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RESEARCH ARTICLE

Time dependent difference effects of MgO and ZnO nanoparticles on the serum and hippocampus Mg^{2+}, Zn^{2+}, $Fe^{2+/3+}$ and Ca^{2+} levels in the stressed rats

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ABSTRACT

Objective(s): Stress is a physiological response that can disrupt body elements homeostasis and lead to neurophysiological abnormality. This study has been investigated the serum and hippocampus Mg^{2+}, Zn^{2+}, $Fe^{2+/3+}$ and Ca^{2+} level changes in two times after MgO NPs and ZnO NPs single injection following restraint stress in the male rat.

Methods: Animals were divided into two main groups that each of them includes: control, restraint of 90, 180 and 360 min+ saline, MgO NPs and ZnO NPs 5 *mg/kg* alone and with a restraint of 90 min. In one group, 30 min and in another 120 min after intraperitoneally injections of components or stress induction elements levels were measured in the serum/ hippocampus.

Results: Elements level changed in the serum and hippocampus following injections of MgO and ZnO NPs depend on acute time after injections. ZnO NPs induced a positive correlation between serums $Fe^{2+/3+}$ levels in two acute times. Different times of stress induction have different effects on elements level changes in the serum and hippocampus, 30 and 120 min after induction and nanoparticles could alleviate these changes depend on the time. In restraint groups, there were positive and negative significant correlations between two different times measurements of $Fe^{2+/3+}$ or Ca^{2+} in the serum and hippocampus.

Conclusion: it seems that time is an important factor in ameliorative MgO NPs and ZnO NPs effects on elements disruption induced by stress, but their exact interaction with stress systems containing ions level changes needs to more investigation.

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INTRODUCTION

Acute and chronic immobilization stress can affect elements homeostasis and change their distribution in the different parts of the body, especially in the brain [1, 2]. Immobilization stress was decreased endogenous Zn^{2+} and $Fe^{2+/3+}$ concentrations in different parts of the brain such as hippocampus 24 hours after the stress induction [3]. On the other hand, trace elements such as Mg^{2+}, Zn^{2+}, $Fe^{2+/3+}$ and Ca^{2} are essential for living cells and body systems functions[4-6] and can change balance of each other in the body[7,8]. Magnesium

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and zinc have key roles in the central nervous system and hippocampus functions [9, 10].

Both of them work on some similar receptors, like N-methyl-D-aspartate (NMDA), that block or reduce its activity [11]. It has been shown that in rats under Zn^{2+} restriction Mg^{2+}, $Fe^{2+/3+}$ and Ca^{2} levels in the serum have increased significantly and decreased Zn^{2+} concentration in the serum and hippocampus, while could not affect Mg^{2+}, $Fe^{2+/3+}$ and Ca^{2+} levels in the rat's hippocampus[12]. Magnesium oxide and zinc oxide nanoparticles (MgO NPs and ZnO NPs), as novel sources of Mg^{2+} and Zn^{2+}, are widely used in medicine and pharmacology, by the development of nanotechnology [13, 14]. Benefit and toxic effects of these components have been investigated in the various living cells and systems, because of the unique properties of them [13, 15-18].

Some studies have shown that nanoparticles can change ions level in the central nervous system and neural cells [16, 19, 20]. Amaraet al. (2013) have shown that in the rat brainZnO NPs change elements levels including$Fe^{2+/3+}$, Zn^{2+}, and Ca^{2+} [19]. Also, ZnO NPs increase intracellular Ca^{2+} level and affect neural cell by increasing Zn^{2+} ions [16, 20]. Ion releasing is one of the most important cytotoxic factors of metal oxide nanoparticles and their primary particle size or surface area did not affect cellular functions directly [13].

Ben-Slama and et al. (2015) have indicated that oral exposure to ZnO NPs decreased the brain Ca^{2+} concentration [21]. Our previous study has shown that ZnO NPs can increase Zn^{2+} level in the serum and decrease anxiety-like behaviors in animal models [22].

In this work we investigated and compared the MgO NPs and ZnO NPs effectson Mg^{2+}, Zn^{2+}, $Fe^{2+/3+}$, and Ca^{2+} level changes in the serum/ hippocampus of adult male rats attwo different acute times following acute stress induction.

MATERIAL AND METHODS

Animals grouping and treatments

In this experimental work, male Wistar rats (220 ± 10 g) were purchased from animal house of faculty of veterinary in the Shahid Chamran University of Ahvaz.Experiments were carried out under ethical code of EE/96.24.3.88369/scu.ac.ir. MgO and ZnO nanoparticles (USnano., CO, USA) (Fig. 1), suspensions were prepared before experiments and injected intraperitoneally in a single dose of 5 *mg/kg* and a volume of 1 *mL/kg* [22, 23]. Both nanoparticles didn't formed large aggregates that blocked the syringe during injections. Rats were divided into 16 groups, which included two sub-groups, 1) non- restraint rats: control,MgO NPsand ZnO NPs 5 *mg/kg*and2) restraint rats: restrained for90 , 180 and 360 min+ saline (ST 90 min, ST 180 min and ST 360 min) andST 90 min+ MgO orZnO NPs 5 *mg/kg*. In all restraint groups, components were injected immediately after restraint stress induction, then in on main group(including, 8 groups) 30 min and in the other (including, 8 groups) 120 min after components injections or restraint stress induction animals were killed for a measure of ions concentrations in the serum and hippocampus.The number of rats in each group was six.

Acute stress *induction*

Rats were restrained for 90, 180 and 360 min in the plexiglass tubes, then immediately received saline (1*ml/kg*) or MgO NPs and ZnO NPs 5 *mg/kg*.

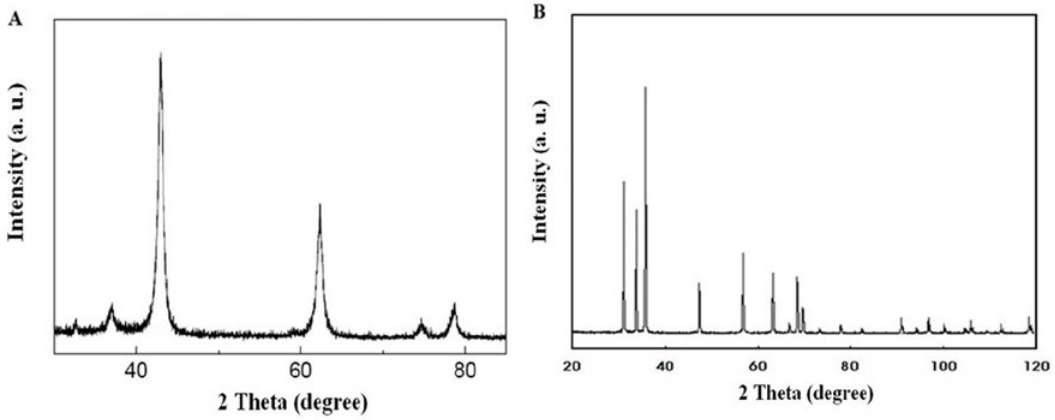

Fig. 1. XRD patterns of MgO NPs (A) and ZnO NPs (B).

Serum/ hippocampus sampling and assessment of elements contents

In the first 8 groups after 30 min and in the second 8 groups after 120 min, all rats scarified then serums and hippocampus homogenates of them obtained.Elements contents measured by a flame atomic absorption spectrophotometer apparatus in all samples, and results expressed as a *µg/ mL* of the serum and *mg/g* of wet hippocampus tissue.

Statistical analysis

One way ANOVA with Tukey post-hoc was used for comparing among groups and Student's t-test was used for comparing the means of unpaired data by using SPSS 16 software. Pearson correlation coefficient was calculated between elements contents of the serum/ hippocampus in 2 acute different times. Differences with a p value of <0.05 was considered statistically significant. Results are presented as the mean ± standard error of the mean and graphs are plotted with the Excel software.

RESULTS AND DISCUSSION

Nanoparticles size detection by XRD patterns

Fig. 1 is XRD patterns of the MgO NPs (A) and ZnO NPs (B) and indicates that the sizes of both nanoparticles were lower than 100 *nm* before injections.

Assessment of Mg^{2+} concentration

As seen in Fig. 2A, MgO NPs (30 min (P=0.002) and 120 min (P<0.0001)) and ZnO NPs (30 min (P<0.001) and 120 min (P=0.003)) significantly increased Mg^{2+} level in the serum 30 and 120 min after injections. Also, in MgO NPs group Mg^{2+}level 120 min after injection was significantly higher than 30 min (P=0.0018).Level of Mg^{2+} in serum was increased 30 min after ST 90 (P=0.0064) and ST 180 min induction (P=0.038) and was decreased and reached to the control group at 120 min. ST 360 min did not affect the level of Mg^{2+} significantly after 30 and 120 min compared to the control groups but was seen significant difference between

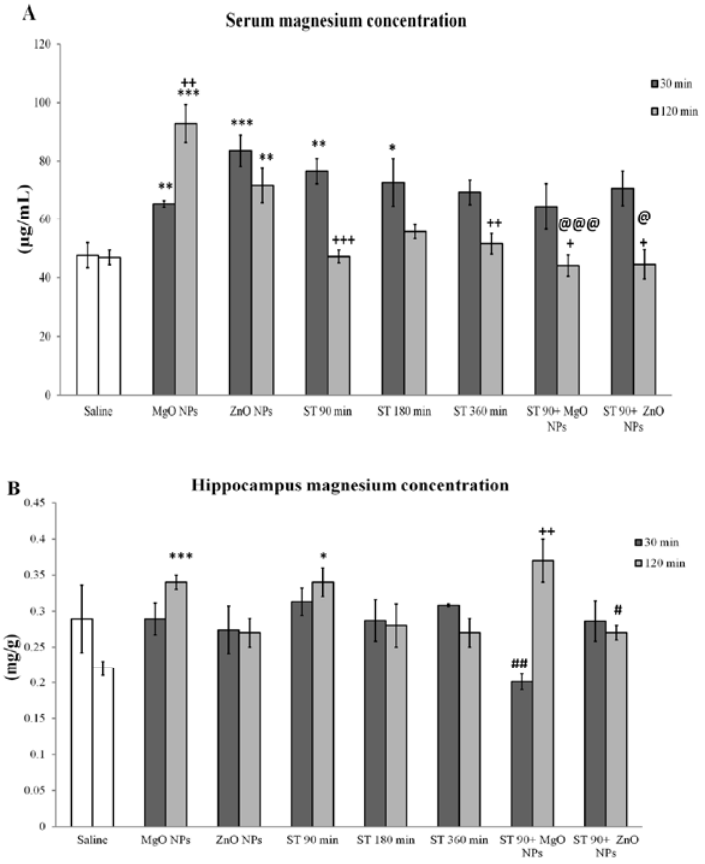

Fig. 2. Assessment of Mg^{2+} concentration. *P<0.05, **P<0.01 and ***P<0.001 are in comparison with the control group at the same time (30 and 120 min). +P<0.05, ++P<0.01 and ++P<0.001 are between equal treatment groups in two different times. #P<0.05 and ##P<0.01 are in comparison with ST 90 min groups at the same time (30 and 120 min). @P<0.05 and @@@P<0.001 are in comparison with MgO NPs or ZnO NPs groups at the same time (30 and 120 min). All bars are means ± standard error of the means.

30 and 120 min (P=0.0092).

In the restraint groups, MgO NPs and ZnO NPs did not change Mg^{2+} level in comparison with ST 90 min group after 30 min and 120 min, but following injection of both nanoparticles Mg^{2+}level after 120 min was decreased in comparison with after 30 min (P=0.042). Data analysis showed that ST 90 min has a reductive effect on the MgO NPs (P<0.0001) and ZnO NPs (P=0.0167) effects on serum magnesium concentration 120 min after injection.

Fig. 3B showed that MgO NPs (P=0.0004) and ST 90 min (P=0.041) increased hippocampus magnesium level after 120 min. While MgO NPs acted significantly in opposite directions in the presence of ST 90 min at two different times of 30 and 120 min (P=0.0030). MgO NPs in the presence of stress after 30 min reduced magnesium compared with the administration of MgO NPs alone but increased it after 120 min. This effect was not observed for ZnO NPs.

These results show that time duration after MgO NPs injection is an important factor in the release of Mg^{2+} from it in the serum and hippocampus. Also, stress has a dual role in the release of Mg^{2+}, in a short time can increase Mg^{2+} in the serum and while with passing the time increase it in the hippocampus.

Assessment of Zn^{2+} concentration

MgO NPs significantly decreased Zn^{2+} level after 120 min (P=0.0002), while ZnO NPs increased Zn^{2+} level in the serum after 30 (P=0.013) and 120 min (P=0.040). Stress was decreased Zn^{2+}level in a time-dependent manner 120 min after induction (ST 90 min (P<0.05), ST180 min (P<0.01) and ST 360 min (P<0.001)). In the restraint groups, MgO NPs (P=0.0075) and ZnO NPs (P=0.030) have increased Zn^{2+} level after 30 min, while decreased it after 120

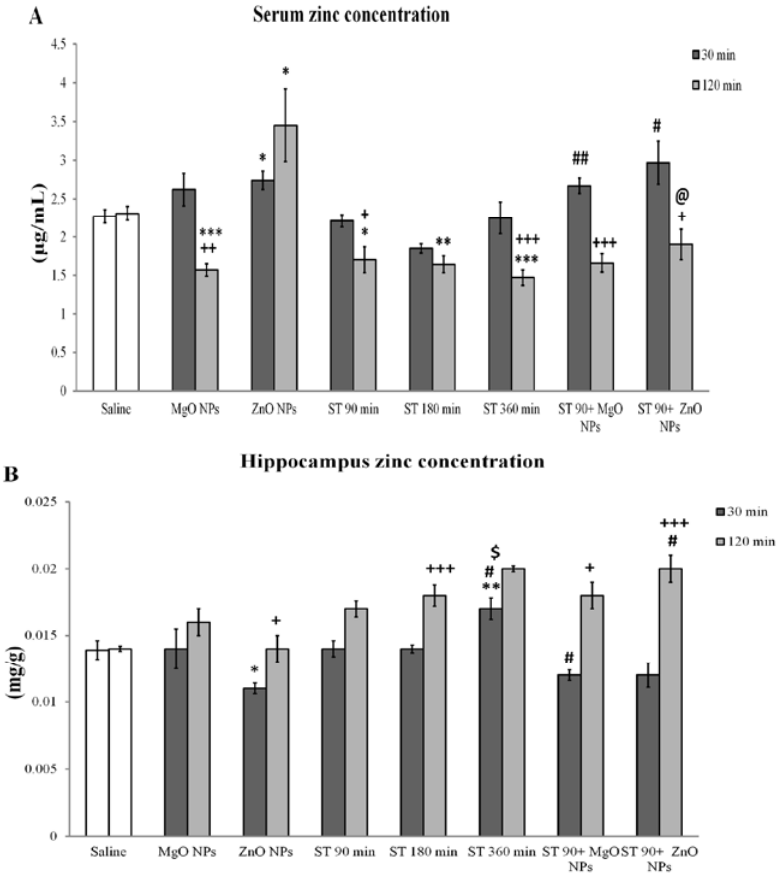

Fig. 3. Assessment of Zn^{2+} concentration. *P<0.05, **P<0.01 and ***P<0.001 are in comparison with the control group at the same time (30 and 120 min). +P<0.05, ++P<0.01 and ++P<0.001 are differences between equal treatment groups in two different times (30 and 120 min). #P<0.05 and ##P<0.01 are in comparison with ST 90 min groups at the same time (30 and 120 min). $P<0.05 shows a significant difference in comparison with ST 180 min group at the same time (30 min). @P<0.05 shows difference in comparison with ZnO NPs group at the same time. All bars are means ± standard error of the means.

min in comparison with 30 min after injections (MgO NPs (P<0.001) and ZnO NPs (P<0.05)). Stress 90 min decreased the serum zinc level in the ZnO NPs group (P=0.013) after 120 min that show negative effect of stress on ZnO NPs efficacy especially (Fig. 3A).

ZnO NPs was decreased Zn^{2+} level in the hippocampus after 30 min (P=0.015). Stress increased partially Zn^{2+} level 30 and 120 min after induction in all groups and it was significant 30 min after induction of ST 360 min (P=0.0058). In restraint groups, MgO NPs and ZnO NPs have increased Zn^{2+} level after 120 min and it was significant in the ZnO NPs group (P=0.044) (Fig. 3B).

These results show that except in one group (ZnO NPs) in all the other groups decrease of Zn^{2+} in serum was parallel to increase of it in the hippocampus, 120 min after treatments.

Assessment of $Fe^{2+/3+}$ concentration

MgO NPs increased serum $Fe^{2+/3+}$level in the stressed (P<0.0001)and non-stressed(P=0.0005) animals after 30 min, while ZnO NPs decreased $Fe^{2+/3+}$ level partially. Ironlevel decreased after 120 min in ST 360 min group (P=0.011). In the restraint animals MgO NPs significantly decreased $Fe^{2+/3+}$ level after 120 min in comparison with 30 min (P<0.0001) (Fig. 4A).

MgO NPs (P<0.0076) and ZnO NPs (P=0.0018) significantly increased $Fe^{2+/3+}$ level in the hippocampus of non-restraint animals after 30 min.Also stress increased $Fe^{2+/3+}$ level in all duration after 30 min (ST 90 and 180 min (P<0.001) and ST 360 min (P<0.05)) and decreased it after 120 min. In the restraint animals MgO NPs decreased $Fe^{2+/3+}$ level after 120 min in compared with 30 min (P=0.0012). On the other hand, ZnO

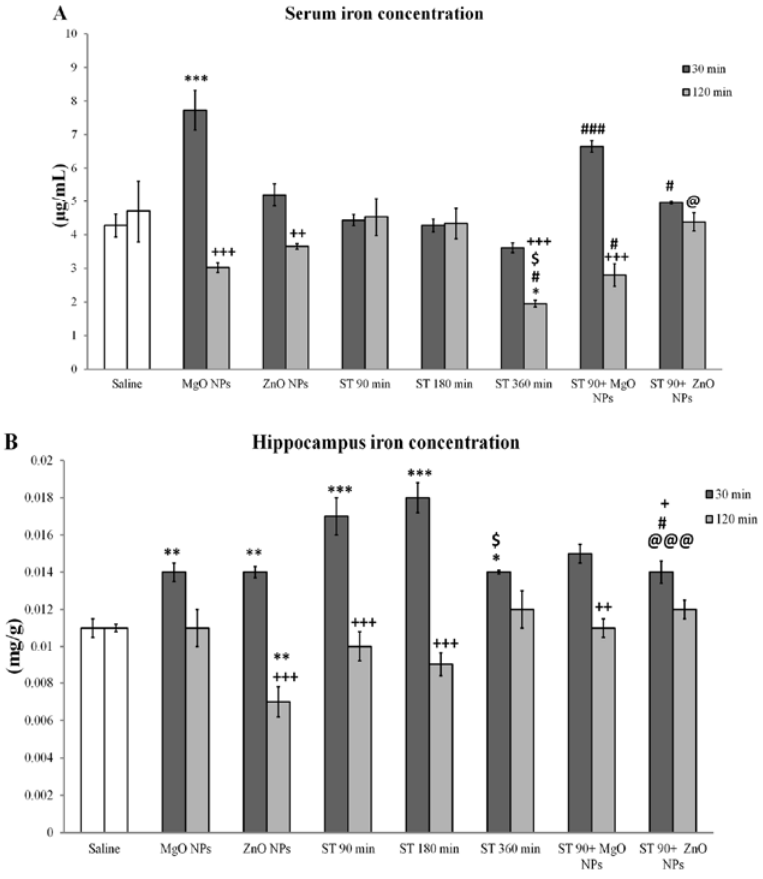

Fig. 4. Assessment of $Fe^{2+/3+}$ concentration. *P<0.05, **P<0.01 and ***P<0.001 are in comparison with the control group at the same time (30 and 120 min). +P<0.05, ++P<0.01 and +++P<0.001 are differences between equal treatment groups in two different times (30 and 120 min). #P<0.05and ###P<0.001 are differences in comparison with ST 90 min groups at the same time (30 and 120 min). $P<0.05 is a significant difference in comparison with ST 180 min group at the same time (30 and 120 min). @P<0.05 and @@@ P<0.001 are differences in comparison with ZnO NPs group at the same time. All bars are means ± standard error of the means.

NPs significantly decreased $Fe^{2+/3+}$ level in the non-restraint (P=0.0031) after 120 min (Fig. 4B).

According to these results, it seems that acute injection of both nanoparticles could change *the* $Fe^{2+/3+}$ balance in two of measurement sites and stress influences their effects.

Assessment of Ca^{2+} concentration

In the serum, MgO NPs increased Ca^{2+} concentration after 30 min (P=0.0106), while ZnO NPs increased it after 120 min (P=0.012). The ST 90 min significantly decreased Ca^{2+} in 120 and 30 min after induction (P<0.01), while ST 360 min increased it and was significant after 30 min (P<0.05). In the restraint animals, MgO NPs was increased Ca^{2+} level after 30 min and decreased it after 120 min (P<0.0001), while in these animals ZnO NPs was increased Ca^{2+} level in both times after injection (30 min (P<0.0001) and 120 min (P=0.0021)). Also, in MgO NPs (P=0.0002) and ZnO NPs recipients groups stress had negative effect on calcium level and decreased it in comparison with nanoparticles injections alone after 120 min (P=0.0106).

MgO NPs significantly was increased Ca^{2+} level in the hippocampus, after 120 min (P=0.008), while ZnO NPs increased it after 30 min (P=0.0054) (Fig. 5 A and B). Stress in all duration increased Ca^{2+} level after 30 min and it was significant in the ST 180 min group (P=0.037). In the restraint animals, MgO NPs decreased Ca^{2+} level after 30 min (P=0.0105), while ZnO NPs decreased it after 120 min (P=0.0042) (Fig. 5B).

Based on these findings, MgO NPs and ZnO NPs effects on Ca^{2+} level balance, in the restraint and non-restraint rats, were completely adverse in two different acute times.

Assessment of Pearson correlation between ions concentration in two acute times (30 and 120 min)

Data on Table 1 show that there were significant

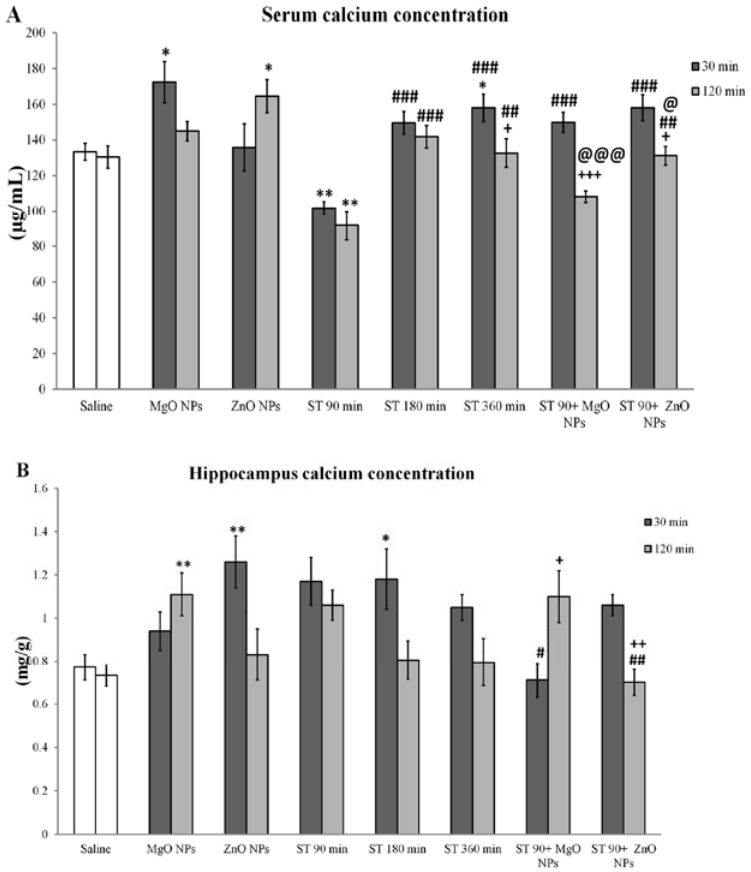

Fig. 5. Assessment of Ca^{2+} concentration. *P<0.05 and **P<0.01 are differences in comparison with the control group at the same time (30 and 120 min). +P<0.05, ++P<0.01 and +++P<0.001 are differences between equal treatment groups in two different times. #P<0.05, ##P<0.01and ###P<0.001 are differences in comparison with ST 90 min groups at the same time (30 and 120 min). @P<0.05 and @@@P<0.001 are differences in comparison with MgO NPs or ZnO NPs groups at the same time. All bars are means ± standard error of the means.

Table 1. Pearson correlation between elements contents at the two times

A	In the serum											
Groups	Saline		ST 90, 180 and 360 min+ saline		MgO NPs		ZnO NPs		ST 90 min+ MgO NPs		ST 90 min+ ZnO NPs	
Elements	R	P	R	P	R	P	R	P	R	P	R	P
Mg^{2+}	0.672	0.14	-0.14	0.574	0.258	0.621	0.221	0.674	0.316	0.541	0.211	0.689
Zn^{2+}	0.754	0.08	-0.29	0.242	0.424	0.402	-0.700	0.122	0.087	0.869	0.065	0.903
$Fe^{2+/3+}$	-0.39	0.44	0.607	0.008**	0.441	0.381	-0.673	0.143	-0.015	0.978	-0.700	0.122
Ca^{2+}	-0.52	0.28	0.626	0.005**	-0.532	0.277	0.225	0.669	-0.569	0.238	-0.509	0.303
B	In the hippocampus											
Groups	Saline		ST 90, 180 and 360 min+ saline		MgO NPs		ZnO NPs		ST 90 min+ MgO NPs		ST 90 min+ ZnO NPs	
Elements	R	P	R	P	R	P	R	P	R	P	R	P
Mg^{2+}	0.417	0.41	0.186	0.461	0.39	0.442	0.230	0.661	0.392	0.442	0.356	0.488
Zn^{2+}	0.147	0.78	0.043	0.865	0.30	0.556	0.214	0.684	-0.060	0.910	0.170	0.748
$Fe^{2+/3+}$	-0.57	0.22	-0.47	0.04*	-0.79	0.057	-0.313	0.545	-0.370	0.471	0.661	0.153
Ca^{2+}	0.275	0.59	-0.16	0.511	0.80	0.052	0.844	0.035*	-0.550	0.258	0.471	0.346

*=P<0.5 and **=P<0.01

positive correlations between both of $Fe^{2+/3+}$ (R=0.0607, P=0.008) and Ca^{2+} (R=0.626, P=0.005) level changes in the serum, 30 and 120 min after stress induction. There was a negative correlation between $Fe^{2+/3+}$ contentof the hippocampus in two different times after stress induction (R=-0.471, P=0.049).Also, in ZnO NPs group there was a positive correlation between Ca^{2+} level changes in the hippocampus, at two different acute times (R=0.844, P<0.035).

Results have indicated that efficacy of MgO and ZnO NPs on ions level changes in the serum and hippocampus could be different with passing the time. Since metal oxide nanoparticles are dissolved easily in acidic environments, probably ZnO NPs can dissolve in the lysosomes and release Zn^{2+} ions [18, 24, 25].This is a possible way to increase of Mg^{2+} and Zn^{2+} in the serum during the times after nanoparticles injections.Oxide salts are less reactive and release of ions from them is slow [26]. Previously we have indicated that Zn^{2+} concentration increased in the serum of male rats following injection of ZnO NPs and conventional ZnO and retention of Zn^{2+} ions in the serum of ZnO NPs group was higher than conventional ones after 24 hours; so that probably in the rat body ZnO NPs clearance was less than conventional forms [22]. This retention of nanoparticles in the body can affect their efficacy with passing the time.

Injections of nanoparticles could change the balance of elements too. Magnesium is a natural Ca^{2+} antagonist and can regulate Ca^{2+} channels with an important role in the active transport of Ca^{2+} ions through the cell membranes [27, 28]. On the other hands, there is a divalent metal transporter 1 that transports divalent metals including Mg^{2+}, Zn^{2+} and Ca^{2+} by a proton-coupled mechanism [29]. Some Zn^{2+} transporter proteins can facilitate non-transferrin bound $Fe^{2+/3+}$ -mediated delivery in cultured cells and similar trans membrane pores conduct $Fe^{2+/3+}$ and Ca^{2+} through the membranes [6]. Consumption of a Ca^{2+} supplement decreased the total $Fe^{2+/3+}$absorption, primarily by reducing the initial uptake of heme $Fe^{2+/3+}$[30]. Transferrin receptor (TfR)-mediated $Fe^{2+/3+}$ transport by the blood-brain-barrier and$Fe^{2+/3+}$ concentration ishigh in the hippocampus of the normal brain and TfR in the cerebral endothelial of the hippocampus is about 3–7 folds higher than in the cortex [31].

All of these studies indicated that MgO NPs and ZnO NPs could affect the balance of other elements in the serum and hippocampus, it's while maybe nanoparticles directly change the balance of elements, that this needs too more investigation.At the following results have indicated that restraint stress has different effects on elements changes in the serum and hippocampus depend on the acute time passing after stress induction.

Karakoc and et al. (2003) have shown that acute immobilization stress causes endogenous Zn^{2+} release from the brain and may enhance production of the brain iron transport proteins [1]. In all over the world iron deficiency anemia is a popular nutritional deficiency anemia and it has been reported that Zn^{2+} supplementation prevents stress effects and a stress-induced decrease in $Fe^{2+/3+}$ level [32, 33]. However, usage of a modest Zn^{2+} supplement induce a cellular $Fe^{2+/3+}$ deficiency and

probably further reduce of the $Fe^{2+/3+}$ statue [34].

Also, it has been shown that in the rat hippocampus stress increases Ca^{2+} current amplitude [35]. In this study MgO NPs and ZnO NPs could improve $Fe^{2+/3+}$ and Ca^{2+} concentration changes in the serum and hippocampus following stress induction and their effects depend on the acute time passing after injection.

CONCLUSION

It seems that rather than the elements level changes by nanoparticles, the efficacy of MgO and ZnO NPs on ions level imbalance induced by restraint stress depend on the acute time passing after stress induction. But more investigation needs to find exact effects of nanoparticles on body ions balance in healthy and stressful situations as well as in different acute and chronic times.

ACKNOWLEDGMENT

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CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest.

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