Hemodynamic Effects of Exogenous and Endogenous Vasopressin at Low Plasma Concentrations in Conscious Dogs

JEAN-PIERRE MONTANI, JEAN-FRANÇOIS LIARD, JOSIANE SCHOUN, AND JAN MÖHRING

SUMMARY The possibility that vasopressin plays a role in cardiovascular control arouses increasing interest. We studied in unanesthetized dogs the hemodynamic consequences of 1-hour vasopressin infusions that modified plasma concentrations over a range similar to that found in physiological situations. We also examined the cardiovascular events following the stimulation of endogenous vasopressin release by an increase in plasma osmolality. In dogs with baroreceptor reflexes intact, vasopressin infusions which increased plasma vasopressin concentration by 2-20 fmol/ml did not affect mean arterial pressure. However, they significantly decreased cardiac output (measured by an electromagnetic flowmeter) and increased total peripheral resistance. After baroreceptor denervation, vasopressin infusion rates as low as 40 fmol/kg per min (0.017 mU/kg per min) led to an increase in mean arterial pressure. Changes in total peripheral resistance were very similar to those calculated in dogs with intact baroreceptors.

THE cardiovascular actions of vasopressin were recognized very early (Nakano, 1974), but a commonly held view is that they are elicited only by concentrations far higher than those required for antidiuresis and are incidental effects subserving no physiological requirement in mammals. However, several findings indicate that the vasoconstrictor properties of vasopressin may have physiological significance. First, concentrations of vasopressin comparable to those found in plasma under various conditions are capable of evoking responses on a variety of blood vessels in vitro (Altura and Altura, 1977, Monos et al., 1978). Second, cardiovascular effects in animals at moderately increased plasma concentrations of vasopressin have been described repeatedly. For instance, Szczepanska-Sadowska (1973) has reported that small rates of infusion of vasopressin could induce in conscious dogs an increase of mean arterial pressure and a decrease of heart rate and cardiac output. Cowley et al. (1974) concluded that vasopressin infused so as to approximate physiological secretion rates could significantly affect systemic resistance vessels in conscious dogs. They drew attention to the greatly enhanced pressor sensitivity to vasopressin following baroreceptor denervation. Schmid et al. (1974) indicated that direct constrictor effects in dogs resulted from moderate increases of vasopressin concentration. Pang et al. (1979) reported that hypophysectomy caused an increase in mesenteric conductance in the anesthetized cat, suggesting that vasopressin had a measurable impact on the cardiovascular system. Cowley et al. (1980) have recently established that vasopressin can function as a rapid and potent system to control arterial pressure under some conditions. Finally, Möhring (1978) has summarized evidence that vasopressin plays an important role in the pathogenesis of various forms of hypertension. It therefore appears from these and many other reports that vasopressin does affect the circulation at concentrations within the range found in various pathophysiological states, such as hemorrhage and surgical stress, or even at lower levels.

The present study was undertaken to answer the following questions. First, do hemodynamic changes resulting from infusions of vasopressin at rates which modify its plasma concentration in a range similar to that found in physiological situations? And second, is it possible to detect hemodynamic changes following the release of endogenous vasopressin in response to an increase in plasma osmolality? To answer these questions, it was necessary to use...
conscious, chronically instrumented animals and to measure the concentrations of vasopressin in the plasma as well as mean arterial pressure, cardiac output, and heart rate during vasopressin infusions and stimulation of the endogenous system. As the baroreceptor reflex appears important in determining the cardiovascular effects of vasopressin (Cowley et al., 1974), the experiments were conducted before and after baroreceptor denervation.

**Methods**

**Animal Preparation**

A total of 33 mongrel dogs (28 male, five female) were selected initially for these experiments. Sixteen were rejected for various reasons, including insufficient baroreceptor denervation (six dogs). The 17 remaining dogs (initial body weight 23.0 ± 0.7 kg, mean ± SEM) underwent one or several of the experimental protocols described later.

All surgical interventions were conducted under pentobarbital anesthesia (30 mg/kg, iv) and sterile conditions. They were not always performed in the same order, nor were all necessarily conducted in each dog. First, catheters were inserted into the aorta and the inferior vena cava through the iliac vessels for blood pressure measurements, blood sampling, and intravenous infusions. Second, an electromagnetic flow transducer was placed round the root of the aorta through a thoracotomy at the 4th intercostal space for cardiac output measurement. Third, a small nonobstructive Tygon catheter was inserted in the right common carotid artery by the technique of Herd and Barger (1964). All cables and catheters were exteriorized on the back of the animal and protected by a jacket. Fourth, baroreceptor denervation was performed by a technique previously described (Liard et al., 1974) that involved surgical stripping of both carotid sinuses, painting of the area with phenol, and total resection of the left and partial resection of the right vagosympathetic trunk in the neck. In three dogs, the technique of Edis and Shepherd (1971) was used for aortic denervation. Six dogs were studied both in the intact and baroreceptor denervated state.

Criteria for accepting dogs as baroreceptor denervated included: (1) similar changes in arterial pressure following bilateral carotid occlusion below or above the carotid sinus (this was tested under anesthesia before and after destruction of the sinus and aortic depressor nerves), (2) absence of pressure response to sodium cyanide, 0.2 mg/kg, injected into the root of the aorta immediately before the animal was killed, and (3) loss of reflex bradycardia in response to intravenous injections of pressor agents (norepinephrine, vasopressin) as tested in the conscious state. Failure to meet one or more of these criteria caused rejection of the preparation. However, we make no claim that the dogs included in this study had a complete destruction of all baroreceptor afferents.

**Measurement of Hemodynamics**

The experiments were conducted in an isolated room on conscious dogs, which were housed in a pen equipped for continuous recording of hemodynamic variables without interference from the observer (Cowley et al., 1973). We measured arterial blood pressure (mean and pulsatile), aortic blood flow, cardiac output [computed from the beat-to-beat integration of the aortic flow signal over 4-second periods, as described by Ferrario et al. (1969)], and heart rate (using a tachometer triggered by the pulsatile flow signal). The analysis of the recorded data was performed in the following manner: a value for each variable was read from the paper record every 20 seconds and used for subsequent calculation of mean values and standard deviations. This procedure was necessary because of the great variability in blood pressure characteristic of baroreceptor denervated animals (Cowley et al., 1973); it allowed a precise determination of even small changes in pressure, output, and heart rate induced by experimental maneuvers.

**Other Measurements**

All blood samples were taken from the aortic catheter. Plasma vasopressin concentration was measured by a radioimmunoassay (Möhring and Möhring, 1975). Purified arginine-vasopressin (AVP) from bovine neurohypophysis was used as standard in the radioimmunoassay. As for rat plasma, linearity of the assay was demonstrated in serial dilutions, linear regressions going through zero. The recovery for AVP extraction from dog plasma was 72.7 ± 4.3% (SD) (n = 20) as assessed by adding known amounts of AVP to pooled plasma. The intraassay coefficient of variation was 3.5% in the range of standards used.

Plasma sodium and potassium concentrations were obtained by flame photometry. In the case of sodium, the coefficient of variation (SD/X) was 0.11% for 20 determinations of a sample in the range 130-150 mEq/L, and 0.09% for K+ in the range 3-5 mEq/L. Plasma osmolality was determined by a freezing-point depression osmometer (coefficient of variation 0.32% in the range 280-320 mOsm/kg H2O for 20 determinations). Hematocrit was obtained by microcentrifugation.

**Experimental Protocols**

The experiments were performed only after the dogs had been trained to lie quietly in the recording pen for several hours. Food, but not water, was withdrawn 12 hours before an experiment. All infusions were given with a syringe pump at a rate of 0.2 ml/min. The arginine-vasopressin infused was a synthetic preparation kindly supplied by Ferring, Malmö. Mainly for the purpose of accurate calculation of metabolic clearance, standard and Ferring AVP were compared quantitatively by radioimmunoassay and by a fluorometric technique (Gruber...
were chosen to increase plasma osmolality by an amount of about 60 and 30 mOsm, respectively. These loads were given either intravenously or into the right carotid artery of denervated dogs (four of which had been studied as intact). Two dogs with intact baroreceptors received a 1-hour infusion of AVP at a rate of 1000 fmol/kg per min. Arterial blood samples were taken before and 30, 45, and 60 minutes after the start of the infusion, and 2.5, 5, 10, 20, 40, and 80 minutes after the end of the infusion for plasma AVP concentration determination.

**Pharmacokinetics of Arginine-Vasopressin**

Four dogs with intact baroreceptors received a 1-hour infusion of AVP at a rate of 1000 fmol/kg per min. Arterial blood samples were taken before and 30, 45, and 60 minutes after the start of the infusion, and 2.5, 5, 10, 20, 40, and 80 minutes after the end of the infusion for plasma AVP concentration determination.

**Hemodynamic and Humoral Effects of Arginine-Vasopressin Infusions**

Following a control period of about 1 hour, a 1-hour infusion of AVP was started at one of the following rates: 40, 100, 200, 1000, and 5000 fmol/kg per min; alternately isotonic saline was used. These six infusions were given on different days in a random order. Hemodynamic variables were monitored continuously during the control and infusion period and for 1 hour thereafter. A blood sample for AVP, Na⁺, K⁺, osmolality, and hematocrit determinations was taken during the control period and after 30 and 60 minutes of infusion. The hemodynamic effects of the infusions were assessed in the following manner. For mean arterial pressure, cardiac output, heart rate, and total peripheral resistance (calculated as the ratio of mean arterial pressure and cardiac output), a control value was obtained by averaging all the values sampled during the control period and after 30 and 60 minutes of infusion. The hemodynamic effects of the infusions were assessed in the following manner. For mean arterial pressure, cardiac output, heart rate, and total peripheral resistance (calculated as the ratio of mean arterial pressure and cardiac output), a control value was obtained by averaging all the values sampled during the control period (100-200 for each variable). The value during infusion was obtained by averaging all the values sampled from the 20th until the 60th minute of infusion. The difference between control and infusion value was calculated. No values are reported for the postinfusion period because of the slow disappearance rate of AVP from the plasma (see Results).

A total of 36 infusions were given to seven intact dogs, and a total of 36 infusions to six baroreceptor denervated dogs (four of which had been studied as intact).

**Hemodynamic and Humoral Effects of Hypertonic Saline Infusions**

In an attempt to stimulate the endogenous release of vasopressin, the following solutions were given either intravenously or into the right carotid artery: NaCl, 2.52 M and 1.26 M, at a rate of 0.2 ml/min for 60 minutes, providing a total osmotic load of about 60 and 30 mOsm, respectively. These loads were chosen to increase plasma osmolality by approximately 4 and 2 mOsm/kg H₂O, assuming that total body water would be affected homogeneously. In all other respects, the protocol was identical with that just described for vasopressin infusions. A total of 27 infusions were given to eight intact dogs, among which five also received AVP infusions. A total of 21 infusions were given to seven baroreceptor-denervated dogs, among which three had received hypertonic solutions as intact and three also received AVP infusions as barodenervated dogs. For seven infusions in intact dogs and for two infusions in baroreceptor denervated dogs, no hemodynamic measurements were collected.

**Statistical Analysis**

Results are given as mean values ±1 SEM. Comparison between groups was made by unpaired t-tests unless stated otherwise. Changes were considered significant for \( P < 0.05 \). Linear regressions were calculated with the least-squares method.

**Results**

**Control, Preinfusion Values**

**Hemodynamics**

In each dog, a mean control value was obtained, for each variable and for its standard deviation, by averaging all the control values for periods preceding the various infusions (up to 10 per dog in the intact and in the barodenervated state). These mean control values were used to calculate the average control values listed in Table 1.

Mean arterial pressure, its standard deviation (an index of variability), and heart rate were significantly greater in the baroreceptor denervated dogs. The difference in arterial pressure proved to be not significant in paired analysis of the six dogs studied in the intact as well as in the barodenervated state.

**Humoral Variables**

As there were no significant differences between preinfusion values in intact and barodenervated dogs for any measured variable, the results have been combined. Plasma vasopressin concentration was 1.85 ± 0.22 fmol/ml; plasma sodium, 143.6 ± 0.49 mM; potassium, 3.68 ± 0.04 mM; osmolality, 296.9 ± 0.9 mOsm/kg H₂O; and hematocrit, 38.3 ± 0.9% (n = 20). As for the hemodynamic variables, these control mean values are based upon one average value per dog in the intact (n = 10) or in the barodenervated (n = 10) state.

**Vasopressin Infusions**

**Plasma Vasopressin Concentration Changes and Pharmacokinetics**

In the four dogs studied that received an infusion of 1000 fmol/kg per min, plasma AVP concentration rose to 57.1 ± 4.5 fmol/ml after 30 minutes, 63.0 ± 4.7 after 45 minutes, and 65.4 ± 4.9 after 60 minutes. Thus, the rise between 30 and 60 minutes was only...
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TABLE 1 Hemodynamic Values during the Control Preinfusion Periods in Intact and Baroreceptor-Denervated Dogs

<table>
<thead>
<tr>
<th></th>
<th>Intact (n = 10)</th>
<th>Barodenervated (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean arterial pressure</td>
<td>101.2 ± 3.2</td>
<td>111.4 ± 30*</td>
</tr>
<tr>
<td>(mm Hg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standard deviation</td>
<td>6.01 ± 0.41</td>
<td>15.93 ± 1.49*</td>
</tr>
<tr>
<td>Cardiac output</td>
<td>107.9 ± 7.0</td>
<td>121.6 ± 7.6</td>
</tr>
<tr>
<td>(ml/kg per min)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standard deviation</td>
<td>10.5 ± 0.72</td>
<td>12.2 ± 1.61</td>
</tr>
<tr>
<td>Heart rate</td>
<td>91.7 ± 2.9</td>
<td>118.1 ± 7.0*</td>
</tr>
<tr>
<td>(beats/min)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standard deviation</td>
<td>6.03 ± 0.76</td>
<td>9.73 ± 1.76</td>
</tr>
<tr>
<td>Total peripheral resistance</td>
<td>1001.3 ± 93.1</td>
<td>975.2 ± 92.6</td>
</tr>
<tr>
<td>(mm Hg kg min/liter)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standard deviation</td>
<td>115.3 ± 16.7</td>
<td>123.5 ± 11.6</td>
</tr>
</tbody>
</table>

Values are means ± SEM.
* Significantly different from value in dogs with baroreceptors intact.

about 10% of the total rise, and a plateau was definitely reached by 60 minutes.

Following the end of the infusion, plasma AVP concentration decreased rapidly. A best-fit curve was constructed which included three exponentials for each dog. The average curve, indicating AVP concentration at time $t$ and expressed in percent of the final level reached by 60 minutes, was $AVP(t) = 27.59 e^{-0.5221} + 55.15 e^{-0.1491} + 17.26 e^{-0.0152}$.

The half times corresponding to the three exponentials were 1.6, 5.5, and 50.9 minutes, respectively.

In the intact and baroreceptor-denervated dogs also studied for hemodynamics, the changes in plasma AVP concentration measured after 60 minutes of vasopressin infusion are summarized in Figure 1. There was a close correlation between infusion rate and plasma AVP concentration changes ($r = 0.989$ for intact and 0.976 for barodenervated dogs). The two coefficients of regression were not significantly different from 1. At 40 fmol/kg per min, the change in AVP concentration was significantly less in intact than in baroreceptor-denervated dogs.

Plasma clearance for AVP was calculated for all groups studied as $Cl_{AVP} = \text{infusion rate/AVP}_{0 \text{ min}}$ neglecting endogenous secretion rate. With an infusion rate of 5000 fmol/kg per min, $Cl_{AVP}$ was 12.3 ± 0.9 ml/kg per min in seven intact and 12.6 ± 0.9 ml/kg per min in six baroreceptor-denervated dogs. Clearances calculated from other infusion rates were not significantly different, except for the clearance calculated for the barodenervated dogs receiving vasopressin at a rate of 40 fmol/kg per min, which was 7.9 ± 0.7 ml/kg per min.

Hemodynamic Effects in Intact Dogs

Table 2 summarizes the hemodynamic changes induced by vasopressin or isotonic saline infusions. Significant increases in mean arterial pressure were not observed until plasma levels of vasopressin of 77.7 ± 13.0 fmol/ml were reached with an infusion rate of 1000 fmol/kg per min. On the other hand, clear-cut changes in cardiac output and peripheral resistance occurred even with the lowest infusion rate, which increased plasma AVP by 2.0 ± 0.4 fmol/ml from a control value of 1.9 ± 0.33 fmol/ml ($n = 6$). Heart rate decreased, although the change was not significant with 40 fmol/kg per min. There was a significant correlation between the changes in cardiac output and heart rate measured during the five different vasopressin infusions ($r = 0.87$, $n = 29$).

The changes in cardiac output ($\Delta CO$) exhibited a negative correlation with the changes in mean arterial pressure ($\Delta MAP$) as illustrated in Figure 2. The linear regression depicted was $\Delta CO = -1.18 \Delta MAP - 14$ ($r = -0.73$, $n = 29$). However, this correlation did not exist for the three lowest infusion rates alone ($r = -0.03$, $n = 16$, unfilled circles), where substantial changes in cardiac output took place with no significant increases in mean arterial pressure.

We also noted that the changes in heart rate ($\Delta HR$) showed a negative correlation with the increments in mean arterial pressure: $\Delta HR = -0.65 \Delta MAP - 8.2$ ($r = -0.7$, $n = 29$). The significant correlation did not exist when only the three lowest infusion rates were considered ($r = 0.12$).

The linear regression of the changes in mean...
**Table 2** Changes in Mean Arterial Pressure (ΔMAP), Cardiac Output (ΔCO), Heart Rate (ΔHR), and Total Peripheral Resistance (ΔTPR) Induced by iv Infusions of Vasopressin in Dogs with Intact Baroreceptors

<table>
<thead>
<tr>
<th>Rate of vasopressin infusion (fmol/kg per min)</th>
<th>Isotonic saline (n = 7)</th>
<th>40 (n = 6)</th>
<th>100 (n = 4)</th>
<th>200 (n = 6)</th>
<th>1000 (n = 6)</th>
<th>5000 (n = 7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ΔMAP (mm Hg)</td>
<td>±0.5</td>
<td>±1.0</td>
<td>±3.3</td>
<td>±1.6</td>
<td>±7.7*</td>
<td>±17.1*</td>
</tr>
<tr>
<td>ΔCO (ml/kg per min)</td>
<td>±1.75</td>
<td>±0.68</td>
<td>±0.6</td>
<td>±1.1</td>
<td>±2.88</td>
<td>±4.16</td>
</tr>
<tr>
<td>ΔHR (beats/min)</td>
<td>±1.7</td>
<td>±2.04</td>
<td>±1.03</td>
<td>±2.0</td>
<td>±4.13</td>
<td>±3.81</td>
</tr>
<tr>
<td>ΔTPR (mm Hg kg min/liter)</td>
<td>±22.81</td>
<td>±28.05</td>
<td>±48.66</td>
<td>±40.7</td>
<td>±161.68</td>
<td>±190.15</td>
</tr>
</tbody>
</table>

Values are means ± SEM.
* Significantly different from change following isotonic saline infusion.

arterial pressure on the logarithm of the changes in plasma vasopressin concentrations (values measured at 30 and 60 minutes being combined) for the two higher infusion rates (above threshold) was $\Delta$MAP = 12.2 log $\Delta$AVP − 14.7 ($r = 0.49, n = 13$). The line crosses the abscissa (“threshold” for mean arterial pressure change) at a plasma AVP concentration of 16 fmol/ml.

The changes in cardiac output and heart rate exhibited negative correlations with the logarithm of the changes in plasma vasopressin concentrations ($r = -0.85$ in both instances, $n = 29$). Total peripheral resistance (TPR) exhibited nonlinear changes with infusions of 1000 and 5000 fmol/kg per min. For that reason, the regression of the changes in resistance on the logarithm of plasma AVP concentration changes has been calculated only for the three lowest infusion rates and was ATPR = 134 log $\Delta$AVP + 77.8 ($r = 0.57, n = 16$).

**Hemodynamic Effects in Baroreceptor-Denervated Dogs**

Table 3 summarizes all the results obtained with various infusion rates and shows that a significant increase in mean arterial pressure was observed already with the lowest infusion rate which increased plasma AVP concentration by only 4 ± 0.31 fmol/ml after 60 minutes. Heart rate showed no significant fall, compared with the group receiving isotonic saline, even with the highest infusion rate. Cardiac output did not fall with the lower infusion rates but decreased significantly with the highest rate. However, the changes in output were not as pronounced as in the intact dogs, even in the latter case. Total peripheral resistance increased for all vasopressin infusions, the changes being similar to those observed in intact dogs for similar alterations in plasma vasopressin concentration.

The changes in mean arterial pressure correlated significantly with the logarithm of the changes in plasma vasopressin concentration, and the linear regression calculated for the five infusion rates was $\Delta$MAP = 11.22 log $\Delta$AVP + 5.18 ($r = 0.63, n = 29$). This line crosses the abscissa (“threshold”) at a plasma concentration of 0.34 fmol/ml, about 50 times less than in intact dogs. The slope is not significantly different from that of the same regression calculated for intact dogs above threshold.
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<table>
<thead>
<tr>
<th>TABLE 3  Changes in Mean Arterial Pressure (ΔMAP), Cardiac Output (ΔCO), Heart Rate (ΔHR), and Total Peripheral Resistance (ΔTPR) Induced by iv Infusions of Vasopressin in Baroreceptor-Denervated Dogs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rate of vasopressin infusion (fmol/kg per min)</td>
</tr>
<tr>
<td>Isotonic saline</td>
</tr>
<tr>
<td>(n = 7)</td>
</tr>
<tr>
<td>ΔMAP (mm Hg)</td>
</tr>
<tr>
<td>ΔCO (ml/kg per min)</td>
</tr>
<tr>
<td>ΔHR (beats/min)</td>
</tr>
<tr>
<td>ΔTPR (mm Hg kg min/liter)</td>
</tr>
</tbody>
</table>

Values are means ± SEM.
* Significantly different from change following isotonic saline infusion.
† Significantly different from change measured in intact dogs following the same infusion.

There was no significant correlation between changes in heart rate and mean arterial pressure (r = 0.12, n = 29) or between changes in cardiac output and pressure (r = -0.29, n = 29).

Humoral Changes
Hematocrit decreased in intact dogs in a dose-related manner. With the highest infusion rate, the change was about 10% (—3.73 ± 0.63 hematocrit units). There were no significant changes in hematocrit in the baroreceptor-denervated dogs.

In both intact and barodenervated dogs, a progressive fall in plasma sodium concentration was measured with increasing rates of vasopressin. With 5000 fmol/kg per min, the change was —0.76 ± 0.22 mM (n = 13, intact and barodenervated combined). The accompanying change in plasma osmolality was —1.05 ± 0.68 mOsm/kg H2O (not significant).

Hypertonic Saline Infusions
Plasma Vasopressin Concentration Changes
From control values reported previously, the infusions of hypertonic saline induced the changes summarized in Table 4. Values for dogs for which no hemodynamic data were collected have been included. Due to the large variability of the responses, many apparent differences did not reach statistical significance. The following trends were observed. First, hypertonic saline infusions induced an increase in plasma AVP concentration. Second, the infusions given into the carotid artery produced changes in plasma AVP concentration that were faster and larger than equivalent infusions given intravenously. In animals in which both routes of administration were used, the difference at 30 and 60 minutes was significantly different in paired analysis. Third, baroreceptor-denervated dogs exhibited larger increases in AVP concentration than did intact dogs in response to hypertonic saline infusion (significant only for infusions of 1.26 M NaCl in paired analysis). Finally, the increase in AVP was larger after 60 than after 30 minutes, but this usually was not significant. Therefore, an average value for the change in plasma AVP concentration was used in the analysis of the hemodynamic effects, as was the case with the vasopressin infusions.

<table>
<thead>
<tr>
<th>TABLE 4  Changes in Plasma AVP Concentration (fmol/ml) Induced by Infusions of Various NaCl solutions into a Carotid Artery (iv) or Intravenously (iv) after 30 and 60 Minutes in Intact and Baroreceptor-Denervated Dogs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infusion</td>
</tr>
<tr>
<td>------------------------------------------------</td>
</tr>
<tr>
<td>n</td>
</tr>
<tr>
<td>0.15 m, iv</td>
</tr>
<tr>
<td>2.52 m, ic</td>
</tr>
<tr>
<td>2.52 m, iv</td>
</tr>
<tr>
<td>1.26 m, ic</td>
</tr>
<tr>
<td>1.26 m, iv</td>
</tr>
</tbody>
</table>

Values are means ± SEM.
* Significantly different from change following infusion of isotonic saline.
† Significantly different from change measured after 30 minutes with the same infusion.
‡ Significantly different from change following the same infusion in intact dogs.
with all infusions, significantly so with the 2.52 M infusion into the carotid artery (ic) (−6.88 ± 2.04 ml/kg per min, n = 7). Total peripheral resistance increased with all infusions, significantly so with 2.52 M ic (+99.32 ± 26.44 mm Hg kg min/liter, n = 7) and with 2.52 M iv (+77.62 ± 15.31 mm Hg kg min/liter, n = 5). Heart rate decreased, but not significantly.

With all four infusions taken together, there were significant correlations between the logarithm of the changes in plasma vasopressin concentration and the changes in cardiac output (r = −0.45, n = 20) on one hand, and total peripheral resistance (r = 0.44, n = 20) on the other hand. The linear regression, ATPR = 40.5 log AAVP + 69.4, had a slope significantly lower than that calculated for vasopressin infusions over a similar range of plasma concentrations (see above). This is illustrated by the finding that total peripheral resistance increased in a similar manner following either a 2.52 M saline infusion into the carotid artery or an intravenous infusion of vasopressin at a rate of 40 fmol/kg per min, even though plasma vasopressin concentration increased about twice as much with the former.

In baroreceptor-denervated dogs, all hypertonic infusions induced an increase in mean arterial pressure that was significant when compared with the isotonic saline infusion for a 2.52 M solution given into the carotid artery (+14.9 ± 5.4 mm Hg, n = 6). Cardiac output and heart rate tended to increase, but not significantly. Resistance increased, significantly so with 2.52 M (+122.9 ± 47.8 mm Hg kg min/liter, n = 6) and 1.26 M (+99.7 ± 45.0 mm Hg kg min/liter, n = 4) into the carotid artery. When we compared intact and baroreceptor-denervated dogs, we found that the four hypertonic saline infusions led to significantly different changes in two instances for mean arterial pressure and heart rate, and in three instances for cardiac output, but in none for resistance.

The changes in mean arterial pressure for the four infusions correlated positively with the logarithm of the changes in plasma AVP concentration in baroreceptor-denervated dogs: ΔMAP = 22.02 log ΔAVP + 1.15 (r = 0.6, n = 19). The slope of this regression was not significantly different from that calculated for exogenous vasopressin infusions. There was also a positive correlation between changes in total peripheral resistance and the logarithm of the changes in plasma AVP concentration, ΔTPR = 179.7 log ΔAVP + 1.1 (r = 0.52, n = 19). The regression coefficient was not significantly different from that found for exogenous vasopressin infusions.

Figure 3 represents the hemodynamic changes observed during the infusion of 2.52 M NaCl into a carotid artery in both intact and barodenervated dogs and compares them with those following two rates of vasopressin infusions producing changes in plasma AVP concentration of comparable magnitude (Fig. 1, Table 4). There is a great similarity in the changes in mean arterial pressure, cardiac output, and total peripheral resistance induced by both types of infusions.

Humoral Changes
Following hypertonic saline infusions, plasma sodium concentration and osmolality increased. The changes in plasma sodium concentration were similar after a given hypertonic infusion into a carotid artery or intravenously, and were also similar in intact and baroreceptor-denervated dogs. The results have therefore been combined in Table 5. The regression of the changes in plasma osmolality (ΔOsm) on the changes in plasma sodium concentration (ΔNa⁺) measured after 60 minutes for all hypertonic and isotonic infusions in intact and baroreceptor-denervated dogs was ΔOsm = 1.48 ΔNa⁺ − 0.39 (r = 0.71, n = 64).
We found that plasma vasopressin changes correlated significantly with plasma sodium and osmolarity changes, but the correlation was higher with sodium. In both intact and baroreceptor-denervated dogs, the slope of the linear regression of AVP changes on plasma sodium changes was significantly steeper for the intracarotid than for the intravenous infusions, especially for the changes measured after 30 minutes. For instance, in barodenervated dogs, the relation at 30 minutes was \( \Delta \text{AVP} = 3.31 \Delta \text{Na}^+ - 0.7 \) \((r = 0.53)\) for all intracarotid infusions and \( \Delta \text{AVP} = 0.76 \Delta \text{Na}^+ + 0.10 \) \((r = 0.57)\) for all intravenous infusions of hypertonic solution. This indicates that the mechanism responsible for AVP release in response to plasma sodium concentration changes was stimulated more with the intracarotid infusion.

Second, the slope of the regression of \( \Delta \text{AVP} \) on \( \Delta \text{Na}^+ \) tended to be higher in barodenervated than in intact dogs. Thus, the relation for all intracarotid infusions of hypertonic solutions in intact dogs at 30 minutes was \( \Delta \text{AVP} = 1.9 \Delta \text{Na}^+ + 0.21 \) \((r = 0.44)\), with a smaller coefficient of regression than that observed in barodenervated dogs (see above). However, the difference was not significant.

Plasma potassium tended to decrease with hypertonic saline infusions, but this was significant in only a few instances. Hematocrit did not change.

**Discussion**

Our study demonstrates that infusions of vasopressin which merely double its plasma concentration have significant hemodynamic effects in conscious dogs. Our results also suggest that similar hemodynamic changes follow the release of vasopressin in response to osmotic stimuli.

In dogs with intact baroreceptor reflexes, no sizeable changes in mean arterial pressure were induced by vasopressin concentration changes thought to represent the physiological range of variation in osmotic regulation (a 10-fold increase from control value corresponding to maximal antidiuresis according to Robertson et al., 1978). However, cardiac output decreased and total peripheral resistance increased for increments of plasma vasopressin well within this range. Destruction of the baroreceptor feedback loop made the cardiovascular impact of these physiological levels of vasopressin even more evident since blood pressure increased. Our results therefore confirm the tremendous increase in sensitivity (about 50 times) to the pressor action of vasopressin which follows baroreceptor denervation, described by Cowley et al. (1974). As these authors did not measure plasma vasopressin levels in their animals and did not use infusion rates as low as those given in the present study, our results add strength to their assumption that physiological levels of vasopressin do increase arterial pressure in barodenervated dogs. On the other hand, our data disprove the suggestion by Cowley et al. that baroreceptor-denervated dogs might have depressed control levels of vasopressin which could explain the enhanced pressor sensitivity to infused vasopressin.

Cowley et al. (1974) did not find any significant difference in the cardiac output response to vasopressin in two dogs before and after barodenervation. This result implied markedly different changes in total peripheral resistance in the two states, because blood pressure increased much more following baroreceptor denervation. We had anticipated the same result because the baroreceptor reflex should, in response to a pressor agent, decrease sympathetic tone to various cardiovascular target organs, including arterioles. Thus, for a similar degree of drug-induced arteriolar constriction, animals with intact reflexes should exhibit lesser increases in vascular resistance.

However, we found that total peripheral resistance increased similarly in intact and baroreceptor-denervated dogs. Another result which may be difficult to interpret is the fall in cardiac output resulting from small amounts of vasopressin in intact dogs. As there is no such decrease in output following baroreceptor denervation, this would appear to be a reflex change, especially when one considers the accompanying fall in heart rate. However, there was no significant increase in mean arterial pressure with the three lowest infusion rates of vasopressin, and no significant correlation between cardiac output and arterial pressure changes.

These results suggest that vasopressin and the baroreceptor reflex interact in a particular way, as recently discussed (Liard, in press). The hypothesis is that vasopressin acts somewhere along the baroreceptor feedback loop to modify the effect of ar-
terial pressure on the activity of the vasomotor center and the center controlling vagal tone in such a way that a greater inhibition of the sympathetic tone and/or a greater stimulation of the vagal tone be obtained for a given pressure at the receptor level. The finding that resistance increases as much in the intact as in the barodenervated animals suggests that vasopressin does not act at the level of the baroreceptor nerve endings but, instead, acts centrally, predominantly on components controlling heart rate and cardiac output. Thus, the effect of low infusion rates of vasopressin would be a centrally mediated fall in cardiac output and a peripherally determined increase in vascular resistance, amounting to unchanged pressure. Suppression of the central effect by removing the baroreceptor afferents would leave only the effect on peripheral resistance and produce an increase in arterial pressure. This is what has been observed in barodenervated dogs. Conversely, central application of vasopressin in this hypothesis should lead to a decrease in cardiac output and arterial pressure. There are some indications that such a central effect exists. Nashold et al. (1962) reported that injection of vasopressin into the left lateral ventricle of anesthetized cats produced a prompt fall in blood pressure (although a larger dose increased the pressure). Varma et al. (1969) indicated that vasopressin had a central stimulating action on the cardioinhibitory neurons in the region of the vagal nuclei. The effect of vasopressin on heart rate in the study by Youmans et al. (1952) persisted after sinoaortic denervation. Apparently, our infusion rates were too low to elicit such an effect.

It should be noted that, with large infusion rates, part of the fall in cardiac output clearly is not related to the baroreceptor reflex, since it occurs also in baroreceptor-denervated dogs. This may result from increased afterload, from increased resistance to venous return to the heart, or from an effect of vasopressin on myocardial contractility (Nakano, 1974).

The present results also suggest that vasopressin released in response to osmotic stimuli may have hemodynamic effects in normal animals. Intracarotid hypertonic infusions were used to increase vasopressin release for a similar change in systemic osmolality and to detect hemodynamic effects unrelated to changes in vasopressin concentration. Despite the fact that the range of variation was rather limited, the significant correlation between AVP and hemodynamic changes in both intact and barodenervated dogs indicates that at least part of the hemodynamic effects were brought about by vasopressin. Still, other factors could have contributed to the cardiovascular action of hypertonic infusions into the carotid artery, since a variety of effects result from this type of maneuver (Zucker and Kaley, 1976; Wood et al., 1977; Gallego and Belmonte, 1979; Feldberg and Wei, 1979).

In dogs with intact baroreceptor reflexes, the changes in peripheral resistance for a given vasopressin concentration increase were not as pronounced following hypertonic saline solutions as after exogenous vasopressin. This was not the case in baroreceptor-denervated dogs, which seems to exclude the possibility that plasma sodium or osmolality changes partially blunted the effects of vasopressin. One possible explanation is that the hypothetical mechanism of vasopressin acting centrally also involves nervous projections (possibly vasopressinergic) on central structures of the baroreflex. These projections would be activated when an osmotic stimulus releases vasopressin and acts to limit blood pressure changes. Such vasopressin pathways are known to be present, although their functional significance is not clear (Buijs, 1978; Sofroniew and Weindl, 1978).

Bie (1977) recently has questioned the localization of the osmoreceptors in the area supplied by the common carotid arteries in dogs, established by Verney (1947). On the whole, our results support Verney’s conclusions, especially when one considers the difference in plasma vasopressin concentration at 30 minutes after intravenous or intracarotid administration of hypertonic saline.

The study of the disappearance rate of vasopressin indicated that this substance persisted for prolonged periods following the end of an infusion, and we found a component with a much longer half-life than most published values, which are usually around 5 minutes in dogs (Lauson, 1974). Similar results were recently reported by Cowley et al. (1980). The values for the plasma clearance found in this study are consistent with most previously reported data (Lauson, 1974). Contrary to a recent report by Weitzman and Fisher (1978), we found no evidence that clearance varied with increasing rates of infusion, with the one exception of the baroreceptor-denervated dogs receiving 40 fmol/kg per min. However, this may result from failure to take into account the endogenous secretion rate. Calculated from the average clearance found with high infusion rates (when endogenous secretion is negligible) and the control plasma concentration of vasopressin preceding the 40 fmol/kg per min infusion, endogenous secretion was 17.3 ± 3.5 fmol/kg per min. Added to the nominal infusion rate, this secretion changed the calculated clearance to 11 ± 0.6 ml/kg per min, a value that did not differ from all other clearances calculated. On the other hand, when we added the calculated endogenous secretion rate (25.5 ± 5.3 fmol/kg per min) to the nominal infusion rate of 40 fmol/kg per min in dogs with intact baroreceptors, we found a clearance of 18.3 ± 2.2 ml/kg per min, a value significantly above those found with higher infusion rates. We interpret these results as indicating that plasma clearance of vasopressin is actually constant and that, in intact dogs, the infusion of vasopressin suppresses the
release of endogenous vasopressin whereas, in barodenervated dogs, it leaves it largely unaffected. This would indicate that a negative feedback of plasma vasopressin concentration on its release is lost at least partly dependent upon afferents destroyed by our denervation procedure. The results obtained with hypertonic saline infusions suggest that such a mechanism might operate also in response to osmotic stimuli (see Table 4).

In conclusion, we have measured in conscious dogs hemodynamic effects associated with plasma concentrations of vasopressin previously thought to be devoid of cardiovascular action. Our study does not indicate that vasopressin normally is involved in blood pressure control, since its pressor effect is antagonized so effectively by the baroreflex. However, a similar antagonism does not necessarily exist in hypotensive situations, when both the baroreceptor reflex and vasopressin release could act together to correct the blood pressure change. This is clearly suggested by the findings by Laycock et al. (1979) that vasopressin plays an important role in the regulation of pressure following hemorrhage. It is possible that failure of the baroreceptor reflex to antagonize the pressor effects of vasopressin in response to stimuli such as plasma osmolality changes accounts for the role of vasopressin in maintaining high blood pressure in some forms of experimental hypertension (Möhring, 1978). Another intriguing possibility is that vascular effects of vasopressin are of physiological importance only in some regional beds.

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