Disturbed Calcium Metabolism in Offspring of Hypertensive Parents

Hiroshi Yamakawa, Hiromichi Suzuki, Makoto Nakamura, Yoichi Ohno, and Takao Saruta

To assess a possible heritability of a disturbed calcium metabolism in relation to blood pressure regulation, 28 young normotensive offspring of either hypertensive or normotensive parents were studied while administered a defined diet with daily sodium chloride of 6 and 20 g/day for 7 days each. Before the high salt diet was begun, the cytosolic calcium concentration ([Ca\textsuperscript{2+}]) in platelets was elevated in offspring of hypertensive parents, whereas serum electrolytes, plasma renin activity, plasma catecholamines, and 24-hour urinary excretion of sodium and calcium showed no difference between the two groups. On exposure to a high salt diet, the mean blood pressure increased (from 80±2 to 85±2 mm Hg, p<0.05) in offspring of hypertensive parents. These changes in mean blood pressure were positively correlated with the basal platelet [Ca\textsuperscript{2+}], (r=0.61, p<0.01), whereas [Ca\textsuperscript{2+}] did not demonstrate any significant changes. When the subjects were administered the high salt diet, plasma ionized calcium decreased (from 2.75 to 2.21 meq/l, p<0.05) and 1,25-dihydroxyvitamin D3 increased (from 32.7 to 40.8 pg/ml, p<0.05) with a transient relative hypercalciuria in offspring of hypertensive parents. This increase of 1,25-dihydroxyvitamin D3 was significantly correlated with the changes in mean blood pressure (r=0.62, p<0.01). Disturbed intraplatelet and systemic calcium metabolism may be of predictive value in the development of hypertension. (Hypertension 1992;19:528–534)

KEY WORDS • calcium • vitamin D • parathyroid hormone • sodium-dependent hypertension • genetics

Disturbed calcium metabolism has become a focus in investigating the major contributing factors in the pathogenesis of essential hypertension. However, it still remains controversial as to what levels and what kinds of disturbance of the calcium metabolism are mainly involved. Several previous reports have suggested the presence of an increased cytosolic calcium concentration ([Ca\textsuperscript{2+}]) in platelets from hypertensive humans,\textsuperscript{1–5} which may reflect an increased [Ca\textsuperscript{2+}], in other cells, including vascular smooth muscle cells. Recently, calcium regulating factors, such as parathyroid hormone (PTH) and 1,25-dihydroxyvitamin D\textsubscript{3} [1,25-(OH)\textsubscript{2}D\textsubscript{3}], have been reported to be intimately involved in interactions with blood pressure (BP) regulation. Although PTH has been reported to influence the calcium current through the cell membrane in vitro,\textsuperscript{6,7} the effect of this hormone on BP in vivo has yet to be identified. 1,25-(OH)\textsubscript{2}D\textsubscript{3} is known to modulate the cardiovascular function, and administration of this hormone increases the contractile force-generating capacity of the resistance arteries.\textsuperscript{8} In addition to such alterations in calcium-regulating factors, an increased urinary calcium excretion has been observed in hypertensive patients.\textsuperscript{9–11} Further, calcium supplementation has been reported to reduce BP in essential hypertension\textsuperscript{12} and in experimental hypertensive animals.\textsuperscript{13} In addition to the above mentioned disturbances of the calcium metabolism in essential hypertension, some abnormalities have been suggested to reflect inherited characteristics since there is a strong familial component to essential hypertension. Thus, young normotensive persons with a family predisposition to hypertension have been of particular interest in investigations because they may provide an insight into the development of essential hypertension. In addition, the relation between salt and calcium metabolism in the progression of hypertension has also been examined.\textsuperscript{14–18}

The purpose of the present study was to determine whether alterations of calcium metabolism might tend to appear in normotensive subjects with a strong genetic background of hypertension and further whether such abnormalities could potentially contribute to salt-induced changes of BP in the subjects. To this end, we compared the platelet [Ca\textsuperscript{2+}], plasma ionized calcium, total calcium, PTH, 1,25(OH)\textsubscript{2}D\textsubscript{3}, and urinary calcium excretion in normotensive subjects, with or without a family history (FH) of parental hypertension, in response to 7 days of high dietary salt intake.

**Methods**

**Subjects**

Twenty-eight healthy Japanese male adolescents, who had BP below 140/85 mm Hg at three visits performed over a 2-month period and who had not experienced previous episodes of high BP or revealed any clinical or laboratory findings of renal diseases, were studied. The subjects were divided into two groups based on FH of essential hypertension. The positive FH group included 14 subjects whose parents both suffered...
from essential hypertension with a BP in excess of 160/90 mm Hg; secondary forms of hypertension in the parents were excluded with the usual investigations. The negative FH group included 14 subjects whose parents and siblings had not experienced any previous episodes of BP in excess of 140/85 mm Hg or myocardial or cerebral ischemic disease. The FH was assessed by measuring the parents’ BP in an outpatient clinic and from information obtained by direct personal communication with the respective physicians. All subjects were volunteers, and written informed consent was obtained before undertaking the present investigations.

**Protocol**

Isocaloric diets were consumed in a metabolic ward with sequential daily salt intake of 6 g and 20 g for 7 days each. The intake of calcium (400 mg/day) and potassium (70 meq/day) were maintained constant during the entire study period. The subjects were placed on the low salt diet (6 g/day sodium chloride) for 1 week as an equilibration period and were placed on the high salt diet (20 g/day sodium chloride) for the next week with the addition of 14 g sodium chloride to the low salt diet. Throughout the high salt-intake period, body weight, BP, and 24-hour urinary excretions of sodium and calcium were determined. Every morning at 8 AM, after an equilibration period of 30 minutes in the supine position under quiet and ambient conditions, BP and heart rate were measured using an automatic BP recorder (Nippon Colin BP-246NP, Aichi, Japan) with an appropriate size cuff on the right arm. The BP and heart rate were determined every minute for 30 minutes, and the average of measurements for the last 20 minutes was retained for analysis.

**Measurements**

Blood sampling was performed after an overnight fast on the seventh day of each sodium diet period. A heparin locked indwelling cannula was inserted into the antecubital vein in the left arm, and venous blood samples were drawn while the subject was in the supine position. The serum sodium, potassium, total calcium, and phosphate were measured with an autoanalyzer (System E4A, Beckman Instruments, Inc., La Brea, Calif.). Samples for measurement of the plasma ionized calcium were collected anaerobically in 3-ml tubes and assayed using an ion-selective electrode (Nova 8, Nova Biochemical, Newton, Mass.). Samples for the plasma renin activity (PRA) were collected in iced tubes containing ethylenediaminetetraacetic acid (EDTA) and assayed by the radioimmunoassay method. The plasma epinephrine and norepinephrine were determined by high-performance liquid chromatography and the trihydroxynandole fluorometric method. The serum concentration of PTH was measured by a radioimmunoassay method (Nichols Institute Diagnostics, San Juan Capistrano, Calif.) that recognized the intact PTH(1–84), 1,25-(OH)₂D₃ was assayed by the radioreceptor method (Mitsubishi Yuka Bio-clinical Laboratories, Tokyo). The platelet [Ca²⁺] was estimated using fura-2 with methods similar to those described previously. Blood samples were collected from inflow tubing, transferred to syringes containing ⅓ their volume of acid-citrate-dextrose (0.8 g citric acid, 2.2 g sodium citrate, and 2.2 g dextrose in 100 ml water), and centrifuged at 140g for 15 minutes. The platelet-rich plasma was removed and layered onto a 2.5×10.0-cm Sepharose CL-2B (Pharmacia, Uppsala, Sweden) column that had been equilibrated with elution buffer containing (mM) N-(2-hydroxyethyl)piperazine-N’-2-ethanesulfonic acid (HEPES) (10) Sigma Chemical Co., St. Louis, Mo.), NaCl 145, KCl 5, Na₂HPO₄ 1, MgSO₄ 0.5, dextrose 6, with the pH 7.4 at 37°C. The filtrated platelet-rich plasma was incubated in 5 μM fura-2-acetoxymethyl ester (Molecular Probes, Inc., Eugene, Ore.) at 22°C for 45 minutes. The suspension was again gel-filtrated on the Sepharose CL-2B column to remove extracellular dye. After filtration, the platelets were adjusted to 1.5–2×10⁴/ml and were incubated at 37°C for 30 minutes after addition of CaCl₂ to a final concentration of 1 mM. The fluorescence was measured with a fluorescence spectrophotometer (F-2000, Hitachi, Tokyo) thermostat-controlled at 37°C. The platelet suspension placed in a quartz cuvette was excited alternately with 340 nm and 380 nm, and the fluorescent emission intensity was monitored at 510 nm. At the end of each experiment, the platelets were lysed with 50 μM digitonin to obtain the fluorescent signal at maximal calcium saturation of the dye. Then ethylene glycol bis[β-aminoethyl ether]-N, N’, N’’-tetraacetic acid (EGTA) (10 mM as final concentration, adjusted the pH to 8.4 with NaOH) was added to chelate the calcium. The fluorescent emission ratio for 340/380 nm excitation was calculated after subtraction of autofluorescence, and the [Ca²⁺] values were calculated as described by Grynkiewicz et al. Measurements were performed in duplicate and, to adjust autofluorescence, a blank sample of unloaded cells was processed in parallel with loaded samples through each step. The time elapsed between obtaining the blood samples from the subjects and the measurement of [Ca²⁺] was approximately 2 hours. The coefficient of variation between repeat measurements in the same subjects had a mean value of 3.6%.

**Statistical Methods**

The results are expressed as the mean±SEM. Analysis of variance with repeated measurements was followed by the Scheffe F test. Comparisons within groups were performed with the paired two-tailed Student’s t test. All statistical computations were carried out using the JMP program (SAS Institute Inc., Cary, N.C.) on a Macintosh Ici computer (Apple Computer Inc., Calif.). Statistical significance was defined as a value of p<0.05.

**Results**

The characteristics of the FH negative and positive groups are summarized in Table 1. Mean and range of ages in the two groups did not differ: 21±2 (range, 20–22) years for both groups. At the end of the 6-g/day salt diet, the BP, heart rate, and body weight did not differ significantly between the two groups. Table 2 lists the biochemical variables for both study groups. The only difference between the FH positive and negative groups was that the former had higher platelet [Ca²⁺] (116.7±2.3 versus 107.2±1.8, p<0.05). The plasma ionized calcium, PTH, and 1,25-(OH)₂D₃ were within the normal ranges and did not differ significantly between the two groups. The serum electrolytes, the PRA, and
plasma catecholamine levels were within the normal ranges and did not differ between the two groups.

Throughout the high salt diet period, neither the body weight nor heart rate showed any significant changes in the two groups. Both the systolic and diastolic BP underwent an increase in the FH positive group (from 113±3 to 120±2 mm Hg, p<0.05 and from 64±2 to 68±3 mm Hg, p<0.05, respectively) but not in the FH negative group (from 112±2 to 113±3 mm Hg and from 63±2 to 64±2 mm Hg, respectively) when the diet was changed from low to high salt. Figure 1 shows the mean BP, which was calculated as the diastolic BP increased significantly in the FH positive group (from 80±2 to 85±2 mm Hg, p<0.05) but remained unchanged in the FH negative group on the seventh day of high salt intake. Neither the FH positive nor the FH negative group revealed significant changes in platelet [Ca2+] with a high salt intake. However, subjects who showed an increase in mean BP had a significantly higher platelet [Ca2+], (Figure 2). A significant positive correlation was observed between the changes in urinary sodium and calcium excretion during a high salt intake in the two groups.

**Table 1. Characteristics of Study Groups**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>NaCl (6 g/day)</th>
<th></th>
<th>NaCl (20 g/day)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FH negative subjects (n=14)</td>
<td>FH positive subjects (n=14)</td>
<td></td>
<td>FH negative subjects (n=14)</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>66.2±2.1</td>
<td>67.6±2.3</td>
<td>66.0±2.3</td>
<td>67.7±2.5</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>112±2</td>
<td>113±3</td>
<td>113±3</td>
<td>120±2*</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>63±2</td>
<td>62±2</td>
<td>64±2</td>
<td>68±3*</td>
</tr>
<tr>
<td>Mean blood pressure (mm Hg)</td>
<td>79±2</td>
<td>80±2</td>
<td>81±1</td>
<td>85±2*</td>
</tr>
<tr>
<td>Heart rate (beats per minute)</td>
<td>66±3</td>
<td>65±2</td>
<td>67±2</td>
<td>67±2</td>
</tr>
</tbody>
</table>

Values are mean±SEM. FH, family history. *p<0.05 compared with FH negative.

**Table 2. Biochemical Variables in Study Groups**

<table>
<thead>
<tr>
<th>Variables</th>
<th>NaCl (6 g/day)</th>
<th></th>
<th>NaCl (20 g/day)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FH negative subjects (n=14)</td>
<td>FH positive subjects (n=14)</td>
<td></td>
<td>FH negative subjects (n=14)</td>
</tr>
<tr>
<td>Platelet [Ca2+] (nmol)</td>
<td>107.2±1.8</td>
<td>116.7±2.3*</td>
<td>106.3±2.2</td>
<td>117.8±2.4†</td>
</tr>
<tr>
<td>Plasma ionized calcium (meq/l)</td>
<td>2.38±0.05</td>
<td>2.37±0.05</td>
<td>2.37±0.05</td>
<td>2.31±0.06†</td>
</tr>
<tr>
<td>PTH(1–84) (pg/ml)</td>
<td>26.3±2.2</td>
<td>27.3±1.9</td>
<td>27.2±2.4</td>
<td>28.3±2.6</td>
</tr>
<tr>
<td>1,25-(OH)2D3 (pg/ml)</td>
<td>31.5±1.9</td>
<td>32.7±2.3</td>
<td>31.7±2.8</td>
<td>40.8±2.7§</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>48.3±2.1</td>
<td>47.8±2.8</td>
<td>48.8±1.5</td>
<td>48.6±2.0</td>
</tr>
<tr>
<td>Serum total calcium (mg/dl)</td>
<td>9.1±0.3</td>
<td>9.1±0.4</td>
<td>9.1±0.4</td>
<td>9.1±0.3</td>
</tr>
<tr>
<td>Serum phosphate (mg/dl)</td>
<td>3.3±0.3</td>
<td>3.2±0.3</td>
<td>3.4±0.1</td>
<td>3.3±0.3</td>
</tr>
<tr>
<td>Serum sodium (meq/l)</td>
<td>142.3±1.4</td>
<td>143.1±1.6</td>
<td>142.6±1.2</td>
<td>142.8±1.4</td>
</tr>
<tr>
<td>Serum potassium (meq/l)</td>
<td>4.2±0.2</td>
<td>4.1±0.1</td>
<td>4.0±0.4</td>
<td>4.0±0.3</td>
</tr>
<tr>
<td>Serum creatinine (mg/dl)</td>
<td>1.0±0.1</td>
<td>1.0±0.1</td>
<td>0.9±0.1</td>
<td>1.0±0.1</td>
</tr>
<tr>
<td>Plasma renin activity (ng/ml/hr)</td>
<td>2.5±0.3</td>
<td>2.4±0.2</td>
<td>1.6±0.3</td>
<td>1.5±0.2</td>
</tr>
<tr>
<td>Plasma epinephrine (pg/ml)</td>
<td>26.3±1.7</td>
<td>27.0±1.9</td>
<td>18.8±2.2</td>
<td>17.9±2.4</td>
</tr>
<tr>
<td>Plasma norepinephrine (pg/ml)</td>
<td>167.3±3.1</td>
<td>168.6±3.9</td>
<td>87.8±3.2</td>
<td>89.8±3.8</td>
</tr>
</tbody>
</table>

Values are mean±SEM. FH, family history; [Ca2+], cytosolic calcium concentration; PTH(1–84), intact parathyroid hormone; 1,25-(OH)2D3, 1,25-dihydroxyvitamin D3.

*p<0.05 compared with FH negative on 6 g NaCl intake.

†p<0.05 compared with FH negative on 20 g NaCl intake.

§p<0.05 compared with FH positive on 6 g NaCl intake.

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Before the high salt intake, the 24-hour urinary sodium excretion did not differ between the FH positive and negative groups (92±14 versus 90±12 meq, respectively) nor did 24-hour urinary calcium excretion (56±12 versus 55±14 mg, respectively). The urinary sodium excretion then increased in the same manner in both groups to reach levels in excess of 300 meq/day on the third day of high salt intake. In the FH negative group, the urinary calcium excretion roughly paralleled the increase in sodium excretion; however, the amount of calcium excretion was more increased in the FH positive group than in the FH negative group on the third (145±13 versus 122±11 mg, p<0.05), fourth (140±12 versus 121±14 mg, p<0.05), and fifth (134±14 versus 122±12 mg, p<0.05) days of high salt intake, whereas the levels of urinary sodium excretion were similar in both groups. Subsequently, the difference in calcium excretion ceased to be significant between the FH negative and positive groups on the sixth (124±10 mg versus 120±8 mg) and seventh (125±10 mg versus 122±11 mg) days of high salt intake.

Discussion

The present study attempted to elucidate the changes in BP in relation to calcium metabolism in normotensive young subjects in response to salt loading. In this study, the salt loading was associated with a relatively low calcium intake (400 mg/day), which was suggested to emphasize the effects of salt on BP regulation.\(^21\) The results obtained clearly demonstrated that short-term salt loading in normotensive young subjects with a strong FH of hypertension tended to induce a mild but significant elevation of BP. This BP elevation was significantly correlated with the basal value of the platelet \([Ca^{2+}]_{pl}\), which did not increase in response to the salt loading.

The numerous previous studies investigating salt sensitivity in humans have used widely varying methodologies and different criteria for salt sensitivity.\(^22\) In the present study, the magnitude of the elevation of the mean BP induced by salt loading was significantly correlated with the basal values of the platelet \([Ca^{2+}]_{pl}\). Intracellular ions and several ion transport systems, which are proposed to be related to salt sensitivity in patients with essential hypertension, have yielded conflicting data.\(^23\) –\(^25\) However, our findings suggest that the levels of \([Ca^{2+}]_{pl}\) play at least in part a role in the salt sensitivity in normotensive subjects. Further, in young
normotensive subjects with a positive FH, the basal values for the platelet \([\text{Ca}^{2+}]\) were significantly higher than those in subjects without a positive FH. In view of the relative similarity of calcium-dependent contractile processes shared by platelets and vascular smooth muscle cells, the platelet \([\text{Ca}^{2+}]\) might reflect the intracellular calcium levels of the vascular smooth muscle cells. Although, to date, minor information on calcium handling in vascular muscle cells is available, sensitivity to extracellular calcium seems to be increased at least in resistance arteries of the mesenteric bed in spontaneously hypertensive hypertensive rats. These findings, in addition to the observation that calcium channel blockers have a greater blood-pressure-lowering effect and vasodilator action in essential hypertension than in control subjects, have been interpreted to indicate that the cell membrane of vascular smooth muscle is more permeable to calcium ion in the hypertensive state. Resultant elevated \([\text{Ca}^{2+}]\), could increase the muscle contraction of the vascular bed, resulting in an enhanced vascular reactivity, BP elevation, or both. In hypertensive patients with salt sensitivity, a hyperreactivity or an enhanced vascular reactivity, or both, have been demonstrated using the forearm vascular resistance as a measure. Such observations would support the notion that an increased platelet \([\text{Ca}^{2+}]\), contributed to elevation of the BP in response to salt loading in the subjects examined in the present study.

Few reports have investigated the levels of \([\text{Ca}^{2+}]\) in young normotensive subjects with a FH of parental hypertension, although an elevation of the platelet \([\text{Ca}^{2+}]\) levels in essential hypertension has been widely established. The data obtained in the present study suggest that an elevation of the platelet \([\text{Ca}^{2+}]\) levels might precede the development of hypertension and be determined genetically, although a large number of subjects need to be examined before a concrete conclusion can be reached. Previous studies have indicated an inherited nature in salt-sensitive subjects who are prone to be hyperreactive to stress. In patients with essential hypertension, it has been demonstrated that salt loading can induce an increase in platelet \([\text{Ca}^{2+}]\). Despite the basic agreement with previous studies, several discrepancies do exist between their studies and ours. These are probably related to the fact that 1) we used normotensive subjects instead of hypertensive patients, 2) younger subjects were enrolled as compared with older people, and 3) all of our subjects were men; women were not included in the present study.

The calcium excretion in subjects with a positive FH was increased on the third, fourth, and fifth days of salt loading when the BP began to rise. The factors that increase the excretion of urinary calcium are suggested to include volume expansion, natriuresis, and BP elevation. Salt loading can induce volume expansion and give rise to an elevation of BP. This process may contribute to increases in calcium excretion. In subjects with a positive FH, the BP rose with the same amount of sodium excretion as observed in subjects without a negative FH. Based on the theory of pressure–natriuresis, natriuresis in subjects with a positive FH may be achieved by BP elevation in response to salt loading. It is possible, therefore, that such natriuresis accompanies calciresis. However, on the final day of salt loading when the BP attained the highest levels, there were no increases in calcium excretion as compared with the negative FH group. These data imply that more complex mechanisms other than volume expansion and pressure–natriuresis might facilitate calcium excretion. In addition to the factors controlling calcium excretion, calcium leak from the kidney has been proposed in patients with essential hypertension. Such calcium leak is further suggested to increase PTH. Indeed, previous investigations have demonstrated the elevation of PTH in essential hypertension. However, we failed to detect any significant changes in PTH levels. It is possible that the elevation of PTH may be transient or that repeated stimuli such as a long-term administration of salt loading can eventually induce an elevation of PTH. For example, in patients with chronic renal failure the serum levels of PTH are frequently within the normal ranges in spite of dynamic alterations of calcium and phosphate. Similar mechanisms may have contributed in our present study where the PTH levels of our subjects were normal. It is also possible that elevation of \(1,25-(\text{OH})_2\text{D}_3\) suppresses PTH synthesis in subjects with salt loading since several recent reports have shown the negative effect of \(1,25-(\text{OH})_2\text{D}_3\) on PTH synthesis.

The levels of plasma ionized calcium in the subjects with a positive FH were significantly lower after a high salt intake. Slight calcium leak, which was observed on the third, fourth, and fifth days, could have been responsible for a reduction of plasma ionized calcium levels. These findings support the previous report by McCarron that in patients with essential hypertension, plasma ionized calcium is decreased.

In connection with the elevation of \(1,25-(\text{OH})_2\text{D}_3\) in these subjects, similar observations, in which patients with low renin hypertension revealed significantly higher than average circulating levels of \(1,25-(\text{OH})_2\text{D}_3\), albeit appropriate for lower serum ionized calcium levels, have been reported previously. Compared with the relation between PTH and BP regulation, the role of \(1,25-(\text{OH})_2\text{D}_3\) in hypertension has been less well investigated. Bukoski et al. showed that in vivo treatment with \(1,25-(\text{OH})_2\text{D}_3\) for 72 hours increased the contractile force-generating capacity of the resistance arteries. The mechanism by which \(1,25-(\text{OH})_2\text{D}_3\) can exert its vasoactive effects remains to be determined, although an in vitro study has suggested that \(1,25-(\text{OH})_2\text{D}_3\) increases \([\text{Ca}^{2+}]\) in vascular smooth muscle cells. Further, in the present study, changes in the \(1,25-(\text{OH})_2\text{D}_3\) response to salt loading were significantly correlated with the changes in mean BP, and the ability...
of salt to elevate the BP may be correlated with its ability to stimulate the 1,25-(OH)2D3 levels. In the present study, the [Ca2+]i in the platelets failed to reveal any significant changes in spite of an increased BP on exposure to high salt intake. The significance of a lack of change of [Ca2+]i in the platelets remained uncertain because 7 days of high salt diet might not be long enough to allow a full turnover of newly released platelets into the circulation and reflect accurately changes of [Ca2+]i, in the platelets.

Our findings indicate that systemic (plasma ionized calcium, 1,25(OH)2D3, organ-specific (kidney), and cellular (platelet) calcium metabolism are disturbed in young normotensive men at risk of developing hypertension based on FH. These disturbances of calcium metabolism are predictive of a rise in BP with salt loading in these individuals at risk. Salt-sensitive individuals are characterized by higher basal [Ca2+]i in platelets and disturbed calcium metabolism with salt loading: a decrease in plasma ionized calcium and an increase in 1,25-(OH)2D3 accompanied a transient urinary calcium leak. Such findings indicate that these disturbances of calcium metabolism precede the development of hypertension and therefore may be of pathophysiological importance. The findings also lend additional support to the notion that both dietary and pharmacological interventions that impact on the regulation of cellular calcium transport may have specific pathophysiological indications in both the prevention and treatment of essential hypertension.

The constellation of findings that we observed would suggest that a strong genetic component to essential hypertension may be attributable to intracellular disturbances especially related to calcium metabolism. It is evident that additional work is required to pursue these promising findings as a means to further our understanding of the pathological basis of increased arterial pressure in a subset of humans.

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