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Correction of magnesium deficiency in the body with balneological means: experimental studies

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Abstract
In the modern world, a lack of magnesium in the body is one of the most common deficient conditions in humans. Low levels of magnesium have been associated with a number of chronic diseases. This work is devoted to the study of the effect of the use of the balneological means "Magnesium oil" for the correction of the manifestations of experimentally induced magnesium deficiency. The experiment was conducted on 50 white female rats of the Wistar auto-breeding line which were divided into 3 equal groups: (1) control, (2) model of magnesium deficiency, (3) received "Magnesium oil". As a result of modeling the state of magnesium deficiency, significant changes are observed in the central nervous system, vegetative nervous system, and kidneys of animals. The use of balneological means "Magnesium oil" can significantly reduce the negative manifestations of magnesium deficiency.

Key words: *magnesium deficiency, nervous system, kidneys, rats,*

Introduction

Magnesium is one of the most important nutrients. It is the fourth most common mineral in the human body after calcium, sodium, and potassium and is the second most common intracellular cation after potassium. Magnesium has several functions in the human body. It acts as a cofactor for more than 300 enzymes, regulating a number of fundamental functions such as muscle contraction, neuromuscular conduction, glycemic control, myocardial contraction, and blood pressure (1, 2**)**. Moreover, magnesium also plays a vital role in energy production, active transmembrane transport for other ions, synthesis of nuclear materials, and bone development (3, 4). Because of magnesium's many functions within the body, it plays a major role in disease prevention and overall health. Low levels of magnesium have been associated with a number of chronic diseases including migraine headaches, Alzheimer's disease, cerebrovascular accident (stroke), hypertension, cardiovascular disease, and type 2 diabetes mellitus (5, 6, 7, 8)

Magnesium must be continuously replenished through foods and water intake because it is not synthesizable. Chronic inadequate intake of magnesium over long period of time can manifest as latent magnesium deficiency with symptoms such as muscle weakness, cramps, fatigue, neurological and cardiovascular dysfunctions, reduced bone mineralization and strength. Reports published by WHO have estimated that ~two thirds of Americans and French have magnesium intake below the recommended amounts but only a small numbers are overtly depleted (9).

In the modern world, a lack of magnesium in the body is one of the most common deficient conditions in humans. The concentration of magnesium in the body decreases under the influence of various factors: living conditions and nutrition, age, physical activity, physiological (pregnancy, lactation) and pathological conditions (disease of the cardiovascular, urinary systems, digestive organs, endocrine glands). Today, two definitions are used to indicate magnesium metabolism disorders: "magnesium deficiency" - a decrease in the total magnesium content in the body and "hypomagnesemia" - a decrease in the concentration of magnesium in the blood serum of less than 0.75-1.2 mmol/l (10, 11).

A moderate deficiency of magnesium in the body is evidenced by its levels in the blood serum of 0.5-0.7 mmol/L, expressed (life-threatening) - below 0.5 mmol/L (12).

Currently, a whole pharmaceutical industry is working to fill the magnesium deficiency. However, the use of drugs is not always effective, may be accompanied by side effects, which makes it relevant to a search for new non-drug treatment strategies. In this context, it seems reasonable to use mineral water (MW) in complex treatment, because, in its therapeutic effects, MW often exceeds many medicines. However, they do not have side effects and allergic reactions, overloading the patient's body with chemicals (13, 14, 15, 16).

This work is devoted to the study of the effect of the use of the balneological means "Magnesium oil" for the correction of the manifestations of experimentally induced magnesium deficiency. The "Magnesium oil" is a natural balneological product containing 95% magnesium chloride. The main attention was directed to studying the dynamics of the state of the nervous system and kidney function, since, according to published data, they mainly suffer the most with deficiency of magnesium in the body (17-26).

Materials and methods.

The experiment was conducted on 50 white female rats of the Wistar auto-breeding line with a bodyweight of 180 - 210 g. The studies were conducted in accordance with the rules established by the Directive of the European Parliament and the Council (2010/63 / EU) and the order of the Ministry of Education and Science, Youth and Sports of Ukraine dated 24.03.2012 No. 249 "On approval of the Procedure for conducting scientific experiments, experiments on animals" (27, 28). Reproduction of a model of magnesium deficiency (MMD) in the body of experimental animals was carried out with the involvement of a special diet. White rats were kept on a magnesium-depleted diet containing 30% casein, 45% potato starch, 10% corn oil, 20% white breadcrumbs. The diet was prepared in distilled water, the same water was used as drinking water. This diet was obtained from the background of the development of chronic psycho-emotional immobilization stress (distress), exacerbated by situational components, for which the animals were periodically immobilized for 3 hours each day by placing rats in a special device consisting of individual cells restricting the movement of animals. The emotional component of distress was reproduced by adding to the above methodology situational components, namely, by changing the mode of feeding, lengthening the daylight, overpopulation. The experimental pathology was reproduced for 70 days.

Before the start of the study, rats were divided into 3 equal groups:

Group 1 (20 pcs.) Is an intact animal that serves as a control group;

Group 2 (10 pcs.) - in which the state of magnesium deficiency is reproduced

Group 3 (10 pcs.) - animals that received a solution of the balneological product "Magnesium oil" with a concentration of magnesium 0.5g/l from the 70th day, in the mode of internal use, against the background of the MMD development. The solution was introduced into the esophagus by animals with a soft probe with olive once a day (in the afternoon) at a dose of 1% of body weight at a rate of 7 days in a row.

The evaluation of the development of the pathological model and the study of the effect of balneological agent "Magnesium oil" on the body of experimental animals were performed by the following tests.

Effects on the nervous system of rats were investigated using the "open field" method, which is a prognostic criterion of the central nervous system (CNS) condition, which is characterized by the ratios of orientational-research behavior, displaced and motor activity. The condition of the vegetative nervous system (VNS) was assessed by changes in emotional activity.

When studying the behavior of animals in the device, the number of exits to the center, intersecting squares, racks, peeps into minks, clearings (grooming), movements and seats in place (boluses and urinations) were recorded. When processing the results, the following totals dates were calculated:

— Motor activity (MA) - the sum of the number of exits to the center and the number and duration of animal stops;

— Orienteering Research Behavior (ORB) - the sum of the number of squares crossed, uprights, mink views;

— Emotional activity (EA) is the sum of the number and duration of grooming (cleansing) sum of urinations, bowel movements (boluses);

- The functional state of the kidneys was evaluated by the influence on the urinary function (glomerular filtration rate, tubular reabsorption, diuresis), on the excretory function (on the excretion of creatinine and urea) and ion-regulating function (on the concentration and daily excretion of ions. Determined the acid-alkaline reaction of daily urine in terms of the concentration of hydrogen ions;

- The concentration of sodium, potassium, calcium and chloride ions in whole blood and urine was determined on an instrument for the determination of electrolytes in biological fluids of AEK-01 "Kwer".

The statistical processing of the obtained data was carried out by the method of indirect differences, while the significant shifts were those that were within the probability of the Student's criterion P <0.05.

Results and discussion

Table 1 shows the data that determine the functional state of the CNS and the emotional activity of rats with the MMD model when conducting experiments in the device "open field".

Table 1. Functional state of the CNS and emotional activity of rats, (M ± m)

Indicators	Group 1 ($M_1 \pm m_1$)	Group 2 ($M_2 \pm m_2$)	Group 3 ($M_3 \pm m_3$)
Number of exits to the center, n	1.85 ± 0.25	0.70 ± 0.02 P1 < 0.001	1.79 ± 0.27
Stops, n	2.04 ± 0.14	3.03 ± 0.01 P1 < 0.01	2.07± 0.03 P2 > 0.5
Stops, s	66.78 ± 7.55	146.50±0.54 P1 < 0.01	257.83± 2.83 P2 < 0.01
Number of squares crossed, n	69.82 ± 2.39	31.47±0.12 P1 < 0.01	10.49 ± 0.42 P2< 0.01
Number of uprights, n	14.37 ± 1.07	6.59±0.03 P1 < 0.001	3.00± 0.07 P2 < 0.01
The number of peeps in minks, n	13.52 ± 0.84	6.11± 0.02 P1 < 0.01	3.17± 0.14 P2 < 0.01
Grooming, n	5.44 ± 0.60	3.06±0.01 P1 < 0.01	2.10± 0.05 P2 < 0.01
Grooming, s	33.00 ± 3.20	27.21±0.07 P1 < 0.05	43.81± 0.24 P2< 0.01
Number of defecation acts (boluses), n	2.52 ± 0.28	0.38±0.004 P1 < 0.01	1.15± 0.05 P2< 0.01
Number of urination acts, n	5.52 ± 0.70	5.04±0.11 P1 > 0.5	3.72± 0.05 P2 < 0.01

Note. 1. ($M_1 \pm m_1$), ($M_2 \pm m_2$)and ($M_3 \pm m_3$)are arithmetic averages with errors of indices;

2. P_1 - calculated between ratios ($M_1 \pm m_1$) and ($M_2 \pm m_2$) groups of rats;

3. P_2 - calculated between ratios ($M_1 \pm m_1$) and ($M_3 \pm m_3$) groups of rats.

As a result of modeling the state of magnesium deficiency, significant changes are observed in the central nervous system and vegetative nervous system of animals. Significantly, 2.4 times (p <0.001), a decrease in the number of animal exits to the center and a significant increase in the number of stops by 1.5 times and their duration by 2.2 times (p <0.01 and p <0.01) , which together indicates a significant decrease in motor activity of animals. Relatively lower in comparison with the control data, the indicators characterizing the orientational-research behavior of rats, namely, the number of crossed squares, uprights and peeping in minks are reduced on average 2.2 times (p <0.001, p <0.001 and p <0, 01 respectively). At the same time, against the background of the development of a magnesium deficiency state, the emotional activity of animals is significantly reduced. The number and duration of grooming acts decreased by 1.8 times (p <0.05 and p <0.01), which, combined with a known decrease of 6.6 times in bowel movements (boluses), indicates a worsening of emotional animal conditions. The animals looked frightened and inhibited, practically did not move around the area of the experimental setup. That is, when the animals one by one found themselves in an unfamiliar environment (placing the device in an "open field"), they showed extremely depressed behavior. On the contrary, when analyzing visual observations of animals with MDS, when they were next to other animals in the cage, the rats were nervous, fussed, jumped into the corner of the cage with little noise or movements, that is, they were in an overexcited state. It should be noted that the above changes in the emotional activity of animals indicate an imbalance in the processes of excitation/inhibition (or an imbalance between the processes of excitation and inhibition) in the central nervous system.

Thus, the development of the magnesium deficiency state is characterized by inhibition of motor activity and orientational research behavior and inhibition of the emotional activity of animals.

The use of magnesium oil solution in rats leads to the restoration of two of the three indicators characterizing the motor activity of animals (Table 1). The number of exits to the center of the instrument and the number of stops of animals does not differ from the control data. But the duration of stops, which has been increased in animals with MMD, is increasing even more, by almost 100%. The animal ORB, characterized by the number of crossed squares, uprights, and staring, were reduced in animals with MMD relative to control, on average, twice, under the influence of the internal course with "magnesium oil" decreases even more (by an average of 50%). At the same time, the emotional activity of the creatures has significantly improved, however, their duration exceeded not only the decreased level in rats with MMD but also exceeded the control values 1.3 times ($p < 0.01$). The established fact indicates that most of the experiment the animals almost did not move around the device, were engaged in grooming (washing), did not fuss, and looked calm. The number of bowel movements recovered (increased) almost to the level of control ($p < 0.01$), and the number of urinations, on the contrary, decreased one and a half times ($p < 0.05$), that is, the emotional stress of the animals decreased.

Consequently, the internal use of "magnesium oil" against the background of the development of a magnesium deficiency state has a powerful calming effect on the animals' ORB, slightly increases motor activity and leads to the restoration of vegetative reactions and a marked improvement in emotional activity.

In the study of the functional state of the kidneys, the following data were obtained. In rats with MMD, the volume of daily diuresis was significantly increased ($p < 0.001$) compared with the control data, but this is due to a noticeable activation of the process of water reabsorption in the renal tubules ($p < 0.001$), while the tubular filtration rate decreases ($p < 0.001$) (Table 2). Excretion of creatinine is also reduced ($p < 0.001$), which indicates a decrease in renal excretory function. Significantly, the concentration and 9-fold decrease in excretion with daily urine of potassium ions decreases by a factor of 11 ($p < 0.01$ and $p < 0.001$), while the concentration of magnesium ions is 1.2 times, and excretion with daily urine of magnesium ions is 2.4 times higher relative to the control data ($p < 0.05$ and $p < 0.001$, respectively), while the concentration and excretion with daily urine of sodium ions and chloride ions does not change.

The following changes are observed under the influence of “magnesium oil” in experimental animals: If the volume of daily diuresis in animals with MMD is increased by 1.3 times ($p < 0.001$) due to a significant decrease in tubular reabsorption, then under the influence of the internal course of the solution “magnesium oil »It increases by 2.4 times ($p < 0.001$) due to a significant decrease in tubular reabsorption.

Table 2. Functional state of the rat kidney, ($M \pm m$)

Indicators	Group 1 ($M_1 \pm m_1$)	Group 2 ($M_2 \pm m_2$)	Group 3 ($M_3 \pm m_3$)
Daily diuresis, ml / dm^2 of body surface	1.18 ± 0.13	1.57 ± 0.005 $P_1 < 0.001$	2.78 ± 0.003 $P_2 < 0.001$
The glomerular filtration rate, ml / (dm^2 · min)	0.11 ± 0.008	0.09±0.0001 $P_1 < 0.001$	0.09± 0.02 $P_2 < 0.001$
Tubular reabsorption, percentage to filter, %	99.26 ± 0.06	98.78 ±0.002 $P_1 < 0.001$	97.78± 0.01 $P_2 < 0.001$
Withdrawal of creatinine, mmol	0.011 ± 0.0008	0.09 ± 0.001 $P_1 < 0.001$	0.09 ± 0.0001 $P_2 < 0001$
Urea excretion, mmol	0.64 ± 0.07	0.69 ± 0.001 $P_1 > 0.2$	1.31 ± 0.02 $P_2 < 0.001$
Elimination of chlorides, mmol	0.48 ± 0.03	0.63 ± 0.004 $P_1 < 0.001$	0.53 ± 0.002 $P_2 < 0.001$
pH of daily urine, u	7.67 ± 0.38	7.04 ± 0.002 $P_1 > 0.5$	6.18 ± 0.007 $P_2 < 0.001$
Concentration of potassium ions in daily urine, mmol / l	176.88 ± 11.35	16.17 ± 0.05 $P_1 < 0.01$	21.35 ± 0.13 $P_2 < 0.01$
Daily excretion of potassium ions, mmol	0.19 ± 0.02	0.021± 0.001 $P_1 < 0.001$	0.060 ± 0.001 $P_2 < 0.001$
Concentration of sodium ions in daily urine, mmol / l	73.81 ± 4.28	67.75 ± 0.30 $P_1 > 0.5$	113.72 ± 0.69 $P_2 < 0.001$
Daily excretion of sodium ions, mmol	0.09 ± 0.02	0.10 ± 0.001 $P_1 > 0.5$	0.31 ± 0.002 $P_2 < 0.001$
Concentration of chloride ions in daily urine, mmol / l	321.03 ± 20.42	315.06 ± 1.94 $P_1 > 0.5$	95.64 ±0.97 $P_2 < 0.001$
Daily excretion of chloride ions, mmol	0.28 ± 0.06	0.30 ± 0.003 $P_1 > 0.2$	0.27 ± 0.004 $P_2 > 0.5$
Concentration of magnesium ions in daily urine, mmol / l	3.39 ± 0.02	4.15 ± 0.004 $P_1 < 0.05$	3.48 ± 0.01 $P_2 > 0.5$
Daily excretion of magnesium ions, mmol	0.0033± 0.0003	0.0080±0.0002 $P_1 < 0.0001$	0.0100±0.0001 $P_2 < 0.001$

Note. 1. ($M_1 \pm m_1$), ($M_2 \pm m_2$)and ($M_3 \pm m_3$)are arithmetic averages with errors of indices;

2. P_1 - calculated between ratios ($M_1 \pm m_1$) and ($M_2 \pm m_2$) groups of rats;

3. P_2 - calculated between ratios ($M_1 \pm m_1$) and ($M_3 \pm m_3$) groups of rats.

The glomerular filtration rate and creatinine excretion remained at the same reduced level as rats with MMD ($p < 0.001$ and $p < 0.001$), but urea excretion increased 2-fold ($p < 0.001$). The pH response of the urine shifts slightly to the acidic direction ($p < 0.001$). Significantly reduced concentration and excretion of potassium ions recovered somewhat under the influence of the conducted course ($p < 0.001$ and $p < 0.001$). An increase of 1.5 times the urine concentration of sodium ions and an increase of 3.4 times their excretion with daily urine ($p < 0.001$ and $p < 0.001$)

were observed, although the concentration in the urine of chloride ions decreased 3.8 times ($p < 0.001$). The concentration of magnesium ions in the urine recovered to the level of control, but their excretion, which was increased by 2.4 times in the background of MMD, under the influence of "Magnesium oil" increased by 3 times ($p < 0.01$ and $p < 0.01$, respectively)).

The data in Table 3 show the changes in the electrolyte composition of the blood of rats with MMD and rats, which in the background of the development of MMD received a solution of "Magnesium oil".

Table 3. Indicators of electrolyte blood composition, (M ± m)

Indicators	Group 1 ($M_1 \pm m_1$)	Group 2 ($M_2 \pm m_2$)	Group 3 ($M_3 \pm m_3$)
Concentration of magnesium ions in blood, mmol / l	0.90 ± 0.03	0.59 ± 0.05 $P_1 < 0.001$	0.80 ± 0.06 $P_2 > 0.2$
Concentration of potassium ions in the blood, mmol / l	3.75 ± 0.31	3.05 ± 0.001 $P_1 < 0.05$	3.46 ± 0.24 $P_2 > 0.2$
Concentration of sodium ions in the blood, mmol / l	132.00 ± 0.13	138.08 ±0.02 $P_1 < 0.001$	132.83± 0.81 $P_2 > 0.5$
Concentration of calcium ions in the blood, mmol / l	1.81 ± 0.02	1.40 ± 0.03 $P_1 < 0.001$	1.52 ± 0.001 $P_2 < 0.001$
Concentration of ionized calcium in the blood, mmol / l	2.62 ± 0.01	2.15 ± 0.02 $P_1 < 0.001$	1.96 ± 0.02 $P_2 < 0.001$
Concentration of chloride ions in blood, mmol / l	146.77 ± 1.41	0.130 ± 0.004 $P_1 < 0.001$	124.70 ± 1.54 $P_2 < 0.001$

Note. 1. ($M_1 \pm m_1$), ($M_2 \pm m_2$) and ($M_3 \pm m_3$)are arithmetic averages with errors of indices;
2. P_1 - calculated between ratios ($M_1 \pm m_1$) and ($M_2 \pm m_2$) groups of rats;
3. P_2 - calculated between ratios ($M_1 \pm m_1$) and ($M_3 \pm m_3$) groups of rats.

The electrolyte composition of the blood of rats with magnesium deficiency is characterized by a decrease in the concentration of magnesium ions by 35%, potassium ions by 19%, and chlorine ions by 12%. At the same time, the concentration of sodium ions increased by 5%. The concentration of calcium ions and ionized calcium significantly decreased by 23% and 18% respectively. The internal use of the magnesium oil solution led to a complete restoration of the concentration of magnesium, potassium and sodium ions. However, the concentration of chlorine ions, calcium ions, and ionized calcium significantly decreased, both in comparison with the group of rats with pathology and in comparison with the control group - by 15%, 16%, and 25%.

So, the established effects from the use of the solution of "magnesium oil" indicate a restoring effect on changes in the electrolyte composition of the blood and the functional state of the kidneys of rats with MMD. An increase in urea excretion by 104% indicates an increase in detoxification function and an increase in excretion of sodium ions by 244% is associated with a significant decrease in tubular reabsorption, which in turn leads to an increase in daily urine output by 135%. Against this background, an even greater increase in the excretion of magnesium ions in comparison with the MMD model and the level of control (against the background of the restoration of its content in the blood serum) indicates a significant decrease in magnesium deficiency in the body, which is confirmed, although by a slight, but significant increase in the excretion of potassium ions and indicates the restoration of electrolyte balance in the body of rats.

Conclusions

An experimental model of magnesium deficiency in rats caused by a prolonged hypo-magnesium diet is characterized by significant changes in the functional state of the nervous system and kidneys. The use of balneological means "Magnesium oil" can significantly reduce the negative manifestations of magnesium deficiency. This makes it possible to test this technique in clinical practice.

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