The Calcium Paradox of Essential Hypertension

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Three disparate observations—that calcium mediates vascular smooth muscle contraction, that calcium channel blockers lower blood pressure, and that increased dietary calcium intake can also ameliorate hypertension—constitute somewhat of a paradox. The complex interrelationships between calcium metabolism and essential hypertension are discussed in this review. Recent evidence suggests possible defects in intracellular calcium transport or in calcium binding in essential hypertension. This evidence, and the paradoxical therapeutic efficacy of both calcium channel blockers and supplemental dietary calcium, can be integrated into a single theoretic construct.

The past five years have witnessed a new perspective in the pathogenesis and treatment of essential hypertension. Disordered calcium metabolism lies at the center of this perspective [1,2]. As with any emerging area in science, however, previous observations concerning hypertension do not appear consistent with this more current interpretation. It will be necessary to resolve this paradox to fully understand the role of calcium metabolism in essential hypertension. The paradox does not truly reflect a dichotomy between truth at one end and error at the other, but rather the gaping holes remaining in our understanding.

EXTRACELLULAR VERSUS INTRACELLULAR FREE CALCIUM

Extracellular ionized or ultrafilterable calcium values are decreased in essential hypertension [3–5]. Comparable decreases also occur in several laboratory models of essential hypertension, most importantly, the spontaneously hypertensive rat [6,7]. Paradoxically, several reports now demonstrate that intracellular free calcium concentrations of platelets both from patients with essential hypertension and from spontaneously hypertensive rats are increased [8,9]. The collective evidence suggests that these observations concerning extracellular and intracellular free calcium are relevant to the underlying pathophysiology of hypertension.

Extracellular ionized calcium levels in both hypertensive humans and experimental animals revert to normal values with the provision of supplemental dietary calcium [6,10]. It is unclear, however, whether the normalization of ionized calcium is an essential step in the lowering of blood pressure, and in the presumed reduction in peripheral vascular resistance and smooth muscle contractility. In our experience, the rise in extracellular ionized calcium often precedes the lowering of blood pressure [6].

In contrast to extracellular ionized calcium, intracellular free calcium, which is elevated before treatment, tends to decrease as blood pressure is lowered by any of several pharmacologic interventions [8]. Once again,

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whether a reduction in intracellular free calcium is a prerequisite for blood pressure reduction or simply a marker of changes in intracellular calcium metabolism is unknown. Current data suggest that treatment of essential hypertension, whether by dietary calcium intervention or by pharmacologic agents such as calcium channel blockers, corrects the discordance between extracellular and intracellular free calcium concentrations. Furthermore, these findings suggest that there is not an obligatory increase in the intracellular free calcium concentration with increases in extracellular ionized calcium. If this were the case, blood pressure should not decrease as extracellular free calcium approaches the normal range, since increased intracellular calcium in the vascular smooth muscle cell would result in increased contractility. Somehow both non-pharmacologic interventions, such as dietary calcium, and pharmacologic treatment with calcium channel blockers allow the vascular smooth muscle to become more efficient or more effective in handling intracellular free calcium. The cell is then able to maintain cytosolic free calcium at a lower concentration.

REDUCED DIETARY CALCIUM INTAKE VERSUS THE RENAL LEAK OF CALCIUM

Within the past four years, 16 reports have linked a low intake of dietary calcium to an increased risk of hypertension in adults [5,11–25]. Paradoxically, the renal excretion of calcium appears to be elevated in essential hypertension [26,27]. The low intake of dietary calcium is thus further exacerbated by the inappropriate renal leak of the cation.

Some investigators have previously interpreted the simple observation of an increased urinary calcium excretion as evidence of increased dietary intake [28]. However, as noted earlier, remarkable consistency has emerged from epidemiologic surveys documenting that the average dietary calcium intake is lower in patients with mild to moderate hypertension than in normotensive control subjects [5,11–25]. Several possibilities could account for the discrepancy between dietary intake and renal excretion of calcium. Resnick and his colleagues [29] have suggested that in "salt-sensitive" essential hypertensive patients, the increased urinary calcium excretion may relate to increased dietary sodium chloride ingestion. In one of our early studies, we also noted that subjects with hypertension excrete more calcium than do normotensive subjects at comparable levels of urinary sodium excretion [26]. Indeed, in experimental models of sodium chloride-induced hypertension, extra dietary salt leads to hypercalciuria [30].

The second theoretic possibility is that a primary defect exists in the renal reabsorption of calcium in humans and animals with hypertension. The evidence to support this hypothesis is fragmentary at this time. Active calcium transport in the nephron is partially dependent upon a calcium ATPase pump. Although this pump has not been measured in renal tissue from humans or from animals with essential hypertension, it has been measured in vascular smooth muscle and red blood cells from both experimental models and human hypertensive subjects [31,32]. Active calcium transport is diminished in the spontaneously hypertensive rat's intestine, an organ that shares many of the biochemical characteristics of active calcium transport with the nephron [33,34]. As a consequence, the spontaneously hypertensive rat exhibits a simultaneous impairment in both intestinal and renal transport of calcium. Direct evidence that the nephron of the spontaneously hypertensive rat is unable to normally reabsorb calcium is that either a low dietary calcium intake or vitamin D deficiency results in a further increase in urinary calcium excretion, rather than the anticipated reduction observed in the normotensive Wistar Kyoto rat [35,36].

In humans with essential hypertension, supplemental calcium does not result in increased urinary calcium excretion, although it does normalize the extracellular ionized calcium concentration [10]. This latter observation suggests that the renal leak improves with exposure to increasing amounts of dietary calcium. This can be inferred from the fact that the filter load of calcium actually increases. Glomerular filtration rate remains constant while the concentration of ionized calcium increases. Since renal calcium excretion does not increase, the percent reabsorption of calcium by the nephron must rise with dietary calcium supplementation [10]. Therefore, the data suggest a primary defect in the active reabsorption of calcium in the kidneys of the laboratory models and human hypertensive subjects. This defect in active calcium transport may exist not only in the kidney, but also in other tissues such as enterocytes, platelets, white blood cells, and vascular smooth muscle.

IMPAIRED VITAMIN D METABOLISM VERSUS REDUCED INTESTINAL CALCIUM TRANSPORT

The role of vitamin D in essential hypertension remains an area with insufficient data to permit accurate interpretation. Resnick et al [29] have demonstrated that sodium loading stimulates formation of vitamin D in salt-sensitive hypertensive subjects, concurrent with a reduction in extracellular ionized calcium concentrations. However, it is unclear whether this increase of 1,25-dihydroxyvitamin D_3 represents an abnormal response.

In the spontaneously hypertensive rat, 1,25-dihydroxyvitamin D_3 levels are significantly lower than in Wistar Kyoto control rats [37]. Feeding the spontaneously hypertensive rat a low-calcium diet, while stimulating production of 1,25-dihydroxyvitamin D_3, does not stimulate it maximally or to the degree observed in the normotensive Wistar Kyoto rat [37]. The low levels of 1,25-dihydroxyvitamin D_3 in the spontaneously hypertensive rat are particularly noteworthy because they occur in the presence of

decreased serum ionized calcium concentrations, increased circulating parathyroid hormone levels, and decreased serum phosphate levels. All of these factors should serve as potent stimuli to increase 1,25-dihydroxyvitamin D_3 production. This pathologic decrease in circulating levels of 1,25-dihydroxyvitamin D_3 is particularly aberrant given the markedly reduced intestinal calcium transport in the spontaneously hypertensive rat [33,34]. Pharmacologic doses of 1,25-dihydroxyvitamin D_3 given for only four days correct this intestinal calcium transport defect [37].

A possible explanation for the paradoxical failure of 1,25-dihydroxyvitamin D_3 production to increase in response to physiologic stimuli in the spontaneously hypertensive rat may partially lie in the elevated intracellular free calcium levels seen in essential hypertension and in laboratory models [8,9]. Cytosolic free calcium and mitochondrial calcium are critical signals to the regulation of 1-alpha-hydroxylase in the proximal tubular cell of the kidney. An abnormal increase in intracellular free calcium values may be read by the 1-alpha-hydroxylase enzyme system as a signal to suppress production.

VASODILATING EFFECTS OF PARATHYROID HORMONE VERSUS HYPERPARATHYROIDISM-ASSOCIATED HYPERTENSION

A body of previous evidence suggests that hyperparathyroidism carries an associated risk of hypertension [38]. Although it was previously proposed that this association represents a vasoconstrictive action of circulating parathyroid hormone, more recent evidence suggests just the opposite [39]. First, parathyroid hormone is a potent vasodilatory agent in both systemic and regional infusion studies [40,41]. Second, the short-term suppression of endogenous parathyroid hormone by a calcium infusion results in increased blood pressure [42]. Third, infusion of physiologic levels of parathyroid hormone partially inhibits the vasoconstrictor response to angiotensin II in laboratory models, an effect incompatible with a vasoconstrictor effect of parathyroid hormone [43]. Finally, clinical observations suggest that hyperparathyroidism may emerge as a long-term complication of hypertension [26,44] rather than as a cause of hypertension.

This latter conclusion is based on several observations. Increasing dietary calcium intake, within the normal range, significantly reduces abnormally elevated circulating parathyroid hormone levels in individuals with "primary" hyperparathyroidism [45]. Parathyroid hormone values are increased both in humans and in animal models of essential hypertension [6,26,46]. As noted earlier, dietary calcium intake is chronically low in hypertensive patients, raising the possibility that the elevated parathyroid hormone levels reflect long-term reductions in calcium exposure. Providing extra calcium in the diet suppresses the circulating parathyroid hormone elevations in the laboratory setting [46]. Last, and perhaps most important, reduction of parathyroid gland mass in the setting of hyperparathyroidism and hypertension is not necessarily associated with normalization of blood pressure. The only long-term follow-up study in such patients actually demonstrates an increase in blood pressure two to five years postoperatively [44].

ACUTE HYPERCALCEMIC BLOOD PRESSURE RESPONSE VERSUS CHRONIC CALCIUM-LOADING BLOOD PRESSURE RESPONSE

A number of studies in humans and animal models demonstrate that acute hypercalcemia induces a rise in blood pressure [47,48]. However, chronic dietary calcium loading both in laboratory animals and in humans is associated with reduced blood pressure [6,10,33,49,50]. Short-term infusion of calcium produces hypercalcemia, yet long-term calcium supplementation does not increase serum calcium levels above the normal range; this may be the critical distinguishing characteristic. A variety of observations suggest that the short-term effects of calcium on the vasculature are opposite to those of a long-term increase in dietary calcium exposure. This conclusion is reinforced by the emerging evidence from seven clinical trials reporting reversal of hypertension in some individuals by supplemental calcium intake [10,23,50–54]. Thus, the short-term effects of hypercalcemia must not be confused with the opposite blood pressure response observed with long-term increases in dietary calcium intake.

CALCIUM MEDIATION OF VASOCONSTRICTION VERSUS VASORELAXATION

Cytosolic free calcium or activator calcium is critical in initiating the contractile response of vascular tissue [55]. Nevertheless, observations spanning more than 20 years of laboratory investigation suggest that raising extracellular calcium levels in vitro results in a relaxation of vascular tissue [56]. This latter finding is supported by more recent studies from our laboratory demonstrating changes in the functional properties of vascular strips removed from calcium-supplemented spontaneously hypertensive rats [57]. These functional changes include a normalization of the reactivity to provocative stimuli, such as 40 mmol of potassium chloride and norepinephrine, as well as significant changes in vascular compliance. This improvement in the vascular reactivity of the spontaneously hypertensive rat through calcium supplementation is consistent with the membrane stabilization induced by short-term changes in extracellular calcium [56]. Webb and Bohr [56], in their in vitro studies, induced comparable vascular changes, via profound increases in extracellular bath calcium concentration. We achieved these changes by simply providing long-term supplementary dietary calcium intake for up to 16 weeks. These recent observations indicate a direct effect of dietary calcium on vascular function.

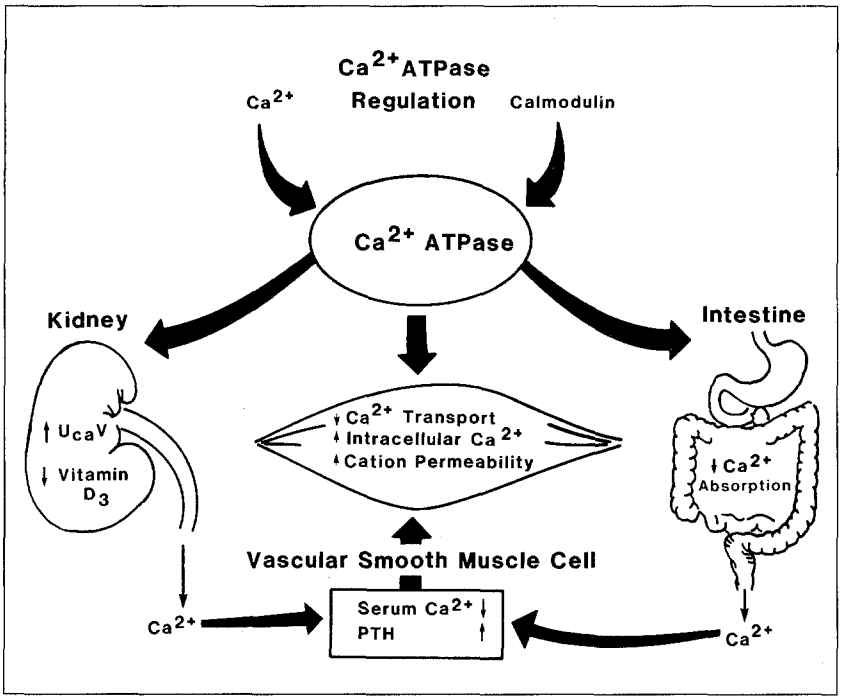

Figure 1. *The calcium paradox in hypertension. $U_{ca}V$ = urinary calcium excretion; PTH = parathyroid hormone.*

CALCIUM CHANNEL BLOCKERS VERSUS DIETARY CALCIUM IN LOWERING BLOOD PRESSURE

Both calcium channel blockers and supplemental dietary calcium lower blood pressure in patients with essential hypertension. Within the past two years, seven studies have shown a favorable blood pressure response to supplemented dietary calcium in patients with essential hypertension [10,23,50–54]. One of those studies demonstrated a reduction in systolic blood pressure over a four-year period [23] in older women. In our randomized, placebo-controlled, double-blind trial, we recently reported that 44 percent of patients with essential hypertension had significant reductions in both systolic and diastolic blood pressures with 1,000 mg of elemental calcium for eight weeks, compared with eight weeks of placebo therapy [10]. Luft and colleagues [50] have also recently demonstrated significant reductions in a crossover protocol utilizing either 1,000 mg of calcium or placebo for only a period of eight days in patients with mild essential hypertension. Finally, the preliminary results of a second intervention trial at the Oregon Health Science University confirm that treatment with 1,000 mg of elemental calcium results in significant reductions in systolic and diastolic pressures in elderly (mean age, 60) hypertensive patients with primary elevations of systolic blood pressure [54]. One preliminary report did not show any significant overall effect of dietary calcium on blood pressure in hypertensive patients, although the authors acknowledge that some subjects did experience a substantial reduction in arterial pressure [58].

CALCIUM TRANSPORT IN HUMAN AND EXPERIMENTAL HYPERTENSION

The paradox that both added dietary calcium and calcium antagonists will lower blood pressure and theoretically lower the concentration of intracellular free calcium remains a major intellectual challenge. In recent experiments, we demonstrated that providing supplemental calcium to spontaneously hypertensive rats resulted in significant changes in calcium influx [59]. We isolated vascular strips obtained from animals treated with a 2 percent calcium diet for 16 weeks. A significant reduction in arterial pressure was demonstrable in these rats. The initial calcium influx in the strips was actually increased in the animals provided with supplemental calcium. The fact that basal tone did not increase in these vessels is consistent with an effect of supplemental calcium: to improve the ability of the vascular tissue to handle cytosolic calcium. The initial increase in calcium influx would otherwise be associated with an increase in basal vascular tone. We hypothesize that supplemental calcium in the spontaneously hypertensive rat either increases intracellular binding of calcium or sequestration by either activating an intracellular binding site or increasing the activity of an intracellular calcium pump.

We and others have noted significant differences in calcium ATPase pump activity in hypertensive subjects [31,32]. In our initial calcium intervention trial, calcium ATPase pump activity of red blood cell lysates was significantly lower in hypertensive than in normal subjects prior to calcium supplementation [10,32]. The reduced activity

of the calcium ATPase pump correlates with mean arterial pressure, which also correlates with dietary calcium intake. The differences in calcium ATPase pump activity between hypertensive and normal subjects were no longer evident after eight weeks of calcium supplementation. These findings are consistent with the hypothesis that dietary calcium supplementation influences primary intracellular mechanisms regulating cytosolic free calcium concentrations.

THEORETIC RESOLUTION OF THE CALCIUM PARADOXES

These data indicate that cellular handling, particularly in vascular tissue, is abnormal in both experimental and essential hypertension. The evidence suggests that calcium ATPase pump activity is reduced both in essential hypertension and in the spontaneously hypertensive rat. This decreased pump activity then contributes to an accumulation of intracellular free calcium, to an abnormal increase in vascular reactivity and, ultimately, to an increase in peripheral vascular resistance and blood pressure. In addition, this deregulation of the calcium pump may contribute to the reduced calcium transport of the intestine and inappropriate renal losses of calcium. Failure to absorb intestinal calcium, coupled with increased renal losses, would further exacerbate the effects of low dietary calcium intake.

Since increasing dietary calcium normalizes extracellular calcium and blood pressure as well as the vascular properties of the spontaneously hypertensive rat, the quantity of calcium intake may play a critical role in intracellular calcium regulation [7]. The abnormal intracellular calcium regulation reflected in the reduced calcium ATPase activity may simply reflect inadequate dietary calcium exposure and resulting failure of pump activation. Conversely, a genetic defect in the intracellular binding of calcium to specific binding sites in a calcium binding protein, calmodulin, may be important. Preliminary studies in the spontaneously hypertensive rat do suggest a modification of calmodulin's binding activity in this animal's brain [60,61].

Low intake of calcium, coupled with decreased intestinal transport and renal reabsorption, could thus initiate a chain of events resulting in increased parathyroid hormone, decreased extracellular free calcium, and increased intracellular cytosolic calcium (**Figure 1**).

Further studies are needed to verify that supplemental calcium normalizes intracellular free calcium and improves the cell's handling of calcium, either through active transport or through binding of the cation. It will also be necessary to determine whether restriction of dietary calcium further exacerbates the organ and cellular defects of calcium metabolism. Another question is whether calcium supplementation in either the laboratory or the clinical setting actually normalizes these defects in calcium transport, either in cells such as platelets or in organs such as intestine and kidney. When these data become available, the seeming paradox that blood pressure is lowered both by increased calcium intake and calcium channel blockers may be resolved. The current utility of calcium channel blockers in the management of essential hypertension may partially depend upon abnormal calcium handling by cells. This abnormality may partially reflect long-term reduced exposure to calcium.

ACKNOWLEDGMENT

We are indebted to Gloria Ellis for assistance in preparing the manuscript.

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