Effects of synthetic atrial natriuretic factor on renal function and renin release

JOHN C. BURNETT, JR., JOEY P. GRANGER, AND TERRY J. OPGENORTH
Departments of Medicine and of Physiology and Biophysics,
Mayo Medical School, Rochester, Minnesota 55905

BURNETT, JOHN C., JR., JOEY P. GRANGER, AND TERRY J. OPGENORTH. Effects of synthetic atrial natriuretic factor on renal function and renin release. Am. J. Physiol. 247 (Renal Fluid Electrolyte Physiol. 16): F863-F866, 1984.—Studies were performed in anesthetized dogs (n = 5) to determine the effects of synthetic atrial natriuretic factor on renal function and renin release. Intrarenal infusion of synthetic atrial natriuretic factor (ANF) (0.3 µg·kg⁻¹·min⁻¹) resulted in a transient increase in renal blood flow (126 ± 8 to 148 ± 11 ml/min). The duration of this transient vasodilation was 3.1 ± 0.4 min. Continued infusion was followed by a slight decrease in renal blood flow (126 ± 8 to 117 ± 8 ml/min) and an increase in glomerular filtration rate (23.1 ± 3.5 to 30.7 ± 1.9 ml/min), with filtration fraction thus being increased (0.19 ± 0.04 to 0.27 ± 0.03). These hemodynamic alterations were associated with increases in fractional sodium excretion (0.6 ± 0.2 to 5.8 ± 0.8%), fractional potassium excretion (30.8 ± 9.4 to 56.3 ± 7.4%), fractional lithium excretion (32.2 ± 7.1 to 60.3 ± 5.7%), and fractional phosphate excretion (8.7 ± 3.5 to 41.6 ± 11.7%). Intrarenal infusion of synthetic ANF markedly suppressed renin secretion rate (295.5 ± 84.6 to 17.2 ± 10.6 ng/min) despite a slight reduction in arterial pressure (123 ± 9 to 118 ± 9 mmHg). Our studies demonstrate that synthetic ANF results in a marked natriuretic response that is in part mediated by an increase in glomerular filtration rate. The increase in fractional lithium and phosphate excretion suggests that this factor may also have an action on proximal tubule reabsorption. Further, these studies demonstrate that synthetic ANF markedly inhibits renin secretion.

sodium excretion; proximal tubule; renal hemodynamics

CRUDE EXTRACT OF ATRIA when infused into the renal artery results in a marked natriuresis. Previous investigations of the effects of atrial extract on renal hemodynamics and tubular reabsorption during the natriuretic response conflict. Studies have demonstrated either increases or no change in glomerular filtration rate and renal blood flow (3, 6, 15, 17, 19). Distal tubular blockade, micropuncture, and microcatheterization studies, all performed in the rat, have suggested no effect of the extract on proximal tubular reabsorption (3, 15, 17).

Recent purification, sequencing, and synthesis of atrial natriuretic factor (ANF) have resulted in the availability of a synthetic peptide composed of the 26 amino acids from residues 8 to 33 of ANF. This synthetic peptide has been found to have the same biological activity as the native peptide (10). Synthetic ANF now permits further elucidation of the precise action of this factor on renal function. In vitro studies with atriopeptin II, a purified peptide of 23 amino acids, have established a relaxing action on intestinal and aortic smooth muscle strips (7). Preliminary dose-response studies have reported that increasing doses of synthetic ANF result in a respective stepwise increase in fractional sodium excretion (16). In the latter study the natriuretic response occurred in the absence of a significant alteration in glomerular filtration rate or renal blood flow, suggesting a direct tubular effect independent of any hemodynamic action. A recent investigation, however, in the isolated perfused kidney preparation that employed semipurified atrial extract supports a critical role for a hemodynamic effect in the natriuretic response (6).

The present study, therefore, was designed to investigate the effects of synthetic ANF on renal function and renin release. Specifically, these studies were designed to focus on the effect of synthetic ANF on renal blood flow, glomerular filtration rate, renal interstitial hydrostatic pressure, proximal tubule reabsorption, and renin release.

METHODS

Experiments were performed in mongrel dogs of both sexes weighing 14-21 kg. Polyethylene matrix capsules for measurement of renal interstitial hydrostatic pressure were implanted in the left kidney 3-4 wk preceding the acute experiment, as previously described (4).

On the day of the acute experiment, the dogs were anesthetized with pentobarbital sodium (30 mg/kg, i.v.). The femoral artery and vein were cannulated and catheters were inserted for measurement of mean arterial pressure and infusion of insulin in isotonic saline at a rate of 1 ml/min to achieve plasma levels of 50 mg/dl. The left kidney was exposed via a subcostal incision. The ureter was isolated and cannulated for timed urine collections. An electromagnetic flow probe was placed on the renal artery and connected to a flowmeter (Micron
Instruments, model RC1008) for measurement of renal blood flow. A curved 22-gauge needle was inserted into the renal artery and connected to a syringe pump (Sage Instruments, model 391A), which delivered isotonic saline at a rate of 1 ml/min. A curved needle (20-gauge) was also inserted into the renal vein for sampling of renal venous blood. Tubing from the chronically implanted renal interstitial capsules was located and placed in a holder for measurement of renal interstitial hydrostatic pressure with a servo-nulling device (Instruments for Physiology and Medicine, model 4A).

After completion of surgery, the dogs were allowed to stabilize for approximately 1 h. Three 15-min control clearances were obtained, followed by intrarenal infusion of synthetic ANF (Merck, West Point, PA) at a rate of 0.3 µg·kg⁻¹·min⁻¹ for a total of 45 min. Fifteen minutes after initiation of synthetic ANF infusion, three 10-min clearances were obtained. The infusion was then stopped. Following a 30-min washout period, three 15-min recovery clearances were obtained.

Glomerular filtration rate was measured by the clearance of inulin. Inulin concentrations were measured by the anthrone method (8). Renin secretion rate was calculated from the product of renal plasma flow and the renal arteriovenous plasma renin activity difference. For clarity of presentation, the renin secretion rate units of nanograms angiotensin I per hour per minute were simplified to nanograms per minute. Plasma renin activity was measured by radioimmunoassay (11). Samples for plasma renin activity were obtained in the last two clearances of each period. Concentrations of sodium and potassium were measured using ion-selective electrodes (Beckman E2A analyzer). Phosphate was measured according to the method of Chen et al. (5). Osmolality of urine and plasma was determined by a vapor pressure osmometer (Wescor, model 5100).

Whole kidney proximal tubular reabsorption of sodium was estimated by the lithium-clearance technique. This technique has been shown to be a reliable method for estimating proximal tubular handling of sodium, since lithium is reabsorbed exclusively by the proximal tubule (12, 18). The dogs were given 300 mg of lithium (orally) the night before each experiment. Lithium concentration in plasma and urine was measured by flame emission spectrophotometry (Instrumentation Laboratory, model 357).

All data from the three clearances in control, ANF, and recovery periods were averaged and are expressed as means ± SE. The data were analyzed using Dunnett's paired t test for simultaneous multiple comparisons.

RESULTS

Table 1 summarizes the renal hemodynamic and excretory function data during control, intrarenal infusion of synthetic ANF, and recovery for five normal dogs.

Hemodynamics. A slight decrease in mean arterial pressure (123 ± 9 to 118 ± 9 mmHg, P < 0.05) and renal blood flow (126 ± 8 to 117 ± 8 ml/min, P < 0.01) was observed during synthetic ANF infusion. Renal vascular resistance was unchanged. However, initiation of the

<table>
<thead>
<tr>
<th>MAP, mmHg</th>
<th>Control</th>
<th>ANF, 0.3 µg·kg⁻¹·min⁻¹</th>
<th>Recovery</th>
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<tr>
<td>123 ± 9</td>
<td>118 ± 9</td>
<td>118 ± 9</td>
<td>124 ± 7</td>
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<tr>
<td>126 ± 8</td>
<td>117 ± 8</td>
<td>117 ± 8</td>
<td>115 ± 11</td>
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<tr>
<td>30.3 ± 3.5</td>
<td>30.7 ± 1.9†</td>
<td>21.8 ± 1.4</td>
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<tr>
<td>0.99 ± 0.11</td>
<td>1.04 ± 0.13</td>
<td>1.13 ± 0.13</td>
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<thead>
<tr>
<th>FF</th>
<th>Control</th>
<th>ANF, 0.3 µg·kg⁻¹·min⁻¹</th>
<th>Recovery</th>
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<tr>
<td>0.19 ± 0.04</td>
<td>0.27 ± 0.03†</td>
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<tr>
<td>Pi, mmHg</td>
<td>3.8 ± 0.5</td>
<td>2.9 ± 1.0</td>
<td>3.6 ± 0.7</td>
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<td>V, ml/min</td>
<td>0.18 ± 0.02</td>
<td>2.20 ± 0.06†</td>
<td>0.24 ± 0.02</td>
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<td>UₕNaV, µg/min</td>
<td>19.6 ± 6.2</td>
<td>263.0 ± 32.4†</td>
<td>28.2 ± 5.6</td>
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<td>FE₂Na</td>
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<td>5.8 ± 0.8†</td>
<td>1.0 ± 0.1</td>
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<tr>
<td>UₕNa, µg/min</td>
<td>3.0 ± 0.6</td>
<td>61.6 ± 8.0†</td>
<td>32.0 ± 7.7</td>
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<td>FE₂Ex</td>
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<td>36.3 ± 7.4†</td>
<td>34.6 ± 7.4</td>
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<td>FE₂Na</td>
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<td>60.3 ± 5.7†</td>
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</tr>
<tr>
<td>FE₂po</td>
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<td>41.6 ± 11.7†</td>
<td>13.6 ± 4.7†</td>
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<tr>
<td>UₕNaH₂O, moles/kg H₂O</td>
<td>1.101 ± 126</td>
<td>359 ± 28†</td>
<td>963 ± 177</td>
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<td>CₕH₂O, ml/min</td>
<td>-0.41 ± 0.08</td>
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<td>-0.45 ± 0.11</td>
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<td>RSR, %</td>
<td>295.5 ± 84.6</td>
<td>17.2 ± 10.6†</td>
<td>405.3 ± 210.2</td>
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ANF infusion was characterized by a transient increase in renal blood flow. Renal blood flow increased from 126 ± 8 to 148 ± 11 ml/min, P < 0.05. The duration of this transient vasodilation was 3.1 ± 0.4 min. A representative tracing of this renal vasodilation response is illustrated in Fig. 1. Glomerular filtration rate increased from 123 ± 9 to 118 ± 9 mmHg, P < 0.05. No change was observed, however, in free water clearance, RSR, renin secretion rate. P values compare results with control: * P < 0.05; † P < 0.01.

![Fig. 1. Renal blood flow tracing during initiation of intrarenal infusion of synthetic atrial natriuretic factor (ANF) that demonstrates transient renal vasodilation.](http://ajprenal.physiology.org/ by 10.2203.34.4 on August 27, 2017)
renal effects of synthetic ANF

Fractional sodium excretion, fractional lithium excretion, and glomerular filtration rate before, during, and following intrarenal infusion of synthetic atrial natriuretic factor (ANF).

Control ANF Recovery

FIG. 2. Fractional sodium excretion, fractional lithium excretion, and glomerular filtration rate before, during, and following intrarenal infusion of synthetic atrial natriuretic factor (ANF).

Intrarenal infusion of synthetic ANF caused a decrease in renin secretory rate from 295.5 ± 84.6 to 17.2 ± 10.6 ng/min, P < 0.01. Renin secretion returned to control values after synthetic ANF infusion was discontinued.

DISCUSSION

Intrarenal infusion of synthetic ANF causes a marked increase in urine volume and sodium excretion. This marked natriuresis and diuresis were associated with significant increases in glomerular filtration rate and fractional sodium excretion and with decreases in proximal tubule reabsorption as estimated by changes in lithium excretion and renin secretion.

A unique renal blood flow response to intrarenal administration of synthetic ANF that has not been previously reported was observed during the present investigation. We noted a significant transient increase in renal blood flow despite continued infusion of synthetic ANF. The transient increase in renal blood flow was followed by a slight but significant decrease in renal blood flow that persisted, with no change in total renal vascular resistance as compared with preinfusion levels.

The mechanism mediating this biphasic renal blood flow response is unclear. However, previous studies reported a vasodilating or vasoconstricting action of atrial natriuretic factor. Oshima et al. (14) reported that bolus injections of atrial extract result in a decrease in renal vascular resistance. Camargo et al. (6) reported that sustained infusion of semipurified atrial natriuretic factor in the isolated perfused kidney results in an increase in renal vascular resistance.

Glomerular filtration rate significantly increased during synthetic ANF infusion. The observed decrease in renal blood flow and increase in filtration fraction support the interpretation that the increase in glomerular filtration rate was associated with an increase in postglomerular arteriolar resistance. In view of these renal hemodynamic effects, synthetic ANF may have produced a balanced effect to decrease preglomerular resistance and increase postglomerular resistance. A direct effect, however, of ANF to increase GFR and thus increase glomerular filtration rate cannot be excluded. These studies suggest that the natriuresis observed during intrarenal infusion of synthetic ANF was in part mediated by an augmentation of glomerular filtration.

Intrarenal infusion of synthetic ANF also resulted in a significant increase in the fractional excretion of lithium. Several laboratories have established lithium as a marker for proximal sodium reabsorption (12, 18). In support of this observation, we also observed a significant increase in the fractional excretion of phosphate (9). Although the present studies suggest that synthetic ANF may have a proximal tubular effect in the dog, the increased filtered load of these ions may have also contributed to the increased excretion of lithium and phosphate. The absence of an increase in renal interstitial hydrostatic pressure as well as the increase in filtration fraction imply that a proximal tubular action would be independent of alterations in physical factors.

Synthetic ANF decreased urine osmolality and increased potassium excretion. Urine osmolality decreased with no associated increase in free water clearance. The absence of an increase in free water clearance indicates that the decrease in urine osmolality was the result of an increase in urine volume. The increased urine volume
may also explain the increased potassium excretion such that an increased tubular flow rate enhanced tubular potassium secretion within the distal nephron. Interestingly, despite the marked decrease in urine osmolality during synthetic ANF infusion, urinary osmolality returned to control values during recovery, suggesting that medullary washout did not occur. Nevertheless, the decrease in urinary osmolality in the absence of an increase in free water clearance suggests a decrease in interstitial tonicity, supporting medullary washout as reported by BoreNSTEIN et al. (2) employing atrial extracts in the rat.

Recent investigations have reported that ANF inhibits angiotensin II-induced release of aldosterone from rat zona glomerulosa (1). The present studies extend these observations and demonstrate a marked action of synthetic ANF on the secretion of renin. We observed, despite a decrease in arterial pressure, a significant reduction in renin secretory rate. The mechanism by which administration of synthetic atrial natriuretic factor results in marked inhibition of renin release is unclear. Previous studies have established an inverse relationship between sodium chloride delivery to the macula densa and renin secretory rate (13). Probable enhanced delivery of sodium chloride to the macula densa during intrarenal synthetic ANF infusion thus would be expected to signal the juxtaglomerular cells to decrease renin release. An alternative explanation for the suppression of renin release is that synthetic ANF may have a direct inhibitory effect on juxtaglomerular cells. It is possible that suppression of the renin-angiotensin system by synthetic ANF may partially contribute to the observed natriuresis. Further, delivery of sodium chloride to the macula densa would be expected to activate tubuloglomerular feedback. This may explain the observed reduction in renal blood flow that followed the initial transient vasodilation following the onset of synthetic ANF infusion.

In summary, our studies demonstrate that intrarenal administration of synthetic atrial natriuretic factor results in a significant natriuretic response. This natriuretic response is associated with an increase in glomerular filtration rate and a decrease in proximal tubule reabsorption as determined by the clearance of lithium. These studies also demonstrate that intrarenal administration of synthetic atrial natriuretic factor results in marked inhibition of renin release.

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REFERENCES


