Inhibition of Muscle Sympathetic Nerve Activity in Humans by Arginine Vasopressin

JOHN S. FLORAS, PHILIP E. AYLWARD, FRANÇOIS M. ABBoud, AND ALLYN L. MARK

SUMMARY Arginine vasopressin, a potent vasoconstrictor, does not raise arterial pressure in normal humans even at pathophysiological plasma levels. To examine whether the pressor effect of vasopressin in humans is buffered by baroreceptor reflex inhibition of sympathetic nerve activity, we recorded postganglionic muscle sympathetic nerve activity directly from the peroneal nerve in 12 normal men before, during, and after a 20-minute intravenous infusion of vasopressin, 4 ng/kg/min, that increased mean plasma concentrations from 6.2 ± 0.6 to 320 ± 68 (SE) pg/ml. During the first 5 minutes (n = 8), mean arterial pressure increased from 91 ± 3 to 97 ± 4 mm Hg (p<0.05) and integrated sympathetic nerve activity decreased from 271 ± 45 to 156 ± 33 units (p<0.05). At 15 minutes (n = 12), arterial pressure did not differ from control values whereas forearm vascular resistance fell (p<0.05) and central venous pressure and heart rate increased (p<0.05). Sympathetic nerve activity remained below control levels throughout the infusion (202 ± 31 vs 254 ± 40 units before infusion; p<0.05). An effect of vasopressin on ganglionic transmission was excluded, since the sympatoexcitatory response to apnea was not attenuated during vasopressin. Thus, pathophysiologic levels of vasopressin in humans cause inhibition of muscle sympathetic nerve activity that is not due to a ganglionic blocking action. The sympathoinhibition may be caused in part by the modest increases in mean arterial and central venous pressures and attendant stimulation of arterial and cardiac baroreceptors. The reflex decrease in sympathetic nerve activity would be expected to buffer the direct vasoconstrictor effects of vasopressin. (Hypertension 10: 409-416, 1987)

KEY WORDS • baroreceptor reflexes • microneurography • vascular resistance

ARGINine vasopressin (AVP) is a potent vasoconstrictor in vitro, but it does not raise blood pressure when given intravenously to conscious animals or humans with intact nervous systems. A marked pressor effect of AVP is unmasked by sinoaortic denervation in dogs and other species. This augmentation is greater than the potentiating effect of sinoaortic denervation on the pressor response to other vasoconstrictor drugs, such as angiotensin, norepinephrine, or phenylephrine. The pressor response to AVP is markedly exaggerated in patients with autonomic failure and orthostatic hypotension and in normal subjects after ganglionic blockade. To explain these findings, it has been suggested that AVP facilitates arterial and cardiopulmonary baroreceptor reflexes, such that the direct vasoconstrictor effect of this peptide is countered by a reflex reduction in heart rate, cardiac output, and peripheral resistance.

This hypothesis has received support from studies in animals that have shown that AVP facilitates reflex inhibition of sympathetic nerve activity (SNA) both by sensitizing baroreceptor afferents and through a central neural action on the area postrema. We have recently shown that AVP (4 ng/kg/min) infused intravenously in normal subjects decreased resting forearm vascular resistance. This response was accompanied by increases in central venous pressure, but mean arterial pressure and pulse pressure did not rise. In addition, AVP facilitated reflex forearm vasodilation during increases in venous return and central venous pressure produced by sudden release of lower body negative pressure. These observations suggest that in humans, as in animals, the direct pressor effect of AVP may be buffered by inhibition of efferent...
SNA. The present experiments were done to test this hypothesis in normal subjects by measuring efferent SNA during intravenous infusions of AVP.

**Subjects and Methods**

**Subject Selection**
Twelve healthy male volunteers, aged 22 to 35 years (mean age, 24.2 years) were studied. Informed written consent was obtained after the rationale, nature, and potential risks of this research were explained. This protocol was approved by the Human Subjects Review Committee of the University of Iowa.

**Procedures**
Subjects were studied supine. The electrocardiogram and respiratory excursions were recorded continuously. Blood pressure was measured in the left arm by sphygmomanometry (diastolic pressure = Korotkoff Phase V). Central venous pressure was measured by means of a catheter introduced into an antecubital vein of the left arm and advanced to an intrathoracic position (Statham Gould P23ID transducer; Gould Instruments, Cleveland, OH, USA). A point 10 cm anterior to the back of the subject was used as zero reference for central venous pressure. This catheter was also used for AVP infusion and blood sampling. A belt coupled to a Statham Gould P23ID transducer was used to record respiratory excursions.

Forearm blood flow was measured in the right arm by venous occlusion plethysmography. The arm was elevated and supported so that the proximal part of the forearm was approximately 10 cm above the anterior chest wall. During measurements of forearm flow, circulation to the hand was interrupted by inflating a cuff around the wrist to 180 mm Hg. A second cuff was wrapped loosely around the arm above the antecubital crease and intermittently inflated to 40 mm Hg. Inflation and deflation of this cuff was timed to give four measurements of forearm blood flow each minute. A Whitney strain gauge was applied approximately 5 cm distal to the antecubital crease over the area of greatest forearm muscle mass. Forearm vascular resistance (expressed as resistance units) was calculated by dividing mean arterial pressure (diastolic pressure plus one third of the pulse pressure [mm Hg]) by forearm blood flow (ml/min/dl of forearm volume).

Multiunit recordings of postganglionic efferent SNA were obtained from a muscle fascicle of the right peroneal nerve posterior to the fibular head using a microneurographic technique. Recordings were made with tungsten microelectrodes 200 μm in diameter in the shaft, tapering to a 1- to 5-μm uninsulated tip. A reference electrode was inserted subcutaneously 1 to 3 cm from the recording electrode. Electrodes were connected to a preamplifier with a gain of 1000 and an amplifier with a gain that could be varied from 50 to 90 as required in a subject. Amplification was constant throughout the study in each subject. Neural activity was fed through a bandpass filter with a band width of 700 to 2000 Hz. The filtered neurogram was routed through an amplitude discriminator to a storage oscilloscope and a loudspeaker. For recording and analysis, the filtered neurogram was fed through a resistance-capacitance integrating network (time constant, 0.1 second) to obtain a mean voltage neurogram of SNA.

There were three criteria for an acceptable recording of muscle SNA. First, weak electrical stimulation (1–3 V, 0.2 msec, 1 Hz) through the electrode in the peroneal nerve elicited involuntary muscle contraction but not paresthesias. Second, tapping or stretching the muscle or tendons supplied by the impaled fascicle elicited afferent mechanoreceptor discharge whereas stroking the skin in the distribution of the peroneal nerve did not. Third, the neurogram contained spontaneous, intermittent, pulse-synchronous bursts that increased during held expiration and Phase 2 and 3 of a Valsalva maneuver. Evidence from earlier studies that such activity represents efferent postganglionic sympathetic activity includes: 1) interruption of activity by local nerve block proximal but not distal to the recording site, 2) reversible elimination of activity by ganglionic blockade, and 3) a conduction velocity approximating 1 m/sec. 

**Arginine Vasopressin**

Synthetic AVP (Pitressin; Parke-Davis, Morris Plains, NJ, USA), 20 pressor units/ml, was diluted in normal saline and infused in a volume of 1.9 ml/min into the central venous catheter at a dose of 4 ng/kg/min using a Harvard constant infusion pump (Model 940; South Natick, MA, USA).

**Protocol**
The protocol included measurements during three sequential periods.

**Control Period**
Once satisfactory determinations of forearm blood flow and efferent SNA were obtained, the subject rested quietly for 10 minutes before starting a 10-minute control period. Central venous pressure, heart rate, and the mean voltage neurogram of muscle SNA were recorded continuously (Model 2800S; Gould); the control values for these variables represent the average values throughout this period. Cuff blood pressure and forearm blood flow, in contrast, were measured intermittently every 2 minutes, and the control values described for these variables represent the mean of these intermittent measurements.
Infusion Period

AVP, 4 ng/kg/min, was infused intravenously for 20 minutes. The infusion did not elicit any symptoms in these subjects. Initial responses during the first 10 minutes of AVP infusion and steady state responses during the second 10 minutes of AVP infusion were examined. The original aim of this study was to examine the effect of AVP on SNA during the steady state period, since it was at this time that we observed a fall in forearm vascular resistance in our previous study.5 However, after review of the first four experiments, it became apparent that sympathoinhibition occurred almost immediately after starting the AVP infusion. Therefore, we added detailed measurements of arterial pressure, central venous pressure, and forearm blood flow every 2 minutes during the initial 10-minute period in the next eight subjects. Central venous pressure was measured intermittently during this period to allow the intravenous infusion of the peptide.

During the second 10 minutes of AVP infusion, responses were at a steady state. Steady state values for heart rate and SNA represent mean values for this period. Arterial pressure, central venous pressure, and forearm blood flow were measured every 2 minutes, and the means of these measurements were used to represent the steady state responses of these variables to AVP.

Recovery Period

Observations continued for 50 minutes after the end of the infusion. Values during this recovery period are reported as average of observations made over five 10-minute periods.

Effect of Apnea

SNA was recorded in eight subjects during held expiration before and at the end of the steady state infusion of AVP. The subjects were instructed to sustain apnea for as long as possible without performing a Valsalva maneuver. This stimulus increased sympathetic discharge and served 1) to determine the stability of the recording site throughout the experiment at times when basal activity was suppressed and 2) to determine whether AVP might inhibit efferent sympathetic activity through a ganglionic blocking action.

Plasma Vasopressin Concentration

Resting AVP levels were calculated as the mean of two samples, obtained at the beginning and end of the control period. For technical reasons, determinations could not be made in one of these 12 subjects. Additional samples were obtained after 10 and 20 minutes of the AVP infusion, and at 20 (n = 11), 30 (n = 10), and 40 (n = 9) minutes after AVP was stopped.

Plasma AVP concentrations were determined by radioimmunoassay.9

Results

Plasma Vasopressin Concentrations

Plasma AVP rose from 6.2 ± 0.6 pg/ml during the control period to 381.7 ± 183.1 and 320.1 ± 67.8 pg/ml after 10 and 20 minutes, respectively, of AVP and was 29.8 ± 16.1 pg/ml 40 minutes after AVP was stopped.

Effects of Infusion

Results obtained during the first 10 minutes of infusion (initial period) and during the last 10 minutes of infusion (steady state period) are described separately.

Initial Infusion Period

Results obtained during the first 10 minutes of infusion are shown in Table 1 and Figure 1. Initially, AVP produced modest, transient increases in arterial pressure (see Table 1). Central venous pressure was not
TABLE 1.  
Hemodynamic Variables and Sympathetic Nerve Activity in the Control State and During the Early Phase of Arginine Vasopressin Infusion (4 ng/kg/min)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control</th>
<th>0–2 min</th>
<th>4–6 min</th>
<th>8–10 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>125 ± 4</td>
<td>130 ± 5*</td>
<td>127 ± 5</td>
<td>124 ± 4</td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>91 ± 3</td>
<td>95 ± 4</td>
<td>97 ± 4*</td>
<td>92 ± 3</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>74 ± 3</td>
<td>78 ± 4</td>
<td>82 ± 4*</td>
<td>76 ± 4</td>
</tr>
<tr>
<td>Pulse pressure (mm Hg)</td>
<td>51 ± 5</td>
<td>52 ± 6</td>
<td>46 ± 5</td>
<td>47 ± 5</td>
</tr>
<tr>
<td>Central venous pressure (mm Hg)</td>
<td>3.1 ± 0.6</td>
<td>3.2 ± 0.6</td>
<td>3.3 ± 0.6</td>
<td>3.5 ± 0.6</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>65 ± 5</td>
<td>59 ± 6*</td>
<td>64 ± 5</td>
<td>70 ± 5</td>
</tr>
<tr>
<td>Forearm blood flow (ml/min/dl)</td>
<td>4.0 ± 0.8</td>
<td>3.8 ± 0.8</td>
<td>3.8 ± 0.8</td>
<td>3.6 ± 0.4</td>
</tr>
<tr>
<td>Forearm vascular resistance (RU)</td>
<td>27.1 ± 4.4</td>
<td>29.2 ± 4.5</td>
<td>30.3 ± 3.8</td>
<td>27.2 ± 2.6</td>
</tr>
<tr>
<td>Sympathetic nerve activity (bursts/min)</td>
<td>22.8 ± 3.1</td>
<td>16.0 ± 2.6*</td>
<td>14.8 ± 2.2*</td>
<td>17.4 ± 2.6*</td>
</tr>
<tr>
<td>Sympathetic nerve activity (bursts/100 heartbeats)</td>
<td>34.9 ± 3.7</td>
<td>26.9 ± 3.5*</td>
<td>23.3 ± 2.9*</td>
<td>24.9 ± 3.1*</td>
</tr>
<tr>
<td>Sympathetic nerve activity (units)</td>
<td>271 ± 45</td>
<td>182 ± 40*</td>
<td>156 ± 33*</td>
<td>203 ± 35*</td>
</tr>
</tbody>
</table>

Values are means ± SE of eight subjects. AVP = arginine vasopressin; RU = resistance units.

*p < 0.05, compared with control values.

altered. Heart rate displayed a biphasic response, falling initially and then tending to increase toward the end of this period. Forearm blood flow did not change. Forearm resistance tended to increase briefly, but this was not significant. SNA, expressed either in terms of bursts per minute or per 100 heartbeats, or in units of integrated SNA, fell significantly within the first 2 minutes of AVP (see Table 1, Figures 1 and 2). In 12 subjects SNA decreased abruptly from 254 ± 40 to 139 ± 27 units (see Figure 1), and in eight of those in whom the hemodynamics were measured every 2 minutes SNA fell from 271 ± 45 to 156 ± 33 units (see Table 1). This inhibition of SNA can be seen clearly in Figure 2.

Steady State Period

Results obtained during the last 10 minutes of infusion are shown in Figures 1, 3, and 4. During the steady state period, neither systolic, mean, nor diastolic arterial pressure was altered from control values. Specifically, diastolic arterial pressure averaged 73.2 ± 2.4 mm Hg during the control period and 75.7 ± 2.6 mm Hg during the steady state. During the steady state, there were increases in both central venous pressure (from 3.1 ± 0.5 to 4.1 ± 0.8 mm Hg; p < 0.05) and heart rate (from 65 ± 3 to 72 ± 3 beats/min; p < 0.05; see Figure 3). Forearm blood flow rose from 3.4 ± 0.6 ml/min/dl in control to 4.1 ± 0.7 ml/min/dl during AVP infusion (p < 0.05), while forearm vascular resistance fell from 34 ± 5 to 29 ± 5 resistance units (p < 0.05; see Figure 3).

SNA was significantly reduced from control values during the steady state infusion of AVP (see Figures 1 and 4). Figure 4 is a record from one of these subjects, illustrating the forearm vasodilation and reduction in SNA during AVP infusion. In this subject, these changes occurred without an increase in either arterial pressure or central venous pressure.

Recovery Period

Results obtained during the recovery period are shown in Figures 1 and 3. Systemic and forearm hemodynamics returned to control levels within 10 minutes after stopping the AVP infusion. SNA, expressed as bursts per minute or as integrated SNA, rose toward control levels and was not significantly different from control levels during recovery. However, SNA adjusted for heart rate remained low (23.2 ± 3.9 bursts/100 heartbeats) 10 minutes after the AVP infusion was stopped (see Figure 1) and then returned to control levels.

Effect of Apnea

A marked increase in SNA was seen consistently during held expiration. Integrated SNA during held expiration was 423 ± 116 units before AVP and 427 ± 104 units during steady state AVP infusion (Figure 5). SNA during apnea was 23.5 ± 1.6 before and 21.4 ± 0.8 bursts/min during AVP infusion. Thus, reflex sympathoneural excitation was not altered by AVP even though resting nerve discharge was significantly attenuated at this time.

Discussion

The key finding in this study was the marked decrease in postganglionic muscle sympathetic nerve discharge during AVP infusion. This observation is consistent with the hypothesis that AVP does not increase...
SYMPATHETIC NEURAL EFFECTS OF VASOPRESSIN

Figure 1. Mean values for continuously recorded heart rate (in beats per minute), integrated muscle sympathetic nerve activity (in units), and sympathetic nerve activity (SNA; expressed as burst frequency per 100 heart beats) before, during, and after a 20-minute infusion of arginine vasopressin (AVP), 4 ng/kg/min (mean ± SE), in all 12 subjects. During the initial 10 minutes of AVP, these values represent means of measurements obtained every 2 minutes. During the control, steady state AVP, and recovery periods, observations represent mean values over 10-minute intervals. AVP elicited a biphasic heart rate response. Muscle SNA was inhibited by AVP. Inhibition of SNA persisted for 10 minutes after AVP was stopped, even though hemodynamic responses to AVP had returned to control levels by this time.

Figure 2. Mean voltage neurogram of sympathetic nerve activity (SNA) from one subject during the control period and after 1 minute of the arginine vasopressin (AVP), 4 ng/kg/min, infusion. SNA is calculated from the frequency and the amplitude of bursts in the mean voltage neurogram. Sympathoinhibition occurred almost immediately after starting the AVP infusion.

Blood pressure in normal humans because reflex sympathetic withdrawal can counteract the direct vasoconstriction seen when AVP is infused directly into a brachial artery. 2

There are several potential explanations for this fall in efferent SNA. First, it could be considered a reflex response to stimulation of arterial or cardiopulmonary mechanoreceptors by increases in either arterial pressure or central venous pressure. Second, AVP may have facilitated inhibition of SNA by sensitizing afferent receptors or by a central neural action. Finally, AVP may have acted as a ganglionic blocker, as suggested by Imaizumi and Thames. 21

To exclude the latter possibility, we studied the reflex response to apnea. AVP did not attenuate the response of postganglionic SNA to apnea. This finding suggests that AVP did not exert a major ganglionic blocking action. One might argue that these observations do not exclude a ganglionic blocking action, since AVP could have increased preganglionic SNA. However, the known effects of AVP on baroreceptor afferents and the central nervous system would be expected to decrease, not increase, preganglionic SNA. Thus, we believe that a preservation of reflex increases in postganglionic SNA after AVP infusion argues against marked ganglionic blockade in these experiments.

Infusion of AVP led to modest, transient increases in arterial pressure followed by a gradual increase in central venous pressure, averaging 1 mm Hg. The sympathoinhibition we observed could be attributed to stimulation of arterial or cardiopulmonary receptors by these changes, resulting in a reflex withdrawal of efferent SNA. Cardiopulmonary reflexes in humans exert a prominent role in the regulation of forearm vascular resistance. 22-24 Marked, sustained increases in efferent muscle SNA are seen when central venous pressure in humans is reduced by lower body negative pressure. 25 These observations would suggest that the increase in central venous pressure that occurred during the second 10-minute period of the infusion might have decreased muscle SNA. In anesthetized 26 and conscious rabbits, 27 vasopressin augments the reflex inhibition of renal nerve activity during volume expansion and elevation in cardiac filling pressure.
FIGURE 3. Mean arterial pressure (MAP), central venous pressure (CVP), and forearm vascular resistance (FVR; expressed as resistance units [RU]), during control, arginine vasopressin (AVP; 4 ng/kg/min) steady state infusion, and recovery periods. Values are means ± SE of 12 subjects. Asterisks indicate significant difference (p<0.05) compared with control values.

At certain times during the infusion a sustained decrease in nerve activity was noted in the absence of any measured increase in either arterial pressure or central venous pressure and despite a tendency for pulse pressure to decrease (see Table 1 and Figure 4). These observations raise the possibility that AVP was inhibiting SNA in part by sensitizing baroreceptor afferents or by a central neural action. However, we cannot exclude the alternative possibility that the inhibition of SNA with AVP was caused entirely by increased (but at times imperceptible) mechanical stimulation of arterial and cardiac baroreceptors.

One way to determine if AVP sensitizes baroreceptor reflex inhibition of SNA would be to compare effects of AVP with those of another pressor agent, such as phenylephrine. This comparison is theoretically simple, but practically we have found it difficult to identify doses of AVP and phenylephrine that produce comparable increases in mean arterial pressure, pulse pressure, and central venous pressure in humans.

During the initial 10 minutes of the AVP infusion, arterial pressure rose, SNA and heart rate fell promptly, but forearm vascular resistance did not change. The lack of change in forearm vascular resistance may be explained by the balance between the direct vasoconstrictor effect of AVP and reflex sympathoinhibition. However, during the steady state period, heart rate increased above control levels, SNA remained below control levels, the forearm vessels dilated, and arterial pressure returned to control levels. The forearm vasodilation may be explained by the sustained inhibition of SNA, which appears to override the direct constrictor effect of AVP in the forearm. The dissociation of changes in heart rate and SNA suggests a selectively greater inhibition of SNA than of heart rate by AVP. The explanation for these divergent responses is not clear. Central venous pressure was rising slowly over the same period. It is known from work in dogs that stimulation of atrial receptors increases heart rate reflexly yet decreases efferent renal SNA. It is also known that, under certain experimental conditions, there is a dissociation in the arterial baroreceptor reflex control of heart rate, vascular resistance, and SNA such that the baroreceptor reflex inhibition of heart rate may be suppressed whereas that of sympathetic activity and vascular resistance is preserved.

This dose of AVP (4 ng/kg/min) increased plasma AVP concentrations well beyond the normal physiological range. Plasma AVP levels similar to those observed in this study have been reported to occur during nausea, vomiting, presyncope, and cardiovascular surgery. In our previous study, we observed forearm vasodilation and a rise in central venous pressure without any increase in mean arterial pressure at a dose of 4 ng/kg/min, but not at 0.4 ng/kg/min. In addition, the increased reflex vasodilator response we observed during infusion of AVP at 4 ng/kg/min in that study led us to propose that if AVP had any effect on efferent SNA, such effect would be most evident at this dose. In the present study, we again observed forearm vasodilation during the steady state period of the AVP infusion when SNA was reduced.

In summary, we have shown that infusion of AVP, 4 ng/kg/min, inhibits efferent muscle SNA. The decreases in SNA did not appear to result from ganglionic blockade. The sympathoinhibition may have resulted principally from mechanical stimulation of cardiac and arterial baroreceptors. However, since the reduction in SNA was not consistently associated with detectable increases in arterial pressure or central venous pressure, we cannot exclude the possibility that AVP decreased SNA in part by sensitizing baroreceptor afferents or by a central neural action.

Sympathoinhibition would appear to be an important mechanism by which the potent pressor effects of AVP are countered in normal humans with intact baroreceptor reflexes. In conditions such as heart failure, hypertension, or autonomic failure that are character-
Mean arterial pressure (MAP), central venous pressure (CVP), forearm blood flow (FBF), and mean voltage neurogram of muscle sympathetic nerve activity (SNA) before and during steady state period (after 10 minutes) of arginine vasopressin (AVP) infusion (4 ng/kg/min). FBF is proportional to and calculated from the slopes of the increase in forearm circumference during intermittent venous occlusion. Integrated SNA is calculated from the frequency and the amplitude of bursts in the mean voltage neurogram. AVP increased FBF and lowered forearm vascular resistance (FVR) and integrated SNA in this subject without changing MAP or CVP.

**Figure 4.**

Mean arterial pressure (MAP), central venous pressure (CVP), forearm blood flow (FBF), and mean voltage neurogram of muscle sympathetic nerve activity (SNA) before and during steady state period (after 10 minutes) of arginine vasopressin (AVP) infusion (4 ng/kg/min). FBF is proportional to and calculated from the slopes of the increase in forearm circumference during intermittent venous occlusion. Integrated SNA is calculated from the frequency and the amplitude of bursts in the mean voltage neurogram. AVP increased FBF and lowered forearm vascular resistance (FVR) and integrated SNA in this subject without changing MAP or CVP.

**Figure 5.**

Mean voltage neurogram of muscle sympathetic nerve activity (MSA) recorded in one subject during held expiration (Exp) in the preinfusion control state (A) and during infusion of arginine vasopressin (AVP; B). AVP had no effect on the response to apnea. Insp = inspiration; ECG = electrocardiogram.

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