A Comparative Study on the Hemodynamic, Renal and Endocrine Effects of 
α-human Atrial Natriuretic Polypeptide in Normotensive 
Persons and Patients with Essential Hypertension

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Alpha-human atrial natriuretic polypeptide (α-hANP), a 28-amino acid polypeptide, identified from human atra and synthesized by Kangawa and Matsuo, has been found to possess a variety of physiological properties. It has potent diuretic, natriuretic and vasodilatory effects. It inhibits the production of aldosterone in adrenal glomerulosa cells and stimulates the production of cyclic GMP in various tissues, such as adrenal capsular cells and vascular walls. Our recent clinical study demonstrated that α-hANP, intravenously infused at successive rates of 0.025, 0.05 and 0.1 mg/kg/min for 20 min each, decreased blood pressure in a dose-dependent manner and appeared to inhibit the secretion of aldosterone, cortisol and arginine vasopressin in healthy male volunteers. However, the diuretic and natriuretic effects of α-hANP were not consistent. These diuretic and natriuretic responses were in contrast to the results of previous studies in which α-hANP was intravenously administered by bolus injection into normotensive persons. In order to further clarify the characteristic physiological properties of α-hANP, this study compared the hemodynamic, renal and endocrine effects of α-hANP in normotensive persons and patients with essential hypertension.

The subjects were 6 normotensive (NT) persons (4 male and 2 female, ranging in age from 21 to 47 years) and 10 patients with essential hypertension (EH; 8 male and 2 female, ranging in age from 30 to 61 years). They were all hospitalized patients and placed on a diet containing 8 to 10 g of salt per day. The normotensive subjects were selected from patients who had been hospitalized because of chance proteinuria or recurrent microscopic hematuria and patients who had been hospitalized for a routine health examination health. No definite abnormalities were found in renal function studies or histological examinations in any of the normotensive subjects.

No subjects had received any drugs for at least 2 weeks prior to examination. After fasting for 14 hours, they were given about 600 ml of water to increase urine output. A central venous catheter and an arterial catheter were introduced into the cubital vein and the brachial artery, respectively. Arterial pressure, central venous pressure and heart rate were recorded in supine subjects with a telemetric manometer. Cardiac output (CO) was determined by the dye-dilution technique using a cuvette, and hemodynamic parameters were calculated as previously described. A lactate-Ringer solution containing 0.94% p-aminohippurate (PAH) was intravenously infused at a rate of 100 ml/hr. Urine was

Key Words:
α-hANP
Systemic hemodynamics
Renal hemodynamics
Plasma renin activity
Plasma aldosterone

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Japanese Circulation Journal Vol. 30, November 1986 1181
collected through a urethral catheter. Glomerular filtration rate (GFR) was determined by renal clearance of endogenous creatinine and renal blood flow (RBF) by renal clearance of PAH and hematocrit. Thirty to forty min after starting infusion of the PAH solution, when blood pressure, heart rate and urino output were stable, urine collection was started and repeated every 20 min throughout the examination. Following two urine collections, α-hANP dissolved in a physiological saline solution was intravenously infused at a rate of 0.025 μg/kg/min for 40 min. Two more urine collections were taken after the infusion of α-hANP was discontinued. Water was intermittently given orally to replete urine output.

Arterial blood samples to measure plasma renin activity (PRA) and plasma concentrations of norepinephrine (PNE) and aldosterone (PA) were obtained before starting the α-hANP infusion and 40 min after cessation of the infusion. PRA, PNE and PA were determined as previously described.

Arterial pressure averaged 122/68 mmHg in the NT group and 178/96 mmHg in the EH group (p < 0.001 for the group differences in systolic and diastolic arterial pressures) before infusion of α-hANP. Arterial pressure gradually declined during infusion of α-hANP and returned to the preinfusion level 40 min after cessation of the infusion. The changes in mean arterial pressure (MAP), heart rate (HR), CO and total peripheral resistance (TPR) were comparable in the NT and EH groups near the end of the infusion of α-hANP; i.e., ∆MAP: −6.2 ± 2.3 (SE)% (p < 0.05) vs −5.4 ± 0.9% (p < 0.01); ∆HR: +14.3 ± 2.6% (p < 0.01) vs +10.8 ± 1.7% (p < 0.001); ∆CO: +6.4 ± 8.2% (ns) vs +6.4 ± 2.6% (p < 0.05); and ∆TPR: −10.7 ± 2.8% (p < 0.05) vs −10.3 ± 3.1% (p < 0.01). Further, central venous pressure was reduced in both groups: −1.8 ± 0.6 mmHg (p < 0.05) in NT and −1.1 ± 0.4 mmHg (p < 0.05) in EH. Urinary volume (UV) and the urinary excretion rate of sodium (U_Na V) were significantly increased only in EH and the changes in these variables were significantly different in NT and EH; ∆UV: +38.2 ± 30.1% (ns) vs +157.3 ± 40.5% (p < 0.01) (p < 0.05 for group difference), and ∆U_Na V: −4.5 ± 19.0% (ns) vs +344.5 ± 60.4% (p < 0.001) (p < 0.001 for group difference) in the second urine collection period during infusion of α-hANP. RBF was decreased similarly in the two groups during or immediately after cessation of the α-hANP infusion, while GFR was increased only in EH: −1.5 ± 2.6% in NT and +19.2 ± 3.9% (p < 0.01) in EH (p < 0.01 for group difference) in the second urine collection period during infusion of α-hANP. There was a significant positive correlation between percent changes in GFR and those in U_Na V (r = 0.71, p < 0.01). Net tubular reabsorption of sodium, which was calculated by subtracting U_Na V from filtered sodium, was definitely increased in EH (+13.1 ± 3.4%, p < 0.01), but not in NT (−4.0 ± 3.1%, ns), with a significant group difference (p < 0.01) in the second urine collection period during infusion of α-hANP.

Although there were no significant changes in PRA in either group during infusion of α-hANP, PA was decreased in both groups with a greater change in NT: −49.2 ± 9.5% (p < 0.01) vs −26.7 ± 3.1% (p < 0.001) (p < 0.05 for group difference). PNE was similarly increased in NT and EH (+28.3 ± 9.8%, p < 0.05, vs +26.4 ± 9.8, p < 0.05). Hematocrit was elevated by 2.2 ± 0.6% (p < 0.05) in NT and by 2.1 ± 0.7% (p < 0.01) in EH near the end of the infusion of α-hANP.

The results of the present study demonstrate that the hypotensive effect of α-hANP was comparable for both NT and EH and that the effect was attributed to the dilatation of the resistance vessels. Although HR was increased during the infusion of α-hANP, the changes in CO were not consistent. The lack of a definite increase in CO may have been due to a decrease in venous return, which was suggested by the reduction in central venous pressure. An increase in sympathetic nerve activity, which is indicated by the increases in HR and PNE, may have been caused by activation of the baroreceptor and cardiopulmonary reflexes.

The absence of diuretic and natriuretic responses to α-hANP in NT was compatible with the results of our previous study. The association of the diuretic and natriuretic responses with the increase in GFR and the enhanced net tubular reabsorption of sodium in EH during infusion of α-hANP support the hypothesis that an increase in GFR is one of the important factors involved in the diuresis and natriuresis following administration of α-hANP or other low molecular-weight ANPs. When the occurrence of diuresis and natriuresis only in EH, the close association of natriuresis with increases in GFR and the slight, but significant, increases in hematocrit during administration of α-hANP are...
combined together, it is likely that the increase in GFR is induced by an increase in capillary permeability, as suggested by the change in hematocrit, being promoted by high arterial pressure.

In spite of the lack of changes in PRA, PA was decreased in both groups. This finding is consistent with the concept that α-hANP directly inhibits the production of aldosterone in adrenal glomerulosa cells.6,8 The decrease in PA induced by the α-hANP infusion was greater in NT than in EH. The responsiveness of the aldosterone system to changes in extracellular fluid volume is known to be altered in patients with essential hypertension; i.e., decreases in PA or urinary excretion of aldosterone in response to salt loading are often smaller in patients with essential hypertension than in normotensive controls.15–17 Recent studies have suggested that ANPs are released in response to hypertension or expansion of extracellular fluid volume, probably via elevation of atrial pressure.18–20 The poorer PA response to α-hANP observed in EH of the present study may underlie the putative altered responsiveness of the aldosterone system to excessive salt intake in EH.

The results of the present study may afford a clue to explore the renal action of α-hANP, and seem to be important to characterize the fundamental pathophysiological aspects of essential hypertension.

Acknowledgement
This study was supported in part by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science and Culture, Japan (No. 59480220).

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