Effect of Intrarenal Bradykinin Infusion on Vasopressin Release in Rabbits

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Electrical stimulation of afferent renal nerves and activation of renal mechanoreceptors increase plasma vasopressin concentration. In the present study, the effect of renal chemoreceptor activation on plasma vasopressin concentration was investigated in anesthetized rabbits. Renal chemoreceptors were activated with intrarenal infusions of bradykinin. With intrarenal infusion of bradykinin at 136 ng/min, plasma vasopressin concentration increased from 4.5±1.5 to 26.8±14.2 pg/ml at 5 minutes (p<0.01), whereas with infusion at 1,360 ng/min, plasma vasopressin increased from 5.9±2.0 to 54.4±16.4 pg/ml at 5 minutes (p<0.01). There was no significant change in plasma vasopressin during intravenous infusion of bradykinin at 136 ng/min. Infusion at 1,360 ng/min increased plasma vasopressin from 2.7±0.5 to 14.8±6.4 pg/ml (p<0.01), but this increase was significantly less than that produced by intrarenal infusion of the same dose of bradykinin. Similar effects on plasma vasopressin were observed during paired intrarenal and intravenous infusions of bradykinin at 136 ng/min. Renal denervation markedly reduced the vasopressin responses to intrarenal infusion of bradykinin at 136 ng/min (2.8±0.5 to 4.0±0.7 pg/ml, p<0.01) and 1,360 ng/min (3.2±0.7 to 7.8±1.8 pg/ml, p<0.05). These results indicate that bradykinin stimulates vasopressin release by an intrarenal action and suggest that this action is mediated by afferent renal nerves. (Hypertension 1992;19:799–803)

KEY WORDS • renal nerves • vasopressin • chemoreceptors • bradykinin • rabbit studies

Electrical stimulation of afferent renal nerves (ARN) increases plasma vasopressin (AVP) concentration1-4 and the activity of neurosecretory cells in the supraoptic5 and paraventricular6 nuclei of the hypothalamus. On the basis of these observations, it has been proposed that the kidneys, acting by way of ARN, participate in the regulation of AVP release.1-4

Two classes of sensory receptors have been identified neurophysiologically in the kidney: mechanoreceptors, which respond to increases in intrarenal pressure,7-15 and chemoreceptors, which respond to renal ischemia or changes in the chemical environment of the renal interstitium.12-15-17 We have reported that activation of renal mechanoreceptors by increasing intrapelvic pressure increases AVP release in the rabbit.18 On the other hand, we were unable to demonstrate an effect of renal chemoreceptor activation on AVP release using retrograde pelvic perfusions of 1 M NaCl, 0.1 M KCl, or 1 M mannitol. However, Knuepfer and Schramm19 have reported that intrarenal injection of bradykinin or capsaicin increases activity in ARN. In addition, Day and Cirillo20 have demonstrated a stimulatory effect of intrarenal bradykinin on neurosecretory cells in the supraoptic nucleus of the hypothalamus. These effects are thought to be mediated mainly by activation of renal chemoreceptors, because bradykinin is known to activate chemosensitive nerve endings.21-24 In the present study, we further investigated the effect of renal chemoreceptor activation on the release of AVP using intrarenal infusion of bradykinin.

Methods

Animal Preparation

Male New Zealand White rabbits weighing 2.4-3.7 kg were used in this study. Food was withheld overnight, but water was allowed ad libitum. All procedures were approved by the University of California, San Francisco, Committee on Animal Research. The rabbits were premedicated with acepromazine maleate (1 mg/kg i.m.) and anesthetized with sodium pentobarbital (20–30 mg/kg i.v.). Catheters were placed in a femoral artery for monitoring of arterial blood pressure and sampling of blood and in a femoral vein for injection of anesthetic, bradykinin, or saline. Isotonic saline was infused intravenously at 0.2–0.3 ml/min to prevent dehydration during surgery. The saline infusion was stopped 30 minutes before the start of an experiment. Each rabbit was placed on its right side. The left renal and adrenolumbar arteries were exposed retroperitoneally through a paravertebral incision. A catheter was inserted retrogradely into the adrenolumbar artery so that its tip was in the bifurcation of the renal and adrenolumbar arteries. This catheter was used for infusions into the left kidney. The catheter consisted of 10-cm PE-10 (Clay Adams, Parsippany, N.J.) connected to 50-cm PE-50. The catheter was fixed in place with silk ligatures. For maintenance of catheter patency, isotonic saline was infused at 14 µl/min. In some rabbits, the left kidney was denervated before adrenolumbar
arterial cannulation as described below. An equilibration period of at least 60 minutes was allowed before the start of an experiment. Arterial blood pressure and heart rate were continuously recorded throughout each experiment with Statham or Cobe pressure transducers and a polygraph (Grass Instrument Co., Quincy, Mass.).

**Experimental Protocols**

The effects of intrarenal and intravenous infusion of bradykinin at 136 and 1,360 ng/min on plasma AVP concentration were investigated according to the following protocols. Two 10-minute infusions of bradykinin were performed in each rabbit. These were given in random order and separated by at least 80 minutes. Bradykinin acetate (Sigma Chemical Co., St. Louis, Mo.) was dissolved in isotonic saline.

**Protocol 1: Intrarenal bradykinin.** After blood pressure and heart rate had stabilized, a vehicle infusion (isotonic saline, 68 µl/min) into the left renal artery was started. This infusion rate is less than 1% of the normal renal blood flow. Thirty minutes later, a 3.5-ml control blood sample was collected via the femoral arterial catheter. Intrarenal saline infusion was then switched to bradykinin infusion (1,360 ng/min, n=7, or 136 ng/min, n=6) at the same flow rate as vehicle infusion. The bradykinin infusion lasted 10 minutes and was followed by vehicle infusion. Additional blood samples were collected 5, 10, and 30 minutes after the start of bradykinin infusion. From each sample, a 2.7-ml aliquot of blood was placed immediately in a chilled tube containing 0.3 ml of 0.3 M EDTA. Plasma was separated by centrifugation at 4°C and frozen until analysis for plasma AVP concentration and plasma renin activity. The remaining 0.8-ml aliquot of blood was placed in a tube containing heparin for the measurement of plasma osmolality. Blood samples were replaced with an equal volume of sterile isotonic saline.

**Protocol 2: Intravenous bradykinin.** In this group of rabbits, the adrenolumbar artery was exposed but not cannulated. Vehicle or bradykinin (1,360 ng/min, n=7, or 136 ng/min, n=7) was infused via the femoral vein catheter over the time course described for protocol 1 as a control for possible recirculation of intrarenally infused bradykinin. Blood sampling was performed as described in protocol 1.

**Protocol 3: Intrarenal and intravenous bradykinin.** To compare the effects of intrarenal and intravenous bradykinin in the same animals, we infused bradykinin (136 ng/min) intravenously and intrarenally in each of 10 rabbits. The infusions were performed as described in protocols 1 and 2 and were separated by at least 80 minutes.

**Protocol 4: Intrarenal bradykinin after renal denervation.** In this series of experiments, the left kidney was denervated to determine if the renal nerves contribute to the AVP response to intrarenal bradykinin. All visible nerve fibers entering the renal hilus were cut, and the adventitia of the renal artery and vein was stripped. The artery and vein were then painted with a solution of 10% phenol in ethanol. Adrenolumbar arterial cannulation, bradykinin infusion (1,360 ng/min, n=7, or 136 ng/min, n=7), and blood sampling were then performed as described in protocol 1.

**Results**

**Intrarenal Bradykinin**

Figure 1 shows the effects of intrarenal bradykinin. With 136 ng/min bradykinin, plasma AVP concentration increased from 4.5±1.5 to 26.8±14.2 pg/ml at 5 minutes (p<0.01), whereas with 1,360 ng/min, it increased from 5.9±2.0 to 54.4±16.4 pg/ml at 5 minutes.
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Figure 2. Line plots show effects of intravenous bradykinin infusion on plasma vasopressin concentration, plasma renin activity, mean arterial pressure, and heart rate. Values are mean±SEM. Open circles, 1,360 ng/min, n=7; closed circles, 136 ng/min, n=7. *p<0.05, **p<0.01 vs. control. Thus, intrarenal bradykinin produced a dose-dependent increase in plasma AVP concentration. Plasma renin activity tended to increase during the bradykinin infusions, but the overall changes were not statistically significant (Figure 1). With the low dose of bradykinin, mean arterial pressure increased gradually in some rabbits but did not change in others. The mean value increased from 75±5 to 81±4 mm Hg at 5 minutes (p<0.05, Figure 1). With the high dose of bradykinin, mean arterial pressure increased more than with the low dose in some rabbits but decreased in other rabbits. As a result, the overall change in mean arterial pressure with the high dose of bradykinin was less than with the low dose of bradykinin (Figure 1). There were no significant changes in heart rate (Figure 1) or plasma osmolality (292.7±3.3 to 292.7±3.2 mosm/kg H2O).

Intravenous Bradykinin

In this group of animals, bradykinin was infused intravenously to determine if the effects of intrarenal infusion were due to an intrarenal action or to systemic recirculation of the peptide. Figure 2 shows the effects of intravenous bradykinin infusion. There was no significant change in plasma AVP concentration with the low intravenous dose of bradykinin. With the high dose, plasma AVP concentration increased from 2.7±0.5 to 14.8±6.4 pg/ml at 5 minutes (p<0.01). This increase in plasma AVP concentration was significantly less than that produced by intrarenal infusion of the same dose of bradykinin (p<0.05). Plasma renin activity increased from 10.9±3.3 to 14.1±4.3 ng/ml/2 hr with the low dose of bradykinin (p<0.01) and from 11.5±2.6 to 27.8±6.5 ng/ml/2 hr with the high dose (p<0.01, Figure 2). The low dose of bradykinin caused no change in mean arterial pressure or heart rate (Figure 2). With the high dose, there was no statistically significant change in mean arterial pressure, but heart rate increased from 206±11 to 239±7 beats per minute (p<0.01, Figure 2). Plasma osmolality did not change (299.3±1.9 to 299.4±2.1 mosm/kg H2O).

Figure 3. Line plots show effects of paired intrarenal and intravenous bradykinin infusions (136 ng/min) on plasma vasopressin concentration, plasma renin activity, mean arterial pressure, and heart rate. Values are mean±SEM. Open circles, intrarenal infusion, n=10; closed circles, intravenous infusion, n=10. *p<0.05, **p<0.01 vs. control.

Intrarenal and Intravenous Bradykinin

Figure 3 shows the effects of paired intrarenal and intravenous infusions of bradykinin at 136 ng/min in the same animals. Intrarenal bradykinin increased plasma AVP concentration from 3.3±0.6 to 11.5±3.8 pg/ml at 5 minutes (p<0.01), but intravenous infusion of the same dose had no significant effect. Plasma renin activity and mean arterial pressure did not change significantly. Heart rate increased with intrarenal bradykinin but did not change with intravenous bradykinin. There were no changes in plasma osmolality.
Intrarenal Bradykinin After Renal Denervation

Renal denervation markedly reduced the increase in plasma AVP concentration produced by intrarenal bradykinin infusion. With infusion at 136 ng/min, plasma AVP concentration increased from 2.8±0.5 to 4.0±0.7 pg/ml (p<0.01), whereas with infusion at 1,360 ng/min, it increased from 3.2±0.7 to 7.8±1.8 pg/ml (p<0.05). In neither case did plasma AVP concentration decrease after cessation of the infusion. Plasma renin activity increased from 12.2±1.8 to 15.6±2.3 ng/ml/2 hr with the low dose of bradykinin (p<0.01) and from 12.1±2.7 to 20.1±3.5 ng/ml/2 hr with the high dose (p<0.01). Heart rate increased by 10 and 23 beats per minute with the low and high doses of bradykinin, respectively, but mean arterial pressure did not change. There were no changes in plasma osmolality.

Discussion

The kidneys are innervated with postganglionic sympathetic fibers and with sensory afferent fibers.13,28 Electrical stimulation of ARN produces a variety of cardiovascular and renal responses, and it has been proposed that ARN plays a role in the control of arterial blood pressure and renal function.15,29 Recently, several investigators have reported that electrical stimulation of ARN increases plasma AVP concentration1-4 and the activity in neurosecretory cells within the supraoptic and paraventricular nuclei of the hypothalamus. These findings support the hypothesis that ARN plays a role in the regulation of AVP release.

Previously, we examined the effects of activation of renal mechanoreceptors and chemoreceptors on the release of AVP.18 Increased pelvic pressure in anesthetized rabbits resulted in a threefold increase in plasma AVP concentration, and renal denervation markedly reduced this AVP response. On the other hand, we were unable to demonstrate an effect of renal chemoreceptor activation on the release of AVP using retrograde pelvic perfusions of 1 M NaCl, 0.1 M KCl, or 1 M mannitol.

Recently, Day and Ciriello20 reported that intrarenal injection of bradykinin increases activity in neurosecretory cells of the supraoptic nucleus of the hypothalamus. This effect was considered to be mediated by activation of renal chemoreceptors, because bradykinin is known to activate a variety of visceral and somatic chemosensitive sensory nerves, including ARN.21-24 Other investigators have also suggested that the hemodynamic effects of intrarenal infusion of bradykinin are due to activation of renal chemoreceptors.25 In the present study, we further investigated the effects of renal chemoreceptor activation on the release of AVP using intrarenal infusion of bradykinin.

Intrarenal infusion of bradykinin increased plasma AVP concentration sixfold to ninefold in a dose-dependent manner. The lower intravenous dose of bradykinin did not change plasma AVP concentration, but the higher dose caused a significant increase. However, the increase produced by the higher intravenous dose of bradykinin was much less than that produced by the same intrarenal dose. These results thus provide evidence for an intrarenal action of bradykinin on vasopressin release. It is possible that there was some recirculation of bradykinin with the higher intrarenal dose, and this may have produced further stimulation of vasopressin release by an extrarenal action.25 It is worth noting, however, that Cicinelli et al13 have reported that the kidney has the highest tissue kininase activity, estimated to be 1,200 times the activity in plasma. Only one pass through the kidney would therefore be expected to destroy most of the bradykinin infused into the kidney. The AVP response to the higher intravenous dose of bradykinin may have been mediated by the kidneys or by an extrarenal action to stimulate AVP release.22

To determine if the renal nerves mediate the vasopressin response to intrarenal bradykinin, we also infused the peptide intrarenally after renal denervation. Denervation almost completely abolished the AVP response to intrarenal bradykinin. These results indicate that bradykinin increases AVP release by an intrarenal action and that this effect is mediated by ARN. Because bradykinin activates chemosensitive nerve endings,21-24 these results provide evidence that activation of renal chemoreceptors results in stimulation of AVP release. However, it is also possible that the AVP response to bradykinin was mediated via mechanoreceptor stimulation.15 Such a mechanism would be consistent with our previous inability to demonstrate an effect of renal chemoreceptor stimulation on AVP release.18

The mechanism of the increase in plasma renin activity produced by intravenous bradykinin was not investigated. A likely possibility is that it was mediated via increased prostaglandin synthesis, because bradykinin stimulates prostaglandin synthesis, and prostaglandins are known to stimulate renin secretion.34 Intrarenal bradykinin also increased plasma renin activity when infused in denervated kidneys but not in innervated kidneys. This suggests that the renal nerves somehow buffer the increase in renin release produced by intrarenal bradykinin. Additional studies are required to investigate this possibility.

In summary, intrarenal bradykinin infusion in anesthetized rabbits produced a dose-dependent increase in plasma AVP concentration, which was blocked by renal denervation. Intravenous bradykinin also increased plasma AVP concentration, but the increase was much less than that produced by the same intrarenal dose of bradykinin. These results demonstrate that bradykinin increases the release of AVP by an intrarenal action and suggest that this action is mediated by ARN. These findings provide further evidence for a role of renal chemoreceptors in the control of AVP release.

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