Role of Arterial Wall Secretion in the Regulation of Blood Pressure

By C. Jiménez Diaz, M.D., P. Barreda, M.D., A. F. Molina, M.D., and R. Alcalá, M.D.

The authors present experiments demonstrating that the hypertension produced by the stimulation of the central end of the vagus nerve is brought about by the appearance of a pressor substance in the circulating blood. The results of these experiments show that such a substance does not come from any gland nor from the central nervous system. The observed facts indicate that its origin is the arterial wall proper, from which it is directly liberated into the circulation. The pharmacologic proofs suggest that this substance is noradrenaline.

In 1947 we showed that electric stimulation of the central ends of the cut vagus nerves produces a vasopressor response accompanied by release of a vasoconstrictor substance which we believed came from arterial walls. We showed subsequently that this vasoconstrictor substance does not come from an endocrine organ, and have reported our views on its origin and nature. This report reviews and extends these observations.

Methods

Mongrel dogs were anesthetized with sodium pentobarbital (32 mg. per kilogram). Blood pressures were recorded on a smoked drum from a cannulated femoral artery connected to a mercury manometer. The vagus nerves were isolated in the neck and cut between ligatures; their central ends were stimulated by applying a silver electrode connected to an inductor. Duration of stimuli was between 10 and 60 seconds at a frequency of 20 to 50 cycles per second with a pulse duration of 3 to 8 milliseconds.

Results

Effect of Vagus Stimulation on Blood Pressure of Cross Transfused Animals

In 20 experiments, the cardiac ends of both carotid arteries were anastomosed to the cardiac ends of the jugular veins of another dog, and the same carotid-to-jugular anastomosis then established in the opposite direction. Thus, blood normally going to the head through the carotid arteries was carried to the right atrium of the opposite dog. Payr- cannulae were used in 10 experiments; heparin was used as an anticoagulant. To exclude the blood pressure effects of unequal exchange of blood between the dogs, a Jouveau transfusion pump was introduced into the perfusion circuit to ensure that both venous and arterial flows were the same.

In all but two experiments, stimulation of the central cut ends of the vagus nerves of one animal caused the arterial pressure of both animals to rise, indicating release of a hypertensive substance into the blood stream which was carried to the opposite animal.

In a second group of experiments, similar carotid-jugular anastomoses were formed between two dogs and a Y tube placed in the circuits so that 40 ml. of blood could be rapidly withdrawn from or injected into either dog. Blood taken during stimulation of the vagus nerve and injected into another animal showed marked pressor activity (fig. 1, table 1).

Effect of Surgical Removal of Various Organs on the Blood Pressure Response to Stimulation of the Vagus Nerves

Stimulation of the central ends of the vagus nerves caused the usual rise in blood pressure in 6 dogs subjected to hypophysectomy, in 14 dogs after hepatectomy, in 13 after bilateral adrenalectomy, and in 11 after bilateral nephrectomy (fig. 2).
REGULATION OF BLOOD PRESSURE

FIG. 1. (a) Withdrawal of 40 cc. of blood from a dog, and (b) reinjection in the same animal. (c) Injection into recipient dog of 40 cc. of blood withdrawn from a dog with the vagi sectioned. (d) Injection in recipient dog of 40 cc. of blood withdrawn from a dog during vagi stimulation.

Effects of Vagus Stimulation in the “Split-Dog” Preparation

We have previously described a method for the vascular isolation and perfusion of the lower half of a dog’s body from a reservoir or donor animal by means of a pump while the nerve supply remains largely intact. The vascular system below the origin of the renal arteries was isolated (“split-dog”) by ligation of all arteries and veins below the kidneys, with the exception of the external iliac arteries and veins. An iron wire tightened around the body secured the isolation. The distal end of the aorta and inferior vena cava were connected with one carotid artery and jugular vein, respectively, of a donor animal, or with a reservoir provided with an oxygenator. The distal portion of the body was then perfused by means of a pump either with blood, oxygenated plasma, saline or saline with 40 per cent red blood cells. That isolation of the two halves of the dog was relatively complete was tested by routinely injecting fluorescein or adrenaline intravenously in the two parts separately at the end of each experiment. There was no evidence of transfer of these substances from one part of the animal to the other.

The vagus nerves were stimulated in 27 such preparations; in 25 there were clear-cut rises in arterial pressure in both halves of the body though there was no mixing of blood in the two parts of the body (fig. 3).

When the lower part of the dog’s body was perfused with oxygenated plasma, the effect was initially unchanged but then it rapidly disappeared. When the perfusion was made with saline solution, the vagal stimulation elicited a pressor response only in the upper but not in the lower part of the body. Our first suggestion was that the arterial wall released an enzyme capable of acting on some substrate present in the plasma. But in further experiments, on perfusing the lower half of the body with red blood cells suspended in saline solution, we found a similar pressor

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<th>No. of Experiment</th>
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<td>(A) Basal blood</td>
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Effect in the upper and lower half, in the same degree as when perfusion was made with oxygenated total blood. In the second place we have seen that Dibenamine (30 mg. per kilogram) abolished the pressor response caused by stimulating the vagus nerves, as well as the hypertension caused by injecting noradrenaline.

**Effect of Section of the Spinal Cord on Pressor Responses to Vagus Stimulation**

A segment of the spinal cord was excised at the level of the fifth cervical vertebra. Stimulation of the vagus nerves immediately and 12 hours after this procedure failed to elicit a pressor response in 50 per cent of animals. In the other half, a pressor response was present, but it was greatly reduced as compared with control responses and was of a different contour.

**Paper Chromatography of Extracts of Arterial Walls**

Extracts of arterial walls were prepared according to the method previously described\(^1\)^\(^,\)\(^2\) and were chromatographed according to a method also previously described.\(^8\) Spots characteristic for adrenaline were more prominent than were those for noradrenaline, suggesting, as do other experiments now in progress, that adrenaline is the main pressor substance contained in arterial walls. Elution of the adrenaline and noradrenaline spots from the paper and bioassay caused typical pressor responses which were abolished or inverted by Dibenamine (fig. 4). A spot on the

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**Fig. 2.** Dog with the hypophysis, kidneys and adrenals removed. At Exc., stimulation of the vagi.

**Fig. 3.** Lower half of body perfused with defibrinated blood; "split dog." Upper graph: perfusion pressure. Lower graph: carotid pressure. At Exc. v., vagal stimulation.
chromatograph just below noradrenaline caused a fall in blood pressure when it was eluted and bioassayed.

**DISCUSSION**

These experiments indicate that electric stimulation of the central ends of the vagus nerves causes a release of hypertensive substance which is similar in all respects to that extracted from arterial walls.

This substance is released into the blood stream, since samples of blood taken during stimulation show activity, and the hypertensive effect is transferred to another dog in cross-circulation experiments. The pressor substance in the arterial wall seems to be adrenaline and/or noradrenaline but mainly noradrenaline in circulating blood, since its activity is interfered with by administration of adrenergic blocking agents; the activity of arterial wall extracts is abolished, or reversed to a depressor effect, by these blocking agents. Paper chromatographs of arterial wall extracts revealed spots in the proper zones for adrenaline and noradrenaline, and elution and bioassay of these spots gave typical adrenaline and noradrenaline responses. There was, in addition, another spot just below those for adrenaline and noradrenaline; the identity of this substance is not known.

Release of hypertensive substances after central stimulation of the vagus nerves is probably largely from blood vessels; heptectomy, nephrectomy or adrenalectomy did not prevent the response. Hypophysectomy also did not prevent the response and it seems apparent that the vagopituitary reflex described by Sattler and Chang and co-workers, which causes the liberation of Pitressin, does not enter into the "vagal hypertension" observed in our experiments. Rather, it seems that release of pressor material from arterial walls after vagus stimulation depends upon a mechanism consisting of excitation of vasomotor centers and sympathetic outflow to the arteries.

In accord with this explanation, it was found that interruption of sympathetic outflow by section of the spinal cord at C-6 largely prevented rise in arterial pressure due to stimulation of the vagus nerves. In some experiments, however, a small rise in pressure persisted after cord section; it is likely that this effect is due to stimulation of the cervical sympathetic trunk, which lies in the vagus sheath in the dog, with release of noradrenaline from arterial walls in the head. On the other hand, these responses, which persisted after spinal cord section, might, in part, be the same as those described by Taylor, Page and Corcoran who found that central vagus stimulation elicited a pressor response after cord section and after adrenergic blockade. They ascribed these responses to release by the brain of a new and unknown pressor material. While this hypothesis is attractive,
we believe that the evidence is not yet complete, and that final proof will await the clarification of certain hemodynamic, respiratory and vasomotor mechanisms that might participate. It is apparent that vagus stimulation can activate several mechanisms that modify arterial pressure. The most important of these would seem to be that one which is mediated over the sympathetic nervous system and provokes the release of pressor amines from blood vessels.

Conclusions

Electric stimulation of the central ends of the cut vagus nerves produces reflex sympathetic stimulation of the arterial walls which release pressor materials. The materials, demonstrated by paper chromatography and characterized pharmacologically, include adrenaline and noradrenaline and at least one other unknown material. It is suggested that the endocrine function of arterial walls plays an integral part in homeostasis.

Sumario Español

Los autores presentan experimentos demostrando que la hipertensión producida por el estímulo del terminal central del nervio vago se debe a la aparición de una substancia presora en la circulación sanguínea. Los resultados de estos experimentos demuestran que esta substancia no proviene de ninguna glándula o del sistema central nervioso. Los hechos observados indican que su origen es de la pared vascular propia, de donde se libera directamente a la circulación. Las pruebas farmacológicas sugieren que esta substancia es noradrenalina.

REFERENCES

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