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Original Article:

Effects of Chronic Administration of Nickel on Memory Function, Hippocampal Neuronal Morphology and Oxidative Stress Factors in Male Adult Rats

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Abstract

Introduction: Nickel (Ni) is a toxic heavy metal that can damage the brain structure, especially the hippocampus which is an important complex brain structure with a major role in memory and learning. Recent studies showed that heavy metals can alter some brain functions and disrupt hemostasis in central nervous system (CNS). The role of chronic Ni administration on memory and leaning, survival of neurons in CA1 hippocampus and the level of oxidative stress marker in rats.

Materials and Methods: In total 24 rats (n=6) were allocated to four groups: Group (I): vehicle received intraperitoneal (IP) normal saline (0.9% NaCl), Group (II, III ,IV): received 0.25 mg/kg, 0.5 mg/kg and 1 mg/kg IP NiCl2 for eight weeks, respectively. During this timespan, the rats were examined in the Morris water maze and novel object recognition test to evaluate memory and learning. Finally, the hippocampus of the rats was extracted and survived neurons were evaluated by Nissl staining; oxidative stress was determined using malondialdehyde (MDA) level and catalase enzyme activity.

Results: Results showed that dose-dependent Ni administration decreased memory and leaning in behavioral studies and caused degenerative and morphological changes in neurons by elevating MDA and catalase enzyme activity as the most important oxidative stress markers.

Conclusion: Ni induces changes in the structure of hippocampal neurons and disrupts memory and learning function in hippocampus in adult rats by an increase in oxidative markers.

Keywords: Heavy metals, Hippocampus, Memory, Nickel, Oxidative stress

1. Introduction

Nickel (Ni) is a key element to have a healthy life [1, 2]. It is a trace element in the body that plays crucial physiological roles such as immunity, cell division, protein synthesis, glucose and lipid metabolism, reproduction, growth and an essential cofactor for many enzymes [1, 3] However, a high level of Ni causes many health problems because of toxicity of the liver, lungs, brain, and kidneys [4]. Recent studies on animals have indicated that being exposed to high levels of Ni can affect CNS, especially animal memory and behavior [5-7]. Ni is abundant in water, soil and air. Hemostatic imbalance of Ni, either as Ni overload or deficiency, can be a source of danger for human health[8, 9]. Recent studies have indicated that high Ni

concentration is found in industrial waste water which can enter ground or surface waters [10, 11]. There is also a high Ni concentration in polluted air that can enter human body by inhalation [12, 13]. Therefore, in some regions, people receive high doses of Ni through environment factors [14, 15]. In vicinity to nickel mines, the levels as high as 200 µg/litre have been measured in drinking-water that can be hazardous for human health [16]. Ni may disrupt many physiological functions and cause anemia, dysfunction of enzymes, gastric irritation, and disrupt glucose and lipid metabolisms [17, 18]. Cytogenic studies also showed Ni is possibly carcinogenic to humans [19]. It can pass through blood-brain barrier (BBB) and cause dysfunction of different parts of CNS [20, 21]. Recent studies revealed that there is a direct connection between nickel exposure during life and increased risk of CNS disorders like Parkinson's or Alzheimer's disease [22, 23]. Ni can create neurological diseases like Parkinson's and Alzheimer's diseases, and vascular dementia [24]. Many studies reported an increase in neurodegenerative disorders in the youth living in regions with high Ni concentrations in drinking water [25-27]. Unfortunately, there are few studies on the impact of environmental factors on CNS and its associated disorders. For this reason, the effects of consuming high levels of Ni on memory function, hippocampus neuron structure and oxidative stress factors in rats were assessed in this study.

2. Materials and Methods

Animals

Twenty-four rats (weight: 200-250 gm) were used in this study. They were kept in light/dark cycle (12h) under controlled temperature condition. There rats received adequate water and food. The Ethics Committee at Tehran University of Medical Sciences (ID: IR.TUMS.MEDICINE.REC.1398.745) approved the study. The rats were assingned to four groups (n = 6 per group). Group (I): vehicle received intraperitoneal (IP) normal saline (0.9% NaCl), Group (II, III ,IV): received 0.25 mg/kg, 0.5 mg/kg and 1 mg/kg $NiCl_2$ (Sigma-Aldrich, St. Louis, MO, USA) respectively dissolved in 0.9% Nacl through single intraperitoneal daily injection for 8 weeks [28]. After 8 weeks, behavioral studies were conducted. Afterwards, three randomly selected rats were anesthetized intraperitoneally using Xylazine (5 mg/kg) and ketamine (90 mg/kg) and then the brains were extracted and kept at -70 °C for measuring oxidative stress. In order to evaluate the histochemistry of hippocampal tissue, three other rats from each group for transcardial perfusion using normal saline. In addition, 10% formaldehyde solution was utilized for fixing the brain tissues. Afterwards, the brains were extracted and kept in 10% formaldehyde solution at room temperature for 24 hours.

Novel Object Recognition Test for Evaluating Recognition Memory in Rats

One of the standard methods to examine recognition memory of rats is novel object recognition test. It is designed based on the instinctive responses of rats which are interested in having more time examining new objects. This test was carried out in three stages, namely 1- habituation, 2- training, and 3- testing. In the first stage, the rats were placed in a box (30×70×70 cm) every day for five minutes to habituate to the test environment. In the second stage, the animals were placed alone in a box containing two objects each on one corner at the same distance from the animal and the animals were given five minutes to examine the objects. The animals were brought back to the box once more after 1 hour, where a new object had replaced one of the objects with the same height and different shape and color. At this stage, the time for examining each item was measured using a chronometer [29, 30]. Eventually, for each object the preference index was determined (novel and familiar objects) as follows:

$$PI = \frac{T_N}{T_N + T_F} \times 100$$

where, T_N represents time spent exploring a new object; T_F represents the time spent examining a familiar object):

Detection of Survival Neurons in Hippocampus by Cresyl Violet Staining

After being randomly selected, three rats were anesthetized using pentobarbital sodium and then sacrificed and perfused transcardially using 0.1 mol/liter PBS and 4% paraformaldehyde. The paraffin-embedded sliced section used was 5 µm in diameter stained for 10 minutes using cresyl violet (400 ml distilled water and 0.4 mg cresyl violet powder (Sigma Alderich); afterwards, gradual dehydration was carried out using graded alcohol (Asiapajohesh Co., Iran). To examine the neurons, a microscope (400X) was used and the results were examined using Image J 1.51 [30, 31].

Measurement of Malondialdehyde Levels and Catalase Activity to Assess Oxidative Stress in Hippocampus

Malondialdehyde levels were detected by thiobarbituric acid (TBA) in hippocampus. In total, six

rats were chosen in each group and the hippocampus was taken out and homogenized using ice and 0.1 M phosphate buffer. Then the sample were centrifuged (4000 rpm; 10 min; at 4°C). Afterwards, to examine the MDA activity, the supernatants were collected. To assess malondialdehyde levels in supernatant, MDA TCA kit (Nalondi™-Lipid Peroxidation Assay Kit-MDA) was utilized. In order to measure catalase activity, colorimetric catalase activity assay kit (Abcam, United Kingdom) was utilized. In the catalase activity measurement with colorimetric methods, the catalase in specimens and hydrogen peroxide (H_2O_2) react and yield oxygen and water. The unconverted H_2O_2 can be detected by probe and measured colorimetrically at optic density (OD) of 570 nm. Briefly, 100µL buffer was optimized and mixed with 10 µL of each sample and incubated at 25ºC for 5 minutes. Then, 10µL H_2O_2 was mixed to the samples and incubated for 30 minutes at 25ºC. Then, 10 µL clearing agent and 100µL chromogen powder were mixed to the solution and incubated for 10 minutes at 25ºC. Finally, results were analyzed with microplate reader at 570 nm.

Statistical Analysis

GraphPad Prism 7.0 was used for data analyses and represented using Mean ± SEM. To make comparisons across the groups, one-way ANOVA was used (P-value<0.05).

3. Results

Chronic Nickel Administration Impaired Recognition Memory in Novel Object Recognition

The NOR study showed lack of any significant difference in terms of the time needed to examine novel and familiar objects in the group that received 1 mg /kg Ni (Figure 1), while in the vehicle and groups that received 0.25 mg/ kg and 0.5 mg/kg Ni, novel object recognition time significantly increased compared to familiar object recognition (*** P<0.001, ** P<0.01, * P<0.05). The preference index (PI) indicated a decrease in the group that received 1 mg/kg Ni in comparison with vehicle group (** P<0.01) (Figure 2). The results indicated that memory declined with chronic 1 mg/kg Ni administration.

Animals in vehicle group, needed longer to examine new objects because of their instinctive behavior (*** P<0.001). Animals in 0.25 mg/kg and 0.5 mg/kg Ni groups also needed longer time with new object instead of familiar one (** P<0.01, * P<0.05). However, in 1 mg/kg Ni group, novel vs. familiar objects were not significantly different. Statistical analysis was done utilizing one-way ANOVA Tukey's post-hoc test and the results were reported as Mean ± SEM (n = 6), F (3, 4) = 38/13, P = 0/0006.

There were no differences in PI between vehicle vs. 0.25 mg/kg and 0.5mg/kg Ni groups. However, PI diminished in 1 mg/kg Ni group in comparison with the vehicle group (**P<0.01). Statistical analysis was done utilizing one-way ANOVA Tukey's post-hoc test and the results were reported as Mean ± SEM (n = 6), F (3, 4) = 1/797 P=0.025.

Chronic Nickel Administration Significantly Decreased Survival Neurons in Hippocampus in Nissl Staining

Nissl staining was used to assess survival neurons in CA1 hippocampus in different groups. Results of this study indicated no changes in the morphology of neurons in the vehicle group and in 0.25 mg/kg Ni

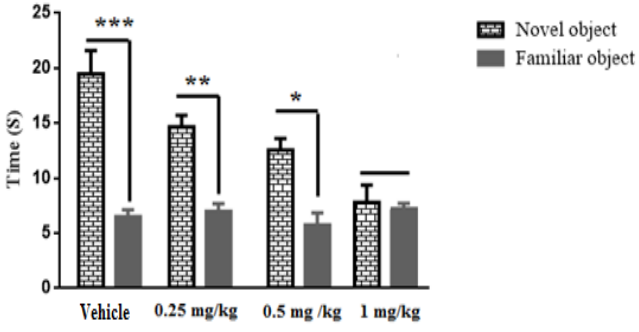


Figure 1. Time needed to examine novel and familiar objects in all groups

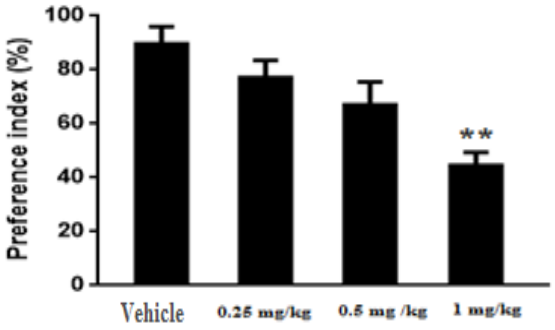


Figure 2. Preference index (PI) in recognizing new object test

group. However, in comparison with the vehicle group, in 0.5 mg/kg and 1 mg/kg Ni groups, morphological and structural changes were induced in hippocampus of rats ($P<0.05$, $P<0.01$). It was observed that high Ni dose administration for 8 weeks caused neuronal loss in CA1 hippocampus (Figure 3).

There were no morphological changes in neurons in vehicle and 0.25 mg/kg Ni groups. However, in 0.5 mg/kg and 1 mg/kg Ni groups, neuronal changes were spotted (*$P<0.05$, **$P<0.01$) (arrows show changes in neuronal morphology). Statistical analysis was done utilizing one-way ANOVA Tukey's post-hoc test and the results were reported as Mean ± SEM (n = 3), F (3, 4) = 12.14, P=0.0175.

Chronic Ni Administration Augmented Malondialdehyde Levels (MDA) and Reduced Catalase Activity

To assess oxidative stress, Malondialdehyde (MDA) and catalase activity were measured as an antioxidant enzyme. Expectedly, there were no changes in MDA levels (a key oxidative marker) and catalase activity between vehicle and 0.5 mg/kg Ni injection (Figure 4).

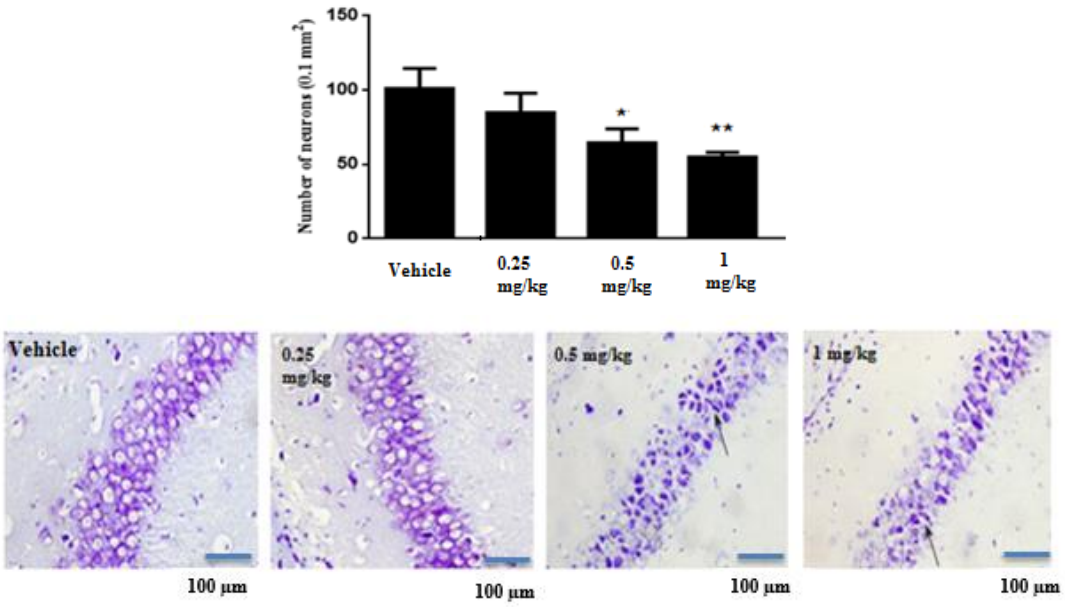
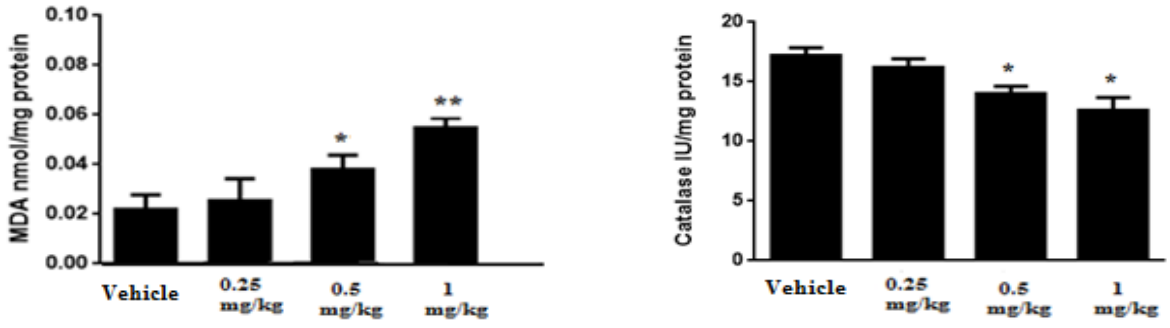


Figure 3. Survival neurons of CA1 hippocampus in Nissl staining (×400)



(A) (B)

Figure 4. Effect of Ni administration on MDA levels and catalase activity. (A): There was no significant difference in MDA levels between 0.25 mg/kg Ni group and vehicle group. However, in 0.5 mg/kg and 1 mg/kg Ni groups, MDA increased significantly compared with vehicle group (*$P<0.05$,**$P<0.01$), $F(3,4)=8.14$, $P=0.0025$. (B): As shown in this figure, there were no changes in catalase activity in 0.25 mg/kg Ni group in comparison with vehicle group. However, administration of 0.5 mg /kg and 1 mg/kg Ni to rats could significantly increase catalase activity level (*$P<0.05$). Statistical analysis was done utilizing one-way ANOVA Tukey's post-hoc test and the results were reported as Mean ± SEM (n = 3), F (3,4) = 8.58, P= 0.0156

However, in comparison with the vehicle group, 0.5 mg/kg and 1 mg/kg Ni administration indicated a significant increase in MDA levels (*P<0.05, **P<0.01). Moreover, 0.5 mg/kg and 1 mg/kg Ni administration lowered the level of catalase activity compared to vehicle group (*P<0.05) (Figure 4-B).

4. Discussion

It is well established that Ni as a toxic heavy metal is crucial for a healthy body. Human body needs small amount of this metal to function properly [32]. Ni may disrupt many physiological functions and cause anemia, dysfunction of enzymes, gastric irritation, and disrupt glucose and lipid metabolisms [17, 18]. Nevertheless, the exact function in the body is not clear yet. Ni-induced toxicity was reported in several studies [32-34]. The effects of chronic Ni administration in various doses on memory function, hippocampal neuron structure and oxidative stress factors were investigated. Administration of high Ni doses showed cognition impairment and memory deficit in novel object recognition in rats. In addition, hippocampal structure was evaluated with Nissl staining. Results indicated that administration of high Ni doses may significantly disrupt neuron structure in CA1 hippocampus. Additionally, Ni-induced MDA production as an important factor for advancement of oxidative stress pathways and reduce catalse enzyme levels as an essential anti-oxidant enzyme in the brain that catalyzes hydrogen peroxidase (H_2o_2) to reduce its cytotoxic effects [35].

Reduced CAT activity shows the failure of brain to remove H_2O_2 produced by Ni metabolism [1]. It seems that much damage to the CA1 region in histological studies originate from imbalance of oxidant and anti-oxidant markers in brain. In addition, Ni-induced oxidative stress in CNS was related to the increase in nitric oxide and free radical levels in the brain that may contribute to apoptotic pathways activation in the brain and damage to the structure of important parts in CNS [36, 37]. In addition, the findings indicated that Ni administration may damage CNS depending on the dose. When 0.5 and 1 mg/kg Ni was injected, significant changes were observed in the levels of oxidative markers. In histological studies, damage to CA1 hippocampus was completely obvious in the pictures. Intraperitoneal Ni was injected in rats for 8 weeks and injuries may be more severe with prolonged use. Other studies approved our results [1, 3, 38]. In a study, compromised behavior and brain morphology was observed after exposure to Ni with a higher level of oxidative stress markers like SOD (Superoxidase), LPO (Lipoperoxidase), MDA levels and modifications of NO systems [1]. In another study, it was indicated that Ni can enhance Zn-induced neuronal loss and promote endoplasmic reticulum stress response [3]. Clearly, CAT and SOD form a supportive team before free radicals. Studies showed that the diminished antioxidant enzymes activity by Ni can be rooted in the direct binding between Ni and sulfhydryl groups of enzymes. In addition, oxidative modifications in amino acid chains and changes the structure of enzyme and inactive or decrease the activity of enzyme [39, 40]. Consequently, when the brain antioxidant system activity decreases, free radicals are accumulated and the LPO level incases, which in return increases the oxidative risk to the tissues. The present study and other similar studies confirmed that high doses of Ni can disrupt CNS function. Also, recent studies indicated that oxidative stress can lead to the death of 5-HT and other neurotransmitter neurons, and thus a decline in 5 HT levels of brain. Following an exposure to Ni, the levels of dopamine, 5-HT, and noradrenaline decrease in brain regions [41]. Therefore, people in regions that intake more Ni are more susceptible to different CNS disorders like Alzheimer's or Parkinson's disease [38, 42, 43] This study only assessed the CNS dysfunction in prolonged administration of Ni. It may make changes in other important organs, cause imbalance in oxidative stress markers and induce dysfunctions in other parts of the human body. Therefore, it is required to assess various effects of Ni and other heavy metals on human health to determine precise functions of Ni and other trace elements in human body.

5. Conclusion

In this study, the effect of administrating different Ni doses on memory function, hippocampus structure and oxidative stress markers in CNS was assessed. Results indicated that memory dysfunction and morphological changes occurred in hippocampus with an increase in oxidative stress after Ni administration for 8 weeks which could be worse depending on the doses. Therefore, nickel consumption from natural sources like water or air should be reduced by taking advantage of methods for environmental treatment.

Ethical Considerations

Compliance with ethical guidelines

There were no ethical considerations to be considered in this research.

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Author's contributions

All authors have equally contributed to preparation of this article.

Conflict of interest

The authors declare no conflict of interest.

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