Efficacy of Oral Magnesium Administration on Decreased Exercise Tolerance in a State of Chronic Sleep Deprivation

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We have previously reported that chronic sleep deprivation causes a deficiency of intracellular magnesium (Mg) and decreased exercise tolerance. The aim of this study was to clarify whether oral administration of Mg could be effective in restoring the exercise tolerance that is decreased by chronic sleep deprivation. A bicycle ergometer cardiopulmonary exercise test was performed by 16 healthy volunteers (mean age 21.9 years). They were divided into 2 groups: 8 received doses of 100 mg of Mg orally per day for 1 month (Mg group) and the remaining 8 received no Mg and served as the control group. The study conditions were designed as follows: (1) the usual state (good sleep); and (2) the sleep-deprived state (sleeping time up to 60% less than the usual state for 1 month). The ratio of intracellular Mg content of the sleep-deprived state to the usual sleep state was significantly higher in the Mg group ($p < 0.05$) than the untreated control group. There was no difference between the sleep-deprived state and the usual state with regard to anaerobic threshold and peak oxygen uptake in the Mg group, whereas both of these decreased in the sleep-deprived state in the control group. These results indicate that decreased exercise tolerance observed in the sleep-deprived state could be improved by oral Mg administration. (*Jpn Circ J* 1998; 62: 341–346)

Key Words: Erythrocyte magnesium; Exercise tolerance; Magnesium administration; Norepinephrine; Sleep deprivation

B etween 300,000 and 400,000 people die suddenly in the United States every year[1] and many of these do so in apparently good health without any prior evidence of coronary heart disease[2] It is well known that sudden cardiac death frequently occurs in apparently healthy people as well as in cardiac patients with chronic fatigue[3] The mechanism of sudden cardiac death occurring in patients with chronic fatigue is controversial from the medical and social standpoints.

Against this background, we investigated the various influences of chronic sleep deprivation as a model of chronic fatigue on the plasma concentration of norepinephrine (NE) and exercise tolerance. Attention was also directed toward magnesium (Mg) dynamics because many patients with vasospastic angina, which is suggested as an etiology of sudden cardiac death, exist in Japan. The mechanism has been speculated to be Mg deficiency in the smooth muscle of the coronary artery[4] and coronary arterial spasm is inhibited by the administration of Mg[5]

In our previous investigations, chronic sleep deprivation caused decreased NE secretion during exercise and de-creased exercise tolerance[6] Chronic sleep deprivation also led to a deficiency in intracellular Mg content[7]

There are several reports regarding the relation between Mg dynamics and NE secretion[8,9] In our previous report about the relation between intravenous Mg administration and NE concentration or exercise tolerance, we suggested that Mg plays an important role in the secretion of NE and that intravenous additive Mg administration could restore the secretion of NE and exercise tolerance during chronic sleep deprivation[10] The aim of this study is to clarify whether oral Mg administration could be effective in improving decreased exercise tolerance caused by chronic sleep deprivation. In addition, plasma NE concentration was measured in association with changes in exercise tolerance.

Methods

The subjects for this study were 16 apparently healthy male volunteers (college students); mean age 21.9 ± 1.3 years. Subjects were assigned to 2 groups at random, ie, 8 subjects (mean age 22.0 ± 1.4 years) treated with oral administration of 100 mg of Mg per day during chronic sleep deprivation for a month by drinking 4 bottles of a cold beverage (provided by Takeda Food Products), each containing 25 mg of Mg and 50 mg of Ca (referred to below as the Mg-treated group), and 8 untreated control subjects (mean age 21.9 ± 1.4 years).

Test conditions were defined as follows: (1) the usual state, a day following a night of good sleep; (2) chronic sleep deprivation, a day preceded by a month during which sleep occupied than 60% of the usual state because of studying for an examination. No restrictions other than banning alcohol ingestion, which influences Mg excretion, were imposed on the daily life of the subjects. Hours of sleep in each state were investigated by a precise interview questionnaire.

Written informed consent for participation was obtained from each subject before the study.

Methods of Cardiopulmonary Exercise Testing

Symptom-limited cardiopulmonary exercise testing used the ramp protocol with a bicycle ergometer (1 W/3 sec) to measure anaerobic threshold (AT), peak oxygen uptake (peak $\dot{V}O_2$) and peak exercise time was undertaken. After a 4-min rest on the bicycle ergometer, exercise began with a 4-min warm-up (20 W) followed by an increase in load (1 W/3 sec). Subjects were monitored by a 12-lead ECG during exercise testing, and heart rate (HR), ST-T change, and arrhythmia were followed carefully. Blood pressure was measured by the cuff method at 1-min intervals. Oxygen uptake ($\dot{V}O_2$), carbon dioxide production ($\dot{V}CO_2$), and minute ventilation ($\dot{V}E$) were measured throughout using a RM-300 respiromonitor and a MG-360 gas analyzer (Minato Ikagaku). The measurement system for cardiopulmonary exercise testing was carefully calibrated before starting each study. The expired gas was sampled using a breath-by-breath method.

From these measurements, the ventilatory equivalent for O_2 was calculated by $\dot{V}E/\dot{V}O_2$, that for CO_2 by $\dot{V}E/\dot{V}CO_2$, and the gas exchange ratio by $\dot{V}CO_2/\dot{V}O_2$. These calculations were made using a personal computer (NEC PC-9801). AT was determined by the following conventional criteria:[11] (1) $\dot{V}E/\dot{V}O_2$ increased after holding constant or decreasing, whereas $\dot{V}E/\dot{V}CO_2$ remained constant or decreased, and (2) the gas exchange ratio started to increase steeply. Blood samples for determining the plasma concentration of NE were drawn after 30 min of rest and immediately after the exercise test. Blood samples for determining the erythrocyte concentration of Mg and serum concentration of Mg and calcium (Ca) were also drawn after 30 min of rest.

Measurement of Erythrocyte Concentration of Mg and Serum Concentration of Mg and Ca

Samples of heparinized blood for measuring erythrocyte Mg concentration were centrifuged at 3000 g at 4 °C for 10 min. After removal of plasma and the buffy coat, the erythrocyte sediment was washed 3 times with 9% NaCl solution and centrifuged at 4 °C at 3000 g for 10 min. After removal of the supernatant, 9% NaCl solution was added until the total sample volume reached 4 ml; this volume was divided equally into 2 samples. Part of a sample was used to count erythrocytes. The remaining part of that sample was centrifuged at 3000 g at 4 °C for 10 min. After removal of the supernatant fluid, distilled water was added until the total sample volume reached 2 ml to hemolyze the erythrocytes. Erythrocyte Mg concentration was measured by the atomic absorption method and the value obtained was corrected for the number of erythrocytes; Mg concentration was expressed per $400 \times 10^4/mm^3$. Serum Mg and Ca concentrations

were measured by conventional chemical assay.

Measurement of Plasma Concentration of NE

For analysis of plasma concentration of NE, blood samples were collected into polypropylene tubes containing EDTA. Samples were centrifuged at 3000 g for 10 min and plasma was extracted. The plasma concentration of NE was analyzed using a high-performance liquid chromatography (HPLC) method. All data are expressed as mean values ± SD. The Mg-treated group and untreated control group were compared by the unpaired t test, and the paired t test was used for comparisons within the same group. A value of $p < 0.05$ was considered significant.

Results

Temporal Changes in Erythrocyte Concentration of Mg, Serum Mg, and Serum Ca

In the Mg-treated group, the mean values of erythrocyte concentration of Mg in the usual state and chronic sleep deprivation were 2.12 ± 0.26 mg/dl and 2.21 ± 0.23 mg/dl, respectively, as compared with the corresponding values of 2.40 ± 0.62 mg/dl and 2.09 ± 0.24 mg/dl in the untreated group. The mean serum Mg concentrations were 2.00 ± 0.14 mg/dl (usual state) and 1.95 ± 0.13 mg/dl (chronic sleep deprivation) in the Mg-treated group, as compared with the corresponding values of 2.02 ± 0.13 mg/dl and 1.92 ± 0.12 mg/dl, respectively, in the untreated group. The mean serum Ca concentrations were 9.23 ± 0.50 mg/dl and 9.48 ± 0.32 mg/dl in the Mg-treated group, as compared with the corresponding values of 9.24 ± 0.35 mg/dl and 9.41 ± 0.24 mg/dl, respectively, in the untreated group. There were no significant differences with regard to erythrocyte concentration of Mg, serum Mg, and serum Ca between chronic sleep deprivation and the usual state in both groups. Fig 1 shows the ratio of erythrocyte concentration of Mg, serum Mg, and Ca of chronic sleep deprivation to usual sleep state in both groups. Ratio of erythrocyte concentration of Mg in the Mg-treated group was significantly higher than the untreated group ($p < 0.05$), whereas the ratio of serum Mg and Ca concentration was not different in both groups.

Temporal Changes in Exercise Tolerance (Figs 2 and 3)

In the Mg-treated group, the mean values of AT for the usual state and for chronic sleep deprivation were 18.9 ± 3.7 ml/min per kg and 18.9 ± 2.8 ml/min per kg, respectively, as compared with the corresponding values of 21.0 ± 3.2 ml/min per kg and 18.0 ± 3.6 ml/min per kg in the untreated group. The untreated group revealed a significant decrease in AT ($p < 0.01$), whereas the Mg-treated group revealed no temporal change in AT.

The mean exercise times from commencement of the ramp exercise test until attainment of the AT were 296.9 ± 67.1 sec (usual state) and 264.3 ± 56.7 sec (chronic sleep deprivation) in the Mg-treated group, as compared with the corresponding values 281.5 ± 64.9 sec and 201.3 ± 46.3 sec, respectively, in the untreated group; the shortening in the untreated group was significant ($p < 0.01$).

Regarding the temporal changes in peak $\dot{V}O_2$, the means for the usual state and chronic sleep deprivation were 40.0 ± 5.0 ml/min per kg and 41.2 ± 5.7 ml/min per

serum-Mg · NS

serum-Ca · NS

erythrocyte-Mg · p<0.05
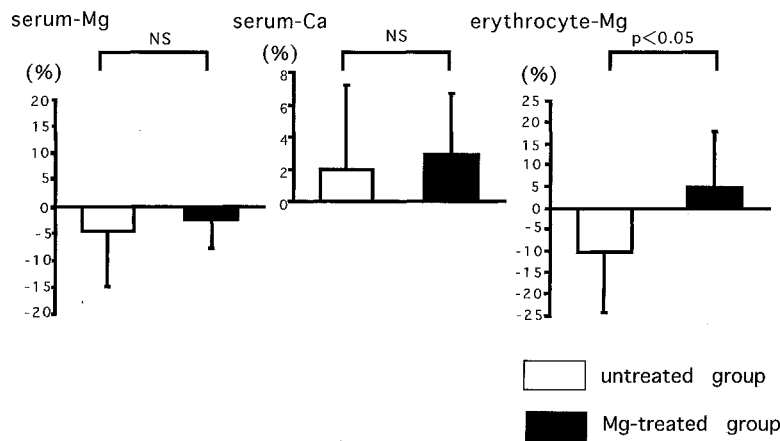
□ untreated group

■ Mg-treated group

Fig 1. Ratios of erythrocyte concentration of Mg and serum Mg and Ca in chronic sleepless state to the usual state. The ratio of erythrocyte concentration of Mg in the Mg-treated group was significantly higher than in the untreated group, whereas the ratios of serum Mg and Ca concentration were not different in both groups. Data are presented as means±SD.

AT
(ml/min/kg)

AT time
(sec)

Control Chronic sleep deprivation Control Chronic sleep deprivation
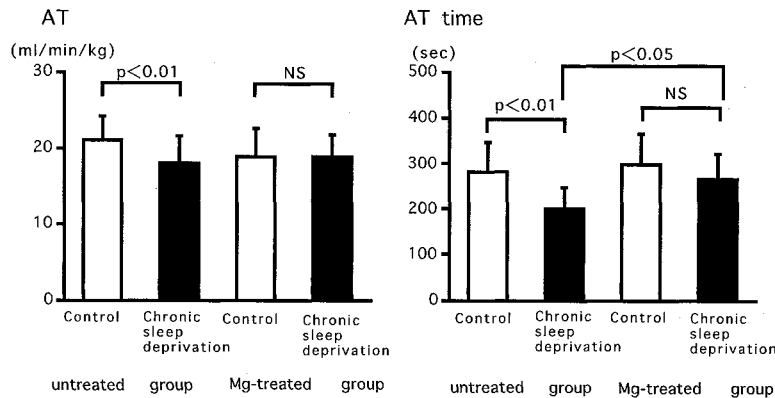
untreated group Mg-treated group

Fig 2. Serial changes in AT and exercise times to attain AT. The untreated group revealed a significant decrease in AT and exercise times to attain AT, whereas the Mg-treated group revealed no temporal change. Data are presented as means±SD.

peak oxygen uptake
(ml/min/kg)

peak exercise time
(sec)

Control Chronic sleep deprivation Control Chronic sleep deprivation
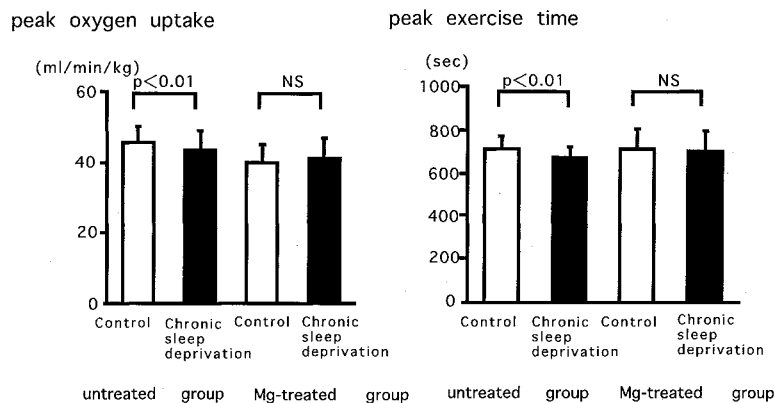
untreated group Mg-treated group

Fig 3. Serial changes in peak oxygen uptake and peak exercise times. The untreated group revealed a significant decrease in peak oxygen uptake and peak exercise times, whereas the Mg-treated group revealed no temporal change. Data are presented as means±SD.

kg, respectively, in the Mg-treated group as compared with 45.5±4.5 ml/min per kg and 43.6±5.1 ml/min per kg, respectively, in the untreated group. The decrease in peak $\dot{V}O_2$ in the untreated group was significant (p<0.01).

The peak exercise times for the usual and chronic sleep deprivation groups were 710.8±91.1 sec and 703.5±93.3 sec, respectively, in the Mg-treated group, as compared with 711.8±57.4 sec and 675.3±45.8 sec, respectively, in the untreated group. The shortening in peak exercise time in the untreated group was also significant (p<0.01).

In comparing exercise tolerance in the Mg-treated group and the untreated group, the mean exercise times until attainment of the AT at chronic sleep deprivation in the Mg-treated group was significantly longer than that in the untreated group (p<0.05). There was no significant

difference between the 2 groups with respect to AT, peak $\dot{V}O_2$, or peak exercise time.

Heart Rate and Blood Pressure Changes Induced by Exercise

In the Mg-treated group, the mean values of resting heart rate for the usual state and chronic sleep deprivation state were 82.9±14.1 beats/min and 81.1±8.7 beats/min, respectively, as compared with the corresponding values of 79.2±4.0 beats/min and 87.5±11.2 beats/min in the untreated group. The mean peak heart rates were 192.1±8.5 beats/min (usual state) and 192.9±9.4 beats/min (chronic sleep deprivation) in the Mg-treated group, as compared with the corresponding values 190.0±9.2 beats/min and 194.3±11.1 beats/min, respectively, in the untreated group; comparison between both states was not
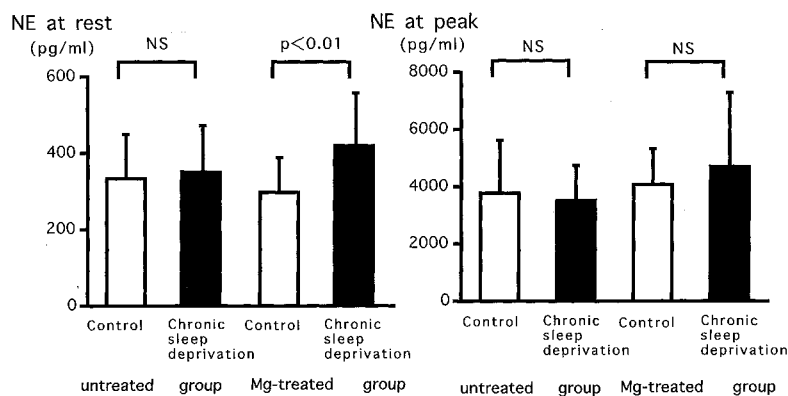
Fig 4. Serial changes in NE concentrations. Plasma NE concentration at rest in the Mg-treated group revealed a significant increase after chronic sleep deprivation. Data are presented as means±SD.

significant in both groups.

In the Mg-treated group, the mean values of resting systolic blood pressure in the usual and chronic sleep deprivation states were 129.3 ± 13.3 mmHg and 130.0 ± 10.5 mmHg, respectively, as compared with the corresponding values of 120.0 ± 7.7 mmHg and 121.4 ± 9.9 mmHg in the untreated group; comparison between both states was not significant in both groups. The mean peak systolic blood pressure was 224.6 ± 24.1 mmHg (usual state) and 233.4 ± 28.6 mmHg (chronic sleep deprivation) ($p < 0.05$) in the Mg-treated group, as compared with the corresponding values 217.0 ± 23.5 mmHg and 221.6 ± 21.4 mmHg (not significant), respectively.

Temporal Changes in NE Concentration

Fig 4 shows the NE concentrations at rest and during peak exercise. Resting NE concentrations for the usual state and the chronic sleep deprivation state were 295.9 ± 90.8 pg/ml and 410.9 ± 147.4 pg/ml in the Mg-treated group, as compared with 332.6 ± 116.6 pg/ml and 342.4 ± 129.8 pg/ml, respectively, in the untreated group. The corresponding NE concentrations at peak exercise were 4078.5 ± 1247.8 pg/ml and 4673.9 ± 2617.9 pg/ml in the Mg-treated group, as compared with 3756.0 ± 1843.6 pg/ml and 3519.5 ± 1207.6 pg/ml, respectively, in the untreated group. Both values at rest and peak exercise in the Mg-treated group revealed a tendency toward an increase in NE concentration at chronic sleep deprivation, and this increase was significant under resting conditions ($p < 0.01$).

In comparing NE concentrations at rest and during peak exercise in the Mg-treated group and the untreated group, there was no significant difference between the 2 groups in both the usual state and the sleep-deprived state.

Discussion

Exercise Tolerance in Chronic Sleep Deprivation

According to our previous report on exercise tolerance in chronic sleep deprivation, peak exercise time in the chronic sleep deprivation state is shorter than in the usual state[6] However peak exercise time in temporary sleep deprivation, which was defined as a day preceded by sleeping less than 3 h, was maintained. The tendency toward an increased ratio of NE concentration during exercise was higher in the temporary sleep deprivation state than in the state of chronic sleep deprivation. It has been suggested that NE secretion during exercise is a compensatory mechanism to maintain blood flow to active muscle. Our previous studies of exercise tolerance suggested that peak exercise capacity in temporary sleep deprivation could be maintained by the compensatory mechanism of NE secretion, but it did not work in chronic sleep deprivation. In the present study, the same tendency was observed with regard to AT, peak $\dot{V}O_2$, and exercise time in the sleep-deprived state in the control group, whereas these parameters were unchanged in the Mg-treated group.

Mg Dynamics in Chronic Sleep Deprivation

The mechanism of sudden cardiac death in chronically fatigued subjects is controversial both socially and medically. Epidemiologic studies suggest that myocardial hypomagnesemia may predispose to sudden cardiac death[12] Also, death from ischemic heart disease is inversely correlated with Mg intake[13] Several studies have shown that Mg content decreased in the infarcted portion of myocardium compared with non-infarcted segments[14,15] These findings support the hypothesis that myocardial Mg deficiency can predispose to sudden death from ischemic heart disease. Studies in vitro show that Mg deficiency induces constriction of isolated canine coronary arteries and that repletion of Mg dilates them[16] We have previously reported that mean erythrocyte magnesium content is lower in patients with variant angina than in control patients and that its value is lower in patients with more frequent episodes of angina[5] We have also demonstrated that measurement of erythrocyte Mg concentration is useful for determining the risk of vasospasm in patients with variant angina[17] Thus, coronary arterial spasm may be related to Mg dynamics in the coronary arteries. Against this background, to investigate the relation between sudden cardiac death and Mg, we also examined whether Mg dynamics are affected by chronic sleep deprivation as a model of chronic fatigue and found that chronic sleep deprivation leads to a cellular Mg deficiency? We used erythrocyte concentration of magnesium as an index of total body magnesium content. Only about 1% of total body magnesium is in the extracellular space, so assessments of the magnesium content of muscle, lymphocytes, and erythrocytes, the magnesium tolerance test, and measurements of daily urinary output of magnesium have been used as indices of magnesium deficiency. The magnesium content of muscle may well be the best gauge of total body magnesium stores but, because it is impracticable in the usual clinical setting, we chose erythrocyte magnesium content as an

index of total body magnesium content.

As far as the mechanism of the reduction in erythrocyte Mg concentration is concerned, repeated stress induced by chronic sleep deprivation may be a factor. Such stress, by increasing catecholamine secretion, would be expected to liberate free fatty acids in the blood[18] Altura and Altura[19] suggested that an apparent Mg-deficient state might result from two major events: (a) the formation of insoluble salts via chelation of Mg with free fatty acids; and (b) the excretion of Mg via the kidneys because of overproduction of catecholamines. Henrotte et al[20] reported that type A subjects have lower levels of erythrocyte Mg and serum Mg than type B subjects. And we have reported that the increased ratio of NE concentration that is found during exercise tends to be higher during temporary sleep deprivation and lower during chronic sleep deprivation[6] During temporary sleep deprivation, the tendency for the change ratio of NE concentration to increase during exercise was related to a reduction in erythrocyte Mg concentration because of loss of Mg via the kidney attributable to overproduction of NE. During chronic sleep deprivation, repeated stress such as temporary sleep deprivation would further reduce the erythrocyte Mg concentration in the early phase of chronic sleep deprivation[7]

Relationship Between Mg Administration and NE Secretion

Leppert et al[8] reported a relationship between Mg administration and NE secretion in patients who had suffered disabling primary Raynaud's phenomenon and control subjects. In that study, control subjects demonstrated a significant increase in plasma NE concentration after 50 ml of $MgSO_4$ diluted with 200 ml of isotonic NaCl was administered for 60 min. Leppert et al suggested that the mechanism of increase in plasma NE concentration after $MgSO_4$ infusion could be due either to an increased release or to an altered clearance. Conversely, James et al[9] reported the reverse relationship with regard to the relation between Mg administration and NE concentration. In that study, the effects of pretreatment with 60 mg/kg body weight $MgSO_4$ on catecholamine release associated with tracheal intubation were measured in normal subjects and saline solution-pretreated control subjects. After intubation, NE levels in the control group were significantly higher than in the Mg-pretreated group. The report concluded that $MgSO_4$ could attenuate NE secretion. In this regard, there was no agreement in the literature. Our previous study demonstrated that chronic sleep deprivation leads to a deficiency of intracellular Mg[7] decreased NE concentration[6] and decreased exercise tolerance. We have also investigated NE concentration in $MgSO_4$ (482 mg)-pretreated normal subjects during chronic sleep deprivation and saline solution-pretreated control subjects[10] That study was designed to clarify whether intravenous Mg administration could be effective in restoring NE secretion during exercise and whether it could improve the decreased exercise tolerance caused by chronic sleep deprivation. At each point during the exercise procedure, plasma NE concentration tended to be higher in patients experiencing chronic sleep deprivation than in those pretreated with saline solution and experiencing chronic sleep deprivation or on a normal day following a night of good sleep. Our report concluded that Mg plays an important role in the secretion of NE

and that additive Mg administration can restore secretion of NE and exercise tolerance in chronic sleep deprivation. In the present study, the effects of oral administration of Mg on exercise tolerance were measured using the same experimental model of chronic sleep deprivation. The ratio of intracellular Mg content in the sleep-deprived state to the usual sleep state was significantly higher in the Mg-treated group, and there was no difference between the sleep-deprived state and the usual state with regard to AT and peak $\dot{V}O_2$ in the Mg-treated group, whereas both of these decreased in the sleep-deprived state in the untreated control group. Also, resting plasma NE concentration was significantly higher in the sleep-deprived-state in the Mg-treated group. Plasma NE concentration immediately after exercise in the Mg-treated group also tended to increase, but the effect was insignificant. The reason for this is considered to be the administration of a smaller amount of Mg or a difference in the method of Mg administration compared with our previous report. The present results are consistent with our previous report with regard to exercise tolerance in the Mg-treated group. These findings may support the hypothesis that Mg plays an important role in maintaining exercise tolerance, and that additive oral Mg administration could improve decreased exercise tolerance in chronic sleep deprivation.

Conclusion

These results indicate that decreased exercise tolerance observed in the sleep-deprived state could be improved by oral Mg administration.

Study Limitations

In the present study, evaluation of intracellular Ca content was not performed because it had not been detected in the erythrocyte sediment. However, our results on exercise tolerance in the Mg-treated group revealed the same tendency as our previous study with regard to the effects of intravenous Mg administration in chronic sleep deprivation. We therefore conclude that Mg plays an important role in maintaining exercise tolerance in the chronic sleep-deprived state.

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