STUDIES ON THE MECHANISM OF "EXAGGERATED NATRIURESIS" IN ESSENTIAL HYPERTENSION

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Prompt and exaggerated natriuresis and diuresis were seen one to two hours after the starting of an infusion of 300 ml of 3% saline for one hour in patients with essential hypertension on a high sodium chloride intake. There were no significant differences in urinary volume and sodium excretion after the saline load in patients with normal and low plasma renin activity. The inhibition of angiotensin converting enzyme with SQ 14225 in patients with normal plasma renin activity did not produce additional natriuresis and diuresis after the saline load. Mean arterial blood pressure and/or changes in mean arterial blood pressure after the saline load showed a positive correlation with urinary volume and sodium excretion in each collection period in hypertensive subjects. Free water reabsorption in hypertensives was lower at high levels of osmolar clearance than that in control subjects.

These results suggest that "exaggerated natriuresis" in essential hypertension is due to a decrease in tubular sodium reabsorption, which may be the result of intrarenal hemodynamic changes related to high blood pressure per se. The decreased medullary osmolar gradient is a possible contributing factor in the enhanced sodium and water excretion, while the renin-angiotensin-aldosterone system does not seem to play an important role.

IT is known that many patients with essential hypertension excrete more sodium at a faster rate than do normotensive control subjects in response to an acute saline load. While this "exaggerated natriuresis" may be the result of a decrease in sodium reabsorption along the renal tubule, the exact mechanism responsible for this phenomenon is not well understood. Some investigators postulate that elevated blood pressure per se decreases tubular sodium reabsorption via intrarenal hemodynamic and/or secondary humoral changes, while others consider that exag-

gerated natriuresis is a characteristic feature of hypertension with renin suppression and that high blood pressure itself is not the sole factor.

We have already reported "exaggerated natriuresis" after a hypertonic saline load in patients with normal plasma renin activity on a high sodium chloride intake whose urinary sodium excretion paralleled changes in mean arterial blood pressure.¹

In the present study, we compared the sodium excreting ability after a hypertonic saline load in hypertensive subjects with normal and low plasma renin activity under the same strict dietary conditions and also tested the effect of blockade of angiotensin II formation by oral converting enzyme inhibitor, SQ 14225, on urinary sodium excretion by normal renin patients. Short-term changes in renin and aldosterone were also exam-

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TABLE I URINE VOLUME (UV) AND SODIUM EXCRETION (UNaV) IN EACH COLLECTION PERIOD FOLLOWING HYPERTONIC SALINE INFUSION IN CONTROL SUBJECTS AND HYPERTENSIVE PATIENTS WITH NORMAL (NREH) AND LOW PLASMA RENIN ACTIVITY (LREH) ON 16g OF NaCl DAILY

Period		0		1		2		3		4		5	
		UV ml/min	UNaV μEq/min	UV	UNaV	UV	UNaV	UV	UNaV	UV	UNaV	UV	UNaV
control	M	1.12	199	1.30	280	1.00	262	1.17	314	1.12	317	0.95	280
(5)	±SEM	0.20	66.2	0.20	64.9	0.35	64.9	0.16	91.1	0.12	87.6	0.13	87.9
NREH	M	1.40	204	1.89**	385*	1.81*	420*	1.19	318	0.98	266	0.74	200
(11)	±SEM	0.44	48.7	0.31	63.0	0.56	110.3	0.38	81.6	0.27	62.2	0.29	66.5
LREH	M	1.41	182	1.70*	335*	1.76*	427*	1.30	301	1.04	262	0.93	221
(5)	±SEM	0.64	53.9	0.47	116.9	0.39	166.0	0.33	126.6	0.14	104.1	0.42	108.3

Statistically significant difference from control (* $p < 0.05$, ** $p < 0.01$).

ined to evaluate the role of the renin-angiotensin-aldosterone system in sodium excretion following an acute saline load. Free water reabsorption (TCH_2O) during hydropenia was determined as an indirect index of sodium reabsorption along the loop of Henle, although free water clearance (CH_2O) could not be assessed in this type of experiment.

MATERIALS AND METHODS

Of 16 hospitalized patients with benign essential hypertension eleven had a normal response of plasma renin activity after four hours in the upright posture following a low sodium diet for three days (1g of sodium chloride was added to daily food materials), while five patients had a poor response. All antihypertensive drugs had been discontinued at least two weeks before the start of the observations. There was no significant difference between the two groups as to age (49.5 ± 7.5 vs 50.7 ± 4.5 , mean ± 1 SD), blood pressure ($176 \pm 16.8/108 \pm 14.8$ vs $179.5 \pm 15.3/105 \pm 10.6$ mmHg), or renal function (GFR: 105 ± 21.7 vs 102 ± 13.7 ml/min; eff. RBF: 693 ± 209 vs 716 ± 202 ml/min). Five age-matched normotensive subjects served as controls. The subjects were then placed on a regular diet containing 16g of sodium chloride and 60–80 mEq of potassium daily for seven days prior to the infusion study. These subjects then fasted for 11 hours and kept in a recumbent position throughout the study. At 7:30 am, the bladder was catheterized with a Foley catheter. A 1-hour

Fig. 1. Mean arterial blood pressure (MAP), urine volume (UV) and sodium excretion (UNaV) following hypertonic saline infusion in hypertensive patients with normal (NREH) and low plasma renin activity (LREH) on 16g of NaCl daily. Statistically significant difference from those in control subjects (* $p < 0.05$, ** $p < 0.01$).

urine specimen (8:00 to 9:00 am) was examined for sodium, potassium, creatinine and osmo-

Fig.2. Changes in serum total protein (TP), sodium concentration (SNa), plasma renin activity (PRA) and aldosterone concentration (PA) following hypertonic saline infusion in hypertensive patients with normal (NREH) and low plasma renin activity (LREH).

Fig.3. Correlation between changes in mean arterial blood pressure (Δ MAP) and urine volume (UV), or sodium excretion ($UNaV$) after an acute hypertonic saline load in hypertensive subjects.

Fig.4. Hypertonic saline load during hydropenia. Effect on free water reabsorption ($T^C H_2O$) and osmolar clearance (C_{osm}).

lality, and blood sample was drawn for measurement of serum total protein (TP), osmolality (S_{osm}), sodium (S_{Na}) and potassium (S_K) and plasma renin activity (PRA) and aldosterone (PA). Then 300 ml of 3% saline solution was infused intravenously for one hour. Blood samples were obtained 30, 60, 120, 180 and 240 minutes after the start of the infusion. Urine was collected every hour after the start of the infusion for five hours. The above parameters were determined in all samples. Blood pressure and pulse rate were measured at short intervals. In five of the patients with normal plasma renin activity, the same infusion study was performed after a daily sodium chloride intake of 8g. Within a week, the same infusion study was repeated after these patients had received 50 mg of SQ 14225 at 7:30 am orally with a minimum amount of water. The parameters listed above were again determined. Glomerular filtration rate (GFR) and renal blood flow (RBF) were determined before and after SQ 14225 administration.

Sodium and potassium concentrations in serum and urine were determined by flame photometry, utilizing lithium as an internal standard. Serum and urine creatinine levels were measured by autoanalyzer. Glomerular filtered load of sodium was expressed as the product of serum sodium concentration and endogenous creatinine clearance. Osmolality of plasma and urine was measured by freezing point depression with a Fiske osmometer. Osmolar clearance (C_{osm}) and free water reabsorption ($T^C H_2O$) were calculated by standard methods. GFR and RBF were obtained from the renal clearance of sodium thiosulfate and sodium para-amino hip-

TABLE II URINE VOLUME (UV) AND SODIUM EXCRETION (UNaV) FOLLOWING HYPERTONIC SALINE INFUSION IN PATIENTS WITH NORMAL PLASMA RENIN ACTIVITY (NREH) ON 8g OF NaCl DAILY WITH AND WITHOUT SQ 14225 ADMINISTRATION

Period		0		1		2		3		4	
		UV ml/min	UNaV μEq/min	UV	UNaV	UV	UNaV	UV	UNaV	UV	UNaV
SQ(-)	M	0.95	150	1.10	218	1.29	294	1.14	272	0.88	208
	±SEM	0.66	104.2	0.60	137.5	0.52	145.2	0.41	132.8	0.34	87.9
SQ(+)	M	0.78	103	0.78	123	0.80*	160*	0.83	173	0.64	137
	±SEM	0.29	41.7	0.18	46.0	0.26	75.7	0.14	50.9	0.14	39.1

Statistically significant difference from the corresponding period without SQ 14225 (* $p < 0.05$).

purate, respectively, by a single injection method.

PRA was determined by radioimmunoassay of angiotensin I with a CEA-IRE-SORIN kit after incubation of plasma at pH 5.7 (37°C) for three hours. Patients whose basal PRA in the morning during maintenance on a daily intake of 8g of sodium chloride for at least five days ranged from 0.40 to 2.91 ng/ml/hr and responded to salt restriction (1g daily) for three days and a 4-hour standing position by increasing to 1.67 to 7.60 ng/ml/hr were placed in the normal renin group, while patients whose basal PRA was less than 0.4 ng/ml/hr and rose to less than 1.67 ng/ml/hr after stimulation were placed in the low renin group. Plasma aldosterone concentrations (PA) were measured by radioimmunoassay as described elsewhere¹. Statistical analysis was performed by Student's t-test. The correlation coefficient was calculated by the classical method. Differences were considered to be significant when p value was less than 0.05.

RESULTS

In the control period, the mean urine volume and sodium excretion were statistically the same in the control, normal and low renin hypertensive groups. Mean arterial blood pressure rose significantly in hypertensive patients after hypertonic saline infusion, while it changed little in the control subjects. There was no significant difference in blood pressure responses between the normal and low renin groups. In response to the hypertonic saline infusion, seven of 11 patients with normal PRA and three of the five with low PRA had a more prompt and exaggerated diuresis and natriuresis than the controls within the first two hours after the start of the infusion. The

mean urinary volume and sodium excretion of each hypertensive group in the first and second 1-hour period were significantly greater than in the control subjects. There was no statistical difference in sodium and water excretion between the renin subgroups (Table I, Fig. 1). The cumulative water and sodium excretion in five hours was the same in all three groups. Urinary potassium excretion increased in parallel with

Fig.5. Mean arterial blood pressure (MAP), urine volume (UV) and sodium excretion (UNaV) following hypertonic saline infusion in patients with normal plasma renin activity (NREH) with and without SQ 14225 administration. Statistically significant difference from those in corresponding period without SQ 14225 (* $p < 0.05$).

Fig. 6. Changes in serum total protein (TP), sodium concentration (SNa), plasma renin activity (PRA) and aldosterone concentration (PA) following hypertonic saline load in 5 normal renin patients with and without SQ 14225 administration.

sodium excretion in each group, but there was no statistical difference between the controls and the hypertensive subjects.

After 300 ml of 3% saline infusion, the mean TP in each group decreased by 8% and serum sodium concentration increased by 3%. The glomerular filtered load increased but there was no significant difference between the control and the hypertensive groups. PRA decreased in both the controls and the patients with normal PRA after one hour of infusion and remained unchanged thereafter. PRA in the patients with low PRA was significantly lower than in the other groups and changed little after saline infusion. PA in the hypertensives was higher than in the controls, but statistically not significant; it was decreased after one hour of infusion and remained unchanged thereafter (Fig. 2).

In the hypertensive subjects, a significantly positive correlation was found between changes of urine volume and mean arterial blood pressure (MAP) ($p < 0.01$), and between changes of urinary sodium excretion and MAP ($p < 0.01$) in each collection period. No such correlation was found in the control subjects (Fig. 3).

Fig. 7. The mean glomerular filtration rate (GFR) remained unchanged and effective renal blood flow (eff. RBF) increased, filtration fraction (FF) being decreased after SQ 14225 in 5 normal renin patients although these changes were statistically insignificant.

$\text{TC}_2\text{H}_2\text{O}$ in each collection period was plotted against the corresponding C_{osm} (Fig. 4). The $\text{TC}_2\text{H}_2\text{O}$ of the hypertensive subjects was lower than that of the normotensive controls at any C_{osm} level greater than 2.5 ml/min. The difference was statistically significant.

In five patients with normal PRA on a daily sodium chloride intake of 8g, MAP fell from 113 to 95 mmHg 90 minutes after the 7:30 am dose of SQ 14225. MAP at the start of the hypertonic saline infusion and one hour later was significantly lower than when SQ 14225 was not given [113 ± 5.3 vs 95 ± 8.3 mmHg ($p < 0.05$), 116 ± 7.1 vs 95 ± 7.9 mmHg ($p < 0.05$)]. Urine volume and sodium excretion did not increase, but were lower in all patients than in the control study although the statistical difference was only seen at 2 hours after the start of the infusion (Table II, Fig. 5), while urinary potassium excretion remained the same.

After one hour of 300 ml of saline infusion, TP decreased by 8% and SNa increased by 3% and the glomerular filtered load of sodium increased in a similar manner both with and without SQ 14225 treatment. PRA increased and PA decreased after SQ 14225 administration indicating effective blockade of angiotensin II forma-

Fig. 8. Correlation between mean arterial blood pressure (MAP) and urine volume (UV), or sodium excretion (UNaV) following hypertonic saline infusion on daily intake of 8g of NaCl in 5 normal renin patients with and without SQ 14225 administration.

tion (Fig. 6).

The GFR increased in two patients, decreased in one and was unchanged in the remaining two patients, so the mean value for this group was unchanged. The RBF increased in three and was unchanged in two, the mean value increasing from 650 to 790 ml/min. The filtration fraction (FF) decreased in three and was unchanged in two, the mean value decreasing from 26.9 to 19.3%. These were not statistically significant changes (Fig. 7).

There were statistically significant positive correlations between MAP and urine volume ($p < 0.05$) and sodium excretion ($p < 0.01$) in the corresponding collection periods with and without SQ 14225 treatment (Fig. 8). There was also a significantly positive correlation between the changes in MAP and urinary sodium excretion ($p < 0.05$) (Fig. 9).

DISCUSSION

In the present study, prompt and enhanced diuresis and natriuresis were observed following

Fig. 9. Correlation between changes in mean arterial blood pressure (ΔMAP) and urine volume (UV), or sodium excretion (UNaV) following hypertonic saline infusion on 8g of NaCl daily in 5 normal renin patients with and without SQ 14225 administration.

hypertonic saline infusion in hypertensive patients on a high salt intake, irrespective of renin status. A similar increase in the glomerular filtered load of sodium in both normal and hypertensive subjects suggests that an alteration in renal tubular sodium handling in the hypertensives is a contributing factor in the exaggerated natriuresis. A similar decrease in the serum total protein concentration in all three groups suggests that the infusion of 300 ml of 3% saline solution causes a similar degree of blood volume expansion in both normal and hypertensive subjects. Our previous study² showed that the circulating blood volume, corrected by the "leanness index"³, in patients with essential hypertension did not differ from that of normotensive controls and also that no statistically significant difference was found between the renin subgroups on a daily intake of 8g of sodium chloride.

To our knowledge, there are only a few reports describing the acute response of the renin-aldosterone system to an acute saline load in patients with essential hypertension. Kem et al⁴

have shown that patients with essential hypertension responded by a decrease in PRA and PA in a similar manner to control subjects after a 4-hour infusion of isotonic saline infusion. Recently, Tuck et al⁵ found that in sodium restricted state, 60% of patients with normal PRA essential hypertension showed no significant decline in PRA or PA until 120–240 minutes after the start of an isotonic saline infusion, while the remainder showed normal renin suppression. Sodium excretion was significantly less in the delayed response subgroup than in the subgroup with normal renin suppression. They suggested that the delayed suppression subgroup had a diminished ability to respond to the sodium ion. The mean decrease in PRA and PA in our normal renin patients after saline infusion did not differ from that in control subjects. The reason for the difference between our observation and those of Tuck et al⁵ is unclear. The main difference in procedure was that we infused 300 ml of 3% saline solution within a 1-hour period while they infused 500 ml of isotonic saline per hour. The larger amount of sodium chloride and higher serum sodium concentrations might explain the consistent PRA suppression in our patients, since Tuck's subgroup with delayed renin suppression showed virtually "normal" renin suppression 120–240 minutes after the start of the infusion. More recently, Pederson and Kornerup⁶ reported that the fall in plasma renin and aldosterone concentrations in hypertensive patients did not differ significantly from the fall in the normotensive group after the infusion of 500 ml of 5% saline solution for 40 minutes.

Some investigators have emphasized the role of renin suppression in the exaggerated natriuresis of hypertensive patients. Krakoff et al⁷ and more recently Luft et al⁸ reported that the renin unresponsive group excreted more sodium in the urine than did the renin responsive group after an acute isotonic saline load. They concluded that exaggerated natriuresis was characteristic of patients with low plasma renin activity and these findings were comparable with those in patients with primary hyperaldosteronism,⁸ spontaneously hypertensive rats (SHR),⁹ salt hypertensive rats,¹⁰ and in the contralateral kidney of animals with experimental renovascular hypertension.¹¹ Schalekamp et al¹² also reported profound natriuresis in patients with a mild decrease in renal blood flow and low plasma renin concentration after an acute hypertonic saline infusion.

The mean urinary sodium excretion in our

five low renin patients with essential hypertension did not differ from that in the normal renin group, and no patients excreted more sodium than did normal renin patients who showed a most prominent natriuresis. Furthermore, the reduced formation of plasma angiotensin II by angiotensin converting enzyme inhibitor SQ 14225 did not increase, but urine volume and sodium excretion decreased with the reduction of blood pressure in these normal renin patients. Although converting enzyme inhibitor has been reported to produce increased water and sodium excretion in sodium depleted animals^{13,14} and in man under certain conditions,^{15,16} none of our normal renin patients showed an enhanced natriuresis after SQ 14225 on a daily intake of 8g of sodium chloride. Above results clearly indicate that the reninangiotensin-aldosterone system does not play an important role in the exaggerated natriuresis of essential hypertension. Muirhead et al¹⁴ reported that MAP was lowered by SQ 14225 in SHR, but water, sodium and potassium excretion and cardiac indices did not change when they were fed an ordinary diet.

A similar change in the glomerular filtered load of sodium in normal and hypertensive subjects suggests that an alteration in renal sodium handling in hypertensives is a contributing factor in exaggerated natriuresis. The site of decreased sodium reabsorption along the renal tubule after an acute salt load remained to be elucidated.

A number of investigators^{17–20} have reported that sodium reabsorption in the proximal tubules is impaired after volume expansion with isotonic saline infusion. Although the precise mechanism remains unclear, increased peritubular hydrostatic pressure, decreased peritubular plasma oncotic pressure, increased back leak of sodium and some humoral substances are considered to be related factors. However, Stumpe et al²¹ found in chronically hypertensive rats that sodium and water reabsorption in the proximal tubule remained unchanged with increasing arterial pressure. More recently, Dibona and Rios²² using micropuncture technique, found that the proximal tubular sodium handling in SHR did not differ from that in control rats when isotonic saline was infused.

Increased RBF and unchanged GFR after converting enzyme inhibition in some patients in our study were in agreement with previous studies.^{23–25} The decrease in filtration fraction after SQ 14225 might indicate a predominant post-glomerular locus of angiotensin II to control

GFR in some patients with normal renin essential hypertension. Although our experimental design could not assess the proximal tubular sodium handling, the decrease in filtration fraction which should result in the decreased peritubular plasma oncotic pressure did not increase sodium and water excretion, suggesting that a decrease in proximal tubular sodium reabsorption does not play an important role in exaggerated natriuresis in essential hypertension. Plasma bradykinin levels which should be increased by converting enzyme inhibition^{13,26} also did not seem to act much as a natriuretic factor in the exaggerated natriuresis seen in these experimental conditions. Vinci et al²⁷ found that parenteral converting enzyme inhibitor SQ 20881 had no effect on plasma bradykinin levels but increased prostaglandin E.

Another possible mechanism contributing to decreased tubular sodium reabsorption during a salt load in hypertensive subjects is suggested by our findings that the TCCH_2O in hypertensives is lower at any C_{osm} above 2.5 ml/min than in control subjects with a daily intake of 16g of sodium chloride. TCCH_2O is a function of medullary sodium accumulation during hydropenia, and the contributory factors in the decreased in TCCH_2O are: decreased sodium reabsorption in the ascending limb of the loop of Henle, decreased permeability to water in the collecting duct due to decreased ADH activity or the change in sensitivity of collecting duct to ADH, and augmented "washout" caused by the increased medullary blood flow. There is no direct evidence that ADH plays a role in enhanced sodium excretion after a saline load in essential hypertension. Buckalew et al²⁸ observed decrease in the TCCH_2O in hypertensives during hydropenia when compared to that in normotensive controls after a hypertonic saline infusion while they were received vasopressin administration.

There is evidence that renal cortical blood flow is well auto-regulated, while renal medullary blood flow is not. Kramer et al²⁹ and Miyamoto and Gordon³⁰ found that during a sudden rise in renal perfusion pressure, the medullary blood flow increased, while renal cortical and total blood flow were little changed. Therefore, an increase in "medullary washout" secondary to an increase in medullary blood flow can be expected in hypertensive subjects after an acute saline load. The prompt and enhanced natriuresis of hypertensive subjects observed in the present study can thus be explained, at least in part, by the de-

crease in sodium reabsorption in the ascending limb of the loop of Henle due to an increase in "medullary washout".

Stumpe et al²¹ studied the function of the loop of Henle in the rats with chronic hypertension by means of micropuncture. They found a continuous decrease in transit time of Lissamine green through the loop of Henle and fractional sodium reabsorption with increasing blood pressure. They concluded that the increase in sodium and water excretion with chronic elevation of arterial blood pressure was caused by a decrease of sodium and water reabsorption along the loop of Henle. DiBona and Rios²² also studied the mechanism of the exaggerated diuresis and natriuresis in SHR by renal clearance and micropuncture techniques. They found that the fractional and absolute sodium reabsorption in Henle's loop was less in SHR than in controls during experimental hydropenia and volume expansion, whereas sodium handling along the proximal and distal tubules and collecting ducts did not differ from that in the control animals. Although they did not measure PRA in their rats, the SHR used in their study were 14–16 weeks in age and their PRA was comparable to that of control rats, according to Bagby et al^{31,32}

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