EDITORIALES

Sodium and calcium metabolism in the pathophysiology of essential hypertension

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In recent years the role of sodium and calcium in the pathogenesis of essential hypertension has been extensively investigated. In this manuscript we will review the evidence pointing to a role of sodium and the controversies surrounding the role of calcium in the pathogenesis of essential hypertension.

1. SALT AND HYPERTENSION

Epidemiologic Studies

Several epidemiologic cross-sectional studies of isolated populations have shown a relationship between dietary sodium intake and the prevalence of hypertension [1-14]. On the other hand, most studies of individuals within populations have failed to show a causal relationship between sodium intake and blood pressure [15-17]. This may be due to the small number of individual studied, the large day-to-day variation of sodium intake and the limited range of sodium intake. Indeed, studies of populations with a larger range of salt intake, such as the Japanese, the Koreans and Indians, have shown a relationship between the daily urinary sodium excretion and blood pressure [15, 18, 19].

More recently, the Intersalt Study has evaluated 10,079 men and women from 29 to 59 years of age, sampled from 52 centers around the world [20]. This study has shown a weak, albeit significant, correlation between, 24-hr urinary sodium excretion and blood pressure, even when age, body mass index and alcohol consumption were taken into account.

Intervention studies add further support to the notion of a causal relationship between sodium intake and hypertension. Moderate sodium restriction to a level of 60-90 mmol/day lowers blood pressure in a large number of patients and the degree of fall in blood pressure is related to pretreatment blood pressure levels: the greater the baseline blood pressure, the greater the decrease following sodium restriction [21].

In Belgium and Japan extensive educational campaigns aimed at reducing the daily salt consumption have resulted in a decrease in the prevalence of hypertension and cerebrovascular accidents [22, 23].

Very recently, it has been suggested that the chloride ion may be equally important. Kurtz et al. [24] have compared the effects of sodium chloride and sodium citrate on blood pressure in a double-blind, placebo controlled, cross-over trial in 5 men with hypertension. The administration of 240 mmol of sodium chloride per day for one week induced a significant expansion of plasma volume and an increase in blood pressure, whereas the administration of an equimolar amount of sodium as sodium citrate resulted in no change in plasma volume and in blood pressure.

Salt-Sensitivity and Salt-Resistance

Kawasaki et al. [25] were the first to study the effect of a very low (10 mEq/day) or of a high (200 mEq/day) dietary sodium intake on blood pressure in patients with essential hypertension kept on a metabolic ward. They observed that approximately half of their patients displayed a rise in blood pressure greater than 10 % when fed a high dietary sodium intake. We also found that in only 60 % of patients with essential hypertension a high dietary sodium intake increases blood pressure more than 10 % (salt-sensitive), whereas blood pressure remained unchanged in the remaining patients (salt-resistant) [26].

The mechanisms linking sodium intake with hypertension are complex. Some have postulated a genetic defect involving the ability of the kidney to excrete a sodium load. As consequence of this defect, when susceptible subjects are exposed to a high dietary sodium intake, they would retain sodium and expand their blood volume. This, in turn, would stimulate the secretion of an inhibitor of the sodium pump which, on one hand, it would cause natriuresis and re-establish sodium balance, on the other hand would enhance sodium entry into smooth muscle

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cells and into sympathetic nerve terminals, causing increased vascular contraction and increased norepinephrine release[27].

Several lines of evidence point to a primacy of the kidney in the genesis of hypertension. Renal cross-transplant studies in different strains of genetically hypertensive rats, have shown that hypertension is transferred with the "hypertensive kidney"[28-30]. Isolated kidneys from Dahl's salt-sensitive prehypertensive rats excrete sodium much slower than kidneys from resistant rats[31]. Moreover, Na, K-ATPase activity was increased in 5 week old SHR compared with WKY[32]. Transplantation of kidneys from normotensive donors resulted in normalization of blood pressure in hypertensive recipient patients[33]. Finally, normotensive siblings of hypertensive patients excrete an acute salt load more slowly than siblings of normotensive patients[34].

On the other hand, ample evidence is available both in human subjects as well as in animals, to support the notion that the renal defect in sodium excretion and the rise in blood pressure in response to sodium loading, may be related to enhanced activity of the sympathetic nervous system. An inverse relationship between urinary sodium excretion and plasma levels of norepinephrine was present in normal but not in hypertensive subjects[35]. Plasma norepinephrine concentrations were not different among normal subjects, salt-resistant and salt-sensitive patients while ingesting a low-sodium diet. However, plasma norepinephrine concentration decreased in normal subjects and in salt-resistant patients, but not in salt-sensitive patients during high salt intake. A significant correlation was found between the changes in plasma norepinephrine and the changes in blood pressure observed during the 2 diets[26]. The data suggest that the response of the sympathetic nervous system to high dietary sodium intake is abnormal in salt-sensitive patients and that it may contribute to the genesis of hypertension in this subset of patients. Evidence from animal studies, also support this concept[35-39].

The mechanisms responsible for the greater activation of the sympathetic nervous system during high dietary sodium intake are not clear. Winternitz and Oparil[39] have shown increased norepinephrine content in the dorsomedial and anterior hypothalamic nuclei suggesting a central mechanism. Kopke and DiBona[37] observed that high sodium intake potentiated the increase in renal sympathetic nerve activity and the decrease in urinary sodium excretion resulting from air-stress in conscious SHR, suggesting a centrally mediated facilitation of sympathetic neural outflow to the kidney. Chen et al.[40] have recently shown that high dietary sodium intake in salt-sensitive SHR may elevate blood pressure by reducing neuroadrenergic input to depressor neurons in the anterior hypothalamus and by increasing noradrenergic input to neurons in the pons.

Dietz et al.[41] observed that high dietary sodium intake caused a reduction in norepinephrine uptake in the sympathetic nerve terminals of stroke-prone SHR, pointing to a peripheral mechanism of activation of the sympathetic nervous system.

We have recently proposed that salt sensitivity may be related to a deranged modulation of the sympathetic and of the renin-angiotensin-aldosterone systems in reponse to a high dietary sodium intake[42]. In normal subjects, normal sodium balance is maintained by increased activity of the renin-angiotensin and the sympathetic nervous systems during a low sodium diet and by decreased activity of these two systems during high dietary sodium intake. Blood pressure, under those circumstances, does not change.

In salt-resistant hypertensive patients, the modulatory influence of dietary sodium on the renin-angiotensin and the sympathetic nervous systems remains unchanged, albeit it is reset to a greater level of blood pressure. This reset is probably dependent upon an increase in renal vascular resistance. In salt-sensitive patients, the increase in renal vascular resistance causes a similar shift to the right of the pressure-natriuresis curve. However, these patients also display abnormalities in tubular reabsorption of sodium causing a depression of the slope of the pressure-natriuresis curve. The cause of this derangement in salt-sensitive patients is probably related to an abnormal modulation of the sympathetic and renin-angiotensin systems in response to changes in dietary sodium. In response to a low dietary sodium intake, salt-sensitive patients display a blunted increase in plasma norepinephrine and renin, leading to less sodium retention and to more negative sodium balance. During ingestion of excessive sodium, these patients have less suppression of plasma renin and an increase, rather than a decrease, in plasma norepinephrine levels, leading to blunted natriuresis, to a positive sodium balance, and to a further rise in blood pressure.

2. CALCIUM AND HYPERTENSION

Calcium is an important mediator of the activity of several hormones on the cardiovascular system, thus contributing to blood pressure regulation.

In recent years, evidence has been accumulating to suggest that abnormalities of calcium metabolism may play an important role in the pathogenesis of essential hypertension.

A wide range of abnormalities of calcium metabolism have been shown both in human subjects, as well in rats with spontaneous hypertension. These derangments include: hypercalciuria, decreased in-

testinal absorption of calcium, low calcium intake, reduced serum ionized calcium, increased cytosolic calcium, increased serum levels of parathyroid hormone, reduced serum levels of Vitamine D_3, and abnormalities in cell membrane transport of calcium.

Hypercalciuria has been shown both in patients with essential hypertension, as well as in SHR [43-48]. McCarron [49] suggested that hypercalciuria may be secondary to renal tubular calcium leak. Hypercalciuria, in fact, seems to occur independently of urinary sodium excretion [49].

However, some investigators have suggested that hypercalciuria may be secondary to volume expansion since it occurs in the animal model of DOCA-salt hypertension and it persists even when urinary sodium excretion reaches steady-state [50].

Intestinal calcium absorption in SHR has been found to be reduced in some studies [51, 52], but normal or even increased in others [53, 54]. We have recently evaluated intestinal calcium absorption in a group of patients with essential hypertension and we were unable to detect any abnormality of intestinal calcium absorption in this group of patients [55].

Recently, based on an analysis of the U. S. National Health and Nutrition Examination Survey I (NHANES I), it has been proposed that the lesser the dietary intake of calcium in a given population, the greater is the probability of developing hypertension [56]. Other investigators, however, have analyzed the same data and reached different conclusions. Feinleb et al. [57] found no difference in dietary calcium intake between normotensive and hypertensive subjects when corrections were made for age and body weight. Harlan et al. [58] found an inverse relationship between dietary calcium intake and diastolic blood pressure in women, but a direct correlation with systolic blood pressure in men.

Two other epidemiologic studies have failed to show a significant correlation between dietary calcium intake and the prevalence of hypertension [59, 60]. Witteman et al. [61], on the other hand, surveyed 58,000 U. S. females and found an inverse relationship between dietary calcium intake and prevalence of hypertension even when age, body weight and alcohol consumption was taken into account.

Severe calcium restriction (0.25-0.5 %) aggravates hypertension in SHR, whereas mild calcium restriction has no effect on the development of hypertension in these animals [62]. It must be pointed out that severe dietary calcium restriction also results in deficiency of other dietary constituents, such as magnesium, and in increased levels of parathyroid hormones which, per se, can result in aggravation of blood pressure [63, 64].

Hypocalcemia has been described both in human subjects with essential hypertension, as well as in SHR [49, 65]. McCarron [65] was the first to describe decreased serum ionized calcium in human subjects with essential hypertension. Resnick et al. [66], on the other hand, observed decreased serum ionized calcium only in patients with low renin, but not in those with normal or high renin. Other investigators have been unable to confirm these findings, even when renin levels were taken into consideration [67-69]. Total serum calcium is usually normal [65] or even increased [70] in patients with essential hypertension.

Inconsistencies on serum ionized calcium are also present in animal studies. Some investigators have observed reduced serum ionized calcium in SHR [49]; wereas, others have found increased levels when serum ionized calcium was measured at midnight, after the animals had ingested their meals [47].

Hypocalcemia has also been observed in other forms of experimentally induced hypertension, such as in the DOCA-salt and in the 5/6 nephrectomy models [70], suggesting that hypocalcemia may be a secondary rather than a primary phenomenon.

Effect of calcium supplementation on blood pressure. The ultimate proof for a role of calcium deficiency in hypertension should derive from intervention studies. If the abnormalities of calcium metabolism in hypertension were related to calcium deficiency, adequate calcium supplementations capable of maintaining a positive calcium balance should result in normalization or in improvement of blood pressure.

Experiments in several animal models of hypertension appear to support this notion. Calcium supplementations reduce blood pressure in SHR [49, 71], in Dahl's salt-sensitive rats [72], in DOCA-salt hypertensive rats [73], and in the two-kidney-one-clip model of renovascular hypertension [74]. SHR pups fostered at birth to high-calcium (2 %) SHR dams developed significantly lower levels of blood pressure that pups fostered to low-calcium (0.01 %) dams [75].

Less convincing are the results from intervention trials in human subjects with essential hypertension. Belizan et al. [76] have shown that calcium supplementations (1 g/day) significantly reduced blood pressure in normal subjects.

McCarron and Morris [77], however, showed no effect of calcium supplementation (1 g/day for 8 weeks) on blood pressure in normal subjects, but a significant decrease in patients with essential hypertension.

The decrease in blood pressure was significant only during the upright posture.

Several other investigators have evaluated the effect of calcium supplementations on blood pressure in patients with essential hypertension reaching conflicting conclusions. Some have found a significant reduction in blood pressure [76-79], wereas others could not find any significant beneficial effect of this intervention [80-83]. Resnick et al. [84] observed a significant reduction in blood pressure in patients with low, but not in those with normal or high renin. Zemel et

al.[85] found that calcium supplementatins reversed the rise in blood pressure caused by high dietary sodium intake in six black hypertensive patients.

In this study, the antihypertensive action of calcium supplementation was attributed to natriuresis and to a reduction in blood volume.

In conclusion, the available data indicate that the antihypertensive action of calcium in human subjects is minimal and possibly limited to salt-sensitive patients with essential hypertension.

3. POSSIBLE RELATION BETWEEN ABNORMALITIES OF SODIUM AND CALCIUM METABOLISM IN ESSENTIAL HYPERTENSION

The abnormalities of calcium metabolism and the antihypertensive efficacy of calcium supplementations appear to be evident primarely in salt-sensitive patients with essential hypertension. This raises the possibility that there may be a link between the abnormalities of sodium and those of calcium metabolism in essential hypertension.

A current hypothesis to explain the link between high dietary sodium intake and hypertension suggest the presence of a defect in sodium-linked cellular calcium transport, perhaps mediated by an inhibitor of the Na-K-ATPase pump[27]. This derangement of cellular sodium and calcium transport may result in shift of calcium inside the cells, when a patient ingest a diet with high sodium content. This could possibly explain the decrease in serum ionized calcium in salt-sensitive patients. Moreover, an increase in intracellular calcium in the juxtaglomerular cells may lead to inhibition of release of renin, since calcium is an inhibitory second messenger in the renin secretory process[86]. An increase of cytosolic calcium in the sympathetic nerve terminals could stimulate norepineprine release[87, 88], and it could potentiate vascular response to pressor agonists[89] (Fig. 2).

References

1. Prior IAM, Evans JG, Harvey HPB, Davidson F and Lindsey M: Sodium intake and blood pressure in two Polynesian populations. *New Engl J Med* 279:515-520, 1968.
2. Page LB, Danion A and Moellering RC Jr: Antecedents of cardiovascular disease in six Solomon Islands societies. *Circulation* 49:1132-1146, 1974.
3. Oliver WJ, Cohen EL and Neel JV: Blood pressure, sodium intake and sodium related hormones in the Yanomamo Indians, a "no-salt" culture. *Circulation* 52:146-151, 1975.
4. Sinnett PF, White HA and Whyte HM: Epidemiological studies in a total highland population, Tuki Senta, New Guinea: cardiovascular disease, relevant clinical, electrocardiographic radiological and biochemical findings. *J Chronic Dis* 26:265-290, 1973.
5. Prior IAM, Grimley-Evans J, Harvey HPB, Davidson F and Lindsey M: Sodium intake and blood pressure in two Polynesian populations. *N Engl J Med* 279:515-520, 1968.
6. Dahl LK: The possible role of chronic excess salt consumption in the pathogenesis of essential hypertension. *Am J Cardiol* 8:571-575, 1961.
7. Staessen J, Fagard R, Lijnen P, Amery A, Bulpitt C and Joossens JV: Salt and blood pressure in Belgium. *J Epidemiol Community Health* 35:256-261, 1981.
8. Strazzullo P, Trevisan M, Farinaro E et al.: Characteristics of the association between salt intake and blood pressure in a sample of male working population in southern Italy. *Eur Heart J* 4:608-613, 1983.
9. Beevers DG, Hawthorne BM and Padfield PL: Salt and blood pressure in Scotland. *Br Med J* 281:641-642, 1980.
10. Tuomilehto J, Karppanen H, Tanskanen A, Tikkanen J and Vuori J: Sodium and potassium excretion in a sample of normotensive and hypertensive persons in eastern Finland. *J Epidemiol Community Health* 34:174-178, 1980.
11. Takamatsu M: Figure of body fluid of farmers in the northeastern districts viewed from angle of water and salt metabolism. *J Sci Lab* (Rodo Kagaku) 31:349-370, 1955.
12. Isaacson LC, Modlin M and Jackson WPU: Sodium intake and hypertension. *Lancet* 1:946, 1963.
13. Fukuda T: Investigation on hypertension in farm villages in Akita Schiba Igakki, Szasshi. *Chiba Med Soc* 29:490-502, 1954.
14. Simpson FO: Salt and hypertension: current data, attitudes and policies. *J Cardiol Pharmacol* 6:S4-S9, 1984.
15. Kesteloot H, Park BC, Lee CS, Brems-Heyns E and Joossens JV: A comparative study of lood pressure and sodium intake in Belgium and in Korea. In: Kesteloot H and Joossens JV (eds). *Epidemiology of arterial blood pressure*. The Hague: Martinus Nijhoff, 453-470, 1980.
16. Ljungman S, Aurell M, Hartford M, Wikstrand J, Wilhelmsen I and Berglund G: Sodium excretion and blood pressure. *Hypertension* 3:318-326, 1981.
17. Simpson FO, Waal-Manning H, Bolli P, Phelan EL and Spears GFS: Relationship of blood pressure to sodium excretion in a population survey. *Clin Sci Mod Med* (suppl) 55:373s-375s, 1978.
18. Yamori Y, Kihara M, Nara Y et al.: Hypertension and diet: multiple regression analysis in a Japanese farming community. *Lancet* 1:120, 1981.
19. Mir MA, Mir F and Khosla T: High incidence of hypertension in heavy salt consuming population of northern Kashmir (Abstract). *Circulation* 70 (suppl II):II-359, 1984.
20. Intersalt Cooperative Research Groupe. Intersalt: an international study of electrolyte excretion and blood pressure. Results for 24 hours urinary sodium and potassium excretion. *Brit Med J* 297:319-328, 1988.
21. MacGregor GA: Sodium is more important than calcium in essential hypertension. *Hypertension* 7:638-637, 1985.
22. Joossens JV and Geboers J: Salt and hypertension. *Prev Med* 12:53-59, 1983.
23. National Nutritional Survey. Ministry of Health & Welfare, Koseisho, Japan, 1981.
24. Kurtz TW, Al-Bander HA and Morris RC Jr: Salt-sensitive essential hypertension in men: is the sodium ion alone important? *N Engl J Med* 317:1043-1048, 1987.
25. Kawasaki T, Delea CS, Bartter FC and Smith H: The effect of high-sodium and low-sodium intakes on blood pressure and other related variables in human subjects with idiopathic hypertension. *Am J Med* 64:193-198, 1978.
26. Campese VM, Romoff MS, Levitan D, Saglikes Y, Friedler RM and Massry SG: Abnormal relationship between sodium intake and sympathetic nervous activity in salt-sensitive patients with essential hypertension. *Kidney Int* 21:371-378, 1982.
27. Blaustein MP: Sodium ions, calcium ions, blood pressure regulation and hypertension: A reassessment and a hypothesis. *Am J Physiol* 232:165-173, 1977.

28. Dahl LK and Heine M: Primary role of renal homografts in setting blood pressure levels in rats. *Circ Res* 36:692-696, 1975.
29. Kawabe K, Watanabe TX, Shiono K and Sokabe H: Influence on blood pressure of renal isografts between spontaneously hypertensive and normotensive rats, utilizing the F_1 hybrids. *Jap Heart J* 19:886-893, 1978.
30. Bianchi G, Fox U, DiFrancesco GF, Giovannetti AM and Pagetti D: Blood pressure changes produced by kidney cross-transplantation between spontaneously hypertensive rats (SHR) and normotensive rats (NR). *Clin Sci Mol Med* 47:435-448, 1974.
31. Tobian L, Lange J, Azar S, Iwai J, Koop D, Coffee K and Johnson MA: Reduction of natriuretic capacity and renin release in isolated blood-perfused kidneys of Dahl hypertension-prone rat. *Circ Res* 43 (suppl 1):92, 1978.
32. Cangiano JL, Rodríguez-Sargent C, Opava-Stitzer S and Martínez-Maldonado M: Renal Na^+-K^+-ATPase in weanling and adult spontaneously hypertensive rats. *Proc Soc Exp Biol Med* 177:240-246, 1984.
33. Curtis JJ, Luke RG, Dustan HP et al: Remission of essential hypertension after renal transplantation. *N Engl J Med* 309:1009-1015, 1983.
34. Grim CE, Luft FC, Miller JZ, Brown PL, Gannon MA and Weinberger MH: Effects of sodium loading and depletion in normotensive first-degree relatives of essential hypertension. *J Lab Clin Med* 94:764-771, 1979.
35. Katholi RE: Renal nerves in the pathogenesis of hypertension in experimental animals and humans. *Am J Physiol* 245:F1-F14, 1983.
36. Lundin S and Thoren P: Renal function and sympathetic activity during mental stress in normotensive and spontaneously hypertensive rats. *Acta Physiol Scan* 115:115-124, 1982.
37. Koepke JP and DiBona GF: High sodium intake enhances renal nerve and antinatriuretic responses to stress in spontaneously hypertensive rats. *Hypertension* 7:357-363, 1985.
38. Winternitz SR, Katholi RE and Oparil S: Role of the renal sympathetic nerves in the development and maintenance of hypertension in spontaneously hypertensive rat. *J Clin Invest* 66:971-978, 1980.
39. Winternitz SR and Oparil S: Sodium-neural interactions in the development of spontaneous hypertension. *Clin Exp Hypertension* 4:751-760, 1982.
40. Chen YF, Meng Q, Wyss JM, Jin H and Oparil S: High NaCl diet reduces hypothalamic norepinephrine turnover in hypertensive rats. *Hypertension* 11:55-62, 1988.
41. Dietz R, Schomig A, Rascher W, Strasser R and Kubler W: Enhanced sympathetic activity caused by salt loading in spontaneously hypertensive rats. *Clin Sci* 59:171s-173s, 1980.
42. Campese VM: Effects of calcium antagonists on deranged modulation of the renal function curve in salt-sensitive patients with essential hypertension. *Am J Cardiol* (in press, 1988).
43. McCarron DA, Pingree PA, Rubin RJ, Gaucher SM, Molitch M and Krutzik S: Enhanced parathyroid function in essential hypertension, a homeostatic response to a urinary calcium leak. *Hypertension* 2:162-168, 1980.
44. Kesteloot H and Geboers J: Calcium and blood pressure. *Lancet* 1:813-815, 1982.
45. Staessen J, Bulpitt C, Fagard R, Joossens JV, Lunen P and Ailery A: Four urinary cations and blood pressure: A population study in two belgian towns. *Am J Epidemiol* 117:676-687, 1983.
46. McCarron DA, Yung NN, Ugoretz BA and Krutzik S: Disturbances of calcium metabolism in the spontaneously hypertensive rat. *Hypertension* 3 (suppl I):I162-I167, 1981.
47. Lau K, Zikos D, Spirnak J and Eby B: Evidence for an intestinal mechanism in hypercalciuria of spontaneously hypertensive rats. *Am J Physiol* 247:E625-E633, 1984.
48. Binchi G, Ferrari P, Salvati P et al.: A renal abnormality in the Milan hypertensives train of rats and in humans predisposed to essential hypertension. *J Hypertens* 4 (suppl 3):S33-S36, 1986.
49. McCarron DA: Is calcium more important than sodium in the pathogenesis of essential hypertension? *Hypertension* 7:607-627, 1985.
50. Massry SG, Coburn JW, Chapman LW and Kleeman CR: The effect of long-term desoxycorticosterone acetate administration on the renal excretion of calcium and magnesium. *J Lab Clin Med* 71:212-219, 1968.
51. Lucas PA, Brown RC, Drueke T, Lacour B, Metz JA and McCarron DA: Abnormal vitamin D metabolism, intestinal calcium transport, and bone calcium status in the spontaneously hypertensive rat compared with its genetic control. *J Clin Invest* 78:221-227, 1986.
52. McCarron DA, Lucas PA, Shneidman RS and Drueke T: Blood pressure development of the spontaneously hypertensive rat following concurrent manipulation of the dietary Ca^{2+} and Na^+: Relation to intestinal Ca^{2+} fluxes. *J Clin Invest* 76:1147-1154, 1985.
53. Lau K, Langman LB, Gafter V, Dudeja PK and Brasitus TA: Increased calcium absorption in prehypertensive spontaneously hypertensive rat. Role of serum 1,25-Dihydroxy vitamin D_3 levels and intestinal brush border membrane fluidity. *J Clin Invest* 78:1083-1090, 1986.
54. Gafter U, Kathpalia S, Zikos D and Lau K: Ca fluxes across duodenum and colon of spontaneously hypertensive rats. Effect of $1,25(OH_2)D_3$. *Am J Physiol* 251:F278-282.
55. Gadallah M, Massry SG and Campese VM: Intestinal absorption of calcium in patients with essential hypertension. Am Soc Nephrol 22nd Ann Meet, Dec. 3-6, 1989.
56. McCarron DA, Morris CD, Henry HJ and Stanton JL: Blood pressure and nutrient intake in the United States. *Science* 224:1392-1397, 1984.
57. Feinleib M, Lenfant C and Miller SA: Hypertension and calcium. *Science* 226:384-389, 1984.
58. Harlan WR, Hull AL, Schmouder RL, Landis JR, Larkin FA and Thompson FE: High blood pressure in older Americans: The First National Health and Nutrition Examination Survery. *Hypertension* 6:802-809, 1984.
59. Gruchow HW, Sobocinski KA and Barboriak JJ: Alcohol, nutrient intake, and hypertension in US adults. *JAMA* 253:1567-1570, 1985.
60. Reed D, McGee D, Yano K and Hankin J: Diet, blood pressure, and multicollinearity. *Hypertension* 7:405-410, 1985.
61. Witteman JCM, Willett WC, Stampfer MJ et al.: Dietary calcium and magnesium and hypertension: a prospective study (Abstract). *Circulation* 76 (suppl IV):35, 1987.
62. McCarron DA: Calcium metabolism and hypertension. *Kidney Int* 35:717-736.
63. Altura BM, Altura BT and Gebrewold A: Magnesium deficiency and hypertension: correlation between magnesium-deficient diets and microcirculatory changes in situ. *Science* 223:1315-1317, 1984.
64. Rosenthal FD and Roy S: Hypertension and hyperparathyroidism. *Br Med J* 4:396-397, 1972.
65. McCarron DA: Low serum concentrations of ionized calcium in patients with hypertension. *N Engl J Med* 307:226-228, 1982.
66. Resnick JM, Laragh JH, Sealey JE and Alderman MH: Divalent cations in essential hypertension: relations between serum ionized calcium, magnesium and plasma renin activity. *N Engl J Med* 309:888-891, 1983.
67. Kesteloot H, Geboers J, Math L and Van Hoof R: Epidemiological study of the relationship between calcium and blood pressure. *Hypertension* 5 (suppl II):52-56, 1983.
68. Strazzullo P, Nunziata V, Cirillo M, Giannattasio R, Ferrara LA, Mattioli PL and Mancini M: Abnormalities of calcium metabolism in essential hypertension. *Clin Sci* 65:137-141, 1983.
69. Freeman RM, Lawton WJ, Friedlander MA and Fitz AE: Cal-

cium, sodium, magnesium and renin interrelationship in hypertension (Abstract). *Circulation* 72 (suppl III):III-421, 1985.
70. Wright GL and Rankin GO: Concentration of ionic and total calcium in plasma of four models of hypertension. *Am J Physiol* 243:H365-H370, 1982.
71. Stern N, Lee DBN, Silis V, Beck FW, Deftos L, Manolagas SC and Sowers JR: Effect of high calcium intake on blood pressure and calcium metabolism in young SHR. *Hypertension* 6:639-646, 1984.
72. Peuler JD, Morgan DA and Mark AL: High calcium diet reduces blood pressure in DAHL salt-sensitive rats by neural mechanisms. *Hypertension* 9 (suppl III):159-165, 1987.
73. Kurtz TW and Morris RC: Attenuation of deoxycorticosterone-induced hypertension by supplemental dietary calcium. *J Hypertension* 4 (suppl 5):S182-S191, 1986.
74. Kageyama Y, Suzuki H, Arima K and Saruta T: Oral calcium treatment lowers blood pressure in renovascular hypertensive rats by suppressing the renin-angiotensin system. *Hypertension* 10:375-382, 1987.
75. Muntzel MS, Hatton DC, Metz JA and McCarron DA: Dietary calcium alters blood pressure in neonatal spontaneously hypertensive rats. *Am J Hypertension* 2:158-162, 1989.
76. Belizan JM, Villar J, Pineda O et al.: Reduction of blood pressure with calcium supplementation in young adults. *JAMA* 249:1161-1165, 1983.
77. McCarron DA and Morris CD: Blood pressure response to oral calcium in persons with mild to moderate hypertension. *Ann Intern Med* 103:825-831, 1985.
78. Luft FC, Aronoff GR, Sloan RS, Fineberg NS and Weinberger MH: Short-term augmented calcium intake has no effect on sodium homeostasis. *Clin Pharmacol Ther* 39:414-419, 1986.
79. Tabuchi Y, Ogihara T, Hashizume K et al.: Hypotensive effect of long-term oral calcium supplement in elderly patients with essential hypertension. *J Clin Hypertension* 3:254-262, 1986.
80. Strazzullo P, Siani A, Galletti F et al.: A controlled clinical trial of long term oral calcium supplementation in arterial hypertension (Abstract #512). In *Program of the 2nd European Meeting on Hypertension*. Milan. University of Milan, 1985.
81. Singer DR, Markandu ND, Carpuccio FP et al.: Does oral calcium lower blood pressure: a double blind-study. *J Hypertens* 3:661-671, 1985.
82. Meese RB, González DG, Casparian JM, Ram CV, Pak CY and Kaplan NM: Failure of calcium supplements to relieve hypertension (Abstract). *Clin Res* 34:218A, 1986.
83. Cappuccio FP, Markandu ND, Singer DRJ, Smith SJ, Shore AC and MacGregor GA: Does oral calcium supplementation lower high blood pressure? A double blind study. *J Hypertens* 5:67-71, 1987.
84. Resnick LM, Nicholson JP and Laragh JH: Dietary Salt, Calcium Metabolism, and the Antihypertensive Efficacy of Calcium Channel Blockade. *Kidney Int* 29:257, 1986.
85. Zemel MB, Gualdoni SM and Sowers JR: Sodium excretion and plasma renin activity in normotensive and hypertensive black adults as affected by dietary calcium and sodium. *J Hypertens* 4 (suppl 6):S343-345, 1986.
86. Churchill PC: Calcium channel antagonists and renin release. *Am J Nephrol* 7 (suppl 1):32-38, 1987.
87. Rubin RP: The role of calcium in the release of neutrotransmitter substances and hormones. *Pharmac Rev* 22:389-427, 1970.
88. Blaustein MP, Ratzlaff BW and Kendrick NK: The regulation of intracellular calcium in presynaptic nerve terminals. *Ann NY Acad Sci* 307:195-211, 1978.
89. Johansson B: Vascular smooth muscle reactivity. *Ann Rev Physiol* 43:359-370, 1981.