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EFFECT OF SODIUM INTAKE ON BLOOD PRESSURE, SERUM LEVELS AND RENAL EXCRETION OF SODIUM AND POTASSIUM IN NORMOTENSIVES WITH AND WITHOUT FAMILIAL PREDISPOSITION TO HYPERTENSION

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1. Seventeen normal volunteers aged 19 to 22 were randomly subjected, in a trial of cross-over design, to three distinct regimens of sodium chloride intake: high (16 to 20 g), normal (8 to 12 g) and low (0.5 to 1 g). Each regimen lasted nine days, with determination of blood pressure and heart rate (in the supine position and after sudden rising), body weight, and urinary output of creatinine, sodium and potassium on the third, sixth and ninth days. In addition, plasma levels of creatinine, sodium and potassium were determined on the ninth day so that sodium and potassium clearance and fractional excretion could be calculated.

2. Eleven of the volunteers had a family history of hypertension. Compared to the six without such a history, these subjects showed: 1) higher supine systolic blood pressure on the third day of sodium overload (124.7 ± 3.0 *vs* 112.3 ± 2.9 mmHg, $P < 0.02$); 2) higher supine diastolic blood pressure on the third day of sodium overload (76.5 ± 2.8 *vs* 64.5 ± 4.3 mmHg; $P < 0.05$); 3) higher supine diastolic blood pressure on the sixth day of sodium overload (73.7 ± 2.3 *vs* 63.8 ± 3.2 mmHg, $P < 0.05$); 4) lower supine heart rate on the ninth day of sodium overload (61.0 ± 3.1 *vs* 72.7 ± 4.6, $P < 0.05$), and 5) lower plasma potassium on the ninth day of sodium overload (4.10 ± 0.05 *vs* 4.28 ± 0.06 mEq/l, $P < 0.05$).

3. These results suggest that normal individuals whose familial history places them at risk for the development of hypertension differ from those not at risk during their adaptation to sodium load by suffering a transient elevation of blood pressure within a few days of the increase in load. The low levels of plasma potassium observed in these volunteers after a period of sodium load may be due

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to the operation of different renal mechanisms of sodium excretion in this group, leading to increased kaliuresis, and may explain the high vascular reactivity of such individuals.

Key words: hypertension, sodium intake, blood pressure, potassium.

Introduction

Dietary sodium overload and potassium deficiency have been cited as environmental promoters of essential hypertension in persons with familial predisposition to this syndrome (MacGregor, 1983; McCarron *et al.*, 1983). These persons appear to have difficulty in excreting a sodium overload (Guyton, 1977; Kaplan, 1979). Current understanding of the body's compensatory mechanisms for this difficulty points to secretion of a natriuretic hormone. This hormone, besides increasing sodium excretion by the kidney, elevates blood pressure (De Wardener and MacGregor, 1982). Experimentation with diets that differ in sodium and/or potassium load in normotensive individuals familially at-risk or not-at-risk for essential hypertension is one approach that has been used to evaluate postulated differences in renal salt clearance (Editorial, 1983). Results of such experiments to date support the hypothesis of differences in renal salt clearance to varying degrees (Kirkendall *et al.*, 1976; Miller *et al.*, 1983; Hofman *et al.*, 1983; Fuchs *et al.*, 1983).

The purpose of this study was to determine whether normal young people familially at-risk for developing essential hypertension respond differently from those not-at-risk to a series of diets that vary in sodium chloride content.

Material and Methods

Volunteers, diets, and study setting

Seventeen male and female medical students aged 19 to 22 were studied. All had unremarkable physical exams, and normal urinalyses and creatinine clearances. Eleven of the volunteers (at-risk) were classified as familially at-risk for developing essential hypertension, based on a family history of essential hypertension either in one parent or in two uncles or aunts. The six remaining subjects (not-at-risk) had no parents, uncles or aunts suffering from hypertension. Mean ages, weights and body surfaces were similar in both groups. Each group contained three females.

Each volunteer underwent three distinct trial periods in randomly allocated sequences. Each period involved either regular, high or low sodium chloride intake and lasted nine days, with a wash-out period of six days between periods.

Diets were established and maintained as follows: usual sodium and potassium intakes were determined by dietary history. Volunteers were furnished charts of sodium and potassium contents of foods and were instructed to maintain their intake of these minerals constant throughout each study period. During the period of regular sodium chloride intake, volunteers thus followed their usual eating pattern, consuming meals having an adequate nutrient distribution and prepared by adding the usual quantity of salt in the kitchen. A daily intake of 8 to 12 grams of sodium chloride was expected during this period. During the period of low sodium chloride intake, the volunteers continued their normal diets except that meals were prepared and consumed without addition of table salt, and foods with high natural sodium chloride content were excluded. A daily intake of 500 to 1000 mg of sodium chloride was expected during this period. During the period of high sodium chloride intake, the volunteers ate their usual diets and supplemented salt intake with 8 grams of sodium chloride administered as enteric release capsules (Laboratório Farmoquímica, Porto Alegre, RG) for an expected total intake of 16 to 20 grams of sodium chloride daily. Volunteers were instructed to maintain potassium intake constant during all trial periods. Compliance with prescribed intakes of sodium and potassium was monitored by determination of urinary electrolytes, as described below.

No volunteer took any medication during the research. None smoked. The volunteers were instructed to perform their usual daily activities throughout the experiment and were not hospitalized.

Measurements of effects

The parameters analyzed were blood pressure and heart rate, both measured in the supine position and after sudden rising, body weight, plasma and urinary sodium and potassium, and the fractional excretion of sodium and potassium.

Body weight, heart rate and blood pressure were determined on the third, sixth and ninth days of each trial period in an air-conditioned and acoustically isolated room. Blood pressure and heart rate were checked twice daily, at 11:00 a.m. and 5:00 p.m. The average of these two measurements was used for statistical analysis, in order to minimize daily blood pressure variability (Pickering, 1977). Blood pressure was measured by the stethoacoustic method using a mercury sphygmomanometer, with systolic pressure defined as the first phase of Korotkoff's sounds and diastolic pressure as the fifth (Kirkendall *et al.*, 1980). Blood pressure and heart rate were obtained with the subject in the supine position after a five-min rest and then immediately after sudden rising. Two observers, blind to the trial conditions of the volunteers and the purposes of the study, performed all measurements. During the nights preceding these measurements, the volunteers collected 10-h overnight urines. Additionally, on the ninth day of each experimental period, aliquots of venous blood were taken from the forearm.

Sodium and potassium concentrations in urine and plasma were measured by flame spectophotometry (Corning Spectrophotometer, model 450), plasma creatinine as described by Chasson *et al.* (1960) with a Technicon Autoanalyzer II, and urine creatinine by the modified Folin-Wu method (MacFate *et al.*, 1954). Technicians performing these tests were also unaware of the experimental conditions of the volunteers and the purposes of the investigation. All measurements were performed in duplicate. Sodium and potassium clearance and fractional excretion of sodium and potassium were calculated for day 9.

Statistical methods

The means of the various parameters observed in the at-risk and not-at-risk groups on the various measurement days were compared using the Student *t*-test for independent samples. Comparisons of the means of the groups stratified by gender were similarly performed. In addition, the differences in parameters within each experimental group were compared using analysis of variance with the classification criterion being the differing dietary loads. Here, comparison of means, when indicated in the F test, was carried out using the Student-Newman-Keuls test (SNK test) (Zar, 1974). Results are presented as means ± SEM.

Results

Tables 1 and 2 show systolic and diastolic blood pressure, heart rate, body weight, and urinary sodium and potassium in the familially at-risk and not-at-risk groups during the different dietary periods. Supine systolic blood pressure was higher for the at-risk group (124.7 ± 3.0 mmHg) than for the not-at-risk group (112.3 ± 2.9 mmHg) on the third day of sodium overload. Supine diastolic blood pressure was higher for the at-risk group than for the not-at-risk group on the third day (76.5 ± 2.8 and 64.5 ± 4.3 mmHg, respectively) and on the sixth day (73.7 ± 2.3 and 63.8 ± 3.2 mmHg, respectively) of sodium overload. Supine heart rate was lower in the at-risk group (61.0 ± 3.1) compared to the not-at-risk group (72.7 ± 4.6) on the ninth day of sodium overload.

Comparisons of multiple means demonstrated the following mean values to differ significantly ($P < 0.05$ to $P < 0.001$) from those obtained from the same group on other days: 1) for the at-risk group only, supine systolic and diastolic blood pressures were higher on the third day of salt overload, standing systolic blood pressure was lower on the third day of the low sodium diet, supine heart rate was lower on the ninth day of overload, standing heart rate was higher on the third and sixth days of low sodium diet, and the quantity of potassium in the urine was greater on the sixth day of the low-sodium diet; 2) for both groups, body weight was lower during the low sodium days, endogenous creatinine clearance was higher on the ninth day of the high sodium diet and the quantity of sodium in the urine was less during the low-sodium diet and greater during the high-sodium diet.

Table 3 presents the mean plasma concentrations and fractional excretions of sodium and potassium for the last day of each dietary period. A lower concentration of potassium in plasma in the at-risk group (4.10 ± 0.05 mEq/l) in relation to the not-at-risk group (4.28 ± 0.06 mEq/l) during the high sodium chloride period was the only difference of statistical significance between the two groups ($P < 0.05$). Although differences between the two groups in fractional potassium excretion were not statistically significant, excretion during sodium overload increased 17.4 ± 9.5 percent in those at risk and decreased 24.9 ± 8.2 percent in those not at risk as compared to the regular diet period ($P < 0.01$). As expected, fractional excretion of sodium increased with increasing sodium load ($P < 0.01$) for both groups. For the at-risk group only, the fractional excretion of potassium during the low-sodium diet was greater than during the other two periods ($P < 0.01$).

Table 1 - *Blood pressure, heart rate and body weight of 11 volunteers familially at-risk (AR) and 6 volunteers familially not-at-risk (NAR) for developing essential hypertension, during diets of varying sodium chloride loads.*

Results are reported as means ± SEM. *P < 0.05, **P < 0.02 for the comparison of AR and NAR (t-test).

Variable	Group/ day	Low NaCl 3	Low NaCl 6	Low NaCl 9	Regular NaCl 3	Regular NaCl 6	Regular NaCl 9	High NaCl 3	High NaCl 6	High NaCl 9
BLOOD PRESSURE (mmHg)										
Systolic, supine	AR	115.1 ± 2.2	114.1 ± 1.9	117.3 ± 3.5	119.1 ± 3.2	114.2 ± 1.9	118.8 ± 3.5	124.7** ± 3.0	118.3 ± 3.4	118.4 ± 2.8
	NAR	114.8 ± 2.7	113.0 ± 2.6	110.7 ± 3.4	113.3 ± 2.4	112.2 ± 3.4	116.7 ± 3.6	112.3 ± 2.9	111.8 ± 2.9	116.5 ± 1.8
Diastolic, supine	AR	70.6 ± 3.1	71.8 ± 2.9	68.4 ± 2.4	67.3 ± 2.7	71.5 ± 3.2	69.1 ± 2.9	76.5* ± 2.8	73.7* ± 2.3	67.4 ± 2.0
	NAR	66.5 ± 2.4	65.8 ± 4.5	70.0 ± 2.4	65.5 ± 1.2	67.8 ± 3.0	67.7 ± 1.4	64.5 ± 4.3	63.8 ± 3.2	67.0 ± 2.2
Systolic, after sudden rising	AR	97.4 ± 4.2	102.9 ± 3.6	100.8 ± 2.7	107.4 ± 3.7	104.4 ± 4.4	103.2 ± 2.7	110.0 ± 4.1	108.4 ± 3.2	101.2 ± 4.0
	NAR	99.8 ± 4.9	96.7 ± 5.8	102.2 ± 3.9	103.8 ± 6.9	98.2 ± 5.0	107.5 ± 6.7	101.3 ± 4.9	99.2 ± 4.8	98.3 ± 3.9
Diastolic, after sudden rising	AR	68.7 ± 2.5	67.4 ± 2.4	59.9 ± 3.5	66.4 ± 3.2	66.6 ± 3.6	65.6 ± 2.9	69.3 ± 4.0	67.9 ± 3.8	65.4 ± 3.5
	NAR	63.7 ± 2.6	58.8 ± 2.1	58.8 ± 3.6	61.3 ± 4.5	60.2 ± 4.7	62.5 ± 5.1	56.3 ± 4.0	59.5 ± 3.8	57.8 ± 2.4
HEART RATE (beats/min)										
Supine	AR	70.0 ± 2.5	70.7 ± 2.2	65.5 ± 3.1	65.4 ± 2.6	69.2 ± 2.1	66.4 ± 2.3	66.7 ± 2.1	69.2 ± 2.0	61.0* ± 3.1
	NAR	74.3 ± 4.3	66.8 ± 4.6	69.0 ± 4.1	68.3 ± 4.3	72.3 ± 2.4	73.7 ± 4.6	70.0 ± 2.9	69.3 ± 4.6	72.7 ± 4.6
After sudden rising	AR	92.2 ± 4.8	88.2 ± 3.5	80.3 ± 3.9	78.1 ± 3.1	85.1 ± 2.9	82.2 ± 4.4	78.0 ± 2.8	78.9 ± 2.6	76.5 ± 2.8
	NAR	91.8 ± 4.2	85.0 ± 3.2	86.7 ± 3.9	83.2 ± 6.8	80.5 ± 3.7	88.7 ± 4.2	80.7 ± 1.5	83.7 ± 4.1	86.3 ± 4.7
BODY WEIGHT (kg)	AR	64.9 ± 3.1	64.4 ± 3.0	64.1 ± 3.0	65.9 ± 2.9	65.6 ± 2.9	65.9 ± 3.0	66.2 ± 3.0	65.9 ± 3.0	65.8 ± 2.9
	NAR	61.8 ± 2.7	61.5 ± 2.8	61.8 ± 2.8	62.5 ± 2.9	62.2 ± 2.8	62.3 ± 2.9	62.9 ± 3.1	62.5 ± 2.7	62.7 ± 2.8

Table 2 - *Urinary sodium and potassium of 11 volunteers familially at-risk (AR) and 6 volunteers not-at-risk (NAR) for developing essential hypertension, during diets of varying sodium chloride load.*

Results are reported as means ± SEM. *P < 0.05 for the comparison of AR and NAR (*t*-test).

Variable	Group/day	Low NaCl			Regular NaCl			High NaCl		
		3	6	9	3	6	9	3	6	9
Sodium (mEq/10 h)	AR	12.8* ± 1.6	5.8 ± 1.3	6.9 ± 2.0	54.2 ± 3.4	58.8 ± 8.0	46.1 ± 6.1	90.1 ± 9.5	100.1 ± 8.9	99.8 ± 8.3
	NAR	7.3 ± 0.6	5.1 ± 2.0	3.5 ± 1.1	46.7 ± 8.0	43.1 ± 6.8	43.6 ± 5.4	85.8 ±13.3	71.8 ±12.1	102.1 ±18.0
Potassium (mEq/10 h)	AR	14.8 ± 2.4	22.5 ± 3.1	20.6 ± 3.0	14.0 ± 2.5	14.8 ± 2.2	11.8 ± 1.3	13.1 ± 1.5	16.6 ± 2.4	14.9 ± 1.3
	NAR	12.6 ± 1.7	20.2 ± 7.1	17.6 ± 4.2	10.6 ± 2.8	10.2 ± 1.2	13.3 ± 1.6	12.5 ± 4.6	9.7 ± 1.2	13.3 ± 1.7

Table 3 - *Plasma sodium and potassium and fractional sodium and potassium excretion in 11 volunteers familially at-risk (AR) and 6 familially not-at-risk (NAR) for developing essential hypertension, on the ninth day of diets of varying sodium chloride load.*

Results are reported as means ± SEM. *P < 0.05 for the comparison of AR and NAR (*t*-test).

Variable		Diet		
		Low NaCl	Regular NaCl	High NaCl
Creatinine clearance (ml/min)	AR	59.2 ± 3.3	65.9 ± 4.8	76.9 ± 5.4
	NAR	56.9 ± 3.2	62.2 ± 4.3	76.2 ± 7.8
Plasma sodium (mEq/l)	AR	145.0 ± 1.5	142.2 ± 2.0	141.5 ± 1.4
	NAR	144.2 ± 2.6	138.2 ± 0.7	145.7 ± 1.5
Plasma potassium (mEq/l)	AR	4.25 ± 0.11	4.22 ± 0.08	4.10 ± 0.05*
	NAR	4.23 ± 0.18	3.90 ± 0.15	4.28 ± 0.06
Fractional sodium excretion	AR	0.0014 ± 0.0004	0.0085 ± 0.0009	0.0167 ± 0.0015
	NAR	0.0007 ± 0.0002	0.0096 ± 0.0013	0.0168 ± 0.0024
Fractional potassium excretion	AR	0.149 ± 0.078	0.076 ± 0.031	0.086 ± 0.032
	NAR	0.137 ± 0.034	0.102 ± 0.011	0.077 ± 0.012

The comparison of means in analysis stratified by gender revealed no substantial differences.

Discussion

The measurements of blood pressure, heart rate and body weight during days 3, 6 and 9 of each diet were designed to observe variations before, during and after the establishment of sodium chloride balance, which occurs around the fifth day (Luft *et al.*, 1982). Plasma concentrations and fractional excretions of electrolytes were measured on the ninth day to observe possible steady state differences in renal handling of sodium and potassium.

The absence of statistically significant differences between the experimental groups in weight, body surface, or any of the measures of effect during the regular diet period, combined with the fact that gender did not substantially influence the results, makes it likely that the differences observed between the two groups can be attributed to familial at-risk status.

The low sodium chloride diet produced similar responses in both experimental groups, suggesting that, for this age group, familial predisposition to hypertension does not alter renal or pressor adaptation to moderate sodium chloride restriction. However, the higher sodium excretion observed on the third day of sodium chloride restriction in the at-risk group could be due to a delayed urinary sodium excretion by this group. The increase observed in supine blood pressure in the at-risk group during saline overload suggests that pressor mechanisms in subjects familially at-risk for developing hypertension respond more slowly to an additional sodium load. These results partially confirm those of some previous studies (Pietinen *et al.*, 1979; Fuchs *et al.*, 1983) although they contradict, or at least potentially contradict the results of others. The study by Pietinen *et al.* (1979), in which the volunteers did not follow a planned diet, is only one which shows a positive correlation between blood pressure and the amount of sodium in urine, exclusively for at-risk individuals.

For the at-risk group, supine heart rate on the ninth day of high sodium chloride intake was lower than on the other days of the experiment and lower than that observed in the not-at-risk group. It is possible that at-risk individuals present a delayed adaptation to the increase in blood pressure which occurs secondarily to sodium overload.

The marked differences between the protocol of the present study and those of other studies, may explain the contradictory results. Murray *et al.* (1978) and Luft *et al.* (1979), who reported a positive correlation between sodium intake and blood pressure for both sodium restriction and overload, used diets with a much larger range of sodium intake which varied from 0.5 to 87 g of sodium chloride per day. Kirkendall *et al.* (1976), who found no effect of variable sodium intake on blood pressure, studied 8 older volunteers (24-47 years of age), only two of whom had a demonstrable family history of hypertension. Burstyn *et al.* (1980) and Luft *et al.* (1982), who also failed to observe such an effect, made no reference to the familial predisposition to hypertension of their volunteers. Additionally, they measured sitting blood pressure only. The higher levels of blood pressure with salt overload, as compared to those measured in a diet with a salt

restriction, may be due to the decline of blood pressure during the salt restriction phase, as was observed by Skraball *et al.* (1981).

The present finding of a lack of difference between groups in body weight reduction during the low-sodium diet is consistent with the results of Skraball *et al.* (1981). The lack of a difference between groups in body weight gain during the saline overload fails to support the proposal of Guyton (1977) that familially at-risk subjects retain greater volumes of fluid when exposed to sodium chloride overload.

Support for the attractive hypothesis that differential renal handling of sodium and potassium is responsible for the difference of blood pressure responses seen during the first half of the sodium overload period is not found in the renal and plasma parameters measured here. Neither, however, do the results refute this hypothesis, as these parameters were determined only for the ninth day.

The idea that dietary sodium overload and potassium deficiency are two environmental promoters of hypertension in predisposed subjects suggests a possible interactive effect. The finding of a differential fractional potassium excretion, although not closely linked temporally to the differential blood pressure responses, suggests a new hypothesis regarding the pathophysiologic mechanisms of essential hypertension: subjects who are familially at-risk may have more difficulty in renally preserving potassium when sodium-excreting mechanisms are activated by sodium chloride overload. The resulting differences in plasma concentrations could explain, by means of some of the mechanisms suggested elsewhere (Overbeck *et al.*, 1974; Hermsmeyer, 1976; Dietz *et al.*, 1981; Iimura *et al.*, 1981; Battarbee *et al.*, 1983), the greater vascular reactivity of predisposed subjects given saline overload. Rado *et al.* (1980) demonstrated a similar differential fractional potassium excretion in response to a saline overload in hypertensives, as compared to normal subjects, but did not comment on this finding. Furthermore, the hypothesis that potassium retention is less effective in at-risk subjects is compatible with the findings of Beretta-Piccoli *et al.* (1981), who demonstrated inverse correlations between blood pressure and exchangeable and total plasma potassium in young people with hypertension. This hypothesis should be investigated further.

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