Effect of Oral Calcium on Blood Pressure Response in Salt-Loaded Borderline Hypertensive Patients

Komei Saito, Hiroshi Sano, Yutaka Furuta, and Hisashi Fukuzaki

To clarify the mechanism of the antihypertensive effect of oral calcium loading, we studied the effect of low versus high calcium intake on salt-induced blood pressure elevations in patients with borderline hypertension. After a 7-day period of dietary salt restriction (50 meq/day), 27 patients were placed on a high salt (300 meq/day), low calcium (250 mg/day) diet for 7 days; 14 of these patients were given 2,160 mg/day of supplementary calcium (Ca group), and 13 patients were given placebo (non-Ca group). With a high salt intake, the percent increase in mean blood pressure was smaller in the Ca group than in the non-Ca group (+2.85±1.22% vs. +8.63±1.66%, respectively, p<0.01). The Ca group showed a smaller weight gain (p<0.05) and a greater urinary excretion of sodium (/»<0.005) than the non-Ca group. In the Ca group, but not in the non-Ca group, high salt intake resulted in an increase in intraerythrocyte magnesium content (p<0.01), which was correlated inversely with the salt-induced changes in mean blood pressure (r=-0.54, p<0.05). While the increase in cellular magnesium was greater in the Ca group, the changes in red blood cell sodium and sodium/potassium ratio were not different between the two groups. The results suggest that oral calcium supplementation may prevent a rise in blood pressure in patients on a high salt, low calcium diet by attenuating the sodium retention. The intracellular magnesium level may, in part, be involved in the regulation of salt-induced blood pressure response, although the pathophysiological mechanism remained unexplored. (Hypertension 1989; 13:219-226)

Abnormalities of calcium homeostasis have recently been considered to be important in the pathogenesis of essential hypertension. Clinical studies indicate enhanced urinary calcium leak1 and lower levels of serum ionized calcium, especially in those with low plasma renin activity.2,3 Epidemiological studies have also suggested an inverse relation between the level of calcium intake and the incidence of hypertension.4 All of these reports suggest an important role for calcium deficiency in genetic hypertension, and intervention studies have indicated that oral calcium supplementation is associated with a lowering of blood pressure in young normotensive adults,5 normal pregnant women,6 and patients with mild to moderate hypertension,7-9 although the mechanism of the hypotensive effect of oral calcium remains unclear.

It has been well established that excess salt intake, in contrast to calcium, increases blood pressure in a subset of patients with essential hypertension and that abnormal renal handling of sodium with the resultant relative sodium retention may be involved in its mechanism.10 Recent reports have also demonstrated that the reduction of cell membrane sodium-potassium adenosine triphosphatase (Na,K-ATPase) activity with the resultant increase in intracellular sodium may be responsible for the salt-induced increase in blood pressure in essential hypertension.11,12 Although it has been suggested such abnormalities in renal and cell membrane sodium handling are associated with sodium susceptibility in human hypertension, it has not been fully elucidated whether calcium supplementation can affect extracellular and intracellular sodium metabolism and salt-induced blood pressure elevations. Therefore, the present study was designed to evaluate how calcium supplementation can moderate the rise in blood pressure with high salt, but low calcium, intake. The present study also attempted to clarify whether a change in sodium metabolism is involved in the mechanism of the antihypertensive effect of oral calcium administration in patients with borderline hypertension.
Patients and Methods

Twenty-seven patients with borderline hypertension, 21 men and six women, ages 39 to 67 years, were studied in the Department of Internal Medicine, Hidaka Hospital. For at least 2 weeks before the study, antihypertensive medications were withheld. Patients were considered to have borderline hypertension according to the World Health Organization criteria (1962) if, during three subsequent visits to the outpatient clinic, their blood pressure at times exceeded but at other times was lower than 160/95 mm Hg. All subjects were admitted, and blood pressures on admission were determined after the subjects had sat quietly for 5 minutes; the fifth phase Korotkoff sound was used for diastolic blood pressure. None of the patients had abnormal renal function or secondary causes of hypertension, which were ruled out by the usual screening examinations, including history, physical examination, urinalysis, blood chemistry, and when appropriate, radiologic examination.

Protocol

The diets were designed by a dietician to provide approximately 70 g/day protein, 40 g/day fat, and 260 g/day carbohydrates throughout the study period. The patients were studied for 1 week with their usual diet containing 150 meq/day sodium, then for 1 week with low salt diet (50 meq/day sodium), and finally for 1 week with high salt diet (300 meq/day sodium). The sodium intake during the three experimental periods was changed by dietary means; the normal and high salt diets were achieved by adding 100 meq and 250 meq of sodium chloride, respectively, to the low salt diet. Except for sodium intake, the composition of the dietary electrolytes remained constant, containing 60 meq potassium, 250 mg calcium, and 800 mg phosphate. The level of calcium intake selected was purposely low to make a definite comparison between the effect of low calcium intake and that of sufficient calcium supplementation on blood pressure. The calcium restriction was achieved by eliminating food rich in calcium from the diet and by not using milk for cooking or drinking.

During the high sodium period, the subjects were randomly assigned to two treatment groups, and the treatment assignment was made in a double-blind fashion. The calcium-supplemented patients (Ca group; n=14) received two tablets of 1.0 g calcium gluconate (Calcium-Sandoz, Tokyo, Japan) three times per day. Each tablet contained 360 mg of elemental calcium and, therefore, the patients were prescribed 2,160 mg/day of calcium as a supplement to the low calcium, high salt diet. The placebo-treated patients (non-Ca group; n=13) received the same amount of placebo tablets. Before administration, the tablets were dissolved in 100 ml of water, and the placebo solution was identical in appearance to the calcium solution so that the patients and the medical staff were unaware of the type of medication administered.

Blood pressure and pulse rate were recorded early in the morning on the seventh day of each period by an automatic sphygmomanometer (Nippon Colin, Inc., Aichi, Japan) every 5 minutes while the patients were supine for 30 minutes. After that, blood samples were taken for determinations of serum concentration of electrolytes (sodium, potassium, calcium, phosphate, and magnesium), plasma ionized calcium, plasma renin activity, and aldosterone concentration, together with measurements of intracellular sodium, potassium, and magnesium. Serum electrolytes were measured by the AutoAnalyzer (System E4A, Beckman Instr., Inc., La Brea, California) technique and ionized calcium levels were measured with use of a specific calcium ion electrode (Orion SS 20, Orion Res. Inc., Boston, Massachusetts). Plasma renin activity and aldosterone concentration were measured by radioimmunoassay. Throughout the study periods, body weight and daily excretion of sodium, potassium, calcium, and phosphate were determined every morning.

Red Blood Cell Sodium, Potassium, and Magnesium Contents

Intraerythrocyte sodium and potassium contents were determined by the method of Kaya et al13 with little modification. An aliquot of venous blood (50 μl) was injected into a microhematocrit capillary tube (75 mm length) and centrifuged at 11,000 rpm for 5 minutes at room temperature. After the determination of hematocrit, the tube was cut at the boundary between packed cell and plasma. The packed erythrocytes were then diluted in 1 ml of "diluted lithium solution," and sodium and potassium concentration of the hemolysate was determined by flame photometry (FLM 3, Radiometer Copenhagen, Inc., Copenhagen, Denmark). Further dilution of the hemolysate was performed (200×) for the measurement of red blood cell magnesium content, which was determined by polarized atomic absorption spectrometry (Zeeman Z-7000, Hitachi, Ltd., Tokyo, Japan). Trapped intracellular plasma was 3%, as determined by 113I radioactive human serum albumin, and a correction was made for this value in calculating intraerythrocyte cation contents. All the measurements were performed in duplicate and the accuracy of this technique was confirmed by the preliminary study through repeated determinations.12,14 The interassay reproducibility, as determined by the coefficient of variation, was 4.6%, 2.7%, and 13.0% for the red blood cell sodium, potassium, and magnesium, respectively. Plasma ionized calcium was measured with an ionized calcium analyzer (model SS-20, Orion Res. Inc.).

Statistical Analysis

The values were expressed as the mean±SEM. The analysis of the data was performed by Student’s paired t or unpaired t test as appropriate.
when the data was normally distributed. Regression coefficients were calculated by using the method of least-squares regression. Difference was considered significant when \( p<0.05 \).

**Results**

There were no differences in age and sex between the Ca group and the non-Ca group. At the end of the normal sodium period, there were also no differences in blood pressure, pulse rate, body weight, serum concentration of electrolytes including ionized calcium level, plasma renin activity, and aldosterone concentration (Table 1).

Figure 1 shows the percent change in mean blood pressure level during the course of the low and high salt diets, which lasted 7 days each after the 7-day normal sodium period. Although body weight decreased from the last day of the low salt diet to the seventh day of the high salt diet was significantly smaller in the Ca group than in the non-Ca group (+2.94±1.25 kg vs. +8.08±1.56 kg, \( p<0.02 \), Table 1). The increase in body weight for the Ca group was statistically significant and was smaller than that for the non-Ca group (+2.80±0.20 kg vs. +1.50±0.30 kg, \( p<0.02 \)).

Pulse rate did not show any change throughout the study periods. Although body weight decreased on the low salt diet in both groups, it increased in the Ca group (+4.5±1.6 mm Hg, \( p<0.05 \)) but remained unchanged in the non-Ca group (+2.4±1.1 mm Hg, NS, respectively) when the diet was changed from low to high salt. The mean blood pressure increase from the last day of the low salt diet to the seventh day of the high salt diet was significantly smaller in the Ca group than in the non-Ca group (+14.8±3.1 mm Hg, \( p<0.001 \) and +4.5±1.6 mm Hg, \( p<0.05 \), respectively), but were not increased in the Ca group (+4.4±2.2 mm Hg and +2.2±1.1 mm Hg, NS, respectively) when the diet was changed from low to high salt. The mean blood pressure increase was smaller for the non-Ca group (+2.46±3.17%, not significant). When compared with the last day of the low salt diet, the percent increase in mean blood pressure was smaller in the Ca group than in the non-Ca group (+2.85±1.22% vs. +8.63±1.66%, \( p<0.01 \)).

The average systolic and diastolic blood pressure values were increased in the non-Ca group (+14.8±3.1 mm Hg, \( p<0.001 \)) and +4.5±1.6 mm Hg, \( p<0.05 \), respectively), but were not increased in the Ca group (+4.4±2.2 mm Hg and +2.2±1.1 mm Hg, NS, respectively) when the diet was changed from low to high salt. Mean blood pressure increased from the last day of the low salt diet to the seventh day of the high salt diet was significantly smaller in the Ca group than in the non-Ca group (+2.94±1.25 mm Hg vs. +8.08±1.56 mm Hg, \( p<0.02 \), Table 1). Pulse rate did not show any change throughout the study periods. Although body weight decreased on the low salt diet in both groups, it increased in the non-Ca group \( (p<0.05) \) on the high salt diet (Table 1). The increase in body weight for the Ca group was not statistically significant and was smaller than that for the non-Ca group \( (+0.80±0.20 kg vs. +1.50±0.30 kg, p<0.05) \).

When the diet was changed from low to high salt, serum sodium was increased and potassium decreased in both groups. Serum calcium and magnesium levels were decreased in the non-Ca group \( (p<0.05) \) after the high salt regimen but remained unchanged in the Ca group. Serum phosphate and plasma ionized calcium levels did not show any significant changes throughout the three dietary periods. Plasma renin activity increased \( (p<0.05) \) on the low salt diet and decreased \( (p<0.001) \) on the high salt diet in both groups, and aldosterone con-

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**TABLE 1. Clinical and Laboratory Findings During Three Experimental Periods**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Calcium-supplemented group</th>
<th>Placebo group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal sodium</td>
<td>Low sodium</td>
</tr>
<tr>
<td>Age (years)</td>
<td>...</td>
<td>49.7±2.1</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>...</td>
<td>11/3</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>130.0±5.0</td>
<td>126.6±5.0</td>
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<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>80.2±3.8</td>
<td>79.8±3.7</td>
</tr>
<tr>
<td>Mean blood pressure (mm Hg)</td>
<td>97.0±4.0</td>
<td>96.0±3.9</td>
</tr>
<tr>
<td>Difference (mm Hg)</td>
<td>-0.92±2.90</td>
<td>+2.94±1.25</td>
</tr>
<tr>
<td>Pulse rate (beats/min)</td>
<td>58.6±1.5</td>
<td>57.9±1.3</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>58.8±1.6</td>
<td>58.2±1.5§</td>
</tr>
<tr>
<td>Difference (%)</td>
<td>-0.92±0.39</td>
<td>+0.80±0.20</td>
</tr>
<tr>
<td>Serum Sodium (meq/l)</td>
<td>139.5±0.5</td>
<td>138.0±0.4</td>
</tr>
<tr>
<td>Potassium (meq/l)</td>
<td>4.3±0.1</td>
<td>4.3±0.1</td>
</tr>
<tr>
<td>Calcium (mg/dl)</td>
<td>8.5±0.1</td>
<td>8.6±0.1</td>
</tr>
<tr>
<td>Phosphate (mg/dl)</td>
<td>3.3±0.1</td>
<td>3.3±0.1</td>
</tr>
<tr>
<td>Magnesium (mg/dl)</td>
<td>2.1±0.1</td>
<td>2.2±0.1</td>
</tr>
<tr>
<td>Ionized calcium (meq/l)</td>
<td>2.19±0.05</td>
<td>2.07±0.10</td>
</tr>
<tr>
<td>Difference (meq/l)</td>
<td>-0.12±0.14</td>
<td>+0.04±0.10</td>
</tr>
<tr>
<td>Plasma renin activity (ng/ml/hr)</td>
<td>1.4±0.2</td>
<td>2.8±0.4‡</td>
</tr>
<tr>
<td>Plasma aldosterone (pg/ml) 90.7±7.6</td>
<td>92.6±7.0</td>
<td>66.3±4.8*</td>
</tr>
</tbody>
</table>

\*\( p<0.001 \), †\( p<0.05 \) versus values in low sodium regimen; ‡\( p<0.05 \) versus values in normal sodium regimen; §\( p<0.02 \), ||\( p<0.05 \) versus values in calcium-supplemented group.
Normal Sodium
Low Sodium
High Sodium

FIGURE 1. Line graph showing percent change in mean blood pressure (MBP) during low and high sodium periods for 14 calcium-supplemented (Ca group) patients (●) and 13 placebo (non-Ca group) patients (○). Oral calcium supplementation (2,160 mg/day) was given to the 14 patients of the Ca group during the high sodium diet, but not to the 13 patients of the non-Ca group. N.S., not significant.

The hypotensive effect of oral calcium supplementation in patients with essential hypertension has been debated and the mechanism has remained unclear. In a randomized, double-blind, placebo-controlled, crossover trial, McCarron and Morris \(^7\) and Strazzullo et al \(^8\) observed a fall in blood pressure after 8 and 15 weeks, respectively, of oral calcium supplementation, 1 g/day, in hypertensive outpatients. However, other studies \(^15\)\(^16\) of similar design failed to reproduce these results. We suppose that one of the reasons for the discrepancy is that the subjects were studied in the outpatient clinic and their dietary sodium intake was ad libitum. A recent experimental study \(^17\) suggested that the antihypertensive action of dietary calcium loading may be specific for or potentiated by the salt-loaded state in spontaneously hypertensive rats. Resnick et al \(^18\) have reported that high calcium, but not low calcium, diets lowered blood pressure in salt-loaded deoxycorticosterone acetate hypertensive rat model, whereas calcium loading elevated blood pressure in the renin-dependent two-kidney, one clip Goldblatt hypertensive rat model. Studies in patients with essential hypertension have also demonstrated a link between dietary salt intake and calcium, and it has been suggested that the hypotensive efficacy of oral calcium is enhanced in the salt-loaded \(^19\)\(^20\) and low-renin state. \(^21\) In the present study, to evaluate the precise effect of oral calcium on salt-induced blood pressure change and on sodium metabolism, we studied hospitalized patients who had a constant dietary electrolyte intake that

Red Blood Cell Sodium, Potassium, and Magnesium Concentrations

Intraerythrocyte sodium was decreased with salt restriction, and its increase during the high sodium regimen was statistically significant in the placebo-treated patients, but not in the calcium-supplemented ones. The degree of change in the intracellular sodium/potassium ratio was, however, not significantly different between the Ca group and the non-Ca group. As for the intraerythrocyte magnesium, the Ca group showed a significant decrease \((p<0.05)\) on the low salt diet and an increase \((p<0.005)\) on the high salt diet, whereas the non-Ca group showed no significant increase during high salt intake. The increase in red blood cell magnesium for the Ca group was significantly greater than that for the non-Ca group.

Figure 4 shows the relation between the change in mean blood pressure and the change in red blood cell cation contents for the calcium-supplemented patients when the diet was changed from low to high salt. The change in mean blood pressure for the Ca group correlated positively with the change in the red blood cell sodium/potassium ratio \((r=0.62, p<0.02)\) and negatively with the increase in cell magnesium contents \((r=-0.54, p<0.05)\). Such relations were not observed in the non-Ca group. A significant relation was also observed between the change in the red blood cell sodium/potassium ratio and the increase in magnesium contents \((r=-0.68, p<0.01)\).

Discussion

The hypotensive effect of oral calcium supplementation in patients with essential hypertension has been debated and the mechanism has remained unclear. In a randomized, double-blind, placebo-controlled, crossover trial, McCarron and Morris \(^7\) and Strazzullo et al \(^8\) observed a fall in blood pressure after 8 and 15 weeks, respectively, of oral calcium supplementation, 1 g/day, in hypertensive outpatients. However, other studies \(^15\)\(^16\) of similar design failed to reproduce these results. We suppose that one of the reasons for the discrepancy is that the subjects were studied in the outpatient clinic and their dietary sodium intake was ad libitum. A recent experimental study \(^17\) suggested that the antihypertensive action of dietary calcium loading may be specific for or potentiated by the salt-loaded state in spontaneously hypertensive rats. Resnick et al \(^18\) have reported that high calcium, but not low calcium, diets lowered blood pressure in salt-loaded deoxycorticosterone acetate hypertensive rat model, whereas calcium loading elevated blood pressure in the renin-dependent two-kidney, one clip Goldblatt hypertensive rat model. Studies in patients with essential hypertension have also demonstrated a link between dietary salt intake and calcium, and it has been suggested that the hypotensive efficacy of oral calcium is enhanced in the salt-loaded \(^19\)\(^20\) and low-renin state. \(^21\) In the present study, to evaluate the precise effect of oral calcium on salt-induced blood pressure change and on sodium metabolism, we studied hospitalized patients who had a constant dietary electrolyte intake that

Ca Supplement
included either low (50 meq/day) or high (300 meq/day) sodium for 1 week each. Moreover, the level of calcium intake selected in the present study was purposely low to differentiate the effect of calcium supplementation from that of low calcium intake on blood pressure.

The present results indicate that only 7 days of calcium supplementation while the patient is on the high salt, low calcium diet can attenuate both systolic and diastolic blood pressure increases. Under the circumstances of excess salt intake, as we12 and others10,22 have previously reported, approximately half of the patients showed a definite increase in mean blood pressure within a week; in the present study six of 13 patients without calcium supplementation showed more than a 10% increase in mean blood pressure. In contrast, in our calcium-supplemented patients, only two of 14 patients showed a definite mean blood pressure increase, as well as an increase in systolic and diastolic pressure. The difference in this salt-induced blood pressure response may not be caused by the different proportion of salt-sensitive to salt-resistant patients in each group. The effect of salt restriction on blood pressure was equable for the two groups. The differences in basal clinical characteristics that can affect sodium sensitivity, which include age, sex, blood pressure level before salt loading, renal function, and plasma renin activity on normal and low sodium intake, were not different between the two groups. Thus, the observed prevention of thepressor action of sodium is considered to be due to the calcium supplementation.

The present balanced study showed that, during the high salt regimen, our placebo-treated patients excreted less sodium (up to 200 meq/day while...
ingesting 300 meq/day) from the fourth to the seventh
day. They also had a smaller increase in the urinary
sodium/potassium ratio and gained more weight on
the last day than did calcium-supplemented patients.
The greater increase in blood pressure with sodium
loading observed in our placebo-treated patients
may be attributed to greater sodium retention with a
resultant increase in body weight. It is possible that
extremely low calcium intake (250 mg/day) and a
calcium deficient state may be responsible for the
impaired natriuresis in the non-Ca group. Urinary
sodium excretion may increase with increasing cal-
cium excretion, since calcium and sodium excretion
are related to each other for common transport
pathways for reabsorption in the proximal tube and
the Loop of Henle.23 Stern et al24 have observed an
increase in urinary sodium during oral calcium
supplementation in salt-loaded spontaneously hyper-
tensive rats. Clinical studies have also indicated an
enhanced sodium excretion during isotonic saline
infusion25 and an increased cumulative urinary
sodium loss during oral calcium supplementation
for 5 days.26 A chronic increase in urinary sodium20
has also been demonstrated when calcium was added
to either low or high salt diets. However, it is
still controversial whether modifications of calcium
intake are followed by changes in sodium excretion
in the same direction. Lau et al27 reported that the
antihypertensive effects of a high calcium diet in
spontaneously hypertensive rats are mediated by
PO4 deficiency, but not by volume contraction. Oth-
ers28,29 have also indicated that calcium supple-
mentation failed to influence sodium or potassium
excretion in both normotensive and hypertensive
subjects. These discrepancies might be caused by the
difference in the level of sodium intake adopted
in the different studies. At least, it is possible that,
with the high salt intake, sufficient calcium intake
may be needed simultaneously to excrete the loaded
sodium and achieve an adequate sodium balance.
Our calcium-supplemented group appeared to be in
balance by the fourth day of high sodium intake.
The prevention of the marked sodium retention,
and hence a smaller weight gain may, at least in
part, contribute to the attenuation of blood pressure
rise with salt loading.

As for extracellular electrolyte changes, a signif-
ificant decrease in calcium and magnesium concen-
tration during high salt intake was observed in the

\[
\begin{array}{l|c|c|c|c|c|c|c}
 & \text{Calcium-supplemented group} & & & \text{Placebo group} & \\
 & \text{Normal} & \text{Low} & \text{High} & \text{Normal} & \text{Low} & \text{High} \\
\hline
\text{RBC sodium (meq/l cell)} & 10.36±0.27 & 9.95±0.27* & 10.41±0.36† & 10.43±0.38 & 9.91±0.36* & 10.31±0.36† \\
\text{Difference} & -0.40±0.19 & +0.47±0.21 & & -0.52±0.24 & +0.40±0.10 \\
\hline
\text{RBC potassium (meq/l cells)} & 100.3±1.5 & 98.2±1.6 & 99.03±1.0 & 98.5±1.2 & 98.7±1.5 & 98.1±1.5 \\
\text{Difference} & -0.89±1.07 & +0.87±1.42 & & +0.15±0.91 & -0.65±0.95 & \\
\hline
\text{Sodium/potassium ratio (×10^{-1})} & 1.051±0.034 & 1.018±0.038* & 1.053±0.038 & 1.058±0.036 & 1.005±0.035* & 1.052±0.036* \\
\text{Difference} & -0.019±0.019 & +0.035±0.018 & & -0.052±0.019 & +0.047±0.016 & \\
\hline
\text{RBC magnesium (mg/dl cells)} & 6.20±0.40 & 5.28±0.33* & 6.65±0.47† & 6.24±0.75 & 5.62±0.63 & 5.89±0.73 \\
\text{Difference} & -0.92±0.37 & +1.37±0.40† & & -0.62±0.71 & +0.22±0.33 & \\
\end{array}
\]

*p<0.05 versus values in normal sodium regimen; †p<0.05, ‡p<0.005 versus values in low sodium regimen; §p<0.05 versus values in placebo group. RBC, red blood cell.
non-Ca group and a decrease in serum potassium in both groups. Although the reductions in serum calcium and magnesium in the non-Ca group were statistically significant, the values for the two groups while on the high salt diet do not appear different so that such minimal changes may not be biologically meaningful. Certain changes in intraerythrocyte electrolytes were also observed in the present study. There were significant increases in red blood cell sodium content in both groups and in the sodium/potassium ratio in the placebo-treated patients. Recent reports suggest that suppression in membrane-active transport for sodium with the resultant increase in intracellular sodium and sodium/potassium ratio may be involved in the mechanism of the volume-expanded form of human hypertension and may be related to salt sensitivity. While the increase in the cellular sodium/potassium ratio in the non-Ca group was statistically significant, this may be due simply to the slightly lower value at low sodium intake in this group. The degree of accumulation of cellular sodium as well as that of the sodium/potassium ratio during a high salt regimen was not different between the two groups. Thus, it may be difficult to conclude that the hypotensive action of oral calcium was mediated to the attenuation of salt-induced intracellular sodium retention.

In contrast to cellular sodium accumulation in our calcium-supplemented patients, a significant increase in intraerythrocyte magnesium content was observed during the high sodium period. The degree of intracellular magnesium accumulation was significantly greater in the Ca group than in the non-Ca group. Although the mechanism remains unclear at the moment, this is consistent with the finding of Resnick et al that a high calcium diet induces an elevation in the intracellular free magnesium level by more than 35% in salt-loaded hypertensive rats. They also reported that untreated patients had consistently lower levels of intraerythrocyte free magnesium than did normotensive subjects and that adequate antihypertensive therapy resulted in an increase in intracellular magnesium. We also have demonstrated that oral magnesium supplementation resulted in a further decline in blood pressure in hypertensive patients receiving long-term thiazide diuretics as well as in untreated patients. The hypotensive action of oral magnesium was associated with the increase in red blood cell magnesium, which was accompanied by an increase in membrane active sodium efflux with the resultant decrease in intracellular sodium content. In the present study, the only finding likely to explain a link between cellular magnesium and blood pressure was the relation between the increase in intraerythrocyte magnesium and the attenuation of either the salt-induced red blood cell sodium/potassium ratio elevation or blood pressure rise in the Ca group. However, the overall changes in the red blood cell sodium and sodium/potassium ratio were not different between the two groups, and cell membrane sodium transport was not determined. Thus, the observed relations in our calcium-supplemented patients merely suggest that cellular magnesium may, at least in part, be involved in the regulation of blood pressure response to salt loading only when the patients receive sufficient calcium intake. It was not determined whether the increase in cellular magnesium is responsible for the depressor action of oral calcium through an activation of Na,K-ATPase. The molecular mechanism and the pathophysiological role of intracellular magnesium in the regulation of salt-induced high blood pressure during low versus high calcium intake remain unexplored.

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References


25. Lasaridis AN, Sofos AB: Calcium diet supplementation increases urinary sodium excretion in essential hypertension. Nephron 1987;45:250


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