Effects of Chronic Intracerebroventricular Infusion of Angiotensin II on Arterial Pressure and Fluid Homeostasis

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SUMMARY Male albino rabbits received continuous (24 hr/day) infusions of angiotensin II (All) at doses of 1 or 3 μg/hr into a lateral cerebral ventricle (i.v.t.) for 10 consecutive days. Infusions were preceded by a 5-day control period and followed by a 5-day recovery period. Water intake, urine output, water “balance” (water intake minus urine output), urinary sodium and potassium excretions were determined daily. Arterial pressure, heart rate, plasma electrolytes (sodium and potassium), plasma volume, and extracellular fluid volume were determined at 5-day intervals. Chronic i.v.t. infusion of All resulted in reversible, dose-dependent increases in arterial pressure, water intake, and urinary sodium excretion, and decreases in plasma sodium, plasma potassium, and water balance. Infusions of normal saline i.v.t. (n = 5) did not significantly alter any of the above values. Intravenous infusion of the same doses of All raised arterial pressure to a similar degree as that from i.v.t. administration, but did not significantly affect any of the other measured variables. In an additional group of 10 rabbits, All was infused at 3 μg/hr i.v.t. for 5 days, and the acute cardiovascular actions of i.v.t. saralasin (10 μg), i.v. saralasin (4 μg/kg/min), and “total” autonomic blockade were compared to the effects of these treatments in five saline-infused rabbits. No significant differences in responses of the two groups were found. In another series of 10 rabbits, 5-day i.v.t. infusion of All (3 μg/hr) was shown to be associated with increased pressor sensitivity to norepinephrine, but not to All or vasopressin. A similar experiment in four additional rabbits revealed that plasma vasopressin concentration was not altered by i.v.t. infusion of All. We conclude that chronic i.v.t. infusion of All in rabbits can cause a sustained hypertension that is not dependent on salt or water retention, “leak” of All into the peripheral vasculature, increased release of vasopressin in the circulation, or increased autonomic nervous system activity.

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KEY WORDS • angiotensin II • fluid balance • electrolyte balance • arterial pressure

SEVERAL converging lines of evidence suggest that an action of angiotensin II (All) on the central nervous system (CNS) contributes to the development of arterial hypertension. Antagonists of the renin-angiotensin system have been reported to lower blood pressure when given directly into the brain of animals with various types of experimental hypertension.1-4 Including rats with genetic hypertension.4-8 Brain lesions that attenuate CNS responsiveness to All also have been shown to prevent or attenuate the development of some forms of experimental hypertension.8 In addition, the chronic administration of All into the brain via either the cerebral blood supply6-8 or cerebral ventricles6 has been demonstrated to produce a sustained rise in arterial pressure.

The mechanism of the hypertension caused by All acting on the CNS is unclear. It is now believed that All can activate CNS pressor mechanisms either by: 1) stimulating specific brain areas capable of responding to changes in blood levels of All; or 2) influencing perhaps separate brain areas as a result of generation of All within brain tissue itself.9 Most studies on hypertension produced by long-term infusion of All into the cerebral blood supply indicate that the mechanism of this effect is increased sympathetic nervous system activity.4-8 Although increased sympathetic activity also undoubtably contributes to the pressor effect of acute injections of All into the cerebral ventricles,11 the contribution of this factor to hypertension caused by chronic intracerebroventricular (i.v.t.) infusion of All is less certain.8 In this regard, it should be pointed out that the most profound effect of All...
acting on the CNS is not changes in blood pressure, but rather alterations in fluid and electrolyte regulation.12

The purpose of our present experiments was to elucidate the etiology of hypertension development in animals given chronic, continuous infusions of All directly into the cerebral ventricles. Particular attention was paid to possible contributions of altered salt/water homeostasis and/or autonomic nervous system activity to the pathogenesis of this form of experimental hypertension.

Methods

Male albino rabbits weighing 2 to 3 kg were used in all studies. Rabbits were housed in large, metal metabolism cages in air-conditioned, light-cycled quarters throughout the experiment except during cardiovascular measurements every fifth day. At least 1 week prior to the initiation of experiments, 23 g stainless steel cannulas were permanently fixed in either one or both lateral ventricles of each rabbit under sodium pentobarbital anesthesia (30 mg/kg, i.v.). Cannula position was verified prior to experimentation by demonstrating a short-latency pressor response to an acute i.v.t. injection of 100 ng of All.

Chronic Intracerebroventricular (i.v.t.) Infusion of All in Conscious Rabbits

Continuous infusion of All into the lateral ventricle was achieved using osmotic minipumps (Alzet Model 2001, Alza Company, Palo Alto, California). Under light sodium pentobarbital anesthesia (10-20 mg/kg, i.v.), a small incision was made in the skin of the neck, and the pump was placed subcutaneously (s.c.). A small length of polyvinyl chloride tubing (tunneled s.c. to the head) was used to connect the prefilled and primed minipump to a previously implanted ventricular cannula. The skin incision was closed with 4-0 silk suture, and the cannula and tubing were covered with dental cement. Minipump replacement was accomplished by reopening the skin incision (under local anesthesia provided by injection of a 2% lidocaine solution), and removing the old pump from the polyvinyl chloride tubing and attaching a new prefilled minipump. Normal saline (0.9% NaCl), 1 or 3 mg/ml All in saline, were infused continuously by the pumps at a rate of 1 µl/hr. Intravenous infusions were accomplished in a similar manner, with the exception that the polyvinyl tubing was inserted (at the time of minipump placement) into the right atrium via a small branch of the jugular vein.

Cardiovascular and Fluid/Electrolyte Measurements

Mean arterial pressure (MAP) was measured directly in conscious rabbits, restrained loosely in a head stock, by percutaneous needle puncture of a dilated central ear artery.14 The needle was connected to a pressure transducer (Statham P23AC) by plastic tubing and pulsatile arterial pressure was recorded for at least 30 minutes on a polygraph. Heart rate was counted directly from the pressure tracing. Some recording sessions were carried out using direct catheterization of the ear artery under local anesthesia (2% lidocaine), when the experiment required arterial pressure and heart rate recordings for several hours.

Plasma volume (PV) and extracellular fluid volume (ECFV) were estimated using the 10-minute distribution space of Evan’s blue dye and the 30-minute distribution space of sodium thiocyanate, respectively.18 Hematocrit (Hct) was measured in triplicate by microcentrifugation. Plasma sodium (PNa) and plasma potassium (Pk) were determined in triplicate by flame photometry.

Daily water intake (WI) was measured using calibrated drinking tubes, and urine output (UO) was determined by 24-hour urine collections. Food intake was measured daily, although the rabbits were limited to a maximum food intake of 100 g/day (Purina High-Fiber Rabbit Chow). Electrolyte content of food (ashed in nitric acid) and urine were determined by flame photometry. Water “balance” (WB) was calculated as daily water intake minus urine output (WI – UO), assuming “insensible” water loss to be constant throughout the experiment.

Experimental Protocol

Chronic All Infusion

At least 1 week after placement of the ventricular cannulas, arterial pressure, heart rate, plasma volume, extracellular fluid volume, plasma sodium, plasma potassium, and hematocrit were determined in the conscious rabbits. Five days of daily fluid/electrolyte measures were then obtained, after which a second series of control cardiovascular and fluid volume measurements were performed. Infusions (either i.v.t. or i.v.) of saline or All were then begun and daily fluid/electrolyte measurements were continued. After 5 days, cardiovascular/volume determinations were repeated, the minipumps were replaced, and another 5 days of daily measurements obtained. At the end of this period, cardiovascular/volume values were again measured, and the ventricular cannula was either plugged or connected to a minipump containing only saline. Finally, another 5 days of daily fluid/electrolyte variables were determined, and a final series of cardiovascular/volume parameters were measured on the fifth day.

“Reversal” of All-Induced Hypertension

At least 1 week after ventricular cannula placement, arterial pressure and heart rate were determined in conscious rabbits, and an i.v.t. infusion of either All (3 µg/hr) or saline was begun. Measurements of arterial pressure and heart rate were repeated on the first, third, and fifth days of infusion; on the fifth day, they were determined by direct catheterization of the central ear artery. Subsequently, their peak steady-state responses to the three following treat-
ments were obtained: 1) a 30-minute i.v. infusion of the All-antagonist saralasin (4 μg/kg/min); 2) a 10 μg i.v.t. bolus (20 μl) of saralasin; and 3) "total" autonomic blockade achieved by sequential i.v. administration of guanethidine sulfate (12 mg/kg), atropine sulfate (1 mg/kg), propranolol hydrochloride (1 mg/kg), and phentolamine hydrochloride (2 mg/kg). The term "total autonomic blockade" is used here in the usual sense of blocking presumably all types of autonomic effector types, as opposed to more selective block of either sympathetic or parasympathetic effectors. The "completeness" of blockade obviously can never be total with competitive pharmacological antagonists. The duration and extent of autonomic blockade produced by the above regimen in rabbits has been documented repeatedly by West and colleagues111 (and references therein). At least 1 hour separated each of the above three tests. In four additional rabbits, All (3 μg/hr) was infused continuously i.v. for 10 days. Measurements of arterial pressure and heart rate were performed on the 2 days prior to initiation of the infusion, and Days 5 and 10 of the infusion period. On Day 10, the response of arterial pressure and heart rate in the conscious rabbits to a 30-minute i.v. infusion of saralasin (4 μg/kg/min) was determined.

Pressor Sensitivity
Rabbits received either All (3 μg/hr) or saline continuously i.v.t. for 5 days, as described above. Arterial pressure and heart rate were determined immediately prior to start of the infusion, and then on Day 5 of the infusion, when the central ear artery and vein were catheterized. Steady-state arterial pressure and heart rate responses to 5-10 minutes of norepinephrine bitartrate infusion (0.3, 1.0, and 3.0 μg/min), All infusion (0.03, 0.1, and 0.3 μg/min), and arginine vasopressin infusion (10, 30, and 100 mU/min) were determined in each rabbit; 30 minutes were allowed for recovery between each different drug infusion.

Plasma Vasopressin Concentration
In four rabbits, plasma arginine vasopressin concentration was determined prior to, during, and following a 5-day i.v.t. infusion of angiotensin (3 μg/hr). On 2 consecutive days, arterial pressure was measured from the ear artery in the conscious rabbits while they sat in a head stock. In addition, 2 ml blood samples were drawn at the end of each recording period. All then was infused i.v.t. for 5 continuous days via previously implanted ventricular canulas, and blood samples and arterial pressure measurements were repeated on Days 1, 3, and 5 of the infusion. The infusion was terminated, and a final blood sample and pressure measurement were obtained 2 days later. Vasopressin was determined in plasma samples (frozen at −20°C until assay) by radiimmmunoassay according to a previously described technique.25

Statistical Analyses
Repeated measurements within rabbits were analyzed using randomized blocks analysis of variance. Individual comparisons were performed using the criterion of least significant differences (l.s.d.). Two sample comparisons were performed using the t test. Pressor sensitivity data were analyzed using a split-plot analysis of variance and Tukey's test for nonconfounded comparisons. Potency ratio was calculated using regression analysis on a 3 X 3 parallel line bioassay model. A probability level of 0.05 was the criterion of statistical significance.

![Figure 1](http://hyper.ahajournals.org/)

**Figure 1.** Cardiovascular and fluid/electrolyte alterations in a rabbit receiving an intracerebroventricular infusion of angiotensin II (3 μg/hr). Dashed lines and open bars represent periods of no infusion; solid lines and black bars represent periods of angiotensin II infusion. Bars represent daily measurements, while dots indicate measurements obtained at 5-day intervals. WI = water intake; PV = plasma volume, ECFV = extracellular fluid volume, UnaV = urinary sodium excretion; UkV = urinary potassium excretion, Pna = plasma sodium, Pk = plasma potassium.
Results

Chronic Infusion of Angiotensin II

Typical results (with the exception of the arterial pressure changes) from a single rabbit receiving a continuous 10-day infusion of 3 μg/hr All i.v.t. are illustrated in figure 1. After initiation of the infusion, arterial pressure rose from 71 to 99 mm Hg by Day 5, and to 102 mm Hg by Day 10 of the infusion. Return of arterial pressure to the control range occurred within 5 days of pump removal. Water intake rose steadily during the 10-day infusion, but returned to control levels between 1 and 2 days after the All infusion was stopped. In this particular rabbit, both plasma and extracellular fluid volumes rose slightly during the first 5 day infusion period, but both returned to control levels by Day 10. Urinary excretion of sodium was increased above control levels for 8 of the 10 days of All infusion, and a rebound decrease in excretion occurred on the second and third postinfusion days. Urinary potassium excretion was increased only slightly during All infusion in this rabbit. Plasma sodium and potassium both fell markedly during All infusion, but had returned to or near control values by 5 days postinfusion.

A summary of the measured variables in all 25 rabbits used in this part of the study (with daily measures expressed as 5-day averages) is shown in figures 2 and 3. In general, the responses to All infused at 1 μg/hr were similar to those observed during 3 μg/hr infusion, but were of a lesser magnitude. Average arterial pressure rose from 75 to 87 mm Hg in rabbits infused with 3 μg/hr All, but exhibited only a transient increase of about 8 mm Hg in rabbits infused with 1 μg/hr All i.v.t. Saline infusion i.v.t. produced no significant changes in arterial pressure. No significant changes in heart rate occurred during any of the infusions. No change in plasma volume was measured in All or saline-infused rabbits, but extracellular fluid volume (on a volume/body weight basis) increased by about 9% during the first 5 days of All infusion at 3 μg/hr i.v.t. However, no correlation was discernible between increases in arterial pressure and increases in extracellular fluid volume in individual rabbits (r = 0.21). A significant, reversible increase in water intake occurred in both groups of All-infused rabbits which was more pronounced when water intake was expressed as a ratio to food intake, since in some rabbits infused with All a modest reversible decrease in food intake was found during the infusion period. (The average decrease in food intake over the 10-day infusion period was 21% in rabbits receiving 3 μg/hr All, and 8% in rabbits receiving 1 μg/hr All). Despite increased water intake during All infusion, urine output increased to an even greater degree, thus producing a decrease in water balance in All-infused animals (significant only in rabbits given 3 μg/hr All). Urinary sodium excretion was increased dramatically in both groups of All-infused rabbits, and fell below control levels in both groups when the All infusion was halted. This event was reflected in All-infused animals by a significant fall in plasma sodium, which tended to return to control values after infusion. Although urinary potassium excretion did not change significantly in the All-infused rabbits, plasma potassium fell significantly in the rabbits given 3 μg/hr All. Body weight was relatively stable in all the rabbits studied, although rabbits receiving 3 μg/hr All i.v.t. tended to lose weight during the first 5 days of the infusion. A small decline in hematocrit in all rabbits is...
indicative of the repeated blood sampling to which they were subjected (about 6 ml every 5 days).

Rabbits given infusions of 1 μg/hr AII i.v. (n = 5) exhibited no significant changes in any of the measured parameters. Rabbits that received 3 μg/hr AII i.v. (n = 5) showed a significant rise in arterial pressure from a control value of 73 mm Hg to 77 mm Hg by Day 5 of the infusion, and to 83 mm Hg by Day 10 of the infusion. Average arterial pressure had returned to 74 mm Hg by 5 days postinfusion. However, no significant change in any other measured parameter was observed in this group of rabbits.

Figure 3. Fluid and electrolyte changes in the same rabbits described in figure 2. Symbols are the same as in figure 2. Points represent 5-day interval measurements for plasma sodium (Pna), plasma potassium (Pk), body weight (B Wt.), and hematocrit (Hct.), and 5-day averages for urinary sodium excretion (UnaV), urinary potassium excretion (UkV), and water/food intakes.

"Reversal" of AII-Induced Hypertension

In five saline-infused rabbits, arterial pressure was 76 ± 3 mm Hg and heart rate was 178 ± 16 bpm before infusion. After 5 days of i.v.t. saline infusion, arterial pressure was 79 ± 3 mm Hg and heart rate was 199 ± 15 bpm. In 10 rabbits given 3 μg/hr AII i.v.t., arterial pressure and heart rate prior to infusion were 75 ± 4 mm Hg and 192 ± 19 bpm, respectively. After 5 days of infusion, arterial pressure was 90 ± 4 mm Hg and heart rate was 204 ± 19 bpm. The effect on arterial pressure of central and peripheral AII antagonism, and "total" autonomic blockade, in these two groups of rabbits are illustrated in figure 4. The depressor actions of 30-minute i.v. infusion of saralasin (4 μg/kg/min), a 10 μg bolus injection of saralasin i.v.t., and "total" autonomic blockade were not significantly different in saline- and AII-infused rabbits. The response of heart rate to these procedures was also identical in the two groups of animals (not shown). The effect of saralasin infusion on arterial

Figure 4. "Reversal" of angiotensin II-induced hypertension. Top graph illustrates changes in mean arterial pressure (MAP) during 5 days of intraventricular infusion of AII (3 μg/hr; n = 10) or saline (n = 5). C = control. ΔMAP = change in mean arterial pressure. Brackets represent SEM. Asterisks (*) indicate a significant (p < 0.05) difference from the group control value.
pressure and heart rate in four additional rabbits receiving 3 μg/hr All i.v. for 10 days is shown in table 1. In these animals, saralasin produced a significant, reversible fall in arterial pressure without a change in heart rate.

Pressor Sensitivity in All-Infused Rabbits

In five rabbits in which saline was infused i.v.t. for 5 days, prior to infusion arterial pressure was 78 ± 4 mm Hg and heart rate, 214 ± 17 bpm; and after 5 days were 78 ± 2 mm Hg and 205 ± 19 bpm. In 5 rabbits given 3 μg/hr All i.v.t., arterial pressure was 78 ± 2 mm Hg and heart rate 199 ± 21 bpm prior to infusion, and after 5 days were 91 ± 2 mm Hg and 182 ± 8 bpm. Figure 5 demonstrates the steady-state pressor and heart rate responses of these two groups of conscious rabbits to i.v. infusions of norepinephrine, All, and vasopressin. Rabbits given 3 μg/hr All i.v.t. exhibited a significant increase in pressor responses to norepinephrine infusion, but not to All or vasopressin, compared to the control rabbits. Rabbits receiving All i.v.t. also had a modest, but significant, decrease in heart rate slowing in response to equivalent pressor stimuli when compared to control animals.

**TABLE 1. Cardiovascular Effect of Saralasin Infusion (4 μg/kg/min) in Four Conscious Rabbits After a 10-Day Infusion of Angiotensin II (3 μg/hr, i.v.)**

<table>
<thead>
<tr>
<th>AP (mm Hg)</th>
<th>HR (bpm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C1</td>
<td>C2</td>
</tr>
<tr>
<td>73 ± 1</td>
<td>73 ± 3</td>
</tr>
<tr>
<td>207 ± 13</td>
<td>192 ± 17</td>
</tr>
</tbody>
</table>

*Significantly different from the C1 value, p < 0.05.
†Significantly different from the All2o value, p < 0.05.

AP = arterial pressure; HR = heart rate; C = control day; All = angiotensin II i.v. day. Values are means ± SEM.

**FIGURE 5** Change in mean arterial pressure (MAP) and heart rate (HR) to intravenous infusion of norepinephrine (NE), angiotensin II (All), and vasopressin (ADH) in rabbits given intraventricular (i.v.t.) infusions of saline (n = 5) or All (3 μg/hr, n = 5) for 5 days. Units for the drug doses are μg/min (NE) and mU/min (ADH). Asterisks (*) indicate a significant (p < 0.05) difference from the response of saline-infused rabbits to the same drug infusion rate. Potency ratios (with 95% confidence limits) of the pressor response to norepinephrine was 1.59 (1.26 - 1.99). Potency ratios for pressor responses to All and ADH were not significantly different from unity.
There were no significant changes in vasopressin blood which plasma vasopressin concentrations were measured during a 5-day i.v.t. infusion of All (3 μg/hr). Furthermore, at a time when arterial pressure is still rising (5 days), plasma volume is not increased. Extracellular fluid volume is elevated on the average in rabbits made hypertensive by i.v.t. All, but the relevance of this finding is uncertain in light of the fact that extracellular fluid volume expansion to correlate with rises in arterial pressure. Chronic i.v.t. infusion of All also is associated with a marked and persistant natriuretic effect sufficient to cause significant hyponatremia. Thus, it appears clear that this form of experimental hypertension is not the direct result of salt or water retention, or vascular volume expansion.

The decrease in arterial pressure produced by autonomic blockade in rabbits made hypertensive by i.v.t. All is identical to that observed in normotensive control rabbits. In other words, blockade of autonomic cardiovascular control does not reverse the hypertensive effects of chronic i.v.t. All. Therefore, hypertension caused by chronic i.v.t. All does not appear to be maintained solely by increased sympathetic nervous system activity. A similar conclusion resulted from two previous studies of this model. However, our experiments do not address the possibility that increased sympathetic activity contributes to the rise in arterial pressure at some early stage of hypertension development.

What then is the mechanism of the hypertension associated with chronic i.v.t. infusion of All? An obvious possibility to be considered is "leak" of All out of the brain into the vascular system, since intravascular infusion of All is known to cause persistent hypertension in rabbits. Although plasma All levels were not measured in our study, several results suggest that an increased intravascular All level is an unlikely cause of the hypertension observed here. First, direct i.v. infusion of All produced only a pressor response roughly equivalent to that observed during i.v.t. infusion of the same dose, despite evidence that little if any of the All infused i.v.t. escapes into the circulation. Thus, leak of All during i.v.t. infusion would be expected to produce a much smaller rise in pressure than that seen during direct i.v.t. infusion of the same dose. Second, the i.v. administration of the angiotensin antagonist saralasin (4 μg/kg/min) did not lower the arterial pressure in rabbits during chronic i.v.t. infusion of All, although similar doses of saralasin are known to effectively lower arterial pressure in rabbits with chronically increased plasma renin activity (and thus presumably raised blood All levels). Furthermore, we confirmed the antagonist potency of this dose of saralasin in our own rabbits that had received direct intravenous infusions of All for 10 days (table 1). Finally, an unaltered pressor response to All infused i.v. in the hypertensive rabbits also is inconsistent with significantly elevated resting concentrations of blood All.

Another possible explanation for the rise in pressure in All-infused rabbits, based on acute responses to i.v.t. All, is an increased rate of secretion of vasopressin. However, the failure to observe alterations in fluid balance consistent with increased blood vasopressin levels, such as plasma or extracellular fluid volume expansion, in the rabbits studied here argue strongly against such a mechanism. Nevertheless, the vasopressin concentrations were directly assessed in four rabbits during a 5-day i.v.t. infusion of All (3 μg/hr), and indeed showed no significant change. This result, combined with an apparently normal pressor sensitivity to vasopressin in rabbits infused chronically with All (figure 5), suggests that the pressor action of vasopressin does not mediate the hypertensive response to chronic i.v.t. infusion of All. Similar findings concerning plasma arginine vasopressin have been reported during chronic i.v.t. infusion of All in rats, as long as access to water was not restricted.

Increased vascular responsiveness to exogenous norepinephrine has been reported previously in dogs made hypertensive by chronic i.v.t. injection of All.

### Table 2. Plasma Arginine Vasopressin (AVP) Concentration in Four Rabbits Receiving Chronic Intracerebroventricular Infusions of Angiotensin II (3 μg/hr)

<table>
<thead>
<tr>
<th>Days</th>
<th>C1</th>
<th>C2</th>
<th>A1</th>
<th>A2</th>
<th>A3</th>
<th>A4</th>
<th>R</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP (mm Hg)</td>
<td>78 ± 2</td>
<td>78 ± 2</td>
<td>84 ± 4</td>
<td>93 ± 2*</td>
<td>86 ± 1*</td>
<td>73 ± 4</td>
<td></td>
</tr>
<tr>
<td>AVP (μU/ml)</td>
<td>2.04 ± 0.27</td>
<td>2.65 ± 0.32</td>
<td>2.79 ± 0.44</td>
<td>1.78 ± 0.24</td>
<td>2.61 ± 0.44</td>
<td>2.51 ± 0.22</td>
<td></td>
</tr>
</tbody>
</table>

C = two consecutive control days; A = 5 days of angiotensin infusion; R = recovery day, 2 days after cessation of angiotensin infusion. Values represent means ± SEM. Asterisks indicate a significant difference from the average of the two control values. MAP = mean arterial pressure.
Our study also revealed an augmented pressor response of conscious rabbits to i.v. norepinephrine. It is of considerable interest that a similar augmentation of pressor sensitivity to norepinephrine has been observed in rabbits during the development of renal hypertension. However, it is hard to reconcile a postulate of increased pressor responsiveness as a pathogenetic factor in i.v.t. AII-induced hypertension with the failure of autonomic blockade to normalize arterial pressure in these animals. Nonetheless, the cardiovascular actions of exogenous norepinephrine may not mimic precisely the effects of norepinephrine released at sympathetic nerve terminals, and it remains a possibility that vascular smooth muscle function could be significantly affected in rabbits infused with AII i.v.t., especially in light of the profound derangement in electrolyte regulation associated with this model.

Finally, as a matter of practical note, it should be pointed out that a bolus i.v.t. injection of the angiotensin antagonist saralasin did not cause an acute reversal of hypertension in rabbits infused chronically with AII i.v.t., although such treatment will abolish the pressor response to a maximal dose of AII injected as a bolus (unpublished observations). This finding is not completely surprising since the onset of hypertension during i.v.t. infusion of AII at the doses used here can take 1-3 days to become manifest, and the return of AP to normal following cessation of infusion also can be delayed for over 5 days, suggesting a more slowly developing mechanism for the hypertension of chronic AII infusion, as opposed to the rapid hypertensive response to acute i.v.t. injections of AII. Thus, one might be led to question the interpretation of studies in which the possibility of a central pressor action of AII in various forms of hypertension is inferred from acute depressor responses to a single i.v.t. bolus of saralasin.

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