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Original article

Effect of lacosamide on ethanol induced conditioned place preference and withdrawal associated behavior in mice: Possible contribution of hippocampal CRMP-2

Nidhi Sharma, Saima Zameer, Mohd Akhtar, Divya Vohora*

Neurobehavioral Pharmacology Laboratory, Department of Pharmacology, School of Pharmaceutical Education and Research, Jamia Hamdard, New Delhi, India

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ABSTRACT

Background: Excessive consumption of ethanol is known to activate the mTORC1 pathway and to enhance the Collapsin Response Mediator Protein-2 (CRMP-2) levels in the limbic region of brain. The latter helps in forming microtubule assembly that is linked to drug taking or addiction-like behavior in rodents. Therefore, in this study, we investigated the effect of lacosamide, an antiepileptic drug and a known CRMP-2 inhibitor, which binds to CRMP-2 and inhibits the formation of microtubule assembly, on ethanol-induced conditioned place preference (CPP) in mice.

Methods: The behavior of mice following ethanol addiction and withdrawal was assessed by performing different behavioral paradigms. Mice underwent ethanol-induced CPP training with alternate dose of ethanol (2 g/kg, *po*) and saline (10 ml/kg, *po*). The effect of lacosamide on the expression of ethanol-induced CPP and on ethanol withdrawal associated anxiety and depression-like behavior was evaluated. The effect of drug on locomotor activity was also assessed and hippocampal CRMP-2 levels were measured.

Results: Ethanol-induced CPP was associated with enhanced CRMP-2 levels in the hippocampus. Lacosamide significantly reduced the expression of ethanol-induced CPP and alleviated the levels of hippocampal CRMP-2 but aggravated withdrawal-associated anxiety and depression in mice.

Conclusion: The present study demonstrated the beneficial effect of lacosamide in attenuation of expression of ethanol induced conditioned place preference *via* reduction of hippocampal CRMP-2 level. These findings suggest that lacosamide may be investigated further for ethanol addiction but not for managing withdrawal.

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Introduction

Lacosamide is a novel antiepileptic drug (AED) which was first approved in 2008 as an adjunctive therapy for partial-onset seizures in adults [1]. It acts through enhancement of slow inactivation of sodium channels and through modulation of CRMP-2. Lacosamide interacts with CRMP-2 and inhibit CRMP-2-induced microtubule assembly as well as neurite growth [2]. Systemic administration of the CRMP-2 inhibitor, lacosamide, or knockdown of CRMP-2 in the NAc decreases excessive alcohol intake in alcohol two bottle drinking paradigm [3]. It was also reported that lacosamide significantly elevated intracranial self-stimulation thresholds and thus reduced the reward impact of medial forebrain bundle stimulation and attenuated the reward facilitating effects of cocaine [4]. However, the effect of lacosamide on ethanol-induced conditioned place preference (CPP) is not known. The present study, thus, examines the effect of lacosamide on ethanol-induced CPP in mice and the role of CRMP-2 in mediating the observed effects. Further, the effect of lacosamide on ethanol-withdrawal associated anxiety and depression-like behavior was also evaluated.

Material and methods

Animals

Swiss albino male mice (five in each group) weighing between 25–35 g, raised at the central animal house facility of Jamia Hamdard were used. The animals were housed in polypropylene

* Corresponding author.
E-mail addresses: divyavohora@hotmail.com, dvohra@jamiahamdard.ac.in (D. Vohora).

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cages in group of 4 mice per cage and kept under controlled environmental conditions (temperature: 20-25 °C; natural light/dark cycle). The animals were given free access to food and water. All experiments were performed during day time on healthy animals. The experiments were carried out as per the guidelines of Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA).

Drugs and doses

Ethanol 20% (8 PM ROYALE, 42.8%) *po* and lacosamide (Torrent Pharmaceuticals, India) were used. The dose of ethanol (20%, 2 g/kg *po*) was chosen was as per our previous report in mice [5]. The lacosamide doses (20 and 40 mg/kg *ip*) were chosen as per the previous report of cocaine reward in rat [4] and also by converting human dose (200 mg/day) to mice dose [6]. Drugs were administered orally (*po*) or intraperitoneally (*ip*) using oral feeding gavage tubes or 1 ml tuberculin syringe respectively.

Experimental design

The sample size was calculated using data from previous study performed in our lab using G-power software version 3.1.9.2 taking effect size (d) 17.46, type 1 error (α) 0.05 and power 0.95. The calculated sample size was 4. Therefore, we used five mice in each group in the present study. Following assessment of behavioral parameters, mice in each group were euthanized and their hippocampal CRMP-2 levels were estimated using mouse DPYSL 2 (Dihydropyrimidinase Protein 2) ELISA Kit (Wuhan fine Biological Technology Co., ltd). The study was conducted in three parts. The first part of the experiment included induction of ethanol-CPP in mice. In the second part, CPP-induced mice were divided into 4 groups with 6 animals per group. Animals in group I received vehicle, normal saline (0.9% w/v of NaCl) as neutral drug in post-conditioning phase (as described under CPP), group II animals received lacosamide A (20 mg/kg *ip*) as test drug in post-conditioning phase and group III and IV animals received lacosamide B (40 mg/kg *ip*) and lacosamide C- (40 mg/kg *ip*) respectively as test drug in post-conditioning phase and group V received ethanol (20%, 2 g/kg *po*) for eight days following post-conditioning phase. After the completion of post-conditioning phase, the animals of groups I, II and III were sacrificed and their hippocampal CRMP-2 levels were estimated using ELISA Kit. Group IV and V were used for third part of the study in order to assess withdrawal associated anxiety and depression-like behavior as well as CRMP-2 level after eight days following post-conditioning phase. Animals were then euthanized for collection of hippocampus in order to estimate CRMP-2 level.

Conditioned place preference

The method comprised of following phases (also depicted in Fig. 1):

Habituation

Animals received normal saline (0.9% w/v of NaCl) and it lasted for 1 day. This phase was designed to evaluate drug-free baseline preference for the compartment. In this phase, animals were placed in neutral chamber and have free access to whole apparatus for 15 min. It was observed that mice spent more time in black chamber as compared to white chamber and this was regarded as chamber bias. Therefore, we adopted biased method of CPP [7,8].

Conditioning phase

During ethanol conditioning (days 2–9), the mice received alternate doses of normal saline (0.9% w/v of normal saline) and

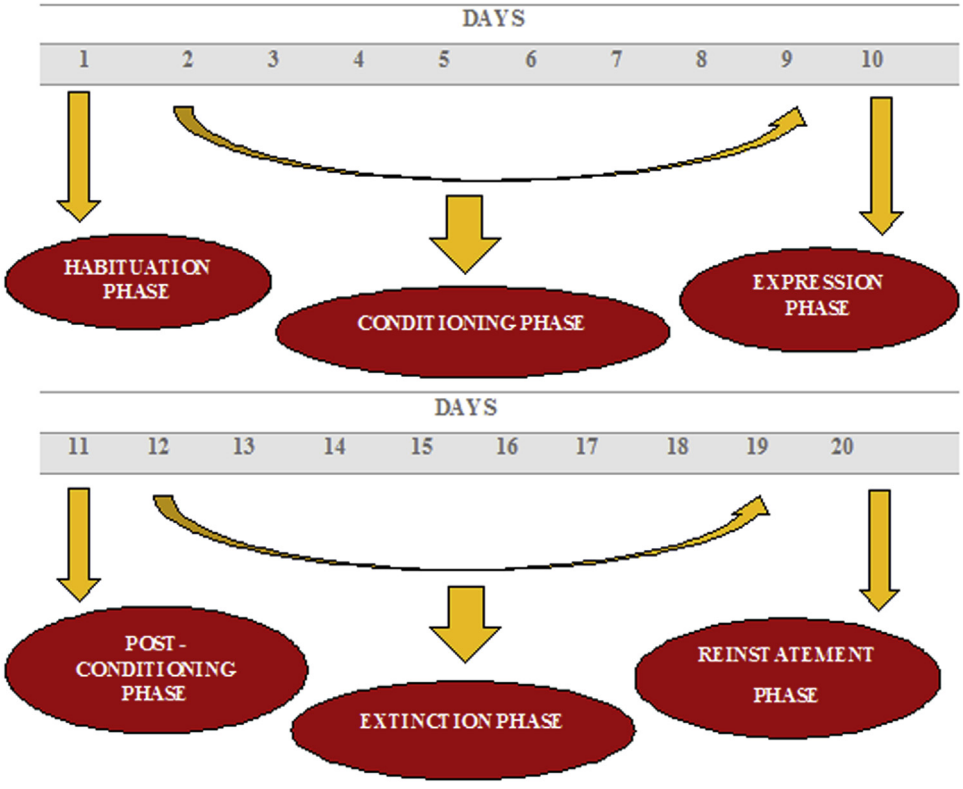

Fig. 1. Experimental Schedule. This figure is representing the time points at which different phases of conditioned place preference (CPP) paradigm was performed.

ethanol (2 g/kg *po*). They received ethanol in non-preferred chamber and normal saline in preferred chamber.

Expression phase

On 10th day, the effect of place conditioning was examined in mice with no treatment after conditioned training. Mice were placed in the center chamber with free access to both test chambers for 15 min, and the time spent in each test chamber was automatically recorded.

Post-conditioning phase

It was conducted 24 h after the expression phase *i.e.* on the 11th day. In this phase, mice were divided into four groups as detailed in Section 2.3 under experimental design. After that, mice were placed in the center compartment with free access to both test chambers for 15 min, and the time spent in each test chamber was automatically recorded.

Elevated plus maze test [9]

The maze made of wood painted gray was 50 cm high and had a central platform (8 cm x 8 cm) from which radiate four symmetrical arms (23.5 cm long x 8 cm wide x 10 cm high). The opposite arms were covered with plastic roof to assess effects on anxiety. Mice were placed in the central platform of the maze individually (which made the neutral zone), with head facing towards the open arm, and the number of entries made by the animal in the open and enclosed arms and the time spent in open arm and enclosed arms were recorded for a period of 5 min. Confinement to closed arms was associated with anxiety like behavior.

Modified forced swimming test [10]

The apparatus for modified forced swimming test was a cylinder which was 40 cm high and 15 cm in diameter. In this cylinder, fresh water was filled to a height of 30 cm and maintained at a temperature of 22–24°. Two training sessions (1 each day of 15 min) were conducted and 24 h after the last training session, the test was conducted. In the test session, each mouse was re-exposed to swimming conditions in the similar environment for 6 min. The total duration of immobility in the last 5 min of test session was recorded for each animal.

Locomotor activity [11]

This test was performed to analyze the locomotor activity of the animal. The locomotor activity was observed in an open field arena consisting of an acrylic box and the horizontal locomotor activity was recorded by lower frame (2.5 cm above arena floor) while rearing was recorded by upper frame (15 cm above the floor). Then the open field chamber was joined to a computer running software (Truscan 2.0 version, Coulbourn Instruments) and average distance per move (cm), mean velocity (cm/s) were recorded for 20 min.

Statistical analysis

The results were statistically analyzed by one-way ANOVA by using Graphpad instat software version 5.1. *Post-hoc* Tukey-Kramer Multiple Comparison Test was performed only when ANOVA showed statistical significance ($p < 0.05$). During habituation phase and post-conditioning phase, analysis was done by Student's unpaired *t*-test. All the results following *post-hoc* test were expressed as mean ± SEM. All differences at $p < 0.05$ were considered to be significant.

Results

Effects of chronic ethanol administration on CPP expression

During the habituation phase, it was observed that, each mouse spent significantly more time in black chamber as compared to white chamber and regarded as chamber biasing (df = 24, 24 F = 14.70 $p < 0.001$) (Fig. 2A). Hence, we used biased method of CPP. In expression phase, after eight days of conditioning training, mice spent more time in ethanol-paired chamber (Zone A) than the non-ethanol paired chamber (Zone B) (df = 24, 24 F = 16.90 $p < 0.001$) (Fig. 2B). Student's unpaired *t*-test showed that mice had significant expression of CPP.

Effects of lacosamide on ethanol-induced CPP in post-conditioning phase

The result showed that lacosamide reduces the expression of ethanol-induced CPP in mice. Lacosamide administered mice spent significant more time in non-ethanol paired chamber (Zone B) as compared to ethanol-paired chamber (Zone A) (lacosamide

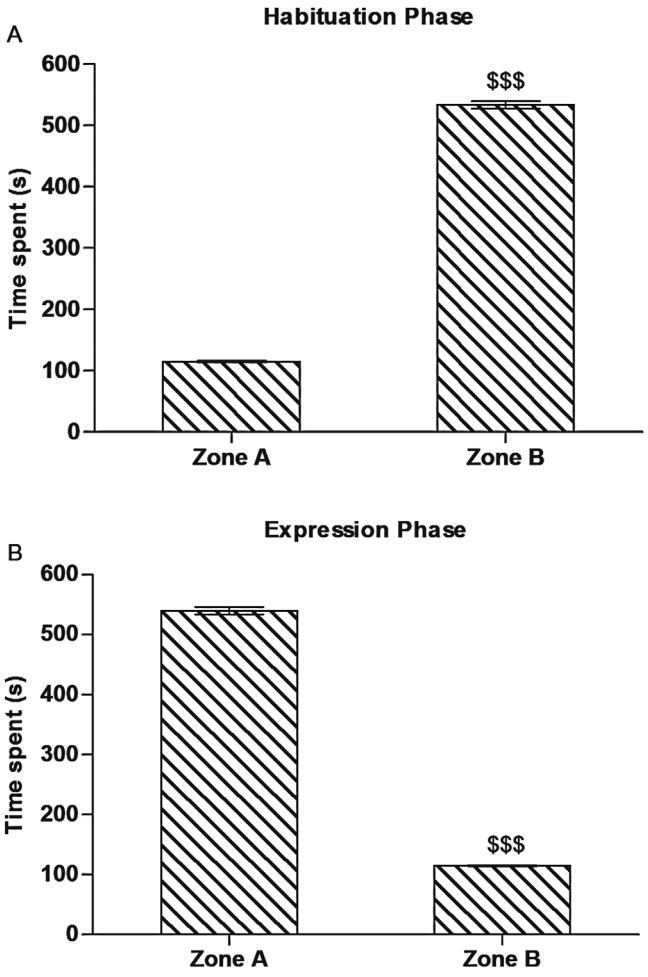

Fig. 2. Habituation and expression phase. The figure shows the A. habituation and B. expression phase. Initially, zone A represents white chamber and zone B represents black chamber. The result showed that mice spent more time in black chamber as compared to white chamber during habituation phase (day 1). Hence, we used biased method of CPP. On 10th day during expression phase, mice spent more time in ethanol-paired chamber (zone A) than the normal saline paired chamber (zone B); this suggested that CPP was induced in mice. Values are represented as mean ± SEM. as calculated statistically using student unpaired *t*-test The marker $^{\$\$\$}p < 0.0001$ represents significant difference in comparison to Zone A.

20 mg/kg; df = 4, 4 F = 33.83 $p < 0.001$ and lacosamide 40 mg/kg; df = 4, 4 F = 11.63 $p < 0.001$) (Fig. 3). It was also noted that test drug was effective in extinguishing the CPP when compared to Group I in Zone A and B individually (as indicated by one-way ANOVA followed by *post-hoc* Tukey-Kramer Multiple Comparison test) (df = 2, 12 F = 143.7 $p < 0.001$).

Effects of lacosamide on anxiety and depression-like behavior and on locomotor activity

Elevated plus maze test

In EPM test, after CPP induction in the expression phase and after eight days of post-conditioning phase, it was observed that mice belonging to ethanol and ethanol withdrawal group spent more time in the closed arm as compared to mice treated with saline (df = 2, 12 F = 232.0 $p < 0.001$) (Fig. 4A). After one-way ANOVA *post-hoc* Tukey-Kramer Multiple Comparison test was carried out which revealed a significantly more time spent by mice of ethanol withdrawal group in closed arm in comparison to ethanol administered mice ($p < 0.001$). This showed that induction of CPP enhanced anxiety-like behavior which was further increased on withdrawal at the end of post-conditioning phase phase.

Modified forced swim test

During modified forced swim test, in comparison to saline group it was observed that immobility time of the animals (ethanol and ethanol withdrawal group) was increased significantly as assessed by one-way ANOVA (df = 2, 12 F = 739.4 $p < 0.001$) (Fig. 4B) which showed that induction of CPP enhanced depression-like behavior in mice. Furthermore, *post-hoc* Tukey-Kramer Multiple Comparison test) indicated increased immobility time on ethanol withdrawal when compared to ethanol treated mice at the end of experiment (as indicated by ($p < 0.001$).

Locomotor activity

No significant change was observed in the mean velocity (df = 2, 12 F = 0.4908 $p > 0.05$) and distance travelled (df = 2, 12 F = 0.2830 $p > 0.05$) (Fig. 4C and D) in mice of all groups. This clearly showed that locomotor activity did not influence the results of elevated plus maze as well as of modified forced swimming test.

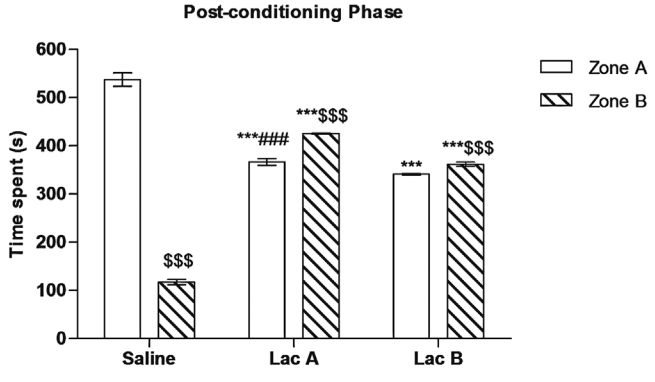

Fig. 3. Post-conditioning phase (11th day). The post-conditioning phase showed that Lac A and Lac B (Group III and IV respectively) reduces the expression of ethanol-induced CPP in mice as assessed by significantly decreased and increased time spent in Zone A and Zone B respectively as compared to Group I (as indicated by one-way ANOVA followed by *post-hoc* Tukey-Kramer Multiple Comparison test). Student's unpaired *t*-test represented the significant increase in time spent in Zone B than Zone A following test drug treatment. Values are represented as mean ± SEM. Zone A represents white chamber and Zone B represents black chamber. The asterisks show significance $^{***}p < 0.001$ *vs.* Group I; $^{###}p < 0.001$ *vs.* Group III and $^{$$$}p < 0.001$ *vs.* Zone A. Lac A: Lacosamide 20 mg/kg and lac B: Lacosamide 40 mg/kg.

Effects of various phases of CPP on hippocampal CRMP-2 levels

During expression phase, it was observed that ethanol-induced CPP resulted in enhanced hippocampal CRMP-2 levels ($p < 0.001$) in comparison to saline. In post-conditioning phase, after the administration of lacosamide 20 mg/kg and 40mg/kg *ip*, the CRMP-2 levels significantly decreases (df = 4, 20 F = 977.7 $p < 0.001$) as analyzed statistically by one-way ANOVA followed by *post-hoc* Tukey-Kramer Multiple Comparison test. This clearly showed that lacosamide has beneficial role in case of ethanol induced reward and drug-seeking behavior. But lacosamide did not show any dose-dependent effect ($p > 0.05$). (Fig. 5).

Discussion

Excessive consumption of ethanol activates the mTORC1 pathway, which further increases the CRMP-2 levels in the limbic regions of rodents. This increased CRMP-2, when binds with the microtubule, form microtubule assembly and this assembly is linked to drug taking and seeking or addiction-like behavior. Therefore in this study, we administered lacosamide, a CRMP-2 inhibitor, which itself binds with the CRMP-2 inhibiting the formation of microtubule assembly and thus playing a beneficial role in ethanol addiction.

Since long time, a line of research has been focusing on compulsive use of drugs of abuse which is supposed to be influenced by a number of factors. The different degree of development of as well as recovery from ethanol dependence in laboratory animals has been reported to be due to sex differences. It was demonstrated that ethanol administration influence neurochemical mechanism including GABA-A and NMDA receptor subtypes depending on sex differences, which are involved in modulation of several neurobehavioral functions [12]. Additionally, it was cited that estrogen in female rodents plays a crucial role in transition from recreation use of drug to compulsive drug seeking behavior [13]. By considering the role of gonadal hormones, male mice were used in the present study in order to avoid any biasing from female hormones in ethanol seeking behavior.

Conditioned place preference (CPP) is widely used to assess the reinforcing properties of ethanol. The conditioned response to drug of abuse is relevant to human drug-seeking behavior as well as relapse conditions [14,15]. We used CPP, a standard preclinical behavioral model, to assess the effect of lacosamide on rewarding effects of ethanol. The biased or unbiased method of CPP was determined by observing the preference of animal in the habituation phase. Thus, we observed that each mouse spent significantly more time in a black chamber as compared to a white chamber, and regarded as chamber biasing. Hence we adopted the biased method of CPP. The present finding is in line with previous studies reporting that biased method is an efficient model for studying those animals which have preference over a particular chamber [7,8,16,17]. However, after eight days of conditioning training (administration of ethanol 20%v/v, in the dose of 2 g/kg alternating with normal saline), this preference was reversed *i.e.* mice spent more time in drug-paired chamber (white) than the non-drug paired chamber (black). This clearly showed that mice had significant expression of CPP and that CPP paradigm is a useful model for studying ethanol's rewarding effects in mice as reported previously in several studies [18–20]. In post-conditioning phase after 24 h of expression phase, test drug *i.e.* lacosamide was administered and then it was observed that mice spent a significant more time in the non-drug paired chamber (Zone B) than the drug-paired chamber (Zone A). This showed that test drug was effective in extinguishing the CPP. The present finding is in agreement with other studies [2–4] reporting

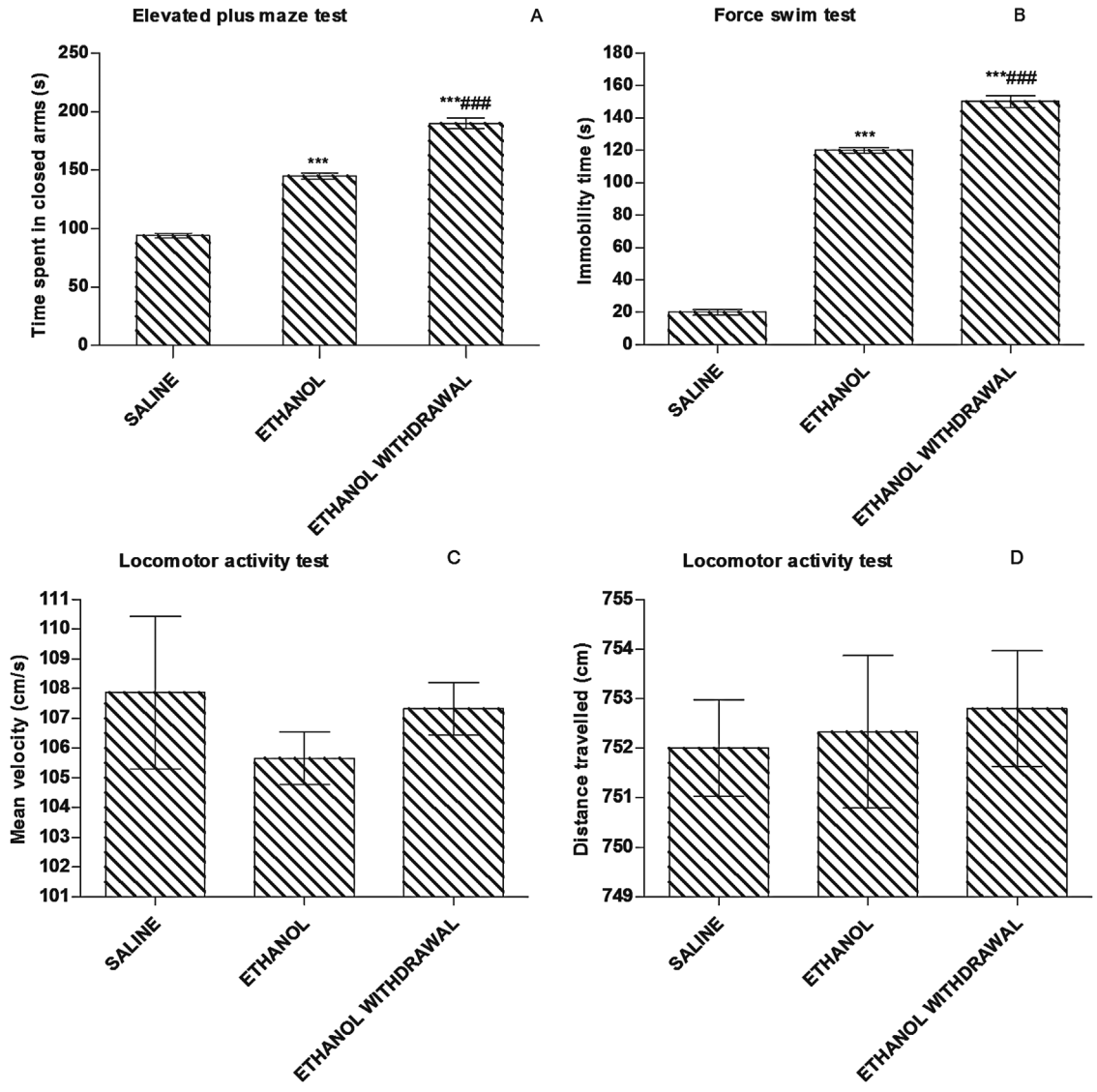

Fig. 4. Anxiety and depression like behavior. This figure is depicting the A. time spent in close arm (elevated plus maze test), B. immobility time (modified forced swim test) and C. and D. mean velocity and distance travelled respectively (locomotor activity test). Significant increase in time spent in closed arm and immobility time was observed following chronic administration of ethanol and withdrawal of ethanol as well, indicating the increased level of anxiety-like behavior in mice. On the contrary, no changes were noticed during locomotor activity test in mice. Each bar is indicating the mean of six mice and is represented as mean ± SEM. The statistical analysis by one-way ANOVA followed by *post-hoc* Tukey-Kramer Multiple Comparison test indicates significant difference $^{***}p < 0.001$ *vs.* saline group and $^{\#\#\#}p < 0.001$ *vs.* ethanol group.

the efficacy of lacosamide in case of excessive ethanol drinking and ethanol-induced drug seeking behavior.

Exposure to diverse classes of drugs of abuse (including ethanol) leads to activation of mammalian target of rapamycin complex 1 (mTORC1) kinase in the limbic system which further causes an increased levels of collapsin response mediator protein-2 (CRMP-2) [3]. It was reported recently that nicotine consumption leads to increased level of CRMP-2 in the hippocampus [2]. In the present study, CRMP-2 level following ethanol administration was assessed in hippocampus. It has been reported that ethanol exposure enhances hippocampal function and formation of the augmented drug-context associations which in turn triggers the development of addiction [21]. Studies have shown that excessive consumption of ethanol blocks the phosphorylation of CRMP-2 which in turn results in increase in the microtubular content of CRMP-2 [2,22,23]. The increased microtubular content of CRMP-2 leads to formation of microtubule assembly that maintains the morphology of neurons and have important role in structural plasticity which involves formation, stabilization and elimination of synapse and is linked to compulsive drug taking and seeking. Hence CRMP-2 mediated microtubule assembly participate in the development and/or maintenance of excessive alcohol drinking behaviour. In accordance with this, administration of ethanol (after CPP induction), in our study, resulted in increased CRMP-2 levels in the hippocampus. The present finding is in consistent with previous studies reporting increased levels of CRMP-2 in ethanol drinking behavior and has confirmed that ethanol addiction ethanol drinking behavior has taken place in our study [2,22–24]. Lacosamide administration (at both 20 and 40 mg/kg) reverted the enhanced CRMP-2 levels in post-conditioning phase (after 24 h of expression phase), and was also effective in extinguishing the CPP as animals spent significantly more time in a non-drug paired chamber than the drug-paired chamber. Our results on lacosamide in alleviating effect of ethanol administration are in agreement with other studies [2,3]. For instance, systemic administration of lacosamide, or knockdown of CRMP-2 in the NAc, was reported to reduce excessive alcohol intake. In addition to ethanol, lacosamide was also studied for cocaine addiction. It was reported that

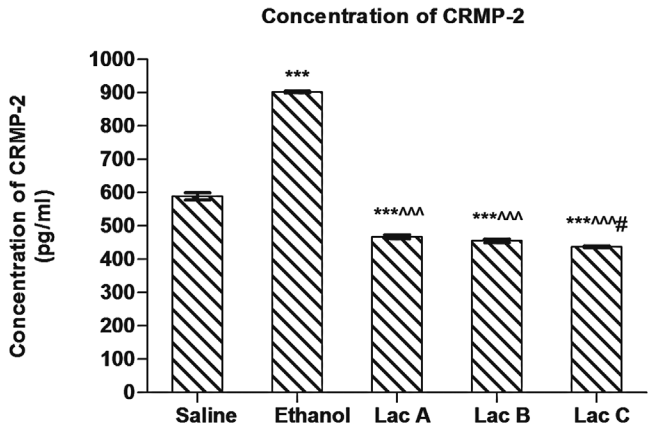

Fig. 5. Hippocampal CRMP-2 levels. CRMP-2 level increased after ethanol-CPP and reduced after administration of lacosamide. It suggested that lacosamide was effective in the treatment of ethanol addiction. CRMP-2 level remained reduced after eight days following post-conditioning phase indicating that lacosamide has anti-relapse activity. Statistical values (as given by one-way ANOVA followed by *post-hoc* Tukey-Kramer Multiple Comparison test) are represented as mean ± SEM. $^{***}p < 0.001$ *vs.* saline group and $^{\wedge\wedge\wedge}p < 0.001$ *vs.* ethanol group and $^{\#}p < 0.05$ *vs.* Lac A. Lac A: Lacosamide 20 mg/kg; Lac B: Lacosamide 40 mg/kg and Lac C: Lacosamide (40 mg/kg) after post-conditioning phase.

lacosamide (30 mg/kg) significantly elevated intracranial self-stimulation (ICSS) thresholds, indicating that it reduced the rewarding impact of medial forebrain bundle stimulation. Lower doses (3–10 mg/kg) did not alter ICSS, but blocked the cocaine-induced lowering of ICSS thresholds [4]. Though the exact mechanism by which lacosamide is effective in addiction remains obscure, our study shows that modulation of CRMP-2 might play a role. The drug is a CRMP-2 inhibitor and is reported to interact with CRMP-2 induced microtubule assembly as well as neurite growth and thus reduces the microtubular CRMP-2 content which is responsible for addiction and drug-seeking behaviour. Previously, studies have reported that decreased levels of CRMP-2 are responsible for treating addiction-like behavior [3,2,4]. Further, the results of Liu and co-workers also suggested that CRMP-2 in the NAc was a convergent point that receives inputs from two signalling pathways, mTORC1 and GSK-3β that in turn drives excessive alcohol-drinking behaviors [3].

CRMP-2 possess putative binding sites that may modulate the effect of lacosamide on voltage-gated sodium channels [25]. It was reported that CRMP-2 alanine mutants (resembling wild-type) has a potential to attenuate the lacosamide-mediated effects on the ability of endogenous Na + channels to transition to a slow inactivated state. The latter finding demonstrated that CRMP-2 can coordinate lacosamide binding thus making it more effective on its primary clinical target [24]. In view of the link between CRMP-2 and voltage-gated sodium channels and the fact that the primary targets of lacosamide are Nav channels, it is possible that the same might have contributed to the effect of lacosamide on CPP in our study. Though this aspect was not studied, it is reported that ethanol disrupts lipid structure of membrane which is a critical factor for functioning of sodium channels. Ethanol, by altering environment of sodium channels, alters neuronal functions [26] and thus effect of lacosamide on sodium channels in mediating the effects observed in our study remains to be determined. Moreover, we used the R-lacosamide which targets both CRMP-2 and selectively enhancing sodium channel slow inactivation.

Anxiety was the first parameter undertaken to study the behavioral effect of ethanol withdrawal. The elevated plus maze is a behavioral test which reliably detects all major classes of anxiogenic as well as anxiolytic drugs. In this test, on daily administration of ethanol (20% v/v in a dose of 2 g/kg *po*) for eight days, it was observed that the anxiety level increased. Furthermore, on withdrawal of ethanol, abruptly increased in the level of anxiety was observed. This showed that induction of CPP enhanced anxiety-like behavior which was further increased on withdrawal at the end of post-conditioning phase. Numerous studies show that acute alcohol exposure elevates serotonin levels in the brain [27,28] which is responsible for its anti-anxiety effects. But the chronic exposure of ethanol-induced persistent changes in circuit function in the brain [29,30] which contributes to subjective feelings of stress and anxiety during alcohol withdrawal. Our results are thus in agreement with numerous studies reporting anxiety as one of the important symptoms following ethanol withdrawal and ethanol addiction [31–36].

Depression was the second parameter undertaken to study the behavioral effect of ethanol withdrawal. The forced swim test (FST) is a behavioral test which reliably detects antidepressant-like behavior. In this test, on daily administration of ethanol (20% v/v in a dose of 2 g/kg *po*) for eight days, it was observed that the immobility time was increased. This showed that induction of CPP enhanced depression-like behavior which was further increased on withdrawal at the end of post-conditioning phase. Our results are in agreement with other studies reporting depression as one of the important symptoms following ethanol withdrawal and addiction [37,38]. Acute ethanol intake causes an immediate release of neurotransmitters like NA, 5-HT, and dopamine in the CNS which contributes to its antidepressant action. Chronic intake of ethanol lowers the levels of serotonin in the brain, a chemical that helps to regulate our mood and thus it leads to depressive-like behavior. As there is more than normal amount of neurotransmitter present postsynaptically, these chronically increase levels of neurotransmitters causes down regulation of α receptors and 5-HT receptors and thus, during withdrawal, their level in the brain falls to a greater extent which is responsible for the development of withdrawal state [39–41]. It was also reported that lacosamide has anti-anxiety and mood stabilizing effects [42–44] but such an effect was not observed in our study indicating that lacosamide is not able to treat ethanol-induced anxiety and depression. However, one of the reasons could be that antianxiety and antidepressant effects were evaluated after eight days of post-conditioning phase while the drug administration was done at the time of post-conditioning day.

Locomotor activity was the third parameter undertaken to study the behavioral effect of ethanol withdrawal following chronic administration. In locomotor activity test, on daily administration of ethanol (20% v/v in a dose of 2 g/kg *po*) for eight days, it was observed that there was no significant difference in normal saline as well as in ethanol-treated mice. Furthermore, it was also observed that, on withdrawal of ethanol, there was no change in the locomotor activity. The present data showed that the locomotor activity did not affect the results of elevated plus maze and modified forced swimming test. The previous studies [44–47] contradict our finding as ethanol withdrawal has previously been reported to induce hyperactivity thereby increasing the locomotor activity. But the reason behind this contradiction might be due to the hypoactivity produced by the lacosamide as previously reported [48]. Therefore it might nullify the effect of hyperactivity produced during ethanol withdrawal.

It is concluded that lacosamide reduces ethanol-induced conditioned place preference in mice possibly by alleviating the levels of CRMP-2 in the hippocampal region of mice and hence could be explored further in the treatment of ethanol addiction. It was also, however, observed that ethanol withdrawal-induced anxiety and depression-like behavior in mice was aggravated by lacosamide. The study, thus, demonstrates that lacosamide does not have a role in the management of the ethanol withdrawal symptoms but suggests an exciting therapeutic potential of

lacosamide in the treatment of excessive ethanol drinking and ethanol-induced drug seeking behavior.

Conflict of interest

The authors declare no conflict of interest.

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