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THE AFFERENT PATHWAY OF THE BEZOLD REFLEX: THE LEFT VAGAL BRANCHES IN DOGS

BY

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In experiments on cats Jarisch and Richter (1939) and Jones (1953) had difficulty in locating the afferent pathway for the Bezold reflex. Even on the right side, which was the simpler, the distribution was not easy to follow. Several difficulties were encountered in these experiments, among which was the doubt that existed in any given cat as to whether a particular dose of the veratrum alkaloids was causing a fall of blood pressure and heart rate by the Bezold reflex or by a central action. In the dog it is comparatively easy to cannulate the main branches of the left coronary artery, and hence to localize the site of action more certainly.

This paper describes experiments which have identified the afferent pathway on the left side in dogs, and also describes the nature of some afferent fibres from these nerves, but probably not those responsible for the Bezold reflex.

METHODS

Forty-six dogs were used in these experiments. They were anaesthetized with sodium pentobarbitone 32 mg./kg. administered intravenously. Artificial ventilation was applied through a tracheal cannula; the chest was opened down the midline and the incision extended between the third and fourth ribs on the left side to allow adequate access to the heart. The blood pressure was recorded from a femoral artery either by a mercury manometer or by a condenser manometer having a frequency response of 200 cycles/second or better.

The peripheral end of the left circumflex coronary artery was cannulated at its origin (see insert to Fig. 2) and connected by a short length of flexible rubber tubing to the central end of the right internal mammary artery, so as to facilitate repeated injections of not more than 0.1 ml. veratridine hydrochloride dissolved in physiological saline. The dog was heparinized.

Small nerve-slips were dissected off branches of the vagus after they had left the main trunk, and action potentials were recorded from these, using a resistance-capacity amplifier, and were displayed on a cathode-ray oscilloscope. The amplifier had a maximum discrimination factor of 1:50,000, an equivalent noise resistance of 6,000 ohms, a high pass filter (cut off 75 c/s), and a low pass filter (cut off 5,000 c/s). One of the principal difficulties in recording action potentials from small fibres so near the heart is the relative size of the electrocardiogram, which is also picked up. In most experiments this source of interference was reduced to a reasonable level by using this type of amplifier, which has an exceptionally high discrimination for out-of-phase signals, and by earthing the tissues around the insulated dissecting platform. In some later experiments a polished stainless steel dissecting platform was earthed, and a single electrode used for recording the action potentials. The electrocardiogram was recorded from leads 1 or 2.

RESULTS

The Afferent Nerve Path of the Bezold Reflex

Preliminary observations showed that there were three problems to be overcome if experimental results were to be of value.

1. It is known (Krayer, Wood, and Montes, 1943) that veratridine injected into dogs causes a fall of blood pressure and heart rate, both by an action on receptors in the coronary vessels (the Bezold reflex) and by a central action. Consequently, the intravenous injection of veratridine in some dogs leads to a fall of blood pressure which is not entirely abolished by cutting the vagi. Therefore, after a few preliminary experiments in which the central effect of veratridine was encountered, we restricted our observations to dogs in which veratridine was administered only into the left circumflex coronary artery. The dose required to cause a fall of blood pressure on intracoronary arterial injections is about 1 μg., one-tenth to one-twentieth that required on intravenous injection.

2. The fall of blood pressure on injection of veratridine is due not only to peripheral vasodilatation (Krayer, Moe, and Mendez, 1944; Moe, Bassett, and Krayer, 1944; Dawes, Mott, and Wid-

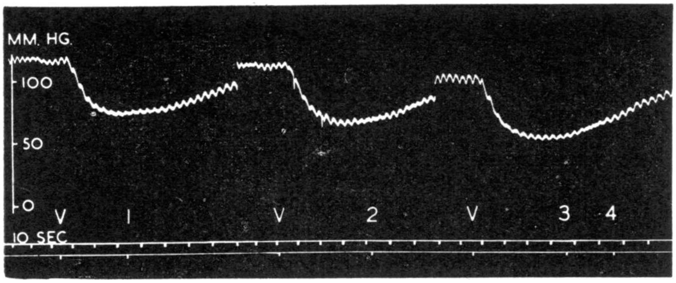

FIG. 1.—Dog, 11 kg.; pentobarbitone anaesthesia. R. vagus cut. Record of femoral arterial pressure with a mercury manometer. Injection of 1 μg. veratridine (at V) into the left circumflex coronary artery at 10 min. intervals caused a fall of blood pressure, which was not affected by section of the main left vagal trunk below the aortic arch (at 1), of the left anterior cardiac branches (at 2) or left depressor branches (3 and 4).

dicombe, 1951), but also to cardiac slowing. Hence, if section of a vagal branch leads to a reduction in the fall of blood pressure observed after administration of veratridine, it might be objected that this would result from interference with efferent nerves to the heart. However, we have repeatedly observed that, in dogs in which the *right* vagus is cut, injection of veratridine into the left circumflex coronary artery causes a fall of blood pressure without any significant change in heart rate (Fig. 3). In one experiment, for instance, the heart rate and P–R interval (measured from the electrocardiogram) changed by less than 5%, which was within the limits of accuracy of the measurements.

Although, therefore, we share the widespread impression that the afferent fibres of the Bezold reflex in the dog travel up both vagus nerves, we have confined our observations to the left vagus. The right vagus was cut early in the course of every experiment.

3. The injection of repeated doses of the veratrum alkaloids leads rapidly to decreasing responses. Veratridine has been used for these experiments because it is less liable to cause tachyphylaxis than other veratrum alkaloids. The doses administered have been as small as possible (about 1 μg.) consistent with obtaining an adequate fall of blood pressure (30–50 mm. Hg). Experience showed that a time interval of ten minutes between doses was a reasonable compromise between the dangers of tachyphylaxis and deterioration of the preparation. Even so, tachyphylaxis was observed occasionally; such experiments have been excluded from further consideration.

In the first eight successful experiments the main thoracic branches of the left vagus were cut in succession (the right had of course been cut at the beginning of the experiment). The procedure adopted was not exactly the same in all experiments, deliberately, since the risk of encountering tachyphylaxis progressively increased with time. A good experiment is illustrated in Fig. 1, in which it is seen that section of the main left vagal trunk below the arch of the aorta (after it had given off its cardiac branches but before reaching the root of the lungs) and section of the left depressor branches from the aorta (running medially towards the origin of the brachiocephalic artery, Fig. 2) did not reduce the size of the Bezold reflex. In five dogs there was conclusive evidence that the main afferent pathway of the Bezold reflex did not run in the main left vagal trunk below the arch of the aorta, in four dogs the aortic depressor nerves were excluded, and in six dogs the anterior cardiac nerves, which run across the pulmonary artery to the left atrium and ventricle, were also

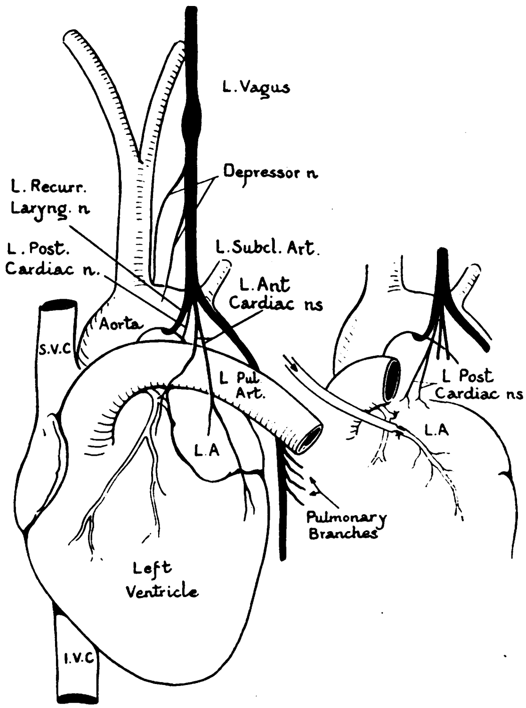

FIG. 2.—Anterior view of the heart to show the distribution of the principal branches of the left vagus. The insert shows the disposition of the left posterior cardiac nerves in relation to the left pulmonary artery and left atrium (L.A.); the left circumflex coronary artery has been cannulated.

excluded. In two dogs the observations suggested that the afferent pathway lay among vagal branches which dived down between the aortic arch and the left pulmonary artery (Fig. 2).

In the next series of five successful experiments attention was concentrated on these posterior cardiac branches of the vagus. Section of this group of nerves, sometimes including the left recurrent laryngeal, at the point where they cross the aortic arch, abolished the Bezold reflex. But it was thought that the afferent nerve fibres only joined the left recurrent laryngeal at the level of the aortic arch, since in two of the five dogs the section did not include the latter.

In order to establish as far as possible the origin of the afferent nerve fibres, a more extensive dissection was undertaken. The left pulmonary artery was tied and divided, together with all vagal branches running anteriorly to it, and the main vagal trunk below the aortic arch (see insert to Fig. 2). This exposed the inferior aspect of the aortic arch, with the left recurrent laryngeal, cardiac, and other branches of the vagus running round it. A few (usually two) very small nerves were seen running to the aortic arch from the base of the left atrium. In all five dogs in which this preparation was completed the Bezold reflex was present, in spite of the extensive dissection and the section of main vagal trunk described. In all five, cutting the fine nerves running from the left atrium abolished the reflex (Fig. 3).

Action Potentials

Twenty-one single and multifibre preparations were made from the aortic depressor branches of the vagus. Intravenous injections of 30–40 μg. veratridine did not sensitize any of these endings.

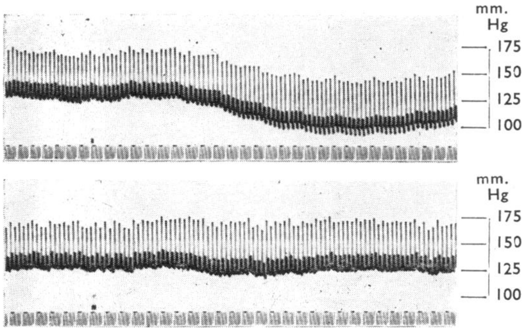

FIG. 3.—Dog, 9 kg.; pentobarbitone anaesthesia. R. vagus cut; left pulmonary artery divided and retracted to gain access to the nerves running beneath it. Record of femoral arterial pressure with a condenser manometer; time signals in 1/10 seconds, interrupted once per second. At the signal marks 1 μg. veratridine was injected into the left circumflex coronary artery. Between the upper and lower records there was a 10 minute interval during which the left posterior cardiac branches of the vagus were divided.

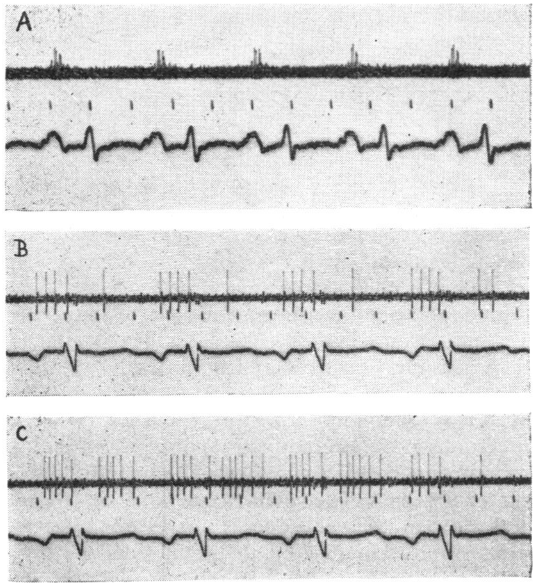

FIG. 4.—Records of action potentials recorded from the left posterior cardiac nerves (above), time marks at 1/10 sec. intervals, and the electrocardiogram (below). The upper record (A) shows a fibre which discharged only between the P and QRS deflections of the E.C.G. The lower record (B and C) shows a fibre which discharged both before and after the QRS complex, the discharge frequency varying with different phases of the respiration.

From the small cardiac branches of the vagus running behind the left pulmonary artery from the back of the heart, 14 single and multifibre preparations were made. The spontaneous activity recorded in the majority of these preparations was similar to that described for atrial pressure or volume receptors by other workers (Paintal, 1953). Some discharged only immediately after the P wave of the electrocardiogram (Fig. 4, A), others discharged both between the P and QRS waves and again about the T wave (Fig. 4, B and C). A few only discharged at or after the T wave. These fibres discharged more frequently on intravenous injection of saline, but were not sensitized by the injection of 30–40 μg. veratridine intravenously, or 1–2 μg. veratridine into the left circumflex coronary artery. In all these preparations both vagi were cut in order to exclude reflex changes in the circulation. In three preparations, however, injection of veratridine into the left circumflex coronary artery caused an audible and visible increase in background activity ; the characteristic spontaneous discharge of the fibres responsible for this phenomenon could not be identified. We had the impression, since we were at the time recording from very small nerve strands, that these nerve fibres must have been small. In addition, on several occasions we encountered single fibre preparations from these nerves which showed spontaneous activity with cardiac and/or respiratory rhythms which we were unable to classify with known types of receptor.

Discussion

We have confined our attention to the vagal branches of the left side of the heart in dogs because preliminary experiments showed that, when the right vagus was cut, injection of veratridine into the left coronary arteries no longer caused any significant bradycardia. Thus, with the right vagus cut, the Bezold reflex is presumably due almost entirely to peripheral vasodilatation. Section of branches of the left vagus then causes a reduction in the Bezold reflex only by interruption of afferent nerve fibres, and not by interruption of efferent vagal cardio-inhibitory nerve fibres. The delineation of the afferent pathway on the left side is therefore a simpler proposition than that on the right side.

Progressive section of the left vagal branches showed that the afferent nerve fibres for the Bezold reflex accompany the left recurrent laryngeal nerve as it runs across the aortic arch, and then run posterior to the left pulmonary artery towards the back of the left atrium. Comparison of the distribution of these branches with the anatomical studies of Schurawlew (1928) shows no exact correspondence with those which he described; the nearest seem to be the "rami cardiaci sin_3 zum 4 Geflecht" (r.r.c.s_3 of his Fig. 1). We propose to refer to these nerves as the left posterior atrial branches of the vagus. They are thus distinguished from the vagal branches to the heart which run anterior to the left pulmonary artery; the term atrial should not be taken to imply that the nerve fibres end in the atrium only.

It was disappointing to find that the only fibres encountered in any number, which almost certainly originate from atrial pressure or volume receptors, were not sensitized by veratridine. While there is good reason to believe that there are other types of fibres running among these nerves, it is not surprising that under the particular experimental conditions smaller nerve fibres were not isolated. In so far as these observations can be compared with those of Jarisch and Zottermann (1948) on the right atrial vagal nerve fibres of the cat, they would agree in the general conclusion that the Bezold afferent nerve fibres are probably of small diameter and accompany the vagal branches to the atria.

Summary

The afferent pathway for the Bezold reflex has been defined on the left side in dogs by injecting veratridine directly into the left circumflex coronary artery; the right vagus was cut. The afferent nerves run from the vicinity of the left atrium beneath the left pulmonary artery to join the left recurrent laryngeal nerve as it crosses the aortic arch.

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