Effect of Salt Loading On the Cardiovascular Response to Stress in Adolescents

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SUMMARY This study investigated, in normotensive adolescents, three accepted risk factors for essential hypertension (EH): stress, dietary salt, and parental history (genetic risk). The cardiovascular response to mental stress was evaluated before and after salt loading in eight subjects without, and in seven with, a family history (FH) of EH. The effect of salt loading on the FH positive group was to increase significantly the stress-induced systolic and diastolic pressure while the heart rate response decreased. Salt loading resulted in no change in cardiovascular response to stress in the FH negative group.

(Hypertension 3 (suppl II): II-195-II-199, 1981)

KEY WORDS • salt • stress • blood pressure • adolescents • genetics

Many factors that influence blood pressure (BP) control have been investigated individually or in relation to other factors as potential contributors to essential hypertension (EH). Epidemiologic evidence, experimental animal studies, and clinical experience indicate a familial role in the determination of BP. In humans, genetic factors place an individual at a certain risk level for EH, with environmental factors acting to modulate the prevalence and intensity of the disorder.

Stress is an environmental factor known to act as a modulator of EH. The physiologic impact of stress on BP regulation in genetically vulnerable subjects has been demonstrated in experimental models. A relationship of chronic environmental stress to higher prevalence of EH has been reported. Variations in BP response to stress have also been observed in young subjects who have a strong genetic potential for EH.

Dietary sodium is another significant environmental factor in the development of EH. Different cultural or geographic dietary patterns of sodium intake are related to the prevalence of EH in various populations. Although high sodium intake is an accepted risk factor for EH, the quantity and duration of excess diet sodium that provokes EH in susceptible individuals is not known. It is suggested that dysregulatory mechanisms are operative before EH is identified.

The purpose of this study was to investigate the interaction of stress and dietary sodium on BP regulation in adolescents who vary in genetic risk for EH. Our hypothesis was that salt loading will alter the cardiovascular response to mental stress in normotensive adolescents with a high genetic risk for EH, while adolescents with a low genetic risk will be resistant to its effects.

Methods

Subjects

Healthy female adolescents were recruited for the study. All participants were normotensive with casual seated systolic and diastolic BP below the 90th percentile. Subjects were divided into two groups on the basis of a family history (FH) of hypertension: 1) the FH positive group in which individuals had at least one parent and also other relatives with documented EH; and 2) the FH negative group in which there was no identified EH in siblings, parents, or parents' siblings, or in grandparents under age 60. No subject was included if the FH was either not clearly positive (one parent with EH) or negative. This report presents the data on the eight females who met the criteria for FH negative and seven females who met the criteria for FH positive. The two groups were matched for age, race, and height. The mean weight for the FH positive group was somewhat greater than that of the FH negative group because there were two obese females; the baseline BP and heart rate (HR) of these two individuals did not vary from the mean, however.
Protocol

The plan was to first determine the cardiovascular response to mental stress in each subject, then administer oral salt loading for 2 weeks, and repeat the testing of cardiovascular response to mental stress.

Before the initial testing, a timed overnight urine sample was collected for sodium, potassium, and creatinine determination. On the day of initial testing, a detailed set of instructions was given and informed consent obtained. Weight and casual seated BP were obtained. A small indwelling butterfly needle was placed into a peripheral vein. The subject then rested supine in a quiet room for 30 minutes, after which a 5 cc blood specimen was obtained for catecholamine determination. Monitoring was then begun utilizing an arteriosonde indirect BP monitor (Roche). Systolic pressure (SBP), diastolic pressure (DBP), and HR were recorded at 1-minute intervals. Baseline SBP, DBP, and HR were derived from the mean of five consecutive determinations. Mental stress was then applied using methods previously described. Subjects were quickly engaged in performance of mental arithmetic consisting of difficult subtraction problems for a period of 10 minutes, after which the subject was told that she had performed well. The investigator administering the stress test had no knowledge of the BP or HR measurements obtained. Monitoring was continued during an additional 5 minutes designated as the recovery period. After recovery, a second 5 cc blood specimen was obtained through the indwelling needle for catecholamine determination.

Each subject then consumed 10 1-g NaCl tablets per day for the next 14 days. They were instructed to maintain their usual diet patterns and were encouraged to drink more fluids. Overnight urine collections for sodium, potassium, and creatinine determination were obtained on the 7th and 14th day of salt loading. Any subject whose urine sodium did not reflect the augmented sodium intake or in whom non-compliance was suspected was dropped from the study. On the last day of salt loading the mental stress test was repeated. All BP values presented in this report were obtained by the Arteriosonde in the supine position. Plasma catecholamines were determined by radioenzymatic assay according to the method of Passon and Peuler.11

Results

The baseline data on the two study groups are presented in table 1. Also presented are the urine sodium excretions and urine sodium:potassium ratios before and after salt loading. These values reflect the augmented urine sodium excretion in the two groups during the salt loading. The mean SBP, DBP, and HR in response to mental stress in the FH positive and FH negative groups before and after salt loading are presented in figure 1. Differences between groups were tested for significance with a two-tailed Student's t test. A paired t test was used to test for significance of the effect of salt loading in each group. Before salt loading the FH positive group had a higher baseline SBP than the FH negative group (105 vs 91 mm Hg, p < 0.05). However, the absolute increase with stress was similar in the two groups. Following the salt loading, no change was apparent in the FH negative group in the baseline SBP response to stress or recovery SBP. After salt loading, the FH positive group had a significantly higher SBP compared to FH negative at baseline (p < 0.05), stress (p < 0.05), and recovery (p < 0.02).

The DBP response for the two groups is also presented in figure 1. No significant difference in DBP response to stress was present between the two groups prior to salt loading although the FH positive group had higher mean values. Following the salt loading, in the FH negative group the DBP at baseline, during stress, and recovery was essentially unchanged from the pre-salt values. Salt loading in the FH positive group produced an increase in DBP at baseline, stress, and recovery. Following the salt loading the difference between FH positive and FH negative become significant for both stress (p < 0.05) and recovery (p < 0.05) DBP.

The third panel of figure 1 shows that the HR response to stress before salt loading was consistently higher in the FH positive group but became significant only after stress (88 ± 4.1 vs 74 ± 2.0, p < 0.05). No change in HR was present in the FH negative group after salt loading. In the FH positive group the HR was lower after the salt loading, and although still greater than the FH negative group, no significant difference was present. The paired t test demonstrated a significant effect of salt loading in the FH positive group for SBP (p < 0.025), DBP (p < 0.01), and HR (p < 0.02). In the FH negative group no significant difference was found between values before and after salt loading.

Table 1. Baseline Data

<table>
<thead>
<tr>
<th>Data</th>
<th>Family history negative (mean ± SEM)</th>
<th>Family history positive (mean ± SEM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>15.8 ± 0.8</td>
<td>16.0 ± 0.9</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>56.4 ± 4.0</td>
<td>75.0 ± 7.8</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>164 ± 3.1</td>
<td>162 ± 1.5</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)*</td>
<td>91 ± 4.6</td>
<td>106 ± 3.8</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)*</td>
<td>61 ± 3.5</td>
<td>67 ± 3.3</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>73 ± 2.6</td>
<td>85 ± 5.7</td>
</tr>
<tr>
<td>Urine Na+(mEq/hr) preloading</td>
<td>2.1 ± 0.5</td>
<td>2.9 ± 0.6</td>
</tr>
<tr>
<td>Urine Na+(mEq/hr) postloading</td>
<td>5.3 ± 1.3</td>
<td>6.4 ± 1.3</td>
</tr>
<tr>
<td>Urine Na+/K+ preloading</td>
<td>4.1 ± 0.8</td>
<td>3.5 ± 0.4</td>
</tr>
<tr>
<td>Urine Na+/K+ postloading</td>
<td>8.4 ± 1.5</td>
<td>5.7 ± 1.4</td>
</tr>
</tbody>
</table>

*pBaseline blood pressures were obtained by arteriosonde in the supine position following 30 minutes' rest.
The mean SBP, DBP, and HR are presented in figure 2 for each subject during stress before and after salt loading. The FH negative subjects exhibited very little change in stress SBP or DBP after the salt loading while the FH positive subjects demonstrated a greater stress SBP and DBP after salt loading. In the FH negative group, individual HR responses to stress after salt loading varied, but the group mean stress HR was unchanged. The FH positive individuals showed a significant decrease in stress HR following the salt loading.

Comparison of the changes of mean showed significant differences between the FH positive and FH negative groups: stress SBP change (in mm Hg) was $-2.3 \pm 2.7$ vs $9.4 \pm 3.5$, $p < 0.02$, and stress DBP change was $-1.4 \pm 2.9$ vs $7.7 \pm 2.7$, $p < 0.01$. Stress HR change in beats per minute (bpm) was $-0.3 \pm 3.8$ vs $-13.0 \pm 0.5$, $p < 0.02$. Therefore, the salt loading significantly raised the SBP and DBP response to stress and lowered HR in the FH positive group. The possibility that the lower HR in the FH positive group reflected acclimatization to the stress seems unlikely in view of the higher BP. Also the HR did not decrease, suggesting that no acclimatization was present in the FH negative group.

The overnight urine collections in the FH negative group demonstrated an approximate twofold increase in sodium excretion during the salt loading, but little change in the levels of plasma catecholamine. In the FH positive group, plasma catecholamine levels decreased somewhat following salt loading, but not significantly.

**Discussion**

The data demonstrate that normotensive adolescents with at least one hypertensive parent responded to salt loading by manifesting a greater BP elevation and decreased HR response to mental stress than adolescents without a family history of EH. In fact, three FH positive subjects developed casual seated BP in a hypertensive range following the salt loading. Neither of the two obese subjects developed casual BP levels in the hypertensive range. Also, their stress response change was less than the normal weight subjects of the FH positive group. Thus, adiposity per se did not account for the observed differences. Plasma catecholamine levels did not reveal any significant difference between or within the groups before or after the salt loading. We previously reported that normotensive offspring of EH parents have a greater SBP, DBP, and HR response to mental stress. While the SBP, DBP, and HR of the FH positive group in this study was higher prior to salt loading, the...
difference in the response to stress was not significant. However, as previously reported⁸ the offspring of hypertensives consisted of some high responders and some low responders. Our findings were similar in the present study prior to salt loading. Therefore, the lack of significant differences in stress response prior to salt loading may be due to the limited number of subjects.

The link between genetics and sodium intake is quite firm in some experimental models.⁹ However, in humans the evidence to firmly establish this link has been more elusive. Evidence of genetic influences on renal excretion of sodium based on observations in twins has been reported by Grim et al.¹⁰ These investigators found that the influence of heredity on BP was most apparent during volume contraction, while the genetic effect on sodium excretion was most apparent during conditions of volume expansion. Thus, these findings suggest that renal regulation of sodium and potassium excretion is in part influenced by genetic factors.

Guyton et al.¹¹ have proposed that the kidney functions as the final common pathway for BP regulation by its control of salt and water excretion in both the hypertensive and normotensive state. Changes in renal blood flow have been reported in patients with mild hypertension¹² along with evidence of sympathetic nervous system involvement in the variability of renal blood flow.¹³ Recently, Hollenburg et al.¹⁴ have reported a decrease in renal plasma flow with a concordant rise in plasma renin activity in hypertensive patients under the stimulus of mental stress.¹⁴ Similar responses were also observed in normotensive offspring of hypertensives. Thus, there is evidence that the kidney’s regulation of sodium excretion is influenced to some degree by genetics or the central nervous system. However, some caution to this conclusion is necessary since hemodynamic studies during volume expansion in anephric patients and patients with end stage renal disease have demonstrated different patterns of hemodynamic response. For example, in some patients the BP increase was associated with an increase in cardiac output only with no subsequent increase in peripheral resistance. But in some other cases the BP rise was associated with an increase in peripheral resistance without an initial increase in cardiac output.¹⁵

Relative to this issue are the recent in vitro studies that have demonstrated differences in sodium movement across cell membranes. Garay and Meyer¹⁶ reported data showing that red blood cells of hypertensive patients extruded sodium at a slower rate than did the red cells of normotensive subjects. Canessa et al.¹⁷ found that the normal rate of lithium-sodium counter transport is increased in patients with essential hypertension, while there is no appreciable alteration in cell sodium. In both these studies investigators found similar in vitro changes in first degree relatives of the hypertensive patients. The relationship between these differences in sodium flux across cell membranes and the pathogenesis of EH is obscure. It is suggested that such differences in red cell sodium transport reflect abnormalities in sodium transport in other cells, including vascular smooth muscle cells which produce variations in vascular tone.

**Figure 2.** Effect of the salt loading on the stress response for each subject. During stress, the mean values of systolic pressure, diastolic pressure, and heart rate are presented before salt loading and connected to the stress value after salt loading, thus reflecting the direction of change. The group mean values are depicted by the wavy line in each column.
Others have investigated the interaction of neurogenic influences and vascular tone. Hemodynamic studies performed on patients with borderline hypertension by Safar et al. demonstrated that total peripheral resistance may be abnormal in borderline hypertension, but only during upright tilt and exercise. They concluded that two main disorders were important in the early stage of hypertension: an abnormality of blood volume and impaired neurogenic activity. The effect of sodium loading on patients with borderline hypertension were investigated by Mark et al. by measuring forearm blood flow and forearm vascular resistance during high and low sodium intake. During high sodium intake, forearm vascular resistance increased as it did in response to vasoconstrictor agonists (norepinephrine) and lower body negative pressure. Also, the magnitude of reflex tachycardia during lower body negative pressure was less during the sodium loading.

To some degree the findings in our FH positive subjects, some of whom may be prehypertensives, correspond to those of Mark et al. A possible explanation is that, in genetically susceptible individuals, salt loading may alter the vascular response to centrally mediated stimuli. It is also possible that these variations may be used in identifying a prehypertensive state.

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Effect of salt loading on the cardiovascular response to stress in adolescents.
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doi: 10.1161/01.HYP.3.6_Pt_2.II-195

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

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