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Reduction of Methylphenidate Induced Anxiety, Depression and Cognition Impairment by Various doses of Venlafaxine in Rat

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ABSTRACT

Background: Methylphenidate (MPH) is a neural stimulant agent, which its neurochemical and behavioral effect remain unclear. Venlafaxine is a serotonin-norepinephrine reuptake inhibitor antidepressant, which was used for management of depression and anxiety. In this study, protective effects of venlafaxine on MPH induced anxiety, depression and cognition impairment were investigated.

Methods: Forty-eight adult male rats were divided randomly to 5 groups. Group 1, received normal saline (0.2 ml/rat) for 21 days and served as control group. Group 2, received MPH (10 mg/kg) for 21 days. Groups, 3, 4, 5 and 6 concurrently were treated by MPH (10 mg/kg) and venlafaxine at doses of 25, 50, 75 and 100 mg/kg respectively for 21 days. On day 22, elevated plus maze (EPM), open field test (OFT), forced swim test (FST) and tail suspension test (TST) were used to investigate the level of anxiety and depression in animals. In addition, between days 17 and 21, Morris water maze (MWM) was used to evaluate the effect of MPH on spatial learning and memory.

Results: MPH caused depression and anxiety in a dose-dependent manner in FST, OFT, EPM and TST, which were significantly different compared with control group. Furthermore, MPH can significantly attenuate the motor activity in OFT. Venlafaxine in all doses can attenuate MPH induced anxiety, depression and motor activity alterations. MPH also can disturb learning and memory in MWM, but venlafaxine did not alter this effect of MPH.

Conclusions: We conclude that venlafaxine can be protective in the brain against MPH induced anxiety and depression.

Keyword: Anxiety, cognition impairment, depression, methylphenidate, venlafaxine

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INTRODUCTION

Methylphenidate (MPH; Ritalin) is an agent with a neural stimulant activity, which administrated for the treatment of attention - deficit/hyperactivity disorder in children.[1,2] Chronic abuse of MPH and its neurochemical and behavioral consequence in adult and children remain unclear.[3] Mechanism of

MPH is that it binds the dopamine, norepinephrine, and lesser extent serotonin transporter and inhibit reuptake of these amine into synaptic terminals, thus stimulates their receptors.[3,4] This agent functionally and pharmacologically is similar to amphetamine and cocaine.[5,6] MPH has a high potential for abuse and addiction due to its pharmacological similarity to cocaine and amphetamines.[7,8] Some unpleasant property of stimulant therapy may emerge during durable therapy, but there is the very little research of the chronic effects of MPH. Chronic administration of MPH can induce behavioral alteration such as anxiety and depression-like behavior in the animal model experiment.[7-9] The behavioral change, which observed after chronic abuse of to MPH consists of increases in depressive-and anxiety-like behaviors and also cognition (learning and memory) impairment.[2,7,8] Experimental studies have demonstrated the potential effect of MPH and other amphetamine-like agent on brain development and functional change, this study showed that chronic usages of MPH has a role in neurodegeneration of some parts of brain cells such as hippocampus and cerebral cortex, which was responsible for cognition and anxiety.[10,11]

Venlafaxine is an antidepressant of the serotonin-norepinephrine reuptake inhibitor (SNRI), which was used for management of depression and anxiety.[12] Many previous studies demonstrated that this agent can be effective as sedative and anxiolytic agent.[12,13] Previous studies also demonstrated that venlafaxine due to its effect on both serotonin and norepinephrine can act as a complete antidepressant with low side-effect on the brain.[13,14] This studies showed that this agent can interfere with some major neurotransmitters such as serotonin, norepinephrine, and dopamine, and this mechanism is responsible for some of its applications such as anxiolytic, antidepressant and neuropathic pain relief.[15,16] These studies suggested that because venlafaxine has both anxiolytic and antidepressant effect, thus itis one of the best choices in situations where there are both anxiety and depressive depression like as amphetamine and other psychostimulant abuse.[13,14] A previous study demonstrated that venlafaxine can potentate and increase motor activity, and it has not side effect on cognition activity.[17] Venlafaxine has been demonstrated to be neuroprotective and can act against some neurotoxin and neurodegenerative agents.[18,19] It also can be effective in the treatment of alcoholic and other drug abuse.[20] Our previous study demonstrated that venlafaxine can be effective against morphine dependency and can be effective as pain killer and anxiolytic in the withdrawal period.[15] Many studies demonstrated that serotonin (5-HT) and a number of serotonergic receptor agonists have anxiolytic and antidepressant effect, these results suggest that the serotonergic agent can be effective against methamphetamine-induced anxiety and depression.[21] Furthermore, it was demonstrated that the adrenergic system has a major role in depression, anxiety, and cognition.[22] Co-administration of venlafaxine with some neurotoxin can diminish this harmful agent effects in some parts of the brain especially in the area, which serotonin and dopamine have protective role.[20] The aim of the study was to evaluate the possible role of pretreatment with venlafaxine, as SNRI, on the modulation of MPH induced stress, anxiety, depression, motor activity and cognition impairment.

METHODS

Animals

A total of 48 adult male Wistar rats, weighing between 250 g and 300 g, were provided from the animal house of Iran University of Medical Sciences. They were housed in an adjusted temperature (22 ± 0.5°C) with 12-h light/dark cycle and had free access to food and water. Our experimental protocol was approved by the Ethical Committee of Research Deputy of Iran University of Medical Sciences.

Drugs

Methylphenidate and Venlafaxine was purchased from Sigma-Aldrich Co. All agents were freshly prepared just before use.

Experimental design

Group 1, received normal saline (0.2 ml/rat) for 21 days and served as control group. Group 2, received MPH (10 mg/kg i.p.) for 21 days. Groups, 3, 4, 5 and 6 concurrently were treated by MPH (10 mg/kg) and venlafaxine at doses of 25, 50, 75 and 100 mg/kg as i.p. respectively for 21 days. On day 22, elevated plus maze (EPM), open field test (OFT), forced swim test (FST) and tail suspension test (TST) were used to investigate the level of anxiety and depression in animals. In addition between days 17 and 21, Morris water maze (MWM) was used to evaluate the effect of MPH on spatial learning and memory. On 16th day, some standard behavioral methods such as EPM, OFT, FST and TST were used to investigate anxiety and depression level of experimental animals. In addition, a standard behavioral protocol by Morris water maze was applied to evaluate spatial learning and memory in animals between 17th and 21st days.

Behavior tests

Open field test

Open field test used as a standard test for assessment of anxiety and locomotor activity in rodents. For the performance of the test, an apparatus used with

bottom divided to 16 equally spaced squares bordered by opaque high walls of 65.90 cm. All parts of the bottom were painted with black color, except the 6 mm broad white lines that divided the ground into 16 squares. During the experiment all parts of the room except for the open field were kept dark, the apparatus was illuminated by a 100 W bulb that focused on the field from a height of about 110 cm from the ground. For assessment of anxiety and locomotors activity, each animal was centrally positioned in the field for a maximum of 5 min to monitor the following behaviors.

- Ambulation distance: Frequency with which the rat crossed one of the grid lines with all four paws
- Line crossing (ambulation) distance: Distance which rat crossed of the grid lines
- Center square entries: Frequency with which the rat crossed one of the red lines with all four paws into the central square
- Center square duration: Duration of time the rat spent in the central square
- Rearing: Frequency with which the rat stood on their hind legs in the maze.

Forced swim test

Forced swim test, frequently used for evaluation of depressant like behavior in rodents. The apparatus is composed of a transparent plexiglass cylinder with 30 cm diameter and 65 cm height, which filled with water up to 30 cm. The day before the experiment, in order to have adaptation of animals, all animals were individually located to swim for a period of 15 min, On the day of experiment, animals were positioned individually for a period of 6 min in plexiglass cylinder, filled with water. The swimming duration was 6 min. Swimming activity is a marker of nondepressive behavior.

Elevated plus maze

Elevated plus maze is another test, which used for assessment of anxiety in experimental animals. The equipment includes two opposite arms 60 cm × 20 cm, which joined with a central square (10 cm × 10 cm), this apparatus form was a plus sign. Two arms were kept open while other arms were closed with 40 cm elevated walls. All parts of apparatus were kept in 50 cm height above the ground. All subjects were situated individually in the center of the maze in front of a closed arm. The time which animal spent on the open arms were recorded during 5 min for each rat. Spent more time in open arm considered as non-depressive behavior.

Tail suspension test

In this test, animal hang up from tail with tape, which stick to 4/5 of the tail length and suspended from a metal rod, which was fixed 50 cm above the surface area. The duration of immobility and heave of animal was recorded for 5 min period. Immobility is considered as depressive-like behavior.

Morris water maze task

Morris water maze was composed of a circular black-colored water tank (150 cm in diameter and 85 cm in height) which was set up in the center of the small room. This apparatus was divided into four quadrants (North, East, West and South). The tank was filled by water to the height of 50 cm. The operator stay in the North-East part of the room. A platform disk with 12 cm diameter (made of Plexiglas), which is invisible was inserted 1 cm beneath the surface of the water. In the first 4 days of the experiment, which called training procedure the platform was constantly located in one of the quarter. An automated infrared tracking system (CCTV B/W camera, SBC-300 [P], Samsung Electronic Co., Ltd., Korea) recorded the position of the animal in the tank. The camera was mounted 2.3 m above the surface of the water.

Handling

Before the start of experiment, on the first day, rats were located on the tank that was filled with water, room temperature (25 ± 2°C) and the operator guided the rat for swimming to reach to the platform placed quarter. The platform was located on South-West quarter of the tank.

Training procedure

Some distinguish landmarks (such as picture, window, door, etc.) as set up in the extra maze in the room for spatial cues for learning of platform's position for animals. The position of the platform was settled in the Southwest quarter of MWM tank with 25 cm distance from the edge of the tank, and 1 cm beneath the surface of the water. Each rat was experimented for four trials in a day. Each animal was tested randomly from four quarters (North, East, West and South). If the rats found the platform within the 60 s, the trial was automatically stopped by computer. In this experiment, two parameters were evaluated.

Time to find the hidden platform which was called escape latency

- Time to find the hidden platform which was called escape latency., and
- Distance traveled to the hidden platform which was called traveled distance were recorded.

On the 5th day, probe day, platform was removed and animal was thrown into water from one of the above-mentioned directions (East) and the percentage of presence of animal in the target quarter (South-West quarter) was recorded.

Statistical analysis

The data were analyzed using GraphPad PRISM v. 6 Software and averaged in every experimental group and expressed as means ± standard deviation. Then the differences between control and treatment groups

were evaluated by ANOVA. To evaluate the severity of behaviors, the differences among averages in each group were compared using the Tukey test at a significant level ($P < 0.05$).

RESULTS

Results of open field test in control and treatment groups

As shown in Table 1 rats under treatment by MPH (10 mg/kg) had less rate of central square entries and also spent less time in the central region of the OFT in comparison with negative control group ($P < 0.05$). Our study indicates that venlafaxine inhibited this effect of MPH in a dose-dependent manner and increased the frequency of central square entries and also time spent in the central region of the OFT in MPH treated group. This difference was statistically significant in comparison with MPH (10 mg/kg) treated group ($P < 0.05$) [Table 1].

Negative control animals in comparison with MPH (10 mg/kg)-treated group has a higher frequency of rearing and longer ambulation distance in OFT ($P < 0.05$). Also, animals treated by venlafaxine (25, 50, 75 and 100 mg/kg) caused a significant increase in ambulation distance in MPH (10 mg/kg) treated group. This increase was statistically significant in comparison with group receiving MPH (10 mg/kg) alone ($P < 0.05$) [Table 1]. Also, Venlafaxine at high dose (100 mg/kg) caused a significant increase in rearing in MPH (10 mg/kg) treated animals. This increase was statistically significant in comparison to group administrated by MPH (10 mg/kg) alone ($P < 0.05$) [Table 1].

Results of forced swim test in control and treatment groups

Animals in MPH treated group (10 mg/kg) compared to negative control group had less swimming time in FST ($P < 0.05$) [Figure 1], While venlafaxine in all doses inhibited this effect of MPH and increased swimming time, however venlafaxine just in doses of 75 and 100 mg/kg can increase significantly the time of swimming compared to the group receiving MPH (10 mg/kg) alone ($P < 0.001$) [Figure 1].

Results of elevated plus maze in control and treatment groups

Negative control group spent more time in open arms of EPM in comparison to group under treatment by 10 mg/kg MPH ($P < 0.05$) [Figure 2]. The result of our study indicated that animals treated with venlafaxine with doses of 50 and 75 mg/kg remarkably increased the presence of animal in open arm of EPM with $P < 0.05$ as opposed to the MPH (10 mg/kg) treated group, while in dose of 100 mg/kg of venlafaxine, this significant level was $P < 0.001$ in contrast with MPH (10 mg/kg) treated group [Figure 2].

Results of tail suspension test in control and treatment groups

Duration of immobility in MPH (10 mg/kg) treated group was significantly increased compared to animals in the control group in TST ($P < 0.05$). Decrease in the immobility due to venlafaxine with doses of 75 and 100 mg/kg was statistically significant in comparison with rats receiving 10 mg/kg of MPH ($P < 0.001$) [Figure 3].

Evaluation of escape latency and traveled distance during training days in the Morris water maze

Escaped latency and traveled distance during 4 days training in the MWM for group under treatment by MPH with dose of 10 mg/kg was statistically significant compared with negative control group ($P < 0.05$) [Figures 4 and 5]. Although venlafaxine in all doses inhibited MPH induced reduction in escape latency and traveled distance but this effect of venlafaxine was not noteworthy as opposed to MPH (10 mg/kg) treated group [Figures 4 and 5].

Evaluation of swimming speed during training days

The swimming speed was not altered during training trials in any of the animal groups, suggesting that exposure to MPH (10 mg/kg) alone or in combination with venlafaxine with doses of 25, 50, 75 and 100 mg/kg did not cause any motor disturbances [Figure 6].

Evaluation of percentage presence in target quarter in probe trial

Results indicated that there was a significant increase in percentage of the presence of animals in target quarter

Table 1: Effect of various doses of venlafaxine on open field exploratory and anxiety like behavior in rat under treated by 10 mg/kg of MPH

Group	Ambulation distance	Central square entries	Time spent in central square (s)	Number of rearing
Control	435±15	25±2	170±10	14±2
MPH (10mg/kg)	320±16[a]	12±1.5[a]	120±8[a]	6±1[a]
MPH (10mg/kg)+venlafaxine (25 mg/kg)	370±20[b]	14±1[b]	140±11[b]	6±2
MPH (10mg/kg)+venlafaxine (50 mg/kg)	380±20[b]	15±1.2[b]	145±10[b]	8±1
MPH (10mg/kg)+venlafaxine (75 mg/kg)	385±25[b]	20±1[b]	160±9[b]	8±2
MPH (10mg/kg)+venlafaxine (100 mg/kg)	410±21[b]	21±1.2[b]	161±6[b]	9±1[b]

[a]$P<0.05$ versus control groups, [b]$P<0.05$ versus 10 mg/kg of MPH. MPH=Methylphenidate

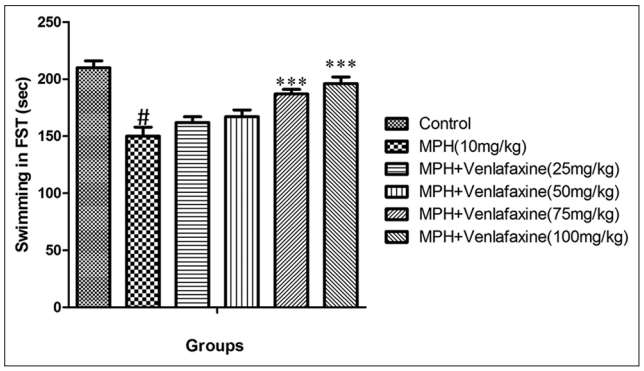

Figure 1: Swimming time (seconds) in forced swim test in control group, and groups under treated by 10 and 20 mg/kg of MPH and 10 and 20 mg/kg of MPH in combination with forced exercise. All data are expressed as mean ± standard deviation (*n* = 8). ***P < 0.05 versus 10 mg/kg of MPH. **P < 0.05 versus 20 mg/kg of MPH. #P < 0.05 versus control groups. MPH: Methylphenidate

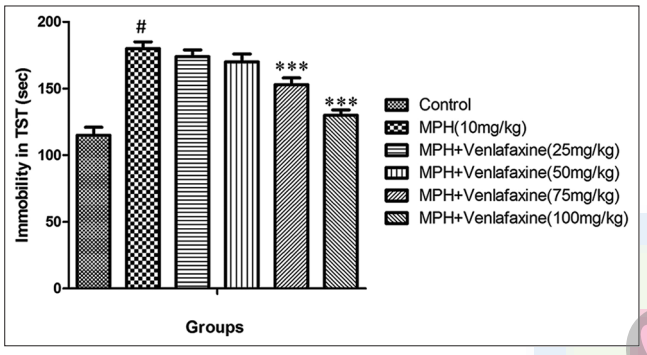

Figure 3: Duration of time stayed in immobility (seconds) in tail suspension test in control group and groups under treated by 10 and 20 mg/kg of MPH and 10 and 20 mg/kg of MPH in combination with forced exercise. All data are expressed as mean ± standard deviation (*n* = 8). ***P < 0.05 versus 10 mg/kg of MPH. **P < 0.05 versus 20 mg/kg of MPH. #P < 0.05 versus control groups. MPH: Methylphenidate

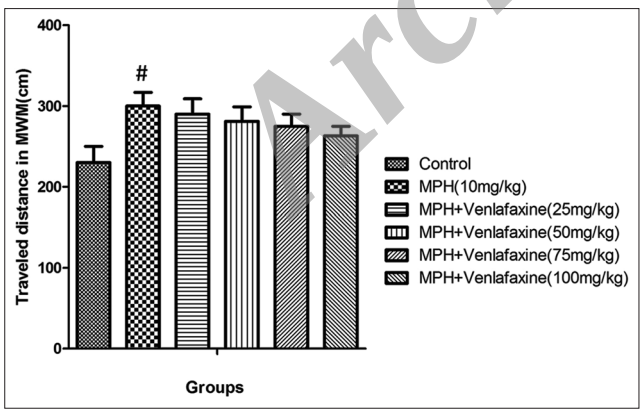

Figure 5: Average of traveled distance in control group and groups under treated by 10 and 20 mg/kg of MPH and 10 and 20 mg/kg of MPH in combination with forced exercise across all training days using Morris water maze in rats. Data are shown as means ± standard deviation. **P < 0.05 versus 20 mg/kg of MPH. #P < 0.05 versus control groups. MPH: Methylphenidate

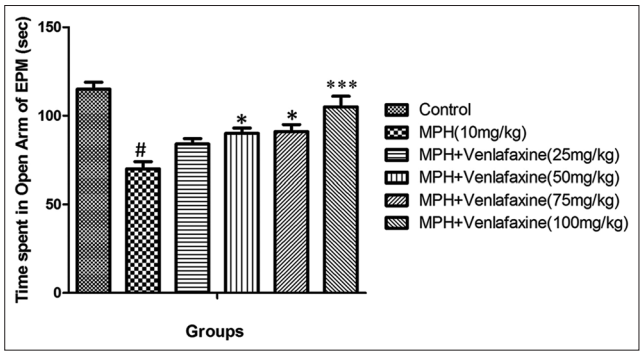

Figure 2: Duration of time spent in open arms (seconds) in elevated plus maze test in control group and groups under treated by 10 and 20 mg/kg of MPH and 10 and 20 mg/kg of MPH in combination with forced exercise. All data are expressed as mean ± standard deviation (*n* = 8). ***P < 0.05 versus 10 mg/kg of MPH. **P < 0.05 versus 20 mg/kg of MPH. #P < 0.05 versus control groups. MPH: Methylphenidate

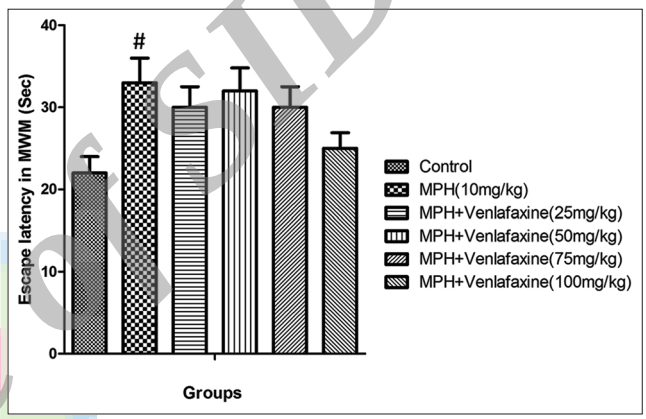

Figure 4: Average of escape latency in control group and groups under treated by 10 and 20 mg/kg of MPH and 10 and 20 mg/kg of MPH in combination with forced exercise across all training days using Morris water maze in rats. Data are shown as means ± standard deviation. **P < 0.05 versus 20 mg/kg of MPH. #P < 0.05 versus control groups. MPH: Methylphenidate

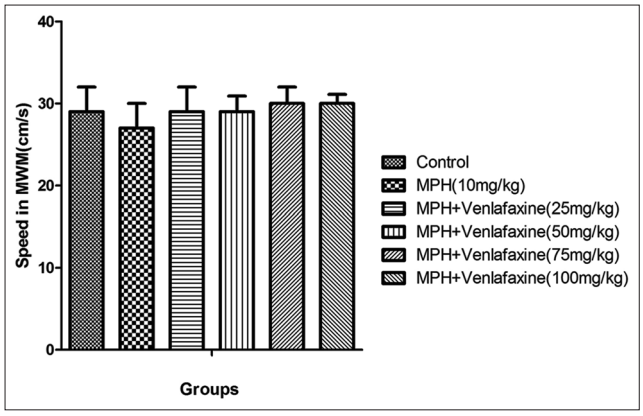

Figure 6: Average of swimming speed in control group and groups under treated by 10 and 20 mg/kg of MPH and 10 and 20 mg/kg of MPH in combination with forced exercise across all training days using Morris water maze in rats. Data are shown as means ± standard deviation, MPH: Methylphenidate

in MPH treated group (10 mg/kg) in comparison with negative control group ($P < 0.05$) [Figure 7]. Also, venlafaxin at all doses used could diminish this effect of MPH, but this effect in any of the doses had not visible/

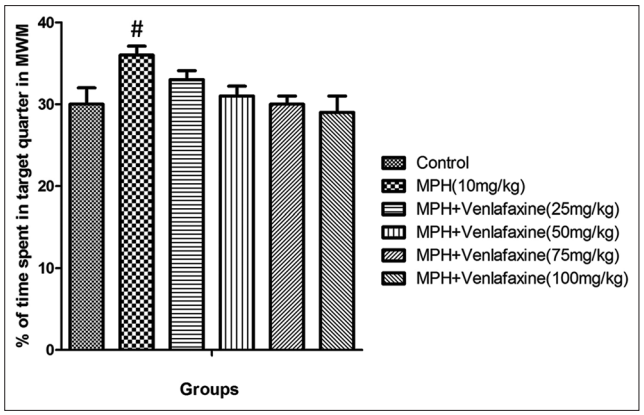

Figure 7: Percentages of time spent in target quarter in probe trial in control group and groups by 10 and 20 mg/kg of MPH and 10 and 20 mg/kg of MPH in combination with forced exercise across all training days using Morris water maze in rats. Data are shown as means ± standard deviation.$P < 0.05$ versus 20 mg/kg of MPH. \#$P < 0.05$ versus control groups. MPH: Methylphenidate**

noticeable difference in comparison with MPH (10 mg/kg) treated group [Figure 7].

DISCUSSION

This study demonstrated that various doses of venlafaxin can alter MPH induced anxiety, depression, and but not the learning and memory disturbances. MPH administration caused an increase in anxiety and depression-like behavior in FST (swimming) and EPM (open arm entry). MPH in various doses can also alter behavioral parameters in OFT (central area entry, central area duration, ambulation distance and rearing). MPH in a dose of 20 mg/kg deteriorates learning and memory. MPH is a neural stimulant which was used for management of hyperactivity in attention-deficit/hyperactivity disorder in children. This agent acts like amphetamine derivatives, like methylen-dioxymethamphetamine. MPH binds the dopamine, and to a lesser extent the norepinephrine transporter, and inhibits reuptake of dopamine and norepinephrine into presynaptic terminals. Because of similarity to cocaine and amphetamine, abuse of MPH increased in recent years in adults.[20,23] However, the chronic neurobehavioral and neurochemical consequences of it remains unclear.[23] Venlafaxine is an antidepressant of the SNRI class. It is used primarily for the treatment of depression, general anxiety disorder, social phobia, panic disorder and vasomotor symptoms.[12]

Our previous study indicated that venlafaxine can be effective for the treatment of morphine dependency.[15] Previous studies demonstrated that venlafaxine significantly decreased the side effects and depression of cocaine dependency.[24,25] Also, another study suggested venlafaxine to be effective in the treatment of alcohol abuse, and furthermore it seems to be useful to decrease the severity of problems related to the alcohol use.[20] The results of this study demonstrated that MPH with a dose of 20 mg/kg cause a decrease in central square entry and time spent in Central Square in OFT. This study suggested that mentioned dose of MPH can induce a depressive-like behavior. Also our findings suggest that 20 mg/kg of MPH cause disturbance in ambulation distance and rearing, as a result, we can discuss that this doses of MPH cause disturb in the motor activity in test animals. We can discuss this results with effect of MPH on dopamine level in brain, many previous studies showed that dopamine has important role on brain motor function, these results indicated that dopamine receptor blockade or decrease in dopamine level by abuse of some drugs such as amphetamine, cocaine and other psycho-stimulants is responsible for disturbance in motor activity which appear in subjects with drug abuse. Probably by abuse of MPH the dopamine level decreased and thus motor activity was disturbed.[3,26,27] On the other hand, our results showed that venlafaxine in all mentioned doses decreased the type of depression in OFT and increased central square entry and time spent in the central square in rats treated by MPH. Also, venlafaxine can abolish the MPH-induced decrease in motor activity. This anti-depressant agent can increase ambulation distance in MPH treated rats. Our results can be compared with a previous study, which demonstrated that venlafaxine as potent SNRI can alter depression-like behavior in OFT in rats.[28] Many previous clinical trials and experimental tests showed that venlafaxine can act as an antidepressant and modulate many depressive-like behavior in depressed patients and subjects showing drug withdrawal syndrome.[13,29,30] Venlafaxine also can improve motor activity and depressive-like behavior by increase in neurotransmitters such as adrenaline, serotonin, and dopamine, we can compare our data with this concept, which by administration of venlafaxine the disturbance of mentioned neurotransmitters induced by MPH were diminished.[16,27,31] Another study indicated that venlafaxine can be used for the treatment of methamphetamine craving in humans; this study suggests that this effect of venlafaxine mediated by its antidepressant activity.[32] It was demonstrated that venlafaxine could modulate the cortical excitability and improve motor activity and reaction speed, which greatly related to the increase of contralateral motor cortical excitability.[17] Our data are consistent with results showing venlafaxine enhancement of motor activity. Thus it can modulate motor activity disturbance, induced by drug abuse. Results of our data showed that MPH (10 mg/kg) decreases swimming period in FST, while venlafaxine in all doses used (25, 50, 75 and 100 mg/kg) decrease immobility and increase the swimming time (period) in FST. Venlafaxine due to its anti-depressive activity can increase serotonin and dopamine in synapses in the brain and modulate rats' depressive-like behavior. We can compare our data with previous results, which supported

the role of venlafaxine even at sub-therapeutic doses in affecting the result of FST and increase in swimming time (period). Our previous study demonstrated that venlafaxine can act as pain killer and antidepressant in morphine withdrawal syndrome, our previous data suggest that antidepressant and anti-anxiety effects of venlafaxine is the major reason for its use in management of withdrawal syndrome.[15] The present study indicated that MPH in mentioned dose can decrease the duration of time spent in open arms (seconds) in EPM and also can increase immobility behavior in TST, while venlafaxine in all doses used (25, 50, 75 and 100 mg/kg) can increase duration of time spent in open arms (seconds) in EPM in rats pretreated by MPH. Also, venlafaxine with the same doses can decrease immobility time in TST. We can argue these results with the basic concept that many antidepressant and anxiolytic compounds and agents could alleviate anxiety-and depression-like behaviors.[33] Several previous studies suggested that SSRIs and SNRIs antidepressants can modify anxiety and depression in experimental tests and clinical trials.[33,34] In our study, venlafaxine as potent SNRI alleviate MPH cessation induced anxiety and depression. Our study showed that MPH cause depletion of dopamine and serotonin and thus augmented anxiety and depression-like behavior after its cessation. In addition, we have found that venlafaxine by its antidepressant and anxiolytic effect inhibited the effect of MPH. Many previous studies demonstrated that venlafaxine can act as neuroprotective agent, this result suggested that venlafaxine can increase amount of antioxidant enzymes such as superoxide dismutase and glutathione peroxidase and also brain-derived neurotrophic factor and BCl2 and decrease Bax in brain regions, in other words, MPH and other methamphetamine like compounds can increase Bax and oxidative marker such as malonil dialdehyde, Protein carbonyl and decrease antioxidant defenses.[18,19,35-37] We can suggest that venlafaxine by a protective mechanism can alleviate MPH induced brain degeneration and induction of anxiety and depression. As mentioned before, our previous study also demonstrated that venlafaxine can reduce blood cortisol level in morphine withdrawal syndrome.[15] According to our findings, we can suggest that venlafaxine can act as a potent antidepressant and anxiolytic agent, which can be used in MPH and other drug abuse. Our study also alluded that chronic administration of MPH (20 mg/kg) can decrease escaped latency and traveled distance in MWM in learning time, this data suggested that MPH at mentioned dose can decrease learning activity and also in probe day, decreases percentage of presence in target quarter in MWM. And suggested that long-term injection of MPH can alter memory in the experimental animal model. This confirms the result of previous studies showing that chronic administration of MPH decreases learning and memory in immature rats.[38-40] Also, other study showed that Methamphetamine like compound caused the release of dopamine, serotonin and adrenaline in the brain and caused depletion of brain region from this amines, a consequence of this phenomenon is cognition impairment.[41] On the other hand, our data showed that venlafaxine at each of mentioned doses could not alter spatial learning and memory. Many previous studies indicated that venlafaxine and other SNRI and antidepressants have not significant effects on learning and memory. However some other studies demonstrated that this agent can improve cognition.[42,43]

CONCLUSIONS

Overall, from obtained data we can conclude that chronic administration of MPH in adult rats caused an increase of anxiety and depression-like behavior and can disturb learning and memory activity. The results of the present study support the hypothesis that venlafaxine may be effective against MPH induced depression, anxiety and motor activity disturbance, but it has no effect against MPH induced cognition impairment. venlafaxine can be suggested for clinical use in patients with MPH abuse and suffering from its behavioral side-effects. These data could be helpful in human MPH abusers. However, further studies are required with human subjects.

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