Influence of Endogenous Angiotensin on the Renovascular Response to Norepinephrine

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The purpose of this study was to elucidate the role of endogenous angiotensin II in mediating the renovascular effects of renal adrenergic stimulation. Six conscious dogs instrumented for monitoring of renal blood flow were subjected to step increases every 10 minutes in the rate of norepinephrine infusion into the renal artery. Under control conditions, infusion of norepinephrine (10–40 ng/min per milliliter per minute of control renal blood flow) increased plasma renin activity and decreased renal blood flow progressively by −10–75%. When increments in angiotensin II during norepinephrine infusion were abolished by fixing plasma levels of angiotensin II at either normal or high concentrations by chronic infusion of captopril plus angiotensin II, renal blood flow responses to adrenergic stimulation were greatly attenuated at rates of norepinephrine infusion that decreased renal blood flow up to −40% under control conditions. Thus, acutely generated angiotensin II appeared to contribute to the renovascular effects of norepinephrine. However, when endogenous levels of angiotensin II were suppressed to low levels by chronic infusion of captopril alone, norepinephrine induced severe renal ischemia at much lower rates of infusion than occurred when the renin-angiotensin system was intact. Since this enhanced sensitivity to norepinephrine did not occur during chronic captopril infusion when angiotensin II was given simultaneously at rates that restored mean arterial pressure to normotensive levels or higher, low arterial pressure during chronic captopril administration may predispose the kidneys to excessive renal vasocostriction during renal adrenergic stimulation.

KEY WORDS • norepinephrine • angiotensin II • renal circulation • angiotensin converting enzyme inhibitors

There is considerable evidence that the sympathetic nervous system is involved in the acute control of renal function and renin release.

Because both norepinephrine (NE) released from adrenergic nerve terminals and angiotensin II (Ang II) generated in response to renal nerve stimulation have potent direct effects on renal hemodynamics and sodium excretion, blockers of the renin-angiotensin system have been given in a number of studies to determine the contribution of increased Ang II generation to the renal hemodynamic and antinatriuretic effects of renal adrenergic stimulation. The most consistent finding from these studies has been that Ang II, presumably by preferentially constricting the efferent arterioles, plays a significant role in the maintenance of glomerular filtration rate during reductions in renal blood flow (RBF) produced by neural stimulation. The role of generated Ang II in mediating the RBF and sodium excretory responses produced by renal adrenergic stimulation, however, has been more controversial. In some studies, the contribution of Ang II to these renal functional effects of neural stimulation has been substantial, whereas in others it has been nonsignificant.

In contrast to the acute studies mentioned above, we observed in recent experiments that the renovascular responses to long-term intrarenal infusions of NE lasting hours to days were enhanced during chronic administration of the converting enzyme inhibitor captopril. That is, when endogenous Ang II was chronically suppressed to very low levels, there were greater reductions in renal plasma flow in response to NE, not smaller responses as some previous acute studies have shown. There are several potential explanations for this discrepancy: 1) the contribution of Ang II to the renovascular effects of NE may be both dose and time dependent, 2) the renin secretory and renovascular responses to adrenergic stimulation in anesthetized, surgically stressed animals may be quite different than in conscious, resting animals with low basal rates of renin secretion and sympathetic activation, and 3) the renal responses to NE during chronic blockade of the renin-angiotensin system may be influenced by changes in renal hemodynamics, sodium balance, and arterial pressure that would be relatively insignificant in acute studies.

Because converting enzyme inhibitors are so widely used in the treatment of chronic diseases such as hypertension and congestive heart failure and because most of our understanding of neural interactions with the renin-angiotensin system in the control of renal function is based on the results from acute studies in...
anesthetized animals, additional long-term studies of the interactions between the sympathetic and renin-angiotensin systems are warranted. The main objective of the present study was to determine whether chronic captopril administration predisposes the kidneys to excessive renal vasoconstriction during acute episodes of renal adrenergic stimulation and, if so, to determine whether this increased renal sensitivity to NE can be abolished by preventing the chronic natriuretic and hypotensive effects of captopril by long-term infusion of Ang II. By chronically fixing plasma Ang II concentration in this manner, we were able to determine whether inappropriate plasma levels of Ang II and the attendant changes in body fluid volumes, arterial pressure, and renal hemodynamics influence the renovascular response to acute adrenergic stimulation.

Methods

Six male dogs weighing 20±1 kg were used in this experiment, and all procedures were in accordance with institutional guidelines. The dogs were sedated with acepromazine (3 mg/kg) and then anesthetized with pentobarbital sodium (30 mg/kg i.v.). A right nephrectomy was performed, and chronic indwelling catheters made of Tygon microbore tubing (0.05 in. i.d., 0.09 in. o.d.), Norton Plastics, Akron, Ohio) were implanted both in femoral arteries and in veins. The tips of the femoral arterial and venous catheters were advanced into the lower abdominal aorta and vena cava, respectively. An externally inflatable Silastic occluder was placed around the aorta immediately cephalad to the origin of the renal arteries, and a Tygon catheter (0.04 in. i.d., 0.07 in. o.d.) was implanted in the renal artery of the remaining kidney by using the technique of Herd and Barger.14 Finally, a precalibrated electromagnetic flow probe (Carolina Medical Electronics, Inc., King, N.C.) was placed around the renal artery proximal to the renal arterial catheter. All catheters, occluders, and electromagnetic flow probes were tunneled subcutaneously and exteriorized between the scapulae. Except during acute infusions, both arterial catheters were maintained by flushing daily with sterile isotonic saline and by filling the catheters with heparin (1,000 units/mL); the femoral catheters were flushed two to three times weekly and filled with heparin. One week after surgery the dogs were placed in metabolic pens in a room maintained at 22±2°C with a 12-hour light/dark cycle. They were fitted with an aluminum and canvas backpack housing a pressure transducer (model P23 ID, Statham Laboratories, Inc., Hato Ray, Puerto Rico) at heart level. The electrical connections to the blood pressure transducers and the electromagnetic flow probes were brought to the top of the cage through a flexible tube attached to the top of the backpack. Isotonic saline was infused continuously via ~10 feet of Tygon tubing (0.06 in. i.d., 0.19 in. o.d.) into one of the femoral vein catheters by means of a Sage tubing pump (model 375A, Sage Instruments, Cambridge, Mass.) at rates of 226 ±3 mL/day. Additionally, 45 mL isotonic saline containing 1,000 units heparin was infused continuously each day into the renal arterial catheter using a Harvard infusion pump (model 944, Harvard Apparatus, South Natick, Mass.). For the infusion into the renal artery, 100 feet of polyethylene (PE-50) tubing was used. The high resistance provided by this tubing prevented intermittent fluctuations in the renal arterial infusion that would have occurred during changes in arterial pressure or during vertical positional changes of the dogs. A disposable Millipore filter (Cathivex Millipore, Bedford, Mass.) was connected in series with both the intravenous and the renal arterial infusion lines to prevent passage of bacteria and other contaminants.

During the entire experiment, the dogs were given free access to water and maintained on a fixed daily diet of two 12-oz cans of prescription heart diet (H/D, Hills Pet Products, Inc., Topeka, Kan.) supplemented with 5 mL vitamin syrup (V.A.L. Syrup, Fort Dodge Laboratories, Fort Dodge, Iowa). Two cans of H/D provide less than 5 mmol sodium and ~60 mmol potassium. Thus, with the saline infusion, sodium intake was ~40 mmol/day. Water consumption was monitored, and 24-hour urine samples were collected at noon, 15 minutes after feeding. Body temperature was measured daily, and amoxicillin (250 mg b.i.d.; Warner Chilcott Laboratories, Morris Plains, N.J.) and dicloxacillin (250 mg b.i.d.; Bristol Laboratories, Evansville, Ind.) were given prophylactically.

Experimental Protocols

During the postoperative period, the dogs were trained to lie quietly in their cages for 2–3 hours and were conditioned to handling. This training and equilibration period usually lasted 10–14 days. During the 2–3-hour training period, mean arterial pressure (MAP), RBF, and heart rate were measured continuously. MAP was recorded from the femoral arterial catheter using a Grass polygraph (model 7D, Grass Instruments Co., Quincy, Mass.). RBF was measured with an electromagnetic flowmeter (Carolina Medical Electronics, Inc., King, N.C.). Zero RBF was achieved by infusing the suprarenal aortic occluder and by administering a bolus (1–2 µg) of Ang II ([Asp7,Val1]Ang II, Ciba Geigy Corp., Summit, N.J.) directly into the renal artery. This was done at the beginning and the end of each training session to ensure that there was no baseline drift in the flow probe during the 2–3-hour period. Although others have given bolus injections of Ang II into the aorta to obtain zero flow in the renal arteries of dogs,15,16 in several of the dogs in the present study RBF was 10–30 mL/min higher after bolus injection of Ang II into the renal artery than after occlusion of the aorta immediately after Ang II administration. Therefore, we used the above mechanical and pharmacological methods in combination to achieve a reference zero flow. Because the reference zero flow did not vary in any animal during the 2–3-hour training period, zero flow was produced only at the end of each experiment described below. If the reference zero flow was different from the zero reading on the flowmeter, the value for RBF was adjusted accordingly.

After the training and equilibration period, at which time MAP, heart rate, and RBF were stable from day to day, RBF dose–response curves were determined during intrarenal infusion of NE (norepinephrine bitartrate, Levophed, Winthrop Pharmaceuticals, New York). Experiments were conducted between 9 AM and noon, 21–24 hours after feeding. During this experiment, the length of the polyethylene tubing between the
infusion pump and the dog was decreased from 100 to 10 feet, and the rate of saline infusion into the renal artery was increased from 0.031 mL/min (48 mL/day) to 0.167 mL/min —1 hour before NE infusion. After the dogs had been resting quietly for at least 30 minutes and MAP, heart rate, and RBF had stabilized, an arterial blood sample (~2 mL) was taken for determination of plasma renin activity (PRA), hematocrit (Hct), and plasma sodium, potassium, and protein concentration. Then NE was added to the intrarenal infusion of isotonic saline. The initial infusion rate of NE was 10 ng/min per milliliter per minute of control RBF. The initial infusion rate of NE was based on control RBF rather than body weight to achieve more comparable initial concentrations of NE in the renal arterial plasma from dog to dog. In a dog weighing 20 kg and having a control RBF of 200 mL/min, the above initial infusion rate of NE would be equal to 0.1 μg/kg per minute. Subsequently, the pump rate was increased to raise the rate of NE infusion by 5 ng/min per milliliter per minute of control RBF every 10 minutes until RBF was reduced to <15% of control or until the rate of NE infusion exceeded 40 ng/min per milliliter per minute of control RBF. Then, after another arterial blood sample was taken, the NE infusion was discontinued immediately and the renal arterial catheter was cleared of NE; once again, saline was infused at 48 mL/day. RBF was monitored for an additional 30 minutes after terminating the NE infusion.

With the above experimental protocol, NE-RBF dose–response relations were determined under the following six conditions: 1) control, 2) acute intravenous infusion of captopril (E.R. Squibb and Sons, Inc., Princeton, N.J.) plus 1-2 ng Ang II per kilogram per minute (acute captopril plus Ang II), 3) chronic intravenous infusion of captopril alone (captopril), 4) chronic intravenous infusion of captopril plus 1–2 ng Ang II per kilogram per minute (captopril plus Ang II), 5) chronic intravenous infusion of captopril plus 5–8 ng Ang II per kilogram per minute (captopril plus high Ang II), and 6) recovery. Two to three NE-RBF dose–response curves were determined on separate days (at least 48 hours apart) during the control period. Then, to determine the role of endogenously generated Ang II in mediating the renovascular response to NE, NE was infused intrarenally, as above, 45 minutes after acute administration of captopril (20 mg bolus, 14 μg/kg per minute infusion) plus Ang II (1–2 ng/kg per minute) to fix plasma Ang II at control levels. Before NE infusion, there were no significant changes in either MAP or RBF during captopril plus Ang II infusion (see below).

After this experiment where the renin-angiotensin system was fixed acutely at control levels, captopril was infused chronically at 14 μg/kg per minute. This infusion rate of captopril blocks Ang II formation chronically. For 3–5 days captopril was infused alone (captopril condition). Additionally, Ang II was infused simultaneously with captopril at either 1–2 ng/kg per minute (captopril plus Ang II) or 5–8 ng/kg per minute (captopril plus high Ang II), for 2–3 days each, to achieve normal and high plasma levels of Ang II, respectively. NE-RBF dose–response relations were determined on the last day of each of these three long-term infusion protocols (after daily sodium balance had been achieved). Thus, the renovascular responses to intrarenal infusion of NE were determined after the renin-angiotensin system had been fixed chronically at low, normal, and high levels. The chronic infusions of captopril with and without Ang II were done in random order in different dogs, and the infusion rates of NE for each dog were the same for all six conditions (as established during control). In these experiments, captopril and Ang II were made fresh daily and added to the intravenous infusion of saline. Finally, several recovery NE-RBF dose–response curves were determined 4–10 days after discontinuation of captopril and Ang II infusion.

**Analytical Methods**

PRA was measured by radioimmunoassay according to the method of Haber et al., and PRA is expressed as nanograms Ang I generated per milliliter plasma per hour of incubation. Plasma and urine concentrations of sodium and potassium were determined by flame photometry (IL 943, Instrumentation Laboratories, Lexington, Mass.), plasma protein concentration by refractometry (American Optical, Buffalo, N.Y.), and Hct by a micromethod (Autocrit II, Clay Adams, Franklin, N.J.).

The vulnerability of the renal vasculature to NE-induced renal ischemia under the different conditions was evaluated in two ways. First, the infusion rates of NE that caused severe reductions in RBF (to <15% of control) under the different conditions were compared. Second, comparisons were made of the calculated steady-state renal arterial plasma concentrations of NE achieved in the different conditions at the NE infusion rate that immediately preceded that which caused severe renal ischemia (RBF <15% of control). Steady-state concentrations of NE in the renal arterial plasma at each infusion rate of NE were calculated according to the following:

\[
[\text{NE}] = \frac{\text{rate of NE infusion}}{[\text{RBF} \cdot (1 - \text{Hct})]}
\]

When severe reductions in RBF did not occur at the highest infusion rate of NE used (40 ng/min per milliliter per minute of control RBF), the dose of NE causing severe renal ischemia was assigned a value of 45 ng/min per milliliter per minute of control RBF.

**Statistical Analysis**

Results are expressed as mean±SEM. The values reported for MAP and RBF are the averages of the results obtained during the last 5 minutes of each 10-minute infusion period. When more than one experiment was performed in a condition, the values from all experiments were averaged. Because the initial values for MAP, RBF, and renal resistance varied quantitatively under some conditions, the responses to NE infusion were expressed as percentage of control. Differences in the effect of a dose of NE on MAP, RBF, and renal resistance (MAP/RBF) within and between conditions were assessed using two-way analysis of variance (ANOVA), repeated one way. This was followed by a planned comparison or contrast using an appropriate mean square as an error to determine at which infusion rates of NE there were differences between conditions and differences within a condition. Comparisons of all preinfusion values among the differ-
ent conditions and comparisons of the NE infusion rates and renal arterial plasma concentrations of NE that caused severe reductions in RBF were performed using one-way ANOVA for repeated measures and contrast. Differences were considered statistically significant when p<0.05.

Results

Table 1 shows the baseline values for renal hemodynamics under the six different conditions studied. When the high rate of Ang II (5–8 ng/kg per minute) was infused along with captopril for 3 days, there was a significant reduction in RBF and increases in MAP and renal resistance. On the other hand, when captopril was infused for 3–5 days without Ang II, these variables changed in the opposite direction; however, only the reductions in MAP and renal resistance were statistically significant. In contrast, when captopril was infused either acutely or chronically along with a rate of Ang II (1–2 ng/kg per minute) sufficient to produce approximately normal circulating levels of the hormone, MAP, RBF, and renal resistance were restored to control levels. Also, during the recovery period, none of these measured variables were significantly different from control. Finally, under control conditions, baseline values for the plasma concentrations of sodium, potassium, and protein; hematocrit; and urinary sodium and potassium excretion were 146±1 mmol/L, 4.1±0.1 mmol/L, 6.2±0.2 mg/dL, 41±1%, 40±2 mmol/day, and 66±2 mmol/day, respectively. Except for a small increase in hematocrit when captopril was infused without Ang II (to 38±2%), the values for these variables in the other five conditions were not significantly different from control. It should be noted that NE–RBF dose–response curves were determined only after sodium and potassium balance had been achieved in each condition.

Figure 1 illustrates the changes in MAP, RBF, and renal resistance that occurred in response to graded increments in the intrarenal infusion rate of NE under control conditions and during acute and chronic captopril plus Ang II infusion. Included in Figure 1 are only the lower doses of NE (<25 ng/min per milliliter per minute of control RBF) that did not produce drastic reductions in RBF in any of the dogs under control conditions. Because marked reductions in RBF did occur in some dogs at these infusion rates of NE when captopril was administered without Ang II replacement (as discussed below), the RBF responses to NE during captopril administration alone are not presented in Figure 1. Under control conditions, PRA increased from a preinfusion value of 1.0±0.2 to 7.3±2.7 ng Ang I per milliliter per hour at the highest rate of NE infused (25–40 ng/min per milliliter per minute of control RBF).

Under control conditions, step increases in the infusion rate of NE produced progressive increases in MAP and renal resistance and reductions in RBF (Figure 1); within-group comparisons indicate that these changes were significant at all but the lowest infusion rate of NE (10 ng/min per milliliter per minute of control RBF). When the renin-angiotensin system was inhibited either acutely or chronically with captopril and the plasma levels of Ang II were fixed at either normal or elevated
levels, the changes in MAP, RBF, and renal resistance in response to NE were markedly attenuated. In fact, during the three conditions where captopril and Ang II were administered simultaneously, within-group comparisons indicated that there were no significant changes in either RBF or renal resistance in response to these rates of NE infusion that produced 11–33% reductions in RBF under control conditions. Figure 1 emphasizes between-group comparisons and illustrates that reductions in RBF in response to NE averaged only about 40% of the control response under the three conditions where plasma Ang II was fixed by infusion during captopril administration. Finally, the hemodynamic responses to NE were not significantly different during control and recovery conditions (not shown in Figure 1).

Figures 2 and 3 show the relation between RBF and the calculated steady-state concentrations of NE in the renal arterial plasma at all infusion rates of NE under control and recovery conditions (Figure 2) and during administration of captopril with (Figure 3) and without (Figure 2) Ang II replacement. In these figures, the number of points for each condition reflects the total numbers of infusion rates that could be achieved in all six dogs before RBF decreased to <15% of control. The control and recovery dose–response curves were virtually identical to each other (Figure 2), suggesting that renal function was stable over the 2 weeks of the experimental period and that any deviation from control was not the result of time-dependent changes but the result of specific treatments. The RBF response to NE tended to be reduced relative to control when plasma levels of Ang II were fixed at either normal or high levels (Figure 3). This was particularly evident at concentrations of NE in the renal arterial plasma that produced up to 40–50% reductions in RBF under control conditions. However, at higher renal arterial plasma concentrations of NE, reductions in RBF appeared comparable during captopril plus Ang II infusion and control conditions. In marked contrast, when captopril was administered chronically without simultaneous infusion of Ang II, RBF responses to NE did not appear to be attenuated in spite of the inability to generate Ang II (Figure 2). In fact, responses appeared to be enhanced relative to control. Moreover, during captopril infusion alone, there were abrupt (within 1 minute) and precipitous reductions in RBF at infusion rates of NE that had only moderate effects on RBF under the other conditions of the study. As illustrated in Figure 2, during captopril infusion alone, only a total of 20 infusions in six dogs could be achieved before RBF decreased markedly (versus 31 infusions during control).

Figure 4 shows that when captopril was chronically administered without Ang II, RBF fell to critically low levels at either NE infusion rates (27±3 ng/min per milliliter per minute of control RBF) or calculated renal
arterial plasma concentrations of NE (60±10 ng/mL) significantly lower than those required to produce renal collapse under control conditions (37±2 ng/min per milliliter per minute of control RBF and 186±50 ng/mL, respectively). Taken together, Figures 2, 3, and 4 indicate that the concentration of NE in renal arterial plasma that caused severe renal ischemia during captopril administration (60±10 ng/mL) reduced RBF to only ~60% of control when the renin-angiotensin system was intact. Thus, when captopril was administered alone, the kidney was much more sensitive to the vasoconstrictor effects of NE. This renal sensitivity to NE during chronic captopril administration was abolished by Ang II replacement.

Discussion

The role of Ang II in mediating the renal actions of renal adrenergic stimulation is controversial.3-13 In previous studies, acute blockade of the renin-angiotensin system either has attenuated or has had no effect on the RBF response to adrenergic stimulation. In contrast, in two earlier studies from our laboratory we observed that long-term administration of captopril actually increased the sensitivity of the renal vasculature to chronic intrarenal infusions of NE, causing severe renal ischemia at rates of NE infusion that produced only moderate reductions in renal plasma flow in dogs with a functional renin-angiotensin system.6,13 The two major findings in the present study were that 1) chronic captopril administration predisposes the kidneys to exaggerated reductions in RBF even during brief periods of adrenergic stimulation, and 2) the enhanced renal sensitivity to adrenergic stimulation induced by captopril is abolished when the chronic natriuretic and hypotensive effects of captopril are prevented by fixing plasma Ang II concentration at either normal or high levels. In fact, under these latter conditions, our data indicate that the RBF responses to NE are attenuated as a result of the inability to generate Ang II.

The results of the present study clarify the duration of renal adrenergic stimulation required to cause severe renal ischemia during chronic captopril administration. In previous studies, we observed that captopril enhanced the renovascular response to intrarenal infusions of NE that produced 20-40% reductions in renal plasma flow when the renin-angiotensin system was intact.6-13 However, since renal plasma flow was determined only after hours to days of continuous renal adrenergic stimulation, the significance of these findings is unclear because it is uncertain that neurally induced reductions in RBF of this magnitude would be sustained for such long periods of time under either physiological or pathophysiological conditions. The present results, on the other hand, showed that severe renal ischemia may occur very abruptly during moderate increments in renal adrenergic stimulation when the renin-angiotensin system is chronically blocked with captopril. When captopril was administered alone, RBF decreased to very low levels (to <15% of control) within 1 minute of step increases in the rate of NE infusion into the renal artery that reduced RBF to only about 60% of control when the renin-angiotensin system was functional. This would indicate that the exaggerated renovascular responses to NE that we previously observed during captopril administration are not dependent on chronic time-dependent effects of renal adrenergic stimulation such as changes in hormones, body fluid volumes, or arterial pressure. The present findings are also of significance because transient neurally induced reductions in RBF of the magnitude observed under control conditions are physiologically relevant.20-21 Thus, the current findings indicate that chronic captopril administration may enhance neurally induced reductions in RBF in response to stimuli such as excitement20 and exercise.21

An important observation in the present study was that the enhanced sensitivity to acute adrenergic stimulation during long-term captopril administration was abolished when Ang II was infused simultaneously with captopril at rates of Ang II infusion that maintained MAP either at or above normal levels. In an earlier study, we found that chronic intravenous infusion of Ang II at the same hypertensive rate as used in the present study (5 ng/kg per minute) prevented captopril-induced deterioration of renal function during infusion of NE into the renal artery over a period of several days.6 The current findings indicate that even normal levels of Ang II prevent enhanced renovascular responses to acute adrenergic stimulation when captopril is administered chronically. In the absence of Ang II replacement, how might chronic captopril administration predispose the kidneys to excessive renal vasocostriction during acute intrarenal NE infusion?

The enhanced renovascular response to acute renal adrenergic stimulation during chronic captopril administration may be due to the lowering of MAP by
captopril. Studies in both anesthetized and conscious dogs have shown that reflex activation of the renal nerves22 electrical renal nerve stimulation,23 and intra-renal NE infusion24 all impair the ability of the kidneys to autoregulate RBF during reductions in renal perfusion pressure. This effect of renal adrenergic stimulation on renal autoregulation is independent of the renin-angiotensin system because Ang II does not affect RBF autoregulation.25,26 In a recent study in conscious dogs, it was shown that reflex activation of the renal nerves by bilateral carotid occlusion, although having no effect on basal RBF, shifted the lower limit of RBF autoregulation (by ~25 mm Hg) to higher pressure levels.22 Thus, even mild increments in renal nerve activity that do not alter renal hemodynamics under basal conditions increase the threshold pressure for autoregulation of RBF to a level that is only 15–20 mm Hg below MAP.22 Based on these findings, we hypothesize that as the rate of NE infusion was increased in the present study, there was a progressive shift in the lower limit of RBF autoregulation to higher pressure levels. Because severe renal ischemia occurred during captopril administration at rates of NE infusion that decreased RBF by ~40% under control conditions, it is possible that at this level of adrenergic stimulation, the threshold pressure for renal autoregulation was sufficiently altered to induce a precipitous fall in RBF in the presence of the hypotension induced by captopril administration. In support of this, the ischemic response did not occur at comparable degrees of renal adrenergic stimulation when plasma activity that do not alter renal hemodynamics under control conditions.26–28 In this study, Ang II did not affect the lower limit of autoregulation of MAP at control levels. However, the ischemic response was observed at a threshold pressure (20 mm Hg below MAP) that was ~10 mm Hg lower than that observed in conscious control dogs22 and is consistent with previous findings in anesthetized dogs.26–28 Thus, the results of the present study support the hypothesis that renal ischemia occurs at lower thresholds of adrenergic stimulation when the renin-angiotensin system is intact and when it is chronically abrogated. For example, it has been reported that captopril reduces the sensitivity of the tubuloglomerular feedback mechanism, an effect that is partially restored by Ang II.29 This and other evidence indicate that Ang II augments tubuloglomerular feedback.29 Therefore, it is possible that the premature renal collapse induced by NE during captopril administration was due to impaired autoregulatory reductions in tubuloglomerular tone in association with decreased distal tubular sodium chloride delivery during NE infusion. Also, since both Ang II and NE increase renal prostaglandin secretion,30 it would be of interest to determine whether chronic captopril administration modifies the compensatory release of vasodilatory eicosanoids in response to renal adrenergic stimulation. Although these experiments were designed to elucidate the mechanisms that account for the exaggerated renovascular response to acute adrenergic stimulation during chronic blockade of the renin-angiotensin system, the present findings also provide insight into the role of acutely generated Ang II in mediating the RBF responses to NE. The RBF responses to exogenous infusion of NE into the renal artery in the present study indicate an important interaction between NE and the renin-angiotensin system in mediating the renal vasoconstrictor effects of NE. At the lowest infusion rates of NE used, which decreased RBF 11–33% under control conditions, there was a pronounced reduction in the renal vasoconstriction produced by NE when plasma levels of Ang II were fixed at control levels, relative to the response before captopril administration when Ang II was capable of increasing above control levels (Figure 1). Because these low rates of NE infusion into the renal artery increase renin release,13 it is likely that increased generation of Ang II normally contributes to the renal vasoconstriction produced by NE. This is consistent with the findings of Pelayo et al9 during electrical renal nerve stimulation in rats. In the study, Ang II blockade greatly attenuated the renal vasoconstriction induced by a level of renal nerve stimulation that reduced renal plasma flow by ~40% under control conditions. Furthermore, this pronounced blunting of the renal vasoconstrictor effects of renal nerve stimulation occurred without affecting the magnitude of the renal NE overflow response to adrenergic stimulation. This would indicate that endogenous Ang II does not contribute importantly to the renovascular effects of renal adrenergic stimulation by presynaptic facilitation of NE release, as suggested in early studies.31 Thus, it appears that a significant component of the renovascular response to moderate degrees of renal adrenergic stimulation is indirectly mediated via increased generation of Ang II, which then acts to evoke renal vasoconstriction. Although Ang II contributed significantly to the RBF responses evoked by moderate degrees of renal adrenergic stimulation, Figure 3 illustrates that at the highest infusion rates of NE, which decreased RBF to less than 60% of control, RBF responses to NE were comparable during captopril plus Ang II infusion and control conditions. This indicates that at high levels of adrenergic stimulation, the renal vasoconstrictor effects of Ang II were diminished relative to those of NE. Based on the pronounced increases in PRA achieved at the highest infusion rates of NE used in the present study and our previous measurements of PRA during intrarenal NE infusion,5,13,32 it is unlikely that the diminished role of Ang II in mediating the renal vasoconstriction at more intense degrees of renal adrenergic stimulation was due to an inability to achieve additional increments in Ang II. Rather, the diminished effects of Ang II on RBF, relative to those of NE, may be due to the differential sensitivity of pregglomerular and postglomerular vessels to these vasoconstrictors. Studies by Johns and his group3–5 indicate that endogenously generated Ang II has substantial effects on efferent arterioles at intensities of renal nerve stimulation and infusion rates of NE into the renal artery that produce only mild (16% or less) reductions in RBF. As the degree of adrenergic stimulation increases, however, the pregglomerular vasculature responds more than the postglomerular vessels.33–35 This relative increase in pregglomerular versus postglomerular resistance at increasing levels of adrenergic stimulation would appear to be due to the direct actions of NE because NE has considerably more pronounced effects on pregglomerular vessels than does...
Further, at higher degrees of adrenergic stimulation, NE may exert a proportionately greater effect, relative to Ang II, on postglomerular resistance. It is also possible that the diminished renal vasoconstrictor effects of Ang II at higher levels of adrenergic stimulation might be secondary to alterations in tubuloglomerular feedback. That is, because distal tubular delivery of sodium chloride is greatly reduced at high rates of adrenergic stimulation, tubuloglomerular feedback would be expected to be operating at or near the plateau range where further changes in tubular flow have minimal influence on afferent arteriolar resistance. Therefore, at high rates of NE infusion, any vasoconstrictor effects of Ang II on the afferent arterioles would be diminished to the extent that they occur and are mediated via the tubuloglomerular feedback system.

In conclusion, the present results indicate that the renin-angiotensin system has both important short-term and long-term renal actions that influence the renovascular response to acute adrenergic stimulation. It appears that the Ang II generated acutely during renal adrenergic stimulation contributes significantly to the renal vasoconstrictor response to intrarenal NE infusion. Furthermore, the contribution of Ang II to neurally induced vasoconstriction appears to be greatest at degrees of renal adrenergic stimulation that produce mild-to-moderate reductions in RBF; at higher levels of adrenergic stimulation, the direct vasoconstrictor effects of NE appear to predominate over those of Ang II. However, in spite of the role of Ang II in mediating the acute renal actions of NE, when endogenous levels of Ang II are suppressed to very low levels during chronic captopril administration, the renal vasculature becomes very sensitive to adrenergic stimulation. This sensitivity to NE is abolished when Ang II is chronically infused simultaneously with captopril at rates that restore MAP to normotensive levels or higher. Thus, when the chronic antinatriuretic effects of Ang II are abolished during long-term captopril administration, the resultant low MAP may predispose the kidneys to renal ischemia during renal adrenergic stimulation. These findings may be especially relevant to conditions such as heart failure where there is both increased sympathetic tone and reduced arterial pressure. Indeed, drastic neurally induced falls in RBF have been documented in conscious dogs with experimentally produced heart failure.

The present results suggest that neurally induced renal vasoconstriction may be exaggerated even more during administration of captopril or other converting-enzyme inhibitors that are now widely used in the treatment of heart failure.

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