Characterization of High and Low Pressure Baroreceptor Influences on Renal Nerve Activity in the Primate Macaca fascicularis

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SUMMARY We characterized the influence of high pressure and low pressure intravascular receptors on renal nerve activity in the pentobarbital sodium-anesthetized nonhuman primate Macaca fascicularis. Epinephrine-induced increases in arterial pressure were used to stimulate high pressure receptors, and intravascular volume expansion was used to stimulate both high and low pressure receptors. In addition, the intravascular mechanoreceptors were stimulated directly by intravenous veratrine administration. All interventions produced large decreases in renal nerve activity in the intact state. Denervation of the carotid sinus or bilateral cervical vagal section diminished, whereas sino-aortic denervation with vagotomy completely abolished all responses of renal nerve activity to these interventions. We conclude that the nonhuman primate possesses very sensitive renal nerve sympathetic reflexes that are modulated by intravascular mechanoreceptors whose afferents traverse the carotid sinus nerves and the vago-aortic trunks. The carotid sinus nerves and the vago-aortic trunks appear to be equally effective in inhibiting renal nerve activity in response to increases in arterial pressure. In addition, there are no afferent pathways mediating intravascular mechanoreceptor modulation of renal nerve activity outside the carotid sinus nerves and the vago-aortic trunks. Circ Res 46: 726-730, 1980

IT HAS BECOME increasingly evident that renal sympathetic nerves are capable of reflexly modifying renal function in the face of circulatory challenges. The basic characteristics of renal sympathetic nerve reflexes have been studied extensively in a number of species including the rabbit (Clement et al., 1972), the rat (Colindres and Gottschalk, 1978), the dog (Prosnitz and DiBona, 1978), and the cat (Ninomiya and Irisawa, 1969). However, there is little, if any, direct information concerning factors which modulate renal nerve activity in the nonhuman primate.

Previous work from this laboratory has called into question the suitability of nonprimate species as human models of reflex cardiovascular-renal control. For example, the renal responses of the monkey to left atrial balloon distension are substantially different from those seen in the dog (Gilmore and Zucker, 1978). These differences were ascribed, in part, to a lower sensitivity of left atrial low pressure receptors compared to the dog (Zucker and Gilmore, 1975). In addition, Weaver (1977) has questioned the role of the classical baroreceptor afferent pathways of the feline carotid sinus and vago-aortic nerves in modulating renal sympathetic nerve discharge. She found that a sino-aortic and vagal-denervated cat still will respond to increases in central venous pressure induced by blood volume expansion with a decrease in renal nerve activity. This is in contrast to the results of Clement et al. (1972) who found that volume expansion in sino-aortic and vagal-denervated rabbits fails to modify renal sympathetic activity. If the difference between the results of Weaver and Clement et al. derives from species differences, then no assumptions can be made about reflex control of renal nerve activity in the primate.

The relative sensitivity of the high and low pressure baroreceptors undoubtedly plays an important role in the renal responses of the primate to physiological stimuli. Therefore, we undertook studies to determine the contribution of high and low pressure receptors to the modulation of efferent renal nerve activity in the monkey.

Methods

We studied eight Macaca fascicularis monkeys weighing 4.5-5.5 kg. They were anesthetized with sodium pentobarbital (40 mg/kg, iv) after induction with ketamine (16 mg/kg, im). Supplemental pentobarbital (0.8 mg/kg, iv) was given as needed.

The femoral artery and vein on one side were catheterized. A femoral vein was cannulated for infusion of drugs and for blood volume expansion and a femoral artery for withdrawing blood. A Millar catheter-tipped pressure transducer was inserted to the level of the aortic arch via the other femoral artery for measurement of arterial blood pressure (AP). The trachea was cannulated and the...
monkey ventilated with a positive-pressure respirator using room air supplemented with oxygen. Arterial PO₂, PCO₂, and pH were monitored throughout the experiment. The animal was paralyzed with Flaxedil (2.2 mg/kg, iv) to minimize respiratory movements. The chest was opened and a Millar catheter-tipped pressure transducer was introduced into the left atrium via a branch of the pulmonary vein.

To record renal sympathetic nerve activity (RSNA), the left kidney was approached via a retroperitoneal flank incision. The peritoneum was retained intact and was used to hold a mineral oil pool over the renal nerves. The renal nerves were located running adjacent to the renal artery, and approximately 1 cm of nerve was freed from connective tissue and placed on a bipolar platinum hook electrode. Once the activity of the nerve had been verified, the distal end of the nerve was crushed so that only efferent activity would be recorded. Crushing the nerve often resulted in an immediate small elevation of blood pressure which lasted several seconds.

RSNA was differentially amplified and filtered with a Tektronix R 5031-3A9 oscilloscope and was quantified with an “RC” integrator with a time constant of 3.84 seconds. Zero RSNA was obtained at the end of the experiment by crushing the central end of the nerve. The unprocessed RSNA, integrated RSNA, AP, and left atrial pressure (LAP) were recorded on a Honeywell 1858 Visicorder.

The carotid arteries on both sides were isolated, and the vago-aortic trunks running alongside the carotids were identified. The medial branch of the left vago-aortic trunk could be traced down into the chest and was seen to originate in the area of the aortic arch. Recordings from the peripheral end of the medial branch were found to consist almost entirely of pulsatile baroreceptor discharges which varied directly with the level of AP. In contrast, recordings from the lateral branch of the vago-aortic trunk yielded activity with predominantly respiratory rhythms not varying with changes in AP. Accordingly, bilateral section of the medial branches of the vago-aortic trunk, along with carotid sinus denervation, was denoted as sino-aortic denervation. Bilateral section of both lateral and medial branches of the vago-aortic trunk, along with caudal vagotomy yielded activity with predominantly respiratory rhythms not varying with changes in AP.

Veratrine (Unitensin) was administered to some of the monkeys intravenously in doses of 10–40 μg. The effects of veratrine required several minutes to achieve full expression. However, almost 90% of the response was achieved after 1 minute. Therefore, RSNA, AP, and LAP data were averaged over 20 seconds, 1 minute after veratrine administration, and were expressed as the changes compared to a 20-second interval just prior to veratrine.

When epinephrine was given, the average RSNA, AP, and LAP in the first 20 seconds after epinephrine were expressed as the change from a 20-second control interval just prior to epinephrine administration. The changes in the first 20 seconds after epinephrine included the rapid rise in AP, the peak rise in AP, and part of the sustained AP elevation following the peak. These data showed much less variability than if only the peak responses were recorded.

Data were collected similarly during bolus volume expansions with isotonic-isoosmotic dextran solution (Dextran 70) or with homologous blood. The first 20-second interval after volume expansion was compared to a 20-second interval just prior to volume expansion. There was no difference between the responses to dextran solution or to homologous blood. After volume expansion, the monkey was hemorrhaged back to control levels.

Data were processed in the following manner: to minimize variations due to respiratory and cardiac rhythms inherent to RSNA, AP, and LAP, the responses over a 20-second interval were averaged to obtain a value representative of that interval. Since the absolute electrical activity representing RSNA varies substantially among animals, depending on the size of the nerve, the degree of electrical contact between the electrode and the nerve, and the degree of nerve signal amplification, no absolute measure of whole nerve RSNA can be obtained (Aars and Leraand, 1968). Therefore, the relative changes in integrated RSNA compared to an integrated control level of RSNA with a known zero RSNA level were used to compare data among animals.

The completeness of baroreceptor denervation was evaluated by observing the effect of bilateral carotid occlusion on AP and on RSNA. Also, a sensitive test for baroreceptor denervation was the absence of RSNA changes in response to epinephrine-induced increases in AP. If denervation was incomplete, the carotid sinus area was painted with either 2% phenol or a 2% lidocaine solution. In all cases, this resulted in complete abolition of the carotid sinus reflex. Baroreceptor reflexes could be restored partially by washing the lidocaine out of the carotid sinus area.

Analysis of variance was used to test the significance of differences between group means, and Student’s paired t-test was used to test the significance of paired data when there was large variation of responses among animals. The data are expressed as means ± se. The n’s of the average data are signified as the total number of interventions in the total number of animals examined (in parentheses).
Results

The response of intact monkeys to 0.5-5.0 µg of intravenous epinephrine was an increase in AP which was accompanied by a fall in RSNA proportional to the rise in AP. LAP showed little or no change after epinephrine. In Figure 1 is shown the average percent change in RSNA per mm Hg rise in AP in monkeys that were either intact, vagal-denervated, carotid-sinus-denervated, sino-aortic-denervated, or vagal- and carotid-sinus-denervated. RSNA in the eight intact monkeys was quite sensitive to rises in AP. This sensitivity was significantly reduced after vagotomy (P < 0.005) or carotid-sinus denervation (P < 0.01). The percent change in RSNA per mm Hg rise in AP in the vagal-denervated animals was not significantly different from that seen in the carotid-sinus-denervated animals (P > 0.5). When the medial branch of the vagus was cut bilaterally in the carotid-sinus-denervated animals, the sensitivity of RSNA to rises in AP was further diminished. This response was significantly less than in the vagotomized state (P < 0.025). Finally, the average change in RSNA per mm Hg rise in AP of eight vagotomized, sino-aortic-denervated monkeys was not significantly different from zero (P > 0.5).

In six monkeys, the effects of bolus intravenous volume expansion on RSNA was examined. In the intact animal, an 8-12% intravascular volume expansion with either isotonic-isoosmotic dextran or homologous blood resulted in a rise in AP of 11-20 mm Hg, a rise in LAP of 6-12 cm H2O, and a decrease in RSNA. The average percent change in RSNA per unit rise in LAP was not significantly different from zero (P > 0.5). Likewise, the average percent change RSNA per unit rise in AP was not significantly different from zero (P > 0.5).

In six monkeys, veratrine was given intravenously in doses of 10-40 µg. The response of the intact animals included a prolonged fall in RSNA and a decrease in AP. No significant changes in CVP were noted. The decrease of both RSNA and AP with veratrine showed a good dose-response relationship.

The average responses of AP and RSNA per microgram of veratrine is shown in Figure 3. In the intact state, substantial decreases in both AP and RSNA occurred. The responses of the vagal-denervated animals were similar, although the change in RSNA per microgram of veratrine was significantly less than in the intact monkeys (P < 0.001), as was the change in AP (P < 0.025). The average responses of the vagal-denervated, sino-aortic-denervated animals were not significantly different from zero when expressed as either change of AP per microgram of veratrine (P > 0.5) or as change of RSNA per microgram veratrine (P > 0.5).
The epinephrine data clearly show the influence of high pressure receptors on renal nerve activity in the monkey. In addition, the relative influence of the classical baroreceptor afferent pathways can be seen as they are progressively denervated. The finding that the RSNA responses to epinephrine in the vagal-denervated and the carotid sinus-denervated states are both significantly less than the intact state, but not significantly different from each other, is consistent with the results of Ninomiya and Irisawa (1969) who observed in the cat that the carotid sinus and the vago-aortic baroreceptor afferents exert approximately equal effects on sympathetic discharge. In the vagal- and sino-aortic-denervated animals, the responses of RSNA to rises in AP were not significantly different from zero. These data support the conclusion that, over a physiological range of increases in AP, the vago-aortic trunks and the carotid sinus nerves are the only high pressure baroreceptor afferents modulating RSNA in the primate. Also supported is the conclusion that the sensitivity of RSNA to changes in AP is dependent on the total number of baroreceptor afferent pathways that are intact. The sum of the RSNA responses of the vagal and sino-aortic-denervated animals, the responses of RSNA to rises in AP were not significantly different from zero. These data support the conclusion that, over a physiological range of increases in AP, the vago-aortic trunks and the carotid sinus nerves are the only high pressure baroreceptor afferents modulating RSNA in the primate.

In another study (Echtenkamp and Gilmore, unpublished data), the sensitivity of RSNA in chloralose-anesthetized cats to rises in AP were examined under conditions similar to those described in this paper. Thus, it is possible to compare the influence of high pressure receptors on RSNA between the cat and the monkey. Figure 4 shows the percent change in RSNA per mm Hg rise in AP in the intact cat and intact monkey. AP changes for both animals were limited to the range from 0 to 30 mm Hg. The sensitivity of the monkey was not significantly different from that of the cat ($P > 0.1$). This is in spite of the fact that the monkey was anesthetized with pentobarbital, whereas the cat was anesthetized with chloralose. These data support the conclusion that the influence of high pressure receptors on RSNA is essentially the same in the cat and the monkey.

In contrast to epinephrine, volume expansion stimulated both low and high pressure receptors. The decrease in response after vagotomy and the complete abolition of any RSNA response to volume expansion after vagotomy with sino-aortic denervation support the conclusion that afferent pathways which signal the volume-loaded state and reflexly inhibit RSNA are confined to the carotid sinus and the vago-aortic trunks in the monkey. This finding is similar to the results of Clement et al. (1972) who showed that, when the rabbit undergoes vagal and sino-aortic denervation, no changes in RSNA occur with volume expansion. However, these data are contradictory to those of Weaver (1977), who reported that vagal and sino-aortic-denervated cats showed a significant inhibition of RSNA when volume expanded. Differences in species, anesthetic, extent of volume expansion, and preparation make it difficult to resolve these differences. However, we reported in a parallel study (Echtenkamp and Gilmore, in press), that volume expansion in cats, using essentially the same anesthetic agent and protocol as Weaver, resulted in no RSNA inhibition in the vagal and sino-aortic-denervated animal.

Veratrine exerts its reflex effects on sympathetic activity by direct stimulation of intravascular mechanoreceptor endings (Benforado, 1967). Our results using veratrine further support the view that all important intravascular mechanoreceptor input which modulates RSNA has been eliminated by vagotomy with sino-aortic denervation. To our knowledge, a separate aortic nerve has not been
The medial branch of the left vagus was found to originate in the vicinity of the aortic arch. In addition, recordings from the peripheral end of the medial branch in the neck revealed a predominantly pulsatile discharge which varied directly with changes in AP. By contrast, the lateral branch of the vagus showed discharges that were predominantly modulated by respiration and that were not altered by changes in AP. The data in Figure 1 show that section of the medial branch of the vagi removed a significant amount of baroreceptor input to RSNA. However, when both carotid sinus and medial vagus branches were cut, leaving only the lateral branches of the vagus intact, there still remained a significant amount of RSNA inhibition with rises in AP. Therefore, it is likely that the medial branch of the vagus constitutes only part of the “aortic nerve” of the monkey with the remaining baroreceptor afferents from the aortic arch and heart being carried via the lateral branch of the vagus. Thus, in the monkey, it appears that the “aortic nerve” is not completely separate from the vagus, as is the case with the rabbit. However, a large proportion of the aortic nerve fibers is carried in a separate medial branch of the vagus in *Macaca fascicularis*.

Taken together, the data from the present study show that the nonhuman primate possesses very sensitive renal nerve sympathetic reflexes that are modulated by intravascular mechanoreceptors whose afferents traverse the carotid sinus nerve and vago-aortic trunks. Furthermore, the carotid sinus and the vago-aortic trunk afferents appear to be equally effective in inhibiting RSNA in response to rises in AP. In addition, the data from vagal and sino-aortic-denervated animals during volume expansion, epinephrine administration, or veratrine administration all support the concept that there are no afferent pathways mediating intravascular mechanoreceptor modulation of RSNA outside the carotid sinus nerves and the vago-aortic trunks. Thus, it is possible that changes in RSNA in response to circulatory challenges in the nonhuman primate may be important in relation to the changes in renal function seen in the intact state.

**References**


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