

## Aging and Salt-Sensitivity

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(Presented by Academy Member V. Okujava)

**ABSTRACT.** Salt sensitivity was assessed in normotensive 48 young and 62 elderly males. Salt sensitivity was assessed by the difference of mean arterial pressure (MAP) on high (200 mmol Na/day) vs. low (40 mmol Na/day) sodium diet. Plasma rennin activity (PRA) was assessed during both diets. High salt diet led to significant increase in systolic blood pressure and MAP only in salt-sensitive subjects with peak levels in the elderly. Only salt-resistant subjects responded adequately during high salt diet by decrease in PRA which was significantly lower compared to basal levels. In salt-sensitive groups, especially in the elderly, PRA decreased to a lesser extent. Final clarification of mechanisms of salt-sensitivity in normotensive elderly calls for further investigations. © 2009 Bull. Georg. Natl. Acad. Sci.

**Key words:** salt-sensitivity, elderly, plasma rennin activity.

Since ancient times it has been well known that excessive consumption of salt is somehow related to health deterioration. Chinese physician Huang Ti Nei Ching Su Wein (1700 BC) stated that “if large amounts of salt are taken, the pulse will stiffen and harden” [1]. Later it became evident that increase in salt intake in salt sensitive persons may lead to the development of arterial hypertension that is considered to be due to genetics. It was estimated that about 26% of normotensive subjects and 51% of hypertensives appear to be salt sensitive. In subjects whose kidneys genetically failed to excrete an increased amount of sodium the latter retained in the body and gradually led to hypertension [1-3]. The distribution of salt sensitivity and resistance in normal and hypertensive subjects is bell shaped (Gaussian distribution) and in both the proportion of individuals who become salt sensitive, increases with age [3, 4]. Up to now little has been known about the mechanisms of salt sensitivity as well as causes of increasing frequency of salt-sensitivity and its distribu-

tion in elderly population [5, 6]. Interestingly enough, presently existing primitive societies that consume less than 3 g salt daily maintain normal range of blood pressure despite age [1-5].

Data regarding activation of the rennin-angiotensin-aldosterone system in the elderly are quite controversial and remain to be clarified. A number of studies showed increased plasma rennin activity (PRA) while others indicate decreased rennin levels [7, 8]. Numerous methods of assessment of salt sensitivity [4, 7-10] are mostly based on changes in mean arterial pressure (MAP) after being on various salt diets (low, normal and high salt intake). Most of the salt sensitivity study protocols imply administration of a low (9 to 80 mmol/day) sodium diet from 4 to 14 days, followed by a high (220 to 300 mmol/day) sodium intake from 4 to 14 days. If MAP increases more than 3 mmHg, a person is considered to be salt sensitive.

Based on the aforementioned, the study aimed at assessing salt-sensitivity in normotensive young and elderly men and assessing their rennin profile.

## Materials and Methods

Salt sensitivity was assessed in normotensive (blood pressure < 139/89 mm Hg) 48 young and 62 elderly males with mean age  $34.6 \pm 5.23$  yrs and  $69.5 \pm 3.41$  yrs respectively. Salt sensitive subjects were divided into two groups in accordance with age (middle age salt-sensitives – SS1, elderly salt-sensitive subjects – SS2; respectively, salt resistant subjects were divided into two groups: SR1 and SR2). Salt sensitivity was assessed by the difference of mean arterial pressure (MAP) on high (200 mmol/day) vs. low (40 mmol/day) salt diet [9]. During the first week the subjects were placed on high sodium diet (200 mmol/d per 70 kg) both by adding 100 mmol directly to the food and by administering 100 mmol in capsules ingested 3 times daily with meals. Next week subjects were placed on a low-salt diet aimed at a maximum intake of 40 mmol sodium per day. Compliance with the diet was confirmed by measurement of 24-hour urinary sodium excretion during the last 2 days of both weeks. On the seventh day of both weeks the diastolic blood pressure (DBP) and systolic blood pressure (SBP) were measured in sitting position at 2-minute intervals for 1 hour by automatic Blood Pressure Monitor BP A100 Plus (Microlife, Switzerland). Mean arterial blood pressure (MAP) was calculated as DBP plus one-third of the difference between DBP and SBP. Salt sensitivity of blood pressure was defined as the difference of MAP between the average of 30 readings during the high and low salt periods. Salt sensitivity was considered when difference between MAP exceeded 3 mm Hg. All subjects were volunteers and nonsmokers. They did not use any medicine and did not have history of cardiovascular, respiratory, liver, renal diseases and diabetes. All patients signed an informed consent.

Plasma rennin activity (PRA) was assessed during both diets in recumbent position by radioimmunoassay (Sorin, Italy). Sodium levels in blood plasma and urine were measured with flame photometry.

Statistical analyses were performed using SPSS software. All data are presented as mean  $\pm$ SD. Statistical comparison among groups was performed by Student's *t* test. The value of  $p < 0.05$  was considered significant.

## Results

Results of salt sensitivity test are presented in Table. Fourteen (29.2%) of middle aged 48 subjects and 29 (46.8%) of elderly 62 subjects were salt sensitive (Groups SS1 and SS2 respectively). Those who did not respond to sodium diets by changes in MAP ( $\leq 3$ mmHg) were considered salt resistant (Groups SR1 and SR2).

By the end of low salt diet SBP, DBP and MAP of salt-sensitive middle-aged subjects (SS1) did not differ from those of Group SS2. High salt diet induced significant elevation of SBP and MAP in both salt-sensitive groups, predominantly in elderly subjects (SS2). Whereas the difference between basal and post-loading MAP in SS1 was  $5.5 \pm 0.43$  mm Hg,  $p < 0.05$ ), in SS2 it became more prominent ( $13.2 \pm 0.31$ mm Hg,  $p < 0.01$ ). Predictably, in salt resistant subjects, blood pressure parameters including MAP did not change significantly in both groups. After salt loading urinary sodium excretion increased both in salt-sensitive and salt-resistant subjects irrespective of their age.

Changes in PRA were similar in all groups, increasing during low-salt and becoming significantly lower after salt loading. However, we noticed that in salt-sensitive subjects, especially in the elderly (SS2 group) PRA decreased to a lesser extent than in salt-resistant subjects ( $5.2 \pm 0.88$  vs.  $3.7 \pm 0.61$ ,  $D1.6 \pm 0.42$ ng/ml/h,  $p < 0.05$  in SS1 group;  $5.7 \pm 1.2$  vs.  $4.6 \pm 0.83$ ,  $D1.1 \pm 0.44$  ng/ml/h,  $p < 0.05$  in SS2 group;  $5.2 \pm 3.1$  vs.  $2.1 \pm 0.22$ ,  $D3.1 \pm 0.28$  ng/ml/h,  $p < 0.01$  in RS1;  $6.1 \pm 2.4$  vs.  $1.9 \pm 1.8$ ,  $D3.1 \pm 0.18$ ng/ml/h.  $p < 0.001$ ).

During low salt diet PRA inversely correlated with daily sodium excretion in groups as well as in salt resis-

Table

Blood pressure and biochemical measurements in SS and SR Groups (M $\pm$ SD)

Variables	SS1		SS2		SR1		SR2	
	low salt	high salt	low salt	high salt	low salt	high salt	low salt	high salt
n	14		29		34		33	
SBP, mm Hg	112.5 $\pm$ 1.2	122.2 $\pm$ 1.3 <sup>a</sup>	116.8 $\pm$ 1.5	131 $\pm$ 1.6 <sup>b*</sup>	116.8 $\pm$ 1.4	121.5 $\pm$ 1.7	123.4 $\pm$ 1.6	124 $\pm$ 1.4
DBP, mm Hg	73.6 $\pm$ 1.2	77.1 $\pm$ 1.1	72.2 $\pm$ 1.1	80.4 $\pm$ 1.1 <sup>a</sup>	74.9 $\pm$ 1.2	76.7 $\pm$ 1.4	75.8 $\pm$ 1.2	78.3 $\pm$ 1.2
MAP, mm Hg	86.7 $\pm$ 0.98	92.4 $\pm$ 1.1 <sup>a</sup>	86.1 $\pm$ 1.2	99.3 $\pm$ 1.3 <sup>a*</sup>	89.2 $\pm$ 1.1	91.5 $\pm$ 1.5	92.3 $\pm$ 1.4	94.3 $\pm$ 1.4
UNa/day, mmol	32.3 $\pm$ 6.3	167 $\pm$ 26.1 <sup>c</sup>	27.4 $\pm$ 4.9	164 $\pm$ 31.5 <sup>c</sup>	28.6 $\pm$ 6.4	173.3 $\pm$ 24.7 <sup>c</sup>	30.4 $\pm$ 4.8	181.5 $\pm$ 19.6 <sup>c</sup>

a -  $p < 0.05$ ; b -  $< 0.01$ ; c -  $< 0.001$  vs. low salt diet. \* -  $< 0.05$  vs. middle aged group(SS1)

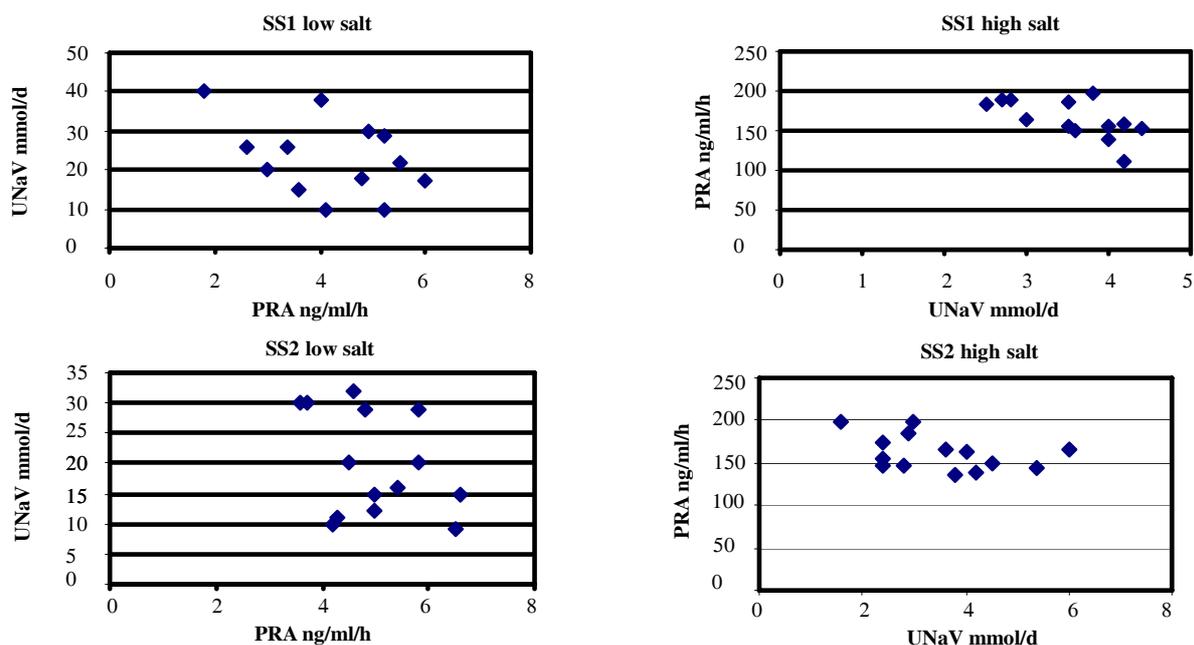


Fig. Correlations between PRA and urinary sodium excretion in salt sensitive subjects

tant subjects irrespective of age. After sodium loading the correlation between PRA and urinary sodium excretion remains significantly negative in salt resistant subjects ( $r = -0.33$  and  $r = -0.31$ ,  $p < 0.01$  and  $r = -0.47$ ,  $p < 0.01$  in SR1 and SR2 groups respectively) became non-significant (Fig.) in salt sensitive groups ( $r = -0.28$ ,  $p > 0.05$  and  $r = -0.11$ ,  $p > 0.05$ ).

## Discussion

Salt-sensitivity, despite being a subject of long-term discussions, remains an actual problem [1-3]. Our findings confirm results of numerous studies that demonstrate age dependence of salt sensitivity [4-6] – we found that high salt diet led to significant increase in SBP and MAP only in salt-sensitive subjects, with peak levels in the elderly. However, our primary interest was focused on investigating whether any differences exist in normotensive middle-age and elderly subjects who are salt-sensitive, and salt with respect to changes in blood pressure, urinary sodium excretion and plasma rennin activity during sodium restriction and salt loading. Though all subjects were normotensive. SBP after salt loading in salt-sensitive elderly subjects reached pre-hypertension/high normal levels, which is associated with moderate risk of cardiovascular morbidity.

Insufficient suppression of the circulating rennin-angiotensin-aldosterone system was postulated as a cause underlying the increase in blood pressure resulting from salt retention [3,4,7,8]. In agreement with this possibility, some investigators found that, contrary to the predicted

downregulation of the rennin-angiotensin-aldosterone system in a state of controlled extracellular expansion, rennin levels were normal [7]. However, other investigators reported appropriately decreased rennin levels [6,8].

In contrast to studies indicating decreased PRA in aged population [6,8], our results showed that PRA did not decrease in the elderly compared to middle-age salt-sensitive as well as in salt-resistant subjects during low-salt diet. Despite similar PRA response to high salt diet only salt-resistant subjects responded adequately by decrease in PRA, which was significantly lower compared to basal levels. In salt-sensitive groups, especially in the elderly, PRA decreased to a lesser extent ( $p > 0.05$ ). On the other hand, renal sodium excretion after salt loading in salt-sensitive groups 5-6 times exceeded natriuresis during low-salt diet. Correlative analysis also showed that significant inverse correlation between PRA and urinary sodium excretion during low-salt diet in salt-sensitive subjects became non-significant after salt loading, in contrast to salt-resistant groups. Based on these findings, it is suggestive that in salt sensitive subjects urinary sodium excretion on low-salt diet largely depends on PRA, while the latter contributes to a lesser extent to increase in natriuresis after switching to high salt diet. Such relationship becomes more evident in salt sensitive elderly. Logically, it remains questionable which factors/mechanisms lead to increase in urinary sodium excretion in salt-sensitive subjects keeping high-salt diet. One of suggestive assumptions might be the study conducted recently by D.Anderson et al. [10].

According to this study, high sodium diet elicited a sustained increase in endogenous sodium pump inhibitor marinobufagenin excretion that directly correlated with an increase in the fractional sodium excretion and

was inversely related to age and to an age-dependent increase in salt-sensitivity. Final clarification of mechanisms of salt-sensitivity in normotensive elderly calls for further investigations.

### სამედიცინო მეცნიერებანი

## სიბერე და მარილმგრძობელობა

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(წარმოდგენილია აკადემიკოს ვ. ოკუჯავას მიერ)

მარილმგრძობელობა შეისწავლებოდა ნორმალური არტერიული წნევის მქონე 48 საშუალო ასაკის და 62 ხანდაზმულ მამაკაცში. მარილმგრძობელობა განისაზღვრებოდა საშუალო არტერიული წნევის სხვაობის საფუძველზე მაღალ (200 მმოლი ნატრიუმი დღეში) და დაბალმარილიან (40 მმოლი ნატრიუმი დღეში) დიეტაზე ყოფნის დროს. პლაზმის რენინის აქტივობა განისაზღვრებოდა ორივე დიეტის დროს. მაღალმარილიანი დიეტა იწვევდა სისტოლური და საშუალო არტერიული წნევის მატებას მხოლოდ მარილმგრძობიარე პირებში მაქსიმალური მაჩვენებლებით ხანდაზმულებში. მაღალმარილიან დიეტაზე ყოფნისას მხოლოდ მარილისადმი რეზისტენტულ პირებს აღენიშნებოდათ რენინის ადეკვატური დინამიკა. რაც გამოიხატებოდა მისი აქტივობის მნიშვნელოვანი დაქვეითებით ბაზალურ დონესთან შედარებით. ნორმალური არტერიული წნევის მქონე ხანდაზმულებში მარილმგრძობელობის გამომწვევი მექანიზმები შემდგომ დაზუსტებას საჭიროებს.

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