Inhibitory Effects of Proadrenomedullin N-terminal 20 Peptide on Antidiuresis and Norepinephrine Overflow Induced by Stimulation of Renal Nerves in Anesthetized Dogs

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ABSTRACT
The effects of proadrenomedullin N-terminal 20 peptide (PAMP) on changes in renal function and norepinephrine (NE) overflow induced by renal nerve stimulation (RNS) were examined in anesthetized dogs. The intrarenal arterial infusion of PAMP (10, 50, 100 ng/kg/min) did not influence basal levels of systemic and renal hemodynamics, or urine formation. RNS at a low frequency (0.5–2.0 Hz) caused significant decreases in urine flow and urinary excretion of sodium, and increases in NE secretion rate (NESR), without affecting renal hemodynamics. RNS at a high frequency (2.5–5.0 Hz), which diminishes renal hemodynamics, elicited more potent decreases in urine formation and increases in NESR. The low frequency RNS-induced reductions in urine formation and increases in NESR were almost completely abolished by the intrarenal arterial infusion of PAMP at 50 ng/kg/min, a dose that produced no alterations on basal renal hemodynamics and excretory responses. In contrast, high frequency RNS-induced renal vasoconstriction and reductions in urine formation, and increases in NESR were not affected by infusion of the peptide. We next examined the effect of PAMP on exogenously applied NE-induced renal actions, to determine if PAMP functions suppressively at postjunctional sites. The intrarenal arterial infusion of NE (100–150 ng/kg/min) produced a significant renal vasoconstriction and a reduction in urine formation, responses not affected by the administration of PAMP (50 ng/kg/min). From these findings, we suggest that PAMP functions as an inhibitory modulator of renal noradrenergic neurotransmission, via prejunctional mechanisms, and plays an important role in regulating renal functions.

Adrenomedullin is a peptide isolated from human pheochromocytoma (Kitamura et al., 1993). The DNA sequence encoding the adrenomedullin precursor, preproadrenomedullin, has been identified in human as well as rat tissues (Kitamura et al., 1993; Sakata et al., 1993). Preproadrenomedullin contains 185 amino acids, and cleavage at the signal peptide between amino acids Thr21 and Ala22 yields a shortened propeptide with 164 amino acids, which contains adrenomedullin. Adrenomedullin is produced by a proteolytic processing at paired basic amino acids (Lys93-Arg94 and Arg148-Arg149) (Kitamura et al., 1993). In addition, a unique 20 amino acids peptide followed by a typical amidation signal of Gly42-Lys43-Arg44 is present in the N-terminal portion of proadrenomedulin (Kitamura et al., 1993; Shimosawa et al., 1995). This peptide was sequently termed PAMP (Kitamura et al., 1994).

Nuki et al. (1993), Ishizaka et al. (1994), Shimekake et al. (1995) have shown that adrenomedullin causes vasodilation by a direct action on vascular smooth muscle or by activating endothelial NO synthase via elevation of intracellular calcium levels, thus increasing the production of NO to induce vasodilation. The i.v. administration of PAMP also produces a rapid and strong hypotensive effect in anesthetized rats (Kitamura et al., 1994). The peptide was found to induce vasodilation by inhibiting the release of norepinephrine from adrenergic nerve endings in the rat mesenteric vascular bed (Shimosawa et al., 1995; Shimosawa and Fujita 1996). In contrast, Champion et al. (1996, 1997) reported that vasodilator responses to PAMP are due to a direct effect mediated by an increase in cAMP rather than by inhibiting the release of adrenergic transmitter from nerve endings, in the cat hindlimb and mesenteric vascular beds.

Although tissue concentrations of PAMP in the adrenal medulla are extremely high, the peptide is detectable also in plasma and in the heart, kidney and brain (Washimine et al., 1994). Indeed, adrenomedullin mRNA is strongly expressed...
in the kidney as well as in adrenal glands, as determined by RNA blot analysis (Kitamura et al., 1993; Sakata et al., 1993). Because both PAMP and adrenomedullin are derived from the same precursor peptide, these peptides may tonically function as a modulator of renal function. Adrenomedullin elicits a pronounced renal vasodilation and diuresis, events mediated by the release of NO (Miura et al., 1995; Majid et al., 1996). Nevertheless, the effects of PAMP on renal function have remained to be examined. Our study was done to examine the effects of PAMP on basal renal function, and to investigate whether this peptide can modulate renal hemodynamic and excretory responses to stimulation of renal sympathetic nerves and to exogenously applied NE, in anesthetized dogs.

**Materials and Methods**

**Animal Preparation**

Experiments were done on adult mongrel dogs of either sex weighing 9 to 16 kg. These dogs were anesthetized with sodium pentobarbital (30 mg/kg i.v.), given maintenance doses as needed and placed on a heated surgical table that maintained the rectal temperature between 37 and 38°C. After tracheal intubation, respiration was supported by artificial ventilation with room air, using a Harvard respirator. Polyethylene catheters were placed in the right brachial artery and vein for arterial blood sampling and for infusion of saline containing 0.45% inulin, respectively. MAP and HR were monitored with a pressure transducer (Nihon Kohden, Tokyo, Japan, AP601G) connected to a catheter placed in the abdominal aorta via the right femoral artery. The left kidney was exposed retroperitoneally through a flank incision and the renal artery was isolated from surrounding tissue. All visible nerve fibers along the renal artery were isolated, ligated and cut. For RNS, the distal cut portion was surrounded tissue. All visible nerve fibers along the renal artery for 15 min. During the first 5 min of the drug infusion, urine was not collected to take into account dead space in the collection system; a urine sample was then collected for 10 min. Another curve 18-gauge needle connected to a polyethylene catheter was inserted into the left renal vein for venous blood sampling. Finally the left ureter was cannulated for urine collection. After completion of the surgical procedures, a priming dose of inulin (20 mg/kg) was given, followed by a sustaining infusion of 0.9% saline containing 0.45% inulin for the measurement of GFR, at a rate of 2.0 ml/min. MAP, HR and RBF were recorded continuously on a polygraph (Nihon Kohden, RM6000G). About 90 to 120 min were allowed for stabilization.

**Experimental Protocol**

**Experiment A.** Effects of intrarenal arterial infusion of PAMP on basal renal function were examined in 15 dogs. After equilibration, urine samples were collected during 10-min control clearance periods. Following the control period, PAMP (10, 50 or 100 ng/kg/min) was infused into the renal artery over a 35-min period. During the first 5 min after the start of the peptide infusion, urine was not collected, to take account of the dead space in the collection system. Urine samples were then collected during 10-min clearance periods (experimental periods). At the end of the third experimental period, PAMP infusion was stopped, and a 10-min recovery period was attained 5 min after the cessation of PAMP infusion. Arterial blood samples (3 ml) were obtained at the midpoint of each period. After measurement of the systemic arterial hematocrit by the microcapillary method, plasma was separated immediately by centrifugation.

**Experiment B.** Four RNS experiments were performed on each of five dogs. Each experiment included a 10-min control period and a 10-min RNS period. Blood samples (3.0 ml) were taken at 5 min in the control period, 1 and 9 min in the RNS period, from the right brachial artery and left renal vein, respectively. Urine samples were collected during the latter 5 min in each period.

The first RNS experiment was performed at a low frequency (0.5–2.0 Hz, duration, 1.0 msec and supramaximal voltage, 10–25 V) during the RNS period. The second stimulation experiment was started after a 30-min equilibration interval. In this experiment, renal nerves were stimulated at a high frequency (2.5–5.0 Hz). These RNS experiments were performed under conditions of intrarenal arterial infusion of saline, at a rate of 0.48 ml/min. Approximately 60 min after termination of the second experiment, intrarenal arterial infusion of PAMP (50 ng/kg/min) was started. Fifteen min after drug infusion, two RNS experiments (the third, low frequency RNS; the fourth, high frequency RNS) were repeated during the infusion of PAMP, in the same manner as described above. To estimate reproducibility of renal actions induced by repeated RNS, separate experiments were done using saline instead of PAMP during the third and fourth experiments.

**Experiment C.** We also evaluated the effect of PAMP on exogenous NE-induced renal actions using five dogs. After an equilibration period, a urine sample was collected during a 10 min control period. After the control period, NE (100–150 ng/kg/min) was infused into the renal artery for 15 min. During the first 5 min of the drug infusion, urine was not collected to take into account dead space in the collection system; a urine sample was then collected for 10 min. Approximately 30 min after termination of NE infusion, PAMP (50 ng/kg/min) was infused intravenously. Fifteen min after peptide infusion, urine collections were repeated during the infusion of PAMP, in the same manner as described above. Blood samples (3.0 ml) were taken at the midpoint of each 10-min urine collection period. To estimate reproducibility of the renal actions induced by repeated NE infusion, separate experiments were done using saline instead of PAMP.

**Analytical Procedures**

GFR was determined from inulin clearance. Urine and plasma inulin levels were measured spectrophotometrically (Hitachi, 650–660) according to Vurek and Pegram (1966). Urine and plasma sodium concentrations were determined using a flame photometer (Hitachi, 205D). NO metabolites (NOx) in urine was measured using an autoanalyzer (Tokyo Kasei Kogyo, TCI-NOX 1000, Tokyo, Japan). Urine was diluted with carrier solution (0.07% ethylenediamine tetra acetic acid in 0.3% NH4Cl) and passed through a cadmium reduction column to reduce from NO3 to NO2, which reacts with the Griess reagent (1% sulfanilamide and 0.1% N-1-naphthylenediamine dihydrochloride in 5% HCl). The absorbance at 540 nm was measured using a flow-through visible spectrophotometer (Tokyo Kasei Kogyo, S-3250). NO2 served as standard. Plasma NE concentration was measured by high-performance liquid chromatography with an amperometric detector (Eikom, Kyoto, Japan, EC-100), as reported (Hayashi et al., 1991). NESP was calculated by:

\[
\text{NESP} \, (\text{pg/g/min}) = \left( \frac{\text{NE}_{V} - \text{NE}_{A}}{\text{RPF}} \right) \, \text{RPF}
\]

where RPF is renal plasma flow (ml/g/min), NEV is renal venous plasma NE concentration (pg/ml), and NEA is renal arterial plasma NE concentration (pg/ml).

**Drugs**

PAMP was purchased from Peptide Institute, Inc. (Osaka, Japan) and was dissolved in saline solution containing 0.1% heat-inactivat-
ing bovine serum albumin. Other chemicals were obtained from Nacalai Tesque, Inc. (Kyoto, Japan) and Wako Pure Chemical Industries, Ltd. (Oaka, Japan).

Statistical Analysis
Data are expressed as mean ± S.E.M. For statistical analysis, we performed repeated measures one-way ANOVA combined with Dunnett’s multiple range test for multiple comparisons in experiment A. In experiments B and C, we used paired Student’s t test for two-sample comparisons and one-way ANOVA followed by a Bonferroni’s multiple comparison test for multiple comparisons. For all comparisons, differences were considered significant at P < .05 and .01.

Results
Effects of Intrarenal Arterial Infusion of PAMP on Renal Function (Experiment A). When PAMP was administered intrarenally at 10, 50 and 100 ng/kg/min, there were no significant changes in systemic (MAP and HR) and renal hemodynamics (RBF, RVR, GFR and FF). UF, UNaV, FENA and UNOX were also constant throughout the experimental period, in all doses (Results obtained with 100 ng/kg/min were described in Table 1).

Effects of PAMP on Renal Actions Induced by RNS (Experiment B). As shown in figure 1, RNS at a low frequency significantly decreased UF, UNaV and FENA, by about 50%, Table 2). Intrarenal arterial infusion of PAMP (50 ng/kg/min) did not influence the basal levels of UF and UNaV. When PAMP was administered intrarenally, the low frequency RNS-induced reductions in urine formation (UF, UNaV and FENa) to the RNS were also reproducible. In addition, significant renal vasoconstriction was also observed (RBF, GFR and FF decreased by about 35, 55 and 35%, respectively, and RVR increased by about 50%, Table 2). Intrarenal arterial infusion of PAMP (50 ng/kg/min) did not influence the basal levels of systemic, renal hemodynamics and urine formation, in the same manner as seen in experiment A. In the presence of PAMP, the low frequency RNS-induced reductions in urine formation were almost completely abolished. Observed changes in UF, UNaV and FENA by the RNS during PAMP infusion were only −11.1 ± 6.8, −2.0 ± 6.4 and −1.8 ± 6.1%, respectively, compared with each control value (Fig. 1). In contrast to the case of low frequency RNS, PAMP did not significantly attenuate the high frequency RNS-induced renal actions. During PAMP infusion, UF, UNaV and FENA decreased by 75.7 ± 6.7, 74.8 ± 7.2 and 53.3 ± 12.3%, respectively, compared with each control value; these are essentially levels similar to those observed with no PAMP infusion (Fig. 1). Also, PAMP infusion failed to suppress the high frequency RNS-induced decreases in RBF, GFR and FF and increase in RVR (Table 2).

Effects of PAMP on RNS-Induced Increases in NESR (Experiment B). The low frequency RNS significantly increased NESR from a control value of −88 ± 82 to 423 ± 168 and 419 ± 168 pg/g/min at 1 and 9 min after the start of RNS, respectively. In the case of high frequency RNS, NESR increased markedly from a control value of −153 ± 60 to 768 ± 98 and 792 ± 173 pg/g/min at 1 and 9 min after the start of RNS, respectively. The PAMP administration did not affect the basal levels of NESR, i.e., control values during PAMP infusion were −191 ± 87 and −133 ± 130 pg/g/min in the low and high frequency RNS experiments, respectively. In the following results, RNS-induced increases in NESR from control are indicated as ΔNESR, to clarify changes in NESR induced by RNS. Intrarenal arterial infusion of PAMP significantly decreased ΔNESR during low frequency RNS (from 547 ± 75 and 507 ± 104 to 15 ± 27 and 11 ± 25 pg/g/min at 1 and 9 min after the start of RNS, respectively). In contrast, the inhibitory effect of PAMP on RNS-induced NE release was not observed in the case of high frequency RNS (from 921 ± 58 and 943 ± 132 to 901 ± 190 and 810 ± 139 pg/g/min at 1 and 9 min after the start of RNS, respectively, Fig. 2).

Effects of Repeated RNS on Systemic and Renal Hemodynamics, Urine Formation and NESR (Experiment B). Reproducibility of renal actions induced by repeated RNS was estimated without administration of PAMP. Systemic and renal hemodynamic responses to repeated RNS were similar both in low (the first and the third RNS) and high (the second and the fourth RNS) frequency RNS (data not shown). As shown in figure 3, the excretory responses (UF, UNaV and FENA) to the RNS were also reproducible. In addition, changes in NESR in response to low or high RNS were reproducible (data not shown).

Effects of PAMP on Renal Actions Induced by Exogenous NE (Experiment C). As shown in Table 3, intrarenal arterial infusion of NE (100–150 ng/kg/min) produced significant decreases in RBF, GFR and FF and increase in RVR. In addition, NE infusion also elicited significant decreases in UF and UNaV. When PAMP was administered intrarenally, there were no effects on systemic and renal hemodynamics, and urine formation in the same manner as experiment A.

<p>| TABLE 1 |
| Effects of intrarenal arterial infusion of PAMP (100 ng/kg/min) on systemic and renal hemodynamics, and urine formation |
| PAMP (100 ng/kg/min) i.r.a. |</p>
<table>
<thead>
<tr>
<th>MAP (mmHg)</th>
<th>C (-10–0 min)</th>
<th>E₁ (5–15 min)</th>
<th>E₂ (15–25 min)</th>
<th>E₃ (25–35 min)</th>
<th>R₁ (40–50 min)</th>
</tr>
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<tbody>
<tr>
<td>123 ± 4</td>
<td>123 ± 4</td>
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<td>123 ± 4</td>
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<td>160 ± 8</td>
<td>160 ± 8</td>
<td>162 ± 9</td>
<td>162 ± 9</td>
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<tr>
<td>28.5 ± 2.2</td>
<td>28.5 ± 2.2</td>
<td>28.5 ± 2.3</td>
<td>28.7 ± 2.3</td>
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<tr>
<td>0.95 ± 0.09</td>
<td>0.93 ± 0.09</td>
<td>0.94 ± 0.09</td>
<td>0.96 ± 0.11</td>
<td>0.94 ± 0.10</td>
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<td>37.5 ± 3.0</td>
<td>36.5 ± 3.1</td>
<td>37.0 ± 3.2</td>
<td>37.3 ± 3.6</td>
<td>36.7 ± 3.2</td>
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<tr>
<td>20.7 ± 7.7</td>
<td>19.8 ± 7.3</td>
<td>20.2 ± 7.4</td>
<td>20.5 ± 7.6</td>
<td>21.2 ± 8.3</td>
<td></td>
</tr>
<tr>
<td>5.16 ± 2.14</td>
<td>4.59 ± 1.98</td>
<td>5.21 ± 2.08</td>
<td>5.13 ± 2.01</td>
<td>5.15 ± 1.94</td>
<td></td>
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<tr>
<td>3.60 ± 1.49</td>
<td>3.62 ± 1.48</td>
<td>3.74 ± 1.50</td>
<td>3.64 ± 1.50</td>
<td>3.68 ± 1.42</td>
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<tr>
<td>0.89 ± 0.13</td>
<td>0.86 ± 0.12</td>
<td>0.91 ± 0.15</td>
<td>0.83 ± 0.09</td>
<td>0.80 ± 0.10</td>
<td></td>
</tr>
</tbody>
</table>

Each value represents the mean ± S.E.M. of five dogs. i.r.a., Intrarenal arterial infusion; C, control period; E₁, E₂, E₃, experimental period; R₁, recovery period.
NE-induced renal vasoconstriction and reductions in urine formation were not affected by the peptide infusion, compared with those observed with the case of NE in the absence of PAMP.

**Discussion**

In our study, low frequency RNS elicited a decreased urine formation without affecting systemic and renal hemodynamics, although high frequency RNS produced more potent antidiuretic and antinatriuretic actions, in addition to reductions in RBF, GFR and FF. Intrarenal arterial infusion of PAMP (50 ng/kg/min) abolished the renal responses to low frequency RNS, whereas high frequency RNS-induced renal vasoconstriction and marked diminution in urine formation were not affected by the peptide. To clarify mechanisms underlying these effects, we determined NESR during the RNS, with or without PAMP infusion. Our results clearly indicated that intrarenal administration of PAMP attenuated markedly the NE overflow induced by low frequency RNS but not by high frequency RNS. In addition, PAMP did not affect exogenous NE-induced renal vasoconstriction and antidiuresis. Taken together, it seems likely that the suppressive action of PAMP on renal responses to low frequency RNS is due to the inhibition of NE release from renal sympathetic nerves.

Shimosawa and Fujita (1996) reported that intravenous
administration of PAMP (10–50 nmol/kg) to conscious rats produced a hypotensive effect, the potency of which is similar to that seen with adrenomedullin (0.1–1.0 nmol/kg). In their study, however, the hypotension evoked by PAMP was accompanied by less reflex tachycardia than that evoked by adrenomedullin. In addition, they demonstrated that PAMP but not adrenomedullin failed to reduce blood pressure in pithed rats. When pithed rats were electrically stimulated, PAMP as well as adrenomedullin could produce a hypotensive effect. Furthermore, plasma NE levels were reduced in the presence of PAMP but not adrenomedullin (Shimosawa and Fujita, 1996). From these findings, they suggested that the hypotensive effect of PAMP is mainly due to inhibition of peripheral sympathetic nerve activity. Actually, PAMP but not adrenomedullin inhibited the NE release by periarterial electrical nerve stimulation in perfused rat mesenteric arteries (Shimosawa et al., 1995). Taken together with the findings of the present study, it seems likely that PAMP plays an important role in various tissues as a sympatho-inhibitory modulator, at the prejunctional level.

PAMP did not influence the high frequency RNS-induced renal actions and NE overflow, in contrast to the case of the low frequency RNS. One possibility is that the dose of PAMP used (50 ng/kg/min) was too low to inhibit the high frequency RNS-induced actions. Therefore, we did additional experiments using 100 ng/kg/min of PAMP, but the results were essentially the same as seen with the low dose. Takagi et al. (1991) reported that intrarenal arterial infusion of endothelin (0.3–3.0 ng/kg/min) suppressed increases in NE efflux induced by low-frequency RNS but not high-frequency RNS. By way of explanation, they suggested that the intense activation of the neural NE release mechanism by the high-frequency nerve stimulation might overcome the presynaptic inhibitory effect of endothelin. This may be applicable to our findings.

NE release is regulated mainly by the intracellular calcium level through entry of Ca$^{2+}$ into the presynaptic terminal. The principal entry sites of Ca$^{2+}$ are the voltage sensitive N-type calcium channels. There is one report of data obtained in in vitro studies. PAMP reduced Ca$^{2+}$ influx entering the cell via N-type sensitive Ca$^{2+}$ channels in NGF-treated PC 12 cells (Takano et al., 1996). Therefore, the N-type Ca$^{2+}$ channel may account for PAMP-induced inhibition of NE release.

We also examined the effects of PAMP on antidiuretic and renal vasoconstrictor responses elicited by exogenous NE, to determine if PAMP functions suppressively at postjunctional sites. NE (100–150 ng/kg/min) was administered in a dose, which elicited reduction in UF, to the same extent as seen in low frequency RNS. In this case, intrarenal arterial infusion of PAMP (50 ng/kg/min) failed to suppress exogenous NE-induced renal vasoconstriction and reduction in urine formation. Similar results were obtained using the rat mesenteric arteries. Shimosawa et al. (1995) reported that the vasoconstrictive response to exogenous NE at a lower doses (1, 3 and

![Fig. 2. Effects of PAMP (50 ng/kg/min) on RNS-induced increases in NESP. Each value represents the mean ± S.E.M. of five dogs. †$P < .05$ versus ΔNESP at 1 min after the start of low frequency RNS during saline infusion. ‡$P < .01$ versus ΔNESP at 9 min after the start of low frequency RNS during saline infusion.](image)

![Fig. 3. Effects of repeated RNS on urine formation. Each value represents the mean ± S.E.M. of five dogs. *$P < .05$, **$P < .01$ versus each control value.](image)
TABLE 3
Effects of PAMP (50 ng/kg/min) on exogenous NE-induced systemic and renal hemodynamics, and urine formation in anesthetized dogs

<table>
<thead>
<tr>
<th></th>
<th>MAP (mm Hg/min)</th>
<th>HR (beats/min)</th>
<th>RR (mm Hg)</th>
<th>IVR (mm Hg/kg/min)</th>
<th>UF (µl/g/min)</th>
<th>FF (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saline infusion</td>
<td>130.8±6.5</td>
<td>148.6±5.9</td>
<td>72.5±6.3</td>
<td>14.9±2.6</td>
<td>0.0±0.0</td>
<td>125±7</td>
</tr>
<tr>
<td>Control 1</td>
<td>130.0±6.4</td>
<td>146.8±5.4</td>
<td>72.0±6.4</td>
<td>14.8±2.6</td>
<td>0.0±0.0</td>
<td>125±7</td>
</tr>
<tr>
<td>Control 2</td>
<td>128.0±5.3</td>
<td>143.0±4.9</td>
<td>70.5±6.1</td>
<td>14.5±2.5</td>
<td>0.0±0.0</td>
<td>125±7</td>
</tr>
<tr>
<td>PAMP infusion</td>
<td>123.0±6.0</td>
<td>131.0±5.6</td>
<td>69.0±6.0</td>
<td>14.0±2.5</td>
<td>0.0±0.0</td>
<td>125±7</td>
</tr>
<tr>
<td>PAMP infusion</td>
<td>120.0±5.2</td>
<td>129.0±5.2</td>
<td>67.5±5.9</td>
<td>13.5±2.4</td>
<td>0.0±0.0</td>
<td>125±7</td>
</tr>
</tbody>
</table>

Each value represents the mean ± SEM of 5 of 6 dogs of each group. *P<0.05 versus each control (NS, not significant).

10 µmol) was not suppressed by 10 pmol/ml of PAMP, a dose that did not alter the basal perfusion pressure. In contrast to the effect of PAMP on the exogenous NE-induced pressor response, adrenomedullin (10 pmol/ml) suppressed the vasocostrictive response induced by exogenous NE. Therefore, it is not likely that PAMP affects renal actions caused by exogenous norepinephrine. In contrast, Champion et al. (1996, 1997) reported that administration of PAMP as well as adrenomedullin caused dose-related decreases in the basal perfusion pressure in the cat hindlimb and mesenteric vascular bed, although the effect of PAMP was 100-fold less than that seen with adrenomedullin. These discrepancies may be due to the differences in species and/or tissues.

In our study, the renal plasma concentration of PAMP after intrarenal arterial infusion of PAMP at rates of 10 to 100 ng/kg/min was estimated to be about 1 to 20 ng/ml, because the renal plasma flow was 6 to 8 ml/min/kg body weight. It has been reported that the plasma concentration of PAMP was in the order of femtomoles per milliliter (equal to picograms per milliliter) in human healthy subjects (Eto et al., 1996). The doses of PAMP, we used in this study, are much higher than those under physiological conditions. However, because adrenomedullin mRNA was found to be strongly expressed in the kidney as well as adrenal glands (Kitamura et al., 1993; Sakata et al., 1993), its local concentration in the kidney may reach pharmacological concentrations.

In summary, the intrarenal administration of PAMP inhibited the low frequency RNS-induced increased response of NE release from renal noradrenergic nerve endings and suppressed antidiuretic and antinatriuretic responses to this RNS. In addition, PAMP did not suppress the exogenous NE-induced renal vasoconstriction and reductions in urine formation. These findings strongly suggest that PAMP plays an important role as an inhibitory modulator of renal noradrenergic neurotransmission through the direct inhibition of NE release at prejunctural mechanisms.

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References


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