Central Role for Vasopressin in Cardiovascular Regulation and the Pathogenesis of Hypertension

Kathleen H. Berecek and Bruce H. Swords

In recent years the role of neuropeptides in the central regulation of arterial pressure and the pathogenesis of hypertension has been the subject of considerable attention. Of all the neuropeptides, vasopressin (AVP) has been one of the most widely studied. The availability of sophisticated immunocytochemical and biochemical methods has permitted localization of AVP in areas of the brain known to be involved in cardiovascular regulation. In addition, specific AVP receptors with high affinity have been found in these brain areas.

Several lines of evidence suggest that central AVP plays a role in the control of blood pressure and heart rate in both normotensive and hypertensive animals. Administration of AVP into the central nervous system produces changes in arterial pressure and heart rate that can be reversed by competitive antagonists. AVP interacts with neurotransmitters such as catecholamines, which are involved in arterial pressure regulation. It is also a potent releasing factor for adrenocorticotropic hormone (ACTH)—corticosterone, which in turn acts on the cardiovascular system. Agents that inhibit the interaction of AVP with its receptors have cardiovascular effects. Furthermore, levels of AVP and its receptor are altered in hypertensive states. Finally, increased sensitivity to the pressor effects of AVP has been described in experimental models of hypertension.

This review will focus on evidence for a central role for AVP in cardiovascular regulation and the pathogenesis of hypertension, and discussion will mainly focus on work done in rats. It should be noted that there is increasing evidence for species differences in responsiveness to AVP and mechanisms of action of AVP. For a more detailed discussion of the neuroanatomy, biochemistry, molecular biology, and physiology of this peptide, the reader is referred to several excellent and comprehensive monographs and books.1-5

Localization of Vasopressin in the Central Nervous System

AVP, together with its precursor neurophysin, is synthesized in the magnocellular neurons of the supraoptic (SON), paraventricular (PVN), and suprachiasmatic (SCN) nuclei of the hypothalamus. Neurophysin and AVP are produced as part of a single precursor molecule, packaged into neurosecretory granules, and transported axonally to nerve endings located in the neurohypophysis where they are stored and secreted into the systemic circulation. Numerous anatomic studies have demonstrated that the hypothalamic AVP synthesizing nuclei send AVP-containing fibers to a number of central neural target areas in addition to the neurohypophysis. AVP-containing fibers and terminals have been observed in the entire neuroaxis from the olfactory bulb to the caudal end of the spinal cord.6-7

As can be seen from Figure 1 and Table 1, a number of areas innervated by AVP-containing fibers are involved in cardiovascular regulation. These include the locus coeruleus, nucleus tractus solitarius (NTS), dorsal motor nucleus of the vagus, anterior ventral region of the third cerebral ventricle (AV3V region), central gray, and the intermediolateral column of the spinal cord.6-7,14-16 The highest density of vasopressinergic fibers is in the NTS and dorsal motor nucleus of the vagus, whereas only scattered fibers are present in the cerebral cortex. Because AVP-containing projections make axosomatic and axodendritic contacts with these target areas, AVP may modulate the activity of neuronal pathways involved in blood pressure regulation.7 Immunohistochemistry at the electron microscopic level has demonstrated that these contacts have the characteristics of true synapses.17 In addition, AVP has been identified in synaptosomes of extrahypothalamic nerve terminals.18 and there is evidence for synaptic release of AVP in extrahypothalamic target areas.19,20 Recently, other sites of AVP synthesis have been revealed after treatment of animals with colchicine, a substance that inhibits axoplasmic transport...
and causes an accumulation of secretory products. These include the bed nucleus of the stria terminalis, dorsal medial hypothalamus, medial amygdala, and locus coeruleus. Quantitative measurements of AVP/neurophysin in discrete regions of the brain and spinal cord by radioimmunoassay generally support the findings from immunohistochemical studies. AVP has also been demonstrated in the cerebrospinal fluid (CSF), suggesting that it is found in neurons or fibers located near the ventricular system. The physiological stimuli that release AVP into the CSF are poorly understood. Dehydration causes...
<table>
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<th>Region</th>
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<th>Origin</th>
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AVP, vasopressin; BST, bed nucleus of the striae terminalis; PVN, paraventricular nucleus; SCN, suprachiasmatic nucleus; SON, supraoptic nucleus. AVP density of brain areas: ++++ and ++++, high density; ++, moderate density; +, low density.
release of AVP into the plasma but does not change CSF levels of AVP. In contrast, hemorrhage and electrical stimulation of the hypothalamus cause a release of AVP into the CSF as well as the plasma. There is a pronounced diurnal rhythm of AVP in CSF, and much of the peptide cleared from the CSF reaches the bloodstream in a biologically active form. The physiological function of AVP in the CSF is not known, but there has been evidence that suggests it may be involved in intracranial pressure control. In addition to synaptic release of AVP, several papers have reported actions of this peptide on neuronal firing rate in several brain regions. Localization of AVP in areas of the brain that control sympathetic outflow and baroreceptor reflex activity, demonstration of synaptic release of AVP, and the finding that this peptide has an action on neuronal firing rate in several brain regions, together with the observation of AVP binding in the same regions, strongly suggest that AVP may act as a neurotransmitter in these regions.

The PVN and SON not only innervate areas of the brain known to be involved in cardiovascular regulation, but they receive afferent projections from cardiovascular centers. These nuclei contain catecholaminergic terminals derived from the A1 (noradrenergic) and C1 (adrenergic) cell groups of the ventral lateral medulla (VLM), the A2, C2, and C3 cell groups of the dorsal medial medulla (DMM) and the A6 cell group of the locus coeruleus (LC). See text for further details.

Central Cardiovascular Effects of Vasopressin

AVP and vasotocin have been demonstrated in extrahypothalamic brain regions in all classes of vertebrates from the most primitive (Agnathans) to mammals, including humans. The finding that AVP or AVP-related peptides are maintained throughout evolution supports the hypothesis that this peptide has physiological significance. Moreover, the diverse origin and widespread distribution of AVP-containing fibers suggest that AVP is involved in the regulation of a variety of central neural functions. Several studies have been carried out to determine whether release of AVP into the circula-
tion is coupled to release of this peptide in extrahypothalamic areas. These studies have given evidence that each of the sites in which AVP is produced is influenced by different stimuli, suggesting that there is spatially controlled release of AVP.

In addition to its peripheral vasoconstrictor and renal functions, AVP has recently been shown to produce cardiovascular effects that are mediated by the central nervous system. Intracerebroventricular injection, intrathecal injection, or microinjection of picomolar quantities of AVP into areas of the brain such as NTS, median preoptic nucleus of the hypothalamus, and locus coeruleus, produce long lasting increases in blood pressure and heart rate. The cardiovascular responses of AVP are due to a central effect and not due to leakage of the peptide into the peripheral circulation as they are blocked by central but not peripheral administration of specific AVP receptor antagonists. The cardiovascular responses to central administration of AVP appear to be mainly due to stimulation of sympathetic vasomotor activity, as they are significantly attenuated by ganglionic blocking agents, α-adrenergic and β-adrenergic receptor antagonists. These studies have led to the hypothesis that AVP may be involved in regulation of sympathetic outflow.

Further evidence for this hypothesis has come from studies on the direct action of AVP on components of the sympathetic nervous system. AVP, acting on V₁ receptors, was found to excite lateral horn cells, which contain a number of preganglionic sympathetic neurons, in in vitro slices of neonatal rat spinal cord. This excitatory effect came about by direct depolarization and an indirect effect via the release of excitatory transmitters. This depolarizing action of AVP on lateral horn cells is in agreement with studies in cats showing that electrical stimulation of neurons in the PVN increased sympathetic outflow, and iontophoresis of AVP onto single sympathetic preganglionic neurons in the intermediolateral nucleus of the spinal cord increased the firing rate of these neurons. In a recent study, using an in vitro slice preparation from the rostroventrolateral medullary reticular nucleus, it was found that AVP produced dose-dependent excitation of the pacemaker neurons. These pacemaker cells are believed to be a source of tonic excitatory drive to sympathetic vasomotor preganglionic neurons, and the basal discharge of the cells can be upregulated or downregulated by a number of neuroregulatory peptides. The reports of AVP immunoreactive fibers and terminals in the rostroventrolateral medulla, the presence of specific V₁ receptors on pacemaker neurons, and the finding of an excitatory effect of AVP on the discharge rate of these neurons suggest that central AVP may alter arterial pressure via an effect on these neurons.

AVP may also influence sympathetic outflow via the locus coeruleus. This region receives vasopressinergic innervation, and microinjection of AVP into this nucleus produces an increase in arterial pressure and heart rate, which is mediated by AVP receptors and increased sympathetic outflow. Microiontophoresis of AVP in the locus coeruleus increases the discharge rate of neurons in this area. Bilateral electrolytic lesions of the locus coeruleus attenuate the pressor and abolish the tachycardiac response to intracerebroventricular AVP. Taken together, these findings suggest that AVP may also act on the locus coeruleus to increase sympathetic outflow.

There is increasing evidence that AVP and the baroreceptor reflex are intricately linked. Neuroanatomic studies have shown that hypothalamic AVP-synthesizing nuclei receive neural projections from the region of the NTS and, in turn, send projections to cardiovascular centers in the medulla, NTS, and spinal cord. Functional studies have shown that the baroreceptor reflex is involved in regulation of AVP secretion, with decreased baroreceptor activity producing an increase and enhanced baroreceptor activity producing a decrease in AVP release. Accordingly, excitation of the baroreceptor reflex has been found to produce a decrease in single unit activity in the PVN and SON, whereas a decrease in baroreceptor reflex activity produced an increase in single unit activity.

The effect of AVP or AVP-containing neurons on baroreceptor function is less certain. There are differences between the effects of peripheral and central AVP on baroreceptor reflex function. Moreover, recent studies have identified important species differences in the effect of AVP on baroreceptor reflex function. The initial study, suggesting an effect of AVP on the baroreceptor reflex, came from Cowley et al and showed that the pressor response to AVP was augmented more than norepinephrine in baroreceptor-denervated dogs. This work was confirmed by Montani et al in conscious dogs and extended by Liard et al, who demonstrated that AVP given into the vertebral artery produced pronounced bradycardia and vasodilation, whereas a similar dose given intravenously had little effect. Taken together, these data suggest that AVP enhances the inhibitory effect of the arterial baroreceptor reflexes on heart rate and sympathetic outflow and does this by a central mechanism of action. Studies in rabbits confirmed the findings in dogs and, in addition, showed that the area postrema was critical for AVP-induced augmentation of baroreceptor reflex inhibition of peripheral sympathetic nerves. Imaizumi and Thames showed that AVP in the CSF, unlike that in the plasma, failed to alter sympathetic activity during increases in carotid artery pressure, but it did facilitate reflex increases in sympathetic activity during carotid hypotension. Hence, the actions of AVP in the plasma and cerebrospinal fluid appear to differ. In contrast to studies in rabbits and dogs, work done in rats and cats have shown that central AVP may exert an inhibitory influence on baroreceptor reflex function. The finding of pressor responses associated with increases in heart rate and sympathetic nerve activity after
central AVP administration suggests that central AVP can override or inhibit the baroreceptor reflex response to increases in arterial pressure. This is further supported by the findings that microinjection of AVP into the NTS produced increases in blood pressure and heart rate in anesthetized and conscious rats suggesting an inhibitory action of AVP on neurons of the NTS. Most studies in the NTS have been performed using nanogram quantities of AVP. In a recent study, Brattstrom et al observed that microinjections of picogram quantities of AVP into the NTS produced a dose-dependent decrease in blood pressure and heart rate. Whether this discrepancy is due to a true dose-response-related phenomenon or to differences in anesthetic used or experimental protocol remains to be tested. Brattstrom et al observed that the effects of picogram amounts of AVP took several minutes to develop. This suggests that AVP may be stimulating the release of or interacting with another transmitter such as glutamate, norepinephrine, or β-endorphin, which are present in the NTS and have been shown to decrease blood pressure and heart rate when injected into the NTS. Studies of Unger et al have demonstrated that intracerebroventricular injection of subpressor doses of AVP produced an attenuation in baroreceptor reflex control of heart rate, whereas injection of a V₁ AVP receptor antagonist at a dose that had no intrinsic action on the cardiovascular system produced an increase in the sensitivity of baroreceptor reflex control of heart rate. These results suggest that neuronal AVP can decrease the sensitivity of the baroreceptor reflex by acting on V₁ AVP receptors in the brain.

Studies assessing baroreceptor reflex activity and the effect of exogenous AVP on baroreceptor reflex function in Brattleboro rats homozygous for diabetes insipidus (DI), which are unable to synthesize AVP, have presented equivocal results. Three different laboratories have presented evidence that DI rats show an increase, a decrease, or no difference in baroreceptor reflex sensitivity in comparison with their controls, the Long-Evans rat. The reason for these discrepancies is not known; however, it may rest with differences among the various colonies of DI rats.

Although it was not the goal of this report to discuss the other neurohypophyseal hormone oxytocin, it should be mentioned that there is increasing evidence that this peptide may also play a role in cardiovascular regulation. Systemic administration of this peptide produced a decrease in blood pressure and cardiac output. Oxytocin was found to reduce pressor responses to mesencephalic stimulation and norepinephrine and, when injected into the dorsal motor nucleus of the vagus, produced bradycardia via activation of neurons in this region. Furthermore, there appears to be an interaction between oxytocin and the baroreceptor reflex as sinoaortic denervation increased both basal release and osmotically induced release of oxytocin.

**Vasopressin Receptors**

The actions of AVP are mediated by membrane-bound receptors of two subtypes. The V₁ receptor mediates the vasoconstrictor and hepatic glycogenolytic actions of AVP via phosphatidyl inositol hydrolysis. The V₂ receptor mediates the antidiuretic effect of AVP on renal collecting ducts via adenylyl cyclase. The AVP receptor in the central nervous system is most similar to the V₁ receptor. However, the anterior pituitary AVP receptor involved in vasopressin-induced corticotropin release differs from the vascular, hepatic, and brain V₁ receptor and has been designated as a V₁b receptor. Several studies using tritiated AVP ([³H]AVP), tritiated V₁-selective ligands, and a radioiodinated (iodine-125) specific V₁ receptor antagonist have localized AVP receptors in the brain using quantitative autoradiography. Results of these studies using the different ligands have not been consistent. Previous studies of autoradiographic localization of AVP in brain using [³H]AVP have been limited by poor resolution, long exposure time, and possible binding to neurophysins. However, several brain regions identified as containing sites for the ¹²⁵I-AVP V₁ receptor antagonist have been shown to contain AVP receptors by [³H]AVP autoradiography. These are the lateral septum, central nucleus of the amygdala, nucleus accumbens, bed nucleus of the stria terminalis, NTS, and hippocampus. However, this was not the case for all brain areas. Studies using [³H]AVP have reported AVP receptors in the SON and PVN and median eminence; however, binding in these areas was not found using ¹²⁵I-d(CH₂)₅ Sar⁷ AVP. Studies of Phillips et al using ¹²⁵I-d(CH₂)₅ Sar⁷ AVP confirmed the findings of Van Leeuwen et al who, also using a V₁-specific ligand [³H]d(CH₂)₅ Tyr(Me)² AVP, found novel V₁ binding sites in the arcuate nucleus, supra-hippocampal nucleus, and superior colliculus. In addition, the investigators found new regions of AVP receptor binding. These regions include the area postrema, fundus striate, lateral hypothalamic nucleus, zona incerta, stigmoid hypothalamic nucleus, interpeduncular nucleus, subgenulate nucleus, medial accessory oluomotor nucleus, subthalamic nucleus, intermediate reticular nucleus, nucleus of the spinal trigeminal tract, subcoeruleus nucleus, and parts of the thalamus and inferior olivary nuclei.

Interestingly, AVP receptors have not yet been identified in some areas of the brain receiving AVP innervation, such as the subformical organ, organum vasculosum of the lamina terminalis, and locus coeruleus. The lack of AVP receptors in these areas is perplexing as they are densely innervated with AVP-containing fibers. In addition, microiontophoresis or microiontophoresis of AVP into the locus coeruleus produces immediate increases in arterial pressure and neuronal activity, respectively. These effects are...
blocked by pretreatment with a selective V₁ AVP antagonist. The reason for the discrepancies between receptor binding and immunocytochemical and functional studies is not known but may relate to the properties of the ligand and its affinity for the V₁ and other peptide receptors, multiple receptor subtypes, and cross-reacting antibodies in immunocytochemical studies.

Factors that modulate AVP receptors are poorly understood. Further, there have been few studies on changes in AVP receptor binding in hypertension. The renal V₂ receptor has been reported to undergo desensitization in response to acute elevations in AVP, but little is known about AVP modulation of the V₁ receptor. In DI rats, V₁ binding site concentration in the liver and septum has been shown to be greater than in Long-Evans control rats, whereas the V₂ [³H]AVP binding site concentration has been shown to be similar in both strains. In recent studies by Shewey and his group, a comparison of [³H]AVP binding between Long-Evans, homozygous DI, and heterozygous DI (partial inability to synthesize AVP) rats showed that the maximal binding capacity and affinity for [³H]AVP in the septum was different among these groups. Heterozygous DI and Long-Evans rats exhibited comparable Kᵦ values, whereas homozygous DI rats had a Kᵦ nearly twofold greater. Binding site concentration of homozygous DI rats was twice that observed in the heterozygous group but was similar to that measured in Long-Evans control tissue. These authors also reported AVP-stimulated phosphoinositide hydrolysis from septal slices from these rats paralleled the binding site concentration data. Central administration of AVP decreased the Kᵦ of AVP receptors in the septum of homozygous but not heterozygous DI rats, and the decrease in receptor number was accompanied by a decrease in the postreceptor response to AVP, as measured by AVP stimulation of [³H]inositol 1-phosphate accumulation. It appears from these studies that the influence of AVP on its receptor is highly complex. If the number of AVP receptors was inversely related to AVP concentration, homozygous DI rats should have had more receptors than heterozygous DI rats, which should have had a greater number than Long-Evans controls. This was not the case in the rats studied by Shewey and coworkers.

Ijima and Malik reported that dexamethasone-induced hypertension in rats was associated with enhanced responses of mesenteric arteries to AVP but not to norepinephrine or angiotensin II, suggesting increased sensitivity or number of AVP binding sites. The effect of steroids on AVP binding is not known with certainty, but adrenalec- tomy decreased AVP binding in the pituitary (V₁b), an effect that was inhibited by corticosterone. Adrenal steroids exert a dual action on AVP-sensitive adenylate cyclase in the kidney increasing the number of binding sites and increasing the efficiency of receptor-enzyme coupling. Our laboratory has recently reported that DOCA treatment of rats increased the number of AVP receptors in the hypothalamus. It has also recently been reported that the number of renal AVP receptors (V₂) is also increased in DOCA-treated rats.

To date, purification of either the V₁ or V₂ receptor subtype to homogeneity has not been accomplished. This has been due, in part, to lack of suitable affinity ligands, which covalently label the receptor, relatively low abundance of receptor in AVP-responsive tissues, and difficulty in solubilizing the receptor in a form that binds AVP.

The cellular and molecular mechanisms of action of AVP are not well understood. To gain an understanding of how the binding of AVP to its specific receptor mediates a precise biochemical effect and how the AVP receptor is regulated, the AVP receptor or AVP receptor subtypes from various tissues (i.e., brain, vascular tissue, kidney) will have to be cloned, expressed, and characterized. The molecular cloning and expression of the AVP receptor will greatly facilitate the biochemical characterization of this receptor and improve our understanding of the mechanism of action of AVP in normal cardiovascular regulation and in hypertension.

Central Vasopressin in Hypertension

The role of AVP in the pathogenesis of hypertension has been controversial. Although plasma levels of AVP have been reported to be increased in many models of hypertension, it has not been possible to demonstrate that chronic administration of AVP, at levels similar to that seen in hypertension, can sustain an elevated arterial pressure by either vasoconstriction or expansion of plasma volume or even total body fluid volume. Furthermore, it has not been possible to consistently demonstrate that administration of pressor antagonists of AVP cause more than a transient fall in blood pressure in any model of experimental hypertension. Thus, it is unlikely that AVP plays a pathogenic role in hypertension through its peripheral vasoconstrictor or antidiuretic effects. Nevertheless, numerous studies have suggested a potential central role for AVP in hypertension. It has been postulated that AVP plays a role in hypertension through its ability to increase sympathetic outflow. Sympathetic overactivity has been established for most models of hypertension. In genetic models of hypertension, inborn hyperactivity of the AVP system may lead to central and peripheral sympathetic hyperactivity. In acquired models of hypertension, AVP may serve as the factor linking salt and DOCA-salt to the sympathetic nervous system.

Deoxycorticosterone Acetate–Salt Hypertension

The DOCA-salt model of hypertension has been one of the most extensively studied, and there is strong evidence in this model for a possible central role of AVP in hypertension. Destruction of central adrenergic structures with 6-hydroxydopamine (6-OHDA) or electrolytic lesion of selective areas of
the brain\textsuperscript{93} in rats before treatment with DOCA and salt prevents the development of hypertension. These findings have led to the hypothesis that there is a centrally located "trigger" mechanism for the initiation of DOCA-salt hypertension. It has been speculated that this central mechanism participates in the development of hypertension by increasing peripheral sympathetic outflow.\textsuperscript{94} Recent studies suggest that AVP is a strong candidate for participation in the centrally located trigger mechanism.\textsuperscript{95–98}

A primary role for AVP in the pathogenesis of DOCA-salt hypertension was first suggested by Friedman et al,\textsuperscript{95} who found that surgical ablation of the median eminence prevented the development of DOCA-salt hypertension, whereas administration of large doses of the peptide hastened its onset. Subsequently, elevations in plasma and urinary AVP levels were reported in DOCA-salt–treated rats in both early and chronic stages of hypertension.\textsuperscript{96,97} Administration of an AVP antagonist or antiserum directed against AVP produced an acute reduction in arterial pressure in DOCA-salt hypertensive rats.\textsuperscript{96,97} Moreover, hypertension failed to develop in DI rats when treated with DOCA-salt but did develop when replaced with the AVP.\textsuperscript{98,99} Although evidence strongly suggests participation of AVP in DOCA-salt hypertension, its mechanism of action is unclear. DOCA-salt–treated rats showed significantly greater increases in mean arterial pressure and heart rate in response to intracerebroventricular administration of AVP than did control rats. Moreover, a more than 10-fold lower threshold dose of AVP was required to produce cardiovascular changes in DOCA rats (0.025 ng) compared with controls (2.5 ng).\textsuperscript{40} Microinjection of AVP into the locus coeruleus produced increases in arterial pressure and heart rate due to stimulation of sympathetic outflow.\textsuperscript{50} Moreover, microiontophoresis of AVP onto noradrenergic neurons of the locus coeruleus in DOCA-salt-treated rats produced a significantly greater increase in firing rate of these neurons than in control rats.\textsuperscript{100} Increased sensitivity in response to locus coeruleus stimulation was seen not only in the established phase of DOCA-salt hypertension but also during the prehypertensive stage.\textsuperscript{100}

The findings that the central effects of AVP involved stimulation of sympathetic outflow\textsuperscript{14,36,37,43} and that the sensitivity and responsiveness of DOCA-salt hypertensive rats to centrally administered AVP were markedly increased\textsuperscript{40} suggested that AVP might stimulate the sympathetic nervous system at a central level in this model. Further support for this hypothesis comes from studies in DI rats with or without lesion of the AV3V,\textsuperscript{101} an area that receives vasopressinergic innervation.\textsuperscript{7} Supplementation of AVP restored the capacity of DI rats to develop DOCA-salt hypertension but not rats with AV3V lesions, although plasma levels of AVP were similar in sham and lesioned rats and comparable with normal, intact rats treated with DOCA-salt. In addition, lesions in the area postrema\textsuperscript{102} or the locus coeruleus,\textsuperscript{103} areas also receiving vasopressinergic innervation, prevented or attenuated the development of DOCA-salt hypertension. Taken together, these results suggest a link between AVP and the sympathetic nervous system in DOCA-salt hypertension. AVP may play a role in hypertension by a direct action via vasopressinergic innervation on central neural centers controlling sympathetic outflow.

A hallmark of hypertension is a resetting or alteration of the arterial baroreceptor reflex. Rapid downward resetting can occur when blood pressure is decreased to normal, suggesting that resetting is not due exclusively to structural abnormalities in the arterial receptors themselves.\textsuperscript{104,105} The findings that central administration of vasopressin\textsuperscript{40,41} and increased activity of the PVN and SON attenuate baroreceptor reflex activity\textsuperscript{52} suggest that alterations in the function of these nuclei or AVP may participate in the resetting of the baroreceptor reflex in hypertension. In addition, AVP may stimulate sympathetic outflow in DOCA-salt hypertension by resetting the baroreceptor reflex.

**Genetic Hypertension**

Genetic models of hypertension such as the spontaneously hypertensive rat (SHR), the Dahl salt-sensitive rat, and the Sabra rat are characterized by increased sympathetic activity or alterations in brain catecholamines.\textsuperscript{106–108} There are conflicting reports concerning the role for AVP in genetic hypertension. There are reports in the literature of high central and peripheral levels of AVP and increased AVP gene expression in SON and PVN in these rats at various ages as well as a fall in blood pressure in response to administration of AVP antagonists.\textsuperscript{109–112} There are also reports in the literature showing opposite effects (e.g., low central and peripheral levels of AVP and lack of a fall in blood pressure in response to AVP antagonists\textsuperscript{113–115}. Studies with administration of antagonists showing lack of effect on blood pressure are difficult to interpret and do not necessarily present conclusive evidence against a role for central AVP in hypertension. Central AVP may be contributing to hypertension at an earlier age than when the treatment is usually begun (less than 4 weeks). Alterations in AVP content have been reported in primary neuronal cultures from brains of 1-day-old SHR and Wistar-Kyoto (WKY) rat pups. In addition, SHR show abnormalities in the distribution of central catecholaminergic and vasopressinergic neurons in comparison with normotensive rats.\textsuperscript{116} DI rats have also shown abnormalities (fewer fluorescent varicosities) in noradrenergic innervation of hypothalamic nuclei.\textsuperscript{117} Taken together, these studies suggest that AVP may be essential for normal catecholaminergic innervation of the brain and that an increase in AVP activity in fetal or newborn SHR might alter the pattern and density of catecholaminergic innervation and underlie the increase in sympathetic activity that characterizes this hypertensive model.
Another factor that must be considered with use of peripheral AVP antagonists is that they may not penetrate the blood–brain barrier and reach sites in the central nervous system that are relevant to regulation of blood pressure. The studies with intracerebroventricular injection of AVP suggest that peripheral AVP antagonism does not block the response to central administration of AVP. Additional opposition to the hypothesis that AVP plays a role in genetic hypertension is the study of Lang et al who crossbred DI rats with SHR of the stroke-prone substrain (SHRSP). Lang et al found that hypertension still developed in these AVP-deficient SHRSP-DI rats. However, results from studies in these rats may not present conclusive evidence against a role for AVP in the development of hypertension in SHR that are not stroke-prone. SHRSP have not shown alterations in AVP that are similar to SHR not prone to strokes. In addition, DI rats show pronounced changes in other hormones, namely, increases in the renin-angiotensin II system and a pronounced activation of oxytocin, which might participate in maintaining hypertension in this strain in place of AVP.

In conclusion, there is strong evidence for a central role for AVP in normal cardiovascular regulation and in the pathogenesis of hypertension. Central administration of AVP produces cardiovascular responses attributable to stimulation of sympathetic outflow. Because most models of hypertension have been characterized by hyperactivity of the sympathetic nervous system, AVP may, in early stages of hypertension, alter sympathetic outflow via an effect on central neural structures controlling the sympathetic nervous system. Central administration of AVP also produces an increase in heart rate; thus, the peptide appears to override the ability of the baroreceptor reflex to buffer changes in arterial pressure. Hence, AVP may participate in baroreceptor reflex resetting in hypertension and alter sympathetic outflow via effects on the baroreceptor reflex.

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