Contribution of Vasopressin to Hypertension

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SUMMARY The contribution of vasopressin to the hypertensive process has been examined in a number of models of hypertension. Vasopressin is essential for the production of DOC-salt hypertension in the rat. It is likely that vasopressin is required in the early stages of this model of hypertension for its antidiuretic activity and contributes to the later stages of the hypertension as a pressor agent. Vasopressin secretion is increased in SHR, but there may be some differences between the SHR and stroke-prone SHR strains. The pressor action of vasopressin appears to be important in the stroke-prone SHR with well-established hypertension, but not in the young SHR. Vasopressin secretion is greater in Dahl S rats on a high salt diet than in similarly treated R rats. Blockade of vasopressin’s pressor activity failed to lower blood pressure in these S rats, unless they were pretreated with captopril. There is insufficient information to determine whether vasopressin has a role in the hypertension in NZGH rats. Vasopressin appears to function as a pressor agent in some, but not all, rats with two-kidney, one clip hypertension. Although vasopressin is not essential for the production of one-kidney, one clip hypertension, it apparently contributes to the hypertension by virtue of its antidiuretic activity. Vasopressin secretion is elevated in partial nephrectomy-salt hypertension, and here, too, it is needed for its antidiuretic action. The question of whether vasopressin secretion is elevated in human essential hypertension is controversial, and its role remains to be determined.


KEY WORDS • vasopressin • hypertension • antidiuretic hormone

THE mechanisms of most forms of clinical and experimental hypertension are still incompletely understood. It is, then, reasonable to consider the possibility that vasopressin, because of its particular biological properties, may be a pathogenetic factor in hypertension. Vasopressin is the mammalian antidiuretic hormone. By virtue of its ability to promote water reabsorption by the kidney, it could be a factor in those forms of hypertension that are dependent on an expansion of blood volume. However, the primary focus of attention in recent years has been on the possibility that the role of vasopressin in hypertension is as a pressor agent, even though, until recently, it was generally considered that the pressor action of vasopressin is of pharmacological rather than physiological importance.

Cardiovascular Actions of Vasopressin

Vasopressin is a potent pressor agent. In the conscious rat, its pressor activity is as great as that of angiotensin II (All). In vitro the rat mesenteric resistance vessels are at least three orders of magnitude more sensitive to vasopressin than to All. This difference in potency between the actions of vasopressin in vivo and in vitro may be due to the restraining influence of the baroreceptor reflex in the intact animal. Cowley et al. showed that, in the conscious dog, denervation of the baroreceptors resulted in a 60- to 100-fold increase in the pressor sensitivity to exogenous vasopressin. These findings have been extended by Montani et al. It has also been demonstrated that in humans with idiopathic orthostatic hypotension and impaired baroreceptor reflexes, there is a marked increase in the pressor sensitivity to vasopressin. Particularly striking is the report by Möhring et al. that a 1000 times greater increase in plasma vasopressin concentration is necessary in normal human subjects to increase arterial pressure by 10 mm Hg than in patients with impaired baroreceptor reflexes. In the impaired patients, pressor responsiveness to All and norepinephrine was only two to eight times greater than in normal subjects.

Möhring et al. suggested that vasopressin increases the gain of the baroreceptor reflexes in the normal individual. Their hypothesis is supported by Montani et al. who reported that very small increases in plasma vasopressin levels in conscious dogs, of the order of those produced by dehydration, increased total peripheral resistance; blood pressure did not rise because of an offsetting decrease in cardiac output. This latter effect was presumably due to a central action of vasopressin on the reflex-control of cardiac function, since the effect of vasopressin on cardiac output was
greatly attenuated in baroreceptor-denervated dogs. Small increases in plasma vasopressin concentration that are maintained over a long period of time appear to be more effective in exerting hemodynamic effects. Lohmeier et al. infused vasopressin intravenously (i.v.) in conscious dogs for 12 days at a rate that increased plasma vasopressin levels five- to sixfold. Mean arterial blood pressure increased 30 mm Hg over the first 6 days and then fell to a level that was 13 mm Hg above control values by the 12th day. The major cardiovascular actions of vasopressin in these experiments were further indicated by the observation that blood pressure fell approximately 40 mm Hg over a period of 8 hours when the vasopressin infusion was discontinued!

Vasopressin, at plasma concentrations that are themselves nonpressor, may also increase arterial pressure by potentiating the pressor action of catecholamines. The physiological importance of this action has not been adequately determined.

**DOC-Salt Hypertension**

The form of hypertension that has been most intensively studied with respect to vasopressin is DOC-salt hypertension in the rat. Because of the variety of techniques that have been used in these studies, they best illustrate the approaches that are currently available for evaluating the role of vasopressin in hypertension. Friedman et al. showed that the development of this form of hypertension could be accelerated by treating the rats with small doses of Pitressin, whereas surgically induced diabetes insipidus prevented the development of hypertension. Subsequently, we have found that DOC-salt hypertension cannot be produced in the Brattleboro rat with hereditary hypothalamic diabetes insipidus (fig. 1).

There is evidence that the secretion of vasopressin from the neurohypophysis is elevated in DOC-salt hypertension. Möhring et al. reported that plasma vasopressin levels were elevated threefold during the benign phase and tenfold in the malignant phase of the hypertension. We have found a much smaller increase in plasma vasopressin levels during the benign phase, but these experiments were carried out in a different strain of rats and with a different dosage schedule for DOC. There was also an increased 24-hour urinary excretion of vasopressin (fig. 2), an index of changes in vasopressin release from the posterior pituitary, which roughly paralleled the increase in blood pressure. Urinary excretion of vasopressin also increased, although to a lesser extent, in unilaterally nephrectomized rats that were given 1.0% saline to drink, but these rats did not become hypertensive (fig. 2). On the other hand, unilaterally nephrectomized rats that were treated with DOC but given water to drink instead of saline also became hypertensive, but the urinary vasopressin excretion did not increase until well after the hypertension developed (fig. 2).

**Figure 1.** Systolic blood pressure (SBP) in Long-Evans (DOC-LE) and diabetes insipidus (DOC-DI) subjected to unilateral nephrectomy (Nephrex) and treated with deoxycorticosterone and salt. Asterisks above or below the lines indicate significant differences from Week 1. Asterisks between the lines indicate significant differences between the groups (see ref. 8).

**Figure 2.** Systolic blood pressure (SBP; A) and the 24-hour urinary excretion of vasopressin (U\textsubscript{ADH}; B) in unilaterally nephrectomized rats that were untreated (H\textsubscript{2}O), given 1% NaCl to drink (1% NaCl), treated with DOC and given 1% NaCl to drink (DOC + 1% NaCl), or treated with DOC alone (DOC). Asterisks above the lines or bars indicate significant differences from Week 1. Asterisks between the lines or within the bars indicate significant differences from the H\textsubscript{2}O group (see ref. 1).
one series of experiments demonstrated that an increased secretion of vasopressin per se is not sufficient to induce hypertension, and some forms of hypertension can develop without an increased secretion of vasopressin.

Blockade of vasopressin with either a vasopressin antiserum or analogs of vasopressin that specifically block its pressor, but not its antidiuretic, action substantially lowered blood pressure in rats with established DOC-salt hypertension. In the perfused hindquarters of the rat with established DOC-salt hypertension, the vasoconstrictor responses to vasopressin and the vasodilator responses to a vasopressin pressor antagonist were enhanced. On the basis of these findings, it would appear that vasopressin contributes to DOC-salt hypertension in the established phase by virtue of its pressor activity. However, plasma vasopressin levels in DOC-salt hypertension, although elevated, are far below vasopressin concentrations that are required to increase blood pressure in the normal individual. This paradox could be explained if there were a marked increase in pressor responsiveness to vasopressin in the rat with DOC-salt hypertension. To test this possibility, we measured pressor responsiveness to vasopressin in DOC-salt hypertensive rats at 3 to 5 weeks and 6 to 8 weeks after the start of treatment. Increased pressor responsiveness to vasopressin was demonstrated in only one of nine rats in the former group and in only five of 11 rats in the latter group.

Similarly, Matsuguchi and Schmid have found that in rats with DOC-salt hypertension, pressor responsiveness to vasopressin was normal after 5 to 7 days of treatment with DOC, and increased after 15 to 17 days of treatment. The more rapid development of increased pressor responsiveness to vasopressin in these experiments may reflect the use of younger animals, larger doses of DOC, and a different strain of rat than in our experiments. These findings strongly suggest that vasopressin functions as a pressor agent only in the later stages of DOC-salt hypertension in the rat, and not during the development of this form of hypertension. Consistent with this view is the recent observation by Rascher et al. that a vasopressin pressor antagonist was without effect on blood pressure in rats with DOC-salt hypertension in the fourth week of treatment. However, in these experiments the vasopressin antagonist did decrease peripheral resistance and increase cardiac output.

Matsuguchi and Schmid have presented data that support the hypothesis that systemically administered vasopressin increases the gain of the baroreceptor reflex in the normal subject. They have further proposed that in the rat with established DOC-salt hypertension, the increased pressor responsiveness to vasopressin is due to an impairment of this action combined with an increased vascular responsiveness to this hormone. Rabito et al. reported that a vasopressin pressor antagonist failed to lower blood pressure in rats in the malignant phase of DOC-salt hypertension. However, these rats were tested with AII, norepinephrine, and vasopressin (dose-response curve), and were given a total of 1.8 ml of normal saline prior to administration of the antagonist. These manipulations could have affected endogenous vasopressin release and pressor responsiveness to vasopressin. We have no other explanation for the variance of their report with ours.

Vasopressin is essential for the development of DOC-salt hypertension in the rat, but what is its role in the initial stages of this syndrome? An answer may be provided by the work of Saito et al. in which they produced DOC-salt hypertension in the rat with hereditary hypothalamic diabetes insipidus by including dDAVP in the salt solution the rats were given to drink. dDAVP is a potent antidiuretic analog of vasopressin that has minimal cardiovascular effects. Thus, vasopressin apparently functions as an antidiuretic agent in the development of DOC-salt hypertension, making possible the expansion of blood volume that is necessary for this model of hypertension.

Genetic Forms of Hypertension

Vasopressin has been studied in three forms of genetic hypertension in the rat, the spontaneously hypertensive rat (SHR) of Okamoto and Aoki, the New Zealand genetically hypertensive (NZGH) rat, and the Dahl salt-sensitive (S) and salt-resistant (R) rat. In the SHR, we have found evidence for increased secretion of vasopressin, indicated by increased urinary excretion and plasma levels of the hormone, in the weanling rat and during the development of hypertension as the rat matured (fig. 3). Our finding of an elevated plasma concentration of vasopressin in the SHR has been confirmed by Morris in the 10-week-old SHR and by Möhring et al. in the stroke-prone SHR 22 to 28 weeks of age. We have no explanation for the report by Rascher et al. that plasma vasopressin levels are depressed in young and adolescent stroke-prone SHR, other than differences in strain of SHR. Pressor responsiveness to vasopressin is increased in the SHR. Although we found that a vasopressin pressor antagonist decreased blood pressure only 9 mm Hg in 9-week-old SHR, Möhring et al. reported that a specific vasopressin antiserum lowered blood pressure substantially in 22- to 28-week-old stroke-prone SHR. Thus, all of the elements are present for a role for vasopressin in the hypertension in the SHR: increased vasopressin secretion, increased pressor responsiveness to vasopressin, and reduction in blood pressure in response to vasopressin blockade. However, the contribution of vasopressin to the early stages of this form of hypertension is still not clear.

The situation with respect to vasopressin is similar but more complicated in the Dahl rat. In response to a high-salt diet, there were greater increases in the plasma vasopressin concentration and the urinary excretion of vasopressin in the S than in the R rat. The pressor responsiveness to vasopressin was also greater in the S than in the R rat. However, a vasopressin pressor antagonist failed to lower blood pressure in the S rat made hypertensive by treatment with a high-salt diet, unless the rats were pretreated with the angiotensin-converting enzyme inhibitor, captopril. These findings suggest that vasopressin is a factor in the
hypertension produced in the Dahl S rat by an elevated salt intake, and that when the pressor action of vasopressin is blocked, the renin-angiotensin system does take over.

In contrast to the SHR and Dahl S rats, vasopressin secretion is not elevated in the NZGH rat. During the development of hypertension, the urinary excretion of vasopressin in young NZGH rats did not differ from that in normotensive NZNR rats, and at age 13 to 14 weeks, plasma vasopressin concentrations in these two groups of rats were not different. On the other hand, the pressor responsiveness to vasopressin is markedly enhanced in NZGH rats. Although it seems unlikely that vasopressin was an important factor in this genetic model of hypertension, a definitive conclusion cannot be reached until a determination is made of the blood pressure response to a vasopressin pressor antagonist.

Renal Hypertension

Plasma vasopressin levels, on the average, were elevated in rats with two-kidney, one clip hypertension. The average increase was greater in rats in the "malignant" than in the "benign" phase of the hypertension. However, plasma vasopressin concentrations in half the benign and malignant hypertensive rats were within the normal range. A vasopressin antiserum lowered blood pressure in only half the malignant hypertensive rats that were tested, whereas saralasin lowered blood pressure in all of these rats. Thus, vasopressin appeared to exert a significant vasoconstrictor action in only half of the rats with malignant two-kidney, one clip hypertension. Möhring et al. suggested that the hypertension in these rats was due to the combined actions of vasopressin and the renin-angiotensin system. Rabito et al. failed to find an effect of a vasopressin pressor antagonist on blood pressure in rats with malignant two-kidney, one clip hypertension, but, as was pointed out above, this could have been due to the treatments these rats received prior to the administration of the antagonist.

In unilaterally nephrectomized dogs, constriction of the remaining renal artery resulted in only a transient twofold increase in the plasma vasopressin concentration, although there was a substantial sustained increase in blood pressure. It seems likely, therefore, that the increased plasma vasopressin levels were an important factor in the elevated blood pressure. However, these dogs were studied for only 6 days, so that a role for vasopressin in the later stages of one-kidney, one clip hypertension cannot be ruled out. Be that as it may, vasopressin is not essential for the production of one-kidney, one clip hypertension in the rat, since it can be produced in a rat that lacks vasopressin, the Brattleboro rat with hereditary hypothalamic diabetes insipidus (fig. 4). However, rats with diabetes insipidus did not become as hypertensive as did rats with normal neurohypophysial function. This may have been due to the impaired growth in the Brattleboro rat. This could have resulted in a smaller increase in diameter of the renal artery with time and a consequent smaller relative constriction of the renal artery in the diabetes insipidus rats than in the normal rats. On the other hand, vasopressin may indeed contribute to one-kidney, one clip hypertension by virtue of either its antidiuretic activity, permitting the expansion of blood volume that apparently is necessary for the chronic stage of the hypertension, or its pressor activity. Effects due to derangements in water and electrolyte metabolism in the Brattleboro rat also cannot be ruled out.

Although hypertension in the chronic phase of one-kidney, one clip hypertension in rats with normal neurohypophysial function is not dependent upon the renin-angiotensin system, this is not the case in diabetes insipidus rats with this form of hypertension. In these rats, blockade of the renin-angiotensin system with
saralasin substantially lowered blood pressure. Indeed, blood pressure fell to normotensive levels in four of the six rats studied. Saralasin was without effect on the blood pressure of normal rats with one-kidney, one clip hypertension; the initial rise in blood pressure was accompanied by an increased plasma renin activity. Within a few days, plasma renin activity returned to normal, and plasma volume was expanded.

The expanded blood volume was presumably responsible for the chronic elevation in blood pressure, and may have been responsible for the return of plasma renin activity to normal levels. It would appear that, in the absence of vasopressin, expansion of blood volume necessary for the hypertensive state was maintained, and plasma volume was expanded. Within a few days, plasma renin activity returned to normal, and plasma volume was expanded.

Partial nephrectomy-salt hypertension is another form of renal hypertension in which vasopressin may function as an antidiuretic agent, making possible the expansion of blood volume necessary for the hypertension to develop. This model of hypertension was produced by reducing renal mass by 70% and substituting 1% saline for drinking water. Rats prepared in this way (fig. 5) rapidly became hypertensive, and there were marked increases in the plasma vasopressin concentration and the urinary excretion of vasopressin. Treatment with a vasopressin pressor antagonist had only a small effect on arterial pressure. On the other hand, a sustained hypertension could not be produced with the partial nephrectomy-salt protocol in rats with hereditary hypothalamic diabetes insipidus (unpublished observations), although transient increases in blood pressure were observed in four of the five rats studied.

Essential Hypertension in Humans

There have been only a few studies of vasopressin in human essential hypertension. Although Padfield et al. and Shimamoto et al. have reported that the plasma vasopressin concentration was slightly lower in patients with benign essential hypertension than in normal subjects, Cowley et al. found that plasma levels of vasopressin were elevated 80% in patients with moderate hypertension. The cause of this difference in results is not readily apparent. The severity of the hypertension and the conditions of the study were similar in all three reports, with the following exceptions. In the studies by Padfield et al. and Shimamoto et al., the patients included both males and females, and they were studied recumbent. All of the patients in the study by Cowley et al. were male, and blood samples were obtained while the subjects were seated quietly. In all three studies, the plasma vasopressin concentrations of many of the patients were within the normal range. In patients with malignant hypertension, plasma vasopressin levels were approximately twice those in normal subjects. Here too there was considerable overlap between hypertensives and normals. In the patients with malignant hypertension there was no correlation between the plasma vasopressin concentration and arterial pressure. On the other hand, Cowley et al. found that multivariate regression analysis indicated a significant correlation among diastolic blood pressure, urinary sodium concentration, and the plasma vasopressin concentration in their patients with moderate essential hypertension. There was also a correlation between urinary sodium excretion and the plasma vasopressin concentration in patients older than 50 years. Cowley et al. suggested that the elevated plasma vasopressin concentration in the hypertensive patients could have been a compensatory response to the impaired concentrating ability found in these patients.

In young men with "very mild" essential hypertension, the urinary excretion of vasopressin did not differ from that in normal subjects when all of the subjects had unrestricted access to fluid (urine osmolality 0 to 400 mOsm/kg H2O). However, in response to mild hydrenephnia (urine osmolality 400 to 800 mOsm/kg H2O), there was a greater increase in the urinary vasopressin excretion in the hypertensive patients than in the normal subjects. These findings indicate that fluid deprivation for as little as 8 hours (the exact time period cannot be determined from this report) could result in a greater increase in vasopressin release from the hypertensive than the normotensive individual, and this would presumably result in a greater increase in the plasma vasopressin concentration in the hypertensive.
Conclusions

It is quite clear that one cannot generalize about the role of vasopressin in hypertension. The role depends upon the model of hypertension and, for a given model, the stage of hypertension. The situation in this regard is similar to that for the renin-angiotensin system. Be that as it may, vasopressin secretion has been found to be elevated in most models of hypertension in which it has been studied, but the contribution of vasopressin to the hypertensive process is controversial.

Padfield and his colleagues\(^{13,41}\) contend that vasopressin is not important in the pathogenesis of hypertension. In support of their position, they cite their observation that patients with the syndrome of inappropriate antidiuretic hormone secretion, in whom the plasma vasopressin concentration was three times higher than in the patients with malignant hypertension, were not hypertensive.\(^{41}\) When vasopressin was infused acutely in normal human subjects, to achieve plasma vasopressin levels that were up to 5 times the highest values found in the patients in the malignant phase of hypertension, blood pressure was not elevated.\(^{13}\) There is no doubt that increases in plasma vasopressin levels of the order of magnitude observed in experimental and clinical hypertension are insufficient to account for the elevated blood pressure by virtue of the pressor activity of vasopressin per se. For vasopressin to contribute to hypertension, there must be a sufficiently increased pressor responsiveness to vasopressin for the circulating levels of vasopressin to cause an increase in blood pressure. Indeed, increased pressor responsiveness to vasopressin has been reported in the SHR,\(^{24,25}\) the rat with DOC-salt hypertension,\(^{1}\) the Dahl S rat,\(^{26}\) and the NZGH rat.\(^{28}\) Increased pressor sensitivity to vasopressin may result from an increased responsiveness of vascular smooth muscle,\(^{41}\) an impairment of baroreceptor activity, or a combination of these phenomena. If vasopressin does indeed increase baroreceptor gain in the normal individual,\(^{3,4,6}\) it is possible that this action may be deficient in some forms of hypertension. In that event, the increases in

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**Figure 5.** Systolic blood pressure (SBP; A) and the 24-hour urinary excretion of vasopressin (U\(_{\text{ADH}}\); B) in partially nephrectomized (PN) and sham-operated rats. Significant differences from 0-time are shown by asterisks above the line and bars. Significant differences between groups are shown by asterisks between the lines or bars (see ref. 36).
plasma vasopressin levels seen in many forms of hypertension would be sufficient to increase blood pressure appreciably. Furthermore, it is apparent from the work of Montani et al. that small increases in the plasma vasopressin concentration can produce important hemodynamic effects, even in the absence of changes in arterial pressure.

If vasopressin does function as an important pressor factor in some forms of hypertension, the interrelationship of this pressor system with others, particularly the renin-angiotensin system, merits further study. We observed in the hypertensive Dahl S rat on a high-salt diet that a vasopressin pressor antagonist lowered arterial pressure only after the renin-angiotensin system was blocked with captopril. This suggests that under certain circumstances, blockade of vasopressin can be compensated for by an increased activity of the renin-angiotensin system. In a somewhat similar vein, one-kidney, one clip hypertension is volume-dependent in the chronic phase in the rat with normal neurohypophysial function, perhaps requiring the antidiuretic action of vasopressin; in the rat with diabetes insipidus, the hypertension is dependent upon the renin-angiotensin system.

Although the primary focus, so far, has been on the possibility of a pressor role for vasopressin in hypertension, an antidiuretic role for vasopressin in some forms of hypertension should not be overlooked. Thus, in partial nephrectomy-salt hypertension and during the development of DOC-salt hypertension, vasopressin appears to be necessary as an antidiuretic factor to make possible the expansion of blood volume that these forms of hypertension are dependent upon. It is also possible that the role of vasopressin can change during the development of the hypertension, e.g., vasopressin does have significant pressor activity in the later stages of DOC-salt hypertension. A definitive investigation of the antidiuretic function of vasopressin in hypertension will probably await the development of analogs of vasopressin that block its antidiuretic activity, but not its pressor activity.

It is premature to attempt an evaluation of the role of vasopressin in human essential hypertension. Additional work is required with particular attention given to the following: sodium intake; integrity of renal function; the stage of the hypertension; and interactions between vasopressin and the renin-angiotensin system, the sympathetic nervous system, and adrenocortical hormones. Studies of the effects on blood pressure of analogs of vasopressin that specifically block either its pressor or antidiuretic actions will be of particular value.

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Contribution of vasopressin to hypertension.
L Share and J T Crofton

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