Role of Vagal Afferents in the Control of Renal Sympathetic Nerve Activity in the Rabbit

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ABSTRACT
The influence of vagal afferents on renal sympathetic nerve activity was studied in nine rabbits anesthetized with sodium pentobarbital and artificially ventilated with oxygen. Arterial Pco₂ and pH were kept normal. The aortic depressor and the carotid sinus nerves were cut. The mean impulse frequency was determined from multifiber preparations of the renal nerve. Blood volume was altered either by bleeding or by infusing dextran. With vagi intact, an increase in blood volume of approximately 10% caused the nerve activity to decrease 41 ± 4%; it returned toward the control level after withdrawal of the same volume. A similar decrease in volume increased the nerve activity 33 ± 7%; it decreased toward the control level after reinfusion. These changes were unaffected by cutting the vagi at the diaphragm but were abolished or markedly attenuated by cooling or cutting the vagi in the neck. Interruption of vagal afferents resulted in a 21 ± 2% increase in nerve activity, indicating that the afferents exerted a continuous inhibition on the sympathetic outflow to the kidney. These experiments demonstrated a role for the low-pressure intrathoracic receptors in the control of renal sympathetic nerve activity in response to changes in blood volume.

KEY WORDS low-pressure receptors blood volume control cardiopulmonary receptors hemorrhage vagal cooling hypervolemia bilateral vagotomy

Evidence is accumulating that, in response to hemorrhage, receptors in the cardiopulmonary area are important in the control of the renal resistance vessels (1, 2). However, the magnitude of the renal response to the same hemorrhage can be strikingly different depending on the technique used to determine the reactions of the renal vessels (2, 3). Local factors in the kidney, such as autoregulation, may cause these differences and make it difficult to assess the role of renal sympathetic nerve activity in determining the magnitude of the response. In the present experiments, electroneurographic recordings from the renal nerve were made to establish more directly the relationship between the impulse frequency in the renal sympathetic nerves and the activation of the low-pressure mechanoreceptors during increases and decreases in blood volume.

Kezdi and Geller (4) have shown an inverse relationship between the carotid sinus pressure and the frequency of renal sympathetic nerve discharge. The influence of the receptors subserved by the vagal afferents on renal sympathetic nerve activity in response to alterations in blood volume has not yet been investigated.

Methods
Preparation.—Nine rabbits, weighing 3–4.5 kg, were anesthetized with sodium pentobarbital (40 mg/kg, iv); anesthesia was maintained by administering additional doses of sodium pentobarbital (6 mg/kg) hourly. The rabbits were artificially ventilated with oxygen at 30–35 cycles/min; the arterial PO₂ was kept above 400 mm Hg and Pco₂ between 30 and 40 mm Hg.

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Bicarbonate was administered to maintain the arterial pH between 7.35 and 7.45. Arterial blood pressure was monitored continuously by a catheter inserted in the femoral artery and connected to a Statham P23De strain-gauge transducer, and the pressure was recorded on an ultraviolet Visicorder (Honeywell 1508). The rabbits were given heparin (5 mg/kg) and paralyzed with gallamine triethiodide (3 mg/kg). In every rabbit, before observations were made, both the aortic depressor and the carotid sinus nerves were identified by recording their nerve activity, and then the nerves were cut.

Recording Renal Nerve Activity.—The left renal nerve was isolated between the renal artery and vein and dissected free over a length of 2 cm under a dissecting microscope. Fat and connective tissue, as well as the outer nerve sheath, were removed. Efferent sympathetic nerve activity was recorded from multifiber preparations of the central end of the nerve with a pair of platinum electrodes 2–3 mm apart. The preparation was immersed in mineral oil to prevent drying out of the nerve fibers.

**FIGURE 1**

Changes in renal nerve activity with an increase in blood volume estimated to be 10%; arterial baroreceptors denervated. With vagi intact (top), renal nerve activity decreased during the increase in blood volume and returned toward control level after withdrawal of the infused volume. After vagotomy (bottom), infusion of the same volume did not change renal nerve activity. Note that the scale of integrated activity is different in the top and bottom of the figure.
The nerve signals were amplified (amplifier A-105 and a-c amplifier A-103/B, Lexington Instruments, Inc.) and transformed into standardized pulses. At the beginning of each experiment, the record was visually inspected to determine the noise level as judged by the background activity during the quiet periods between the bursts of impulses. A discriminator was then set up to prevent this noise from being counted. The impulse frequency was integrated over 5-second periods. The time-response characteristics of the equipment permitted counting of signals at 0.25-msec intervals. A difficulty inherent in the use of multifiber preparations is that, at higher frequencies, spike summation can occur; counting the nerve impulse frequency then results in an underestimation of the nerve activity (5). To minimize this possibility, the nerve fibers were dissected to obtain a level of activity below 100 impulses/sec.

Changes in Blood Volume.—An increase in blood volume was obtained by infusing low-molecular-weight dextran into the femoral artery. The amount infused was calculated to be 10% of the blood volume assuming the latter to be 54 ml/kg body weight (6). After 1–2 minutes, the same amount of blood was withdrawn and used for subsequent infusions. To decrease the blood volume, an amount of blood estimated to be 10% of the total volume was withdrawn.

The changes in blood volume were made before and after cooling or cutting the cervical vagi. When cooling was used, thermodes were applied to both nerves and perfused with ice water to block nerve conduction. The surface temperature of the thermodes was monitored by thermocouples, and cold block was assumed to be complete when a temperature of 2–5°C was obtained. The block was reversed by perfusing the thermodes with water at 30–40°C. At the end of each experiment, cold block was again instituted and the vagi were severed caudal to the thermodes. Since no further changes occurred in blood pressure or renal nerve activity with vagal section, the cold block was assumed to be effective.

When the cervical vagi were cut, 10 minutes was allowed for nerve activity and arterial blood pressure to reach a steady state before any tests were performed.

Analysis of Data.—To standardize the results, the changes in impulse frequency were expressed as a percent of the control level. Increases and decreases in blood volume were performed randomly three times in each rabbit. The changes in renal nerve activity measured during the changes in blood volume were averaged for each rabbit, and the mean was used to calculate the mean change for the group. Statistical analysis of the data was performed using Student's paired t-test. The data are expressed as means ± SE.

Results

Blood Volume Increase.—In nine rabbits, the control mean impulse frequency was 94 ± 10 impulses/sec and the control mean aortic blood pressure was 118 ± 5 mm Hg.

With the vagi intact, the increase in blood volume caused the renal nerve activity to decrease 41 ± 4% (P < 0.001) and the aortic blood pressure to increase 31 ± 7 mm Hg. After withdrawal of the same volume of blood, mean renal nerve activity increased toward its initial value (102 ± 3%) (Figs. 1, 2). After interruption of the cervical vagi, there was no significant change in renal nerve activity (3 ± 3%, P > 0.2) during the increase in blood volume, but the aortic blood pressure increased 30 ± 6 mm Hg.

In five of the nine rabbits, cooling was used to block the vagi. Increasing blood volume during the block did not change the renal nerve activity, but rewarming the vagi during...
the period when the blood volume was still increased resulted in a decrease in renal nerve activity relative to the control level (Fig. 3).

Heart rate was unaffected by the increased blood volume, averaging 284 beats/min during the control period and 282 beats/min during the period when blood volume was increased ($P > 0.05$) both before and after interruption of the vagi.

In two rabbits, the vagi were cut below the diaphragm at the beginning of the experiment. In these rabbits, the increase in blood volume caused a decrease in renal nerve activity of 46%. This decrease was abolished by interruption of the vagi in the neck.

**FIGURE 3**

Effect of changes in blood volume on renal nerve activity during vagal cooling. TEMPERATURE indicates temperature of thermodes applied to vagi. Vagal cooling (top) caused an increase in aortic blood pressure and in nerve activity. An increase in blood volume during vagal cooling did not decrease nerve activity. Rewarming the vagi (bottom) during this period of increased blood volume caused nerve activity to decrease below the control level. Nerve activity returned to the control level after withdrawal of the infused volume. Note the changes in bursting activity when the vagi were rewarmed.
Blood Volume Decrease.—The effect of a decrease in blood volume on renal nerve activity was studied in seven rabbits. With the vagi intact, the decrease caused the renal nerve activity to increase $33 \pm 7\% \ (P < 0.01)$ and the aortic blood pressure to decrease $44 \pm 6 \text{ mm Hg}$. Reinfusing the same amount of blood resulted in a return of mean renal nerve activity toward its control level ($96 \pm 5\% \ (P < 0.01)$) (Figs. 2, 4). After interruption of the cervical vagi, the decrease in blood volume caused only a minor increase in renal nerve activity ($3 \pm 1\%, \ P < 0.05$) that was significantly smaller than the change obtained with the vagi intact ($P < 0.01$). The decrease in blood volume caused the aortic blood pressure to decrease $45 \pm 9 \text{ mm Hg}$ after vagal interruption.

In the five rabbits in which cooling was used, the decrease in blood volume during cooling did not change the renal nerve activity. Rewarming the vagi during the period when the blood volume was decreased resulted in an increase in nerve activity relative to the control level.

Heart rate was unaffected by the decreased blood volume, averaging 284 beats/min during the control period and 288 beats/min.

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**FIGURE 4**

Changes in renal nerve activity with a decrease in blood volume estimated to be 10%; arterial baroreceptors denervated. With vagi intact (top), renal nerve activity increased during the decrease in blood volume and returned toward control level after reinfusion. After vagotomy (bottom), the change in renal nerve activity during the decrease in blood volume was markedly attenuated. Note that the scale of integrated activity is different in the top and bottom of the figure.
during the period when blood volume was decreased ($P > 0.05$) both before and after interruption of the vagi.

In the two rabbits in which the vagi were cut below the diaphragm, the decrease in blood volume caused an increase in renal nerve activity of 42%, which was abolished by vagal interruption in the neck.

At the end of each experiment, the ability of sympathetic nerve activity to increase after vagotomy was verified by ventilating the rabbits with 10% CO$_2$. This procedure resulted in an increase in nerve activity that averaged $38 \pm 10\%$ of control.

**Effect of Vagal Interruption on Renal Nerve Activity.**—Vagotomy (seven rabbits) immediately increased renal nerve activity $41 \pm 10\%$ ($P < 0.02$). However, this level of activity was not sustained, and after 5 minutes it stabilized at a lower level, $21 \pm 3\%$ above control ($P < 0.001$). Cooling of the vagi (five rabbits) increased renal nerve activity $21 \pm 2\%$. This increase was reversed by rewarming the vagi. After interruption of the vagal afferents, the bursting activity observed in the renal nerve became more regular.

**Discussion**

The results indicate that the changes in blood volume had an inverse effect on renal sympathetic nerve activity. The afferent pathway of the reflex was mediated by vagal fibers, since interruption of the vagi either by cutting or by cooling abolished or markedly attenuated the response. This diminished response was not the result of a deterioration in the condition of the rabbit. Reversibility of the effects was demonstrated by the experiments in which cooling was used to block the vagi: the response of renal nerve activity to changes in blood volume was abolished during cooling but was restored as soon as the vagi were rewarmed. The ability of sympathetic nerve activity to increase after vagotomy was demonstrated by ventilating the rabbits with 10% CO$_2$.

Vagotomy and vagal cooling produced the well-documented increase in arterial blood pressure (7-9) along with an increase in renal nerve traffic. A more regular pattern of bursting activity was observed after interruption of the vagal afferents. This change in bursting activity after vagotomy was also observed by Cohen and Gootman (10) in the splanchnic nerve and presumably reflects the activity of the central sympathetic nervous system freed from its peripheral afferent inputs.

Chalmers et al. (11) observed that after sinoaortic denervation in the rabbit a 26% hemorrhage produced a small but sustained increase in renal vascular resistance. Öberg and White (1) demonstrated that after sinoaortic denervation in the cat a 20-ml hemorrhage caused an increase in the vascular resistance in the kidney greater than that in the muscular bed. Recently, Pelletier et al. (2) showed that in the dog receptors subserved by the vagal afferents played a role in the circulatory control of the splanchnic arterial and venous beds and the renal arterial bed but had little effect on the hind-limb circulation, which was predominantly controlled by the high-pressure receptors. The present experiments offered more direct information about the sympathetic outflow to the kidney because renal nerve activity was measured. Our results confirmed the previous conclusion that hemorrhage causes a reflex increase in the sympathetic nerve activity to the kidney. In addition, they demonstrated that a decrease in sympathetic nerve activity can be evoked by increasing the blood volume. This finding suggests that the receptors involved have a buffering function.

Öberg and White (1) concluded that cardiac receptors were involved in the compensatory response to hemorrhage since the responses were small or absent after avulsion of the cardiac nerves. Recently, Karim and associates (12) showed that balloon distention of the pulmonary vein–left atrial junction in the dog caused a decrease in renal nerve activity. The present experiments showed that the receptors for this reflex were situated in the cardiopulmonary area (13, 14), because the reflex response was present after section of the vagi at the diaphragm. The experiments

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did not permit a more precise location of the receptors concerned.

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**References**


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