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Research Paper:

The Effects of Pentoxifylline on Memory in Male Rats Treated with Zinc Oxide NPs

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ABSTRACT

Background: Zinc oxide Nanoparticles (NPs) present irreversible effects on the nervous system, memory, and learning.

Objective: The current study aimed to investigate the effects of pentoxifylline on memory impairments, CA1 hippocampal pyramidal cells, and blood serum antioxidant enzymes in male rats treated with zinc oxide NPs.

Methods: Male Wistar rats were divided into the control, zinc oxide NPs (1.25 mg/kg), pentoxifylline (50 mg/kg), and pentoxifylline with zinc oxide NPs groups. In all study groups, saline, zinc oxide NPs, and pentoxifylline were intraperitoneally injected 30 minutes before training. In the co-treatment group, pentoxifylline was injected one hour before injecting Zno NPs. After performing the behavioral test, the tested animals' brains were fixed and the number of healthy neurons in the CA1 region of the hippocampus was counted. In all research groups, malondialdehyde levels, total antioxidant power, superoxide dismutase levels, and glutathione peroxidase in blood serum were measured.

Results: Zinc oxide nanoparticles decreased memory and the number of healthy neurons in the CA1 region of the hippocampus and increased oxidative stress in blood serum, compared to the controls. In the co-treatment group, using pentoxifylline improved the above-mentioned factors and reached the level of the control group. Pentoxifylline alone presented no significant effect on the aforementioned characteristics, compared to the control group.

Conclusion: ZnO NPs may decrease memory retrieval and cause cell death in the pyramidal neurons of the CA1 region of the hippocampus by increasing oxidative stress. Pentoxifylline, as a potent antioxidant, can prevent the harmful effects of ZnO NPs.

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1. Introduction

Memory is the ability to learn and retrieve the information and events that have been previously learned. The learning process can facilitate interneural communication by cellular stimulation and molecular modifications; it is the basis of information stored in the memory network [1].

Inhibitory avoidance task is a test used to evaluate learning as well as short-term and long-term memories in laboratory animals. Evidence suggests that the hippocampus plays a key role in inhibitory avoidance consolidation. However, numerous modulatory systems, originating from various parts of the brain, enter the hippocampus and affect inhibitory avoidance memory [2].

With the development of new industries, harmful compounds tend to enter the environment; in some cases, their effects are irreparable on human health and the environment. Nanoparticles metal oxides are vastly used in industrial and domestic practices. Zinc nanoparticles are applied in various industries, such as the food industry, pharmaceutical and sanitarian industries, e.g., toothpaste and sunscreen production, textiles, rubber manufacturing, electronic industries, and so on [3]. Special photoelectric properties of zinc oxide nanoparticles make them appropriate for the gas sensors, gas turbine receptors, visible and UV lasers, and oxidized conductive envelopes with high conductance for solar cells [4]. Given their unique features, zinc oxide nanoparticles are among the main medicinal compounds, i.e., used extensively. For instance, they can be used as drug carriers; agents stimulating enzymes; some neurotransmitters, like serotonin and GABA (gamma-Aminobutyric acid), antimicrobials in antibacterial drugs, and recently, as analgesics [4]. Additionally, for their small sizes, zinc oxide nanoparticles pass through the blood-brain barrier, enter the brain cells; eventually, they present destructive effects on different parts of the nervous system. Zinc oxide nanoparticles can cause apoptosis in pyramidal neurons in the CA1 region of the hippocampus. Such a process leads to decreased memory retrieval by increased oxidative stress [5].

Pentoxifylline was known as a vasodilatory agent used for treating vascular disorders in the mid-60s. This drug is a member of the methylxanthine group and inhibits xanthine oxidase. Xanthine oxidase is among the cellular detrimental molecules which facilitate free radical production [6]. Pentoxifylline has been used to treat infertility for increasing the testes' blood flow. It also inhibits the phosphodiesterase enzyme and enhances cellular cAMP and ATP; ultimately, it promotes sperm motility [7]. Pentoxifylline is an effective treatment in apoptosis. This aim is achieved by affecting cellular and vascular events and inhibiting inflammatory cells. Accordingly, this process leads to the attenuating inflammatory storms of cytokines includinginterlukine-1α, interlukine-8, interlukine-6β and tumor necrosis factor–α, as well as growth factors [8].

It has been demonstrated that zinc oxide nanoparticles are closely associated with human health status. These nanoparticles can enter the brain and present irreparable effects on the nervous system, memory, and learning. To reduce their detriments, using antioxidants as a therapeutic strategy, can be essential. Pentoxifylline has a remarkable capability in clearing Reactive Oxygen Species (ROS). Furthermore, ample evidence has revealed that antioxidants provide a potent impact on various disorders. The present study aimed to investigate the effects of pentoxifylline on memory dysfunction, pyramidal cells in the CA1 region of the hippocampus, and serum antioxidant enzymes in male rats treated with zinc oxide nanoparticles.

2. Materials and Methods

This original study was conducted in the Faculty of Sciences of Arak University in 2018-2019. Moreover, Wistar male rats (prepared in Iran Pasteur Institute) weighing 220-250 gr were used in this research. The explored animals had access to a day-night period of 12 h (day starts at 7 AM), the temperature of 22±2°C, and the experiments were performed at a specific time of the day. The study groups included control, zinc oxide nanoparticles (1.25 mg/kg), pentoxifylline (50mg/kg), and co-treated group pentoxifylline+zinc oxide nanoparticles. In this study, all ethical rules, approved by Arak University were considered.

The memory evaluator device was made of plexiglass (manufactured by Tehran Borjsanat Company) with two separate rooms including dark (20×20×30 cm) and bright (20×20×30 cm) sides; they were connected by a guillotine door (7×9 cm) placed in the medial wall. At the bottom of the dark side, there were metal bars with 2.5 mm diameter. When the device was turned on, 1 mA electricity was appointed for 3 seconds in dark side metal bars.

A passive avoidance learning test was conducted by step-through latency over two days. On the training day, each examined animal was firmly put on the bright

side of the device and the guillotine door was opened after 5 seconds. The entered time to the dark side was recorded. The explored rats with >100 seconds delay were excluded from the experiment. The trends were repeated after 30 minutes; however, this time, after entering the dark side, the door was closed and the study animal's feet were stimulated by an electric shock for 3 seconds. Then, the examined animal was picked up and transferred to its cage. These steps were repeated after two minutes. If the animal entered the dark side in <120 seconds, it would receive electrical shock for the second time (but with less intensity). Otherwise, passive avoidance learning was formed in the animal's memory. On the test day (24 hours later), the animal was placed on the bright side of the device. Accordingly, after 5 seconds, the guillotine door was opened and the animal's Step-Through Latency (STL) was recorded as a criterion for memory retrieval. The maximum latency time was considered 300 seconds. The animal received no shock on the test day [5].

Zinc oxide nanoparticles (manufactured by Tecnan in Spain with 99.9% purity and particle size of 20-30 nm) were solved in the 0.9% physiologic serum. This measure was performed 30 minutes before the experiment with the dose of 1.25 mg/kg/day; before each injection, it was diffused with an ultrasonic bath and re-mixed with a shaker device for one minute [5]. Pentoxifylline (Sigma Aldrich, made in Germany) was also dissolved in normal saline at a concentration of 50 mg/kg [9].

The injections occurred Intraperitoneally (IP) half an hour before the learning phase of the experiment. In the pentoxifylline+zinc oxide nanoparticles group, initially, the pentoxifylline, then 60 minutes later, the zinc oxide nanoparticles were injected into the peritoneum. Besides, 30 minutes later, the learning phase began. After performing the memory test, the study animals in each group were randomly divided into two groups (n=6/group). One group was used for blood tests and another group underwent cerebral perfusion and tissue studies.

For the perfusion study, first, 0.9% physiologic serum, then, the 40% paraformaldehyde solution was injected in the examined animal's left ventricle. This measure was conducted after the animal was anesthetized and the right atrium was cut with a scissor to expel the blood. After fixing the brain, the following steps were taken: tissue passage, hippocampus CA1 sectioning with a microtome device, hematoxylin-eosin staining, and observation by a light microscope. Images of the samples were randomly captured in ≥4 visual fields in each lam. Then, normal and necrotized neurons were counted by Image J software [10].

After the bleeding, blood serum was separated by centrifuge (Universal model, made in Germany); it was divided as necessary and frozen at -80°C. Thiobarbituric Acid (TBA) method was used to measure the amount of lipid peroxidation. In this method, aldehydes entered a reaction with thiobarbiturate and formed pink complexes. This complex can be measured by spectrophotometry in 535 nm wavelength [11]. To measure the antioxidant capacity of the whole plasma, Benzic et al.'s method was applied. In this method, a blue complex was formed by reducing ferric to ferru in acidic pH with the presence of specific reagents. This complex could be measured in 593 nm wavelengths [12]. Superoxide dismutase level was also measured by a compound, called Pyrogallol. Pyrogallol can be rapidly autoxidized in an aqueous or alkali solution. Superoxide dismutase enzyme can prevent this autoxidation; subsequently, it would be used for measuring this enzyme's level in 240 nm [13]. Glutathione peroxidase activity was measured by Rotrac et al.'s method. In this approach, this enzyme is simultaneously oxidized and hydrogen peroxide is reduced to water. This reaction results in the formation of a colored compound which can be measured by spectrophotometer in a 420-nm wavelength [14].

Data analysis of behavioral experiments was performed by SPSS v. 16. The significance level was determined by the one-way Analysis of Variance (ANOVA) and Tukey's test. Tissue examination data were analyzed by Prism using one-way ANOVA. The significance level was considered at $P<0.05$.

3. Results

One-way ANOVA and Tukey's test results revealed a significant difference [$F(3,36)=185.54$, $P<0.001$] in STL between the experimental groups. Injecting zinc oxide nanoparticles(1.25 mg/kg), 30 minutes before the learning phase, reduced the time for entering the dark side of the device (Figure 1) ($P<0.001$), compared with the control group that demonstrated reduced levels of memory. Tukey's test data indicated that injecting pentoxifylline (50 mg/kg), an hour before the injection of zinc oxide nanoparticles, can significantly increase STL (Figure 1) ($P<0.001$), compared with zinc oxide nanoparticles alone. In other words, pentoxifylline could compensate for the memory deficiency caused by the injection of zinc oxide nanoparticles in the controls. The data of the injection of pentoxifylline alone revealed no differences in STL, compared with the control group ($P<0.05$).

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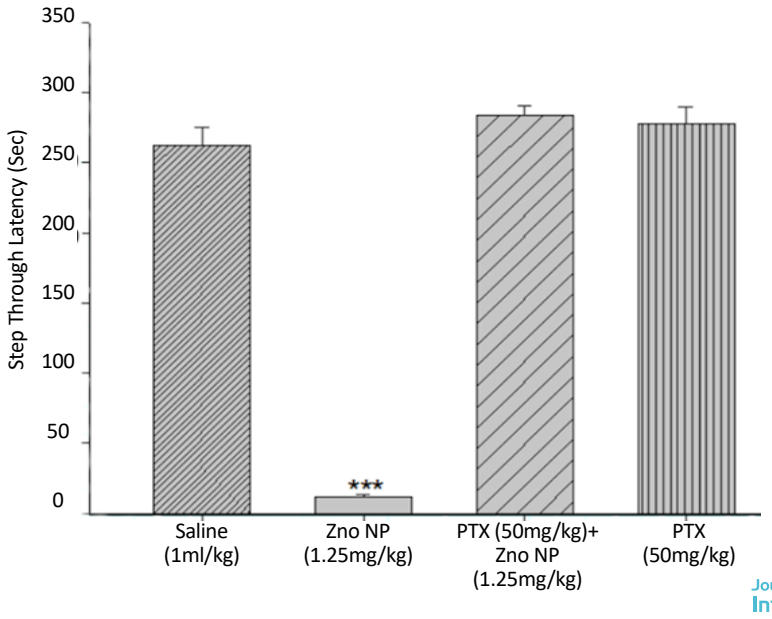

Figure 1. Effect of zinc oxide nanoparticles and pentoxifylline on memory retrieval, compared with the control group

Zinc oxide nanoparticles reduced STL, compared with the control group. Injecting pentoxifylline an hour before the injection of zinc oxide nanoparticles, significantly increased STL, compared with the zinc oxide nanoparticles group. Injecting pentoxifylline alone presented no difference in STL, compared with the control group. The obtained results are expressed as Mean±SEM by one-way ANOVA and Tukey's test for 12 animals. Statistical analysis was performed using one-way ANOVA followed by Tukey's posthoc test (***P<0.001).

Tissue sections attained from the samples of the control group demonstrated that the neurons in the CA1 region of the hippocampus are spherical cells with the nucleus in the middle of them and the density of the neurons is very high in this region (Figure 2-A). However, these neurons were necrotized and transformed in the rats receiving zinc oxide nanoparticles (1.25 mg/kg) and the density of the neurons was significantly reduced in this region, compared with the controls (P<0.001) (Figure 2-B). Tissue sections from the pentoxifylline (50 mg/kg)+zinc oxide nanoparticles (1.25 mg/kg) group signified that the number of normal neurons in the tissue section of hippocampus CA1 was significantly increased, compared with the group that only received zinc oxide nanoparticles (P<0.001) (Figure 2-C). Nevertheless, the number of normal neurons in this region of the brain presented no significant difference in the group that only received pentoxifylline (50 mg/kg) (P>0.05) (Figure 2-D).

Counting the healthy neurons in the hippocampus CA1 region in the tissue sections of different groups suggested that the number of these neurons was significantly reduced in the group receiving zinc oxide nanoparticles (1.25 mg/kg), compared to the controls (P<0.001). In the group receiving pentoxifylline+zinc oxide nanoparticles (50 mg/kg & 1.25 mg/kg, respectively), injecting pentoxifylline, 60 minutes before the injection of zinc oxide nanoparticles, significantly increased the number of healthy neurons, compared with the group that only received zinc oxide nanoparticles (P<0.001). The number of healthy neurons in the CA1 region of the hippocampus in the group of pentoxifylline alone indicated no significant difference, compared with the controls (P>0.05) (Figure 3).

The one-way ANOVA data indicated that the IP injection of zinc oxide nanoparticles (1.25 mg/kg) significantly increased the amount of malondialdehyde [F(3,20)=2.367, P<0.001] and decreased total antioxidant capacity [F(3,20)=5.675, P<0.001]; this measure also decreased the level of superoxide dismutase enzyme [F(3,20)=460.311, P<0.001] and glutathione peroxidase [F(3,20)=239.225, P<0.001] in the blood serum, compared with the controls (P<0.001). The IP injection of pentoxifylline (50 mg/kg) 60 minutes before the injection of zinc oxide nanoparticles (1.25 mg/kg) significantly decreased the amount of malondialdehyde; it also increased the total antioxidant potency and the levels of the enzymes superoxide dismutase and glutathione peroxidase in the blood serum, compared with the group that only received zinc oxide nanoparticles (1.25 mg/kg). Moreover, these results were similar to those of the control group. Injecting pentoxifylline alone (50 mg/kg) did not significantly change the blood serum properties, compared with the control group (P>0.05) (Table 1).

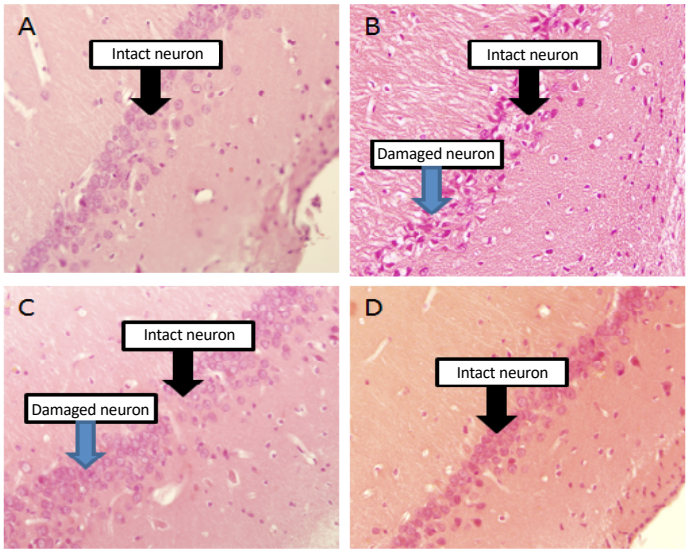

Figure 2. Tissue sections of CA1 pyramidal neurons in experimental groups

A: Control group; B: Zinc oxide nanoparticles group; C: The group treated with pentoxifylline+Zinc oxide nanoparticles; and D: The group that only received pentoxifylline. Black arrows illustrate intact cells and red arrows present degenerating pyramidal cells. Hematoxylin-eosin staining, original magnification ×40.

4. Discussion

The present study data indicated that the IP injection of zinc oxide nanoparticles, half an hour after the training, decreased STL and caused memory destruction on the test day, compared with the controls. Previous studies supported the results obtained from this study. The IP injection of zinc oxide nanoparticles reduced memory and learning in the passive avoidance learning model in a dose-dependent manner [5]. Zinc oxide nanoparticles decreased special cognition destruction in the hippocampus and significantly reduced the time for stepping down from the platform in the step-down model [15]. Acute and chronic exposure to zinc oxide nanoparticles resulted in abnormal cognitive function and pathologic neuronal changes in the hippocampus [5, 15-18].

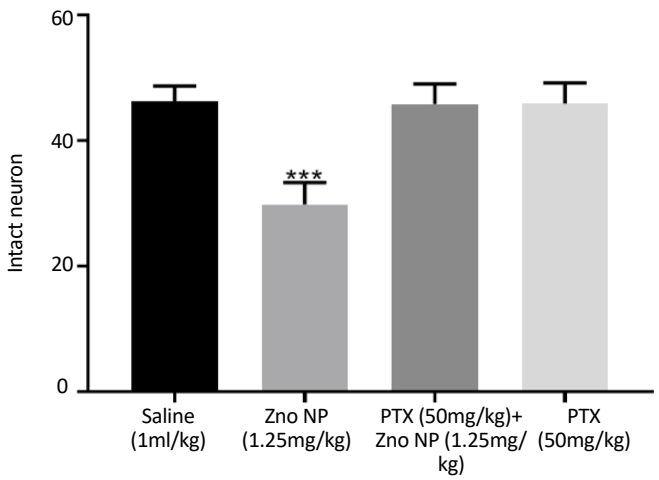

Figure 3. Neuron density in the CA1 area of the hippocampus in the brains of all study samples

In the group of zinc oxide nanoparticles, the number of intact neurons significantly decreased, compared with the control group. In the group of pentoxifylline+zinc oxide nanoparticles, the number of intact neurons significantly increased, compared with the zinc oxide nanoparticles group. The number of normal neurons in the CA1 region of the hippocampus in the group of pentoxifylline alone indicated no significant difference, compared with the control group. The collected results are expressed as Mean±SEM for 12 study animals. Statistical analysis was performed using one-way ANOVA followed by Tukey's posthoc test (***P<0.001).

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Table1. Comparison of serum analysis in the experimental groups

Groups / Factor	Mean±SD			
	Saline (1 mL/kg)	Zno NP (1.25 mg/kg)	PTX+Zno NP (50mg/kg+1.25 mg/kg)	PTX (50 mg/kg)
MDA (nmol/mL)	1.919±0.024[a]	12.59±0.188[b]	2.29±0.093[a]	1.59±0.047[a]
FRAP (mmol/L)	1.64±0.009[a]	0.23±0.014[b]	1.62±0.003[a]	1.64±0.004[a]
SOD (U/ml)	1.541±0.048[a]	0.133±0.024[b]	1.44±0.022[a]	1.618±0.028[a]
GPX (U/L)	38.59±1.054[a]	15.82±0.467[b]	36.66±0.467[a]	38.98±0.733[a]

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The values with different superscript letters within the same row significantly differ at P<0.001. Malondialdehyde (MDA); total antioxidant capacity (TAC) of Plasma; Ferric Reducing Ability of Plasma (FRAP); superoxide dismotase (SOD); glutathione peroxidase (GPX).

Additionally, in this study, the injection of pentoxifylline, one hour before the injection of zinc oxide nanoparticles, increased STL. Besides, it could compensate for memory deficiency caused by injecting zinc oxide nanoparticles into the controls. Injecting pentoxifylline alone suggested no significant change, compared to the control group. Consistent with our results, some investigations revealed that pentoxifylline can ameliorate the animals' learning ability and oxidative stress in the brain hippocampus in adult male Swiss rats [19]. Pentoxifylline can reduce the severity of the hippocampus CA1 legions by anti-edema and protective effects and ameliorates motor neurological defects in the acute phase of temporary cerebral ischemia in rats [20]. Pentoxifylline can ameliorate learning and memory caused by glutamate damage in rats [9].

In this study, the number of healthy neurons in the hippocampus CA1 in the tissue sections presented a significant decrease in the group receiving zinc oxide nanoparticles, compared with the controls. In the zinc oxide nanoparticles+pentoxifylline group, a significant increase was observed in the number of healthy cells in the tissue section. Pentoxifylline alone revealed no significant effect on the number of healthy neurons in the CA1 region of the hippocampus, compared with the control group. Previous studies also supported the present study data. Zinc oxide nanoparticles caused apoptosis in the pyramidal neurons of the hippocampus CA1 region [5]. The IP injection of zinc oxide nanoparticles reduces memory by neuronal destruction in the CA3 and DG region of the hippocampus [15]. The IP injection of pentoxifylline can ameliorate the destruction of the pyramidal neurons in the hippocampus CA1 region in cerebral ischemia and elevate the number of these cells in ischemic rats [20]. Pentoxifylline can recover the destruction of the hippocampal neurons caused by high-dose glutamate [9].

In this study, zinc oxide nanoparticles enhanced the level of malondialdehyde and significantly decreased the total antioxidant potency, superoxide dismutase, and glutathione peroxidase enzyme in the blood serum, compared with the controls. Treatment with pentoxifylline, before the injection of zinc oxide nanoparticles significantly decreased the level of malondialdehyde and increased the total antioxidant potency and the mentioned enzymes in the blood serum, compared with the zinc oxide nanoparticles group. Injecting pentoxifylline alone provided no significant changes in the measured factors in the blood serum, compared with the control group. Similar studies also supported our results. Zinc oxide nanoparticles adversely impacted the level of antioxidant enzymes, like catalase and superoxide dismutase [5, 16, 21]. The obtained results indicated that zinc oxide nanoparticles, in high concentrations, can elevate the level of malondialdehyde, necrosis, fibrosis, and cellular lysis in the kidney tissue [22]. Pentoxifylline can significantly decrease oxidative stress and the level of malondialdehyde in the blood serum of diabetic rats, also in diabetic patients [23].

Zinc plays an essential role in synaptic transmission, gene regulation, structural maintenance, and enzymatic activity. Anxiety and cognitive disturbances occur along with zinc deficiency, followed by oxidative stress and changes in the enzymes in the brain. Zinc deficiency can activate NO synthase and mitochondrial dysfunction and oxidative stress. Moreover, zinc deficiency can impair memory and learning by reducing neurogenesis and increasing neuronal apoptosis [24]. Some studies represented that zinc consumption increases the neu-

rons' myelin; however, other investigations revealed that zinc accumulation can cause neuronal toxicity, oxidative stress, and cognition destruction. These conflicts might result from the difference between the doses used in these studies. Very low and very high amounts of zinc are related to oxidative stress; intermediate amounts present protective effects in the neurons [24].

Studies demonstrated that injecting zinc oxide nanoparticles causes an accumulation of zinc in the glutamatergic synapses and the inhibition of of n-methyl-d-aspartic acid receptors; ultimately, it leads to decreased long-term potentiation as well as acquisition and learning [25]. LTP inhibition can also be attributed to the blockage of the calcium channels in the synaptic clefts which decreases the amplitude of EPSP (excitatory postsynaptic potential). By affecting the postsynaptic receptors, an increase in the concentration of zinc and glutamate can cause the entrance of positive ions, like zinc and calcium into the cell and trigger the apoptosis mechanisms [26]. Zinc oxide nanoparticles can decrease the integrity of the lipid membrane by lipid peroxidation; therefore, they lead to calcium influx deficiencies through the membrane [26]. Increased calcium concentration in the cell can result in the production of free oxygen radicals and nitrogen by activating the enzymes; accordingly, this process is followed by the thiol-dependent inactivation of the calcium pumps and intensifying calcium concentration in the cell. Free radicals and hypercalcemia result in severe primary metabolic defects; they eventually decrease ATP levels and cause apoptosis [27]. The exposure of cells to zinc oxide nanoparticles can activate JNK kinases and increase the production of TNF-α and IL-8. This increase in the proinflammatory cytokines results in apoptosis [28]. Zinc oxide nanoparticles can release zinc ions; therefore, they convert anionic superoxide into hydroxyl radicals and harm the DNA [29]. Furthermore, zinc oxide nanoparticles stimulate autophagy. This is performed by entering the lysosome and stimulating the production of free radicals. Autophagy can then destruct the antiapoptotic proteins or DNA repairing proteins, leading to cellular toxicity [30].

Pentoxifylline is a drug with various effects, including inhibiting Phosphodiesterase (PSES) and increasing cAMP; it can activate Protein Kinase A (PKA), stop the transcription of inflammatory and proinflammatory genes [31], and reduce the levels of TNF-α and IL-6. Moreover, it is useful for treating some autoimmune diseases, like rheumatoid arthritis, multiple sclerosis, and systemic lupus erythematosus [32]. Pentoxifylline can increase the intracellular cAMP level in various cells, such as mononuclear phagocytes, microglia, neutrophils, vascular smooth muscle, and endothelium; therefore, it affects gene transcription and presents protective effects by its anti-inflammatory properties, including inhibiting neutrophils and monocytes, activating microglia, and decreasing the production of inflammatory intermediates [33]. Studies indicated that pentoxifylline can cause antioxidant balance which can play an essential role in the prevention of the dysfunction caused by mitochondrial oxidative damage in the brain [34]. Pentoxifylline reduces platelet aggregation and fibrinogen. Pentoxifylline can prevent the peroxidation of lipids and decrease the superoxide dismutase and catalase activity caused by malathion in the liver of diabetic patients [35].

5. Conclusion

Numerous mechanisms were stated to be responsible for the memory impairment caused by zinc oxide nanoparticles; however, zinc oxide nanoparticles might cause a reduction in memory retrieval and increase the cellular toxicity and apoptosis in the hippocampus in response to the elevated levels of oxidative stress. Pentoxifylline, a potent antioxidant, can decrease the level of active oxygen species in the pyramidal neurons of the CA1 region and prevent the zinc oxide nanoparticles destructive effects. Therefore, if individuals are exposed to zinc oxide nanoparticles contaminants, their harmful effects can be prevented by the consumption of antioxidants.

Ethical Considerations

Compliance with ethical guidelines

This study obtained ethical approval from the Arak University of Medical Sciences (Code: IR.ARAKMU.REC.1398.142).

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Authors' contributions

Writing - original draft and Data analysis: Niloufar Darbandi and Zeynab Vasheghani Farahani; Writing - review & editing and Project administration: Niloufar Darbandi; Resources and review: Hamidreza Momeni.

Conflict of interest

The authors declared no conflicts of interest.

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References

[1] Ghadiri T, Modarres Mousavi SM, Alipour F, Mohammad Sadeghi Sh. Cellular and molecular pathways of learning and memory. Neurosci J Shefaye Khatam. 2014; 2(2):81-8. [In Persian] [DOI:10.18869/acadpub.shefa.2.2.81]

[2] Wright A. Limbic system: Hippocampus [Internet]. 2020 [Updated 2020 October 10]. Available from: https://nba.uth.tmc.edu/neuroscience/m/s4/chapter05.html

[3] Kesmati M, Torabi M, Ghandizadeh-Dezfuli M. Nanoparticles of zinc oxide reduces acute somatic pain in adult female wistar rats. Zahedan J Res Med Sci. 2014; 16(2):24-8. https://sites.kowsarpub.com/zjrms/articles/1714.html

[4] Cui Zh, Lockman PR, Atwood CS, Hsu CH, Gupet A, Allen DD, et al. Novel D-penicillamine carring nanoparticles for metal chelation therapy in Alzheimer's and other CNS diseases. Eur J Pharm Biopharm. 2005; 59(2):263-72. [DOI:10.1016/j.ejpb.2004.07.009] [PMID]

[5] Darbandi N, Khosravi S, Momeni HR. Effect of zinc oxide nanoparticles on memory retrieval, hippocampal CA1 pyramidal neurons and some serum oxidative stress factors in male Wistar rats. Stud Med Sci. 2018; 29(6):450-63. [In Persian] http://umj.umsu.ac.ir/article-1-4402-fa.html

[6] Tripathi R, Mishra DP, Shaha Ch. Male germ cell development: Turning on the apoptotic pathways. J Reprod Immunal. 2009; 83(1-2):31-5. [DOI:10.1016/j.jri.2009.05.009] [PMID]

[7] Kheradmand N, Soleimani Mehranjani M, Mahmoodi M. The effect of pentoxifyllin on histoligical change of testis and spermatogenesis indexes in mouse treated with dexamethasone. Qom Univ Med Sci J. 2019; 13(7):29-41. [In Persian] [DOI:10.29252/qums.13.7.29]

[8] Marrama P, Baraghini GF, Carani C, Celani MF, Giovenco P, Grandi F, et al. Further studies on the effects of pentoxifylline on sperm count and sperm motility in patients with idiopathic oligo-asthenozoospermia. Andrologia. 1985; 17(6):612-6. [DOI:10.1111/j.1439-0272.1985.tb01728.x] [PMID]

[9] Cunha GM, Bezerra PJ, Saldanha MD, Cavalcante MC, De Brun VM, Viana GS. Pentoxifylline improves learning and memory in glutamate-lesioned rats. Pharmacol Biochem Behav. 2000; 66(4):687-94. [DOI:10.1016/S0091-3057(00)00279-3] [PMID]

[10] Liu J, Wang A, Li L, Huang Y, Xue P, Hao A. Oxidative stress mediates hippocampal neuron death in rats after lithium-pilocarpine-inducedstatus epilepticus. Seizure. 2010; 19(3):165-72. [DOI:10.1016/j.seizure.2010.01.010] [PMID]

[11] Ramezani AR, Moonikh Kh. Effect of quercetin supplementation on oxidative stress and exhaustion in male soccer players. J Med Plants. 2017; 16(62):136-44. [In Persian] http://jmp.ir/article-1-1400-en.html

[12] Gohari AR, Hajimehdipoor H, Saeidnia S, Ajani Y, Hadjiakhoondi A. Antioxidant activity of some medicinal species using FRAP assay. J Med Plants. 2011; 10(37):54-60. http://jmp.ir/article-1-233-en.html

[13] Rukmini MS, D'Souza B, D'Souza V. Superoxid dismutase and catalase activities and their correlation with malondialdehyde in schizophrenic patients. Indian J Clin Biochem. 2004; 19(2):114-8. [DOI:10.1007/BF02894268] [PMID] [PMCID]

[14] Mohajeri D, Monadi AR, Kaffashi Elahi R, Neshat Gharamaleki M. Study on the protective effects of Quercetin on Methotrexate-induced small intestinal damage in the rat. J Comp Pathobiol. 2015; 12(2):1637-48. [In Persian] https://jcp.srbiau.ac.ir/article_7559.html

[15] Issapare N, Kesmati M, Mohammadi T. Comparison of the effects of pre-training administration of zinc oxide and zinc oxide nanoparticles on long-term memory of adult male mice. J Babol Univ Med Sci. 2016; 18(1):37-43. [In Persian-English] [DOI:10.22088/jbums.18.1.37]

[16] Tian L, Lin B, Wu L, Li K, Liu H, Yan J, et al. Neurotoxicity induced by zinc oxide nanoparticles: Age-related differences and interaction. Sci Rep. 2015; 5:16117. [DOI:10.1038/srep16117] [PMID] [PMCID]

[17] Han D, Tian Y, Zhang T, Ren G, Yang Z. Nano-zinc oxide damages spatial cognition capability via over-enhanced long-term potentiation in hippocampus of Wistar rats. Int J Nanomedicine. 2011; 6:1453-61. [DOI:10.2147/IJN.S18507] [PMID] [PMCID]

[18] Valipour Chahardahcharic S, Kesmati M, Vahdati A, Hoseini SE. The effects of acute administration of zinc oxidenanoparticles on long term memory in the presence and absence of vitamin C in adult male rat. Adv Environ Biol. 2014; 8(13):260-6. https://www.researchgate.net/publication/267032206

[19] Ahmad M, Abu-Taweel GM. Attenuating effects of pentoxifylline on memory, oxidative stress and monoamine levels in the hippocampus of seizure induced mice. J Adv Biol. 2014; 4(2):404-13. https://www.rajpub.com/index.php/jab/article/view/5578

[20] Panahi Khezri N, Nadia Sharifi Z, Shafaroodi H, Ansarian G, Movassaghi S. The effect of pentoxifylline on global ischemia/reperfusion induced spatial memory impairment in estrous phase of female Wistar rat. Med Sci J Islam Azad Univ Tehran Med Branch. 2014; 24(1):14-21. [In Persian] http://tmuj.iautmu.ac.ir/article-1-766-en.html

[21] Valipour-Chahardah-Charic S, Kesmati M, Vahdati A, Hoseiny SE. Oxidative stress indices in rat hippocampus using the memory deficit model induced by zinc oxide nanoparticles. Feyz. 2015; 19(1):38-46. [In Persian] http://feyz.kaums.ac.ir/article-1-2538-en.html

[22] Hosseini SM, Amani R, Razavimehr SV, Moshrefi AH, Aghajanikhah MH. Histopatologic and biochemical study of zinc oxide nanoparticles effect on renal tissue in rats. Sci J Ilam Univ Med Sci. 2018; 26(3):177-86. [In Persian] [DOI:10.29252/sjimu.26.3.177]

[23] Najar A, Piryae A, Babaei S, Bayat M. Effect of pentoxifylline on Sertoli and Leydig cells count of experimentally induced type 1 diabetes in male rats. Ann Mil Health Sci Res. 2013; 11(3):e65100. [In Persian] https://sites.kowsarpub.com/amhsr/articles/65100.html

[24] Hafez MH, Gad SB. Zinc oxide nanoparticles effect on oxidative status, brain activity, anxiety-like behavior and memory in adult and aged male rats. Pak Vet J. 2018; 38(3):311-5. [DOI:10.29261/pakvetj/2018.069]

[25] Takeda A, Fuke S, Ando M, Oku N. Positive mudolation of long-term potentiation at hippocampal CA1 synapses by low micromolar concentrations of Zinc. Neuroscience. 2009; 158(2):585-91. [DOI:10.1016/j.neuroscience.2008.10.009] [PMID]

[26] Huang CC, Aronstam RS, Chen DR, Huang YW. Oxidative stress, calcium homeostasis, and altered gene expression in human lung epithelial cells exposed to ZnO nanoparticles. Toxicol in Vitro. 2010; 24(1):45-55. [DOI:10.1016/j.tiv.2009.09.007] [PMID]

[27] Xiong D, Fang T, Yu L, Sima X, Zhu W. Effects of nano-scale TiO_2, ZnO and their bulk counterparts on zebrafish: Acute toxicity, oxidative stress and oxidative damage. Sci Total Environ. 2011; 409(8):1444-52. [DOI:10.1016/j.scitotenv.2011.01.015] [PMID]

[28] Xie Y, Wang Y, Zhang T, Ren G, Yang Zh. Effects of nanoparticle zinc oxide on spatial cognition and synaptic plasticity in mice with depressive-like behaviors. J Biomed Sci. 2012; 19(1):14. [DOI:10.1186/1423-0127-19-14] [PMID] [PMCID]

[29] Saliani M, Jalal R, Goharshadi EK. Mechanism of oxidative stress involved in the toxicity of ZnO nanoparticles against eukaryotic cells. Nanomed J. 2016; 3(1):1-14. https://nmj.mums.ac.ir/article_6191.html

[30] Scherzad A, Meyer T, Kleinsasser N, Hackenberg S. Molecular mechanisms of zinc oxide nanoparticle-induced genotoxicity short running title: Genotoxicity of ZnO NPs. Materials. 2017; 10(12):1427. [DOI:10.3390/ma10121427] [PMID] [PMCID]

[31] Donate-Correa J, Tagua VG, Ferri C, Martín-Núñez E, Hernández-Carballo C, Ureña-Torres P, et al. Pentoxifylline for renal protection in diabetic kidney disease. A model of old drugs for new horizons. J Clin Med. 2019; 8(3):287. [DOI:10.3390/jcm8030287] [PMID] [PMCID]

[32] de Oliveira Garcia FA, Rebouças JF, Balbino TQ, da Silva TG, de Carvalho-Júnior CHR, Cerqueira GS, et al. Pentoxifylline reduces the inflammatory process in diabetic rats: Relationship with decreases of pro-inflammatory cytokines and inducible nitric oxide synthase. J Inflamm. 2015; 12:33. [DOI:10.1186/s12950-015-0080-5] [PMID] [PMCID]

[33] Karimi J, Tavilani H, Ranjbar A. Ameliorative effect of pentoxifylline a phosphodiesterase-5 on acrolein induced oxidative damage. Zahedan J Res Med Sci. 2015; 17(9):e1060. [DOI:10.17795/zjrms-1060]

[34] Ranjbar A, Ghahremani MH, Sharifzadeh M, Golestani A, Ghazi-Khansari M, Baeeri M, et al. Protection by pentoxifylline of malathion-induced toxic stress and mitochondrial damage in rat brain. Hum Exp Toxicol. 2010; 29(10):851-64. [DOI:10.1177/0960327110363836] [PMID]

[35] Ranjbar A, Baeeri M. The effect of pentoxifylline on malathion-induced mitochondrial damage in rat liver. J Shahrekord Univ Med Sci. 2013; 15(4):83-92. [In Persian] http://78.39.35.44/article-1-1331-en.html

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