Influence of Vasopressin and Angiotensin on Baroreflexes in the Dog

Allen W. Cowley Jr., David Merrill, John Osborn, and B. J. Barber
From the Department of Physiology, Medical College of Wisconsin, Milwaukee Wisconsin

SUMMARY. Cardiovascular responses to step-changes of carotid sinus pressure were evaluated at normal and elevated levels of plasma arginine vasopressin in anesthetized neurohypophysectomized dogs (n = 12). Arginine vasopressin influenced autonomic function in two ways: first, maximum carotid reflex gain increased; second, cardiac output was decreased. The enhancement of reflex strength was observed only in response to decreases of intrasinus pressure below the equilibrium point (pressures of between 60 and 105 mm Hg). Aortic pressure rose twice as high for a given decrease of intrasinus pressure, elevations of total peripheral resistance responses were triple those observed at normal plasma arginine vasopressin. In this way, arginine vasopressin more than doubled the ability of the carotid reflexes to return a drop in arterial pressure to normal. Arginine vasopressin enhancement of reflex gain was not observed with elevations of intrasinus pressures above the equilibrium point. Elevation of aortic pressure expected from the vasoconstrictor actions of infused arginine vasopressin were buffered by associated reductions in cardiac output. Vagally mediated bradycardia was consistently observed with elevated arginine vasopressin, but the reflex response of heart rate to step-changes of intrasinus pressure was unchanged. Time control studies in five neurohypophysectomized dogs indicated no significant change in carotid reflex response over the 3- to 4-hour protocol. Comparison of reflex responses in anephric dogs (n = 8) at low and elevated levels of angiotensin II indicated that this vasoactive peptide did not significantly alter reflex responsiveness. We conclude that arginine vasopressin enhances the ability of the carotid reflexes to normalize decreases of arterial pressure, but buffers a rise in pressure from its own vasoactive properties by initiating a fall of cardiac output. (Circ Res 54:163-172, 1984)

The present studies were designed to determine the influence of arginine vasopressin (AVP) on the carotid baroreceptor reflex control system. It has long been known that ganglionic blockade could enhance vasopressin pressor activity, an observation which was applied to increase the sensitivity of pressor AVP bioassay procedures in the past (Saameli, 1968). More recently, comparison of AVP dose-response relationships in conscious normal vs. sinoaortic baroreceptor-denervated dogs has shown an enhancement of pressor sensitivity that is far greater than that observed with either angiotensin II or norepinephrine (Cowley et al., 1974; Cowley and DeClue, 1976; Mohring et al., 1980; Montani et al., 1980). These studies have suggested that AVP could in some manner enhance the strength of the autonomic reflexes to buffer changes of arterial pressure induced by its vasoconstrictor actions.

In the normal state, the inability of even large elevations of plasma AVP to substantially increase arterial pressure is clearly related to the presence of the sinoaortic baroreflex system (Cowley et al., 1974; Cowley and DeClue, 1976; Montani et al., 1980). Studies in conscious dogs by Montani et al. (1980) demonstrated that AVP administration resulted in a reflex-mediated fall of cardiac output offsetting the elevation of arterial pressure, which would otherwise be expected with the observed increase in total peripheral resistance. In chronic sinoaortic baroreceptor-denervated dogs, the AVP-induced decrease in cardiac output did not occur, so that elevations of arterial pressure were observed with only slightly elevated plasma AVP levels (10 pg/ml). The extent to which these observed responses were directly dependent on AVP-induced alterations of the baroreflex sensitivity is unknown.

The present studies were designed to quantify the influence of elevations of plasma AVP on the open-loop feedback gain of the carotid sinus baroreflexes. Anesthetized neurohypophysectomized dogs were studied with the carotid sinus regions isolated bilaterally and blood perfused. The systemic hemodynamic reflex responses to step-changes of intrasinus pressure were determined at normal and elevated levels of plasma AVP. Changes of plasma AVP over the physiological range were achieved in the neurohypophysectomized dogs with intravenous infusion of AVP. These results were compared with those obtained in an anephric group of dogs with low and elevated levels of plasma angiotensin II (AII). Time control studies were also performed.

Methods

Selective Neurohypophysectomy

Three to 4 days before the acute experimental studies, 12 mongrel dogs were anesthetized with sodium pentobarbital (30 mg/kg), and the neurohypophyses were re-

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moved using a transpharyngeal approach. For this procedure, the adenohypophysis was transected in an anterior to posterior direction and the underlying neurohypophysis removed selectively with a small suction pipette. The postoperative physiological state was used to determine the success of this procedure, since gross examination of histological sections was not definitive. Post-surgical daily urine excretion rates ranged from 3 to 8 liters/day over the 3 days of recovery, with urine osmolalities ranging from 40 to 60 mOsm/kg. The 3-day recovery period enabled natural repletion of body fluid volumes by drinking, and enabled better maintenance of arterial pressure during the control period of the acute experimental procedures. Steroid replacement was not required, since the major portions of the adenohypophysis remained intact. Plasma cortisol levels measured in three of the dogs ranged from 0.5 to 0.8 μg/100 ml.

Protocol for Vasopressin Study

Mongrel dogs (n = 12) were anesthetized with sodium pentobarbital (30 mg/kg), and catheters were placed in the abdominal aorta and inferior vena cava from the femoral vessels. An intravenous saline drip (0.9%) was started immediately at a rate of 2-3 ml/min and continued until the time of AVP infusion when it was decreased to 1 ml/min. A left thoracotomy was performed in six of the 12 dogs for placement of an electromagnetic flow probe on the root of the ascending aorta for measurement of cardiac output. The chest was then closed, evacuated, and the animal permitted to breathe spontaneously.

The carotid sinus regions were then isolated bilaterally so that intrasinus pressure and systemic arterial pressure could be controlled independently. The external carotids were catheterized to divert blood flow back to the systemic circulation via a jugular vein. An extruded glass tube was placed in the circuit to elevate outflow resistance. Catheters were placed in the proximal portions of the common carotids at the base of the neck, from which blood was diverted to a peristaltic infusion pump (Renal Systems Inc., model RS-7800). Blood was returned by the pump to the common carotids at a slightly more distal site. All other branches of the carotid arteries were ligated, including the thyroid branches. The internal carotid and occipital arteries were ligated 8-10 mm from their origin to avoid disruption of neural innervation of the carotid sinus regions. The left vagal-sympathetic nerve and the medial one-third portion of the right vagal-sympathetic bundle then were transected in the lower portion of the neck. We have shown in previous studies that this procedure removes the major portion of the aortic arterial baroreceptor control (Liard et al., 1974).

Intrasinus pressure was determined by the rate of blood flow returning from the pump to the distal portion of the common carotids with a fixed outflow resistance. Pulsa-

tions from the peristaltic movement of the pump resulted in a constant pulse pressure of nearly 40 mm Hg with a pulse frequency ranging from 30 to 70 pulsations per minute over the ±40 mm Hg range of intrasinus pressures used in the study. Flow rates ranged from 50 to 250 ml/min. The same procedure was used during both the control curves and experimental (AVP and All) curves. In four dogs, results were compared with those in which mean intrasinus pressure was determined only by altering resistance in the outflow line using a constant pump speed. Although the influence of frequency per se was not rig-
orously evaluated, the aortic pressure responses to changes of intrasinus pressure did not appear to differ from similar changes made by altering pump speed. Dogs were hepa-
rinized with 6000 USP units of heparin just before per-
fusion of the carotid sinus regions was begun.

Intrasinus mean pressure was brought into equilibrium with the mean aortic pressure in the open-loop state by appropriate adjustment of the perfusion pump, and this pressure level was defined as the "equilibrium point" of the baroreflex system. That is, intrasinus pressure elevations above the "equilibrium point" resulted in lowering of systemic arterial pressure, and intrasinus pressures below that point raised systemic arterial pressure. Step-decreases or increases of 10-20 mm Hg, each 5 minutes long, were then applied between intrasinus pressures of 40 and 160 mm Hg. The choice of initially decreasing or increasing carotid sinus pressures was determined randomly. Intrasinus and systemic arterial pressures were brought into equilibrium each time before the ISP was forced into the opposite direction. In this way, both hys-
teresis and time-related changes in the "equilibrium point" of the reflex could be assessed at the beginning, midpoint, and end of each forcing function. Changes in aortic pressure were determined from the initial "equilibrium point" for the first half of the curve and the "mid-equilib-
rium point" for the second part of the curve. If this value differed by more than 10 mm Hg during the course of each complete curve, the data were discarded. The entire results of experiments on eight dogs were eliminated on the basis of a progressive decline of the equilibrium pres-
sure level throughout the protocol. At the end of each forcing function, a 7-ml arterial blood sample was taken for analysis of plasma AVP, using radioimmunoassay techniques developed in our laboratory and described previously (Cowley et al., 1981).

The control carotid sinus forcing functions were first performed at the plasma AVP level determined by pre-

ving secretion rates from the severed stalk of the neu-
rohypophysis. Synthetic arginine vasopressin (Parke-
Davis; 85% purity) was then infused at either 0.5-1.0 or

5.0-10.0 ng/kg per min for 1 hour prior to and during the next forcing function. Aortic pressure responses to step-
changes of carotid sinus pressure were again evaluated at the elevated plasma AVP level, and a plasma sample was again obtained for analysis of AVP at the end of the forcing function.

The open-loop feedback gain of the baroreceptor reflex control of arterial pressure was determined by the ratio of the change in mean arterial pressure to the corresponding change in mean intrasinus pressure, as defined by linear control theory (Milhorn, 1966). Cardiac output was determined using a Gould-Statham electromagnetic flow meter. Integrated mean flow was recorded at each step of the forcing function, together with phasic aortic flow, which provided an estimation of base line throughout the period of measurement based on end-distolic aortic blood flow. Systemic arterial and intrasinus pressures were recorded using Statham (model DC23) arterial pressure transducers. Signals from both flow and pressure transducers were recorded using a Grass polygraph (model 7D). Total per-

ipheral resistance was calculated as the quotient of mean arterial pressure (mm Hg) divided by mean cardiac output (ml/min). For graphic presentation of these data (Figs. 4 and 5), we first normalized arterial pressure and flow by setting each control value equal to the group average and 5), we first normalized arterial pressure and flow by setting each control value equal to the group average and setting each control value equal to the group average.
Protocol for "Time Control" Study

Five dogs underwent selective neurohypophysectomy as described above and, on the 3rd day of recovery, were anesthetized with sodium pentobarbital (30 mg/kg). The carotid sinus regions were isolated for perfusion, and two complete reflex function curves were determined at 60- to 90-minute intervals in the absence of infused AVP. As with the AVP studies, intravenous infusion of isotonic saline at a rate of 2–3 ml/min was started upon insertion of the femoral venous catheter and continued throughout the first control curve. During the remaining time, 1 ml/min was administered. Mean right atrial pressure was recorded continuously throughout the study in three dogs from a catheter inserted from a femoral vein.

As described for the preceding studies, changes in aortic pressure were determined from the initial "equilibrium point" for the first half of the curve and the "mid-equilibrium point" for the second part of the curve. If this value differed by more than 10 mm Hg during the course of each complete curve, the data were discarded.

Protocol for Angiotensin Study

Another group of six mongrel dogs were anesthetized with sodium pentobarbital (30 mg/kg) to study the influence of angiotensin on carotid reflex function. Catheters were first placed in the abdominal aorta and inferior vena cava from a femoral artery and vein, as before. A bilateral nephrectomy was then performed using retroperitoneal flank incisions. A 0.9% saline drip at 2.0 ml/min was administered until completion of the nephrectomy. The carotid sinus regions were bilaterally isolated, and the left cervical vagal-sympathetic trunk and medial one-third portion of the right vagal-sympathetic trunk and medial one-third portion of the right vagal-sympathetic bundle were cut as before. Two hours following nephrectomy, intrasinus arterial pressure was varied in steps above and below the equilibrium point in identical fashion to the AVP and "time control" studies. Following the control curve, a 1-hour infusion of angiotensin II (Ciba; 85% purity) at 20 ng/kg per min was begun and the reflex responses were determined again.

All data are reported as mean ± SEM. Student's t-test for paired data was used to compare the changes from the equilibrium pressure at each level of carotid sinus pressure during both the control and experimental states. Probability was considered significant if the P value was less than 0.05.

Results

Response to Vasopressin

Carotid sinus reflex responses were studied at the three levels of plasma AVP indicated in Figure 1. Endogenous plasma AVP measured at the end of the control period averaged 6.3 ± 1.2 pg/ml (n = 12). One hour AVP infusion at a rate of 0.5–1.0 ng/kg per min yielded average plasma AVP levels of 51.6 ± 15.0 pg/ml (n = 7), whereas infusions at a rate of 5–10 ng/kg per min yielded levels of 455 ± 91 pg/ml (n = 4). Since no significant differences were seen in reflex responses at plasma AVP concentrations between 51 and 455 pg/ml, the results of these two groups were combined and will be referred to as the "elevated AVP* group.

Figure 2 compares the average 3- to 5-minute steady state responses of mean arterial pressure to changes of intrasinus pressure at normal and elevated levels of plasma AVP. The control mean arterial pressure level (equilibrium point) averaged 105 ± 2 mm Hg, and this pressure level was not changed statistically by the infusions of AVP. At normal levels of AVP, a typical inverse sigmoidal relationship was observed relating changes in intrasinus and mean aortic pressure. Elevations of plasma AVP resulted in substantial enhancement of aortic pressure responses in each of the 12 dogs when intrasinus pressure was decreased from the "equilibrium point." The rise of aortic pressure was 2 to 3 times as great as the input change in intrasinus pressure. Thus, for each mm Hg decrease of intrasinus pressure, aortic pressure rose 2 to 4 mm Hg. The enhancement of the systemic pressure response was significantly greater (P < 0.05) at all levels of intrasinus pressure less than 105 mm Hg. However, systemic responses to increases in intrasinus pressure above the equilibrium point were not altered by elevations of plasma AVP.
The aortic pressure responses observed during the initial 30–45 seconds after the step-changes of intrasinus pressure were also determined. As seen with the steady state responses, elevation of AVP enhanced the reflex gain only when intrasinus pressure was lowered from the equilibrium point. At normal levels of plasma AVP, a mild overshoot was sometimes observed, but this initial response was not statistically greater than the steady state response except at the intrasinus pressure steps in the range of ±50 mm Hg (i.e., the extreme range of the curve). Infusion of AVP resulted in greater initial decreases in aortic pressure when intrasinus pressure was raised which significantly exceeded (P < 0.05) the steady state responses. These responses exceeded the steady state responses by 35–40% at each of the intrasinus step-changes between +10 and +60 mm Hg above the equilibrium point. Such differences between the initial and steady state aortic pressure responses were not observed when intrasinus pressure was lowered in steps below the equilibrium point. In about one-third of the dogs, in the presence of elevated AVP, aortic pressure often continued to increase over the entire 3 minutes following the step-decrease of intrasinus pressure so that the steady state response was, on the average, greater than the initial response. It was also observed that infusion of AVP often resulted in arterial pressure oscillations (±10–15 mm Hg) with a frequency of 20–30 seconds.

Figure 3 compares the average open-loop feedback gain of carotid baroreflexes at normal and elevated levels of AVP between mean intrasinus pressures of 40 to 160 mm Hg. The maximum reflex gain obtained at normal plasma AVP levels averaged 1.8 ± 0.2, and increased to 3.9 ± 0.7 at elevated plasma AVP levels (P < 0.001). This enhancement of reflex strength with elevations of plasma AVP occurred at intrasinus pressures between 85 and 105 mm Hg. At normal plasma AVP levels, the maximum gain was extended over a wider range than at elevated AVP levels. The differences in reflex gain at normal and elevated AVP levels were significantly greater (P < 0.05) at all levels of intrasinus pressure less than 105 mm Hg.

The relationship between total peripheral resistance (TPR) and intrasinus pressure at normal and elevated plasma AVP is summarized in Figure 4. Several things are apparent from these data. First, elevation of plasma AVP to 116 ± 67 pg/ml resulted in a significant increase of systemic vascular resistance (P < 0.05) at all levels of intrasinus pressure. Second, a 50% elevation of TPR occurred in the absence of a significant change in the control level of mean arterial pressure. Third, with decreases of intrasinus pressures from equilibrium point, the increases of TPR were nearly 3 times greater at elevated plasma AVP than the changes observed at normal AVP levels. Fourth, with elevations of intra-
sinus pressures above the equilibrium point, the corresponding changes of TPR were less than those seen when intrasinus pressure was lowered and nearly equal at both levels of plasma AVP.

Figure 5 summarizes the changes of cardiac output as intrasinus pressure was changed at the two levels of plasma AVP. It is seen that at normal levels of plasma AVP cardiac output remained relatively unchanged at intrasinus pressures between 60 and 130 mm Hg, above which there was a tendency to decrease. Elevation of plasma AVP resulted in a substantial reduction of cardiac output from an average of 1241 ± 179 to 866 ± 70 ml/min at the equilibrium point (P < 0.05). Flow was only minimally influenced by changes of intrasinus pressure over the range that was studied. At higher levels of intrasinus pressure, cardiac output tended to increase, but these changes were not statistically significant.

Figure 6 summarizes the average changes of heart rate with changes of intrasinus pressure at normal and elevated levels of plasma AVP. An inverse relationship was obtained between intrasinus pressure and heart rate at both normal and elevated AVP levels. Elevation of plasma AVP, however, resulted in a significant decrease in heart rate from 156 to 133 beats/min (P < 0.05) at the equilibrium point. This difference in heart rate between normal and elevated AVP levels was maintained over the entire range of intrasinus pressures. Unlike the systemic vascular responses, a nearly parallel shift of the curve was observed, indicating that reflex heart rate responses were not enhanced by elevations of plasma AVP. In addition, it was observed in five of these dogs that, when the remaining right vagal-sympathetic nerve trunk was totally transected at the completion of the study, heart rate returned to the values seen at the normal plasma AVP levels despite continued infusion of AVP. Total vagotomy in these dogs did not substantially alter the reflex induced changes of heart rate seen with changes of intrasinus pressure, however. As intrasinus pressure was lowered ±40 mm Hg in steps above and below the equilibrium point, heart rate changed an average of ±22 beats/min (P < 0.05) from the average control of 164 ± 15 beats/min. These changes were comparable to those seen in Figure 6 before total elimination of the right cervical vagus nerve.

**“Time Control” Study**

To ensure that the above results seen with AVP infusion were not time-dependent changes in the strength of the reflex mechanisms, time control studies were performed in another group of neurohypophysectomized dogs. The results of these studies summarized in Figure 7 indicate a slight decline...
in the strength of the reflexes over a 3-hour experimental period following the completion of surgery. However, no statistical difference was observed at any of the step-changes between curves number 1 and 2, run 60–90 minutes apart. Dogs in which equilibrium pressures exceeded 10 mm Hg within individual curves were discarded. Control equilibrium pressure valves did differ between curve 1 and 2, averaging 117 ± 6.0 mm Hg before the first reflex curve, compared with 90 ± 7 mm Hg at the completion of the second reflex curve (P < 0.05). This decline was not observed in dogs infused with either AVP or All. Heart rate responses were similar to those shown in Figure 6 during the control period. Mean right atrial pressure averaged 5.0 ± 0.2 mm Hg during the first control reflex curve and 4.5 ± 0.2 mm Hg during the second control reflex curve, but the difference did not reach statistical significance. Plasma AVP averaged 8.9 ± 2.5 and 11.3 ± 0.7, respectively, at the completion of first and second reflex curves (not statistically different). These results support our impression that there was a general tendency for a gradual decline of the strength of the reflexes in these studies. The observed enhancement of the reflex gain with elevated AVP therefore probably underestimates the AVP enhancement of the reflex gain shown in Figures 2–4.

**Angiotensin Infusion**

The influence of angiotensin II on carotid sinus reflex gain is summarized in Figure 8. At low post-nephrectomy plasma All levels, the equilibrium pressure for the control curves averaged 98.6 ± 4.7 mm Hg compared to 107 ± 4.8 (P < 0.05) during the All infusion period. No substantial differences were observed in the carotid reflex responses between low and elevated levels of All. There was a tendency for the amplitude of the aortic pressure rise to be diminished at intrasinus pressures below the equilibrium point, but this reached statistical significance only at one step (ISP = −20 mm Hg).

Heart rate averaged 124.8 ± 5.9 beats/min at equilibrium pressures for the control curves and 123.6 ± 7.4 beats/min at elevated levels of All. No significant differences in heart rate responses were observed with elevation of All. Heart rate changed an average of ±16 beats/min as intrasinus pressure was varied ±40 mm Hg around the equilibrium point, similar to those seen during the control curve of Figure 2.

**Discussion**

The present study was designed to determine whether physiological changes in plasma AVP could alter baroreceptor reflex function. Two major influences on autonomic function were observed—one upon maximum carotid reflex gain and the other upon cardiac output. An enhancement of reflex gain was observed in response to decreases of intrasinus pressure below the equilibrium point. Elevation of plasma AVP more than doubled the maximum strength of the reflex system between intrasinus pressures of 60–105 mm Hg. That is, aortic pressure rose twice as high for a given decrease of intrasinus...

![Figure 7](image_url) **FIGURE 7.** Time control study comparing response of the mean arterial pressure (±SEM) to changes of mean intrasinus pressure (ΔISP ± SEM) in five anesthetized neurohypophysectomized dogs. "Control #1" curve was run first, followed by "Control #2" curve 60–90 minutes later.

![Figure 8](image_url) **FIGURE 8.** Response of the systemic mean aortic pressure (±SEM) to step-changes of intrasinus pressure (ΔISP ± SEM) at normal and elevated levels of angiotensin II. The equilibrium point at low concentrations of All averaged 98.6 ± 4.7 mm Hg compared to 107 ± 4.8 at elevated levels of All.

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pressure. AVP influence on reflex responsiveness was even more apparent when represented as changes in total peripheral resistance. Peripheral resistance responses with elevated AVP were triple those observed at normal AVP. This does not appear to be characteristic of vasoconstrictor agents in general, as seen by the failure of comparable amounts of angiotensin II to alter the strength of the reflex. This appears to be the case with norepinephrine as well, which we studied in three anephric dog preparations in the same manner as AlI. Norepinephrine infused at 0.19 ng/kg per min increased the equilibrium pressure nearly 15 mm Hg and tended to decrease the maximum gain of the carotid sinus reflex. We are unaware of any other circulating hormone that is capable of influencing the reflex system to the extent observed with AVP.

The time control studies indicated that over the 3-hour period of the study, the reflex responses of the neurohypophysectomized dogs remained relatively constant, although there was a tendency for the reflex to decline in strength. These data indicate that the enhanced strength of the baroreceptor reflex observed at elevated levels of plasma AVP was indeed a result of the vasopressin per se, and not due to time-related changes either in the reflex controllers or physiological state of the dogs.

AVP enhancement of carotid reflex gain was not observed with step increases of intrasinus pressures above the equilibrium point. Elevations of aortic pressure expected from the vasoconstrictor actions of AVP were buffered by a second major mechanism. Specifically, there was a reproducible decrease of cardiac output when plasma AVP was increased. A fall of cardiac output and the associated bradycardia (Figs. 5 and 6) has been observed previously (Szczepanska-Sadowska, 1973; Montani et al., 1980) with moderate increases of plasma AVP. Suppression of cardiac output did not occur in conscious dogs in which the sinoaortic baroreceptors had been surgically removed (Montani et al., 1980). This influence of AVP somewhere upon the reflex pathway appears to provide a potent neural pathway whereby elevations of arterial pressure in response to AVP vasoconstrictor actions can be effectively blunted. Thus, although AVP enhancement of carotid reflex gain was not observed as intrasinus pressure was raised above the equilibrium point, the net effect of AVP was to initiate changes in autonomic function which buffered the rise of aortic pressure. In the absence of all autonomic reflexes, we have shown that the elevations of plasma AVP reached at the lower level of infusion in the present study (50 pg/ml, Fig. 1) result in elevations of mean arterial pressure in excess of 40 mm Hg (Cowley et al., 1980; Cowley, 1982).

The precise mechanisms whereby AVP induced alterations of autonomic function and a decreased cardiac output were not determined in the present study. We have presented recently a theoretical analysis of the potential mechanisms which could be mediating this response (Cowley and Barber, 1983).

The average equilibrium point in the present study was undoubtedly influenced by a number of factors including the barbiturate anesthetic and the pulsatile nature of the carotid perfusion system (Sagawa, 1983). Furthermore, the reflex changes observed in these studies were probably influenced to some extent by the increased frequency of the perfusion pump at the higher levels of carotid sinus pressure. Although this would tend to flatten the curve as pressure was varied first with pump speed and then by altering outflow resistance at a fixed pump speed and only minor differences (between 5 and 10 mm Hg) were observed. Since pulsatile pressures were applied in the identical way during all forcing functions, this should not explain the enhanced gain observed at elevated plasma AVP levels.

As we and others have observed previously, elevations of plasma AVP were associated with a vagally mediated bradycardia (Varma et al., 1969; Cowley et al., 1974; Montani et al., 1980). Unlike the reflex control of arterial pressure, however, heart rate responses to changes of intrasinus pressure were similar at both normal and elevated levels of plasma AVP, as seen by the relatively parallel shift of the curves in Figure 6. Since similar reflex-mediated changes in heart rate were observed with total cervical vagotomy, it appears that most of the reflex changes associated with changes of intrasinus pressure were sympathetically mediated, whereas the generalized bradycardia was vagally mediated.

### Importance of Neurohypophysectomy

Preliminary studies in our laboratory indicated that it was important to eliminate the endogenous AVP secretion associated with the surgical preparation of these studies. In a preliminary study with four normal anesthetized dogs, intravenous infusion of AVP appeared to have no effect on systemic arterial pressure response to complete occlusion of the common carotid arteries. This was not particularly surprising, in view of the surgical stress of the procedures, since we had shown previously that intramuscular administration of Pitressin before intravenous AVP infusions obviated expected changes of arterial pressure in conscious baroreceptor-dener- vated dogs (Cowley et al., 1974). It is assumed that the high level of AVP receptor occupancy probably accounted for the lack of pressor responsiveness in these studies. Therefore, in the present studies, selective neurohypophysectomy was performed to enable the plasma AVP levels to be maintained within normal physiological limits during characterization of the reflex gain. Although this procedure did not
completely inhibit AVP release during surgical stress, the response was greatly blunted, and plasma AVP levels were maintained within a range seen in normal conscious dogs. It is presumed that these AVP levels resulted from portions of neuronal fibers remaining in the region of the median eminence.

**Influence of Angiotensin**

Elevation of plasma angiotensin II did not result in a significant change in the overall strength of the carotid sinus reflexes. Mild attenuation of baroreceptor-mediated reflex vasodilation and enhanced baroreceptor-mediated reflex vasoconstriction has been reported by others (Goldstein et al., 1974; Sweet and Brody, 1970). The amount of AVI infused in the present study has been shown to result in a substantial increase of total peripheral resistance (35%), elevation of arterial pressure (25%) and a 10% decrease in cardiac output (Heyndricks, 1976). The results obtained with AVI and the preliminary data with norepinephrine (n = 3 dogs) indicate that it is unlikely that a generalized change of vascular wall diameter accounted for the observed increases in reflex sensitivity with AVP.

**AVP Interaction with Autonomic Pathways**

The precise mechanism whereby AVP influences the baroreceptor reflexes or autonomic functions remains to be determined. Preliminary observations by Guo et al. (1982, 1983) indicate that vasopressin augments baroreflex inhibition of lumbar sympathetic nerve activity in rabbits. However, other potential sites of action cannot be excluded at this time, including the carotid sinus receptors, various regions of the CNS where AVP could gain access, or components of the efferent side of the reflex system, such as ganglion or nerve terminals.

There is increasing evidence that AVP may act directly on the central nervous system (CNS) (Cowley, 1982). Liard et al. (1981) have demonstrated that vertebral artery infusions of AVP in unanesthetized dogs induced a greater decrease in heart rate and lesser increase in mean arterial pressure than intravenous infusions which achieved the same systemic plasma AVP levels. Potentially, AVP could influence the CNS through regions devoid of a blood brain barrier, such as the area postrema, organum vasculosum of the lamina terminalis, subfornical organ, pineal, and the posterior pituitary gland itself. CNS actions of AVP have been demonstrated by Tanaka et al. (1977), who reported that cerebroventricular administration of AVP in rats increased norepinephrine turnover in the medullary-pontine catecholamine neurons and that AVP antiserum had opposite effects. Matsuguchi et al. (1982) have reported dose-related blood pressure and heart rate increases with AVP injections into the nucleus tractus solitarius. There is neuroanatomical evidence for AVP efferent monosynaptic axon projections from the paraventricular nucleus to the brainstem and spinal cord (Swanson, 1977; Ciriello and Calaresu, 1980a; Ciriello and Calaresu, 1980b; Sofreniew and Weinid, 1981; Zimmerman, 1981). Although the organization and function of these pathways remain obscure, these studies, together with the present observations, represent increasing evidence for potential central actions of AVP on autonomic pathways.

There is evidence that AVP can augment the vasoconstrictor effects of sympathetic nerves by actions on either the ganglion, sympathetic terminals, or sympathetic adrenergic receptors (Kepinow, 1912; Bartelstone and Nasmyth, 1965; Altura et al., 1965; Diana and Masden, 1965; Commarato and Lum, 1969; Erker and Chan, 1977), but the physiological relevance of these interactions is yet unknown.

The present studies indicate a complex interaction of AVP on the functional elements of the baroreflex system. For example, AVP influenced efferent vagal nerve activity, as seen by the lowered heart rate. AVP appeared to influence this portion of the reflex system by adding to the tonic vagal output, rather than by multiplicatively enhancing the sensitivity of the reflex, (i.e., parallel shift of the curve seen in Fig. 6). However, AVP did not alter the changes of heart rate in response to changes in intrasinus pressure. These reflex changes appeared to be sympathetically mediated, since they were not abolished by vagotomy. We have shown previously that AVP exerts little direct effect on heart rate in the complete absence of the nervous system (Cowley et al., 1974). A second element of the reflex which is modified by AVP appears to be one which enhances changes of total peripheral resistance when intrasinus pressure is decreased below the equilibrium point of the baroreceptors. In contrast to the vagal effects, it would appear that this effect is—at least in part—multiplicative, because the slope of the response is increased nearly 3-fold. Finally, the data indicate that a portion of the overall reflex response remains unaffected by elevations in plasma AVP, since the reflex system responded normally when intrasinus pressure was increased above the equilibrium point. Evidence for multiple CNS elements influencing baroreceptor reflex responses was reported by Reis and Cuenod (1965). Two functional types of neuron pools were proposed: one which responded to increases and the other to withdrawal of baroreflex activity. Since a mutual independence of pressor and depressor responses was observed in their studies, it is possible that AVP could differentially modulate the activity of these two types of neuron pools.

**Integrated Role of AVP in Short-Term Stabilization of Arterial Pressure**

The role of AVP in the control of cardiovascular function has become increasingly apparent, based on recent studies demonstrating that physiological changes in plasma AVP can produce substantial alterations of systemic vascular resistance and con-
FIGURE 9. Proposed manner by which AVP and arterial baroreceptor reflexes work together to compensate for a rapid fall in arterial pressure. A decrease of arterial pressure, in this example, would be buffered immediately by baroreceptor reflexes, returning the pressure about 65% toward control levels. Further compensation of pressure would be obtained by AVP enhancement of baroreceptor gain, which would double the strength of the reflexes from —1.5 to —3.0, and enhance the fractional compensation of pressure to 75%. Finally, the direct vasoconstrictor actions of AVP with a gain greater than —2.0 would give a combined gain of greater than —5.0 with a net compensation of arterial pressure of nearly 85%.

Utilizing principles of linear control theory, which assume that the feedback gains of the different controllers acting on arterial pressure are additive, one can make the following predictions of the combined actions of AVP and the baroreflexes. After a decrease of arterial pressure, as shown in Figure 9, the baroreceptor reflexes would respond rapidly to return arterial pressure about 65% back toward control levels, based on an open-loop feedback gain of —1.8. Further compensation of arterial pressure would be obtained by AVP enhancement of baroreflex gain. Since, as seen in the present study, AVP appears to double the strength of the reflexes, this would result in a net feedback gain of nearly —3.6. This would increase the fractional compensation of arterial pressure to 78% of control values. Finally, the potent direct vasoconstrictor actions of AVP must also be considered. We have reported previously that the direct vasoconstrictor effects resulting from release of AVP, in the absence of baroreceptor reflexes and the renin-angiotensin system, can return a decrease of pressure about 70% of the way back toward control values. These direct vasoconstrictor actions resulted in an open-loop feedback gain of —2.2 (Cowley et al., 1980). The combined overall gain of the AVP-stimulated baroreflex effects, together with direct AVP vasoconstriction, would yield a total net gain of —5.8, equivalent to nearly an 85% compensation of arterial pressure. When other reflex responses, such as aortic and cardiopulmonary stretch receptors, are also considered, together with mechanisms such as renin release, capillary fluid redistribution, and stress relaxation, it is not surprising that greater than 10% of an animal's blood volume can be removed before detectable changes are observed in arterial pressure.

Finally, alterations of the carotid reflex gain per se do not appear to account for the potent buffering of elevations of arterial pressure that occur with AVP in the normovolemic state. Failure of pressure to rise is related to AVP-induced lowering of cardiac output, which appears to offset observed elevations of total peripheral resistance.

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Address for reprints: Dr. Allen W. Cowley Jr., Ph.D., Chairman, Department of Physiology, Medical College of Wisconsin, 8701 Watertown Plank Road, Milwaukee Wisconsin 53226.

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References


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Influence of vasopressin and angiotensin on baroreflexes in the dog.
A W Cowley, Jr, D Merrill, J Osborn and B J Barber

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