Vasopressin Elevation in Essential Hypertension and Increased Responsiveness to Sodium Intake

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SUMMARY  The relationship of arterial pressure (AP) to plasma arginine vasopressin (AVP) and sodium (Na) intake was determined in untreated essential hypertensive (H) and normotensive (N) subjects. The AP of H subjects averaged 147/101 mm Hg and that of N subjects, 124/79 mm Hg. Plasma AVP was elevated significantly in H subjects, averaging 8.5 pg/ml compared to 4.7 pg/ml in N subjects. Multivariate regression analysis yielded a significant correlation (r² = 0.34) between diastolic pressure, urine Na concentration, and changes in plasma AVP. Plasma Na of H subjects averaged 2.0 mEq/liter less and urine Na concentration 22 mEq/liter less than in N subjects. Sodium intake appeared to have no influence on the plasma AVP of N subjects, but H subjects excreting Na in excess of 250 mEq/day averaged a plasma AVP twice as high as that in H subjects excreting less than 150 mEq/day. In H subjects, the influence of Na intake appeared to be related to age. In subjects less than 50 years of age, Na intake did not appear to influence chronic levels of plasma AVP, while in subjects older than 50 years who were excreting Na in excess of 250 mEq/day, plasma AVP levels were twice (13.5 pg/ml) those observed in hypertensives of the same age excreting less than 150 mEq/day (6.5 pg/ml). The data indicate that plasma AVP tends to be elevated in moderate essential hypertension. Reduced concentrating ability of the kidneys of these subjects is suggested by decreased urine Na concentrations despite elevated plasma AVP. The observed increases of plasma AVP could be exerting a direct influence on extra- and intravascular volumes by renal and systemic vasoconstriction.

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KEY WORDS • vasopressin • sodium intake • plasma arginine vasopressin • essential hypertension • age • kidney • vasoconstriction

THE role of arginine vasopressin (AVP) in human hypertension is poorly defined. Since the advent of adequately sensitive AVP assay procedures there have been only two efforts to characterize AVP in human hypertension. Khokhar and Slater1 reported increased urinary excretion of AVP in mild essential hypertension. Padfield et al.,2 however, concluded that plasma AVP was suppressed in mild hypertension but elevated from three- to fivefold in the malignant phase of the disease. In several experimental forms of hypertension, plasma AVP is clearly elevated and exerts significant vasoconstrictor activity.3,4

The present study was undertaken to resolve these conflicting reports and to better characterize plasma AVP concentrations in human subjects with benign essential hypertension. In addition, the influence of sodium intake was evaluated to determine if hypertensive subjects responded differently to excess daily sodium intake than normal subjects. Since no one had yet determined the influence of chronic alteration of sodium intake on plasma AVP, a group of normal subjects was studied to determine what the appropriate concentrations would be at normal and high levels of sodium intake.

Subjects and Procedures

Three groups of subjects were evaluated: Group 1: normal medical students, average age 23 ± 1 years, and 23% female; Group 2 = normal men (exclusive of subjects from Group 1), average age 46 ± 2 years, with 12 black and 35 white subjects; Group 3 = moderate-hypertensive men, part of VA Cooperative Study 127, average age 50 ± 1 years, and a nearly equal racial mix of black (n = 37) and white (n = 35). All medication was withdrawn 2 weeks prior to the study.

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Acute Sodium Load in Normal Subjects

Subjects from Group 1 were evaluated to determine the acute AVP response to oral ingestion of 200 mEq hypertonic NaCl. Similarly, a time-control group without NaCl was evaluated. Experiments were performed at 11:00 a.m., 4 hours after a light breakfast after which no coffee or smoking was permitted. Control venous blood samples were withdrawn after subjects had been seated comfortably for a period of 30 minutes. Following determination of arterial pressure and heart rate, 200 mEq NaCl was diluted in one cup of beef broth (55 mEq/liter Na; 0.3 mEq/liter K), and ingested over a 20-minute period. Following a 2-hour period with water intake restricted to no more than 120 ml (one 4-ounce cup), blood samples and arterial pressure were again obtained. Students were free to move about and carry on normal activities within the confines of the laboratory except for the 30-minute period preceding blood samples when they remained seated. Plasma samples were analyzed for Na, K, osmolality, and AVP concentration.

Chronic Sodium Load in Normal Subjects

Other students in Group 1 volunteered to participate in a 1-week study in which daily NaCl was either increased by 200 mEq or maintained at normal levels. Subjects were instructed not to change their daily dietary habits but to either add the excess prescribed salt to regular meals (“high-salt”) or maintain their normal dietary intake (“time-control”). Two 24-hour urine samples were collected, one during the day prior to the start of the high Na period and one during the 7th day of the experimental period. Blood samples were taken 4 hours after a light breakfast with the subjects seated for 30 minutes, their last high-salt meal having been taken the prior evening. Subjects were instructed not to smoke or drink coffee for 4 hours prior to blood withdrawal. Plasma was analyzed for Na, K, osmolality, and AVP concentration. Daily urine excretion was determined, and urine was analyzed for Na, K, and osmolality.

Comparison of Hypertensive and Comparably Aged Normal Subjects

Hypertensive subjects on unrestricted sodium diet were included in the study when after 2 weeks of no medication diastolic pressure on three separate determinations exceeded 95 mm Hg and was less than 115 mm Hg. Pressures were taken by a trained clinical assistant. At the end of this 2-week period, urine volume, electrolyte and creatinine clearance were determined on an outpatient basis from 24-hour urine collections. All electrolyte and creatinine analyses were performed on the same instruments and in the same laboratory. Arterial pressure and blood samples were obtained after overnight fasting between 8:00 and 10:00 a.m. with the subject seated quietly for 30 minutes. Subjects were instructed not to drink coffee or smoke for 3 hours prior to blood withdrawal. The comparably aged group of normotensive adults were similarly evaluated. Subjects with a history of alcoholism were excluded from the study.

Analysis

Plasma arginine vasopressin (AVP) was determined using an assay modified from a procedure developed in our laboratory. Plasma samples (1 ml), which were deproteinized with 2 ml acetone, were taken to complete dryness using a centrifugation-vacuum-concentrating system (Savant Instruments, Hicksville, New York) and assayed as previously reported. The percent of $^{125}$I-AVP bound to the antibody was determined by the ratio of the supernatant bound fraction

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**Figure 1.** Comparison of the average of three extracted "AVP-suppressed" human plasma standard curves; 12 extracted "AVP-free" dog plasma standard curves; nine extracted saline standard curves. The parallelism of the three curves indicates minimum interference of plasma elements in either dog or human plasma with the assay. Between assay variability was determined using a curvilinear least squares fit analysis of the 12 extracted dog plasma curves and yielded the equation $Y = -0.33 X^3 + 1.69 X^2 - 19.70 X + 100.65$ ($r = 0.96$), with a significance fit of $p < 0.01$. The between assay variability was predicted by the confidence intervals at each respective standard as follows: (0.0 pg = 3.8% ) (0.13 pg = 3.8% ) (0.26 pg = 3.5% ) (0.52 pg = 3.2% ) (1.30 pg = 2.9% ) (2.6 pg = 2.9% ) (5.19 pg = 4.1% ) (13.0 pg = 5.6% ) (26.0 pg = 7.0% ) (52.0 pg = 7.1% ).
to the total counts in the supernatant and residue after background count subtraction. The bound fraction of each individual plasma sample was corrected for "nonspecific binding" (NSB), which represented the amount of binding of ²⁸²⁴⁰AVP to plasma constituents in the absence of antiserum. This value (NSB) was determined for each individual subject using 1 ml plasma processed in an identical manner to plasma unknowns. The NSB was found to average 5.1% ± 0.8% standard error (SE) in a group of 200 normal and hypertensive subjects.

For each analysis, standard curves were determined using the USP Posterior Pituitary Reference Standard in concentrations ranging from 0.26 to 52.0 pg/ml. As explained below, standard curves were determined using both saline and plasma. Each concentration was determined in triplicate and processed at the same time in the same manner as the unknown plasma samples. Figure 1 compares the average of nine separate standard curves determined in normal saline with 1% BSA to the average of 12 separate standard curves determined in AVP-free dog plasma as previously reported. Plasma standard curves have now been determined using nonpooled human plasma collected from three individuals who drank 20 ml H₂O/kg over a 20 to 30-minute period. The average of these three human standard curves is shown in figure 1 superimposed on the results obtained using saline and dog plasma.

Since the difference between absolute maximum binding obtained from extracted saline to which no AVP was added and the AVP-suppressed human plasma to which no AVP was added was less than the minimum detectable level of the assay, no correction was made for these blank values as graphed in figure 1. With corrections for NSB, and the loss of AVP associated with protein precipitation, it can be seen that these average standard curves exhibit close parallelism and near identity. Both the extracted saline and human plasma curves fell within the predicted confidence intervals determined by a curvilinear regression analysis of the 12 individual dog plasma curves (see fig. 1 legend). Plasma protein precipitation resulted in a 23% (coefficient of variation ± 1.4) loss determined with both ²⁸²⁴⁰AVP and AVP. Previous dog plasma values reported from this laboratory were read directly from extracted plasma standard curves so no corrections for losses were necessary.

The near identity of extracted saline, dog, and human plasma standard curves following correction for extraction losses demonstrated that there was no significant interference with AVP binding in the assay system. Unknown plasma samples in the present study were therefore read from the extracted saline standard curves. Reported values were corrected for a 23% extraction loss and therefore represent the concentrations in the original 1 ml plasma sample. As previously reported, the between-assay variability based on 12 separate standard curves averaged ± 4.4%, based on the confidence intervals of the standard curves shown in figure 1. The intraassay coefficient of variation averaged ± 4.0%. The least detectable AVP concentration in the original plasma averaged 0.3 pg/ml, and the midrange of the assay averaged 6.5 pg/ml.

Urine and plasma electrolyte concentrations were determined by flame photometry (Instrumentation Laboratory Model 343). Serum and urine osmolality were determined in triplicate with an Advanced Instrument osmometer (Model 3R). Plasma samples for determination of electrolytes and osmolality were collected in lithium-heparin tubes (Becton-Dickinson). All values in the text are reported as means ± SEM; paired and unpaired Student's t test was used when appropriate. Correlation coefficients were calculated by the method of least squares and by a multiple regression analysis.

Results

Figure 2 relates the diastolic pressures to plasma AVP concentrations of all hypertensive and com-

![Figure 2. Relationship between diastolic arterial pressure and plasma AVP obtained in 61 hypertensive subjects (age 50 ± 1 years) and 43 comparably aged normotensive subjects (age, 46 ± 2 years).](http://hyper.ahajournals.org/)}
parably aged normotensive subjects. A clear tendency toward elevated plasma AVP levels is seen at diastolic pressures exceeding 95 mm Hg. A multivariate regression analysis of all measured variables indicated that only diastolic pressure and urine Na concentration were correlated significantly ($r^2 = 0.34$) with plasma AVP ($p < 0.01$). Changes in age, weight, urine volume, plasma Na, or urine Na excretion did not correlate significantly with plasma AVP.

Table 1 summarizes the average values of comparably aged normotensive and hypertensive subjects. Plasma AVP concentration averaged 8.5 ± 1.0 pg/ml in 61 hypertensive subjects and 4.7 ± 0.5 pg/ml in 51 normotensive subjects of comparable age ($p < 0.05$). Blood pressure and plasma and urinary Na concentration were the only other variables that differed significantly between the two groups. It was noted, however, that the daily urine volume of these groups exceeded ($p < 0.05$) that of the younger student population by nearly 600 ml/day (table 2). The multivariate analysis indicated that race did not significantly contribute to the observed elevation of plasma AVP in hypertensive subjects. Thus, hypertensive subjects were characterized by elevated plasma AVP, a slightly lower plasma Na concentration, and a lower urine Na concentration.

### Influence of Sodium Intake on Plasma AVP

#### Levels in Normotensive Student Subjects

**Acute Response**

The acute response to an oral salt load of 200 mEq of sodium chloride was determined in 13 normotensive students. Two hours following the ingestion of salt, plasma Na concentration increased from an average of 138.4 ± 0.5 to 143.3 ± 0.5 mEq/liter ($p < 0.01$), plasma osmolality from 288.4 ± 0.9 to 296.6 ± 1.3 mOsm/kg ($p < 0.001$), and plasma AVP concentration from 3.1 ± 0.5 to 7.0 ± 1.3 pg/ml ($p < 0.05$). A group of four “time control” students exhibited no significant changes over the same time period in the same environment.

**Chronic Response**

The influence of a high Na intake (200 mEq/day) maintained for 1 week in a group of normotensive students is summarized in table 2. Twenty-six students took the high Na diet and 40 maintained their regular diet to serve as “time controls.” Plasma AVP was not altered significantly by chronic high Na intake nor in the “time control” subjects. Thus, despite a mild but reproducible elevation of $P_{Na}$ concentration associated with a twofold increase in Na intake, the

### Table 1. Comparison of Moderate Essential Hypertensives to Comparably Aged Normotensive Subjects

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Normotensive controls</th>
<th>Hypertensives</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average age (yrs)</td>
<td>46 ± 2</td>
<td>50 ± 1</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>83 ± 3</td>
<td>87 ± 2</td>
</tr>
<tr>
<td>$P_{Na}$ (mEq/liter)</td>
<td>142 ± 0.4</td>
<td>140.1 ± 0.4*</td>
</tr>
<tr>
<td>$P_{K}$ (mEq/liter)</td>
<td>4.2 ± 0.6</td>
<td>4.2 ± 0.65</td>
</tr>
<tr>
<td>$P_{AVP}$ (pg/ml)</td>
<td>4.7 ± 0.4</td>
<td>8.6 ± 1.0*</td>
</tr>
<tr>
<td>Urine volume (ml/day)</td>
<td>1416 ± 114</td>
<td>1531 ± 96</td>
</tr>
<tr>
<td>Sodium excretion (mEq/day)</td>
<td>189.5 ± 19.3</td>
<td>161.4 ± 9.5</td>
</tr>
<tr>
<td>Urine sodium (mEq/liter)</td>
<td>141.4 ± 11.2</td>
<td>118.6 ± 6.2*</td>
</tr>
<tr>
<td>C_{creatin} (ml/min)</td>
<td>91.4 ± 8.2</td>
<td>96.8 ± 5.0</td>
</tr>
<tr>
<td>Arterial pressure (mm Hg):</td>
<td></td>
<td></td>
</tr>
<tr>
<td>systolic</td>
<td>123.5 ± 2</td>
<td>147 ± 2*</td>
</tr>
<tr>
<td>diastolic</td>
<td>79.4 ± 1.5</td>
<td>101 ± 0.6*</td>
</tr>
</tbody>
</table>

* $p < 0.05$.  

### Table 2. Comparison of Effects of Normal (“Time Control”) and High Sodium Diet (1 week) in Normotensive Student Subjects

<table>
<thead>
<tr>
<th>Group</th>
<th>$P_{Na}$ (mEq/liter)</th>
<th>$P_{osm}$ (mOsm/kg)</th>
<th>$P_{AVP}$ (pg/ml)</th>
<th>Urine volume (ml/day)</th>
<th>Sodium excretion (mEq/day)</th>
<th>Urine sodium (mEq/liter)</th>
<th>Arterial pressure (mm Hg):</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (n = 26)</td>
<td>138.7 ± 0.4</td>
<td>288.1 ± 0.8</td>
<td>6.2 ± 1.0</td>
<td>742 ± 41</td>
<td>135 ± 13</td>
<td>127.9 ± 10.4</td>
<td>130 ± 3</td>
</tr>
<tr>
<td>High salt (200 mEq)</td>
<td>140.0* ± 0.5</td>
<td>289.1 ± 0.9</td>
<td>4.9 ± 0.8</td>
<td>989* ± 69</td>
<td>269* ± 18</td>
<td>197.3* ± 9.7</td>
<td>121 ± 2</td>
</tr>
<tr>
<td>Control (n = 40)</td>
<td>135.5 ± 0.3</td>
<td>287.3 ± 0.7</td>
<td>4.9 ± 0.5</td>
<td>896 ± 71</td>
<td>149 ± 9</td>
<td>134.1 ± 7.5</td>
<td>131 ± 3</td>
</tr>
<tr>
<td>Time control</td>
<td>139.3 ± 0.4</td>
<td>289.1 ± 0.8</td>
<td>5.2 ± 0.8</td>
<td>812 ± 54</td>
<td>137 ± 9</td>
<td>133.9 ± 8.4</td>
<td>121 ± 2</td>
</tr>
</tbody>
</table>

* $p < 0.05$.  

$tp < 0.001$.  

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steady-state plasma AVP concentration was unchanged in normal student subjects.

Relationship Between Sodium Intake and Plasma AVP in Hypertensive Subjects

Sodium intake, as determined from daily Na excretion, appeared to have no influence on plasma AVP in normotensive subjects of all ages, as seen in figure 3. In contrast to the normotensive students, these values do not necessarily represent a steady-state level of Na intake. Plasma AVP of normotensive subjects \((n = 15)\) excreting 113 ± 6.0 mEq Na/day was 4.4 ± 0.5 pg/ml \((n = 15)\) compared to the plasma AVP of 5.5 ± 0.8 pg/ml \((n = 18)\) of normotensive subjects excreting 280 ± 19 mEq Na/day. Hypertensive subjects were characterized by plasma AVP levels significantly higher than normotensive subjects at both low and high levels of Na intake \((p < 0.05)\). In contrast to normotensive subjects, plasma AVP in hypertensive subjects appeared to be influenced by increased Na intake. In those excreting an average 106 ± 7 mEq Na/day, plasma AVP averaged 6.8 ± 0.8 pg/ml. This compared to a plasma AVP of 11.2 ± 2.1 pg/ml \((p < 0.07)\) in those excreting 273 ± 12 mEq Na/day.

Influence of Age on Plasma AVP of Hypertensive Subjects

The relationship between Na intake and plasma AVP appeared to be influenced by age. As seen in figure 4, plasma AVP was not related to the Na intake in hypertensive subjects less than 50 years of age. In contrast, a significant relationship was observed between Na intake and plasma AVP in hypertensive subjects greater than 50 years of age. Plasma AVP averaged 6.5 ± 1.3 pg/ml in those subjects excreting 115 ± 7.0 mEq Na/day compared to 13.5 ± 3.4 pg/ml in those excreting 265 ± 16 mEq Na/day \((p < 0.05)\).

Figure 3. Contrasts the relationship between sodium excretion and plasma AVP observed in normotensive (upper) and hypertensive subjects (lower). Plasma AVP was significantly higher in hypertensive subjects at both levels of sodium excretion compared to normotensive subjects \((p < 0.05)\). Hypertensive subjects exhibited a strong tendency toward elevated plasma AVP at high levels of sodium excretion \((p < 0.07)\). Mean ± SEM is represented.

Figure 4. Comparison of relationship between sodium excretion and plasma AVP on hypertensive subjects under and over 50 years of age. Subjects older than 50 exhibited significantly higher levels of plasma AVP at high levels of Na excretion \((p < 0.05)\). Mean ± SEM is represented.
Discussion

The present data demonstrate a clear tendency toward elevated plasma AVP in hypertension. The results of the multivariate correlation analysis did not suggest the cause of these elevations, which could not be explained on the basis of age, sex, race, or sodium intake. Life style and diet were not evaluated. A difference between normal and hypertensive subjects was also observed when the influence of sodium intake on plasma AVP was examined. To better interpret the meaning of the observed plasma AVP concentrations in hypertensive subjects, it was necessary to know how plasma AVP responds to varying levels of dietary sodium intake in normal subjects, a relationship not previously determined. The data obtained from the medical student population was particularly useful in this regard since these subjects could be maintained on high Na intake for 7 consecutive days in a relatively well-controlled manner (table 2) whereas Na intake in normal Veterans Administration subjects could only be estimated by a single 24-hour urine collection (fig. 3). The data from both normal groups, however, indicate that plasma AVP was not influenced by daily levels of sodium intake, although transient postprandial elevations were clearly observed several hours following oral ingestion of salt. Results indicated that enhanced thirst appeared to normalize plasma AVP concentrations in subjects on a high sodium intake, as seen by the 33% increase in daily urine excretion (table 2), a response we have also observed in dogs. 10

A different relationship was obtained between daily sodium excretion and plasma AVP in hypertensive subjects. Hypertensive subjects excreting Na in excess of 250 mEq/day exhibited nearly twice the levels of AVP compared to those excreting less than 150 mEq/day. Thus, although plasma AVP was significantly higher in hypertensive than in normotensive subjects at both low and high levels of Na excretion, hypertensive subjects exhibited an even greater tendency toward increased plasma AVP levels with a high Na diet.

Hypertensive subjects were then analyzed to determine if significant subgroups could be identified, since, as seen in figure 2, plasma AVP was relatively normal in many hypertensive subjects. The data indicated that the AVP hyperresponsiveness to Na excess was related to age. In persons less than 50 yrs of age, Na intake appeared to have no influence on plasma AVP, but in persons older than 50, plasma AVP was twice as high in those excreting more than 250 mEq Na/day compared to those excreting less than 150 mEq Na/day. Although this response could be unique to hypertensive subjects, it should be recognized that an insufficient number of older normotensive subjects excreting Na in excess of 250 mEq/day were obtained for analysis. Thus, it is unclear whether the relationship between plasma AVP and Na excretion was unique to hypertensive subjects or also to the age of the subject. Exaggerated AVP responses to acute intravenous hypertonic saline infusions have been observed in older normotensive subjects. 11 However, the opposite has been observed in senescent rats by a number of investigators, 12, 13 so age-related AVP responsiveness remains unclear.

A second subgroup of hypertensive subjects was analyzed in which a multivariate analysis was used to compare subjects with plasma AVP levels greater than 10 pg/ml to those with less than 10 pg/ml. The few differences that distinguished these two groups did not suggest a reason for differences in AVP, but rather appeared to be a result of observed concentrations of plasma AVP. Specifically, urine Na concentration and daily Na excretion was mildly elevated in those subjects with plasma AVP levels greater than 10 pg/ml (p < 0.05).

Elevated plasma AVP in hypertension could be of primary or secondary origin. Increased secretion of AVP could be part of an overall neurohormonal pattern of central nervous system dysfunction in essential hypertension. Such a primary excess AVP secretion could account for the mild hyponatremia observed in hypertensive subjects, as seen in patients with SIADH syndrome. 14 Alternately, elevated AVP could be secondarily related to a renal concentrating defect, as suggested by the observation in this study that hypertensive subjects were unable to concentrate urine Na as effectively as normotensive subjects despite elevated levels of plasma AVP. An inability of the kidneys to respond to AVP could have led to a compensatory oversecretion of AVP. It has long been known that decreased urine specific gravity is a sign of renal injury in hypertension. 15 Similar findings were reported by Khokhar et al. 1 who observed a primary renal resistance of hypertensive subjects to the concentrating actions of endogenous AVP.

Our present study did not suggest any other secondary factors that may have been responsible for elevation of AVP. Plasma Na concentration was actually less in hypertensive subjects than in normotensive subjects, which would tend to suppress rather than elevate plasma AVP. Elevated arterial pressure per se in hypertension should, if anything, reflexly suppress plasma AVP although adaptation of the baroreceptors would probably negate any such effects. 16 Similarly, it is unlikely that cardiopulmonary stretch receptors would account for elevation of plasma AVP since central blood volume appears to be increased rather than decreased in essential hypertension, 17 and these receptors appear to adapt like the high pressure receptors. 18

Potential Consequence of Elevated AVP in Hypertension

Elevated plasma AVP could potentially alter arterial pressure by influencing the rate of renal water excretion or by altering systemic vascular tone, or both. Maximum concentration of urine is achieved in dehydrated man and dog at plasma AVP levels between 15 to 20 pg/ml, a three- to fivefold increase above normal plasma AVP levels. 19, 20 So, compared to the plasma concentrations of AVP to which the renal tubules normally respond, the two- to fivefold in-
crease of plasma AVP levels observed in hypertensive humans must be considered a biologically significant elevation.

Recent evidence indicates that systemic vascular resistance also can be influenced by comparable elevations in plasma AVP. In normotensive animals and man, the vasoconstrictor actions of AVP are effectively buffered by cardiovascular reflex mechanisms so that elevations of arterial pressure are observed only at plasma concentrations far in excess of those required for maximum antidiuretic activity. In dogs without cardiovascular reflexes, however, the arterial pressure-AVP dose-response curve is displaced to the left by a factor of 5 at threshold doses and by a factor of 4000 for doses that increased blood pressure by 50 mm Hg. The significance of this was recently demonstrated by the observation that endogenous AVP release can function in the dog as a rapid and potent arterial pressure control system in hypovolemic states.

We have reported that, in the absence of autonomic control, increases in plasma AVP as small as 10 to 20 pg/ml can elevate arterial pressure 20 to 30 mm Hg. Recently, Möhring et al. reported the dose-response relationships in several patients with idiopathic orthostatic hypotension. In normal subjects, an increase of plasma AVP up to 450 pg/ml raised arterial pressure by only 5 to 7 mm Hg, while in subjects with greatly reduced activity of cardiovascular reflexes, a 5 pg/ml increase of plasma AVP was associated with nearly a 30 mm Hg rise of arterial pressure. The results indicated that a 10 mm Hg increase in pressure would require doses or concentrations of AVP about 1000 times higher in normal subjects than in those with automatic insufficiency. Similar pressor responsiveness to Pitressin infused in subjects with idiopathic hypotension was earlier reported by Wagner and Braunwald. Recent experiments by Montani et al. in conscious dogs indicate that the vasopressor actions of AVP are in large measure masked by strong activation of the vagus nerve and associated bradycardia under normal conditions. These data suggest that the plasma levels of AVP observed in human hypotension could exert a considerable influence on the cardiovascular system provided there was some type of associated alteration in the CNS and/or autonomic reflex control system.

It is relevant that enhanced pressor sensitivity to plasma AVP has been demonstrated in various types of experimental hypertension. Acute blockade of vasopressin in DOC-salt hypertension in rats and the hereditary SHR rat model, in which circulating levels of AVP ranged from three to tenfold above normal, resulted in a 30 to 100 mm Hg fall of arterial pressure, indicating nearly a 1000-fold increase in sensitivity. Crofton et al. also reported enhanced pressor responsiveness to infused AVP in rat DOC-salt hypertension, but only an 80- to 100-fold increase in sensitivity was observed.

Despite increasing evidence that relatively small changes in plasma AVP can acutely alter vascular tone, the role of AVP in the long-term control of arterial pressure is far from clear. Smith et al. attempted to produce sustained hypertension with a continuous infusion of AVP that maintained plasma levels nearly 10 times normal, but hypertension was not sustained beyond 2 weeks. Lohmeier and Cowley observed that excess AVP did not increase the severity of angiotensin II- or aldosterone-induced hypertension. In contrast to the latter studies, sustained hypertension has been produced with infusions of AVP in dogs with impaired renal function. Hypertension in these dogs was associated with an expansion of blood volume and hyponatremia, although this may have been accompanied by AVP-induced alterations of vascular smooth muscle tone.

Evidence therefore suggests that elevated plasma levels of AVP in the presence of reduced renal function could contribute to the severity of hypertension by volume expansion. Structural vascular change in the form of microvascular disease is usually demonstrable in kidneys of subjects with essential hypertension. Average resting renal blood flow has been found to be reduced in many patients with benign essential hypertension in the presence of normal or slightly reduced GFR. Although the precise changes in renal function remain to be longitudinally defined in human essential hypertension, it is clear that a variety of intrinsic and extrinsic factors may alter renal glomerular tubular balance. Consequent reduced renal function in the presence of excess AVP could lead to or aggravate an existing state of hypertension. Reduced renal ability of hypertensive subjects to reabsorb filtered water could enhance secretion of AVP.

In summary, our present study indicates a clear tendency toward elevated plasma AVP in moderate essential hypertension. Hypertensive subjects also appear to differ from normal subjects in that chronic changes of sodium intake can exert a greater influence on observed plasma AVP levels. This relationship could be related to age as well as hypertension. Renal concentrating ability appears to be diminished in hypertension despite elevated plasma AVP. The observed elevations of plasma AVP could be a compensatory response attempting to offset the loss of tubular concentrating ability. Given the observed elevations of plasma AVP in hypertension and the demonstrated direct vascular and renal responses to AVP at similar plasma concentrations, the data would seem to warrant a closer look at the role of this peptide in the etiology of human hypertension.

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References

PATHOPHYSIOLOGY OF HYPERTENSION


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