EFFECTS OF $\alpha$-HUMAN NATRIURETIC PEPTIDE ON RENAL HEMODYNAMICS AND DIURESIS IN DOGS AND PERFUSED RAT KIDNEYS

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Effects of $\alpha$-human atrial natriuretic polypeptide ($\alpha$-hANP) on renal function were studied in anesthetized dogs and isolated perfused rat kidneys. Two doses of $\alpha$-hANP were used to determine whether renal hemodynamics or tubular reabsorption is the major factor in the diuretic action of $\alpha$ hANP. The excretion rates of sodium (Na) and inorganic phosphate (PO$_4$) were evaluated to determine the site of diuretic action in the renal tubule. In dogs that received the smaller dose of $\alpha$-hANP (5 ng.kg$^{-1}$.min$^{-1}$) infused into the renal arteries without changes in systemic or renal hemodynamics, urine volume (UV) and urinary Na excretion (UNaV) increased significantly. Fractional excretion of Na (FENA) was increased, while fractional excretion of PO$_4$ (FEPO$_4$) was unchanged, following the infusion of $\alpha$-hANP. The calculated fractional Na reabsorption in the distal tubule (DTRNa) during the infusion of $\alpha$-hANP was significantly suppressed. In dogs that received the larger dose of $\alpha$-hANP (50 ng.kg$^{-1}$.min$^{-1}$), the glomerular filtration rate (GFR), UV, and FENA were increased and DTRNa was decreased. In isolated rat kidneys perfused at a constant pressure, a lower concentration of $\alpha$-hANP (0.5 ng.ml$^{-1}$) in the perfusate caused diuresis and increased Na and PO$_4$ excretion without any renal hemodynamic alterations. A higher concentration of $\alpha$-hANP (5 ng.ml$^{-1}$) increased GFR, Na and PO$_4$ excretion. Since PO$_4$ reabsorption is believed to occur primarily in the renal proximal tubule, these findings suggest that the diuretic action of $\alpha$-hANP in smaller doses is induced by direct action on renal distal nephron. However, the site of action of $\alpha$-hANP in larger doses was not determined in the renal tubule because GFR and FEPO$_4$ increased and DTRNa decreased following infusion of $\alpha$-hANP.  

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In 1981, de Bold et al! demonstrated that mammalian atrial extracts given intravenously produce a potent diuresis, i.e., natriuresis accompanied by a smooth muscle relaxation. Many forms of atrial natriuretic factors and peptides (ANF and ANP) with similar biological activities have been purified and identified from rat atrium. The term ANP will be used in this report. In 1984, Kangawa and Matsuo2 purified peptides from atrial extracts of humans and determined amino-acid sequences of one of three different peptides ($\alpha$-human atrial natriuretic peptide ($\alpha$-hANP)). The pharmacological and physiological effects of ANP and $\alpha$-hANP on vascular smooth muscles, systemic and renal hemodynamics, and

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sodium excretion have been investigated and reviewed in detail.\(^3\)–\(^5\)

Strong natriuretic effects of α-hANP have been well established in rats\(^2\) and dogs\(^6\)–\(^8\) but the precise mechanism of sodium diuresis has not been fully clarified. Changes in renal hemodynamics, particularly an increase in the glomerular filtration rate (GFR), inducing natriuretic action, are possible mechanisms based on animal studies.\(^6\)–\(^9\),\(^10\) Other reports have suggested that renal effects are not mediated by a change in GFR, but rather by redistribution of blood flow\(^5\),\(^8\) or by direct inhibition of tubular sodium reabsorption.\(^11\),\(^12\)

In this animal study, we used smaller doses of α-hANP, which did not affect renal hemodynamics, to evaluate the role of tubular reabsorption on the natriuretic action of α-hANP. Changes in the sodium (Na) and inorganic phosphate (PO\(_4\)) levels were particularly evaluated to determine the active site of α-hANP in the renal tubule.\(^13\)

Since reabsorption of PO\(_4\) is believed to occur primarily at the early proximal renal tubule, increased quantities in the urine suggests proximal activity of the drug. Moreover, fractional distal reabsorption of Na was calculated from fractional excretion of PO\(_4\) (FEPO\(_4\)) and Na (FENa). This value enabled us to determine the difference between proximal and distal tubular transport of electrolytes. In the first experiment, α-hANP was infused into the renal artery of dogs to eliminate systemic hemodynamic effects. In the second experiment, we examined isolated perfused rat kidneys to rule out extrarenal neural or hormonal effects that may influence renal hemodynamics and tubular electrolyte reabsorption.

MATERIALS AND METHODS

Institutional approval of the experimental protocol was obtained and the guidelines of the National Institute of Health for the care and use of laboratory animals were followed.

Experiment 1. (in vivo Study in Dog)

The technique for drug infusion into the dog’s renal artery has been described previously.\(^13\) In this experiment, 16 mongrel male dogs weighing 9 to 13 kg were anesthetized with pentobarbital. A polyethylene catheter was then inserted into the femoral artery for measuring blood pressure and blood sampling and another catheter was inserted into the femoral vein for fluid and drug administration. The dog’s abdomen was opened through a midline incision and the right kidney was removed. The left ureter was cannulated and urine was collected every 20 minutes throughout the study. A curved 22-gauge needle, attached to polyvinyl tubing was inserted into the left renal artery. After surgery, 40–60 min were allowed for stabilization before the experiments were begun. Ringer’s lactate solution (containing 0.1% paraaminohippuric acid (PAH)) was administered intravenously at 10 ml.kg\(^{-1}\).hr\(^{-1}\) throughout the study. The dogs were divided into two groups. After two 20 min control periods while saline was infused into the left renal artery, α-hANP (Suntory Pharmaceutical LTC, Japan) was infused into the left renal artery at 5 ng.kg\(^{-1}\).min\(^{-1}\) (Group 1) or 50 ng.kg\(^{-1}\), min\(^{-1}\) (Group 2). These two infusion rates were calculated to provide increases in renal plasma concentrations of 0.5 ng.min\(^{-1}\) and 5 ng.min\(^{-1}\), respectively.

Following the 20 min stabilization period, two 20 min clearance periods for α-hANP infusion were obtained. Urine was collected for each of the 20 min periods and blood was drawn at the midpoint of each period. The urine and plasma concentrations of PAH, creatinine (Cr), and PO\(_4\) were determined colorimetrically. Concentrations of Na and potassium (K) were determined by flame photometry, and plasma osmolarity was measured by a freezing point technique using a Knauer osmometer.

Experiment 2. (in vitro Study in Rats)

Eight male Wistar rats weighing 280 to 330 g were anesthetized with pentobarbital (50 mg.kg\(^{-1}\) intraperitoneally) and their kidneys were isolated and perfused according to the methods of Nishiiutsuji-Uwo, et al.\(^4\)

The perfusate was composed of a Krebs-Henseleit buffer which contained 6.7 g.dl\(^{-1}\) of fraction V bovine serum albumin, 20 essential amino acids\(^5\) 5 mmol.l\(^{-1}\) of glucose and 50 mg.l\(^{-1}\) of Cr. Following kidney isolation, 120 ml of perfusate was recirculated at 37°C and continuously oxygenated with 95% O\(_2\)/5% CO\(_2\). Renal perfusion flow

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(RPF) was measured by an electromagnetic flowmeter and the perfusion pressure was monitored at the renal artery through a double lumen needle. The perfusion pressure was continuously maintained at 120 mmHg throughout the experiment and urine was collected through a ureteral catheter.

Following a 10 min stabilization period, two 10 min control clearance periods were obtained. Two doses of α-hANP were then added to the perfusate consecutively to obtain a lower perfusate concentration (0.5 ng.ml⁻¹: ANP-1 period) and a higher concentration (5 ng.ml⁻¹: ANP-2 period), and two 10 min experimental clearance periods were obtained during each period. Urine was collected during each 10 min clearance period and perfusate was collected at the midpoint of each clearance period. Urine and perfusate concentrations of Cr, PO₄, Na, and K were determined as in experiment 1.

**ANALYTICAL METHODS**

**Experiment 1**

The free water clearance (CH₂O), and fractional excretion of Na (FENa), K (FEK) and PO₄ (FEPO₄) were calculated from the following formulae:

\[
CH₂O = UV \times (1-Uosm/Posm)
\]

\[
FENa = (UV \times UNa)/(Ccr \times PNa) = UNaV/(Ccr \times PNa)
\]

\[
FEK = (UV \times UK)/(Ccr \times PK) = UKV/(Ccr \times PK)
\]

\[
FEPO₄ = (UV \times UPO₄)/(Ccr \times PPO₄) = UPO₄V/(Ccr \times PPO₄)
\]

where \(UV\) is the urine volume in ml.min⁻¹, and \(Uosm\) and \(Posm\) are urine and plasma osmolarities, respectively. \(UNa\), \(UK\), and \(UPO₄\) are the concentrations of Na, K and PO₄ in urine and PNa, PK and PPO₄ are the plasma concentrations of Na, K and PO₄, respectively. \(UNaV\), \(UKV\) and \(UPO₄V\) are the urinary excretion volume of Na, K and PO₄, respectively. \(Ccr\) is creatinine clearance in ml.min⁻¹ and estimates GFR. Filtration fraction (FF) was calculated by dividing \(Ccr\) by CPAH. CPAH is the paraaminohippuric acid clearance in ml.min⁻¹.

The fractional Na reabsorption in the distal tubule (FDRNa) and the distal tubular rejection fraction of Na (DTRFNa) were estimated by FDRNa(%) = (FEPO₄ - FENa) / (FEPO₄) x 100, and DTRFNa(%) = 100 - FDRNa.

**Experiment 2**

Renal vascular resistance (RVR) was calculated by dividing RPF by perfusion pressure, which was 120 mmHg in this study. Other parameters were determined as in experiment, but PNa, PK and PPO₄ were the perfusate concentrations of Na, K and PO₄, respectively. \(Ccr\) was calculated by renal extraction data for creatinine:

\[
Ccr = RPF \times ((PACr - PVCr)/PACr)
\]

where \(PACr\) and \(PVCr\) represent the concentrations of creatinine in the perfusate of the renal artery and vein, respectively.

**Statistical Analysis**

The significance of changes was assessed by the Wilcoxon matched-pairs singled-ranks test between the two periods in each group and by the Mann-Whitney test between the control periods in two groups. The Friedman test was used to compare the differences among the three periods in each group. The spearman rank correlation was used calculate the correlation coefficient. Values are presented as mean ± SD, and a value of p < 0.05 was considered significant.

**RESULTS**

**Experiment 1**

Neither blood pressure nor heart rate changed in either Group 1 or Group 2 during the study. There was no significant difference in renal function between the two groups during the control period (Table I). In Group 1, although CPAH and \(Ccr\) did not change, \(UV\), \(UPO₄V\), \(UNaV\) and \(UKV\) increased significantly compared to the control period (Table I). In Group 2, CPAH did not change, but \(Ccr\) increased significantly. As a result, during α-hANP infusion, the filtration fraction rose from a control value of 0.30 ± 0.05 to 0.36 ± 0.08. \(UV\) and \(UNaV\) also increased significantly more in Group 2 than in Group 1 (Fig. 1). FENa increased significantly in Groups 1 and 2, two-fold and four-fold, respectively. However, FEPO₄ increased only in Group 2. The relationship
### TABLE I EFFECTS OF $\alpha$-hANP INFUSION (5 ng.kg$^{-1}$.min$^{-1}$: GROUP 1, 50 ng.kg$^{-1}$.min$^{-1}$: GROUP 2) ON RENAL FUNCTION IN DOGS. (mean±SD, n=8, RESPECTIVELY)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control (mmHg)</th>
<th>$\alpha$-hANP (mmHg)</th>
<th>Control (ml.min$^{-1}$)</th>
<th>$\alpha$-hANP (ml.min$^{-1}$)</th>
<th>Control (ml.min$^{-1}$)</th>
<th>$\alpha$-hANP (ml.min$^{-1}$)</th>
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<th>Control (ml.min$^{-1}$)</th>
<th>$\alpha$-hANP (ml.min$^{-1}$)</th>
<th>Control (ml.min$^{-1}$)</th>
<th>$\alpha$-hANP (ml.min$^{-1}$)</th>
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<tbody>
<tr>
<td>MAP (mmHg)</td>
<td>control 112.9±13.5</td>
<td>$\alpha$-hANP 114.8±8.8</td>
<td>control 105.2±13.6</td>
<td>$\alpha$-hANP 113.8±12.7</td>
<td>control 165.5±12.0</td>
<td>$\alpha$-hANP 163.9±15.5</td>
<td>control 62.9±13.6</td>
<td>$\alpha$-hANP 66.7±13.8</td>
<td>control 57.9±17.2</td>
<td>$\alpha$-hANP 66.8±15.3</td>
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<td>HR (ml.min$^{-1}$)</td>
<td>control 0.21±0.14</td>
<td>$\alpha$-hANP 0.18±0.08*</td>
<td>control 0.36±0.24**</td>
<td>$\alpha$-hANP 1.02±0.58**</td>
<td>control 66.7±13.8</td>
<td>$\alpha$-hANP 66.8±15.3</td>
<td>control 18.5±4.0</td>
<td>$\alpha$-hANP 19.5±4.4</td>
<td>control 18.3±5.1</td>
<td>$\alpha$-hANP 23.2±5.1**</td>
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<td>$\text{Ccr}$(ml.min$^{-1}$)</td>
<td>control 22.8±13.9</td>
<td>$\alpha$-hANP 56.1±25.5***</td>
<td>control 0.90±0.60</td>
<td>$\alpha$-hANP 0.86±0.40</td>
<td>control 110.2±27.0</td>
<td>$\alpha$-hANP 168.4±49.4**</td>
<td>control 118.5±33.4</td>
<td>$\alpha$-hANP 148.5±70.6</td>
<td>control 9.85±4.75</td>
<td>$\alpha$-hANP 9.22±3.03*</td>
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<tr>
<td>$\text{UNaV}$(µEq.min$^{-1}$)</td>
<td>control 2.24±1.09**</td>
<td>$\alpha$-hANP 110.1±48.8**</td>
<td>control 118.5±33.4</td>
<td>$\alpha$-hANP 148.5±70.6</td>
<td>control 8.95±2.88</td>
<td>$\alpha$-hANP 7.90±2.71</td>
<td>control 9.03±4.33</td>
<td>$\alpha$-hANP 88.9±4.5</td>
<td>control 12.8±1.6</td>
<td>$\alpha$-hANP 15.3±4.5</td>
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<td>$\text{FEPO}_4$(%)</td>
<td>control 76.4±10.9**</td>
<td>$\alpha$-hANP 60.3±10.5**</td>
<td>control 16.8±4.7**</td>
<td>$\alpha$-hANP 20.6±2.9**</td>
<td>control 22.3±5.4</td>
<td>$\alpha$-hANP 24.3±6.9</td>
<td>control 25.9±9.3</td>
<td>$\alpha$-hANP 28.5±9.3</td>
<td>control -0.03±0.18</td>
<td>$\alpha$-hANP -0.08±0.08</td>
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<tr>
<td>$\text{FDRNa}$(%)</td>
<td>control 89.3±4.75</td>
<td>$\alpha$-hANP 88.9±4.5</td>
<td>control 12.8±1.6</td>
<td>$\alpha$-hANP 15.3±4.5</td>
<td>control 22.3±5.4</td>
<td>$\alpha$-hANP 24.3±6.9</td>
<td>control 25.9±9.3</td>
<td>$\alpha$-hANP 28.5±9.3</td>
<td>control -0.03±0.18</td>
<td>$\alpha$-hANP -0.08±0.08</td>
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<tr>
<td>$\text{UKV}$(µeq.min$^{-1}$)</td>
<td>control 22.3±5.4</td>
<td>$\alpha$-hANP 24.3±6.9</td>
<td>control 25.9±9.3</td>
<td>$\alpha$-hANP 28.5±9.3</td>
<td>control -0.03±0.18</td>
<td>$\alpha$-hANP -0.08±0.08</td>
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<tr>
<td>$\text{FEK}$(%)</td>
<td>control 22.3±5.4</td>
<td>$\alpha$-hANP 24.3±6.9</td>
<td>control 25.9±9.3</td>
<td>$\alpha$-hANP 28.5±9.3</td>
<td>control -0.03±0.18</td>
<td>$\alpha$-hANP -0.08±0.08</td>
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<tr>
<td>$\text{CH}_2\text{O}$(ml.min$^{-1}$)</td>
<td>control -0.03±0.18</td>
<td>$\alpha$-hANP -0.08±0.08</td>
<td>control -0.03±0.18</td>
<td>$\alpha$-hANP -0.08±0.08</td>
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*: $p<0.05$, **: $p<0.01$; compared to the values of the control period in each group.

Fig.1. Changes (%) in urine volume (UV) and urinary Na, K and PO$_4$ excretion (UNaV, UKV and UPO$_4$V) due to $\alpha$-hANP infusion into left renal artery of dogs (5 ng.kg$^{-1}$.min$^{-1}$: Group 1, 50 ng.kg$^{-1}$.min$^{-1}$: Group 2). *: $p<0.05$, **: $p<0.01$, compared with the values in Group 1.

between the increase in FEPO$_4$ ($\Delta$FEPO$_4$) and that in Ccr ($\Delta$Ccr), that were calculated from the difference between the respective control values and those during $\alpha$-hANP infusion in Group 2, is shown in Fig.2. FDRNa significantly decreased at both concentrations of $\alpha$-hANP (Table I). Free water clearance (CH$_2$O) did not change in either Group 1 or 2.

**Experiment 2**

Results of the isolated perfused rat kidney study are shown in Table II. During this experiment, renal perfusion flow (RPF) did not change significantly at either of the perfusate concentrations of $\alpha$-hANP at a constant perfusion pressure. Therefore, renal vascular resistance (RVR) was not influenced by $\alpha$-hANP. Ccr increased only during the ANP-2 period. UV, UNaV, and UPO$_4$V increased significantly in a dose-dependent manner (Table II). FEPO$_4$ slightly increased...
only during the ANP-2 period.

DISCUSSION

In this study, we showed that the infusion of 50 ng.kg\(^{-1}\).min\(^{-1}\) \(\alpha\)-hANP into the renal artery produced a marked increase in GFR, FF and natriuresis in the absence of changes in systemic circulation. An increase in GFR induced by ANP has been reported by others\(^5,9,10\) but the mechanism by which \(\alpha\)-hANP increases GFR has not yet been clarified. A selective vasoconstriction of efferent arterioles and vasodilatation of afferent arterioles of the glomerulus, which induce an increase in glomerular capillary

\[\text{TABLE II EFFECTS OF } \alpha\text{-hANP (0.5 ng.ml}^{-1}\text{; ANP-1 PERIOD, 5 ng.ml}^{-1}\text{; ANP-2 PERIOD) ON RENAL FUNCTION IN ISOLATED PERFUSED RAT KIDNEYS (mean} \pm \text{SD)}\]

<table>
<thead>
<tr>
<th></th>
<th>control period</th>
<th>ANP-1 period</th>
<th>ANP-2 period</th>
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<tbody>
<tr>
<td>(UV) ((\mu l.min}^{-1}))</td>
<td>53.0±12.3</td>
<td>95.6±28.4*</td>
<td>173.8±58.8**</td>
</tr>
<tr>
<td>(RPF) (ml.min}^{-1}))</td>
<td>20.7±3.0</td>
<td>20.8±2.5</td>
<td>20.8±2.6</td>
</tr>
<tr>
<td>(CCr) (ml.min}^{-1}))</td>
<td>0.72±0.15</td>
<td>0.71±0.16</td>
<td>1.05±0.45*</td>
</tr>
<tr>
<td>(FF)</td>
<td>0.035±0.007</td>
<td>0.035±0.008</td>
<td>0.050±0.002*</td>
</tr>
<tr>
<td>(UNA\text{V (nEq.min}^{-1}))</td>
<td>3.59±1.40</td>
<td>7.43±2.29**</td>
<td>13.01±5.23**</td>
</tr>
<tr>
<td>(FENa) (%)</td>
<td>3.79±1.93</td>
<td>7.66±3.01*</td>
<td>9.48±4.28*</td>
</tr>
<tr>
<td>(UPOA\text{V (nEq.min}^{-1}))</td>
<td>0.16±0.05</td>
<td>0.21±0.08</td>
<td>0.47±0.22*</td>
</tr>
<tr>
<td>(FEPOA\text{ (%)})</td>
<td>16.0±6.1</td>
<td>21.0±9.7</td>
<td>30.9±13.9*</td>
</tr>
<tr>
<td>(UKV) (nEq.min(^{0})-))</td>
<td>1.05±0.37</td>
<td>1.26±0.41</td>
<td>1.61±0.55*</td>
</tr>
<tr>
<td>(FEK) (%)</td>
<td>28.0±9.9</td>
<td>33.6±11.5</td>
<td>32.4±16.7</td>
</tr>
<tr>
<td>(CH_2O) ((\mu l.min}^{-1}))</td>
<td>23.9±9.0</td>
<td>41.3±16.4</td>
<td>82.4±29.6**</td>
</tr>
<tr>
<td>(FDRNa) (%)</td>
<td>76.3±7.2</td>
<td>61.3±10.5*</td>
<td>67.9±12.4</td>
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</table>

*: \(p<0.05\); **: \(p<0.01\); compared to the values of the control period in each parameter.
pressure, have been suggested to play a role in this process. The vasodilatory activity of α-hANP may be due to the activation of guanylate cyclase and an increase of guanosine 3',5'-cyclic monophosphate (cGMP). Additionally, an indirect vasodilatory activity, by antagonizing the renal vasoconstrictive action of the sympathetic nervous system and angiotensin II has been reported. The finding that α-hANP increased GFR in dogs and isolated perfused rat kidneys suggests that α-hANP has a direct effect on glomerular circulation. The vasoconstrictive action of α-hANP in the efferent arterioles may be mediated by an agonistic action on renal vasculature or reflex sympathetic activity. In isolated perfused rat kidneys, GFR and FF increased with addition of α-hANP. The increase in FF might be mediated by a change in the glomerular capillary ultrafiltration coefficient (Kf) or glomerular capillary hydrostatic pressure. If Kf remained constant, then a rise in the glomerular capillary hydrostatic pressure mediated by vasoconstriction of efferent arterioles and vasodilatation of afferent arterioles of the glomerulus, must have occurred. The changes in the efferent and afferent resistance had to be reciprocal, since RVR did not change. Therefore, α-hANP may have a direct vasoconstrictive action in the efferent arterioles. The increase in GFR induced by α-hANP is one of the causes of natriuretic action with high dose infusions. However, smaller doses of α-hANP caused natriuresis in the absence of renal hemodynamic changes in dog and isolated perfused rat kidney studies. These findings suggest that the direct tubular effects of α-hANP are the primary reasons for natriuresis in this experiment. Since DTRNa significantly decreased, the primary natriuretic action site is the distal nephron which includes the thin descending, and thin and thick ascending limbs of Henle's loop, the distal convoluted tubule, collecting tubule and collecting ducts. Free water clearance was considered an index of a sodium and chloride reabsorption by the cortical thick ascending limb of the loop of Henle during water diuresis. In this study, smaller doses of α-hANP did not significantly affect the free water clearance. There is also no evidence of a decrease in solute transport in this segment due to the infusion of α-hANP. Additionally, FEK did not change by α-hANP infusion and the UKV increase was small compared to the change in UNaV. Since potassium excretion is dependent on sodium reabsorption in the collecting duct, α-hANP appears to affect sodium transport by inhibiting Na+K+-ATPase or Na channels in the collecting duct.

A micropuncture study showed that ANP inhibited sodium reabsorption in the collecting duct. An autoradiography and binding assay using I-labeled ANP showed that high affinity binding sites for ANP were localized in the glomerulus and inner medullary collecting ducts. In this study, inhibition of sodium reabsorption was seen in isolated perfused kidneys. These findings suggest that α-hANP directly inhibits sodium reabsorption in the distal nephron and collecting duct without affecting antidiuretic hormones or aldosterone, which affect water and Na reabsorption. Rocha et al showed that ANP inhibits direct Na absorption in the in vitro microperfused inner collecting duct, which may be mediated by cGMP.

Inhibition of proximal reabsorption of sodium by ANP has also been reported. In this study, a larger dose of α-hANP increased FEPO4 and GFR. GFR is one of the primary factors in the inhibition of PO4 reabsorption in the proximal tubule. On the other hand, a smaller dose of α-hANP induced sodium diuresis without affecting FEPO4 or GFR. These findings suggest that ANP may have an indirect effect on proximal reabsorption by inhibition of angiotensin II, which enhances sodium and fluid reabsorption in the proximal tubules. In human studies, the site at which α-hANP acts on the renal tubule has not been determined due to the presence of anesthesia and surgical stress, which modify the renin-angiotensin aldosterone system, and renal sympathetic activities, which affect proximal and distal tubular fluid and electrolyte reabsorption.

A larger dose of α-hANP increased free water clearance in isolated rat kidney. Although the mechanism for this effect is not entirely clear, renal hemodynamic changes may play a role in this increase. In conclusion, smaller doses of α-hANP
produced natriuresis without causing renal hemodynamic changes. The results in the isolated rat didney suggest that the primary site of tubular action of α-hANP is the distal nephron is the absence of extrarenal hormonal and neural influences.

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