OVER the last few years, several studies have suggested a vasopressor role for arginine vasopressin (AVP) in the pathogenesis of different forms of hypertension in the rat. Rats with hypertension secondary to unilateral renal artery constriction (two-kidney, one clip hypertension) or DOCA-salt treatment, as well as spontaneously hypertensive rats, have elevated plasma levels of AVP and increased urinary excretion rates of AVP.\(^1\,^4\) Furthermore, the hypertension tends to be most severe in rats with the highest plasma AVP concentration and, at least in the spontaneously hypertensive rat, arterial pressure correlates with plasma AVP concentration.\(^1\,^3\,^4\) Moreover, blockade of plasma AVP by intravenous injection of either AVP-antiserum or competitive antagonists that block the pressor but not the antidiuretic activity of AVP lowers arterial pressure transiently in these high-AVP hypertensive states.\(^1\,^2\,^3\,^4,\,^8\)

Although high plasma levels of AVP have very pronounced vasoconstrictor effects that are important in the maintenance of arterial blood pressure under acute conditions such as hemorrhage,\(^6,^9\) it is well established from states of chronic AVP excess that AVP might interact with angiotensin II and aldosterone to influence the severity of the hypertension,\(^11\) and patients with essential hypertension\(^13\) and malignant hypertension\(^19\) have high plasma levels of AVP or increased urinary excretion rates of AVP.

In light of the very interesting and provocative hypertensive rat studies mentioned above, which suggest a role for AVP in the pathogenesis of hypertension associated with high plasma levels of angiotensin II (two-kidney, one clip hypertension) or high plasma levels of mineralocorticoid (DOCA-salt hypertension), we have attempted to determine how AVP might interact with angiotensin II (AII) and aldosterone to influence the severity of the hypertension achieved with these sodium-retaining hormones. Additionally, we think the interrelationships between
these hormones might be of particular interest because a chronic excess of AVP can produce fairly marked hypertension when renal excretory capacity is compromised. Finally, and most important, since we were interested in how these hormones might interact in the pathogenesis of hypertension, we have emphasized the chronic as well as the short-term effects of AVP on mean arterial pressure (MAP), and water and electrolyte metabolism.

Methods

Twelve male dogs weighing 21.0 ± 1.3 (SE) kg had chronic indwelling catheters of Tygon tubing (Norton) placed in the femoral artery and vein. The tip of the femoral artery catheter was advanced into the aorta distal to the origin of the renal arteries, and the end of the femoral vein catheter was positioned in the vena cava. A Silastic elbow prevented kinking of the catheters in the femoral area. The catheters were tunneled subcutaneously and exteriorized in the posterior thoracic region.

Two weeks after surgery the dogs were placed in metabolic pens and fitted with an aluminum and canvas backpack housing a Statham arterial blood pressure transducer (Model P23 ID) at heart level. The electrical connections to the transducer and an intravenous infusion line were brought to the top of the cage through a flexible tube attached to the top of the backpack. Continuous intravenous infusions were made through the femoral vein catheter by means of a Sage tubing pump (Model 375A), and the MAP was recorded continuously 24 hours per day from the femoral artery catheter on a Grass polygraph (Model 7D).

During the entire experiment, the dogs were given free access to water and maintained on a fixed daily diet of two 15.5 oz cans of h/d prescription diet (Riviana Foods Inc.). Two cans of h/d provide < 5 mEq of sodium and 45 to 50 mEq of potassium. Isotonic saline was infused at a rate of 800 ml/day (124 mEq Na/day). When appropriate, daily hormonal supplements of AII, aldosterone, and/or AVP were added to the saline. Body temperature was measured daily, and ampicillin (Principen, E. R. Squibb and Sons) and a trimethoprimsulfamethoxazole combination (Bactrim, Roche Laboratories) were given prophylactically. To promote accurate measurements of 24-hour urinary sodium and potassium excretion rates, the urinary bladder was catheterized daily using aseptic techniques. The bladder was washed with a nitrofurazone solution (Vet Products Company) to prevent bacterial infection.

Experimental Protocol

Two groups of five dogs each were subjected to the sequence of infusions shown in table 1.

<table>
<thead>
<tr>
<th>Infusion</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Saline</td>
<td>Saline</td>
<td>10-14 days</td>
</tr>
<tr>
<td>2</td>
<td>AII</td>
<td>Aldosterone</td>
<td>14 days</td>
</tr>
<tr>
<td>3</td>
<td>AII + AVP</td>
<td>Aldosterone + AVP</td>
<td>14-15 days</td>
</tr>
<tr>
<td>4</td>
<td>AII</td>
<td>Aldosterone</td>
<td>4-7 days</td>
</tr>
<tr>
<td>5</td>
<td>Saline</td>
<td>Saline</td>
<td>5-7 days</td>
</tr>
<tr>
<td>6</td>
<td>AVP</td>
<td>AVP</td>
<td>12 days</td>
</tr>
<tr>
<td>7</td>
<td>Saline</td>
<td>Saline</td>
<td>9 days</td>
</tr>
</tbody>
</table>

Days of aldosterone + AVP infusion (Step 3) when the rate was increased to 560 µU/kg per min. Finally, two of the five dogs from each group were subjected to AVP infusion alone (Steps 5-7); two additional dogs were infused with AVP at 140 µU/kg/min for 12 days, as in Group 1 and 2 dogs (Steps 5-7).

In all animals, 5 ml blood samples were taken periodically for measurement of plasma renin activity (PRA), plasma sodium and potassium concentration, and hematocrit. Additionally, in four of the dogs, 5 ml blood samples were taken intermittently for measurement of plasma AVP concentration; these samples were taken only during infusions 5-7. All blood samples were taken at 8-9 a.m., 18-20 hours after feeding. Twenty-four-hour urine collections were made at noon immediately after bladder catheterization and just prior to feeding. Daily water consumption was also monitored.

Analytical Methods

The PRA was measured by radioimmunoassay for angiotensin I (A1) (E.R. Squibb and Sons), expressed as nanograms of A1 generated per milliliter of plasma per hour incubation (ng A1/ml/hr). Plasma and urine concentrations of sodium and potassium were determined by flame photometry (Instrumentation Laboratory, IL 343). Plasma AVP concentration was determined using a specific and highly sensitive radioimmunoassay procedure developed in our laboratory. Minimum sensitivity of the assay with 1-ml plasma samples was 0.1 µU/ml. Intraassay coefficient of variation averaged ± 4.0%. All samples were analyzed in duplicate.

The MAP was recorded continuously on the Grass recorder and simultaneously on a PDP 11/70 Digital Equipment Corporation computer using an analog-to-digital converter. The analog signal from the Grass recorder was sampled every 60 seconds, and the digitized information was used by the computer to calculate hourly values for MAP based on 60 sample points/hr. The daily values presented for MAP are calculated from the 960 data points generated during the 16-hour period extending from 4 p.m. to 8 a.m.

All values presented are means ± SE. Control data were compared with experimental data by using Dunnet's paired t test for multiple comparisons. Statistical significance was considered to be p < 0.05.
Results

Effects of AVP Infusion in Dogs with All-Induced Hypertension

After 2 weeks of All infusion at a rate of 5 ng/kg/min, the MAP was elevated from a control value of 109 ± 2 mm Hg to 152 ± 4 mm Hg (p < 0.05); plasma sodium concentration was unchanged; plasma potassium concentration was reduced 0.5 ± 0.1 mEq/liter (p < 0.05); and the PRA was suppressed to undetectable levels (fig. 1). Quantitatively, these results are similar to those reported in an earlier study in which dogs were subjected to the same infusion rate of All and were maintained on a comparable sodium and potassium intake.16

In all dogs, infusion of AVP at 140 μU/kg/min along with the All did not alter the MAP either acutely or chronically (figs. 1 and 2). In contrast, when AVP administration was terminated on Day 29, while the All infusion was maintained, there was an immediate and precipitous fall in MAP of 35 to 40 mm Hg, which persisted for several hours (fig. 3); within 15 to 18 hours, however, the MAP returned to its previous hypertensive level. Thus, the high plasma levels of AVP did not produce any long-term changes in MAP.

During AVP infusion, there was an increase in both urinary sodium and potassium excretion, which was most prominent during the first 24 hours of AVP infusion (fig. 2). The net loss of sodium and potassium achieved during AVP infusion was reflected in the values for plasma electrolytes: after 2 weeks of AVP infusion, plasma sodium and potassium concentration were reduced 9 ± 2 mEq/liter (p < 0.05) and 0.7 ± 0.1 mEq/liter (p < 0.05) respectively (fig. 1). When AVP infusion was discontinued on Day 29, sodium and potassium retention occurred for 1 to 2 days, and subsequently plasma sodium and potassium concentration returned to their pre-AVP infusion values.

During the 2-week period of AVP infusion, both urine excretion and water consumption decreased, but there was no measurable retention of water (fig. 2). In fact, during the initial 24 hours of AVP infusion, water balance was even slightly negative in some animals. Further, body weight was unchanged after 14 days of AVP infusion. During the 48-hour period following termination of AVP infusion, water balance was clearly positive (250 to 500 ml), not negative (fig. 2). Thus, in dogs with All-induced hypertension, AVP infusion failed to promote water retention and MAP was unchanged. The MAP did fall precipitously when AVP infusion was terminated; however, this fall was followed by salt and water retention and, within 24 hours, a return to the previous hypertensive MAP level.

Effects of AVP Infusion in Dogs with Aldosterone-Induced Hypertension

After 2 weeks of aldosterone infusion at a rate of 9 μg/kg/min, the MAP was elevated from a control value of 104 ± 2 to 114 ± 3 mm Hg (p < 0.05); the plasma sodium concentration was increased 2 ± 1 mEq/liter (p < 0.05); plasma potassium concentration was reduced 1.6 ± 0.2 mEq/liter (p < 0.05); and PRA was suppressed to undetectable levels (fig. 4). These results are quantitatively similar to those of an earlier study in which dogs were subjected to the same infusion rate of aldosterone and maintained on a comparable sodium and potassium intake.16

As in dogs with All hypertension, changes in plasma AVP levels were associated with only transient changes in MAP (figs. 4 and 5). The MAP increased during the initial days of AVP infusion (at 140 μU/kg/day), but within 10 days returned to the pre-AVP infusion level (fig. 5). With subsequent infusion of AVP at the higher infusion rate (360 μU/kg/day), the MAP once again increased transiently for several days but within 5 days returned to the level achieved with aldosterone infusion alone. As in the dogs with All-induced hypertension, when AVP administration was terminated (on Day 30) while the aldosterone infusion was maintained, there was an immediate and precipitous fall in MAP of 35 to 40 mm Hg (to hypertensive levels with respect to the original control pressure), which was only transient (fig. 6) — within 48 hours MAP returned to prior hypertensive levels.

As in the dogs chronically infused with All, AVP administration in dogs with aldosterone-induced hypertension produced both a natriuresis and a kaliuresis, which were most prominent during the initial 24 hours following each level of AVP infusion (fig. 5); when AVP infusion was discontinued, sodium and potassium retention occurred for 2 days. Simultaneously with the changes in sodium and potassium
balance, when AVP was infused at 140 \( \mu \)U/kg/min, plasma sodium and potassium concentration fell 5 ± 1 (p < 0.05) and 0.3 ± 0.1 mEq/liter (p < 0.05) respectively, from the values achieved during aldosterone infusion alone (fig. 4). When AVP was infused at the higher rate, plasma sodium and potassium concentration fell an additional 4 ± 1 (p < 0.05) and 0.1 ± 0.1 mEq/liter (p < 0.05) respectively. Within 4 days after termination of AVP infusion, the values for plasma sodium and potassium concentration were similar to those observed prior to AVP infusion.

In dogs with aldosterone-induced hypertension, both urine excretion and water consumption decreased during AVP infusion but, as in dogs with AII hypertension, there was no indication from the water balance data of net water retention, and body weight was unchanged (fig. 5). In fact, water balance was negative to a small extent for several days after initiation of each infusion rate of AVP. Following termination of AVP infusion, water balance was very clearly positive for 2 days (700 to 1000 ml) and, once again, the return of MAP to the hypertensive level achieved prior to AVP infusion was associated with both sodium and water retention (fig. 5).

**Effects of AVP Infusion in Normotensive Dogs**

On the 2 days prior to and on Days 7 and 12 of AVP infusion, plasma AVP concentration was 0.5 ± 0.1, 0.3 ± 0.1, 4.9 ± 0.5, and 6.0 ± 1.1 \( \mu \)U/ml respectively. That is, infusion of AVP at 140 \( \mu \)U/kg/min increased plasma AVP concentration to about 14 times control. The recovery values for plasma AVP concentration (Day 9 post-AVP infusion) were similar to control.

During AVP infusion in normotensive dogs, the MAP increased progressively for 6 days to a level 30 mm Hg above control and then gradually decreased.
throughout the remainder of the infusion period, so that on Day 12 of AVP infusion the MAP was increased only 13 mm Hg above control (fig. 7). Therefore, even though the dogs were infused with fairly liberal amounts of both sodium and water, there was only a modest increase in MAP after 12 days of AVP infusion, and at this time the MAP was still declining. During AVP infusion, PRA was suppressed to undetectable levels.

The AVP infusion alone, as when given simultaneously with either AII or aldosterone, induced both a natriuresis and a kaliuresis (fig. 8); however, in contrast to dogs with either AII- or aldosterone hypertension, in normotensive dogs the natriuresis was more pronounced and protracted (lasting 6 days). In dogs given only AVP, sodium excretion exceeded intake by 85 mEq after 12 days of AVP infusion. In dogs with AII- and aldosterone-induced hypertension, net sodium loss for the same rate of AVP infusion totalled 50 and 30 mEq respectively. Similarly, the kaliuretic response to AVP infusion was more gradual and prolonged when AVP was infused alone. For the first 6 days of AVP infusion, potassium excretion increased progressively in parallel with the rise in MAP.

Plasma sodium and potassium concentration fell considerably more when AVP was infused alone than when infused in combination with either AII or aldosterone (figs. 1, 4, and 7). This was particularly true for plasma sodium concentration. When AVP was infused alone, plasma sodium concentration fell 25 ± 2 mEq/liter vs 9 mEq/liter or less when AVP was infused in combination with either AII or aldosterone. In comparison with dogs having either AII- or aldosterone-induced hypertension, the fall in plasma sodium concentration during AVP infusion alone was disproportionately greater than the net sodium loss because of the concomitant water retention (see below), which did not occur when the dogs had prior hypertension.
In contrast to when AVP was infused with either AII or aldosterone, net water retention occurred when AVP was infused alone (fig. 8). During the initial 4 to 5 days of AVP infusion when MAP was increasing, water balance was positive; however, during Days 6–12 when MAP was falling, the net water balance was negative. Apparently, since daily sodium balance was maintained during the last week of AVP infusion, the negative water balance during this time accounted for the 116 mEq/liter to 120 mEq/liter on Day 12 of AVP infusion (fig. 7). Nevertheless, in spite of compensatory effects tending to reduce the amount of water retained, after 12 days of AVP infusion, the water balance was positive and body weight was increased 0.4 ± 0.1 kg (p < 0.01); further, water balance was distinctly negative (600 to 1200 ml) during the 24-hour period following cessation of AVP infusion.

During the 24-hour period following AVP infusion, the MAP gradually decreased for several hours to hypotensive levels (with respect to the original control pressure) and remained low for at least 18 hours (fig. 9). This gradual fall in MAP from hypertensive to hypotensive levels (with respect to the original control pressure) was associated with a loss of body water; it is in marked contrast to the 24-hour-off transient response observed in dogs with either AII- or aldosterone-induced hypertension in which, after termination of AVP infusion, the MAP fell precipitously but transiently, and water was retained not lost. During the second post-AVP day, all dogs retained water (260–600 ml) and MAP increased approximately 10 mm Hg. Thereafter, although daily sodium and water balance was achieved and PRA returned to control levels, the MAP fell a few mm Hg and remained 5–10 mm Hg below control level for the duration of the recovery period.

Discussion

The data demonstrate very clearly that chronic increases in plasma AVP concentration do not exacerbate the hypertension associated with long-term infusion of either AII or aldosterone. Further, very high plasma levels of AVP (14 to 15 times control) produced only very moderate hypertension after 12 days (13 mm Hg) even in normotensive dogs subjected to fairly high salt and water intakes. In contrast, infusion of AII at 5 ng/kg/min, a rate that would be expected to increase plasma AII concentration to only 2 to 3 times that of control, increased MAP 43 mm Hg. It should be emphasized that acute infusions of AVP at 140 and 560 μU/kg/min, although having no pressor effects in conscious intact dogs, increased MAP in conscious dogs without baroreceptor reflexes about 20 and 40 mm Hg respectively. Since the arterial baroreceptors adapt to a sustained increase in arterial pressure, during prolonged infusions of AVP at these levels the vasoconstrictor effects of AVP should produce hypertension, provided the kidneys cannot compensate for the rise in arterial pressure by increasing renal fluid excretion. Apparently, in dogs with either AII- or aldosterone-induced hypertension, the AVP did not alter the functional capability of the kidneys to excrete body fluid. In these animals, any pressor effects associated with AVP infusion were compensated for by increased renal salt and water excretion, and, therefore, arterial pressure was unchanged chronically.

Although AVP failed to produce any long-term changes in MAP in AII- and aldosterone-induced hypertensive dogs, transient changes did occur, which were particularly pronounced when AVP infusion was terminated. The transient changes in MAP that occurred with variations in plasma AVP concentration
could be explained on the basis of arteriolar resistance and/or vascular capacitance changes. First, both the arterial and venous vascular beds are responsive to the vasoconstrictor properties of physiological levels of AVP. Second, it is well established that there are great differences in regional blood flow responses to AVP. For example, the splanchnic bed is particularly sensitive to the vasoconstrictor properties of AVP, whereas the renal bed is apparently much less sensitive. Little or no change in renal blood flow has been reported in conscious dogs infused either acutely or chronically with lysine vasopressin or AVP at rates used in the present study. In fact, in one study it was found that renal blood flow actually increased in conscious hydropenic dogs when lysine vasopressin was infused at 166 μU/kg/min. Thus, the transient MAP increase observed during AVP infusion in dogs with aldosterone hypertension could be accounted for by both increased arteriolar constriction and/or decreased vascular capacitance. Increased arteriolar constriction of predominately nonrenal arterioles and/or decreased vascular capacitance would favor an increase in MAP which would, in turn, be expected to result in a renal pressure diuresis and eventually a return in MAP to the initial arterial pressure level. This is precisely what occurred during AVP infusion in dogs with aldosterone-induced hypertension. Failure to observe even a transient increase in MAP following AVP infusion in dogs with AI-induced hypertension may have been due to the high vasoconstriction state prior to AVP administration. Accordingly, in both dogs with AI- and aldosterone-induced hypertension, the marked fall in MAP immediately after termination of AVP infusion could then be explained by a decrease in arteriolar resistance and/or an increase in vascular capacitance. Thus, alterations in plasma AVP concentration may be associated with rather marked hemodynamic effects, which include transient changes in MAP.

Theoretical and experimental evidence indicates that a prerequisite for sustained chronic hypertension is an alteration in the relationship between arterial pressure and urinary excretion of salt and water such that a higher arterial pressure level is required to achieve fluid balance. Thus, long-term changes in arterial pressure are associated with alterations in the setpoint of the renal-arterial pressure control system — the value to which the renal-arterial pressure control system adjusts or controls arterial pressure. Only when arterial pressure is equal to the setpoint value is there an equilibrium between fluid intake and output. When arterial pressure is greater than the renal setpoint, urinary output of salt and water becomes greater than intake. Consequently, there is a decrease in body fluid volume, and arterial pressure returns to the setpoint value. Presumably, this is what occurred in the present study when AVP was infused in animals with prior hypertension. On the other hand, when arterial pressure falls below the renal setpoint, fluid intake becomes greater than urinary output, and body fluid volume continues to increase until arterial pressure rises high enough to achieve balance between urinary output and intake. Again, this is precisely what occurred when AVP infusion was terminated in dogs with either AI- or aldosterone-induced hypertension. Thus, apparently, AVP failed to alter the setpoint of the renal-arterial pressure control system in dogs with prior hypertension, and, therefore, long-term changes in arterial pressure failed to occur.

Since blockade of plasma AVP by intravenous injection of either AVP antiserum or competitive antagonists that block the pressor but not the antidiuretic activity of AVP lowers the arterial pressure dramatically in hypertensive rats with elevated plasma AVP concentration, it is clear that the vasoconstrictor effects of AVP do play a significant role in at least the short-term maintenance of the hypertension. However, it should be emphasized that all these studies were acute, lasting no longer than 1 hour; therefore, they only provide information relating to the role of AVP in the short-term maintenance of arterial pressure and do not necessarily reveal the role of AVP in long-term arterial pressure control, which involves changes in body fluid balance via the renal-arterial pressure control system. For example, opening an arteriovenous fistula is associated with an immediate fall in total peripheral resistance and therefore arterial pressure, but the hypotension is only transient because the setpoint of the renal-arterial pressure control system has not changed. Subsequently, the kidneys retain salt and water, and over a period of hours to days, arterial pressure returns to that of control. Similarly, in the present study as well, when AVP infusion was terminated in dogs with either AI- or aldosterone-induced hypertension, there was a precipitous fall in MAP because of diminution of the vasoconstrictor effects of AVP. However, the fall in arterial pressure was compensated for by both salt and water retention, and within several hours to days the MAP returned to the previous hypertensive level.

It should be emphasized that such hemodynamic and renal excretory responses are in marked contrast to those that occur with reductions in plasma AI concentration in hypertensive states associated with high plasma levels of AI. Like AVP, AI increases peripheral resistance, but, additionally, AI has potent renal effects that alter the setpoint of the renal-arterial pressure control system in such a way that a higher arterial pressure level is required to achieve fluid balance. Consequently, when plasma AI concentration is reduced in hypertensive states associated with high plasma levels of AI, there is an immediate fall in arterial pressure due to a decrease in peripheral resistance (similar to the AVP response in the present studies). However, in the case of AI, this fall in arterial pressure cannot be compensated for by salt and water retention because of the diminished renal effects of AI, which favor natriuresis and diuresis — there is a shift in the setpoint of the renal-arterial pressure control system to a lower pressure value for long-term arterial pressure control. Therefore, the arterial pressure remains reduced rather than returning to the previous high level.

Thus, in light of the present data, which suggest that
AVP is much more important in the short-term maintenance of arterial pressure than in the long-term control of arterial pressure, it would be particularly interesting and important to know whether chronic blockade of endogenous AVP in high AVP hypertensive states would result in a permanent amelioration of the hypertension. If the hypertensive response to AVP blockade is not maintained chronically and arterial pressure returns to prior hypertensive levels such as occurred in the present study when AVP infusion was terminated, this would indicate that, in these hypertensive states, AVP is not a particularly important hypertensive hormone.

The changes in MAP observed during AVP infusion in normotensive dogs were expected. First, although 1 to 2 days out of phase, changes in MAP and fluid balance paralleled one another. During the initial days of AVP infusion, MAP increased progressively as water balance became increasingly positive; subsequently, daily water balance became negative and MAP gradually fell for the duration of AVP infusion. Similarly, in dogs chronically infused with comparable amounts of AVP, Smith et al.\(^\text{10}\) reported a significant correlation between increases in MAP and plasma volume. Second, after 12 days of AVP infusion, the rise in MAP was very moderate — only 13 mm Hg above control. This is consistent with the observations that usually arterial pressure is either not elevated markedly or not at all in patients with the syndrome of inappropriate AVP secretion. It is significant that we attempted to optimize conditions for achieving hypertension during AVP infusion by subjecting the animals to fairly high salt and water intakes. In spite of a forced salt and water load of 100% and 45% greater respectively than that employed by Smith et al.,\(^\text{10}\) hypertension was no more severe in our study. Finally, during the initial days of AVP infusion, both the retention of water and the attendant hypertension were fairly pronounced. The reason for the subsequent unloading of much of this retained water together with the marked fall in arterial pressure is unclear. These transient changes in water balance and arterial pressure also occur in animals infused chronically with dDAVP (personal observations) and are unique in that they do not occur in other models of volume-loading hypertension. The loss of body water over time may in part be related to "washout" of the concentration gradient in the renal medullary interstitium due to the volume expanded, high arterial pressure state, or some other effect related to the protracted loss of various electrolytes in the urine. For example, it is well established that potassium depletion is associated with a renal concentration defect that is vasopressin resistant.\(^\text{28-30}\) This concentrating defect may be related to the interaction of AVP and prostaglandins since, at least in the dog, prostaglandin \(E_2\) secretion is increased during potassium depletion\(^\text{30}\) and prostaglandins have been shown to antagonize the hydroosmotic effects of vasopressin.\(^\text{30, 31}\)

Hyponatremia, increased sodium excretion, water retention, and suppressed PRA were all observed in the dogs when AVP alone was infused. In both man and dog, these perturbations are characteristically seen in the syndrome of inappropriate AVP secretion or during vasopressin administration.\(^\text{9, 10, 28-30}\) Additionally, in the dog but not in man, hypokalemia and kaliuresis are typical findings in the syndrome of inappropriate AVP secretion or during AVP administration.\(^\text{9, 10, 28, 34, 35}\) There are undoubtedly several factors that contribute to AVP-induced natriuresis, although the relative importance of these factors in mediating sodium loss is unresolved. It is clear from the present study, however, that when plasma levels of All or aldosterone cannot be suppressed during AVP administration (as in the dogs with All- or aldosterone-induced hypertension), the natriuretic effects of AVP are attenuated. Further, it is apparent from the dogs with All- and aldosterone-induced hypertension that neither water retention nor increased arterial pressure are prerequisites for AVP-induced salt loss. Finally, it is widely recognized that the changes in plasma electrolytes observed during AVP administration in inappropriate AVP secretion reflect not only the dilutional but also the urinary electrolyte changes. In dogs infused with 77-140 \(\mu\)U AVP/kg/min, Smith et al.\(^\text{10}\) found after 15 days that most of the decrease in plasma sodium concentration was accounted for by the cumulative negative sodium balance rather than retention of water. Similarly, in the present study, the fall in plasma sodium concentration during AVP infusion was much milder in dogs with All- and aldosterone-induced hypertension than in dogs infused with AVP alone, not only because they excreted less sodium, but also because they failed to retain water.

In summary, in the hypertensive models studied, high plasma levels of AVP had relatively weak hypertensive effects. Although variations in plasma AVP concentration were associated with rather pronounced acute changes in arterial pressure, the long-term arterial pressure effects of AVP were either minimal or, in the case of animals already hypertensive, nonexistent. This study emphasizes the importance of evaluating not only the transient but also the chronic arterial pressure effects associated with alterations in plasma AVP concentration. Future studies achieving long-term blockade of endogenous AVP in hypertensive states with elevated plasma AVP concentration should prove particularly valuable in determining whether AVP is, in fact, an important hypertensive hormone.

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References

In their paper, Lohmeier and colleagues have attempted to evaluate vasopressin as a hypertensive agent in the conscious dog by determining the effect on arterial pressure of an infusion of vasopressin superimposed upon pressor infusions of either angiotensin II (AII) or aldosterone. They concluded that, in these models of hypertension, vasopressin is a relatively weak hypertensive agent.
First, when the vasopressin infusion was superimposed upon a preexisting infusion of All, there was no further increase in arterial pressure; when the vasopressin infusion was combined with a preexisting infusion of aldosterone, there was only a small further increase in arterial pressure, which was maintained for only a few days. It is difficult, however, to evaluate adequately the possible role of vasopressin in these models of hypertension in the absence of information concerning the effects on plasma vasopressin concentrations of the infusions of All and aldosterone alone, as well as in combination with the infusion of vasopressin. Although Lohmeier et al. did measure the plasma concentration of vasopressin when it was infused alone, this is not adequate, since either All or aldosterone could affect the rates of secretion or clearance of vasopressin.

Second, Lohmeier et al. found that, when vasopressin infusion was discontinued while infusion of All or aldosterone was continued, the arterial pressure fell 35 to 40 mm Hg within 1 hour and did not return to previous hypertensive levels until 18 to 48 hours later. On the basis of this observation, as well as other data to which I shall return later, Lohmeier et al. concluded that vasopressin is more important in the short-term than long-term regulation of arterial pressure. An alternative view, which I believe is more consistent with these data, is that during the 14 days of vasopressin infusion the vasopressin assumed the major role for the maintenance of the elevated blood pressure. Thus, when the vasopressin infusion was terminated, arterial pressure fell precipitously, even though the infusion of All or aldosterone was continued. That arterial pressure eventually returned to hypertensive levels only indicates that the mechanisms originally responsible for the hypertension again came into play.

Third, when vasopressin alone was infused, arterial pressure gradually increased to 30 mm Hg and then fell to a value only 13 mm Hg above the control level on the twelfth day of infusion. Although the increase in arterial pressure at the end of the vasopressin infusion was modest, it could be of considerable pathological importance if it were maintained for a prolonged period of time. This is of particular relevance since the increase in the plasma levels of vasopressin achieved in these experiments is of the same magnitude as that observed in dogs after 2 days of dehydration. Furthermore, there is a marked increase in the pressor responsiveness to vasopressin in several models of experimental hypertension, e.g., DOC-salt hypertension, the SHR, and Goldblatt hypertensive rat. In comparing the pressor potencies of All and vasopressin, Lohmeier et al. point out that in their experiments the plasma vasopressin concentration was increased 14-fold, but claim that the plasma All concentration was increased only two- to threefold, even though All was infused at a rate 14 times that of vasopressin. However, Lohmeier et al. did not measure the plasma All levels but relied on measurements made by others.

It has been shown by several other groups of investigators that the bolus intravenous (i.v.) injection of a vasopressin antiserum or a vasopressin analog that blocks the pressor but not the antidiuretic action of vasopressin results in a substantial, transitory reduction in arterial pressure. No report has yet been made of an attempt to achieve a long-term reduction of arterial pressure by this means. In the absence of such a demonstration, Lohmeier et al. state that these data can only be used as evidence for a role of vasopressin in the short-term regulation of arterial pressure. The logic here seems faulty. If, in the chronic stage of a given form of hypertension, blockade of the pressor action of vasopressin results in a fall in arterial pressure, it is obvious that vasopressin was at least partially responsible for the long-term maintenance of the hypertension. This conclusion would not be altered even if it should be shown that sustained blockade of vasopressin does not result in a sustained reduction in arterial pressure; this would merely indicate that some other pressor mechanism can take over to maintain the hypertension while vasopressin is blocked.

In conclusion, although Lohmeier and his colleagues have chosen to do otherwise, the data they have presented in the preceding paper can be used as evidence that vasopressin, as a pressor agent, does indeed play an important role in the maintenance of the elevated arterial pressure in the two rather specialized models of hypertension they have chosen to study. It is certainly premature to attempt to delineate fully the role of vasopressin in hypertension or in the normal regulation of arterial pressure. The data obtained by Lohmeier et al. and others clearly indicate that vasopressin is a major factor in the development or maintenance of some forms of hypertension, e.g., DOC-salt hypertension, two-kidney, one clip hypertension, and in the SHR.

References

Is vasopressin an important hypertensive hormone?
T E Lohmeier, M J Smith, Jr, A W Cowley, Jr, R D Manning, Jr and A C Guyton

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