Effects of Dietary Magnesium Supplementation on Diurnal Variations of Blood Pressure and Plasma Na⁺, K⁺-ATPase Activity in Essential Hypertension

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SUMMARY

To evaluate the antihypertensive and hormonal effects of oral magnesium supplementation, 17 inpatients with untreated, uncomplicated mild-to-moderate essential hypertension (EH) and 8 age-matched normotensive controls (controls) were given MgO orally 3 times a day at a daily dose of 1.0 g (0.6 g per day as Mg) for a period of 2 weeks. Supplementation of MgO elicited a significant fall in averaged mean blood pressure calculated with a 24-h ambulatory blood pressure monitoring system (MBP) in EH from a baseline value of 104.3 ± 12.2 to 99.5 ± 11.6 mmHg ($p < 0.05$), while controls remained unaltered from a baseline value of 85.1 ± 11.5 to 84.5 ± 13.3 mmHg. The percentage reductions in systolic and diastolic blood pressures were similar during daytime and nighttime in EH. According to the extent of reduction in MBP with magnesium supplementation, EH patients were divided into 2 groups, responder and nonresponder. The level of plasma renin activity (PRA) in the responder group was significantly higher than that of the nonresponder group ($p < 0.05$). After 2 weeks of magnesium supplementation, the plasma level of Na⁺, K⁺-ATPase inhibitory activity (PATPI), defined as equivalency to ouabain, was reduced significantly from 0.75 ± 0.54 to 0.40 ± 0.30 μ mol ouabain/ml ($p < 0.05$) in the responder group, while it remained unaltered in controls and the nonresponder group. PRA, plasma aldosterone concentration, urinary epinephrine and norepinephrine excretion, and urinary sodium excretion did not change significantly in either control subjects or EH (responder and nonresponder groups). A significant negative correlation existed between the pretreatment PRA and changes in MBP after magnesium supplementation in EH ($r = -0.65$, $p < 0.01$), and there was a significant positive correlation between changes in PATPI and changes in MBP as a whole ($r = 0.41$, $p < 0.05$). These results support the view that oral magnesium supplementation is a useful approach to treatment of patients with uncomplicated essential hypertension, especially those with high plasma renin activity. It appears that magnesium suppresses circulating Na⁺, K⁺-ATPase inhibitory activity to attenuate vascular tone, and thereby re-

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duces blood pressure in EH.

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SEVERAL investigators have demonstrated that magnesium supplementation prevented development of hypertension and/or attenuated blood pressure levels in various animal models which include spontaneously hypertensive rats,¹⁾ two-kidney, one-clip Goldblatt hypertensive rats,²⁾ and deoxycorticosterone acetate-salt hypertensive rats.³⁾ Dyckner and Wester⁴⁾ also confirmed the salutary effects of magnesium supplementation in patients with essential hypertension. Although the rationale of magnesium's hypotensive action remains unsettled, several proposed mechanisms for the antihypertensive effects of magnesium are 1) competition with Ca²⁺ for binding sites in vascular smooth muscle cells (VSMC), thereby preventing Ca²⁺-induced vasoconstriction,⁵⁾ and 2) activation of the sodium pump through suppression of Na⁺, K⁺-ATPase inhibitor in the VSMC and subsequent reductions in the vascular resistance and vascular reactivity to constrictor agonists such as norepinephrine and angiotensin II.⁶⁾ In addition, experimental evidence suggests that magnesium produces a fall in blood pressure as a result of inhibiting angiotensin II-induced aldosterone production⁷⁾ and stimulating vasodilatory prostaglandin I₂ release from vascular tissues.⁸⁾

On the other hand, recent studies have strongly indicated the presence of Na⁺, K⁺-ATPase inhibitory substance in the circulation.⁹⁾⁻¹¹⁾ Although its origin as well as chemical structure are as yet unknown, accumulating evidence implicates such an inhibitor in the pathogenesis of essential hypertension.¹²⁾⁻¹⁴⁾ In this context, Motoyama et al¹⁵⁾ reported that the blood pressure-lowering effect of oral magnesium correlated inversely with the ouabain-sensitive sodium efflux rate of erythrocytes in essential hypertensive patients, leading to a hypothesis that oral magnesium treatment is effective in lowering high blood pressure through suppression of the circulating Na⁺, K⁺-ATPase inhibitor. To date, however, few data are available to explain the exact mechanism of the hypotensive action of oral magnesium supplementation in essential hypertension.

This study was designed to evaluate the effects of oral magnesium supplementation on blood pressure, plasma Na⁺, K⁺-ATPase inhibitory activity, renin and aldosterone profiles, urinary output of catecholamines and electrolytes in patients with essential hypertension, and then to elucidate the hypotensive mechanism and therapeutic efficacy of oral magnesium.

PATIENTS AND METHODS

Patients

After informed consent was obtained, 17 inpatients (7 men and 10 women) with untreated, uncomplicated mild-to-moderate essential hypertension and normal renal function, aged 30–69 years (53.4 ± 11.8 years, mean $\pm$ SD), and 8 age-matched healthy volunteers (6 men and 2 women; hereafter termed controls) were enrolled in this study. The patients had stages I or II hypertension according to the World Health Organization hypertension criteria.

These subjects were admitted to the Third Department of Internal Medicine, Fukushima Medical College, and received a constant sodium diet (7 or 9 g of sodium chloride/day) for at least 2 weeks before the study was initiated.

Study protocol

After the baseline evaluation, including measurements of blood pressure, heart rate and biomedical variables, patients and controls were given oral magnesium supplementation 3 times a day in the form of magnesium oxide (MgO) 1 g/day (600 mg Mg daily) for 2 weeks and received no other medications until the completion of the study.

Since the decremental mean value of averaged 24-h MBP after magnesium supplementation was approximately 5 mmHg, patients with essential hypertension were then classified as responders when their averaged 24-h MBP fell by 5 mmHg or more, and as nonresponders when the MBP fell by less than 5 mmHg. According to this criterion, 7 patients were included in the responder group, and the remaining 10 in the nonresponder group. The following measurements were performed for each subject before entry into the study and at the end of the study. Blood pressure and pulse rate were measured every 30 min for 24 h using an indirect ambulatory blood pressure monitoring system (ABPM type 630, Nihon Colin Co., Ltd., Tokyo) by the oscillometric method. In this context, “daytime” was defined as the period from 6:30 to 22:00 and “nighttime” as the period from 22:30 to 6:00. Venous samples were obtained from the subjects at 8 AM after an overnight fast to measure serum sodium, potassium, chloride and magnesium; plasma renin activity (PRA); plasma aldosterone (PAC); and plasma Na^+ , K^+ -ATPase inhibitory activity (PATPI). A 24-h urine sample was collected at 4°C and analyzed for urinary volume and sodium, magnesium, epinephrine and norepinephrine excretion.

Analytical methods

The PATPI was assayed by the photometric method essentially similar to that reported by Hamlyn.¹²⁾ Briefly, the plasma sample (2 ml) was boiled for 10 min and centrifuged for 30 min as 12,000 rpm. The supernatant was applied to a Sep-Pak C₁₈ cartridge (Waters, Milford, MA) which had been prewashed with 0.1% N-trifluoroacetic acid-d, l-methionine methylester (TFA-MM) followed by petroleum ether. The cartridge was then eluted with a mixture of acetonitrile, distilled water and TFA-MM (80:19.9:0.1, vol/vol), and the eluate was evaporated to dryness in a vacuum centrifuge. The dried material was dissolved in assay buffer consisting of (in mM) KCl (2.1), NaCl (120), NaHCO₃ (26), CaSO₄ (2.5), K₂HPO₄ (1.2), MgSO₄ (1.2), and EGTA (3.4). The buffer contained 0.08% bovine serum albumin. To each tube containing 500 μ l of the sample were added 0.02 unit of ATP disodium salt (Sigma Chemical, St. Louis, MO) dissolved in tris-hydroxymethyl-2-aminoethanesulfonic acid (TES) buffer containing 20 mM KCl, 100 mM NaCl, 4.5 mM MgSO₄, and 5 mM EDTA-Na₂ and 500 μ l of aliquot containing ATP (3 mM), phosphoenol pyruvate (1.2 mM), lactate dehydrogenase (1.2 units), pyruvate kinase (1.2 units) and NADH (0.25 mM). Tubes not containing the plasma extract were used for control. The decrease in absorbance (340 nm) due to NADH oxidation in the reaction mixture was recorded photometrically for the sample and control. The PATPI was calculated according to the following formula:

$$\text{PATPI} = 100 - (\text{sample } A_{340} \text{ nm} / \text{control } A_{340} \text{ nm}) \times 100^{12)}$$

The PATPI was defined as equivalency of ouabain which was used as a standard, and expressed as μ mol of ouabain/ml.

The PRA¹⁶⁾ and PAC¹⁷⁾ were determined by radioimmunoassay as described previously. Urinary epinephrine and norepinephrine were measured by an electrochemical detection method coupled with high-performance liquid chromatography. Serum and urinary sodium and potassium, and urinary magnesium all were measured by flame photometry.

Statistical analysis

Data are expressed as means $\pm$ SD. Statistical analysis was performed by chi-square test and Student's *t*-test (paired and unpaired samples) when appropriate. A *p*-value below 0.05 was accepted as a significant level.

RESULTS

Figure 1 summarizes the effect of magnesium supplementation on averaged mean blood pressure (MBP) calculated with a 24-h blood pressure monitoring system both in patients with essential hypertension and control subjects. Averaged 24-h MBP in patients with essential hypertension decreased significantly after 2 weeks of magnesium supplementation, from a baseline value of 104.3 ± 12.2 to 99.5 ± 11.6 mmHg ($p < 0.05$), while MBP remained unchanged in control subjects from a baseline value of 85.1 ± 11.5 to 84.5 ± 13.3 mmHg.

Figure 2 shows the daily profile of systolic and diastolic blood pressures and pulse rate in patients with essential hypertension before and after magnesium supplementation. Systolic and diastolic blood pressures and pulse rate fell significantly at only limited points of the day. However, each of the averaged 24-h, daytime and nighttime systolic and diastolic blood pressures was significantly lower after than before magnesium supplementation. The percentage reductions in systolic and diastolic blood pressures after magnesium supplementation were similar during daytime and nighttime (Fig. 3). In contrast, systolic and diastolic blood pressures and pulse rate did not change significantly following magnesium supplementation in control subjects, as shown in Fig. 4.

Table I shows the clinical and laboratory profiles of the 2 groups of patients with essential hypertension, as well as control subjects. Averaged 24-h

Fig. 1. Effect of oral magnesium supplementation on averaged 24-h mean blood pressure measured with a noninvasive blood pressure monitoring system in hypertensives (EH) and control subjects.

Fig. 2. A 24-h profile of systolic and diastolic blood pressures and pulse rate averaged every 30 min before (closed circles) and after magnesium supplementation (open circles) in hypertensives. Asterisks indicate p values for the differences between before and after oral magnesium treatment.

MBP of hypertensives (nonresponder and responder groups) was higher than that of control subjects ($p < 0.05$ and $p < 0.01$, respectively). The responder group showed higher MBP as compared with the nonresponder one ($p < 0.05$). Whereas PRA of the responder group was higher than that of the nonresponder one ($p < 0.05$), other variables examined did not show significant differences among the groups.

After 2 weeks of magnesium supplementation, serum magnesium concentration rose in each group slightly, but significantly ($p < 0.05$). However, other serum electrolyte concentrations (Na, K and Cl) were unaffected by magnesium supplementation in any group (Table II).

Urinary magnesium excretion (U-Mg) significantly increased in each group ($p < 0.01$), but no differences in changes of U-Mg were observed among the groups (Table III).

Table IV shows the effects of magnesium supplementation on PRA,

* $P < 0.01$ vs. before magnesium administration

Fig. 3. Percentage reductions in daytime and nighttime blood pressures after oral magnesium supplementation in hypertensives. Asterisks indicate p values for the differences between before and after oral magnesium treatment.

PAC and PATPI. PRA was unchanged after 2 weeks of magnesium supplementation in each group. PAC in the responder group showed a tendency to rise ($p=0.08$), while it did not change in the other 2 groups. On the other hand, PATPI in the responder group significantly decreased from a baseline value of 0.74 ± 0.54 to $0.40 \pm 0.30 \mu\text{mol ouabain/ml}$ ($p < 0.05$), whereas changes in PATPI in the other 2 groups were not significant.

Urinary excretion of epinephrine (U-E) and norepinephrine (U-NE) did not change after 2 weeks of magnesium supplementation in each group (Table V).

Urinary sodium (U-Na) in the responder group tended to increase after 1 week of magnesium supplementation, but shifted toward baseline levels after 2 weeks; the extent did not reach a statistically significant level. There were no significant changes in U-Na in control subjects and the non-responder group during magnesium supplementation (Table VI).

There was a significant negative correlation between pretreatment PRA and changes in averaged 24-h MBP in EH as a whole population ($r = -0.65$, $p < 0.01$, Fig. 5), and a significant positive correlation was also found between changes in PATPI and in averaged 24-h MBP in EH and control subjects as entire groups ($r = 0.41$, $p < 0.05$, Fig. 6).

Diarrhea or other side effects were not encountered in any patients or

Fig. 4. A 24-h profile of systolic and diastolic blood pressures and pulse rate every 30 min before (closed circles) and after magnesium supplementation (open circles) in control subjects.

Table I. Clinical and Laboratory Profiles of Hypertensives and Control Subjects

	Control	Hypertensives	
		Nonresponder	Responder
Number (male/female)	8 (6/2)	10 (5/5)	7 (3/4)
Age (years)	52.8 $\pm$ 9.8	51.7 $\pm$ 12.8	55.7 $\pm$ 9.7
MBP (mmHg)	85.1 $\pm$ 11.5	99.1 $\pm$ 9.8*	111.6 $\pm$ 12.6**†
Body weight (kg)	57.9 $\pm$ 4.8	60.4 $\pm$ 10.1	53.4 $\pm$ 5.2
s-Mg (mg/dl)	1.88 $\pm$ 0.13	1.91 $\pm$ 0.17	1.89 $\pm$ 0.22
PRA (ng/ml/hour)	1.44 $\pm$ 1.82	0.52 $\pm$ 0.19	1.41 $\pm$ 0.99†
PAC (pg/ml)	98.5 $\pm$ 69.4	86.9 $\pm$ 54.2	108.2 $\pm$ 71.5
PATPI (μ mol oua./ml)	0.33 $\pm$ 0.19	0.53 $\pm$ 0.39	0.75 $\pm$ 0.54
U-NE (μ g/day)	35.2 $\pm$ 20.2	42.0 $\pm$ 21.6	34.2 $\pm$ 15.8

Values are mean $\pm$ SD. * $P < 0.05$, ** $p < 0.01$, versus control group. † $P < 0.05$ versus non-responder group. MBP=24 hour averaged mean blood pressure; PRA=plasma renin activity; PAC=plasma aldosterone concentration; PATPI=plasma Na^+ , K^+ -ATPase inhibitory activity; U-NE=urinary norepinephrine excretion.

Table II. Serum Electrolyte Concentration Before and After 2 Weeks of Magnesium Supplementation in Hypertensives (Responder and Nonresponder Groups) and Control Subjects

	Before			
	Na (mEq/L)	K (mEq/L)	Cl (mEq/L)	Mg (mg/dl)
Control	140.5±2.0	4.26±0.25	108.3±2.2	1.88±0.13
EH Nonresponder	141.6±2.0	4.17±0.29	106.9±1.6	1.91±0.17
Responder	140.0±1.9	4.36±0.45	105.9±2.6	1.89±0.22

	After			
	Na (mEq/L)	K (mEq/L)	Cl (mEq/L)	Mg (mg/dl)
Control	138.8±3.1	4.33±0.36	107.4±2.1	2.00±0.15*
EH Nonresponder	142.1±1.5	4.37±0.45	106.4±2.4	2.23±0.46*
Responder	139.7±2.2	4.44±0.66	106.6±2.4	1.99±0.25*

Values are mean±SD. *P<0.05 versus before magnesium administration.

Table III. Urinary Magnesium Excretion Before and After 2 Weeks of Magnesium Supplementation, and Changes in Urinary Magnesium Excretion in Hypertensives (Responder and Nonresponder Groups) and Control Subjects

	Mg supplementation		Changes in urinary Mg
	Before	After	
Control (mg/day)	95.0±30.6	180.0±57.0*	85.0±66.6
EH Nonresponder (mg/day)	75.4±26.4	149.1±62.7*	73.8±46.2
Responder (mg/day)	83.4±28.8	145.9±32.4*	62.0±40.9

Values are mean±SD. *P<0.01 versus before magnesium supplementation.

subjects during the study.

DISCUSSION

These results are consistent with the previous observation that, in patients with uncomplicated essential hypertension, oral magnesium supplementation in the form of MgO 1 g/day (600 mg Mg daily) produced a significant reduction in blood pressure.¹⁵⁾ In addition, our results seem to be the first documentation that magnesium supplementation causes antihypertensive action without altering diurnal variation of blood pressures, inasmuch as both averaged daytime and nighttime blood pressures were reduced significantly during supplementation compared with the pretreatment period.

Table IV. Plasma Renin Activity (PRA), Plasma Aldosterone Concentration (PAC) and Plasma Na⁺, K⁺-ATPase Inhibitory Activity (PATPI) Before and After 2 Weeks of Magnesium Supplementation in Hypertensives (Responder and Nonresponder Groups) and Control Subjects

	Before		
	PRA (ng/ml/hr)	PAC (pg/ml)	PATPI (μmol oua./ml)
Control	1.44±1.82	98.5±69.4	0.33±0.19
EH Nonresponder	0.52±0.19	86.9±54.2	0.53±0.39
Responder	1.41±0.99	108.2±71.5	0.75±0.54
	After		
	PRA (ng/ml/hr)	PAC (pg/ml)	PATPI (μmol oua./ml)
Control	1.12±1.19	83.1±41.0	0.29±0.25
EH Nonresponder	0.67±0.60	92.1±53.2	0.48±0.47
Responder	1.58±1.18	136.4±98.4	0.40±0.30*

Values are mean±SD. *P<0.05 versus before magnesium supplementation.

Table V. Urinary Epinephrine Excretion (U-E) and Urinary Norepinephrine Excretion (U-NE) Before and After 2 Weeks of Magnesium Supplementation in Hypertensives (Responder and Nonresponder Groups) and Control Subjects

	Before		After	
	U-E (μg/day)	U-NE (μg/day)	U-E (μg/day)	U-NE (μg/day)
Control	6.9±2.4	35.3±20.2	8.9±7.4	28.0±22.1
EH Nonresponder	7.4±5.5	42.0±21.6	8.2±6.6	52.3±28.8
Responder	8.7±5.9	34.2±15.8	8.8±6.7	41.5±15.9

Values are mean±SD.

Table VI. Urinary Sodium Excretion (U-Na) Before and During Magnesium Supplementation in Hypertensives (Responder and Nonresponder Groups) and Control Subjects

	1 week before (mEq/day)	After 1 week (mEq/day)	After 2 weeks (mEq/day)
Control	143.8±24.8	140.7±24.4	142.1±32.4
EH Nonresponder	126.5±17.0	130.2±15.2	123.5±15.9
Responder	125.7±21.2	140.6±25.7	136.8±31.4

Values are mean±SD.

Fig. 5. Relationship between pretreatment plasma renin activity (PRA) and changes in averaged mean blood pressure (MBP) after oral magnesium supplementation in hypertensives.

Fig. 6. Relationship between changes in averaged mean blood pressure (MBP) and changes in plasma Na^+ , K^+ -ATPase inhibitory activity (PATPI) after oral magnesium supplementation in hypertensives as a group and control subjects.

Further, in keeping with earlier investigations,^{15),18)} the form and dose of magnesium used in this study appeared to be well tolerated as there were no reports of diarrhea or other untoward side effects.

Although the present study did not compare the antihypertensive effect of oral magnesium supplementation with that of placebo, it has increasingly become clear that placebo does not lower ambulatory blood pressure.¹⁹⁾ Thus the results obtained in this study indicate that oral magnesium supplementation indeed exerts an antihypertensive effect in patients with essential hypertension.

At present, there are several possible explanations for the mechanism of action of magnesium to lower blood pressure.^{6),20)–23)} One human study evaluating systemic hemodynamics has shown that the blood pressure-lowering effect of magnesium was associated primarily with peripheral vasodilation and a consequent decrease in total peripheral resistance.²³⁾ Thus, although the hemodynamic changes following magnesium supplementation were not determined in the current study, it is conceivable that the reduction in blood pressure observed in our patients was partly due to the vasodilating mechanisms.

Urinary sodium excretion in the responder group tended to increase after 1 week of magnesium supplementation, suggesting that magnesium has the potential to increase the renal output of sodium. These results show the contributory role of the natriuretic effect of magnesium in its hypotensive action. Berthlot and Esposito¹⁾ also have demonstrated that magnesium has the potential to increase the renal output of sodium, along with an increment in urine volume, probably through potentiating renal prostacyclin synthesis.⁸⁾

PAC did not change after magnesium treatment. Atarashi et al⁷⁾ reported that intravenous infusion of magnesium suppressed angiotensin II-induced increase of aldosterone production, suggesting that magnesium treatment exerts its antihypertensive effect through inhibition of aldosterone production. The reason for this different effect of magnesium on aldosterone production requires further study, but differences in the administration route of magnesium (i.e., oral supplementation versus intravenous infusion), which may result in a difference in plasma concentrations of magnesium, or differences in the duration of administration could be possible explanations.

Oral magnesium supplementation did not affect urinary noradrenaline excretion in either controls or hypertensive patients; therefore, the suppression of peripheral sympathetic nervous activity does not seem to contribute to its antihypertensive mechanisms. On the other hand, Luthringer et al²⁴⁾

have reported that a highly magnesium enriched diet prevented the development of hypertension in spontaneously hypertensive rats, the effect being concomitant with an increase in dopamine levels in the brain stem. These findings may indicate some role of the central nervous system in the antihypertensive mechanism of magnesium. The results from the present study that the pulse rate of hypertensives, but not controls, was reduced slightly by magnesium supplementation may support the hypothesis that the modification of central catecholamines by magnesium treatment contributes to the hypotensive mechanisms.

The finding that PRA in responders was significantly greater than that in nonresponders and a significant negative correlation existed between pretreatment plasma renin activity and changes in MBP in hypertensives, indicates that reduction in blood pressure is much greater in patients with high-renin hypertension than in those with low renin hypertension.

Magnesium has been shown to inhibit cellular calcium influx *in vitro*.²⁵⁾ Because of this trait, magnesium has been proposed as a physiological calcium antagonist. An abnormality of calcium homeostasis has been postulated to exist in low-renin hypertension.²⁶⁾ Patients with low-renin essential hypertension have been shown to have lower serum ionized calcium, and higher parathyroid hormone and 1, 25 vitamin D₃ levels than patients with high-renin hypertension.^{26),27)} Both parathyroid hormone and 1, 25 vitamin D₃ have been shown to increase intracellular and/or cytosolic calcium in some tissues.²⁸⁾⁻³⁰⁾ Such alterations may lead to an increase in smooth muscle cytosolic calcium, and thus enhance vasoconstriction. Therefore, magnesium may have a preferential blood pressure-lowering effect in low-renin hypertension by blocking smooth muscle cellular calcium entry. However, our data do not support the concept that magnesium supplementation exerts a more pronounced antihypertensive effect in low-renin hypertensive patients than it does in patients with high renin activity. Resnick et al have reported that while serum magnesium levels were higher in patients with low-renin hypertension and lower in patients with high-renin hypertension than those with normal-renin hypertension, serum levels of ionized calcium were lower in patients with low-renin hypertension and higher in patients with high-renin hypertension than in those with normal-renin hypertension. Additionally, they demonstrated a negative correlation between the plasma renin activity and the serum magnesium level, and also a positive correlation between the plasma renin activity and the serum ionized calcium level.²⁶⁾ Thus, assuming that reduced levels of extracellular magnesium reflect increased levels of intracellular calcium, which would account for the arteriolar vasoconstriction, these observations may explain convincingly that magne-

sium supplementation exerts blood pressure-lowering action more effectively in patients with higher levels of plasma renin activity than it does in patients with lower renin activity, as observed in the current study, through inhibiting calcium influx across the cell membrane. However, since serum magnesium concentrations in the responder group did not significantly differ from those in the nonresponder one, possibly because of the limited numbers of patients studied, further studies will be needed to elucidate this important mechanism.

Recently, a new hypothesis has emerged for explaining the role of a circulating sodium pump inhibitor in the pathogenesis of essential hypertension.¹²⁾⁻¹⁴⁾ Although the molecular structure of the inhibitor is as yet unidentified, Motoyama et al¹⁵⁾ showed that the extent of reduction in mean blood pressure induced by oral magnesium supplementation positively correlated with the levels of 'pump activator' of erythrocytes which was defined as the ouabain-sensitive ^{23}Na efflux rate constant in patients with essential hypertension. Their results are consistent with our observations. Magnesium inhibits the release of calcium from sarcoplasmic reticulum by competition for a calcium receptor on a calcium-regulated efflux channel and drives calcium into the sarcoplasmic reticulum through stimulation of Ca^{2+} -ATPase.³¹⁾ Efflux of calcium from the arterial smooth muscle cell is accomplished by Ca^{2+} -ATPase activity and by the sodium-calcium exchange system.³²⁾ Magnesium has also been known to activate not only Ca^{2+} -ATPase³³⁾ but also Na^{+} , K^{+} -ATPase.^{34),35)} The activated Na^{+} , K^{+} -ATPase produces a decrease in intracellular sodium concentration in smooth muscle cells, as a result of which the sodium-calcium exchange mechanism is activated,³⁶⁾ thus decreasing the intracellular calcium concentration and reducing the tension of the muscle.⁹⁾ Therefore, if Na^{+} , K^{+} -ATPase inhibitor is suppressed, then vascular smooth muscle tone is reduced via a decrement in the intracellular calcium concentration. Our data seem to have provided clinical evidence for such a mechanism for the antihypertensive effect of oral magnesium supplementation, since magnesium treatment produced a significant decrease in the plasma PATPI of the responder group. More importantly, a significant positive correlation existed between the decrement in plasma PATPI and that in MBP in hypertensive patients as a whole population, suggesting a contributory role of magnesium supplementation in suppression of plasma PATPI and concomitant reduction in blood pressure in patients with essential hypertension.

CONCLUSION

The present study suggests that oral magnesium supplementation produces a significant decrease in plasma sodium pump inhibitory activity, accompanied by a reduction in blood pressure without altering diurnal variations in patients suffering from mild to moderate essential hypertension. These observations also show the therapeutic efficacy of appropriate oral magnesium intake as a nonpharmacological approach to the treatment of essential hypertension.

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