Brief Review

Dietary Calcium and Blood Pressure in Experimental Models of Hypertension

A Review

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Restricted dietary calcium intake has been linked to elevated blood pressure in a number of epidemiologic studies. These findings, in conjunction with indications of calcium deficiency in clinical hypertension, suggest that repletion of dietary calcium may have a beneficial effect on blood pressure. This possibility has been explored extensively in both humans and animal models of hypertension. In this article, we review the animal work relating dietary calcium to blood pressure and examine some of the mechanisms that may be responsible. Much of the content is based on published experiments and earlier reviews by our laboratory on this subject.[1-3]

Background

Calcium Metabolism in Experimental and Essential Hypertension

More than 20 epidemiologic investigations have reported an inverse relation between dietary calcium intake and blood pressure status.[4-28] The increased risk of elevated blood pressure with lower calcium intake appears to be related to an apparent deficit in calcium metabolism that occurs in a subset of hypertensive individuals. That deficit appears systemically as a small increase in circulating parathyroid hormone (PTH)[29,30] levels, reduced serum phosphorus,[31] and increased urinary calcium excretion.[32-38] At the cellular level, the deficit in calcium metabolism is reflected in elevated intracellular free calcium levels, as indicated by studies examining platelets isolated from individuals with essential hypertension.[39-47]

The alterations in calcium metabolism observed in hypertensive humans are mirrored in experimental models of hypertension. Plasma ionized calcium has been reported to be decreased in the spontaneously hypertensive rat (SHR) relative to the normotensive Wistar-Kyoto (WKY) rat,[48-51] whereas PTH has been observed to be either elevated or unchanged.[49,51] End-organ responsiveness to PTH appears to be abnormal based on findings of hypercalciuria,[51-54] decreased basal and stimulated 1,25-dihydroxyvitamin D_3 [1,25$(OH)_2$ vitamin D_3] production,[55-58] and low to normal urinary nephrogenous cyclic AMP in the presence of elevated PTH.[52,59,60] At the cellular level, SHR exhibit depressed ATP-dependent calcium uptake capacity in crude microsomal fractions of aorta as well as in more purified sarcolemmal fractions of the mesenteric artery.[61-66] Therefore, it has been suggested that the vascular myocyte may not be able to maintain normal levels of intracellular calcium or properly remove calcium after activation.[67] It appears that the cell membrane of the SHR as exemplified by platelets and lymphocytes may be hyperpermeable to calcium because both basal and agonist-stimulated calcium uptake have been found to be elevated in the SHR.[68-71] Consequently, the SHR has abnormally high intracellular free calcium levels, as has been observed in essential hypertensive patients.

The inverse relation between dietary calcium and blood pressure identified through epidemiologic investigations suggests that supplemental dietary calcium may lower blood pressure. Numerous studies have tested this possibility. Of the published studies of calcium supplementation in humans, 24 reported a significant reduction in blood pressure[72-95] in at least a segment of the study population, and 13 reported no difference in blood pressure.[96-108] Recent reviews of these data[109,110] indicated a modest, dose-dependent effect of calcium supplementation on blood pressure that may be most important in certain subsets of the population. These subsets include African Americans,[111-113] women with gestational hypertension,[83-88] or salt-sensitive individuals.[90-92] Low calcium intake may be an especially important indicator because very low calcium diets (<400 to 600 mg/d) are most closely associated with elevated blood pressure,[5,20-22,24,27,114,115] and work with experimental models indicates that low calcium diets elevate blood pressure (see below).

Dietary Calcium in Experimental Models of Hypertension

The outcome of calcium supplementation in experimental models of hypertension is much more consistent than it is in humans. As shown in Table 1, more than 80 studies have manipulated dietary calcium and measured blood pressure. Most have found an inverse relation between calcium intake and blood pressure. This relation has been found in a variety of genetic and experimental models of hypertension, including SHR; stroke-prone SHR; Dahl salt-sensitive (DS) rats; Lyon hypertensive rats; deoxycorticosterone-saline (DOC-saline) rats; one-kidney, one clip rats; and remnant kidney

Received May 25, 1993; accepted in revised form December 15, 1993.

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TABLE 1. Studies of Dietary Calcium and Blood Pressure in Experimental Animal Models

Study	Model	Calcium Diet	Age of Animal/ Treatment Length, wk*	Result in mm Hg SBP	Focus
Ambrozy et al 1991[116]	Zucker rat	0.5-1.5%	8/4	~↓ 30 in lean, ~↓ 20 in obese, $P<.05$	Vascular reactivity, VSM Ca^{2+} efflux
Anderson et al 1986[117]	Dog	$CaCl_2$, 115 mEq	2	No effect	Diet-stress interaction
Anderson et al 1983[118]	SHR (n=7-8)	0.02-4.0%	16/2	↓ 19 MAP, $P<.005$	Calcium balance, PTH
Ando et al 1991[119]	SD/Ang II/salt	1.17-4.07%	12 days	↓ 35 MAP, $P<.01$	SNS
Ayachi 1979[54]	SHR/WKY	1.2-2.5%	4/14	~↓ 21, $P<.05$	Metabolic study
Baksi 1988[120]	SD	0.005/0.17/1.4/ 2.8%	4/8	~↓ 30, $P<.05$	Pressor response
Baksi 1989[121]	SD	0.005/0.17/1.4/ 2.8%	4/8	↓ 34 MAP, $P<.05$	CNS NE
Baksi 1988[122]	SD/PTX	0.005/1.4/2.8%	4/8	↓ 43, $P<.05$	PTH
Baksi et al 1989[123]	SD	0.005-1.4%	4/8	~↓ 100, $P<.01$	RAS
Belizán et al 1981[124]	Pregnant SD (n=5,6)	0.0-0.6%	20/12	↓ 20, $P<.001$	Pregnancy-induced hypertension
Belizán et al 1984[125]	PTX Wistar (n=9)	0.0-0.6%	8/10	↓ 19, $P<.005$	PTH
Blakeborough et al 1990[126]	♀ SHR/WKY	0.06-0.6%	8/10	~↓ 16, $P<.05$	Intestine and kidney membrane enzyme
Bogden et al 1991[127]	Wistar rat	0.02-4.0%	~4/31	~↑ 10 MAP, $P<.05$	Lead-Ca^{2+} interaction neoplasia
Bukoski et al 1989[128]	SHR/WKY	0.5/1.0/2.0%	6/6 or 12	~↓ 12, $P<.05$	Vascular contractility
Bukoski and McCarron 1986[129]	SHR/WKY	1.0-2.0%	6/8 or 15	↓ 19, $P<.05$	Vascular contractility
DiPette et al 1990[130]	SD/DOC-salt	0.6-2.5%	~6/8	↓ 14 MAP, $P<.05$	Calcium-regulating hormones
Doris 1985[131]	♀ WKY/saline	1.0-2.5%	~8/26	↓ 10, $P<.01$	NaCl-Ca^{2+} interaction
Doris 1988[132]	♀ WKY/saline	1.0-2.0%	12/26	~↓ 7, $P<.05$	NE and PTH
Evans et al 1990[133]	SHR (n=9)	0.075/0.5/2.5%	8/23	~↓ 35, $P<.001$	Mg^{2+}-Ca^{2+} interaction
Fujito et al 1991[134]	SHR/WKY (n=5)	0.1/0.6/4.0%	6/14	~↓ 12, $P<.01$	Erythrocyte sodium transport
Furspan et al 1989[135]	SHRSP/WKY (n=6)	1.0-2.5%	10/9	↓ 58, $P<.05$	Membrane stability
Ganguli et al 1986[136]	DS rat (n=18)	0.5-3.0%	8/15	↓ 7 MAP, $P<.01$	$CaCO_3$ vs $CaHPO_4$
Geiger et al 1988[137]	SHR/PTX	0.1-3.0%	4/4	↓ 26, $P<.05$	ANP
Hano et al 1991[138]	SHR/WKY (n=10)	1.2% $CaCl_2$ in water	4/3	~↓ 25, $P<.01$	NE, platelet $[Ca^{2+}]_i$
Hatton et al 1986[139]	SHR (n=12/21)	0.1-2.0%	Prenatal/4	↓ 30 MAP, $P<.01$	Early diet experience
Hatton et al 1987[140]	SHR/WKY (n=8)	0.1/1.0/2.0%	6/13	~↓ 20, $P<.05$	Diet-stress interaction
Hatton et al 1988[141]	SHR (n=8)	0.1/1.0/2.0%	3/1	↓ 14 MAP, $P<.01$	Plasma volume, vascular contraction
Hatton et al 1989[142]	SHR/WKY (n=8)	0.1/1.0/2.0%	4/12	~↓ 20 MAP, $P<.01$	SNS

SBP indicates systolic blood pressure; VSM, vascular smooth muscle; SHR, spontaneously hypertensive rats; MAP, mean arterial pressure; PTH, parathyroid hormone; SD, Sprague-Dawley rats; Ang II, angiotensin II; SNS, sympathetic nervous system; WKY, Wistar-Kyoto rats; CNS, central nervous system; NE, norepinephrine; PTX, parathyroidectomy; RAS, renin-angiotensin system; DOC, deoxycorticosterone; SHRSP, stroke-prone SHR; DS, Dahl salt-sensitive; ANP, atrial natriuretic peptide; ACI, American Cancer Institute; BP, blood pressure; LVH, left ventricular hypertrophy; PHF, parathyroid hypertensive factor; SHR-S, salt-sensitive SHR; SHR-R, salt resistant SHR; LHR, Lyon hypertensive rats; 2K1C, two-kidney, one clip hypertensive rats; ADX, adrenalectomized rats; and aldo, aldosterone.

*Unless noted otherwise.

rats. Normotensive rats, such as WKY, Wistar, Fisher 344, and Sprague-Dawley rats, are also responsive to dietary calcium, but the changes in blood pressure are smaller and take prolonged periods of time to develop.

The most common method of manipulating dietary calcium has been by altering $CaCO_3$ in dry food. However, $CaCl_2$ in the drinking water has proved to be an effective means of altering blood pressure as well. The

TABLE 1. Continued

Study	Model	Calcium Diet	Age of Animal/ Treatment Length, wk*	Result in mm Hg SBP	Focus
Hatton et al 1991[143]	SHR (n=8)	0.1-2.0%	3/1	~↓ 10 MAP, $P<.01$	Hematocrit
Hatton et al 1993[144]	SHR (n=8/7)	0.1-2.0%	3/2	↓ 13 MAP, $P<.005$	Adrenergic receptors
Hattori et al 1991[145]	Wistar/DOC-salt (n=9/12)	2.0% $CaCl_2$ in water	5/4	↓ 56	Endogenous opioids
Hermsmeyer et al 1990[146]	SHRSP	0.2-2.0%	4/8	~↓ 25, $P<.01$	Calcium channels
Huie et al 1987[147]	Fisher 344, Wistar-Furth, ACI	0.1-1.0%	4/25	↓ 15, $P<.05$, Fisher 344	Genetic variability
Huie et al 1987[148]	SHR (n=8/10)	0.1/1.0/2.0%	6/13	~↓ 27	Stress-diet interaction
Jirakulsomchok et al 1990[149]	SHR/WKY high salt	0.68-2.0%	7/2.5	↓ 42, $P<.05$	Natriuresis, diuresis
Jones et al 1986[150]	Wistar (n=9)	1.0-2.5%	~4/6	↓ 27, $P<.01$	Electrolyte interaction
Jones and Huibonhoa 1988[151]	Wistar (n=8)	0.2/0.3/0.4/ 0.5%	~4/19	No effect	Marginal calcium diet
Kageyama et al 1986[152]	SHR/WKY (n=10)	1.5% $CaCl_2$ in water	6/3	↓ 26, $P<.01$	Vascular reactivity
Kageyama et al 1987[153]	2K1C (n=30)	1.5% $CaCl_2$ in water	~7/3	↓ 53, $P<.005$	RAS
Kageyama et al 1987[154]	Wistar/DOC-saline (n=6/8)	1% $CaCl_2$ in water	~8/3	~↓ 18, $P<.01$	Vascular reactivity
Kageyama and Bravo 1987[155]	Dog/DOC-saline (n=7)	0.4-1.7%	Adult/15 days	↓ 24 MAP, $P<.01$	Peripheral resistance
Kang et al 1990[156]	DS rat (n=10)	1.0-2.0%	11/30	↓ 17, $P<.05$	Sodium transport
Karanja et al 1987[157]	SHR (n=7)	0.1/0.25/0.5/ 1.0/2.0%	6/14	↓ 13, $P<.05$	Calcium-BP dose response
Karanja et al 1989[158]	SHR (n=10)	0.25-2.0%	3/26	↓ 16, $P<.01$	Fat/calcium
Kohno et al 1989[159]	SHR/WKY (n=30)	0.4-2.9%	10/3	↓ 22, $P<.05$	ANP
Koide and Tuan 1989[160]	Chick embryo (n=8-9)	0%	Prenatal	↓ 3 MAP, $P<.05$	Adrenergic regulation
Kurtz and Morris 1986[161]	DOC-saline (n=7-9)	0.5-4.0%	4/9	↓ 26 MAP	DOC-calcium interaction
Lau et al 1984[162]	♀ SHR/WKY multiple groups	0.22/1.2/4.3%	Multiple experiments	~↓ 15, $P<.05$	PTX, PO_4, volume, hypercalcemia
Lau et al 1986[163]	♀ SHR (n=10)	0.87-2.0%	3/12	↓ 16, $P<.05$	NaCl-Ca^{2+} interaction, RAS
Lau et al 1986[164]	SHR/WKY (n=11-46)	0.35/0.87/ 1.35%	3-15/5-11	No effect	Calcium balance
Lee et al 1984[165]	Turkey (n=10)	0.98/1.96%	33/15	↓ 29 MAP, $P<.005$	LVH, stress
Lewanczuk et al 1990[166]	SHR (n=10)	0.02/0.6/2.0%	4/4-8	↓ 33 MAP, $P<.01$	PHF
Luft et al 1988[167]	SHRSP, WKY (n=20)	0.25-4.0%	6/16	↓ 24, $P<.05$, no effect of higher Mg	Mg homeostasis, catecholamines
Mangiarua et al 1990[168]	SHR/WKY (n=12-60)	0.02/1.0/4.0%	5/8	↓ 24 MAP, $P<.05$	Hypertensive factor
McCarron et al 1981[51]	SHR/WKY (n=12)	0.25/0.5/4.0%	10/38	~↓ 30, $P<.001$	Calcium metabolism
McCarron 1982[169]	WKY (n=12)	0.25/0.5/4.0%	8-10/24-26	↓ 14, $P<.001$	Calcium balance

amount of calcium has varied considerably, ranging from 5% to virtually no calcium in the diet. Most studies have used either 0.5% or 1.0% as the normal value for dietary calcium. The smaller value corresponds to the recommended level of dietary calcium for rats based on the American Institute for Nutrition 1976 report.[201]

TABLE 1. Continued

Study	Model	Calcium Diet	Age of Animal/ Treatment Length, wk*	Result in mm Hg SBP	Focus
McCarron et al 1985[170]	SHR/WKY (n=7)	0.1/1.0/2.0%	6 /14	↓ 56, $P<.01$	Na-Ca^{2+} interaction, Ca^{2+} flux
Muntzel et al 1989[171]	SHR (n=10-14)	0.1/1.0/2.0%	Prenatal/28 days postnatal	~↓ 14 MAP, $P<.01$	Early exposure
Oparil et al 1991[172]	SHR-S, SHR-R, WKY (n=10-12)	0.68-2.0%	8/2	~↓ 14 MAP, $P<.01$	NaCl, SNS
Oshima et al 1992[68]	SHRSP (n=15)	0.2-2.0%	3/6	~↓ 35, $P<.001$	Cellular calcium
Pamnani et al 1990[173]	Wistar/reduced renal mass (n=21)	~1.0-3.0%	~10/5	↓ 40, $P<.05$	Electrolyte metabolism
Pang et al 1992[174]	SHR (n=12)	0.2/0.4/0.8%	12/8	↓ 12 MAP, $P<.05$	Calcium antagonists
Pernot et al 1978[175]	SD DOC-saline (n=7-12)	3.5% $CaCl_2$ in water	~6/10	↓ 25, $P<.01$	PTH
Pernot et al 1985[176]	SD DOC-saline SHR, ♀ LHR	DOC=1.3% $CaCl_2$ in water, SHR=0.3-1.2%, LHR=0.6-2.5%	6/16 DOC, 6/44 SHR, 6/22 LHR	~↓ 30 DOC, ~↓ 18 SHR, ~↓ 16 LHR	Compare models
Pernot et al 1990[177]	LHR (n=7-12)	0.03/0.6/2.5%	4/23	~↓ 22, $P<.01$	Vascular reactivity
Peuler et al 1987[178]	DS rat (n=10-11)	0.4-4.0%	4/6-7	~↓ 30 MAP, $P<.05$	SNS
Peuler and Mark 1989[179]	DS rat (n=10-13)	0.4-2.0%	6/6	~↑ 25, $P<.05$	Calcium BP, SNS
Peuler 1991[180]	♀ SHRSP/DS rat (n=8-13)	0.4-2.0%	4-6/6-22	DS=↑ 17 MAP SHRSP=↓ 38 MAP, $P<.05$	Divergent effects calcium on BP
Peuler and Schelper 1992[181]	♀ SHRSP (n=11-13)	0.4-2.0%	4 Weeks to death	~↓ 45 MAP, $P<.05$	Stroke
Porsti et al 1990[182]	SHR DOC-saline (n=12)	1.5% $CaCl_2$ in water	8/9	↓ 24 MAP, $P<.05$	Vascular reactivity, Ca^{2+}-ATPase
Porsti et al 1992[183]	SHR/WKY (n=16/9)	1.1-3.1%	8/12	↓ 20 MAP, $P<.0001$	Vascular relaxation, platelet $[Ca^{2+}]_i$, Na,K-ATPase
Portsi 1992[184]	SHR/WKY (n=16/9)	1.1-2.1%	8/12	↓ 18 MAP, $P<.0001$	Vascular reactivity, platelet $[Ca^{2+}]_i$
Resnick et al 1986[185]	Wistar DOC-saline/ 2K1C (n=10)	0.2-1.8%	~6/4	↓ 16 DOC, ↑ 21 2K1C, $P<.05$	RAS
Resnick et al 1986[186]	Wistar DOC-saline/ 2K1C	1.2-1.8%	~6/4	↓ 23 DOC, ↑ 18 2K1C, $P<.05$	RAS
Saito et al 1991[91]	WKY DOC-saline (n=8-30)	1.0-4.0% $CaCl_2$	6/4	↓ 55, $P<.01$	Electrolyte balance
Schleiffer et al 1984[187]	SHR (n=7-9)	0.0/0.3/1.2%	5/39	~↓ 18, $P<.05$	BP
Scrogin et al 1991[188]	SHR (n=8-9)	0.2-2.0%	4/8	~↓ 18, $P<.05$	NaCl-Ca^{2+}, BP reactivity
Scrogin et al 1991[189]	SHR (n=8-9)	0.2-2.0%	4/8	↓ 14, $P<.05$	Stress
Semafuko and Morris 1991[190]	SHR/ADX-aldo (n=8-10/4-5)	0.5-2.5%	3/17 SHR, 6/2 SHR/ADX	↓ 20 SHR, ↓ 70 SHR/ADX, $P<.01$	Calcium/aldosterone
Stern et al 1984[50]	SHR/WKY (n=10)	0.4-2.8%	6/4	No effect	Calcium metabolism
Stern et al 1987[191]	SHR (n=18)	0.4-2.5%	10/4	No effect	Vascular reactivity

TABLE 1. Continued

Study	Model	Calcium Diet	Age of Animal/ Treatment Length, wk*	Result in mm Hg SBP	Focus
Tamura 1987[192]	SHR (n=6)	0.8-3.2%	5/4	↓ 19, $P<.01$	Mg^{2+}, phosphorus
Tenner et al 1989[193]	SHR/WKY (n=15-20)	0.02/0.1/0.5/ 2.5%	5/15	~↓ 45, $P<.001$	PTH, vascular reactivity
Togari et al 1990[194]	Wistar (n=6)	0.01-0.3%	3/7	↓ 28	PTH-induced hypotension
Tresham et al 1988[195]	Sheep (n=4)	50-200 mmol	Adult/6	No effect	BP
Wiecek et al 1989[196]	PTX SHR/WKY (n=5-10)	0.95/1.6/2.4/ 3.0%	4/11	No effect in intact rats	PTH, vascular reactivity
Wuorela et al 1990[197]	SHR DOC (n=12)	1.5% $CaCl_2$ in water	9/4	~↓ 21, $P<.01$	Electrolyte balance, Ca^{2+}-ATPase
Wuorela et al 1992[198]	SHR DOC (n=12)	1.5% $CaCl_2$ in water	8/9	↓ 26, $P<.001$	Ca^{2+}-ATPase Na-K ratio
Wyss et al 1989[199]	SHR-S (n=12-18)	0.68-2.0%	7/2	↓ 16 MAP, $P<.05$	Hypothalamic NE
Yang et al 1989[200]	SHR-S (n=6)	0.68-2.0%	7/2	↓ 16 MAP, $P<.05$	Hypothalamic α_2 receptors

However, 1.0% is often considered the normal level because it is the amount contained in major brands of rat chow.

Based on the available literature, it appears that studies which have used fairly substantial differences in calcium intake (5- to 10-fold) between treatment groups have most consistently reported significant differences in blood pressure. Using five diets that ranged between 0.1% and 2.0% calcium, Karanja et al[157] reported a nonlinear inverse relation between the calcium content of the diet and blood pressure in SHR maintained on a concurrent high sodium chloride diet. When calcium was varied by a factor of two or less, differences in blood pressure were less likely.

The overall composition of the diet has varied considerably, reflecting the variety of dietary sources available to researchers around the world. The nutrients that have received the most attention in relation to calcium are other electrolytes. Sodium, chloride, potassium, magnesium, and phosphorus have frequently been modified along with calcium. Less consideration has been given to other factors in the diet, even though other nutrients may influence calcium metabolism. Fiber content is known to influence the absorption of calcium,[202] and the lipid profile of the diet has been shown to interact with calcium to alter blood pressure.[158]

How rapidly blood pressure changes after dietary manipulation depends on the age of the animal as well as the composition of the diet. With normal levels of sodium chloride in the diet, 3-week-old animals show alterations in blood pressure to dietary calcium within 4 to 5 days.[141] At 4 weeks of age, 2 weeks or longer may be required before a change in blood pressure is observed, whereas at 6 weeks of age, more than 2 months may pass without a change in blood pressure.[51] In contrast, the effects of calcium may be apparent within 2 weeks in an 8-week-old salt-sensitive SHR if the animal is on a high sodium chloride diet.[172,199,200]

The diet-related changes in blood pressure do not appear to be due to variations in body weight. Karanja et al[157] reported that weight gain was greatest in SHR consuming 1.0% calcium diets, yet the rate of blood pressure rise was about half that of rats fed 0.25% calcium diets. It is of interest to note that animals on enriched calcium diets eat as much as 30% more but weigh less than animals on normal calcium diets.[203]

Proposed Mechanisms for the Antihypertensive Actions of Calcium

A multitude of potential mechanisms may explain the effect of dietary calcium on blood pressure. As dietary calcium changes, so do PTH, calcitriol, calcitonin, calcitonin gene–related peptide (CGRP), atrial natriuretic peptide (ANP), renin-angiotensin system activity, sympathetic nervous system activity, metabolism of other electrolytes, calcium binding proteins, intracellular free calcium levels, membrane-bound calcium, and electrolyte fluxes. Any one or combination of these changes could be responsible for altering blood pressure. In the following sections, several mechanisms that have been postulated to mediate the effects of dietary calcium on blood pressure will be explored. The proposed mechanisms are summarized in Table 2.

Vascular Smooth Muscle

Calcium plays a key role in vascular smooth muscle function. Calcium influx through receptor- and voltage-operated calcium channels is thought to initiate vascular contraction, and the fall in the intracellular free calcium concentration is thought to result in relaxation or vasodilation. Therefore, how the vascular smooth muscle cell (VSMC) handles calcium is critical to vascular tone and blood pressure. Anything that causes a perturbation in the processes that control cellular regulation of calcium would very likely change vascular tone.

In the following section, the effects of dietary calcium on VSMC regulation of calcium will be considered. In some instances, the effects on vascular smooth muscle are estimated from the effect of dietary calcium on platelets or other cell types. Although there are impor-

TABLE 2. Proposed Mechanisms of Action of Supplemental Dietary Calcium on Blood Pressure in Experimental Models of Hypertension

Site of Action	Mechanism
Cellular	↑ Membrane stabilization
	↑ Na,K-ATPase
	↑ Ca-ATPase
	↑ Calmodulin
	↓ Intracellular calcium
Vascular	↓ Contractility
	↑ Relaxation
Calcium-regulating hormones	↓ PTH
	↓ 1,25(OH)$_2$ vitamin D$_3$
	↑ Calcitonin
Calcium-sensitive hormones	↓ Parathyroid hypertensive factor
	↑ Atrial natriuretic peptide
	↓ Renin-angiotensin system
	↑ CGRP
Sympathetic nervous system	↓ CNS outflow
	↓ Circulating catecholamines
	↓ α_1-Adrenergic receptor–mediated responses
	↑ Natriuresis
Renal	↑ Prostaglandins
	↑ Natriuresis

↑ indicates increase in; ↓, decrease in; PTH, parathyroid hormone; CGRP, calcitonin gene–related peptide; and CNS, central nervous system.

tant differences among cell types, it is assumed that the effect of dietary calcium on cellular calcium regulation is not restricted to VSMCs, and therefore, other cell types can be used as surrogates. This assumption is bolstered by the work of Oshima et al,[68] who observed a decline in platelet and lymphocyte intracellular free calcium in stroke-prone SHR maintained on high calcium/high sodium chloride diets. In their study, stroke-prone SHR were maintained on low or high calcium (0.2% versus 2.0%) and either low or high sodium (0.3% versus 3.1%). Animals on high sodium/low calcium diets had elevated blood pressure and high levels of basal and stimulated intracellular free calcium in both circulating platelets and intrathymic lymphocytes. Supplemental dietary calcium corrected the abnormalities in intracellular calcium. The similarity of findings in two different cell types indicates that the dietary calcium–induced correction of intracellular abnormalities of calcium metabolism may be a generalized phenomenon and not cell specific.

Membrane Stabilization

Based on numerous reports of abnormalities in cell membrane transport systems associated with hypertension, Bohr and colleagues[204] have hypothesized that there is a defect in the lipid bilayer of vascular smooth muscle membrane in hypertensive individuals. This defect results in decreased membrane fluidity and enhanced excitability as a consequence of increased Ca^{2+} flux across the cell membrane. Bohr and coworkers[135,204-209] have provided persuasive evidence that increased extracellular calcium causes a reduction in vascular contractility through a process of membrane stabilization. Increased binding of calcium to the plasma membrane decreases membrane permeability to both monovalent and divalent cations, resulting in diminished vascular contractility.

Membrane stabilization is an attractive hypothesis for explaining the effects of dietary calcium, but most studies of membrane stabilization have been done in vitro using extracellular calcium levels that may not correspond to the magnitude of change that might be expected from manipulations of dietary calcium. To evaluate the effect of dietary calcium on cellular function, Furspan and Bohr[210] fed stroke-prone SHR and WKY rats either 1% or 2.5% calcium diets for 10 weeks. They then measured blood pressure, serum ionized calcium, and lymphocyte intracellular sodium, potassium, and calcium, as well as net passive fluxes of sodium and potassium. They found that supplemental calcium reduced blood pressure, increased serum ionized calcium, reduced net potassium efflux, and reduced free ionized calcium within the lymphocyte. The changes were attributed to increased extracellular calcium and resultant membrane stabilization in the calcium-supplemented stroke-prone SHR.

Na,K-ATPase

In a series of studies, Porsti et al[182-184] reported that increasing dietary calcium lowers blood pressure and improves vascular relaxation in the SHR. They found that supplemental calcium normalized DOC-induced

elevations of blood pressure as well as the increased vascular contractility to norepinephrine that is characteristic of vessels from DOC-treated animals.[182] Dietary calcium did not alter contractility to norepinephrine in SHR not treated with DOC, suggesting that the change in maximal contractility resulted from a calcium-induced modulation of the DOC treatment. On the other hand, supplemental calcium did enhance relaxation to sodium nitroprusside and acetylcholine in both the DOC-calcium group and the calcium-supplemented control SHR. The authors suggest that the improved relaxation may have been a consequence of increased Na,K-ATPase activity. In a previous report, they noted that potassium-induced relaxation of mesenteric arterial rings was augmented by calcium supplementation in SHR.[183] Because ouabain was able to prevent the relaxation, the difference between diet groups was attributed to increased Na,K-ATPase activity. This outcome is consistent with the notion of a reciprocal relation between intracellular calcium and Na,K-ATPase activity; as intracellular calcium declines, Na,K-ATPase activity increases.[211]

The results from Porsti et al[182-184] are commensurate with other findings showing the maximal contractility to norepinephrine in intact vessels is not altered by supplemental dietary calcium. Aorta, mesenteric, and tail arteries from animals fed high calcium diets have not shown diminished reactivity to norepinephrine or potassium chloride (KCl).* If anything, there may be increased contractility. Ambrozy et al[116] found increased sensitivity to phenylephrine in Zucker obese and lean rats fed high calcium diets, whereas Pernot et al[177] found an increase in maximal contractility to norepinephrine in Lyon hypertensive rats on high calcium diets.

Despite the in vitro results, blood pressure reactivity in vivo has been reported to be reduced to norepinephrine in animals fed supplemental calcium. Several investigators have reported diminished pressor responses to norepinephrine in both hypertensive[142,153,180] and normotensive[120,132] rats fed high calcium diets. These results would not appear to be a consequence of diminished vascular contractility given the results from isolated vessels cited above. However, the in vivo results may be related to circulating factors that modify the response to norepinephrine or to difficulties related to vascular relaxation.

Ca^{2+}-ATPase

Just as Furspan and Bohr[210] observed lower levels of intracellular free calcium in lymphocytes from animals on high calcium diets, Porsti et al[183] reported lower levels of intracellular free calcium in platelets isolated from animals maintained on supplemental calcium diets. These favorable changes in intracellular calcium regulation may be related to increased Ca^{2+}-ATPase activity. Porsti et al[182] and Wuorela et al[198] observed an increase in the maximal velocity of calcium transport by "inside-out" red blood cell vesicles from SHR on calcium-supplemented diets. The greater velocity of calcium transport is indicative of increased Ca^{2+}-ATPase activity. Wuorela et al[198] also reported that nitroprusside-induced relaxation of norepinephrine-contracted mesenteric arterial rings was enhanced in calcium-supplemented animals, perhaps as a consequence of an increased ability to extrude calcium from the cell.

Calmodulin

Using duodenal enterocytes, Roullet et al[212] have observed that calmodulin levels are lower in SHR than WKY rats and that increasing dietary calcium eliminates that difference. Subsequent work indicated that dietary calcium can actually upregulate calmodulin levels (C.M. Roullet, personal communication, November 1993). Correction of a defect in calmodulin activity by calcium could provide a mechanism whereby a multitude of molecular and cellular processes might be modified. Calmodulin plays a pivotal role in intracellular calcium regulation and could be responsible for diet-induced variations in Ca^{2+}-ATPase.[213,214]

Calcium-Regulating Hormones

Until recently, calcium-regulating hormones were rarely considered outside of their traditional role in calcium homeostasis. Calcium-regulating hormones exert tight control over serum free ionized calcium levels (for review, see Reference 215). Reductions in serum ionized calcium provoke release of PTH from the parathyroid gland. PTH in turn stimulates the production of calcitriol [1,25$(OH)_2$ vitamin D_3], the most active metabolite of vitamin D, in the proximal convoluted tubule cell. Calcitriol enters the circulation to reach its target tissues, the principal targets being the renal and intestinal epithelia where 1,25$(OH)_2$ vitamin D_3 increases the synthesis of the calcium-binding proteins calbindin and integral membrane calcium-binding protein. An increase in these calcium-binding proteins is reflected by greater intestinal absorption and renal reabsorption of calcium. When serum free ionized calcium levels are too high, calcitonin is released from the thyroid gland. This compound acts to lower serum free ionized calcium by inhibiting osteoclast activity and preventing mobilization of calcium from bone.

It has become increasingly clear that PTH, calcitriol, and perhaps calcitonin possess vasoactive properties and thus may play a role in blood pressure regulation. Furthermore, other vasoactive peptides and hormones have been identified that are responsive to dietary calcium such as CGRP and parathyroid hypertensive factor. Because these compounds are responsive to changes in calcium intake, it follows that variations in calcium-regulating hormones may account for calcium-induced alterations in blood pressure.

Parathyroid hormone. Hyperparathyroidism is associated with elevated blood pressure in humans,[32,216,217] and PTH is elevated in many essential hypertensive patients.[32,35,217-223] These observations suggest that elevated PTH may in some way be responsible for the high blood pressure. If so, dietary calcium may lower blood pressure by suppressing PTH. However, such an effect would be paradoxical because PTH is a potent vasodilator. Intravenous injections of PTH result in a prompt, dose-dependent fall in blood pressure.[224,225] Nevertheless, parathyroidectomy has been consistently shown to lower blood pressure in animal models of hypertension.[226-228] Furthermore, transplantation of parathyroid glands between WKY rats and SHR results in higher

*References 116, 128, 129, 141, 177, 183, 184.

blood pressure in the WKY rat and lower blood pressure in the SHR.[226,229,230]

The resolution of the paradox may be related to a number of factors. First, it should be noted that at physiological concentrations in blood, PTH does not appear to be vasoactive.[231-233] Thus, the influence of PTH on blood pressure may be independent of its vasodilating effects. Second, prolonged exposure to low calcium diets, which elevates circulating PTH levels,[50] diminishes the magnitude of the blood pressure decline after an acute injection of PTH.[118] The potential development of tolerance to the vasodilator effects of PTH may be associated with a simultaneous enhancement in response to other vasoactive drugs. This situation would be analogous to the effect of alcohol exposure on arterial pressure. Acutely, alcohol is a vasodilator, but with continued exposure it is associated with hypertension. Several studies have shown that as the vasodilator effects of alcohol decline, there is an increase in intracellular free calcium in VSMCs that may favor enhanced responses to other agonists (for review, see Reference 234).

PTH may act as a calcium ionophore to promote increased intracellular calcium levels in VSMCs and thereby increase vascular tone. The possibility of PTH as an ionophore in vascular smooth muscle is suggested by findings that low concentrations of PTH induce calcium influx into isolated cardiac cells[235] as well as osteoblasts.[236] The relation between PTH and platelet intracellular calcium has been examined in humans and in rats. Oshima et al[237] could find no effect of parathyroidectomy on platelet free intracellular calcium in SHR. In humans, there is little intercorrelation between intracellular free calcium and PTH activity.[238] Thus, the evidence does not favor the ionophoric effect of PTH in hypertension.

It is possible that PTH has central nervous system effects that promote an elevation of blood pressure. In a brief article, Delbarre et al[239] reported that intracerebral ventricular administration of PTH resulted in significantly elevated blood pressure in the SHR. Although this study is apparently the only one of its kind, there are other indications that PTH has central nervous system effects. Geiger et al[240] reported altered cyclic AMP in various brain regions in the rat that were attributable to variations in PTH. More recently, Islam et al[241] found evidence that PTH diminished synaptosomal phospholipid content in uremic rats. In a subsequent study, Smogorzewski et al[242] reported that PTH was responsible for a higher calcium content in rat brain synaptosomes as well as reduced Na,K-ATPase activity. PTH also modified epinephrine content, uptake, and release.

An additional explanation for the PTH paradox is the putative parathyroid hypertensive factor. Lewanczuk et al[243] have reported the presence of a circulating hypertensive factor that is present in both SHR and human plasma.[244] When injected into normotensive rats for bioassay, the hypertensive factor stimulates vascular smooth muscle calcium uptake and causes an elevation in blood pressure with a time lag of about 2 hours. Parathyroidectomy eliminates the circulating factor, suggesting that the parathyroid gland is the source.[226] If so, this would shift focus away from PTH to the parathyroid gland itself and in so doing would reconcile the disparate blood pressure results that have previously been ascribed to PTH. Pertinent to this review, the purported factor is responsive to variations in dietary calcium. Increased dietary calcium reduces circulating hypertensive factor, whereas restricted calcium increases it.[167]

Calcitriol. As mentioned previously, low calcium diets provoke an increase in the synthesis and release of $1,25(OH)_2$ vitamin D_3, (see Reference 215), which itself may mediate an increase in blood pressure. Receptors for $1,25(OH)_2$ vitamin D_3 have now been demonstrated in vascular tissue.[246,247] Calcitriol has been shown to stimulate Ca^{2+}-ATPase in vascular smooth muscle, suggesting that $1,25(OH)_2$ vitamin D_3 may play a role in regulating cellular calcium metabolism.[248,249] A direct effect of calcitriol on VSMC intracellular free Ca^{2+} has been reported for calcitriol in intact mesenteric resistance arteries as well as isolated VSMCs. Bukoski et al[250] and Xue et al[251] have shown that short-term incubation of intact mesenteric resistance vessels with $1,25(OH)_2$ vitamin D_3 increases the Ca^{2+} transient induced by norepinephrine in the SHR. No effects were seen in the WKY rat. Similar effects are observed after systemic injections of calcitriol. Bukoski et al[128,252] observed that both acute injections and 3-day administration of the vitamin at physiological levels significantly enhanced maximal force generation of isolated vessels from both hypertensive and normotensive animals. These findings suggest direct effects of $1,25(OH)_2$ vitamin D_3 on Ca^{2+} metabolism of intact resistance vessels. They further suggest that the observed response to calcitriol differs depending on whether the vascular tissue is isolated from the normal or hypertensive animal.

Despite evidence of direct effects on vascular smooth muscle, observations of elevated blood pressure as a consequence of exposure to $1,25(OH)_2$ vitamin D_3 have been inconsistent. The animals that Bukoski et al[252] examined for vascular contractility did not have elevated blood pressure as a consequence of exposure to calcitriol. Likewise, Hatton et al[253] found evidence of enhanced vascular contractility in vessels from animals given $1,25(OH)_2$ vitamin D_3 injections for 7 consecutive days, but there were no changes in blood pressure. Using a higher concentration of $1,25(OH)_2$ vitamin D_3, Shimosawa et al[254] did observe a potentiation of pressor responses to both norepinephrine and angiotensin II in animals treated with calcitriol or the noncalcemic analogue 22-oxacalcitriol for 14 days.

Most recently, Bukoski and Xue[255] found evidence that daily injections of $1,25(OH)_2$ vitamin D_3 over a 28-day period caused sustained elevations in blood pressure in normotensive Wistar rats. However, chronic administration of $1,25(OH)_2$ vitamin D_3 in SHR produced only a transient elevation in blood pressure after 5 weeks of treatment, suggesting a modest effect of the hormone on blood pressure.[256] As reported in previous studies, vascular contractility was significantly enhanced in the SHR.

Thus, considering the direct effects on the vasculature, the observation of potentiated pressor responses, and recent reports of elevated blood pressure, $1,25(OH)_2$ vitamin D_3 should be considered as an agent that has the potential to alter blood pressure. Further

work is needed to understand the cellular events underlying the vascular smooth muscle response to calcitriol.

Calcitonin. In general, the effects of calcitonin on calcium regulation are opposite to those of PTH and $1,25(OH)_2$ vitamin D_3. Although supplemental dietary calcium can be expected to elevate calcitonin levels, calcitonin has not been routinely measured in studies of the effect of dietary calcium manipulations on blood pressure. Nevertheless, there is evidence that calcitonin may have vasoactive properties.

There have been conflicting reports on the relation of calcitonin to blood pressure. Bindels et al[49] found significantly elevated calcitonin in young SHR, along with reduced serum ionized calcium and elevated $1,25(OH)_2$ vitamin D_3. Presumably, the disparate results between elevated calcitonin in the presence of reduced serum ionized calcium were related to phosphate metabolism. These findings suggest that calcitonin is associated with elevated blood pressure. In fact, Clementi et al[257] reported elevated blood pressure after intracerebroventricular administration of 0.4 IU salmon calcitonin. The increased blood pressure was accompanied by increased plasma renin activity. It is unlikely that the increased plasma renin activity contributed to the elevation of blood pressure, because intravenous and intramuscular administration of calcitonin elevated plasma renin activity without altering blood pressure.

Other investigators have found conflicting evidence. Delbarre et al[239] observed a reduction in blood pressure with intracerebroventricular administration of calcitonin but an elevation of blood pressure with peripheral administration. Wegener and McCarron[258] were unable to detect any effect of calcitonin on blood pressure through intravenous administration.

Additional research will be needed to assess the effects of calcitonin on blood pressure and its relation to dietary calcium. Calcitonin may well have an influence on blood pressure via the central nervous system. Although calcitonin is a thyroid hormone, a number of calcitonin receptors in the brain[259] mediate a variety of effects, including anorexia,[260] analgesia,[261] and altered pituitary release of hormones.[262] However, at the present time there is insufficient evidence to evaluate the possibility that calcitonin modulates blood pressure via the central nervous system.

Calcitonin gene–related peptide. In contrast to calcitonin, CGRP is known to be vasoactive. This 37–amino acid neuropeptide results from alternative processing of the calcitonin gene. It is widely distributed in the central and peripheral nervous systems[263] and is one of the most potent vasodilators yet discovered. Intravenous infusion of CGRP produces marked hypotension through a reduction in total peripheral resistance.[264,265] Central nervous system administration of CGRP produces variable effects depending on the dose and site of administration. For example, injection of 0.2 pmol CGRP into the nucleus tractus solitarius produced a depressor response, whereas 2 pmol resulted in a pressor response.[266] Likewise, injections into the central nucleus of the amygdala resulted in a pressor response,[267] but intrathecal injections caused a reduction in blood pressure.[268]

Of particular interest are observations that levels of CGRP in spinal cord vary with dietary calcium. DiPette et al[269] demonstrated that low levels of dietary calcium reduced dorsal horn CGRP content, and supplemental calcium increased CGRP levels. Although DiPette et al[269] did not assess circulating levels of CGRP in their study, others[270] have found it to be lower in SHR than WKY rats. Given the vasoactive properties of CGRP and its presence in central and peripheral nervous system sites involved in cardiovascular regulation, CGRP may be involved in the blood pressure alterations that result from dietary calcium manipulations.

Sympathetic Nervous System

There are consistent reports of altered sympathetic nervous system activity associated with variations in dietary calcium. Winternitz et al[271,272] and Oparil et al[273] have reported that increased sodium chloride causes an elevation of blood pressure in salt-sensitive SHR. The increased blood pressure is associated with elevated circulating norepinephrine and reduced hypothalamic norepinephrine.[274] Provision of supplemental calcium reverses the increased blood pressure induced by sodium chloride while normalizing circulating and central nervous system changes in catecholamines.[172,199,200] Peuler et al[178] reported that 4.8% calcium diets reduce blood pressure in DS rats by attenuating sympathetic nervous system outflow. Interestingly, 2% calcium diets aggravated hypertension in this strain[179] while reducing blood pressure in the stroke-prone SHR.[180]

There are several possible mechanisms through which calcium may modify the sodium chloride effect on sympathetic nervous system outflow. One possibility is that the electrolytes may interact within the central nervous system. Infusion of sodium chloride into the cerebral ventricles[275] or nucleus tractus solitarius[276] has been shown to cause an elevation of blood pressure. In contrast, intracerebroventricular calcium causes a reduction in blood pressure.[277] Therefore, it appears that both calcium and sodium chloride are reciprocally vasoactive in the central nervous system. There is evidence that manipulations of dietary calcium result in altered levels of central nervous system calcium. Long-term alterations in dietary calcium have been shown to change cerebrospinal fluid and brain levels of calcium in rats. Harris et al[278] found the reduction in calcium levels to be greatest in the brain stem (24%) after 4 weeks of restricted dietary calcium (0.02%), with the soluble and microsomal fractions of calcium selectively reduced. Likewise, Tai et al[279] found that calcium fluxes into brain and cerebrospinal fluid were linearly related to plasma ionized calcium. Thus, it appears that although the brain is protected from acute changes in serum ionized calcium by low cerebrovascular permeability to calcium, long-term changes in dietary calcium can alter brain levels of calcium, albeit to a lesser extent than the changes in serum calcium.[280]

The interaction between sodium and calcium may occur at the receptor level. Gavras[281] has hypothesized that sodium may directly influence neural activity and cause increased sympathetic nervous system outflow by attenuating the affinity of α_2-adrenergic receptors for their agonists. Because activation of hypothalamic α_2 receptors causes inhibition of sympathetic outflow, reduced affinity would result in disinhibition of the sympathetic system. In contrast to sodium, divalent cations such as calcium increase the affinity of the receptors for the ligand.[282]

Whether changes in central nervous system calcium levels are responsible for alterations in central catecholamine levels remains to be demonstrated. Nevertheless, reductions in dietary calcium comparable to those used to modify central nervous system calcium levels are reported to alter central nervous system norepinephrine levels. Baksi[122] reported that 8 weeks of a 0.005% calcium diet reduced hypothalamic norepinephrine and dopamine content in Sprague-Dawley rats. Restricted dietary calcium has also been reported to alter peripheral catecholamine levels. Baksi and Hughes[283] and Hagihara et al[284] reported altered adrenal catecholamine levels with reduced calcium diets, and Luft et al[167] observed reduced epinephrine levels and epinephrine responses to stress in stroke-prone SHR on high calcium diets. Scrogin et al[188] also observed diminished circulating epinephrine in calcium-supplemented SHR. Felicetta et al[285] observed an increased urinary dopamine-norepinephrine excretion ratio during a high calcium/high sodium chloride diet. Other investigators have reported no difference in circulating catecholamines as a consequence of altered calcium diets.[142,152,191]

Responses to norepinephrine have been reported to be potentiated by restricted calcium diets and dampened by high calcium diets. Hatton et al[142,144] reported diminished pressor responses to exogenous norepinephrine in SHR on high calcium diets. The reduced pressor response did not occur in response to angiotensin II, suggesting that it was not due to a generalized change in vascular responsiveness. Doris,[132] Kageyama et al,[152-154] Baksi,[121] and Peuler[180] have reported similar results with regard to norepinephrine.

The reduced responsiveness to norepinephrine may be related to altered adrenergic receptor activity. Hatton et al[144] demonstrated that dietary calcium specifically modulates the α_1-adrenergic receptor. Blockade of α_1-adrenergic receptors with phentolamine or prazosin eliminated the difference in blood pressure that prevailed in animals on high and low calcium diets. Blockade of α_2-, β_1-, or β_2-adrenergic receptors had no such effect. Likewise, pharmacologic reduction of blood pressure with CGRP, sodium nitroprusside, or the converting enzyme inhibitor captopril had no differential effect on blood pressure. The results of this study strongly suggest that dietary calcium modifies the α_1-adrenergic receptor. The nature of the effect remains to be determined, but preliminary data indicate that there may be a difference in receptor expression because binding to tritiated prazosin was greater in kidneys from animals fed low calcium diets.

Electrolyte Interactions

A change in the level of one dietary electrolyte can have extensive ramifications on other dietary electrolytes. Increased dietary calcium, for example, can increase sodium excretion, reduce magnesium absorption, and reduce circulating phosphorus levels. Likewise, increasing sodium chloride in the diet causes calcium wasting, but if sodium levels are altered independently of chloride, calcium is unaffected. Consequently, when manipulation of a dietary electrolyte is shown to have an effect on blood pressure, the possibility exists that the blood pressure effect is due to reciprocal changes in other electrolytes.

Phosphate depletion. Early in the study of the effect of dietary calcium on blood pressure, Lau and coworkers[163] proposed that calcium-induced phosphate depletion accounted for the blood pressure reduction. However, rather than a positive relation between phosphate and blood pressure as predicted by Lau et al,[162] Bindels et al[49] demonstrated that supplementing the SHR diet with phosphate results in a blood pressure reduction during mid-adolescence. To specifically determine the role of phosphorus in calcium-induced reductions in blood pressure, Tamura[192] varied both calcium and phosphate and found that calcium lowered blood pressure regardless of serum phosphate levels. Thus, it would appear that the effect of calcium on blood pressure is relatively independent of phosphate.

Magnesium. Dietary calcium intake can have a pronounced effect on magnesium metabolism.[192] With increased dietary calcium intake, serum magnesium levels decline. Furthermore, observations of increased intracellular calcium with low calcium diets suggest that intracellular magnesium may be reduced.[244] Because of the interactive effects of dietary calcium and magnesium, it has been suggested that some of the effect of calcium on blood pressure may be mediated through alterations in magnesium. Indeed, Tamura[192] found a significant positive correlation of serum magnesium levels with systolic blood pressure across groups receiving different levels of dietary calcium. However, in a factorial study of calcium and magnesium, Evans et al[133] found no effect of magnesium on blood pressure and no interactive effects of the two cations on blood pressure.

Sodium chloride/calcium interactions. Numerous studies have found that calcium attenuates sodium chloride–dependent, low-renin hypertension. Calcium lowers blood pressure in several salt-sensitive models of hypertension, including DOC-saline rats,[91,130,145,154,176,186] reduced renal mass/saline rats, DS rats,[156,173,178,182] salt-sensitive SHR,[149,172,199,200] salt-fed WKY rats,[131,132] angiotensin II–salt rats,[119] and adrenalectomy/aldosterone–induced hypertension.[190] The mechanisms through which calcium attenuates salt-induced forms of hypertension have not been identified, but numerous candidates have been suggested.

Calcium-induced natriuresis. Increasing dietary calcium facilitates natriuresis in a number of ways. Increased circulating ANP, reduced sympathetic nervous system outflow, reduced α_1-adrenergic receptor activity, reduced angiotensin II receptor expression, reduced circulating PTH, and direct effects of calcium on sodium excretion at the proximal tubule may all play a role. The most familiar natriuretic effect of calcium is the interaction that occurs at the renal level. Increasing calcium facilitates natriuresis and diuresis in part by inhibiting sodium reabsorption in the proximal tubule.[286] Conversely, reducing serum ionized calcium levels by acute volume expansion retards natriuresis and diuresis.[287] This occurs, at least in part, as a consequence of increased circulating PTH acting on the tubules to alter production of prostaglandins, with a resultant reduction in sodium excretion[288] as well as direct effects of calcium on prostaglandin production. Less well known are the effects of increasing dietary calcium on other systems that promote natriuresis. Geiger et al[137] and Kohno et al[159] have reported increased circulating ANP after supplemental calcium diets. Such an increase in ANP

would promote natriuresis as well as cause peripheral vasodilation and reduced blood pressure. Levi and Henrich[289] recently reported that high calcium diets reduced angiotensin II binding in renal brush-border membranes and decreased brush-border membrane Na-H antiport activity in SHR. Angiotensin II increases proximal tubular sodium transport by increasing Na-H antiport activity. Decreased activity in this system would enhance sodium excretion.

The effect of calcium on sympathetic nervous system activity would also facilitate sodium excretion. The reduction in sodium chloride–induced increases in sympathetic nervous system outflow that have been reported[172] can be expected to result in increased sodium excretion, as would the diminished α_1-adrenergic activity during high calcium diets, as reported by Hatton et al.[144]

Given the multiple mechanisms through which increased dietary calcium facilitates sodium excretion, it is not surprising that increasing the proportion of calcium in the diet results in natriuresis.* In some models of hypertension, natriuresis may be an important component of the antihypertensive effect of dietary calcium. This would apply regardless of how sodium chloride might provoke hypertension, because removal of sodium chloride would remove the initial stimulus for elevated blood pressure.

Not all evidence favors a natriuretic explanation for the blood pressure effects of dietary calcium. In SHR that are not salt sensitive, increasing dietary sodium chloride does not alter blood pressure. However, increasing dietary calcium does lower blood pressure. Studies from our laboratory[170] and that of Hamet et al[290] have demonstrated that the antihypertensive action of calcium may actually be enhanced by simultaneous sodium chloride supplementation. This interactive effect of these nutrients is not likely to be related to natriuresis because, as mentioned above, manipulation of sodium chloride alone does not alter blood pressure in these animals.

Thus, it may be necessary to distinguish between hypertensive models when assessing the interactive effects of dietary calcium and sodium chloride. For models in which calcium prevents a sodium chloride–induced elevation in blood pressure, such as in DOC-saline hypertension, natriuresis might be suspected. Otherwise, natriuresis seems less likely. Even when natriuresis is an unlikely cause for the blood pressure–lowering effect of dietary calcium, as in the SHR, sodium chloride and calcium may interact to potentiate the antihypertensive effects of supplemental calcium.

Sodium chloride–induced calciuresis. Just as calcium promotes natriuresis, sodium chloride promotes calciuresis. Consequently, as sodium chloride is increased in the diet, more calcium is excreted. Resnick and colleagues[244,291,292] hypothesize that this dietary sodium chloride–induced calciuresis results in reduced serum ionized calcium and increased circulating levels of calcium-regulating hormones including calcitriol, PTH, and/or parathyroid hypertensive factor. In turn, these hormones stimulate cellular calcium uptake and disrupt cellular electrolyte balance, resulting in elevated blood pressure. According to this hypothesis, calcium supplementation increases available calcium, prevents the fall in ionized calcium that provokes the increase in calcium-regulating hormones, and reverses the salt-induced hypertension.

Favoring this hypothesis are indications that increased dietary sodium chloride causes renal wasting of calcium[293,294] and stimulates calcitriol and PTH production.[293] Elevated calcitriol and PTH have been found in low-renin human hypertension[292] as well as in experimental forms of hypertension.[91] Kotchen et al[295] reported that after 5 days of a high salt diet, young DS rats exhibited increased calcium excretion in both urine and feces, whereas ionized calcium was reduced and calcitriol and PTH were elevated relative to Dahl salt-resistant rats. The differences in calcium excretion occurred with no changes in blood pressure. The excessive calcium excretion could be avoided by sodium loading with anions other than chloride, suggesting that the combination of sodium and chloride is critically important to the calciuresis that occurs. It is notable that high sodium diets that do not contain chloride also do not cause hypertension in the DS rat. Similarly, Kurtz and Morris[161] found increased calcium excretion in DOC-saline hypertension when the animals were fed sodium chloride. However, if an equimolar amount of sodium bicarbonate was substituted for sodium chloride, the increases in both calcium excretion and blood pressure were reversed.

To test the hypothesis that sodium chloride causes hypertension as a consequence of alterations in calcium-regulating hormones, Resnick et al[186] fed supplemental dietary calcium to low-renin, DOC-salt hypertensive rats and to renin-dependent Goldblatt hypertensive rats. Calcium excretion was substantially greater in the DOC-salt rats relative to the two-kidney, one clip Goldblatt rats. Modest increases in dietary calcium (1.2% versus 1.8%) caused a reduction of blood pressure in the DOC-salt animal but resulted in an increase in blood pressure in the Goldblatt model of hypertension.

Although these results are dramatic, other investigators have found that supplemental dietary calcium reduces renovascular hypertension. Kageyama et al[153] reduced blood pressure in two-kidney, one clip Goldblatt hypertensive rats by providing supplemental calcium (1.5%) in the drinking water. The reduction in blood pressure was accompanied by a suppression of plasma renin and aldosterone as well as diminished pressor responses to norepinephrine, leading the authors to conclude that the reduction in blood pressure may have been a consequence of reduced renin-angiotensin system activity.

Nonvascular Mechanisms

Nonvascular mechanisms must also be considered in explaining the role of dietary calcium in blood pressure regulation. Tordoff and colleagues[296,298] have provided important new insights as to potential nonvascular mechanisms. Their studies in three genetically distinct animal models indicate that dietary calcium regulates sodium chloride appetite or intake. Low dietary calcium stimulates sodium chloride intake, and higher intakes of calcium suppress sodium chloride appetite. Thus, while volume may not be changed at higher calcium intakes,

*References 54, 91, 119, 131, 137, 149, 156, 159, 173, 190, 191, 286-288.

exposure to sodium chloride is reduced with potentially important effects on sodium-regulating hormones such as renin, aldosterone, and angiotensin II.

Change in blood viscosity is another nonvascular mechanism potentially affected by dietary calcium. Hatton et al[143] have measured changes in hematocrit that occur with calcium supplementation as an indirect assessment of viscosity. They found that there is an inverse relation between calcium intake and hematocrit. However, the changes in blood pressure observed with the higher calcium intake were independent of changes in hematocrit.

Hamet and Tremblay[299] have linked correction of the abnormal HSP70 gene expression of experimental hypertension to increased dietary calcium intake. The HSP70 gene, which exists in the major histocompatibility complex and segregates closely with hypertension, has its expression corrected (suppressed) by dietary calcium.[299]

Summary

More than 80 studies have reported lowered blood pressure after dietary calcium enrichment in experimental models of hypertension. The evidence presented here suggests that dietary calcium may act concurrently through a number of physiological mechanisms to influence blood pressure. The importance of any given mechanism may vary depending on the experimental model under consideration.

Supplemental dietary calcium is associated with reduced membrane permeability, increased Ca^{2+}-ATPase and Na,K-ATPase, and reduced intracellular calcium. These results suggest that supplemental calcium may limit calcium influx into the cell and improve the ability of the VSMC to extrude calcium. This could be a direct effect of calcium on the VSMC or an indirect effect mediated hormonally.

The calcium-regulating hormones have all been found to have vasoactive properties and therefore may influence blood pressure. Furthermore, CGRP and the proposed parathyroid hypertensive factor are both vasoactive substances that are responsive to dietary calcium. Therefore, diet-induced variations in calcium-regulating hormones may influence blood pressure.

Modulation of the sympathetic nervous system is another important way that dietary calcium can influence blood pressure. There is evidence of altered norepinephrine levels in the hypothalamus as a consequence of manipulations of dietary calcium as well as changes in central sympathetic nervous system outflow. Dietary calcium has also been shown to specifically modify α_1-adrenergic receptor activity in the periphery.

In some experimental models of hypertension, dietary calcium may alter blood pressure by changing the metabolism of other electrolytes. For example, the ability of calcium to prevent sodium chloride–induced elevations in blood pressure may be attributed to natriuresis. However, natriuresis does not account for all of the interactive effects of calcium and sodium chloride on blood pressure. Sodium chloride–induced hypertension may be due in part to calcium wasting and subsequent elevation of calcium-regulating hormones. Chloride is an important mediator of this effect because it appears that sodium does not cause calcium wasting when it is not combined with chloride.

More attention to the central nervous system effects of dietary calcium is needed. Not only can calcium itself influence neural function, but many of the calcium-regulating hormones appear to affect the central nervous system. The influence of calcium and calcium-regulating hormones on central nervous system activity may have important implications for blood pressure regulation and also may extend to other aspects of physiology and behavior.

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KEY WORDS • Ca^{2+}-transporting ATPase • parathyroid hormones • calcitriol • sympathetic nervous system • natriuresis • muscle, smooth, vascular

Dietary calcium and blood pressure in experimental models of hypertension. A review.

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Hypertension. 1994;23:513-530
doi: 10.1161/01.HYP.23.4.513
Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0194-911X. Online ISSN: 1524-4563