STATE OF THE ART REVIEW

Role of vasopressin in cardiovascular homeostasis and hypertension

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Introduction

In 1895 Oliver & Schäfer [1] reported that extracts of the pituitary were pressor when injected into anaesthetized animals, and 3 years later Howell [2] established that the active pressor material arose from the posterior pituitary. For this reason and because later pressor bioassay became the method of standardization for the pharmacopoeia, the substance was named vasopressin. Ironically, in early physiological studies in animals administration of pituitary extracts was associated with diuresis. It was not until early in the 20th century that two physicians, linking the pathological changes found in the pituitary gland to diabetes insipidus, administered pituitary extracts to patients with diabetes insipidus and showed a decrease in urine flow. The classic studies of Starling & Verney [3] on the isolated kidney established that pituitary extracts were antidiuretic but it was not until Du Vigneaud [4] isolated and synthesized vasopressin that it was clearly shown that the same peptide had both pressor and antidiuretic properties. For a full account of the historical background the reader is referred to Heller [5].

Until recently the vasoconstrictor action of vasopressin was regarded as a pharmacological property of little physiological or pathological importance. The reason for its neglect in cardiovascular homeostasis is difficult to ascertain, for as early as 1937, Page & Sweet [6] showed that hypophysectomy reduced experimental renal hypertension and Ellis & Grollman in 1949 [7] reported increased levels of antidiuretic hormone in the urine of hypertensive patients and experimental dogs. In 1960, Friedman et al. [8] demonstrated that administration of vasopressin accelerated DOCA-salt hypertension. Further, interrelationship between catecholamines and vasopressin and the potentiation by vasopressin of the vasoconstrictor effects of catecholamines were established by the 1960s [9, 10]. Also by that time haemorrhage, with its cardiovascular consequences, was known to be a potent stimulus to vasopressin release [11]. Finally, vasopressin was shown in vitro to be the most powerful vasoconstrictor agent known, more potent even than angiotensin [12]. Thus, similar to the actions of angiotensin, vasopressin was known to vasoconstrict (pressor) as well as conserve volume (antidiuresis). Whereas these two biological actions were used to support the concept of a role for the renin–angiotensin system in blood pressure regulation and hypertension, similar arguments were not advanced for vasopressin. The recent interest in vasopressin as a pressor hormone is largely due to the tenacity and imaginative experimental work of Jan Möhring (1940–1979).

Vasoconstrictor and pressor activity of vasopressin

Vasopressin in doses as low as 10⁻¹² mol/l can cause contraction of isolated vascular smooth muscle in vitro [13]. Circulating plasma levels of vasopressin in hydrated subjects are of a similar order (1–5 fmol/ml), but only double with dehydration. However, in vivo, the dose of vasopressin needed to produce a rise in blood pressure is 10–100-fold those required to produce maximum antidiuresis [14, 15]. In rats [16], dogs [17–19] and man [20], infusion of exogenous synthetic arginine-vasopressin (AVP), sufficient to increase the blood pressure significantly, result in plasma vasopressin levels some 20–100 fold higher (100 fmol/ml) than are found in physio-
logical conditions or in hypertensive states (see below).

It is apparent therefore that for endogenous vasopressin to act as an important vasopressor hormone in blood pressure control either circulatory reflex mechanisms normally buffer its vasoconstrictor activity or sensitization to the vasoconstrictor activity of vasopressin must occur in a variety of physiological and hypertensive conditions.

Cowley et al. [17] showed that the pressor effect of vasopressin was greatly attenuated by the baroreceptors and the sympathetic nervous system. These studies have been recently extended by Pullan et al. [21], who showed that in anaesthetized dogs, when the sympathetic nervous system was pharmacologically blocked, very low infusion rates of vasopressin, sufficient to raise the plasma vasopressin levels only to 20–40 fmol/ml, significantly increased the blood pressure. In normal dogs with an intact sympathetic system, although blood pressure did not increase with these small elevations in plasma vasopressin heart rate significantly decreased and plasma renin was suppressed [21] (Fig. 1). This suggests that, even under normal conditions, vasopressin in very low concentrations has circulatory effects that may dampen its hypertensive action. Vasopressin has previously been shown to reduce plasma renin both in vivo[22, 23] and in vitro [24] by a direct effect on the juxtaglomerular apparatus.

The interaction between vasopressin and catecholamines can also be demonstrated at the level of the vascular smooth muscle. Decreased sympathetic tone increases vasopressin-induced vasoconstriction, whereas increased sympathetic tone blunts vasoconstriction induced by vasopressin. The reverse effect is also well established; small doses of vasopressin enhance vasoconstriction as well as the rise in blood pressure caused by sympathetic stimulation or infused catecholamines [25, 26].

Vasopressin also interacts with the renin–angiotensin system. Mention has already been made of vasopressin directly suppressing renin release. Other studies [27–29] have demonstrated that intraventricular, in contrast to intravenous, infusions of angiotensin release vasopressin from the posterior pituitary and that the vasopressin released may participate in the hypertensive response to intracerebral angiotensin infusions [30]. Of more importance in the overall regulation of blood pressure are the observations of McNeil et al. [31] that vasopressin and angiotensin, rather than the sympathetic system, are the important determinants of mesenteric vasoconstriction after haemorrhage or volume reduction with diuretics [32]. Furthermore, there was a reciprocal relationship between these two hormonal systems such that, when the vasopressin vasoconstriction was abolished by hypophysectomy, the resistance was maintained by heightened activity of the renin–angiotensin system and vice versa [33]. A similar interaction between vasopressin and angiotensin has recently been demonstrated in the recovery of blood pressure after haemorrhage in the dog by Cowley et al. [34]. Andrews & Brenner [35] have also reported a similar phenomenon in the dehydrated rat where blood pressure was maintained by the combined effect of angiotensin and vasopressin. Blocking the effect of either vasoactive hormone led to a compensatory increase in vasoconstriction by the other vasoactive peptide (see below).

These complex interactions between the sympathetic nervous system, the renin–angiotensin system and vasopressin, together with blood and extracellular volume, make the cardiovascular actions of vasopressin [25] difficult to interpret in the closed loop system of the intact organism.

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**Fig. 1.** Changes in mean arterial blood pressure (MAP), heart rate and plasma renin with increasing infusion rates of vasopressin in conscious intact dogs. Values are plotted against measured elevations in the plasma vasopressin.
does suggest that vasopressin may be part of an integrated system for the control of blood pressure [36].

Vasopressin shares with the renin–angiotensin–aldosterone system the dual attributes of vasoconstriction and antidiuresis [37]. Both these responses are important in the defence against volume depletion whether this be in orthostasis, salt and volume depletion or haemorrhage. Vasopressin's phylogenetic longevity [37] also lends credence to it being involved in the process of preserving body fluid volumes and blood pressure. It is probably no coincidence that vasopressin release from the posterior pituitary gland is under both osmotic [14, 39] as well as volume [40] and baroreceptor control [41].

### Vasopressin receptors and antagonists

Similar to other peptide hormones specific membrane receptors have been demonstrated for vasopressin in vascular smooth muscle, myometrium and a variety of epithelial tissues [42]. It is now apparent that vasopressin acts on smooth muscle and epithelial cells by two distinct biochemical mechanisms; the antidiuretic action is via the classical cyclic AMP 'second messenger' pathway [43, 44] whereas the vasoconstrictor action is probably via changes in intracellular calcium ions [12, 45]. Over several years, careful structural modifications of the parent compounds, vasopressin and oxytocin, have given rise to a variety of structural analogues with enhanced oxytocic, antidiuretic and vasopressor potency [46]. More recently, selective peptide receptor antagonists for the oxytocic and vasopressor activity have been developed. Two of the more promising selective antagonists to the pressor and vasoconstrictor activity of vasopressin, which have been synthesized by Manning and tested by Sawyer and his colleagues, are 1-(β-mercaptop-β-cyclopentamethylenepropionic acid),4-valine,8-d-arginine vasopressin [cycloDVPAP] and 1-deamino- penicillamine-2-(O-methyl)tyrosine] arginine vasopressin [dPtyr(Me)AVP] [47, 48]. Both are potent vasopressor antagonists and weak oxytocin antagonists with less than 2.5% antidiuretic potency. They should therefore prove to be very useful in helping to define the role of vasopressin in regulating blood pressure in a variety of physiological and pathological states. Some of the preliminary studies employing these vasopressin receptor antagonists are discussed in the relevant sections. Caution should be exercised, however, in interpreting the results from the use of these antagonists, for although they are specific for vasopressin, they may possibly have independent actions other than those antagonizing the action of vasopressin at the vascular receptor. One is reminded that for a variety of reasons use of the competitive angiotensin II receptor antagonists has not proved to be as illuminating as first hoped.

### Vasopressin in orthostasis and syncope

The maintenance of blood pressure during postural changes involves reflex activation of the sympathetic nervous system and the renin–angiotensin system. Davies et al. [49] have shown that, in man, standing upright leads to an increase in plasma vasopressin levels, and this rise can be dissociated from the increased renin activity that also occurs [50]. The rise in plasma vasopressin was more apparent in dehydrated subjects. Tilted patients who suffer syncope have very striking increases in plasma vasopressin levels [49, 51], increases to levels capable of causing vasoconstriction and rises in blood pressure in normal man. Therefore in man vasopressin clearly is released in response to a fall in blood pressure. Similar large increases in plasma vasopressin have been reported in subjects who suffer nausea and vomiting [14, 52]. However, what contribution vasopressin makes to maintenance of blood pressure under these conditions cannot be decided. Studies with the competitive vascular receptor antagonists to vasopressin would help assess the effect of vasopressin in these conditions.

### Vasopressin in dehydration

Dehydration in both animals [14] and man [52] leads to a small rise in plasma osmolality and a doubling in plasma vasopressin levels. Robertson & Athar [53] and Weitzman et al. [54] have clearly shown a close direct relationship between plasma osmolality and plasma vasopressin levels. However, the very small increase in plasma vasopressin levels to 10 fmol/l after dehydration could not ordinarily be expected to exert any haemodynamic effects. Recent reports employing a specific vasopressin receptor antagonist, dPtyr(Me)AVP, raise the possibility that vasopressin may help to maintain blood pressure during dehydration. In a preliminary report, Aisenbrey et al., [55] demonstrated that intravenous administration of dPtyr(Me)AVP to dehydrated rats with elevated plasma vasopressin levels significantly lowered the blood pressure. These results have been extended by Andrews & Brenner [35], who showed that a similar vasopressin vascular receptor antagonist,
d(CH₃)₂VDAVP, had no hypotensive effect in rats undergoing a water diuresis but produced a transient 8 mmHg fall in mean arterial pressure in dehydrated anaesthetized rats. The hypotensive effect was maintained and prolonged in rats given both the vasopressin antagonist and an angiotensin receptor antagonist, saralasin, suggesting that blood pressure compensation after vasopressin blockade was mediated by endogenous angiotensin II. This serves again to emphasize the close interrelationship between the renin–angiotensin system and vasopressin.

**Vasopressin in haemorrhage**

Haemorrhage has been known for many years to be a potent stimulus to vasopressin release [56, 57]. As the amount released is far in excess of that required for maximal antidiuretic activity, several investigators have suggested that vasopressin may play a role in maintaining arterial blood pressure after non-hypotensive haemorrhage [58, 59]. Pullan et al. [21] found plasma vasopressin reached levels up to 500 fmol/l after haemorrhage in anaesthetized dogs and that such levels were pressor when exogenous vasopressin was infused into dogs. Furthermore, plasma vasopressin levels rose before arterial blood pressure fell but not before there was a decrease in right atrial pressure. In a series of elegant experiments Cowley et al. [34] have recently provided definitive evidence that vasopressin plays a crucial and quantitative role in maintaining blood pressure after haemorrhage in the dog. In bilaterally nephrectomized dogs whose central sympathetic nervous system had been ablated, the compensatory rise in blood pressure after acute haemorrhage could be abolished either by hypophysectomy or by injection of the vasopressin antagonist (dPVDAVP). As the dogs had both their sympathetic nervous system and renin–angiotensin system functionally abolished, vasopressin acted as the sole vasoconstrictor agent. The authors state that by a simplified system analysis, with calculations of the open-loop feedback gain, the results suggest that the vasopressin pressure control system is equal to the renin–angiotensin or baroreceptor sympathetic system in acutely restoring blood pressure towards normal after haemorrhage. Laycock et al. [60] reported that blood pressure compensation after haemorrhage was less efficient in the Brattleboro rat, which is genetically deficient in vasopressin, than in the normal Long–Evans rat. A similar study showing the differences in blood pressure after haemorrhage in Long–Evans and Brattleboro, diabetes insipidus, rats is illustrated in Fig. 2. However, the Brattleboro rats also had lower plasma renin activity and plasma angiotensin II after haemorrhage, so the result may not be as clear cut as first reported.

**Vasopressin in experimental hypertension**

Möhring et al. [61–63] were the first clearly to establish that the levels of plasma vasopressin were elevated in experimental models of hypertension. They also pointed out that the levels were higher in malignant hypertension than in benign hypertension. Subsequently, many reports have confirmed these findings in rats with DOCA–salt hypertension, two-kidney, one-clip Goldblatt hypertension, the spontaneously hypertensive rat (SHR) and experimental hypertension in the dog (see Table 1).

However, in all the reports the plasma levels of vasopressin in hypertension are only slightly elevated compared with normal plasma levels (Table 2) and are below pressor levels achieved with exogenous infusions of vasopressin. Möhring was aware of this difficulty and proposed the hypothesis that a specific sensitization to the pressor response of vasopressin occurred in the hypertensive state, either by a reduced gain of the baroreceptor pressure reflex or via increased sensitivity of the vascular smooth muscle [15, 16]. Crofton et al. [64] have also demonstrated
an increased sensitivity to vasopressin in some rats with DOCA–salt hypertension. However, this increased sensitivity was not specific for vasopressin and has not been confirmed in another model of steroid ACTH hypertension in the sheep [65]. It can also be demonstrated that the vasoconstrictor activity of vasopressin is dependent upon the ambient plasma concentration of vasopressin, such that chronically elevated plasma levels of vasopressin will dampen the vasoconstrictor response to exogenous vasopressin and vice versa [66]. This ‘down regulation’ of peptide receptors is common to many peptide hormones and has clearly been shown for the vascular effects of angiotensin [67]. Elevated levels of vasopressin as occur in hypertension would therefore lessen, not accentuate, the vascular response.

Further evidence for a role of vasopressin in DOCA–salt hypertension was the inability of Crofton et al. [68] to produce DOCA–salt hypertension in the Brattleboro rat genetically deficient in vasopressin. This group also showed that a vasopressin receptor antagonist transiently lowered the blood pressure in DOCA–salt hypertension [68] as well as in the spontaneously hypertensive rat [69]. However, Brattleboro rats do not drink 1% sodium chloride solution, they are volume deplete, and vasodilatation, necessary to measure their blood pressure, lowers the blood pressure, so these experiments are not conclusive.

Möhring et al. [61–63, 70] transiently lowered the blood pressure in a variety of models of experimental hypertension in rats by the use of a specific vasopressin antiserum. However, these experiments need to be interpreted with some caution as the possibility exists that, when unpurified antibody is used, the hypotensive effect is due to some other non-specific effect rather than vasopressin blockade.

We have recently produced two-kidney, one-clip hypertension and one-kidney, one-clip Goldblatt hypertension in homozygous Brattleboro rats with hereditary hypothalamic diabetes insipidus [71] (Fig. 3). Interestingly, the blood pressure in the diabetes insipidus rats with one-kidney, one-clip hypertension did not reach the same absolute level of blood pressure as in the control Long–Evans rats. However, administration of DDAVP, a synthetic vasopressin analogue with antidiuretic activity but no pressor activity, corrected the water and electrolyte balance and elevated the blood pressure in the diabetes insipidus rats to the same hypertensive level as that seen in the control rats (Table 3; Fig. 3). These results suggest that the vasoconstrictor activity of vasopressin is not essential for the development of renal hypertension, but that the

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<th>TABLE 1. Vasopressin levels in human and experimental hypertension</th>
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<th>TABLE 2. Systolic blood pressure and plasma and pituitary vasopressin levels in normotensive rats and rats with one-kidney, one-clip (1K–1C) Goldblatt hypertension and two-kidney, one-clip (2K–1C) Goldblatt hypertension</th>
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<td>Mean results ( \pm \text{ SEM} ) are shown, with the numbers of rats given in parentheses. * ( P &lt; 0.0125 ); ** ( P &lt; 0.001 ); † ( P &lt; 0.05 ); ‡ ( P &lt; 0.01 ).</td>
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antidiuretic action of vasopressin, by maintaining fluid volume, may be important in determining the absolute hypertensive level [71].

Finally, Rabito et al., [72] have recently reported that an infusion of the vasopressin receptor antagonist, dPVDAVP, failed to lower the blood pressure in rats with adrenal regeneration hypertension, malignant DOCA-salt hypertension and malignant two-kidney, one-clip Goldblatt hypertension (Fig. 4).

In summary, although plasma vasopressin levels are elevated in most models of experimental hypertension, their relationship to the pathogenesis of hypertension must await further studies employing the new specific vasopressin pressor antagonists. The ubiquitous elevation of vasopressin in so many different experimental models of hypertension also raises the possibility that the increase is a result of the hypertension rather than the cause of the increase in blood pressure.
Vasopressin and blood pressure

Ellis & Grollman in 1949 [7] first reported that patients with hypertension had increased antidiuretic activity in their urine. More recently Khokhar et al. [73] reported that urinary vasopressin was increased in patients with mild essential hypertension. However, Padfield et al. [20] reported that although the plasma vasopressin was increased in patients with malignant hypertension, it was normal or even low in those with benign essential hypertension. A preliminary report by Cohen et al. [74] confirms that plasma vasopressin levels appear to be normal in patients with essential hypertension. Padfield et al. [20] suggested that the increased levels of plasma vasopressin they observed in malignant hypertension may be a result of the severe hypertensive process, with its metabolic consequences of salt and volume depletion, rather than the cause. However, Khokhar et al. [75] found, in a patient with nephrogenic diabetes insipidus who was gradually dehydrated, that the blood pressure rose when the already elevated levels of plasma vasopressin were further increased. They also showed that infusions of vasopressin into normal subjects raised the diastolic blood pressure when plasma vasopressin levels were only 14.5 fmol/ml. Thus a relationship between increased plasma levels of vasopressin and elevated blood pressure was suggested. In contrast, Padfield et al. [20] showed, in studies similar to the experiments on hypertension in animals, that in man exogenous administration of vasopressin to plasma levels some 10-fold higher than those found in hypertension did not result in an elevation of blood pressure. Thus, in hypertension where the plasma levels of vasopressin are only moderately elevated, a sensitization to the cardiovascular effects of vasopressin would need to be postulated before vasopressin could assume a pathogenic role in hypertension in man.

Patients with the syndrome of inappropriate antidiuretic hormone secretion (SIADH) [76] are not hypertensive (see Table 4) and we could find no correlation between the level of plasma vasopressin and blood pressure in such patients. Many such patients with continuous ectopic secretion of vasopressin from a malignant tumour have extremely high plasma vasopressin levels (>450 fmol/l). Although the syndrome is associated with the metabolic consequences of excessive antidiuretic hormone (hyponatraemia and hypoosmolality, low blood urea, expanded blood and extracellular fluid with continued urinary sodium excretion) blood pressure is not elevated [20]. It is possible that other cardiovascular homeostatic mechanisms may dampen down the blood pressure elevation from vasopressin’s vasoconstrictor action or desensitization to vasopressin’s pressor action may occur. However, plasma vasopressin levels of this magnitude achieved by exogenous infusions are usually pressor. Why sensitization to vasopressin does not occur in this condition but does in hypertension would also need to be explained, if the hypothesis that excess vasopressin causes hypertension is valid.

The lack of a persistent increase in blood pressure to prolonged excessive secretion of vasopressin is in contrast to the hypertension that results from excessive renin production from a
The role of vasopressin in various forms of human hypertension will need to be defined by further studies of plasma vasopressin levels in hypertension and will have to await the development of longer-acting specific vasopressin vascular antagonists. Studies in humans, using the recently developed short-acting vasopressin antagonists, are awaited with great interest.

**Vasopressin and hypertensive vascular disease**

There are two major theories on the pathogenesis of the vascular lesions and fibrinoid necrosis found in hypertension. At one extreme, pressure alone, particularly the rate of rise in blood pressure, is held to be responsible and, at the other end, hormonal or ‘vascular permeability factors’ are thought to be the cause (for recent reviews see [77, 78]). Vasopressin can cause extensive pathological arteriolar changes when injected into animals in very high doses [78–80] but it also raises the blood pressure. Möhring [78] has suggested that vasopressin may be important in the pathogenesis of hypertensive vascular damage. Aorticligature between the renal arteries in the rat produces a particularly severe form of malignant hypertension characterized by extensive fibrinoid necrosis, high plasma renin and death [81]. We (R. Woods, P. Kincaid-Smith & C. I. Johnston, unpublished work) have recently produced this form of malignant hypertension in the homozygous Brattleboro rat with hereditary hypothalamic diabetes insipidus, which completely lacks vasopressin. Malignant hypertension was characterized by functional changes, including weight loss, increased fluid intake, rise in packed cell volume and high plasma renin. Typical arterial lesions of malignant hypertension were found in the diabetes insipidus rat, identical in both incidence and extent with those seen in control Long–Evans hypertensive rats. A very good relationship was found between the functional changes and the presence of fibrinoid necrosis: no animal without the functional changes had fibrinoid necrosis or the typical arteriolar lesions in either the normal or diabetes insipidus hypertensive rats, and the majority of hypertensive rats with functional changes of malignant hypertension demonstrated the vascular lesions. It has been postulated that in the diabetes insipidus hypertensive rat the renin–angiotensin system may compensate for the vasopressin lack and be responsible for the elevated blood pressure and vascular lesions. In this group of diabetes insipidus rats with malignant hypertension from aortic ligature, the plasma renin and angiotensin levels were elevated relative to controls but only to the same extent as the Long–Evans hypertensive rats.

This suggests that vasopressin is not an essential prerequisite for hypertensive or vascular lesions but does not establish whether pressure or vascular permeability factors are more important. Probably neither is the sole mechanism that causes hypertensive vascular disease.

**Conclusions**

Vasopressin has two major biological actions, vasoconstriction and antidiuresis, that are important variables in the control of blood pressure. However, the concentrations of vasopressin required for antidiuresis are 10–100 times less than those required to elevate the blood pressure in the intact organism. Vasoconstrictor potency of vasopressin in vitro, however, is of the same magnitude as the antidiuretic potency. This suggests that in the closed loop system in vivo vasopressin’s pressor action is largely buffered by other cardiovascular homeostatic mechanisms. It has been clearly demonstrated that one such damping mechanism is the sympathetic nervous system, and there is evidence that there is a quantitative interplay between vasopressin and angiotensin, such that the sum of their combined pressor effects is constant.

There is increasing evidence that the vasoconstrictor action of vasopressin may play a role in the integrated cardiovascular response to orthostasis and volume depletion. Vasopressin is also of great importance in the response to haemorrhage and is essential for the compensatory rise in blood pressure after blood loss.

Most studies agree that plasma vasopressin levels are elevated in experimental and human hypertension. Vasopressin has been postulated to be involved in the pathogenesis of hypertension. It could be involved by one of three mechanisms: (1) as a direct vasoconstrictor, (2) by its antidiuretic activity and hence by maintaining blood and extracellular volume, or (3) by modulating and enhancing other vasopressor mechanisms.

If it is to act as a direct vasoconstrictor some mechanisms of sensitization to the pressor effect of vasopressin needs to be postulated. As yet there is very little evidence on this point. Furthermore, one needs to ask why in hypertension there is sensitization, whereas patients with high plasma vasopressin levels from SIADH do not develop sensitivity and are normotensive?
Studies with the Brattleboro rat with genetic hypothalamic diabetes insipidus, as well as with the new specific competitive antagonists to the pressor actions of vasopressin, appear to rule out a direct vasconstrictor role for vasopressin in experimental hypertension. Its role in the pathogenesis of essential hypertension is still undecided.

References


