The effect of aerobic exercise and psilocybin following methamphetamine induction on gene expression of some cerebral cortex semaphorins in female Wistar *rats*

Running title: The effect of aerobic exercise and psilocybin following methamphetamine induction

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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 some cerebral cortex semaphorins in female Wistar *rats*.

Methods: In this experimental study, 40 female *rats* were placed in five groups; control (C), amphetamine (A), amphetamine-aerobic (AA), amphetamine-psilocybin (AP), amphetamine-psilocybin-aerobic (AAP). Methamphetamine was injected at a dose of 15 mg/kg for 5 days in the morning. Psilocybin was injected at a dose of 1mg/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, the genes expression was measured by 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). 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). AAP group had a significant decrease in the average expression of semaphorin 3A gene compared to AA and AP groups (P=0.001). Also, the AAP group showed a significant decrease in semaphorin 7A compared to the AP group (P=0.007).

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

Keywords: methamphetamine, aerobic exercise, psilocybin, semaphorins, cerebral cortex tissue structure, rats

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 also facilitates the release of these single amines into the synaptic space (2). Studies show that this drug causes a decrease in the ability of stem cells to reproduce and self-regenerate in particular parts of the brain, causes a change in their differentiation path from the usual way to abnormal ways, and also causes a difference in the process of formation, growth, and differentiation of cells. It becomes stem or neural precursors (3).Recently, microRNAs have been identified to play critical roles in various cellular processes. The expression levels of some miRNAs are altered after methamphetamine administration, which may affect the transcription of target genes to regulate methamphetamine toxicity or addiction (1). One of the targets of microRNAs is axon guidance molecules such as semaphorins. These molecules were shown to be useful for the development of drug reward and addiction (4). SEMA3A changes 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 and produce soluble proteins (6). Semaphorin signaling is mainly mediated through plexin receptors and leads to changes in the cytoskeleton and adhesion apparatus that regulate cell morphology (6, 7). In addition to plexins and neuropilins, other molecules act as receptors for some semaphorins (8). Such as CD72 and T cell, immunoglobulin, and mucin domain protein that interact with Sema 4D (CD100) and Sema 4A, respectively, in the immune system (9), and integrins that act as transmitters of Sema 7A signals in the nervous and immune systems act (10). Semaphorin 4D also participates in mast cell functions, B lymphocyte functions, and T cell-mediated immunity. Sema 4D causes inhibitory synapse formation and acts as an axon guidance factor. Somatic and dendritic inhibitory synapses respond equally to Sema 4D signaling. Semaphorin 7A also plays a role in T cell-macrophage communication (11). Sema3 is expressed by activated T cells and DCs. Sema3A receptor i.e., Pelexin A1, is expressed in other immune cells such as macrophages, B and, T cells at low or undetectable levels. Studies conducted using RNA interference showed that Pelexin A1 is involved in the communication between T cells and DCs and causes the activation of T cells by DCs. Semaphorin 3A is involved in immunosuppressive roles and functions of dendritic cells (11). In the nervous system, semaphorins can play the role of repulsion or attraction for axons to the target tissue (12). On the other hand, it has been shown that sports activity can create a non-invasive and non-pharmacological protective effect against neuromuscular diseases and disabilities, and also, it is very important to maintain the function and structure of the synapse and in addition to the recovery of damaged neurons (13). Today, exercise is considered one of the influential and essential factors in the mental, and mental stability of people and it can have positive effects on people's behavior. Aerobic exercise significantly increases the length of the nerve terminal branch. Also, it can maintain the standard size of the end plate (14). Sports activity exerts some of its effects on peripheral nerves and NMJ by stimulating the expression of growth factors, increasing mitochondrial biogenesis, and increasing the speed and amount of axonal transmission (15). Recently, psilocybin (4-phosphoryloxy-N, N-dimethyltryptamine), a natural hallucinogen and a primary compound in umbelliferae, has been shown to have significant effects (16, 17). After consumption by humans, psilocybins turn into psilocin, which has psychoactive properties. The short-term use of psilocybin has been proven in the

treatment of patients with borderline or bipolar personality disorders and the treatment of depression and migraines (18). The appropriate dose for most people ranges from 1 to 3.5 grams of dried mushrooms or 10 to 15 grams of fresh mushrooms. Psilosybin mushroom sometimes increases heart rate and blood pressure in people (19). Psilocybin has various physical and psychological symptoms during stimulation of 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 Rowland et al, shows that taking just one high dose of psilocybin can cause long-lasting changes in the user's personality (21). Until today, the role of psilocybins and also the effect it can have on semaphorins have not been determined in detail, also what effects psilocybins can have with exercise is not fully known, so in this research, we seek to investigate the impact of psilocybins. Aerobic exercise and psilocybin are looking for the induction of methamphetamine on the gene expression of some cerebral cortex semaphorins in female Wistar *rats*.

Methods

The present research is experimental. *Rats* were obtained from Shahrood University of Medical Sciences. The weight of the *rats* were 155-180 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)), 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 with the principle of ethics IR.IAU.AMOL.REC.1401.104.

The dose of methamphetamine and psilocybin was chosen based on previous studies. The dose of methamphetamine was injected intraperitoneally at the rate of 15 mg for four days every 12 hours (22), and the amount of psilocybin was considered 1mg/kg intraperitoneally (19, 23).

The training consisted of an 8-week running program of increasing intensity. The total running time was increased from 20 minutes to 30 minutes. The maximum daily speed was increased from 20 m/min to 25 m/min, and in the fourth week, a 5% slope was considered. Exercises were done at 8-10 AM. To determine the evaluation of the training effect, VO2max factor equalized in rats and comparison between groups was used (24).

In order to more accurately confirm the creation of methamphetamine-addicted rat’s model, behavioral data was also used. For this purpose, Y-maze tests were considered (Figure 4, Figure 5).

After eight weeks of applying the independent variable, all the samples with completely similar conditions and in baseline conditions (48 hours after the last training session), they were anesthetized by intraperitoneal injection of a combination of ketamine (60 mg/kg) and xylazine (5 mg/kg). To check the expression of the desired genes, the real-time PCR method, the Step One model, made in Italy, was measured. The sequence of primers is shown in Table 1. Glyceraldehyde 3-phosphate dehydrogenase (GAPDH) was used for internal control.

Table 1. The primer pattern of semaphorins

Genes	Forward primers	Reverse primers	Tm°c
semaphorin 3A	GACATCTATGGCAAAGCCT GTGC	GTGAGTCAGTGGGTCTC CATTC	56
semaphorin 7A	CTTCTTCCGAGAGGACAAT CCTG	GTGTTCCACTTGGAGAC TGACAG	57
semaphorin 4D	CCAGATAGTGGTAGACAGG ACC	GTCTCCTCGATGACATG CACCT	56
GAPDH	AAGTTCAACGGCACAGTCA AGG	CATACTCAGCACCAGCA TCACC	57.5

To compare between 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 were considered statistically significant (P<0.05).

Results

The results of the table show that the weight changes from the first to the eighth week in the groups that exercised were less than the other groups. Also, the values of vo2max show the effectiveness of the exercise. The groups that had exercise showed higher values of vo2max (Table 2).

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).

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 had 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). 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).

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.

Behavioral data

The comparison between before and after methamphetamine induction in the variable of the total number of entering arms shows a significant difference (Figure 1; P<0.0001). Also, the comparison before and after methamphetamine induction shows a significant difference in the non-repetitive interval count variable (Figure 2; P<0.0001).

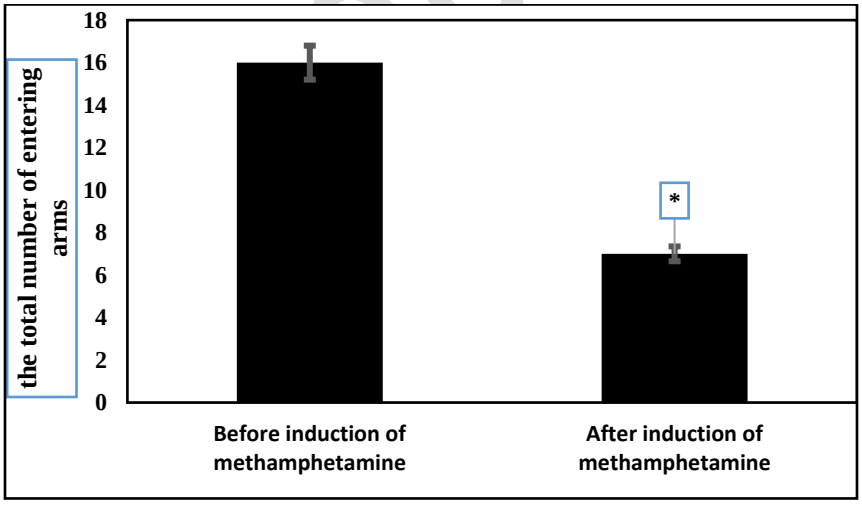

Figure 1: The mean and standard deviation of the total number of entering arms before and after methamphetamine induction. * Significant decrease compared to the before induction of methamphetamine

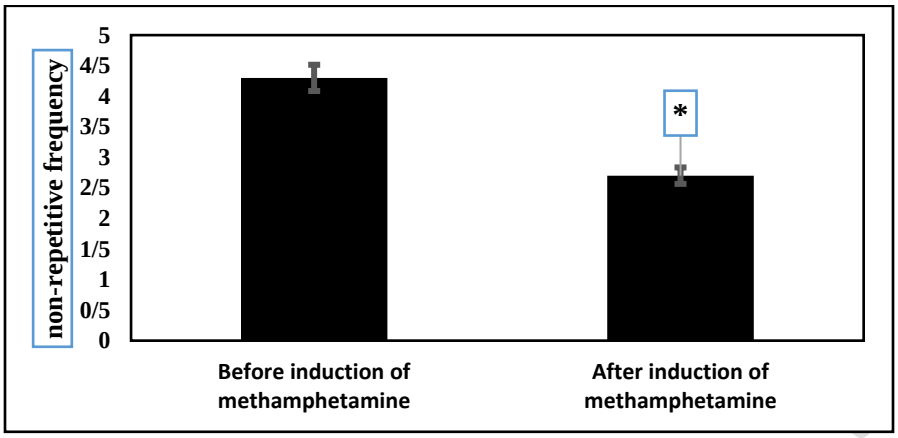

Figure 2: The mean and standard deviation of the non-repetitive frequency before and after methamphetamine induction. * Significant decrease compared to the before induction of methamphetamine

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 to mitochondrial dysfunction and increased production of ROS and nitric oxide (26). Another result of the research was the reduction of 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), another protein that may play an important role in the induction of class 3 semaphorins, especially Sema3B. It is a motor suppressor protein (p53). In research it has been shown that high expression of Sema3B in the presence and even absence of p53 can have an apoptotic effect on cancer cells. It has been shown that Sema3B induced apoptosis in these cells through the activation of the caspase three enzyme (28). Moretti and his colleagues stated in research that Sema3A signaling controls apoptosis by fas (CD95) through the transfer of fas into lipid rafts (29). In the study of Fazelzadeh, it was shown that four weeks of voluntary exercise caused a significant decrease in the concentration of H2B2 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 has stated in 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 direction through the adaptations it creates on 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 (BDNF) 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. Also, psilocybin has regulatory effects on methamphetamine-induced alterations of behavior in rat 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 lead to a decrease in semaphorins 3A, 4D, and 7A in the cortex of female rats, and the best results in the combined group of exercise and psilocybin was obtained, 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.

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Ethics approvals

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Authors' contributions

FR: original draft, methodology. AAD: writing, review and editing, project management. JZ: Methodology. AA: Analysis.

Conflict of interest

The authors have no conflict of interest with the presented results.

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