Central Vasopressin Raises Arterial Pressure by Sympathetic Activation and Vasopressin Release

Philip Janiak, Barry G. Kasson, and Michael J. Brody

Although central administration of arginine vasopressin (AVP) has been reported to increase arterial pressure mediated by activation of the sympathetic system, we found that peripheral blockade of sympathetic transmission did not attenuate this pressor response. To elucidate the mechanism, rats were pretreated with either phentolamine (3 mg/kg), chlorisondamine (2.5 mg/kg), a vasopressin V₁ receptor antagonist d(CH₂)₅Tyr(Me)AVP (AVP-X) (10 μg/kg), or the combinations of phentolamine and AVP-X or chlorisondamine and AVP-X. The pressor response to intracerebroventricular injection of AVP in unrestrained conscious rats was reduced but not significantly altered by intravenous injection of phentolamine or AVP-X; however, combined treatment with these agents abolished the response. To determine that the amount of central AVP leaked to the periphery did not contribute to the pressor effect, tritiated AVP and AVP (100 ng total) were injected intracerebroventricularly. Blood samples collected at 0, 3, and 30 minutes after injection showed that radioactivity in plasma was primarily metabolites and that the amount of intact AVP estimated to leak from the brain was too low to produce a pressor effect. Comparative regional hemodynamic studies between intracerebroventricular and intravenous injection of AVP performed in conscious rats instrumented with Doppler flow probes demonstrated a qualitatively similar pattern of increased resistance in the renal, mesenteric, and hindquarters beds. These data suggest that central pressor action of AVP is mediated by both activation of the sympathetic system and release of AVP. (Hypertension 1989;13:935-940)

Recently we demonstrated that the chronic central infusion of aldosterone selectively abolished the pressor response mediated by intracerebroventricular injection of arginine vasopressin (AVP).1 Despite the number of papers related to central actions of AVP, the mechanism of the pressor action induced by this centrally injected peptide remains unclear.

AVP-containing neurons project from the paraventricular and supraoptic nuclei to brainstem regions such as the nucleus tractus solitarius (NTS). Also, in several regions of the brain specific binding sites for AVP that play a role in central regulation of arterial pressure have been reported.2 Microinjections of AVP in the NTS raise arterial pressure3,4 and increase turnover of catecholamine in this nucleus.5 AVP is stored in the neural lobe of the pituitary gland and can be released into the bloodstream by several central6-9 and peripheral10 stimuli. It has also been indicated that this peptide is present in the cerebrospinal fluid.11

It has been reported that the increase in arterial pressure produced by central injection of AVP is mediated by increased sympathetic outflow.12,13 If this were the only mechanism, then blockade of sympathetic transmission should prevent this pressor effect. However, in recent studies, we found that neither ganglionic nor α-adrenergic blockade significantly altered the pressor response. Therefore, the purpose of the present study was to characterize the mechanism of the pressor action evoked by intracerebroventricular injection of AVP.

Materials and Methods

We used male Sprague-Dawley rats (Bio-lab Corp., St. Paul, Minnesota) weighing 300–400 g for our experiments. After surgical procedures, the rats were placed in individual cages and were housed in a
light-controlled room with rat chow (Teklad Test Diets, Madison, Wisconsin) and tap water ad libitum.

Surgical Procedures

The rats were anesthetized by intraperitoneal injection of a mixture of ketamine (140 mg/kg) and acepromazine (14 mg/kg). A polyethylene (PE-50) catheter (PE-10 at tip) was introduced in the abdominal aorta via the femoral artery and another in the femoral vein for blood pressure measurement and drug administration. Both catheters were filled with heparin saline and exited at the back of the neck. Using a Kopf stereotaxic apparatus (Tujunga, California), we implanted a 20-gauge guide cannula in a lateral ventricle and plugged it with a 25-gauge obturator.

For the hemodynamic study, miniaturized pulsed Doppler flow probes were implanted around the abdominal aorta and the mesenteric and renal arteries as reported in detail elsewhere.14 Arterial pressure was measured with a pressure transducer (model CP-01, Century Technol. Co., Inc., Pomona, California) connected to a Beckman R611 Dynograph recorder (Beckman Instr., Inc., Fullerton, California), and heart rate was determined with a Beckman 9857B cardiotachometer. Flows were measured with a pulsed Doppler flowmeter (University of Iowa, Bioengineering Facility, Iowa City, Iowa). All hemodynamic parameters were acquired via an IBM PC-XT every 5 seconds for 20 minutes and analyzed as described elsewhere.15 The placement of the cannula in the lateral ventricle was verified postmortem by intracerebroventricular injection of Evans Blue dye.

Pressor Antagonists

Three days after surgery, freely moving rats were pretreated with a bolus intravenous injection of one of the following: saline (0.2 ml), chlorisondamine (2.5 mg/kg), phentolamine (3 mg/kg), a vasopressin V1 receptor antagonist d(CH2)5Tyr(Me)AVP (AVP-X) (10 µg/kg), captopril (10 mg/kg), a combination of phentolamine (3 mg/kg) and AVP-X (10 µg/kg), or chlorisondamine (2.5 mg/kg) and AVP-X (10 µg/kg). In another group, bilateral adrenal demedullation was performed with ketamine-acepromazine anesthesia. The efficacy of adrenergic and vasopressin receptor blockade was checked with intravenous phenylephrine (5 µg/kg) (+48±5 mm Hg) and AVP (100 ng) (+72±6 mm Hg). AVP (100 ng) and saline (3 µl) were then administered intracerebroventricularly. Antagonist pretreatments and administration of saline and AVP were performed in a randomized order. On a given day, the rats received only one intracerebroventricular injection of AVP.

Intracerebroventricular Injection of Tritiated Arginine Vasopressin

The purpose of our experiment was to determine whether AVP leaked into the bloodstream when administered intracerebroventricularly. A solution of [3H]AVP (11.5 ng, 70 Ci/mmol, New England Nuclear, Boston, Massachusetts) and cold AVP (88.5 ng) was injected intracerebroventricularly in conscious unrestrained rats while measuring mean arterial pressure (MAP) and heart rate. Blood samples (0.5 ml) were collected before (time 0) and 3 and 30 minutes after administration of AVP. The plasma was separated by centrifugation and divided into two fractions to count radioactivity and to perform a reverse-phase thin-layer chromatography (RPTLC) as described elsewhere.16 An estimated peak plasma level of AVP was calculated according to the radioactivity measured and the percent of pure AVP detected in each sample. Plasma samples at 0 and 3 minutes were counted for tritium. The 3-minute samples were chromatographed to determine the percentage of tritium representing [3H]AVP. The difference in radioactivity between time 0 and the 3-minute samples was then corrected for the percentage of intact [3H]AVP, total plasma volume (assumed to be 33.5 ml/kg17), the fraction of [3H]AVP/total AVP (11.5%), and specific activity (70 Ci/mmol) to determine the amount of AVP that leaked from the brain to the bloodstream.

Hemodynamic Study

MAP, heart rate, hindquarter, mesenteric, and renal blood flow was monitored in freely moving rats during intracerebroventricular injections of saline (3 µl) and AVP (10 ng) and intravenous administrations of saline (0.2 ml) and AVP (100 ng/kg).

Analysis

Data are presented as mean±SEM. Statistical analysis was performed by one-way analysis of variance in randomized blocks followed by Student's t test with a Bonferroni correction.

Results

As shown in Figure 1, administration of AVP (100 ng i.c.v.) produced a significant increase in MAP associated with tachycardia. Pretreatment with either AVP-X or phentolamine alone did not alter the pressor response evoked by central injection of AVP, whereas the combined treatment abolished the effect. A summary of these data is shown in Figure 2, which also reports that intravenous pretreatment with captopril did not significantly alter the response to centrally injected AVP. Although not shown, identical findings were obtained with chlorisondamine, which did not affect the pressor response when given alone but abolished it when combined with AVP-X. Adrenal demedullation (n=6) also failed to alter the pressor effect of AVP but reversed the heart rate response to a significant bradycardia (−105±24 beats/min).

As previously observed in Figure 1, central administration of radioactive AVP (100 ng composed of 11.5 ng [3H]AVP and 88.5 ng AVP) produced an increase in MAP (Figure 3) in an average time of 3
FIGURE 1. Blockade of pressor response produced by intracerebroventricular (IVT) injection of arginine vasopressin (AVP). Shown are responses after pretreatment with saline, a vasopressin V₁ receptor antagonist d(CH₂)₅Tyr(Me)AVP (AVP-X) (10 μg/kg), phentolamine (3 mg/kg), or the combination of AVP-X and phentolamine. Traces of heart rate (HR), mean arterial pressure (MAP), and pulse pressure (PP) are shown.

FIGURE 2. Summary of cardiovascular responses (heart rate [HR] and mean arterial pressure [MAP]) to intracerebroventricular (ICV) injection of arginine vasopressin (AVP) (100 ng) after pretreatment with one of the following i.v.: phentolamine (Phent) (3 mg/kg), d(CH₂)₅Tyr(Me)AVP (AVPX) (10 μg/kg), phentolamine and AVPX, or captopril (10 mg/kg). Values are mean±SEM.
Centrally injected AVP (10 ng) produced an increase of MAP and a slight bradycardia associated with decreased flows in hindquarters and renal and mesenteric beds. The cardiovascular effects obtained with administration of AVP (100 ng/kg i.v.) were qualitatively similar but more pronounced (Figure 5). These data are summarized in Figure 6.

**Discussion**

Several studies have reported that central administration of AVP increases arterial pressure and heart rate. Pittman et al. showed in anesthetized rats a pressor effect produced by intracerebroventricular injection of AVP that was associated with a delayed increase in urine conductivity and a decrease in urine flow, effects that are consistent with the release of AVP into the circulation. Direct injection of AVP into the fourth ventricle or in the NTS evoked a pressor response mediated by an increase of the sympathetic outflow. Recently, Rohmeiss et al. reported that central administration of AVP produced an increase in MAP, heart rate, and splanchnic nerve activity. These effects were blocked by pretreatment with phentolamine, suggesting that intracerebroventricular injection of AVP activates the sympathetic nervous system. Matsuguchi et al. showed that microinjections of AVP in the NTS of anesthetized rats raised arterial pressure and heart rate and that these cardiovascular responses were abolished by ganglionic blockade.

In our experiments neither ganglionic nor \(\alpha\)-adrenergic blockade significantly reduced the pressor effect induced by intracerebroventricular injection of AVP. Only combined treatment with phentolamine and AVP-X or chlorisondamine and AVP-X abolished the increase in MAP. We believe that our failure to block the pressor effect with phentolamine cannot be attributed to inadequate blockade of adrenergic receptors since the dose was sufficient to abolish a 48 ± 5 mm Hg pressor effect of phenylephrine. The renin-angiotensin system did not seem to be involved in the cardiovascular action of central AVP since blockade of converting enzyme by captopril did not change the pressor response and no residual pressor effect potentially attributable to angiotensin was found after combined blockade of the sympathetic and vasopressin systems.
These data suggested that the pressor response could be attributed to both activation of the sympathetic nervous system and release of AVP into the bloodstream. Although AVP was not measured to quantify the amount in plasma, the partial contribution of AVP to the pressor effect was identified with the receptor antagonist. To determine the amount of AVP that leaked to the periphery from the brain after intracerebroventricular injection and the contribution of this leak in the pressor response, [3H]AVP was injected into the lateral ventricle. Radioactivity in the plasma at 3 minutes (average time to peak pressor response) after central administration indicated a plasma level of AVP much lower than that required to produce a pressor effect. These data allowed us to rule out the possibility that
the vasopressinergic component of the pressor effect of centrally administered AVP was due to a leak of the peptide into the circulation.

Therefore, under our experimental conditions, central injection of AVP appears to induce the release of AVP from the pituitary concurrent with activation of the sympathetic nervous system. Both of these effects act in concert, in an apparent synergistic fashion, to increase MAP. Our data could help explain the increase in urine conduction and drop in urine flow that occurred about 15 minutes after intracerebroventricular injection of AVP, as described by Pittman et al. These actions could be attributed to release of AVP into the bloodstream.

Administration of AVP (100 ng i.c.v.) induced in some rats (15%) a motor disturbance called "barrel rotation." Thus, for the hemodynamic study, we used a smaller dose of AVP (10 ng) that did not evoke this motor abnormality because the phenomenon could have hidden effects on the regional blood flow, particularly in that of the hindquarter. Intravenous AVP increased MAP and regional resistance, especially in the mesenteric and renal beds. To a lesser extent, qualitatively similar effects were obtained with intracerebroventricular AVP.

The present findings indicate that AVP as well as other centrally acting pressor agents produce their effects by two mechanisms: activation of the sympathetic nervous system and release of AVP. Thus, it may be proposed that central actions of AVP can exert positive feedback on its own pressor action in addition to the negative feedback mediated centrally via the area postrema. Several questions remain to be answered. First, is there a functional relation between the central effects of vasopressin mediated on the one hand via the cerebroventricular system or binding sites in selected brain regions and on the other hand by circulating vasopressin that reaches the brain via the circumventricular organs? Second, is the dual mechanism of increased sympathetic outflow and release of AVP a function of the concentration of AVP in the cerebroventricular system? Overall, these data suggest a novel central action of vasopressin, that of promoting its own release in amounts sufficient to contribute to the cardiovascular effects of the peptide.

References


Key Words · arginine vasopressin · peptides · central nervous system · hemodynamics
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