres. From above downwards, e.c.g.; impulses in gastric afferent fibres; time in $\frac{1}{10}$ sec, and in *A* and *B*, injection signal. At signal in *A*, 130 μ g phenyl diguanide was injected into the aorta. In *B*, a similar injection was given after sub-diaphragmatic vagotomy; note absence of any response. Records *B* and *C* are continuous.

DISCUSSION

It is known that there are a number of vagal afferent fibres that show irregular bursts of activity without either respiratory or cardiovascular rhythm. Some of these are no doubt chemoreceptors (Paintal, 1953*b*), which are easily recognized by their response to anoxia. They are stimulated by nicotine and lobeline (Neil, Redwood & Schweitzer, 1949) as is also the case with gastric stretch receptors (Paintal, 1953*c*). It is believed that there are chemoreceptors in the abdominal viscera (Hollinshead, 1946; Bean, 1952) and lungs (Pi-Suner,

1947), and the method described in this paper could be conveniently used to determine their exact location. These fibres could first be recognized by their response to anoxia or carbon dioxide excess and then tracked down by the drugs that stimulate them. In fact, by simply noting the effect of injecting the drug into the abdominal aorta it can be determined at once whether the receptors are situated by the thorax or the abdomen. Subsequent exact location by injections into different vascular channels should present little difficulty. This method could also be used to determine more accurately the location of those receptors responsible for persistent discharges in vagal afferent fibres (Adrian, 1933), provided a suitable drug could be found to stimulate these receptors.

Finally there are the vagal afferent fibres which are concerned in the production by drugs of certain reflex effects such as the well-known Bezold reflex (Bezold & Hirt, 1867) produced by veratrine and the ones more recently observed by Dawes, Mott & Widdicombe (1951) as reflex effects of derivatives of guanidine and of isothioureia. In spite of the great deal of information which exists regarding the reflex effects of these drugs and although there is much evidence to suggest that the receptors are situated in the heart and lungs (Dawes, 1947; Jarisch & Zotterman, 1948; Dawes *et al.* 1951), nothing definite is known regarding the exact location of these receptors or their normal function. Nevertheless, when recording from vagal afferent fibres, it will be necessary to exclude the abdominal viscera as the possible location of the receptors, a conclusion that has been well borne out by the results of the present investigation. One other obvious advantage of the method is that it is more convenient to work on the main vagal trunk than on its branches, most of which are not conveniently accessible for recording impulses. Also, it is possible to obtain from the trunk a much more complete knowledge of the distribution of the receptors.

Although the situation of the intestinal receptor at the attachment of the peritoneum to the intestine and the receptor's response to digital compression suggest that it might have been located in a Pacinian corpuscle, there is, however, no direct evidence of this. It is suggested that since this receptor was sensitive to intra-aortic injections of phenyl diguanide, experiments on the effect of local application of this drug to intestinal Pacinian corpuscles might yield valuable results.

SUMMARY

1. A method of locating the receptors of visceral afferent fibres has been described. It consists in injecting drugs, capable of stimulating receptors, into different vascular channels and noting their effects on the activity of afferent nerve fibres.

2. The method has been successfully used to determine the situation of

certain receptors, stimulated by phenyl diguanide; most of these have been located in the wall of the stomach, some in the intestines.

3. The possible applications of the method have been discussed.

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