Timeline (Bioavailability) of Magnesium Compounds in Hours: Which Magnesium Compound Works Best?

Article *in* Biological Trace Element Research · January 2019

DOI: 10.1007/s12011-018-1351-9

CITATIONS
14

READS
7,234

9 authors, including:

Nazan Uysal
Dokuz Eylul University
88 PUBLICATIONS **2,255** CITATIONS
SEE PROFILE

Servet Kizildag
Dokuz Eylul University
31 PUBLICATIONS **292** CITATIONS
SEE PROFILE

Güven Güvendi
Dokuz Eylul University
26 PUBLICATIONS **220** CITATIONS
SEE PROFILE

Sevim Kandis
Dokuz Eylul University
19 PUBLICATIONS **115** CITATIONS
SEE PROFILE

Biological Trace Element Research
https://doi.org/10.1007/s12011-018-1351-9

Timeline (Bioavailability) of Magnesium Compounds in Hours: Which Magnesium Compound Works Best?

Nazan Uysal[1,2] · Servet Kizildag[2] · Zeynep Yuce[3] · Guven Guvendi[1] · Sevim Kandis[1] · Basar Koc[1] · Aslı Karakilic[1] · Ulas M. Camsari[4] · Mehmet Ates[2]

Received: 27 December 2017 / Accepted: 13 April 2018

Abstract
Magnesium is an element of great importance functioning because of its association with many cellular physiological functions. The magnesium content of foods is gradually decreasing due to food processing, and magnesium supplementation for healthy living has become increasingly popular. However, data is very limited on the bioavailability of various magnesium preparations. The aim of this study is to investigate the bioavailability of five different magnesium compounds (magnesium sulfate, magnesium oxide, magnesium acetyl taurate, magnesium citrate, and magnesium malate) in different tissues. Following a single dose 400 mg/70 kg magnesium administration to Sprague Dawley rats, bioavailability was evaluated by examining time-dependent absorption, tissue penetration, and the effects on the behavior of the animals. Pharmacokinetically, the area under the curve calculation is highest in the magnesium malate. The magnesium acetyl taurate was found to have the second highest area under the curve calculation. Magnesium acetyl taurate was rapidly absorbed, able to pass through to the brain easily, had the highest tissue concentration level in the brain, and was found to be associated with decreased anxiety indicators. Magnesium malate levels remained high for an extended period of time in the serum. The commonly prescribed dietary supplements magnesium oxide and magnesium citrate had the lowest bioavailability when compared to our control group. More research is needed to investigate the bioavailability of magnesium malate and acetyl taurate compounds and their effects in specific tissues and on behavior.

Keywords Magnesium acetyl taurate · Magnesium malate · Magnesium citrate · Magnesium oxide · Magnesium sulfate · Anxiety · Brain · Muscle

Introduction

Magnesium is the eight most common element found on our planet [1]. It is also the fourth most abundant element in vertebrates and the second most common element in the cell following potassium in eukaryotic cells. There is an average of 0.4 g/kg (total of 24 g in a 70-kg adult) magnesium in the human body [2]. Approximately 99% of the total body magnesium is localized in the bone, muscle, and the soft tissue surrounding them; of which 50–60% is found in the bones [3]. One third of the magnesium found in bones tissue act as a reservoir, regulated to maintain normal blood magnesium levels [4]. The magnesium content of the bone decreases with age, leading to a decline in its storage function [1]. Extracellular magnesium constitutes 1% of the total body magnesium and is mostly found in serum and red blood cells. Seventy percent of the magnesium in serum is ionized, 20% is protein-bound, and 10% is bound to anions such as phosphate, bicarbonate, citrate, and sulfate [3, 4].

Magnesium is a vital component of cells, involved in many physiological functions [2]. It is the most frequently found metal ion cofactor in enzymatic systems, including DNA/RNA polymerases and all enzymes functioning in ATP metabolism. In cells, the presence of magnesium is critical for the stability of polyphosphate compounds. Under normal conditions, biologically active ATP is bound to a magnesium ion [2,

✉ Nazan Uysal
nazan.uysal@deu.edu.tr

[1] Medical Faculty, Department of Physiology, School of Medicine, Dokuz Eylul University, Balcova, Izmir, Turkey

[2] College of Vocational School of Health Services, School of Medicine Izmir, Dokuz Eylul University, İzmir, Turkey

[3] Department of Medical Biology and Genetics, School of Medicine, Dokuz Eylul University, Izmir, Turkey

[4] Department of Psychiatry and Psychology, Mayo Clinic, Rochester, MN, USA

Published online: 21 April 2018

4]. ATP metabolism is essential for muscle contraction and relaxation, normal neurological function, and release of neurotransmitters. Mg affects muscle performance through its fundamental role in muscle contraction/relaxation and energy metabolism [5]. The most common manifestation of magnesium deficiency is muscular cramps. In addition, it is essential in the regulation of vascular tone, heart rhythm, platelet-activated thrombosis, and bone formation [6]. It has been suggested that magnesium deficiency has related with both anxiety and depressive disorders. Some studies demonstrated magnesium's anxiolytic effects in both rodent models and humans [7].

Approximately 30–40% of the dietary magnesium is absorbed from the digestive tract with a variability between ~ 10 and 65% depending on the physiological need. Absorption occurs mostly in the small intestine, but also continues in the colon. In humans, magnesium absorption particularly occurs in the distal segment of the small intestine; however, radioisotope-labeled magnesium has been detected in plasma 1 h after ingestion, indicating that absorption begins in the upper regions of the small intestine, such as duodenum and jejunum [8]. The presence of fibers in the diet that can be fermented by intestinal bacteria increases Mg absorption from the large intestine [9]. Following absorption from the digestive tract, magnesium enters the bloodstream. However, the rate of magnesium transport across cell membranes is not the same in all tissues of the human body; the rate is higher in the heart, liver, and kidney and lower in the skeleton, red cells, and brain [10]. Magnesium easily crosses the blood-brain barrier [2].

The recommended daily dose of magnesium is 310 mg for women 19–30 years of age and 320 mg for women 31+ years old and 400 mg for men aged 19–30 and 420 mg for men 31+ years [11]. Food and water are the major sources of magnesium intake. It is abundant in green leafy vegetables, cereals, nuts, and legumes. Nonetheless, the magnesium content of foods has decreased in the last century [12, 13]. Processed and refined foods are poor sources of the nutrient, reducing its content up to 85%. Cooking (especially boiling) also decreases the magnesium content in foods [14]. In addition to a magnesium-poor diet, deficiency can occur secondary to chronic alcohol usage, lengthy hospitalizations, or chronic diseases such as type 2 diabetes, obesity, and metabolic syndrome. Magnesium uptake can be increased by a magnesium-rich diet or magnesium supplementation. Decreased intake or absorption and chronic diseases caused magnesium deficiency, in which taking a dietary supplement becomes necessary.

The magnesium element forms compounds with organic or inorganic molecules and mostly exists as magnesium salts in nature. Organic and inorganic compounds are the two main classes of chemical compounds. With a few exceptions, an organic compound is defined as containing C-H bonds and is associated with living organisms and life processes. Inorganic compounds include salts, metals, minerals, and other elemental compounds that do not contain carbon and are not associated with living matter. Production of inorganic compounds is cheaper and they break down very easily in the digestive tract. Yet they have a lower absorption rate when compared to organic substances. When magnesium minerals are consumed, they are quickly released and free to bind other compounds such as phytates found in nuts, grains, and some vegetables. Thus, the resulting new compounds are excreted without absorption. The unbound magnesium mineral can also irritate the digestive system and cause a laxative effect or diarrhea [15–17].

Information on the bioavailability and efficacy of different magnesium compounds is limited. The aim of this study is to investigate the bioavailability of different organic (magnesium citrate, magnesium acetyl taurate, and magnesium malate) and inorganic (magnesium oxide and magnesium sulfate) magnesium compounds. Magnesium citrate and magnesium oxide are the most prescribed Mg compounds as dietary supplements. Magnesium acetyl taurate was shown to have an effect on an experimental cataract model and is also recommended for the treatment of migraine. Magnesium malate is used in the treatment of fibromyalgia. We compared the bioavailability of these widely used magnesium compounds and parenteral usage to oral intake.

Materials and Methods

Animals

Forty-nine adult outbred male Sprague Dawley rats (Dokuz Eylul University School of Medicine, Experimental Animal Laboratory, Izmir, Turkey) were used in this study. All rats were housed in individual cages with free access to water and laboratory chow. They were kept in a 12-h light/12-h dark cycle at constant room temperature (22 ± 1 °C) and humidity (60%). Dokuz Eylul University School of Medicine Animal Care Committee approved all experimental procedures.

Rats were divided into six groups: (1) Control group (n = 7), (2) magnesium sulfate (n = 7), (3) magnesium oxide (n = 7), (4) magnesium citrate (n = 7), (5) magnesium acetyl taurate (n = 7), (6) magnesium malate (n = 7).

Experimental Design The details of experiment are summarized in Fig. 1. The effects of magnesium on the body were investigated 6 h after magnesium administration (400 mg/70 kg—recommended daily dose for men) [18]. Elementary magnesium levels of all compounds were calculated and then dissolved using phosphate-buffered saline (PBS). Also, our aim was to compare parenteral form with peroral; therefore, magnesium sulfate was administered intraperitoneally, while the other magnesium compounds were given orally. The magnesium sulfate group was subject to the experiments 2 h after

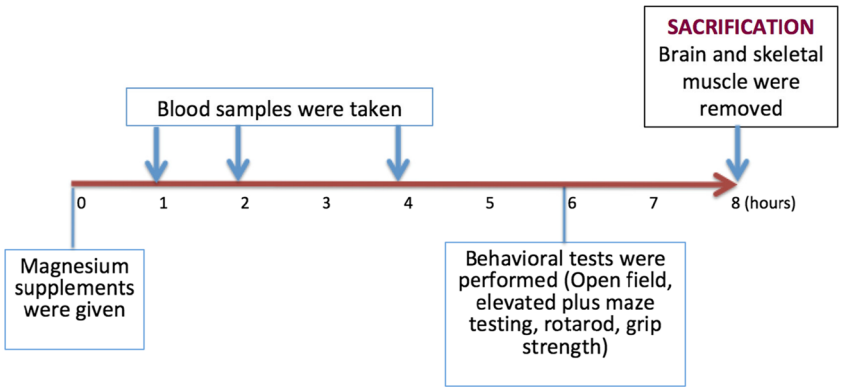


Fig. 1 Timeline of experiments

magnesium administration. All magnesium compounds were given in 1-ml volume/each rat. Control animals were given the same volume of PBS orally.

We looked at different tissues to assess the bioavailability of magnesium. We utilized two established animal anxiety models to assess the effects of magnesium in the brain tissue: open-field arena and elevated plus-maze apparatus. The recording and analyses were completed by 4.1.106 version Noldus Ethovision XT video-tracking system. In order to assess the effects of magnesium in the muscle tissue, we assessed locomotor activity, muscle strength levels, and motor coordination. Eight hours after administration of magnesium [19], blood samples were drawn under carbon dioxide anesthesia; later, brain was separated from the cerebellum and magnesium level was measured in the whole brain. While measuring Mg in muscle tissue, gastrocnemius was removed because it contains muscle fibers of type 1 and type 2.

Open-Field Test

This test has been commonly used to assess spontaneous locomotor activity and anxiety. As part of our series of experiments, exploratory behavior of the rodents was evaluated in the open-field test. The open field consists of an area of 1 × 1 m surrounded with a wall 50 cm in height, and a video camera installed 2.5 m above the apparatus. Each rat was placed in the center of the open field and then locomotor activity (ambulation) was measured for 5 min in a soundproof observation room illuminated with controlled light (100 lx) [20].

Elevated Plus Maze

This is another established model for anxiety in rodents. This test causes anxiety in the animal and therefore is more accurate for the assessment of anxiety. The elevated plus-maze apparatus consists of a central platform (5 cm × 5 cm) with two open arms (50 cm long, 10 cm wide, and 0.5 cm high borders) and two closed arms (50 cm long, 10 cm wide with 40 cm high walls) that were elevated 50 cm above the ground. Rats were placed on the platform facing the open arm and were observed for 5 min. The total number of entries into the open and closed arms as well as the time spent in each arm was measured [21].

Forelimb Grip Strength Measurement

The muscle strength of the subjects was measured using a muscle strength meter. Rats were lifted from the tail to hold the device bar with the forearms and then pulled gently from their tail. The value given by the digital force indicator before the release of the rod was defined as the grip force. The test was repeated three times in succession and the highest value was regarded as the holding force [22].

Rotarod: Assessment of Motor Coordination

The rotarod test device consists of 3-cm diameter cylinders, separated by panels to prevent animals from seeing each other. Five animals can be tested at the same time. The speed of the bar was linearly increased from 4 to 20 rpm for 180 s. The animals were trained to walk on the accelerating rotarod. Each walking performance on the rotarod was timed by the counter until the animal lost balance and fell down [23].

Blood, Brain, and Muscle Tissue Magnesium Levels

Blood, brain, and muscle samples were stored at − 85 °C until they were analyzed. Magnesium level in the brain, plasma, and muscle tissues was determined by atomic absorption spectrophotometry (following microwave oven digestion—210 VGP model, East Norwalk, Connecticut, USA), 8 h post administration. Magnesium level was measured at different time points using a Beckman Coulter AU 5800 analyzer (Beckman Coulter, Brea, CA). Tissue magnesium concentration was calculated per wet weight. Protein analysis was performed as per manufacturer's description of BCA protein assay kit (Cat No E- BP-500, Elabscience, Wuhan, China). The erythrocyte magnesium levels were calculated per protein (hemoglobin).

Calculation of the Area Under the Curve

Bioavailability refers to the fraction of drug systemically absorbed and it can be measured by quantifying area under the curve (AUC) of a serum concentration against a time plot. We calculated the AUC of the plot of serum magnesium levels determined at different time points. (AUC = (C1 + C2)/(t2-t1) + (C2 + C3)/(t3-t4) + (C3 + C4)/(t5-t4)).

Statistical Evaluation

All statistical procedures were performed by SPSS software for Windows, Version 11.0 (SPSS, Chicago, IL). Differences between groups were analyzed using one-way ANOVA with the Bonferroni post hoc test when a statistically significant difference was found between groups. Correlations among groups were calculated using the Pearson correlation analysis. Results are presented as mean ± S.E.M, where $p < 0.05$ was considered statistically significant.

Results

All results are summarized in Table 1. In the open-field test, the magnesium acetyl taurate group demonstrated more activity in the center of the open-field arena compared to the magnesium sulfate, magnesium oxide, magnesium citrate, and control groups ($p < 0.05$ for magnesium sulfate; $p < 0.001$ for the other experimental groups) (Fig. 2a).

The magnesium acetyl taurate group demonstrated more activity in the open arms of elevated plus-maze test when compared to the magnesium malate, magnesium citrate, magnesium oxide, and control group rats ($p < 0.05$ for magnesium malate and magnesium citrate; $p < 0.001$ for magnesium oxide, and control groups) (Fig. 2b).

No difference was observed in muscle strength or rotarod performance between the experimental groups and control (Fig. 2c, d).

As early as 4 h post administration, blood magnesium levels were high in rats administered with magnesium malate (indicating fast intestinal absorption), but no statistical difference was found between the magnesium malate and magnesium acetyl taurate groups. At the eighth hour, blood magnesium levels were significantly higher in the magnesium malate group when compared to all other groups ($p < 0.001$) (Fig. 3a). No difference was observed in erythrocyte magnesium levels between the experimental and control groups (Fig. 3b).

The area under the magnesium curve is the difference between all magnesium compounds. Magnesium malate's AUC is much higher than all other groups ($p < 0.0001$). Magnesium acetyl taurate and magnesium sulfate's AUC are higher than magnesium oxide and citrate (both $p < 0.0001$) (Fig. 3c).

Brain magnesium levels were highest in the magnesium acetyl taurate group when compared with others (comparison with magnesium citrate $p < 0.05$; for other groups $p < 0.0001$) (Fig. 4a). On the other hand, muscle magnesium levels were lower in the magnesium acetyl taurate group when compared with magnesium sulfate, magnesium oxide, magnesium citrate, and control groups (all of $p < 0.001$) (Fig. 4b).

We found strong positive correlations between brain magnesium levels and time spent in open arms of the elevated plus maze ($r = 0.541$, $p = 0.0001$). We also found intermediate negative correlations between muscle magnesium levels and distance in the open-field arena and also open arms of the elevated plus maze ($r = -0.446$, $p = 0.005$; and $r = -0.468$, $p = 0.003$, respectively).

Discussion

This study compared the bioavailability of three organic and two inorganic (intraperitoneal and peroral) Mg compounds. Bioavailability was assessed by investigating tissue magnesium levels and also evaluated behavioral effects.

To understand the bioavailability of Mg in the brain, we conducted two established experimental anxiety models for rodents, and Mg has been previously used with success in these models in reducing anxiety in rodents. We were able to demonstrate that among the magnesium preparations we tested, the magnesium acetyl taurate group demonstrated the lowest anxiety indicators as per open-field test and elevated plus-maze test markers (by entering more often into the center cells of the open-field arena and by spending more time in the open arms of elevated plus-maze test); the magnesium acetyl taurate group also had the highest Mg concentration in brain tissue after 8 h, strongly indicating an efficient blood-brain barrier passage. However, blood and muscle magnesium levels were low in the magnesium acetyl taurate group when compared to the other experimental groups. Serum levels were the highest in the magnesium malate group.

Literature on the bioavailability of various Mg compounds is limited. To our knowledge, there is no previous study investigating and comparing the immediate physiological and behavioral effects of various magnesium preparations and their corresponding blood/tissue magnesium levels. Most studies so far have compared the bioavailability of up to three different magnesium compounds and bioavailability has been measured through the urinalysis [24–26]. After oral administration, magnesium is absorbed from the intestines, and increased levels in the blood would not suffice, it would need to pass through the cell membrane and get inside the cell in order to participate in normal physiological functions. Therefore, we have used both peroral and parenteral administration of inorganic magnesium supplements. In our experiments, we did not observe any differences between the control

Table 1 Behavioral tests results and tissue and blood magnesium levels in 8 h

	OF Time spend in middle area (sec)	T-maze Time spend open arms (sec)	Blood Mg (mg/dL)	Muscle Mg (mg/g tissue)	Brain Mg (mg/g tissue)
Control	5.2 ± 0.2	8.8 ± 1.6	3.3 ± 0.5	327.4 ± 1.4	189.3 ± 1.6
MgSO4	6.3 ± 0.6	38.6 ± 5.6**	3.4 ± 0.3	328.5 ± 2	178.6 ± 3.7
MgAT	11.4 ± 2.1*	39.8 ± 5.5*	3.1 ± 0.7	296.9 ± 8.8*	216.9 ± 2.9*
MgO	5.3 ± 0.7	8.0 ± 0.8	3.2 ± 0.7	326.2 ± 3.4	182.9 ± 1.5
MgC	3.8 ± 0.4	23.2 ± 2.9	3.4 ± 1.1	324.9 ± 2.5	198.8 ± 7.1
MgM	10.0 ± 1.1	21.9 ± 2.5	3.7 ± 0.8*	333.4 ± 5.6	180.6 ± 3.9

*$p < 0.05$ compared with control; **$p < 0.001$ compared to control and MgO

group and the inorganic magnesium groups (magnesium oxide and magnesium sulfate), which can be interpreted as the low bioavailability of these compounds [15, 17]. We showed that the magnesium acetyl taurate (an organic compound) group had the highest brain magnesium levels, followed closely by magnesium malate. Magnesium is an essential mineral for the homeostasis of all living cells. It is a cofactor in over 300 biochemical reactions, regulating nucleic acid and protein synthesis, ATP synthesis, nerve and muscle cell functions, and body temperature [2, 27]. Magnesium is also important in psychoneuroendocrine systems that attenuate stress hormone release and modulate the activity of the hypothalamus–pituitary–adrenocortical axis [7, 28].

Magnesium depletion is associated with affective mood disorders, anxiety, and depression. It was previously shown that increased magnesium levels in the brain were associated with anxiety-related behavior in mice [29]. Magnesium treatment was shown to reduce anxiety in other rodent studies [30, 31]. In Poleszask's study, organic and inorganic magnesium compounds were compared and while magnesium sulfate did

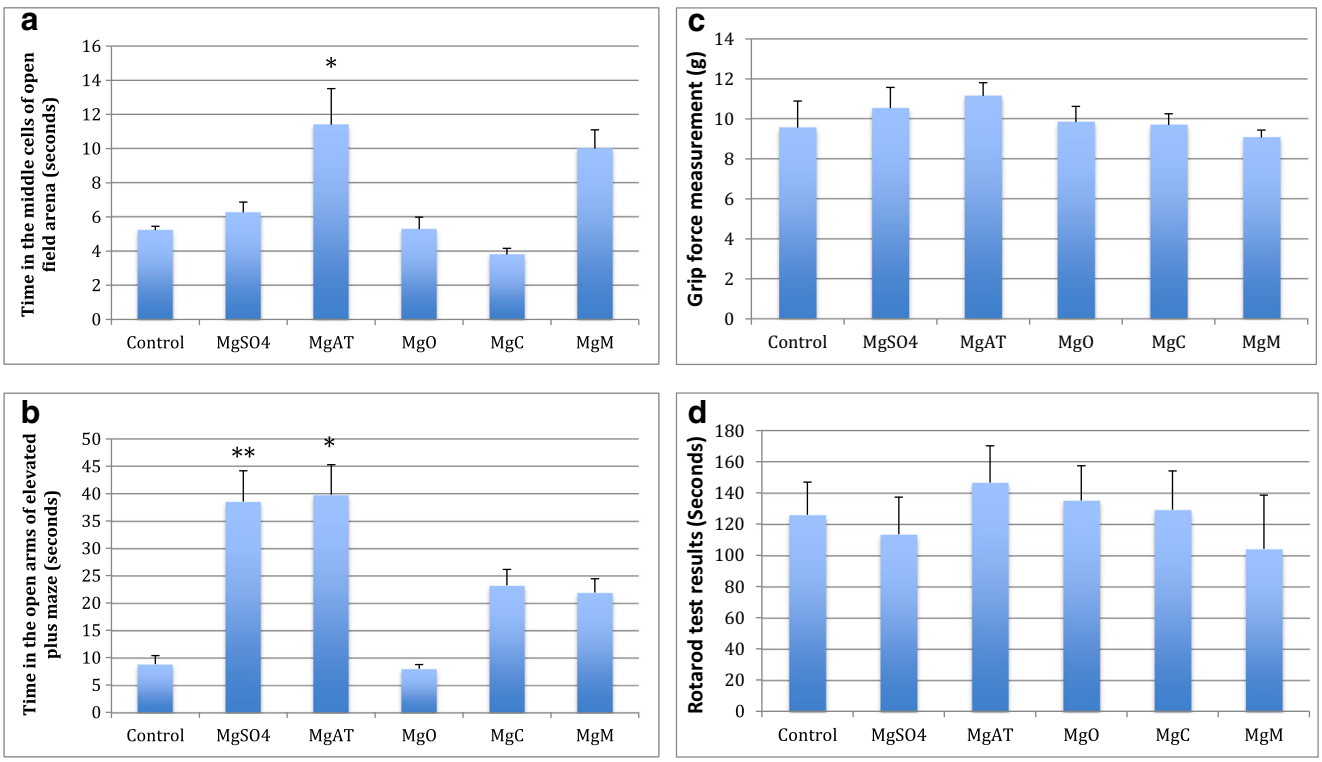
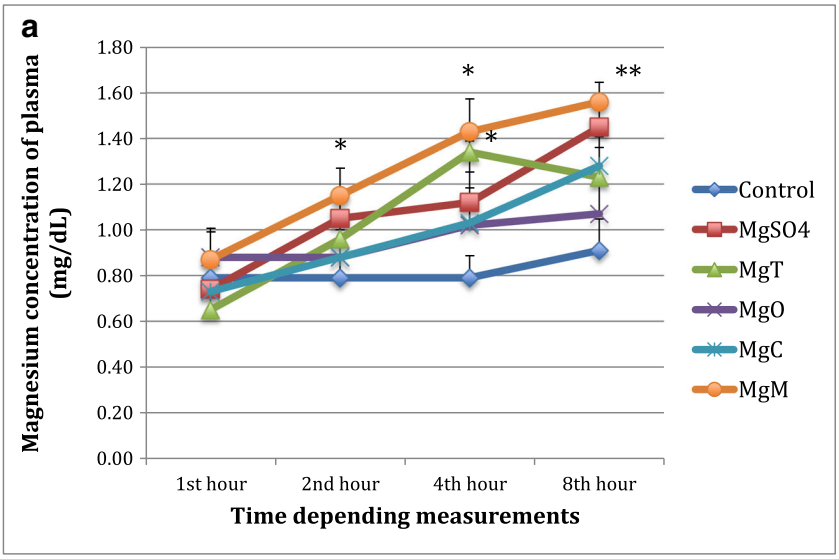
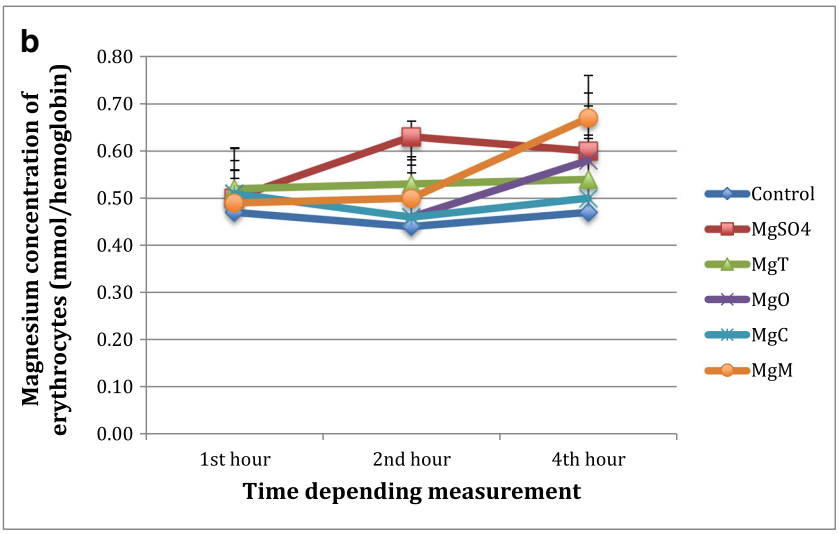


Fig. 2 Behavioral test results. **a** Open-field test result, percentage of moving-time in open-field test. Asterisk indicates $p < 0.05$ compared to other groups. **b** Elevated plus-maze test result, total entries to open arms of elevated plus maze. Single asterisk indicates $p < 0.001$ compared to control, MgC, MgO, and MgM. Double asterisks indicate $p < 0.001$ compared to control and MgO. **c** Forelimb grip strength measurement results. **d** Rotarod test results. MgSO4 magnesium sulfate, MgT magnesium acetyl taurate, MgO magnesium oxide, MgC magnesium citrate, MgM magnesium malate





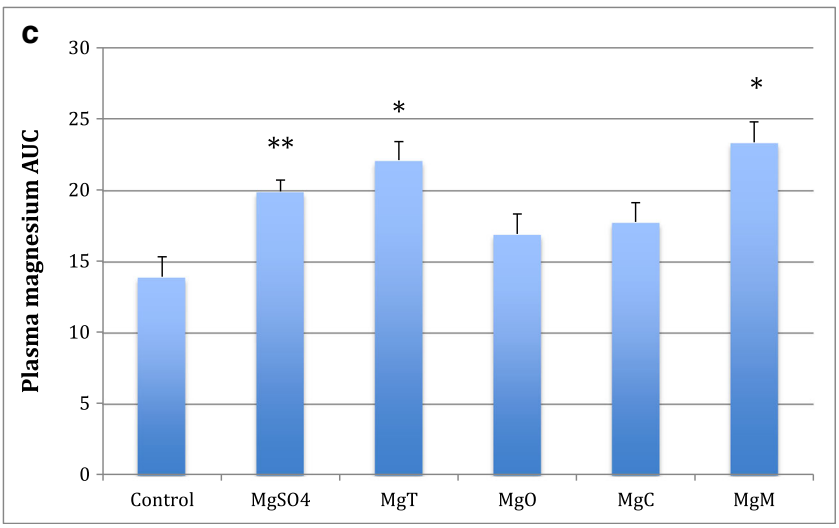


Fig. 3 **a** Serum magnesium levels. **a** Time point measurements of serum magnesium levels. Single asterisk indicates $p < 0.001$ compared with control, Double asterisks indicate $p < 0.01$ compared to MgT. **b** Time point measurements of erythrocyte magnesium levels. **c** Plasma magnesium AUC calculation results. Single asterisk indicates $p < 0.001$ compared to other groups, Double asterisks indicate $p < 0.001$ compared to control, MgO, MgC, MgT, and MgM. AUC the area under the curve, MgSO4 magnesium sulfate, MgT magnesium acetyl taurate, MgO magnesium oxide, MgC magnesium citrate, MgM magnesium malate

not affect anxiety, magnesium hydroaspartate (an organic compound) was shown to decrease anxiety levels in mice [30]. Consistent with these results, in our study, inorganic compounds did not affect anxiety either while magnesium acetyl taurate—an organic compound—reduced anxiety. Other organic magnesium compounds (magnesium citrate

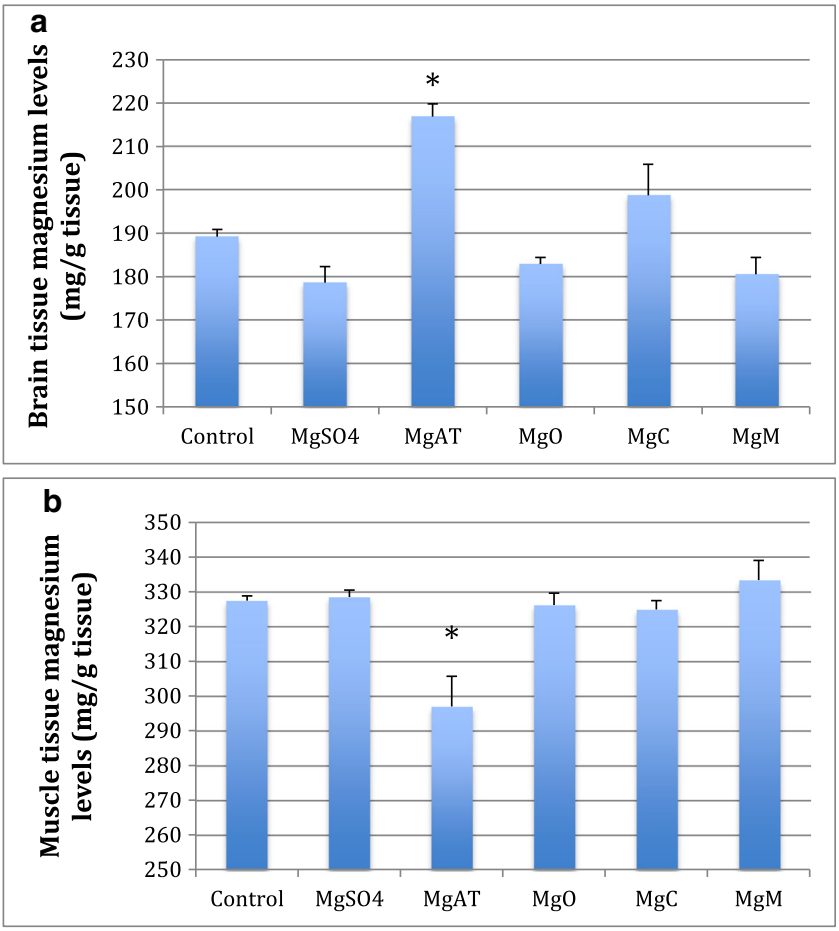


Fig. 4 Tissue magnesium levels. **a** Brain tissue magnesium levels. **b** Muscle tissue magnesium levels. Asterisks indicate $p < 0.05$ compared to other groups. MgSO4 magnesium sulfate, MgT magnesium acetyl taurate, MgO magnesium oxide, MgC magnesium citrate, MgM magnesium malate

and magnesium malate) had no effect on anxiety indicators. There were differences in the magnesium administration method of our study and Poleszask's [30]. In Poleszask et al., all organic magnesium compounds were given intraperitoneal. In our study, we mainly used oral administration. Level in brain tissue was only shown to be increased in the magnesium acetyl taurate group.

We did not observe any effect on muscle tissue after magnesium supplementation in the acute period. There are some reports on magnesium supplementation in fibromyalgia patients. A magnesium reduction in the muscle cells of fibromyalgia has previously been reported [32]. Abraham and Flechas treated fibromyalgia patients with a daily magnesium malate supplementation of 300–600 mg, for 8 weeks, and reported improvement in the fibromyalgia symptoms of the patients [33]. In our study, acute magnesium administration did not affect muscle tissue magnesium levels in our magnesium malate group. We also did not find any difference in muscle strength of the magnesium malate group when compared to its controls. Our results support a previous study data demonstrated no correlation between that serum magnesium level and muscle strength [34]. Magnesium is distributed to the bone, muscle, and brain tissue after getting into the bloodstream through the gastrointestinal tract [35]. Therefore, we particularly chose to investigate its bioavailability in muscle tissue directly and in brain tissue through its presumed behavioral manifestations.

One limitation of our study is that we could not collect urine to measure excretion of magnesium. In order for us to do this, rats must have been kept alone in metabolism cages for collection of urine. This would have caused isolation stress and would have likely adversely affected our behavioral test results. Being able to measure urine magnesium would have allowed us to calculate the entire magnesium metabolism.

In our study, we were surprised to find magnesium oxide and magnesium citrate compounds—commonly prescribed by doctors—had the lowest bioavailability measured, and in most cases, no significant difference from the control group was observed. It is known that magnesium is rapidly separated from the compound in both of these magnesium forms and free magnesium quickly binds to many intestinal contents such as food. During our experiments, our rats had free access to food; thus, our findings may indicate a lower bioavailability of the magnesium compound.

Conclusion

Today, the reduced nutrient content of foods makes micronutrient reinforcement necessary. Magnesium is one of the microelements that must be taken as supplement if it is deficient in the body. In this study, we demonstrated that orally administered magnesium acetyl taurate detected in the brain was quickly absorbed, able to pass through to the brain easily, and had measurable effects on anxiety indicators as specifically evidenced by strong positive correlation between brain magnesium levels and time spent in open arms of the elevated plus maze. Another notable findings were that magnesium taurate levels remained high for a long time in the serum. We used single dosing (daily recommended dosing) in this study; dose-dependent responses of these magnesium compounds would require further investigation. In addition, further work is needed to explain the effects of these magnesium compounds on the body of long-term applications.

Compliance with Ethical Standards

The experiments were carried out according to the Guiding Principles in the Use of Experimental Animals and approved by the Animal Care and Use Committee of the Dokuz Eylul University, School of Medicine.

Conflict of Interest The authors declare that they have no conflict of interest.

References

1. Maguire ME, Cowan JA (2002) Magnesium chemistry and biochemistry. Biometals : an international journal on the role of metal ions in biology, biochemistry, and medicine 15(3):203–210
2. Swaminathan R (2003) Magnesium metabolism and its disorders. The Clinical biochemist Reviews / Australian Association of Clinical Biochemists 24(2):47–66
3. Elin RJ (2010) Assessment of magnesium status for diagnosis and therapy. Magnes Res 23(4):S194–S198
4. Jahnen-Dechent W, Ketteler M (2012) Magnesium basics. Clin Kidney J 5(Suppl 1):i3–i14
5. Scott D, Blizzard L, Fell J, Giles G, Jones G (2010) Associations between dietary nutrient intake and muscle mass and strength in community-dwelling older adults: the Tasmanian Older Adult Cohort study. J Am Geriatr Soc 58(11):2129–2134
6. Cunningham J, Rodriguez M, Messa P (2012) Magnesium in chronic kidney disease stages 3 and 4 and in dialysis patients. Clin Kidney J 5(Suppl 1):i39–i51
7. Boyle NB, Lawton C, Dye L (2017) The effects of magnesium supplementation on subjective anxiety and stress—a systematic review. Nutrients 9(5)
8. Verhas M, de la Gueronniere V, Grognet JM, Paternot J, Hermanne A, Van den Winkel P, Gheldof R, Martin P, Fantino M, Rayssiguier Y (2002) Magnesium bioavailability from mineral water. A study in adult men. Eur J Clin Nutr 56(5):442–447
9. Coudray C, Bellanger J, Vermorel M, Sinaud S, Wils D, Feillet-Coudray C, Brandolini M, Bouteloup-Demange C, Rayssiguier Y (2003) Two polyol, low digestible carbohydrates improve the apparent absorption of magnesium but not of calcium in healthy young men. J Nutr 133(1):90–93
10. Rude RK (1993) Magnesium metabolism and deficiency. Endocrinol Metab Clin N Am 22(2):377–395
11. c (1997) National research, DRI (dietary reference intakes) for calcium, phosphorus, magnesium, vitamin D, and fluoride. National Academy Press, Washington
12. Mayer A-M (1997) Historical changes in the mineral content of fruits and vegetables. Br Food J 99(6):207–211
13. Thomas D (2007) The mineral depletion of foods available to us as a nation (1940-2002)—a review of the 6th edition of McCance and Widdowson. Nutr Health 19(1–2):21–55
14. Fawcett WJ, Haxby EJ, Male DA (1999) Magnesium: physiology and pharmacology. Br J Anaesth 83(2):302–320
15. Coudray C, Rambeau M, Feillet-Coudray C, Gueux E, Tressol JC, Mazur A, Rayssiguier Y (2005) Study of magnesium bioavailability from ten organic and inorganic Mg salts in Mg-depleted rats using a stable isotope approach. Magnes Res 18(4):215–223
16. Bertinato J, Plouffe LJ, Lavergne C, Ly C (2014) Bioavailability of magnesium from inorganic and organic compounds is similar in rats fed a high phytic acid diet. Magnes Res 27(4):175–185
17. Schuchardt JP, Hahn A (2017) Intestinal absorption and factors influencing bioavailability of magnesium—an update. Current nutrition and food science 13(4):260–278
18. Bohn T (2008) Dietary factors influencing magnesium absorption in humans. Curr Nutr Food Sci 4(1):53–72
19. Schuette SA, Lashner BA, Janghorbani M (1994) Bioavailability of magnesium diglycinate vs magnesium oxide in patients with ileal resection. JPEN J Parenter Enteral Nutr 18(5):430–435
20. Casarrubea M, Sorbera F, Crescimanno G (2009) Multivariate data handling in the study of rat behavior: an integrated approach. Behav Res Methods 41(3):772–781
21. Handley SL, Mithani S (1984) Effects of alpha-adrenoceptor agonists and antagonists in a maze-exploration model of 'fear'-motivated behaviour. Naunyn Schmiedeberg's Arch Pharmacol 327(1):1–5
22. Meyer OA, Tilson HA, Byrd WC, Riley MT (1979) A method for the routine assessment of fore- and hindlimb grip strength of rats and mice. Neurobehav Toxicol 1(3):233–236
23. Dunham NW, Miya TS (1957) A note on a simple apparatus for detecting neurological deficit in rats and mice. Journal of the American Pharmaceutical Association American Pharmaceutical Association 46(3):208–209
24. Walker AF, Marakis G, Christie S, Byng M (2003) Mg citrate found more bioavailable than other Mg preparations in a randomised, double-blind study. Magnes Res 16(3):183–191
25. Morris ME, LeRoy S, Sutton SC (1987) Absorption of magnesium from orally administered magnesium sulfate in man. J Toxicol Clin Toxicol 25(5):371–382
26. Bohmer T, Roseth A, Holm H, Weberg-Teigen S, Wahl L (1990) Bioavailability of oral magnesium supplementation in female students evaluated from elimination of magnesium in 24-hour urine. Magnesium and trace elements 9(5):272–278
27. Morais JB, Severo JS, Santos LR, de Sousa Melo SR, de Oliveira Santos R, de Oliveira AR, Cruz KJ, do Nascimento Marreiro D (2017) Role of magnesium in oxidative stress in individuals with obesity. Biol Trace Elem Res 176(1):20–26
28. Murck H, Steiger A (1998) Mg2+ reduces ACTH secretion and enhances spindle power without changing delta power during sleep in men—possible therapeutic implications. Psychopharmacology 137(3):247–252
29. Laarakker MC, van Lith HA, Ohl F (2011) Behavioral characterization of A/J and C57BL/6J mice using a multidimensional test: association between blood plasma and brain magnesium-ion concentration with anxiety. Physiol Behav 102(2):205–219

30. Poleszak E, Szewczyk B, Kedzierska E, Wlaz P, Pilc A, Nowak G (2004) Antidepressant- and anxiolytic-like activity of magnesium in mice. Pharmacol Biochem Behav 78(1):7–12
31. Iezhitsa IN, Spasov AA, Kharitonova MV, Kravchenko MS (2011) Effect of magnesium chloride on psychomotor activity, emotional status, and acute behavioural responses to clonidine, d-amphetamine, arecoline, nicotine, apomorphine, and L-5-hydroxytryptophan. Nutr Neurosci 14(1):10–24
32. Magaldi M, Moltoni L, Biasi G, Marcolongo R (2000) Changes in intracellular calcium and magnesium ions in the physiopathology of the fybromyalgia syndrome. Minerva Med 91(7–8):137–140
33. Abraham GE, Flechas JD (1992) Management of fibromyalgia: rationale for the use of magnesium and malic acid. Journal of Nutritional Medicine 3(1):49–59
34. Dominguez LJ, Barbagallo M, Lauretani F, Bandinelli S, Bos A, Corsi AM, Simonsick EM, Ferrucci L (2006) Magnesium and muscle performance in older persons: the InCHIANTI study. Am J Clin Nutr 84(2):419–426
35. Jahnen-Dechent W, Ketteler M (2012) Magnesium basics. Clin Kidney J 5(Suppl_1):i3–i14