Release of Renin by the Carotid Baroreflex in Anesthetized Dogs

Role of Cardiopulmonary Vagal Afferents and Renal Arterial Pressure

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SUMMARY In 3 of 10 anesthetized dogs with aortic nerves sectioned and renal arterial pressure maintained constant, reduction to 40 mm Hg of the pressure in the vascularly isolated carotid sinuses resulted in an increase in renin secretion. After section of the vagus nerves, carotid sinus hypotension resulted in an increase in renin secretion in 9 of the 10 dogs. Vagal nerve section in these 10 dogs with carotid sinuses vascularly isolated and maintained at a pressure equal to existing aortic pressure resulted in significant increases in basal levels of plasma renin activity and renin secretion. The increase in renin secretion found during carotid sinus hypotension in vagotomized dogs was totally or substantially inhibited when renal arterial pressure was not maintained constant but allowed to increase equally with systemic arterial pressure. The increase in renin secretion observed during carotid hypotension in vagotomized dogs with renal arterial pressure held constant was abolished by renal denervation. We conclude that the carotid baroreflex is involved in the neural control of renin release. However, a concomitant activation of cardiopulmonary receptors and/or a substantial rise in renal arterial pressure can suppress the reflex increase in the secretion of renin induced by carotid sinus hypotension.

IN THE LAST FEW YEARS increasing attention has been given to the neural control of renin release. Stimulation of selected areas in the medulla1-3 and hypothalamus4 and an increase5, 6 or decrease7, 8 in afferent nerve traffic from vagally innervated cardiopulmonary receptors can excite or inhibit the secretion of renin. These effects are abolished by renal denervation. Zanchetti and Stella9 have shown that the release of renin in such diverse situations as suprarenal aortic stenosis, administration of the diuretic furosemide, and tilting to the upright position is dependent on neural mechanisms in considerable degree. In view of these observations, it is surprising to find disagreement regarding the role of the carotid baroreceptors in the control of renin secretion. Three studies10-12 reported an increase in renin secretion during carotid occlusion and three studies13-15 reported that renin secretion was not affected by changes in carotid sinus pressure.

In a recent study it was shown that, when the carotid sinus was free to exert its buffering influence, complete interruption of afferent vagal nerve traffic from cardiopulmonary receptors did not result in an increase in renin secretion in 17 of 20 dogs.16 Because it has been shown that the inhibitory influence of vagally innervated cardio-

pulmonary receptors becomes more pronounced as that of the carotid baroreceptors is reduced,17 it seemed possible that this interaction between the two receptor systems might act to inhibit the release of renin during carotid sinus hypotension.

The following studies were carried out to investigate this question.

Methods

Dogs weighing 16-20 kg were maintained on a daily intake of 65 mEq of Na+ and 55 mEq of K+ for 5 days before study. Anesthesia was induced with sodium thio-
pental (30 mg/kg, intravenously) followed by a-chloralose (80 mg/kg dissolved in 5% dextrose in water and administered intravenously). Suplemental doses of chloralose (5-10 mg/kg) were given hourly. Gallamine triethiodide (Flaxedil; 3 mg/kg, iv) was used to obtain muscle relaxation during the surgical procedures. A cuffed endotracheal tube was inserted and the dog was mechanically ventilated with oxygen, using a respiratory frequency of 12/min and a tidal volume of 20 ml/kg. Measurements of Pao2, Paco2, and pH were made at intervals (IL Blood Gas Analyzer). Paco2 was maintained between 30 and 40 mm Hg by adjustment of respiratory frequency, and pH was main-
tained between 7.3 and 7.4 by intravenous infusion of sodium bicarbonate. Body temperature was kept at or above 37°C by use of a heating blanket.

Surgical Procedures

The aortic nerve and the cervical sympathetic nerve on each side were identified and sectioned.18 Both carotid sinuses were vascuarily isolated and maintained at selected nonpulsatile pressures.9, 19 Silastic-covered cooling coils
were placed around each cervical vagus nerve. Right and left lumbar incisions allowed the dog to be suspended in the prone position with the ventral abdominal wall clear of the table top by using the technique of Hosie. The right lumbar incision was sufficiently large to allow retroperitoneal exposure of the right renal artery and vein. A noncannulating square wave electromagnetic flow transducer (Carolina Medical Electronics) and a mechanical occluder were placed around the right renal artery. A 27-gauge needle connected to a Statham P23Db strain gauge was used to record renal arterial pressure downstream from the mechanical occluder. A 25-gauge needle with a terminal side hole was positioned in the right renal vein for blood sampling. Patency of the needle was maintained by a constant infusion of 5% dextrose in water at a rate of 0.25 ml/min. The suspension of the dog in the position described allowed the weight of the kidney to elongate the renal pedicle and greatly facilitated the placement of the flow transducer, occluder, and the needle for recording renal arterial pressure.

Renin Measurements

Renin activity of plasma separated from systemic arterial and renal venous blood samples was measured by radioimmunoassay by the method of Haber et al. The accuracy and reproducibility of the method have been reported previously. The hematocrit was measured from at least two arterial samples and the secretion of renin calculated as the product of the venous-arterial renin difference and the renal plasma flow. Sample blood loss was replaced with 5% dextrose in water.

Hemodynamic Measurements

A catheter introduced into the femoral artery and positioned in the abdominal aorta was used to record systemic arterial pressure (Statham P23Db). Mean blood pressure was obtained by electronic damping of the pulsatile signal. Another catheter was placed in the descending aorta via the common carotid artery and used to obtain samples of arterial blood. Systemic and renal arterial pressure and renal blood flow were recorded continuously on an ultraviolet recorder (Honeywell Visicorder model 1508). On completion of the experiment, a pump-reservoir system was used to calibrate the flow transducer in situ by timed volume collections of the dog’s own blood.

Protocols

Following completion of the surgical procedures, the dog was left undisturbed for a period of 1 hour. Three types of experiments were performed. The major experiment examined the effect of a reduction in carotid sinus pressure to 40 mm Hg on the release of renin before and after vagotomy in dogs with aortic nerves sectioned and renal arterial pressure maintained constant with a mechanical occluder. Immediately before the vagus nerves were cut, the carotid sinus pressure was reduced to 40 mm Hg. After the vascular response had stabilized, the cervical vagus nerves were cooled to 0°C. Four to 5 minutes later, they were divided on the cardiac side of the cold block and the carotid sinus pressure was restored to the control level. This experiment was done to provide evidence that, during carotid sinus hypotension, cardiopulmonary receptors subtended by vagal afferents exerted an inhibitory influence on the vasomotor center. Prior cold block also prevented afferent discharge from the cut ends of the nerves.

Subsequent to vagotomy the effect of controlled and uncontrolled renal arterial pressure on the secretion of renin was studied at two different levels of carotid sinus hypotension. Also in vagotomized dogs the effect of carotid sinus hypotension on the release of renin was examined before and after renal denervation. In these experiments, renal arterial pressure was maintained constant.

Data Analysis

Grouped data are presented as means ± SEM. Statistical analysis was carried out by Student’s t-test for paired observations and by the χ² test. The level of significance was taken as 0.05. Measurements made before and 20 minutes after terminating the period of carotid sinus hypotension were compared with those made during the period of hypotension. The effect of vagotomy on resting levels of arterial blood pressure, renal blood flow, plasma renin activity, and release of renin was determined. Measurements of these variables made before and 20 minutes after terminating carotid sinus hypotension were averaged, and the values were considered as representative of basal conditions in the dog with intact vagus nerves. These data were compared with averages obtained similarly after vagotomy.

Results

Figure 1 shows individual data on the secretion of renin during control conditions, during the 4th minute of carotid sinus hypotension, and 20 minutes after returning carotid sinus pressure to the control value in 10 dogs with aortic nerves sectioned. In seven dogs, reducing the pressure in the carotid sinus to 40 mm Hg did not result in an increased secretion of renin with the vagi intact but did so after vagotomy. In two dogs (nos. 1 and 3), there was an increase in renin secretion during sinus hypotension both before and after vagotomy. In one dog (no. 6), sinus hypotension caused an increase in renin secretion before but not after vagotomy. Analysis of these data on renin release before and after vagotomy with the χ² test and a 2 × 2 contingency table showed 0.01 > P > 0.005.

The grouped data (mean ± se) are given in Figure 2. The mean increase in arterial blood pressure of 44 mm Hg during sinus hypotension before vagotomy was significantly less than that (70 mm Hg) recorded after vagotomy. Renal blood flow decreased significantly during carotid hypotension after vagotomy (mean decrease = 53 ml/min) but not before (mean decrease = 11 ml/min). Renal perfusion pressure was less well controlled before (13 mm Hg mean increase) than after vagotomy. This was due principally to the fact that, in dogs no. 1 and no. 10, reduction of carotid sinus pressure to 40 mm Hg with the vagi intact resulted in an immediate reduction in renal blood flow to more than 50% of control levels. For this
FIGURE 1 Secretion of renin in ng/min during control (C), the fourth minute of carotid sinus hypotension of 40 mm Hg (T), and 20 minutes after carotid sinus pressure had been restored to the control level (R) in 10 dogs with aortic nerves cut and renal arterial pressure held constant. ○ = data obtained before vagotomy; • = data obtained after vagotomy.

FIGURE 2 Grouped data (means ± SEM) on systemic arterial blood pressure (ABP), renal arterial pressure (RPP), renal blood flow (RBF) and secretion of renin (RR) during control (C), carotid sinus hypotension of 40 mm Hg (T), and recovery (R) in 10 dogs with aortic nerves cut and renal arterial pressure controlled by means of a mechanical occluder. Data obtained before vagotomy shown in upper panel, after vagotomy i lower panel. Asterisk indicates that test situation is significantly different from control and recovery.

reason, renal perfusion pressure was less rigorously controlled in these two animals. The mean difference in renin secretion during control conditions and during carotid sinus hypotension was not significant before vagotomy (562 ng/min) but was so after vagotomy (1374 ng/min). The magnitude of the difference in the levels of renin secretion during control and sinus hypotension with intact vagus nerves was due principally to dogs no. 3 and no. 6. If these values are not included in the analysis, the mean difference in renin secretion during control conditions and during sinus hypotension was 155 ng/min before vagotomy and 1610 ng/min after vagotomy.

In the group of 10 dogs with aortic nerves sectioned, reduction in carotid sinus pressure to 40 mm Hg caused a mean increase in arterial blood pressure of 50 ± 11 mm Hg and a mean decrease in renal blood flow of 17 ± 7 ml/min. Cold block of the vagus nerves at this sinus pressure resulted in a further mean increase in arterial blood pressure of 30 ± 10 mm Hg and a further mean decrease in renal blood flow of 42 ± 11 ml/min. Renal blood pressure was maintained throughout the experiment at the level recorded prior to carotid hypotension. Section of the vagus nerves during vagal cold block did not change arterial blood pressure or renal blood flow. After vagus nerve section, restoration of carotid sinus pressure to control levels was followed by a return of arterial blood pressure and a renal blood flow to levels similar to those recorded prior to vagotomy.

In the group of 10 dogs with aortic nerves sectioned, carotid sinuses vascularity isolated, and vagus nerve intact, the mean resting levels (average of pre- and postcarotid occlusion values) of arterial blood pressure and renal blood flow were 154 ± 5 mm Hg and 3.9 ± 0.2 ml/g per min, respectively. Forty minutes after vagotomy, corresponding values were 140 ± 7 mm Hg and 3.8 ± 0.2 ml/g per min. These changes in blood pressure and flow were not significant. There were, however, significant increases in the concentration of renin in arterial blood samples.
(10 ± 2 ng/ml per hr before and 24 ± 6 ng/ml per hr after vagotomy) and in the secretion of renin (653 ng/min before and 1279 ng/min after vagotomy).

The effect of controlling or not controlling renal arterial blood pressure on the release of renin during carotid sinus hypotension was examined in 4 of the 10 dogs after section of the vagus nerves. The grouped data are shown in Figure 3. When sinus pressure was reduced to 40 mm Hg (upper panel), maintaining renal arterial pressure constant resulted in a significant decrease in renal blood flow and a significant increase in renin release. This did not occur when renal arterial pressure increased equally with systemic arterial pressure. Similar data were obtained when sinus pressure was reduced to a lesser degree (mean decrease = 22 ± 5 mm Hg). As shown in the lower panel, the increase in the secretion of renin was significant only when renal arterial pressure was maintained constant.

The effect of renal denervation on the release of renin during the carotid sinus hypotension was studied in four other dogs from the group. The vagus nerves had been sectioned and renal arterial pressure was maintained constant. The right kidney was denervated by section of the right splanchnic nerve and stripping the renal artery from its origin at the aorta to its termination at the renal pelvis. Absence of a change in renal blood flow during reduction in carotid sinus pressure to 40 mm Hg was accepted as proof of denervation. With the renal nerves intact, peak decreases in blood flow were obtained 30-40 seconds after reducing carotid sinus pressure and were −70, −36, −26, and −16 ml/min, respectively. The maximal reduction in renal flow was not sustained. Comparable values during carotid sinus hypotension after denervation were +20, −3, +1, and −6 ml/min, respectively. In each dog, renal denervation abolished the increase in the secretion of renin previously observed on reducing the carotid sinus pressure to 40 mm Hg (Fig. 4). Mean arterial blood

**Figure 3** Mean data (± SEM) on systemic arterial pressure (ABP), renal arterial pressure (RPP), renal blood flow (RBF), and renin secretion (RR) in four dogs with aortic and vagal nerves sectioned and with renal pressure controlled (C) and not controlled (NC). Data in upper right panel obtained in control period (C) and during 4th minute of reduction in carotid sinus pressure from a mean value of 150 ± 2 mm Hg to 40 mm Hg (C). Data in bottom panel obtained in control (C) and during the 4th minute following reduction in carotid sinus pressure by 22 ± 5 mm Hg from a control level of 154 ± 3 mm Hg (C). Significant difference indicated by an asterisk.

**Figure 4** Individual data on renin secretion and renal blood flow, and mean data (± SEM) on systemic arterial pressure in four dogs with aortic and vagal nerves sectioned. Data obtained in control (unfilled symbols) and during 4th minute of reduction in carotid sinus pressure to 40 mm Hg (filled symbols) with renal nerves intact (left panel) and after renal denervation (center panel). Data shown in right panel obtained during mechanical reduction in renal arterial pressure and renal blood flow in vagotomized dogs with denervated kidneys. Each dog is indicated by a separate symbol.
pressure increased from 119 ± 10 mm Hg to 165 ± 7 mm Hg during carotid sinus hypotension with the renal nerves intact, and from 117 ± 11 mm Hg to 188 ± 20 mm Hg after nerve section. Mean renal blood flow decreased from 121 ± 20 ml/min to 97 ± 15 ml/min during carotid sinus hypotension with the renal nerves intact and was not changed by this procedure after nerve section (118 ± 12 ml/min before and 122 ± 20 ml/min after denervation). The ability of the denervated kidney to release renin was tested in these dogs by mechanically reducing renal arterial pressure. Carotid sinus pressure was maintained constant (mean sinus pressure = 140 ± 10 mm Hg). Mean renal arterial pressure decreased from 116 ± 1 to 62 ± 1 mm Hg and renal blood flow from 137 ± 25 to 109 ± 10 ml/min. Renal arterial hypotension was accompanied by an increase in the secretion of renin in each dog.

Discussion

The present findings expand previous observations on the interaction of carotid and cardiopulmonary mechanoreceptors in the neural control of renin secretion and show that vagally innervated cardiopulmonary receptors can inhibit the increased secretion of renin due to withdrawal of carotid baroreceptor inhibition. Thus, while both reflex systems are capable of changing efferent renal sympathetic nerve activity and, thereby, the secretion of renin, in certain circumstances withdrawal of the inhibitory influence of one system may augment that of the other, so that the secretion of renin is unaffected.

There is considerable evidence that vagally innervated cardiopulmonary receptors tonically inhibit the vasomotor neurons that control efferent sympathetic nerve traffic, particularly when carotid baroreceptor inhibition is reduced or withdrawn. There are, in addition, data to suggest that vagally innervated cardiopulmonary receptors are preferentially oriented toward renal vasomotor neurons. The findings of this study are in agreement with these earlier observations. Vagal cold block at a carotid sinus pressure of 40 mm Hg caused a mean increase of 30 mm Hg in systemic arterial pressure and a mean decrease of 42 ml/min in renal blood flow. Before vagotomy, carotid sinus hypotension increased arterial blood pressure by 44 mm Hg; the increase after vagotomy was 70 mm Hg. With the vagus nerves intact, carotid sinus hypotension was accompanied by a nonsignificant decrease in renal blood flow of 11 ml/min. After vagotomy, the decrease was 53 ml/min.

However, the circumstances of the present experiment may have augmented the inhibitory influence of the cardiopulmonary receptors. In a previous study, Öberg and Thorén showed that carotid sinus hypotension increased the frequency of discharge of vagally innervated cardiac receptors that exerted a tonic inhibitory influence on the vasomotor neurons controlling the efferent sympathetic discharge to muscle and renal resistance vessels. In the present study, vagal cold block with carotid sinus pressure reduced to 40 mm Hg resulted in a mean increase in arterial blood pressure of 30 ± 10 mm Hg. This is significantly greater than the mean increase of 9 ± 2 mm Hg (n = 20) previously observed during vagal cold block with the carotid sinuses free to exert their buffering influence. The possibility thus exists that an increase in the secretion of renin could result from withdrawal of carotid sinus inhibition if this caused no change or only a modest increase in the activity of the vagally innervated cardiopulmonary receptors. In the present study there was an increased secretion of renin in three dogs during carotid sinus hypotension with the vagus nerves intact. The increases of 8 and 10 mm Hg in arterial blood pressure during vagal cold block with the carotid sinuses maintained at 40 mm Hg in two of these dogs were the lowest for the group of 10 dogs. This would suggest that in these two dogs there was less activation of cardiopulmonary receptors during carotid sinus hypotension than in the other dogs of the group.

The study on the control of renal arterial pressure revealed a further constraint on the release of renin during carotid hypotension. When renal arterial pressure was allowed to rise equally with systemic arterial pressure, either there was no increase in the secretion of renin or it was markedly reduced from that observed with renal arterial pressure held constant. This is in accord with the earlier findings by McPhee and Lakey that control of renal perfusion pressure resulted in greater renin secretion during carotid occlusion than when renal arterial pressure was uncontrolled.

It could be argued that the less effective control of renal arterial pressure in the studies before vagotomy compared to those conducted after vagotomy was the reason that carotid sinus hypotension did not result in an increase in the secretion of renin with the vagus nerves intact. However, in the three dogs that did release renin during carotid sinus hypotension with vagus nerves intact, there were increases in renal arterial pressure of 10, 18, and 20 mm Hg. Six of the seven dogs that did not demonstrate an increase in renin secretion during carotid sinus hypotension with intact vagus nerves had increases in renal arterial pressure of less than 15 mm Hg. Also, in the study by Mancia et al., vagal cold block resulted in an increase in the secretion of renin accompanied by a mean increase of 18 mm Hg in renal arterial pressure.

The interaction between carotid and cardiopulmonary receptors in the neural control of renin release also is demonstrated by the change in the basal rate of renin secretion following vagotomy. In this study in dogs with the carotid sinus vasculature isolated and thus prevented from exerting a buffering influence, there was a significant increase in basal values of plasma renin activity following vagal nerve section (10 ± 2 ng/ml per hr before; 24 ± 6 ng/ml per hr 40 min after vagotomy). This is in contrast to the previous observation that vagal nerve section did not result in a significant increase in plasma renin activity in dogs with undisturbed carotid sinuses (16.6 ± 4.7 ng/ml per hr before; 20.7 ± 11.6 ng/ml per hr after). The above findings can explain the previous divergent observations on the effects of carotid sinus hypotension on the secretion of renin. In two of the three studies in which renin secretion was not influenced by the carotid baroreflex, the vagi were intact and renal perfusion either was not controlled or not controlled in every experiment. In the third study, the dogs were vagotomized but renal arterial pressure was not controlled. In two of the
three studies in which carotid sinus hypotension resulted in an increase in renin secretion, the dogs were vagotomized and renal arterial pressure was maintained constant.12, 13

Failure of carotid sinus hypotension to increase renin secretion after renal denervation in vagotomized dogs with renal arterial pressure maintained constant demonstrated that the efferent limb of the reflex was the renal sympathetic nerves. However, in vagotomized dogs with renal arterial pressure maintained constant, carotid sinus hypotension invariably resulted in a reduction in renal blood flow, often of considerable magnitude (mean reduction 30%, maximum 74%). Thus, although the carotid baroreceptors participate in the neural control of renin secretion, the intrarenal mechanism for renin release is still to be determined; the same is true for the reflex control of renin release mediated by vagally innervated cardiopulmonary receptors.

In summary, reduction in carotid sinus pressure can result in an increased secretion of renin; this indicates that the carotid baroreflex participates in the neural control of renin release. However, a concomitant activation of cardiopulmonary receptors and/or a substantial increase in renal arterial pressure may partially or totally inhibit the reflex release of renin.

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