The Effects of Intravenous Injection of α -Human Atrial Natriuretic Polypeptide on Blood Pressure, Renal Hemodynamics and Urinary Kinin Excretion in Anesthetized Rabbits

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NUSHIRO, N., ABE, K., SEINO, M., OMATA, K. and YOSHINAGA, K. *The Effects of Intravenous Injection of α -Human Atrial Natriuretic Polypeptide on Blood Pressure, Renal Hemodynamics and Urinary Kinin Excretion in Anesthetized Rabbits.* Tohoku J. exp. Med., 1987, **151** (2), 221-231 — Studies were performed in anesthetized rabbits to examine the effects of α -human atrial natriuretic polypeptide (α -hANP) on blood pressure, renal hemodynamics and urinary kinin excretion. Intravenous bolus injection of α -hANP at a dose of 5 μ g resulted in a transient increase in renal blood flow from 26.6 ± 2.2 to 33.7 ± 2.2 ml/min ($p < 0.05$) and a decrease in mean arterial pressure from 113 ± 1.8 to 107 ± 2.2 mmHg ($p < 0.01$). The calculated renal vascular resistance decreased from 4.50 ± 0.34 to 3.28 ± 0.20 mmHg/ml/min ($p < 0.05$). This vasodilatory effect of α -hANP was immediate and lasted for 30 min. These hemodynamic alterations were not associated with the changes in glomerular filtration rate estimated by creatinine clearance. Intravenous injection of α -hANP also produced marked increases in urine volume from 1.99 ± 0.43 to 5.7 ± 1.20 ml/10 min ($p < 0.01$), urinary sodium from 42.2 ± 7.6 to 243 ± 54 μ Eq/10 min ($p < 0.01$), urinary potassium from 37.5 ± 5.5 to 74.8 ± 10.3 μ Eq/10 min ($p < 0.01$), and urinary kinin excretion from 3.44 ± 0.49 to 5.26 ± 0.82 ng/10 min ($p < 0.05$). The observed natriuretic effect of α -hANP lasted only for 30 min, whereas diuretic and kaliuretic effects were sustained for 120 min. Hematocrit levels did not change significantly throughout the experiment. These results indicate that α -hANP is a potent vasodilator substance and that the natriuretic effect induced by the bolus injection of α -hANP is mediated mainly through its renal vasodilatory action. It is also suggested that the renal kinin, at least in part, contributes to the natriuretic effect of α -hANP. — α -human atrial natriuretic polypeptide (α -hANP); renal hemodynamics; fluid and electrolyte excretion; urinary kinin excretion

It is well informed that mammalian atrial extract when administered to rats produces a marked natriuresis and diuresis (de Bold et al. 1981; Briggs et al. 1982; Keeler and Azzarolo 1983; Pollock and Banks 1983; Camargo et al. 1984;

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Beasley and Malvin 1985), but the effects of atrial extract on renal hemodynamics are controversial. Some studies have suggested an increase in renal blood flow (Keeler and Azzarolo 1983; Vaughan et al. 1983), and others have indicated no effect on renal blood flow (Keeler 1982; Pollock and Banks 1983; Beasley and Malvin 1985). These conflicts of the mechanism of action of atrial extract include use of crude, unpurified extracts of the right atrium that may contain contaminants. Recent purification, sequencing, and synthesis of atrial natriuretic substance extracted from rats or humans have resulted in the availability of new synthetic polypeptides composed of the 28 amino acids which are referred to as α -rat (Kangawa and Matsuo 1984) or α -human atrial natriuretic polypeptide (Kangawa et al. 1984). These synthetic polypeptides have been thought to have the same biological activity as the native peptides, but the mechanisms by which α -hANP produces a diuresis and natriuresis are still unclear. The present study was designed to examine the effects of intravenous injection of α -hANP on blood pressure, renal hemodynamics, fluid and electrolyte excretion in anesthetized rabbits. We also examined a role of the renal kinin in α -hANP-induced natriuresis, since it has been demonstrated that the renal kinin contributes to a potent natriuresis.

MATERIALS AND METHODS

Experiments were performed on six female albino rabbits weighing 3.0-3.2 kg. The animals were raised on standard rabbit chow which provided 9.1 mEq sodium/100 g and 63.4 mEq potassium/100 g, and were allowed free access to water. The rabbits were fasted

Protocol

Fig. 1. Experimental protocol in the present experiments. MAP, mean arterial pressure; RBF, renal blood flow; Hct, arterial hematocrit; P_{cr} , plasma creatinine concentration; UV, urine volume; $U_{Na}V$, urinary sodium excretion; U_KV , urinary potassium excretion; $U_{Cr}V$, urinary creatinine excretion; $U_{kin}V$, urinary kinin excretion.

overnight (20 hr) and water was allowed at libitum. The rabbits were anesthetized with urethan (450 mg/kg i.v.) and α -chloralose (45 mg/kg i.v.). Tracheotomy was undergone and the trachea was intubated for spontaneous breathing. The left jugular vein was cannulated with polyethylene tubing (PE 50) and a catheter (PE 50) was inserted into the inferior vena cava through the left femoral vein for an infusion of 5% dextrose solution or injection of α -hANP. A third polyethylene catheter (PE 60) was placed into the abdominal aorta adjacent to the renal arteries through the left femoral artery for arterial pressure recording and collection of arterial blood sample. The left renal artery was then exposed through a left peritoneal flank incision and gently isolated. A non-cannulating electromagnetic flow probe (2.0 mm, Nihon Kohden, Tokyo), connected to an electromagnetic flow meter (MF-27, Nihon Kohden), was placed around the renal artery for the monitoring of renal blood flow. Arterial pressure was monitored with a pressure transducer and amplifier (Biophysigraph, 180 system, San-ei, Tokyo), and recorded on a pen oscillograph with renal blood flow. The left ureter was then cannulated with tubing for collection of urine. Solution of 5% dextrose was infused intravenously to the extent of 2% of body weight as a priming infusion and then followed by a sustained infusion at a rate of 0.425 ml/min throughout the experiment. α -Human atrial natriuretic polypeptide (α -hANP) (Protein Research Foundation, Osaka) stored at -20°C was dissolved in distilled water to the appropriate concentration of $5\text{ }\mu\text{g/ml}$ for intravenous administration. After the completion of surgery, at least 60 min were allowed for stabilization of arterial blood pressure and renal blood flow. Then a priming dose of 50 mg/kg of creatinine in 4 ml of 5% dextrose solution was given through the left jugular vein catheter and was followed by a prolonged infusion of 0.5 mg/kg/min in 0.425 ml/min of 5% dextrose solution throughout the experiment to determine glomerular filtration rate. Twenty min after the priming injection of creatinine, experimental protocol was started.

Fig. 1 illustrates the present experimental protocols. Each experiment consisted of a 30-min control period at the end of which urine collection and 5 ml of arterial blood sample were taken. Urine volume (UV), urinary excretion of sodium ($U_{\text{Na}}V$), potassium ($U_{\text{K}}V$), kinin ($U_{\text{kin}}V$) and creatinine ($U_{\text{cr}}V$), systemic arterial hematocrit (Hct), and plasma creatinine concentration (P_{cr}), were determined as the controls. Then α -hANP was inject-

Fig. 2. Effect of intravenous injection of α -human atrial natriuretic polypeptide on mean arterial pressure. * $p < 0.05$ compared with before ** $p < 0.01$ compared with before.

Fig. 3. Effect of intravenous injection of α -human atrial natriuretic polypeptide on renal blood flow. * $p < 0.05$ compared with before.

Fig. 4. Effect intravenous injection of α -human atrial natriuretic polypeptide on renal vascular resistance. * $p < 0.05$ compared with before. ** $p < 0.01$ compared with before.

ed intravenously at a dose of $5 \mu\text{g}$ through the femoral vein catheter. After the injection, six consecutive 10-min urine collections were taken, then two consecutive 30-min urine collections were followed. UV , $U_{Na}V$, U_KV , $U_{Cr}V$ and $U_{kin}V$, were also determined in each urine sample. Arterial blood samples were drawn at 30, 60 and 120 min after the α -hANP injection. After each blood sample collection, the same amount of arterial blood drawn from another donor rabbits was supplemented at the rate that did not have a volume effect on renal blood flow. Glomerular filtration rate was estimated from the clearance of

Fig. 5. Typical effects of intravenous injection of α -human atrial natriuretic polypeptide (α -hANP) on mean arterial pressure and renal blood flow.

creatinine. Plasma and urinary concentrations of creatinine were determined by cleanerlizer (VS-700 s, Nihon Denshi, Tokyo). Urinary concentrations of sodium and potassium were also determined by autoanalyzer (STAT/ION-II, Nihon Technicon, Tokyo). Urinary kinin concentration was measured by radioimmunoassay described elsewhere (Abe et al. 1978). Renal vascular resistance (RVR) was calculated by dividing mean arterial pressure by renal blood flow, and was expressed as mmHg/ml/min.

UV, $U_{Na}V$, U_KV , $U_{cr}V$ and $U_{kin}V$ excreted during the 30-min period were expressed as average value for 10-min excretion.

All data in the control period were compared with those in the experimental period using Student's paired t test. Statistical significance was considered to be $p < 0.05$. All data in figures and tables are expressed as means $\pm$ s.e.

RESULTS

Figs. 2, 3, and 4 illustrate the effects of intravenous injection of α -hANP on mean arterial pressure (MAP), renal blood flow (RBF), and renal vascular resistance (RVR), respectively.

MAP decreased significantly from 113 ± 1.8 to 109 ± 2.1 , 107 ± 2.3 , 108 ± 2.1 , 110 ± 2.1 and 111 ± 2.1 mmHg at 1, 2, 5, 10, 20 and 30 min after the α -hANP injection, respectively. Then MAP gradually returned to the initial control level at 40 min after the injection of α -hANP. As shown in Fig. 3, RBF increased markedly from 26.6 ± 2.2 to 32.1 ± 2.0 and 33.7 ± 2.2 ml/min at 1 and 2 min after the α -hANP injection, respectively, and returned slowly to the control level.

The calculated renal vascular resistance declined significantly from $4.50 \pm$

TABLE 1. *Effect of intravenous injection of α -human atrial natriuretic polypeptide on glomerular filtration rate (GFR)*

	Control	Time after injection (min)		
		30	60	120
GFR (ml/min)	4.5 ± 1.1	4.3 ± 0.4	4.9 ± 0.5	4.7 ± 0.8

Values are expressed as mean $\pm$ s.e.

Fig. 6. Effect of intravenous injection of α -human atrial natriuretic polypeptide on urine volume. ** $p < 0.01$ compared with the control value.

0.34 to 3.73 ± 0.22 , 3.42 ± 0.18 , 3.28 ± 0.20 and 3.38 ± 0.22 mmHg/ml/min at 1, 2, 3 and 4 min after the α -hANP injection, and returned gradually to a control level (Fig. 4). Fig. 5 shows typical effects of intravenous injection of α -hANP on MAP and RBF.

Changes in glomerular filtration rate (GFR) as estimated by creatinine clearance throughout the experiment are summarized in Table 1. GFR did not change significantly at either 30, 60, or 120 min after the α -hANP injection as compared with the control value. Figs. 6, 7 and 8 illustrate the effects of intravenous injection of α -hANP on UV, $U_{Na}V$, and U_KV , respectively. UV increased significantly from 1.99 ± 0.43 to 5.70 ± 1.2 ml/10 min in the first 10 min period after the α -hANP injection, and this significant increase in UV was sustained for 120 min. After the injection of α -hANP, $U_{Na}V$ increased significantly from 42.2 ± 7.6 to 243 ± 54 ($p < 0.01$), 143 ± 25 ($p < 0.01$), and 83.2 ± 12 μ Eq/10 min ($p < 0.01$) at each period of 10, 20 and 30 min, respectively. U_KV also increased significantly from 37.5 ± 5.5 to 74.8 ± 10 μ Eq/10 min ($p < 0.01$) in the first 10 min period after the injection of α -hANP, and this significant increase in U_KV lasted to the end of the experiment.

Fig. 7. Effect of intravenous injection of α -human atrial natriuretic polypeptide on urinary sodium excretion. ** $p < 0.01$ compared with the control value.

Fig. 8. Effect of intravenous injection of α -human atrial natriuretic polypeptide on urinary potassium excretion. * $p < 0.05$ compared with the control value. ** $p < 0.01$ compared with the control value.

Fig. 9 illustrates the effect of intravenous injection of α -hANP on $U_{kin}V$. Intravenous injection of α -hANP elicited a significant increase in $U_{kin}V$ from a control value of 3.44 ± 0.49 to 5.26 ± 0.82 ng/10 min ($p < 0.05$) in the second 10 min period after the α -hANP injection. This increase in $U_{kin}V$ by α -hANP was sustained for 60 min, and $U_{kin}V$ returned to the control level at 120 min.

Fig. 9. Effect of intravenous injection of α -human atrial natriuretic polypeptide on urinary kinin excretion. * $p < 0.05$ compared with the control value.

DISCUSSION

Intravenous injection of α -hANP at a dose $5 \mu\text{g}$ resulted in a significant decrease in MAP with a marked transient increase in RBF. These renal vasodilatory effects of α -hANP are consistent with the observations by Keeler and Azzarolo (1983), Borenstein et al. (1983), Wakitani et al. (1985) and Hintze et al. (1985) that atrial extracts or atriopeptin II and III elicited renal vasodilation in anesthetized rats or dogs, or in conscious dogs. In the present experiment, the natriuretic effect of α -hANP was not associated with changes in glomerular filtration rate estimated at 30 min after the injection of α -hANP. However, glomerular filtration rate may have increased immediately after the intravenous injection of α -hANP, and this increase in GFR may have been transient, therefore, resulting in failure of determination for a period of 30 min after the α -hANP injection. In fact, Keeler and Azzarolo (1983) reported an increase in GFR only during the first 5-min period following the injection of atrial extract in spite of a fall in mean arterial pressure. There have been some different reports concerning the effects of atrial extracts on GFR. In *in vivo* studies in which atrial extracts have been reported to fail to affect GFR (de Bold et al. 1981; Keeler 1982; Sonnenberg et al. 1982; Nemeh and Gilmore 1983; Pollock and Banks 1983), a bolus injection of atrial extracts was given, and the subsequent natriuresis was both rapid in onset and transient. On the other hand, an increase in GFR was observed in studies in which atrial extract or atrial natriuretic factor was infused intrarenally or intravenously at a constant rate (Burnett et al. 1984; Maack et al. 1984; Beasley and Malvin 1985; Huang et al. 1985; Hammond et al. 1985; Hirata et al. 1985). Bolus injections of atrial extracts or atrial natriuretic factor

lead to transient that could not be detected if the clearance period exceeds the transient time. In our present experiment, intravenous injection of α -hANP might have resulted in a transient increase in GFR that could not have been detected in the 30-min period. Ultimately, we could not estimate the accurate changes in GFR produced by α -hANP in the present experiment. However, we recently observed a significant increase in GFR by 24 and 28% at 30 and 60 min after an intravenous constant infusion of α -hANP at a rate of 0.05 $\mu\text{g/kg/min}$ (Nushiro et al. unpublished data).

In the present study, intravenous injection of α -hANP at a dose of 5 μg resulted in a sustained increase in UV for 120 min and this increase in UV was associated with a sustained increase in U_KV , whereas increased $U_{Na}V$ elicited by the injection of α -hANP was transient. It has been reported that intravenous injection of atrial extracts produces a diuresis and kaliuresis of short duration (de Bold et al. 1981; Borenstein et al. 1983; Keeler and Azzarolo 1983; Vaughan et al. 1983; Thibault et al. 1984). These discrepancies of duration of diuresis and kaliuresis between in our experiment and in others might have been caused by the different volume status of animals. In the present experiment, 5% dextrose solution was infused intravenously to the extent of 2% body weight as a priming infusion and then was followed by a sustained infusion at a rate of 0.425 ml/min during the experiment. Therefore, in our present experiment, the diuresis and kaliuresis might have been persistent for 120 min after the intravenous injection of α -hANP. Another possible mechanism by which the prolonged diuresis and kaliuresis was produced by α -hANP is medullary washout. Borenstein et al. (1983) reported that injection of atrial extract into anesthetized rats increased total and medullary blood flow in the kidney. In the present study, the prolonged kaliuresis was accompanied by the diuresis, which suggests that urine flow into the distal tubule may have increased after the injection of α -hANP, since it has been shown that potassium secretion is increased when flow into the distal tubule is increased (Malnic et al. 1966; Morgan and Berliner 1969; Kunau et al. 1974; Khuri et al. 1975; Reineck et al. 1975; Diezi et al. 1976). This increase in urine flow into the distal tubule could have been elicited by the dissipation of corticomedullary osmotic gradient by medullary washout.

It has been demonstrated that the renal kinin possesses a potent natriuretic action. Therefore, we examined whether the renal kinin contributes to the natriuresis induced by α -hANP, although it has been shown that kallikrein is a proteolytic factor of atrial natriuretic substance (Briggs et al. 1984; Thibault et al. 1984).

Intravenous injection of α -hANP resulted in a significant increase in $U_{kin}V$. This increase in $U_{kin}V$ was accompanied by the marked diuresis and natriuresis, and lasted for 60 min. In the present study, it is not clear whether the kallikrein-kinin system in the kidney contributed to the diuresis and natriuresis produced by α -hANP, but since the renal kinin has been shown to have potent natriuretic

action, it seems likely that the renal kinin, at least in part, contributes to the natriuresis produced by α -hANP, and that the renal kallikrein-kinin system is not a proteolytic factor in vivo.

In summary, intravenous injection of α -hANP resulted in a transient increase in RBF and in a decrease in MAP. These hemodynamic alterations were accompanied by a marked diuresis and natriuresis, and an increase in $U_{\text{kin}}V$.

These results suggest that α -hANP is a potent renal vasodilator substance and that the natriuretic effect of α -hANP is mediated primarily through the renal vasodilatory action, although the contribution of the renal kinin is not excluded completely.

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