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CALCIUM AND HYPERTENSION

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INTRODUCTION

The concept that hypertension can be managed through dietary means, first popularized by Kempner (1) and others, has re-evolved into an area of active research within the past 5 years. With the advent of potent antihypertensive agents in the 1950s, nutritional aspects of blood pressure regulation became less important as areas of investigation.

The current interest is a result of a number of developments. First, several decades of experience with antihypertensives medications indicate that, despite their ability to control hypertension effectively, they may precipitate untoward side effects. Some of the side effects such as hyperlipidemia and hyperglycemia are just as likely as hypertension itself to hasten the time course for developing cardiovascular complications. Secondly, individuals not normally classified as hypertensive carry a greater than normal risk of experiencing a cardiovascu-

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lar-related event. The latter group of individuals includes adults with "high-normal" blood pressures and children with blood pressures in the upper deciles of normal for their respective age and size. The demographics of these subgroups are poorly defined; however, it is clear that they add substantially to the ranks of those likely to experience a cardiovascular-related event at some point in their lives. Consequently, they, along with those experiencing mild forms of hypertension, are prime candidates for dietary intervention to control their respective conditions, as dietary intervention may be most effective in lowering the very modest increases in blood pressure that they experience.

Most authorities agree that essential hypertension constitutes a genetic disorder characterized by increased peripheral vascular tone that may, or may not be accompanied by hemodynamic changes and enhanced sensitivity of the autonomic nervous system. It is further accepted that this disorder depends on environmental factors such as stress and diet for expression. These facts imply that stress management and/or dietary intervention can be used in a prophylactic manner to preempt the occurrence of hypertension or to control it once it has occurred.

As with anemia, it is now acknowledged that essential hypertension is not a single disorder. As such, it responds differently to different medications and may behave in the same manner where diet is concerned. Hence, some individuals may benefit from a single nutrient manipulation, while others may be harmed by such a manipulation. This insight has extended the dimension of blood pressure regulation by diet beyond sodium restriction as the only valid dietary maneuver in hypertension control. In synchrony with this idea, other nutrients and dietary factors such as fiber and alcohol are actively being investigated as blood-pressure-regulating agents. Among these, dietary calcium has commanded considerable attention within the last three years.

The purpose of this review is to summarize the data that have led to this interest, and to define directions of future research within this area. This approach is not intended to suggest that the role of other nutrients is less important; indeed, as will become clear throughout the review, the effect of calcium on blood pressure is probably mediated through the action of many other nutrients and nonnutrient factors.

EPIDEMIOLOGY OF CALCIUM INTAKE AND HYPERTENSION

A link between calcium intake and blood pressure was postulated as early as 1930 in studies of gestational hypertension (2). Recent epidemiologic data indicate that women in societies where calcium consumption is 1000 mg or more experience low rates of preeclamptic hypertension, despite limited prenatal care and a diet generally poor in other respects (3–5). While such

population observations have failed to control for confounding variables and utilized crude measures of calcium intake, they serve as a general stimulant for more precise analysis of the role of calcium in nongestational essential hypertension. They have further put into context the earlier epidemiologic work of Kobayashi (6) and Schroeder (7), who reported that cardiovascular mortalities in hard-water (high in calcium and magnesium) areas were lower relative to regions with soft water.

Table 1 is a summary of epidemiologic studies that have reported an inverse correlation between calcium intake and blood pressure (8–17). A distinct feature of these studies is that they used the ethnic and regional diversity of the United States as well as techniques that control for obvious confounders such as age, sex, race, and body mass index to draw their conclusions. Despite the variation in blood pressure definition, statistical approaches, and different methods of collecting intake data, these studies establish a statistical association between low levels of potassium, magnesium, phosphorus, and calcium with a greater risk of elevated blood pressure. In one report (8) that analyzed data from a cross-sectional sample of the entire US population, calcium was the strongest correlate of blood pressure. It was estimated that a person consuming less than 300 mg of calcium per day carried an 11–14% risk of developing hypertension. This chance was reduced 3–6% if the individual's intake was 1200 mg per day.

It is difficult to distinguish the singular effects of calcium on blood pressure from the effects of other nutrients that track closely with calcium in foods. Thus, in analyzing data from the Honolulu cardiovascular disease tracking program, Reed et al (14) could not separate the effects of protein, milk, and potassium from those of calcium on blood pressure. The authors attribute this to the fact that protein, potassium, and calcium all occur in relatively high proportions in dairy products. In any case, dairy products or calcium were found to be protective against hypertension.

An intriguing relationship between hypertension and the existence of mandibular interdental canals was recently reported. Patni et al (19), examining radiographs, found a higher incidence of interdental canals in 97 hypertensive patients compared to 111 normotensive individuals. Although these structures are considered normal by some investigators, others have correlated them with a variety of other conditions, among them, calcium deficiency. It would be instructive to examine further interrelationships involving calcium intake, bone loss syndromes, and hypertension.

Despite the strong negative association made by this body of data relating dietary calcium to hypertension, a number of epidemiologic studies have reported a positive correlation between serum total (12, 20) and ionized (21) calcium and blood pressure, while others have noted lower ionized calcium values in hypertension (21a). These findings would appear to be inconsistent

Table 1 Epidemiological studies relating calcium intake to hypertension

Ref.	Location	Dietary data[a]	Statistics[b]	Calcium source	BP Def.	Age (yr)	Sex	No.	Other nutrients[c]
9	Portland, OR	24 hr	t-test	Dairy	MAP<105	25–65	M,F	96	Mg
8	US/HANES I	24 hr	DA	Dietary Ca	SPB>140, 160	18–74	M,F	10,419	K, Vit C
10	San Diego, CA	Ques.	ANOVA t-test	Dairy prod.	DBP>95, SBP>160	30–79	M,F		Not reported
11	Puerto Rico	24 hr	MR	Diet Ca/ milk	continuum	45–64	M	7,932	ETOH, coffee
12	US/HANES I	24 hr	MR	Dietary Ca	continuum	25–74	M,F	2,055	ETOH, PO_4
13	US/HANES II	24 hr	MR	Dietary Ca	continuum	25–74	M,F		ETOH
14	Honolulu, HI	24 hr	MR	Dietary Ca milk	continuum	46–65	M	6,496	PO_4, protein
15	Chicago, IL	DH	MR	Dietary Ca	continuum	40–56	M	1,976	PUFA, ETOH
16	Zutphen, Netherlands	DH	MR	Dietary Ca	continuum	45–70	M	605	PO_4, ETOH
17	Pittsburgh, PA	FF	MR	Dietary Ca	continuum	34–56	M,F	1,939	Not reported

[a]Dietary data: 24 hr = 24-hour recall; Ques. = questionnaire; DH = diet history; FF = food frequency; FR = food record.
[b]Statistics: MR = multiple regression; DA = discriminant analysis.
[c]Nutrients: ETOH = alcohol; PUFA = polyunsaturated fatty acid; K = potassium; PO_4 = phosphorus; MG = magnesium.

with the notion of a decreased calcium intake in hypertension. While no immediate explanation for this discrepancy is available, the most likely interpretation is that total calcium levels are dependent on plasma proteins, which are increased in hypertensives. It is also well established that serum calcium, especially the ionized component, is regulated by a variety of factors. Among these are bioavailability, as it may be affected by other dietary components (fiber, oxalates, phosphorus) and hormonal influences [PTH, calcitonin, $1,25,(OH)_2D_3$]. The large sample sizes used in surveys make a complete appraisal of these modifiers logistically impossible. An example of these confounding variables is the influence of thiazide diuretics, which likely accounted for the increased serum ionized calcium in one study (21). Consequently, it is unlikely that this information can be used to negate the current interpretation of the previously outlined inverse associations between dietary calcium intake and blood pressure.

DIETARY CALCIUM SUPPLEMENTATION IN ANIMALS

The hypothesis formulated from epidemiological associations that supplemental dietary calcium plays an ameliorative role in hypertension has been tested in animal models of hypertension and in humans. In interpreting the available data, it is important to distinguish between acute administration of calcium provided through intravenous infusions and graded exposure, as might be afforded by a high-calcium diet. Clearly, the two modes of administration engage different physiological pathways. As such, they cannot be expected to have comparable effects on blood pressure. As an example, acute calcium infusions appear to cause transient increments in blood pressure that return to baseline levels after infusion in patients with normal or mildly impaired renal function (22). In contrast, chronic dietary exposure to diets ranging in calcium content from 0.59 to 4.3% have repeatedly been shown to attenuate the rate at which blood pressure develops in normal, pregnant, and hypertensive rats, as well as in other species (25–37). Belizan and his coworkers (25) fed a diet deficient in calcium to pregnant Wistar rats and compared their blood pressures to those of pregnant rats maintained on 0.59% calcium diet for nine weeks. The animals on a calcium-deficient diet showed a steady increase in blood pressure that was significantly higher than that of rats fed adequate amounts of calcium. Similar results have been reported in normotensive Wistar rats (26) and in Wistar Kyoto (WKY) rats bred from the same stock as the spontaneously hypertensive rats (SHR) (27).

The greatest effects of dietary calcium on blood pressure, however, have been reported in animal models of hypertension. In weanling rats, supplemental calcium in the diet slows down the rate at which blood pressure rises with age. It is important to note that dietary calcium does not eliminate hypertension per se.

In a preliminary report (28) (Figure 1), the rate of blood pressure development as a function of increasing doses of dietary calcium was evaluated in post-weanling (6-week-old) rats. At a dietary concentration of 0.25%, the rate of increase was 7.14 mm Hg every two weeks, compared to 3.28 mm Hg at a dietary calcium concentration of 2.0%, during the first 18 weeks of life. Consequently, even though both groups became hypertensive by the end of this period, systolic pressure of the calcium-supplemented groups stabilized to lower levels than those of rats fed suboptimal amounts of calcium. This finding is in keeping with the earlier work of McCarron (32) indicating that early exposure to dietary calcium results in a greater attenuation in blood pressure compared to intervention initiated at a later time.

Recently, Hatton et al (31) expanded this concept even further. They evaluated blood pressure in SHR pups born to mothers receiving either 0.1 or 2% calcium during pregnancy. Pups born to mothers on the low-calcium diet were subsequently cross-suckled to mothers maintained on a high-calcium diet during pregnancy and vice versa. Mean arterial pressures, measured by intraarterial catheters, were higher in pups fostered to dams maintained on a low-calcium diet compared to pups fostered to mothers maintained on a high-calcium diet from gestation up until the pups were 21 days old (Table 2). Similarly, total and ionized calcium were higher in pups suckled to dams

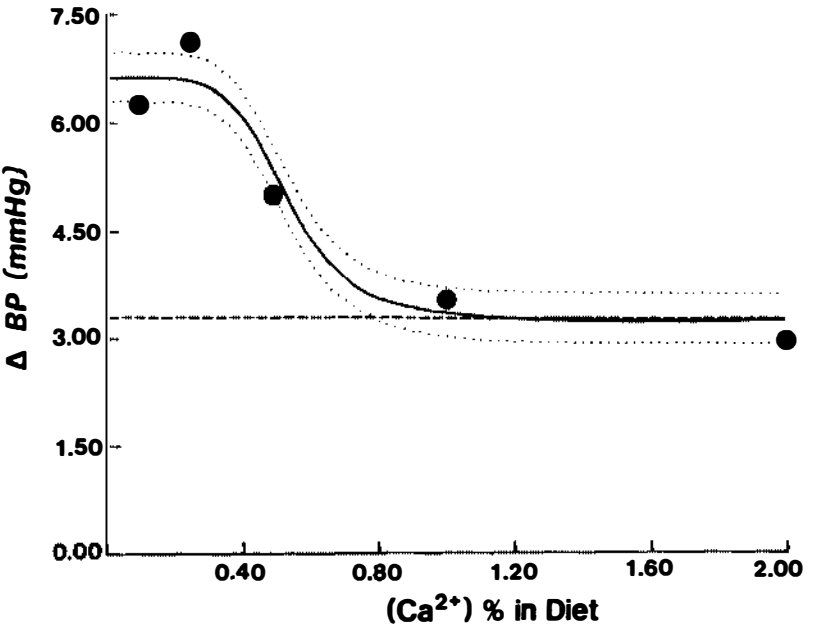

Figure 1 The effect of dietary calcium concentration on blood pressure rise in SH rats. Each point represents the mean of seven rats. Dotted lines are the 95% confidence interval.

Table 2 Blood pressure and serum calcium levels based on postnatal dietary Ca^{2+} (mean ± SD)

	Supplemented $n = 12$	Restricted $n = 21$
MAP (mm Hg)	105 ± 15	135 ± 22[a]
Serum ionized Ca^{2+} (mMol/liter)	1.13 ± .13	0.92 ± .10[a]
Serum total calcium (mg/dl)	10.20 ± .93	8.80 ± 1.15[a]

[a]Significant difference between diet groups $p<0.01$.

maintained on a high-calcium diet. Presumably, intrauterine exposure to calcium does not influence the blood pressure of offspring as much as postnatal exposure through the mothers milk. Interestingly, total elimination of calcium from the diets of recently weaned rats produces a paradoxical decrease in blood pressure. Five-week-old SH rats fed 0% calcium have been reported to experience a rapid blood pressure rise, followed by a reversal of this trend after two weeks on the diet (33). This reduction in blood pressure occurs concomitantly with a severe curtailment in growth.

Supplemental dietary calcium may also lower blood pressure in rats with hypertension artificially induced with deoxycorticosterone acetate (DOCA) and sodium chloride (34) and in other species (35). Mature turkeys, *Meleagris gallopavo,* provided with twice (1.96%) the amount of calcium normally found in the diet of these birds experienced mean arterial pressures that were lower than turkeys fed normal levels (0.98%) of calcium. In addition to these pressure changes, mean total heart weights were lower in calcium-supplemented birds than in those receiving the regular diet. Similarly, the heterophil/lymphocyte ratio (a crude measure of stress in domestic avian species) was higher in the supplemental group (35). These results indicate that calcium may regulate blood pressure in part by reducing left ventricular hypertrophy and stress.

The notion that stress can be ameliorated by a high-calcium diet may be too presumptive at this point. Nevertheless, preliminary data appear to support such a notion. Spontaneously hypertensive rats and mice exposed to psychosocial stress through manipulation of group housing exhibit blood pressures that are higher than those of nonstressed animals. Spontaneously hypertensive rats exposed to similar stress were reported to have lower blood pressures when their diets contained 2% calcium than those whose diets contained 0.1% calcium (36). This concept requires further investigation.

Findings of an ameliorative role for dietary calcium supplementation are not unequivocal. Stern et al (38) evaluated blood pressures in post-weanling rats (6 weeks old) fed either 0.4 or 2.8% calcium. After 28 days of feeding, blood pressure values from both groups were not significantly different, even though the high-calcium diet increased serum ionized calcium. It is not clear why these reports differ from those of other workers. The possibility that the rapid weight gain associated with this phase of growth may have masked the hypotensive

effects of calcium exists. Certainly, supplementation beyond this rapid growth phase would have made the results more comparable with those of others. Nevertheless, the bulk of experimental data in animals seems to support the view that dietary calcium modulates the rate at which hypertension develops. Still, conclusive statements regarding blood pressure and calcium can only come from experimental data in humans. This is true of calcium more than other nutrients because calcium requirements in most other species are considerably higher than in humans.

DIETARY CALCIUM SUPPLEMENTATION IN HUMANS

Unlike the data generated from animals, data on calcium intervention in human hypertension are limited. To date, a total of five studies have supplemented the diets of normal (39), pregnant (40), or hypertensive (18, 18a, 41) subjects with calcium and reported significant decreases in blood pressure. Belizan et al (39) studied 57 normal volunteers aged 18–35 years in a double blind trial employing either 1 g of elemental calcium or placebo for 22 weeks. Blood pressure fluctuated for the first 9 weeks in women and 6 weeks in men. After this time, diastolic blood pressure stabilized to lower values in both sexes receiving supplemental calcium compared to those on placebo. For women, a 5% decrease in supine diastolic pressure was reported. The comparable value for males was 9%. Systolic blood pressures were not affected.

Blood pressure reductions of a magnitude similar to that seen in nonpregnant women have been reported in pregnant women given 1 or 2 g of calcium, compared to a group treated with placebo. The women given 1 g of calcium experienced lower diastolic and systolic blood pressure from 15 weeks of gestation until the end of the second trimester of pregnancy. After this time, 1 g calcium could not prevent the characteristic rise in blood pressure typical of the third trimester of pregnancy. In contrast, the blood pressures of women ingesting 2 g calcium remained low until delivery (40).

The first randomized, double-blind crossover trial of calcium as therapy for mild to moderate essential hypertension has recently been reported (41). In this study, 48 hypertensive and 32 matched normotensives received either 1 g of calcium per day (provided as calcium carbonate) or placebo for eight weeks. Treatments were then switched for an additional eight weeks after an interim "washout" period of four weeks when placebo was ingested. Compared to placebo (Figure 2), calcium significantly reduced average systolic pressure by 5.6 mm Hg and average diastolic blood pressure by 2.3 mm Hg in hypertensive subjects. As in the study by Belizan et al (39), steady changes did not become apparent until the 6th week of supplementation. After this time, blood pressure started to decline and was still declining when the study was terminated. As with any trial, some of the patients in this study did not respond to therapy

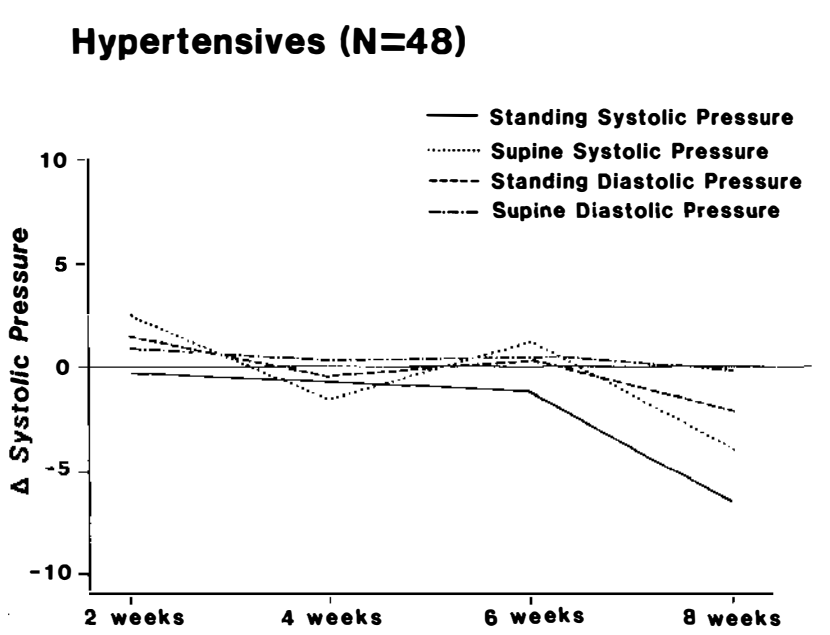

Figure 2 Blood pressure change by week in 48 patients with hypertension receiving 1 g of calcium per day.

within the eight weeks of supplementation. At the inception of the trial, the authors defined response as a 10-mm Hg decrease in systolic blood pressure with calcium compared to placebo. Using this criterion, they found that 21 of 48 (44%) hypertensive participants experienced a decrease of 10 mm Hg or more. For normotensive subjects the response rate was 19%. The authors point out that these differential responses may reflect the etiological heterogeneity of hypertension.

Two other recent reports have also demonstrated an antihypertensive effect of supplemental calcium. Johnson and colleagues (18) reported that 16 hypertensive postmenopausal women who received 1.5 g/day of Ca^{2+} for four years experienced a significant reduction in their systolic blood pressure compared to a control group of 18 women who received placebo. Luft et al (18a) supplemented 16 hypertensives for two weeks with 1 g of calcium and noted modest but significant decreases in blood pressure compared to the two weeks on placebo.

Collectively, these trials in humans indicate that calcium can reduce blood pressure in selected patients, and that these nonpharmacologic doses can theoretically be achieved through the diet (<2500 mg). Whether calcium actually supplied through dietary sources would have the same effects remains undetermined.

POSSIBLE DEFECTS OF CALCIUM METABOLISM IN HYPERTENSION

A number of biochemical abnormalities associated with hypertension have been reported in both hypertensive animals and humans. These include decreased serum ionized calcium with attendant elevations in parathyroid hormone, and increased fractional and total urinary calcium excretion. As outlined in a recent review, however, these findings have not been found to exist in all studies to the same extent (24). While any number of explanations could be invoked for these discrepancies, it is likely that they are indicators of different stages of more profound disturbances of calcium metabolism, occurring within the major organ systems that regulate calcium balance and the vascular smooth muscle cell. Thus, subnormal handling of calcium in the gastrointestinal tract, the kidney, or bone will invariably affect the manner in which calcium is made available to the smooth muscle cell, the site at which cation appears to contribute to the regulation of vascular tone and thereby blood pressure. These possible defects are discussed in the next sections.

The Gastrointestinal Tract, the Kidney, and Bone

Inasmuch as the gastrointestinal (GI) tract acts as the first delimiter of nutrient bioavailability, it is not surprising that this organ system is receiving considerable attention in the study of calcium balance in hypertension. In considering the complex mechanisms that govern calcium absorption, four loosely defined points can be identified where defects may occur.

First, the uptake of calcium across the brush border membrane into the cell may be impaired. The movement of calcium at this point is actively mediated and depends on the vitamin D status of the animal. Transport is further dependent on the ability of the cell to synthesize proteins, such as calcium binding protein, that act as carriers of calcium into the cell. Other nutrients such as sodium, magnesium, and phosphorus may further modify this process (42). Consequently studies attempting to identify defective calcium absorption in hypertension may need to characterize one or all of the following: (*a*) ability of the enterocyte to synthesize binding proteins, (*b*) number and capacity of cytosolic receptors for vitamin D and, (*c*) the activity of brush border membrane bound enzymes such as alkaline phosphatase.

Once calcium has penetrated the brush border membrane, the enterocyte must effectively translocate it to the basolateral membrane for extrusion into the blood stream (42). This phase constitutes a second point where calcium handling may be defective in hypertension. The ability of intracellular organelles successfully to buffer and move calcium to the basolateral membrane must therefore be examined.

Extrusion of calcium through the basolateral membrane is an energy-requiring process (42) thought to be mediated by a calcium-dependent ATPase and a non-ATP-dependent Ca^{2+}/Na^{+} exchange mechanism (43–45). The activity of these enzymes needs to be investigated within the context of hypertension.

Lastly, calcium absorption occurs through nonenergy-, gradient-dependent, largely passive pathways that need to be characterized for possible defects.

Preliminary investigations into possible defects of calcium absorption have been reported. Studies suggest that active transport is impaired in the SHR. However, the nature of this impairment is controversial. In an initial study, Toraason & Wright (47) reported a higher serosal/mucosal (S/M) ratio of calcium concentration in duodenal sacs prepared from 12-week-old SHR relative to age-matched WKY rats. Calcium uptake was similarly higher in SHR compared to WKY rats in vivo. Administration of $1,25(OH)_2D_3$ elicited an increase in duodenal calcium transport in WKY but not SH rats. Whether this decreased transport of calcium was due to the high S/M ratio of calcium concentration demonstrated in the SHR or due to an impairment of the vitamin D adaptive process is not clear.

In a protocol similar to that used by Toraason et al, Schedl and his coworkers (48) reported opposite findings. Young (5-week-old) and older (12-week-old) SHR exhibited significantly lower S/M concentrations of ^{45}Ca, compared to age-matched WKY rats. Furthermore, a kinetic analysis of calcium transport in in situ segments of the small intestine revealed that maximal velocity (V_{max}) for calcium was higher in WKY relative to SH rats. Despite these differences serum concentrations of $1,25(OH)_2D_3$ were similar in both strains. These findings suggest that the SHR may produce sufficient quantities of 1,25-dihydroxycholecalciferol, but its GI tract may be refractory to vitamin D's effects. It is noteworthy that both studies utilized dietary calcium and phosphorus levels that were more than adequate by NRC criterion.

In a recent communication Lucas et al (49) examined the vitamin D response in SHR and WKY rats fed low (0.1%) or adequate (2%) calcium diets from the age of 6 weeks up until they were 12–14 weeks old. Decreased levels of $1,25(OH)_2D_3$ were seen in SHR maintained on adequate amounts of calcium in relation to WKY rats. The calcium-deficient diet stimulated by 80% the level of serum $1,25(OH)_2D_3$ in both strains. However, the SHR's initial $1,25(OH)_2D_3$ were low, and absolute adaptive values were also lower than those of WKY rats. Accordingly, mucosal to serosal calcium flux rose nonsignificantly from 29.5 ± 4.2 on a 2.0% calcium diet to 37.2 ± 8.1 nmol·cm^{-2}hr^{-1} on the 0.1% calcium diet in an older (20–24-week-old) group of rats. Similar values were from 30.6 ± 4.0 to 83.1 ± 10.5 nmol·cm^{-2}hr^{-1} in WKY rats, which was a highly significant increase. Similar values were found by McCarron et al (50) but are not supported by calcium balance studies (37, 38).

Calcium fluxes have been examined in isolated enterocytes of SH and WKY rats. Preliminary evidence suggests that ^{45}Ca efflux constants are lower in SHR than in WKY rats (51). The efflux rate constant reflects calcium ATPase activity in the basolateral membrane. This pump has been found to be deficient in other cells from hypertensive animals and humans. Calcium absorption has not been evaluated in human subjects with hypertension.

The kidney may also contribute to the biochemical abnormalities in hypertension, especially hypercalciuria. Unfortunately, the nature, characteristics, and cellular processess governing calcium reabsorption in the various segments of the nephron are not well understood and have been minimally studied in hypertension. Nevertheless, mechanisms of calcium reabsorption in the kidney are remarkably similar to those of calcium absorption in the GI tract. Consequently, defective calcium transport is likely to occur at those sites along the kidney where active transport is most prevalent. Within the proximal convoluted tubule, only about 12% of the filtered load of calcium is actively transported, with 48% moving passively following water and sodium reabsorption. Active transport similarly governs calcium reabsorption in the pars recta and in the distal convoluted tubule. About 20% of the filtered load of calcium is reabsorbed at these two latter sites. Theoretically then, only about 35% of the filtered calcium load is reabsorbed actively; the rest is absorbed passively through concentration or electrical gradients (52). As with the intestine, it is likely that a variety of enzyme systems responsible for calcium transport are partially ineffective as a result of either (*a*) diminished synthesis or diminished binding to receptors or (*b*) rapid degradation. A negative correlation between Na^+/K^+ ATPase activity and blood pressure has been reported in renal cortical segments of both SHR and WKY rats (22a). Investigations designed to explore further these aspects of calcium transport in the kidney in hypertension are therefore urgently needed.

The contribution of bone to overall calcium homeostasis in hypertension is poorly characterized. Based on the previously outlined defects in intestinal absorption and renal reabsorption, it can be anticipated that mineralization in the SHR is abnormal. In a preliminary study, Izawa et al reported that bone density was decreased in tibial trabecular bone of male SH relative to age-matched WKY rats. Although a similar difference could not be demonstrated for tibial cortical bone, mean femur dry weight and ash weight per unit of bone volume were significantly reduced in the SHR (53). Preliminary studies from our laboratory indicate that femoral cortical bone density in 54-week-old male SH rats is reduced (52a). This latter observation indicates that osteopenia is progressive in the SHR and may go undetected in cortical bone of younger rats (26 weeks old) such as those studied by Izawa et al. Nevertheless it is clear that some aspect of bone mineralization and modeling is defective in SHR. The precise nature of this defect and its contribution to the availability of calcium and blood pressure regulation require further experimentation.

Cellular Handling of Calcium

Defects involving cellular calcium handling in hypertension have been partially characterized, and were reviewed in a recent publication (53a). Three basic abnormalities that contribute to increased basal active tension in the smooth muscle cell of hypertensive animals have been indentified. First, increased sensitivity to vasoactive substances such as norepinephrine has been noted in mesenteric resistance vessels from SHR compared to those from WKY rats. This increased sensitivity is associated with increased permeability to calcium in vascular smooth muscle cells (54–57). Secondly, the rate of relaxation after an agonist is removed is lower in arteries obtained from hypertensive rats relative to normotensive controls (58, 59). Lastly, red blood cells and adipocytes obtained from hypertensive rats and humans have higher than normal intracellular concentrations of calcium (60, 61, 64). These abnormalities are consistent with dysfunctional calcium influx, intracellular sequestration/release, and efflux pathways.

Increased permeability of the hypertensive membrane to calcium is thought to be due to a reduction of binding sites rather than a reduced affinity of these sites to calcium (53a). Theoretically possible sites where calcium may bind within the cell membrane include carboxylic acid residues of acidic amino acids (aspartate and glutamate) as well as negatively charged membrane phospholipids such as phosphotidylserine. To date, there is little evidence that these particular components are altered in hypertension. The composition of the main membrane lipids for example is similar in hypertensive and normotensive humans (64a). Secondly, despite the observation that band III protein, which constitutes ~30% of all erythrocyte proteins, is increased in SHR (53a), direct evidence for a reduction in glutamate and/or aspartate in hypertensive membranes is lacking. Irrespective of the precise nature of membrane alterations in hypertension, the increased permeability in these membranes (62) presumably destabilizes the membrane, which in turn promotes the entry of cations, especially calcium, into the cell.

The rate of relaxation and rebound of elastic elements depends upon rate of calcium efflux and sequestration by subcellular organelles. The calcium pump ATPase and the Na^+/Ca^{2+} exchanger, present in both the plasma membrane and in subcellular membranes, are responsible for this phase.

Data on the operational nature of the Na/Ca^{2+} exchanger in hypertension are lacking. The apparent absence of this enzyme in cells traditionally studied for calcium handling (erythrocytes, adipocytes, and hepatocytes) has resulted in a scarcity of knowledge regarding the role of this system on cellular calcium handling and distribution in hypertension. Nevertheless, the activity of the Na^+/K^+ ATPase is decreased in hypertensive rats and humans. While this enzyme does not directly regulate calcium transport in the VSMC, it causes sodium to accumulate within the VSMC and thereby hampers the ability of the Na^+/Ca^{2+} exchanger to extrude calcium (63, 65, 66).

Recent reports indicate further that the more ubiquitous calcium pump ATPase is similarly hampered in hypertension. Microsomes harvested from aortas and mesenteric arteries of SHR, DOCA, and renovascular models of hypertension show diminished calcium pump ATPase activity (67–69). In humans, basal unstimulated activity of this enzyme in lysates of red blood cells (RBCs) is reduced in untreated hypertensive subjects compared to normotensives (70). These changes occur despite the observation that the calmodulin content and distribution of RBC's are normal (70a). Furthermore, the ability of calmodulin to activate calcium pump ATPase is reduced in hypertensive human subjects (70b). These observations are consistent with a basic defect in the manner in which this universal Ca^{2+} binding protein interacts with calcium in hypertension. Postonov & Orlov (53a) postulate that factors that modify the calmodulin-Ca^{2+}-ATPase interaction, such as the release of calcium-dependent phospholipases and proteases, may play a role in the observed defects of this enzyme system. Presumably these enzyme modifications would in turn modify the hydrophobic regions of both calmodulin and Ca^{2+}-ATPase by altering the ratio of free to bound forms of unsaturated fatty acids and probably peptides (53a). Dysfunctions of the Ca^{2+}-ATPase system tend to occur in very young (3–5-wk-old) rats and may be absent in pregnancy-induced hypertension (71, 72). Furthermore, when renovascular hypertension is treated, these abnormalities disappear in rats with the latter form of hypertension compared to SHR (72). This latter observation indicates that the abnormalities of the Ca^{2+}-ATPase system are genetically determined.

MECHANISMS ASSOCIATED WITH THE ANTIHYPERTENSIVE ACTION OF DIETARY CALCIUM

The precise nature of the antihypertensive action of dietary calcium is not known beyond the finding that additional calcium in the diet increases serum ionized calcium and does not exacerbate the calciuria. Two distinct theories for the antihypertensive action of dietary calcium have been advanced. Both are fraught with inconsistencies with the current knowledge and understanding of the hypertensive process and are subject to modification with additional research.

Feeding supplemental calcium causes marked decreases in serum and urine phosphorus levels in normal adult males, decreases that are accompanied by significant increases in fecal phosphorus (73). Similar changes in serum and urine, but not feces, phosphorus values have been noted in hypertensive rats and humans not receiving supplemental dietary calcium (74). Lau et al (29) tested the hypothesis that supplemental dietary Ca^{2+} lowers blood pressure through decreasing serum and urine, and increasing fecal phosphate. Female SHR (22-wk-old) were fed a diet containing 4.3% calcium and given daily in-

jections of $NaPO_4$ or sham injections of NaCl for ten days. Serum and urine phosphorus values remained normal in the calcium- and phosphate-supplemented group with no dectable change in blood pressure. The rats receiving NaCl and supplemental dietary calcium exhibited significantly lower urine and phosphorus values and lower blood pressure. Subsequent phosphate injections in this latter group for an additional 16 days reversed their phosphorus chemistries and increased blood pressures to levels similar to a control group receiving 1.2% dietary calcium.

Based on these findings, the authors concluded that dietary calcium lowered blood pressure by depleting phosphate. Two criticisms make this conclusion untenable at this point in time. First, the level of dietary calcium, and consequently the Ca:P ratio (9:1), was far in excess of levels required to lower blood pressure and therefore the phosphate "depletion" may have been a reflection of the unbalanced provision of the two nutrients. Secondly, injected phosphate is metabolized differently from ingested phosphate. Consequently, the implications for blood pressure regulation by this route are limited. Nevertheless, the theory is worthy of further research, especially as it may affect cellular energy utilization, since one of the major function of phosphorus is to provide the cell with sufficient energy.

The second theory proposes that dietary calcium may lower blood pressure through VSMC membrane stabilization. The theory is based on early in vitro observations that high concentrations of calcium are able to relax aortic preparations made to contract with norepinephrine (75). Similar results have been reported in the New Zealand strain of genetically hypertensive rats using lower ranges of calcium in hindlimb preparations (76). It is postulated that the observed relaxation occurs because excess extracellular calcium inhibits its own flux rate into the cell, in essence acting much in the same manner as the calcium channel blockers do. This postulate is strengthened by observations that the rate of calcium entry into VSMC (77) and cardiac cells (78) governs the release of intracellular calcium stores. By the same token, a decreased influx rate would presumably decrease intracellular calcium.

The major drawbacks of this theory are (*a*) the levels of calcium used are far in excess of what is physiologically attainable even with increased dietary calcium intake, and (*b*) in vitro preparations do not reflect steady-state conditions. While the latter criticism cannot be easily overcome, the first criticism can be. Recently, Bukoski et al (79) tested the hypothesis that dietary calcium can alter functional properties of aortic smooth muscle. Isometric force development, apparent membrane stability, and elastic properties were evaluated in SHR maintained on either a 2 or 1% diet from 6 weeks of age either until 13–14 weeks or until 20–23 weeks of age. While aortic properties remained essentially unchanged for the two diet groups in the younger rats, significant alterations were observed in aortas isolated from the rats maintained on the 2% diet for 15 weeks. The changes included a decrease in sensitivity to KCl, an

increase in apparent membrane stability, and a normalization of vessel wall stiffness. These findings are consistent with an effect of dietary calcium intake on vascular smooth muscle. In a preliminary report utilizing a similar protocol, these results could not be substantiated in tail arteries isolated from 15-week-old SH rats maintained on either 0.4% or 2.8% Ca^{2+} in the diet for 4 weeks (79a). The comparative value of these findings is limited by differences in the ages of the animal used. Further experimentation is required, however.

Calcium may also alter the activity of the sodium-potassium pump. Smooth muscle cells cultured from the carotid artery and incubated in a calcium-deficient media accumulate more sodium than do cells incubated in media containing 0.5, 2.0, or 4.0 mM calcium (80). In view of the effects of increased intracellular sodium on the Ca^{2+}/Na^{+} exchange mechanism alluded to earlier, this aspect requires further experimentation with particular attention to dietary calcium intake.

CONCLUSIONS AND FUTURE RESEARCH

The thesis that increased dietary calcium protects against pervasive hypertension has been tested intensely through epidemiological studies, animal experiments, and human clinical trials. Consideration of available data indicates that a causal relationship exists between lower dietary calcium intake and a higher risk of hypertension. Still, large areas of this relationship are not clearly delineated. Several aspects need to be evaluated further. Epidemiologically, it would be interesting to find out why the prevalence of hypertension is low in regions of the world where calcium intake is also low. Since this may be a reflection of the interaction of calcium with nutrients and/or environmental contaminants, it might help to define which nutrients should be experimentally studied. The relationship between hypertension, dietary calcium, and other calcium-losing syndromes (peridontal gum disease, osteoporosis, etc) needs clarification, especially in children and young adults.

In intervention trials, the role of dietary calcium as opposed to calcium from nonnutrient dietary supplements needs to be examined in humans. This is especially important as the nutrient mixtures in foods may modify the effects of calcium on blood pressure. The role of nutrients that track closely with calcium physiologically and in foods (such as magnesium, phosphorus, vitamin D, and potassium) and their effects on blood pressure also need clarification. The implied role of calcium in reactivity to environmental stress is another area where future research efforts should be directed.

Research is most critically needed in the area of physiological mechanisms associated with the antihypertensive action of dietary calcium. A clarification of these mechanisms would greatly advance our knowledge not only of how dietary calcium acts to reduce pressure, but also of how other nutrients may

modify blood pressure. Until these issues are fully resolved, it is premature to make recommendations regarding dietary calcium intake other than supporting the current recommendation of the National Academy of Sciences (800 mg calcium per day). Unfortunately, the vast majority of adult women and over half of the adult males in the American society are below this level, thereby increasing their cardiovascular risk.

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