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Selegiline alleviates the depressive-like behaviors of methamphetamine withdrawal syndrome through modulating mitochondrial function and energy hemostasis

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Abstract

Background: Methamphetamine (METH) is considered the second most commonly abused drug in the world. There is limited or no evidence concerning the effective treatment of METH withdrawal symptoms, such as depression and anxiety. Mode of action of selegiline (increase of the brain neurotransmitter activity) suggests that it might be useful in METH withdrawal syndrome treatment, being capable of diminishing the preference and depression involved in drug degeneration and addictive activities. **Methods:** Mice were randomly divided into 10 groups (n= 10): five METH-nondependent groups treated with normal saline intraperitoneal (i.p) for two weeks, to which, from the 15th day, selegiline (10, 20 and 40 mg/kg; i.p) or fluoxetine (5 mg/kg; i.p) was administrated for 10 consecutive days. Other groups injected METH (2 mg/kg, at 12-h intervals) for 14 days. From the 15th day, the 10-day period of METH abstinence started and the above-mentioned doses of selegiline or fluoxetine were injected. Then, the mice were evaluated for depression and biochemical assessments from the 25th day of the study. **Results:** Our data indicated that post-treatment with selegiline (10-40 mg/kg; i.p) for 10 days reversed METH-induced depressive-like behaviors in the forced swimming test (FST), tail suspension test (TST), and splash test with exerting no effects on the locomotor activity. Furthermore, none of the previously proposed treatments affected the behavioral abnormality in the control animals. Moreover, both selegiline and fluoxetine as standard antidepressant drug, substantially improved the levels of mitochondrial reduced glutathione (GSH), malondialdehyde (MDA), and adenosine triphosphate (ATP). **Conclusion:** Our findings demonstrated that selegiline produced antidepressant-like effects following METH withdrawal and prevented the mitochondrial dysfunction in the male mice.

Keywords: Selegiline, Methamphetamine(METH), Fluoxetine, Depression, Mitochondrion, Oxidative stress

Introduction:

The selective and irreversible monoamine oxidase (MAO)-B inhibitor, selegiline, is one of the therapeutic approaches for the management of Parkinson's disease (PD) in the early stages[1]. It has been shown that selegiline blocks dopamine reuptakes and enhances dopamine release on the dopaminergic neurons terminal[2]. Numerous fundamental studies have suggested neuroprotective actions of selegiline in different neurons[3-5]. In addition, it has been reported that selegiline can cause pro-trophic, antioxidant, antidepressant effects[6], anti-anxiolytic impact[7] through mechanisms independent of its MAO-B inhibitory action[8-10].

It has been indicated that the neuroprotective effect of selegiline is dependent on its effects on the cellular antioxidant system and mitochondrial enzyme[8]. A similar report in the human dopaminergic neuroblastoma and rat striatum has confirmed that selegiline prevents the depletion of the glutathione level induced by 1-methyl-4-phenyl pyridinium[11]. Previous studies indicated that selegiline could be an efficient and safe adjunctive cure for cocaine, opioid and alcohol addiction and smoking cessation[12-15].

Since the past decade, methamphetamine (METH) has been a major drug problem in the world [16, 17]. METH, also known as ice, is a strong neurotoxin with psychostimulant and addictive effects[18, 19]. Although METH is prescribed for attention deficiency hyperactivity disorder in children [20], its chronic abuse resulted in neurotoxicity, cognitive, mood and motor impairments[21-23]. In function and pharmacological aspects, it is similar to cocaine [24].

Accumulating studies have demonstrated that chronic METH abuse diminishes the serotonergic and dopaminergic nervous terminal activity in various regions of the brain, such as the hippocampus, occipital cortices, nucleus accumbens and caudate-putamen[25-28]. It's worth noting that, METH not only enhances the dopamine concentration in the synaptic cleft, but also increases the oxidation of dopamine via monoamine oxidase and catechol-o-methyltransferase, and finally raises the reactive oxygen species (ROS) level [29, 30]. Furthermore, the intracellular bilayers organelle, mitochondria, which plays the main role of an energy generator, is one of the major sits of the METH induced ROS generation within neural cells[31, 32].

A large number of studies indicate that prolong abuse and precipitate cessation of METH trigger depression, anxiety and other neurobehavioral disturbances [33, 34]. Since selegiline attenuates the oxidative stress on the dopaminergic nervous terminal, and oxidative stress mediators like ROS contribute to the depression induced by METH withdrawal, we, in the present study, aim to investigate the effect of selegiline on the METH post-depression by focusing on mitochondria and stress oxidative markers.

Material and Methods:

Chemicals: All analytical grade chemicals were provided from Merck Co. (Germany).

Animals: Male NMRI mice (25-30 g) provided by Pasteur Institute, Tehran, Iran were housed under standard conditions. After acclimation, the behavioral test was done between 10:00 and 14:00h. The study was approved in accordance with Animal Ethics Committee in Zanjan University of Medical Sciences(ZUMS.REC.1395.224).

Methamphetamine (METH)-induced withdrawal syndrome models: In the present research, METH was initially dissolved in sterile normal saline (0.9%). IP administered of METH (2mg/kg) was done twice a day for 14 consecutive days as described by a previous study[35].Subsequently, the treated animals were kept in cages for 10 days without any METH injections so that the withdrawal syndrome term would be induced in mice, which was confirmed through behavioral or molecular assessments. Saline injection in the control animals was done in order to exclude solvent effects as the sham group.

Experimental design: Mice were distributed into 10 groups (10 mice in each group): Group 1: control mice received normal saline; Group 2: animals which received METH (2 mg/kg) twice a day for 14 consecutive days so that the withdrawal syndrome could be induced; Group 3, 4, 5: in these groups, normal mice received 10, 20 and 40 mg/kg selegiline daily for 10 consecutive days after receiving of normal saline for two weeks ; Group 6: Normal mice received 5 mg/kg fluoxetine (FLX) on a daily basis for 10 consecutive days after receiving of normal saline for two weeks ; Group 7, 8, 9: METH-induced withdrawal mice received 10, 20 and 40 mg/kg selegiline on a daily basis for 10 consecutive days after induction of withdrawal syndrome in 14 days period time; Group 10: METH-induced withdrawal mice received 5 mg/kg FLX on a daily basis for 10 consecutive days after 14 days. At the end of the treatments, the animals were subjected to the behavioral test including OFT and TST, FST and Splash test between 10:00 AM and 14:00 PM. Ultimately, the animals were sacrificed under mild anesthesia according to our previous studies[36, 37] and then, their hippocampi were dissected on an ice-cold surface and immediately immersed in liquid nitrogen, and then stored at -80 °C until mitochondrial function assay. The timeline of the procedure, treatment, behavioral and mitochondrial tests is represented in Figure.1.

Behavioral assessments:

Forced swimming test (FST): The immobility time was considered as a biomarker in depressive-like behavior in rodents[37]. Briefly, 26 days following the test, mice were put in cylinders containing water for 6 min. The immobility time for the period of the last 4 min was measured once the mice remained floating motionlessly in the water. It is worth noting that the reaction of each mouse was assessed by an observer who was not alert of the nature of the treatment.

Splash test: Motivational and self-care difficulties were considered as anhedonia behaviors in the rodents[36]. Therefore, the grooming behavior of the mice was regarded as an indirect amount of spraying delicious solution intake (10% sucrose) on the dorsal of mice for 5 min by a blinded investigator[38].Therefore, body grooming nose/face grooming, and head washing was measured in the grooming behaviors.

Tail suspension test (TST): According to Can et al., study the decrease in the duration of immobility time was considered to assess the antidepressant-like efficacy of drug treatments in mice[39].The animals were suspended by their tail for 6 min and the immobility posture period was considered as a depressive-like behavior when they were exposed to an inescapable situation[40].

Open-field test (OFT): The locomotor activity of the mice in response to withdrawal syndrome and different treatments was assessed using OFT based on our previous published study[41],in order to certify that the changes in the duration of immobility time were not due to the changes in the locomotor activity of mice. The animals were retained separately on the corner of the Plexiglas OFT box (50×50×40cm) that was dimly illuminated during the test and their activities

were documented with a camera for 5 min so that we could measure the distance they moved or their horizontal activity.

Mitochondrial and biochemical assessments:

Preparation of mitochondria*:* The mice were decapitated 24h after the completion of behavioral tests and their brains were fast divided out and rinsed utilizing isotonic PBS, and were soaked in the liquid nitrogen and kept at a –80 ºC freezer until the assays. The isolation of hippocampal mitochondria was performed as said by our prior investigation[37].The final isolated mitochondria pellet obtained from a two-time centrifuge was re-suspended in Tris buffer. The uniformity of the experimental condition was done employing Coomassie blue method by adjusting to 0.5 mg mitochondrial protein per ml in each sample[42].

GSH assay: GSH amount was measured using DTNB [5, 5'-dithiobis- (2-nitrobenzoic acid)] as the indicator[43]. 0.5 mL of supernatant was primarily added into 0.5 mL TCA (10%) and centrifuged in 8000 g for 5 min. Afterwards, 0.5 ml supernatant was added to 1.25 ml Tris buffer and 0.25 ml of DTNB (0.04%) in a total volume of 2.0 mL (pH 8.9). The developed color was measured at 412 nm with a spectrophotometer. GSH content was stated as µg mg^{-1} protein.

MDA assay: The thiobarbituric acid reactive substances (TBARs) assay is widely utilized to measure lipid peroxidation or MDA level and tetra methoxy propane (TEP) as a standard of calibration curve[37]. In sum, 0.5 mL of supernatant was added into 2.5 mL TCA (20%) and centrifuged in 8000 g for 5 min and kept in temperature room for 10 min. 0.5 ml supernatant was then added to 2.5 ml sulphuric acid (0.05M) and 2 ml of TBA (0.2%). The developed yellow color was assessed at 532 nm with a spectrophotometer and MDA content was represented as µM.mg^{-1} protein.

ATP assay: Briefly, 50 mg of hippocampus was homogenate with 0.5 mL TCA (6%) and centrifuged in 12000 g for 10 min in 4□C. Subsequently, potassium hydroxide (4M) was added to supernatant to reach pH=6.5 to neutralization and samples were immediately stored at -80° C. Finally, the ATP levels were measured by ATP assay kit based on the phosphorylation of glycerol in order to generate a product that can be easily quantified by calorimetrically assay (OD 570 nm) based on the instructions of company.

Statistical Analysis: Results have been accessible as mean ± SD. All statistical analyses were done by SPSS 17 software. Statistical significance was performed by one-way ANOVA test, followed by the post-hoc Tukey test. $P<0.05$ was considered to be statistically significant.

Results

Selegiline attenuated the depressive-like behaviours of METH withdrawal in mice

Our data in FST revealed no significant differences concerning the immobility time in the mice treated with selegiline (10,20&40mg/kg) according to our present protocol, compared to that in untreated animals ($P>0.05$; data not shown). Afterwards, the effect of selegiline on the behavioral assessment was assessed in our samples. Our results revealed that in METH withdrawal induced mice the immobility time significantly increased in the FST (Fig.2a; $p<0.05$) and TST (Fig.2b; $p<0.05$). In the splash test, in METH withdrawal induced mice the grooming activity time of the mice significantly decreased compared to the control counterparts (Fig.2c; $p<0.01$). Moreover, no significant differences were identified concerning the locomotor activity in METH withdrawal induced mice compared to those in normal animals on the OFT (Fig.2d; $p>0.05$).

To investigate the impacts of selegiline on depressive-like behaviors observed in METH withdrawal mice, we treated the animals applying selegiline (10, 20 and 40mg/kg). One-way ANOVA analysis illustrated that significantly decline in the immobility time in selegiline treated compared to METH withdrawal mice in FST [$F(9,62) = 14.402$; ***$p<0.001$]. The similar data regarding the decrease in the immobility time was observed in selegiline treated groups compare to METH withdrawal mice in TST [$F(9,62) = 10.843$; ***$p<0.001$]. Administration of selegiline caused a significant increase in the grooming activity time of METH withdrawal mice in the splash test [$F(9,62) = 38.266$; ***$p<0.001$]. Furthermore, there were no significant effects of treatments on the distance moved in OFT in comparison to the control mice [$F(9,62) = 2.903$; $p>0.05$].

Depressant effects of METH withdrawal mice were reversed by selegiline treatment in mitochondrial function

Our data revealed that there was a significant decrease in mitochondrial reduced glutathione amounts in the hippocampus of METH withdrawal mice in comparison to the control group (Fig.3a, ***$p<0.001$). Statistically analysis established significant differences among all treated groups in GSH level in the hippocampus following the administration of selegiline [$F(9,20) = 5.529$, $p<0.05$; Fig.3a]. Also, a significant rise in mitochondrial GSH levels was found in the hippocampus of METH withdrawal mice compared to the control group based on one-way ANOVA analysis (Fig.3a, ***$p<0.001$). In addition, the administration of selegiline in normal rats did not induce significant difference in GSH amount in compared with the control animals (Fig.3a, $p>0.05$).

Post-hoc analysis exhibited significant difference among experimental groups regarding mitochondrial MDA levels in the hippocampus after the treatment with selegiline [$F(9,20)=12.093$,***$p<0.001$; Fig.3b]. It revealed that a significant rise in mitochondrial MDA amounts in the hippocampus of animals following METH withdrawal mice compared to the control group (Fig.3b, ***$p<0.001$). According to our results, post-treatment with selegiline significantly decreased MDA levels compared to METH withdrawal mice (Fig.3b, ***$p<0.001$).

Statistical analysis implied significant differences in mitochondrial ATP amounts between experimental groups after the treatment with selegiline [$F(9,20) = 299.874$, $p<0.001$; Fig.3c]. Statistical analysis showed a significant decline in mitochondrial ATP levels concerning the hippocampus of mice following METH treatment (Fig.3c, **$p<0.01$). The findings revealed that post-treatment with selegiline significantly increased ATP levels compared to METH withdrawal mice in the hippocampus (Fig.3c, #$p<0.05$). Furthermore, there are no significant difference between selegiline administration in normal mice and control groups in mitochondrial ATP amounts (Fig.3c, $p>0.05$). Similarly, we observed a significant rise in mitochondrial ATP levels in the hippocampus of METH withdrawal mice following selegiline treatment in comparison with METH withdrawal mice (Fig.3c, ***$p<0.001$).

Discussion:

For the first time, the results of the present study indicated that selegiline as a MAO inhibitor effectively attenuated the METH induced post-depression. The results also demonstrated that selegiline could attenuate the mitochondrial dysfunction and oxidative stress in the hippocampus following METH (2 mg/kg) administration in the male mice. Our data showed that METH (2 mg/kg) could diminish the swimming time during FST and the agitation time in TST, while the

selegiline (10- 40 mg/kg) significantly decreased the immobility time in FST and TST. Our findings are consistent with previous information[6]. Moreover, the probability effects of selegiline (10- 40 mg/kg) revealed non-significant difference in distance moved in OFT when compared to the METH-dependent or METH-independent mice, demonstrating that neither METH nor selegiline altered the horizontal activity of the mice. It is supposed that the selegiline (20mg/kg) can be used as maximum effective dose to reverse depression-like behavior following METH post-depression due to observation of aggressive and restless behavior in some treated animals.

It is noteworthy that abstinence of METH following prolong exposure may deplete dopamine, the neurotransmitter undertakes in depressive behavior. Also, selegiline can compensate the dopamine depletion and increase the level of the dopamine in the synapses and attenuate the depressive behavior[44]. Our data are consistent with previous findings suggesting that selegiline can attenuate the immobility time in the animal models of the behavioral despair [6, 45]. Our data revealed that METH withdrawal syndrome decreased the grooming activity time, indicates the self-care difficulties and motivation problem in rodent, in the splash test which may reflected the METH post-depression behaviors. Numerous fundamental studies have indicated that depression and poor motivation are key factors in the relapse of METH usages[36, 46, 47].

Interestingly, 10 days after the administration of selegiline (but not dose-dependent) during METH withdrawal significantly, the depressant-like effect was reversed during the splash test in the mice. In line with our behavioral findings, the mitochondrial and biochemical results illustrated that repeated administration of METH (2 mg/kg) following 10-day withdrawal might promote the MDA level, as a lipid peroxidation marker, and reduced the amount of GSH and ATP in the hippocampus tissue of the male mice. Certain evidence obtained from previous

investigations revealed that in depressive-like behaviors, the hemostasis imbalance and biochemical alteration play the main role in the neuronal damage [37, 46-48].

Additionally, emerging lines of research illustrated that METH elevated reactive oxygen and nitrogen species (ROS &RNS) generation and inhibited the electron transport chain and Krebs cycle on mitochondria. These harmful effects caused to DNA damage, activation of proteases and promoting the cell death signaling of the neural cells[49-53]. Induction of oxidative stress, apoptosis, mitochondrial dysfunction and pro-inflammatory mediators have been reported in the animal model of the METH induced neurotoxicity, and considerable results have been reported [54-58]. Some previous investigations have demonstrated that selegiline can inhibit the oxidative stress, prevent from apoptosis, improve mitochondrial enzyme activity and reduce neuroinflammation and neurotoxicity[59-61].

. In this regard, our present study results are consistent with those of previous studies indicating that selegiline could augment the GSH level and diminish the MDA level; this correlates with the increased amount of the ATP generation by the mice hippocampus mitochondria in the METH post-depression period. The current research revealed that selegiline might improve the mitochondrial membrane potential collapse in the mice hippocampus induced by METH via attenuating the lipid peroxidation and betterment of the antioxidant enzyme activity. Interestingly, it is worth noting that during the METH post-depression period, the effects of 20 mg/kg selegiline on improving the mitochondrial function and the recovery of the behavioral disturbances were better than the effects of the other doses and similar to the effects of the standard antidepressant drug fluoxetine.

According to the previous studies, methamphetamine in the lower doses can induce neuroprotective effects[62, 63].

Our initial hypothesis was that the metabolites of selegiline could alleviate the depressive-like behaviors of methamphetamine withdrawal syndrome. The dose-independent pattern of the present study results may be associated with the accumulation of selegiline metabolites. Indeed, as presented in ATP, MDA and GSH results, the accumulation of amphetamine and methamphetamine by administration of 40 mg/kg selegiline during methamphetamine withdrawal syndrome reverses the beneficial effects of selegiline. The present study has clearly indicated that the maximum effective dose of selegiline to alleviate the depressive-like behaviors of methamphetamine is 20 mg/kg.

Conclusion: We found that selegiline is capable of mitigating depressive-like behaviors following METH in the male mice. In addition, selegiline can reverse oxidative stress conditions, such as a rise in the GSH level, a decline in the MDA amount, and an increase in the energetic ATP level, playing a pivotal role in the METH withdrawal induced depression. This research practically suggests the use of selegiline (particularly in doses less than 20 mg/kg) as a neuroprotective agent in the clinical stages for patients with stimulant-withdrawal syndrome.

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Ethical issues: This work was supported by the Ethics Committee of Zanjan University of Medical Sciences (ZUMS.REC.1395.224).

Authors' contribution: Conceived and designed the experiments and the study protocol: MJH & HG; Performed the experiments: Sima Asghari; Analyzed and Interpretation of the data: MJH & HG; Wrote the paper: MJH & HG. Critical review of the manuscript: MJH & HG & SA.

Conflict of Interest: The authors declare that there is no conflict of interest.

Figures legend

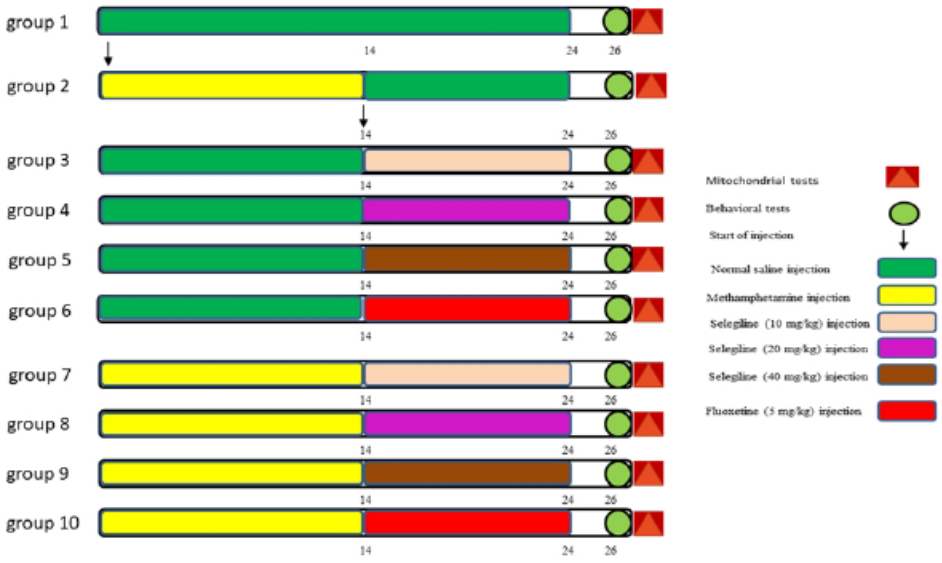
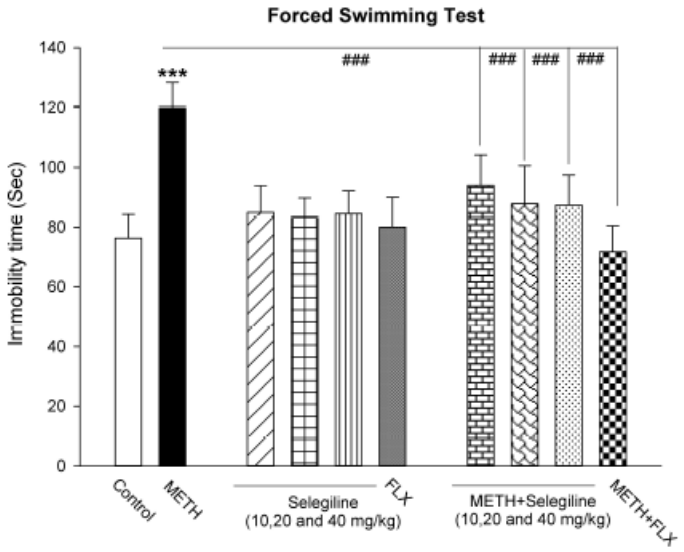
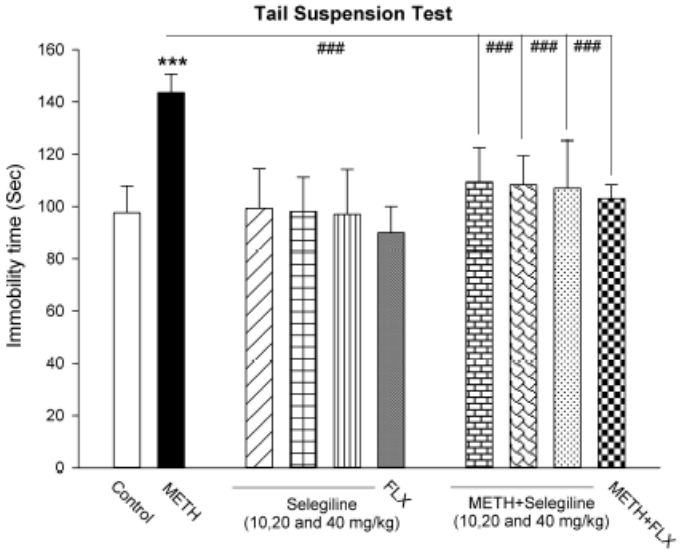


Fig. 1. Schematic timeline of METH withdrawal, treatment, behavioral and mitochondrial tests




Tail Suspension Test
Immobility time (Sec)
160
140
120
100
80
60
40
20
0
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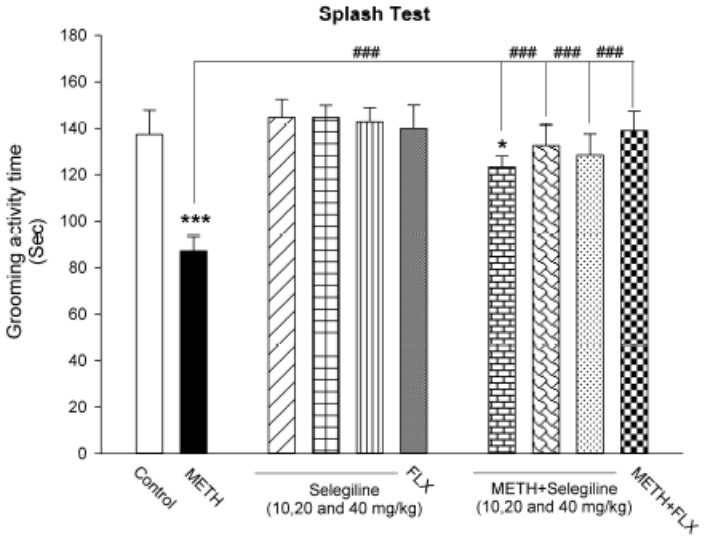
Control
METH
Selegiline
(10,20 and 40 mg/kg)
FLX
METH+Selegiline
(10,20 and 40 mg/kg)
METH+FLX


Splash Test
Grooming activity time (Sec)
180
160
140
120
100
80
60
40
20
0
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Control
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Selegiline
(10,20 and 40 mg/kg)
FLX
METH+Selegiline
(10,20 and 40 mg/kg)
METH+FLX

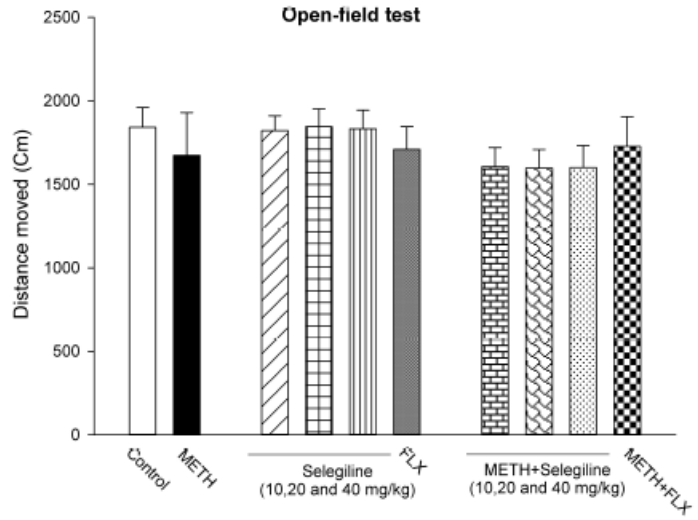
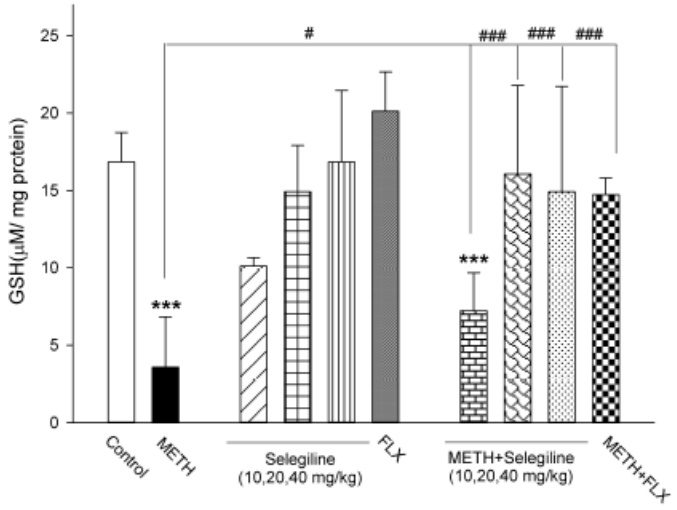


Fig. 2. Effects of selegiline (10, 20 and 40 mg/kg) on despair behavioral in the (a)FST, (b) TST, (c) splash test and (d) OFT. Values are expressed as the mean ± SD and were analyzed using one-way ANOVA followed by Tukey's post hoc test (n=6-8). * P<0.05, ** P<0.01 and *** P<0.001 compared with control group. #P<0.05 and ##P<0.01 and ### P<0.001 compared with METH-withdrawal treated groups.



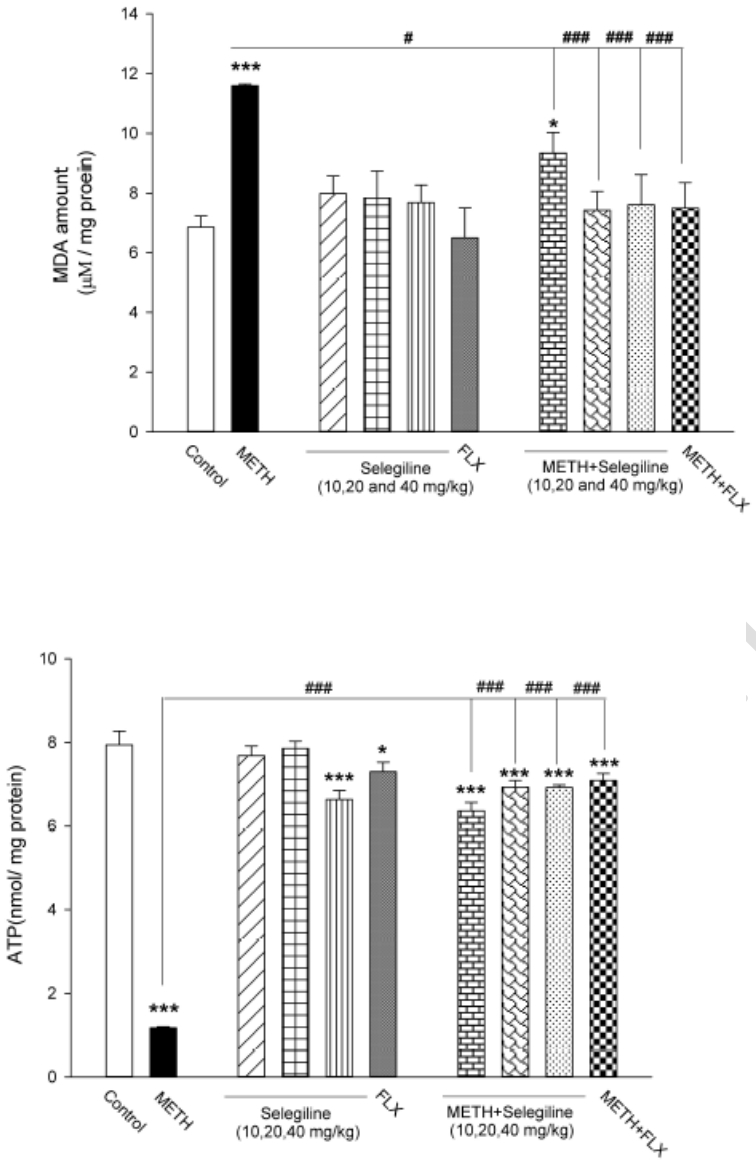


Fig. 3. Effects of selegiline(10, 20 and 40 mg/kg) on oxidative stress paramters including (a) GSH, (b) MDA and (c) ATP level in Hippocampus. Values are expressed as the mean ± SD and were analyzed using one-way ANOVA followed by Tukey's post hoc test (n=6-8). * P<0.05, ** P<0.01 and *** P<0.001 compared with control group. #P<0.05 and ##P<0.01 and ### P<0.001 compared with METH-withdrawal treated groups.

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