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Neuroprotection by dexpanthenol in a single-dose methotrexate mouse model

Tek doz metotreksat modelinde dexpanthenolün nöroprotektif etkileri: dişi fare çalışması

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ABSTRACT

Aim: Methotrexate (MTX) used in ectopic pregnancy can induce neurotoxicity and cognitive deficits. We evaluated whether dexpanthenol (DEX) mitigates anxiety-/depression-like behaviors and learning/memory impairment following single-dose MTX.

Materials and Methods: Female mice were assigned to three groups (n=7/group): Control (saline), MTX (40 mg/kg, i.p.), and MTX+DEX (500 mg/kg, i.p., 1 h before MTX). Twenty-four hours after MTX, animals underwent open field (OF), tail suspension (TST), and novel object recognition (NOR) tests. Data were analyzed by one-way ANOVA with Tukey's post hoc test (α=0.05).

Results: MTX reduced time spent in the OF center, increased immobility in TST, and lowered the NOR discrimination index. DEX significantly attenuated these MTX-induced changes, decreasing anxiety-/depression-like behaviors and improving cognitive performance.

Conclusion: DEX shows neuroprotective effects against single-dose MTX-induced behavioral and cognitive deficits in female mice, supporting its potential to mitigate chemotherapy-related neurotoxicity.

Keywords: methotrexate; dexpanthenol; anxiety; depression; cognitive function; mice

ÖZ

Amaç: Ektopik gebelikte yaygın kullanılan metotreksatın (MTX) nörotoksik etkileri öğrenme ve hafıza bozukluklarına yol açabilir. Bu çalışma, tek doz MTX uygulaması sonrası ortaya çıkan bilişsel ve duygudurum değişikliklerine karşı deksapantenolün (DEX) olası koruyucu etkilerini araştırmayı amaçladı.

Gereç ve Yöntemler: Dişi fareler üç gruba ayrıldı (n=7/grup): Kontrol (SF), MTX (40 mg/kg, i.p.) ve MTX+DEX (DEX 500 mg/kg, i.p., MTX'ten 1 saat önce). MTX enjeksiyonundan 24 saat sonra açık alan (OF), kuyruk süspansiyon testi (TST) ve yeni nesne tanıma (NOR) testleri uygulandı. Veriler tek yönlü ANOVA ve Tukey testi ile değerlendirildi (p<0,05).

Bulgular: MTX, OF'de merkezde kalma süresini azalttı ve TST'de hareketsizlik süresini artırdı; NOR ayrım indeksinde düşüşe yol açtı. DEX, bu MTX-ilişkili etkileri anlamlı olarak hafifletti; anksiyete ve depresyon benzeri davranışları azalttı ve bilişsel performansı iyileştirdi.

Sonuç: DEX, tek doz MTX uygulaması sonrası gelişen anksiyete/dep. benzeri davranışlar ve bilişsel bozulmaya karşı nöroprotektif etki göstermiştir. Bulgular, kemoterapiye bağlı nörotoksisiteyi azaltmada DEX'in potansiyel bir tedavi seçeneği olabileceğini düşündürmektedir.

Anahtar Kelimeler: metotreksat; deksapantenol; anksiyete; depresyon; bilişsel işlev; fare

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INTRODUCTION

Ectopic pregnancy is a condition in which the embryo implants in an abnormal location outside the uterus, usually in the fallopian tube, and can pose serious life threats if left untreated. Such pregnancies can be medically treated with antineoplastic drugs such as methotrexate, which inhibit cellular division by targeting trophoblast cells, which usually multiply rapidly (1). Methotrexate, or MTX, amethopterin, and 4-amino-10-methylfolic acid is an antineoplastic drug used in the cure of numerous solid tumors, inflammatory disorders, molar pregnancy and hematologic malignancies, including breast cancer (2) In ectopic pregnancy, methotrexate is administered intramuscularly in single dose, double dose and variable (multiple) doses (1). In addition to these, direct injection into the mass is also available. Multiple methotrexate and folic acid are administered as an alternative regimen (1mg/kg methotrexate on days 1, 3, 5 and 7, folinic acid on days 2, 4, 6 and 8) (3). After the demonstration of treatment efficacy, the single-dose regimen has become one of the most commonly used treatment methods due to fewer side effects, fewer complications, and better patient compliance.

Nonetheless, the anticipated reduction in cancer mortality rates due to advancements in early identification and combined treatment modalities and success of methotrexate in the treatment of ectopic pregnancy presents healthcare professionals with the challenge of a rising incidence of Alzheimer's disease (3.2%), a complex condition (4). Cognitive pathologies due to MTX neurotoxicity are manifested by memory deficits, impaired spatial and non-spatial learning, distractibility, impaired emotional learning, and decision-making skills (5). Widely used in animal studies, MTX has been reported to impair cognitive functions after intraperitoneal injection in both rats and mice, as well as male and female animals with and without cancer (6-7-8-9-10). The neurotoxic effects of MTX are generally attributed to physiopathological conditions such as oxidative stress, neuroinflammation, and associated apoptosis and impaired neurogenesis. Therefore, targeting this toxicity with antioxidant and anti-inflammatory therapies may help to reduce the adverse effects of toxicity.

Dexpanthenol (DEX), which protects cells from free radical damage by protecting against lipid peroxidation through the synthesis of coenzyme CoA in cells, is actually an alcohol derivative of pantothenic acid, a B5 vitamin. DEX, which protects cells against apoptosis by raising glutathione levels, is known to protect tissues exposed to oxygen, such as skin, lungs, and eyes, as well as in wound healing (11-12). Recent studies have shown that DEX has neuroprotective effects in experimental animal models, and the number of reports in the literature supporting these findings continues to grow. DEX prevented colistin-induced brain tissue damage by inhibiting oxidative stress and inflammation (13) and also reduced malondialdehyde production and restored glutathione levels in middle cerebral ischemia-reperfusion injury (14) . It also reduced peripheral traumatic nerve injury (15) and improved cognitive functions by regulating inflammation and cholinergic pathways in the Alzheimer rat model (16). It improved lipopolysaccharide-induced brain injury by reducing oxidative stress and inflammation, restoring BDNF/CREB pathways, and inhibiting apoptosis (17). It ameliorated spinal cord ischemia-reperfusion (18) and traumatic brain injury (19-20), as well as hypoxic-ischemic encephalopathy (21), by regulating oxidative stress and inhibiting apoptosis. The literature on the effects of DEX on cognitive functions in neurodegenerative disease models is insufficient, and there is no study that we know of investigating the effects of this substance in female rodents against MTX-induced neurotoxicity. In this study, we tested the hypothesis that MTX-induced anxiety, depression, and learning-memory disorders can be treated with DEX, which has strong antioxidant and anti-inflammatory properties, and aimed to contribute to the development of a new treatment strategy against the neurotoxic effects of MTX.

MATERIALS AND METHODS

Methodology of research and group formation

This study was conducted using female mice aged 12 to 14 weeks, obtained from the Aksaray University Experimental Animal Research and Application Center. This unit, which is accredited by the appropriate governmental authorities, provided standardized environmental conditions for the animals, including temperature, lighting, and ventilation. The mice had unrestricted access to standard laboratory rodent chow and tap water throughout the study. At the onset of the experiment, all mice were randomly assigned to groups and housed in cages of identical size. A ten-day acclimatization period was observed before the study commenced, following approval from the local ethics committee. A total of 21 mice were utilized, with seven mice allocated to each group. The group assignments and the associated procedures executed are as follows: The initial group was identified as the control (CON) group; mice in this group did not receive any treatment as in the others but received saline injections in the same volume as the administered drug. The second group (MTX) consisted of mice treated with methotrexate. All mice were injected intraperitoneally (i.p.) with methotrexate (Metoart Con, Kocak Farma Drug and Chemical Industry A.Ş., Istanbul, Turkey) at a dose of 40 mg/kg 24 h before behavioral tests (22). The last group (MTXDEX) included mice treated with DEX. Mice in this group were injected with DEX (500 mg Bepanthene ampul, Bayer Corp., Leverkusen, Germany) at

a dose of 500 mg/kg i.p. 1 hour before MTX injection. All shots were administered by the same individual at the same time each day.

Behavioral Tests

Behavioral testing was conducted by the same researcher, commencing 24 hours post-MTX injection and continuing for a duration of two days. The mice were placed in the testing room one hour prior to the start of the procedure to allow for acclimatization to the new environment. Every effort was made to minimize the influence of external factors (such as noise, odors, lighting, etc.) on the behavioral assessments. Following each trial, the testing arena was sanitized with a 70% alcohol solution to eliminate potential confounding variables from previous subjects.

Open Field test

The open field test (OF) is employed to assess locomotor and anxiety-related behaviors in experimental animals. In this context, an empty 45x45x40h cm arena made of dark-colored material was preferred. The floor of the arena was imaginatively divided into 16 equal squares, and the four squares in the center were defined as the 'center' region, while the remaining squares were called the 'periphery'. During the experiment, mice were placed in the center of the OF arena and given 5 minutes to explore. Movements were monitored and recorded through video recordings. Locomotor activity was evaluated by measuring the total distance traveled and average speed of the mice, while the duration spent in the center was utilized to gauge anxiety levels (23).

Tail Suspension Test

Depression-like behavior of mice was analyzed using the tail suspension test. For this purpose, a 50 cm high maze was used, each placed 15 cm apart and with a hook at the top to suspend the mouse by its tail. The maze had the capacity to evaluate 4 mice at the same time, and screens were placed between the mice to prevent them from seeing each other. All mice were suspended with medical tape on their tails, and their behavior was video recorded for 6 minutes. The first 2 minutes of the video recordings were excluded from the analysis and the time the mice remained motionless was measured and used as a criterion to identify depression-like behaviors (24).

Novel Object Recognition Test (NOR)

The novel object recognition (NOR) test was employed to evaluate the learning and memory performance of mice. This test was conducted in an open-field arena, one day following the open field (OF) test, with the OF serving as the familiarization phase. The following day, two identical objects were affixed to the arena floor with double-sided tape, and the mice were allowed 5 minutes for unrestricted exploration. After a 1.5-hour interval, one of the objects was replaced with a novel object, and the mice were allowed to explore the arena for an additional 5 minutes. The total time spent interacting with the novel object and the familiar object was recorded. Interaction was defined as either touching the objects or approaching them within 2 cm with the nose. The discrimination index was calculated based on these times and used for inter-group comparisons. Discrimination index = (time of interest in the novel object - time of interest in the familiar object) / (time of interest in the novel object + time of interest in the familiar object) (25).

Dose selection and safety

The MTX dose (40 mg/kg, i.p.) was chosen based on prior mouse work showing acute hippocampal dysfunction and behavioral deficits after a single injection. The DEX dose (500 mg/kg, i.p., 1 h prior) was selected in line with multiple rodent neuroprotection studies that used 500 mg/kg i.p. and reported functional and histological benefits without study-period mortality (e.g., traumatic brain injury, head injury, Parkinson's model, and neonatal hypoxic-ischemic encephalopathy). Additionally, safety data indicate very low acute toxicity for dexpanthenol (oral LD50 >10,000 mg/kg in rats), supporting a wide therapeutic margin; nevertheless, dose-route differences were considered and animals were monitored by a veterinarian throughout the protocol (19-20-21).

Statistical Analysis

Data were analyzed in IBM SPSS v26.0. One-way ANOVA was used for comparisons among three independent groups, followed by Tukey's HSD for pairwise contrasts. Results are presented as mean ± SD. For figures/tables, groups sharing the same superscript letter do not differ significantly; different letters indicate $p<0.05$.

RESULTS

Overall toxicity and changes in body weight

We recorded the body weights of all mice before and at the end of the study. Nonetheless, no statistically significant difference was detected between the groups regarding weight alterations from the commencement to the conclusion of the study (Fig. 1, $p > 0.05$). Furthermore, no mice were lost during the study period due to MTX toxicity. A veterinary surgeon regularly examined the mice every day, observing no macroscopic health problems.

Effect of DEX on anxiety-like behaviour

In our study, a single intraperitoneal injection of 40 mg/kg methotrexate induced an elevation in anxiety-like behaviors in mice. The duration spent in the central zone, utilized as an indicator of anxiety in the OF test, was seen to be diminished in MTX-treated mice relative to the control group (Fig. 2, $p<0.05$). Furthermore, DEX therapy alleviated this MTX-induced issue, resulting in a statistically significant increase in the total time spent in the center by the MTX

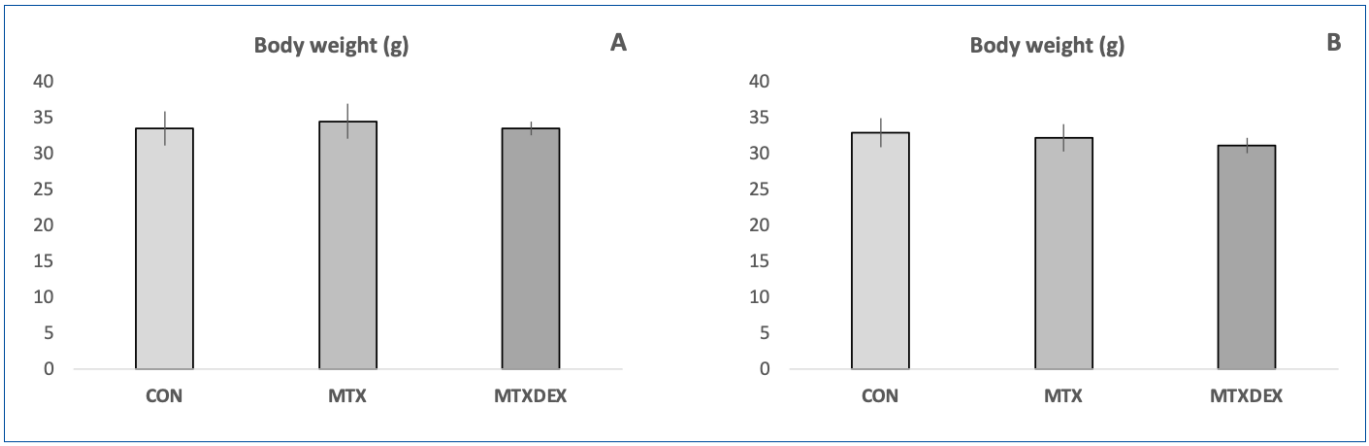

Figure 1. The body weight of the mice was unaffected by both MTX and DEX in this study. (A) Body weights before Mtx administration, (B) Body weights at the end of the study. The data are expressed as the means ± SD. There was no difference between the averages expressed with the same letter index, while the group averages expressed with different letter indices were statistically different (one-way ANOVA followed by Tukey's post hoc test).

group (Fig. 2, $p<0.05$). No substantial difference was seen between the groups concerning the two measures utilized for assessing locomotor activity in the OF test. The overall distance traveled and the average speed of the mice in the arena exhibited no significant differences across all groups (Fig. 2, $p > 0.05$).

DEX improves depression-like behaviour

In our experiment, we used the tail suspension test maze to assess depression-like behavior. The difference between the immobility times recorded in each mouse during the test was investigated. Statistical analysis revealed that mice in the MTX group exhibited

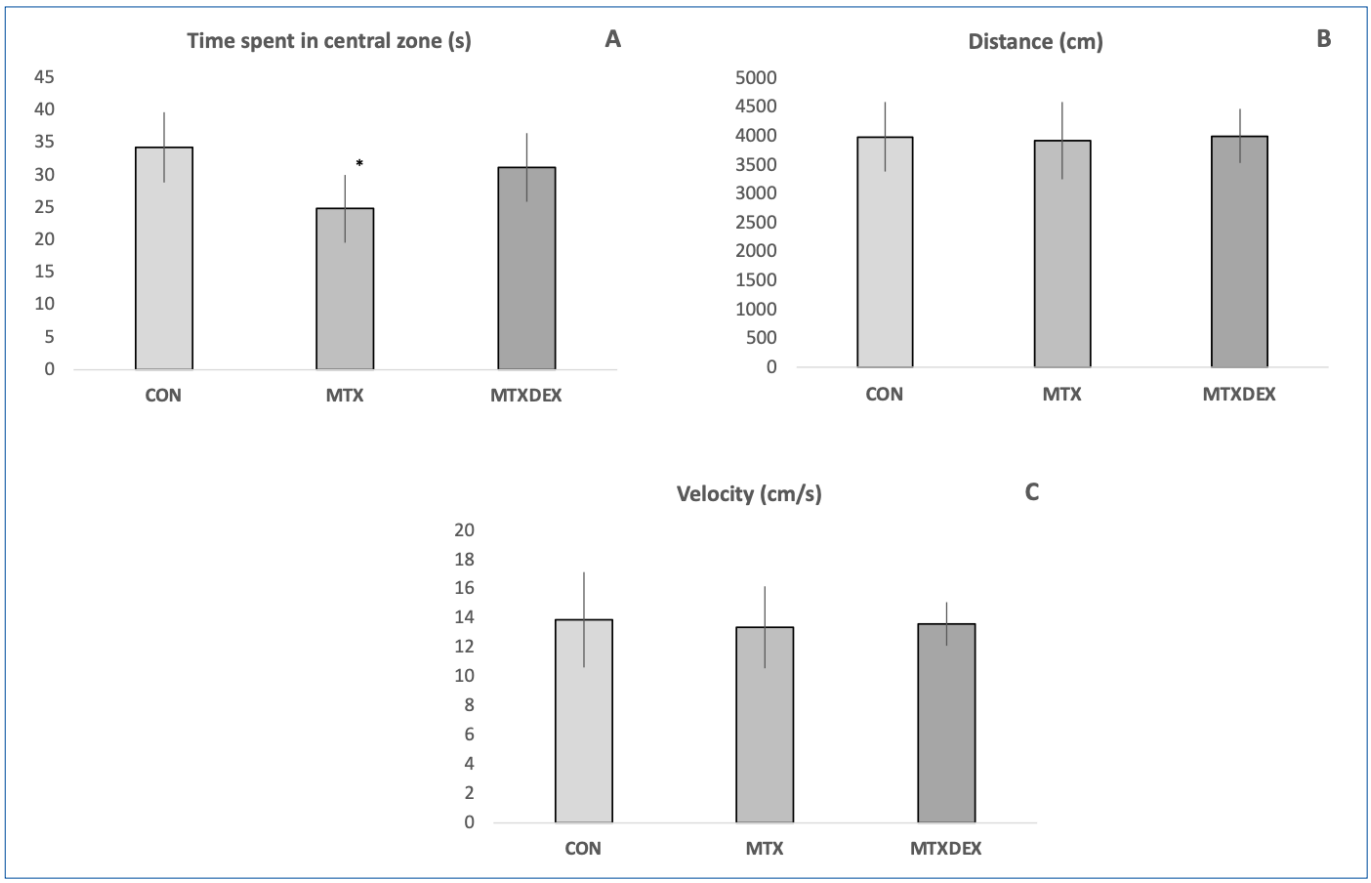

Figure 2. Effect of DEX on Mtx-induced impaired anxiety-like behaviors on the open field data:, the time spent in central zone (A), total distance traveled (B) and average movement velocity data in female mice. Data were expressed as mean ± SD. Asterisk (*) indicates significance compared with other groups ($p < 0.001$), (one-way ANOVA followed by Tukey's post hoc test).

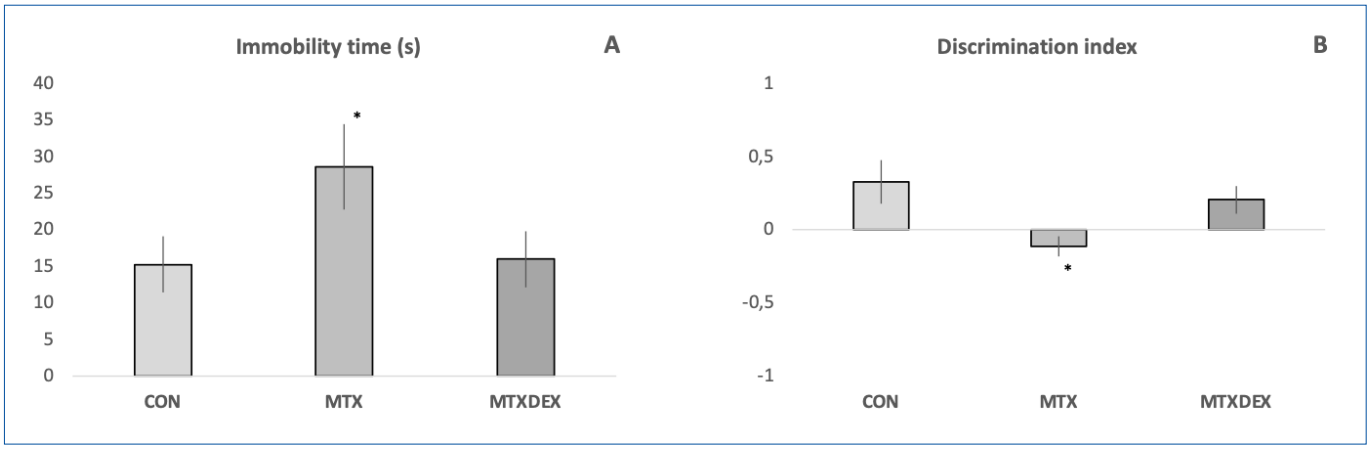

Figure 3. Effect of Dex on Mtx-induced impaired depression-like behaviors and learning and memory activities. Immobility time (A) in tail suspension test and discrimination index (B) in novel object recognition test. Data were expressed as mean ± SD. Asterisk (*) indicates significance compared with other groups ($p < 0.001$), (one-way ANOVA followed by Tukey's post hoc test).

more immobility behavior. Based on this, it was determined that mice in this group exhibited a behavior more similar to that of depressed mice compared to the control group. This depression-like behavior induced by MTX was alleviated by DEX treatment, which resulted in a significant reduction in the amount of time spent sedentary during the test (Fig.3A).

Effect of DEX on MTX-induced cognitive impairment

The assessment of the cognitive and memory functions of mice was conducted utilizing the new object recognition test. In this test, an OF arena is used, and all mice are kept in the arena with two similar objects for at least 5 minutes during the training phase. One of the objects is replaced after 1.5 hours, and if more interested behavior is observed with the new object, the cognitive activity of that mouse is considered normal. In our study, we found that MTX treatment impaired learning and memory activity assessed by the NOR test, and the discrimination index used in this test was lower in the MTX group compared to the control (Fig. 3B, $p<0.05$). However, DEX treatment ameliorated this MTX-induced impairment, as the discrimination index was closer to the control group than to the MTX group. The discrimination index was statistically increased in the DEX group compared to the MTX group (Fig. 3B, $p<0.05$).

DISCUSSION

Ectopic pregnancy (EP) accounts for between one and two percent of all pregnancies, and ruptured EP is responsible for two and a half percent of all deaths that occur during pregnancy. This presents a substantial challenge to public health. Pharmacological intervention is the primary treatment for EP, with methotrexate (MTX) being the therapeutic method that undergoes the most widespread application (26-27). Although chemotherapeutic drugs, especially MTX, are effective in the treatment of pathologies such as EP, they may cause a number of undesirable side effects. One of these side effects is cognitive impairment, which can seriously affect the quality of life of patients. This has led health professionals to increase their efforts to understand and manage cognitive dysfunctions. Although recent research has focused on developing solutions to reduce these side effects, the physiopathological mechanisms underlying these disorders need to be examined in more depth in order to design effective interventions. DEX is known as a compound with potent anti-inflammatory and antioxidant properties. In this study, we investigated the potential ameliorative effects of DEX on MTX-induced cognitive side effects. In the study, the effects on anxiety and depression-related behaviors and cognitive functions pertaining to learning and memory following MTX administration were evaluated using a mouse model. The findings revealed that MTX exposure led to a significant increase in anxiety and depression-like behaviors and impaired learning and memory functions. However, treatment with DEX was effective in preventing these cognitive problems, and these results suggest that DEX may be a therapeutic option against MTX-induced neurotoxicity.

MTX-induced neurotoxicity has been extensively described in experimental animal models. MTX (37.5 mg/kg) administered to female rats caused impairments in cognitive functions such as spatial memory, task acquisition, and processing speed during the subacute period. Another study reported that MTX-induced cognitive impairment was associated with decreased hippocampal cell division, impaired neuronal cell survival, and decreased number of immature neurons (28). In another study in rats, it was reported that MTX-induced cognitive impairment was associated with a decrease in hippocampal neural stem cells, oxidative stress, and

apoptosis (29). MTX induces microglial activation and apoptosis by causing oxidative stress and neuroinflammation, and this is accompanied by cognitive impairment (9). MTX also shows effects at the maternal level. MTX injection to mother rats on day 17 of gestation caused behavioral changes in the offspring 6-9 weeks after birth. A significant increase in anxiety-like behavior was observed in the offspring. In addition, a significant increase in the immobility time of the pups was detected in the forced swimming test in which depression-like behaviors were evaluated (30). The neurotoxic effects of MTX are not only acute but also persist in a chronic manner. MTX treatment of both male and female rat pups leads to impairment of cognitive functions even approximately 1 year after treatment. This impairment was associated with decreased neurogenesis, increased neuronal apoptosis, and increased microglial activation. Furthermore, the most important finding of this study was the observation that female rats were more affected by the MTX treatment protocol compared to male rats (31). In our study, a single administration of 40 mg/kg ip MTX to mice resulted in heightened anxiety-like behaviors measured by the OF test, the induction of depression-like behaviors evaluated by the TST test, and a decline in learning and memory capabilities assessed by the NOR test, corroborating findings from prior research in our laboratory (32-33). Neurotoxicity caused by MTX is strongly linked to oxidative stress and neuroinflammation. These physiological and pathological processes play a big role in cognitive function impairment through side effects like apoptosis and microglial activation. In this context, modulation of oxidative stress and neuroinflammation may be considered as a potential therapeutic approach to reduce MTX toxicity.

DEX is an oxidized derivative of pantothenic acid found in peripheral tissues and has anti-inflammatory and antioxidant effects in nerve cells. Studies have demonstrated the neuroprotective potential of this compound by reducing inflammatory cytokine levels and oxidative stress (34). In neurotoxicity induced by a chemotherapeutic agent in female rats, DEX was reported to activate the CREB/BDNF pathway, thereby modulating oxidative stress, apoptosis, and inflammation (34). Through the use of a rat model of hypoxic ischemic encephalopathy, DEX was able to control the levels of TNF-alpha and IL-6 cytokines, prevent neuronal death, and reduce oxidative stress (21). In a rat model of Parkinson's disease induced by rotenone, it has been reported that the neuroprotective property of DEX is associated with reduced neuronal loss in the striatum and prevention of oxidative damage and inflammation (35). In rats with traumatic brain injury, DEX reduced injury-induced lipid peroxidation, prevented oxidative stress and apoptosis, and activated the antioxidant defense system, and less neuronal damage was observed in histopathological evaluation (20). In LPS-induced neuroinflammation, a neuroprotective effect was reported by modulating the BDNF/CREB pathway by reducing oxidative stress and apoptosis (17). Streptozotocin-induced neuronal injury reduced inflammation and modulated the cholinergic pathway (16, Erdogan et al., 2022). Potential protective efficacy has been reported in cerebral ischemia-reperfusion injury by reducing oxidative stress and enhancing the antioxidant defense system (14). As mentioned above, although the neuroprotective properties of DEX have been demonstrated in various studies on chemotherapeutic agent-induced neurotoxicity, there is no research in the literature that we know of that examines the effects of this compound on chemotherapy-induced anxiety, depression, and cognitive dysfunctions. In this context, our study is the first to address the potential role of DEX in the management of chemotherapeutic treatment-induced neurological disorders through behavioral parameters. In our study, DEX decreased MTX-induced anxiety and depression-like behaviors and improved impaired learning-memory activity. However, although our study contributes important information to the literature in this field, it has some limitations. Firstly, there is no laboratory study to reveal the exact mechanism of the potential effect of DEX in MTX-induced cognitive impairment, but the fact that our study is the first report in this field will inspire new studies in this field. Secondly, female rodents were used in our study, and it is claimed that the short menstrual cycle in rodents would not significantly affect the metabolic effects of chemotherapy and DEX (34).

Limitations

This study has limitations. First, we did not perform an a priori power calculation; the sample size (n=7/group) was based on feasibility and alignment with prior behavioral studies. Second, only behavioral outcomes were assessed; mechanistic assays (oxidative stress, neuroinflammation, apoptosis, neurogenesis) were not measured. Replication with larger cohorts, mechanistic readouts, and both sexes is warranted.

CONCLUSION

In conclusion, in this study, we observed that the chemotherapy-induced cognitive impairment model induced by MTX led to a significant decrease in learning and memory functions as well as anxiety and depression-like behaviors. However, DEX treatment effectively prevented these neurological complications, significantly reduced anxiety and depression-like symptoms, and improved cognitive functions. These findings support that DEX, as a neuroprotective agent, provides significant protection against chemotherapeutic neurotoxicity. In the future, a more detailed investigation of the mechanisms of action of DEX at the molecular level, especially the pathways associated with neuroinflammation

and oxidative stress, has great potential for the development of more targeted therapeutic strategies. Furthermore, the need for larger studies for clinical applications will further confirm the role of DEX in the management of chemotherapy-induced neurological disorders. These findings provide an important basis for the development of new therapeutic approaches for the prevention of chemotherapy-induced neurological side effects. Although folinic acid treatment is applied in terms of toxic effects in multidose methotrexate treatments, we believe that our research, which started with the question of whether antioxidants should be added to the treatment to avoid possible toxic effects after single-dose methotrexate treatment, will shed light on future studies and treatment protocols.

Ethical Statement: The study was approved by the Aksaray University Institutional Ethics Committee for Animal Experimentation and Use (Protocol number:2024/9/58).

Author Contributions: Conceptualization, I.O.A and M.O.; investigation, M.O., and I.O.A.; methodology, M.O. and I.O.A.; validation, I.O.A., E.O., M.O., and H.E.; writing—original draft, I.O.A.; writing—review & editing, I.O.A., E.O., M.O., and H.E. All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest: The authors declare no conflict of interest.

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