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Effect of Nifedipine on Endocrine and Cardiovascular Responses to Angiotensin II in SHR Fed with Different Sodium Diets

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= ABSTRACT=

Effects of a voltage-dependent calcium channel antagonist, nifedipine, on the responses of blood pressure, and secretion of atrial natriuretic peptide (ANP) and aldosterone to angiotensin II (Ang II) were compared in male Wistar and spontaneously hypertensive rats (SHR).

A low-, control- or high-sodium diet (2, 10 or 25 mmol Na/100 g diet) was fed for 6 weeks from the age of 6 weeks. On the morning of the experiment, catheters were inserted under ether anesthesia in the femoral artery for pressure recording and blood sampling, and in the femoral vein for drug infusion. Ang II was infused at a rate of 250 ng/kg/min for 20 min. Nifedipine mixed with Ang II was infused at a rate of 16 μg /kg/min for 20 min. Arterial blood samples were collected before and after infusion of Ang II with or without nifedipine.

The control plasma level of aldosterone was inversely related to the amount of salt intake, whereas the plasma ANP level was not different between the salt groups. SHR showed a higher basal plasma ANP but a lower aldosterone concentration than Wistar rats. Infusion of Ang II produced a significant increase in blood pressure and plasma levels of aldosterone and ANP: The % increase was not significantly different either between the salt groups or between SHR and Wistar rats. SHR showed a greater pressor response to Ang II but a remarkably smaller decrease in heart rate after Ang II infusion than Wistar rats. With increasing sodium intake, the effect of Ang II on aldosterone secretion was decreased, whereas that on ANP secretion or blood pressure was not changed. Nifedipine decreased the responses of blood pressure and heart rate to Ang II in all groups. Nifedepine caused almost a complete inhibition of Ang II induced ANP secretion, but only a partial inhibition of Ang II induced aldosterone secretion or vasoconstriction.

These results indicate that calcium-dependent processes were involved in Ang II-induced vasoconstriction, and secretions of aldosterone and ANP. However, the calcium-dependent process for ANP secretion was considerably different from that for aldosterone secretion or vasoconstriction evoked by Ang II. The Ang II-induced increase in ANP secretion appeared to be caused primarily by activating voltage-dependent calcium channels, whereas Ang II-induced aldosterone secretion and vasoconstriction was not.

Key Words: Ang II, Aldosterone, ANP, Nifedipine, SHR

INTRODUCTION

The most important hemodynamic distur

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bance in patients with hypertension is an increase in peripheral vascular resistance. Therefore, antihypertensive vasodilators, which directly decrease peripheral vascular resistance, are useful for the therapy of essential hypertension. In experimental hypertension, the calcium channel antagonist drugs nifedipine, verapamil and diltiazem produce a greater hypotensive effect than in normotensive animals (review: Wadsworth, 1990). Enhanced vasoconstriction in hypertension seems to be maintained by calcium channel activity. Thus, calcium channel antagonists have been developed and established as useful for the treatment of hypertension both experimentally and clinically.

Considerable evidence from in vivo and in vitro studies has demonstrated that voltage-dependent calcium channels are present in most cell types (Lory et al, 1991). Calcium channels transiently permeabilize the cell membrane to extracellular calcium, triggering cellular response such as excitation-contraction coupling, neurotransmitter release and stimulation or inhibition of hormone secretion (review; Pelzer et al, 1990).

Angiotensin II produces important physiological roles in a variety of tissues, specifically, the adrenal cortex, the heart, vascular endothelial and smooth muscle cells, the brain, and the sex organs. Although it is generally accepted that calcium plays a crucial intermediate role in the actions of angiotensin II (review: Palant & Ross, 1991), the mechanisms responsible for calcium entry through a variety of target cell membranes are not clear.

The present study was designed to examine the effects of a voltage-dependent calcium channel antagonist, nifedipine, on the responses of blood pressure, and secretions of aldosterone and atrial natriuretic peptide to angiotensin II. The effects were compared in normotensive Wistar rats and spontaneously hypertensive rats fed with different amounts of sodium for 6 weeks.

METHODS

Male spontaneously hypertensive rats (SHR) and normotensive Wistar rats at 6 weeks of age were divided into 3 groups. The rats were maintained on either low, medium or high sodium diets (2, 10, or 25 mmol/100 g diet) for 6 weeks. On the morning of the experiment, rats were anesthetized with ether and the right femoral artery and vein were catheterized by the method described previously (Lee-Kwon, 1984). Then each rat was placed in a restraining cage and the arterial line was connected to a Statham pressure transducer (P50). Blood pressure and heart rate were displayed continuously throughout the experiment on a Narco Physiograph (model MK-IV-P). After the rats regained consciousness and the blood pressure had been stabilized, 2 ml of the control blood sample were collected throught the arterial line and the same volume of blood was transfused simultaneously through the venous line with the method described in a previous study (Lee-Kwon, 1984).

After blood sampling, the arterial line was reconnected to the pressure transducer and angiotensin II (Ang II) was infused at a rate of 250 ng/kg/min for 20 min. In order to examine effects of a calcium channel blocker on Ang II-induced responses, a 10-min infusion of nifedipine (16 μg/kg/min) preceded concomitant infusion of ang II with nifedipine. Arterial blood was collected at the end of a 20-min infusion of Ang II with or without nifedipine.

The blood drawn was collected in tubes containing the following protease ihibitors (final concentration): EDTA, 5 mg/ml; aprotinin, 200 KIU/ml; soybean trypsin inhibitor, 50 BAEE/ml. The samples were immediately centrifuged at 2500 rpm at 4℃ for 20 min and the plasma was stored at −20℃ for hormone assay.

Plasma concentrations of ANP were measured by radioimmunoassay after prior extraction on Sep-Pak C_{18} cartridges. For extraction,

approximately 1 ml plasma was acidified with 10% plasma volume of 1 N HCl and was run slowly through a Sep-Pak C_{18} cartridge pre-washed with 5 ml methanol, 5 ml 8 M urea and 10 ml double distilled water. Then the cartridge was washed with 10 ml water-and 10 ml 4% acetic acid. ANP was eluted with 3 ml ethanol-acetic acid-water (90 : 4 : 6). The eluate was dried under an air stream at 37℃, and stored at −20℃ until assayed. The sample was reconstituted with 250 μl 0.2 mol/L sodium phosphate buffer (pH 7.3) containing 1 g bovine serum albumin (Sigma 7888), 3 g NaCl and 1 ml triton X-100 per liter.

For radioimmunoassay, 100 μl of plasma-extract or standard was mixed with 100 μl antibody (Research and Diagnostic Antibodies, Berkeley, CA) at 4℃ in polypropylene tubes. The mixture was allowed to incubate for 24 hr at 4℃. Then, 50 μl of tracer solution (8000 cpm) was added, and incubated for a further 24 hr at 4℃. Separaction of bound and free hormone was achieved by addition of 1 ml charcoal solution at 4℃ and centrifugation at 2200 rpm at 4℃ for 20 min. Radioactivity of the supernatant was counted in a gamma counter.

Table 1. Baseline values for mean arterial blood pressure (MABP), heart rate (HR), plasma concentrations of aldosterone and atrial natriuretic peptide (ANP) in Wister (Ws) and SHR fed with different sodium diets (2, 10 or 25 mmol/100 g diet) for 6 weeks and infused with nifedipine (Nif)

	Na 2	Na 10	Na 25
MABP, mmHg			
Ws: Control	124.5±2.5	120.0±2.1	120.9±4.2
Nif	11.7±2.2	108.0±4.7	108.3±3.3
SHR: Control	166.0±2.9##	166.0±3.0##	169.8±3.7##
Nif	150.9±2.9##	148.3±2.8##	151.0±3.2##
HR, beat/min			
Ws: Control	474±11.1	468±13.3	464±7.1
Nif	496±25.2	463±10.2	474±15.2
SHR: Control	395±6.9#	386±6.3##	384±11.5##
Nif	414±11.9#	392±12.6##	395±16.9##
Aldosterone, ng/dl			
Ws: Control	120.9±8.7	91.6±8.6*	48.1±5.4*
Nif	130.1±14.7	87.8±12.0*	56.6±4.1*
SHR: Control	83.3±4.0#	56.9±5.7*#	38.1±5.0*
Nif	88.2±7.3#	63.0±9.9	34.6±2.9*
ANP, pg/ml			
Ws: Control	43.4±9.4	37.7±5.4	47.2±5.2
Nif	50.6±8.4	46.1±9.1	55.4±5.8
SHR: Control	72.5±6.3#	92.5±6.1##	101.0±10.2#
Nif	88.4±9.5#	85.8±6.5#	102.4±9.3#
n, Ws	6	6	7
SHR	7	7	8

Values are mean±SE.
*$p<0.01$, Na 2 vs. Na 10 or Na 25.
#$p<0.05$, ##$p<0.01$, Ws vs. SHR.

Plasma concentration of aldosterone was measured by using the radioimmunoassay kit (Diagnostic Inc.).

RESULTS

Mean arterial blood pressure (MABP) was significantly higher in SHR than in Wistar rats: averages were 167.5±1.9 (n=19) and 121.7±1.8 mmHg (n=22), respectively ($p<0.01$) as shown in Table 1. However, SHR showed significantly lower heart rates than Wistar rats: 335.2±4.87, 395±5.4 beat/min, respectively. Baseline values for MABP and heart rate were not different between the salt groups of SHR and Wistar rats respectively. Nifedipine produced a significant decrease in baseline MABP, −12.4±0.1 mmHg in Wistar rats and −17.5 ±0.2 mmHg is SHR ($p<0.05$), but did not alter the heart rate significantly.

Infusion of Ang II increased MABP (Fig. 1), but decreased heart rate (Fig. 2). The pressor response to Ang II was not significantly different between the salt groups. SHR produced significantly greater pressor responses to Ang II than Wistar rats: average increase was 49.9 ± 1.47 and 39.5±1.90 mmHg ($p<0.05$), respectively, Nifedipine diminished the pressor response to Ang II in all groups. Reductions in pressor response to Ang II by nifedipine were greater in SHR (−15.7±0.5 mmHg) than in Wistar rats (−7.6±0.6 mmHg).

Reductions in heart rate during Ang II infusion were not different between the salt groups. However, the reduction in heart rate was much less in SHR than in Wistar rats: average decrease was 32.5±3.1 and 72.9±6.8 beats/min ($p<0.01$), respectively.

Baseline values for plasma concentration of aldosterone were inversely related to the amount of sodium intake, whereas plasma ANP levels were not different between the sodium groups (Table 1). SHR showed lower plasms aldosterone, but higher ANP concentration than Wistar rats. Plasma concentration of aldosterone in SHR was about 70% of that in Wistar rats, whereas that of ANP in SHR was approximately 2-fold higher than that in Wistar rats. A ten-min infusion of nifedipine did not alter the basal plasma concentrations of aldosterone and

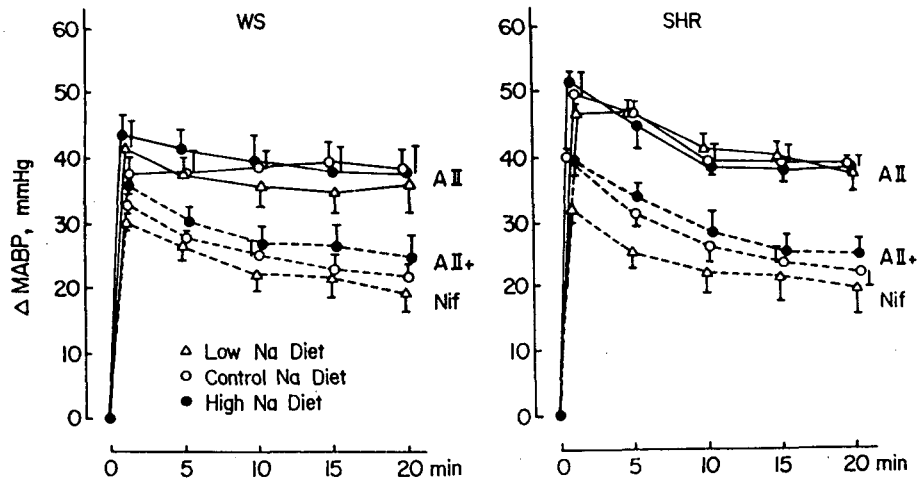

Fig. 1. Changes in mean arterial blood pressure (△MABP) during infusion of Ang II (250 ng/kg/min) for 20 min with (---) or without (——) nifedipine (16 μg/kg/min) in Wistar rats (Ws) and spontaneously hypertensive rats (SHR) fed with different Na diets (2, 10, 25 mmol/100 g diet) for 6 weeks.

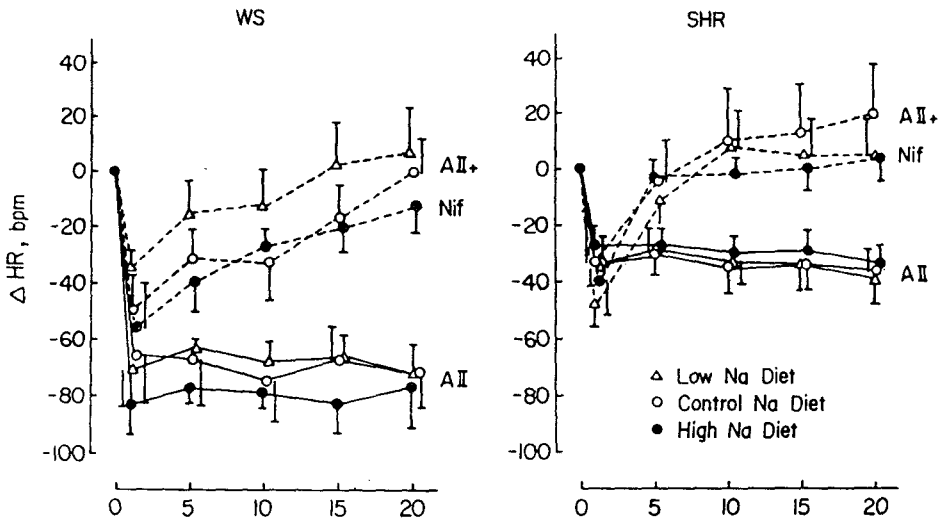

Fig. 2. Changes in heart rats (△HR) during infusion of Ang II (250 ng/kg/min) for 20 min with (---) or without (——) nifedipine (16 μg/kg/min) in Wistar rats (Ws) and spontaneously hypertensive rats (SHR) fed with different Na diets (2, 10, 25 mmol/100 g diet) for 6 weeks.

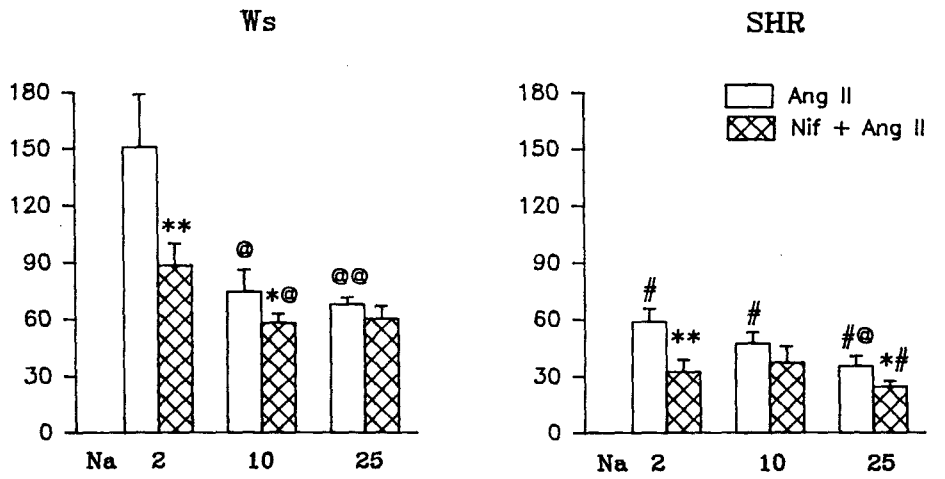

*Fig. 3. Increase in plasma aldosterone concentration after infusion of Ang II (250 ng/kg/min) with or without nifedipine (16 μg/kg/min) in Wistar rats (Ws) and spontaneously hypertensive rats (SHR) fed with different Na diets (2, 10, 25 mmol/100 g diet) for 6 weeks. *p<0.05, **p<0.01, Ang II vs. Ang II+Nif. @p<0.05, @@p<0.01, Na 2 vs. Na 10 or Na 25. #p<0.05, Ws vs. SHR.*

ANP.

Infusion of Ang II was associated with about a 2-fold rise in plasma aldosterone concentration (Fig. 3). The aldosterone response to Ang II was significantly greater in the low sodium diet group than the higher sodium diet groups.

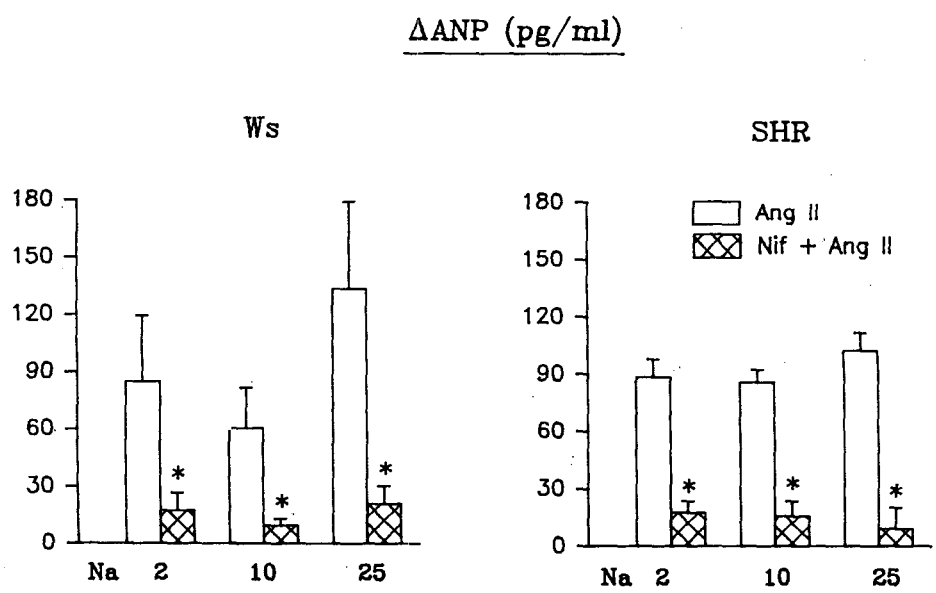

*Fig. 4. Increase in plasma atrial natriuretic peptide (ANP) concentration after infusion of Ang II (250 ng/kg/min) with or without nifedipine (16 μg/kg/min) in Wistar rats (Ws) and spontaneously hypertensive rats (SHR) fed with different Na diets (2, 10, 25 mmol/100 g diet) for 6 weeks. *p<0.01, Ang II vs. Ang II+Nif.*

Aldosterone release after Ang II infusion was significantly attenuated in SHR than in Wistar rats. Treatment of nifedipine significantly suppressed the aldosterone response to Ang II. Average percent inhibition of the aldosterone response to Ang II was 32.6±4.7% in Wistar rats and 36.6±2.8% in SHR.

Plasma concentration of ANP increased remarkably after Ang II infusion (Fig. 4). ANP response to Ang II was not different between the sodium diet groups of Wistar rats and SHR respectively. Nifedipine suppressed the Ang II-induced ANP release almost to the basal level. Average percent inhibition of the ANP response to Ang II was 83.1±7.2% in Wistar rats and 86.4±5.4% in SHR.

DISCUSSION

The pressor dose of Ang II in the present study produced a marked increase in the release of aldosterone and ANP. Infusion of the voltage-sensitive calcium channel antagonist nifedipine blocked the Ang II-stimulated ANP secretion close to the basal level. In contrast, aldosterone release and pressor response to Ang II were only partially inhibited by nifedipine. Our results support the contention that a calcium-dependent mechanism is a part of the physiological responses to Ang II, but indicate the existance of local differences in Ang II mechanisms at specific target cells such as cardiocytes, adrenal glomerulosa and vascular smooth muscle cells.

In vascular smooth muscle cells, calcium has been recognized as the primary messenger regulating contraction (review: Wadsworth, 1990). Ang II appears to increase cytoplasmic free calcium initially by rapid formation of inositol-1, 4, 5-triphosphate to release calcium from the endoplasmic reticulum (Smith et al, 1985; Griendling & Alexander, 1990), and subsequently by transmembrane calcium influx. Influx of extracellular calcium could be mediated by either ligand-operated channels or voltage-

dependent channels. Vascular smooth muscle appears to contain both types of channels (Zschauer et al, 1987), but their relative contribution to Ang II-stimulated calcium influx remains uncertain. Ang II depolarizes vascular smooth muscle (Casteels et al, 1977; Zelcer & Sperelakis 1981, Haeusler & De Peyer, 1989), but it is not known whether this change in membrane potential activates volatage-dependent calcium influx. The partial inhibition of Ang II-stimulated vasoconstriction by nifedipine observed in the present study may indicate the relative importance of calcium influx through calcium channels other than voltage-dependent channels, but this has to be investigated further.

A partial inhibition of Ang II-stimulated aldosterone secretion by the voltage-sensitive calcium channel antagonists was also observed in conscious ewes (Johnson et al, 1988) and in isolated perfused canine adrenal glands (Radke et al, 1989). However, potassium-stimulated aldosterone secretion was completely inhibited by nifedipine (Radke et al, 1989). Several other investigators have also reported a difference in the sensitivity to voltage-sensitive calcium channel antagonists between Ang II- and potassium-stimulated aldosterone secretion (Capponi et al, 1984; Johnson et al, 1984; Lobo & Marusic 1982) which was dependent on increased cytoplasmic calcium (Pratt et al, 1989, Spät et al, 1991). Ang II-stimulated aldosterone secretion by adrenal glomerulosa cells was triggered by the rapid formation of inositol triphosphate which, in turn, mobilizes calcium ions from a non-mitochondrial intracellular pool (review: Spät, 1988). In contrast to the initial phase, the sustained phase of hormone production is absolutely dependent on transmembrane calcium influx (Farese et al, 1984; Capponi et al, 1984; Pratt et al, 1989). Recently, Spät et al (1989) found in isolated rat glomerulosa cells that calcium influx stimulated by potassium was sensitively inhibited by nifedipine, whereas that stimulated by Ang II was not sensitive to nifedipine, but was strongly inhibited by an inhibitor of the Na^+/Ca^{++} antiport. The increased calcium influx by Ang II might be the predominant function of the Na^+/Ca^{++} antiport. Results of ours and the above authors suggest that, in contrast to potassium, Ang II does not cause of full activation of the dihydropyridine-sensitive calcium influx pathway in the adrenal glomerulosa cells.

Ang II has shown to promote ANP release in vivo (Lachance & Garcia, 1988; Volpe et al, 1990) as in the present study and in in vitro studies (Veress et al, 1988; Focaccio et al, 1990). The literature on the actions of Ang II on ANP release is somewhat contradictory. It is not clear whether its effect is due to direct receptor stimulation (volpe et al, 1990) or secondary to hemodynamic chages leading to increased atrial stretch (Lachance & Garcia 1988; Shenker et al, 1988). It is well known that atrial contraction and passive stretch, which stimulate ANP secretion (Ledsome et al, 1985; Matsubara et al, 1988), are associated with transmembrane calcium influx (Gibbons, 1986; Macchia & Page, 1987). Whatever the mechanism is, the present results clearly show that Ang II-stimulated ANP secretion is almost completely blocked by the calcium channel antagonist nifedipine, indicating its specificity. These data suggest that the increase in calcium influx via voltage dependent calcium channels is involved in the mechanism of ANP secretion stimulated by Ang II.

Several abnormalities in vascular reactivity, and in aldosterone and ANP axis have been observed in SHR compared with normotensive rats. We found that both the hypertensive action of angiotensin and hypotensive action of nifedipine were enhanced in SHR. These suggest that the influx of calcium into vascular smooth muscle cells is enhanced in the hypertensive rats. SHR at their hypertensive stage showed significantly lower plasma concentration of aldosterone but higher ANP than comparably aged Wistar-Kyoto rats (Gutkowska et al, 1986; Kim et al, 1989) as observed in Wistar rats of the present study. In SHR, aldosterone release was blunted in response to Ang II (Williams et al, 1982), but was augmented in

response to potassium infusion (Kim et al, 1991). ANP release after Ang II infusion was similar between normotensive and hypertensive rats, but ANP release after blood volume expansion was impaired in SHR (Kim et al, 1989; Pattersson et al, 1985). The blunted aldosterone response to Ang II in SHR has been attributed to an impaired capacity to increase the number of Ang receptors in adrenal glomerulosa cells (Williams et al, 1982; Bradshaw & Moore, 1988), However, the mechanisms responsible for the abnormal aldosterone and ANP axis in SHR are not certain.

It has been well documented that the renin-angiotensin-aldosterone system is sensitively affected by changes in dietary sodium intake (Sagnella et al, 1985) as clearly shown in the present study. However, the effects of chronic changes in dietary sodium intake on plasma ANP are contradictory. We have shown (Kim et al, 1989) along with others (Raine et al, 1985; Salazar et al, 1986) that plasma ANP levels were not altered after chronic changes in sodium intake. In contrast, other studies reported parallel changes in plasma ANP levels and dietary Na intakes (Sagnella et al, 1985). The reason for the discrepant results might be related to phasic changes in ANP release during long-term sodium loading. Both human (Ogihara et al, 1988) and rat (Lattion et al, 1988) studies showed that the ANP system was activated during short-term adaptation to high sodium intake, but was not sustained during long-term sodium loading.

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