Stimulus-Response Curve of the Renal Baroreceptor: Effect of Converting Enzyme Inhibition and Changes in Salt Intake

Eli R. Farhi, James R. Cant, William C. Paganelli, Victor J. Dzau, and A. Clifford Barger

We investigated the effect of converting enzyme inhibition (CEI) on the relationship between renal perfusion pressure (RPP) and steady-state plasma renin activity (PRA) in uninephrectomized conscious dogs on normal-salt (80 meq Na\(^+/\)day) and low-salt (10 meq Na\(^+/\)day) diets. Stimulus-response curves for the renal baroreceptor were determined by measuring the steady-state PRA while the RPP was lowered and then held constant by an inflatable cuff placed around the renal artery. On each diet the control stimulus-response curve can be described by two lines intersecting at a threshold pressure; in the higher pressure range PRA is relatively insensitive to changes in RPP, while in the lower pressure range PRA is very responsive to changes in RPP. On the normal-salt diet CEI significantly increases the sensitivity of PRA to RPP in the responsive range without affecting the threshold pressure itself or the values of PRA at pressures greater than the threshold pressure. On the low-salt diet CEI also increases the sensitivity of PRA to RPP significantly in the responsive range; we were unable to determine the effect of CEI on PRA at RPPs greater than the threshold pressure in the low-salt state because CEI causes a significant drop in blood pressure under these circumstances. The effect of CEI was significantly greater in the dogs on the low-salt diet than in the dogs on the normal-salt diet. Thus, CEI and salt depletion interact synergistically to increase the sensitivity of the renal baroreceptor only in the responsive range of the stimulus-response curve, i.e., at renal perfusion pressures below the threshold pressure. (Circulation Research 1987;61:670-677)
describes not only the effects of each individual stimulus on renin secretion but also the interactions between various stimuli such as renal perfusion pressure, salt intake, and circulating catecholamines. In this paper, we report on the results of similar experiments designed to examine the mechanisms of the inhibitory effects of angiotensin II on PRA and to include these negative feedback loops into an integrated model of the control of plasma renin activity in the conscious animal.

Materials and Methods

Seven male mongrel dogs (25–35 kg) were trained to lie quietly on a padded table in an experiment room for 2 to 3 hours. Then, during a sterile procedure under intravenous pentobarbital anesthesia, catheters were implanted in the aorta, inferior vena cava (caudal to the kidney), and one renal artery, using the technique of Herd and Barger, and an inflatable silastic cuff (Hazen Everett, Mahwah, N.J.) was placed around the renal artery proximal to the tip of the renal arterial catheter. The contralateral kidney was removed. The animals were given at least 10 days to recover from surgery before any experiments were performed. The catheters were flushed daily with isotonic dextrose and then filled with heparin.

The dogs were housed in individual cages and were fed either a normal-salt diet (approximately 80 meq Na+/day) or a low-salt diet (approximately 10 meq Na+/day) with the same potassium content. Urinary collections were analyzed daily to determine the total urinary sodium excretion, which ranged between 70 and 90 meq Na+/day on the normal-salt diet and between 2 and 10 meq Na+/day on the low-salt diet. In addition, dogs beginning the low-salt diet were given furosemide (40 mg orally twice a day for three days). The dogs were allowed 10 days to equilibrate, as documented by urinary sodium excretion, after a change in salt intake prior to any experiments.

The renal baroreceptor stimulus–response curves were determined as described in previous papers. Briefly, the dog was brought into an experiment room where it would lie quietly as the aortic and renal arterial catheters were connected to Statham P23Dc pressure transducers. After a 20-minute control period, two blood samples were drawn at 5-minute intervals for later determination of PRA. The constrictor cuff around the renal artery was then inflated to decrease the renal perfusion pressure by a predetermined amount (15, 20, or 25 mm Hg); this pressure was then kept constant for 30 minutes by continuous adjustment of the cuff as needed. At the end of this time, when mean arterial pressure had stabilized, two blood samples were drawn 5 minutes apart for later analysis of PRA. Then, if the dog was still relaxed, the cuff was inflated further to decrease the renal perfusion pressure by another 15 mm Hg, and the procedure was repeated. The renal perfusion pressure was decreased in this manner in sequential steps until the dog became restless or the next constriction would have resulted in a perfusion pressure of less than 40 mm Hg.

To determine the effect of angiotensin converting enzyme inhibition on the stimulus–response curve of the renal baroreceptor, the procedure described above was modified after the control period by giving a 15 mg intravenous bolus of the converting enzyme inhibitor teprotide (SQ 20881), followed by an infusion at 5.4 mg/hr. After another 25-minute control period, the renal perfusion pressure was decreased as described above. The efficacy of the converting enzyme inhibition was tested by determining the pressor response to an intravenous bolus of 1 µg angiotensin I immediately prior to the bolus of converting enzyme inhibitor and at the end of the experiment. In all experiments, the angiotensin I bolus caused the mean aortic pressure to rise transiently by at least 20 mm Hg prior to converting enzyme blockade but did not change mean aortic pressure during CEI infusion.

The blood samples for the PRA assay were drawn into 5-ml EDTA vacutainer tubes. The tubes were kept on ice for less than 10 minutes until they could be spun in a refrigerated centrifuge to remove cells and platelets. Plasma samples were decanted and then frozen until the assays were performed. At the end of an experiment, the red blood cells were suspended in isotonic dextrose and returned to the animal. PRA was measured by the method of Haber et al: the results are expressed as nanograms of angiotensin I generated per milliliter of plasma per hour at pH 7.4.

Four dogs were examined on the normal-salt diet and 5 on the low-salt diet. Of these, 2 were studied on both diets. On each diet, 3 or 4 experiments, each consisting of 3 to 5 successive reductions in the renal perfusion pressure, were performed in every animal over a two-week period, with and without converting enzyme inhibition. From a series of such experiments, we obtained steady-state values of PRA in each dog at each renal perfusion pressure in the presence and the absence of angiotensin II. By averaging all values of PRA obtained within a 5 mm Hg range of RPP and then plotting this average PRA against the renal perfusion pressure we obtained stimulus–response curves for the renal baroreceptor of that dog with and without converting enzyme blockade. As we have previously described, the stimulus–response curves consist of two ranges of renal perfusion pressures separated by a threshold pressure (Figure 1). In the lower range, below the threshold pressure, PRA increases steeply in response to decrements in RPP, while above the threshold pressure PRA is relatively independent of RPP. For purposes of analysis, a straight line was fitted to the data within each range of RPP, and the intersection of the two lines was defined as the threshold pressure. Converting enzyme inhibition did not affect blood pressure during the control period in the dogs on the normal-salt diet but did cause the control arterial pressure to fall to or below the threshold pressure when the dogs were on a low-salt diet; in these cases the data were fit to a single line.

As in our previous papers, the form of the stimulus–response curves was similar in all the dogs in each condition, although the absolute values of PRA and of...
Na⁺lday) in the control state (A, ) and during converting enzyme inhibition (A, —). Plasma renin activity is expressed as ng AI/ml plasma/hour. Each point represents the average of all steady-state values of plasma renin activity within a 5 mm Hg range of renal artery pressure. In each condition, two straight lines were fit to the data by standard regression techniques.

The results of all dogs on the normal-salt diet are summarized in Table 1. In all of the dogs, the slope of the stimulus-response curve at RPPs above the threshold pressure was increased during converting enzyme blockade; this effect was statistically significant \((p<0.05)\) in 3 of the 4 dogs and for the group as a whole. Infusion of converting enzyme inhibitor did not change the threshold pressure significantly in the dogs on a normal-salt diet, nor did it affect the values of PRA at RPPs above the threshold pressure.

CEI decreased blood pressure to below the threshold pressure in the dogs on the low-salt diet so that no PRA was obtained by averaging all the normalized PRA values of each dog (i.e., one value per dog) within each 5 mm Hg interval of renal perfusion pressure as shown in Figure 2.

Comparisons between slopes and intercepts of these lines in the same dog for the different protocols were performed using the analysis of covariance technique for comparison of regression lines described by Sne-decor and Cochran. \(^{10}\) When the normalized curves were compared, the number of degrees of freedom was decreased by one. Direct comparisons of PRA values obtained with and without converting enzyme inhibition at renal perfusion pressures above the threshold pressure were performed using analysis of variance and paired \(t\) tests.

### Results

Using the techniques described above, we generated four sets of stimulus-response curves with and without CEI for dogs on the normal-salt diet (28 experiments) and five sets for dogs on the low-salt diet (33 experiments). Stimulus-response curves of a representative dog on a normal-salt diet with and without CEI are shown in Figure 1, while composite curves, summarizing the results of all the dogs on the normal-salt diet with and without CEI are shown in Figure 2. The results of all dogs on the normal-salt diet are summarized in Table 1. In all of the dogs, the slope of the stimulus-response curve at RPPs below the threshold pressure was increased during converting enzyme blockade; this effect was statistically significant \((p<0.05)\) in 3 of the 4 dogs and for the group as a whole. Infusion of converting enzyme inhibitor did not change the threshold pressure significantly in the dogs on a normal-salt diet, nor did it affect the values of PRA at RPPs above the threshold pressure.

CEI decreased blood pressure to below the threshold pressure in the dogs on the low-salt diet so that no PRA

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### Table 1. Analysis of Stimulus-Response Curves in Individual Dogs on Normal Salt Diet

<table>
<thead>
<tr>
<th>Dog</th>
<th>Control RA constriction</th>
<th>RA constriction during converting enzyme inhibition</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Slope of stimulus-response curve below TP (ng AI/ml/mm Hg), Normalized slope of stimulus-response curve below TP, Average PRA above TP (ng AI/ml/hr)</td>
<td>Slope of stimulus-response curve below TP (ng AI/ml/mm Hg), Normalized slope of stimulus-response curve below TP, Average PRA above TP (ng AI/ml/hr)</td>
</tr>
<tr>
<td>BO</td>
<td>78 (-0.12, -2.6, 0.2)</td>
<td>93 (-0.13, -2.8, 0.3)</td>
</tr>
<tr>
<td>E</td>
<td>90 (-0.08, -1.7, 0.3)</td>
<td>86 (-0.16*, -3.5*, 0.1)</td>
</tr>
<tr>
<td>H</td>
<td>72 (-0.36, -2.9, 0.5)</td>
<td>82 (-0.53*, -4.3*, 0.4)</td>
</tr>
<tr>
<td>X</td>
<td>85 (-0.13, -2.1, 0.2)</td>
<td>84 (-0.19*, -3.1*, 0.2)</td>
</tr>
<tr>
<td></td>
<td>81 (-0.17, -2.1, 0.3)</td>
<td>86 (-0.25, -3.2*, 0.3)</td>
</tr>
</tbody>
</table>

Threshold pressures (TP), slopes of regression lines fit to stimulus-response curves below threshold pressure, and average plasma renin activity (PRA) above threshold pressure during renal artery (RA) constriction in dogs on a normal-salt diet under control conditions and converting enzyme inhibition. Slopes were normalized by expressing each PRA value as a percent of the maximum PRA of the control stimulus-response curve.

\(^*p<0.05\) compared to control.
values could be obtained at renal perfusion pressures equal to or greater than the threshold pressure. As a result, the stimulus-response curves obtained during tetrodote infusion could be modeled with one line rather than two lines intersecting at a threshold pressure. The stimulus-response curve of a typical dog on the low-salt diet is shown in Figure 3, and the composite curves are shown in Figure 4. The results of the individual dogs and the combined curves are summarized in Table 2. At RPPs below threshold pressure, the slopes of the stimulus-response curves increased in each dog; this change was statistically significant (p<0.05) in 4 of the 5 dogs and for the group as a whole.

The normalized control curves for the dogs on the low-salt and normal-salt diets are shown in Figure 5. As in our previous paper,13 the two curves are indistinguishable when expressed as a percentage change in PRA. The effect of converting enzyme inhibition, however, is different in dogs on the two salt diets. Figure 6 shows that during converting enzyme inhibition, the normalized values of PRA at renal perfusion pressures below the threshold pressure are greater in the

<table>
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<tr>
<th>Dog</th>
<th>Control RA</th>
<th>RA conduction during converting enzyme inhibition</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TP (mm Hg)</td>
<td>Slope of stimulus response curve below TP (ng Al/ml/mm Hg)</td>
</tr>
<tr>
<td>BO</td>
<td>80</td>
<td>-0.35</td>
</tr>
<tr>
<td>BR</td>
<td>85</td>
<td>-0.72</td>
</tr>
<tr>
<td>S</td>
<td>77</td>
<td>-0.63</td>
</tr>
<tr>
<td>X</td>
<td>81</td>
<td>-0.25</td>
</tr>
<tr>
<td>Z</td>
<td>85</td>
<td>0.17</td>
</tr>
<tr>
<td>Mean</td>
<td>82</td>
<td>-0.42</td>
</tr>
</tbody>
</table>

Threshold pressures (TP), slopes of regression lines fit to stimulus-response curves below threshold pressure, and average plasma renin activity (PRA) above threshold pressure during renal artery (RA) constriction in dogs on a low-salt diet under control conditions and converting enzyme inhibition. Slopes were normalized by expressing each PRA value as a percent of the maximum PRA of the control stimulus-response curve.

*p<0.05 compared to control.
Figure 4. Stimulus-response curves of the renal baroreceptor: average results from 5 dogs on a low-salt diet (33 experiments). Individual values of plasma renin activity are expressed as a percent of the maximum value of the stimulus-response curve (normalized plasma renin activity), as described in the text. Points at each renal artery pressure represent the mean of 5 dogs at that pressure in the control state (○, ——) and during converting enzyme inhibition (○, •••). Dogs on the low-salt diet (p<0.05). As the figure demonstrates, this effect appears to be due to an increase in the slope of the stimulus-response curve at RPPs below the threshold pressure; during CEI infusion, the slope was steeper in the dogs on the low-salt diet, although the difference in slopes did not reach statistical significance (p = 0.07).

Figure 5. Stimulus-response curves of the renal baroreceptor under control conditions; average results from 4 dogs on the normal-salt diet (▲) and 5 dogs on the low-salt diet (○). Individual values of plasma renin activity are expressed as a percent of the maximum value of the stimulus-response curve (normalized plasma renin activity), as described in the text.

Discussion

We determined nine sets of stimulus-response curves with these experiments, showing the effect of converting enzyme inhibition in dogs on normal-salt and low-salt diets. On both diets, the shape of the control curves was similar to those seen in our previous experiments, consisting of two ranges of pressures. PRA is relatively unresponsive to changes in renal perfusion pressure at higher pressures, while below a certain threshold pressure small changes in RPP cause large changes in systemic PRA. Although the form of the stimulus-response curve was the same in each dog, the absolute values (the slope of the curves above and below the threshold pressure and the threshold pressure) varied from dog to dog as shown in Tables 1 and 2. Because of this, we normalized the stimulus-response curves, expressing them as a percent change rather than as absolute values. This decreased the interanimal variability and also allowed us to compare the groups of dogs on the different salt diets.

Figures 1 and 2 show that in the dogs on the normal-salt diet, converting enzyme inhibition increased the slope of the stimulus-response curve at RPPs below the threshold pressure without changing the threshold pressure itself or the stimulus-response curve at RPPs above the threshold pressure. This is consistent with earlier data from our laboratory, which demonstrated that CEI does not affect blood pressure in recumbent man or in dogs on a normal-salt diet at control blood pressure, while at a decreased RPP converting enzyme inhibition causes a significant increase in PRA in the dog.

As Figures 3 and 4 demonstrate, converting enzyme inhibition increases the slope of the stimulus-response
curve at RPPs below threshold pressure in dogs on the low-salt diet; this effect is qualitatively similar to that seen in dogs on the normal-salt diet. Because of the hypotensive effect of CEI in low-salt dogs, we were unable to obtain values of PRA at renal perfusion pressures close to the control blood pressure. Thus, we could not determine the nature of the stimulus-response curve at RPPs above threshold pressure, or even the threshold pressure itself, in low-salt dogs during CEI infusion. From inspection of Figure 4, it would appear that the threshold pressure itself is unchanged by converting enzyme inhibition in the dogs on the low-salt diet, although we were not able to confirm this statistically given the nature of our experiments.

Previous work done in our laboratory may be helpful in determining the nature of the stimulus-response curve at RPPs above threshold pressure in dogs on a low-salt diet after converting enzyme inhibition. Sanchez et al.11 found that converting enzyme inhibition caused an increase in PRA in normal subjects on a low-salt diet without causing a significant decrease in blood pressure. Samuels et al.12 reported that in conscious, sodium-depleted dogs, CEI caused a significant increase in PRA associated with a drop in blood pressure. After CEI, infusions of phenylephrine sufficient to return blood pressure back to control levels did not prevent the rise in plasma renin activity seen in the salt-depleted dogs. These data indicate that, in some salt-depleted animals, CEI increases PRA at RPPs close to the control blood pressure. One must, however, be very careful in extrapolating these results to our stimulus-response curves for at least two reasons. First, the experimental models were considerably different from ours. Sanchez et al.11 reported that there was a transient period of hypotension after converting enzyme inhibition in their experiments; this may have been a sufficient stimulus for an increase in renin release. In the experiments of Samuels et al., the dogs were adrenalectomized and were very salt-depleted, so that the control mean arterial pressure was approximately 70 mm Hg; this value would be below the threshold pressure in our dogs. Second, the interpretation of the results of Samuels et al. depends on the assumption that α-adrenergic agents do not themselves stimulate renin secretion; this is currently a subject of some controversy.19

Previous experiments from our laboratory14 have demonstrated that changes in salt intake affect the scale of the renal baroreceptor, multiplying the PRA at any renal perfusion pressure by a constant factor. In that study, the scaling factor (the ratio of the low-salt PRA to the normal-salt PRA at any renal perfusion pressure) was 3.0; the scaling factor for the present study is 2.8. This scaling factor is independent of the renal perfusion pressure, so that while the absolute values of PRA at any renal perfusion pressure are greater on a low-salt diet than on a normal-salt diet, the percentage change in PRA produced by any change in RPP is the same in both salt states. This is demonstrated in Figure 5, which shows that the control stimulus-response curves, expressed as a percentage change in PRA, are the same in dogs on the normal-salt and the low-salt diets.

The effect of converting enzyme inhibition, however, is different in dogs on the two salt diets. Figure 6 shows that, after CEI, the normalized PRA values at renal perfusion pressures below the threshold pressure are greater in the dogs on the low-salt diet than in the dogs on the normal-salt diet. This effect may be related to the fact that the aortic pressure fell considerably when converting enzyme inhibitor was given to the dogs on the low-salt diet, but did not change when given to the dogs on the normal-salt diet. Previous work in our laboratory has demonstrated that decreasing the pressure sensed by the carotid baroreceptors during renal hypotension increases PRA.20 Thus, the fall in blood pressure seen after CEI in the dogs on the low-salt (but not the normal-salt) diet would be sensed by the systemic baroreceptors, which could stimulate renin release when the renal perfusion pressure is decreased.

From inspection of Figure 6, this increase in PRA seen in the dogs on the low-salt diet when compared to those on the normal-salt diet appears to be due to a steeper slope of the stimulus-response curve at renal perfusion pressures below the threshold pressure. The difference in slopes, however, did not achieve statistical significance (p = 0.07). The lack of statistical significance could be due to two reasons. One is that the slopes are, in fact, different but that we were unable to confirm this statistically because of the small number of animals, the relatively large interanimal variability, and our inability, because of the nature of our experiments, to determine the threshold pressure in the low-salt animals during converting enzyme inhibition. The other explanation is that the slopes are actually not significantly different and that the values of PRA are increased by a different mechanism, such as a shift of the stimulus-response curve to the right. This last possibility would be consistent with the hypothesis raised earlier involving an interaction of carotid and renal baroreceptors during CEI infusion in low-salt animals; the effect of systemic baroreceptors on PRA is likely to involve the sympathetic nervous system, which is associated with a rightward shift of the stimulus-response curve.11

These results have a number of physiologic and pathophysiologic consequences. First, they raise methodologic questions about studies in which renin secretion rates are measured prior to the attainment of a steady state; our data indicate that changes in renin secretion rates in response to an acute stimulus might well be time dependent, decreasing as circulating levels of renin and angiotensin II increase (particularly in response to a hemodynamic stimulus such as decreased renal perfusion pressure). The data also have some physiologic implications: for example, the fact that the stimulus-response curves are increased when the renal perfusion pressure is decreased suggests that angiotensin II may inhibit renin release by the renal baroreceptor (i.e., renin released in response to a lowered renal perfusion pressure) to a greater degree than it inhibits renin release by other mechanisms (such as salt depletion at control renal perfusion pressures).
Most importantly, these results provide a framework that can be used to analyze the effects of blockade of the renin-angiotensin system in terms of PRA, salt and volume status, and renal perfusion pressure. This model has many potential applications; one example would be in understanding the effects of various interventions on the renal vein renin ratio, a clinical tool commonly used in the evaluation of renal artery stenosis. First proposed by Judson and Helmer, the renal vein renin ratio is the ratio of the PRA in the renal vein of the kidney with the stenosed renal artery (S) to that in the renal vein of the normal kidney (N); higher ratios often indicate significant renal artery stenosis. This is demonstrated in Figure 7 where, assuming an arbitrary gradient of approximately 40 mm Hg across the renal artery of the stenosed kidney, the renal vein renin ratio would be S/N; a tighter stenosis would further reduce the RPP, moving to the left along the control (solid) stimulus response curve to point S', and raising the renal vein renin ratio to S'/N. Because this test as originally proposed had a relatively high number of false-positive results, a number of investigators attempted to increase the sensitivity of the technique by salt depletion or administration of diuretics, but this intervention did not increase the sensitivity of the renal vein renin ratio when evaluated closely. The reason for this is again shown in Figures 5 and 7; changes in salt and volume status alone do not affect the normalized stimulus-response curve, so that the renal vein renin ratio would remain at S/N. Other investigators attempted to increase the sensitivity of the technique by decreasing blood pressure, using upright tilt or vasodilators such as hydralazine or nitroprusside. This intervention had somewhat better results, consistent with our model. Vasodilators or upright tilt decrease renal perfusion pressure; this is shown in Figure 7 by a shift along the control (solid) stimulus-response curve, from N to N1 for the normal kidney and from S to S1 for the stenosed kidney. Both kidneys will therefore increase renin secretion, but the decrease in pressure will only affect the normal kidney once the renal perfusion pressure is below the threshold pressure; thus, assuming the same gradient, there is a slight but definite increase in the renal vein renin ratio (S/N under control conditions compared to S'/N after vasodilators or upright tilt).

Most recently, a number of investigators have attempted to increase the sensitivity of the renal vein renin ratio by using specific antagonists of the renin-angiotensin system such as converting enzyme inhibitors or saralasin, often with concomitant salt depletion. Blockade of the renin-angiotensin system has consistently increased the sensitivity of the renal vein renin ratio; the mechanism for this is demonstrated again in Figure 7. In the normal-salt state, CEI increases the slope of the stimulus-response curve only at renal perfusion pressures below the threshold pressure, as shown by the change in the stimulus-response curve from the solid to the dashed line. Thus, CEI will increase renin secretion from the stenosed kidney (S to S1), but not the normal kidney, causing a larger change in the renal vein renin ratio (from S/N in the control state to S'/N after CEI). In the low-salt state, the effect of CEI is even more pronounced because of two factors. First, the slope of the stimulus-response curve is increased even further (as shown by the dotted line). In addition, CEI causes a drop in blood pressure in the low-salt state but not the normal-salt state. This is associated with a small increase in renin secretion from the normal kidney (N to N1) and a dramatic increase in renin secretion from the stenosed kidney (S to S1), causing a marked increase in the renal vein renin ratio (from S/N after salt depletion). Thus, the change in the slope of the stimulus-response curve at subthreshold pressures, combined with the decrease in renal perfusion pressure, may be the mechanism behind the clinical observation that converting enzyme inhibition will preferentially increase renin secretion from the affected kidney in cases of unilateral renal artery stenosis, and that salt depletion, whether caused by a low-salt diet, diuretics, or both, accentuates this effect.

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