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RESEARCH ARTICLE

EFFECTS OF TOPIRAMATE PRETREATMENT ON KETAMINE INDUCED BEHAVIORS IN RATS

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ABSTRACT

Topiramate has been used as an add-on-drug with typical antipsychotics to treat negative and cognitive symptoms of schizophrenia. The present study investigated if topiramate exhibits atypical antipsychotic-like activity, has any potential to precipitate or exacerbate psychosis and its ability to relieve negative symptoms of schizophrenia.

Aims: To study the effects of topiramate pretreatment on ketamine induced behavioral effects in the rats.

Methods: Hyperlocomotion and stereotyped behaviors were induced in the rats by acute administration of ketamine (25mg./kg. i.p.). Ketamine in low dose (2mg./kg. i.p.) produced social isolation and deficits in the social interaction in the rats. The effect of topiramate (40mg./kg and 80mg./kg. p.o.) pretreatment on hyperlocomotion was evaluated by activity scores measured with automated actophotometer and stereotyped behavior was graded by trained observers. The effect of topiramate pretreatment on ketamine induced deficits in the social interaction in the rats was evaluated by manually performed social interaction test.

Data analysis: Locomotor activity and social interaction scores were analysed by two tailed, unpaired student's 't' - test. Stereotyped Behaviors' highest scores, were evaluated by Mann Whitney U test. Value of $p<0.05$ was considered statistically significant.

Results: Topiramate decreased ketamine induced hyperlocomotion and stereotyped behavior in the rats which was statistically not significant. Topiramate significantly reduced ketamine induced social isolation in the rats.
Conclusion: Topiramate did not exhibit either atypical antipsychotic-like activity or the potential to precipitate/exacerbate psychosis. Topiramate could be effective in relieving negative symptoms of schizophrenia and it appears that topiramate has the potential to improve negative affective states..

INTRODUCTION

Topiramate, an antiepileptic drug, has been used with typical antipsychotic drugs to treat negative and cognitive symptoms of schizophrenia and also to prevent gain in body weight because of antipsychotic drug treatment. Negative and cognitive symptoms of schizophrenia are more resistant and difficult to treat. Topiramate antagonizes glutamate at α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid and kainite (AMPA/KA) receptors and enhances the activity of γ-amino-butyric acid (GABA)[1]- both of these actions address the pathophysiological processes of schizophrenia. Hypofunction of the N-methyl-D-aspartate (NMDA) – glutamate receptors increases the glutamate release at AMPA/KA – glutamate receptors which leads to the development of psychiatric symptoms.[2] Decreased GABA-ergic neurotransmission is also implicated in the pathophysiology of schizophrenia.[3]

In the initial clinical trials, topiramate when used as an adjuvant drug to the typical antipsychotics, either improved the negative symptoms or lacked the therapeutic effects.[4,5,6] On the other hand, topiramate was reported to produce psychiatric adverse events in the treatment of epileptic patients .[7-10]

Here, we examined experimentally the clinical findings of topiramate by investigating the efficacy of topiramate alone in rodent (rats) animal model of ketamine induced positive and

negative symptoms of schizophrenia relevant to NMDA – receptor hypofunction.

MATERIALS AND METHODS

Animals **-** The present animal study was approved by the Institutional Animal Ethical Committee formed as per the guidelines of C.P.C.S.E.A.

Male Wistar rats weighing between 180-280 g were used for the experiments. Animals were maintained in 12 hour dark/light cycle. Animals had free access to food and water, except during the experiments. All the experiments were done between 09.00-15.00 hrs.

The rats were divided into two groups - a control group (vehicle treated) and a test group (topiramate treated.) The total number of rats used was 26.

Drugs and doses **-** Topiramate powder was supplied by Encore Healthcare. Topiramate was given p.o. in the form of suspension prepared with 1% guar gum in water. Topiramate was administered one hour before ketamine administration. Ketamine Inj. (Aneket, Neon) 50mg/ml solution, was supplied by our Hospital Pharmacy.

Ketamine was given by i.p. inj. after one hour in test group and in control group. Ketamine was diluted to suitable concentration with inj. normal saline. Ketamine was given in the dose of 2mg/kg for Social Interaction Test and 25mg/kg for Hyperlocomotion & Stereotyped Behaviors. [11,12] During the experimental procedures the trained observers were blind to the treatment paradigm.

Ketamine induced locomotor hyperactivity and stereotyped behavior in rats

NMDA receptor antagonists such as ketamine produce hyperlocomotion and stereotyped – like activity in rats. These motor effects are related to the positive symptoms of schizophrenia or to the propensity to elicit/exacerbate psychosis.[2,3,12]

The rats were acclimatized to the test arena for three days before the experiment was done. The locomotor activity and stereotyped behavior of rats were recorded individually for each rat in the actophotometer (Dolphin) and by a trained observer, respectively. The locomotor activity is defined as the total photocell beam interruptions monitored using an automated infrared beam based actophotometer. The locomotor activity was measured for 15 minutes duration. The average activity score for 5 minutes duration was used as a measure of locomotor activity.[12,13] Stereotypy was rated separately by a trained observer for 1 minute at every 5 minutes intervals during locomotor study. The score assigned was determined as the highest level of stereotypy consistently observed during rating period. The rating scale is given below:[14]

PCP (phencyclidine) stereotyped behavior: (0) = Stationary, little or no movement,

1. = Active, occasional to frequent movement,
2. = Active with episodes of repetitive forward and head searching (the rat walks forward in a stereotyped manner along the periphery of the arena without engaging in other behaviors),
3. = Continuous forward searching,
4. = Frequent, repetitive rearing, side to side weaving or turning,
5. = Episodes of rapid, jerking, side to side circular or dorsoventral head movements (the rat is usually stationary.)

Ketamine induced social withdrawal and the deficits in social interaction measured in social interaction test

This test helps to show the effectiveness of the test drugs against negative symptoms of schizophrenia. The negative symptoms of schizophrenia are produced by non-competitive NMDA receptor antagonists like phencyclidine, ketamine, MK-801, in rodents which disrupt social interaction and this is considered to be an animal model of negative symptoms of schizophrenia.[12,2]

Very low doses or repeated administration of ketamine produces social isolation in rats, representing negative symptoms of schizophrenia.[11,13]

Naïve rats were housed in pairs for 10 days prior to the start of the test. During the test one cage mate (familiar/resident rat) was removed and a new one (intruder) was placed in the cage for a duration of 10 minutes. The amount of social interaction, between the resident and the intruder rat, was recorded manually for 10 minutes. The social interaction was measured as the total amount of time spent on various elements of interaction eg. sniffing, grooming of the partner, genital investigation and following the partner. Aggressive behavior was not included.[13]

Data Analysis

Locomotor activity and social interaction scores were analysed by two tailed, unpaired student's 't' - test. Stereotyped behaviors' highest scores, were evaluated by Mann Whitney U test. Value of $P<0.05$ was considered statistically significant.

RESULTS

Ketamine induced locomotor hyperactivity and stereotyped behavior in rats

Topiramate pretreatment decreased ketamine induced hyper locomotion and stereotyped behavior in the rats. The reductions were statistically not significant (Table 1 & Table 2, $P > 0.05$)

Table 1 Effect of topiramate (40mg/kg & 80mg/kg) pretreatment on ketamine (25mg/kg) induced hyperlocomotion in rats.

	Topiramate 40mg/kg		
Group	**Number of rats in each group**	**Mean of locomotion score per 5 min ± S.E.M.**	**P - value**
Control	6	83.44±9.67	
Test	6	61.21±12.60	P > 0.05
	Topiramate 80mg/kg		
Control	7	51.30 ± 9.18	
Test	7	42.38 ± 10.57	P > 0.05

Unpaired, two tailed student's 't' – test.
P value < 0.05 considered significant*
Control group = vehicle (1% guar gum in water + ketamine)
Test group = topiramate + ketamine

Ketamine induced social withdrawal and the deficits in social interaction measured in social interaction test

Topiramate reduced ketamine induced social isolation in rats which was highly significant (Table 3, $P^{*}< 0.01$)

Table 2 Effect of topiramate (40mg/kg & 80mg/kg) pretreatment on ketamine (25mg/kg) induced stereotyped behavior in rats.

A – Topiramate 40mg/kg					
Group	**Number of rats in each group**	**Mean rank**	**Sum of ranks**	**Mann Whitney U**	**P - Value**
Control	6	5.17	37.00	10	P > 0.05
Test	6	7.83	47.00		
B – Topiramate 80mg/kg					
Control	7	9.36	65.50	11.50	P > 0.05
Test	7	5.64	39.50		

Mann Whitney U test.
P value < 0.05 considered significant*
Control group = vehicle (1% guar gum in water + ketamine)
Test group = topiramate + ketamine

Table 3 Effect of topiramate pretreatment (40mg/kg and 80mg/kg) on ketamine (2mg/kg) induced social isolation.

A – Topiramate 40mg/kg			
Group	**Number of pairs of rats in each group**	**Time spent in social interaction in seconds per 10 min**	**P - value**
Control	6	5.17 ± 1.362	
Test	6	30.50 ± 8.176	P < 0.01*
B – Topiramate 80mg/kg			
Control	6	3.17 ± 1.302	
Test	7	21.43 ± 5.047	P < 0.01*

Unpaired, two tailed student's 't'-test. P^*< 0.01 highly significant.
P value < 0.05 considered significant*
Control group= vehicle (1% guar gum in water)+ketamine,
Test group = topiramate+ketamine

DISCUSSION

Hyperlocomotion and Stereotyped Behavior (SB)

The atypical antipsychotics block hyperlocomotion and SB produced by NMDA- receptor antagonists more effectively than the typical antipsychotics which block these behaviors at higher doses that suppress normal activity in rodents.[3,15] In our experiment, topiramate (40mg/kg & 80mg/kg) did not block hyper locomotion and SB significantly._ These behaviors in rats produced by NMDA-receptor antagonists are also inhibited by AMPA/KA- receptor blockers and also by increasing the brain levels of GABA.[2,3,15,16] Topiramate antagonizes glutamate at AMPA/KA receptors and facilitates GABA function through non-benzodiazepine $GABA_A$ receptors.[17] In our study, topiramate showed insignificant effects on hyperlocomotion and SB. Clinically, rapid escalation to higher doses of topiramate led to cognitive and psychiatric adverse events. The higher dose of topiramate (80mg/kg) in our experiment decreased hyperlocomotion and SB non-significantly. The results of our experiment indicate that topiramate does not have either antipsychotic -like activity or the potential to elicit/exacerbate psychosis.

Social Interaction Test

Topiramate significantly (P < 0.01) reduced social isolation in rats induced by low dose of ketamine. These results are suggestive of topiramate's potential to reduce negative symptoms of schizophrenia. Hypofunction of dopaminergic system in the Pre Frontal Cortex (PFC) may be responsible for the development of negative symptoms of schizophrenia.[18,19] The atypical antipsychotics increase dopaminergic function in the PFC and are effective in alleviating negative symptoms of schizophrenia.[2,16,18,19] Eltyab *et al* reported that the administration of topiramate or raclopride (D_2 receptor antagonist) alone had slight enhancing effects on dopamine release in PFC which was statistically non-significant. But the dopamine release increased significantly when topiramate and raclopride combination was administered.[20] In the present study, topiramate did not exhibit antipsychotic-like activity and was not administered with D_2 receptor antagonist. Interestingly, topiramate was reported to possibly prevent negative affective state produced by alcohol withdrawal.[21] So, it appears that topiramate has the potential to reduce negative affective states produced by different factors such as administration of ketamine or typical antipsychotics or that induced by alcohol withdrawal. This study was limited only to the behavioral effects induced by acute administration of ketamine.

CONCLUSION

Topiramate did not exhibit either atypical antipsychotic-like activity or the potential to precipitate/exacerbate psychosis. Topiramate could be effective in relieving negative symptoms of schizophrenia and it appears that topiramate has the potential to improve negative affective states.

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