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Renal Nerves Modulate Renin Secretion during Autoregulation (41371)

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Abstract. Efferent stimulation of the renal nerves at a very low frequency (0.25 Hz) which is subthreshold for changes in renal blood flow (RBF), urinary sodium excretion ($U_{Na}V$), and renin secretion has been shown to augment the renin secretion response to reduction in renal arterial pressure to 50 mm Hg by aortic constriction. The present experiments determined whether this modulating influence on renin secretion could be demonstrated during aortic constriction when both RBF and glomerular filtration rate (GFR) were autoregulated. In 9 dogs with renal nerves sectioned, aortic constriction reduced renal arterial pressure from 131 to 98 mm Hg and $U_{Na}V$ from 68 ± 15 to 29 ± 6 μeq/min, did not change RBF or GFR, and significantly increased renin secretion (82 ± 26 to 606 ± 206 ng/min). Aortic constriction during low frequency renal nerve stimulation (0.25 Hz) resulted in similar increases in renin secretion (245 ± 130 to 691 ± 298 ng/min). In 10 dogs with innervated and contralateral denervated filtering kidneys, aortic constriction reduced renal arterial pressure from 131 to 99 mm Hg without changing RBF or GFR and equally decreasing $U_{Na}V$ in innervated and denervated kidneys. Renin secretion increased significantly more ($P < 0.05$) from innervated (1363 ± 669 ng/min) than from denervated kidneys (647 ± 399 ng/min). These results support the view that the prevailing nerve activity which passes to the kidney during aortic constriction exceeds 0.25 Hz of electrical nerve stimulation and is sufficient to augment the renin secretion response to aortic constriction when RBF and GFR are autoregulated.

The influences of the renal sympathetic nerves, the renal vascular baroreceptor, and the tubular macula densa receptor on renin release have been investigated primarily by isolating one of these mechanisms from the remaining two. However, investigators have reported that innervated kidneys secrete more renin than do the contralateral denervated kidneys in response to stimuli for renin release such as aortic constriction (1, 2) and furosemide administration (1–3). The physiologic significance of the influence of the renal nerves on renin secretion from the innervated kidneys was not evident from most of these studies.

Thames and DiBona (2) recently reported that low-frequency stimulation of the renal nerves (10 V, 1 msec, 0.25 Hz) failed to alter renal blood flow, urinary sodium excretion, or the basal rate of renin secretion but augmented the renin secretion response to a reduction of renal arterial pressure to 50 mm Hg (by aortic constriction) and to the administration of furosemide. These authors concluded that low frequency renal nerve stimulation augmented the secretion of renin mediated by nonneural mechanisms. They indicated that this was the probable basis for the difference in renin responses of innervated and denervated kidneys to aortic constriction to 50 mm Hg and to furosemide administration.

This neural modulation of renin secretion mediated by nonneural mechanisms would assume greater physiological importance if such an effect could be demonstrated during moderate reductions in renal arterial pressure. Autoregulation of both glomerular filtration rate and renal blood flow occurs when renal arterial pressure is reduced to only 100 mm Hg (4). The purpose of this study was to determine whether renal nerve activity also modulates renin secretion during reductions of renal arterial pressure to a range in which both renal blood flow and glomerular filtration rate are autoregulated.

Materials and Methods. Experiments were conducted on mongrel dogs weighing 16–23 kg. Animals were anesthetized with

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sodium pentobarbital (30 mg/kg iv) or sodium thiopental (30 mg/kg iv) followed by α-chloralose (80 mg/kg and 10 mg/kg/hr iv). A cuffed endotracheal tube was inserted and the animals were artificially ventilated. Catheters were inserted via a femoral artery into the descending aorta near the level of the renal arteries and into the ascending aorta via a brachial artery. Catheters also were placed in a femoral vein and jugular vein for the infusion of inulin and saline and for the administration of supplemental doses of anesthetic. An inulin solution was infused at 1 ml/min to maintain plasma inulin concentration at approximately 30 mg/dl. Following anesthesia, animals were infused with normal saline at a rate of 4.0 ml/min to replace fluid and urinary losses.

The left kidney was exposed in each experiment using a retroperitoneal flank incision. A catheter was placed in the left renal vein via the left gonadal vein. A flowmeter probe was positioned on the left renal artery and the left ureter was cannulated. A mechanical occluder also was positioned around the aorta above both renal arteries and was used for reducing renal arterial pressure.

In experiments in which the responses of both kidneys were studied, the right kidney was exposed using a midline incision. A polyethylene catheter (o.d. 1.27 mm) was advanced from the left femoral vein into the right renal vein for the collection of renal venous blood samples. A noncannulating electromagnetic flowmeter probe was placed on the right renal artery and the right ureter was cannulated using polyethylene tubing.

In experiments conducted using low-level renal nerve stimulation, the renal nerves were severed so that the only sympathetic nerve activity passing to the kidney was evoked by electrical stimulation. This technique has been shown to abolish the renal vasoconstrictor responses to splanchnic nerve stimulation (2). The distal renal nerve bundle then was placed on platinum electrodes. A marked reduction of renal blood flow during strong renal nerve stimulation (10–30 V, 1 msec, 10 Hz) before and after each experiment verified that the renal nerves remained functional for the duration of the experiment.

Experiments were first conducted in nine dogs anesthetized with pentobarbital. Control urine collections (two) of 5 min duration each were obtained and arterial and renal venous blood samples were collected between the two periods for the determination of renin secretion rate. Renal arterial pressure then was decreased by aortic constriction to 98 ± 2 mm Hg. After 5 min of aortic constriction, arterial and renal venous blood samples were obtained followed by collection of two urine samples of 5 min duration each. The aortic constriction was released and 20 min were allowed for recovery at which time blood and urine samples were collected as described in control. Low frequency renal nerve stimulation (10 V, 1 msec, 0.25 Hz) was begun and after 10 min the protocol was repeated while renal nerve stimulation was continued. In four of these dogs, the renal nerves were stimulated during the first aortic constriction. Since our previous study (2) employed chloralose anesthesia, an additional group of four dogs was anesthetized with chloralose and subjected to the same experimental protocol. The results obtained in this chloralose-anesthetized group were not different from those obtained in the pentobarbital-anesthetized group (vide infra). We have not pooled the results and present only the results obtained in the pentobarbitol-anesthetized group.

Experiments also were conducted in 10 α-chloralose-anesthetized dogs with the left kidney denervated and the right kidney innervated. The experimental protocol was similar to that of the previous experiments except that the renal nerves were not electrically stimulated and a second aortic constriction was not performed. Denervation of the left kidney was accomplished by severing all visible renal nerves and applying phenol solution (10 g/dl) to the renal artery. Absence of changes in renal blood flow during hemorrhage of 20 ml/kg (renal arterial pressure was maintained constant by release of the previously constricted aorta)

or during strong stimulation of the proximal renal nerve bundle (10 V, 1 msec, 10 Hz) was taken as evidence of renal denervation.

Systemic arterial pressure was measured using a pressure transducer (Statham P23Db) and direct writing oscillograph (Beckman Dynograph). Plasma and urinary sodium concentrations were determined by flame photometry. Arterial hematocrit was estimated by a micromethod. Plasma and urinary inulin concentrations were determined colorimetrically (5). Gomerular filtration rate was calculated as the clearance of inulin from the plasma.

Blood for plasma renin determination was collected in chilled tubes containing ethylenediaminetetraacetic acid (EDTA) to achieve a final concentration of 1 mg/ml. Plasma renin activity of arterial and renal venous samples was determined by radioimmunoassay for angiotensin I generated after a 1-hr incubation at 37° (6). Renin secretion rate was calculated as the product of the renal venous−arterial plasma renin activity difference and renal plasma flow.

Data were analyzed using Student's *t* test for paired data. Differences between innervated and denervated kidneys were tested by a paired *t* analysis of the absolute change following aortic constriction. The 0.05 level of probability was utilized as the criterion of significance.

Results. In nine experiments, the aorta was constricted to decrease renal arterial pressure from 131 ± 5 to 98 ± 3 mm Hg. This aortic constriction did not affect renal blood flow or glomerular filtration rate (Fig. 1). Urinary sodium excretion, however, decreased significantly following this reduction of renal arterial pressure (Fig. 1). Aortic constriction increased renin secretion rate from a control value of 82 ± 26 to 606 ± 206 ng/min (Fig. 1). Low-frequency renal nerve stimulation (0.25 Hz) did not significantly alter basal renin secretion. Aortic constriction to a renal arterial pressure of 98 ± 3 mm Hg during renal nerve stimulation did not change renal blood flow or glomerular filtration rate, decreased urinary sodium excretion, and increased renin secretion from 245 ± 130 to 691 ± 298 ng/min.

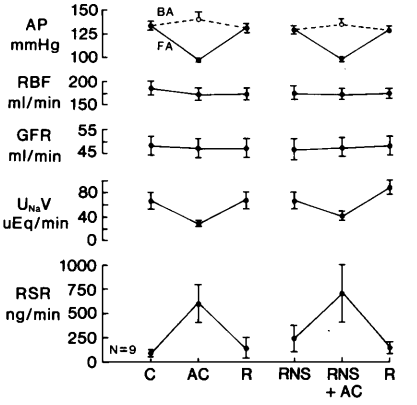

FIG. 1. Changes in mean arterial pressure (AP), renal blood flow (RBF), glomerular filtration rate (GFR), urinary sodium excretion ($U_{Na}V$), and renin secretion rate (RSR) of kidneys with renal nerves sectioned in response to suprarenal aortic constriction (AC) within the range of blood flow and glomerular filtration rate autoregulation performed with and without low level renal nerve stimulation (RNS). Reduction of renal artery pressure to 98 mm Hg equally decreased urinary sodium excretion and increased renin secretion rate before and during low-level renal nerve stimulation. C, control; R, recovery; BA, brachial artery; FA, femoral artery, taken as renal artery.

The increases in renin secretion during aortic constriction with and without nerve stimulation were not different. Following release of the aortic constriction renal arterial pressure, urinary sodium excretion and renin secretion rate returned to values which were not different from control (Fig. 1).

In 10 animals with innervated and contralateral denervated kidneys, the aorta was constricted to decrease renal arterial pressure from 131 ± 3 to 99 ± 2 mm Hg (Fig. 2). Renal blood flow and glomerular filtration rate remained constant in both kidneys throughout each experiment (Fig. 2). Aortic constriction decreased urinary sodium excretion to the same degree in both innervated and denervated kidneys (Fig. 2). Following a 5-min period of reduced renal arterial pressure, renin secretion from the denervated kidneys increased 647 ± 399 ng/min while renin secretion from the innervated kidneys increased 1363 ± 669 ng/

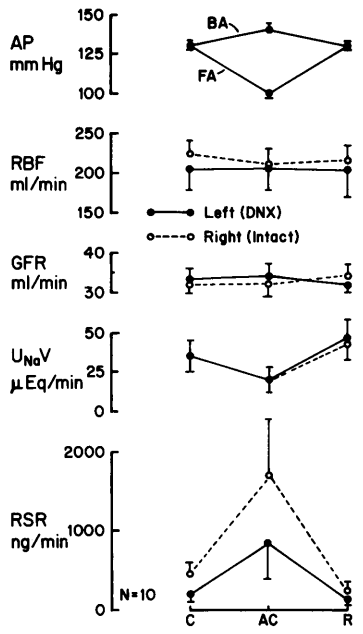

FIG. 2. Changes in mean arterial pressure (AP), renal blood flow (RBF), glomerular filtration rate (GFR), urinary sodium excretion ($U_{Na}V$), and renin secretion rate (RSR) in response to suprarenal aortic constriction (AC) within the range of blood flow and glomerular filtration rate autoregulation performed in denervated (DNX) and innervated (intact) kidneys. Aortic constriction to a renal arterial pressure of 99 mm Hg increased renin secretion 647 ± 399 ng/min in denervated kidneys and 1363 ± 669 ng/min in innervated kidneys. C, control; R, recovery; BA, brachial artery; FA, femoral artery.

min (Fig. 2). The mean increase in renin secretion from innervated kidneys was significantly greater than that from denervated kidneys. Following release of the aortic constriction, renal arterial pressure, urinary sodium excretion, and renin secretion returned toward the previously obtained control values (Fig. 2).

Discussion. Several investigators have reported that kidneys with renal nerves intact have a greater rate of renin secretion during aortic constriction or furosemide administration than do contralateral denervated kidneys (1, 3, 7). Thames and DiBona (2) recently confirmed these findings. In addition, these authors reported that low-level efferent stimulation of the renal nerves at a frequency (0.25 Hz) which did not alter the basal rate of renin secretion, markedly enhanced the renin secretion response to reduction in renal arterial pressure to 50 mm Hg by aortic constriction and to furosemide administration. On the basis of these and other data, it was concluded that the renal nerves modulate renin secretion mediated by nonneural mechanisms.

In the previous experiments utilizing aortic constriction as a stimulus for renin secretion, renal arterial pressure was reduced to 50 mm Hg which is below the range of autoregulation of renal blood flow and glomerular filtration rate. Although the renal nerves were shown to modulate renin secretion during this large reduction of renal arterial pressure, this interaction would assume greater physiological significance if a similar modulating influence could be demonstrated during aortic constriction within the range of renal arterial pressures in which renal blood flow and glomerular filtration rate are autoregulated. Accordingly, experiments were conducted in which renal arterial pressure was reduced to approximately 100 mm Hg by aortic constriction so that both renal blood flow and glomerular filtration rate were autoregulated (Figs. 1 and 2). In the initial studies, low-frequency renal nerve stimulation did not augment renin secretion during aortic constriction to 100 mm Hg (Fig. 1). However, in the latter experiment, renin secretion from innervated kidneys increased significantly more than did renin secretion from the contralateral denervated kidneys when both kidneys were subjected to the same reduction of renal arterial pressure (Fig. 2). In these experiments utilizing aortic constriction as the stimulus for renin secretion, renal arterial pressure, renal vascular resistance, and urinary sodium excretion are decreased. Under these circumstances, renin secretion may be mediated by renal vascular receptors due to the reduction of renal arterial pressure (8) or by tubular macula densa receptors due to the decrease in delivery of sodium chloride to the distal nephron (9). Renal blood flow and glomerular filtration rate remained constant in each experiment and urinary sodium excretion of innervated and dener-

vated kidneys were not different throughout the study. These results indicate that similar stimuli for renin secretion likely were presented to both the vascular and macula densa receptors in both innervated and denervated kidneys. Despite these equivalent nonneural stimuli, renin secretion in response to aortic constriction was enhanced from innervated kidneys. During aortic constriction there was a rise in arterial pressure above the constriction which, as previously shown, reduces the prevailing level of efferent renal sympathetic nerve activity (2). Despite this further reduction in sympathetic activity during aortic constriction, the residual activity in the renal nerves was sufficient to augment renin secretion from the innervated kidney in response to moderate reductions of renal arterial pressure when both renal blood flow and glomerular filtration rate were autoregulated.

It is possible to approximate the prevailing level of efferent renal sympathetic nerve activity passing to the innervated kidney in these experiments (Fig. 2). During the control phase of the experiment, urinary sodium excretion was similar between the intact and denervated kidney whereas renin secretion rate was higher in the intact kidney than the denervated kidney. Our previous studies with direct electrical renal nerve stimulation show that a frequency of 0.5 Hz produces increases in renin secretion rate without a change in urinary sodium excretion (10) whereas a frequency of 1.0 Hz produces both increases in renin secretion rate and decreases in urinary sodium excretion (11); neither frequency affects glomerular filtration rate or renal blood flow (10, 11). Thus, these observations suggest that the range of prevailing efferent renal sympathetic nerve activity passing to the intact kidney in these studies and which produced augmentation of renin secretion was between 0.5 and 1.0 Hz.

The inability of low-frequency renal nerve stimulation (0.25 Hz) to augment renin secretion from filtering kidneys following aortic constriction without associated changes in renal blood flow or glomerular filtration rate may be a function of the modest magnitude of the nonneural stimulus for renin secretion. Abe *et al.* (12) found no significant increase in renin secretion of denervated filtering kidneys when renal arterial pressure was reduced from 142 to 104 mm Hg. In the present studies, renal arterial pressure was reduced only to 100 mm Hg. This reduction of renal arterial pressure can be viewed as a weak nonneural stimulus for renin secretion. We suggest that low-level renal nerve stimulation was not sufficient to augment renin secretion during such a modest nonneural stimulus whereas the prevailing efferent nerve traffic (which presumably is greater than 0.25 Hz) will augment renin secretion during aortic constriction to renal arterial pressures within the range of renal blood flow and glomerular filtration rate autoregulation.

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