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N-methyl-D-aspartate receptor antagonists decrease interferon-alpha induced depressive behavior in mice model of despair

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ABSTRACT

Introduction: Treatment with interferon-alpha (IFNa) can induce depression that is likely the result of its effect on the tryptophan-kynurenine pathway. Kynurenine passes through the blood–brain barrier and breaks to neurotoxic metabolites, such as quinolinic acid, with agonistic effect on N-methyl-D-aspartate receptor (NMDAR). Thus, tryptophan available for serotonin synthesis declines. The aim was to evaluate the effect of NMDAR antagonists on IFNa-induced depression in mice model of despair. **Materials and Methods:** The total immobility time in the forced swimming test (FST) was assessed as an indicator of depression in mice. Depression was induced by IFNa injection (16 × 105 IU/kg) for 6 consecutive days. The optimum dose of dextromethorphan, memantine, and dizocilpine (MK-801) was administered on the 7th day following IFNa injection. **Results:** Immobility time in the FST was increased following IFNa injection (181 s ± 7 vs. control 122 s ± 10, $P < 0.05$) which indicated depression behavior. Dextromethorphan (15 mg/kg) and MK-801 (0.075 mg/kg) administration reduced the immobility time in IFNa-treated animals (57 s ± 14 and 46 s ± 6, respectively). Memantine (5 mg/kg) reduced the immobility time when it was administered alone but failed to decrease the immobility time induced by IFNa. The animals' locomotor activity was normal in the experimented groups. **Conclusion:** Dextromethorphan and MK-801 inhibited IFNa-induced depression. Thus, at least part of IFNa depressive behavior is caused by NMDAR that is stimulated by the production of metabolites in the tryptophan-kynurenine pathway. Administrating NMDAR antagonists should be further evaluated for patients suffering from the neurologic side effects of IFNa.

Keywords: Depression, forced swimming test, interferon-alpha, N-methyl-D-aspartate receptor

INTRODUCTION

Interferon-alpha (IFNa) has an antiviral effect in infected cells by the inhibition of viral replication. IFN-a has ample clinical application, being used in the treatment of conditions such as hepatitis B and C, and different types of cancer. Neuropsychiatric side effects have been identified in cancer patients and hepatitis who received high-dose IFNa therapy, such as dementia that was relieved after treatment cessation,[1] major depressive disorder, and symptoms that resemble sickness behavior induced by cytokines.[2] Neurologic adverse effects of IFNa therapy is caused by alterations in tryptophan-kynurenine pathway.[3,4] IFNa increases the indoleamine 2,3-dioxygenase (IDO) activity, which is responsible for tryptophan breakdown to kynurenine. Stimulated IDO expression causes high level of tryptophan to go through the neurotoxic arm of the pathway.[4] Therefore, kynurenine increases and tryptophan concentration available for serotonin synthesis decreases.[5] Kynurenine passes through the blood–brain barrier and breaks to neurotoxic metabolites, such as quinolinic acid, with agonistic effect on N-methyl-D-aspartate receptor (NMDAR).[3] Commonly NMDAR is composed of two GluN1 subunits and two GluN2 subunits. Normally, glutamate binds to GluN2 subunits and glycine binds to a GluN1 subunits, to cause the opening of the $Na^+/K^+/Ca^{++}$-permeable ion channel.[6] The open NMDA channel is blocked by uncompetitive NMDAR antagonists

memantine, ketamine, and MK-801 by binding inside of the ion channel in an area overlapping the binding site for Mg2+.[7] Receptors comprised of GluN2C/GluN2D have a lower susceptibility to extracellular Mg2+ channel blockade and are more sensitive to channel blockers such as ketamine.[8]

Quinolinic acid acts specifically with NMDAR subtypes containing the GluN2A/GluN2B subunits, causing great calcium entry into neurons. Therefore, quinolinic acid exerts the greatest damage to neurons where these receptor subtypes are present, that is hippocampus and striatum.[9]

The depression symptoms caused by INFa could be managed by antidepressant citalopram, a selective serotonin reuptake inhibitors (SSRIs).[10] However, usual antidepressant drugs mainly mediate the monoamine system that requires 2–3 weeks of treatment to show their therapeutic effects. There is a crucial need for rapid-acting drugs, and the researches performed on ketamine propose that NMDAR antagonist may be a practical therapeutic target.[11] Memantine that has been approved for the treatment of Alzheimer's disease could also exhibit antidepressant activity.[12,13]

Dextromethorphan pharmacodynamics is similar to ketamine, and it has shown prompt antidepressant effects even in the treatment of resistant patients.[14] It has been available as a high margin of safety antitussive drug during the past half-century; therefore, it could be considered as a safer alternative to ketamine. Ample evidence suggests that the glutamatergic system is involved in the pathogenesis of depression, and thus, it is promising for developing the novel treatments for major depressive disorder.[15]

On the basis of IFNa effect on the tryptophan-kynurenine pathway and the production of neurotoxic NMDAR agonists, the objective was to evaluate various NMDAR antagonists' effects on the IFNa-induced depression behavior in mice. The antagonist drugs included in the experiment were the low-affinity NMDAR channel blockers (memantine and dextromethorphan) that are well-tolerated compounds and the widely used inhibitor MK-801 (dizocilpine maleate) that was shown to be a potent NMDAR channel blocker.[6]

MATERIALS AND METHODS

Animals

Male albino mice weighing 28 ± 3 g were housed six animals in each cage at 21 ± 2°C with a 12 h–12 h light-dark cycle (the lights were on from 6 am to 6 pm). Tap water and standard mice chow were available, *ad libitum*. To minimize circadian rhythm influence, all the experiments were performed between 08:00 and 13:00 h in the pharmacology laboratory. Tests were performed only after the mice had acclimated to the environment for at least 24 h. Minimum of six mice were used for each treatment group. All animal procedures were performed in accordance with guidelines for the Care and Use of Laboratory Animals issued by The University of Medical Sciences (Ethical No: IR.MUI.REC.1395.3.857).

Locomotion Test

The motor activity of mice was assessed in a rectangular, open field apparatus (Borj Sanat, Iran) divided by red beams into 15 zones in a 5 × 3 grid formation. Mice were placed facing toward the wall and were allowed to explore the field for 3 min.[16] The total activity was calculated by summing the zone entries (horizontal exploration) that were automatically counted by the apparatus and rears (vertical exploration) that were counted by the experimenter.

Forced Swimming Test (FST)

FST was done according to previously published experiments with some modifications.[17] Briefly, mice were forced to swim for 6 min in 25°C water-filled glass beaker (diameter 12.5 cm). Latency to the first immobility was recorded starting right after placing the mice in the water. The total immobility time in the past 4 min, defined as the time spent while animal was floating staying still or using righting movements, was measured. The whole experiment was recorded by camera and analyzed later. After 6 min, the mice were dried carefully and returned to their home cage. Each animal was first subjected to the locomotor test and then to the FST.

Sucrose Preference Test

This test was carried out to confirm depressive behavior induced by IFNa. As described earlier, in the first 24 h, two bottles of sucrose solution (1% w/v) were placed in each animal cage, and on the following day, one bottle of sucrose solution was replaced with water for another 24 h. After the habituation period, the test was conducted on the 3rd day, in which mice had access to two bottles containing sucrose solution or tap water (100 ml). After 24 h, the amount of sucrose solution and water consumptions was measured and sucrose preference was calculated as sucrose preference (%) = sucrose consumption (ml)/(sucrose consumption [ml] + water consumption [ml]) × 100%.[18] A decrease of sucrose preference measured to a level <65% was taken as a criterion for anhedonia.[19]

Drug Administration

The following drugs were used: IFNa (PDferon-B 5 MIU/ml, Pooyesh Darou, Iran), the stock solution was prepared with distilled water into different aliquots stored at −20°C, 16×10^{5} IU/kg body weight was injected subcutaneously for 6 consecutive days, and tests were performed on the 7th day.[16] Memantine HCl (Sobhan Darou, Iran) 2.5, 5, and 7 mg/kg;[12] dextromethorphan HBr (Gift from Amin industry, Isfahan, Iran) 7.5, 15, and 30 mg/kg;[14] and (+)-MK-801 (Sigma-M107, USA) 0.05, 0.075, and 0.1 mg/kg[20] were all administered ip 30 min before testing, and after the optimal dose of each drug was evaluated, it was injected on the 7th day following IFNa therapy. Fluoxetine HCl (Sigma-Aldrich, USA) 20 mg/kg (ip) was used as the reference antidepressant drug to validate FST. All of the drugs were dissolved in normal saline, and they were prepared daily on demand.

Data Processing and Statistical Analysis

Results were expressed as group mean ± standard error of mean (SEM). All results were analyzed by one-way analysis of variance (ANOVA), followed by the appropriate multiple comparison tests, $P < 0.05$ was considered to be statistically significant. The software programs used for data analyzing and making graphs were Excel 2010 and the GraphPad Prism 6.

RESULTS

The Effect of NMDA Antagonists on Total Activity during the Locomotor Test

Animal activity in the open field increased significantly by exposure to dextromethorphan 30 mg/kg (251 ± 18 total activity vs. 175 ± 11, $P < 0.01$) as presented in Table 1. Memantine slightly decreased total locomotor activity that was not significantly different from the saline group. The highest dose of MK-801 also increased total animal movements in our experiments [Table 1].

The Effect of NMDA Antagonists on Depressive Behavior during the FST

Figure 1a shows that each of dextromethorphan doses has significantly reduced the immobility time during the FST compared with the control group (145 s ± 14, $P < 0.001$). The immobility time was 63 s ± 12 for the dose of 15 mg/kg. Memantine considerably decreased the immobility time following the administration of the doses, 5 and 7.5 mg/kg to 53.6 s ± 15 and 65 s ± 15, respectively ($P < 0.01$ compared with the control group), and no change was observed with the lowest dose during the FST [Figure 1b]. There was a noticeable decrease in the immobility time in the FST with different doses of MK-801. As Figure 1c illustrates, immobility was very low with 0.075 mg/kg MK-801 and it was the dose selected for further experiments (13 s ± 7, $P < 0.001$). Therefore, the drug doses that reduced the immobility in the FST and did not cause significant effect on animal locomotor activity were selected as the optimum doses, to exclude the risk that their antidepressant-like effects are due to their adverse effects on the locomotor activity.

The Effect of NMDA Antagonists following IFNa Administration on Total Activity during the Locomotor Test

The total locomotor activity in the open field following IFNa administration did not differ from the control group [Table 2]. By injecting the selected dose of each NMDAR antagonist on day 7, there was no significant change in the total locomotor activity. Therefore, immobility changes observed during the FST could be interpreted as the direct effect of the treatments on depressive behavior.

The Effect of NMDA Antagonists following IFNa Administration on Depressive Behavior during the FST

Animals' immobility time in the FST increased after 6 days of IFNa injection [Figure 2a] indicating animal despair behavior (181 s ± 7 vs. control group, the plain bar 122 s ± 10, $P < 0.05$). This was confirmed by the sucrose preference test which showed anhedonia in the IFNa-treated animals [Figure 2b]. Fluoxetine was used as the reference antidepressant drug, and it significantly reduced the immobility time in animals that were treated with IFNa, indicating its antidepressant effects compared with IFNa alone group, the solid bar [$P < 0.001$, Figure 2a]. Dextromethorphan 15 mg/kg considerably reduced immobility time in IFNa-treated animals (57 s ± 14 vs. 181 s ± 7, $P < 0.001$). Memantine (5 mg/kg) alone although reduced immobility time in the FST but it could not reduce the immobility time when administered following IFNa (146.5 s ± 22), implicating that it could not recover depression induced by IFNa. MK-801 had a meaningful effect on the total immobility time as it reduced the value to 46 s ± 6 ($P < 0.001$ vs. IFNa alone group). Immobility latency values during the FST were not different from control groups in our experiments; therefore, the data are not applied.

Table 1: The number of animal movements in the open field

Treatments	Horizontal movement	Vertical movement	Total movement
Control group	147±17	15±4	175±11
Dex (7.5 mg/kg)	174±25	7.5±3	181±26
Dex (15 mg/kg)	198±12	19±2	216±12
Dex (30 mg/kg)	246±17	5±1*	251±18**
Mem (2.5 mg/kg)	167±19	7±1	174±19
Mem (5 mg/kg)	143±17	6.5±1.7*	150±12
Mem (7.5 mg/kg)	156±15	4±1*	160±15
MK (0.05 mg/kg)	172±4	4±1*	176±4
MK (0.075 mg/kg)	150±18	3.4±1.7	152±17
MK (0.1 mg/kg)	223±15	5±1*	228±16

The zone entries and hind-leg rears were count in mice for 3 min, and the total activity is the sum of zone entries and rears. The number of animals in each group was 6. Control animals received normal saline. The test was performed 30 min after the treatments. Results are expressed as group mean±SEM and analyzed by ANOVA followed by Tukey's comparison tests *P<0.05, **P<0.01 compared with the control group. (Dex: Dextromethorphan, Mem: Memantine, MK: MK-801). SEM: Standard error of mean, ANOVA: Analysis of variance

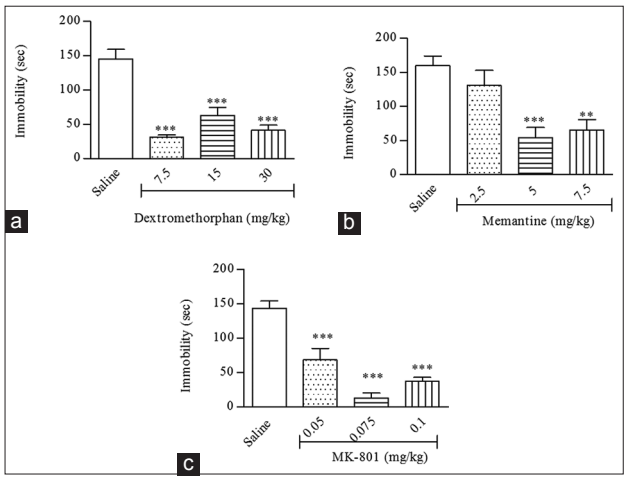

Figure 1: The effect of different N-methyl-D-aspartate receptor antagonists on depression behavior in the FST. Drugs administered were dextromethorphan (a), memantine (b), and MK-801 (c). The immobility time is the total time, animals were immobile during the past 4 min of the total 6 min test. Number of animals in each group was 6. Control animals received normal saline. Results are expressed as group mean ± standard error of mean and analyzed by analysis of variance followed by Tukey's comparison tests. **$P < 0.01$ and ***$P < 0.001$ compared with the control group.

DISCUSSION

Using FST in our experiments that is the most commonly used screening model for antidepressant activity in rodents, IFNa

Table 2: The number of animal movements in the open field

Treatments	Horizontal movement	Vertical movement	Total movement
Control group	156±8.4	14±3	171±11
IFNa (16×10^5 mg/kg)	135±18	13±2	155±12
IFNa+Flx (20 mg/kg)	109±5.6	10±1	119±5.4
IFNa+Dex (15 mg/kg)	202±17	14±1.4	215±18
IFNa+Mem (5 mg/kg)	138±20	5.2±4*	142±23
IFNa+MK (0.075 mg/kg)	121±25	2±1**	131±23

The zone entries and hind-leg rears were count in mice for 3 min, and the total activity is the sum of zone entries and rears. Number of animals in each group was 6. IFNa was administered (16×105 IU/kg, SC) after diluted in normal saline for 6 days. Control animals received normal saline. The drugs were administered on the 7th day 30 min before the test. Results are expressed as group mean±SEM and analyzed by ANOVA followed by Tukey's comparison tests *P<0.05 and **P<0.01 compared with the control group. (Flx: Fluoxetine, Dex: Dextromethorphan, Mem: Memantine, MK: MK-801). SEM: Standard error of mean, ANOVA: Analysis of variance

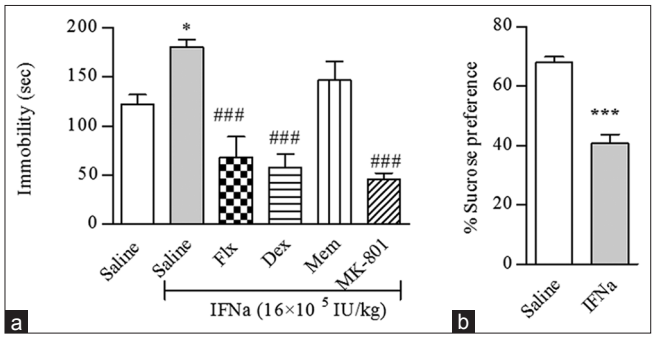

Figure 2: The effect of different N-methyl-D-aspartate receptor antagonists on interferon-alpha (IFNa)-induced depression in the forced swimming test (a), sucrose preference confirmation test for IFNa (b). Number of animals in each group was 6. IFNa was injected for 6 days and the drugs were administered on the 7th day 30 min before the test. Fluoxetine 20 mg/kg, dextromethorphan 15 mg/kg, memantine 5 mg/kg, and MK-801 0.075 mg/kg were administered. Results are expressed as group mean ± standard error of mean and analyzed by analysis of variance followed by Tukey's comparison tests. *P < 0.05, compared with the control group the first column,###P < 0.001 compared with IFNa the solid column

increased animal immobility time in the FST denoting despair behavior. This was also supported by the sucrose preference test, IFNa-treated animals had no sucrose preference over water that indicates anhedonia. Our reference drug fluoxetine obviously decreased the immobility time in IFNa-treated animals. The optimal NMDAR antagonist dose was chosen regarding their unbiased effect on the locomotor activity; the locomotor activity should be tested before behavioral tasks since variations in locomotor activity nonspecifically affect performance in many behavioral tests. The NMDAR antagonists' dextromethorphan and MK-801 administered in our experiments prevented IFNa-induced depression; however, this result was not achieved by memantine.

After six consecutive IFNa administrations, animals showed despair behavior as observed previously.[16] Similar results were obtained following IFNa administration in mice that depressive symptoms were with anxiety-like behavior,[21] while other researchers failed to reproduce the despair behavior.[22] This inconsistency could be a direct result of differences in experimental patterns, including the sort of IFNa used, treatment regimens, animal species, and behavioral tests performed.

Previous findings suggest that aberrations in the tryptophan-kynurenine pathway could be linked to the neuropsychiatric side effects of IFNa.[23] Clinical studies have shown that IFNa therapy increases kynurenine levels in plasma and CSF[24] and decreases plasma tryptophan and serotonin levels.[25] Imbalances in kynurenines and noticeable decrease in serotonin have also been reported in major depression disease.[26] Quinolinic acid levels in CSF correlate with the intensity of depression symptoms;[24] on the other hand, microglia quinolinic acid levels were higher in severe depressed patients following post-mortem.[27] As tryptophan proceeds along the kynurenine pathway, kynurenine is the first stable intermediate formed. Subsequently, several neuroactive intermediates are generated such as the excitotoxin, NMDAR agonist, and quinolinic acid.[28] Researchers proved that antagonists at several NMDAR sites including ligands at glutamate and ionophore recognition sites are successful in models of depression.[29]

In our study, dextromethorphan on its own showed non-dose-dependent antidepressant activity in mice which was realized by the reduced immobility time in the FST by all the doses. Previous studies advocated that dextromethorphan readily induces antidepressant effect in mice FST through NMDAR and L-arginine-NO-cGMP pathway.[30] The important advantage of dextromethorphan over common antidepressants is its possible rapid antidepressant effect.[11] Dextromethorphan has higher affinity for serotonin transporters than ketamine.[31] It mitigated the immobility time induced by IFNa in the FST which could be in part because of its NMDAR antagonist effects. High-dose dextromethorphan induced an increase in the locomotor activity; therefore, the medium dose was experimented with IFNa in the FST. More selective NMDAR antagonists were experimented to realize the effect of NMDAR stimulation in IFNa-induced depression.

As early as 1990, the first evidence of the antidepressant-like effects of NMDAR antagonists including MK-801 and 1-aminocyclopropanecarboxylic acid in the mice FST and tail suspension test was provided.[32] In agreement with previous results different doses of MK-801 in our experiment reduced the immobility time during FST in a non-dose dependent manner. The optimal MK-801 dose that did not cause locomotor aberration diminished IFNa-induced depressive behavior. Therefore, it could be inferred that the NMDAR has a crucial role in IFNa-induced depression that is connected to induction of IDO and a shift from serotonin synthesis to tryptophan-kynurenine pathway metabolism which may ultimately lead to serotonin depletion and overproduction of quinolinic acid that is NMDAR agonist. Previous research showed that, by increasing tryptophan in mice diet, the serotonin yield could be higher which was another approach to prevent IFNa-induced depression.[16] Although on the downside of our research, we did not measure the tryptophan/kynurenines ratio, but this has been proven earlier.[3]

Memantine was also examined here as an uncompetitive NMDAR antagonist. Although memantine alone decreased immobility in the FST, but it was not as effective as

dextromethorphan or MK-801 in reducing the immobility time caused by IFNa. Previous experiments have shown that memantine has synergist effects when used with antidepressant in the FST in rats.[33] Alike dextromethorphan memantine is a low-affinity NMDAR channel blocker, only after channel opening, it can enter the channel and block current flow.[34] Interestingly, magnesium ions reduce the affinity of memantine for NMDA receptor channels, and thus in the presence of physiological levels of Mg^{++} ions, memantine displays approximately 10-fold selectivity for GluN1/GluN2C and GluN1/GluN2D receptors.[34] Therefore, since quinolinic acid is a potent NMDAR agonist, especially for the subtypes containing the GluN2A and GluN2B subunits, it was interpreted that memantine as a low-affinity antagonist is unable to overcome the effect of a potent NMDAR agonist. Definitely further molecular research is warranted to prove the possible interaction between quinolinic acid and memantine on the NMDAR site. The discrepancy of the drugs' effects may be related to the drugs' differences in the mechanism of action on NMDAR subunits. It looks like minor changes in the drug mechanism of action which can translate into great differences in its clinical outcome.

Although IFNa-induced depression could be treated with SSRIs but the somatic symptoms such as fatigue and anorexia are less responsive to SSRIs treatment.[10] On the other hand, the rapid-acting antidepressant effects of NMDAR antagonist make them valuable targets to overcome IFNa neurologic side effects in patients. Therefore, these drugs could be promising therapy for IFNa depression, and their clinical use in patients that suffer IFNa neurologic disadvantage should be further evaluated.

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