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Neuroprotective effects of selenium against cisplatin-induced oxidative damage in the rat hippocampus

Selenyumun sıçan hipokampusunda cisplatin kaynaklı oksidatif hasara karşı nöroprotektif etkileri

Melek Altunkaya, Gülsüm Abuşoğlu, Bahadır Öztürk

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Abstract

Purpose: This study aimed to comprehensively evaluate the cognitive and behavioral effects together with the role of oxidative stress in the hippocampus in order to evaluate the role of selenium as a potential neuroprotective agent against cisplatin-induced central nervous system neurotoxicity.

Materials and methods: Thirty-eight male rats were divided into control, cisplatin, selenium, and cisplatin+selenium groups. A single dose of cisplatin (7.5 mg/kg) was administered intraperitoneally to the rats. Selenium (1 mg/kg) was administered orally once daily by gavage for 21 days. Novel location and object recognition tests were used to test short-term memory (STM) and long-term memory (LTM). The forced swim test was used to measure depression level. Total antioxidant status (TAS), superoxide dismutase (SOD), total oxidant status (TOS), and malondialdehyde (MDA) were measured in hippocampus tissue using the ELISA method.

Results: Cisplatin treatment caused weight loss in rats p=0.001. TOS p=0.02 and MDA p=0.05 levels increased, and TAS p=0.03 and SOD p=0.01 levels decreased in the cisplatin group compared to the control group. No statistically significant change was observed in these oxidative damage parameters in the cisplatin+selenium group compared to the control group. STM and LTM were impaired in the cisplatin group p=0.05. However, some improvement was observed in the LTM impairment in the Cisplatin+selenium group. While depression levels increased in the cisplatin group compared to the control group, they were significantly reduced in the Cisplatin+selenium group p=0.001.

Conclusion: The findings suggest that selenium supplementation may play a potential therapeutic role in alleviating cisplatin-induced neurotoxic effects in the central nervous system in rats.

Keywords: Hippocampus, selenium, oxidative stress, behavioral test.

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Öz

Amaç: Bu çalışma, selenyumun cisplatin kaynaklı merkezi sinir sistemi nörotoksisitesine karşı potansiyel bir nöroprotektif ajan olarak rolünü değerlendirmek amacıyla, oksidatif stresin hipokampüsteki rolüyle birlikte bilişsel ve davranışsal etkileri kapsamlı bir şekilde değerlendirmeyi amaçlamıştır.

Gereç ve yöntem: Otuz sekiz erkek sıçan kontrol, sisplatin, selenyum ve sisplatin+selenyum gruplarına ayrıldı. Sıçanlara tek doz sisplatin (7,5 mg/kg) intraperitoneal olarak uygulandı. Selenyum (1 mg/kg) 21 gün boyunca günde bir kez oral yoldan gavaj yoluyla uygulandı. Kısa süreli hafızayı (KSH) ve uzun süreli hafızayı (USH) test etmek için yeni konum ve nesne tanıma testleri kullanıldı. Depresyon düzeyini ölçmek için zorunlu yüzme testi kullanıldı. Toplam antioksidan durumu (TAS), süper oksidaz dismutaz (SOD), toplam oksidan durumu (TOS) ve malondialdehit (MDA), ELISA yöntemi kullanılarak hipokampüs dokusundan ölçüldü.

Bulgular: Cisplatin tedavisi sıçanlarda kilo kaybına neden oldu p=0.001. Cisplatin grubunda kontrol grubuna göre TOS p=0.02 ve MDA p=0.05 seviyelerinde artış, TAS p=0.03 ve SOD p=0.01 seviyelerinde azalma görüldü. Cisplatin+Selenyum grubunda bu oksidatif hasar parametrelerinde kontrol grubuna kıyasla istatistiksel olarak anlamlı bir değişiklik gözlenmedi. Cisplatin grubunda KSH ve USH'de bozulma görüldü p=0.05. Ancak Cisplatin+Selenyum grubunda USH'daki bozulmada bir miktar iyileşme görüldü. Cisplatin grubunda, kontrol grubuna kıyasla depresyon düzeyinde artış gözlemlenirken, Cisplatin+Selenyum grubunda önemli ölçüde azaldı p=0.001.

Sonuç: Elde edilen bulgular, selenyum takviyesinin sıçanlarda cisplatin kaynaklı merkezi sinir sisteminde nörotoksik etkilerin hafifletilmesinde potansiyel terapötik bir rol oynayabileceğini düşündürmektedir.

Anahtar kelimeler: Hipokampus, selenyum, oksidatif stres, davranışsal test.

Melek Altunkaya, PhD. Department of Vocational School of Health Services, Selçuk University, Konya, Türkiye, e-mail: melek.batakci@selcuk.edu.tr (https://orcid.org/0000-0002-6228-7831) (Corresponding Author)

Gülsüm Abuşoğlu, PhD. Department of Vocational School of Health Services, Selçuk University, Konya, Türkiye, e-mail: gulsum.tekin@selcuk.edu.tr (https://orcid.org/0000-0003-1630-1257)

Bahadır Öztürk, PhD. Department of Biochemistry, Faculty of Medicine, Selcuk University, Konya, Türkiye, e-mail: bahadirozturk@selcuk.edu.tr (https://orcid.org/0000-0003-2654-7621)

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Introduction

Cisplatin, a platinum-based anticancer drug [1], is the most commonly used medication for the treatment of ovarian, bladder, lung, testicular, cervical, and melanoma [2, 3]. Although cisplatin is preferred for cancer treatment, its use is primarily limited by two factors: acquired resistance to cisplatin and severe side effects in normal tissues [3]. The second major reason that limits the use of cisplatin is its toxicity, which includes nephrotoxicity, hepatotoxicity, cardiotoxicity, neurotoxicity, myelosuppression, allergic reactions, and certain reproductive toxicities [2, 4]. Despite long-standing research efforts to mitigate the adverse effects of cisplatin, no effective treatment method has yet been identified. Many substances have been employed to prevent or reduce the neurotoxicity caused by cisplatin (N-acetyl cysteine, curcumin, betaine, vitamin E, etc.) [5-7]. However, no definitive preventive treatment method has yet been identified. Although selenium is known to be an essential element for our body [8], it has also recently been identified as an anticarcinogen and has been shown to partially reduce the side effects of cisplatin [9]. Selenium's protective effects against cisplatin-induced toxicity occur through complex mechanisms, including reducing oxidative stress, modulating inflammatory processes, regulating apoptosis, and strengthening cellular detoxification systems [10]. Specifically, selenium acts as a cofactor for important antioxidant enzymes like glutathione peroxidase and thioredoxin reductase, neutralizing reactive oxygen species [9]. It also reduces inflammation by suppressing pro-inflammatory signaling pathways such as NF-κB, regulates excessive cisplatin-induced apoptosis in healthy cells, and aids in the elimination of toxic metabolites by activating detoxification enzymes like glutathione S-transferase [11-13].

Chemotherapy in cancer patients may affect cognitive and motor functions, such as cognitive deficits, disorientation, visual perception, and hearing impairment [14]. Recent research using animal experimental models to assess cisplatin neurotoxicity has also substantiated the presence of severe mood problems, specifically heightened levels of anxiety [10]. Many tests are used to evaluate learning, memory performance, and depression in rats. Both short-term and long-term memory can be evaluated using the novel location recognition test (NLRT) and the novel object recognition test (NORT) [15, 16]. In the forced swim test (FST), the level of depression is evaluated on the basis of the transition to immobility and the duration of immobility [17]. Oxidative stress is considered to be one of the main mechanisms involved in cisplatin-induced neurotoxicity [18]. Considering the above information, the hypothesis of this study is that selenium supplementation may alleviate cisplatin-induced neurotoxicity, especially memory loss and anxiety-like symptoms, by reducing oxidative stress in the brain. While the neurotoxic effects of cisplatin have been well-documented, the use of selenium as a countermeasure is relatively new. In summary, the novelty of this study lies in its exploration of selenium as a potential neuroprotective agent against cisplatin-induced neurotoxicity, its focus on the role of oxidative stress in the hippocampus measuring total antioxidant status (TAS), superoxide dismutase (SOD), total oxidant status (TOS), and malondialdehyde (MDA), its comprehensive evaluation of cognitive and behavioral effects (NLRT, NORT, FST), and its quantitative assessment of oxidative stress biomarkers.

Therefore, this study aimed to determine whether selenium supplementation could alleviate the neurotoxic effects, including memory impairment and depression-like behavior, caused by cisplatin treatment through its potential to reduce oxidative stress in the brain.

Materials and methods

Experimental animals

The study was conducted at the Experimental Medicine Application and Research Center of Selcuk University and used 38 male Wistar albino rats, aged 60 days and weighing between 180 and 200 g. In experimental studies reported in the literature, a priori power analysis conducted

using GPower 3.1.9.7 found that the required sample size for a multi-group ANOVA was 35 animals (95% confidence interval (1-α), 90% statistical power(1-β), effect size = 1.20). Based on these data and considering the potential risk of animal loss associated with cisplatin administration, the sample size in the present study was planned as 38 rats.The animals were housed in a room with appropriate conditions (temperature: 21°C, humidity: 55%, and 12 h of light/light-dark cycle). This study adhered to the guidelines outlined in the Guide for the Care and Use of Laboratory Animals to ensure the protection of animal rights. Permission was obtained from the Animal Experiments Ethics Committee of the Selcuk University Experimental Medicine Application and Research Center for the study (permission date: January 27, 2023, and permission number: 2023-09).

90 mg/kg ketamine (Ketalar, Eczacıbaşı, Türkiye) and 10 mg/kg xylazine (Rompun, Bayer, Germany) were used for anesthesia. All rats were sacrificed via cervical dislocation when the drug doses were completed. Then, their hippocampus was surgically removed.

The experiment involved four groups of rats: control (Cont), cisplatin (Cis), selenium (Se), and cisplatin+selenium (Cis+Se). The experimental procedure is presented in Figure 1.

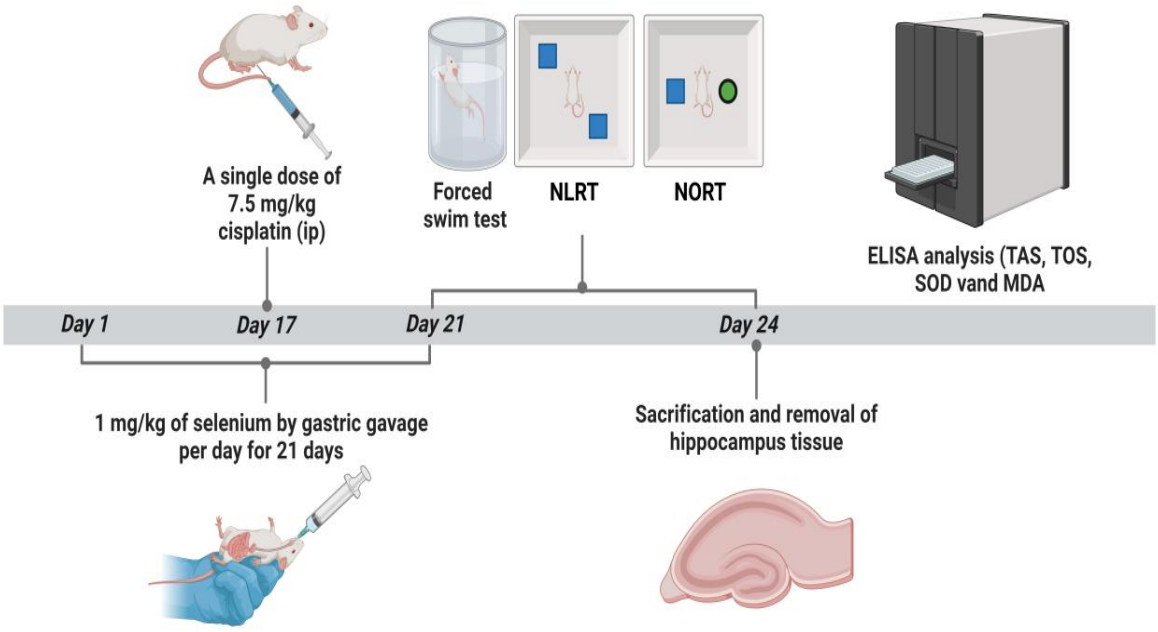

Figure 1. Schematic representation of the timeline of experimental procedures with the start of the experiment taken as day 0

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Experimental groups

Control group (n=8): A single dose of 2 ml physiological saline was administered intraperitoneally, and 1 ml physiological saline was administered by gastric gavage.

Se group (n=10): Selenium (sodium selenite, CAS;10102-18-8, Sigma-Aldrich, Germany) was administered by gastric gavage at a dose of 1 mg/kg for 21 days, and a single dose of 2 ml physiological saline was administered intraperitoneally [19].

Cis group (n=10): Cisplatin (Koçak Farma Co., İstanbul, Türkiye) was administered intraperitoneally at a single dose of 7.5 mg/kg, and for 21 days, 1 ml of physiological saline was administered by gastric tube [20].

Cis+Se group (n=10): A single dose of cisplatin at 7.5 mg/kg was administered intraperitoneally, and selenium was administered by gastric gavage at 1 mg/kg for 21 days [19, 20].

Analysis of TAS, TOS, MDA, and SOD in rat hippocampus tissue using ELISA

Prior to experimentation, total protein content was determined using the Folin-Ciocalteu method. Tissues stored at -80°C were homogenized in 0.01 M phosphate-buffered saline and subsequently analyzed for TAS (Cat no.: E1710Ra), TOS (Cat no.: E1512Ra), MDA (Cat no.: E0156Ra), and SOD (Cat no.: E0168Ra) using commercial rat ELISA kits (BT LAB, Zhejiang, China). After incubation with biotin antibody and horseradish peroxidase conjugate at 37°C, the substrate reagent was added, and absorbance was measured at 450 nm using a Clariostar Microplate Reader.

Novel location recognition tests and novel object recognition tests

Although many models are available to test visual recognition memory in rats, the protocol defined by Ennaceur and Delacour in 1988 was used in this study [21]. For this test, a 50×50×46 cm matte white open space box with a base divided into small squares was used. Objects of different colors and shapes (three identical copies each) were used in the experiment [22]. The objects were fixed to the ground to ensure that they could not be moved by the rats during the experiment. NLRT and NORT were performed on days 61 and 62. To mitigate any anxiety resulting from entering an unfamiliar setting, each animal underwent an acclimatization test consisting of two 20-min sessions before the experiment. Testing began 24 h after the last acclimatization session. First, two identical objects were placed in the box, close to each other (at a distance of 10 cm), aligned with two adjacent edges (recognition session). The rat was then placed in the box and kept in the box for 5 min. Subsequently, the rats were removed. Both objects were replaced by an identical object. Another identical object was placed in a different location inside the box. For short-term memory, the rat was placed back in the box 60 min after the recognition session and kept in the box for five minutes [23]. During both tests, the time the rats spent exploring the objects was recorded. This behavior was defined as the rat moving its nose 2 cm closer to the object and touching the object. To assess long-term memory, 24 h after the recognition session, the same and novel objects were placed (in the same location as the previous objects), the rat was kept in the box for 5 min, and the behavior of exploring the objects was recorded. A rat with good recognition memory is expected to allocate a greater amount of time to the exploration of a novel object than to the exploration of a familiar object. The rats' interactions with familiar and novel objects were measured in seconds using NLRT and NORT. This included the time spent with each object individually and the overall time spent with both objects. The recognition index (RI) is a quantitative measure to remember information about a novel object and is the ratio of the time spent exploring the novel object to the total object exploration time [24]. NLRT, NORT, and FST tests were performed by the same researcher in a quiet and isolated room at the same time every day to minimize daily changes.

The forced swimming test

This test, developed by Wu et al. [22], is widely used among behavioral tests to examine stress responses and screen for antidepressant drugs. In this test, the prolonged period of immobility is generally considered "behavioral despair", which is an animal-like manifestation of human depression. The following experimental protocol was utilized in the current study: On the first training day, each rat was trained for 15 minutes in a cylindrical container. This container had a 27 cm diameter, was 50 cm high, and was filled with 30 cm of water at 24-26°C, ensuring the rats' tails did not touch the bottom. On the second day, rats were immersed in water and analyzed for 5 minutes.

Statistical analysis

Normality of all data was assessed using the Shapiro-Wilk test. Data for FST, NLRT, NORT, TAS, TOS, and SOD were found to be normally distributed and were analyzed using one-way ANOVA, with Student-Newman-Keuls multiple comparison tests performed post-hoc. For MDA, which demonstrated non-normal distribution, the Kruskal-Wallis test was employed, followed by Dunn's multiple comparison test. Descriptive statistics were expressed as mean ± standard error of the mean (SEM) for normally distributed variables, whereas the MDA values, which did not follow a normal distribution, were presented as median (25^{th}–75^{th} percentiles).All statistical analyses were conducted in SigmaStat 3.5, and graphs were created using OriginPro 9.1. A significance level of $p<0.05$ was used for all tests.

Results

Effect of selenium administered for 21 days on weight loss in rats administered a single dose of 7.5 mg/kg intraperitoneal cisplatin

Measures ANOVA was conducted across four groups (Control, Cis, Se, Cis+Se) and three time points (Day 0, Day 1, and Day 2). The analysis revealed a statistically significant interaction effect between the group and day factors [$F_{(6, 68)}$=54.414, p=0.001]. This significant interaction indicates that the weight changes of the groups differed over time. When examining the daily weight changes within each group, both the Control and Se groups showed a statistically significant increase in weight over time (p=0.001). Conversely, the Cis and Cis+Se groups exhibited a statistically significant decrease in weight over time (p=0.001). At the end of the second day, inter-group weight differences were examined, and statistically significant weight differences were found among all group pairs (p=0.001) (Figure 2). These findings align with previous research, confirming that weight loss and decreased appetite are common and early adverse effects associated with cisplatin chemotherapy [25, 26].

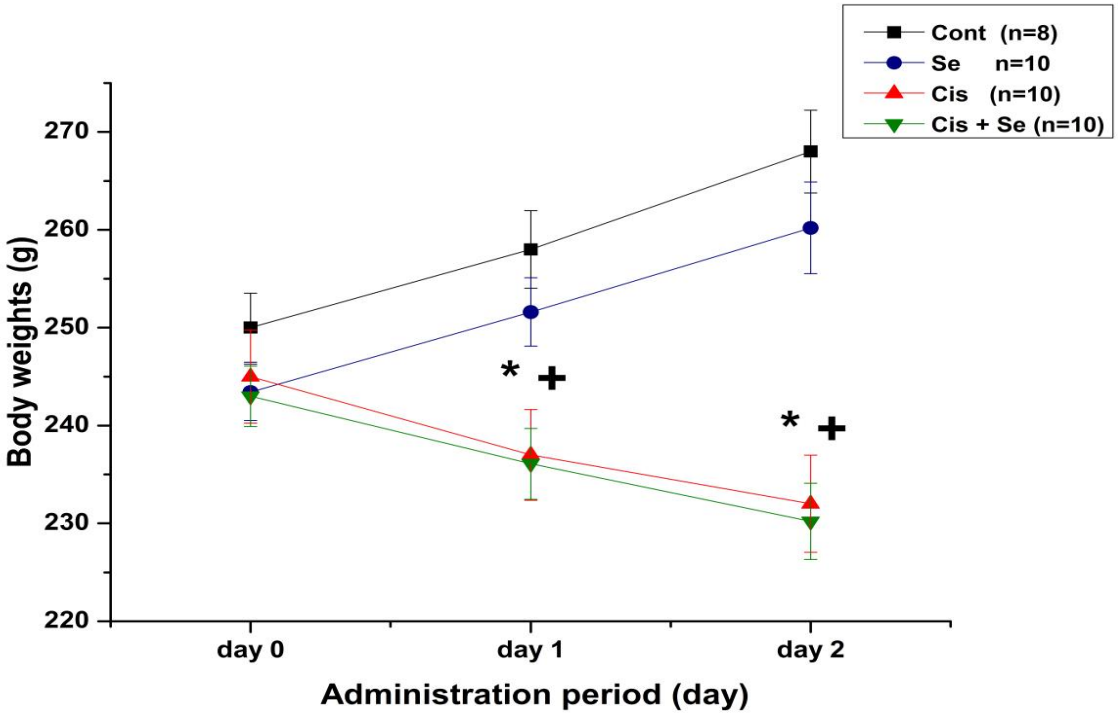

Figure 2. Body weight of control and experimental groups after cisplatin treatment

Values are means±standard error (control: n=8; experimental: n=10)
* indicates significance vs. Cont group, + indicates significance vs. Se group

Mitigation of cisplatin-induced adverse effects on short- and long-term memory by selenium

To evaluate the effect of selenium on cognitive impairment induced by cisplatin administration, we assessed STM using the NLRT and LTM using the NORT. To assess memory performance, we used a discrimination index calculated as the ratio of time spent exploring the novel object to the total exploration time (Figure 3). Results showed a trend towards a lower discrimination index in the experimental groups compared to the Cont group in STM (p=0.05). When LTM was evaluated, Cis significantly reduced the discrimination index compared to the Cont group (p=0.05). However, this decrease was significantly attenuated when selenium was co-administered with cisplatin (p=0.014), suggesting that selenium may have a protective effect against cognitive impairment induced by cisplatin.

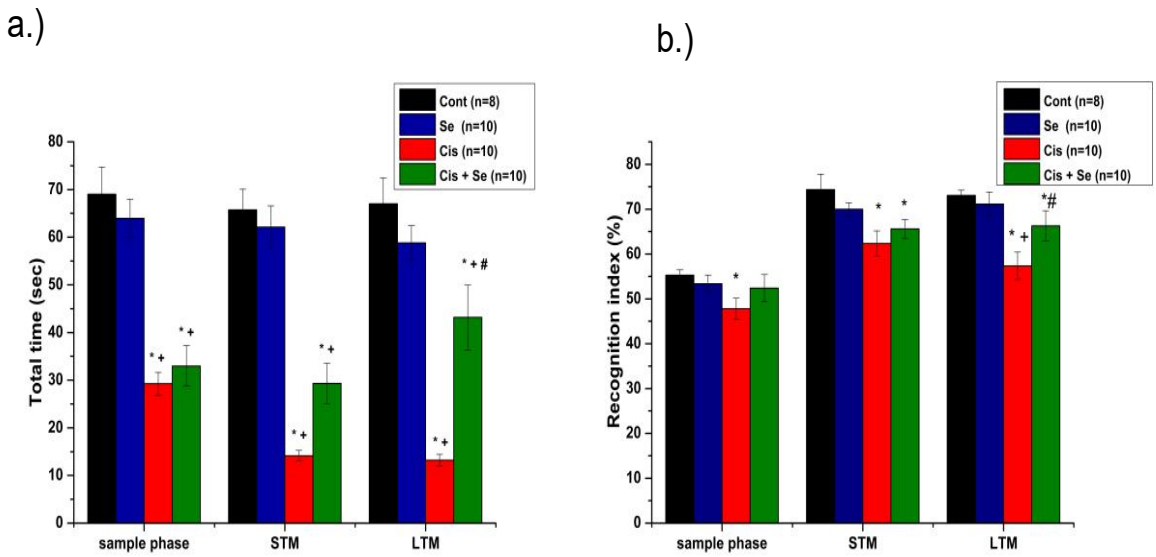

Figure 3. Comparison of the short-term and long-term memory

a. Total times, b. Recognition index % for control and experimental groups. Values are means±standard error (control: n=8; experimental: n=10)
* indicates significance vs. Cont group, + indicates significance vs. Se group, # indicates a significant vs Cis group

Mitigation of cisplatin-induced adverse effects on depression by selenium

After 21 days of selenium supplementation, significant differences were observed in the forced swimming test between the cisplatin-treated groups ($F_{(3,34)}$=53.584, p=0.001). Compared to the Control group, the cisplatin-treated group also showed a significant increase in immobility time (p=0.001). In particular, the Cis+Se group showed a significant decrease in immobility time compared to the cisplatin-only group (p=0.001), suggesting a potential ameliorative effect of selenium supplementation (Figure 4).

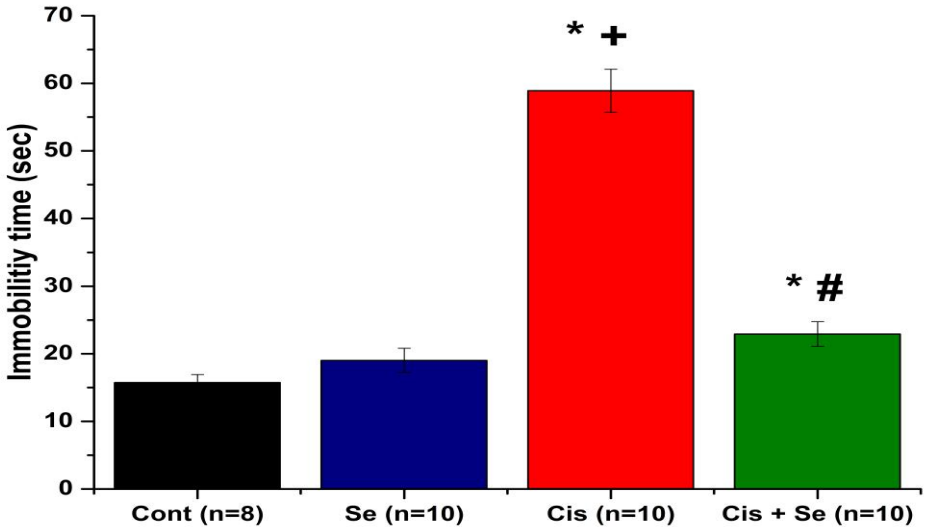

Figure 4. Results of the forced swim test for control and experimental groups

Values are means±standard error (control: n=8; experimental: n=10)
* indicates significance vs. Cont group, + indicates significance vs. Se group, # indicates a significant vs Cis group

Mitigation of cisplatin-induced oxidative stress by selenium

According to the One-Way ANOVA results, statistically significant differences were observed in the levels of TAS [$F_{(3, 34)}$=5.368, p<0.004], TOS [$F_{(3, 34)}$=4.843, p<0.007] and SOD [$F_{(3, 34)}$=5.459, p=0.004]. The Kruskal-Wallis H test for malondialdehyde (MDA) levels also showed a significant difference between the groups [H=12.832, df=3, p=0.005]. There was a significant decrease in the TAS levels of the Cis group compared with the Control and Se groups (p=0.03 and p=0.005, respectively) (Figure 5a), and a parallel significant increase was observed in the TOS levels of the Cis group (p=0.02 and p=0.006, respectively) (Figure 5b). In addition, a significant decrease was observed in the TAS level of the Cis+Se group compared with that of the Se group (p=0.03). A significant increase was observed in the MDA levels of the Cis group compared with the Control and Se groups (p=0.05) (Figure 5c). There was a significant decrease in the SOD levels of this group (p=0.01 and p=0.004, respectively) (Figure 5d). These results indicated that the decrease in TAS and SOD levels and the increase in TOS and MDA levels induced by cisplatin were regulated by selenium treatment (Table 1).

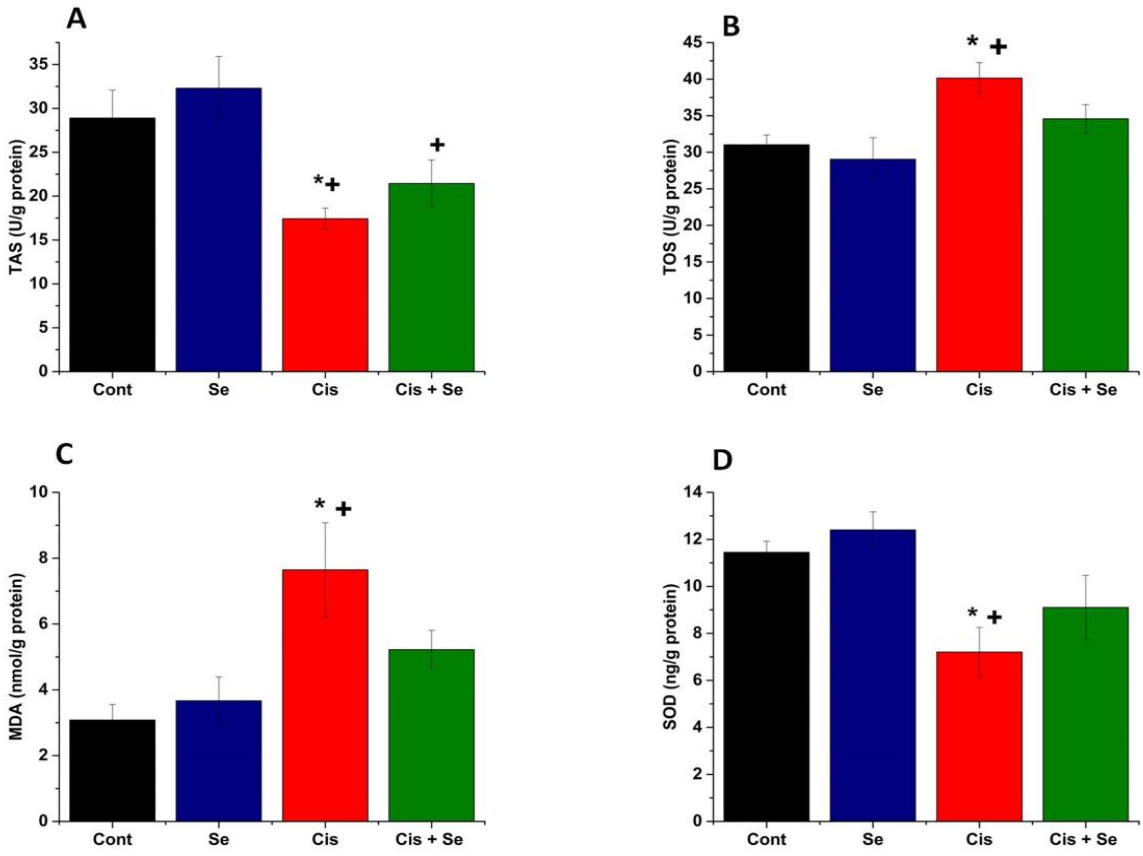

Figure 5. Comparison of the oxidative stress parameters

a. Total antioxidant status b. Total oxidant status c. Malondialdehyde, d. Superoxide dismutase measured in the hippocampus tissue of the rats in control and experimental groups, Values are means±standard error (Control: n=8; experimental: n=10)
* indicates significance vs. Cont group, + indicates significance vs. Se group

Table 1. Comparison of TAS, TOS, MDA and SOD activity

	Cont (n=8)	Se (n=10)	Cis (n=10)	Cis+Se (n=10)	Test Result	Significant Group Comparisons
TAS U/g protein	28.89±3.20	32.30±3.60	17.41±1.21 ***+**	21.43±2.66 **+**	F(3, 34)=5.368, *p*=0.004	*Cis* ↓ *vs Cont p*=0.03 *Cis* ↓ *vs Se p*=0.005 *Cis+Se* ↓ *vs Se p*=0.03
TOS U/g protein	31.01±1.34	29.03±2.96	40.15±2.09***+**	34.56±1.95	F(3, 34)=4.843, *p*=0.007	*Cis* ↑ *vs Cont p*=0.02 *Cis* ↑ *vs Se p*=0.006
MDA nmol/g protein	2.7(2.4-3.9)	3.0(2.0-4.7)	7.0(4.0-8.4) ***+**	5.2(4.0-6.2)	H=12.832, df=3, *p*=0.005	*Cis* ↑ *vs Cont p*=0.05
SOD ng/g protein	11.44±0.47	12.40±0.76	7.24±1.05***+**	9.10±1.37	F(3, 34)=5.459, *p*=0.004	*Cis* ↓ *vs Cont p*=0.01 *Cis* ↓ *vs Se p*=0.004

ANOVA and Student-Newman-Keuls post-hoc analysis were applied for TAS, TOS, and SOD, while Kruskal-Wallis H test and Dunn's post-hoc analysis were used for MDA.Values are presented as mean ± SEM (normal distribution) or median (25^{th}–75^{th} percentiles) (non-normal distribution) ***** indicates significance vs. Cont. group, **+** indicates significance vs. Se group.

Discussion

In our study, the protective effect of selenium on cisplatin-induced neurotoxicity was evaluated by measuring the behavioral effects and oxidative stress parameters by giving a single dose of 7.5 mg/kg cisplatin to rats that were given selenium (1 mg/kg gavage) supplementation for 21 days.

In our study, after two days of weight monitoring, the control group showed a 6% weight increase, and the Se group showed a 7% increase. However, the Cis group experienced a 4.5% weight decrease, and the Cis+Se group experienced a 5% decrease. It is known that gastrointestinal problems caused by cisplatin, such as nausea, vomiting, and slow digestion, contribute to weight loss [27, 28]. This is a well-known side effect of cisplatin, observed in both clinical settings and animal models [28]. Indeed, necropsy findings revealed that the stomachs and intestines of animals administered cisplatin were still full of undigested food. These data suggest that weight loss occurs due to excessive saturation of the gastrointestinal tract and, therefore, reduced intestinal motility.

The hippocampus plays a crucial role in memory formation and spatial processing. In adults, the integration of newly generated neurons into hippocampal circuits is essential for hippocampal neurogenesis and the maintenance of healthy cognitive function [29]. In the current study, in NLRT, performed to evaluate short-term memory, the ability to recognize the same object was impaired in the Cis group when the location of a previously familiarized object was changed. In the rats that were administered Se along with Cis, the results were relatively better than those in the Cis group, but there was no significant difference between these two groups. Many studies have reported that selenium has a neuroprotective effect [30, 31]. A study in which 5 mg/kg of cisplatin was administered to rats once a week for 5 weeks showed that this treatment significantly reduced the time spent recognizing a novel object in NORT [32]. In our study, despite using a different cisplatin dose, the ability to recognize a novel object based on previous experience with a familiar object was impaired in the cisplatin group compared with the control group. Selenium administration alleviated the cisplatin-induced deficit, resulting in a significant difference between the Cis+Se and Cis groups. When evaluated collectively, our results suggest that selenium can mitigate the cognitive deficits induced by the administration of a single 7.5 mg/kg dose of cisplatin.

Recent studies utilizing animal experimental models to evaluate cisplatin neurotoxicity have also confirmed the development of serious mood disorders, such as increased anxiety levels, following cisplatin administration [10, 33]. Similarly, in our study, there was a significant increase in the duration of immobility in the

cisplatin group compared with that in the control group. Interestingly, the duration of immobility in the Cis+Se group was reduced compared with that in the cisplatin group, suggesting that selenium could potentially decrease the level of depression induced by cisplatin. Selenium is known to act as a cofactor in the synthesis of neurotransmitters, especially serotonin and dopamine [34]. It is thought that this cofactor effect is the reason why selenium reduces depression-like effects, thus correcting cisplatin-induced neurotransmitter imbalances and alleviating depression and anxiety symptoms.

The severity of oxidative stress is evaluated by TAS, TOS, MDA, and SOD levels [35, 36]. Reactive oxygen molecules are neutralized by antioxidants [37]. Oxidative stress and depletion of antioxidant enzymes are among the mechanisms by which cisplatin causes damage [38]. Therefore, treatment with antioxidants may help rebalance endogenous antioxidants to normal levels and combat tissue damage from cisplatin. One of the most important antioxidants is selenium, which has been identified as an anti-carcinogen. To understand the possible mechanism of selenium underlying its neuroprotective effects, we also measured the levels of oxidative stress markers, including TAS, TOS, MDA, and SOD. Previous studies have clearly shown that cisplatin increases oxidative stress and depletes antioxidants [39, 40]. Consistently, in our study, the TAS level decreased while the TOS level increased in the cisplatin group. Analysis of parameters such as TAS and TOS allows for a complete assessment of oxidative stress [41]. In other studies in which cisplatin was administered to rats at the same dose as in our study, an increase in the MDA level was found in brain tissue and in the HT-22 mouse hippocampal neuronal cell line [42, 43]. We also observed a significant increase in MDA in the cisplatin group. In the literature, the SOD level was found to be lower in the cisplatin group than in the control group [40]. Consistently, we determined the SOD level to be lower in the cisplatin group in our study. Cisplatin administration resulted in a significant increase in TOS and MDA levels, which are markers of oxidative stress, while TAS and SOD levels showed a marked decrease. However, when selenium supplementation was administered concurrently with cisplatin, no statistically significant changes were observed in these oxidative damage parameters compared to the control group. This finding suggests that selenium may have a potential protective effect against cisplatin-induced oxidative stress. Because selenium is one of the cornerstones of our antioxidant defenses because it is a cofactor that is essential for the functioning of the enzyme glutathione peroxidase (GPx) [44]. Studies have consistently associated selenium deficiency with a reduction in GPx activity, subsequently leading to an increase in oxidative stress [44, 45].

This study has some limitations. First, using only male rats prevented the evaluation of gender-specific effects of cisplatin and selenium. Second, the acute cisplatin dose used may not fully reflect the effects of chronic exposure. In order to address these limitations, it is recommended that both male and female rats be included in the experimental groups in future studies. Furthermore, considering the different doses and frequencies of selenium and cisplatin administered in the literature, it is also important to create experimental groups with acute/chronic doses in future studies. Finally, molecular and histopathological analyses are recommended for a more comprehensive understanding.

The findings from this study showed that selenium supplementation may have partial limited restorative effects on long-term memory impaired by a single dose of 7.5 mg/kg cisplatin. The results of behavioral experiments supported by the measurement of oxidative stress markers showed that selenium may alleviate depression levels. Based on these findings, it is conceivable that selenium could be considered among potential neuroprotective agents against cisplatin, pending further research to determine optimal dosage.

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Author's contributions: M.A. constructed the main idea and hypothesis of the study. M.A. and G.A. conducted the data collection and M.A. performed the processing and analysis of the data collected. The manuscript was written by M.A. B.Ö. provided supervision throughout the research process and performed a critical review of the manuscript.

Conflict of interest: The authors declare that they have no known competing financial interests or personal relationships that could have influenced the work reported in this paper.

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