Magnesium Supplementation Prevents the Development of Alcohol-Induced Hypertension

Shao-Tung Hsieh, Hiroshi Sano, Komei Saito, Yoshihisa Kubota, and Mitsuhiro Yokoyama

The effect of chronic alcohol administration on blood pressure was investigated in 7-week-old Wistar rats. Tail-cuff blood pressure was significantly higher in rats who received 15% ethanol in drinking water than in control rats. Intracellular free calcium concentration of lymphocytes was increased, while magnesium concentration of erythrocyte, aorta, and skeletal muscle and erythrocyte ouabain-sensitive $^{23}$Na efflux rate constant ($K_m$) were decreased in alcohol-induced hypertensive rats but not in control rats. Extracellular fluid volume was also increased in alcohol-administered rats. Oral magnesium supplementation (1% MgO in rat chow) attenuated the development of alcohol-induced hypertension accompanied by increased magnesium concentration of erythrocyte, aorta, skeletal muscle, and $K_m$ and decreased intraerythrocyte sodium concentration. Norepinephrine half-life time of the heart and spleen was also increased in magnesium-supplemented rats. Blood pressure significantly correlated positively with intracellular calcium concentration and extracellular fluid volume, negatively with magnesium concentration of erythrocyte, aorta, skeletal muscle, and $K_m$. These results suggest that increased intracellular calcium, which was partly due to magnesium depletion and suppressed sodium pump activity, and expanded body fluid volume had a possible role in the development of alcohol-induced hypertension. It is also suggested that oral magnesium supplementation had a hypotensive effect on alcohol-induced hypertension possibly through decreased intracellular sodium concentration caused by an activation of sodium pump and decreased sympathetic nervous activity. (Hypertension 1992;19:175–182)

Since the first report by Lian in 1915, an increased prevalence of hypertension has been recognized in chronic alcoholics. Recently, a large number of cross-sectional studies have revealed a positive, independent association between alcohol consumption and blood pressure, but the mechanism by which regular alcohol consumption leads to an elevation in blood pressure is still uncertain.

The most likely mechanism for alcohol-induced hypertension is that alcohol directly affects intracellular calcium levels of vascular smooth muscle cell or sympathetic nerve terminals, but direct measurement of the intracellular calcium level has been lacking.

It is also well known that chronic alcohol consumption may cause several electrolytic abnormalities. Magnesium depletion is especially common and significant during chronic alcohol consumption. An experimental study in rats has reported that dietary magnesium deficiency is associated with the development of hypertension, and that magnesium may be an important determinant of intracellular calcium. Magnesium depletion may play a possible role in the etiology of alcohol-induced hypertension.

Experimental and clinical trials have shown that magnesium could be useful as a hypotensive agent. Oral magnesium supplementation may also have a hypotensive effect on alcohol-induced hypertension.

The present study was designed to investigate the relation between blood pressure and intracellular magnesium, calcium, and sodium metabolism during chronic alcohol administration in rats. The effect of oral magnesium supplementation on alcohol-induced hypertension was also evaluated.

Methods

Animal Preparation

Seven-week-old male Wistar rats were obtained from Clea Japan Inc., Tokyo, and were randomly divided into three groups. The animals allocated to the alcohol (Alc) group ($n=44$) received 15% ethanol in their drinking water ad libitum. They were fed with commercially available normal rat chow (MF Oriental Yeast Co. Ltd., Tokyo) ad libitum. Rats in the alcohol-magnesium (Alc-Mg) group ($n=46$) also received 15% alcohol in their drinking water, but...
they were also given oral magnesium supplementation in the form of 1% magnesium oxide (MgO) in their rat chow. The alcohol concentration of the solution was 5% at the start of the study and then it was elevated gradually to 15% over a 5-day period. Pure ethanol was added to distilled water to make the appropriate dilution. The control group (n=38) received distilled water and normal rat chow ad libitum.

The animals were kept in individual metabolic cages under controlled conditions. Urine samples were collected for 24 hours at the second and fourth week for the determination of urine volume and urinary magnesium excretion. Water consumption, food consumption, and weight gain were determined weekly. Systolic blood pressure (SBP) (mm Hg) was measured weekly with the tail-cuff method using a Narco BioSystems Programmed Electrophysimeter (PE-3000, Houston, Tex.). The total experimental period was 4 weeks.

**Intracellular Electrolytes**

After 4 weeks, 33 animals (control, n=8; Alc, n=12; Alc-Mg, n=13) were killed by decapitation. Trunk blood was collected in heparinized plastic tubes for the determination of intracellular free calcium (Ca \(^{2+}\)) and sodium (Na\(^{+}\)) concentration and erythrocyte sodium pump activity. Plasma electrolyte concentrations were determined by the Auto Analyzer (System E4A, Beckman Instruments, La Brea, Calif.). Erythrocyte electrolyte concentrations were measured by the method of Kaya et al\(^{14}\) with slight modifications. Erythrocyte sodium pump activity was calculated as the erythrocyte ouabain-sensitive \(^{22}\)Na efflux rate constant (\(K_a\)) by the method of Walter et al\(^{15}\) with slight modifications. Both of these methods have been described previously.\(^{16}\) The spleen was excised, and lymphocytes were collected by gradient centrifugation. Briefly, the spleen was minced, pipetted in phosphate-buffered saline (PBS) with a syringe several times, and passed through four layers of gauze to remove connective tissue. The resulting suspension was overlaid on 3 ml Ficoll-Paque (Pharmacia LKB, Uppsala, Sweden) in a centrifuge tube and centrifuged at 1,600 rpm for 30 minutes at room temperature. The middle layer containing lymphocytes was withdrawn and washed twice with PBS.

Intracellular free calcium concentration of lymphocyte (L-[Ca\(^{2+}\)]) (nM) from the spleen was measured using the fluorescent dye Quin-2 by the method of Tsien et al\(^{17}\) with slight modification. The calibration was determined by the method of Hesketh et al.\(^{18}\) The details of these methods have been described elsewhere.\(^{19}\)

The descending aorta and skeletal muscle of hind limb were also removed for the measurement of tissue magnesium content (A-Mg, M-Mg) after nitric acid digestion.

**Body Fluid Measurement**

Extracellular fluid volume (ECFV) was measured in 28 rats (control, \(n=10\); Alc, \(n=9\); Alc-Mg, \(n=9\)). ECFV was evaluated by dilution of sodium thiocyanate. After the rats were anesthetized with an intraperitoneal injection of sodium pentobarbital (50 mg/kg), 5% sodium thiocyanate in 0.5 ml saline solution was injected slowly into the femoral vein by 1.0 ml injection syringe with a 26G needle. Sixty minutes later, 1.0 ml blood was withdrawn for the determination of plasma concentration of the indicator. After the blood was centrifuged at 3,000 rpm for 5 minutes at 4°C, 200 \(\mu\)l plasma was diluted in 800 \(\mu\)l distilled water, then in 400 \(\mu\)l trichloroacetic acid (50% wt/vol). After denatured proteins were sedimented by centrifugation at 3,000 rpm for 10 minutes, 1.0 ml supernatant was withdrawn and complexed in 1.0 ml Crandal-Andersen reagent. The concentration of the indicator was immediately determined by the optical density measured at 480 nm in a spectrophotometer. A calibration curve and a plasma blank were prepared in parallel. ECFV was calculated as the product of the volume of injected thiocyanate by the ratio of its initial concentration to its plasma concentration.

**Norepinephrine Turnover Rate**

In 67 rats (control, \(n=20\); Alc, \(n=23\); Alc-Mg, \(n=24\)), norepinephrine turnover rates were determined after inhibition of norepinephrine synthesis by intraperitoneal injection of DL-\(\alpha\)-methyl-p-tyrosine (Sigma Chemical Co., St. Louis, Mo.). The drug was dissolved in 1N HCl at 75–80°C and was injected at a dose of 200 mg/kg. The animals were killed by decapitation at 0, 4, and 8 hours after injection. The heart and spleen were quickly removed and frozen in liquid nitrogen. Tissue norepinephrine was then extracted, separated by high-performance liquid chromatography, and determined by the trihydroxyindole method.\(^{20}\)

The turnover of norepinephrine was determined by calculating the decline of endogeneous norepinephrine level. Each time point represented the mean value of individual measurement of each group and was expressed as a percent of the initial value; they were logarithmically transformed, curves were derived from least-squares linear regression analysis, and half-life times were calculated. The significance between the turnover curves was calculated using regression analysis test.\(^{21}\)

**Statistical Analysis**

The existence of a significant difference among the groups was examined using analysis of variance followed by a modified \(t\) test for an individual pair of values. Correlation of the data was determined with a least-squares fit linear regression analysis. A value of \(p<0.05\) was considered statistically significant.

**Results**

The development of SBP during the study is shown in Figure 1. In the Alc group, SBP significantly

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increased as compared with the control group in the first week, and it reached a plateau at the third week. The difference in SBP between these two groups remained significant throughout the study. In the Alc-Mg group, SBP also increased significantly as compared with the control group, but it was significantly lower than the Ale group throughout the study. After 4 weeks, SBP for the control group, the Ale group, and the Alc-Mg group was 118.8±7.3, 147.0±9.3, and 128.8±10.4 mm Hg, respectively, and these values were significantly different between groups. The body weight gain is shown in Figure 1. Alcohol administration resulted in gradual retardation of growth as observed in the Ale and the Alc-Mg groups.

The fluid intake was reduced by alcohol consumption. The average daily water consumption in the fourth week was 30.0 ml in the control group, 24.1 ml in the Ale group, and 25.0 ml in the Alc-Mg group. Food intake decreased in both alcohol-administered groups. The daily food consumption was 19.1 g in the control group, 11.4 g in the Ale group, and 13.4 g in the Alc-Mg group. However, the total daily caloric intake calculated was almost equivalent among the groups. (Ethanol was assumed to contain 29.4 kJ/g and rat chow, 14.7 kJ/g). Rats in the Ale group consumed 1.3 g ethanol daily at the start of the study, and they increased their daily ethanol consumption up to 3.6 g in the fourth week. In the Alc-Mg group, the daily ethanol consumption increased from 1.2 g to 3.8 g.

Twenty-four-hour urine volume in the second and fourth weeks was significantly decreased in both the Ale group and Alc-Mg group as compared with the control group (Figure 2). In the Ale group, 24-hour urinary magnesium excretion was significantly increased as compared with the control group, and it was further increased in the Alc-Mg group as compared with the other two groups (Figure 2).

**Intracellular Electrolytes**

Figure 3 demonstrates the scatterplot of L-[Ca^{2+}] in each group. L-[Ca^{2+}] was significantly higher in the Ale group compared with that of the control group (152.1±22.2 versus 128.6±25.2 nM, respectively, p<0.05). In the Alc-Mg group, L-[Ca^{2+}] was 141.7±18.8 nM; this value showed no significant difference with the other two groups. As shown in Figure 4, L-[Ca^{2+}] significantly correlated positively with SBP (r=0.40, p<0.05).

R-Mg, A-Mg, and M-Mg in the Ale group were significantly lower compared with those of the control group and the Alc-Mg group; R-Mg and A-Mg were also significantly lower in the Alc-Mg group than in the
control group (Table 1). There was significant negative correlation between SBP and R-Mg ($r = -0.58, p < 0.001$), SBP and A-Mg ($r = -0.73, p < 0.001$), and SBP and M-Mg ($r = -0.56, p < 0.001$) (Figure 5).

Erythrocyte sodium pump activity calculated as $K_a$ was suppressed in the Alc group compared with that of the control group. In the Alc-Mg group, sodium pump activity was higher than that of the Alc group (Table 1). $K_a$ also significantly correlated negatively with SBP ($r = -0.40, p < 0.05$) (Figure 5).

R-Na in the Alc-Mg group was significantly lower than that of the Alc group (Table 1).

**Extracellular Fluid Volume**

Extracellular fluid volume (ml/kg·body wt) was significantly higher in the Alc group compared with the control group (Table 1). ECFV positively correlated with SBP ($r = 0.38, p < 0.05$) (Figure 6).

**Norepinephrine Turnover**

Chronic alcohol administration did not alter the norepinephrine half-life time of either heart or spleen (Table 2). In the Alc-Mg group, the half-life time of norepinephrine in the heart and spleen was significantly increased compared with the other two groups.

**Discussion**

In this study, chronic alcohol administration for 4 weeks resulted in the development of hypertension in normotensive Wistar rats. In spite of epidemiological investigations and clinical interventions, there have been few reports on the effect of chronic alcohol administration on blood pressure in experimental animals, and the results are controversial. Several studies in spontaneously hypertensive rats (SHR) failed to demonstrate the pressor effect of alcohol. In these studies, chronic alcohol administration resulted in the attenuation of the development of hypertension in SHR or stroke-prone SHR (SHR-SP). In Wistar-Kyoto (WKY) rats, alcohol administration also caused a mild reduction in blood pressure. In contrast, our results are consistent with the study by Chan and Sutter, in which chronic alcohol administration for 12 weeks in normotensive Wistar rats caused the rise of blood pressure. In our study, blood pressure increased rapidly within a week, but it showed a significant increase from week 4 in the study by Chan and Sutter. One explanation for this discrepancy is that the alcohol concentration in the drinking water was rapidly increased within a week in our study but slowly over 3 weeks in the study by Chan and Sutter.

The mechanism by which regular alcohol consumption leads to an elevation in blood pressure is unclear, but the most likely mechanism of alcohol-induced hypertension is alcohol affecting the intracellular calcium level. Indirect evidence from human studies has shown that the pressor effect of acute and chronic alcohol consumption may be due to an increased intracellular calcium accumulation. More direct evidence reported by Altura and Altura showed that chronic alcohol intake in rats resulted in a progressive increase in total calcium content of the aorta and the portal vein, which became progressively reactive to contractile stimuli. The intracellular calcium concentration is critical to the contractile state of vascular smooth muscle. The increase in [Ca$^{2+}$] of vascular smooth muscle cells would produce an increase in vascular tone. In the present study, an increase in L-[Ca$^{2+}$] was observed in rats with alcohol-induced hypertension. A positive correlation was observed between L-[Ca$^{2+}$] and SBP. Recent studies have also reported the increased L-[Ca$^{2+}$] levels of SHR. To our knowledge, this study is the first demonstration of an increase in both blood pressure and [Ca$^{2+}$] during chronic alcohol administration. Although the rela-
tion between hypertension and increases in L-[Ca²⁺], is unclear, alterations in calcium levels are presumably shared by other cells as well, including vascular muscle cells. Hypertension in rats chronically administered alcohol is possibly caused by an elevated vascular tone through increased [Ca²⁺], in vascular smooth muscle cells.

A previous study, which showed a fall in plasma calcium after alcohol ingestion, suggested the possibility of an alcohol-induced shift in intracellular calcium.⁷ Chronic alcohol administration also increases the entry of calcium into cells through the upregulation of voltage-activated calcium channels.³¹ Alcohol is known to inhibit Ca²⁺-ATPase in several tissues, which extrudes calcium from the cell.³² Consequently, chronic alcohol administration would result in an increase in intracellular calcium by influencing the cellular calcium transport system. In addition, alcohol can influence the metabolism of other cellular ions. Acute and chronic exposure to alcohol would increase the permeability of the plasma membrane to sodium, leading to an increase in intracellular sodium.³³ Increased intracellular sodium, in turn, would result in intracellular calcium accumulation through an inhibition of the Na⁺-Ca²⁺ exchange system.³⁴

It has long been known that chronic ethanol ingestion in humans would result in hypomagnesemia and magnesium wasting through an enhancement of renal magnesium excretion.⁹,¹⁰ There was increased urinary excretion of magnesium in a rat model of alcohol-induced hypertension reported by Chan and Sutter.²⁵ In agreement with this report, we found that daily urinary magnesium excretion in the Ale group was threefold greater than that of the control group. A massive increase in urinary magnesium excretion would cause magnesium deficiency in tissue. Altura and Altura²⁶ reported that progressive ingestion of ethanol in rats resulted in a progressive significant reduction in total magnesium content of the aorta and the portal vein. In the present study, not only A-Mg but M-Mg and R-Mg also decreased in the Ale group, suggesting magnesium deficiency in rats chronically ingesting alcohol.

Previous epidemiological studies have demonstrated an inverse correlation between arterial blood pressure and serum magnesium and intraerythrocyte magnesium level.³⁵,³⁶ Experimental study has also shown that dietary deficiency of magnesium may lead to the development of hypertension.¹¹ Since inverse correlations were observed between SBP and R-Mg, A-Mg, and M-Mg, magnesium depletion may play a role in the etiology of alcohol-induced hypertension. Both Ca²⁺-ATPase and Na⁺,K⁺-ATPase activity are known to be magnesium dependent.³⁷,³⁸ Although the magnesium-regulating mechanism of lymphocytes is not well known, magnesium depletion shown in several tissues (erythrocytes, skeletal muscle, and aorta) is supposed to occur also in lymphocytes of the Ale group. Magnesium depletion of lymphocytes would have resulted in increased [Ca²⁺], through the suppression of Ca²⁺-ATPase.³⁹,⁴⁰ The suppression of Na⁺,K⁺-ATPase caused by magnesium depletion would result in an increased [Ca²⁺] level in vascular smooth muscle cell.³⁴ Thus, chronic alcohol administration would increase [Ca²⁺], through the direct effect of alcohol or through magnesium depletion and eventually would lead to increased peripheral vascular tone and result in hypertension.

In the present study, there was an expansion of the ECFV in the Ale group compared with the control group, and ECFV positively correlated with SBP. Plasma volume expansion has been reported and suggested as a cause of alcohol-induced hypertension by Chan and Sutter.²⁵ They suggested that elevated plasma arginine vasopressin and plasma renin activity.

### Table 1. Measurements of Electrolyte Concentrations in the Plasma, Erythrocytes, and Tissue; Erythrocyte Ouabain-Sensitive 26Na Efflux Rate Constant; and Extracellular Fluid Volume

<table>
<thead>
<tr>
<th>Variables</th>
<th>Control (n=8)</th>
<th>Alcohol (n=12)</th>
<th>Alcohol-magnesium (n=13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma Na concentration (meq/l)</td>
<td>147.8±2.5</td>
<td>146.9±1.7</td>
<td>145.1±2.3</td>
</tr>
<tr>
<td>K concentration (meq/l)</td>
<td>5.92±0.72</td>
<td>5.83±0.59</td>
<td>5.75±0.54</td>
</tr>
<tr>
<td>Mg concentration (meq/l)</td>
<td>1.86±0.09*</td>
<td>1.86±0.11*</td>
<td>2.50±0.23</td>
</tr>
<tr>
<td>Intraerythrocyte Na concentration (meq/l • cells)</td>
<td>5.69±0.32</td>
<td>6.22±0.67†</td>
<td>5.10±0.80</td>
</tr>
<tr>
<td>Mg concentration (meq/l • cells)</td>
<td>8.51±0.21</td>
<td>7.53±0.49‡‡§§</td>
<td>8.05±0.52‡‡§§</td>
</tr>
<tr>
<td>Erythrocyte ouabain-sensitive 26Na efflux rate constant (/hr)</td>
<td>0.752±0.054</td>
<td>0.551±0.052‡‡§§</td>
<td>0.681±0.093</td>
</tr>
<tr>
<td>Tissue Mg concentration (mM/kg dry wt)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aorta</td>
<td>18.4±2.93</td>
<td>11.3±1.18*‡‡§§</td>
<td>15.1±2.49‡‡§§</td>
</tr>
<tr>
<td>Muscle</td>
<td>55.0±34.0</td>
<td>30.4±4.63*‡‡§§</td>
<td>52.4±12.2</td>
</tr>
<tr>
<td>Extracellular fluid volume (ml/kg body wt)</td>
<td>285.8±24.7</td>
<td>305.3±13.7‡‡§§</td>
<td>293.6±17.1</td>
</tr>
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Values are represented as mean±SD.

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Altura reported that progressive ingestion of
may contribute to the volume expansion. Expanded ECFV seen in alcohol-ingesting rats in our present study, which may have resulted from the activated renin-aldosterone system or other mechanisms, would be partly responsible for the elevated blood pressure. But further examination is necessary to elucidate the mechanism of ECFV expansion during chronic alcohol administration.

In our present study, the norepinephrine turnover rate in the heart and spleen of the Alc group was similar to that of the control group. Peripheral sympathetic nervous activity seemed to be unchanged by chronic alcohol ingestion. It is unlikely that an increase in sympathetic nervous activity caused the alcohol-induced hypertension of the rats in the present study. Several animal studies have shown that acute alcohol administration produces an elevation in blood and urine catecholamine levels. However, it was shown that chronic alcohol exposure did not alter endogenous norepinephrine levels and its turnover in the heart, suggesting that tolerance can develop to some of the initial sympathostimulatory effect of alcohol on sympathetic neurons in the heart. In human studies, although acute alcohol administration would produce an elevation in blood pressure and a simultaneous increase in plasma norepinephrine, high blood pressure in chronic alcohol drinkers seems not to be associated with an increase in plasma norepinephrine. It is supposed that the acute increase in plasma norepinephrine after acute alcohol ingestion cannot be a cause of the chronic elevation in blood pressure during chronic alcohol consumption. On the other hand, the in situ terminal arterioles from rats maintained on alcohol were shown to result in the potentiation of the constrictor response to locally administered epinephrine. The enhanced vascular responsiveness to catecholamine in alcohol-maintained rats was explained by an alcohol-induced increase in intracellular calcium. Since our present study showed an increase in $\left[Ca^{2+}\right]_i$ in the Alc group, a supersensitivity of blood vessels to catecholamine in alcohol-ingesting rats may account for the elevated blood pressure in this group.

Recently, experimental and clinical studies have demonstrated that oral magnesium supplementation may be useful as a hypotensive agent. The mechanism for the blood pressure-lowering effect of magnesium is supposed to include an inhibition of sympathetic nervous activity and peripheral vasodilation via control of sodium and calcium metabolism. In our study, oral magnesium supplementation has attenuated the development of hypertension in rats administered alcohol. The hypotensive effect of magnesium is supposed to be partly due to the correction of the

![Figure 5](http://ahajournals.org)
magnesium depletion caused by chronic alcohol consumption. But our data, in which R-Mg, A-Mg, and M-Mg were lower in the Alc-Mg group than in the control group, also demonstrated that magnesium depletion was not normalized by magnesium supplementation. There was significant reduction of body weight in the Alc-Mg group, and since blood pressure is supposed to be weight dependent, the decreased blood pressure may be explained by the retardation of growth caused by the magnesium treatment. However, we would prefer not to attribute the blood pressure-lowering effect of magnesium to decreased body weight, because in one of our separate experiments, we could not find any change in body weight in the Alc-Mg group in spite of the blood pressure-lowering effect of magnesium.

Another interesting finding derived from our study was an elevation of Na\(^+\)-K\(^+\) pump activity and a decrease in R-Na in magnesium-supplemented rats. Previously, we have shown that the hypotensive effect of oral magnesium supplementation on essential hypertensive patients was accompanied by an elevation in Na\(^+\)-K\(^+\) pump activity and a decrease in R-Na.\(^47\) In vascular smooth muscle cells, a decreased intracellular sodium may lead to a decrease in intracellular calcium via the Na\(^+\)-Ca\(^2+\) exchange system. Thus, magnesium had a blood pressure-lowering effect on alcohol-induced hypertension in rats as well as on essential hypertension in humans, possibly through a decreased intracellular sodium concentration caused by an activation of cell membrane sodium pump, which concomitantly resulted in a decrease in intracellular calcium in vascular smooth muscle.

Increased norepinephrine half-life time in the heart and spleen of the Alc-Mg group suggests that peripheral sympathetic nervous activity was decreased by magnesium supplementation in rats chronically administered alcohol. Decreased sympathetic nervous activity may partly account for the blood pressure-lowering effect of magnesium supplementation. However, it is not probable that magnesium supplementation counteracted the pressor effect of alcohol through this sympathoinhibitory effect of magnesium because sympathetic activity was not elevated in rats chronically administered alcohol.

In conclusion, chronic alcohol administration resulted in the development of hypertension in normal Wistar rats, which we speculate was caused by an increase in intracellular calcium. Intracellular calcium was elevated partly through magnesium deficiency and suppressed sodium pump and possibly through the direct effect of alcohol. Alcohol-induced hypertension was accompanied by an expansion of ECFV, which may further contribute to the development of hypertension. Oral magnesium supplementation had a hypotensive effect on alcohol-induced hypertension. Decreased intracellular sodium concentration caused by an activation of the cell membrane sodium pump and decreased peripheral sympathetic nervous activity was possibly responsible for this hypotensive effect of magnesium.

References


KEY WORDS • alcohol-induced hypertension • calcium • magnesium • sodium pump