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THE AFFERENT PATHWAY OF THE BEZOLD REFLEX: THE RIGHT VAGAL BRANCHES IN CATS

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In 1867 von Bezold and Hirt showed that intravenous injection of veratrum alkaloids caused a fall of blood pressure and heart rate, which was abolished by cutting the vagi. They attributed the phenomenon to an action on receptors in the heart.

The principal physiological interest of the Bezold reflex lies in the nature of these receptors, and before these can be identified the afferent pathway of the reflex must be established with certainty. In 1939 Jarisch and Richter investigated the afferent pathway of the reflex in cats. On the right side they concluded that it lay among a group of nerves which leave the vagus just as it crosses the right subclavian artery, and which run beneath the aortic arch toward the ventricles; on the left side it was not clearly defined. However, Amann and Schaeffer (1943) observed an increase in the discharge frequency of vagal branches *from the right atrium* after administration of veratrine, and in 1948 Jarisch and Zottermann concluded from similar observations that these branches contain the Bezold afferent nerve fibres. There is therefore a discrepancy in the evidence for the afferent pathway of the reflex.

This paper describes experiments to identify the afferent nervous pathway of the Bezold reflex on the right side in cats. The effects of stimulation of the central ends of these nerves, and of the application of a cold block to the vagus in the neck are also described.

METHODS

Cats were anaesthetized with chloralose, 60 mg./kg. The chest was opened along the midline and artificial ventilation was applied. The blood pressure was recorded with a mercury manometer from the carotid artery. Intravenous injections were made from a cannula in the right external jugular vein.

The vagi were cooled by applying hollow thermodes through which alcohol was circulated from a reservoir in an ice-salt mixture. The thermodes, which were covered with silver foil, were in contact with the nerve for a distance of 1 cm., and their temperatures were recorded from thermocouples in contact with their surface. They were similar to those used by Dawes, Mott, and Widdicombe (1951), and the results obtained are therefore comparable.

Branches of the right vagus running to the right atrium were cut as near to the heart as possible, and their central ends were stimulated with rectangular current pulses using a constant current output. The compound action potentials of the right cervical vagus were recorded with a conventional resistance-capacity coupled differential amplifier having a time constant of about 1 second. They were displayed on a cathode-ray oscilloscope together with time marks of 0.1 and 1 msec. from a crystal-controlled oscillator.

The veratridine used was the same as that used by Dawes (1947) and Dawes, Mott, and Widdicombe (1951), and was obtained from Professor O. Krayer.

RESULTS

The Afferent Pathway of the Bezold Reflex on the Right Side.—Jarisch and Richter (1939) used veratrine, a mixture of alkaloids which is rather liable to cause tachyphylaxis, in their experiments to locate the afferent pathway of the Bezold reflex. In the experiments to be described one of the pure veratrum alkaloids, veratridine, was used throughout. Previous work (Krayer and Acheson, 1946) has shown that this alkaloid does not cause tachyphylaxis so readily, and that its duration of action is short. Injections of 10–25 μg. repeated every 10 min. have given satisfactory responses.

Section of the upper right vagal branches to the heart (Fig. 1, n. I) did not abolish the Bezold reflex, even though the left vagus had been cut. Subsequent injection of the same amount of veratridine into the ascending aorta did not cause a fall of blood pressure and heart rate; hence the effect observed after section of the left vagus and n. I on the right side was not due to a central action. The afferent pathway must therefore lie principally in n. II or n. III (Fig. 1).

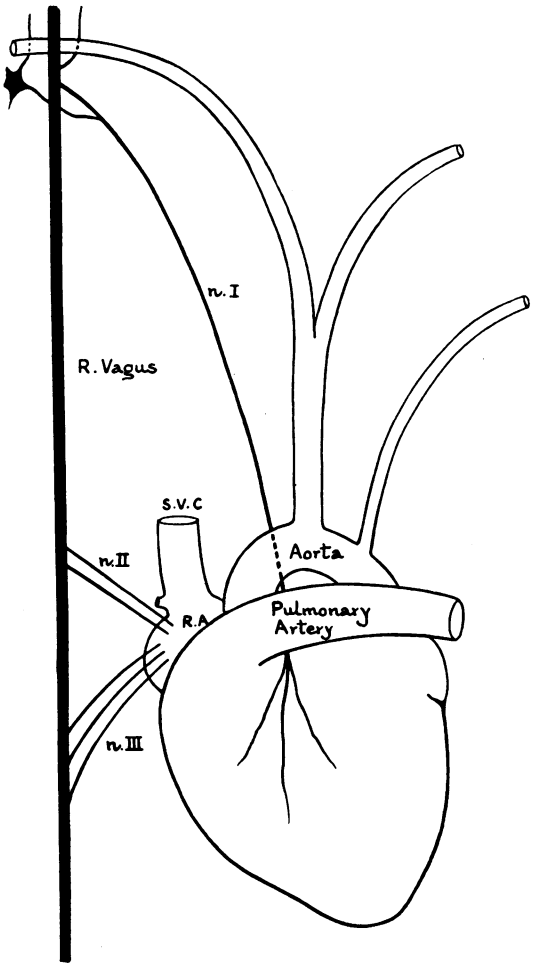

FIG. 1.—Diagram of the distribution of the cardiac branches of the right vagus in the cat.

Although it seems fairly certain that a proportion of the Bezold afferent nerve fibres must run in n. II, which also carries efferent cardio-inhibitory fibres to the right atrium, it is clear that n. III is also of importance. A typical experiment designed to test this point is illustrated in Fig. 2. The first injection of veratridine (A) was given while the *right* vagus was cooled to 8° C., a temperature at which the afferent fibres, but not all the efferent fibres, are blocked (Dawes, Mott, and Widdicombe, 1951). There was only a small fall of blood pressure and heart rate, suggesting that in this particular cat most of the afferent nerve fibres ran in the right vagus. Twenty-five sec. after the injection the right vagus was warmed, and there was an immediate further large fall of blood pressure and heart rate. The right vagal branches, n. I and II, were then cut, and the trachea was scraped to eliminate other branches. The next dose of veratridine (B) was injected while the *left* vagus was cooled to 8° C. There was a considerable fall of blood pressure and heart rate, showing that some afferent nerve fibres were still present on the right side. The left vagus was warmed about 50 sec. after the injection, and there was a further fall of blood pressure. The major part of n. III was then cut, including those nerves running across the right bronchus and through the lymph node at the origin of the latter from the trachea. With the left vagus at 8° C., injection of veratridine still caused a fall of blood pressure and heart rate (C). Finally, a number of nerve fibres running across the right pulmonary vein were destroyed. With the left vagus at 8° C., veratridine now caused a small rise of blood pressure (D). When the left vagus was warmed there was an immediate fall of blood pressure and heart rate, from which it can be seen that the cat had not become appreciably tachyphylactic during the experiment.

Twelve experiments of this type were performed; in six of these the afferent nerve fibres on the right side were destroyed before the cat became relatively insensitive to injections of veratridine. The fall of blood pressure was never completely abolished until n. III had been destroyed; often there was little reduction in the effect when n. I and II were cut. In all but one cat injection of veratridine caused considerable reflex bradycardia while the *right* vagus was cooled to 8° C., indicating that a number of afferent nerve fibres also run in the left vagus.

Electrical Stimulation of the Right Vagal Cardiac Nerves.—Jarisch and Zottermann (1948) caused a fall of blood pressure and heart rate by stimulating the central ends of n. II, which Jarisch and Richter (1939) had thought carried mainly efferent cardio-inhibitory nerve fibres. These observations have been repeated, and the temperature at which the afferent impulses are blocked has been determined by cooling the right vagus in the neck.

The largest vagal branch to the right atrium (n. I) was cut as near to the heart as possible and freed from surrounding tissue for 2 cm., to prevent direct current spread to the heart. In 18 cats stimulation of this nerve caused a fall of blood pressure and heart rate; occasionally this was preceded by a slight rise in blood pressure. In a few cats in earlier experiments only a rise of blood pressure with no consistent change of heart

rate was observed ; the possibility that the nerve had been damaged cannot be excluded.

Stimuli were delivered at a frequency of 20–100 per sec. (usually 77 per sec.) for 5 sec. In most cats the minimum current required to elicit a fall of blood pressure was 0.2 mA with a duration of 5–7 msec. With currents of 0.3–0.4 mA the duration could be reduced to 1.0–0.5 msec. The application of still larger currents did not reduce the duration necessary to elicit a fall of blood pressure.

In eight successful experiments the right vagus was cooled in the neck while the nerve (n. II) was stimulated. In five cats the fall of blood pressure and heart rate was abolished by cooling the right vagus to 10–12° C., and in the other three cats at 8–10° C. The cooling characteristics of these nerve fibres are therefore the same as those of the Bezold afferent nerve fibres. In three cats the *left* vagus was cooled subsequently in order to discover at what temperature the efferent cardio-inhibitory fibres were blocked, when stimulated reflexly. The bradycardia disappeared when the vagus was cooled to between 6 and 8° C.

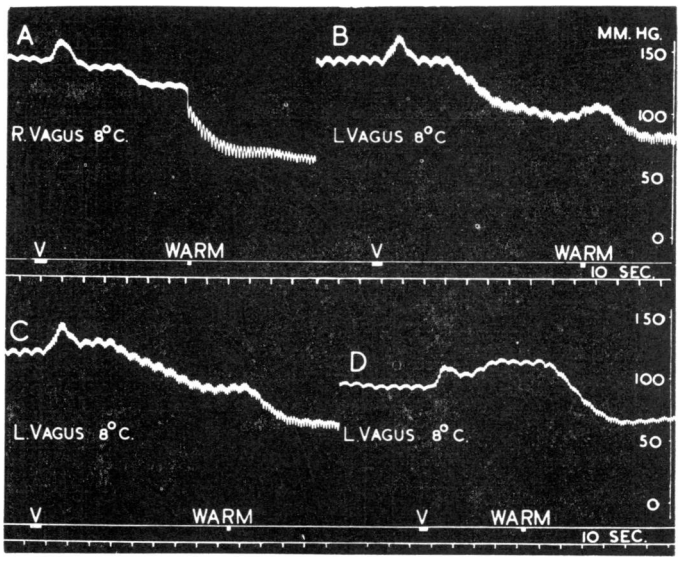

FIG. 2.—Cat, 2.4 kg.: chloralose anaesthesia. Chest opened; artificial respiration; record of carotid arterial blood pressure. At V 25 μg. veratridine was injected intravenously, at intervals of approximately 10 minutes. The right or left vagus was cooled to 8° C. for 2 minutes before each injection; the vagus was warmed at the point indicated. Between A and B, n. I and II (Fig. 1) were cut; between B and C part of n. III, and between C and D the remainder of n. III were cut.

In 26 cats compound action potentials were recorded from the intact vagus in the neck, while the central ends of vagal branches from the right atrium (n. II) were stimulated. The blood pressure was also recorded in order to gauge the effect of stimulation. The experiments were performed with the vagus exposed to air, and so the conduction velocities observed are probably too low. With this reservation, the conduction velocity of the peak elevation was 22–33 m./sec. in five cats. Occasionally a second, smaller elevation of the compound action potential followed the first. It was more prolonged, and the stimulus strength required to cause its appearance was usually well above that required to cause a fall of blood pressure.

DISCUSSION

There are several difficulties in designing a satisfactory type of experiment to define the afferent pathway (or pathways) of the Bezold reflex on the right side in the cat :

1. Successive injections of the veratrum alkaloids cause diminishing effects (tachyphylaxis).

2. Veratrum alkaloids cause a fall of blood pressure and heart rate not only by an action on receptors in the heart (the Bezold reflex), but also by a central action whose precise mechanism (there may be more than one) has not been systematically analysed. While it is certainly possible to limit the site of action of veratridine by injection into the coronary arteries, it is not a practical proposition to combine the extensive dissection which this involves with that required for progressive nerve section. Therefore, doses of veratridine must be chosen which are large enough to excite only the receptors for the Bezold reflex but not to act centrally. This choice may be checked either by injection of veratridine into the ascending aorta (when it should have no effect on blood pressure or heart rate) at the beginning of the experiment, or by intravenous injection when the vagi are cut at the end of the experiment. Both tests have been employed in the work described above.

3. Progressive section of branches of the right vagus not only interrupts afferent nerve fibres, but also efferent cardio-inhibitory nerves. Hence a reduction in the fall of blood pressure and heart rate may be due to section of either afferent or efferent nerves. This makes the attribution of the afferent pathway to a particular vagal branch or branches a difficult problem, so far as nerve-section experiments are concerned.

4. It is equally difficult to interpret action-potential records from vagal branches from the heart, since the veratrum alkaloids are now known to excite many types of nerve ending.

The results obtained in this paper differ in a number of details from those recorded by Jarisch and Richter (1939), but it is believed that the discrepancies can be explained by the fact that the latter were using large doses of veratrine (sometimes as much as 200 μg.), and were not at that time fully aware that such large doses might have a central action as well as an action on receptors in the heart. It was not until 1943 that Krayer, Wood, and Montes showed that veratridine injected into the isolated head circulation caused bradycardia. There is a further point. It is now well known that intravenous injection of *large* doses of the veratrum alkaloids cause a rise of blood pressure when the vagi are cut, partly at least because of a liberation of adrenaline from the adrenal glands (Mendez and Montes, 1943). Some of Jarisch and Richter's (1939) tracings show evidence of this rise of blood pressure, which implies that the doses used must have been sufficient to cause a very widespread and complicated action upon the cardiovascular system, to a degree that would render the analysis of the effects of progressive nerve section most difficult. In these circumstances it is not surprising that different conclusions have been reached.

In spite of the precautions which were observed in the experiments described in this paper it will be seen that the afferent pathway on the right side of the cat has not been localized to a single vagal branch. So far as these experiments allow, we must conclude that the afferent pathway is widespread, scattered over a number of fine branches which run towards the heart between and around the great veins and the right bronchus. Some of these branches also carry the efferent cardio-inhibitory branches to the heart. There is as yet no effective method of distinguishing between the Bezold afferent nerve fibres and the cardio-inhibitory efferent nerve fibres so far as the reaction of the cat's blood pressure and heart rate to veratridine is concerned.

Summary

The branches of the vagus, which carry the afferent nerve fibres for the Bezold reflex, are widely distributed on the right side in cats.

Stimulation of their central ends causes a fall of blood pressure and heart rate which is blocked by cooling to 8–10° C.

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References

Amann, A., and Schaefer, H. (1943). *Pflüg. Arch. ges. Physiol.*, **246**, 757.

Bezold, A. von, and Hirt, L. (1867). *Unters. physiol. Lab. Wurzburg*, **1**, 73.

Dawes, G. S. (1947). *J. Pharmacol.*, **89**, 325.

—— Mott, J. C., and Widdicombe, J. G. (1951). *J. Physiol.*, **115**, 258.

Jarisch, A., and Richter, H. (1939). *Arch. exp. Path. Pharmak.*, **193**, 347, 355.

—— and Zottermann, Y. (1948). *Acta physiol. scand.*, **16**, 31.

Krayer, O., and Acheson, G. H. (1946). *Physiol. Rev.*, **26**, 383.

—— Wood, E. H., and Montes, G. (1943). *J. Pharmacol.*, **79**, 215.

Mendez, R., and Montes, G. (1943). Ibid., **78**, 238.