Effect of Sodium Intake on Responses of Blood Pressure, Renin-Aldosterone and Renal Excretions to Atrial Natriuretic Peptide in Spontaneously Hypertensive Rats*

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(Received October 30, 1990)

ABSTRACT

Effects of atrial natriuretic peptide (ANP) on blood pressure, plasma renin activity, aldosterone and renal excretion were compared in conscious spontaneously hypertensive rats (SHR) and normotensive Wistar rats fed low, medium or high sodium diet (2, 10, 25 mmol NaCl/100g diet) for 6 weeks. ANP infusion (380 ng/kg/min for 20 min) produced reductions in blood pressure, plasma renin activity, and aldosterone level, but marked increases in hematocrit, urine flow, and excretions of sodium and potassium. The low sodium group showed a significantly enhanced aldosterone lowering effect of ANP than the high sodium group. However, three salt groups showed no difference in effects of ANP on blood pressure, plasma renin activity, hematocrit and diuresis. Natriuretic response to ANP was significantly greater in the high salt-than in the low salt-SHR, but was not different between the Wistar salt groups. There were strain differences in effects of ANP: SHR showed greater responses of blood pressure and natriuresis than Wistar rats.

Above results indicate that aldosterone-lowering and natriuretic effects of ANP were modified by different dietary sodium intakes. However, blood pressure- and renin-lowering, or diuretic effects of ANP were not affected by dietary sodium intakes. The mechanisms whereby dietary sodium intakes alter the effects of ANP in the pathogenesis of hypertension are not clear.

Key Words: ANP, Aldosterone, Renin, Natriuresis, Salt, SHR

INTRODUCTION

The earlier studies observed specific granules in the atria of many mammalian species (Kisch 1956, Jamieson & Palade, 1964). In 1981, de Bold et al. discovered that acidic extracts of these granules possess powerful diuretic and natriuretic activities. A larger prohormone molecule is present in the myocytes of the right and left atria, and the 28 amino acid peptide hormone (atrial natriuretic peptide, ANP) is released in response to an increase in atrial pressure (Petersson et al, 1985). Endogenous release of ANP or exogenous administration of the synthetic hormone results in a number of effects; a potent diuresis/natriuresis, vasodilatory effect and an inhibition of the renin-angiotensin-aldosterone system (Atarashi et al, 1985; Garcia et al, 1985; Ishihara et al, 1985). There are also strong indications of its implication in the regulation of both the central (Quirion et al, 1984) and the peripheral nervous system (Debinski et al, 1986).

Basal levels of ANP in various forms of experimental hypertension have been reported as either normal or only slightly elevated (Gutkowska et al, 1986; Imada et al. 1985).

However, acute administration of ANP produced enhanced responses of blood pressure, diuresis and natriuresis in hypertensive patients (Cusson et al, 1987) and animals (Kondo et al, 1985; Hamet & Tremblay, 1989). These studies suggest modified effects of ANP in the pathogenesis of hypertension. Since the physiological responses to ANP may be in part dependent on volume status and renin-angiotensin activity, in the present study the influence of sodium intake on the responses to ANP infusion in normotensive and hypertensive rats was examined.

METHOD

Male spontaneously hypertensive rat (SHR) and normotensive Wistar rats at the age of 6 weeks were divided into three groups. They were fed low, medium or high sodium diet (2, 10 or 25 mmol NaCl/100g diet) and tap water ad libitum for 6 weeks. On the day of the expeiment, rats were anesthetized with ether and polyethylene catheters (Pulled PE 50) filled with heparinized saline (50 U/ml) were implanted in the femoral artery and vein. The free end of the catheters was exteriorized at the back and secured. The urinary bladder was exposed via a median abdominal incision and cannulated (PE 100) for urine collection. Then the rat was placed in a restraining cage and the arterial catheter was attached to a Statham pressure transducer P50 and physiograph (Narco, MK-IV-P) for monitoring atrerial pressure.

When the rat regained consciousness and the arterial pressure had been stabilized, the venous line was connected to a infusion pump and 0.9% saline was infused at a rate of 20 μl/min for 80 min. Control urine sample was collected in a pre-weighed tube during the last 20 min. Then 2.5 ml of control blood sample was collected through the arterial line and the same volume of donor blood was collected through the arterial line and the same volume of blood was given simultaneously through the venous line with the method described in a previous study (Lee-Kwon, 1984).

Rat atrial natriuretic peptide (ANP) was purchased from peninsula Laboratories, Inc. (Belmont, Calif) and was dissolved in 0.1 M acetic acid in a concentration of 0.1 mg/ml, divided into 60 μl aliquots, frozen and stored at −20℃. For each experiment, an aliquot of ANP was diluted in 0.9% saline and infused at a rate of 380 ng ANP/Kg/min (20 μ l/min) for 20 min. Urine samples were collected at 10 -min intervals during and after the ANP infusion. Arterial pressuer was recorded continuously during the experimental period. At the end of the ANP infusion, 2.5 ml of arterial blood was taken.

After measurement of hematocrit, the blood was centrifused at 2000 rpm for 20 min, and the separated plasma was stored at −20℃. Plasma concentration of aldosterone was measured by using the radioimmunoassay kit (Diagnostic Inc.) and renin activity with the radioimmunoassay method described by Kim and Cho (1986). The volume of the urine was measured by weighing the collection tube. Then the urine samples were frozen at −20℃ for later determination for the content of sodium and potassium (flame photometer).

Statistical analysis: Responses to ANP infusion in each group, and differences between Wistar and SHR were tested by Wilcoxon's signed-rank test, and Mann-Whitney U test, respectively. Differences between the three salt groups were assessed by nonparametric one-way analysis of variance (Kruskal-Wallis test). All values are presented as mean±SE. Statistical difference was considered significant when p value was <0.05.

RESULTS

Growth rate was similar between the three salt groups, but the body weight of Wistar rat was heavier than that of SHR (Fig. 1). Baseline mean

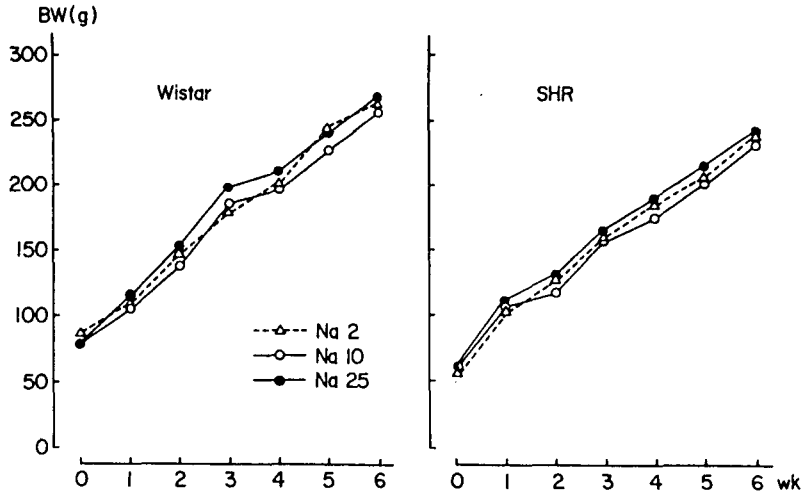

Fig. 1. Growth rate of Wistar rats and SHR fed three different sodium diets (2, 10, 25 mmol NaCl/100 g diet) for 6 weeks.

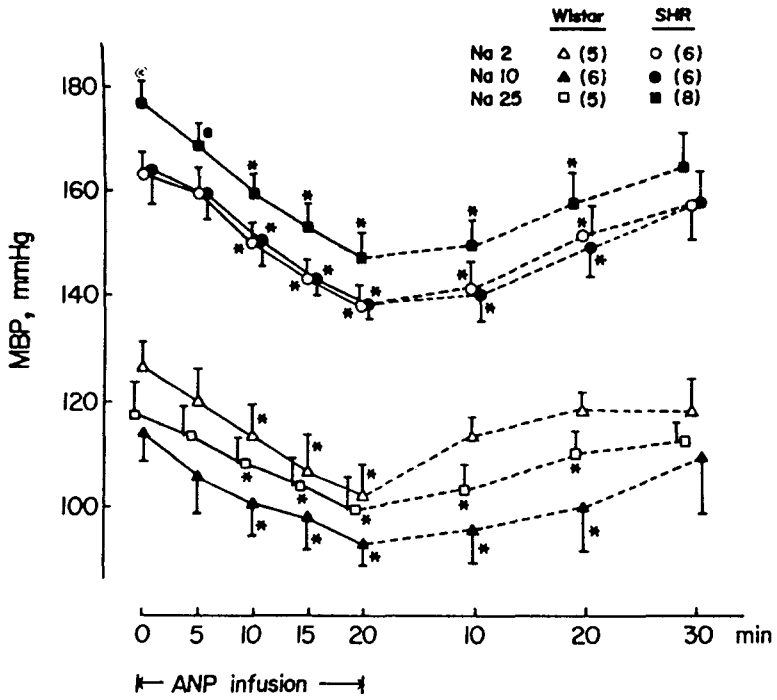

Fig. 2. Effect of ANP infusion (380 ng/kg/min) on mean arterial blood pressure (MABP) of Wistar and SHR fed 3 different sodium diets (2, 10, 25 mmol NaCl/100g diet) for 6 weeks. *$p<0.01$, significantly different from the pre-infusion value. @ $p<0.05$, significantly different from the low sodium group (Na 2).

arterial blood pressure (MABP) of SHR was significantly higher in the high salt group (176±4.0 mmHg) than in the low or medium salt group (163±4.3, 163±6.6 mmHg, respectively, $p<0.05$) (Fig. 2, Table 1). However, MABP of Wistar rats was not significantly different among the three salt groups.

Table 1. Base-line values for mean arterial blood pressure (MABP), plasma aldosterone concentration (Aldo), renin activity (PRC) and hematocrit (Hct). urine flow (V), excretions of sodium (ENa) and potassium (EK), and changes induced by infusion of ANP (380 ng/kg/min) for 20 min in Wistar and SHR fed different sodium diets (2, 10, 25 mmol NaCl/100g diet) for 6 weeks. Shown are the absolute change as well as percent change compared with own basal values

		Base-line		Change		%Change		Number	
		Wistar	SHR	Wistar	SHR	Wistar	SHR	Wistar	SHR
MABP,	Na 2	126±4.7	163±4.3**	−24.8±2.5	−24.8±4.0	−19.4±2.7	−15.1±2.1	5	6
mmHg	Na 10	113±5.2	163±6.6**	−20.7±1.9	−27.4±3.7	−18.3±1.8	−15.2±2.0	6	6
	Na 25	117±6.3	176±4.0**	−19.8±0.6	−30.4±3.5*	−15.6±0.9	−17.2±2.0	5	8
Aldo,	Na 2	217±19.1	140±15.3	−47.7±12.6	−48.5±9.3	−21.3± 5.1	−33.5± 3.1	5	6
ng/dl	Na 10	109±15.4	104±14.2	−21.1±11.3	−23.9±9.0	−13.9±12.3	−21.1± 7.0	6	5
	Na 25	74± 6.7	76±18.1	−17.6± 5.1	−12.6±8.6	−22.5± 6.6	−15.0±11.3	5	7
PRA,	Na 2	33.3±4.5	30.1±4.8	−13.2±4.0	−11.3±3.6	−35.7± 7.4	−33.6± 5.6	5	6
ng AI/	Na 10	35.7±4.4	31.5±4.8	−12.8±5.7	−15.1±5.5	−30.4±11.2	−40.9±12.2	6	5
ml.hr	Na 25	32.6±7.1	26.1±3.2	−10.7±8.3	−5.7±2.8	−32.7±25.4	−17.2± 9.6	5	7
Hct,	Na 2	41.9±0.44	45.7±0.83	2.13±0.34	0.96±0.50	5.08±0.84	2.15±1.11	5	6
%	Na 10	43.6±1.58	44.2±1.06	1.40±0.53	2.09±0.74	3.44±1.43	4.77±1.68	6	5
	Na 25	42.6±0.89	44.6±0.97	1.85±0.75	1.70±0.54	4.30±1.78	3.84±1.23	4	7
V,	Na 2	3.3±1.1	4.5±1.0	27.1±2.1	26.5±6.5	870±193	589±111	6	6
μl/min	Na 10	6.6±1.9	8.7±2.4	17.7±3.7	28.3±6.2	340± 94	326±105	6	6
100g	Na 25	7.1±2.3	9.8±2.9	34.6±8.5	28.8±6.2	494±102	395± 97	4	7
ENa,	Na 2	0.21±0.11	0.12±0.03	4.0±0.5	3.9±0.6	1919±238	3292±952	6	6
μEq/min	Na 10	0.20±0.05	0.73±0.32*	2.9±0.6	5.3±0.9*	1781±217	922±247	6	6
100g	Na 25	0.39±0.15	0.97±0.29*	4.1±0.8	5.9±0.1	1046±152	708±178	4	7
EK,	Na 2	0.37±0.17	0.47±0.11	3.00±0.23	2.31±0.27	657±152	474±103	6	6
μEq/min	Na 10	0.40±0.12	0.78±0.16	2.18±0.24	2.34±0.35	763±114	296± 87	6	6
100g	Na 25	0.27±0.14	0.69±0.21	2.07±0.21	1.55±0.20	767±107	243± 99	4	7

Values are mean±SE.

*$p<0.05$, **$p<0.01$, significantly different between the three salt groups (Kruscal-Wallis one-way ANOVA test).

*$p<0.05$, **$P<0.01$, significantly different between Wistar and SHR (Mann-Whitney test).

Infusion of ANP produced a gradual decrease in MABP as shown in Fig. 2. Maximun reduction in MABP during the infusion of ANP was similar among the salt groups of Wistar rats and SHR (Table 1). When the values of maximum reduction in MABP of the three salt groups after ANP infusion were pooled together, SHR showed significantly greater reduction(−27.3±2.2 mmHg, n=20) than Wistar rats (−21.0±1.3 mmHg, n=16, $p<0.05$). However, percent reduction in MABP by ANP was similar between Wistar (−17.8±1.1%) and SHR (−16.0±1.1%).

Baseline plasma concentration of aldosterone was significantly higher in the low salt group than in the higher salt groups of both Wistar and SHR (Fig 3. Table 1). Baseline plasma renin activity was similar

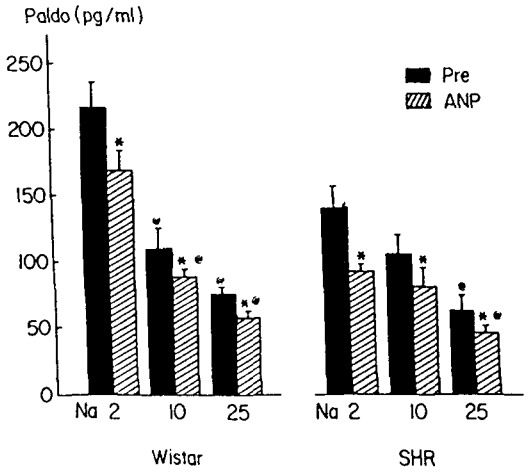

Fig. 3. Changes in plasma aldosterone concentration after ANP infusion (380 ng/kg/min) in Wistar and SHR fed 3 different sodium diets (2, 10, 25 mmol NaCl/100g diet) for 6 weeks. *p<0.01, significantly different from the pre-infusion value. @p<0.05, significantly different from the low salt group (Na 2).

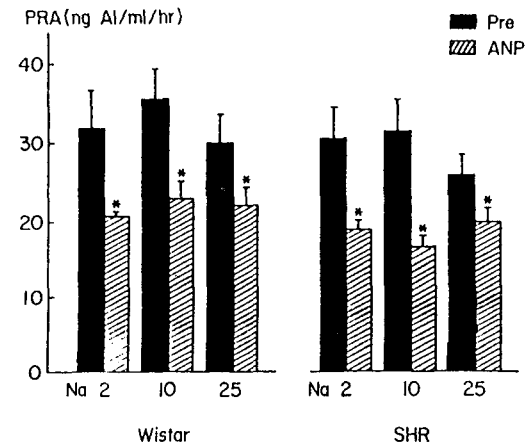

Fig. 4. Changes in plasma renin activity (PRC) after ANP infusion (380 ng/kg/min) in Wistar and SHR fed 3 different sodium diets (2, 10, 25 mmol NaCl/100g diet) for 6 weeks. *p<0.01, significantly different from the pre-infusion value.

between the three salt groups (Fig. 4). ANP infusion produced decreases in plasma aldosterone and renin activity in all groups. The magnitude of the reduction in aldosterone level was significantly greater in the

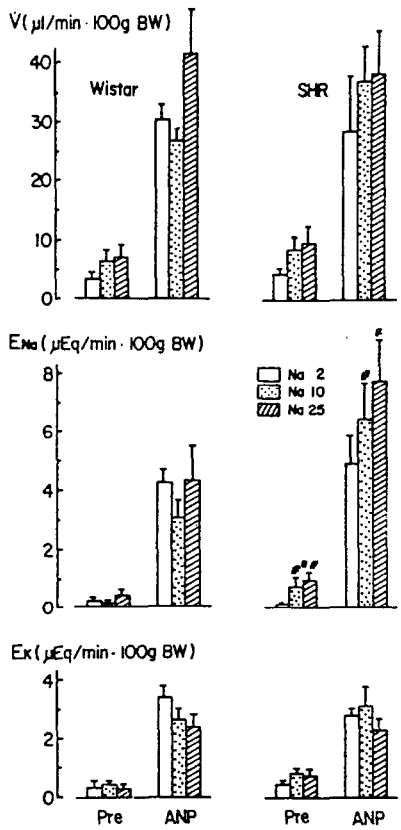

Fig. 5. Urine flow (V), urinary excretions of sodium (ENa) and potassium (EK) before (Pre) and during 20 min infusion of ANP (380 ng/kg/min) in Wistar and SHR fed 3 different sodium diets (2, 10, 25 mmol NaCl/100g diet) for 6 weeks. *p<0.05, significantly different between the 3 sodium groups. #p<0.05, significantly different between the Wistar and SHR.

low salt group than in the high salt group (Table 1). SHR had a lower plasma aldosterone level than Wistar rats.

Baseline hematocrit value was not different between the three salt groups of either in Wistar or SHR (Table 1). When the baseline values of the salt groups were pooled together, the hematorit values were significantly lower in Wistar (42.9±0.8, n=15) than in SHR (44.9±0.5, n=18, p<0.05). ANP infusion produced an increase in hematocirt in similar degrees in all groups.

Baseline urine flow and sodium excretions were greater in the high sodium-than in the low sodium-SHR, but were not different between the three salt groups of Wistar (Table 1, Fig. 5). ANP infusion produced marked increases in urine folw, and sodium and potassium excretions (Fig. 5). In Wistar rats, diuretic and natriuretic responses to ANP were similar among three salt groups. However, in SHR the high salt group produced a significantly greater natriuresis during the ANP infusion than the low salt group. Increase in potassium excretion during the ANP infusion was similar between the three salt groups of Wistar and SHR. Diuretic and Kaliuretic responses to ANP infusion were not different between Wistar and SHR. However, natriuretic response to ANP was greater in SHR than in Wistar.

DISCUSSION

In response to high sodium diet the hypertension in the SHR was aggravated, again demonstrating that this rat strain is moderately sensitive to salt (Kim et al, 1989; Gardin & Persson 1987). Judging from the reduction in blood pressure during ANP infusion, there were no indications that a high sodium diet was associated with a change in vascular response to ANP. This is in agreement with observations made in SHR (Gardin & Persson 1987) and in normotensive man (Weidmann et al, 1986). Contrary to our results, Valentin et al. (1989) observed that normotensive rats fed a sodium deprived diet for 3 weeks showed a markedly greater reduction in blood pressure than high salt rats when a very high dose of ANP (1 μg/kg/min) was infused. The discrepant reports might be due to the more severe degree of salt restriction in their study. They used a sodlum deprived diet, which has been shown to retard growth rate, while we employed, as low sodium diet, 2 mmol/100g diet which is just sufficient to allow the normal growth (Grunert et al, 1950; Toal & Leenen 1983; Choi et al, 1987). There is a possibility that the enhanced vascular response to ANP in the study of Valentin et al. (1989) might be resulted from sodium deficiency. A question whether animals chronically fed different amounts of sodium could result in up- or down-regulation in vascular ANP receptors has to be resolved.

The hypotensive response to ANP was significantly greater in SHR than in Wistar rats (Table 1). Other investigators (Gellai et al, 1986; Kasai et al, 1986) also reported an augmented hypotensive response to ANP in SHR. When different doses of ANP were injected or infused, SHR showed dose-dependent hypotensive response to ANP but normotensive Wistar Kyoto (WKY) rats showed hypotensive response to only the high doses of ANP. On the contrary, Pettersson et al (1988) reported a similar magnitude of reduction in blood pressure in WKY and SHR during ANP infusion. When they studied cardiac performance and central hemodynamics, there were the strain difference in the mechanisms of the blood pressure-lowering effects of ANP. In the normotensive rats the fall in blood pressure after ANP infusion was due only to a reduction in the cardiac output while in the SHR there was a decresase in the cardiac output as well as in total peripheral resistance (Petterson et al, 1988). The reduction in central blood volume and the cardiac output was significantly more pronounced in the normotensive rats than in SHR. Mechanisms of the strain difference in the fall in the toal pheripheral resistance by ANP are not certain.

Cellular mechanism of ANP action on the vasculature appears to be mediated by activation of guanylate cyclase and thus the production of cyclic GMP (cGMP) as a second messenger (Napier et al, 1984; Rapoport et al, 1985; Hamet & Tremblay 1989). The enhanced effects of ANP observed in hypertension seem to be related to a hyperresponsiveness of the effector system, cGMP. Short-term ANP infusion induced an exaggerated increase in cGMP in the plasma and the urince in hypertensive

patients (Cusson et al, 1987) as well as in hypertensive animals (Hamet et al, 1986). The in vitro studies also showed hyperresponsiveness of the cGMP system in different tissues from SHR (Takayanagi et al, 1986). In cultured vascular smooth muscle and endothelial cells, an abnormal responsiveness of the cGMP effector system was maintained even after several generations (Hamet & Tremblay 1989). This may suggest a genetic defect in cellular cGMP system in hypertension. Further studies are required for better understanding of the role of ANP on pathogenesis of hypertension.

ANP infusion produced an increase in hematocrit (Table 1). This could be partly explained by rapid diuresis and consequent reduction in blood volume. In nephrectomized rats, ANP infusion provoked a marked reduction in circulation blood volume (Almeida et al, 1986;Fluckiger et al, 1986; Valentin et al, 1989). This suggests an increased fluid shift from capillary beds to the interstitium. Direct measurement on a single capillary preparation demonatrated that ANP directly and reversibly elevate capillary hydraulic conductivity (Huxley et al, 1987). Hyperfiltration induced by ANP was independent of capillary hydrostatic pressure or surface area. Therefore, ANP decreases blood volume not only by inducing diuresis, but also by increasing systemic transcapillary fluid filtration. In the present study, the magnitude of diuresis and increased hematocrit after ANP infusion was not different either among salt groups or between Wistar and SHR. This result suggests that the degree of fluid shift at the capillaries induced by ANP may not be different among salt groups. On the other hand, SHR had higher baseline hematocrit than Wistar rats, but its physiological significance is not clear.

The degree of ANP-induced natriuresis (approximately 7 to 30 fold increase) was much greater than that of diuresis (approximately 3 to 9 fold increase). Three salt groups of both Wistar and SHR showed similar diuretic response during ANP infusion. However, the natriuretic response to ANP was significantly greater in the high salt than in the low salt SHR. SHR showed significantly greater natriuretic response to ANP than normotensive Wistar rats (Fig. 3). This is in accord with other reports on SHR (Kihara et al, 1985; Kondo et al, 1985) and hypertensive men (Ishii et al, 1986). Pollock and Arendshorst (1990) observed a more pronounced diuretic and natriuretic response to ANP only in 6-week-old SHR than in age-matched normotensive WKY rats, but not in 11-week-old SHR. Reasons for differences in the age-related phenomenon are not clear, but might be related to different rate of development of hypertension in SHR obtained from different sources. Mechanisms for the exaggerated renal response to ANP in SHR are not known. Renal perfusion pressure may account for some of the differences in the renal response to ANP between SHR and WKY. However, increased renal perfusion pressure could not completely account for the exaggerated renal response in young SHR (Pollock & Arendshorst, 1990). There is a possibility that a relatively lower metabolic clearance of exogenously administered ANP (Chevalier et al, 1988) in SHR may produce an enhanced natriuretic response to ANP.

The mechanisml of the well-known potent natriuretic and diuretic responses to ANP remains controversial. Proposed mechanisms include ① increase in renal blood flow (Needleman et al, 1984), ② increase in GFR without an increase, or actual decrease in renal blood flow (Maak et al, 1985), ③ direct tubular effect of ANP (Briggs et al, 1982). It has been generally agreed that filtration fraction is significantly increased by ANP. Hyperfiltration produced by ANP may be due to its newly proposed direct effect on capillary hydraulic conductivity, independently of filtration pressure as demonstrated on a single capillary preparation by Huxley et al (1987), Cellular mechanisms of diuretkc and natriuretic effects of ANP seem to be different from each other. Willenborck et al (1989) dissociate the diuretic and natriur-

etic activities of ANP by using Met-Sulfoxy ANP, an analog of human ANP with the oxidizied form of methionine at the position 110. In contrast to the effect of ANP, the diuretic doses of the ANP analog had no effect on urinary excretions of sodium and cyclic GMP (cGMP). Mechanism of the heterogeneity of the ANP-cGMP effector system has to be elucidated further.

Infusion of ANP appeared to suppress renin and aldosterone release while promothing sodium excretion. This effect of ANP was more obvious when aldosterone was stimulated by low salt diet (Table 1). Similar magnitude of fall in PRA and aldosterone during ANP infusion in the present and other studies (Cuneo et al, 1986; Wiedmann et al, 1986) may suggest the possibility that the decreased aldosterone secretion is in part renin dependent. However, ANP injection in nephrectomized rats did not change plasma renin activity, but decreased plasma aldosterone level (Shionoiri et al, 1986). This result indicates that ANP may have a direct inhibitory effect on aldosterone secretion from the adrenal gland. It is still controversial whether the inhibitory effect of ANP on aldosterone secretion is more or less mediated by changes in plasma renin levels (Vierhapper et al, 1986; Cuneo et al, 1987; Oelkers et al, 1988). There was a strain difference in baseline plasma aldosterone concentration: SHR showed significantly lower level than Wistar rats. This result is in accord with other reports (Kim et al, 1988;Kim et al, 1989).

However it is not clear whether differences in aldosterone level between Wistar and SHR result in differences in regulating salt and body fluid balance.

ACKOWLEDGEMENTS

The authors are grateful to Ms Soon Bock Chang for the expert technical assistance and to Dr. Kyung Woo Cho, Dep't of Physiology at Jeonbug University for the measurement of plasma renin activity at his lab. This work was supported by a grant from Korea Science and Engineering Foundation.

REFERENCES

Almeida JP, Suzuki M & Maak TH (1986). Atrial natriuretic factor increases hematocrit and decreases plasma volume in nephrectomized rats. *Life Sci* 39, 1193-1199

Atarashi K, Mulrow PJ & Gutkowska J (1985). Inhibition of aldosterone production by an atrial extract. *Science* 224, 992-994

Briggs JP, Steipe B & Schubert G (1982). Micropuncture studies of the renal effects of atrial natriuretic substance. *Pflugers Arch* 395, 271-276

Chevalier RL, Gomez RA, Carey RM, Peach MJ & Linden J (1988). Renal effects of atrial natriuretic peptide infusion in young and adult rats. *Pediatric Res* 33, 333-337

Choi BH, Hwang JH, Park JS & Lee WJ (1987). Effect of calcium infusion on pressor responsiveness to angiotensin II and arginine vasopressin in Wistar rats fed high salt diet. *Kyungpook Univ Med J* 28, 143-150 (in Korean)

Cuneo RC, Espiner EA & Nicholls MG (1987). Effect of physiological levels of atrial natriuretic peptide on hormone secretion: inhibition of angiotensin-induced aldosterone secretion and renin release in normal man. *J Clin Endocrinol* 65, 765-772

Cusson JR, Hamet P & Gutkowska J (1987). Pharmacodynamics of infusions of ANP in normotensive and hypertensive subjects. in: *Biologically active atrial peptides.* Vol. 1. edited by BM Brenner and JH Laragh. Raven Press, NY. pp. 602-605

Debinski W, Gutkowska J & Kuchel O(1986). ANF-like peptides in the peripheral autonomic nervous system. *Biochem Biophysics Res Comm* 134, 279-284

de Bold AJ, Borenstein HB, Veress AT & Sonnenberg H (1981). A rapid and potent natriuretic response to intravenous injection of atrial myocardial extract in rats. *Life Sci* 28, 89-94

Fluckiger JP, Waeber B & Matsueda G (1986). Effect of atriopeptin III on hematocrit and volemia of nephrectomized rats. *Am J Physiol* 251, H880-H883

Garcia R, Thibault G & Gutkowska J (1985). Changes in regional blood flow induced by atrial natriuretic

factor in conscious rats. *Life Sci* 36, 1687-1692

Gellai M, DeWolf RE, Kinter LB & Beeuwkes R (1986). The effect of atrial natriuretic factor on blood pressuer, heart rate and renal function in conscious, spontaneously hypertensive rats. *Circ Res* 59, 56-62

Gardin K & Persson B (1987). Renal and cardiovascular effects of atrial natriuretic peptide in Wistar-Kyoto and spontaneously hypertensive rats during a chronic salt loading. *Acta Physiol Scand* 131, 273-281

Grunert RR, Meyer JH & Phillips PH (1950). The sodium and potassium requirements of the rat for growth. *J Nutr* 42, 609-618

Hamet P, Tremblay J & Pang SC (1986). Cyclic GMP as mediator and biological marker of atrial natriuretic factor. *J Hypertens* 4 (Suppl 2), S49-56

Hamet P & Tremblay J (1989). Atrial natriuretic factor, the kidney and high blood pressure. *Clin Invest Med* 12, 329-335

Huxley VH, Tucker VL, Verburg KM & Freeman RH (1987). Increased capillary hydraulic conductivity induced by atrial natriuretic peptide. *Circ Res* 60, 304-307

Imada T, Takayanagi R & Inagami T (1985). Changes in the content of ANF with the progression of hypertension in SHR. *Biochem Biophys Res Comm* 133, 759-765

Ishii M, Sugimoto T & Matsuoka H (1986). The haemodynamic, renal and endocrine effects of alpha-human atrial natriuretic polypeptide in normotensive people and patients with essential hypertension. *J Hypertens 4* (Suppl 6), S542-S545

Ishihara T, Aisaka K & Hattori K (1985). Vasodilatory and diuretic actions of a-human atrial natriuretic polypeptide. *Life Sci* 36, 1205-1215

Jamieson JD & Palade GE (1964). Specific granules in atrial muscle cells. *J Cell Biol* 23, 151-172

Kalil F, Fine B, Kuriyama S, Hatori N, Nakamura A, Nakamura M & Aviv A (1987). Increased atrial natriuretic factor receptor density in cultured vascular smooth muscle cells of the spontaneously hypertensive rat. *Clin Exp Hypertens* [A]9, 741-752

Kasai Y, Abe K & Yasujim M (1986). The augmented hypotensive response to a synthetic atrial natriuretic factor in spontaneously hypertensive rats. *J Hypertens* 4 (Suppl 3). S325-S327

Kihara M, Nakayama K & Nakao K (1985). Accelerated natriuresis induced by synthetic atrial natriuretic polypeptide in spontaneously hypertensive rats. *Clin Exp Hypertens* A7, 539-551

Kim AR, Lee WJ, Choo YE, Kim SH & Cho KW (1989). Dietary sodium effects on responses of atrial natriuretic peptide, aldosterone and renin release to acute volume expansion in SHR. *Kor J Physiol* 23, 253-262

Kim HJ & Cho KW (1986). On the negative feedback control mechanism of the renin release in kidney slices. *Kor J Physiol* 20, 236-248 (in Korean)

Kim SH, Kim SH, Seul KH & Cho KW (1988). Effects of atrial natriuretic peptide on renal and endocrine functions in spontaneously hypertensive rats. *Kor J Physiol* 22:41-53

Kisch B (1956). Electron microscopy of the atrium of the heart. *Exp Med Surg* 14, 99-112

Kondo K, Kida O & Kangawa K (1985). Enhanced natriuretic and hypo-tensive responsiveness to alpha-human atrial natriuretic polypeptide in SHR. *Clin Exp Hypertens* A7, 1097-1107

Lee-Kwon WJ, Share L, Crofton JT & Brooks BP (1984). Effect of angiotensin II on vasopressin in plasma and platelets in SH and WKY rats. *Clin Exp Hypertens* A6, 1653-1672

Maack T, Camargo MJ & Kleinert HD (1985). Atrial natriuretic factor: structure and functional properties. *Kid Int* 27, 607-615

Napier MA, Vandlen RL & Albers-Schonberg G (1984). Specific membrane receptors for atrial natriuretic factor in renal and vascular tissues. *Proc Natl Scad Sci* USA 81, 5946-5950

Needleman P, Currie MG & Geller DM (1984). Potensial mediators of an endocrine relationship between heart and kidney. *Trends Pharmacol Sci* 5, 506-509

Oelkers W, Kleiner S & Bahr V (1988). Effects of incremental infusion of atrial natriuretic factor on aldosterone, renin, and blood pressure in humans. *Hypertens* 12, 462-467

Pettersson A, Ricksten SE, Hedner J & Hedner T (1988). Differential haemodynamic effects of atrial natriuretic peptide (ANP) in normotensive and spontaneously hypertensive rats. *Acta Physiol Scand* 134, 247-251

Pollock DM & Arendshorst WJ (1990). Exaggerated natriuretic response to atrial natriuretic factor in rats

developing spontaneous hypertension. *Hypertens* 16, 72-79

Quirion R, Dalpe M & Dam T-A (1984). Characterization and distribution of receptors for the atrial natriuretic peptides in mammalian brain. *Proc Natl Acad Sci USA* 83, 174-178

Rapoport RM, Waldman SA & Schwartz K (1985). Effects of atrial natriuretic factor, sodium nitroprusside, and acetylcholine on cGMP levels and relaxation in rat aorta. *Eur J Pharmacol* 115, 219-229

Shionoiri H, Yasuda G & Hisashi O (1986). Effects of synthetic alpha-human atrial natriuretic peptide on blood pressure and renin-aldosterone system in both intact and nephrectomized spontaneously hypertensive rats. *J Hypertens* 4(Suppl 3), S329-330

Takayanagi R, Imada T & Grammer RT (1986). Atrial natriuretic factor in spontaneously hypertensive rats: Concentration changes with the progression of hypertension and elevated formation of cyclic GMP. *J Hypertens* 4(Suppl 3). S303-307

Toal CB & Leenen FHH (1983). Dietary sodium restriction and development of hypertension in spontaneously hypertensive rat. *Am J Physiol* 245, H1081-H1084

Valentin JP, Ribstein J & Mimran A (1989). Sodium intake influences the effects of atriopeptin on blood pressure and transcapillary fluid shift in the rat. *Life Sci* 45, 2437-2441

Vierhapper H, Nowotny P & Waldhausl W (1986). Prolonged administration of human atrial natriuretic peptide in healthy man: reduced aldosteronotropic effect of angiotensin II. *Hypertens* 8, 1040-1043

Weidman P, Hellmueller B & Uehllinger DE (1986). Plasma levels and cardiovascular, endocrine and excretory effects of atrial natriuretic peptide during different sodium intakes in man. *J Clin Endocrinol Metab* 62, 1027-1036

Willenbrock RC, Tremblay J, Garcia R & Hamet P (1989). Dissociation of natriuresis and diuresis and heterogeneity of the effects of atrial natriuretic factor. *J Clin Invest* 83, 482-489

= 국문초록 =

소금 섭취량을 달리한 정상 및 고혈압쥐에서 Atrial Natriuretic Peptide가 혈압, Renin-Aldosterone 및 신배설에 미치는 영향

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장기적으로 소금 섭취량을 달리 한 정상 및 고혈압쥐에서 atrial natriuretic peptide (ANP) 가 혈압, renin-aldosterone 및 신배설에 미치는 효과를 비교하였다. 생후 6주된 spontaneously hypertensive rat (SHR)와 Wistar 숫쥐를 각각 저염, 정상염 및 고염 (2, 10, 25 mmol NaCl/100 g diet) 군으로 나누어 실험 식이를 6주동안 먹었다. 실험 당일 아침에 쥐를 ether로 마취시킨 상태에서 대퇴 동맥과 정맥 및 방광에 catheter를 삽입한 다음에 쥐를 restraining cage에 넣어 고정시켰다. 마취가 깨고 혈압이 안정된 후에 정맥관으로 0.9% saline을 0.02 ml/min의 속도로 80분간 주입하고 안정시 뇨와 혈액을 채취하였다. 그후 ANP를 380 ng/kg/min의 속도로 20분간 주입하였으며 그동안 10분 간격으로 뇨를 채취한 다음 채혈하였다. 혈장 aldosterone 농도와 renin 활성도 (PRA)를 방사면역법으로 측정하였다.

ANP를 주입하개 전에 SHR 고염군의 평균동맥압은 정상염이나 저염군보다 유의하게 높았으나, Wistar의 혈압은 소금군 사이에서 차이가 없었다. ANP 주입전의 혈장 aldosterone 농도는 소금 섭취량이 많을수록 유의하게 낮았으며, Wistal 군이 SHR보다 높은 값을 보였다. 혈장 renin 활성도는 소금군 간에 차이가 없었으며, Wistar와 SHR 간에도 차이가 없었다. 요량이나 Na, K 배설률은 소금군 간에 유의한 차이가 없었으나, SHR이 Wistar 보다 높은 경향을 보였다. Hematocrit 값도 소금군 간에 차이가 없었으나, SHR의 값이 Wistar 보다 유의하게 높았다. ANP를 주입하는 동안 혈압이 점진적으로 감소하여 20분후에는 20~30 mmHg 정도 감소하였으나, 각 소금군사이에 차이가 없었다. 그러나, ANP에 의한 혈압 강하 정도는 SHR이 Wistar 보다 유의하게 높았다.

ANP 주입 후에는 모든 군에서 aldosterone과 혈장 renin 활성도가 유의하게 감소하였는데, aldosterone의 감소 정도는 저염군에서 가장 크게 나타났다. ANP의 이뇨 및 Na 배설 항진효과는 Wistar 에서는 소금군 간에 차이가 없었으나, SHR 에서는 고염군의 Na 배설률이 저염군보다 유의하게 높았다. ANP의 혈압강하 효과나 Na 배설 항진효과가 SHR에서 Wistar 보다 유의하게 높게 나타났으나, 이뇨반응, renin 및 hematocrit의 변화에는 차이가 없었다.

이상의 결과에서, 장기적으로 소금 섭취량이 다름에 따라 ANP의 효과 중에서 특히 aldosterone 분비나 SHR의 Na 배설에 차이가 나타났는데 그 작용 기전은 확실치 않다.