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Selenium improves the histochemical pattern of amyloid beta proteins and carbohydrates in cerebellum of rats after ZnO NPs exposure

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ABSTRACT : **Exposure to nanoparticles decreased the activities of reactive oxygen species (ROS)-scavenging enzymes such as glutathione peroxidase (GSH-Px), superoxide dismutase (SOD) and catalase in brain of rats and mice. However, low and intermediate doses of selenium inhibit cancer cell proliferation and has a therapeutic effect on neurological diseases. Four groups of animals, representing control, Se-administered (0.2 mg/kg/day), ZnO NP-exposed (1 g/kg/day for 5 consecutive days), and ZnO NPs + Se-treated, were used in this study. Exposure to ZnO NPs exhibited an intense amyloid β reaction for proteins in those neurons which underwent damage and apoptosis in most of cerebellar areas particularly Purkinje. Also, the exposure to these NPs reduced the total carbohydrate content in the damaged cerebellar neurons. However, administration of selenium prior to ZnO NPs exposure improved the pattern of these histochemical components.The study aimed to investigate the antioxidant effects of selenium in cerebellum of ZnO NPs-intoxicated rats at the histochemical level with special reference to amyloid beta proteins and carbohydrates. We also try to test the potential protctive application of selenium for treatment.**

***KEYWORDS*: ZnONPs; Brain; Amyloid Beta Protein; Total carbohydrates; Albino Rat.**

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I. INTRODUCTION

Amyloid beta (Aβ) is a sticky, starch-like plaques protein that is deposited in brain tissue causing Alzheimer disease (AD). AD, as one of neurodegenerative disorders, will disrupt memory functions, cognitive ability and even personality. Thus, AD will menace human health and minimize life quality (Shankar *et al*., 2007). Previous studies suggested that AD is associated with the extracellular deposition of abnormal Aβ peptides and intracellular aggregates of neurofibrillary tangles (NFT), which are accumulation of hyperphosphorylated tau proteins (Zhang *et al.*, 2011). Aβ protein is associated to the pathogenesis of AD (Yu *et al*., 2014). Aβ-40 and Aβ-42 are the two main forms of Aβ proteins (Triguero *et al*., 2008). Aβ-42, is more hydrophobic, easily to accumulate than Aβ-40 and a major constituent in plaques of AD patients (Vestergaard *et al*., 2005). Neurodegenerative mechanisms relating to exposure to engineered nanomaterials (ENMs), such as CuO NPs, in neurological diseases such as AD can provide rationale for the regulation of these materials. A study recorded that a low-dose of CuO NP exposure has a direct role in activating the Nuclear factor kappa BNFκB signaling pathway and increasing amyloid precursor protein (APP) expression (Shrivastava *et al.*, 2013). Shah *et al*. (2015) recorded toxic effects for nano-alumina that decreasing cell viability by producing ROS in vitro, which finally reach the brain and accumulate in exposed animals, inducing oxidative stress and neurodegeneration. These results indicated that exposure to nano-alumina makes the CNS more vulnerable to amyloid beta-based neurodegenerative disorders, such as AD. Concerning carbohydrates, Almansour *et al.* (2017) reported that partial depletion of glycogen in hepatocytes was illustrated in rats exposed to ZnO NPs (35 nm). This depletion was markedly-observed in degenerated hepatocytes. Also, Alferah (2018) reported that severe glycogen depletion in hepatocytes was observed due to exposure of experimental animals to ZnO NPs. Hence, regulating environmental exposure to these nanoparticles may be necessary to lower the risk of neurodegenerative diseases and promote overall healthy brain aging.

Therefore, the aim of the current study is to investigate the effect of ZnO NPs-exposure of rats on the histochemical pattern of amyloid beta proteins and total carbohydrate contents of cerebellum as two bio indicators reflecting this pathogenesis and evaluating the possible protective role of selenium.

. II. MATERIALS and METHODS

2.1.Chemicals

All chemicals consumed in the study were of high analytical grade and products of Sigma and Merck companies. ZnO NPs (MW: 81.39 g/mol, < 50 nm size, purity > 97% with long lasting effect) and selenium (Sodium Selenite, Na2SeO3) were products of Sigma-Aldrich Corporation (USA) and purchased from the "International Company for Scientific and Medical Supplies", Cairo, Egypt.

2.2. Animals

Forty adult healthy male albino rats (Rattus norvegicus strain) weighing 180-200 g were used for this study. They were equally categorized into four groups (10 animals each). Rats of 10 -12 week age was chosen, since the brain is well-developed at this age (Downes et al., 2013). They were survived in plastic cages under standard conditions of dark / light cycle, temperature (25°C ±1), good ventilation and humidity (55%). Animals were provided with free access to tap water and a standard diet. Four groups of animals, representing control, Se-administered (0.2 mg/kg/day), ZnO NP-exposed (1 g/kg/day for 5 consecutive days), and ZnO NPs + Se-treated, were used in this study.

2.3. Ethics approval and consent to participate

This experimental study was performed with the confirmation of the local ethics committee on use and care for animal experiments at Zagazig University, Faculty of Science, and Zoology Department. State authorities approved the experiment and followed Egyptian animal-protection rules of IACUC at Zagazig University with approval number: ZU-IACUC/F/109/2020.

2.4. Experimental Design

Post acclimatization, animals were categorized into four groups (n= 10); G1: Healthy control, G2: Selenium-given rats, 0.2 mg/kg bw/day, oral gavage (El-Demerdash and Nasr, 2014) and G3-G4: Treated groups, orally-given 1 g/kg b.w/day ZnONPs by gastric tube for 5 consecutive days (Wang et al., 2008 and Nassar et al.,2017) and divided as follows; G3: ZnONPs intoxicated rats., G4: ZnONPs- intoxicated rats with co-administration of selenium daily. Selenium was orally-given (0.2 mg/kg bw /day) for eight consecutive days, 3 days of them before the start of the experiment. After 24 hour of the last dose administration, rats were fasted overnight, euthanized by thiopental and sacrificed.

2.5. Tissue sampling

Brains were quickly excised from skulls after quick cervical dislocation, blotted out with filter paper. Brains were split sagittal into two halves. Cerebella were collected and fixed in 10% neutral buffered formalin at room temperature for 24 h, washed, dehydrated, cleared and embedded in paraffin. Then, sections were cut at 3-4 µm thick.

2.6. For histochemistry:

2.6.1. Amyloid beta protein:

Amyloid Beta proteins could be demonstrated by Congo red stain according to the method of Valle (1986):

Histochemistry of carbohydrates (PAS):

The total carbohydrate content in tissue sections of cerebellum could be detected by Periodic Acid-Schiff's (PAS) reaction according to the method of Bancroft and Layton (2013).

III. RESLUTS and DISCUSSIONS

Resuts

3.1. Amyloid beta protein reaction

The histochemical demonstration of amyloid β – proteins in sections of control rat revealed a slight deposition of this material in the nuclei of the cerebellar cells (Fig. 1).The mean optical density (MOD) value of the amyloid –β protein content in control animals was 1.22(table1, Histogram 1). Animals of Se group exhibited a histochemical pattern for amyloid β – proteins nearly similar to that of control with a MOD of 1.3 % of change (Fig. 2, table 1, Histogram 1). The application of Congo red stain after exposure to ZnONPs exhibited an intense amyloid β reaction for proteins in those neurons which underwent damage and apoptosis in most of cerebellar areas particularly Purkinje (Fig. 3). The MOD values recorded a highly – significant increase in these measurements to reach 13.1 % of change as compared to those of control. Therefore, the image analysis performed for the histochemical stained slides of Congo red confirmed the qualitative results (Table 1 and Histogram1). The co-administration of Se together with ZnONPs decreases the amyloid β content towards the

normal control picture (Fig. 4). The MOD records a significant decrease in these measurements to reach 9.78 % of change as compared to those of ZnONPs group (Table 1 and Histogram 1).

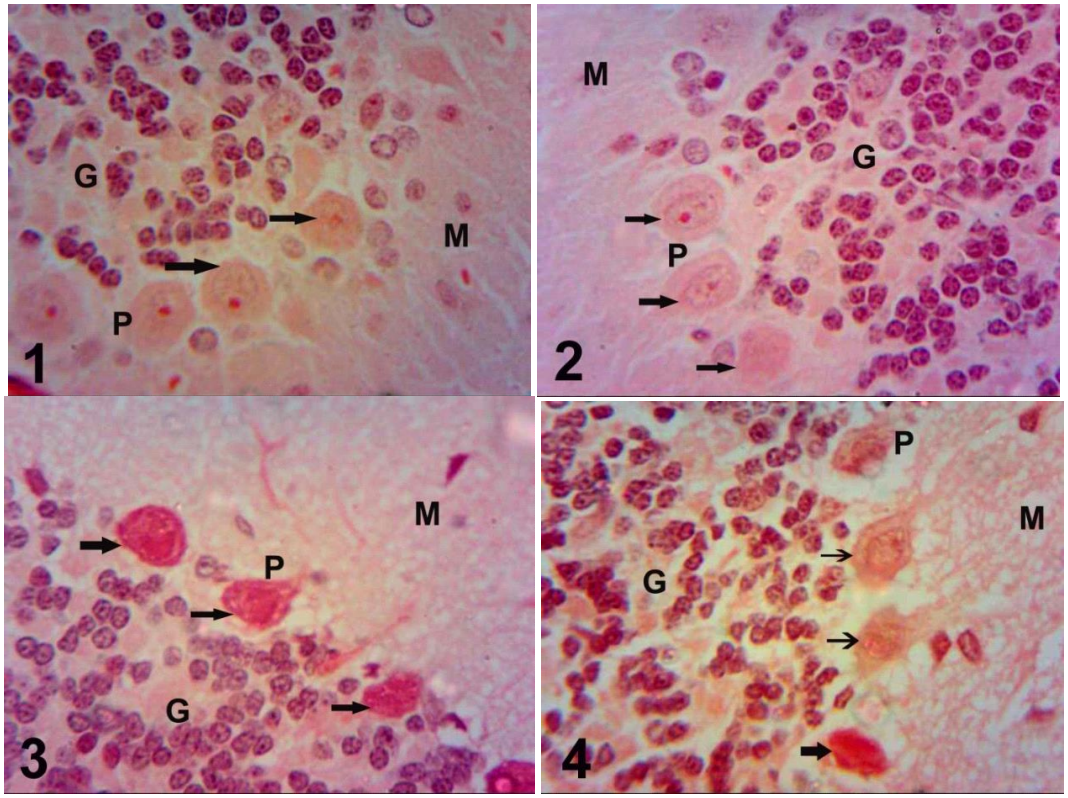

Fig.1:Section of cerebellum of control rat stained with Congo red (x 1000) demonstrating amyloid β protein content revealing; a weak (+) to moderate (++) reaction in the neuronal cells of cerebellum (Purkinje), where the reaction exhibited a slight deposition of amyloid β in the nuclei of these cells (arrows). Fig. 2: Section of cerebellum of rat of Se group stained with Congo red (x 1000) demonstrating amyloid β protein content revealing; a reaction for amyloid in the neuronal cells of cerebellum (Purkinje) nearly similar to that of control (arrows). Fig. 3: Section of cerebellum of ZnONPs-intoxicated rat stained with Congo red for amyloid β protein (x 1000) revealing; an intense ++++ reaction for amyloid in the damaged neuronal cells of cerebellum (e.g. Purkinje) exhibiting a high deposition of this material (arrows). Fig. 4: Section of cerebellum of ZnONPs-intoxicated rat treated with Se and stained with Congo red demonstrating amyloid β protein (x1000) revealing; a strong +++ reaction for amyloid in the neuronal cells of cerebellum (e.g. Purkinje) exhibiting a some sort of restoration towards the normal histochemical picture (arrows).

Table (1) Showing the mean optical density (MOD) values of amyloid β content in the cerebellar tissue of control and experimental animals.

	NC	Se	Zno NPs	Zno NPs+ Se
Average mean	1.22	1.30	13.06	9.78
Standard deviation	0.0044	0.0024	0.051	0.395
P value		≤ 0.903 Non-Sig.	≤ 0.0001 Sig.	≤ 0.0001 Sig.

Histogram (1) showing the % of change of amyloid β protein content of experimental animals relative to the control value.

Total carbohydrate content:

Periodic Acid Schiff's reaction (PAS)

The normal distribution of polysaccharides in the cerebellar tissue of control animals was visualized by Fig.5 in the form of moderate (++) to strong (+++) reaction in the cytoplasm of all neural cells. The MOD of the PAS +ve material in slides of control animals was 0.244 (Table 2, Histogram 2). Animals of Se group exhibited a histochemical pattern nearly similar to that of control with a MOD of 0.255 % of change (Fig. 6, Table 2, and Histogram 2). The exposure to ZnO NPS reduced PAS + ve reaction in the neurons of cerebellum (Fig. 7) where the MOD value of PAS + ve materials in animals of this group was 0.213 % of change to record a significant decrease as compared to control (Table 2 and Histogram 2). The co-administration of Se together with ZnO NPs increased the intensity of PAS + ve material towards the normal control picture (Fig. 8), where the MOD was 0.238 % of change to record a significant increase as compared to those of group-3 (Table 2 and Histogram 2).

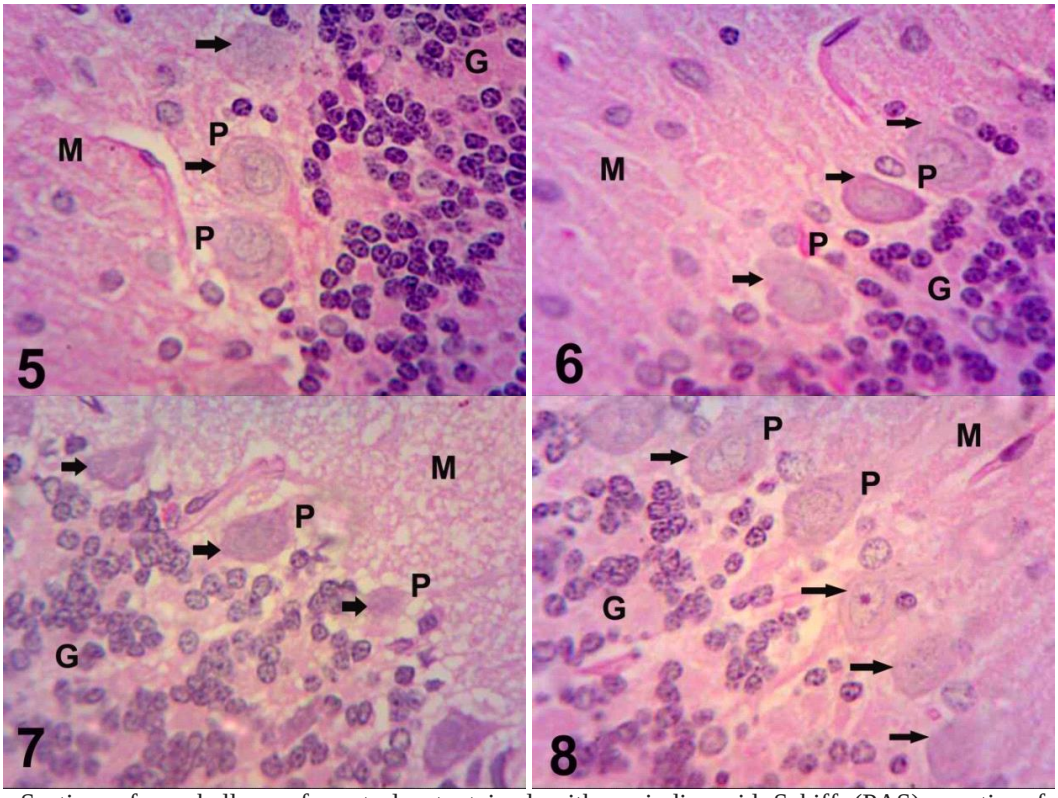

Fig. 5: Section of cerebellum of control rat stained with periodic acid Schiff (PAS) reaction for total polysaccharides (x1000) revealing; a moderate (++) to strong (+++) reaction in the cytoplasm of all neuronal cells (arrows). Fig. 6: Section of cerebellum of Se group stained with periodic acid Schiff (PAS) reaction for total polysaccharides (x1000) revealing; a reaction of PAS nearly similar to that of control group (arrows). Fig. 7: Section of cerebellum of ZnONPs – exposed group stained with periodic acid Schiff (PAS) reaction for total polysaccharides (x1000) revealing; a weak (+) PAS reaction in all damaged neuronal cells (e.g. Purkinje) recording a marked decrease as compared to control. Fig. 8: Section of cerebellum of ZnO NPs-intoxicated rat treated with Se and stained with periodic acid Schiff (PAS) reaction for total polysaccharides (x1000) revealing; a moderate (++) PAS reaction in all neuronal cells recording an increase towards the normal status (arrows).

Table (2) Showing the mean optical density (MOD) values of PAS positive material in the cerebellar tissue of the control and experimental animals.

	NC	Se	Zno NPs	Zno NPs+ Se
Average mean	0.244	0.255	0.213	0.238
Standard deviation	0.0085	0.004	0.0074	0.0048
P value		≤ 0.031 Sig.	≤ 0.0001 Sig.	≤ 0.0001 Sig.

Histogram (2) Showing percent of change of PAS materials of experimental animals relative to the control value.

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IV. DISCUSSION

Recently, a growing interest emerged to study the role of selenium and selenoproteins in neurodegenerative diseases including AD.

Concerning the impact of ZnO NPs intoxication on the amyloid β (Aβ) protein , in the present work, the application of Congo red stain exhibited a significant increase in Aβ proteins in those neurons which underwent damage and apoptosis in most areas of cerebellar tissue particularly Purkinje cells as compared to those of control. The increased intracellular deposition of Aβ in cerebellar neurons leads to their degeneration and the development of different neural diseases such as Alzheimer's Disease (AD). However, co-administration of Se prior to ZnO NPs, in the current experiment, decreases amyloid β content towards the normal status. These current results are in line with previous ones; where investigators reported that there is compelling evidence that nanoparticles contribute to Alzheimer's disease (AD) pathology. Various metal nanoparticles are abnormally abundant in individuals who exhibit Alzheimer's disease, the onset which may be due to their tendency to allow Aβ aggregation (Liu et al., 2006). Also, previous studies reported that AD is associated with the extracellular deposition of abnormal beta amyloid peptides (Aβ) and intracellular aggregates of neurofibrillary tangles (NFT), which are accumulation of hyperphosphorylated tau proteins (Zhang et al 2011). There are many theories to explain the etiology of Alzheimer's disease including; oxidative stress, accumulation of APP forming amyloid-β plaques, hyperphosphorylation of tau protein, changes in cholinergic neurotransmission, immune system dysfunction, genetic factors comprising mutations of APP and presenilin (PSEN) genes and environmental pollution (Wang et al.,2014). Pathologically, the extracellular depositions of Aβ proteins and the presence of intraneuronal neurofibrillary tangles are essential markers for posthumous diagnosis of AD. Aβ is the main protein component of senile plaques in the AD brain and it is composed of spontaneously aggregating peptides of 39-43 amino acids (Kosik, 1992). It was known that microglia is the main source of neuroinflammatory factors and the latter affect the nature of AD (Kosik, 1992). Inflammatory processes are concomitant with reactive oxygen species (ROS) production. Both ROS and reactive nitrogen species (RNS) are considered to play pivotal roles in induction of AD (Nazıroğlu, 2011 and Ajith and Padmajanair, 2015). Selenoproteins are mainly involved in AD prevention, owing to their excellent neuroprotective property (Siddiqui et al 2009). Selenium treatments minimized the levels of oxidative stress and Aβ formation in brain of experimental animal models for AD (Ishrat 2009 and Yin et al 2015). Reduced selenium contents in plasma and hair were reported in the patients with AD and it was found a negative correlation between the selenium content in plasma and incidence of AD (González-Domínguez et al., 2014). Kosik (1992) and Balaban et al. (2016) reported that selenium treatment may decrease the risk of memory deficits in animal models and in AD patients.

As regards the effect of ZnO NPs on the carbohydrate material in cerebellar tissue, the current study concluded that ZnO NPs significantly reduced the PAS + ve material (total carbohydrate content) in cerebellar neurons. The onset which may be attributed to mal absorption of carbohydrates in experimental animals due to oral administration of ZnO NPs . However, the co-administration of Se prior to ZnO NPs increased the intensity of PAS + ve material towards the normal control picture to record a protective role for Se. This is in accordance with Singla and Dhawan (2012) who recorded a reduction of glycogen content for both cerebrum and cerebellum in aluminum toxicity (nanoparticles) in rats. In this respect, Almansour et al. (2017) reported that rats subjected to ZnO NPs demonstrated glycogen depletion which may indicate negative influence on carbohydrate absorption or on enzymes involved in the process of glycogenesis and/or glycolysis. Ermak and Davies (2002) reported that the large surface area of NPs increases their capacity to produce ROS such as hydrogen peroxide and hydroxyl radicals. ROS production leads both to cytotoxicity and to genotoxicity. The accumulation of ROS in tissue cells results in oxidative damage of macromolecules including lipid, protein, and DNA peroxidation. If the oxidative stress occurs in a cell, it can lead to alterations in signal transduction and gene expression for metabolism and mitogen pathways. Also, El-Bestawy et al. (2020) reported that the PAS staining affinity was markedly decreased in TiO2 NPs - exposed animals with faintly-stained cardiac fibers indicating carbohydrate depletion. A highly-significant decrease in the reaction of PAS staining in the treated group as compared to control groups (I and IV).The depletion of glycogen can be explained by the fact that the level of glycogen reserves in the heart is low as most of glucose transported to myocardium is mainly consumed in oxidative glycolysis and a small amount is used for glycogen synthesis according to Pascual and Coleman (2016). Houstis et al. (2006) reported that the muscle would not uptake glucose efficiently due to oxidative stress with a resultant decrease in glycogen synthesis leading to its depletion. They reported also, that oxygen free radicals inhibit mitochondrial energy metabolism making cells unable to store glycogen and convert lactate and pyruvate to glycogen. There was a partial recovery of glycogen and protein including the desmin protein as indicated by some recovery of PAS and bromophenol blue (BPB) staining affinity and a moderate

immunoreactivity to the anti-desmin antibody. This was proved statistically by the increased optical density that showed highly significant difference from the TiO2 NPs treated group.

Conclusion

The results of the current study confirmed the affection of the histochemical pattern of amyloid beta proteins and carbohydrates in cerebellum of rats due to ZnO NPs-exposure and the possible protection role of Se. Hence, management of environmental exposure to NPs may be necessary to lower the risk of neurodegenerative diseases and allow overall healthy brain aging. This study is expected to be a useful one for scientists working in the field of neurodegenerative diseases, oxidative brain injury or selenium as a neuro-protective food supplement.

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