Short- and Long-term Effects of Potassium on Renin-Aldosterone System in Hypertensive Rats Fed with Different Amounts of Sodium

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= ABSTRACT=

To evaluate the acute and chronic effects of potassium on aldosterone response to different amounts of sodium intake, two series of experiments were conducted. In the first series of experiments, when the plasma K level was increased acutely by KCl infusion (20 μg/kg/min for 20 min), plasma aldosterone concentration increased in both low Na and high Na groups. However, the aldosterone response to K infusion was significantly greater in the low Na than in the high Na groups. In the second series of experiments, rats fed a high K diet chronically showed a significantly higher plasma K level than those fed a low K diet. However, plasma Na level was maintained relatively constant independent of the Na intake. Both the plasma renin activity (PRA) and aldosterone levels were inversely related to the Na intake. There was a highly positive correlation between aldosterone level and PRA over a wide range of sodium intakes. However, the slope of the correlation line was distinctly steeper in the K-repleted than in the K-depleted rats. The above results indicate that the adrenotropic action of acute K load was augmented in the presence of high plasma renin levels. However, when plasna K level was elevated chronically by a high-K diet, aldosterone secretion was markedly stimulated, although the plasma renin levels were suppressed.

Key Words: K & Na diet, Aldosterone, Plasma renin, SHR.

INTRODUCTION

The importance of the renin-angiotensin system and plasma potassium concentration in the regulation of aldosterone secretion has been firmly established (Fraser 1979, Sealey & Laragh 1990). Dietary potassium intake and changes in plasma K concetration have a

profound effect on aldosterone secretion (Dluhy et al, 1972, Douglas & Catt 1976). Potassium admi-nistration increases aldosterone secretion whereas potassium depletion retards it. Angiotensin also has a potent stimulating effect on aldosterone secretion in humans (Laragh et al, 1960) and in experimental animals (Carpenter et al, 1961; Mulrow & Ganong 1961). On the other hand, direct effect of sodium on aldosterone secretion is not clear. It is generally agreed that small changes in plasma sodium concentration do not directly alter aldosterone secretion (Fraser et al, 1979; Enyedi & Spat 1981). Thus, the increased aldosterone secretion during sodium

depletion has been mainly attributed to a stimulation of renin-angiotensin system (Oelkers et al, 1974; Sagnella et al, 1989)

Although the separate effects of potassium and angiotensin II on aldosterone secretion have been thoroughly studied, the interaction of the two factors has not been analyzed until recently. When angiotensin II was infused into dogs maintained on three different levels of potassium diet, the stimulatory effect of potassium on aldosterone secretion was greater in dogs with higher angiotensin II levels (Young et al, 1984). An *in vitro* study also showed that the two stimuli augment each other's secretory potential (Pratt et al, 1989).

The present study was undertaken to evaluate acute and chronic effects of potassium on aldosterone releasing response to different amounts of sodium intake in rats. Different plasma level of angitensin II was maneuvered physiologically by changing dietary sodium intake. Two series of experiments were conducted. The first series of experiments compared effects of acute potassium infusion on aldosterone secretion in sodium depleted and repleted rats. Since hypertensive patients (Dluhy et al, 1979) and spontaneously hypertensive rats (SHR) (Bradshaw & Moore 1988; Williams et al, 1982) show a decreased aldosterone response to angiotensin II, both normotensive and hypertensive rats were used. The second series of experments examined the effects of chronic potassium repletion and depletion on aldosterone secretion in rats with various sodium intakes.

METHODS

Series I: Acute effect of potassium

The experiments were carried out in approximately 12-week old male Wistar and spontaneously hypertensive rats (SHR). They were divided into two groups, fed with low- or high-sodium diet (0.5 or 50 mmol Na/100 g diet) containing 10 mmol K/100 g diet and tap water ad libitum for 5 days. On the morn-

ing of the study, catheters were inserted into the femoral artery and vein under ether anesthesia. Then, the rat was placed in a restraining cage. Arterial pressure and heart rate were recorded continuously from the femoral arterial catheter with a Statham P50 strain gauge transducer and a Narco Physiograph. When mean arterial pressure was stable aproximately 2 hr after the surgery, 2.5 ml of the control blood sample was collected through the artrerial catheter and the same volume of donor blood was given simultaneously through the venous catheter as described in the previous study (Lee-Kwon, 1984). Then, potassium chloride (520 μmol/ml of saline) was infused intravenously at a rate of 20 μl/min for 20 min by means of a infusion pump (Sage Instruments, model 351). Blood samples were drawn at 10 and 20 min of potassium infusion and were transferred to test tubes containing 5 mg EDTA at 4°C. Plasma was separated and stored frozen. Plasma aldosterone level was determined with a radioimmunoassay kit (Diagnostic Inc.) and renin activity by the radioimmunoassay method described by Kim and Cho (1986).

Series II: Chronic effect of potassium

This study was performed in 70 female SHR weighing 160-180 g. All rats were fed commercial rat chow (Jinyang, Taegu) and tap water before the study. Then, rats were divided into two groups and fed with low- or high-potassium diet (0.5 or 24 mmol K/100 g diet) containing 0.5 mmol Na/100 g diet during the first 5 days. On the following morning, seven rats in each group were decapitated and trunk blood was collected in a plastic tube containing 0.5 ml sodium heparin (1000 U/ml). After a 5-day equilibration period on the low-sodium diet, the sodium content in the diet was increased stepwise every day (5, 10, 25 and 50 mmol NaCl/100 g diet). Every morning, seven rats in each group were decapitated and trunk blood was collected. Hematocrit was measured and plasma was separated by centrifugation at 2000 rpm for 20 min at 4°C.

Plasma concentrations of sodium and potassium were measured with a microlyte ion selective analyzer (Kone Inc.) and the remaining plasma was stored at $-20°C$. Plasma levels of Na, K, aldosterone and renin activity were measured with the methods described for the Series I.

Statistics

Statistical analysis of the response to potassium infusion in each group was carried out by Wilcoxon's sighed-rank test. Mann-Witney U-test was used to analyze the difference between Wistar rat and SHR. The regressions were obtained by the least-square linear regression methods. Differences among the salt groups were analyzed by nonparametric Kruskal-Wallis's one-way analysis of variance. All values are presented as mean±SE.

RESULTS

Series I: Acute effect of potassium

Average daily intakes of food and electrolytes in rats fed with low- or high-sodium diet shown in Table 1. SHR consumed less food than Wistar rats.

As summarized in Table 2, both the low and high sodium groups showed similar control values for plasma sodium and potassium, hematocrit, mean arterial pressure, and heart rate. However, plasma aldosterone level and renin activity were higher in the low-sodium than in the high-sodium group. The SHR (12 weeks of age) were clearly hypertensive, and showed lower heart rate, higher plasma potassium concentration and hematocrit than
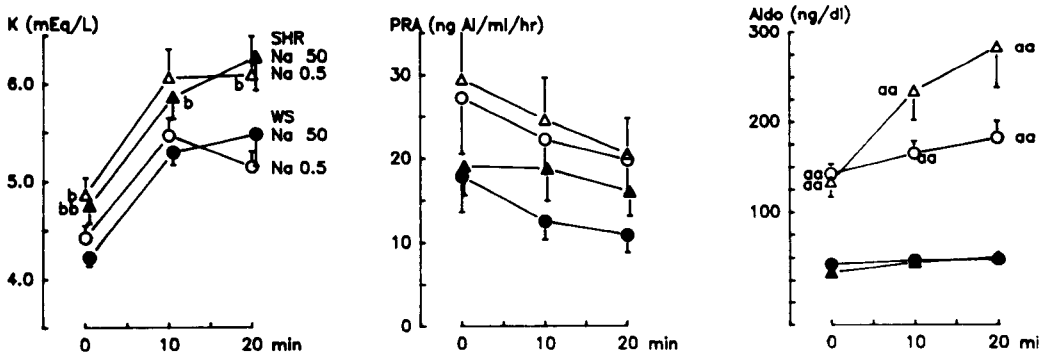
Fig. 1. *Effect of KCl infusion on plasma K, renin activity (PRA) and aldosterone concentration in Wistar and SHR fed low or high sodium diet (0.5 or 50 mmol/100g diet) for 5 days. aa p<0.01, low vs. high Na groups. b p<0.05, bbp<0.01, Wistar vs. SHR.*

Table 1. Average daily intake of food and electrolytes in Wistar and SHR fed low or high NaCl Diet (0.5 or 50 mmol/100 g diet) for 5 days.

	Wistar		SHR	
	Na 0.5	Na 50	Na 0.5	Na 50
Food Intake (gm/day/rat)	24.2±0.7	27.2 ±0.7	19.8 ±2.6	19.4±2.5
Na Intake (mmol/day/rat)	0.1±0.003	13.61±0.36	0.19±0.01	9.72±1.22
K Intake (mmol/day/rat)	2.46±0.07	2.78±0.08	2.04±0.27	1.98±0.25
Cl Intake (mmol/day/rat)	1.13±0.03	13.64±0.36	0.94±0.13	9.74±1.23

Table 2. Effect of KCl infusion on plasma concentrations of Na, hematocrit, mean arterial pressure (MAP) and heart rate (HR) in Wistar (Ws) and SHR fed with low or high Na diet (0.5 or 50 mmol/100 d diet) for 5 Days

	Control	10 min	20 min
Na, mEq/L			
WS Na 0.5	140.4± 0.4	141.4± 0.5	141.1± 0.4
Na 50	141.7± 0.4	141.6± 0.5	141.2± 0.7
	a		
SH Na 0.5	141.5± 0.8	141.9± 0.9	141.9± 0.9
Na 50	141.5± 0.6	141.2± 0.3	140.4± 0.5
Hct, %			
WS Na 0.5	42.4± 0.6	41.5± 0.6	40.7± 0.4**
Na 50	42.5± 0.6	41.6± 0.8*	41.2± 0.7*
SH Na 0.5	47.3± 1.2[bb]	46.4± 1.3[b]	44.9± 1.0**[bb]
Na 50	46.7± 0.9[bb]	45.8± 0.8*[bb]	45.4± 0.7**[bb]
MAP, mmHg			
WS Na 0.5	120.0± 2.0	121.4± 2.7**	122.8± 2.8**
Na 50	126.0± 2.9	128.9± 3.4**	127.1± 3.0**
SH Na 0.5	145.0± 3.5[bb]	152.5± 5.0**[bb]	147.5± 2.1**[bb]
Na 50	149.0± 3.5[bb]	152.8± 4.8**[bb]	157.8± 4.8**[bb]
HR, beats/min			
WS Na 0.5	437.4±12.1	452.2±12.5	440.6±10.9
Na 50	422.9±17.1	428.4±18.0	418.3±18.9
SH Na 0.5	382.0±18.4[b]	402.0±19.0	412.3±26.7
Na 50	405.1±24.3	394.3±22.6	425.7±25.3

Values are mean ± SE.
* $p < 0.05$, ** $p < 0.01$, before vs. after KCl infusion (Wilcoxon's signed-rank test).
a $p < 0.05$, low vs. high NaCl group(Mann-Whitney U-test).
[b] $p < 0.05$, [bb] $p < 0.01$, Wistar vs. SHR (Mann-Whitney U-test).

Wistar rats.

In all groups, infusion of potassium chloride resulted in a significant rise in plasma potassium concentration with no change in sodium concentration and a significant fall in hematocrit (Table 2). The plasma aldosterone concentration was increased but the renin activity was decreased. The increase in aldosterone level was considerably greater in the low-sodium than in the high-sodium group. This result indicates that the potassium-induced aldosterone release was facilitated in the presence of a high plasma level of renin-angiotensin.

The reduction of plasma renin activity dur-

Table 3. Equations and statistics for regression lines between plasma aldosterone and K concentratiom, and between plasma renin activity (PRA) and plasma K concentration in Wistar and SHR fed low or high NaCl diet (0.5 or 50 mmol/100 g diet) for 5 days

	Wistar	SHR
Low Na	Aldo = 10.43 Pk + 110.81 r = 0.15, n = 24 ns	Aldo = 46.87 Pk − 55.10 r = 0.35, n = 26 p < 0.05
High Na	Aldo = 7.73 Pk + 7.15 r = 0.37, n = 24 p < 0.05	Aldo = 6.45 Pk + 7.00 r = 0.42, n = 28 p < 0.05
Low Na	PRA = −0.07 Pk + 23.45 r = 0.003, n = 24 ns	PRA = −0.91 Pk + 28.56 r = 0.07, n = 28 ns
High Na	PRA = −4.09 Pk + 34.17 r = 0.38, n = 24 p < 0.05	PRA = 2.42 Pk + 5.14 r = 0.24, n = 28 ns

(SHR Aldo Low Na and High Na bracketed together: p < 0.05)

Table 4. Average daily Intakes of food and electrolytes in rats fed five different Na diets (0.5-50 mmol/100 g Diet) containing either low or high level of K (0.5 or 24 mmol/100 g Diet)

		Na 0.5	Na 5	Na 10	Na 25	Na 50
Food Intake	K 0.5	15.1±0.3	12.7±0.6	15.5±0.9	14.5±0.2	12.8±0.2
(gm/day/rat)	K 24	13.1±1.0	17.6±1.3	12.8±0.7	12.1±0.9	13.6±0.4
Na Intake	K 0.5	0.08±0.01	0.83±0.03	1.55±0.09	3.62±0.06	6.42±0.08
(mmol/day/rat)	K 24	0.07±0.01	0.88±0.06	1.28±0.07	3.04±0.21	6.78±0.20
K Intake	K 0.5	0.08±0.01	0.07±0.01	0.08±0.01	0.08±0.01	0.06±0.01
(mmol/day/rat)	K 24	3.15±0.23	4.23±0.31	3.06±0.17	2.91±0.20	3.25±0.20
Cl Intake	K 0.5	0.14±0.01	0.69±0.03	1.61±0.20	3.68±0.06	6.48±0.08
(mmol/day/rat)	K 24	1.46±0.11	2.75±0.20	2.63±0.15	4.32±0.30	8.21±0.24

ing potassium infusion was similar in the four groups. Potassium infusion induced a slight increase in mean arterial pressure and heart rate.

Table 3. presents the regression equations for the plasma aldosterone vs. potassium and PRA vs. plasma potassium. The regression of plasma potassium to aldosteronhe concentration was significant only in SHR, the slope of the regression line being significantly greater in the low-sodium group than in the high group. The regression of plasma potassium to PRA was not significant.

Table 5. Plasma Na, K and aldosterone concentrations, and renin activity (PRA) in rats fed with different Na
diets(0.5-50 mmol/100 g diet) containing either low or high K (0.5 or 24 mmol/100 g diet) for 5 days

	Na 0.5	Na 5	Na 10	Na 25	Na 50
Na, mEq/L					
K 0.5	134.6± 1.0	133.9± 0.4	134.2± 0.5	135.9± 0.5	137.2± 0.6*
K 24	134.4± 0.6	133.9± 0.4	135.1± 0.7	137.0± 3.5	136.7± 0.4*
K, mEq/L					
K 0.5	4.2± 0.1	4.5± 0.1	4.1± 0.1	3.9± 0.1	3.9± 0.2
K 24	5.5± 0.2	5.2± 0.1	5.2± 0.2	5.2± 0.1	6.0± 0.1
	aa	aa	aa	aa	aa
Aldo, ng/dL					
K 0.5	87.2±11.6	31.6± 3.4	24.0± 1.8	18.9± 2.8	20.6±2.5**
K 24	147.2±32.5	92.9±16.9	44.8± 6.7	34.3± 4.9	14.6±2.6**
		aa	aa	a	
PRA, ng AI/mL/hr					
K 0.5	179.3±31.6	96.2±10.8	39.0± 6.1	33.9± 4.2	15.3±3.1**
K 24	46.0± 4.9	14.6± 0.8	30.2± 5.0	30.6± 1.6	15.3±2.2**
	aa	aa			
Hct, %					
K 0.5	33.4± 0.6	34.0± 0.5	34.3± 0.8	31.7± 0.9	34.7± 1.0
K 24	33.1± 1.0	32.8± 1.5	34.1± 0.6	34.7± 1.0	32.7± 2.3
				a	
(n)	(7)	(7)	(7)	(7)	(7)

Values are mean±SE.
*p<0.05, **p<0.01, significantly different among the sodium groups (Kruskal-Wallis's one-way
ANOVA).
a p<0.05, aa p<0.01, significantly different between low and high K groups (Mann-Whitney U-test).

Series II: Chronic effect of potassium

Table 4. shows food and electrolyte intakes
in high-and low-potassium diet groups while
changing sodium intake. Food intake was sim-
ilar in all groups, and was not apparently
changed during alterations of sodium intake.

The plasma potassium concentration was
significantly higher in the high-potassium diet
group than in the low-potassium diet group
(Table 5, Fig. 2). However, plasma Na con-
centration and hematocrit were not different
between the two groups.

Alterations in sodium intake did not affect
plasma potassium concentration and hemato-

crit. However, plasma sodium concentration
of the rats fed with the highest level of sodi-
um (50 mmol/100 g diet) was significantly ele-
vated. As the sodium intake was increased,
plasma aldosterone and PRA were gradually
reduced (Fig. 2). Rats fed the high potassium
diet showed significantly higher plasma aldo-
sterone but much lower PRA than those fed
the low potassium diet. In the high-potassium
diet group, plasma aldosterone level was grad-
ually decreased as the sodium intake was in-
creased from 0.5 to 50 mmol/100 g diet.
However, in the low potassium diet group,
plasma aldosterone reduced at the minimum
level when sodium intake increased to 10
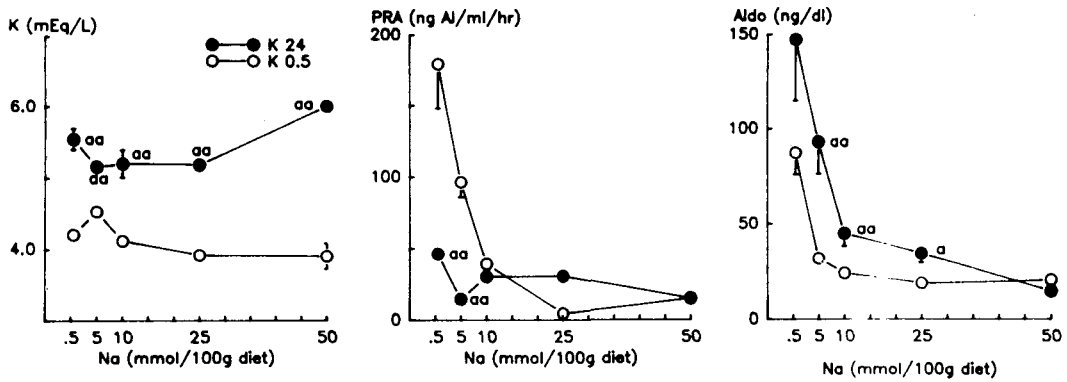mmol/100 g diet. In the low-potassium diet

Fig. 2. *Plasma K, renin activity (PRA) and dldosterone concentration in rats fed with 5 different Sodium diets (0.5-50 mmol/100 g diet) containing either low or high level of potassium (0.5 or 24 mmol/100 g diet). a p<0.05, aa p<0.01, low vs. high potassium groups.*
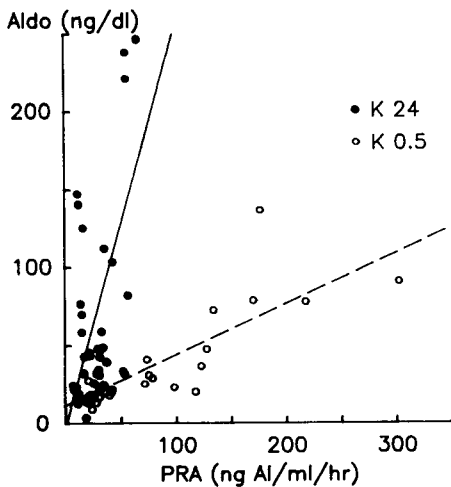

Fig. 3. *Plasma aldosterone concentration data are plotted as a function of plasma renin activity (PRA) in rats fed with 5 different sodium diets (0.5-50 mmol/100 g diet) containing either low or high level of potassium(0.5 or 24 mmol/100 g diet). The regression equations are as follows. High K group: Aldo= 2.58 PRA–3.15(r=0.58 p< 0.01). Low K group: Aldo=0.33 PRA+11. 49(r=0.82, p<0.01).*

group, PRA changed inversely with the sodium intake, but in the high-potassium diet

group, it was significantly suppressed and was not dependent of sodium intake.

When the aldosterone concentration was plotted as a function of PRA (Fig. 3), there was a positive linear relationship in both high-and low-potassium diet groups. However, the slope of the regression line was much greater in the former than in the latter group.

DISCUSSION

The responses of renin and aldosterone secretion to changes in NaCl intake are very rapid and sensitive. In the present study, we observed reductions in plasma aldosterone and plasma renin activity within a day of the increased sodium intake (Fig. 2), in accordance with other reports (Holtzman et al, 1989; Sagnella et al, 1989). In normal humans, plasma renin activity and aldosterone concentration decreased within a day of gradual small increase in sodium intake (Sagnella et al, 1989). Holtzman et al. (1989) observed in rats that plasma renin activity and angiotensin II concentration increased sharply within 8 hours after a shift from a high- to a low-Na diet and then remained unchanged over the next 40 hours, whereas plasma aldosterone continued to rise over 48 hours. These

observations indicate that the response of the renin-angiotensin-aldosterone system to changes in dietary sodium intake is rapid and sensitive.

The plasma potassium concentration of rats in the present study was significantly higher in the rats fed with a high potassium diet than with a low potassium diet (Table 5 & Fig. 2), as observed by others (Dluhy et al, 1974; Young et al, 1984). In contrast, plasma sodium concentration was maintained relatively constant during progressive increase in dietary sodium. It is generally accepted that small changes in plasma sodium concentration do not elicit a significant effect on aldosterone secretion. However, there are some evidences that an increase in plasma sodium concentration may directly inhibit aldosterone secretion (Ball et al, 1981; Schneider et al, 1984). A change in sodium concentration as small as 3 mEq/L showed a marked effect on both angiotenisn II-and potassium-stimulated aldosterone secretion in the isolated canine adrenal gland (Schneider et al, 1984). However, in the absence of angiotensin II or potassium stimuli, changes in sodium concentration had little effect on the aldosterone secretion. In the present study, plasma sodium concentration was slightly elevated (less than 3 mEq/L) only when sodium intake was very high (50 mmol/100 g diet), consequently the renin-angiotensin system was maximally suppressed (Table 5). Therefore, it is likely that plasma sodium concentration has little effect on the aldosterone secretion, and the plasma potassium and angiotensin II play major roles in the regulation of aldosterone secretion when sodium and potassium intakes change.

Augmented adrenotropic action of potassium in the presence of adequate amount of angiotensin II has been demonstrated in dogs (Pratt 1982) and in isolated adrenal glomerulosa cells (Pratt et al, 1989) as well. The present study also showed that the stimulatory actions of potassium and angiotensin II on aldosterone secretion were synergistic. Acute potassium infusion induced only a slight in-

crease in aldosterone secretion when renin-angiotensin system was suppressed by high sodium intake. However, when renin-angiotensin system was stimulated by sodium depletion, potassium produced a much greater increase in aldosterone secretion. This indicates a synergistic interation between potassium and angiotensin II in aldosterone release.

However, acute and chronic effects of potassium on aldosterone secretion appeared to be different in rats fed different sodium diets. When plasma potassium concentration was elevated chronically, aldosterone release was markedly stimulated, although the renin-angiotensin system was suppressed (Fig. 2, 3). Both renin and aldosterone levels were inversely related to sodium intake (Fig. 1 and Brown et al, 1964). There was a highly positive correlation between aldosterone levels and plasma renin activity over a wide range of sodium intake (Fig. 3 and Laragh et al, 1972). However, the slope of the correlation line was distinctly steeper in the potassium repleted rats than in the potassium depleted rats. This suggests that when plasma potassium level is elevated chronically, renal renin release is drastically suppressed but aldosterone release could be remarkably stimulated. The inhibitory effect of potassium on renal renin secretion has long been known in humans (Bauer et al, 1977) and in experimental animals (Abbrecht & Vander, 1970). On the other hand, when potassium intake is restricted and thus plasma potassium remains low, a large increase in plasma renin-angiotensin level results in only a modest increase in aldosterone release. These facts indicate that the adrenotropic action of angiotensin II is sensitively affected by chronic status of potassium.

The interaction of potassium and angiotensin II in stimulating aldosterone secretion has been previouly studied by Young et al. (1984). They determined the aldosterone response to 5-day infusion of 3 levels of angiotensin II in dogs maintained on 3 different potassium diets for 3 weeks and found that a

rise in angiotensin II level increased the slope of the regressions obtained from plotting plasma potassium versus aldosterone concentration without changing the point of intersection. They therefore concluded that two stimuli interact muitipli-catively in stimulating aldosterone secretion. The present study on the aldosterone response to acute potassium infusion (Table 2) agrees well with this notion. That is, in sodium repleted rats thus having a reduced plasma renin-angiotensin II level, an acute increase in plasma potassium produce a slight increase in aldosterone release. On the other hand, when plasma potassium concentration was raised chronically, aldosterone release was markedly increased although plasma renin-angiotensin II level was low (Table 5, Fig. 2). It is, therefore, apparent that the interation between potassium and angiotensin II in regulating aldosterone secretion is different between chronic and acute alterations of plasma potassium level.

The mechanism responsible for the effect of potassium and angiotensin II on aldosterone secretion was not addressed in this study. However, several lines of evience suggest that potassium and angiotensin II share some common features in stimulating aldosterone secretion. In the biosynthetic pathway of aldosterone, both act at an early step (cholesterol to pregnenolone) and a later step (corticosterone to aldosterone) (Müller 1968). Chronic effect of sodium and potassium balance concerns mainly on the later biosynthetic step (Müller et al, 1989). Both potassium and angiotensin II affect aldosterone secretion by increasing cytosolic calcium concentration (Foster et al, 1981; Pratt et al, 1989), although the mechanisms of cytoplasmic calcium change by potassium and angiotensin II seem to be different (Pratt et al, 1989). When calcium influx was blocked by a calcium channel antagonist nitredipine, stimulatory responses to potassium and angiotensin II were completely inhibited. Taken together, potassium and angiotensin II may act together to determine the optimal rate of calcium influx, insuring an appropriate production and secretion of aldosterone. However, the mode of interation between potassium and angiotensin for aldosterone secretion is obscure. Douglas and Catt (1976) reported that the number of angiotensin II receptors on rat adrenal cortical cells is increased after potassium repletion as well as after sodium depletion. The physiological significance of this change remains to be identified.

Sodium depleted SHR showed a considerably greater aldosterone response to acute potassium infusion as compared with Wistar rats (Fig. 1). In contrast, several studies have reported a blunted aldosterone response to angiotensin II in SHR (Williams et al, 1982; Bradshaw & Moore, 1988; Ahn et al, 1989) and in hypertensive patients (Moore et al, 1977). Blunted adrenal response to angiotensin II in sodium restricted SHR has been attributed to an impaired capacity to increase the number of angiotensin II receptors in adrenal glomerulosa cells (Williams et al, 1982; Bradshaw & Moore, 1988). However, the mechanism of the increased adrenal sensitivity to potassium in sodium depleted SHR, as observed in the present study, is not apparent. Potassium probably opens calcium channels by depolarizing the membrane (Quinn et al, 1987) and consequently increases aldosterone secretion. It has long been recognized that hypertensive patients and animals show widespread alterations in cation (i.e., Ca, K, Na, H) transport functions in plasma membranes of a variety of cells (Aoki et al, 1974; Jones 1973). The major pathogenically significant consequence of these alterations is the increase in cytoplasmic free calcium (Bohr & Webb, 1988; Postnov 1990). Increased voltage-dependent Ca influx and decreased calmodulin dependent calcium pump decreased activity have been demonstrated in various cells of SHR. Based on these facts, we tempt to speculate that in SHR high potassium may result in an abnormally high cytoplasmic calcium concentration, leading to a more pronounced aldosterone response than in nor-

motensive rats. Certainly, further studies are required to substantiate this notion.

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