Role of the Renin-Angiotensin System in the Control of Vasopressin Secretion in Conscious Dogs

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SUMMARY. The present studies were designed to evaluate the physiological significance of angiotensin II in the control of vasopressin secretion in conscious dogs. They demonstrated that exogenous angiotensin II (10 ng/kg per min) increased vasopressin secretion more when the pressor effect of angiotensin II was abolished. The fact that endogenous angiotensin II levels are normally increased without an increase in arterial pressure suggests that angiotensin II may play a greater role in the control of vasopressin secretion than was previously thought. The present study also evaluated the role of endogenous angiotensin II in the control of vasopressin secretion during sodium depletion, a state in which angiotensin II levels are elevated. Intracarotid infusion of a low dose of the angiotensin II antagonist, saralasin, decreased plasma vasopressin concentration, suggesting that endogenous angiotensin II acts in an area of the brain perfused by the carotid arteries to stimulate vasopressin secretion in sodium-deprived dogs. Finally, the present experiments evaluated the role of angiotensin II in baroreceptor reflex control of vasopressin secretion. Baroreflex function was assessed by examining the relationship between the change in blood pressure and the log of the change in vasopressin secretion over a range of blood pressure levels. Exogenous angiotensin II (10 ng/kg per min) altered baroreflex function by causing a shift of this relationship to a higher pressure level in sodium-replete dogs. In sodium-depleted dogs, inhibition of the renin-angiotensin system with saralasin or captopril produced an opposite shift. These results suggest that endogenous angiotensin II may be necessary for the maintenance of normal baroreflex control of vasopressin secretion during sodium depletion. Collectively, these results support the hypothesis that endogenous angiotensin II plays a role in the control of vasopressin secretion. (Circ Res 58: 829-838, 1986)

THERE have been reports that intravenous infusion of angiotensin II (All) stimulates vasopressin secretion (Bonjour and Malvin, 1970; Unlich et al., 1975; Padfield and Morton, 1977; Ramsay et al., 1978a; Reid et al., 1982), but it is not clear whether this effect of All is physiologically important. The purpose of the present investigation was to examine the physiological significance of All in the control of vasopressin secretion. Three experimental approaches were used.

Previous attempts to analyze the role of All in the control of vasopressin secretion have evaluated whether doses of All that produce plasma levels within the physiologial range are sufficient to stimulate vasopressin release. For example, Ramsay et al. (1978) reported that physiological concentrations of All were capable of increasing plasma vasopressin levels. However, we and others have observed that supraphysiological doses are required (Padfield and Morton, 1977; Reid et al., 1982). Possibly, high levels of All are needed because the pressor effect of All, by stimulating baroreceptor pathways (Schrier et al., 1979), inhibits the release of vasopressin. This possibility was examined recently by Mitchell et al. (1982), who reported that intravenous All injections inhibited the activity of supraoptic magnocellular neurons. However, after sinoaortic denervation, All increased the firing rate of these neurons (Mitchell et al., 1982). These results were interpreted as evidence that the pressor effect of All, by acting via baroreceptors, counteracts the stimulatory action of All on vasopressin release. The first set of experiments in the present study were designed to test this hypothesis more directly. In these experiments, the effect of All on plasma vasopressin concentration was examined in conscious dogs while the increase in blood pressure produced by All was eliminated by simultaneous infusion of the vasodilator, nitroprusside.

Another approach that has been used to study the role of All in the control of vasopressin secretion involves the administration of antagonists of the renin-angiotensin system to animals with elevated plasma All levels. In previous studies, this approach has provided evidence that All is involved in the release of vasopressin that follows injection of isoproterenol and furosemide, two agents which increase renin secretion (Ramsay et al., 1978b; Siegel et al., 1979; Knepel and Meyer, 1980). In addition, it has been suggested that All may contribute to the elevated vasopressin levels in dehydrated rats (Yamaguchi et al., 1980, 1982; Keil et al., 1983). How-
ever, All has not been implicated in the increase in vasopressin levels provoked by hemorrhage (Claybaugh and Share, 1972, 1973). Our second purpose, in the present study, was to evaluate the role of All in the control of vasopressin secretion during sodium depletion, another state in which plasma All levels are elevated. In these experiments, the All antagonist, saralasin, was infused into the carotid or vertebral arteries of chronically prepared conscious dogs.

The last group of experiments extended the experiments described above in which saralasin was infused into the blood supply to the brain of sodium-depleted dogs. In those experiments, saralasin was also infused intravenously. As expected, this treatment caused hypotension, emphasizing the important role of All in the maintenance of blood pressure during sodium depletion. However, saralasin infusion had no effect on plasma vasopressin concentration despite the fact that hypotension normally stimulates vasopressin secretion (Schrier et al., 1979). Experiments therefore were performed to determine why plasma vasopressin concentration did not increase when blood pressure was decreased by saralasin.

Two hypotheses were tested. One is that baroreflex control of vasopressin secretion is altered by sodium depletion. Sodium-deprived dogs do not exhibit tachycardia in response to carotid occlusion (Rocchini et al., 1977; Szlagy et al., 1981). In addition, the reflex increase in renal nerve activity produced by hypotension is reduced in sodium-depleted dogs (Takishita and Ferrario, 1982). To evaluate whether baroreflex control of vasopressin secretion is also affected, we compared the relationship between blood pressure and plasma vasopressin in sodium-deprived and sodium-replete dogs.

A second hypothesis is that saralasin blocks the reflex release of vasopressin that is elicited by a fall in blood pressure. More specifically, it is possible that endogenous All contributes to the vasopressin response to hypotension in sodium-depleted dogs, and that saralasin blocks this action. To test this hypothesis, we examined the relationship between blood pressure and vasopressin secretion before and after blockade of the renin-angiotensin system in sodium-depleted dogs.

Methods

Mongrel dogs of either sex weighing between 16 and 32 kg were used.

Surgical Preparation

Subcutaneous injections of acepromazine maleate (1 mg/kg; Ayerst Laboratories, Inc.) were administered, and then the dogs were anesthetized with pentobarbital sodium (15 mg/kg, iv). Silastic canulas (0.5 mm i.d.) were placed into a femoral artery and vein and were advanced into the abdominal aorta and vena cava. The dogs then were divided into three groups. In some dogs of the first and third groups, right atrial catheters were placed via a jugular vein, or left atrial catheters were placed via a left thoracotomy. In the second group of dogs, both carotid and both vertebral arteries were exposed, and small Tygon canulas (0 1 or 0 30 mm i.d.) were implanted, without occluding blood flow, into each vessel. Each cannula was held in place with a purse-string suture (Tevdek 4-0 cardiovascular suture). All catheters were led subcutaneously to an area between the scapulae, where they exited and were protected by a nylon jacket (Medical Arts). Vertebral and carotid catheters were flushed daily with isotonic saline and filled with sodium heparin (1000 U/ml); the remaining catheters were flushed 3 times a week. In most dogs, a minimum of 7 days elapsed before the first experiment was performed. Dogs that were subjected to a thoracotomy were allowed at least 2 weeks to recover. All dogs received penicillin and streptomycin (Henry Schein, Inc.; 3 ml/day, im) for 5 days after surgery. After surgery, the dogs were fed one of two diets. Sodium-replete dogs were fed a diet which provided approximately 70 mEq/day sodium. Sodium-deprived dogs were fed two cans H/D Prescription diet (Hills Pet Products), which provided approximately 10 mEq/day sodium, and were injected im with furosemide (20 mg) on alternate days for 1 week.

Experimental Protocols

On the day of the experiment, the dogs were brought to the laboratory where they stood, loosely restrained by a nylon sling. Mean and pulsatile arterial pressure and heart rate were measured via the femoral arterial canula with a Statham Strain gauge and a Grass polygraph. Right and left atrial pressures also were measured. Transducers were placed so that the zero pressure point was at the level of the heart. Because of the difficulty of accurately determining the zero reference point for atrial pressures, we analyzed the atrial pressure data by paired t-test or by analysis of variance for repeated measures, which adjusts for differences in baseline values between dogs (Winer, 1971), and by analyzing the change in atrial pressure from control values.

After a 45-minute equilibration period, one of the following three groups of experiments was performed.

Group I. The Effect of All and Nitroprusside on Vasopressin Secretion

Protocol I. These experiments were performed in sodium-replete dogs (n = 7). Immediately after collection of a control arterial blood sample, an infusion (0.5 ml/min) of All (10 ng/kg per min; Schwarz-Mann or Bachem) dissolved in 5% dextrose was begun. Fifteen minutes later, another arterial blood sample was collected, and an intravenous infusion of nitroprusside (Nipride, Roche Laboratones) dissolved in 5% dextrose at 0.3 μg/kg per min was begun while the All infusion was continued. Every 15 minutes, another blood sample was collected, and the dose of nitroprusside was increased until a total of four doses had been given (0.3, 0.6, 1.5, 3.0 μg/kg per min). All blood samples (13 ml) were replaced with an equal volume of isotonic saline. In control experiments, the dogs received the nitroprusside infusions without All (n = 7), and also received intravenous infusions (0.5 ml/min) of the drug vehicle (n = 5).

Protocol II. Experiments were performed to determine the effect of eliminating the pressor effect of All with another vasodilator, hydralazine (Apresoline HCl, Taylor Pharmcral Co.). Two control arterial blood samples, 15 minutes apart, were collected, and one of three 30-minute infusions was begun. Dogs received either All alone (10
ng/kg per min) (n = 7) or the same dose of All with either nitroprusside (3 μg/kg per min) or hydralazine (15–20 mg bolus). Blood samples (13 ml) were collected 15 and 30 minutes after the experimental infusion was begun. Thirty minutes were allowed after terminating the experimental infusions, and a recovery sample was collected. All and nitroprusside were diluted with 5% dextrose.

**Group II. The Effect of Intracarotid, Intravertebral, and Intravenous Infusion of Saralasin on Plasma Vasopressin Concentration in Sodium-Deprived Dogs**

**Protocol I.** After a control blood sample was obtained [Sar<sup>1</sup>,Ala<sup>8</sup>]-AII (saralasin; Bachem), dissolved in isotonic saline was infused for 30 minutes into both carotid or both vertebral arteries. Three doses (0.1, 0.3, and 1 μg/kg per min per pair of arteries) were infused, each on a different day. The experimental infusion was followed by a 45-minute recovery period. Subsequently, the same dose of saralasin was infused intravenously for 30 minutes, and the experiment ended after a final 45-minute recovery period. In some dogs, the intravenous infusion was performed first. Blood samples were collected immediately before and 15 and 30 minutes after the start of the saralasin infusions, and also at the end of each recovery period.

**Protocol II.** In four dogs, the isotonic saline vehicle was infused either into both carotid arteries, or into both vertebral arteries and intravenously, as described in Protocol I.

**Protocol III.** Experiments were performed to test the effectiveness of the saralasin infusions. First, All (4 ng/kg per min per pair of arteries) was infused for 15 minutes into either both carotid or both vertebral arteries. After a 15-minute recovery period, an infusion of the lowest dose of saralasin (0.1 μg/kg per min) was begun into the same vessels. After 20 minutes, All (4 ng/kg per min per pair of arteries) was again infused for 15 minutes, along with saralasin. Blood samples were collected before, at the end of, and 15 minutes after, each All infusion.

**Group III. Effect of Sodium Depletion and All Blockade on the Relationship Between Blood Pressure and Plasma Vasopressin Concentration**

These experiments were performed in sodium-deprived conscious dogs according to the protocol described in group I, protocol I. A control arterial blood sample was collected and an intravenous infusion of saralasin (1 μg/kg per min) or captopril (20 μg/kg per min following a 1 mg/kg prn: E.R. Squib & Sons, Inc.) dissolved in 5% dextrose was begun. Fifteen minutes later, a second blood sample was collected, and infusion of nitroprusside (0.3 μg/kg per min) was begun, along with saralasin or captopril. Subsequently, the dose of nitroprusside was increased every 15 minutes until a total of four doses were given. Blood samples were collected just before the dose of nitroprusside was changed. In separate experiments, sodium-deprived dogs also received nitroprusside alone. The saralasin and nitroprusside experiment was also repeated in a group of sodium-replete dogs.

In all experiments, blood was collected into chilled, heparinized plastic tubes and centrifuged. Plasma was analyzed for arginine vasopressin by radioimmunoassay (Keil and Severs, 1977).

**Data Analysis**

**Groups I and III**

In experiments in which four doses of nitroprusside were infused, the relationship between blood pressure and plasma vasopressin concentration was obtained. Since this relationship is exponential, a linear relationship is generated when the log (change in plasma vasopressin concentration) is plotted vs. the change in arterial blood pressure. The lines drawn in the figures were obtained by first calculating the mean ± SEM of the change in blood pressure and the log of the mean ± SEM of the change in plasma vasopressin concentration for each dose of nitroprusside. A line of best fit then was calculated for these data by least squares analysis, and this is depicted graphically in the figures. For statistical purposes, a regression equation was calculated by least squares analysis of the log (change in plasma vasopressin concentration) vs. the change in blood pressure for all the individual values collected in each group, and groups were compared by testing for differences in slope and intercept (Winer, 1971). In experiments in which one dose of nitroprusside or hydralazine was administered with All, differences between groups were determined by Student's t-test (Winer, 1971).

**FIGURE 1. Relationship between the change in blood pressure and the log of the change in plasma vasopressin concentration during intravenous infusion of nitroprusside (NP) (n = 7) or nitroprusside and angiotensin II (NP + All) (n = 7). Control blood pressures were 109 ± 1 (NP) and 105 ± 2 (NP + All) mm Hg. Control vasopressin levels were 2.0 ± 0.4 (NP) and 2.1 ± 0.4 (NP + All) pg/ml. n = number of dogs.**
had returned to control levels, and plasma vasopressin concentration was increased by 11.9 ± 1.9 pg/ml (P < 0.001). Thus, All produced a larger increase in vasopressin levels (P < 0.001) when the pressor effect of All was abolished. Also illustrated in Figure 1 is the relationship between blood pressure and plasma vasopressin concentration produced by nitroprusside infusion alone. Plasma vasopressin concentration rose as blood pressure decreased, and the log of the vasopressin change was linearly related to the blood pressure fall (Fig. 1; Table 1). All significantly increased the intercept of this line (P < 0.001) while displacing it to the right (Table 1).

In another group of experiments, a second vasodilator, hydralazine, was used to eliminate the pressor effect of All. A 30-minute infusion of All alone (n = 6) increased blood pressure from 97 ± 2 to 134 ± 2 mm Hg (P < 0.001) and increased plasma vasopressin levels from 3.1 ± 0.3 to 5.1 ± 0.9 pg/ml (P = 0.05). In the presence of hydralazine (n = 8), All had no effect on arterial pressure (101 ± 3 to 103 ± mm Hg; P > 0.10) and increased plasma vasopressin concentration from 3.4 ± 0.3 to 38.8 ± 7.3 pg/ml (P < 0.001). Similarly, with nitroprusside and All infusion (n = 5), blood pressure did not change (103 ± 2 to 104 ± 2 mm Hg; P > 0.10), and plasma vasopressin increased from 3.0 ± 0.4 to 19.1 ± 5.9 pg/ml (P < 0.05). Thus, All produced a larger increase in plasma vasopressin concentration when the pressor response was eliminated by either hydralazine (P < 0.001) or nitroprusside (P < 0.05).

Group II: Effect of Intravertebral, Intracarotid, and Intravenous Saralasin Infusion on Plasma Vasopressin Concentration in Sodium-Deprived Dogs

Neither intravertebral nor intravenous infusion of any dose of saralasin decreased plasma vasopressin

### Table 1

**Effect of Angiotensin II, Saralasin, and Captopril on Baroreflex Function Relationships in Sodium-Replete and -Depleted Conscious Dogs**

<table>
<thead>
<tr>
<th>Protocol</th>
<th>Slope</th>
<th>Intercept</th>
<th>r²</th>
</tr>
</thead>
<tbody>
<tr>
<td>NP (replete)</td>
<td>-0.081</td>
<td>-0.237</td>
<td>0.63</td>
</tr>
<tr>
<td>NP + All (replete)</td>
<td>-0.031*</td>
<td>0.878*</td>
<td>0.46</td>
</tr>
<tr>
<td>NP + SAR (replete)</td>
<td>-0.025*</td>
<td>0.260</td>
<td>0.26</td>
</tr>
<tr>
<td>NP (depleted)</td>
<td>0.054</td>
<td>0.070</td>
<td>0.57</td>
</tr>
<tr>
<td>NP + SAR (depleted)</td>
<td>-0.046</td>
<td>-0.766f</td>
<td>0.45</td>
</tr>
<tr>
<td>NP + CAP (depleted)</td>
<td>-0.049</td>
<td>-1.035f</td>
<td>0.54</td>
</tr>
</tbody>
</table>

Values are slopes and intercepts of the linear equation log (change in plasma vasopressin concentration) = slope - (change in plasma vasopressin concentration obtained from Winer, 1971).

*p < 0.001 compared to NP-replete group
† P < 0.05 compared to NP-depleted group

### Table 2

**Effect of Intravertebral, Intracarotid, and Intravenous Saralasin Infusion on Plasma Vasopressin Concentration in Conscious, Sodium-Deprived Dogs**

<table>
<thead>
<tr>
<th>Dose of saralasin (µg/kg per min)</th>
<th>Control</th>
<th>Intravertebral</th>
<th>Recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1 (6)</td>
<td>2.0 ± 0.5</td>
<td>2.2 ± 0.6</td>
<td>2.4 ± 0.7</td>
</tr>
<tr>
<td>0.3 (6)</td>
<td>2.7 ± 0.8</td>
<td>2.1 ± 0.6</td>
<td>3.0 ± 0.7</td>
</tr>
<tr>
<td>1.0 (4)</td>
<td>2.8 ± 1.0</td>
<td>2.3 ± 0.7</td>
<td>2.2 ± 0.5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Control</th>
<th>Intracarotid</th>
<th>Recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1 (5)</td>
<td>1.2 ± 0.1</td>
<td>2.5 ± 1.1</td>
</tr>
<tr>
<td>0.3 (6)</td>
<td>2.1 ± 0.4</td>
<td>2.4 ± 0.5</td>
</tr>
<tr>
<td>1.0 (4)</td>
<td>1.7 ± 0.1</td>
<td>1.1 ± 0.2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Control</th>
<th>Intravenous</th>
<th>Recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1 (9)</td>
<td>2.5 ± 0.5</td>
<td>2.4 ± 0.7</td>
</tr>
<tr>
<td>0.3 (9)</td>
<td>2.9 ± 0.4</td>
<td>2.7 ± 0.4</td>
</tr>
<tr>
<td>1.0 (7)</td>
<td>2.5 ± 0.7</td>
<td>3.0 ± 1.0</td>
</tr>
</tbody>
</table>

Values are means ± sem of plasma vasopressin concentration (pg/ml) Numbers in parentheses are the number of dogs in each group NS = no significant change (P > 0.05).
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concentration (Table 2). The two lowest doses of saralasin infused into the carotid arteries also failed to affect vasopressin levels; however, the highest dose (1 µg/kg per min) produced a significant decrease (Table 2) \( (P < 0.05) \). The effect of intravertebral, intracarotid, and intravenous saralasin infusion on mean arterial pressure is summarized in Table 3. Saralasin produced a dose-dependent decrease in blood pressure with each route of administration (Table 3).

The saline vehicle was infused intravenously and into the carotid arteries (two dogs) or intravenously and into the vertebral arteries (two dogs). Neither intracarotid, intravertebral, nor intravenous saline infusion altered plasma vasopressin concentration or blood pressure.

We performed experiments in five dogs to verify adequate AII blockade with the doses of saralasin used in these experiments. Infusion of AII (4 ng/kg per min) into the carotid arteries increased plasma vasopressin levels from 1.9 ± 0.6 to 3.7 ± 1.1 pg/ml \( (P = 0.01) \). After a 20-minute infusion of the lowest dose of saralasin (0.1 µg/kg per min), AII had no effect on plasma vasopressin concentration (2.0 ± 0.5 to 2.1 ± 0.7 pg/ml; \( P > 0.10 \)).

**Group III: The Effect of Sodium Depletion and Blockade of the Renin-Angiotensin System on the Relationship between Blood Pressure and Plasma Vasopressin Concentration**

The relationship between plasma vasopressin concentration and blood pressure obtained in sodium-deprived dogs from group II treated with three intravenous doses of saralasin is compared to the relationship obtained from sodium-replete dogs treated with nitroprusside (Fig. 2). Although blood pressure fell by up to 25 mm Hg, vasopressin levels did not increase with saralasin infusion. This result is in marked contrast to the increase in vasopressin produced by nitroprusside in sodium-replete dogs (group I) (Figs. 1 and 2).

The final groups of experiments examined why vasopressin did not rise as blood pressure fell with saralasin in sodium-depleted dogs. One hypothesis

### Table 3

<table>
<thead>
<tr>
<th>Dose of saralasin (µg/kg per min)</th>
<th>Control</th>
<th>Intravertebral</th>
<th>Recovery</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1 (6)</td>
<td>103 ± 1</td>
<td>98 ± 2</td>
<td>96 ± 3</td>
<td>104 ± 4</td>
</tr>
<tr>
<td>0.3 (6)</td>
<td>104 ± 2</td>
<td>96 ± 3</td>
<td>90 ± 3</td>
<td>105 ± 2</td>
</tr>
<tr>
<td>1.0 (4)</td>
<td>104 ± 2</td>
<td>90 ± 3</td>
<td>85 ± 3</td>
<td>101 ± 3</td>
</tr>
<tr>
<td>Control</td>
<td></td>
<td>Intracarotid</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.1 (5)</td>
<td>102 ± 5</td>
<td>101 ± 5</td>
<td>96 ± 4</td>
<td>101 ± 5</td>
</tr>
<tr>
<td>0.3 (6)</td>
<td>105 ± 3</td>
<td>98 ± 4</td>
<td>93 ± 4</td>
<td>104 ± 4</td>
</tr>
<tr>
<td>1.0 (4)</td>
<td>103 ± 5</td>
<td>92 ± 5</td>
<td>83 ± 5</td>
<td>101 ± 3</td>
</tr>
<tr>
<td>Control</td>
<td></td>
<td>Intravenous</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.1 (9)</td>
<td>103 ± 3</td>
<td>97 ± 3</td>
<td>94 ± 3</td>
<td>101 ± 2</td>
</tr>
<tr>
<td>0.3 (9)</td>
<td>105 ± 2</td>
<td>93 ± 3</td>
<td>88 ± 3</td>
<td>101 ± 2</td>
</tr>
<tr>
<td>1.0 (7)</td>
<td>100 ± 3</td>
<td>81 ± 2</td>
<td>75 ± 3</td>
<td>101 ± 3</td>
</tr>
</tbody>
</table>

Values are means ± SEM of blood pressure (mm Hg) Numbers in parentheses are the number of dogs in each group.
was that sodium depletion alters baroreflex control of vasopressin secretion. The relationship between blood pressure and plasma vasopressin concentration following nitroprusside in sodium-replete and sodium-depleted dogs is summarized in Figure 3. Hypotension induced similar increases in vasopressin in both groups of animals (Fig. 3), and the regression lines were not different (Table 1).

A second hypothesis was that saralasin affects baroreceptor control of vasopressin secretion such that a smaller rise in vasopressin is elicited for a given decrease in blood pressure. To test this hypothesis, we examined the relationship between blood pressure and vasopressin in the presence and absence of saralasin (Fig. 4). In saralasin-treated dogs, hypotension elicited a rise in vasopressin secretion; however, the relationship between blood pressure and vasopressin concentration was shifted to the left (Fig. 4) compared to dogs that received nitroprusside alone. There was a significant decrease in intercept without a change in slope (Table 1). Inhibition of AII production with captopril had a similar effect on the line relating blood pressure to the log of the change in vasopressin concentration (Fig. 5; Table 1). Saralasin did not affect the intercept of this line in sodium-replete dogs (Table 1, Fig. 6), although the slope was slightly depressed (Table 1).

Discussion

Does the Pressor Effect of Infused AII Inhibit Vasopressin Secretion?

Bonjour and Malvin (1970) presented the first direct evidence that increases in plasma AII levels stimulate vasopressin secretion. Numerous subsequent reports demonstrated that intracerebroventricular injection of AII also increases vasopressin release (Mouw et al., 1971; Keil et al., 1975); however,
the stimulatory effect of systemic All administration originally observed by Bonjour and Malvin has proved difficult to duplicate. Part of the inconsistency may be due to the fact that some experiments have been performed in anesthetized animals. In these experiments, intravenous infusion of a wide range of doses of All has consistently failed to stimulate vasopressin secretion (Claybaugh et al., 1972; Shade and Share, 1975; Cadnapaphornchai et al., 1975). Another explanation may be species differences, since rats, for example, appear to be relatively insensitive to All (Kneipel and Meyer, 1980).

More consistent results have been obtained in experiments performed in conscious dogs and human subjects. Most investigators agree that intravenous All infusion can increase vasopressin release (Bonjour and Malvin, 1970; Ramsay et al., 1978; Uhlich et al., 1975); however, in some cases, large doses of All were required (Reid et al., 1982; Padfield and Morton, 1977), making the physiological significance of this effect uncertain. It is possible that high levels of exogenous All are needed to increase vasopressin secretion because the pressor effect of All counteracts a direct stimulatory action of All on vasopressin secretion. A major finding of the present study is that intravenous All infusion produces a larger increase in plasma vasopressin concentration when the pressor effect of All is eliminated by a simultaneous nitroprusside infusion. Thus, the rise in blood pressure does appear to interfere with a stimulatory action of All on vasopressin release. Since increases in endogenous All levels usually occur without increases in blood pressure, the stimulatory effect of All on vasopressin...
secretion would normally be unopposed. These results therefore suggest that All may play a greater role in the control of vasopressin secretion than was previously thought.

It is possible that nitroprusside infusion increased the vasopressin response to All by some action other than by counteracting the pressor response. This seems unlikely, however, since hydralazine, another vasodilator, also enhanced the vasopressin response. Furthermore, in preliminary experiments, we observed that the vasopressin response to nitroprusside is eliminated by denervation of both high pressure (carotid sinus and aortic arch) and low pressure (cardiopulmonary) baroreceptors: plasma vasopressin concentration increased during nitroprusside infusion from 5.7 ± 0.9 to 70 ± 25 pg/ml in intact dogs (P < 0.05, n = 4) but was unaltered in denervated dogs [3.9 ± 0.9 to 7.9 ± 2.7; P > 0.10, n = 3 (Brooks, Quillen, Keil, and Reid, unpublished results)]. Thus, it appears that nitroprusside increases vasopressin secretion by lowering blood pressure and by activation of baroreceptor pathways. The enhanced response was also not due to further increases in plasma All levels produced by nitroprusside-induced decreases in blood pressure. Plasma All levels were measured during All infusion and were not altered by simultaneous nitroprusside infusion (Brooks and Reid, 1986). It was shown that nitroprusside lowers right atrial pressure below control levels, both when infused alone and when infused in combination with All (Brooks and Reid, 1986). Thus, it is possible that the additional increase in vasopressin secretion produced by nitroprusside during All infusion was due to stimulation of right atrial stretch receptors. Although this possibility cannot be definitely ruled out, in most cases the smallest dose of nitroprusside decreased right atrial pressure to the lowest level, and higher doses did not increase pressure further. As a result, there was no correlation between the changes in right atrial pressure and plasma vasopressin concentration during either nitroprusside (r² = 0.08, P > 0.10) or nitroprusside and All (r² = 0.09, P > 0.10) infusion. Because a significant correlation was observed between the changes in arterial pressure and vasopressin concentration, this suggests, in agreement with the studies by Brennan et al. (1971) and Schultz et al. (1982), that decreases in right atrial pressure may not have an important influence on vasopressin secretion. The lack of a correlation also suggests that the enhanced vasopressin response to All produced by nitroprusside was not due to a fall in right atrial pressure. Finally, changes in left atrial pressure tended to parallel changes in mean arterial pressure. All increased left atrial pressure, and simultaneous nitroprusside infusion decreased left atrial pressure to control levels (Brooks and Reid, 1986). Since changes in left atrial pressure may have a profound influence on vasopressin release (Schultz et al., 1982), it is probable that nitroprusside amplified the vasopressin response by lowering both elevated arterial and left atrial pressures back to control levels.

A second finding of the present study is that the relationship between blood pressure and plasma vasopressin concentration produced by nitroprusside infusion is shifted to the right during All infusion. This suggests that the effects of All to reset baroreflex control of vasopressin secretion to a higher pressure level are similar to its effects on baroreflex control of heart rate and ACTH (Brooks and Reid, 1986). The slope of the function curve also was depressed during All infusion, but this may be because baroreflex function curves are sigmoid, and a different range of pressures was studied during All and nitroprusside compared to nitroprusside alone.

The mechanism of this shift with All is not clear, but we offer three possibilities. First, it has been demonstrated that arterial stretch receptors rapidly reset to sustained changes in blood pressure, with a shift in the function curves relating blood pressure to baroreceptor activity in the direction of the pressure change (Dorward et al., 1982; Munch et al., 1983; Heesch et al., 1984). Therefore, it is possible that the pressor effect of All caused the shift in the function curves. If this is the case, it would be expected that All would produce a larger increase in plasma vasopressin concentration at control pressure in the experiment in which the pressor effect of All was slowly reduced with increasing doses of nitroprusside, compared to the experiment in which All and the highest dose of nitroprusside were infused simultaneously, and pressure never changed. However, similar increases in plasma vasopressin concentration were observed, suggesting that the vasopressin rise and the shift of the function curves were not dependent on the blood pressure increase. Second, it is possible that All acts on the brain to stimulate vasopressin secretion, and as blood pressure falls when nitroprusside is simultaneously infused, there is an additional and independent stimulation which is mediated by the baroreceptors. Thus, at any given blood pressure, vasopressin secretion would be higher and the relationship between blood pressure and vasopressin would be shifted to the right.

Another possibility is that All acts somewhere within the baroreflex loop to alter baroreceptor control of vasopressin release. The fact that All also affects baroreceptor control of heart rate and ACTH (Brooks and Reid, 1986) and baroreflex control of lumbar sympathetic activity (Guo and Abboud, 1984; Schmid et al., 1985) is consistent with this possibility, and suggests that All may act early in the baroreflex loop. However, there is evidence that All does not exert a direct action on either the carotid sinus or aortic arch baroreceptors (McCubbin et al., 1957; Lumbers et al., 1979; Guo and Abboud, 1984). Therefore, All may act at an area of the brain which is involved in cardiovascular control and which is
Does Endogenous Angiotensin II Affect Vasopressin Levels and Baroreflex Control of Vasopressin Secretion in Sodium-Depleted Dogs?

It previously has been shown that intracarotid ALL infusion stimulates vasopressin secretion, whereas intravertebral infusion of ALL is either ineffective or increases plasma vasopressin levels (Reid et al., 1982). A second purpose of the present experiments was to evaluate whether the elevated ALL levels in sodium-depleted dogs act via either the carotid or vertebral circulation to affect vasopressin release. In these experiments, the competitive ALL antagonist saralasin was infused into the carotid or vertebral arteries of conscious sodium-deprived dogs.

Intracarotid infusion of the two lowest doses of saralasin had no effect on plasma vasopressin concentration; however, the highest dose significantly reduced plasma vasopressin levels. Because neither intravenous nor intravertebral infusion of the same dose of saralasin depressed plasma vasopressin levels, it is possible that chronic elevations in endogenous ALL stimulate vasopressin secretion in sodium-deprived dogs by acting in an area of the brain perfused by the carotid arteries.

It is significant that intravertebral and intravenous infusion of saralasin generally did not affect vasopressin concentration. This result was somewhat surprising, since saralasin also produced large decreases in blood pressure, and hypotension normally stimulates vasopressin secretion (Schrier et al., 1979). The final group of experiments examined why vasopressin secretion did not increase during intravenous saralasin infusion in sodium-deprived conscious dogs.

One possibility is that some aspect of sodium depletion alters baroreflex function. However, a comparison of the relationship between blood pressure and plasma vasopressin concentration revealed no differences between sodium-replete and sodium-depleted dogs. Thus, the release of vasopressin induced by decreases in blood pressure is unchanged by sodium depletion.

Another possibility is that saralasin infusion affects the reflex release of vasopressin elicited by a fall in blood pressure in sodium-deprived dogs. This possibility is supported in the present experiments by the finding that ALL blockade with either saralasin or captopril produced a parallel shift to the left in the relationship between blood pressure and the log of plasma vasopressin concentration without affecting the slope or sensitivity of the relationship. Thus, during ALL blockade, blood pressure was required to fall to a lower level before vasopressin release was elicited, suggesting that endogenous ALL acts to reset the baroreflex during sodium depletion.

Endogenous ALL levels are increased in sodium-depleted animals; therefore, it may seem contradictory that resting vasopressin secretion is not increased, and that baroreflex function curves are not shifted to higher pressure levels in sodium-depleted dogs compared to sodium-replete dogs (Fig. 3), thereby mimicking the effects of exogenous ALL infusion (Fig. 1). This result suggests that some other factor is shifting the curves to a lower pressure level during sodium depletion, and that ALL acts to maintain a normal relationship between blood pressure and vasopressin by shifting the relationship back to the right. The factors that offset baroreflex activity during sodium depletion were not investigated in the current study, but they probably are related to the decreased blood volume of these animals, and may include exaggerated vagal afferent activity (Szilagyi et al., 1981; Takishita and Ferrario, 1982). Thus, the role that the chronically elevated levels of ALL play in maintaining normal baroreflex control of vasopressin secretion is very similar to the role ALL plays in maintaining normal blood pressure via its vasoconstrictor effect.

Saralasin slightly depressed the slope of the relationship between blood pressure and vasopressin concentration in sodium-replete dogs. The antagonist appeared to diminish the reflex release of vasopressin observed with the largest falls in blood pressure, suggesting that increases in plasma ALL levels resulting from large decreases in blood pressure may contribute to the vasopressin rise produced by hypotension in sodium-replete dogs.

The mechanism of the shift produced by saralasin or captopril in sodium-depleted animals is unknown. It was shown that when blood pressure is reduced by nitroprusside, plasma ALL levels increase (Brooks and Reid, 1986). These elevated ALL levels may then act on the brain to release vasopressin. It is possible that saralasin blocked this action and reduced the vasopressin response to a given decrease in pressure. The result would be a shift to the left in the relationship between blood pressure and vasopressin.

A second possible mechanism for the shift produced by ALL blockade is that the elevated levels of ALL in sodium-depleted dogs act within the baroreflex loop to maintain normal control of vasopressin release, and that saralasin and captopril block this
effect. Thus, in the presence of All blockade, the baroreflex setpoint is decreased and blood pressure must fall to a lower level before vasopressin secretion is stimulated. Further experiments are required to distinguish between these possibilities.

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INDEX TERMS: Renin-angiotensin system • Baroreceptor reflex • Saralasin • Captopril • Brain • Carotid and vertebral arteries • Nitroprusside
Role of the renin-angiotensin system in the control of vasopressin secretion in conscious dogs.

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