Influence of Intravenous and Intracerebroventricular Vasopressin on Baroreflex Control of Renal Nerve Traffic

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SUMMARY. We performed experiments in α-chloralose-anesthetized rabbits with vagi sectioned, to determine the influence of intravenous and intracerebroventricular vasopressin on arterial baroreflex control of renal nerve activity. Arterial baroreflex control of renal nerve activity was assessed during phenylephrine-induced increases and nitroglycerin-induced decreases in arterial pressure. Intravenous vasopressin (4 and 40 mU over 1 minute) reduced basal renal nerve activity (from 149 ± 14 to 101 ± 13 and 28 ± 13 impulses/sec) without changing arterial pressure and reduced the sensitivity of the arterial baroreflex control of renal nerve activity. This effect was reversed by vasopressin antagonist (d(CH₂)₅[Tyr(Me):2]AVP) which blocks vasoconstrictor effects of vasopressin. Intracerebroventricular vasopressin (4, 40, or 400 mU) did not alter basal renal nerve activity or arterial pressure but increased the sensitivity of baroreflex control of renal nerve activity. In contrast, the inhibitory influence of intravenous vasopressin on lumbar sympathetic nerve activity was abolished by sinoaortic denervation. Finally, intravenous vasopressin inhibited renal nerve activity (by 43 ± 5%) in six rabbits with spinal cord transection. This effect was abolished by the vasopressin antagonist. We draw the following conclusions from these data: (1) intravenous and intracerebroventricular vasopressin have different effects on basal and baroreflex control of renal nerve activity; (2) these effects are mediated by different vasopressin receptors; (3) the effects of intravenous vasopressin on basal renal nerve activity are not baroreflex dependent, and appear to be mediated by spinal or, possibly, ganglionk mechanisms; and (4) the differing effects of baroreceptor denervation on the response of renal nerves (postganglionic fibers) and lumbar nerves (preganglionic fibers) suggest an effect of intravenous vasopressin on ganglionic transmission. However, another mechanism(s) may account for our observation, since we did not test this possibility directly. (Circ Res 58: 17-25, 1986)

VASOPRESSIN has been shown to have potent systemic vasoconstrictor effects when it is infused intravenously (Schmid et al., 1974; Montani et al., 1980). In striking contrast, administration of large doses of arginine vasopressin (AVP) into the systemic circulation results in only modest increases in arterial pressure (Cowley et al., 1974). This inability of large elevations in AVP to raise arterial pressure is thought to be due to the presence of intact sinoaortic baroreflexes (Cowley et al., 1974). Cowley and colleagues (1974) reported an 11-fold increase in threshold sensitivity and an increase of as much 60- to 100-fold in pressor sensitivity at higher doses of AVP after baroreceptor denervation. In contrast, far less enhancement of the pressor responses to systemic norepinephrine or angiotensin II infusions have been observed after baroreceptor denervation. These observations were taken to indicate a unique interaction between vasopressin and the arterial baroreflex system. Cowley and colleagues (1984) recently reported that systemic administration of vasopressin augmented the gain of the isolated carotid baroreflex (aortic and part of vagal cardiopulmonary baroreceptors denervated) control of arterial pressure, but not of heart rate, in anesthetized hypophysectomized dogs. They indicated that this augmented gain could be due to effects on the central nervous system, on sympathetic ganglia, on sympathetic nerve endings, or to an interaction between norepinephrine and vasopressin at the neuroeffector junction. A direct effect of vasopressin on the baroreceptors was also possible since, in their experiments, the isolated carotid sinuses were perfused with blood obtained from the systemic circulation with high vasopressin levels. Evidence from several sources supports the possibility of a central effect of vasopressin on heart rate (Varma et al., 1969) and blood pressure (Liard et al., 1981), and recent studies by Undesser et al. (1985) and by Guo et al. (1983) provide direct evidence for a central effect on the arterial baroreflexes.

The first goal of our study was to determine whether peripherally administered vasopressin al-
serves the arterial baroreflex control of renal nerve traffic. By recording changes in nerve traffic rather than arterial pressure, we could exclude effects of peripherally administered vasopressin on sympathetic endings and at neuroeffector junctions. The second goal was to determine if the influence of central and peripheral vasopressin administration on basal renal nerve traffic and baroreflex control of the renal nerves is similar. Such a similarity would support a central effect of peripherally infused vasopressin, and would indicate an influence independent of an effect on baroreceptor sensory endings. The third goal of our studies was to determine whether the effects of central or peripheral vasopressin could be blocked with an antagonist that blocks the vasoconstrictor effect of vasopressin. Based on the results of the studies addressing these three goals, we performed additional experiments to elucidate further the mechanism for the effect of peripherally administered AVP on the renal nerves. The results of our experiments support the view that intravenous vasopressin acts to inhibit renal nerve traffic by inhibition of ganglionic transmission.

Methods

Experiments were done in adult New Zealand white rabbits weighing 2.5–3.5 kg. The animals were anesthetized initially with thiopental sodium (25 mg/kg, intravenously), followed by α-chloralose (60 mg/kg, intravenously). Supplemental doses of chloralose (10 mg/kg) were given hourly. During the protocol, muscular activity was abolished with decamethonium bromide. After endotracheal intubation, the animals were ventilated artificially with room air supplemented with oxygen at a tidal volume of 10 ml/kg and at a frequency of 20–25 cycles/min. Arterial blood gases and pH were measured at intervals, and ventilatory rate was adjusted to maintain pH between 7.45 and 7.55, Pco2 between 25 and 40 mm Hg, and Po2 in excess of 100 mm Hg. Body temperature was maintained at 37°C–40°C by external warming.

Denervation Procedures

The vagi were sectioned in all experiments before the protocol was begun. This was done to eliminate the influence of cardiopulmonary vagal afferents.

Sinoaortic denervation was performed by bilateral section of the aortic nerves (which are separate from the vagi), by interruption of all nervous and vascular structures which course between the internal and external carotid artery, and by stripping the adjacent adventitia in the region of the carotid sinus.

In six experiments (see Protocols), we interrupted the spinal cord by carefully exposing the cord at the C1 or C8 level and cauterizing all visible vessels and dividing the cord. After spinal cord interruption, noradrenaline was infused in three experiments at a rate (1–4 μg/min) which maintained arterial pressure at the same level that prevailed before interruption of the spinal cord.

Technique for Intracerebroventricular Injections

These injections were accomplished by placing the rabbit in a stereotaxic frame and by positioning a cannula in a lateral ventricle. The coordinates of the cannula in relation to the bregma were 1.5 mm posterior, 3.3 mm lateral, and a depth of 10 mm. The position of the cannula in the lateral ventricle was confirmed by the staining of all four ventricles after injection of 0.1 ml of methylene blue at the end of the experiment.

Recording and Quantification of Nerve Traffic

The left flank was opened to expose the left renal nerves. A branch of the nerves was separated from surrounding connective tissue, cut distally, desheathed, and covered with mineral oil for subsequent recording of action potentials from the central cut end of the nerve. Recordings of renal nerve traffic were made from small branches of left renal nerves or from a bundle of fibers obtained from the nerves. The nerves were placed on platinum iridium or silver/silver chloride bipolar electrodes for subsequent recording of nerve traffic. The technique for amplification and quantification of renal nerve traffic has been presented previously in detail (Felder and Thames, 1981). In brief, the action potentials in the renal nerves were amplified by a Grass bandpass amplifier (P511J). The amplified signals then were fed into an oscilloscope so that the signals could be viewed, into an audio amplifier so that changes in nerve traffic could be detected by audible signal, and into a nerve traffic analyzer that discriminated each spike which exceeded a selected level (just above the noise) so that the spikes could be counted. Each spike which crossed the lower window discriminator level triggered a voltage step which was independent of spike amplitude. These voltage steps then were integrated by the nerve traffic analyzer, which is digital in design and can integrate linearly at instantaneous spike frequencies of up to 10 kHz. The raw renal electrogram and the integrated output from the spike counter were displayed on a Gould E51000 electrostactive recorder or on a Honeywell 1858 Visicorder. Also displayed on these recordings was the arterial pressure which was obtained via a cannula positioned in the distal aorta via the left femoral artery. In some experiments, changes in the heart rate were assessed by manual counting of the arterial pressure pulse.

In five experiments, recordings were made from the lumbar sympathetic nerves. A transabdominal approach was used to expose the nerves.

Protocols

Four groups of experiments were performed. A 20-minute equilibration period was interposed between the completion of the surgical preparation and the initiation of each of the protocols. This resulted in steady state basal values of arterial pressure and renal sympathetic nerve traffic. The four protocols are outlined below as groups I, II, III, and IV.

Group I: Effect of Bolus Administration of AVP

The input from arterial baroreceptors was increased by short-lasting (30–60 seconds) infusions of phenylephrine (7–15 μg/min) which raised arterial pressure, and was decreased by short-lasting infusions of nitroglycerin (10 μg/min) which decreased blood pressure. These infusions changed arterial pressure by 15–20 mm Hg/min. This allowed us to determine the stimulus response relationship between baroreceptor input and renal sympathetic output. Responses were determined under control conditions, after the intravenous administration of 4 mU of AVP, and after administration of 40 mU of AVP. In both instances,
AVP was infused for approximately 1 minute. Phenylephrine or nitroglycerin was infused immediately after the vasopressin infusion had been completed. Immediately after the effects of the larger dose of AVP on the baroreflex control of renal nerve traffic were examined, an AVP antagonist (10 µg/kg) was administered intravenously, and the protocol was repeated. This antagonist, d(CH2)5[Tyr(Me)2]AVP, blocks the vasoconstrictor effects of vasopressin (10). Because we found that intravenous AVP had a significant effect on renal nerve traffic, all responses of renal nerve traffic in these experiments are expressed as absolute values of impulses per second. This permitted us to examine the whole stimulus response relationship between changes in pressure and changes in traffic.

**Group II: Effect of Intracerebroventricular AVP**

Changes in arterial pressure were induced with phenylephrine and nitroglycerin, as outlined above. Baroreflex control of renal nerve traffic was assessed after the intracerebroventricular administration of vehicle (saline, 0.1 ml), 4 mU, 40 mU, or 400 mU of AVP. These doses were administered in progressively increasing sizes, rather than in randomized fashion. Immediately after the largest dose of AVP was administered, AVP antagonist (3 µg) was administered intracerebroventricularly, and the protocol was repeated.

**Group III: Responses to Intravenous AVP before and after Sinoaortic Baroreceptor Denervation**

The role of the arterial baroreceptors in the responses to intravenous injection of vasopressin was assessed by determining the changes of arterial pressure and renal sympathetic nerve traffic which resulted from bolus injections of AVP (4 mU and 40 mU) before and after sinoaortic baroreceptor denervation. This sinoaortic denervation abolished the inhibition of renal nerve traffic that resulted from phenylephrine-induced increases in arterial pressure. In these experiments, AVP was administered over 1 minute.

**Group IV: Intravenous Infusion of AVP after Spinal Cord Transection**

The animals (n = 6) were permitted to recover from spinal shock for approximately 2–3 hours. Immediately after spinal cord transection, there was virtually no sympathetic nerve traffic. By the time that the protocol was initiated, traffic had returned to approximately 20% of the basal value which preceded the spinal cord transection. The responses to the intravenous bolus injection of AVP (40 mU) were determined only after spinal cord transection. The AVP was infused over approximately 60 seconds, and changes in renal nerve and arterial pressure were recorded. Then, AVP antagonist (10 µg) was administered intravenously, and the protocol was repeated. When necessary, sufficient norepinephrine (1–4 µg/min) was infused throughout the period of time following spinal cord transection to permit the maintenance of an arterial pressure, which was comparable to the pretransection arterial pressure (total dose, 0.25–1.0 mg/experiment).

**Data Analysis**

The responses of arterial pressure and renal nerve traffic to interventions were determined in each group of experiments in which the gain of the arterial baroreflex control of the renal nerves was determined (groups I and II). Since pressure was raised and lowered over a wide range, we were able to generate a stimulus response relationship between these measured parameters. In these two groups of experiments, differences from control responses were determined by analysis of variance. The type of analysis of variance depended on the design of the study. For example, in group I experiments in which the baroreflex control of renal nerve traffic was assessed after the intravenous bolus injection of AVP and after AVP antagonist, a multivariate analysis of variance was performed. In those experiments (group II) in which the responses of blood pressure and renal nerve traffic were assessed following intravenous AVP before and after sinoaortic denervation (SAD), a paired t-test was performed. Least-squares linear regression analyses were done on all stimulus-response relationships in which the baroreflex control of the renal nerve traffic was assessed. These regressions served as an index of the magnitude of the sensitivity (gain) of this reflex, but the actual statistical significance of the differences between these responses was determined by analysis of variance. Data are summarized in the text, tables, and figures as the mean ± 1 se. Values of P less than 0.05 are considered significant.

**Results**

**Group I: Effect of Bolus Administration of AVP**

Under basal conditions, mean arterial pressure was 71 ± 6 mm Hg and renal nerve traffic was 149 ± 14 impulses/sec. Administration of 4 mU of AVP over 1 minute decreased (P < 0.05) renal nerve traffic to 101 ± 13 impulses/sec without changing arterial pressure (70 ± 4 mm Hg). Administration of 40 mU of AVP also failed to raise arterial pressure significantly (80 ± 6 mm Hg), but decreased renal nerve activity to 28 ± 13 impulses/sec. Baroreflex control of renal nerve traffic was tested under control conditions and after each dose of AVP. The results from six experiments are summarized in Figure 1. After the effect of the high dose of AVP on the baroreflex was tested, the AVP antagonist was administered. This raised renal nerve traffic to 160 ± 21 impulses/sec and reduced mean arterial pressure to 65 ± 6 mm Hg. These values tended to be (P < 0.10), respectively, higher and lower than the initial control values at the start of the protocol, but the differences were not statistically significant. Baroreflex control of renal nerve activity was tested again after administration of the antagonist. The mean least squares linear regression slopes (impulses/sec per mm Hg) for the baroreflex control of the renal nerves were: Control, −2.6 ± 0.4; 4 mU AVP, −2.0 ± 0.6; 40 mU AVP, −0.8 ± 0.3; and AVP antagonist, −3.7 ± 0.5. The r values for these linear regressions all were >0.75. Compared with the antagonist slope, the control slope tended to be less (P < 0.09), whereas those obtained after 4 mU and 40 mU of AVP were significantly less (P = 0.03 and 0.0004, respectively). Thus, intravenous AVP decreased basal traffic without significantly changing arterial pressure, and decreased the slope (sensitivity) of the baroreflex control of the renal nerves.
basal levels of AVP must have been sufficient to alter the baroreflex since, after AVP antagonist, the highest level of renal nerve traffic and greatest baroreflex sensitivity were observed.

**Group II: Effect of Intracerebroventricular AVP**

Unlike intravenous AVP, intracerebroventricular AVP had no effect on basal renal nerve activity or arterial pressure (Table 1). Thus, responses of renal nerve activity were normalized for the analysis of these data. Intracerebroventricular AVP altered baroreflex control of the renal nerves (Fig. 2). The mean least squares linear regression slope rationalized with respect to the 0,0 point was \(-2.2 \pm 0.4\% / \text{mmHg}\).

### Table 1

<table>
<thead>
<tr>
<th>AVP</th>
<th>Saline</th>
<th>4 mU ICV</th>
<th>40 mU ICV</th>
<th>400 mU ICV</th>
<th>AVP Ant, 3 mU ICV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>64 ± 4</td>
<td>69 ± 4</td>
<td>68 ± 3</td>
<td>69 ± 3</td>
<td>68 ± 3</td>
</tr>
<tr>
<td>Renal nerve activity (impulses/sec)</td>
<td>88 ± 13</td>
<td>91 ± 13</td>
<td>83 ± 11</td>
<td>94 ± 13</td>
<td>85 ± 11</td>
</tr>
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*Before (B) and after (A) intracerebroventricular (ICV) saline, arginine vasopressin (AVP), or AVP antagonist (Ant).*
Hg after intracerebroventricular saline: $-2.9 \pm 0.5\%/\text{mm Hg}$ after 4 mU intracerebroventricular AVP; $-3.3 \pm 0.5\%/\text{mm Hg}$ after 40 mU intracerebroventricular AVP ($P < 0.04$), and $-3.7 \pm 0.6\%$ after 400 mU intracerebroventricular AVP ($P < 0.001$). The $r$ values for these linear regressions were $\geq 0.80$. Immediately after the baroreflex had been tested, following the highest dose of AVP, the AVP antagonist was administered. The antagonist did not alter the basal traffic (Table 1), nor did it return baroreflex control of renal nerve activity to control ($-3.9 \pm 0.5\%/\text{mm Hg}$, $P < 0.001$). The changes in baroreflex slope were not due to the passage of time, since we have shown previously that baroreflex control of the renal nerves is unaltered after each of four intracerebroventricular injections of saline (Imaizumi et al., 1984). Thus, in contrast to intravenous AVP, which reduced both basal traffic and baroreflex sensitivity, intracerebroventricular AVP failed to alter basal traffic and augmented the gain of the reflex. The effects of intravenous AVP were blocked by the AVP antagonist; those of intracerebroventricular AVP were not.

**Group III: Effect of Sinoaortic Denervation on Responses to Intravenous AVP**

We were struck by the observation that intravenous AVP alone decreased basal renal nerve traffic in the absence of changes in arterial pressure. Such an effect would require the gain of the arterial baroreflexes to be nearly infinite if it were mediated solely by the arterial baroreflexes. This made us wonder whether the decreases in basal renal nerve traffic after intravenous AVP were dependent on baroreflexes. As illustrated in Figures 3 and 4, they were not. Figure 3 is an original record illustrating that intravenous AVP decreased renal nerve traffic before (Fig. 3A) and after sinoaortic denervation (Fig. 3B). Figure 4 summarizes the mean data from seven experiments and illustrates the maximum responses of arterial pressure and renal nerve activity. With sinoaortic baroreflexes intact (vagi sectioned) there were dose-dependent decreases in renal nerve traffic. There also were small increases in arterial pressure. After sinoaortic denervation, intravenous AVP still inhibited renal nerve traffic by percentages
comparable to those observed with baroreflexes intact. In contrast, inhibition of renal nerve traffic during phenylephrine-induced increases in arterial pressure were abolished by sinoaortic denervation. The pressor response to low-dose AVP (4 mU) was significantly augmented after sinoaortic denervation, but the response to the higher dose was not. Although we did not measure cardiac filling pressure, we believe that the failure of sinoaortic denervation to potentiate the pressor response to high-dose AVP (40 mU) resulted from the inability of the rabbit left ventricle to maintain cardiac output with intense peripheral vasoconstriction.

In those experiments in which we recorded from the renal nerves, we also determined the changes in heart rate before and after sinoaortic denervation (vagi sectioned). Injection of 40 mU of AVP decreased heart rate by 78 ± 9 beats/min from a basal heart rate of 351 ± 10 beats/min. After sinoaortic denervation, basal heart rate was 327 ± 10 and decreased by 51 ± 8 beats/min. This response was significantly less (P < 0.02) than that observed under control conditions, and indicates that about one-third of the heart rate response was baroreflex mediated and two-thirds was independent of the baroreflexes.

The failure of sinoaortic denervation to alter the inhibitory influence of intravenous AVP on renal nerve traffic differs strikingly from the results of similar studies performed by Guo et al. (1982). They found that sinoaortic denervation abolished the neural responses to intravenous AVP. However, in their studies, they recorded from lumbar sympathetic nerves. These nerves are mainly preganglionic, in contrast to the postganglionic renal sympathetic nerves from which we recorded. As illustrated in Figure 5, we also found that sinoaortic denervation abolished the responses of the lumbar nerves to intravenous AVP. The figure illustrates the maximum responses to vasopressin. Administration of hexamethonium bromide (10 mg/kg), a ganglionic blocker, failed to alter lumbar nerve traffic significantly (191 ± 31 impulses/sec before and 166 ± 40 impulses/sec after ganglionic blockade), thus confirming its principally preganglionic nature.

**Group IV: Responses of Renal Nerves to Intravenous AVP after Spinal Cord Transection**

The difference between the effect of SAD on responses of renal and lumbar nerves suggested to us that AVP could be acting on the renal nerves by a mechanism that altered ganglionic transmission. We tested this possibility in six rabbits by sectioning the spinal cord and examining the effect of intravenous AVP on renal nerve traffic. Initially, the animals had low blood pressure and essentially no renal nerve traffic (spinal shock), and required intravenous norepinephrine to maintain arterial pressure. Two to 3 hours after spinal cord transection, renal nerve traffic had returned to 7.1 ± 0.5 impulses/sec, and arterial pressure was maintained (68 ± 7 mm Hg) without norepinephrine (n = 3) or with very small doses of norepinephrine (n = 3). These levels of renal sympathetic nerve traffic are similar to those of cardiac sympathetic nerve activity which we have observed previously in dogs following transection of the spinal cord (Felder and Thames, 1981).
venous AVP (40 μl) increased arterial pressure and decreased renal nerve traffic to 4.3 ± 0.4 impulses/sec (43 ± 5% inhibition). These changes were statistically significant. After the response to AVP was determined, AVP antagonist was administered, and the rabbits then were challenged again with AVP. As illustrated in Figure 6, there was no significant change in arterial pressure and only a tendency for a decrease in renal nerve traffic when AVP was administered following the antagonist.

**Discussion**

We report several new and important findings. First, intravenous AVP reduced basal renal nerve activity and baroreflex control of the renal nerves. This effect is reversed by an AVP antagonist known to block the vasoconstrictor effects of AVP. Second, intracerebroventricular AVP does not alter basal renal nerve traffic, but does augment the gain of the baroreflex control of the renal nerves. This effect is not blocked by the AVP antagonist we used. Third, the effects of intravenous AVP on basal renal nerve traffic are not prevented by sinoaortic denervation, or even by sectioning of the spinal cord. In contrast, sinoaortic denervation abolishes baroreflex influences on the lumbar nerves. In the paragraphs that follow, we will discuss each of these points.

We have become increasingly impressed with the complex influences of AVP on the neural control of the circulation (Schmid et al., 1984). Microinjection of AVP into the nucleus tractus solitarii of rats produces cardioexcitatory and vasopressor responses (Matsuguchi et al., 1982). In contrast, intravenous AVP augments the gain of the arterial baroreflex control of the lumbar sympathetic nerves in rabbits (Guo et al., 1983) and of isolated carotid sinus baroreflex control of arterial pressure (but not heart rate) during decreases but not increases in carotid sinus pressure in dogs (Cowley et al., 1984). Little is known about the effects of intravenous AVP on nerve traffic other than the lumbar nerves. By recording sympathetic nerve traffic rather than just arterial pressure or vascular resistance, it is possible to gain clearer insights into the way in which AVP influences the nervous system. In our experiments, intravenous AVP inhibited basal renal nerve traffic and reduced the gain of the baroreflex control of renal nerve traffic. This effect on the baroreflex is strikingly different from that reported by Guo et al. (1982) for the lumbar nerves. As discussed below, this difference has important implications. We found that administration of AVP antagonist reversed the effects of intravenous AVP on basal traffic and on the baroreflex. In fact, the difference between control baroreflex sensitivity and the sensitivity after the antagonist tended to be different, suggesting that the basal levels of AVP were sufficient to alter baroreflex control of the renal nerves. These initial studies did not determine the site at which AVP was working to cause the effects, i.e., baroreceptors, brain, spinal cord, or sympathetic ganglia.

Guo et al. (1983) have reported that intravenous AVP augments the gain of the arterial baroreflex control of lumbar nerves due to a central neural influence of AVP. This conclusion was based primarily on the fact that baroreceptor discharge was similar during phenylephrine- or AVP-induced increases in arterial pressure; yet, the gain of the baroreflex control of the lumbar nerves was enhanced during AVP. Our studies in which AVP was injected intracerebroventricularly indicate that AVP can augment baroreflex sensitivity by an effect on the brain. This finding also is consistent with the observations of others regarding central effects of peripherally administered AVP (Guo et al., 1983; Liard et al., 1981; Schmid et al., 1984; Undesser et al., 1985). Our results suggest that the effect we observed probably is mediated by brain regions in close proximity to the brain ventricles. The central effects of AVP we observed after its intracerebroventricular injection may account for the central effects of AVP on the baroreflex control of the lumbar nerves, suggested by the findings of Guo et al. (1983). However, they do not account for the effects of peripherally administered AVP on the baroreflex control of the renal nerve activity. This suggested to us that there may be at least two completely different mechanisms involved here, one of which is baroreflex dependent, the other baroreflex independent.

The fact that intravenous AVP inhibited renal nerve traffic after sinoaortic denervation (vagi sectioned) points to an effect(s) on the brain, spinal cord, or sympathetic ganglia. The persistence of the

**FIGURE 6.** Mean maximum responses (n = 6) of renal nerve activity (% change, top) and mean arterial pressure (mm Hg, bottom) to intravenous injection of AVP (40 μl) after spinal cord transaction, and, also, after intravenous administration of AVP antagonist (10 g). Significant differences before and after antagonist are so indicated. Data shown as mean ± se.
effects of intravenous AVP on renal nerve traffic after spinal cord transection points to a spinal cord or ganglionic effect. It’s unlikely that its effect is on the spinal cord, because we would have expected both renal and lumbar nerves to be affected in a qualitatively, if not quantitatively, similar fashion. There is an important clue to the localization for the effect of intravenous AVP on basal renal nerve traffic in the differences between our findings and those of Guo et al. The renal nerves are postganglionic sympathetic nerves. The lumbar nerves are mainly preganglionic. The effect on lumbar nerve activity of ganglionic blockade with hexamethonium bromide that we observed confirms this point. It seems likely that intravenous AVP alters ganglionic transmission in a way which reduces basal postganglionic sympathetic nerve activity and baroreflex control of postganglionic nerve activity. This effect seems to dominate the central effect of AVP on baroreflex control of preganglionic sympathetic nerve activity reported by Guo and colleagues (1983), at least for short-lasting infusions and for the doses we used. With longer periods of AVP infusion, the magnitude of the central effect may become enhanced and the net effect of systemic AVP would depend on the balance between its effect on ganglionic transmission and its central effect on the baroreflexes.

Although we did not directly investigate the effect of intravenous vasopressin on ganglionic transmission, our interpretation of these findings is supported by the observations of Wali (1984), who found that vasopressin inhibited ganglionic transmission in the superfused rabbit superior cervical ganglion. Using the conditioning test technique, he found that vasopressin reduced the amplitudes of postganglionic compound action potentials in response to a constant preganglionic stimulus.

Hanley and colleagues (1984) reported recently that there is immunoreactive vasopressin-like peptide in sympathetic ganglia. They suggested that this peptide should be considered as a possible mediator of the nonadrenergic responses to sympathetic stimulation. We suggest that circulatory AVP as well as locally released AVP-like peptide could modulate transmission in sympathetic ganglia.

Whereas it is our view that the effect of vasopressin on basal renal traffic is explained best by an influence on ganglionic transmission, we would like to emphasize that we have not directly tested this possibility. We also acknowledge that there may be other mechanisms which could account for our findings. One possibility is that vasopressin influences postganglionic renal nerve activity by a selective effect on preganglionic renal sympathetic nerves in the spinal cord. It also is possible that there are central effects of vasopressin which are selective for the renal nerves. Such effects could be eliminated by spinal cord transection, only to be “replaced” by spinal or ganglionic effects.

We also would like to acknowledge that the doses of vasopressin we used were large, and probably resulted in plasma vasopressin levels that were very much higher than those observed in response to physiological stimuli for vasopressin release. Although we did not measure the plasma levels of AVP in our experiments, we consider it likely that the doses we used (4 and 40 mU) resulted in plasma levels that are in the range of those observed during severe hemorrhage. This view is supported by unpublished data (Phillip G. Schmid, personal communication).

It is likely that the effect of intravenous AVP on the renal nerves is not unique to this sympathetic outflow. Intravenous AVP decreased heart rate significantly before and after SAD. Since the vagi were sectioned in these experiments, it is unlikely that this bradycardia was mediated by increased parasympathetic nerve activity. Since, after SAD, the heart rate response to AVP was reduced by about one-third, only this reduction can be attributed to baroreflex influences. The remainder of the response is independent of the arterial baroreflexes and may well be due to an effect on sympathetic ganglionic transmission to the heart. This observation should be taken into account when conclusions are drawn regarding the influence of intravenous AVP on baroreflex control of heart rate, which has been reported to be augmented by AVP (Varma et al., 1969).

It should be noted that the effects of peripherally administered AVP were abolished by an AVP antagonist which blocks the vasoconstrictor effects of AVP. However, the effects of centrally administered AVP were not blocked by this antagonist. This suggests that there are at least two different AVP receptors in the brain and in the periphery which mediate the responses we observed.

Our results are different from those reported by Cowley et al. (1984). They found augmented isolated carotid sinus baroreflex control of arterial pressure during decreases, but not increases in carotid sinus pressure following intravenous AVP. We found depressed baroreflex control after intravenous AVP during both increases and decreases in arterial pressure. However, the results we obtained with intracerebroventricular AVP are similar to those of Cowley and colleagues, in that we saw augmented baroreflex gain, primarily during decreases in stimulus to the arterial baroreceptors. These differences may be attributable to important species differences in both the types and magnitudes of the different effects of AVP on the baroreflex control of the circulation.

There are also important differences between our results and those recently reported by Undesser et al. (1985). They examined the effect of intravenous vasopressin on arterial baroreflex control of renal nerve traffic. They found that vasopressin augmented baroreflex inhibition of renal nerve traffic, and that inhibition of renal nerve traffic in response to intravenous vasopressin was markedly reduced by sinoaortic baroreceptor denervation. They also showed that area postrema lesions prevented the sensitization of the baroreflex by vasopressin. There
are several important differences between the design of their study and ours. Our experiments were done in anesthetized rabbits; theirs were done in conscious rabbits. They used only vasopressin to change pressure; we used phenylephrine and nitroglycerin to change pressure after administration of vasopres- sin. We infused vasopressin over 1 minute, after which pressure was changed with vasoactive drugs. They infused vasopressin at different rates for 3 minutes. We would like to emphasize that there also are important similarities between these two studies. Like Undesser et al. (1985), we observed nearly an 80% reduction in renal sympathetic nerve traffic after the administration of vasopressin (40 mU) alone, without a significant concomitant rise in arterial pressure. Thus, both studies indicate a marked inhibitory influence of vasopressin on renal nerve traffic, although the mechanisms suggested are quite different. Undesser et al. attributed the influence of vasopressin on the baroreflex to its influence on the area postrema. Our findings suggest an effect on ganglionic transmission which is independent of baroreflexes. Undesser et al. continued to observe large decreases in renal nerve traffic in response to vasopressin after sinoaortic denervation, which they found to be abolished by vagotomy. We began our studies with the vagi sectioned, and continued to observe inhibition of renal nerve traffic by vasopressin following sinoaortic denervation. We would like to emphasize that we were able to abolish the effect of vasopressin on the lumbar nerves by baro-denervation, as reported by Guo et al. (1982). Our findings were obtained in the same preparation in which Guo et al. (1983) showed that vasopressin augmented baroreflex sensitivity in the control of the lumbar nerves by a central effect. In this same preparation barodenervation plus vagotomy did not abolish the influence of vasopressin on renal nerve traffic. Based on our data and those of Undesser et al. (1985), we feel that it is best to conclude the vasopressin may alter the arterial baroreflex control of the renal nerves by both a central effect and an influence on ganglionic transmission, with the expectation that future studies will sort out the relative importance of these two mechanisms.

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