Effect of Magnesium Chloride and Magnesium L-Aspartate on Seizure Threshold in Rats under Conditions of Dietary Magnesium Deficiency

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We studied the effect of Mg-L-aspartate, $MgCl_2$, and their combinations with vitamin B_6, magneB_6, and $MgSO_4$ on seizure threshold in rats with dietary Mg^{2+} deficiency. Mg^{2+} deficiency was followed by a decrease in the threshold dose of corazol (from 79.20 to 49.48 mg/kg), shortening of the latency of the first jerk (by 33.6%, p=0.012), and reduction of the time to the first episode of clonic seizures (by 32.6%, p=0.011). Seizure threshold and latencies of the first jerk and first episode of clonic seizures increased over 3 weeks after peroral administration of Mg^{2+} salts. The combination of Mg^{2+} salts and pyridoxine was most effective in this respect.

Key Words: *corazol; seizures; magnesium chloride; magnesium L-aspartate; pyridoxine*

Magnesium plays an important role in the development of seizure readiness. Generalized tonic-clonic seizures were shown to be typical of patients with isolated idiopathic hypomagnesemia [3]. Pronounced hypomagnesemia is often revealed in children with epilepsy, which positively correlates with the severity of the disease. It is important to regulate Mg^{2+} metabolism in epileptic patients, since therapy with anticonvulsants (*e.g.*, phenobarbital, hexamidine, and diphenin) can be accompanied by hypomagnesemia.

The severity of corazol-induced seizures increases over the 1st days of dietary Mg^{2+} deficiency. By contrast, Mg^{2+} salts have an anticonvulsant effect [5]. They have different bioavailability, which may increase during combined administration of salts with pyridoxine. In this respect the most effective organic and inorganic salts are Mg-L-aspartate and $MgCl_2$, respectively. However, the influence of Mg^{2+} salts administered alone or in combination with vitamin B_6 on seizure threshold remains unknown.

Here we studied the effects of Mg-L-aspartate, $MgCl_2$, and their combinations with vitamin B_6 on corazol-induced seizures.

MATERIALS AND METHODS

Experiments were performed on 130 male outbred albino rats weighing 170-250 g. The animals were divided into groups. Twenty-five rats were intact. Other rats fed a Mg^{2+}-deficient diet (ICN Biomedicals Inc.) to induce pathological changes associated with dietary Mg^{2+} deficiency. Deionized water was used for drinking and food preparation. Control animals (n=25) fed a normal Mg^{2+} diet (500 mg/kg Mg^{2+}) and drank water with 20 mg/liter Mg^{2+}. The development rate and severity of hypomagnesemia were estimated by a spectrophotometric study of Mg^{2+} concentration in the plasma and erythrocytes from animals (color reaction with titanium yellow). The diagnosis of moderate hypomagnesemia was made from a decrease in Mg^{2+} concentration in erythrocytes and plasma (below 1.4 and 0.7 mmol/

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liter, respectively). The animals of treatment groups perorally received Mg^{2+} salts (Mg-L-aspartate, $MgCl_2$, and their combinations with vitamin B_6). The reference preparations included magneB_6 (Mg lactate and vitamin B_6) and $MgSO_4$ (50 mg elementary Mg^{2+} per kg body weight, 21 days until normalization of Mg^{2+} concentration in the plasma and erythrocytes). Vitamin B_6 in a dose of 5 mg/kg was added to $MgCl_2$ and Mg-L-aspartate (ratio 1:10).

Compensation for Mg^{2+} deficiency (X) was calculated as follows:

$$X=\frac{C_{salt}-C_{diet}}{C_{intact}-C_{diet}}\times 100\%,$$

where C_{salt} is Mg^{2+} concentration in animals after salt administration; C_{diet} is Mg^{2+} concentration in animals feeding a Mg^{2+}-deficient diet; and C_{intact} is Mg^{2+} concentration in animals of the control group.

Seizure threshold was measured on day 21 after administration of salts [1]. The animals received subcutaneous injection of corazol in doses of 50-90 mg/kg. The latency of 4-point seizures (clonic seizures with loss of the turning response; and subsequent tonic seizures with forelimb extension) was measured after administration of corazol in this dose. The dose of corazol that increased the threshold of seizures in 50% animals (TID_{50}) was evaluated by the probit analysis.

Data processing and evaluation of TID_{50} were performed by means of regression analysis.

RESULTS

The decrease in Mg^{2+} concentration in the plasma (by 51%) and erythrocytes (by 56%) was accompanied by body weight loss (by 26.8%), hair bloom, and change in seizure threshold. The decrease in the threshold dose of corazol was accompanied by an increase in seizure readiness (by 30%) on the 7th week of the diet (Table 1). Mg^{2+}-deficient animals were characterized by a decrease in the latency of the first jerk (by 33.6%, p=0.012) and reduction of the time to the first episode of clonic seizures (by 32.6%, p=0.011) in response to treatment with corazol in a dose of 80 mg/kg.

Mg^{2+} concentration in the plasma and erythrocytes returned to normal after peroral administration of Mg^{2+} salts for 21 days.

The rate of compensation for Mg^{2+} deficiency in erythrocytes by salts decreased in the following order: Mg-L-aspartate with vitamin B_6 (133.37±2.53%)≥$MgCl_2$ and vitamin B_6 (130.72±1.82%)>Mg-L-aspartate (120.18±11.91%)≥magneB_6 (111.93±4.15%)>$MgCl_2$ (103.54±2.34%)>$MgSO_4$ (84.24±2.28%, Fig. 1).

The ability of salts to increase (normalize) low value of TID_{50} in animals of the diet group decreased in the following order: Mg-L-aspartate and vitamin B_6 (83.19 mg/kg corazol)≥$MgCl_2$ and vitamin B_6 (81.15 mg/kg corazol)≥$MgCl_2$ (79.32 mg/kg corazol)>Mg-L-aspartate (74.95 mg/kg corazol)>$MgSO_4$ (73.27 mg/kg corazol)>magneB_6 (72.55 mg/kg corazol, Table 1).

TABLE 1. Effect of Mg^{2+} Salts (50 mg Elementary Mg^{2+} per kg Body Weight) on Corazol-Induced Seizure Threshold under Conditions of Dietary Mg^{2+} Deficiency

Preparation	TID_{16}	TID_{50}	TID_{84}
Intact rats	69.60 (64.12-75.56)	79.20 (72.96-85.97)	90.11 (83.01-97.82)
Mg^{2+}-deficient diet	35.27 (33.91-36.69)	49.48 (47.57-51.47)	69.42 (66.74-72.21)
$MgCl_2$	58.59 (50.65-67.78)	79.32 (68.57-91.75)	107.37 (92.82-124.20)
$MgCl_2$+vitamin B_6	59.41 (52.79-66.85)	81.15 (72.12-91.32)	110.85 (98.51-124.74)
MagneB_6	55.02 (51.45-58.83)	72.55 (67.85-77.58)	95.67 (89.47-102.30)
$MgSO_4$	55.37 (51.27-59.79)	73.27 (67.84-79.13)	96.96 (89.78-104.72)
Mg-L-aspartate	57.30 (53.95-60.86)	74.95 (70.57-79.60)	98.02 (92.29-104.11)
Mg-L-aspartate+vitamin B_6	63.63 (56.41-71.77)	83.19 (73.75-93.84)	108.77 (96.42-122.68)

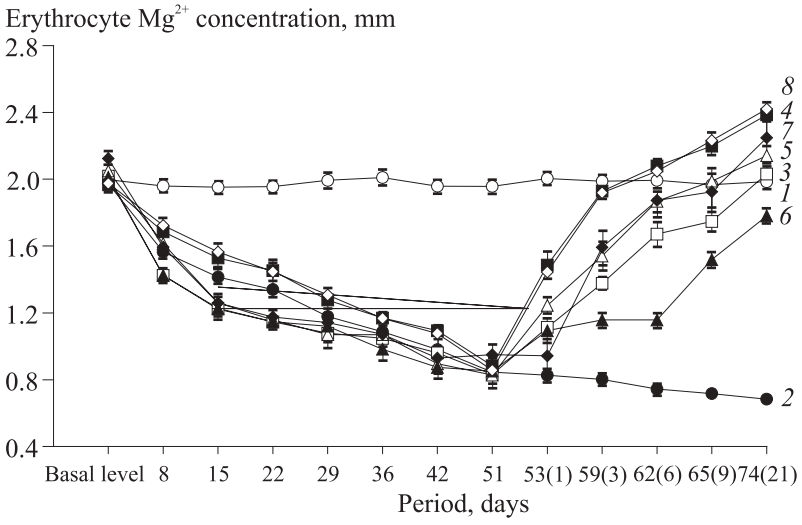

Fig. 1. Mg^{2+} concentration in erythrocytes of Mg^{2+}-deficient animals after administration of magnesium salts. The duration of treatment is shown in brackets. Intact rats (*1*); Mg^{2+}-deficient diet (*2*); $MgCl_2$ (*3*); $MgCl_2$+vitamin B_6 (*4*); magneB_6 (*5*); $MgSO_4$ (*6*); Mg-L-aspartate (*7*); and Mg-L-aspartate+vitamin B_6 (*8*).

The animals receiving Mg^{2+} salts exhibited a higher latency of the first jerk in response to 80 mg/kg corazol compared to rats feeding a Mg^{2+}-deficient diet. This parameter in animals receiving $MgCl_2$ and Mg-L-aspartate in combination with vitamin B_6 was higher than in Mg^{2+}-deficient rats (by 71.8 ($p<0.05$) and 66.6% ($p<0.05$), respectively). The time to the first episode of clonic seizures in animals of these groups decreased by 53.3 ($p<0.05$) and 61% ($p<0.05$), respectively.

We showed that magnesium salts in combination with pyridoxine have the highest anticonvulsant activity. Pyridoxine deficiency may cause seizures in children. Homeostasis of Mg^{2+} and pyridoxine are closely related. On the one hand, pyridoxine provides Mg^{2+} transport and storage in cells. On the other hand, pyridoxine enters the composition of alkaline phosphatase required for supply of tissues with pyridoxal phosphate [6]. Pyridoxine is a cofactor in the synthesis of various neurotransmitters (serotonin, norepinephrine, dopamine, and GABA). These data explain the fact that salts in combination with vitamin B_6 induce the most potent anticonvulsant effect.

Our results indicate that Mg^{2+} salts in combination with vitamin B_6 have the highest anticonvulsant activity. These compounds surpass magneB_6 and $MgSO_4$ in the anticonvulsant effect.

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