Calcium, Magnesium, and Phosphorus Balance in Human and Experimental Hypertension

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SUMMARY The thesis that primary disturbances of divalent ion metabolism contribute to the development and maintenance of hypertension is addressed. Representative interactions of calcium, magnesium, and phosphorus with normal cardiovascular physiology are presented. Established and postulated abnormalities of divalent ion metabolism associated with human and experimental hypertension are reviewed. The influence of calcium balance on blood pressure development in the young spontaneously hypertensive rat is demonstrated by the results of a diet intervention study. Twelve male SHRs were randomized at 4 weeks of age to one of three diets that differed only in the calcium content (0.25%, 0.5%, and 4.0% by weight). The SHRs' blood pressures stratified inversely (p < 0.001) based upon the calcium content. The low calcium animals experienced a more rapid and greater rise in blood pressure between 4 and 20 weeks of age (p < 0.01). Blood pressures of the supplemented SHRs (4%) peaked at a lower value (174 vs 192 mm Hg, p < 0.01). After maturity, the 4% SHRs experienced an attenuation (p < 0.01) of their hypertension (154 ± 7 mm Hg, 4% SHR vs 176 ± 7 mm Hg, 0.5% SHR). It is proposed that membrane-associated bioavailable Ca^{2+} is reduced in the SHR, and possibly in human, hypertension. Dietary calcium supplementation may reverse this defect, resulting in cell membrane stabilization and vascular smooth muscle relaxation.


KEY WORDS • calcium and hypertension • magnesium and hypertension • phosphorus and hypertension • Ca^{2+} and the SHR • spontaneously hypertensive rat • urinary electrolytes and dietary Ca^{2+}

Divalent ions serve critical functions in cardiovascular tissue. This report focuses on three of those ionic species: calcium, magnesium, and phosphorus, and assesses the contributions of changes in their metabolic balance on the pathophysiology of hypertension. While each exerts direct actions on cardiovascular physiology, each also modifies one another's. In addition, the cardiovascular effects of sodium, potassium, and many vasoactive hormones may be influenced by the divalent ions. First, representative actions of these three ions on normal cardiovascular physiology will be reviewed and established, and then postulated abnormalities of divalent ion metabolism associated with hypertension will be assessed.

Calcium, Magnesium, and Potassium in Cardiovascular Physiology

Calcium (Ca^{2+}) is essential to neurohurmoral control, volume regulation, and vascular smooth muscle function. Calcium’s diverse effects on blood pressure control reflect the cation’s central role in both membrane and cytosolic associated events. In conjunction with membrane receptors and intracellular calmodulin, Ca^{2+} regulates cell-cell communication, neurotransmitter synthesis and release, and hormone receptor interactions that initiate cytosolic metabolism. In the central nervous system, Ca^{2+} is essential to the integration of the various components of blood pressure control. In the kidney, Ca^{2+} modifies water and solute excretion through its effects on filtration rate and reabsorptive processes.

Calcium is a critical element in normal vascular tissue physiology. The cation’s contribution to blood pressure regulation is most prominent in its influence on vascular resistance. Membrane receptor binding is dependent on Ca^{2+}. Ion fluxes, including those of sodium and potassium, are altered by their interaction with Ca^{2+}. Calmodulin and Ca^{2+} induce enzymatic pathways that range from phospholipase A to myosin...
light chain kinase which catalyzes the final steps in the activation of the contractile proteins, actin and myosin. Ultimately, the intracellular function of this protein-cation complex is self-regulating, facilitating vascular tissue relaxation under appropriate circumstances.

Like Ca$^{2+}$, magnesium (Mg$^{2+}$) is an essential element in normal cardiovascular physiology. The synthesis and secretion of neurotransmitters is influenced by the cation. Via its direct effects on cardiac conduction and contractility as well as its influencing water and solute excretion, Mg$^{2+}$ can alter both cardiac output and intravascular volume. Magnesium is required for normal vascular smooth muscle physiology. Membrane-associated actions of Mg$^{2+}$ include stabilization of Ca$^{2+}$ channels, activation of Ca$^{2+}$/Mg$^{2+}$ ATPase, and modulation of Na$^{+}$/K$^{+}$ ATPase activity. In the cytosol, the cation functions as a cofactor in the enzymatic generation of cAMP, and catalyzes the actin-myosin-Ca$^{2+}$ interaction, which ultimately determines basal and stimulated vascular tone. Within smooth muscle cell vesicles, Mg$^{2+}$ is important for ATP generation in mitochondria and sequestration of both Ca$^{2+}$ and K$^{+}$. In essence, Mg$^{2+}$ acts as a regulatory cofactor in the cascade of events that is initiated by cell stimulation and proceeds through ion fluxes, enzymatic induction, energy-dependent metabolic responses, and return of the cell to its basal state. Magnesium's cardiovascular effects parallel those of Ca$^{2+}$.

The role of phosphorus (PO$_4^{3-}$) in normal cardiovascular physiology is equally diverse and important as that of Ca$^{2+}$ and Mg$^{2+}$. In all cells and organs, PO$_4^{3-}$ is a prerequisite for normal plasma membrane synthesis and integrity. In addition, most energy requiring metabolic function of a cell is dependent upon PO$_4^{3-}$ through the formation and degradation of high energy bonds in ATP. As a consequence, membrane-associated ion pumps, as well as receptor-ion channel interactions, involve PO$_4^{3-}$. Furthermore, the synthesis, storage, and release of local and systemic hormones that regulate cardiac output and vascular resistance require phosphorus. In vascular tissue, PO$_4^{3-}$ is a vital cofactor in the processes outlined above for Ca$^{2+}$ and Mg$^{2+}$. Functionally, the primary roles of these three ionic species in vascular cell physiology is highly integrated.

**Disorders of Calcium, Magnesium, and Phosphorus Metabolism in Human and Experimental Hypertension**

Abnormalities of Ca$^{2+}$ homeostasis have been identified in both human and experimental hypertension. The human data include clinical and epidemiological observations. Low serum ionized calcium, elevated parathyroid hormone levels, and an increase in renal calcium excretion have been reported in hypertensive humans. Consistent with clinical associations between abnormalities of calcium and PTH homeostasis and human hypertension is the observation that overt hypercalcemia will develop in a subset of hypertensives taking thiazide diuretics. This thiazide-related hypercalcemia is facilitated by PTH.

The established relationship between hypertension and hyperparathyroidism appears to reflect the requisite stimulation of the parathyroid gland axis as a compensatory mechanism to protect calcium balance of hypertensives. This interpretation of recent data is to be contrasted with earlier reports that have concluded that hyperparathyroidism and its attendant hypercalcemia were the cause of hypertension, and, therefore, the primary abnormality linking hypercalcemia with the development of hypertension. Independent of the issue of essential hypertension, it is apparent that some hypercalcemia states may be associated with the emergence of high blood pressure via effects on renal and sympathetic nervous system function.

Comparable disturbances of Ca$^{2+}$ metabolism have recently been characterized in the Aoki-Okamoto, spontaneously hypertensive rat (SHR). For example, abnormalities in Ca$^{2+}$ metabolism has been suggested by the animal's blood pressure response to dietary calcium supplementation. Placing the SHR on a supplemented Ca$^{2+}$ diet will lower its blood pressure. Even though the diet is introduced at 10 to 12 weeks of age after the hypertension is established. The normotensive, Wistar-Kyoto rat's blood pressure is likewise responsive to changes in dietary Ca$^{2+}$, as it tracks inversely based upon the Ca$^{2+}$ content in the diet.

The first suggestion that the dietary intake of Ca$^{2+}$ may be an important factor in the development of hypertension came from the epidemiologic observations that cardiovascular mortality and regional blood pressures were inversely related to water hardness. More recently, a review of the incidence of gestational hypertension worldwide, as well as two preliminary reports from the United States, have suggested that hypertensive individuals' Ca$^{2+}$ intakes are significantly less than those of normotensives.

The accumulated experience with calcium balance and hypertension suggests that a modest reduction in Ca$^{2+}$ intake may exacerbate the abnormalities of Ca$^{2+}$ metabolism associated with hypertension. The relative Ca$^{2+}$ depletion that ensues may alter vascular smooth muscle function and enhance vascular tone. Maintenance of an adequate exposure to Ca$^{2+}$, conversely, may have protective effects on blood pressure regulation.

There is additional circumstantial evidence that relative calcium depletion may increase blood pressure in humans and animals. On a teleological basis, one would reason that, were relative Ca$^{2+}$ depletion to result in an increase in vascular resistance, then the hormone responsible for improving Ca$^{2+}$ balance, if endowed with any vascular effects, would cause vasodilation. Specific vasodilating properties of parathyroid hormone at both physiologic and pharmacologic
concentrations have been demonstrated in experimental models and humans. Magnesium homeostasis has not been characterized in either human or experimental hypertension. This is partly due to Mg being primarily an intracellular cation and, therefore, difficult to assess. Though differing in their total body content and compartmental distributions, Mg and Ca share many common determinants of metabolic balance. The abnormalities of Ca homeostasis described above may have their counterparts in Mg metabolism and hypertension.

Magnesium restriction in experimental animals accelerates cardiovascular disease. In vitro depletion of Mg enhances vascular reactivity to vasoconstrictors. Magnesium excess stabilizes vascular membranes and reduces vascular tone. Epidemiological evidence also suggests that increasing Mg exposure in the diet may afford humans protection against cardiovascular events.

Serum PO₄ is inversely correlated with blood pressure in normotensive individuals. Compared to age-, sex-, and racially-matched controls, serum PO₄ levels of hypertensives are lower. Severe phosphorus depletion is associated with hypotension. The levels of hypophosphatemia required, though, are extreme, producing multiple organ failure.

As noted above, supplementation of the adolescent SHR's diet with Ca, beginning at 10 to 12 weeks of age, lowers blood pressure after the animal reaches maturity. The effects of earlier introduction of dietary Ca supplementation on the development and maintenance of the SHR's hypertension is unknown. In addition, the influence of dietary Ca intake on the daily urinary excretion of other electrolytes is also incompletely defined in experimental hypertension. The following protocol sought to address these questions.

Methods

Twelve male Aoki-Okamoto SHRs were randomized to one of three diet regimens at 4 weeks of age. The synthetic diets differed only in their Ca carbonate content; 0.25%, 0.5%, and 4% Ca by weight of the food. The 0.25% represents a low-normal Ca diet; 0.5%, a normal Ca diet; and 4.0%, a supplemented Ca diet. Beginning at 7 weeks of age, and at 4- to 8-week intervals thereafter up to 39 weeks of age, systolic blood pressures, weights, serum ionized calcium, and 24-hour urinary electrolyte and creatinine excretion were measured. Serum creatinine was measured at only 33 weeks of age.

Urine collections were carried out 1 to 2 days before blood pressure determinations. Tail-cuff systolic blood pressures were recorded on a Narcobiosystem physiograph. Four readings were averaged for each rat. Blood samples (2 ml) were withdrawn the following day via subclavian venapuncture. Serum samples were obtained between 12 and 33 weeks of age. Serum and urine chemistries were determined by previously described techniques. Analysis of variance (repeated measures) and t statistics were used in the data assessment.

Results

Growth was similar for all three diet groups (fig. 1 A). Serum ionized Ca (fig. 1 B) was increased (p < 0.01) by 12 weeks of age compared to the normal diet animals, and then remained significantly (p < 0.001) elevated throughout the duration of the study. No adverse effects of the hypercalcemia were observed in these or previous protocols. Mean serum creatinine was 0.8 ± 0.1 mg%.

![Figure 1](https://example.com/figure1.png)

**Figure 1.** A. Body weight (g ± se). B. Serum ionized calcium (mEq/liter, ± se). C. Systolic blood pressure (mm Hg ± se) in the SHRs on one of three calcium diets, measured at 4- to 8-week intervals between 7 and 39 weeks of age. See text for statistical comparison.
Between 7 and 17 weeks of age, the rise in systolic blood pressure was similar on all three diets. From the 17th week onward, the systolic pressure (fig. 1 C) tracked inversely \((p < 0.001)\) with the \(\text{Ca}^{2+}\) content of the diet. The 4% animals’ hypertension was the lowest, while that of 0.25% SHRs was the highest. At 39 weeks of age, the 4% SHRs’ systolic pressure was 154 ± 7 mm Hg, the 0.5% SHRs’ was 176 ± 7 mm Hg, and the 0.25% SHRs’ was 181 ± 5 mm Hg.

Urinary electrolyte excretions per 24 hours are recorded in table 1. Urinary \(\text{Ca}^{2+}\) excretion increased and the 0.25% SHRs’ was 181 ± 5 mm Hg. Potassium excretion did not vary with the age of the animal. Urinary sodium excretion stratified according to the percentage of \(\text{Ca}^{2+}\) in the diet. Potassium excretion was increased on the 4% \(\text{Ca}^{2+}\) diet \((p < 0.001)\) with the \(\text{Ca}^{2+}\) content of the diet. Potassium excretion stratified inversely based upon the percent dietary \(\text{Ca}^{2+}\). \(\text{U}_{\text{Na}}\) did not change by the \(\text{Ca}^{2+}\) content of the diet. Predictably, \(\text{U}_{\text{Ca}}\) was less on the 0.25% \(\text{Ca}^{2+}\) diet than on either the 0.5% or 4% \(\text{Ca}^{2+}\) diets. As is apparent from table 1, the differences in \(\text{U}_{\text{Na}}\) on the three \(\text{Ca}^{2+}\) diets was evident between all three diets, such that \(\text{U}_{\text{Na}}\) was less on the 4% \(\text{Ca}^{2+}\) diet. Daily sodium excretion varied directly with \(\text{Ca}^{2+}\) content of the diet. Potassium excretion stratified inversely based upon the percent dietary \(\text{Ca}^{2+}\). \(\text{U}_{\text{Mg}}\) decreases as dietary \(\text{Ca}^{2+}\) content increases. The increased \(\text{U}_{\text{K}}\) may reflect either altered renal handling or, more simply, increased \(\text{K}^+\) consumption on the 4% \(\text{Ca}^{2+}\) diet. Daily sodium excretion varied directly with \(\text{Ca}^{2+}\) content of the diet. There was no variation in \(\text{U}_{\text{Na}}\) over time, however, thereby dissociating temporally the effect on \(\text{U}_{\text{Na}}\) from that on the blood pressure attenuation induced by the high \(\text{Ca}^{2+}\) diet. Since the animals were not pair-fed, a change in sodium balance cannot be excluded as a factor in the protective action of the \(\text{Ca}^{2+}\) supplementation diet. Several factors though would suggest changes in sodium balance were not responsible. Body weight was not different among

### Table 1. Urinary Electrolyte Excretion (Mean ± so) per 24 Hours of Spontaneously Hypertensive Rats Grouped by Percentage of Calcium in the Diet

<table>
<thead>
<tr>
<th>Rat group</th>
<th>Urinary electrolyte</th>
<th>Weeks of Age</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(\text{U}_{\text{Ca}})-mEq</td>
<td>7</td>
</tr>
<tr>
<td>SHR 0.25% calcium ((n = 4))</td>
<td>0.006 ± 0.002</td>
<td>0.03 ± 0.005</td>
</tr>
<tr>
<td>SHR 0.50% calcium ((n = 4))</td>
<td>12.00 ± 1.90</td>
<td>8.60 ± 1.60</td>
</tr>
<tr>
<td>SHR 4.0% calcium ((n = 4))</td>
<td>0.08 ± 0.04</td>
<td>0.25 ± 0.14</td>
</tr>
<tr>
<td></td>
<td>(\text{U}_{\text{Na}})-mEq</td>
<td>0.79 ± 0.26</td>
</tr>
<tr>
<td></td>
<td>(\text{U}_{\text{Mg}})-mEq</td>
<td>0.23 ± 0.10</td>
</tr>
</tbody>
</table>

**Discussion**

Modifying \(\text{Ca}^{2+}\) intake in experimental animals will alter their blood pressures. Previous reports in normotensive37, 38 and hypertension rats,19, 36 have demonstrated that supplementation of the diet with \(\text{Ca}^{2+}\) lowers the blood pressure of adult SHRs and Wistar-Kyoto rats. The protective effect occurs in conjunction with the development of mild hypercalcemia in the rat. The current investigation extends these previous observations. Introduction of \(\text{Ca}^{2+}\) supplementation at the time of weaning reduces the peak systolic pressure that develops as well as attenuating the mature animal’s hypertension. In addition, modest \(\text{Ca}^{2+}\) restriction accelerates the early phase of developing hypertension in the young SHR.

Urinary electrolyte excretion is modified by the \(\text{Ca}^{2+}\) content of the diet. Predictably, \(\text{U}_{\text{Ca}}\) rises and \(\text{U}_{\text{Na}}\) decreases as dietary \(\text{Ca}^{2+}\) content increases. The increased \(\text{U}_{\text{Na}}\) may reflect either altered renal handling or, more simply, increased \(\text{K}^+\) consumption on the 4% \(\text{Ca}^{2+}\) diet. Daily sodium excretion varied directly with \(\text{Ca}^{2+}\) content of the diet. There was no variation in \(\text{U}_{\text{Na}}\) over time, however, thereby dissociating temporally the effect on \(\text{U}_{\text{Na}}\) from that on the blood pressure attenuation induced by the high \(\text{Ca}^{2+}\) diet. Since the animals were not pair-fed, a change in sodium balance cannot be excluded as a factor in the protective action of the \(\text{Ca}^{2+}\) supplementation diet. Several factors though would suggest changes in sodium balance were not responsible. Body weight was not different among
the diet groups. Urinary sodium excretion was already increased at 7 to 12 weeks of age at a time when the 4% animals systolic pressures were similar to the other diet groups. Lastly, recent studies in the SHR fed 1% vs 4% Ca2+ have found no change in total body sodium content (Ritz E, University of Heidelberg, West Germany, personal communication, 1982) in the animals chronically fed the 4% diet. This latter observation, combined with our urinary excretion data, suggests that diet consumption increases as the Ca2+ content of the diet increases. The increased UNaV would then simply reflect diet intake and not enhanced excretion. Such an interpretation would be most consistent with the body weight, total body Na+, and blood pressure data. Additional studies are needed to clarify precisely the mechanism whereby UNaV stratifies with the percentage of Ca2+ in the diet.

The specific cellular mechanism(s) whereby increasing dietary calcium lowers blood pressure in experimental animals cannot be addressed by the current study. Drawing upon our observations and recent investigations of cellular Ca2+ metabolism in the SHR, however, a unifying theory can be advanced based upon modifying bioavailable Ca2+ to vascular cell membranes.

Numerous laboratories have reported cellular abnormalities of Ca2+ handling in the SHRs. Defects have been identified in RBC, 33, 44 intestinal epithelial cells, 32 adipocytes, 35 aortic, 54, 55 and vascular smooth muscle cells. 56-59 Mulvaney has recently demonstrated that these are intrinsic to the vascular tissue and not functional changes due to the increase in mean arterial pressure. 60 The cellular abnormalities described to date have included increased Ca2+ permeability of the plasma membrane, 36 reduced 45Ca2+ binding to isolated membranes following incubation, 34, 57 altered intracellular fluxes of Ca2+ between the cytosol and various intracellular compartments, 38 and increased total Ca2+ content of the cell. 59, 61 The observation that total cell Ca2+ is increased, while membrane binding of 45Ca2+ is reduced, suggests that protein binding of Ca2+ is increased, i.e., Ca2+ is bound more avidly to binding sites in the plasma membranes of the cells and its constituent vesicles of cells. Such a proposed defect parallels the documented increases in extracellular binding of Ca2+ noted in the SHR. 18, 19 and humans. 20

Critical to this interpretation of the literature, are the data from the 44Ca2+ membrane binding studies. 33, 34, 53, 57 Those investigations have shown that there is a reduction in the number of available binding sites for 44Ca2+ when the isotope is incubated with plasma membrane preparations. This observation has been extrapolated so as to estimate total binding sites. 33 Several authors have concluded that the total number, occupied and “free,” are also reduced. However, an equally plausible interpretation is that total binding sites are either normal or increased in number, but that “free” sites are reduced, secondary to an alteration in the kinetics of the cation’s binding to membrane proteins. This interpretation reconciles the otherwise disparate observations that total cell Ca2+ is increased while binding of 45Ca2+ to plasma membranes is decreased.

Basal and stimulated vascular smooth muscle tone is dependent upon Ca2+ fluxes through plasma membrane-associated channels. While a variety of endogenous compounds and ions, as well as pharmacologic agents are known to modify Ca2+ channel fluxes, bioavailable calcium in the membrane may be the ultimate regulator of these fluxes. 5, 62, 63 Recent studies have demonstrated a specific inhibition of Ca2+ membrane fluxes by membrane-available Ca2+. 64 Conditions that result in a reduction in bioavailable, membrane-associated Ca2+ may stimulate Ca2+ fluxes, and result in enhanced permeability to Ca2+ and other ions with a consequent increase in vascular tone.

Maintaining an adequate or supplemental Ca2+ intake in the SHR may produce the in vivo counterpart of the in vitro incubation experiments that have demonstrated the specific inhibition by Ca2+ of calcium fluxes in smooth muscle cells. 62, 63 The net effect would be a reduction in both basal and stimulated vascular tone. Restricting Ca2+ intake would theoretically produce the opposite results, as membrane-available Ca2+ decreases, vascular ion fluxes increase, vasoconstriction occurs, resistance rises, and blood pressure goes up. One would predict that such effects would be apparent in normotensive 36, 37 as well as hypertensive animals and humans. The influence of Ca2+ balance, though, may be magnified in the hypertensive animal due to its inherent abnormality(ies) of cellular handling of Ca2+.

These observations of Ca2+ balance, cellular Ca2+ defects, and blood pressure in the experimental model may have several implications for human hypertension. First, as sodium intake, and thereby UNaV increases in humans, obligatory renal losses of Ca2+ ensue. 64 The possibility that sodium exposure in the diet modifies blood pressure in those subjects who are “salt sensitive” via changes in Ca2+ balance needs to be explored. Second, it is noteworthy that several of the societies that clearly differ in their prevalence of hypertension in spite of similar sodium exposures in the diet, also differ in their estimated Ca2+ intake. 65-67 Where average daily Ca2+ intake has been maintained near or above 1000 mg per day, hypertension is infrequent or nonexistent. 56, 67 Third, two established therapeutic modalities that reduce blood pressure in humans also induce positive Ca2+ balance. They are thiazide diuretics 24, 65 and sodium restriction. 69 The possible contribution of these changes in Ca2+ balance to the reduction in blood pressure associated with these treatment regimens should be explored.

Magnesium and PO4 balance may be equally important cofactors in this theoretical construct relating Ca2+ balance to hypertension. As noted above, these two divalent ions would appear to facilitate, or be a prerequisite for, many cardiovascular actions of Ca2+. Factors, such as sodium excretion, which promote renal Ca2+ losses also adversely affect the metabolic balance of Mg2+ and PO4-. As the Ca2+ balance issues in human and experimental hypertension are pursued,
it will be essential to characterize equally as well the roles of Mg\(^{2+}\) and PO\(_4\)^{3-}\) balance.

Conclusions

Divalent ions are critical to normal cardiovascular control. Limited observations in normal and hypertensive humans and experimental animals suggest that alterations in the metabolic balance of Ca\(^{2+}\), Mg\(^{2+}\), and PO\(_4\)^{3-}\) may contribute to long-term variations in blood pressure. In the experimental model these effects, primarily those of Ca\(^{2+}\), may be linked to identified abnormalities in the cellular Ca\(^{2+}\) metabolism of the SHR’s vascular tissue. The influence of positive Ca\(^{2+}\) balance, and the apparent generalized defect in vascular cell’s Ca\(^{2+}\) metabolism, need not be limited to that tissue. They may be applicable to other recently hypothesized mechanisms that are believed to contribute to the development of hypertension. This expanding area of high blood pressure research provides important and obvious interfaces with many established and proposed neurohumoral, renal, and sodium mechanisms that have been associated with hypertension. Rather than alterations of transcellular fluxes and/or intracellular concentrations of Na\(^+\) increasing intracellular Ca\(^{2+}\) and thereby enhancing vascular smooth muscle tone, as proposed by Blaustein, primary abnormalities of cellular Ca\(^{2+}\) metabolism may be responsible for observed differences in cellular sodium and potassium handling linked with hypertension. Correction of the Ca\(^{2+}\) defects may then stabilize cell membranes and modify vascular smooth muscle cell function including ion fluxes. In addition, this hypothesis poses provocative questions concerning possible nutritional measures that could be applicable to both the prevention and therapy of human hypertension.

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