Hypertensive and Renal Effects of Chronic Low Level Intrarenal Angiotensin Infusion in the Dog

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SUMMARY To determine whether the intrarenal sodium-retaining effects of angiotensin II (A II) can produce chronic hypertension, we infused A II at a rate (1 ng/kg per min) that did not cause a measurable immediate rise in mean arterial pressure (MAP) for 10 days directly into the renal artery of five dogs with unilateral nephrectomy. Four additional control dogs with unilateral nephrectomy were infused intravenously with A II for 10 days at 0.5 ng/kg per min. This intravenous infusion rate of A II was calculated to produce an increase in peripheral blood levels of A II at least as great as those achieved with the intrarenal infusion of A II. MAP was recorded continuously, 24 hours/day, and daily values for MAP based on approximately 720 sample points per day were determined by computerized data analysis. Intrarenal A II infusion produced an immediate fall in glomerular filtration rate (GFR), effective renal plasma flow (ERPF), and urinary sodium (UN.V) and potassium (UK.V) excretion. MAP was unchanged during the first day of the infusion period. Both GFR and ERPF remained depressed for at least 6 days of the infusion. However, sodium balance was achieved on day 2 when MAP had increased by 9 mm Hg. Subsequently, MAP continued to increase, reaching + 15 mm Hg at the end of 10 days. In contrast, there was no sodium retention or hypertension during the first 48 hours of intravenous A II infusion; yet, during days 3-10, MAP did rise by 7 mm Hg. After the intrarenal infusion of A II was stopped on day 10, there were immediate increases in GFR, ERPF, UK.V, and especially UN.V, and MAP returned to control levels after a few hours. The data indicate that the intrarenal effects of A II can produce chronic sodium retention and a sustained elevation in MAP and also prevent pressure natriuresis during the hypertension. Circ Res 44:154-160, 1979

IT IS well established that chronic infusion of angiotensin II (A II) at a rate that causes only a small increase in arterial pressure initially, will in time produce prominent hypertension (McCubbin et al., 1965; Dickinson and Yu, 1967; Cowley and DeClue, 1976; Cowley and McCaa, 1976; Lohmeier et al., 1978). Also, it is well accepted that A II plays an important role in the maintenance of some forms of experimental and clinical renal hypertension. However, at present, controversy does exist as to the primary mechanism(s) which sustain A II-induced hypertension.

A II indirectly promotes sodium and water retention via its control of aldosterone secretion, and this action of A II has been evoked frequently to account for the hypertension which persists in states of increased activity of the renin-angiotensin-aldosterone system. However, we recently have shown that the changes in plasma aldosterone concentration which accompany A II infusion have very little influence on the severity of the ensuing hypertension (Lohmeier et al., 1978).

Another possible mechanism to account for A II-induced hypertension and one which has received little consideration in the past is that A II per se acts directly on the kidney to promote sodium and water retention. Several investigators have demonstrated that infusion of A II, either intravenously or directly into the renal artery, at rates too low to cause a measurable acute rise in arterial pressure produces an immediate and a marked decrease in sodium and water excretion (Waugh, 1972; Navar and Langford, 1974; Fagard et al., 1976). More recently, we have shown that intrarenal infusion of A II antagonists in dogs with elevated plasma renin activity (PRA) secondary to sodium depletion or dehydration produces an increase in sodium and water excretion (Lohmeier et al., 1977; Hall et al., 1977; Trippodo et al., 1977). In one of our studies (Lohmeier et al., 1977), the dogs were chronically adrenalectomized and, therefore, the increased sodium and water output during the intrarenal A II blockade had to have been independent of any effects of A II on aldosterone secretion (or the release of adrenal catecholamines).

The purpose of the present study was to determine whether chronic low-level A II infusion could, in fact, produce sustained hypertension through its direct renal effects which promote sodium and water retention. In dogs with unilateral nephrectomy, mean arterial pressure was measured continuously and renal function intermittently during 10 days of intrarenal or intravenous A II infusion.
Methods

Nine dogs weighing 19.2 ± 0.7 kg were anesthetized with sodium pentobarbital (30 mg/kg, iv). A right nephrectomy was performed, and chronic indwelling polyvinyl catheters were implanted in the femoral artery and vein. The tip of the femoral artery catheter was advanced into the aorta distal to the bifurcation of the renal artery and the end of the femoral vein catheter was positioned in the vena cava. In five of the dogs (body weight = 19.6 ± 0.7 kg) a polyvinyl catheter also was implanted in the renal artery. Prior to chronic infusion, patency was maintained by flushing twice daily with sterile isotonic saline and by filling the catheter with heparin (1000 U/ml). In an earlier study we have described the catheters and the techniques used for their implantation (Lohmeier et al., 1977).

During a 1-week convalescent period, the dogs were placed in metabolic pens and conditioned to daily handling and, at the end of the week, were fitted with a plaster of Paris backpack housing a pressure transducer at heart level. While harnessed the dogs had relatively unrestricted movement about the pen and after a few days appeared relaxed in the apparatus. They were given free access to water and maintained on a fixed daily diet of two 15.5-oz cans of h/d prescription diet (Riviana Foods, Inc.). Two cans of h/d provide <5 mEq sodium and 40-50 mEq potassium. Additional 72 ml saline/day (11 mEq sodium) were infused intravenously in the four control dogs at 0.5 ng/kg per min. Mean arterial blood pressure was recorded 24 hours per day from the femoral artery catheter, using a Harvard infusion pump. A disposable Millipore filter (Cathivex) was connected in series with the renal artery infusion line to prevent passage of bacteria and other contaminants. In the control dogs without renal artery catheters, all the saline (792 ml) was infused intravenously by means of a Sage tubing pump (model 375 A) and an additional 72 ml saline/day (11 mEq sodium) were infused into the renal artery catheter, using a Harvard infusion pump. A disposable Millipore filter (Cathivex) was connected in series with the renal artery infusion line to prevent passage of bacteria and other contaminants. In the control dogs without renal artery catheters, all the saline (792 ml) was infused intravenously. Mean arterial blood pressure was recorded 24 hours per day from the femoral artery catheter throughout the experiment by employing a Grass polygraph (model 7D) and Statham arterial blood pressure transducers which were built into the backpacks (Cowley et al., 1973). To provide accurate measurements of 24-hour urinary sodium and potassium excretion rates, the urinary bladder was catheterized aseptically daily. Also, the bladder was washed with a nitrofurazone solution to prevent bacterial infection. Body temperature was measured daily, and ampicillin (500 mg orally, twice daily) was given prophylactically except on days preceding renal clearance measurements.

Experimental Protocol

Following a 5- to 7-day control period, [Asp1, NH2-Val8]angiotensin II (Ciba) was infused for 10 days in the intrarenally infused dogs at 1 ng/kg per min or intravenously in the four control dogs at 0.5 ng/kg per min. This rate for the control dogs was calculated to be equal to or greater than the A II that escaped destruction in the kidneys when infused intrareally, as will be discussed below. A II was prepared fresh daily in saline and added to the intrarenal saline infusion or the intravenous saline infusion for the control dogs. After the 10-day A II infusion period, there was a 4-day recovery period.

Four-milliliter blood samples for measurement of PRA, plasma sodium and potassium concentration, and hematocrit were taken on the last 3 days of the control period, on days 3, 6, and 10 of A II infusion, and on days 1, 2, and 4 of the recovery period. Urine was collected daily for measurement of 24-hour urinary sodium and potassium excretion rates. In dogs subjected to intrarenal infusion of A II, the following two additional measurements to assess renal function were made on the last 2 days of the control period, on days 3, 6, and 10 of A II infusion, and on day 4 of the recovery period: (1) glomerular filtration rate (GFR) determined from the clearance of sodium [125I]iothalamate (Glofile 125, Abbott Laboratories) and (2) effective renal plasma flow (ERPF) from the clearance of p-aminohippurate (PAH, Merck, Sharp and Dohme). In addition, following determination of renal function on the second control day and on day 10 of A II infusion, measurements were made of the acute changes in renal function which occurred 10-40 minutes after initiation and 10-40 minutes after termination of A II infusion, respectively. Priming doses and sustaining infusion rates of sodium [125I]iothalamate and PAH were calculated to give plasma levels of 2000-3000 counts/ml per min and 1-3 mg/100 ml, respectively.

Analytical Methods

PRA was measured by a radioimmunoassay procedure for angiotensin I (E.R. Squibb & Sons) and is expressed as nanograms of angiotensin I generated per milliliter of plasma per hour of incubation (ng A I/ml per hour). Plasma and urine concentrations of sodium and potassium were determined by flame photometry (Instrumentation Laboratory, Inc., IL 343), concentrations of PAH by the method of Smith et al. (1945) and concentrations of iothalamate by gamma emission of sodium [125I]iothalamate in a Nuclear-Chicago gamma well counter. Hematocrit was measured by a micro method. GFR and ERPF were calculated as the clearance of sodium [125I]iothalamate and PAH, respectively. The values presented for GFR and ERPF are the average of three consecutive 15-minute clearance periods. Filtration fraction is expressed as GFR/ERPF.

The automated techniques used in our laboratory for computerized data analysis have been described previously in detail (Cowley et al., 1973). In brief, the continuous mean arterial blood pressure recordings from the Grass polygraph were converted to electrical signals for computer analysis by employ-
A four-channel analog curve-reading system with fiberoptic scanning pens which generated analog voltages from the recorded ink tracings. The analog voltages from the curve tracings were fed into an analog-to-digital converter that changed them to digital signals for analysis by a PDP 11/70 computer. The digitized information was used by the computer to calculate hourly and daily values for mean arterial pressure based on approximately 30 sample points per hour or 720 sample points per day.

All values presented are means ± SE. Student’s t-test for paired observation was used to determine statistical significance. Statistical significance was considered to be \( P < 0.05 \).

## Results

Table 1 shows the 24-hour values for mean arterial pressure (MAP) during the last 3 days of the 7-day control period in the five dogs given intrarenal arterial infusion of A II. As mentioned above, each 24-hour value for MAP represents the average of approximately 720 sample points per day. As shown in Table 1, there is a very small day-to-day variation in the values for MAP for each dog; in four of the five dogs the average 24-hour value for MAP over the 3 days did not vary by more than 1 mm Hg.

### Effects of Intrarenal Arterial A II Infusion on MAP, PRA, Plasma and Urinary Electrolytes, and Hematocrit

Figure 1 illustrates the changes in MAP, PRA, and urinary sodium and potassium excretion which occurred during the 10 days of intrarenal A II infusion. During the first 24 hours of intrarenal A II infusion there was no measurable change in MAP, although both antinatriuresis and antikaliuresis occurred. The average sodium and potassium retention for the first day of A II infusion was 48 ± 8 and 10 ± 4 mEq, respectively. By the second day of A II infusion, however, daily sodium and potassium balance was again achieved, but MAP was elevated by an average of 9 mm Hg or to 60% of the maximum increment observed on day 10. From days 2 to 10 there was a progressive increase in MAP which reached an average of 15 ± 2 mm Hg above control by the last day of intrarenal A II infusion. Daily sodium and potassium balance was maintained from days 2 to 10 of A II infusion, and PRA was depressed to undetectable levels.

### Table 1: Control Values from Continuous Mean Arterial Blood Pressure Recordings

<table>
<thead>
<tr>
<th>Day</th>
<th>Dog 1</th>
<th>Dog 2</th>
<th>Dog 3</th>
<th>Dog 4</th>
<th>Dog 5</th>
<th>Mean ± SE</th>
</tr>
</thead>
<tbody>
<tr>
<td>-2</td>
<td>111</td>
<td>99</td>
<td>111</td>
<td>109</td>
<td>109</td>
<td>108 ± 2</td>
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<tr>
<td>-1</td>
<td>113</td>
<td>98</td>
<td>110</td>
<td>108</td>
<td>108</td>
<td>107 ± 3</td>
</tr>
<tr>
<td>0</td>
<td>110</td>
<td>99</td>
<td>111</td>
<td>108</td>
<td>109</td>
<td>107 ± 2</td>
</tr>
</tbody>
</table>

Each value for mean arterial pressure is the average of 720 sample points per day.

During the 24-hour period following cessation of intrarenal A II infusion, there was an average net urinary loss of 35 ± 10 mEq sodium (\( P < 0.05 \)), and MAP fell to control levels. PRA was still depressed on the first recovery day but increased progressively to control levels thereafter; by the fourth postinfusion day, full restitution of PRA had not been achieved.

Figure 2 shows the hourly changes in MAP which followed termination of A II infusion on day 10. There was no measurable change in MAP for 2 hours and no significant change in MAP for 3 hours following cessation of the A II infusion. Subsequently, there was a fairly abrupt fall in MAP to pre-infusion control levels.

Control values for plasma sodium concentration, plasma potassium concentration, and hematocrit averaged 147 ± 1 and 4.4 ± 0.1 mEq/liter and 39 ± 1%, respectively. These values were unchanged during the infusion of A II and during the subse-
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Figure 3 Acute effects of intrarenal arterial infusion of A II at 1 ng/kg per min on mean arterial pressure (MAP), glomerular filtration rate (GFR), effective renal plasma flow (ERPF), urinary sodium excretion (UNaV), and urinary potassium excretion (UKV).

Figure 4 Effects of chronic intrarenal arterial infusion of A II at 1 ng/kg per min on glomerular filtration rate, effective renal plasma flow, and filtration fraction.

Figure 5 Acute changes in MAP, GFR, ERPF, UNaV, and UKV following cessation of chronic intrarenal arterial infusion of A II at 1 ng/kg per min.

Effects of Intrarenal Arterial A II Infusion on Renal Function

Figure 3 illustrates the acute renal response to intrarenal A II infusion, measured 10-40 minutes after initiation of A II. The mean control values for GFR, ERPF, and filtration fraction were 43 ± 5 ml/min, 151 ± 21 ml/min, and 0.29 ± 0.02, respectively. Intrarenal A II infusion at 1 ng/kg per min produced an acute fall in GFR of 16 ± 2%, in ERPF of 26 ± 4%, and an increase in filtration fraction of 15 ± 4%, whereas urinary sodium and potassium excretion decreased 54 ± 7% and 39 ± 6%, respectively. MAP was unchanged acutely.

Figure 4 shows the long-term effects of intrarenal A II infusion on renal function. In contrast to the more transient effects of intrarenal A II infusion on sodium and potassium excretion, where the excretion of these electrolytes was reduced for only 24 to 48 hours, the acute effects of A II on renal function to decrease GFR and ERPF persisted for at least 6 days of the A II infusion. However, by the 10th day of intrarenal A II infusion, the reduced values for GFR and ERPF were not significantly different from control. The recovery values for renal function measured 4 days after termination of A II infusion were increased slightly but were not significantly different from control.

Figure 5 depicts the immediate changes in renal function (from the day 10 values) which occurred following termination of A II infusion on day 10. Renal function was measured during the period 10-40 minutes after the intrarenal infusion of A II was stopped. Cessation of A II infusion was associated with immediate increases in GFR (10 ± 3%), ERPF (29 ± 7%), urinary sodium (139 ± 29%) and potassium (39 ± 17%) excretion, and a decrease in filtration fraction (14 ± 3%).

Effects of Intravenous A II Infusion on MAP, PRA, Plasma and Urinary Electrolytes, and Hematocrit

The changes in MAP, PRA, and urinary sodium and potassium excretion associated with 10 days of intravenous A II infusion at 0.5 ng/kg per min are shown in Figure 6. Most importantly, the increase in MAP in these dogs was more gradual and moderate than that observed in the dogs subjected to intrarenal A II infusion (Fig. 1). By the last day of intravenous A II infusion, the average increase in MAP above control was 7 ± 2 mm Hg, and this elevation was significantly less (P < 0.05) than that observed (15 ± 2 mm Hg) in the dogs infused with A II intrarenally.

The response of urinary sodium excretion to in-
travenous A II infusion also was distinctly different from that observed in the dogs infused with A II intrarenally. In contrast to the intrarenal infusions where there was marked sodium retention during the first 24 hours of A II infusion, in dogs infused with A II intravenously there was no measurable change in urinary sodium excretion during this period. Further, there were no prominent changes in urinary sodium excretion throughout the remainder of the 10-day A II infusion period. However, as in dogs subjected to intrarenal A II infusion, sodium balance was negative during the 24-hour period following termination of A II infusion. During this 24-hour period, urinary sodium excretion exceeded sodium intake by approximately 20 mEq ($P < 0.05$).

Control values for plasma sodium concentration, plasma potassium concentration, and hematocrit averaged 147 ± 1 and 4.4 ± 0.1 mEq/liter, and 39 ± 1%, respectively. As with the intrarenal infusions, these values were unchanged during intravenous A II infusion and during the subsequent recovery period except for a transient rise in hematocrit to 41 ± 1% ($P < 0.05$) on the first recovery day.

In contrast to the dogs infused with A II intrarenally, PRA fell to undetectable levels in only two of the four dogs during intravenous A II infusion. Further, the return of PRA to control levels during the recovery period was more rapid in the dogs infused with A II intravenously than in the dogs infused with A II directly into the renal artery.

**Macroscopic Examination of the Kidneys in Dogs with Renal Artery Catheters**

The right kidneys weighed 45 ± 3 g when they were removed at surgery. Approximately 4 weeks later, at the end of the experiment, the left kidneys weighed 63 ± 6 g. Gross examination did not reveal any significant damage to the kidneys with the exception of an occasional minute area of infarction.

**Discussion**

The most important finding of this study is that the intrarenal effects of A II which promote sodium and water retention are manifested as well in a sustained elevation in arterial pressure. With intrarenal A II infusion, there was an immediate reduction in urinary sodium excretion to less than 50% of control. This A II-induced antinatriuresis was reflected in the retention of approximately 50 mEq sodium during the first 24 hours of A II infusion and a 9 mm Hg increase in MAP by day 2 of the infusion. That there was no hypertension associated with the fluid retention on day 1 of intrarenal A II infusion was probably mainly a function of baroreceptor compensation (Cowley and DeClue, 1976); subsequently, baroreceptor resetting would be expected (Cowley and DeClue, 1976). In contrast to the intrarenal infusions, intravenous A II infusion failed to produce any measurable sodium retention or hypertension during the first 48 hours of the infusion.

To ascertain whether systemic effects associated with the intrarenal arterial infusion of A II could account for part of the ensuing hypertension, one-half of the intrarenal arterial infusion rate of A II or 0.5 ng/kg per min was infused intravenously for 10 days. This rate was chosen since it has been reported that 50–80% of the A II in renal arterial blood is metabolized in a single pass through the kidney (Oparil and Bailie, 1973; Bailie and Oparil, 1977). Therefore, intravenous infusion of A II at 0.5 ng/kg per min was expected to produce systemic effects at least comparable to those achieved during intrarenal A II infusion. That the maximum increase in mean arterial pressure during intravenous A II infusion was less than half that achieved during the renal artery infusion suggests that the direct renal effects of A II account for the major portion of the hypertension associated with the intrarenal infusion of A II.

In dogs infused either intravenously or intrarenally with A II, there was a progressive and modest increase in MAP of 6–7 mm Hg over the last 8 days of the A II infusion. In the dogs subjected to intravenous A II infusion, this gradual rise in MAP was apparently secondary to A II-induced fluid retention because, although there was not a statistically significant retention of sodium during the 10 days of intravenous A II infusion, in all these dogs natriuresis did accompany termination of the infusion. In contrast to intravenous infusion, this progressive increase in MAP during days 3–10 of intrarenal A II infusion was not accompanied by further sodium and water retention. Instead, in the intrarenally infused dogs, all the sodium retention occurred during days 1–2 of A II infusion. Cowley...
and DeClue also have found that approximately 30% of the final steady state rise in MAP associated with infusion of A II at 5 ng/kg per min occurs after the initial 48 hours of the infusion (Cowley and DeClue, 1976). Finally, it should be pointed out that this gradual late increase in MAP is not specific to A II infusion but also occurs following chronic infusion of both aldosterone and norepinephrine (unpublished observations).

Although plasma aldosterone concentration was not measured in the present study, aldosterone probably played a minor role in mediating the hypertension induced by either the intravenous or intrarenal infusion of A II for the following reasons. First, in dogs maintained on a comparable sodium intake, infusion of A II at a much higher rate (5 ng/kg per min) than that used in the present study produced at best a sustained 2-fold increase in plasma aldosterone concentration (Cowley and McCaa, 1976; Lohmeier et al., 1978). Second, increases in aldosterone concentration during chronic A II infusion are associated with a fall in plasma potassium concentration and an increase in urinary potassium excretion, particularly at higher sodium intakes such as in the present study (Lohmeier et al., 1978). Neither hypokalemia nor kaliuresis was observed with either the intrarenal or intravenous infusion of A II. Finally, we have found in both intact and adrenalectomized dogs, both infused with A II, that increases in plasma aldosterone concentration (by infusion) to as much as three to five times normal have little or no effect on the severity of the hypertension (Lohmeier et al., 1978).

The finding that the average increase in MAP during intrarenal A II infusion was only 15 mm Hg does not indicate that the intrarenal sodium- retaining effects of A II are not a potent or a primary mechanism which sustains A II-induced hypertension. First, by necessity, very low levels of A II were infused intrarenally to minimize systemic effects of A II which would complicate interpretation of the data. Second, compensatory mechanisms may be particularly effective in counteracting the hypertensive effects of A II at this low infusion rate. For example, the intrarenal infusion of A II suppressed PRA to undetectable levels and, therefore, at least some of the potential hypertensive activity of the exogenous A II was required just to compensate for the hypotensive effects associated with suppression of endogenous A II. If in fact the intrarenal infusion of A II at 1 ng/kg per min completely suppressed endogenous renin release, higher rates of A II infusion in the renal artery would be expected to have proportionately greater hypertensive effects than rates less than 1 ng/kg per min (but, unfortunately for the purposes of this present study, greater peripheral effects also). It should be pointed out that during the intravenous infusion of A II, when MAP increased to almost half that achieved with the intrarenal infusion of A II, suppression of PRA was less complete and, therefore, this compensatory mechanism had less of a mitigating influence on the hypertensive response than during intrarenal A II infusion.

The acute renal hemodynamic and urinary electrolyte responses to intrarenal A II infusion were both qualitatively and quantitatively similar to those observed in anesthetized dogs subjected to the same infusion rate of A II into the renal artery (Waugh, 1972; Fagard et al., 1976). The present study extends these acute observations to the chronic state. During chronic intrarenal A II infusion, the acute reductions in both GFR and ERPF (and the increase in filtration fraction) were maintained for at least several days of the infusion, whereas the very pronounced antinatriuresis (and antikaliuresis) which immediately followed intrarenal A II infusion persisted for only about 24 hours (after which time sodium balance was achieved). The data indicate, therefore, that in states in which renin concentration is increased, sodium and fluid balance may be maintained at a reduced GFR. That sodium and fluid balance again were achieved shortly after the first 24 hours of the infusion was probably a function of MAP which had increased by this time. Thus, in spite of the fact that MAP was elevated after day 1, pressure natriuresis did not occur because of the intrarenal sodium-retaining effects of A II. Clearly, on day 10 when the kidney still was exposed to an increased arterial pressure, the sudden removal of the intrarenal sodium retaining effects of A II immediately following cessation of A II infusion allowed pressure natriuresis and diuresis to occur within minutes. Within a few hours, MAP returned to control.

That both GFR and ERPF tended to return to control levels by day 10 of intrarenal A II infusion may have been a function of any or all of the following: (1) increased MAP, (2) renal hypertrophy, and (3) renal autoregulation due to chronic ischemia. That the recovery values for both GFR and ERPF were increased over control would indicate that renal hypertrophy did occur over the 2-week experimental period. However, since PRA had not fully recovered to control levels by the end of the recovery period, the increased values for GFR and ERPF during this time could also have been secondary to a partially suppressed renin-angiotensin system (Lohmeier et al., 1977).

In summary, the present study provides data for the first time, on the chronic intrarenal hemodynamic and electrolyte excretory effects of A II. The present observations in no way exclude the possibility that the intrarenal hemodynamic and antinatriuretic effects of A II are mediated by indirect renal actions of A II. For example, at least in acute experiments, it has been shown that A II enhances the vasoconstrictor responses to adrenergic stimulation in a number of vascular beds including the renal bed (McCubbin, 1974; Zimmerman, 1978). This study does demonstrate, however, that the intrarenal actions of A II that promote sodium and
fluid retention eventuate in a state of chronic hypertension. Unfortunately, due to the limitations inherent in the experimental protocol (as described above), the quantitative importance of these intrarenal effects in the maintenance of Ang II-induced hypertension could not be ascertained, and the hypertensive effects of this mechanism were perhaps underestimated. However, from the quantitative data generated in this study and in one other in which the hypertensive activity of aldosterone was measured (Lohmeier et al., 1978), it appears that the intrarenal sodium-retaining effects of Ang II are considerably more potent for the maintenance of Ang II-induced hypertension than are those mediated via aldosterone secretion.

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References

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