Medical Laboratory Journal
Online ISSN: 2538-4449
Golestan University of Medical Sciences

The effect of aerobic exercise and psilocybin following methamphetamine induction on the gene expression of certain semaphorins in female Wistar rats

Fariba Rasannezhad [1], Asieh Abbassi Daloii [1*], Javad Ziaolhagh [2], Ahmad Abdi [1]

1. Department of Sport Science, Ayatollah Amoli Branch, Islamic Azad University, Amol, Iran
2. Department of Sport Science, Shahrood Branch, Islamic Azad University, Shahrood, Iran
* Correspondence: Name. Department of Sport Science, Ayatollah Amoli Branch, Islamic Azad University, Amol, Iran. Tel: +989111274366;
Email: abbasi.daloii@gmail.com

Abstract

Background: The purpose of the present study was to investigate the effect of aerobic exercise and psilocybin after methamphetamine induction on the gene expression of certain cerebral cortex semaphorins in female Wistar rats.

Methods: In this experimental study, 40 female rats were placed into five groups: control (C), amphetamine (A), amphetamine-aerobic (AA), amphetamine-psilocybin (AP), and amphetamine-psilocybin-aerobic (AAP). Methamphetamine was injected at a dose of 15 mg/kg for 5 days in the morning. Psilocybin was administered at a dose of 1 mg/kg. The aerobic training program included running on a treadmill at 20–25 m/min, three days a week for eight weeks. After eight weeks, gene expression was measured using the Real-Time PCR method. The data were analyzed by one-way analysis of variance and Tukey's post hoc test at a significance level of $P < 0.05$.

Results: The results showed that the average gene expression of semaphorin 3A, semaphorin 4A, and semaphorin 7A in the cerebral cortex of the A group had a significant increase compared to the C group ($P = 0.001$). The AA, AP, and AAP groups showed a significant decrease in the average expression of semaphorin 3A and semaphorin 4A genes compared to the A group ($P = 0.001$). The AAP group had a significant decrease in the average expression of the semaphorin 3A gene compared to the AA and AP groups ($P = 0.001$). In addition, the AAP group showed a significant decrease in semaphorin 7A expression compared to the AP group ($P = 0.007$).

Conclusion: According to the results, aerobic training and psilocybin supplementation can help reduce semaphorin expression in the cerebral cortex of rats induced with methamphetamine.

Article History

Received: 28 April 2024
Received in revised form: 24 July 2024
Accepted: 8 September 2024
Published online: 24 December 2024
DOI: 10.29252/mlj.18.6.36

Keywords

Methamphetamine
Exercise
Psilocybin
Semaphorins
Rats

Article Type: Original Article

Introduction

Methamphetamine abuse is a significant public health concern worldwide due to its strong addictive properties (1). It interrupts the reabsorption of dopamine and other single amine neurotransmitters and facilitates the release of these single amines into the synaptic space (2). Studies show that this drug decreases the ability of stem cells to reproduce and self-regenerate in specific parts of the brain, alters their differentiation pathways from normal to abnormal, and impacts the processes of cell formation, growth, and differentiation into stem or neural precursors (3). Recently, microRNAs have been identified to play critical roles in various cellular processes. The expression levels of certain miRNAs are altered after methamphetamine administration, which may affect the transcription of target genes that regulate methamphetamine toxicity or addiction (1). One of the targets of microRNAs is axon guidance molecules, such as semaphorins, which have been shown to contribute to the development of drug reward and addiction (4). Changes in SEMA3A are negatively correlated with miRNAs, suggesting that SEMA3A expression may be regulated by miRNAs in methamphetamine sensitivity (5). Semaphorin 7A (Sema7A) is linked to the plasma membrane through a glycophosphatidylinositol anchor. Some membrane-bound semaphorins can be proteolytically cleaved to produce soluble proteins (6). Semaphorin signaling is primarily mediated through plexin receptors and leads to changes in the cytoskeleton and adhesion apparatus that regulate cell morphology (6,7). Besides plexins and neuropilins, other molecules act as receptors for some semaphorins (8), such as CD72 and T-cell immunoglobulin and mucin domain proteins. These interact with Sema 4D (CD100) and Sema 4A, respectively, in the immune system (9). Integrins also act as transmitters of Sema7A signals in the nervous and immune systems (10). Semaphorin 4D participates in mast cell functions, B lymphocyte functions, and T-cell-mediated immunity. It causes inhibitory synapse formation and acts as an axon guidance factor, with somatic and dendritic inhibitory synapses responding equally to Sema 4D signaling. Semaphorin 7A plays a role in T cell-macrophage communication (11). Sema3 is expressed by activated T cells and dendritic cells (DCs). Sema3A's receptor, plexin A1, is expressed at low or undetectable levels in other immune cells, such as macrophages, B cells, and T cells. Studies using RNA interference have shown that plexin A1 is involved in communication between T cells and DCs and causes T cell activation by DCs. Semaphorin 3A is associated with immunosuppressive roles and functions of dendritic cells (11). In the nervous system, semaphorins play roles in either repulsion or attraction of axons toward target tissues (12). On the other hand, sports activity has been shown to exert non-invasive and non-pharmacological protective effects against neuromuscular diseases and disabilities. Exercise is crucial for maintaining synaptic function and structure and for the recovery of damaged neurons (13). Today, exercise is considered an essential factor in the mental stability of people, which can have positive effects on people's behavior. Aerobic exercise significantly increases the length of nerve terminal branches and helps maintain the standard size of the endplate (14). It also affects peripheral nerves and neuromuscular junctions by stimulating the expression of growth factors, increasing mitochondrial biogenesis, and enhancing the speed and quantity of axonal transmission (15). Recently, psilocybin (4-phosphoryloxy-N, N-dimethyltryptamine), a natural hallucinogen and primary compound in umbelliferae, has shown significant effects (16,17). After consumption, psilocybin is metabolized into psilocin, which has psychoactive properties. Short-term use of psilocybin has proven effective in treating borderline or bipolar personality disorders, depression, and migraines (18). The appropriate dose for most individuals ranges from 1 to 3.5 grams of dried mushrooms or 10 to 15 grams of fresh mushrooms. Psilocybin mushrooms can sometimes increase heart rate and blood pressure (19). Psilocybin produces various physical and psychological symptoms by stimulating the sympathetic nervous system. As with many psychoactive substances, the effects of psychedelic mushrooms are subjective and can vary considerably between individuals (20). A study by Gotvaldová et al. showed that a single high dose of psilocybin could cause long-lasting changes in personality (21). To date, the precise role of psilocybin and its effects on semaphorins have not been fully determined. Furthermore, the potential synergistic effects of psilocybin and exercise remain unclear. Therefore, this study seeks to investigate the impact of aerobic exercise and psilocybin, in conjunction with methamphetamine induction, on the gene expression of certain cerebral cortex semaphorins in female Wistar rats.

Methods

Rats for this experimental research were obtained from Shahrood University of Medical Sciences. The weight of the rats ranged from 155 to 180 grams. First, 40 female rats were randomly divided into five groups of eight: the first group (Control group (C)), the second group (Methamphetamine group (A)), the third group (Methamphetamine + aerobic group (AA)), the fourth group (Methamphetamine + psilocybin group (AP)), and the fifth group (Methamphetamine + aerobic + psilocybin group (AAP)). The code of ethics for the current research at Islamic Azad University - Ayatollah Amoli Branch was reviewed and approved under the ethical principles IR.IAU.AMOL.REC.1401.104.

The doses of methamphetamine and psilocybin were chosen based on previous studies. Methamphetamine was injected intraperitoneally at a dose of

15 mg every 12 hours for four days (22), and psilocybin was administered intraperitoneally at a dose of 1 mg/kg (19,23).

The training program consisted of an 8-week running regimen with increasing intensity. The total running time was gradually increased from 20 minutes to 30 minutes, and the maximum daily speed was increased from 20 m/min to 25 m/min. Starting in the fourth week, a 5% slope was introduced. Exercises were performed between 8-10 AM. To evaluate the training effect, VO2max was equalized among the rats, and comparisons were made between the groups (24).

To confirm the creation of the methamphetamine-addicted rat model more accurately, behavioral data were also used. For this purpose, Y-maze tests were conducted (Figure 1 and 2)

After eight weeks of applying the independent variables, all samples, under identical conditions and in baseline conditions (48 hours after the last training session), were anesthetized via intraperitoneal injection of a combination of ketamine (60 mg/kg) and xylazine (5 mg/kg). To examine the expression of the target genes, the real-time PCR method (Step One model, made in Italy) was employed. The sequence of primers is shown in Table 1. Glyceraldehyde 3-phosphate dehydrogenase (GAPDH) was used as the internal control.

To compare the groups, a one-way analysis of variance and Tukey's post hoc test were used. All analyses were performed using SPSS V.23 statistical software, and results were considered statistically significant at $P < 0.05$.

Results

The results in the table show that weight changes from the first to the eighth week were less in groups that exercised compared to the other groups. In addition, the VO2max values indicate the effectiveness of the exercise, as the groups that exercised showed higher VO2max values (Table 2).

Expression of Semaphorin 3A gene in cerebral cortex

Based on the findings, the mean expression of the semaphorin 3A gene in the cerebral cortex of the A group increased significantly compared to the C group ($p < 0.0001$). The AA ($p = 0.008$), AP ($p = 0.012$), and AAP ($p < 0.0001$) groups showed a significant decrease compared to the A group. The AAP group exhibited a considerable decline compared to the AA ($p = 0.046$) and AP ($p = 0.031$) groups (Table 3).

Expression of semaphorin 4A gene in cerebral cortex

The findings showed that the mean expression of the semaphorin 4A gene in the cerebral cortex of the A group increased significantly compared to the C group ($p = 0.001$). The AA ($p = 0.001$), AP ($p = 0.005$), and AAP ($p < 0.0001$) groups showed a significant decrease compared to the A group (Table 3).

Expression of semaphorin 7A gene in cerebral cortex

Based on these findings, the mean expression of the semaphorin 7A gene in the cerebral cortex of the A group increased significantly compared to the C group ($p < 0.0001$). The AAP group showed a significant decrease compared to the A ($p = 0.001$) and AP ($p = 0.007$) groups (Table 3).

Behavioral data

The comparison between before and after methamphetamine induction in the variable of the total number of arm entries showed a significant difference (Figure 1; $P < 0.0001$). In addition, the comparison before and after methamphetamine induction showed a significant difference in the non-repetitive interval count variable (Figure 2; $P < 0.0001$).

Table 1. The primer pattern of semaphorins

Gene	Primer sequence (5'→3')		Tm°c
	Forward	Reverse	
Semaphorin 3A	GACATCTATGGCAAAGCCTGTGC	GTGAGTCAGTGGGTCTCCATTC	56
Semaphorin 7A	CTTCTTCCGAGAGGACAATCCTG	GTGTTCCACTTGGAGACTGACAG	57
Semaphorin 4D	CCAGATAGTGGTAGACAGGACC	GTCTCCTCGATGACATGCACCT	56
GAPDH	AAGTTCAACGGCACAGTCAAGG	CATACTCAGCACCAGCATCACC	57.5

Table 2. The mean and standard deviation of the weight (gr) and VO2max (ml/kg/min) of rats of different groups

Variable	Statistics	C	A	AA	AP	AAP
Weight of the first weeks (gr)	Mean± SD	166.667±10.97	164.833±8.117	165.333±10.718	164.85±9.71	165.5±9.853
Weight of the eighth weeks (gr)	Mean± SD	179±9.126	178±10.12	175.833±10.236	176.2±10.445	174.957±11.603
VO2max (ml/kg/min)	Mean± SD	402.5±41.617	398±52.002	405.333±17.152	399.333±52.022	408.5±36.172

Control group (C), methamphetamine group (A), methamphetamine+aerobic group (AA), methamphetamine+psilocybin group (AP), methamphetamine+aerobic+psilocybin group (AAP).

Table 3. The mean and standard deviation of semaphorins gene expression in different research groups

Variable	Statistics	C	A	AA	AP	AAP
Semaphorin 3A (Fold change)	Mean± SD	1±0.19	2.249±0.246 *	1.6±0.503 $	1.643±0.508 $	1.132±0.246 $&#
Semaphorin 4D (Fold change)	Mean± SD	1±0.142	2.215±0.394 *	1.27±0.541 $	1.145±0.363 $	1.053±0.466 $
Semaphorin 7A (Fold change)	Mean± SD	1±0.124	1.772±0.279 *	1.502±0.153	1.65±0.179	1.173±0.249 $#

*: significant increase compared to the C group. $: significant reduction compared to the A group. &: significant reduction compared to AA group. #: significant reduction compared to the AP group.

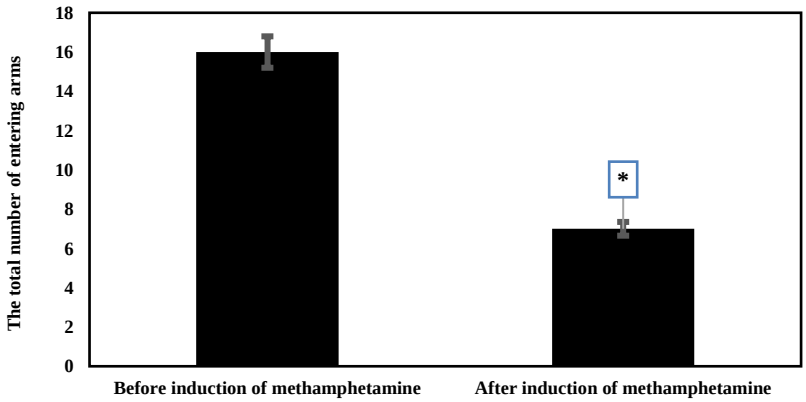

Figure 1. The mean and standard deviation of the total number of arm entries before and after methamphetamine induction.

*Significant decrease compared to before methamphetamine induction

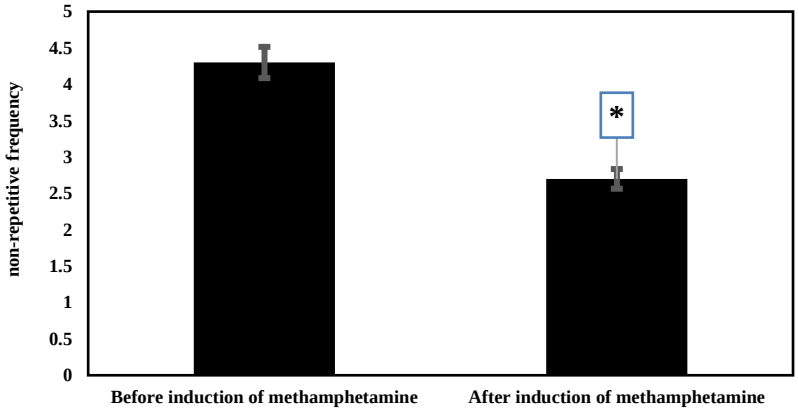

Figure 2. The mean and standard deviation of the non-repetitive frequency before and after methamphetamine induction. *Significant decrease compared to before methamphetamine induction

Discussion

In the present study, the average expression of semaphorin-3A, 4D, and 7A genes in methamphetamine-consuming rats showed a significant increase. Methamphetamine can act as a vasoconstrictor and decrease striatal and cortical blood flow through the dopamine D2 receptor (25). Like alcohol, methamphetamine can also cause long-term damage through mitochondrial dysfunction and increased production of ROS and nitric oxide (26). Another result of the research was the reduction in the average gene expression of semaphorins 3A, 4D, and 7A as a result of performing aerobic exercise alone and in combination with psilocybin in rats consuming methamphetamine. Studies have shown that Sema3A signaling causes a local increase in H2O2 in the dorsal root growth cone of the nerve ganglion through the activation of MICAL1 and MICAL3 (27), with another protein, p53 that is a motor suppressor protein, possibly playing an important role in the induction of class 3 semaphorins, especially Sema3B. In research, it has been shown that high expression of Sema3B, in the presence or even absence of p53, can have an apoptotic effect on cancer cells. It has been shown that Sema3B induces apoptosis in these cells through the activation of the caspase-3 enzyme (28). Moretti and his colleagues stated in their research that Sema3A signaling controls apoptosis through Fas (CD95) by transferring Fas into lipid rafts (29). In the study by Fazelzadeh, it was shown that four weeks of voluntary exercise caused a significant decrease in the concentration of H2O2 and Sema3B, and apoptosis in the hippocampus of diabetic rats (30). Sports training has a positive effect on cognitive function and facilitates neurological rehabilitation after brain injury (31). Van Praag stated in his research that voluntary running on a treadmill causes an increase of 3-4 times, or even more, in the production and survival of new nerve cells in the dentate gyrus of the hippocampus (32). Regular exercise can probably play a role in this process through the adaptations it creates in the activity and expression of some influential factors in regulating apoptosis (33,34). The results of some studies showed that intense periodic training reduced the increased expression of Sema3A in the skeletal muscles of old rats (35). As the present study showed, exercise activity decreased the increased concentration of Sema3B protein in the cerebral cortex of rats consuming methamphetamine. Functional brain regions responsible for processing social inclusion and exclusion are located primarily in the insula, and substance abuse directly damages the neural structures of the insula (36). At the same time, methamphetamine abuse leads to an imbalance in the dopaminergic system, where dopamine type 1 receptor signaling in the ventral tegmental area mediates complex social behavior and the availability of striatal D2/3 dopamine receptors (37). Aerobic exercise promotes the expression of brain-derived neurotrophic factor and other neurotrophic factors that support synaptic plasticity and neuronal survival. This upregulation can counteract the synaptic dysfunction caused by methamphetamine. The modulation of semaphorin gene expression by these neurotrophic factors could help in restoring synaptic function and structural integrity in the brain regions affected by methamphetamine (38). Aerobic exercise has anti-inflammatory effects, reducing the levels of pro-inflammatory cytokines and enhancing the expression of anti-inflammatory cytokines. Since semaphorins also play roles in immune modulation, exercise-induced changes in semaphorin expression could contribute to a reduction in neuroinflammation, thereby protecting neural cells from methamphetamine-induced damage (39). Another result of the present study was the decrease in the mean expression of semaphorins 3A, 4D, and 7A due to the use of psilocybin and the combination of exercise with psilocybin in rats consuming methamphetamine. In recent years, there has been scientific reconsideration of the potential use of psilocybin and other psychoactive substances to treat psychiatric disorders, particularly mood disorders, anxiety, and addiction (40). All symptoms were described as transient, and no patient required specific drug treatment (41). The most essential pharmacological property that psilocybin showed in all trials was the rapid onset of the alleviated effect. This effect can be ameliorated when combined with traditional antidepressant treatment, which has a long latency (42). The antidepressant effects of psilocybin appear biological and context-dependent (19). These natural processes include cell proliferation, increased synaptic connectivity, and anti-inflammatory effects (43). Psilocybin facilitates periodic behavioral flexibility, in which exploration of a non-home environment reduces anxiety during future investigation of a novel environment (19). The more sustained therapeutic effects of a single dose of psilocybin compared to ketamine in an experimental system support the idea that serotonin 5-HT2A receptor-directed therapeutic strategies may be superior to ketamine-based treatments in the depression clinic. In addition, psilocybin has regulatory effects on methamphetamine-induced alterations of behavior in rats via dopamine 2 receptor-mediated signal regulation of extracellular signal-regulated kinase phosphorylation (23). Psilocybin promotes neuroplasticity and synaptogenesis by activating serotonin 5-HT2A receptors. This activation leads to the upregulation of immediate early genes involved in synaptic growth and plasticity. Given that semaphorins are integral to synaptic formation and guidance, psilocybin-induced neuroplasticity could involve modulation of semaphorin gene expression, enhancing synaptic connectivity and repair in methamphetamine-affected regions (38). Similar to aerobic exercise, psilocybin has been found to possess anti-inflammatory properties. By reducing neuroinflammation, psilocybin may alter the expression of semaphorin genes involved in immune responses, thus protecting neural tissues from inflammatory damage induced by methamphetamine. Psilocybin impacts the limbic system and other brain areas involved in stress and emotion regulation. Semaphorins are known to play roles in neural circuit development in these regions. Psilocybin-induced modulation of semaphorin expression could therefore contribute to improved emotional regulation and stress resilience in individuals recovering from methamphetamine abuse (39). The interplay between aerobic exercise and psilocybin in modulating semaphorin gene expression offers a promising avenue for mitigating methamphetamine-induced neurotoxicity. Aerobic exercise supports neuroprotection and synaptic function through metabolic and anti-inflammatory pathways, while psilocybin enhances neuroplasticity and reduces neuroinflammation. Both interventions, by modulating semaphorin gene expression, could provide synergistic benefits in restoring neural health and function in the context of methamphetamine abuse. According to the discussed cases, the beneficial effects of exercise and psilocybin on the reduction of semaphorins 3A, 4D, and 7A were evident in rats consuming methamphetamine, and the best results were obtained when they were used simultaneously, which shows the synergistic effect of exercise and psilocybin.

Conclusion

In general, the results of the present research indicate that exercise training and psilocybin in rats using methamphetamine led to a decrease in semaphorins 3A, 4D, and 7A in the cortex of female rats. The best results were obtained in the combined group of exercise and psilocybin, which shows the synergistic effect of these two interventions. Nevertheless, the current research was associated with limitations, such as the use of female rats and the short duration of the interventions, which requires additional research for better results.

Acknowledgement

This article is taken from the thesis of the doctoral course in sports physiology, approved by Islamic Azad University, Ayatollah Amoly Branch. The authors wish to thank all the people who helped us in the progress of the work.

Funding sources

This article is extracted from a Ph.D. thesis at the Ayatollah Amoli Branch of Islamic Azad University and was personally funded by the authors.

Ethical statement

The code of ethics for the current research at Islamic Azad University, Ayatollah Amoli Branch, was reviewed and approved under the principle of ethics IR.IAU.AMOL.REC.1401.104.

Conflicts of interest

The authors have no conflicts of interest regarding the presented results.

Author contributions

FR: Original draft, Methodology. AAD: Writing, Review and Editing, Project Management. JZ: Methodology. AA: Analysis.

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How to Cite:

Rasannezhad F, Abbassi Daloii A, Ziaolhagh J, Abdi A. The effect of aerobic exercise and psilocybin following methamphetamine induction on the gene expression of certain semaphorins in female Wistar rats. *Med Lab J.* 2024;18(6):36-40.