Plasma Concentration of α -hANP and Renal Responses to α -hANP Infusion in Patients with Congestive Heart Failure and Those with Chronic Renal Failure

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To study the role of α -human atrial natriuretic polypeptide (α -hANP) in body fluid regulation, we measured the plasma concentration of α -hANP and renal function in 9 patients with congestive heart failure (CHF), 10 with chronic renal failure (CRF) and 8 normotensives (NT) before and during α -hANP infusion at 0.025 $\mu\text{g}/\text{kg}\cdot\text{min}$. The plasma concentration of α -hANP was significantly higher in the CHF and CRF than in the NTs (319, 168 and 72 pg/ml, respectively). α -hANP infusion decreased mean blood pressure in a similar manner in the 3 groups (-5% , $p < 0.01$ each). Increases in urinary sodium excretion and glomerular filtration rate during α -hANP infusion, however, were greater in the CHF and CRF than in the NTs. Furthermore, the higher the preinfusion level of renal vascular resistance (RVR), the greater was the reduction in RVR by α -hANP ($r = -0.80$, $p < 0.001$). The metabolic clearance rate (MCR) of α -hANP was significantly smaller in the CHF and CRF than in the NTs (38, 35 and 67 ml/min $\cdot$ kg, respectively). These results suggest that the renal vasodilatory actions of α -hANP seem to be enhanced in patients with increased RVR and that the elevation of the basal plasma concentration of α -hANP in CHF and CRF may be in part due to the low MCR.

RECENT studies on atrial natriuretic polypeptide (ANP) have indicated that this peptide may be involved in the regulation of body fluid volume and blood pressure. The plasma concentration of immunoreactive ANP has been reported to be markedly increased in patients with congestive heart failure¹⁻³ and in those with chronic renal failure^{4,5}. Although ANP exerts potent natriuretic and blood pressure

lowering effects in healthy persons^{6,7} it is possible that the blood pressure and renal responses to the peptide may be modified in such disease conditions. That is to say, the high plasma concentration of ANP may blunt the responses to exogenously administered ANP if this peptide possesses the usual hormone-receptor relationship. Furthermore, it is still unclear if the putative elevation of plasma ANP in cardiac or renal diseases is attributable exclusively to an increase in ANP secretion. The circulating ANP is rapidly degraded⁸ and this degradation seems to take place during the passage through various organs, including the kidneys, because the plasma concentration of ANP is lower in the renal vein

Key words:

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than in the aorta.⁹ Therefore, some organ damage, especially renal damage, may possibly delay the degradation of ANP, resulting in the elevation of the plasma concentration of the peptide. Thus, in the present study we infused synthetic α -human ANP (α -hANP) into patients with advanced cardiac or renal dysfunction and examined the renal responses to the compound, as well as measuring its metabolic clearance rate.

SUBJECTS AND METHODS

The subjects were 9 patients with congestive heart failure (CHF), 10 with chronic renal failure (CRF) and 8 normotensive (NT) persons. The causes of CHF were valvular heart diseases in 6, dilated cardiomyopathy in 2 and arrhythmia in 1 patient. Seven patients belonged to class 3 of the New York Heart Association Criteria and two to class 4. The underlying diseases of CRF were chronic glomerulonephritis in 6 patients and diabetic nephropathy in 4. The diagnosis was based on thorough clinical and laboratory examinations including renal biopsy. None of the patients with CRF had received peritoneal or hemo-dialysis. The NT persons were selected from patients who had been hospitalized because of chance proteinuria or recurrent microscopic hematuria. In these patients, renal function was normal and the histological diagnosis was minor glomerular abnormality according to the WHO criteria.

All subjects were hospitalized and placed on a diet containing 5 to 8 g/day of NaCl. Some patients with CHF were treated with digitalis and/or diuretics, and those with CRF were given diuretics and/or calcium antagonists. The study was started at least 14 hours after the last intake of medicine.

On the day of the examination, catheters were introduced into the radial artery, antecubital vein and bladder. To the supine subjects, 500 ml of water was then given orally and the intravenous infusion of 0.94% paraaminohippuric acid (PAH) dissolved in a lactate Ringer's solution was started at a rate of 100 ml/hr. Following a 30 min equilibration period, urine was collected through the bladder catheter every 20 min. After a 40 min urine collection control period, synthetic α -hANP was continuously infused through the antecubital vein at 0.025 μ g/kg·min for 40 min. A 40 min urine collection was also carried out during and after the infusion. Blood pressure was monitored

through the intra-arterial line, and arterial blood samples were obtained at the mid point of each urine-collection period for measuring the plasma concentrations of PAH, creatinine, immunoreactive α -hANP, cGMP and norepinephrine, and plasma renin activity. Blood samples for PAH and creatinine were heparinized and centrifuged at room temperature. Those for hormone measurements were placed in prechilled test tubes containing EDTA- Na_2 and then centrifuged at 4°C. Aprotinin (500 KIU/ml) was added to the plasma samples for α -hANP and stored at -70°C until assay. The administration of α -hANP was approved by the Ethical Committee of the University of Tokyo Hospital and informed consent was obtained from each patient after detailed explanation of the infusion study.

Variables measured:

Renal blood flow (RBF) and glomerular filtration rate (GFR) were estimated by the PAH clearance and creatinine clearance methods, respectively. Urinary sodium concentration was measured by a flamephotometer. The plasma concentration of α -hANP was determined by radioimmunoassay (RIA) as previously reported.^{3,10} In this assay system, the sensitivity was less than 1 pg/tube and the 50% intercept was 13 pg/tube. The interassay variation was 11.6% for a 50 pg/ml level ($n = 11$) and the intra-assay variation was 3.6% ($n = 10$). The plasma concentration of cGMP was also determined by RIA using a commercially available cGMP assay kit (Yamasa, Chiba, Japan).³ Plasma renin activity and the plasma norepinephrine concentration were assayed by standard RIA and high performance liquid chromatography using a trihydroxy indole method, respectively.¹¹ Renal vascular resistance (RVR) was obtained by dividing mean blood pressure by RBF. The metabolic clearance rate of α -hANP during the infusion period was determined as follows:

$$\text{metabolic clearance rate} = \frac{\text{infused dose of } \alpha\text{-hANP}}{\text{plasma } \alpha\text{-hANP during infusion} - \text{plasma } \alpha\text{-hANP during control}}$$

Statistics:

The differences in means among the three groups were tested by one-way analysis of variance and modified t-test. The differences in means within the group were assessed by the paired t-test. Correlation coefficients were ob-

TABLE I MAIN CLINICAL FINDINGS AND THE CHANGES IN MEAN BLOOD PRESSURE AND RENAL FUNCTION PARAMETERS INDUCED BY α -hANP INFUSION IN NORMOTENSIVE PERSONS (NT), PATIENTS WITH CHRONIC RENAL FAILURE (CRF) AND THOSE WITH CONGESTIVE HEART FAILURE (CHF).

	NT group	CRF group	CHF group
Age (y. o.)	33.4 $\pm$ 3.2	52.8 $\pm$ 1.1 ^d	56.3 $\pm$ 3.3 ^d
plasma Cr (mg/dl)	0.8 $\pm$ 0.1	7.6 $\pm$ 0.2 ^d	1.0 $\pm$ 0.1
PRA (ng/ml·hr)	2.25 $\pm$ 0.47	1.46 $\pm$ 0.38	6.9 $\pm$ 4.17
PNE (pg/ml)	205 $\pm$ 26	497 $\pm$ 65 ^a	985 $\pm$ 245 ^c
MCR (ml/kg·min)	66.3 $\pm$ 8.3	35.7 $\pm$ 3.5 ^c	38.4 $\pm$ 5.2 ^c
basal MBP (mmHg)	85.4 $\pm$ 3.2	121.8 $\pm$ 6.4 ^d	95.2 $\pm$ 7.2 ^c
Δ (%) MBP	-5.2 $\pm$ 1.6 ^g	-6.7 $\pm$ 1.3 ^h	-4.1 $\pm$ 1.1 ^g
basal UV (ml/min·m ²)	2.25 $\pm$ 0.23	0.96 $\pm$ 0.14 ^d	1.08 $\pm$ 0.25 ^d
Δ (%) UV	+54 $\pm$ 28	+114 $\pm$ 32 ^g	+310 $\pm$ 140 ^e
basal UNaV (mEq/min·m ²)	106.8 $\pm$ 18.8	53.2 $\pm$ 10.2	86.6 $\pm$ 25.5
Δ (%) UNaV	+11 $\pm$ 24	+208 $\pm$ 55 ^h	+135 $\pm$ 59 ^e
basal GFR (ml/min·m ²)	67.2 $\pm$ 3.8	4.9 $\pm$ 0.5 ^d	36.8 $\pm$ 5.9 ^c
Δ (%) GFR	-5 $\pm$ 6	+29 $\pm$ 8 ^{c,g}	+30 $\pm$ 4 ^{c,h}
basal RBF (ml/min·m ²)	482.6 $\pm$ 28.7	26.2 $\pm$ 4.2 ^d	238.9 $\pm$ 50.2 ^c
Δ (%) RBF	-12 $\pm$ 5 ^e	+32 $\pm$ 11 ^{b,f}	+22 $\pm$ 7 ^{c,f}
basal RVR (mmHg·min·m ² /ml)	0.18 $\pm$ 0.02	7.08 $\pm$ 2.10 ^c	0.53 $\pm$ 0.10
Δ (%) RVR	+9 $\pm$ 6	-28 $\pm$ 6 ^{d,h}	-19 $\pm$ 5 ^{c,g}

Values are means $\pm$ SE. a: $p < 0.05$; b: $p < 0.02$; c: $p < 0.01$; d: $p < 0.001$, compared with NT; e: $p < 0.05$; f: $p < 0.02$; g: $p < 0.01$; h: $p < 0.001$, compared with the control period. PRA = plasma renin activity; RNE = plasma norepinephrine concentration; Cr = creatinine; MBP = mean blood pressure; UV = urine volume; UNaV = urinary sodium excretion; GFR = glomerular filtration rate; RBF = renal blood flow; RVR = renal vascular resistance

Fig. 1. Plasma concentration of immunoreactive α -hANP in normotensive persons (NT), patients with chronic renal failure (CRF) and those with congestive heart failure (CHF) in the control, infusion and recovery periods.

tained by the least squares method.

RESULTS

Table I shows the ages, basal plasma concentrations of creatinine and norepinephrine, plasma renin activity, metabolic clearance rate, mean blood pressure (MBP) and renal function parameters in the 3 groups. The percent changes in MBP, urine volume (UV), urinary Na excretion (UNaV), GFR, RBF and RVR during α -hANP infusion are also presented. Patients with CRF showed high plasma concentrations of creatinine and norepinephrine, and those with CHF showed high plasma norepinephrine and renin activity. The plasma concentration of α -hANP in the control period was markedly elevated in CHF and CRF patients than in the NT subjects (Fig. 1). The plasma concentration of α -hANP was increased during α -hANP infusion by about 5-fold in each group and was still higher in CHF and CRF patients than in the NT subjects. The metabolic clearance rate of α -hANP was signifi-

cantly lower in the CRF and CHF groups (Table I). As shown in Fig. 2, the plasma concentrations of cGMP were elevated in a similar fashion in CHF and CRF patients, resulting in a close positive correlation between the plasma concentrations of α -hANP and cGMP in the control period ($r = 0.74$, $p < 0.001$). The plasma concentrations of cGMP were markedly increased during α -hANP infusion, but the increases were not different among the three groups.

The MBP and the changes due to α -hANP infusion in the three groups are listed in Table I. Alpha-hANP significantly lowered it by about 5%. Although basal MBP was different among

the groups, the blood pressure responses to α -hANP were comparable in the 3 groups. The increases in UV and UNaV by α -hANP were not consistently observed in NT subjects, whereas both variables increased by 2 to 3-fold in the CHF and CRF groups (Table I). Both basal RBF and GFR were markedly lower in patients with CRF and CHF than in the NT subjects (Table I). Alpha-hANP infusion increased RBF and GFR in CHF and CRF patients, but not in the NT subjects. Similarly, significant decreases in RVR elicited by α -hANP were found only in the CHF and CRF groups. The higher the preinfusion level of RVR, the greater was the reduction in RVR by α -hANP ($r = -0.80$, $p < 0.001$). Blood pressure and renal function returned to basal levels in the recovery period. When the determinants of natriuretic responses to the peptide were assessed, significant positive correlations were found between the changes in UNaV and MBP, or changes in GFR during α -hANP infusion (Fig. 3).

Fig. 2. Plasma concentration of cGMP in normotensive persons (NT), patients with chronic renal failure (CRF) and those with congestive heart failure (CHF) in the control, infusion and recovery periods.

DISCUSSION

CHF and CRF patients showed an elevation in the plasma concentration of α -hANP. This finding is compatible with the results of previous reports.¹⁻⁵ It has been suggested that the secretion of ANP is regulated mainly by atrial pressure.^{12,13} In heart diseases, generally the higher the atrial pressure, the higher is the plasma

Fig. 3. Relationships between changes in urinary sodium excretion and mean blood pressure or changes in glomerular filtration rate during α -hANP infusion. NT = normotensive persons, CRF = patients with chronic renal failure, CHF = patients with congestive heart failure.

concentration of α -hANP.³ Although atrial pressure was not determined in the CRF patients in this study, elevation of the plasma α -hANP concentration seems to have been a result of an increase in the secretion of ANP due to an elevation of atrial pressure which resulted from an increase in body fluid volume.^{4,5} However, the metabolic rate of α -hANP may affect its plasma concentration. Although this peptide rapidly disappears from the circulation,⁸ the exact metabolic process is still unknown. Luft et al¹⁴ have shown that the half life of ANP in plasma is prolonged in anephric rats. However, Katsube et al¹⁵ and Murthy et al¹⁶ reported that nephrectomy did not affect the disappearance time of ANP in rat plasma. Thus, although the kidney is one of the most active sites for the action of ANP, the role of the kidney in ANP metabolism has not been confirmed. On the other hand, Hirata et al¹⁷ suggested that ANP receptors per se may be involved in the degradation of ANP by means of internalization. Furthermore, Almeida et al¹⁸ have recently shown that previously infused α -hANP derivatives delay the half life of α -hANP, resulting in an elevation of the plasma concentration of α -hANP. Accordingly, the long-lasting high plasma concentration of ANP may induce some changes in the metabolism of ANP, especially at the receptor sites. If this is the case in CHF or CRF patients in the present study, it is possible that the metabolic clearance rate of α -hANP may be reduced in patients with markedly increased secretion of α -hANP, and such a low metabolic clearance rate may contribute partly to the further elevation of the plasma concentration.

Patients with elevated plasma α -hANP concentration also showed high plasma cGMP. Cyclic GMP is considered to be an intracellular second messenger of ANP because ANP activity has been demonstrated to occur in parallel with the increase in cGMP concentrations in target organs,¹⁹ and because the ANP binding protein has been co-purified with guanylate cyclase from rat lung²⁰ Although it has already been reported that exogenous ANP markedly increases the plasma concentration of cGMP,²¹ the present study has revealed that an increase in endogenous ANP also elevates plasma cGMP.

During the infusion of α -hANP, UV, UNaV, GFR and RBF increased in the CRF and CHF groups, but not in the NT group (Table I). The RVR was significantly reduced only in the CRF and CHF groups. These findings appear to be

consistent with the hypothesis that an increase in GFR is one of the factors involved in ANP-induced natriuresis.²² Furthermore, in the present study, the UNaV was well correlated with blood pressure. Taken together, as indicated in our previous study,²³ renal perfusion pressure seems to be an important factor for determining the natriuretic response during α -hANP infusion. The importance of renal artery pressure in ANP-induced natriuresis has recently been confirmed by Davis et al.²⁴ If ANP increases GFR, the presence of high renal perfusion pressure can promote the natriuretic activity of the peptide. Furthermore, α -hANP increased UNaV and GFR even in patients with advanced renal failure whose functioning glomeruli might be in the state of "hyperfiltration".²⁵ This implies that α -hANP may be a "glomerular diuretic".

In contrast to normal persons, α -hANP infused at the rate used in this study showed a marked renal vasodilatory action in CHF and CRF patients. Although it is still controversial as to whether or not ANP is a selective renal vasodilator,^{26,27} this suggests that the responses of the renal vessels to ANP can be modified by the disease condition. It has been shown that the vasorelaxing activities of ANP is prominent when the vessels have been previously contracted by vasoconstricting agents, such as angiotensin II and vasopressin.²⁸ On the contrary, atrial extracts are known to increase renal vascular resistance when the vessels are fully relaxed.²⁹ The renal vasodilatory effect of α -hANP may be manifested only in patients with high renal vascular resistance due to organic renal damages, or increased activity of the sympathetic nervous system or renin-angiotensin system.

In conclusion, despite the high plasma concentration of α -hANP, α -hANP infusion induced greater natriuresis in CHF and CRF patients. The enhanced renal responses may be explained at least in part by the high renal perfusion pressure and high renal vascular tone in these patients.

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