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RESEARCH PAPER

Evaluating behavioral, biochemical and histopathological effects of the MgO nanoparticles administration on memory in the Alzheimer-like model of male rat

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ABSTRACT

Objective(s): This study has investigated the effects of acute and chronic administration of MgO nanoparticles (NP), on the memory, serum magnesium ions level, total antioxidant capacity and histopathological changes of the rat hippocampus in the Alzheimer-like model induced by streptozotocin (STZ).

Materials and Methods: Adult male Wistar rats divided into: control, sham (STZ+ saline) and MgO NP 1 and 5 mg/kg groups. To induce Alzheimer's disease, all rats except control group, received STZ (3 mg/kg/ 5 µl of saline) into the lateral ventricles during anesthesia. One week after surgery, passive avoidance learning was started by shuttle box device and saline or MgO NP acutely and chronically was administered after training. Memory tests were done at 90 minutes and 24 hours after training and one week after chronic administration. Immediately after the memory test, serum magnesium levels and total antioxidant capacity were measured, also the brain hippocampus tissue was removed for histopathological evaluation. STZ significantly impairs memory up to a week after the training.

Results: Acute and chronic administration of MgO NP significantly improved short and long-term memory in the Alzheimer's rats. Serum magnesium level decreased in the Alzheimer's rats and MgO NP increased it in a dose-dependent manner. MgO NP 1 mg/kg significantly increased serum total antioxidant capacity. MgO NP improved STZ-induced cell lesions in different parts of the hippocampus.

Conclusions: It seems that MgO NP have the potential to improve brain lesions that have led to loss of memory and can be considered as an important component candidate for Alzheimer's disease.

Keywords: *Alzheimer, MgO, Nanoparticles, Passive avoidance memory, Rat*

How to cite this article

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INTRODUCTION

Alzheimer's disease (AD) is a progressive brain disease that is typically caused by aging [1].In Alzheimer's disease, the structure of the neurons is destroyed, which affects memory and behavior. The β-amyloid plaques formation around neural cells, as well as neurofibrillary filaments within brain cells are some reasons that cause this disease [2,3]. Early signs of Alzheimer's disease are gradually impairing memory, especially spatial memory [4,5]. Reducing and degeneration of neurons in learning and memory related areas, especially in the hippocampus, is one of the symptoms observed in AD [5]. Evidences clearly demonstrated the role of neuronal inflammation and oxidative stress in the pathogenesis of this disease [6]. In fact, Alzheimer's disease is a neuropathologically advanced dementia associated with a significant alteration of hippocampus activity, beta-amyloid protein deposits in the vascular walls and development of neurotic plaques [7]. On the other hands, Magnesium ion level in Alzheimer's patients blood serum is less than that of healthy people and increasing magnesium level returns learning

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in young and old mice, as well as magnesium increases the short-term and long-term synaptic facilitations and improves memory and learning [8]. It has been shown that increased extracellular magnesium has significant protective effects on the Alzheimer-like mouse model; hence, magnesium has therapeutic potential for Alzheimer treatment [9].

In recent years, nanotechnology has grown enormously with new materials that have a wide range of important applications at the cellular and molecular level [10, 11]. Our previous studies on metal oxide nanoparticles such as magnesium oxide nanoparticle (MgO NP) have shown that this nanoparticle could affect behavioral parameters such as learning and memory, pain perception and anxiety and change blood and hippocampus magnesium level [12-14].

It has been shown that MgO NP could improve long-term memory and memory impairment due to peripheral injection of atropine [13,14]. Since in Alzheimer's disease magnesium level decrease [8], so that it seems a sufficient supply of magnesium in the body can be a way to treat brain damage resulting of Alzheimer's disease.

Since the effects of MgO NP on the animal model of Alzheimer has not been investigated, the aim of this study was to evaluate the effects of acute and chronic administration of MgO NP on the short and long term memory, serum magnesium ion concentration and antioxidants capacity as well as hippocampal tissue changes in Alzheimer-like model of rats.

MATERIALS AND METHODS

Animals grouping and treatments

In this experimental study adult male Wistar rats (280-320 mg) were provided from faculty of the Veterinary animal house in the Shahid Chamran University of Ahvaz. All animals were accommodated for one week before surgery in a room at 22 ± 2 *°C*, with controlled 12/12 *h* light–dark cycles and free access to food and drinking water except during the test periods. All the experiments were carried out between 8 PM-14 AM, and in accordance with the institutional guidelines for animal care followed by the Shahid Chamran University of Ahvaz, Ahvaz, Iran. MgO NP (<100 nm, Lolitech Co, Germany) suspension was prepared by sonication in saline before injection. Saline and MgO NP 1 and 5 *mg/kg* injected intraperitoneally in a volume of 1 *ml/kg* [12, 14, 15]. Streptozotocin (STZ) (Zelbio Co, Germany) solution was prepared by dissolving in saline and injected into lateral ventricules in dose of 3 *mg/kg/* 5*μL* [16].

Animals were divided into three main groups that each of them including: controls (saline), sham (STZ +saline), STZ+ MgO NP 1and 5 *mg/kg*.

In the first main group, animals received acute injection of saline or two doses of MgO NP immediately after training and passed the short-term memory testing by the shuttle box test, 90 minutes after injections. In the second group animals received acute injection of saline or two doses of MgO NP 24 hours after training and passed the long-term memory testing1 hour after injections.

In the last group animal received daily injection of saline or two doses of MgO NP, 24 hours after training for 6 constantans days as chronic injections of components and at the 7th day, passed the long-term memory testing 1 hour after last injection. Control group received intra ventricular injection of saline during the surgery and intraperitoneal injection of saline after training. Number of animals in each group was 6 (N=6).

Animal surgery for Alzheimer-like model

Induction of Alzheimer- like model was done by injection of streptozotocin into the lateral ventricles [17].

All rats were anesthetized by intraperitoneal administration of ketamine hydrochloride and xylezine (60:4 *mg/kg*) and placed in a stereotaxic apparatus. Each rat received single injection of STZ solution to the left and right ventricles (anterocaudal: −0.8 *mm*; lateral: ± 1.5 *mm* (with respect to the bregma), vertical: -3.5 *mm* (from the dura) according to the atlas of Paxinos and Watson) in volume of 5 *μL* in each side over a 10 minutes period through an 27 gage syringe connected by polyethylene tubing to a 10 *μL* Hamilton syringe.

After surgery, rats were allowed to recover in their home cage for one week.

Passive avoidance learning protocol

Passive avoidance memory was performed by shuttle box apparatus, that has a white compartment connected to a black one (20×20×30 *cm*) by a sliding door (9×7 *cm*), according to the following protocol.

Habituation and training

On habituation day, the rat was placed in the bright compartment, facing away from the dark compartment and allowed to explore for 10 sec, then door was raised and the rat was allowed to explore freely. When the rat entered in the dark chamber, the guillotine door was closed and the latency to enter was recorded (from the time the door was lifted and if the latency to entrance in dark chamber was more than 100 sec rat is eliminated). Then rat was removed after 30 sec and returned to the home cage. On training day, 30 minutes after habituation, rat was placed in the light compartment, facing away from the dark compartment and was allowed to explore for 10 sec, then the guillotine door was lifted. When rat entered the dark compartment with all four paws, immediately received foot-shock (0.5 Ma and 5 sec duration).

Short and long term memory testing

For short term memory testing, 90 minutes after training or components injection, the rat was returned to the bright compartment and after 10 sec, the guillotine door was lifted. When the rat entered the dark compartment, the latency time to entrance in the dark compartment and the period of staying in the black compartment were recorded. For long-term memory testing, 24 hours or 7 days after training again, the rat was passed this protocol. Then rat was removed and returned to the home cage, if did not cross after 300 sec (18). Each rat was used just for one time.

Serum magnesium concentration and total antioxidant capacity (TAC) assessment

Immediately after long term memory test in groups that received chronic injections, animals were anesthetized with ether and whole blood was collected from the heart and centrifuged to obtain the serum. Magnesium level was measured by magnesium assay kit (*Pars Azmoon kit*, karaj, Iran*). In this way,* 100 *µL* of Xylidyl Blue mixed with 10 *µL* of serum and read of complex absorbance at a wavelength of 546 *nm* by photometer instrument and results were expressed as *mMol/L* of serum. Total antioxidant capacity was evaluated in the serum by the method that used ferric reducing antioxidant power (FRAP). In this way, 30 *µL* of the serum was mixed with 200 *µL* of the FRAP reagent, which containing 2.5 *mL* of 2,4,6-tris(2pyridyl)-*s*-triazine (TPTZ)10 *mM* in HCl 40 *mM* and 2.5 *mL* of FeCl320 *mM* in 25 *mL* of acetate buffer 0.1 *M* (pH= 3.6) and mixture was added with distilled water up to 1 *mL* [19]. After ten minutes of incubation in 37 Cº, the mixture was centrifuged at 10,000 × *g*. Absorbance of colored TPTZ complex was read at a wavelength of 593 *nm* and results were expressed as *µMol/L* of serum.

Histopathological assessment

Animals of groups that received chronic injections scarified and whole brain removed, fixed in formaldehyde 10% solution and common histologic technical stages were done. Then the brain sections which were stained with Hematoxylin- Eosin and were observed under light microscope for evaluating neural changes in different parts of hippocampus including CA1, CA2, CA3 and dentate gyrus (DG).

Statistical analysis

Data were analyzed with Instate 3.0 software and Student's t-test was used for the comparison of the means of unpaired data and one way ANOVA with Tukey post hock was used for multiple comparisons between groups.

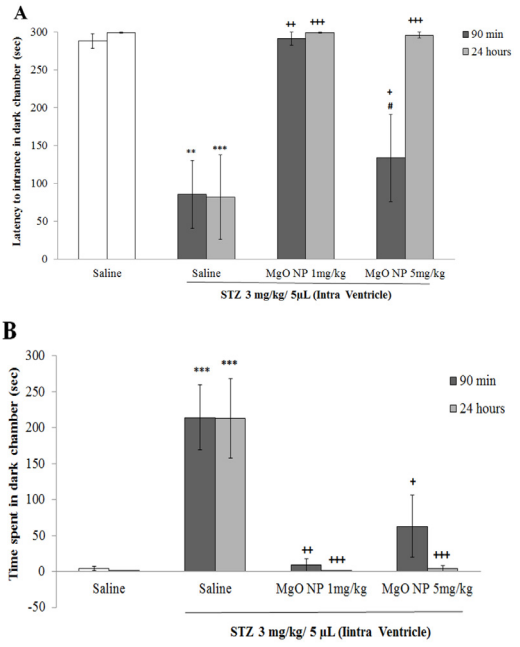

Fig 1. The effects of acute injection of MgO NP on short and long term memory. **P<0.01 and ***P<0.001 are in comparison with control (saline) group. +P<0.05, ++P<0.01 and P<0.001 are in comparison with STZ+ saline group. # P<0.05 is in comparison with STZ+ MgO NP 1 mg/kg group Results are expressed as a mean ± S.E.M

P<0.05 at each point was considered to be statistically significant. Results expressed as a mean ± standard error of the mean (S.E.M) and graphs were drawn by Excel software.

RESULTS

Short and long term memory assessment

Intra ventricular injection of STZ significantly decreased latency time to entrance in dark chamber 90 min (P<0.01) and 24 hours (P<0.001) after training (Fig1A). Also STZ significantly increased time spent in dark chamber 90 minutes and 24 hours after training (P<0.001) (Fig1B). These indicate that STZ could induce Alzheimer-Like model in rats. Acute injection of MgO NP 1 *mg/kg* significantly increased latency time to entrance and decreased time spent in dark chamber 90 minutes (P<0.01) and 24 hours (P<0.001) after training (Fig1A and B). As well as, acute injection of MgO NP 5 *mg/kg* significantly increased latency time to entrance and decreased time spent in dark chamber 90 minutes (P<0.05) and 24 hours (P<0.001) after training (Fig1A and B).

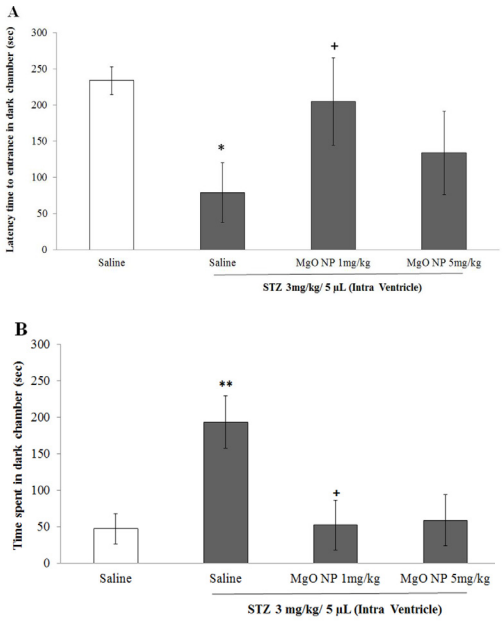

Fig 2. The effects of chronic injection of MgO NP on long term memory. *P<0.05 and **P<0.01 are in comparison with control (saline) group. +P<0.05, is in comparison with STZ+ saline group. Results are expressed as a mean ± S.E.M

Results of Fig 2A and B show that STZ significantly decreased latency time to entrance in dark chamber (P<0.05) and increased time spent in dark chamber (P<0.01). These indicate that STZ could impair long- term memory 7 days after training and induce Alzheimer- like model in rat too. Chronic injection of MgO NP 1 *mg/kg* significantly decreased latency time to entrance in dark chamber and increased time spent in dark chamber (P<0.05). While chronic administration of MgO NP 5 *mg/kg* could not affect long term memory disruption (Fig 2A and B).

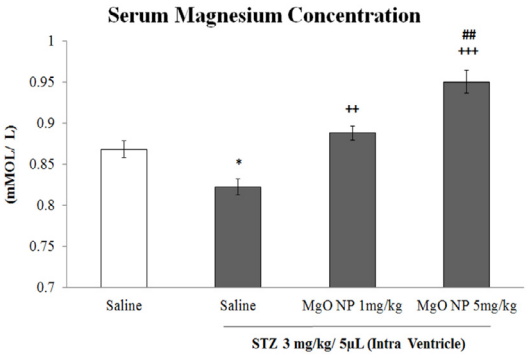

Fig 3. The effects of chronic injection of MgO NP on the serum magnesium concentration. *P<0.05 is in comparison with control (saline) group. ++P<0.01 and +++P<0.001 are in comparison with STZ+ saline group. ## P<0.01 is in comparison with STZ+ MgO NP 1 mg/kg group. Results are expressed as a mean ± S.E.M

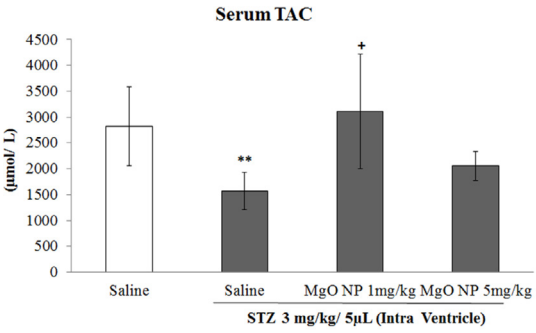

Fig 4. The effects of chronic injection of MgO NP on the serum TAC. **P<0.05 is in comparison with control (saline) group. +P<0.05 is in comparison with STZ+ saline group. Results are expressed as a mean ± S.E.M

Serum magnesium level and total antioxidant capacity assessment

Serum magnesium level and total antioxidant capacity were measured in the animals that received chronic injection of MgO NP and passed long term memory after 7 days. Data in Fig 3 shows that injection of STZ into the lateral ventricles significantly decreased serum magnesium level (P<0.05), while chronic injection of MgO NP 1

and 5 *mg/kg* for one week could improve this reduction in a dose dependent manner (P<0.01 and P<0.001, respectively).

Fig 4 shows that STZ injection into the lateral ventricles significantly decreased TAC in the serum of animals (P<0.01), while chronic injection of MgO NP 1 *mg/kg* could improve this reduction significantly (P<0.05) and MgO NP 5 *mg/kg* did not show significant effect on this reduction.

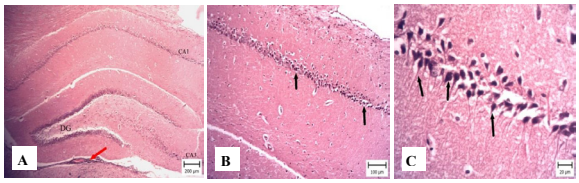

Fig 5. Hippocampus. STZ+ saline group. (Hematoxylin and Eosin). (A): Note to accumulation of inflammatory cells around the ventricle capillary (Red arrow). (B&C): Ischemic changes are obvious in neurons (black arrows). They were small, dark and wrinkle. Note to high number of injured neurons

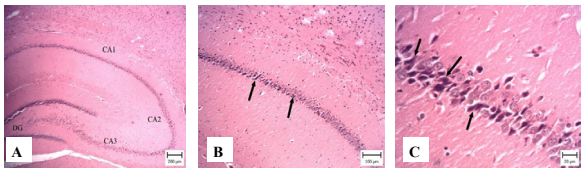

Fig 6. Hippocampus. STZ+ MgO NP 1mg/kg group. (Hematoxylin and Eosin). (A): Different part of hippocampus (CA1, CA2, CA3 and DG) are seen. (B&C): Ischemic changes are obvious in neurons (black arrows). They were small, dark and wrinkle and normal cells have large and visible nucleus. Note to the decreased number of injured neurons in comparison with Fig 5C

Hippocampus histological changes assessment

Hippocampus histological changes were evaluated in the animals that received chronic injection of components and passed long term memory after 7 days. Histopathologic evaluation of the hippocampus showed a wide range of lesions in streptozotocin+ saline group. The neurons of different parts of the hippocampus, including CA1, CA2, CA3, and DG (dentate gyrus), have been affected by ischemic cell changes. These cells were smaller than adjacent healthy cells. The cytoplasm and the nucleus were also more intense (Fig 6). The accumulation of inflammatory cells around the vessels in the ventricular space and increasing the Virchow- Robin space were observed too (Fig 6). In the STZ+ MgO NP 1 and 5 *mg/kg* recipient groups, the observed changes were lower than the streptozotocin group. Cellular ischemic changes in the neurons of STZ+ MgO NP 1*mg/kg* group were less than that of streptozotocin group alone and these were much lower in STZ+ MgO NP 5 *mg/kg* group rather than STZ+ saline or STZ+ MgO NP 1 *mg/kg* ones (Fig 7 and 8). Also, in this group the number of healthy cells in different parts was higher (Fig 8). The lowest changes were observed in the control (saline) group (Fig 5).

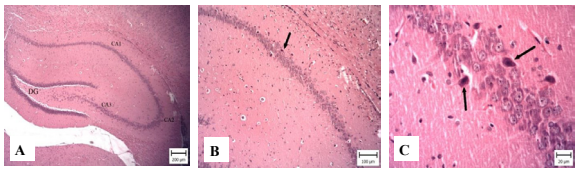

Fig 7. Hippocampus. STZ+ MgO NP 5 mg/kg group. (Hematoxylin and Eosin). (A): Different parts of hippocampus (CA1, CA2, CA3 and DG) are seen. (B&C): Ischemic changes are obvious in neurons (black arrows). They were small, dark and wrinkle and normal cells have large and visible nucleus. Number of normal neurons is more than STZ+ saline and STZ+ MgO NP 1 mg/kg groups

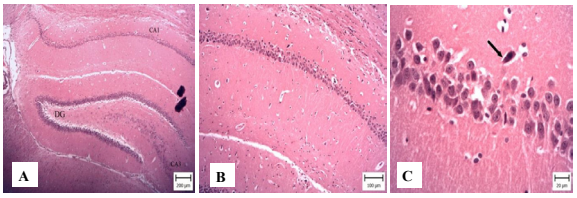

Fig 8. Hippocampus. Control (saline) group. (Hematoxylin and Eosin). (A): Different parts of hippocampus (CA1, CA3 and DG) are seen. (B&C): Note to the normal structure (B) and low number of altered cells (C)

DISCUSSION

Results of this study indicated that STZ could induce Alzheimer-like model and disrupt short and long term memories in male rats. Also, STZ decreased serum magnesium level and total antioxidant capacity. Microscopic observation of the hippocampus tissue in this group revealed a wide range of lesions and ischemic cell changes in different parts of the hippocampus. On the other hand, acute and chronic injection of MgO NP significantly improved short and long term memories, as well as chronic injection increased serum magnesium level and total antioxidant capacity. Also in chronic MgO NP recipient groups microscopic observed changes in hippocampus tissue were less than STZ group alone. Ischemic and inflammatory changes were lower, and the number of healthy cells in different parts of hippocampus was higher than STZ group.

Rats treated with intra ventricle injection of STZ are a suitable model for describing single-blind Alzheimer's disease in human, which is associated

with a gradual deterioration in the memory and metabolism of glucose [20]. It has been shown that administration of STZ under the diabetogenic dose to the brain ventricles leads to cognitive impairment; defects brain cholinergic system activity and oxidative stress markers [21-23].

Deficiency in Cholinergic System activity in The STZ-induced Alzheimer-like model by reducing acetylcholine and increasing acetylcholine esterase in the hippocampus supports the hypothesis that STZ can induce Alzheimer conditions [21]. Although the STZ toxicity mechanism was not well known, the properties of the alkaline metabolism of STZ metabolites cause reactive oxygen species (ROS), oxidative stress, and DNA damage [24]. STZ can reduce brain metabolism and acetylcholine release, which can play an important role in reducing cognitive function in Alzheimer's disease [25]. Studies have been shown that oxidative damage is involved in the development of Alzheimer's disease and in these patients, the antioxidants level in the plasma has decreased [26-28]. Oxidative stress causes lipid peroxidation, DNA, protein and carbohydrates oxidation, that all of which are found in Alzheimer's disease [29]. The use of a variety of antioxidant compounds has been suggested to reduce oxidative stress in Alzheimer's disease [29].

Also, magnesium levels decreased in the serum of AD patients and magnesium to modulate the trafficking and processing of amyloid-β precursor protein, which plays a central role in the pathogenesis of AD [30].

It has been shown that, magnesium deficiency increases oxidative stress and reduces the ability of body antioxidant barriers [26, 28]. Previous studies have indicated that acute injection of MgO NP could change magnesium, zinc, iron and calcium levels in the serum and hippocampus of male rats, as well as change of malondialdehyde level and catalase activity in the whole hippocampus tissue [12, 15]. Magnesium and zinc are involved in the antioxidant defense mechanism and there is a strong correlation between magnesium and iron levels and the antioxidant enzymes activity [26].

Rather than other mechanisms involved in the efficacy of MgO NP on memory that described by previous studies [13,14], it can be possible that intraperitoneal injection of MgO NP, which increases plasma magnesium level, by increasing total antioxidant capacity improved memory disruption in the streptozotocin induced Alzheimer-like model of rats. Javed et al. (2012) have shown that in STZ-induced Alzheimer-like model in rats, the neurons in the hippocampus were abnormal and degenerated, and described lesions were in agreement with this research [16]. There is a relationship between the reduction in magnesium levels and the reduction in the volume of the hippocampus that is common in AD disease [30]. Slutsky et al (2010) have reported that increasing the extracellular concentration of magnesium leads to an increase in long term potential in the neurons of the hippocampus [31]. On the other hand, recently Serita et al., 2019, have reported that magnesium deficiency could impair hippocampus-dependent memories in mice while spine density and morphology of hippocampal neurons were normal in them [32]. So that, probably rather than increasing serum magnesium level after chronic injection of MgO NP and memory improvements, nanoparticle by passing the blood–brain-barriers could reverse STZ effects on hippocampal neural cells directly or with activation of other mechanisms.

CONCLUSION

It is possible that MgO NP by increasing the serum magnesium level, antioxidant capacity and reducing the tissue lesions in the hippocampus can be a good candidate to improve memory disruption in Alzheimer-like model of the rat. Also in chronic usage lower dose of this nanoparticles can be effective than its higher dose. Finding side effects of this nanoparticle require further study.

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