Interaction of Vasopressin and Prostaglandins Through Calcium Ion in the Renal Circulation

MASAHIDE SEINO, KEISHI ABE, KAZUO TSUNODA, AND KAORU YOSHINAGA

SUMMARY To determine whether the effects of arginine vasopressin (AVP) on the renal and systemic vessels are modulated by prostaglandins (PGs), AVP (10, 20, and 50 mU/kg/min) was infused into the renal artery before and after treatment with indomethacin (8 mg/kg) in anesthetized rabbits. Arginine vasopressin elicited a dose-dependent increase in systemic arterial pressure and renal vasoconstriction. However, after cessation of the infusion, significant renal vasodilation was observed. Indomethacin potentiated the systemic and renal vasoconstrictor actions and attenuated the renal vasodilator reaction induced by AVP. These results suggest that endogenously produced PGs buffer the vasoconstrictor action of AVP, and the renal vasodilator reaction induced by AVP could be mediated through PGs. Further, to investigate whether the effects of AVP on the systemic and renal vessels are mediated by calcium ion (Ca$^{++}$), the Ca$^{++}$ entry blocker nifedipine was used. Intravenous administration of nifedipine (50 μg/kg) attenuated the systemic and renal vasoconstrictor action of AVP. The renal vasodilator reaction induced by AVP was also diminished after treatment with nifedipine. These results indicate that the systemic and renal vasoconstrictor actions of AVP are mediated through Ca$^{++}$ influx into the vascular smooth muscle cells. The present study suggests that Ca$^{++}$ participates in the AVP-induced vasodilator reaction, itself probably mediated by PGs.

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KEY WORDS • nifedipine • calcium-ion entry blocker • indomethacin • vascular response

The main physiological role of arginine vasopressin (AVP) is to alter water permeability in the kidney.1 But AVP also possesses a potent vasoconstrictor action.2,3 It has been reported that AVP stimulates renal prostaglandin (PG) synthesis4-6 and that biosynthesized endogenous PGs act as negative feedback modulators to AVP-induced water permeability.4,7 Recently, it has been proposed that the renal vasoconstriction of AVP is modulated by an opposing vasodilative effect of intrarenal PGs triggered by AVP.8-9

Our present study examines whether the renal and systemic vasoconstrictor effect of AVP is modulated by PGs; for this purpose we used the prostaglandin synthesis inhibitor, indomethacin. To induce renal vasoconstriction, pharmacological doses of AVP were infused into the renal artery, since it is reported that infusion of a low or physiological dose of AVP causes renal vasodilation.8,10,11 Furthermore, it has been shown that the calcium ion (Ca$^{++}$) plays an important role in PG synthesis.12 Therefore, we also investigated whether the renal vascular effects of AVP are mediated through Ca$^{++}$ entry into the renal vascular smooth muscle cells. For this purpose we used nifedipine,13 one of the Ca$^{++}$ entry blockers, to determine the effects of a reduction in intracellular Ca$^{++}$.14

Methods

We used 14 female Japanese albino rabbits that weighed 3.2 to 3.7 kg. They were allowed free access to normal laboratory chow and drinking water. Anesthesia was induced by intravenous urethane (450 mg/kg) and α-chloralose (45 mg/kg). Small maintenance doses of the anesthetics were given as needed. The trachea was cannulated, and polyethylene catheters were placed into the abdominal aorta (PE 60) through the femoral artery for arterial pressure recording, and into the inferior vena cava through the femoral vein (PE 50) for nifedipine and indomethacin administration. For blood flow measurements, the left renal artery was exposed through a flank incision, and a non-cannulating electromagnetic flow probe of appropriate diameter (1.5 to 2.5 mm, Nihon Kohden Company, Inc., Tokyo, Japan) was attached around the renal artery. The hindquarters were perfused for 10 min with warm (37°C) saline at a constant pressure of 70 mm Hg. After stabilization of arterial pressure and renal blood flow, AVP (10, 20, and 50 mU/kg/min, 60 min) was infused overnight into the renal artery, and systemic vascular resistance was calculated as the ratio of arterial pressure to renal blood flow.
renal blood flow and is expressed as mm Hg/ml/min analyzed by Student’s paired t-test.

Arterial pressure was monitored with a pressure transducer and amplifier (Biophysiograph, 180 system, SAN-El Company, Ltd., Tokyo, Japan), and renal blood flow was simultaneously recorded on a pen oscillograph. The rabbits were given an infusion of Ringer’s lactate solution equal to 2% of body weight. Arginine vasopressin (Protein Research Foundation, Osaka, Japan) was diluted with 5% dextrose to the appropriate concentration for administration into the renal artery. Indomethacin was supplied by Nippon Merk Banyu Company, Ltd., Tokyo, Japan. Nifedipine (0.2 mg/2 ml) was a gift from Bayer Co. Ltd.

After surgery, at least 1 hour was allowed to elapse to stabilize the arterial pressure and renal blood flow. Then, AVP was administered intrarenally at 10, 20, and 50 mU/kg per minute. In preliminary experiments, the renal vasoconstrictor action of AVP occurred immediately and reached maximal level within 2 min. Therefore, to examine the vasoconstrictor action of AVP, the infusion lasted for 2 minutes. Time control and reproducibility of the AVP effect on renal vascular responses were examined in three rabbits. In six rabbits, following the determination of control series of dose-response curves to AVP, indomethacin (8 mg/kg) was administered intravenously as a bolus injection. In five rabbits, nifedipine (50 μg/kg) was administered intravenously after the determination of dose-response curves to AVP. Extreme care was taken to reduce the exposure of nifedipine to light. Fifteen minutes after indomethacin or nifedipine administration, the determinations of dose response curves were repeated. At least 10 minutes were allowed to elapse between two doses of AVP. Renal vascular resistance was calculated by dividing mean arterial pressure by renal blood flow and is expressed as mm Hg/ml/min. All values are expressed as means ± SEM. Data were analyzed by Student’s paired t-test.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Effect of Intrarenal Arterial Infusion of Arginine Vasopressin (AVP) on Renal Blood Flow (RBF), Renal Vascular Resistance (RVR), and Mean Arterial Pressure (MAP)</th>
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<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>10</th>
<th>20</th>
<th>50</th>
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</thead>
<tbody>
<tr>
<td>RBF (ml/min)</td>
<td>47.5 ± 4.2</td>
<td>40.6 ± 4.1*</td>
<td>34.9 ± 4.4*</td>
<td>27.6 ± 4.0*</td>
</tr>
<tr>
<td>RVR (mm Hg/ml/min)</td>
<td>2.57 ± 0.26</td>
<td>3.13 ± 0.33*</td>
<td>3.90 ± 0.47*</td>
<td>5.67 ± 0.89*</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>110 ± 3.5</td>
<td>113 ± 3.1†</td>
<td>117 ± 2.6*</td>
<td>120 ± 2.9*</td>
</tr>
</tbody>
</table>

Values are means ± SEM (n = 11)

*p < 0.001 vs control values

†p < 0.01

Results

In three time-control rabbits, basal renal blood flow was unchanged during the dose-response curves of AVP infusions, from 41.5 ± 5.8 to 40.6 ± 6.5 ml/min. After the first series of AVP infusions, no significant change in hematocrit was observed, from 44.7% ± 0.9% to 43.6% ± 1.4%. There was no significant alteration in the reproducibility of arterial pressure and renal vascular reactions to AVP.

Table 1 shows the effect of AVP on renal circulation and systemic arterial pressure in the indomethacin- or nifedipine-treated group (n = 11). The intrarenal arterial infusion of AVP caused a reduction in renal blood flow with an increase in renal vascular resistance. The doses of AVP used in this study elicited a significant increase in mean arterial pressure. After the AVP infusions were stopped, the renal blood flow not only returned to the control values but also increased to levels above control. Dose-dependent increases in renal blood flow were observed from control level, 4.4 ± 0.9 (p < 0.01), 8.2 ± 1.2 (p < 0.01), and 11.2 ± 1.4 ml/min (p < 0.001) in the three doses of AVP used respectively (n = 11). After each dose of AVP, arterial pressure and renal blood flow returned to control levels within 10 to 20 minutes.

The administration of indomethacin did not cause a significant change in mean arterial pressure from 109 ± 5 to 110 ± 4 mm Hg. However, the mean basal renal blood flow decreased from 51.5 ± 5.2 to 41.2 ± 7.8 ml/min (p < 0.05), and the renal vascular resistance increased significantly from 2.34 ± 0.28 to 3.36 ± 0.57 mm Hg/ml/min (p < 0.05) with indomethacin. The decrease in renal blood flow was apparent for 90 to 120 minutes until the end of experiment, although it was only slight in two of six animals. Indomethacin significantly potentiated the renal vasoconstrictor action induced by AVP at doses of 10 and 20 mU/kg/min, but there was no significant change with the dose of 50 mU/kg/min (Figure 1). The increases in renal blood flow after cessation of the AVP infusions were diminished significantly by treatment with indomethacin (Figure 1).

Figure 2 shows the effects of indomethacin on the changes induced by AVP on mean arterial pressure, renal blood flow, and renal vascular resistance. The increases in mean arterial pressure induced by AVP at doses of 10 and 20 mU/kg/min were significantly po-
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![Graph](image)

**Figure 1** Changes in renal blood flow induced by AVP infusions before (○○○) and after (●●●) treatment with indomethacin. Hatched columns are changes obtained during the AVP infusion. * = p < 0.05; ** = p < 0.01, compared to the changes in renal blood flow before treatment with indomethacin. n.s = no significance. Values are means ± SEM.

tentiated by treatment with indomethacin but did not reach statistical significance at the dose of 50 mU/kg/min. The decrease in renal blood flow and increase in renal vascular resistance induced by AVP were also potentiated by indomethacin.

Administration of nifedipine decreased the basal mean arterial pressure from 112 ± 3 to 106 ± 3 mm Hg (p < 0.02), but it did not affect the basal renal blood flow, from 41.5 ± 6.6 to 41.0 ± 6.9 ml/min. Figure 3 shows a typical effect of nifedipine on the changes in renal blood flow induced by AVP. Nifedipine attenuated the renal vasoconstrictor action of AVP (Figures 3 and 4). The augmentation in renal blood flow produced by the cessation of AVP infusions was also suppressed by nifedipine (Figures 3 and 4). The effects of nifedipine on the changes in mean arterial pressure, renal blood flow and renal vascular resistance induced by AVP are shown in Figure 5. Nifedipine attenuated the increase in mean arterial pressure caused by AVP. The decrements in renal blood flow and the increments in renal vascular resistance induced by AVP were also attenuated by nifedipine.

**Discussion**

The intrarenal arterial infusion of pharmacological doses of AVP caused an initial vasoconstriction, as expected. However, after withdrawal of the AVP infusions, a characteristic reversed renal vasodilation was produced. The vasodilatory response to AVP infusion is not likely due to a nonspecific action, such as reactive hyperemia. It has been reported that the administration of AVP at low doses induces renal vasodilation, although the mechanism was not clear. Recently, Oliver et al. observed that the intrarenal infusion of physiological and pharmacological doses of AVP produced an increase in renal venous plasma PGE2 concentration in dogs. They further showed that the intrarenal infusion of a physiological dose of AVP caused only renal vasodilation. However, the infusion of a pharmacological dose of AVP induced renal vasoconstriction, although the vasocostriction returned gradually to control level despite continued infusion.

Ichikawa et al. proposed that the renal insensitivity to AVP vasoconstrictor action appears to be due to an opposing vasodilative influence of intrarenal PGs production triggered by AVP in rats. In the present study, to clarify a counteracting renal vasodilation, the intrarenal infusions of pharmacological doses of AVP were stopped after a maximal renal vasoconstriction had been achieved. The increase in renal blood flow was diminished after this by treatment with indomethacin,

![Graph](image)

**Figure 2.** Effect of indomethacin on the changes in mean arterial pressure (MAP), renal blood flow (RBF), and renal vascular resistance (RVR) induced by intrarenal infusion of AVP. Before treatment with indomethacin (○○○); after treatment with indomethacin (●●●). * = p < 0.05; ** = p < 0.01; compared to the changes before treatment with indomethacin. n.s = no significance. Values are means ± SEM.
FIGURE 3. Tracings obtained from the intrarenal arterial infusions of AVP before and after treatment with nifedipine. RBF = renal blood flow, AVP = arginine vasopressin; Nifed (−) = before treatment with nifedipine, Nifed (+) = after treatment with nifedipine.

FIGURE 4. Changes in renal blood flow (RBF) induced by intrarenal infusion of arginine vasopressin (AVP) before (○→○) and after (▲→▲) treatment with nifedipine. Hatched columns show the AVP infusion period. * = p < 0.05; ** = p < 0.01, compared to the changes of RBF before treatment with nifedipine. Values are means ± SEM.

FIGURE 5. Effects of nifedipine on the changes in mean arterial pressure (MAP), renal blood flow (RBF), and renal vascular resistance (RVR) induced by intrarenal infusion of AVP. Before treatment with nifedipine (○→○); after treatment with nifedipine (▲→▲). * = p < 0.05, ** = p < 0.01; compared to the changes before treatment with nifedipine. n.s. = no significance. Values are means ± SEM.
which provided evidence that endogenously formed PGs, perhaps in renal arterioles, participate in the vasodilator reaction.

It is well known that AVP augments PG synthesis in the kidney and endogenous PGs modulate the effect of AVP on water permeability. In our study, the renal vasodilation induced by AVP occurred within a few minutes, which suggested that AVP increases renal PGs synthesis through direct vascular action rather than hydroosmotic effect. After the administration of indomethacin, the intrarenal arterial infusion of AVP produced a significantly greater vasoconstriction.

This finding is compatible with the observation of Walker et al. that the renal vasoconstrictor effect of AVP is potentiated by indomethacin. It also indicates that renal vascular PGs antagonize the vasoconstrictor action of AVP. In the present study, indomethacin potentiated the increase in systemic arterial pressure induced by AVP at doses of 10 and 20 mU/kg/min. However, no significant potentiation was observed at a dose of 50 mU/kg/min. Glänzer et al. reported that exogenous administration of AVP only transiently increased blood pressure in spite of continuous infusion. The tachyphylaxis to AVP of vascular beds may be due to a PG-mediated reaction. Endogenously formed PGs in systemic vasculatures could be important in the regulation of resistance vessels, although it is unclear what kinds of PGs are concerned with the vascular reaction in the present study.

Wennmalm also proposed that endogenous PGs are important in the regulation of systemic vascular resistance. On the other hand, it has been reported that indomethacin failed to potentiate AVP-induced vasoconstriction in the mesenteric vasculature. It was also shown that the vasoconstrictor effect of AVP on renal circulation was weaker than that in other vascular beds. It seems likely that there is an organ specificity in the interaction of AVP and PGs.

Intravenous administration of nifedipine did not affect the basal renal blood flow, as reported previously. Vasoconstrictors, such as renin-angiotensin or catecholamines, might be released secondary to a decrease in systemic arterial pressure. As a result, the vasodilator action of nifedipine could be masked by these vasoconstrictors. Nifedipine attenuated the systemic and renal vasoconstrictor reaction to AVP, which suggests that the vasoconstrictor action of AVP is mediated through a Ca++ influx process in the vascular smooth muscle cells. The renal vasoconstrictor reaction produced by AVP was also diminished by treatment with nifedipine. The underlying mechanisms for the attenuation of the renal vasodilation by nifedipine are not clear. However, the vasodilator effect of AVP could be mediated through PG synthesis, as mentioned above. We have reported that that renal vasodilator effect of exogenously administered PGE2 was not influenced by nifedipine. These results suggest that nifedipine may have some influence on the process of PG synthesis, since already synthesized PGE2 is not affected by this Ca++ entry blocker. There is a possibility that intrarenal PG synthesis triggered by AVP could involve the Ca++ influx process.

Although the blunted vasodilatory reaction by nifedipine appears to be related to the decreased vasoconstriction that preceded it, it is unlikely that the renal vasodilation triggered by the AVP infusion was a nonspecific reaction, because the low AVP dose caused a relatively increased renal blood flow in spite of the small renal vasoconstriction. Further, after treatment with indomethacin, in spite of the potentiated decrease in renal blood flow produced by AVP, the secondary renal vasodilation by AVP was not observed. These results indicate that the blunted renal vasoconstrictor reaction seen with nifedipine is not simply related to the attenuation of the preceding vasoconstriction.

It is not known whether endogenous AVP is involved in the regulation of the renal vascular resistance. The present study suggests that endogenous PGs in renal vascular beds may play an important role in modulating changes in vascular tone in response to exogenous AVP.

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