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DEPRESSION-LIKE EFFECTS OF LEVETIRACETAM WAS HALTED BY PRETREATMENT WITH N-METHYL-D-ASPARTATE RECEPTOR (NMDAR) BLOCKERS IN MICE

Azadeh Mesripour * and Tanin Ahmadi

Department of Pharmacology and Toxicology, School of Pharmacy and Pharmaceutical Sciences, Isfahan University of Medical Sciences, Isfahan, Iran

N-methyl-D-aspartate receptor (NMDAR) stimulation might be responsible for levetiracetam -(Lev) induced depression. The aim of our study is to evaluate the effect of noncompetitive NMDAR blockers, dextromethorphan (Dxt) and dizocilpine (MK801), on Lev-induced depression in mice. Male NMRI mice were daily injected with Lev for 14 days. Pretreatments with Dxt, or MK801 were performed 30 min prior to Lev administration. The locomotor test and the forced swimming test (FST) and the novelty suppressed feeding test (NSFT) were performed. Following Dxt or MK801 pretreatment immobility time during FST was lower than Lev alone. There was no change in the locomotor activity. During NSFT, Lev increased latency, and decreased food intake; while, pretreatment with Dxt or MK801 reversed these effects. To our knowledge this is the first study showing that NMDAR blockers prevented the depressive-like behavior induced by Lev in mice. And proved that, at least in part activation of NMDAR is responsible for Lev induced depression, that warrants further research.

Keywords: *Mice, depression, epilepsy, N-methyl-D-aspartate receptors, levetiracetam*

INTRODUCTION

Epidemiological studies suggest that patients with depression have two to seven-fold increased risk of developing epilepsy, meanwhile epilepsy is also associated with depression[1]. It has also been reported that, antiepileptic drugs such as barbiturates, zonisamide, topiramate, vigabatrin, and levetiracetam (Lev) can further aggravate the depression in epileptic patients[2]. Lev is a second-generation antiepileptic drug with a unique structure and a novel mechanism of action. It is commonly approved for partial seizures with or without secondary generalization; other indications include, adjunctive treatment of myoclonic seizures and primary generalized tonic-clonic seizures[3&4]. Lev effectively prevents epileptic attacks by a different mechanism; probably by binding to synaptic vesicle glycoprotein (SV2A) Lev decreases the transmitter release together with the modulation of ion channels[5].

Indoleamine 2,3-dioxygenase (IDO) enzyme stimulation in distinct brain parts is also related to depression in epilepsy[6]. In pentylenetetrazole induced kindled mice Lev treatment worsens depression related to epilepsy by further increasing IDO activity[7]. Serotonin (5-HT) is a brain neurotransmitter related to epilepsy and depression, it is synthesised by tryptophan hydroxylase[8&9]. Another tryptophan metabolism pathway is the kynurenine pathway, that involves (IDO) enzyme; IDO stimulation leads to a decrease in 5-HT to kynurenine ratio. Kynurenine freely passes through the blood-brain barrier and is further converted to a neuroactive glutamatergic compound, quinolinic acid, that by stimulating the N-methyl-D-aspartate receptor (NMDAR) causes neurotoxic effects[10].

The rapid antidepressant effects of ketamine (a NMDAR antagonist) in patients with major depressive disorder have been previously proven[11]. Dextromethorphan (Dxt)

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*Corresponding author: Azadeh Mesripour, E-mail: a_mesripour@yahoo.com

is an antitussive drug with a high margin of safety structurally related to alkaloid opioids but does not produce classic opioid central effects. In fact, the main site of action of Dxt is NMDAR as a non-competitive antagonist. It was previously shown that Dxt administration prevented interferon-α- induced depression[12]. Interferon-α -induced depression is also related to augmentation of IDO activity, that was prevented by Dxt co-administration[13]. Notably, starting treatment with Dxt/quinidine or increasing the dose to twice daily in resilient depressed patients, has shown rapid mood improvements (1–2 days) in some patients[14].

Prescribing conventional antidepressant drugs such as imipramine (Imi) a tricyclic antidepressant (TCA), or bupropion were reported to lower the seizure threshold in people with epilepsy leaving depression untreated[15]. Moreover, in a chronic model of temporal lobe epilepsy, showed pharmacoresistance to antidepressant effect of selective serotonin reuptake inhibitors (SSRI)[16]. Thus, conventional antidepressant drugs are probably not ideal for depression in epilepsy or induce by antiepileptic drugs and introducing alternative drug therapy for preventing depression is crucial. The objective of this study was to evaluate the efficacy of NMDAR antagonists on the Lev-induced depression behavior in mice. The antagonist drugs used in this experiment were, Dxt a low-affinity noncompetitive NMDAR channel blocker, that is well-tolerated, and dizocilpine maleate (MK801) a potent selective noncompetitive NMDAR antagonist that acts by binding to the pore of the NMDAR channel[17].

MATERIALS AND METHODS

Animals

Male NMRI mice (a Swiss-type mice) weighing 25±3 g, 6-8 weeks old were used and housed at room temperature 21± 2 ºC, on a 12-12 hrs light-dark cycle (lights on at 6 AM), with free access to standard mouse chow and water (provided from disinfected drinking water). Animals were placed in the experimental room 24 hrs before the test for acclimatization. All the experiments were accomplished between 8 AM to 1 PM in the Pharmacology Department laboratory. All animal procedures were performed according to the guidelines for the Care and Use of Laboratory Animals issued by The National Ethical Committee of Iran, evaluated by the Vice-Chancellor in Research Affairs-Medical University of Isfahan (Ethical No: IR.MUI.REC.1399.559, Approval date: 2020-11-14). Between the behavioral tests, mice were put back in their home cage with access to food and water. Mice weight changes were evaluated during the study, experiments were conducted in the way to minimize animal suffering and to reduce the number of animals used in the experiments.

Chemicals

Chemicals included Lev that was purchased from Amin Chemical & Pharmaceutical Company, Iran, the reference antidepressant drug Imi hydrochloride was provided from Sigma-Aldrich, Germany, Dxt hydrobromide was a generous gift from Amin industry, Iran, and MK801 was purchased from Sigma-M107, USA.

Study design

The study comprised of ten groups with seven animals in each group: Lev (20 mg/kg) alone group, the dose was based on a previous study[18] and our previous experiments[19], the control group received normal saline; five groups that received Dxt (15, 30 mg/kg), or MK801 (0.05, 0.075 mg/kg) alone[12], or the vehicle that was normal saline, two groups that were pretreated with Dxt 30, or MK801 0.075 mg/kg along with Lev, the control positive group was pretreated with Imi (10 mg/kg). All the drugs were injected intraperitonealy[12&18], the injection volume was 10 ml/kg.

Firstly, two doses of Dxt, or MK801 were administered in order to choose the best dose with antidepressant-like effect and yet not interfering with the locomotor activity. Animals were injected Lev daily for 14 consecutive days. Pretreatments were performed 30 min before Lev administration starting from the second week (Table 1). The locomotor test and the forced swimming test (FST) were performed on day 7 (30 min after the daily injections) and on day 15 (24 hrs after the last injection) in the same group of animals, fasting was imposed on day 15 at the end of the behavioral tests for 18 hrs, the novelty suppressed feeding test (NSFT) was performed on day 16.

Table 1: Research protocol timeline.

Days	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Lev	-	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	-	-
Dxt, MK	-	✓	✓	✓	✓	✓	✓	✓	-	-	-	-	-	-	-	-	-
Lev-	-	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	-	-
Dxt, Mk, Imi	-	-	-	-	-	-	-	-	✓	✓	✓	✓	✓	✓	✓	-	-
Locomotor activity test	-	-	-	-	-	-	-	✓	-	-	-	-	-	-	-	✓	-
FST	-	-	-	-	-	-	-	✓	-	-	-	-	-	-	-	✓	-
NSFT	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	F	✓

✓: treatment or experiment performed, -: no treatment or experiment, F: fasting at the end of behavior tests, FST: Forced swimming test, NSFT: Novelty suppressed feeding test, Lev: levetiracetam, Dxt: dextromethorphan, MK: MK801, Imi: imipramine.

Locomotor activity test

Mice locomotor activity was measured at the beginning of the behavioral experiments by an open field (Borj Sanat, Iran) that was divided into 15 zones by red beams crossing over the arena floor. Mice were gently put in one corner and allowed to explore the arena for 3 min, by passing through the beams the number of zone entries was counted automatically and hind-leg rears were recorded manually. Total activity, the sum of horizontal and vertical movements were calculated for each mouse[20].

Forced swimming test (FST)

Mice were forced to swim in a 2-liter Pyrex beaker (diameter 12.5 cm, depth 12 cm) filled with 25 ºC water for 6 min. The first 2 min after putting the mouse in water was considered for the habituation period and the immobility time was measured during the last 4 min of the test. The immobility time that indicates the animal despair behavior was considered when no additional activity was observed in animals except those required to keep their head above the water[12]. Swimming and climbing time was also measured to hypothesize the possible neurotransmitter involved in depressive-like behavior[21]. The whole experiment was recorded by a camera and analyzed later. After the experiment animals were dried carefully to avoid hypothermia and returned to their home cage.

Novelty suppressed feeding test (NSFT)

The test was performed in a Plexiglas box (45×45×20 cm), that was covered with 0.5 cm of wooden bedding. Three pieces of mouse chow were weighed and placed in the center of the apparatus on a Petri dish. Each mouse was located in the corner of the box, the latency to feed the pallet was recorded, and finally, after 20 min the total amount of food consumed was measured by weighing the remaining chow. At the end, the mice were returned to their previous cage with free access to food and water.

Data processing and statistical analysis

All statistical evaluation and data processing were carried out by using Excel 2010 and the GraphPad Prism 8 software (La Jolla, CA, USA). Results are expressed as group means ± SEM and analyzed by one-way analysis of variance (ANOVA), followed by Tukey's multiple comparison tests. Values of p less than 0.05 were defined as statistically significant.

RESULTS and DISCUSSION

Results

The effect of drug administrations on animals' weight

According to Fig. 1 the percent of weight changes were lower during pretreatment with Dxt (5.3 ± 1.0 %) following 14 days compared to the control group (12.0 ± 3 %) although it was not significant ($p > 0.05$).

The effect of Dxt pretreatment on the locomotor activity and FST

The immobility time during FST is depicted in Fig.2a, the immobility time following treatment with Dxt alone 15 mg/kg (86.2 ± 9.3 s, $p = 0.0096$), or Dxt 30 mg/kg (56.8 ± 10.0 s, $p < 0.001$) were significantly lower than the control group (125.2 ± 7.5 s),

these changes were in the absence of important changes in the locomotor test (Table 2). Lev alone administration for 7 days did not cause a noticeable change in the immobility time during FST, and following continued treatment with Lev for 14 days immobility time was significantly higher than control (161.4 ± 11.8 s, vs. 109.4±6.0 s, p= 0.002) (Fig.2a). During pretreatment with Dxt 30 mg/kg immobility time was significantly lower than lev alone and the control group (44.3 ± 5.6 s, p<0.001), while the locomotor activity remained evidently unchanged (Table 2). These changes were similar to pretreatment with Imi. Table 3 shows the swimming and climbing time results during FST, Lev significantly reduced the swimming time after 14 days compared to control (p= 0.0176), following pretreatment with Dxt swimming (p< 0.001) and climbing time (p= 0.0034) were significantly higher than the Lev alone group.

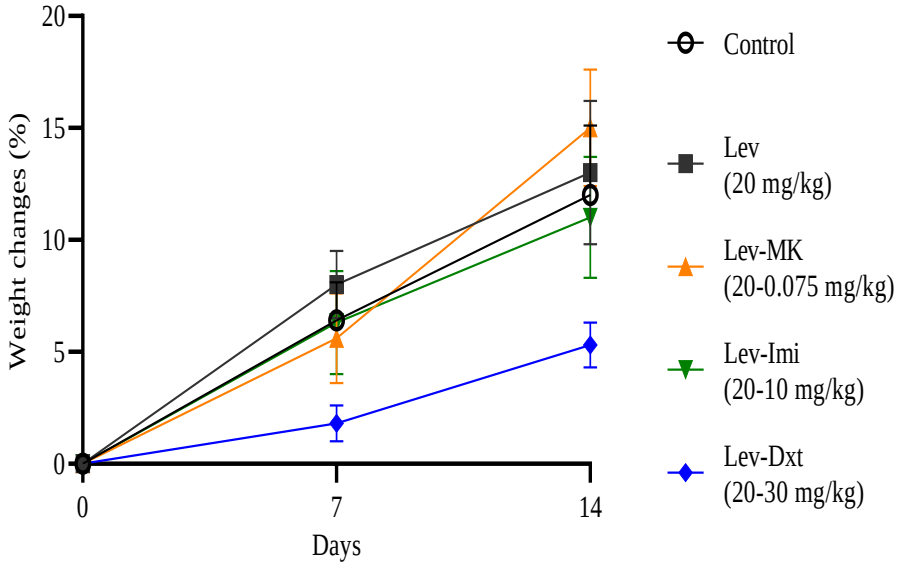

Fig. 1: The percentage of body weight change after 7 and 14 days. Control animals; normal saline. The results represent mean ± SEM for n=7 mice per group, and analyzed by one-way ANOVA, followed by Tukey's multiple comparison tests (p>0.05). Lev: levetiracetam, Dxt: dextromethorphan, MK: MK801, Imi: imipramine.

Table 2: The total activity counted during the locomotor activity test.

Day 7		Day 14	
Groups (n=7)	Total activity (No.)	Groups (n=7)	Total activity (No.)
Control	190.4±20.1	Control	145.1±12.69
Dxt (15 mg/kg)	168.2±23.3	Lev (20 mg/kg)	135.9±12.95
Dxt (30 mg/kg)	169±18.1	Lev-Dxt (30 mg/kg)	140.1±14.56
Mk801 (0.05 mg/kg)	176.3±18.73	Lev-MK801 (0.075 mg/kg)	202.9±18.42
MK801 (0.075 mg/kg)	153.2±12.86	Lev-Imi (10 mg/kg)	126.7±13.47
Lev (20 mg/kg)	146.4±16.22		

Total activity equals horizontal plus vertical activity. Control animals; normal saline. Results are presented as group mean ± SEM and analyzed by one-way ANOVA followed by Tukey's comparison test. Lev: levetiracetam, Dxt: dextromethorphan, MK: MK801, Imi: imipramine.

Table 3: The swimming and climbing time results during FST.

Day 7			Day 14		
Groups (n=7)	Swimming time (s)	Climbing time (s)	Groups (n=7)	Swimming time (s)	Climbing time (s)
Control	64.33±11.36	30.14±12.56	Control	107.7±9.42	22.86±6.27
Dxt (15mg/kg)	96.42±13.37	57.42±12.87	Lev (20mg/kg)	57.57±10.31v	21±5
Dxt (30 mg/kg)	137.7±11.1***	45.5±9.89	Lev +Dxt 30mg/kg)	132.9±13.67###	62.8±11.16vv,##
Mk (0.05 mg/kg)	131.6±9.81*	17.86±1.72	Lev +MK (0.075mg/kg)	139.9±15.24###	36.0±14.5
MK (0.075mg/k)	194±7.9***	20.8±5.7	Lev + Imi (10mg/kg)	134.7±10.03###	21.86±6.26
Lev (20 mg/kg)	81.29±11.72	48.14±16.01			

Control animals; normal saline. The results are presented as mean ± SEM, and analyzed by one-way ANOVA followed by Tukey's multiple comparison tests. * p<0.05, ***p<0.001 compared with the control group (day 7), v p<0.05, vv p<0.01 compared with the control group (day 14), ## p<0.01, ###p<0.001 compared with Lev alone group. Lev: levetiracetam, Dxt: dextromethorphan, MK: MK801, Imi: imipramine.

The effect of MK801 pretreatment on the locomotor activity and FST

As shown in Fig. 2b by administrating MK801 for 7 days, the immobility time during FST was significantly lower than the control group (for a dose of 0.05 mg/kg; 90.5 ± 9.2 s, p= 0.0107, and for a dose of 0.075mg/kg; 25.0±7.0 s, p< 0.001), no important change was observed in the locomotor activity (Table 2). Following Lev pretreatment with MK801 (0.075 mg/kg) the immobility time (53.0 ± 7.04 s) was significantly lower than the control group (p= 0.0019) and Lev (p< 0.001). Changes were not present in the locomotor activity (Table2). As shown in table 3 pretreatment with MK801 significantly increased the swimming time (p< 0.001). The changes were similar to the Imi group.

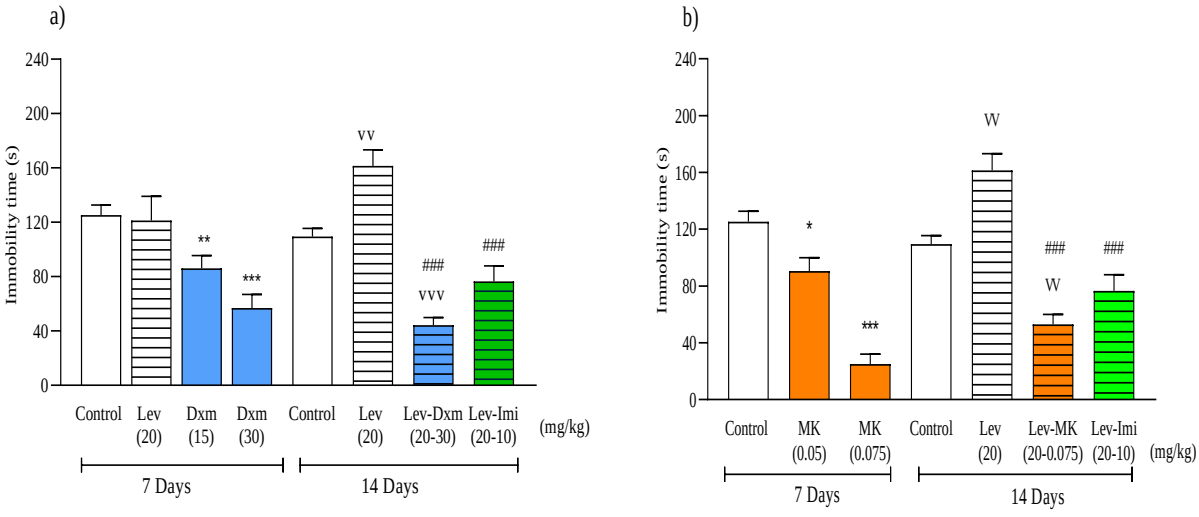

Fig. 2: Effect of (a) dextromethorphan and (b) MK801 pretreatments on Lev immobility time during the forced swimming test. Control animals; normal saline. The results present mean ± SEM (n=7), and analyzed by one-way ANOVA followed by Tukey's multiple comparison tests. * p<0.05, **p<0.01, ***p<0.001 compared with the control group (7 days), vv p<0.01, vvv p<0.001 compared with the control group (14 days), ###p<0.001 compared with Lev alone group. Lev: levetiracetam, Dxt: dextromethorphan, MK: MK801, Imi: imipramine.

The effect of Dxt and MK801 pretreatment on NSFT

As depicted in Fig.3a, Lev significantly increased the starting to eating time during NSFT (159.0 ± 25.1 s vs. control 86.7 ± 9.3 s, p= 0.0047). Latency significantly reduced following pretreatment with Dxt (73.1 ± 5.5 s, p< 0.001), or MK801 (59.9 ± 4.7 s, p< 0.001) compared to the Lev alone group. Food intake during NSFT is shown in Fig.3b, Lev alone significantly reduced food intake after 20 min compared to the control group (8.6 ± 0.7 mg/g body weight, p< 0.001). This value significantly increased during pretreatment with Dxt (12.9 ± 1.7 mg/g body weight, p= 0.0467), or MK801 (13.1 ± 0.8 mg/g body weight, p= 0.0346), the NSFT results in Dxt or MK801 pretreatment were similar to the Imi group.

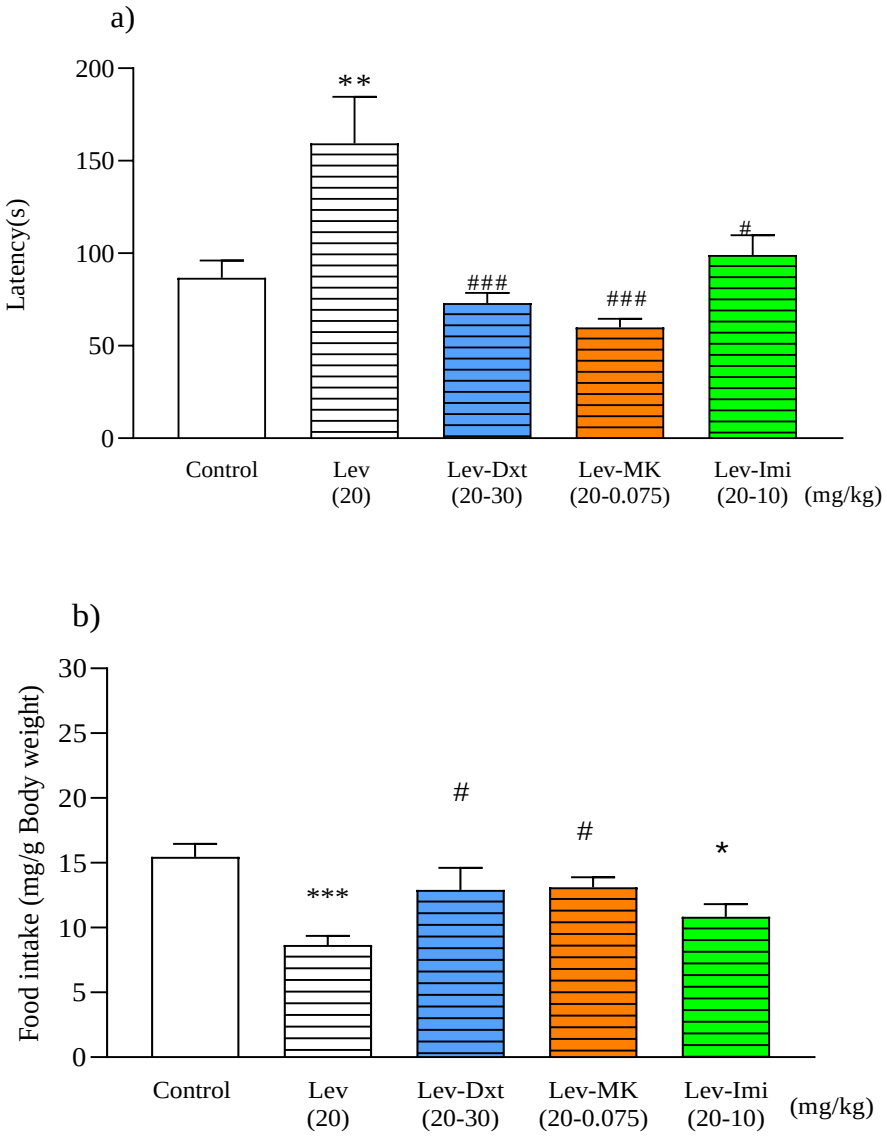

Fig. 3: Effect of dextromethorphan and MK801 pretreatment on Lev latency (a) and food intake (b) during novel feeding test after 14 days. Control animals; normal saline. The results present mean ± SEM (n=7), and analyzed by one- way ANOVA followed by Tukey's multiple comparison tests. * p<0.05, **p<0.01, ***p<0.001 compared with the control group, # p<0.05, ###p<0.001 compared with Lev alone group. Lev: levetiracetam, Dxt: dextromethorphan, MK: MK801, Imi: imipramine.

Discussion

Our results proved that administration of Lev induced depressive-like behavior in mice and the NMDAR blockers (Dxt or MK801) prevented the depressive-like effects. Clinical data indicate that the safety and efficacy of antidepressant drugs are still unreliable in patients with epilepsy[22]. One study has shown that some antidepressant drugs like SSRIs may be useless in alleviating the depression related to chronic epilepsy due to the lack of 5-HT production, related to the activation of IDO and the shift in transforming tryptophan to kyneronic acid instead of 5-HT[6]. In addition, some of these drugs have proconvulsant effects[23], therefore NMDAR blockers could be considered as promising alternative medications.

As an acute model, FST has been used for decades for screening of antidepressant drugs[24&25]. In FST, while animals are forced to swim in a water tank, despair is manifested when the animals become motionless in the inescapable situation. Common antidepressant drugs such as Imi, can efficiently reverse the motionless behavior. On the other hand, evaluation of climbing and swimming time helps to interpret the related neurotransmitters involved in the behavior change[21]. That is, the antidepressants that increase 5-HT level, mostly increases swimming time while improvement of adrenergic neurotransmitter may enhance climbing time, during the FST. NSFT was chosen to evaluate the long term effect of the treatments on depressive behavior. This test involves measuring the eating latency in a novel environment, which could display the level of anxiety, while measuring food consumption displays changes in appetite as another endophenotypes of depression[24&25]. These findings were in the absence of important changes in the locomotor activity, therefore changes in the immobility time during FST or latency during NSFT could be related to depressive behavior.

The common antidepressant drugs such as TCAs (Imi) or selective serotonin reuptake inhibitors (fluoxetine) have been applied in previous behavioral studies in order to verify the accuracy of depression models used for animal studies[21&25]. Therefore, in order to reduce the number of animals used in the experiment, Imi alone was not repeated in this experiment.

During the treatment procedure with Lev alone or the pretreatments with MK801 or Imi the animals normally gained weight, although it was less during pretreatment with Dxt. However, it has been shown previously that Lev can induce weight loss in patients[26]. Housing situation can influence rodents weight changes[27], longer duration of Lev exposure in animals may reveal weight loss.

Depression was not induced in mice after one week of Lev administration, and after continuing the treatment depressive-like effect in mice became prominent on day 14, that was in agreement with previous findings[10]. The depressive-like effects of Lev was deduced from the immobility time that increased during FST; and during NSFT latency increased and food consumption declined . In our set of experiments, Lev 20 mg/kg induced depressive like behavior without causing important changes in the normal locomotor activity and this dose was chosen for further evaluations. Previously, it was shown that patients taking Lev have experienced considerably more psychiatric side effects than patients treated with other antiepileptic drugs[28]. In mice, it was shown that treatment with Lev 40 mg/kg for 15 days in kindled mice significantly increased motionless time in the tail suspension test compared with naïve animals, and significantly reduced the sucrose preference that also indicates anhedonia[10]. Elevated IDO activity in both cortical and hippocampal parts of the mice brain in chronic epileptic animals was proven by elevated kynurenine as well as decreased 5-HT level[10]. Depression was worsened by Lev treatment that further augmented IDO activity[10]. As it was observed during FST following Lev administration, swimming time significantly reduced, that is in agreement with reduced 5-HT level. Kynurenine metabolism leads to the production of quinolinic acid (end-product) that leads to the formation of reactive oxygen species responsible for neuronal apoptosis leading to hippocampal damage and initiating the overstimulation of NMDAR, causing the development of depression[29]. Evidence had proven that glutamatergic neurotransmission imbalance by increasing NMDAR agonist levels, could initiate excitatory activity in most brain circuits

involved in major depression[30]. On the downside, IDO activity, and brain oxidative stress parameter were not evaluated in this behavioral study.

Dxt a non-selective NMDAR channel blocker reduced immobility time during FST, proving its antidepressant-like effect that was in agreement with previous studies[12&31], while swimming was the prominent activity during FST. Dxt (30 mg/kg) alone showed consistent antidepressant-like effect while locomotor activity remained in the normal range; therefore, it was applied following Lev induced depression in mice. Dxt pretreatment prevented Lev anti-motion behavior during FST clearly showed its antidepressant efficacy that was further confirmed by NSFT. After Dxt pretreatment latency decreased and food intake increased compared to the Lev alone group in NSFT.

Dxt may exert its neuroprotective effects by inhibiting the excitatory neurotransmitter-glutamate- induced neurotoxicity by blocking NMDAR. Irregular high glutamate concentrations by increasing toxic amount of cytosolic free calcium ends up in neuronal necrosis or apoptosis[30]. Dxt reduces presynaptic calcium dependent glutamate release. Postsynaptic neuroprotection against excessive glutamate is mediated by Dxt of culminating in a potent neuroprotective effect[32].

On the other hand, treatment with high-dose of Dxt (40 mg/kg) for 2 weeks, in Sprague–Dawley rats have shown augmented depression-like behavior in comparison with the control group[33]. Following repeated treatment with high dose Dxt hippocampus neurogenesis was limited that was proven by decreases in number of proliferative cells[33]. Alternatively, it was proven that Dxt antidepressant actions in part are also related to sigma-1 (σ1) receptor binding, that is also an important target for antidepressant medications[34].

In order to further evaluate the role of NMDAR in Lev induced depression the effect of a more specific NMDAR blocker, MK801, pretreatment was assessed. MK801 is a potent anti-convulsant with anesthetic property, but due to numerous negative side effects, including cognitive disruption and psychotic-spectrum reactions it is only an experimental compound, not used clinically[35]. MK801 (0.075 mg/kg) alone showed reliable antidepressant-like effect while locomotor activity was not significantly different from the control group, therefore it was applied following lev induced depression in mice. Pretreatment with MK801 efficiently had antidepressant-like effects, by reducing the motionless behavior and enhanced swimming time during FST, likewise improved animals' performance during NSFT. The beneficial effects of MK801 were previously shown on interferon-α- induced depression in mice[12]. It was also observed that MK801 enhances lithium antidepressant-like effects in the FST[36].

Conclusion

This study for the first time showed that NMDAR blockers (Dxt and MK801), prevent the depressive-like behavior induced by Lev in mice. In conclusion, preventing depressive-like behavior effects of Lev in mice by Dxt a non-specific NMDAR blocker or MK801 a specific NMDAR blocker shows that at least in part activation of NMDAR is responsible for Lev-induced depression. The NMDAR antagonist should be considered for further studies as alternative therapy for preventing Lev-induced depression initiation.

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إيقاف التأثيرات المشابهة للاكتئاب لدواء ليفيتيراسيتام عن طريق المعالجة المسبقة بمضادات مستقبلات الجلوتامات ن-مثيل-د-أسبارتات (NMDA) فى الفئران آزاده

مسرييور* – تانين أحمدي

قسم علم الأدوية والسموم ، كلية الصيدلة والعلوم الصيدلانية ، جامعة أصفهان للعلوم الطبية ، أصفهان ، ايران

تشير الأبحاث إلى أن تحفيز مستقبلات الجلوتامات ن-مثيل-د-أسبارتات قد يكون مسئولا عن الاكتئاب الناجم عن دواء ليفيتيراسيتام. و قد كان الهدف من هذه الدراسة تقييم تأثير مضادات مستقبلات الجلوتامات ن-مثيل-د-أسبارتات الغير تنافسية؛ ديكستروميتورفان وديزوسيلبين، على الاكتئاب الذى يسببه دواء ليفيتيراسيتام فى الفئران. تم حقن ذكور فئران NMRI يوميًا بدواء الليفيتيراسيتام لمدة ١٤ يومًا، بينما تم معالجة الفئران بديكستروميتورفان أوديزوسيلبين، ٣٠ دقيقة قبل تناول ليفيتيراسيتام. تم إجراء الاختبار الحركي واختبار السباحة القسري (FST) واختبار كبت التغذية الناتج عن التجديد .(NSFT) وقد أظهرت النتائج أن المعالجة المسبقة للفئران بديكستروميتورفان أوديزوسيلبين قد أدت إلى تقليل فترة عدم الحركة فى اختبار السباحة القسري عن تلك التى نتجت عن حقن الفئران بدواء الليفيتيراسيتام وحده. لم يكن هناك تغيير ملحوظ في النشاط الحركي. و من خلال اختبار كبت التغذية الناتج عن التجديد (NSFT) ، أدى دواء الليفيتيراسيتام إلى زيادة فترة الاستجابة، وتقليل تناول الطعام فى الفئران؛ بينما أدت المعالجة المسبقة بديكستروميتورفان أوديزوسيلبين إلى إبطال هذه التأثيرات. و على حد علمنا، تمثل هذه هي الدراسة الأولى من نوعها التي تظهر أن مضادات مستقبلات الجلوتامات ن-مثيل-د-أسبارتات تمنع السلوك الشبيه بالاكتئاب الذي يسببه ليفيتيراسيتام في الفئران، كما تثبت أن تنشيط تلك المستقبلات مسؤولا، على الأقل جزئيًا، عن الاكتئاب الناجم عن ليفيتيراسيتام، و هذا ما يستدعي مزيدًا من الابحاث لدراسته.