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The Effects of Folic Acid on Testicular Histology, Sperm Quality, and Spermatogenesis Indices Following 3,4-Methylenedioxymethamphetamine Exposure in Adult Male Rats

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Original Article

Abstract

Background: There is an increasing concern over acute exposure of amphetamine and its derivative such as 3,4-methylenedioxymethamphetamine (MDMA) on male reproductive toxicity. Supplementary vitamins can reduce the oxidative stresses and repair the damages on reproductive organs. This experimental study was conducted to evaluate the effects of folic acid (FA) on reproductive indices, the antioxidant enzyme activities, and histological changes of testis on adult male rats treated by MDMA.

Methods: This experimental study was conducted on adult male Wistar rats. Animals were divided into 4 groups: control, MDMA, FA, and MDMA + FA. Animals received a dose of 10 mg/kg of MDMA and 1 mg/kg of FA for 7 or 14 days. Rats were anesthetized and sperm quality parameters (number, concentration, motility, and morphology), spermatogenesis indices [the mean seminiferous tubule diameter (MSTD), spermiogenesis index (SI), repopulation index (RI), and tubular differentiation index (TDI)], changes on testicular structure, antioxidant enzyme activities of catalase (CAT), superoxide dismutase (SOD), and malondialdehyde (MDA) beside serum level of luteinizing hormone (LH), follicle-stimulating hormone (FSH), and testosterone were measured. Data were analyzed, using the one-way analysis of variance (ANOVA) and SPSS software.

Findings: MDMA (both 7 and 14 days) caused significant changes in sperm quality ($P < 0.001$), spermatogenesis indices ($P < 0.001$), testicular histopathology, and level of LH, FSH, testosterone beside the antioxidant enzyme activities (SOD, CAT, and MDA) ($P < 0.001$). Supplementation of FA in association with MDMA partially reversed these parameters and made them close to the control group.

Conclusion: The results suggested that FA could reduce the adverse effect of MDMA on reproductive ability in adult male rats.

Keywords: Folic acid; N-Methyl-3,4-methylenedioxyamphetamine; Spermatozoa; Spermatogenesis; Rats

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Introduction

3,4-methylenedioxymethamphetamine (MDMA) is an amphetamine derivative that is called as ecstasy.[1] It is an addictive chemical compound which affects central nervous system (CNS) and is abused as a drug for psychoactive recreational experiences.[2] Ecstasy traditionally comes in pill and powder/crystalline form. Studies have shown that acute abusing of MDMA has negative effects on the normal function of cells and organs of the body in the form of pathophysiological changes. These changes can lead to tissue damage by the production of oxidative stress and they can be as inflammatory infiltrate, necrosis areas toxicity, changes in the antioxidant enzyme activities, and effect on cellular macromolecules like lipids, proteins, and deoxyribonucleic acid (DNA). Cardiac arrhythmias, hypertension (HTN), hyperthermia, liver injury, serotonin syndrome, coma, and death in some cases are some of the main acute effects of MDMA.[1,3-5]

It is estimated that global use of MDMA is as high as 1.2% (24.7 million) in the Middle East, Asia, Oceania, and North America. Ecstasy has become more popular in recent years, especially in young adult population aged 18-35 years, who are at the age of reproduction. The overall number of MDMA users in young adults increased over these years and it is estimated that 6%-12% of them used this drug at least once in their lifetime. Despite the number of MDMA users, there is no universally effective pharmacological treatment for MDMA abuse.[6]

Studies show that MDMA neurotoxicity can affect hypothalamic-pituitary-gonadal axis (HPG axis) which can affect gonadal steroid hormones especially testosterone.[7] In addition, oxidative stress can increase the reactive oxygen species (ROS) that affects the reproductive ability.[8] Long-term use of MDMA can increase DNA damage and histopathology changes in testes.[9]

Proper diets and use of supplements such as vitamins can greatly reduce the damages on cells of the reproductive system. One of these vitamins is folic acid (FA) or vitamin B9 that is necessary for normal synthesis of nucleotides and amino acid and has an important role in cell division.[10] Several studies confirmed the role of FA on normal spermatogenesis and oogenesis on both male and female animal models.[10,11] Low folate in seminal plasma increases DNA damages and may reduce men's reproductive abilities. A systematic review confirmed the beneficial effects of the antioxidants such as zinc, folate, selenium, carnitine, and vitamins on reproductive ability in infertile men.[12]

It is suggested that male-related factors in infertility are nearly 50% of cases. This study was designed to evaluate the effects of MDMA and its combination with FA on the reproductive activity of adult male rats. Accordingly, number, motility, morphology, and concentration of sperm and histopathological changes of testis were checked; besides, serum testosterone, luteinizing hormone (LH), and follicle-stimulating hormone (FSH) levels were determined. For analyzing the antioxidant enzyme activities, we checked superoxide dismutase (SOD), malondialdehyde (MDA), and catalase (CAT) levels in the testicular tissue to evaluate the role of oxidative stress.

Methods

Animals and housing: This experimental study was conducted according to the National Institutes of Health (NIH) guidelines on ethical standards for the investigation of animals, which was approved with the code of IR.KMU.REC.1396.2217. Young adult Wistar rats (2-3 months old) with a weight range of 200-220 g were obtained from Animal Center of Kerman University of Medical Sciences, Kerman, Iran. All animals were kept in a 12-hour light/dark cycle in a climate-controlled room at 25 ± 2 °C with a relative humidity of 55 ± 15%. The rats had free access to standard pellet food and water.

Preparation of drug: MDMA (Pharmaceutics Research Center, Kerman University of Medical Sciences) and FA (Sigma, US, CAS Number: 59-30-3) were dissolved in normal saline [0.9% sodium chloride (NaCl)]; stock solutions were prepared and administered via intraperitoneal (IP) injection for 7 or 14 days.

Experimental groups: To investigate the protective effects of FA on reproductive indices of MDMA (ecstasy)-exposed rats, all animals received treatment for 7 or 14 days. The rats were randomly divided into four treatment groups (7 mice in each) including group I (control) receiving saline (0.9% NaCl, IP), group II (MDMA) receiving MDMA (10 mg/kg/daily, IP),[7] group III (FA) receiving FA (1 mg/kg/daily, IP),[13] and group IV (MDMA, FA) receiving MDMA (10 mg/kg/daily, IP) and FA (1 mg/kg/daily, IP). Immediately 24 hours after the last administration, rats were anesthetized by receiving a ketamine and xylazine mixture (100/10 mg/kg, IP).

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Hormonal analysis: Blood was drawn by cardiac puncture for analysis of the level of LH, FSH, and testosterone. The samples were centrifuged for 5 minutes at 4-6 ºC and 2500 rpm. Hormonal levels of LH, FSH, and testosterone were measured by radioimmunoassay using the enzyme-linked immunosorbent assay (ELISA) technique using a commercial kit (Padgin teb, Iran).

Histological analysis: For evaluation of histological changes, the right testis was removed and fixed in 10% neutral buffered formalin (NBF). After dehydrating, formalin-fixed samples were processed by the conventional paraffin embedding techniques. The samples were sectioned at 5 µm thick slices and stained with hematoxylin and eosin (H&E) for histopathology using a light microscope.

For each testis, 20 seminiferous tubules were randomly selected and the number of spermatogonia, primary and secondary spermatocytes, and Leydig and Sertoli cells was counted. We also measured other spermatogenesis indices including tubular differentiation index (TDI), spermiogenesis index (SI), repopulation index (RI), and the mean seminiferous tubule diameter (MSTD). To determine TDI, we calculated the percentage of tubules with more than three layers of germinal cells (i.e., intermediate or type B spermatogonia, spermatocytes, or spermatids). The RI is the ratio of active spermatogonia to inactive spermatogonia. For the SI, the ratio of seminiferous tubules containing sperm to the tubules without sperm was calculated. MSTD was measured by Image Tools software (version 2).[14]

Sperm quality analysis: For analyzing sperm quality, we checked number, concentration, motility, and percentage of normal morphology and compared these indices between groups. For sperm sampling, a small part of the cauda epididymis was dissected and washed in phosphate-buffered saline (PBS); after that, it was placed in Dulbecco's Modified Eagle's Medium (DMEM)/Ham's F-12 at 37 °C and 5% carbon dioxide (CO_2). The cauda epididymis was cut into small pieces. For calculating the count and concentration of spermatids, one piece of cauda epididymis was transferred in 1 ml of medium and swam up for 1 minute. The spermatozoa were counted by hemocytometer using the improved Neubauer chamber under a light microscope. The sperm concentration was expressed as $\times 10^6$/ml. Sperm motility was examined under a light microscope by counting motility of 100 sperms; it was expressed as a percentage of motile sperm.

Sperm morphology was assessed using alkaline methyl violet stain; the stain was poured off on slides containing diluted semen sample (1:4) for 10 minutes. After washing the slides, 200 spermatozoa were counted under a light microscope and violet color spermatozoa were identified as normal morphology; the data were demonstrated as a percentage of sperm with normal morphology.

Antioxidant profile analysis: For evaluation of the antioxidant enzyme activities, the left testis was divided and frozen in liquid nitrogen. The total SOD, MDA, and CAT activity of the testicular tissue was determined using commercially-available kits (Naxifer Navand lab, Iran).

Statistical analysis was conducted using SPSS software (version 20, IBM Corporation, Armonk, NY) by using one-way analysis of variance (ANOVA) followed by Tukey's honestly significant difference (HSD) post hoc test. Data were expressed as mean ± standard deviation (SD). The level of significance was taken at $P < 0.05$.

Results

Histological changes of testis: The testes weight did not show a significant difference in any of the experimental groups. Histological examination showed numerous structural changes in MDMA groups. The main change in testicular histology has been edema in the interstitial tissue and irregularity in the distribution of spermatogenic cell in seminiferous tubules (Figure 1).

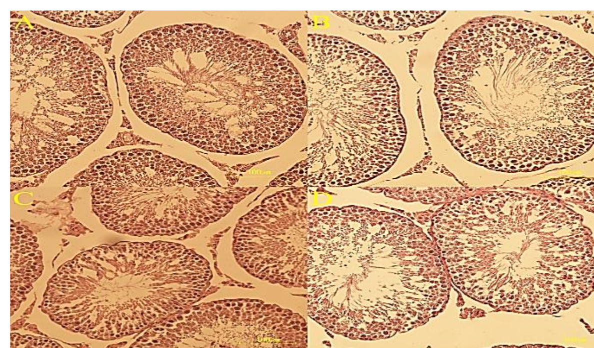

Figure 1. Optical micrographs of testis sections stained with hematoxylin and eosin (H&E) in (A) control with normal spermatogenesis, (B) 3,4-methylenedioxymethamphetamine (MDMA) (10 mg/kg), (C) folic acid (FA) (1 mg/kg), (D) MDMA + FA. No histological changes were seen in the control group; FA alone did not show any significant effects on testes structure. Tubular degeneration and interstitial edema in most seminiferous tubules were observed in the MDMA group compared to the control. Co-administration with FA reversed these effects partially, but not completely.

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Changes in number of seminiferous tubules' cells are shown in figure 2. This result showed a significant decrease in spermatogonia and primary and secondary spermatocytes in MDMA groups compared to control group ($P < 0.001$). However, FA significantly increased these parameters ($P < 0.05$), but in co-administration of MDMA and FA, the adverse effect of the drug did not reserve completely, that has a significant difference with control group ($P < 0.05$) (Figure 2).

Spermatogenesis indices including TDI, SI, IR, and MSTD have been affected by MDMA treatment (both 7 and 14 days) that significantly decreased compared to control group ($P < 0.001$).

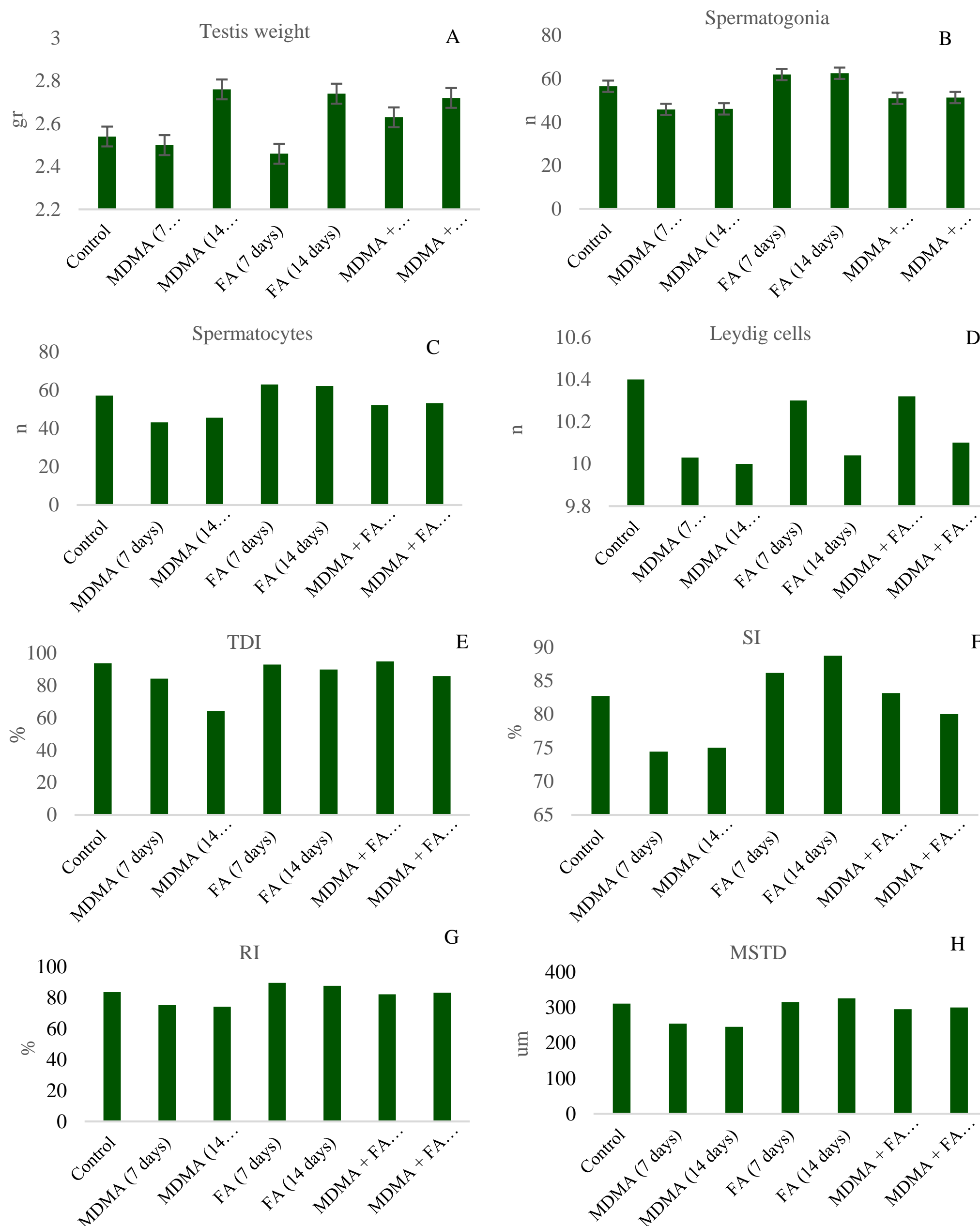

Figure 2. Effects of 7- and 14-day 3,4-methylenedioxymethamphetamine (MDMA) and folic acid (FA) administration compared with their co-administration on (A) testes weight, (B) number of spermatogonia, (C) spermatocytes, (D) Leydig cells and spermatogenesis indices including (E) tubular differentiation index (TDI), (F) spermiogenesis index (SI), (G) repopulation index (RI), and (H) mean seminiferous tubule diameter (MSTD) in male rats. Values are expressed as mean ± standard deviation (SD); *Significant compared to control group ($P < 0.001$)

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FA treatment significantly increased the TDI, SI, IR, and MSTD compared to control group (P < 0.001). In the co-administration treatment, this index did not show a significant difference with control group (P > 0.05) (Figure 2).

Sperm quality: Effect of MDMA, FA, and their combination is shown in figure 3. Our results showed that in MDMA groups (both 7 and 14 days) concentration, motility, and viability significantly decreased compared to control group (P < 0.001). FA significantly increased sperm quality indices (in both 7 and 14 days) compared to control group (P < 0.001).

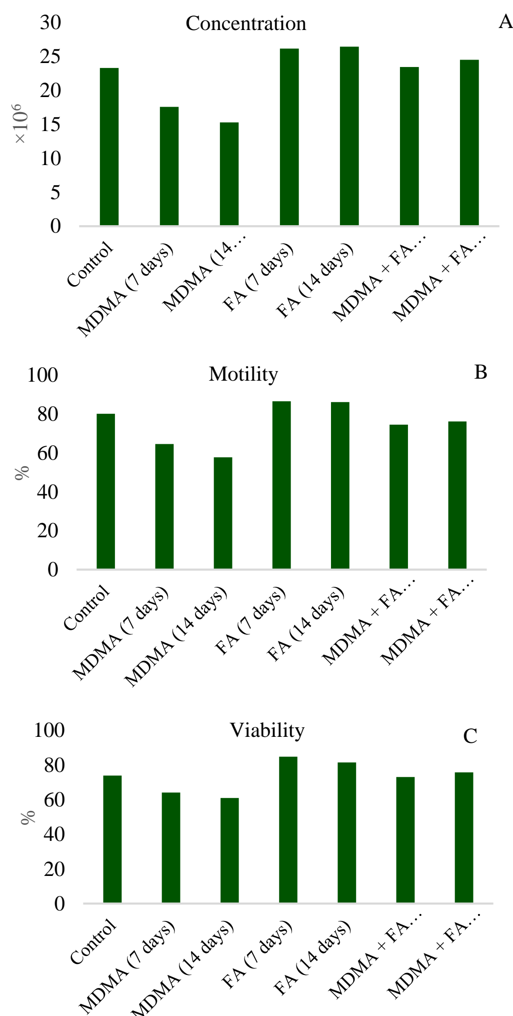

Figure 3. Effects of 7- and 14-day 3,4-methylenedioxymethamphetamine (MDMA) and folic acid (FA) administration compared with their co-administration on semen quality including (A) concentration, (B) motility, and (C) viability. Values are expressed as mean ± standard deviation (SD); *Significant compared to control group (P < 0.001)

In combination of MDMA and FA, the sperm parameters (concentration, motility, and viability) increased compared to control group, which shows that FA can compensate for the effects of MDMA abuse on sperm quality (Figure 3).

Serum hormone levels: Serum level of LH and testosterone in MDMA groups (both 7 and 14 days) increased in comparison with the control group (P < 0.001). However, the serum level of FSH decreased in MDMA group compared to control group (P < 0.001). Despite the effect of FA on serum level of LH, FSH, and testosterone, there was no significant difference with the control group (P > 0.050). In co-administration groups, FA improved serum hormonal indicators compared to the MDMA group, so these indicators were close to the control group and did not have a significant difference with it (P > 0.05) (Figure 4).

Antioxidant profile analysis: The levels of total SOD, CAT, and MDA in the testicular tissues are shown in figure 4. The results showed that the SOD and CAT activities in the testes of MDMA-treated rats were significantly reduced in both 7 and 14 days compared to the control rats, although MDA significantly increased. In FA groups, the CAT activity significantly increased in 7 days-treated rats compared to the control. In co-administration groups, no significant differences were observed between different indices (Figure 4).

Discussion

The results of this study show chronic effects of MDMA on testis structure; consistent with the results of previous studies, abnormalities such as interstitial edema in seminiferous tubules had been seen in MDMA-treated groups that may be resulted from general toxicity of MDMA and its metabolites.

MDMA caused a significant decrease in the mean number of cells in seminiferous tubules as well as a significant change in spermatogenesis indices including MSTD, TDI, RI, and SI compared with the control group. These results confirmed previous reports that showed the adverse effects of amphetamine derivative on reproductive organs in males and females animals.

Saberi et al. reported that using a pure dose of methamphetamine (MAMP) (10 mg/kg) caused a significant decrease in spermatogenesis indices and the average number of seminiferous tubules' cells.[14] Alavi et al. reported that using MAMP for two weeks could affect seminiferous tubules' structure in rat testis and reduced animal fertility activities.[6]

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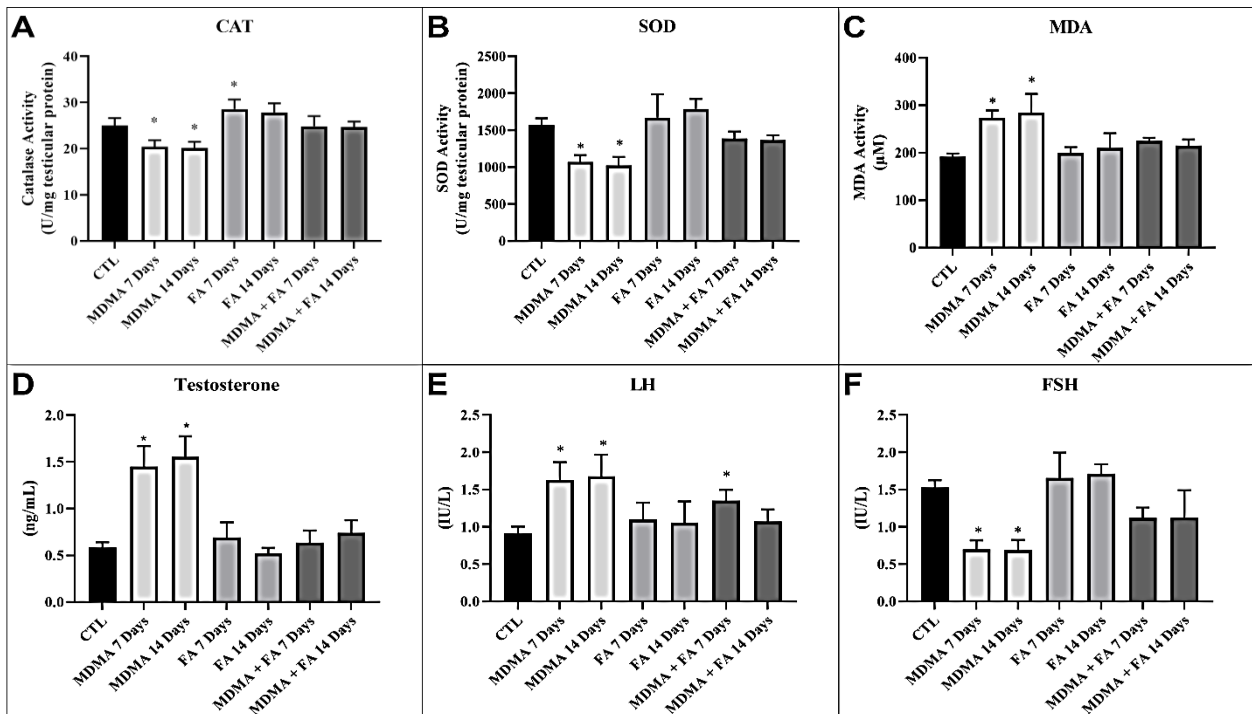

Figure 4. Statue of antioxidant enzymes, (A) catalase (CAT), (B) superoxide dismutase (SOD), and (C) malondialdehyde (MDA) in testicular tissue homogenate of various experimental groups and serum level of hormones, (D) LH, (E) FSH, and (F) testosterone in experimental groups. Values are expressed as mean ± standard deviation (SD); *Significant compared to control group ($P < 0.001$)

These toxic effects induced by MDMA have impacted on the antioxidant enzyme activities in testicular tissue and level of reproductive hormones in rats. SOD, CAT, and MDA as the antioxidant enzyme activities of testis structure and level of LH, FSH, and testosterone as an important hormone influencing males' fertility are significantly different from control group. Changing of these factors play the main role in the pathogenesis of lead toxicity. Normal spermatogenesis and secretory functions of the testis depend on the normal range of testosterone hormone.[15]

Opium, amphetamine, and its components alter the activity of the antioxidant enzymes and increase oxidative activity in animals' organs especially in the nervous system and brain. Besides this, previous studies have shown that reduced levels of serum hormones influence fertility, and induce apoptosis in germ cells and seminiferous tubules' cells. The underlying mechanism(s) is not determined yet; some studies investigated that illicit drug abuse including opium, amphetamines, and ecstasy could affect hypothalamic-pituitary-testicular axis and decrease gonadotropin-releasing hormone (GnRH) and serum testosterone levels.

Lin et al. reported significant changes in the antioxidant parameters [SOD, CAT, glutathione (GSH)] and level of testosterone in MAMP-treated rats.[16]

Sperm quality that determines reproductive ability was evaluated by some biomarkers such as sperm concentration, motility, and morphology. In our study, spermatid counts, sperm motility, and percent of normal spermatozoid in MDMA groups significantly decreased compared to control group. Changes in these biomarkers indicate the role of chemical agents in infertility and changes in testicular functions.

Previous studies have confirmed the effect of drug addiction and its abuse on sperm quality and fertility indicators. Sabour et al. showed that using MAMP increased apoptosis activity in germ cells and caused significant changes in sperm quality.[17] Nudmamud-Thanoi and Thanoi showed that using 4 and 8 mg/kg of MAMP significantly decreased count and percent of normal spermatids in adult male rats.[18]

Besides the toxic effect of amphetamine and its components such as MAMP and MDMA on testicular structure and level of serum hormones,

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these addictive drugs can produce secondary metabolites that affect the molecular activity of cells.[19] These metabolites lead to oxidative damage of DNA structure. Changes in DNA structure can lead to increased mutations and alter the genetic activity of the cell, which in turn, disrupts the process of making regulatory and functional proteins.[20]

DNA repair systems in cells can repair the mutations and other damages on DNA structure; however, with the increase in these damages, the performance of the repair systems will be disrupted. Using an antioxidant regime can help the DNA correctional activity to reduce the side effects of these damages.[21] One of the most important antioxidant groups is vitamins, which have a good effect on reducing damage to the cells. FA is also known as vitamin B9, and it is required to make DNA and ribonucleic acid (RNA) and is necessary for cell division.[10]

The results of this study showed that FA could influence the semen quality and its co-administration with MDMA improved the spermatogenesis indices and improved histological architecture of testis. Using FA can reduce apoptosis induced by hyperthermia or oxidative stress. Similar results were obtained by Shalaby et al. who used FA against methomyl insecticide in rats. FA administration can protect cell from apoptotic damages and its antioxidant and anti-inflammatory activity is important for cell multiplication, differentiation processes, and cell division.[22]

According to the findings of the present study, FA co-administration with MDMA significantly changed the SOD, CAT, and MDA compared to MDMA groups. Moreover, the results showed changes in the level of LH, FSH, and testosterone. This is in agreement with previous studies from other animal models about protection against oxidative damages.

Conclusion

The data show the adverse effects of MDMA on reproductive indices in adult male rats including testicular structure, spermatogenesis indices, sperm quality, and the antioxidant enzyme activities of testes. However, the findings clearly revealed that FA could improve reproductive indicators having protective effects against deleterious impact in MDMA-treated male adult rats.

Conflict of Interests

The Authors have no conflict of interest.

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Authors' Contribution

Collected the data: IR; conceived and designed the analysis, collected the data: AS; other contribution: NSKN; conceived and designed the analysis, wrote the paper: VH; conceived and designed the analysis, collected the data, performed the analysis, wrote the paper: ES; collected the data, performed the analysis: SA; conceived and designed the analysis, other contribution: SN.

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اثرات اسید فولیک بر بافت‌شناسی بیضه، کیفیت اسپرم و شاخص‌های اسپرماتوژنز موش‌های صحرایی نر بالغ تیمار شده با ۳ و ۴ متیلن دی‌اکسی مت‌آمفتامین

ایمان راد[۱]، آرزو صابری[۱]، نجمه سادات کوچک‌زاده نعمت‌الهی[۲]، ویکتوریا حبیب‌زاده[۲]، احسان سالارکیا[۳]، صدیقه امان‌الهی[۳]، سعیده نیکپور[۴]

مقاله پژوهشی

چکیده

مقدمه: امروزه نگرانی در مورد اثرات سوء مصرف ترکیبات حاوی آمفتامین مانند ۳ و ۴ متیلن دی‌اکسی مت‌آمفتامین (۳،۴-Methylenedioxymethamphetamine یا MDMA) بر روی باروری مردان افزایش یافته است. مصرف ترکیبات آنتی‌اکسیدانی همچون ویتامین‌ها، می‌تواند اثرات استرس اکسیداتیو ناشی از مصرف این مواد را بر روی اندام‌های تولید مثلی کاهش دهد. پژوهش حاضر با هدف بررسی اثرات اسید فولیک بر روی شاخص‌های تولید مثلی و فعالیت‌های آنزیم‌های آنتی‌اکسیدانی و تغییرات بافت‌شناسی بیضه موش‌های صحرایی تیمار شده با MDMA انجام شد.

روش‌ها: این مطالعه تجربی بر روی موش‌های صحرایی نر نژاد ویستار انجام شد. حیوانات به ۴ گروه شاهد، گروه مت‌آمفتامین، گروه فولیک اسید و گروه درمان ترکیبی فولیک اسید و مت‌آمفتامین تقسیم شدند. حیوانات به مدت ۷ یا ۱۴ روز دز ۱۰ میلی‌گرم بر کیلوگرم مت‌آمفتامین و ۱ میلی‌گرم بر کیلوگرم اسید فولیک دریافت کردند. در انتها نیز شاخص‌های کیفیت اسپرم (تعداد، غلظت، تحرک و ورفولوژی)، شاخص‌های اسپرماتوژنز شامل میانگین قطر لوله‌های اسپرم‌ساز (Mean seminiferous tubule diameter یا MSTD)، شاخص اسپرموژنز (Spermiogenesis index یا SI)، ضریب بازسازی (Repopulation index یا RI) و شاخص تمایز لوله‌ای (Tubular differentiation index یا TDI)، تغییرات در ساختار بیضه، فعالیت آنزیم آنتی‌اکسیدانی کاتالاز (Catalase یا CAT)، سوپراکسید دیسموتاز (Superoxide dismutase یا SOD) و مالون دی‌آلدئید (Malondialdehyde یا MDA) در کنار سطح سرمی هورمون‌های Luteinizing hormone (LH)، Follicle-stimulating hormone (FSH) و تستوسترون اندازه‌گیری گردید. داده‌ها با استفاده از آزمون one-way ANOVA در نرم‌افزار SPSS مورد تجزیه و تحلیل قرار گرفت.

یافته‌ها: مصرف مت‌آمفتامین به مدت ۷ و ۱۴ روز، منجر به ایجاد تغییرات قابل توجهی در کیفیت اسپرم ($P < ۰/۰۰۱$)، شاخص‌های اسپرماتوژنز ($P < ۰/۰۰۱$)، هیستوپاتولوژی بیضه و سطح LH، FSH و تستوسترون در کنار فعالیت‌های آنزیم آنتی‌اکسیدان CAT، SOD و MDA ($P < ۰/۰۰۱$) گردید. مصرف مکمل فولیک اسید در کنار مت‌آمفتامین تا حدودی این شاخص‌ها را بهبود بخشید و آن‌ها را به گروه شاهد نزدیک کرد.

نتیجه‌گیری: بر اساس نتایج به دست آمده، فولیک اسید می‌تواند اثر سوء مصرف مت‌آمفتامین را در توانایی تولید مثل موش‌های صحرایی نر بالغ کاهش دهد.

واژگان کلیدی: اسید فولیک؛ N-۳ و ۴ متیلن دی‌اکسی مت‌آمفتامین؛ اسپرماتوزوئید؛ اسپرماتوژنز؛ موش‌های صحرایی

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