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EVALUATION OF KYNURENIC ACID ATTENUATES ETHANOL WITHDRAWAL INDUCED HYPEREXCITABILITY IN MICE

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ABSRTACT
The present study was undertaken to investigate the effects of kynurenic acid attenuates hyperexcitability after ethanol withdrawal in mice. Acute and chronic administration of both kynurenic acid and diazepam (or saline) which mice exhibited peak ethanol withdrawal-induced hyper excitability. Treatment with kynurenic acid (50 or 100 mg/kg, i.p.), 30 min prior to peak ethanol withdrawal-induced hyper excitability signs (7 h), significantly reduced ethanol withdrawal-induced hyper excitability sign scores compared with the vehicle treated group, whereas a lower dose (50 mg/kg, i.p.) did not influence the ethanol withdrawal-induced signs. In other experiments, administration of diazepam (1.25 or 2.5 mg/kg, i.p.), 30 min prior to peak (7 h), dose-dependently attenuated the withdrawal signs, whereas a lower dose (0.625 mg/kg, i.p.) did not influence the ethanol withdrawal-induced signs. Acute treatment with kynurenic acid and diazepam in the control liquid-diet groups had no influence on the physical signs of hyper excitability. In line with the above, it was observed that acute effect of kynurenic acid did not show any significant effect on locomotor. The significant effects on locomotor activity compared with the Vehicle treated animals. In contrast, diazepam (2.5 mg/kg, i.p.) significantly reduced chronic treatment with kynurenic acid exhibited prevention in hyper locomotor effect of ethanol withdrawal. The results and evidence suggest that kynurenic acid exhibited an inhibitory influence against ethanol withdrawal-induced hyper excitability signs which could be mediated through its neuromodulatory & neuroprotective action.

KEYWORDS: Kynurenic acid, Hyperexcitability, Ethanol Withdrawal, NMDA Receptor.

1. INTRODUCTION

Kynurenic acid is a product of tryptophan metabolism that is synthesized and released in the brain by astrocytes. Schwarcz R, Pellicciari et al.,(2002);Stone TW. (1993)Kynurenic acid acts as an antagonist of both α-7 nicotinic acetylcholine receptor and glycine site of n-methyl-d-asparted glutamate receptor. Kynurenic acid involved in pathophysiology of schizophrenia, thus, examination of patients with schizophrenia has revealed elevated level of kynurenic acid in both cerebrospinal fluid (CSF) and in post mortem prefrontal cortex. Stone TW. (1993).

Ethanol is one of the most widely abused addictive drugs, and has hazardous health consequences resulting from its chronic use. Ethanol dependence is characterized by an abstinence syndrome in which withdrawal symptoms resulting from central nervous system (CNS) hyper excitability emerge in a time dependent fashion after cessation of drinking (Schuckit *et al*., 1995; for reviews see Olive and Becker, 2008). Much evidence has accumulated to suggest that acute administration of ethanol blocks glutamate receptor activity in the brain. The ethanol – induced reduction of glutaminergic activity appears to be largely mediated through a blocked of glutamate receptors of the N-methyl D- aspartate (NMDA) subtype whereas non NMDA receptor are reported to less sensitive to ethanol. Electrophysiological and biochemical studies have shown that ethanol reduced NMDA –induced stimulation of function Ca^{2+} responses intracellular enzyme activity, and neurotoxicity (Hoffman, 1995; Cebers et al., 1996). In behavioral studies, acutely given ethanol blocks NMDA-convulsions and potentiates the locomotor and /or sedative effects caused by both competitive and non-competitive NMDA receptor antagonists (Kulkarni et al., 1990; Liljequist, 1991a; Robledo et al., 1991; Kuribara, 1994). While the inhibitory effect of ethanol on various

NMDA – induced functional responses have been demonstrated, far less is known about the exact mechanism by which ethanol decrease the activity of NMDA receptors. Results from receptor binding studies indicated that ethanol does not directly influence the binding properties of various glutamate receptor agonist or glutamate receptor modulator agent to their recognition site (Snell et al., 1993), but some reports suggest that ethanol may alter the kinetic of non – competitive NMDA receptor ligand and binding (Snell et al., 1996; Michaelis et al., 1996). Ethanol is not a molecule with a single clear effect on a particular neurotransmitter system but it may affect multiple stages of the neurotransmission cascade of the large majority of neurotransmitters.(De witteP. al.,2003).

Several neurotransmitter systems and plasma membrane ion channels such as glutamate, noradrenaline, dopamine, serotonin, opiates, gamma-amino butyric acid (GABA) and voltage-sensitive calcium channels are implicated in the effects of ethanol (Koob and Nestler, 1997; for reviews see Chastain, 2006. However, the large doses typically used lead to sedation and motor impairments coupled with the potential risk of substance dependence. Thus, there is a need for a drug, which can not only ameliorate the withdrawal effects, but also be free of side effects. Thus, the aim of the present investigation was to study the effects of kynurenic acid on ethanol withdrawal-induced hyper excitability in a mouse model of ethanol withdrawal.

2. MATERIALS AND METHODS

2.1 Subjects

Adult male Swiss mice born and reared in the Animal House of the Institute of pharmaceutical Education and Research from a stock originally purchased from Shree Farms, Bhandara, India were used in the present study. Young healthy male mice (22–26 g) were group housed (four per cage) and maintained at 23 ± 2 °C under 12:12 h light (08.00–2000 h)/dark cycle with free access to rodent chow and tap water. The animal studies were approved by the Institutional Animal Ethics Committee (IAEC), constituted for the purpose of the control and supervision of experimental animals by the Ministry of Environment and Forests, Government of India, New Delhi, India. Animals were naive to drug treatments and experimentation at the beginning of all studies. Each experimental group comprised (6-8) mice.

2.2 Drugs and solutions

Kynurenic acid (Sigma-Aldrich Co, St Louis, MO), diazepam (Calmpose, Ranbaxy, India) and Ethanol (Changshu Yangyuan Chemical, China) used in present study were dissolved in 0.9% saline. Drug solutions were prepared fresh and doses of kynurenic acid are expressed in terms of its freebase. The doses of kynurenic acid and diazepam were selected on the basis of previous reports (Anton Bespalov et al.(1994); Molina C. et al., (2001).

2.3 Induction of ethanol dependence

Ethanol dependence was induced in mice using an earlier reported method (Bhutada *et al*., 2010) with slight modifications. To develop ethanol dependence, the mice were housed individually in small cages (28 ×14×14 cm) and provided with a nutritionally balanced control liquid diet (Novartis India Ltd, Mumbai, India)on day 0 as their sole nutrient source (600 kcal/L). From days 1 to 4, ethanol (3% v/v) was incorporated into the liquid diet, followed by 6% v/v of ethanol (days 5–7) and10% v/v of ethanol (days 8–10). On day 11, at 0800 h, the ethanol liquid diet was replaced with a nutritionally balanced control liquid diet. Mice from the control group were provided with liquid diet without ethanol from days 0 to 10, which was iso-caloric to the ethanol liquid diet on respective days. Liquid diets were daily prepared and replaced at 0800 h. At the end of this feeding pattern, no significant difference was observed in the weights of mice from the ethanol liquid diet and control liquid diet groups.

2.3.1 Assessment of ethanol withdrawal-induced hyperexcitability signs

The ethanol dependence was assessed by scoring the withdrawal-induced physical signs of hyper excitability, graded as shown in Table 1 (Umathe *et al*., 2008; Bhutada *et al*., 2010b). In brief, each mouse was lifted by the tail, spun gently through a 180° arc and held 30 cm away under an angle poise lamp (60watt) for 3 s; ethanol withdrawal-induced physical signs were observed and graded at hourly intervals for 24 h to determine the time of peak withdrawal signs. The observations and grading were made by an experimenter who was unaware of treatment group identity.

2.3.2 Effects of acute treatment with kynurenic acid and diazepam on ethanol withdrawal-induced hyperexcitability signs

Kynurenic acid (50 and 100 mg/kg, i.p.) or diazepam (0.625, 1.25 or 2.5 mg/kg, i.p.) or saline (10 ml/kg, i.p.) was administered 30 min before the time interval at which mice exhibited peak ethanol withdrawal-induced hyper excitability (7 h after withdrawal). Thereafter, ethanol withdrawal-induced physical signs were observed and graded as described above. Similar treatments were given to the control liquid diet groups (*n* = 6-8). Thirty minutes thereafter, ethanol withdrawal-induced physical signs were observed and graded.

2.3.3 Effects of acute and chronic treatment with kynurenic acid and diazepam on ethanol withdrawal-induced hyperlocomotor activity

Increase in locomotor activity or hyperlocomotor activity is one of the sign of ethanol withdrawal which measured by actophotometer. Locomotor activity was monitored with actophotometer of 38 cm diameter and 16 cm height, equipped with photocells that automatically measured the movement of mice. Any movement of the mice that interrupted photo beams was recorded as a motor count. Separate group of animals were made

ethanol dependent as described earlier 24 h post withdrawal condition, during which maximum score for withdrawal symptoms was observed, all animal were subjected to actophotometer for 30 min to assess the locomotor activity. (Bhutada et al., 2011).

Table 1. Rating the scores for Ethanol withdrawal signs

Sr. No.	Withdrawal Sings	Scores
1	Vocalization	1
2	Defecation	1
3	Urination	
4	Caudal Posture (0-3) Limp or normal tail Stiff, curls around the fingers Stiff, curls around the fingers, stays elevated after release Spontaneous abnormal posture of tail such as lift above back, stiff, curls around the fingers and stays elevated after release	 0 1 2 3
5	Tremor (0-3) No tremor Mild tremor in one portion of body i.e. face Occasional generalised tremor Constant generalised tremor	 0 1 2 3
6	Startle (0-3) None Twitch Jump and freeze Exaggerated jump and freeze	 0 1 2 3
7	Convulsions (0-3) None Short duration clonic Multiple clonic Tonic-clonic	 0 1 2 3
8	Death	10

2.3.3 Effects of chronic treatment with kynurenic acid on ethanol withdrawal-induced hyper excitability signs.
In a separate set of experiments, during the induction of ethanol dependence as described above, mice from the ethanol liquid diet group (n = 6-8) were treated twice daily (0800 hand 2000 h) with kynurenic acid (50 and 100 mg/kg i.p.) or diazepam (0.625, 1.25 or 2.5 mg/kg, i.p.) or saline (10 ml/kg, i.p.) from day 1 to day 10. Similar treatments were given to the control liquid diet groups. On day 11, withdrawal induced physical signs of hyper excitability were observed and graded every hour for the next 24h.

3. STATISTICAL ANALYSIS

The data from the present investigations were analyzed by parametric tests (Umathe *et al*., 2008), using either one-way ANOVA followed by Tukey's test or two-way repeat measure ANOVA followed by the Bonferroni test for multiple comparisons. All values are expressed as the mean _ SEM of 6- 8 mice per group. A value of $p < 0.05$ was considered statistically significant in all the cases.

4. RESULTS

4.1 Ethanol withdrawal-induced hyper excitability signs: Figure 1 shows that the ethanol liquid diet group exhibited gradually elevated scores of withdrawal-induced signs between 5 and 9h after the withdrawal of the ethanol diet on day 11, and the peak withdrawal signs appeared at 7 h. Two-way repeat measure ANOVA revealed a significant ethanol withdrawal effect [F (5,30) = 90.96, $p < 0.0001$], [F (5,30) = 1.85, $p < 0.0802$]. Bonferroni post hoc tests revealed that the ethanol diet withdrawal group exhibited significantly higher withdrawal-induced hyper excitability sign scores ($p < 0.05$) from 5 to 9 h compared with the control liquid diet group.

4.1.1 Effects of acute treatment with kynurenic acid and diazepam on ethanol withdrawal-induced hyper excitability signs

Treatment with kynurenic acid (50 or 100 mg/kg, i.p.), 30 min prior to peak ethanol withdrawal-induced hyper excitability signs (7 h), significantly reduced ($p < 0.05$)ethanol withdrawal-induced hyper excitability sign scores compared with the vehicle treated group [F (5,30) 90.96, $p < 0.0001$], whereas a lower dose (50 mg/kg,i.p.) did not influence the ethanol withdrawal-induced signs ($p > 0.05$). In a separate set of experiments, administration of diazepam (1.25 or 2.5 mg/kg, i.p.), 30 min prior to peak (7 h), dose-dependently attenuated the withdrawal signs [F (5, 30) = 5.243, $p < 0.0001$], whereas a lower dose (0.625 mg/kg, i.p.) did not influence the ethanol withdrawal-induced signs ($p > 0.05$). Acute treatment with kynurenic acid or diazepam in the control liquid-diet groups had no influence on the physical signs of hyper excitability ($p > 0.05$) (Fig. 1).

4.1.2 Effects of chronic treatment with kynurenic acid on ethanol withdrawal-induced hyper excitability signs: The ethanol diet mice chronically treated with kynurenic acid (50 or 100 mg/kg, i.p., twice daily for 10 days) showed significantly lower ethanol withdrawal-induced hyper excitability signs scores on day 11. Two-way ANOVA revealed a significant effect of chronic kynurenic acid treatment [F (5, 30) = 22.57, p < 0.0001], [F (5, 30) = 34.53, p < 0.0001] and treatment–time interaction [F (5, 30) = 20.09, p < 0.0001] on withdrawal-induced hyper excitability scores. Chronic treatment with kynurenic acid to the control liquid diet group did not influence the average score of physical signs (Fig. 2).

4.1.3 Effects of acute treatment with kynurenic acid and diazepam on ethanol withdrawal-induced hyperlocomotor activity: The acute effects of kynurenic acid and diazepam on locomotor activity in naive animals are illustrated in Fig.3 Acute effect of kynurenic acid (50 or 100 mg/kg, i.p.) Was devoid of any significant effects on locomotor activity compared with the Vehicle treated animals [F (5, 30) = 0.6668, p = 0.2095]. In contrast, diazepam (2.5 mg/kg, i.p.) significantly reduced [F (5, 30) = 12.51, p < 0.0001] (Fig. 3).

4.1.4 Effects of chronic treatment with kynurenic acid and diazepam on ethanol withdrawal-induced hyperlocomotor activity.

In another set of experiment chronic effect of kynurenic acid (50 or 100 mg/kg, i.p.) and diazepam (2.5 mg/kg, i.p.)Showed significant inhibitory effects on locomotor activity compared with the Vehicle treated animals [F (5, 30) = 0.8760, p < 0.0001] (Fig. 4).

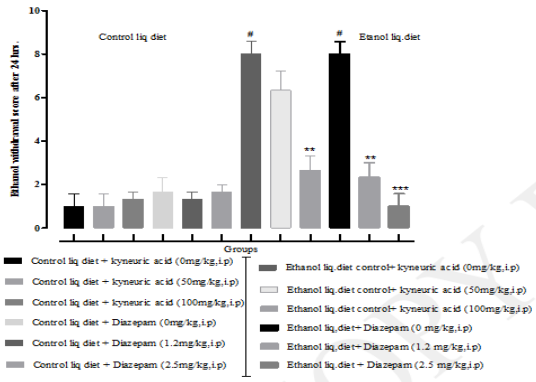

Figure 1. Effects of acute treatment with kynurenic acid and diazepam on ethanol withdrawal-induced hyperexcitability signs. Kynurenic acid (50 and 100 mg/kg, i.p.) or diazepam (1.25 and 2.5 mg/ kg, i.p.) pretreatment, 30 min prior to the peak hour (7 h) significantly reduced ethanol withdrawal-induced signs. Values are mean _ SEM of six observations per group. * p < 0.001 vs respective vehicle treatment in ethanol diet withdrawn group (one-way ANOVA followed by Tukey's post-hoc test).

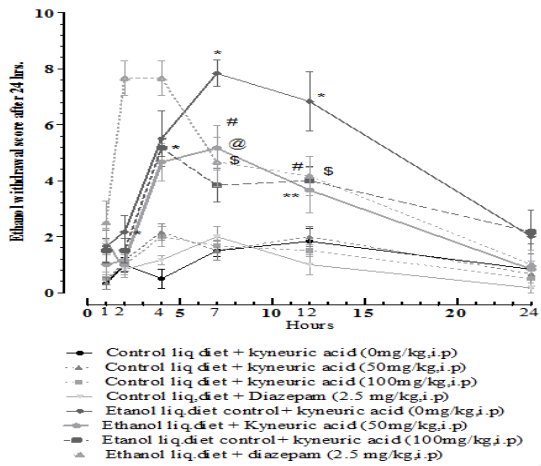

Figure. 2: Effects of chronic treatment with kynurenic acid on ethanol withdrawal-induced hyper excitability signs. Kynurenic acid (50 and 100 mg/kg, i.p., twice daily for 10 days) treatment to ethanol significantly attenuated ethanol withdrawal induced. Values are mean _ SEM of six observations per group * p < 0.001 vs. saline treatment in control diet; @ p < 0.01, # p < 0.001 vs. saline treatment in ethanol diet withdrawn group at respective time interval (two-way ANOVA followed by Bonferroni post-hoc test).

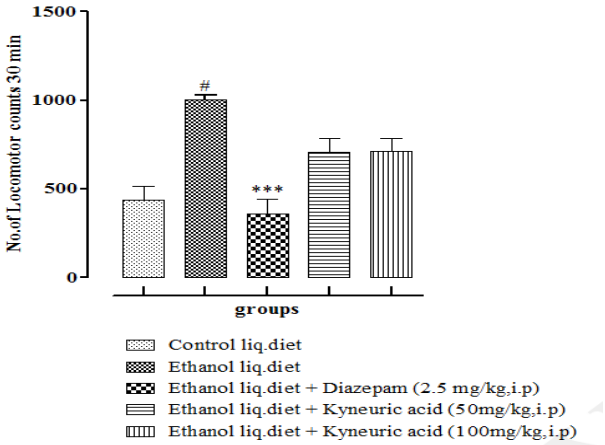

Figure. 3: Effects of acute treatment with kynurenic acid and diazepam on ethanol withdrawal-induced hyperlocomotor activity. Each bar represents mean ± SEM (n=6). ***p<0.001 when compared against ethanol control group. #p<0.001 when compared against liquid diet group. (One way ANOVA followed by Tukey's t test).

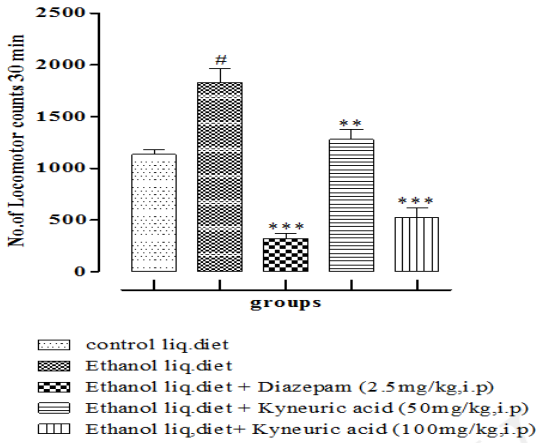

Figure. 4: Effects of chronic treatment with kynurenic acid and diazepam on ethanol withdrawal-induced hyperlocomotor activity. Each bar represents mean ± SEM (n=6). **p<0.01 and ***p<0.001 when compared against ethanol control group. #p<0.001 when compared against liquid diet group. (One way ANOVA followed by Tukey's t test).

5. DISCUSSION

It has been repeatedly demonstrated that acute ethanol consumption causes inhibition of NMDA-receptor and also GABA-receptor function. NMDA-receptor is one of the subtypes of glutamate (major excitatory neurotransmitter in brain) receptor and inhibition of this receptor leads to development of addiction to the ethanol effects. But, long-term exposure to ethanol leads to an imbalance in excitatory and inhibitory (GABA) amino acids. When ethanol consumption is reduced or completely stopped, these imbalances in different amino acids and neurotransmitters are behaviorally expressed in the form of ethanol withdrawal and its symptoms. (Abdelkader D, et. al., 2003) Chronic administration of ethanol results in "up-regulation" of NMDA receptor binding in brain and leads into neurotoxicity result of which is an occurrence of withdrawal symptoms.

The effect of kynurenic acid could be mediated through neuroprotective actions. An exhaustive review by (Trevor W. Stone, 2000). The research data support the view that Kynurenic acid is an endogenous neuroprotective compound. Experimental inhibition of central kynurenic acid synthesis leads to the excitotoxic neuronal loss. (Urbanska et al., 1991) and seizures in rodents. As opposite to the application of KYNA which prevents neurodegenration (Nemeth et al., 2006) Altered central KYNA metabolism was associated with some human neuropathologies (Nemeth et al., 2006). It was shown that CSF and certain brain areas of schizophrenics contains abnormally high levels of KYNA (Erhardt et al., 2007), where as in depression endogenous KYNA content is diminished (Myint et al., 2007).

Previous investigations suggest that compounds that decrease the NMDA-receptor function may inhibit ethanol withdrawal symptoms in rodents. (Fernando V.1997, Silvania Vet al., 2008, Michael G' 1999) The drug used in present study i.e. Kynurenic acid is a NMDA receptor antagonist, (Kyle K et al., 1996) and it is also agonist of dopamine receptor; therefore it may help in preventing the reduction of alcohol craving during the development phase of dependence and therefore reduces withdrawal sings in developmental phase of alcohol dependence. (Tayfun U, Oguz K.1995) It was observed that acute administration of kynurenic acid (50 and 100 mg /kg, i.p.), 30 min prior to the 24 hr interval after the withdrawal of ethanol diet on day 11 markedly attenuated the peak hyper excitability signs. Further in a separate set of experiments, chronic administration of kynurenic acid (50 and 100 mg/kg.i.p, twice daily for 10 days) attenuates the withdrawal induced hyper excitability signs scores at 7, 12, 24 hr. This dosing schedule was adopted as the elimination half life of kynurenic acid from mice plasma is reported to be around 5 hr (Richard W. Jakson 1939). Furthermore it is demonstrated that, (kynurenic acid 50 mg and 100 mg/kg,i.p.) completely blocks morphine-inductedlocomotor sensitization and analgesic tolerance in mice and reduced D1 dopamine and N-methyl- D-aspartate (NMDA)receptor bindingin the cortex. (Anton Bespalaov et.al., 1994).

The daily ethanol consumption higher than 2 g/kg for 10 consecutive days produced physical dependence in mice. (King G, et al., 1994) It was demonstrated that non-competitive NMDA-R antagonist decrease the ethanol consumption as studied using different paradigm such as ethanol deprivation effect, ethanol self-administration, and bottle choice. (Tayfun U, Oguz K,1995, Valentina Vet al.,2005,Przemyslaw Bet al., 2001) The modified liquid diet used in this study is consumed by the mice in amounts equivalent to a range of mean daily ethanol consumption from 10.60± 0.236 to 17.38 ± 1.102g/kg/day. As dopamine plays an important role in dependence as well as in withdrawal syndrome, previous finding also suggest that dopamine level get reduced after chronic administration of ethanol, nicotine, cocaine and all drug of abuse, which results in adverse behavioral effect. Kynurenic acid shows beneficial effect in preventing the adverse behavioral effect which occurs after chronic administration of Morphine. As the mechanism of action of ethanol and morphine is found to be similar in development of dependence and withdrawal, with this line, the drug may also help in preventing behavioral effects after ethanol withdrawal. (Yossef I, et al,. 1999).

Also the kynurenic acid is safe and does not produce any adverse effects such as tolerance, dependence due to its dopamine agonist property. There is a dramatic increase in glutamate levels from the nucleus accumbens was recorded during the first ethanol withdrawal period, particularly aspartate, glutamate, arginine, taurine, alanine and also GABA. (Abdelkader D, et al., 2003).

This results in physical dependence which is characterized by various physical signs hyper excitability sign such as vocalization on handling, defecation on handling, urination on handling, caudal posture, tremor, startle response, and hyper locomotion as characteristic features of ethanol withdrawal syndrome in ethanol dependent mice. With these findings present study demonstrated that, chronic treatment of kynurenic acidproduced inhibitory effects on ethanol withdrawal hyper excitability signs such as vocalization on handling, defecation on handling, urination on handling, caudal posture, tremor, startle response. However administration of kynurenic acid 30 min before ethanol withdrawal did not alter the enhanced hyper excitability signs in ethanol dependent mice.

Thus present investigation revealed that chronic treatment of kynurenic acid along with ethanol exposure prevent the induction of ethanol dependence as characterized by reduction in several hyper excitability signs of ethanol withdrawal and not associated with acute effect of kynurenic acid.

We also initiate the NMDA receptor antagonist treatments after 1 day of ethanol exposure and continued up to 10 days. These treatments of NMDA receptor antagonist also significantly blocked the ethanol withdrawal induced hyper excitability signs and prevent the elevation of glutamate level in ethanol dependent mice. Thus it appears that NMDA receptor antagonist plays pivotal role in prevention of ethanol dependence rather than its withdrawal and seems to be associated with normalization glutamate level. Moreover chronic treatment of kynurenic acid is required for preventing re-addiction process of ethanol.

In addition to “physical” or “hyper excitability” signs, withdrawal from all major drugs of abuse including alcohol is associated with a negative affective state including negative emotions such as dysphoria, irritability, anxiety and depression. (Tayfun U, Oguz K,1995).

In line with the above, it was observed that acute effect of kynurenic acid did not show any significant effect on locomotor.) Was devoid of any significant effects on locomotor activity compared with the Vehicle treated animals [F (5, 30) = 0.6668, p = 0.2095]. In contrast, diazepam (2.5 mg/kg, i.p.) significantly reduced [F (5, 30) = 12.51, p < 0.0001] Chronic treatment with kynurenic acid [F (6, 30) = 521.3; p< 0.001] exhibited prevention in hyper locomotor effect of ethanol withdrawal.

In conclusion, the results and evidence suggest that kynurenic acid exhibited an inhibitory influence against ethanol withdrawal-induced hyper excitability signs which could be mediated through its neuromodulatory & neuroprotective action.

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