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Effect of High Calcium Diet on Magnesium, Catecholamines, and Blood Pressure of Stroke-Prone Spontaneously Hypertensive Rats[1] (42691)

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Abstract. To test the effect of a high dietary calcium intake on blood pressure, we fed stroke-prone spontaneously hypertensive (SHR-SP) and Wistar–Kyoto rats (WKY) diets containing (a) 0.25% Ca/0.08% Mg, (b) 4.0% Ca/0.02% Mg, and (c) 4.0% Ca/0.08% mg, beginning at 6 weeks of age. SHR-SP and WKY rats receiving 4% Ca with the lower Mg content had lower blood pressures, hypomagnesemia, and hypomagnesuria, and grew poorly. SHR-SP receiving 4% Ca and the higher Mg diet had blood pressures no different from those of rats receiving the 0.25% Ca diet, in spite of having lower body weights. Rubidium flux studies in erythrocytes were not influenced by Ca or Mg in the diets. Plasma phosphate values were moderately reduced in rats receiving 4% Ca diets. Epinephrine and norepinephrine values were higher in SHR-SP than in WKY rats. Norepinephrine increased with stress in both strains, independent of diet. Epinephrine values were lower in SHR-SP receiving the 4% Ca diets and showed less of an increase with stress compared to SHR-SP receiving the 0.25% Ca diet. After 26 weeks of diets, SHR-SP and WKY rats were given 0.9% NaCl in their drinking water. NaCl increased blood pressure in SHR-SP irrespective of Ca content of the diet. These data suggest that a high Ca diet influences Mg homeostasis and adrenal medullary function in SHR-SP. Further, SHR-SP appear resistant to any blood pressure lowering effect of Ca irrespective of NaCl intake.

A series of investigations in hypertensive rats, as well as in normal and hypertensive man, suggest that increased dietary calcium intake lowers blood pressure (1–5). Moreover, the blood pressure lowering effect of calcium may be augmented rather than impeded, by a concomitant, generous sodium chloride intake (6). The mechanisms of these effects are not known. The possibility that calcium may act to stabilize vascular smooth muscle membranes, and thereby regulate its own cytosolic homeostasis, has been suggested by McCarron (7). We tested the effect of high calcium intake and variable sodium chloride intake on blood pressure in stroke-prone, spontaneously hypertensive rats (SHR-SP) and their normotensive controls, the Wistar–Kyoto rat (WKY). Since hypertension may be related to a circulating inhibitor of Na/K–ATPase (8, 9), we tested the effects of calcium on the Na/K–ATPase activity of erythrocytes. Further, since SHR-SP have increased sympathetic tone (10, 11), we also examined the effects of high calcium intake on circulating catecholamines. Finally, since a high calcium intake may affect magnesium and phosphorus homeostasis (12), we tested the effect of a high calcium intake at two different levels of dietary magnesium intake.

Methods. SHR-SP and WKY rats, which have been maintained in Heidelberg since 1974, were used in the studies. Following weaning, at 6 weeks of age, the rats were randomly distributed to six groups of 20 rats each. SHR-SP and WKY rats were fed diets (Altromin, Lage, FRG) differing only in their calcium and magnesium contents as follows: (a) 0.25% Ca/0.08% Mg, (b) 4.0% Ca/0.02% Mg, (c) 4% Ca Mg/0.08%, on the basis of weight of the diet. A magnesium content of 0.02% is sufficient for normal growth for rats at a usual calcium intake (13, 14). The sodium content of the Altromin diet is 0.2% Na. The rats were housed two per cage and

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were allowed free access to demineralized water. Blood pressure and body weight were determined biweekly. Blood pressure was measured plethysmographically under light ether anesthesia by a tail cuff technique (11). The relatively large numbers of animals in each group allowed us the sensitivity to identify small differences in blood pressure between the groups. To estimate variability, we examined the sixth and seventh blood pressure measurements in each rat. We found an interclass correlation of 0.81. Thus, we conclude that 34% of the variation in measurements is due to within animal variability, which is influenced by both changes in time and the variability of the measurement. On the other hand, 64% of the variation can be attributed to animal variability. Cronbach's α, a measurement of reliability of the measurement, is 0.89.

At 6 weeks, prior to initiation of the diets, and at 12 weeks (6 weeks of diet), blood was withdrawn from the orbital plexus under ether anesthesia for the determination of extra- and intraerythrocyte electrolytes, and rubidium (Rb) ouabain inhibited, and uninhibited, erythrocyte membrane flux. Rb is transported by erythrocyte membranes in a fashion analogous to that of potassium. By measuring the total Rb influx, and that occurring in the presence of ouabain, the Rb influx attributable to the activity of Na/K–ATPase may be calculated. The electrolytes were measured by automated methods. The rubidium flux methodology is described in detail elsewhere (15, 16). At 12 weeks, the rats were also placed in metabolism cages to permit the collection of 24-hr urine specimens. The first day was used for acclimatization. On the second day, 24-hr urine specimens were collected, while 24-hr water intake was monitored. The excretion of Na, K, Mg, and Ca was determined.

We used norepinephrine and epinephrine values in plasma to reflect sympathetic activity. Femoral arterial catheters were placed in six to eight rats in each group after the animals had received their dietary regimens for 14 weeks. Ether anesthesia was employed, the catheters were exited at the nape of the neck, and the animals were allowed 24 hr to recover. The techniques of catheter placement are detailed elsewhere (17). Each rat was placed in an individual, covered cage and allowed to rest completely quietly for 30 min. Blood samples of 0.5 ml each were gradually withdrawn from the catheters. The animals were then placed in a cold room (4°C) for 30 min, and an additional 0.5 ml of blood was withdrawn. The catecholamines were determined by techniques described previously (11). These animals were then sacrificed. Kidneys from rats receiving the 0.25% Ca/0.08% Mg and 4% Ca/0.08% Mg diets were perfused *in situ* with glutaraldehyde, and the tissue was examined with light and electron microscopy with techniques outlined in detail elsewhere (18).

The rats receiving the lower magnesium intake exhibited blunted growth, and their studies were terminated after 14 weeks of the diet. Four groups of rats were continually studied until 42 weeks of age (36 weeks of diet). These rats received either the 0.25% Ca/0.08% Mg or the 4.0% Ca/0.08% Mg diets. After 28 weeks of the respective diets, the sodium chloride intake of all four groups was augmented by the substitution of demineralized water for a solution of 0.9% NaCl. The investigations were then continued for an additional 8 weeks.

The data were entered into a computerized statistical program (SPSSX). Blood pressure and body weight were analyzed by means of repeated measures analysis of variance. Other variables were compared by means of two- and three-way repeated measures analysis of variance. This approach allowed us to assess interactions among the grouping factors and the repeated measures. When these interactions were significant, the presence of individual group differences was examined. Fiducial limits are expressed as SD. The 95% limits of probability were accepted as significant.

Results. The effects of the regimens on blood pressure are outlined in Fig. 1. Since the data were analyzed with repeated measures analysis of variance, fiducial limits are not shown on the figure. However, the SD did not exceed 15 mmHg in any group. SHR-SP and WKY receiving 4% Ca/0.02% Mg had lower blood pressures than the other groups. Blood pressures of SHR-SP and WKY receiving 4% C/0.08% Mg or 0.25% Ca/0.08% Mg were not different within a

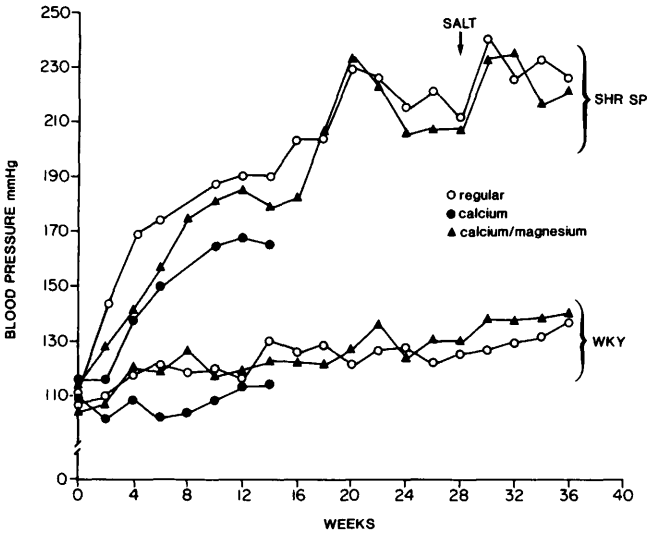

FIG. 1. Effect of 0.25% Ca/0.08% Mg (open circles), 4.0% Ca/0.02% Mg (closed circles), and 4.0% Ca/0.08% Mg (closed triangles) diets on blood pressure in SHR-SP and WKY rats. Only the 4.0% Ca/0.02% Mg diet decreased blood pressure.

strain of rats. When the data were analyzed considering only 8 weeks of the diets, the 4% Ca/0.08% Mg regimen was associated with a rate of blood pressure increase less than that observed with the 0.25% Ca/0.08% Mg dietary intake; however, by 10 weeks, the blood pressures of the two groups were not different. The addition of NaCl to the drinking water increased the blood pressure of both groups of SHR-SP; however, the degree of incresae was not different.

Body weight is outlined in Fig. 2. The SHR-SP and WKY groups receiving the 4% Ca/0.02% Mg diet exhibited bilateral erythema of the base of the ears after 2 weeks of the diet. In some animals, this condition was followed by excoriation of the outer ear with minute hemorrhages, followed by subcutaneous edema and/or the accumulation of crusty serohemorrhagic exudate. These animals exhibited a blunted growth curve, so that by 12 weeks they weighed only half as much as the other groups. For that reason studies in these rats were terminated. WKY rats weighed more than SHR-SP. Further, the groups receiving the 0.25% Ca/0.08% Mg diet gained more weight than groups receiving the 4% Ca/0.08% Mg diet.

Table I contains the electrolyte and Rb flux determinations. At 6 weeks of the diets, the rats receiving 4% Ca/0.02% Mg had higher intraerythrocyte Na values than the other groups. Intraerythrocyte K values, plasma Na, plasma K, and plasma total Ca values were not different among the groups. After the diets were begun, the total calcium values of rats receiving the higher calcium diets increased significantly. Plasma Mg values were decreased in rats receiving the 4% Ca/0.02% Mg diet. The two 4% Ca diets also resulted in lower plasma phosphorus values.

Inhibited and uninhibited Rb flux values did not differ among the groups of SHR-SP regardless of diet. The difference between these values, reflecting Na/K–ATPase activity, also did not differ among SHR-SP regardless of the diet. However, all SHR-SP groups had higher Rb flux values than WKY ingesting the 0.25% Ca/0.08% Mg diet.

Table II shows the 24-hr electrolyte excretion as determined at 12 weeks. Urine Na excretion in SHR-SP receiving the 4% Ca/0.02% Mg diet was less than that of other groups, probably reflecting their poor growth. Magnesium excretion in the groups receiving the 4% Ca/0.02% Mg diet was at the lower limit of our being able to detect it.

Table III shows the plasma norepinephrine and epinephrine values in SHR-SP and

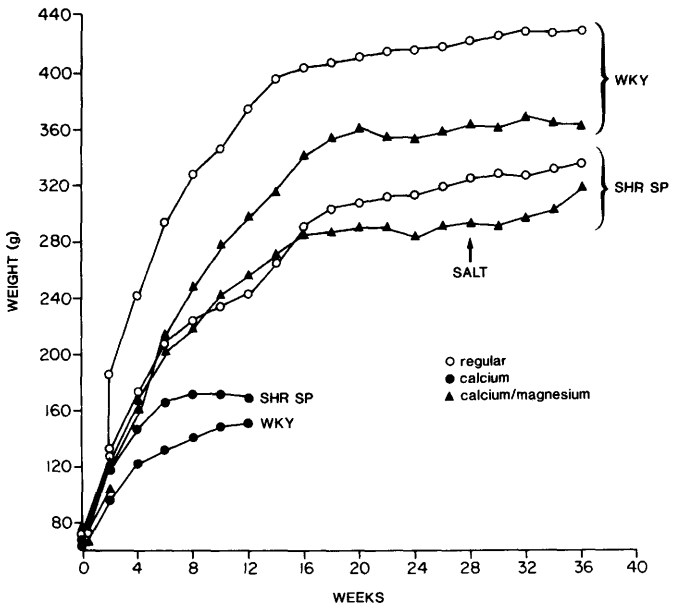

FIG. 2. Effect of 0.25% Ca/0.08% Mg (open circles), 4.0% Ca/0.02% Mg (closed circles), and 4.0% Ca/0.08% Mg (closed triangles) diets on body weight in SHR-SP and WKY rats. The high calcium regimens resulted in lower body weights.

WKY before and after cold stress. These values were greater in SHR-SP than in WKY rats. No effect of the dietary regimens on the stressed norepinephrine values was identified. However, the 4% Ca diets resulted in lower basal epinephrine values in SHR-SP. Further, the response of plasma epinephrine values to cold stress was less in SHR-SP receiving the high Ca regimens than in those receiving the 0.25% Ca diet.

Renal tissue from SHR-SP and WKY rats receiving the 0.25% Ca/0.08% Mg and 4% Ca/0.08% Mg regimens were compared. Electron microscopy of the interlobular and arcuate arteries, as well as the afferent and the efferent arterioles, were normal in these groups which could not be distinguished morphologically on the basis of the regimens. Further, the renin-producing cells of the juxtaglomerular apparatus of animals ingesting 4% Ca showed no changes which would distinguish them from rats receiving 0.25% Ca.

Discussion. Increased amounts of dietary calcium are reported to attenuate the development of hypertension (1, 2), while low levels of dietary calcium appear to accelerate the development of hypertension in SHR (3). A variety of biochemical defects related to calcium metabolism in the SHR, including low serum ionized calcium values (19), elevated parathyroid hormone concentrations (2), hypercalciuria (2, 20), and decreased intestinal absorption of calcium (20) may contribute to this effect. Phosphate depletion has also been suggested as a possible explanation (21). The exact mechanisms responsible for the effects of calcium on blood pressure are unknown. Further, not all investigators have found that increasing dietary calcium intake regularly lowers blood pressure in SHR (22). We found that a 4% calcium intake did not decrease blood pressure in SHR-SP if an adequate amount of magnesium was included in the diet. It may be argued that calcium attenuated the rate of increase in blood pressure; however, the final values obtained were no different with the low and high calcium regimens. Instead, augmented calcium intake may have served to promote magnesium deficiency in animals receiving a diet which was marginal in magnesium content. A definitive statement would require inclusion of a diet containing low calcium and marginal magnesium content, which was not included in this study. However, the pres-

TABLE I. ELECTROLYTE AND RUBIDIUM FLUX VALUES (MEAN ± SD)

Regimens	Weeks	SHR-SP rats			WKY rats
		Normal	High calcium	High calcium, high magnesium	Normal
Na (i) (mmole/liter)	0	4.5 ± 0.2	3.4 ± 0.3	3.0 ± 0.2	3.2 ± 0.3
	6	3.6 ± 0.3	4.6 ± 0.8[a]	4.0 ± 0.4	4.2 ± 0.4
K (i) (mmole/liter)	0	109.0 ± 2.4	108.3 ± 3.5	114.6 ± 4.4	113.9 ± 4.2
	6	104.7 ± 4.6	108.0 ± 1.4	108.8 ± 5.8	111.3 ± 6.0
Uninhibited rubidium flux (mmole/liter/hr)	0	2690 ± 234	2733 ± 220	2910 ± 264	2329 ± 282
	6	2658 ± 183	2778 ± 184	3034 ± 174	2064 ± 162
Inhibited rubidium flux (mmole/liter/hr)	0	852 ± 70	863 ± 76	910 ± 144	754 ± 123
	6	905 ± 80	981 ± 39	964 ± 40	682 ± 88
Na/K ATPase flux difference	0	1839 ± 166	1870 ± 164	1973 ± 340	1575 ± 214
	6	1753 ± 163	1709 ± 117	1867 ± 182	1382 ± 151
Na(ex) (mmole/liter)	0	134.8 ± 0.5	139.5 ± 0.4	141.4 ± 0.5	139.8 ± 1.1
	6	138.0 ± 0.6	137.7 ± 1.0	138.0 ± 0.7	139.1 ± 1.1
K(ex) (mmole/liter)	0	6.36 ± 4.7	6.84 ± 0.7	5.44 ± 2.6	6.24 ± 0.43
	6	5.98 ± 4.9	5.74 ± 9.4	5.26 ± 5.0	4.89 ± 0.64
Ca(ex) (mmole/liter)	0	2.60 ± 0.02	2.65 ± 0.02	2.73 ± 0.04	2.69 ± 0.06
	6	2.73 ± 0.04	2.96 ± 0.16[a]	2.97 ± 0.12[a]	2.59 ± 0.08
Mg(ex) (mmole/liter)	0	0.68 ± 0.06	0.64 ± 0.02	0.67 ± 0.06	0.71 ± 0.03
	6	0.72 ± 0.05	0.30 ± 0.07[a]	0.64 ± 0.09	0.82 ± 0.04
Phosphorous (mmole/liter)	6	1.48 ± 0.18	1.04 ± 0.18[a]	1.06 ± 0.22[a]	1.88 ± 0.16

[a] Different from other groups ($P < 0.05$).

ence of magnesium deficiency was suggested by decreased blood pressure values, failure to grow properly, premature mortality, increased intraerythrocyte sodium values, and clinical signs of magnesium deficiency characterized by erythema and other cutaneous changes of the pinnae. Similar changes have been reported by Evans *et al.* (23) who observed all of the above changes in addition to renal tubular necrosis, interstitial nephritis, and intrarenal mineralization. The likely cause of magnesium deficiency in our animals is not entirely established; however, a high dietary calcium intake may alter magnesium absorption as well as facilitating its renal excretion (24). Our urinary magnesium values in hypomagnesemic rats were very low, perhaps favoring decreased magnesium absorption as the explanation. The effects of a high calcium intake on phosphate homeostasis have been stressed previously (21, 25). Phosphate values in rats receiving a high calcium intake were decreased compared to controls; however, the decreases were modest and not suggestive of phosphate depletion sufficient to influence blood pressure. With the more generous magnesium intake, we observed the rats receiving the high calcium diet still achieved lower body weights than their counterparts receiving the lower calcium intake, although the blood pressure values were no different. We have no explanation for the effect of high calcium intake on body weight. Long-term pair feeding experiments would be necessary to elucidate this issue. We found no evidence of calcium deposition in the vasculature of animals receiving the larger magnesium intake. Such depositions of calcium are particular features of magnesium deficiency (24).

We measured Rb fluxes to reflect Na/K–ATPase activity in our animals before the diets were begun and at 6 weeks thereafter. A circulating inhibitor of Na/K–ATPase has been postulated to be responsible for the development of hypertension by several groups of investigators (8, 9). This inhibitor would promote natriuresis, but would also lead to higher intracellular sodium and calcium concentrations, thereby promoting increased

TABLE II. URINARY ELECTROLYTE EXCRETION IN CALCIUM FED RATS AT 12 WEEKS (MEAN ± SD).

	SHR-SP rats			WKY rats		
	Normal	High Ca	High Ca, high Mg	Normal	High Ca	High Ca, high Mg
Water intake (ml/24 hr)	20 ± 8	8 ± 5	14 ± 4	22 ± 16	17 ± 9	24 ± 13
UV (ml/24 hr)	10 ± 4	6 ± 2	8 ± 3	14 ± 8	14 ± 9	15 ± 9
UNaV (mmole/24 hr)	0.74 ± 0.3	0.64 ± 0.2[a]	1.15 ± 0.4[a]	0.98 ± 0.3	1.12 ± 0.9	1.09 ± 0.5
UKV (mmole/24 hr)	1.14 ± 0.4	1.01 ± 0.3	1.65 ± 0.4	1.42 ± 0.4	1.37 ± 0.8	1.69 ± 0.5
UCaV (mmole/24 hr)	0.01 ± 0.01	0.10 ± 0.10[a]	0.14 ± 0.09[a]	0.01 ± 0.01	0.09 ± 0.08[a]	0.10 ± 0.10[a]
UMgV (mmole/24 hr)	0.01 ± 0.01	<0.001[a]	0.015 ± 0.01	0.01 ± 0.01	<0.001[a]	0.02 ± 0.02

[a] Regimen differs from "normal group" ($P < 0.05$).

vascular reactivity, decreased neuronal uptake of norepinephrine, and other alterations which could lead to the development of hypertension. We previously observed that Na/K–ATPase activity in SHR-SP is decreased by the administration of sodium chloride, but not by the administration of sodium bicarbonate (26). These findings were consistent with a mechanism by which Na/K–ATPase is reduced in response to increased sodium chloride intake. In the present study, Na/K–ATPase activity appeared to decrease with age. Altered calcium intake and different magnesium intakes had no effect on this parameter in the current investigations.

Recently, the effects of calcium on blood pressure were found to be more pronounced if the dietary sodium chloride content was also generous (6). Similarly, diets restricted in calcium and sodium content seemed to be more effective in elevating blood pressure in SHR than diets with restricted calcium but elevated sodium content (6). However, we observed an increase in blood pressure at the higher sodium chloride intake in animals receiving either the high or the low calcium diets rather than a decrease.

Reports of altered sympathetic activity following dietary calcium alterations (25), together with observations of enhanced calcium-mediated release of norepinephrine and increased smooth muscle contractility in SHR (28), suggest that dietary calcium may influence blood pressure by influencing sympathetic tone. Numerous studies have dem-

TABLE III. CATECHOLAMINE RESPONSES IN CALCIUM FED RATS (MEAN ± SD)

	SHR-SP rats			WKY rats		
	Normal	High Ca	High Ca, high Mg	Normal	High Ca	High Ca, high Mg
Norepinephrine (pmole/ml)						
Warm	1.99 ± 0.85	1.94 ± 0.87	1.47 ± 0.38	0.87 ± 0.13	1.31 ± 0.47	0.77 ± 0.33
Cold	3.46 ± 0.78	5.74 ± 0.94	2.70 ± 0.75	1.54 ± 0.81	2.65 ± 1.13	1.83 ± 0.54
N	7	6	7	7	5	7
Epinephrine (pmole/ml)						
Warm	9.52 ± 2.90	3.91 ± 1.97[a]	2.02 ± 2.54[a]	0.89 ± 0.51	1.64 ± 1.38	0.84 ± 0.54
Cold	18.63 ± 8.23	9.94 ± 4.13[a]	6.28 ± 4.91[a]	3.15 ± 3.39	3.45 ± 1.61	2.24 ± 1.72
N	7	6	7	7	5	7

[a] Calcium regimens differ from usual diet ($P < 0.05$).

onstrated increased sympathetic tone in SHR (10), particularly our strain of SHR-SP (11). Recently, a high calcium, high sodium chloride diet was found to attenuate stress-induced blood pressure responses in SHR (25). We used norepinephrine and epinephrine values in SHR-SP before and after cold stress to reflect sympathetic tone. We found that the high calcium diets affected epinephrine but not norepinephrine, both before and after stress. The effects of augmented calcium intake on blood pressure in rats are variable. A decrease in blood pressure has not regularly been found. For instance, Huie *et al.* (28) observed that Fisher 344 rats responded to a high calcium intake with significant correlations among systolic blood pressure and serum ionized and total calcium concentrations, and positive correlations among systolic blood pressure, phosphorus, and magnesium, while no such correlations were identified in either the Wistar Furth rat or the ACI rat. SHR-SP and WKY have been bred in Heidelberg since 1974. This strain is relatively sodium chloride sensitive (29). It is possible that differences in susceptibility to calcium loading are related to strain SHR differences that have developed gradually through time. Our data demonstrate that the effects of calcium on blood pressure in SHR are heterogeneous. The Heidelberg strain of SHR-SP appears to be relatively calcium resistant.

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