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The Natriuretic Response to Acute Saline Loading in the Aged

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ABSTRACT

Studies were performed to evaluate the natriuretic response to acute saline loading in the aged. After overnight fasting, 15 ml/kg of body weight of 0.9% saline was intravenously infused for 1 h in 10 healthy aged (72.8±1.3 years old) and 9 young (22.0±0.5 years old) volunteers. The saline infusion resulted in a gradual increase in urinary sodium excretion rate ($U_{Na}V$) for 4 h in young subjects, while in aged subjects $U_{Na}V$ reached a peak just after the completion of the infusion and decreased thereafter. The amount of sodium excreted for the first 4 h after starting the infusion in aged and young groups was 13.8±1.1 and 20.7±2.2% of loaded sodium, respectively ($p<0.05$). GFR was significantly lower in the aged and did not significantly change throughout the pre- and post-infusion periods in both groups. Fractional sodium excretion (FE_{Na}) was greater in aged subjects than in young subjects during the pre-infusion and the early phase of the post-infusion period, but not in the late phase. Plasma atrial natriuretic peptide (ANP) in the pre-infusion period was significantly higher in aged subjects than in young subjects ($p<0.05$). The saline infusion caused a more marked increase in plasma ANP in the aged group during the early phase of the post-infusion period when compared with the young group (55.6±9.9 vs. 30.9±3.5 pg/ml, $p<0.05$), but significantly decreased thereafter. Furthermore, a significant correlation was found between alterations in $U_{Na}V$ and plasma ANP in the aged during the post-infusion period ($r = 0.79$, $p<0.01$), but not between changes in $U_{Na}V$ and other sodium excretion-regulating factors, such as GFR, blood pressure, plasma oncotic pressure, aldosterone, noradrenaline, dopamine and prostaglandin E_2. The data suggest that the natriuretic response to acute saline loading is retarded in the aged and that this retarded response is partly mediated through alterations in plasma ANP.

INTRODUCTION

It is well known that functioning nephrons in the kidney decrease in number in the aged (Kaplan et al., 1975), with resultant decline in the whole kidney glomerular filtration rate (GFR) (Rowe et al., 1976). Also, the renal capacity to conserve sodium chloride deteriorates with aging (Epstein and Hollenberg, 1976). Crane and Harris (1975) demonstrated that aged subjects excrete more sodium than younger subjects when dietary sodium is restricted to under 10 mEq/day. When sodium chloride is acutely loaded, however, aged people excrete sodium more slowly when compared with younger people (Luft et al., 1979). Nevertheless, the mechanisms for altered natriuretic response to acute saline loading in the aged are poorly understood.

The present work was performed to re-examine whether the natriuretic response to acute saline loading is retarded in the aged, and if so, what is a major determinant of altered natriuretic response.

MATERIALS AND METHODS

Studies were performed on 9 young (mean age 22.0±0.5 years) and 10 aged (mean age 72.8±1.3 years) volunteers. None of them had any history of hypertension, cardiovascular disease or renal disease, or was taking any medication. Blood pressure measurement, urinalysis and electro-cardiogram, examined before starting the studies, did not indicate any abnormal findings. All subjects were taking regular home diet. Informed consent was obtained from all the subjects after the detailed explanation of the study.

After overnight fasting, all subjects were asked to awake at 0600 h, ingest 400 ml of tap water, and then come to our hospital at 0800 h. Following measurements of body weight and height, subjects were kept supine until the end of experiment. After 1 h of the control period, 15 ml/kg of 0.9% saline was intravenously infused at a constant rate between 0900 h and 1000 h. Loaded sodium ranged from 92.3 to

144.5 mEq in the aged and from 124.7 to 184.7 mEq in the young subjects. Urine samples were collected every hour from 0800 h to 1300 h by voluntary voiding. Venous blood samples were taken hourly just before voiding. After every voiding 50–100 ml of tap water was ingested to maintain urine flow.

The percent excretion of loaded sodium (%NaEx) was calculated from the sodium excretion rates during the pre-infusion control period (A) and post-infusion period (B), and the amount of loaded sodium (C) as follows:

$$\%NaEx = (B - A)/C \times 100\%.$$

Mean arterial blood pressure was calculated as diastolic blood pressure plus one-third of pulse pressure.

The sodium concentration in serum and urine samples were measured by flame photometry. Creatinine and albumin concentrations were estimated by means of an automated analyzer. Creatinine clearance adjusted to a standard surface area of Japanese adults (1.48 m^2) was calculated by conventional method. The plasma renin activity (PRA), plasma levels of aldosterone (PAC) and atrial natriuretic peptide (ANP) and urine prostaglandin E_2 (PGE_2) were evaluated by radioimmunoassays, using γ-coat Renin kit (Baxter, Tokyo), Spack-S aldosterone kit (Daiichi, Tokyo), HANP kit (Eiken, Tokyo), and Prostaglandin E_2 kit (New England Nuclear, Tokyo), respectively. Urine dopamine and norepinephrine were measured by high performance liquid chromatography (880-PU, Japan Spectroscopic, Tokyo).

The data are presented as the mean ± SEM. All statistical comparisons were performed using Student's *t*-test.

RESULTS

The urinary sodium excretion rate ($U_{Na}V$) during the pre-infusion control period was higher in the aged than in young subjects (128.7±13.1 vs. 112.8 ±8.5 μEq/min, $p<0.05$) (Table 1). An approximately two-fold increase in $U_{Na}V$ was observed in both groups during the first 2 h after starting the saline loading. Thereafter, $U_{Na}V$ increased progressively in young subjects but decreased in aged subjects. A significant difference was found in $U_{Na}V$ at 4 h after starting the infusion between aged and young subjects (180.2±22.9 vs. 274.3±28.7 μEq/min, $p<0.05$).

The percent excretion of loaded sodium (%NaEx) for 4 h after starting the infusion was lower in aged subjects than in young subjects (13.8±1.1 vs. 20.7±2.2%, $p<0.05$). When the post saline infusion period was divided into the early (from 0 to 2 h after starting the saline infusion) and late phases (from 2 to 4 h), %NaEx in the early phase was not significantly different between aged and young subjects (Fig. 1, left top), but significantly lower in the aged during the late phase. The serum sodium concentration did not significantly change in both groups throughout the observation periods (Table 1).

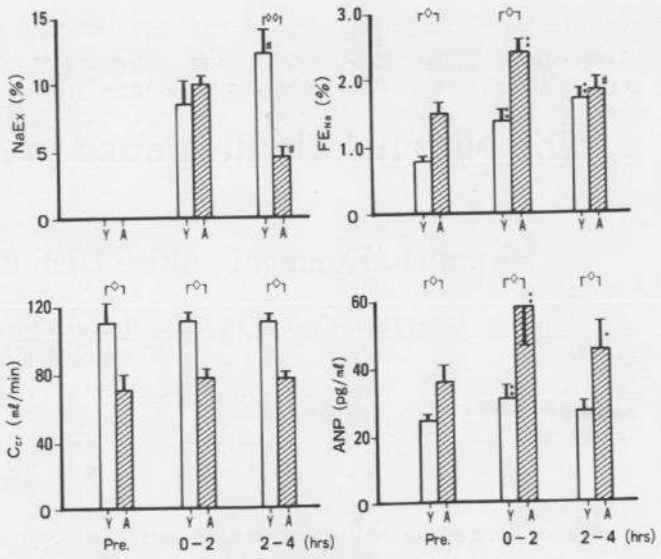

Fig. 1. Effects of the saline infusion on the percent excretion of sodium (%NaEx), creatinine clearance (C_{cr}), fractional sodium excretion (Fe_{Na}) and atrial natriuretic peptide (ANP). A, aged subjects; Y, young subjects. $^{*}p<0.05$, $^{**}p<0.01$, compared with pre-infusion values; $^{\#}p<0.05$, $^{\#\#}p<0.01$, compared with the early phase; $^{\circ}p<0.05$, $^{\circ\circ}p<0.01$, compared with aged subjects.

The creatinine clearance rate (C_{cr}) in the pre-infusion control period was lower in aged subjects than in young subjects. C_{cr} did not significantly change after the saline infusion in both groups (Fig. 1, left bottom).

The fractional sodium excretion (FE_{Na}, $U_{Na}V/s\text{-}Na/C_{cr}$) in the aged was two-fold greater than that in young subjects in the pre-infusion period (Fig. 1, right top). FE_{Na} increased in the early phase of the post-infusion period and thereafter decreased in aged subjects but gradually increased in young subjects. There was no significant difference in FE_{Na}, estimated at 4 h after starting the saline loading between aged and young subjects.

Aged subjects showed slightly but significantly higher blood pressure when compared with young subjects. Blood pressure did not significantly change after the saline infusion in both groups (Table 1).

The pre-infusion level of serum albumin was slightly but not significantly lower in aged subjects than in young subjects. After starting the infusion, serum albumin decreased in both groups. PRA was

TABLE 1

Effects of acute saline infusion on urinary sodium excretion ($U_{Na}V$), mean blood pressure (MBP), serum Na (s-Na), serum albumin (s-alb), plasma renin activity (PRA), plasma aldosterone concentration (PAC), urinary dopamine excretion (u-dopamine), the ratios of urinary dopamine/norepinephrine concentration (u-dopa/nor) and urinary prostaglandin E_2 (u-PGE_2). Values are expressed as means±SEM; *$p<0.05$, **$p<0.01$ compared with the pre-infusion values. #$p<0.05$, compared with the early phase. °$p<0.05$ compared with aged subjects.

		Pre-infusion	0–2 h	2–4 h
$U_{Na}V$ (μEq/min)	Aged	128.7±13.1	241.5±24.6**	182.9±21.5**#
	Young	112.8±8.5°	213.7±26.1**	256.3±28.7**#°
MBP (mmHg)	Aged	91.3±3.5	89.7±2.3	88.9±2.1
	Young	81.9±4.0°	83.3±2.5	82.8±2.4°
s-Na (mEq/l)	Aged	142.1±0.7	143.0±0.8	142.7±0.7
	Young	142.4±0.5	142.0±0.4	141.4±0.4
s-alb (g/dl)	Aged	4.1±0.1	3.7±0.1**	3.7±0.1**
	Young	4.4±0.1	4.0±0.1**°	4.0±0.1**°
PRA (ng/ml/h)	Aged	0.64±0.17	0.61±0.21	0.54±0.16*#
	Young	1.00±0.26	0.50±0.07*	0.48±0.07*°
PAC (pg/ml)	Aged	32.7±4.0	16.3±1.8*	18.0±1.9*
	Young	55.1±8.2°	28.8±3.7*°	26.0±3.6*°
u-dopamine (μg/h)	Aged	13.4±1.2	12.3±1.4	10.1±1.1*
	Young	19.7±2.4°	18.5±1.7°	17.5±1.7*°
u-dopa/nor	Aged	3.4±0.3	3.2±0.3	3.1±0.3
	Young	6.5±1.1°	6.2±0.9°	6.2±1.0°
u-PGE_2 (pg/h)	Aged	24.0±5.2	26.6±5.8	22.8±4.2
	Young	48.8±11.3°	49.2±11.9°	58.6±22.2°

significantly suppressed by saline loading in both groups (Table 1), concomitant with a significant decrease of PAC.

Aged subjects showed significantly higher plasma level of ANP in the pre-infusion period when compared with young subjects (Fig. 1, right bottom). The saline infusion gave rise to a significant increase in ANP in both groups during the early phase of the post-infusion period and a decrease thereafter. A significant positive correlation was found in aged subjects between $U_{Na}V$ and ANP in the range above 35 pg/ml ($r = 0.79$, $p<0.01$). In contrast, an increase in plasma ANP following the saline infusion was smaller in young subjects. A significant correlation was not found between $U_{Na}V$ and plasma ANP in young subjects.

Urinary dopamine excretion, urinary dopamine/norepinephrine ratios and urinary PGE_2 excretion before and after the saline infusion were significantly lower in aged subjects than in young subjects (Table 2), but not significantly affected by the saline infusion in both groups.

DISCUSSION

The present work demonstrated that urinary sodium excretion in the resting state was higher but the natriuretic response to acute saline loading was retarded in the aged. The percent excretion of loaded sodium in the early phase of post-infusion period was not significantly different between aged and young subjects. In the late phase, however, sodium excretion decreased in aged subjects but increased in young subjects, a finding which suggests altered renal handling of sodium in the aged.

Why was the natriuretic response to acute saline infusion retarded in the aged? Increased blood pressure and/or reduced serum albumin concentration should enhance sodium excretion. In our study, blood pressure was higher and serum albumin lower in aged subjects rather than in young subjects throughout the observation periods. Therefore, the retarded natriuretic response in the aged can not be explained by differences in blood pressure and/or serum albumin between aged and young subjects.

On the other hand, Kirkland et al. (1983) suggested that impaired urinary sodium excretion in the aged is attributed largely to an age-related decline in the whole kidney GFR. In our aged subjects, GFR was lower in the pre-infusion control period but FE_{Na} was much higher, with resultant higher sodium excretion. GFR was not affected by the saline infusion in both aged and young groups. FE_{Na} increased significantly in the early phase of the post-infusion period in both groups, with much higher value in the aged. In the late phase, however, FE_{Na} decreased significantly in aged subjects but further increased in young subjects. Taken together the data suggest that suppressed natriuretic response to acute saline loading in the aged is mediated through a decrease in FE_{Na} during the late phase.

FE_{Na} is influenced by multiple factors such as plasma oncotic pressure, aldosterone, ANP, catecholamine and prostaglandins (Epstein, 1978). Lower PAC should enhance sodium excretion. In our aged group, FE_{Na} and $U_{Na}V$ were significantly reduced in the late phase of the post-infusion period, despite maintained lower PAC. Also, urinary excretion of dopamine and PGE_2, and the dopamine/noradrenaline excretion ratios were significantly lower in the aged not only in the pre-infusion period but also in the post-infusion period. Such changes in aged subjects should contribute to a reduction in urinary sodium excretion. However, a significant difference was not found in these factors between the early and late phases despite reduced sodium excretion in the late phase. It is unlikely, therefore, that reduced sodium excretion during the late phase in the aged is attributed largely to alterations in these sodium excretion-regulating factors.

One of the other sodium excretion-regulating factors is ANP (Epstein et al., 1987). In our study, the plasma level of ANP in the pre-infusion control period was significantly higher in the aged than in young subjects, a finding which is compatible with the previous data (Haller et al., 1987). After starting the saline infusion, urinary sodium excretion in the aged group changed synchronously with alterations in the plasma ANP level. Furthermore, a significant positive relationship was found in aged subjects between plasma ANP and FE_{Na}. The findings suggest that plasma ANP plays a causal role in altered natriuretic response to acute saline loading in the aged.

It is unclear, however, why plasma ANP decreased in the late phase of the post-infusion period in the aged, despite most of loaded sodium was still retained in the body. The serum albumin concentration and PRA, indices of changes in the plasma volume, were not significantly different between the early and late phases. It is unlikely, therefore, that the decrease in plasma ANP in the late phase resulted from reduced plasma volume.

In contrast to aged subjects, the increase in plasma ANP following the saline infusion was significantly smaller in young subjects. There was no significant correlation, therefore, between a gradual increase in sodium excretion following the saline infusion and alterations in plasma ANP.

In summary, the natriuretic response to acute saline loading was retarded in the aged. Alterations in urinary sodium excretion changed in a parallel fashion with alterations in plasma ANP in aged subjects but not in young subjects.

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