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Research Article

EVALUATION OF ANTIEPILEPTIC AND MEMORY RETENTION ACTIVITY OF CURCUMIN PER SE AND IN COMBINATION WITH ANTIEPILEPTIC DRUGS.

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ABSTRACT

Antiepileptic activity of curcumin and its combination with phenytoin and sodium valproate were studied in chronic model (14 days) of Maximal Electroshock Seizure (MES) and Pentylenetetrazole (PTZ) induced seizure respectively. Elevated plus maze test was used to study effect of drugs and/or seizures on memory retention in MES and PTZ groups. Curcumin in both doses did not show any significant effect (P = 0.33) on tonic extension, while curcumin 100 mg/kg significantly (P < 0.01) reduced clonic phase compared to vehicle control. Curcumin in 100 mg/kg dose significantly (P < 0.001) inhibited PTZ induced seizure. Addition of curcumin to sub therapeutic dose of sodium valproate showed synergistic effect. Curcumin did not show any effect on memory retention. Inhibition of PTZ induced seizure by curcumin could be due to effect on γ-amino butyric acid receptor (GABA) pathway and its antioxidant property. Curcumin can be effective in absence seizure alone and as add on with sodium valproate.

Keywords: Curcumin, Epilepsy, Memory retention

INTRODUCTION

Epilepsy is a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures and by the neurobiological, cognitive, psychological, and social consequences of this condition.[1] The definition of epilepsy requires the occurrence of at least one epileptic seizure. Epilepsy is second most common neurological disorder after stroke.[2] Approximately 50 million people are suffering from epilepsy worldwide and amongst them 80% are in developing countries. Incidence of epilepsy is 40 – 70 per 100000 per year in developed countries; it is much higher in developing countries. It has prevalence rate of 4 to 10 per 1000 population. Epilepsy affects all the age groups, especially young people in first two decades of life and elderly. People suffering from epilepsy have two to three fold higher chances of mortality, it being even higher in young age group.[3]

Management of epilepsy requires immediate attention and long term treatment. Therefore, it is important that the drugs that are used should have a benign profile of adverse drug events. Phenytoin, sodium valproate, carbamazepine and phenobarbitone are commonly used antiepileptic drugs. About 75-80% of patients with epilepsy are adequately controlled with conventional antiepileptic drugs, while 20-25% develop therapeutic failure and require add on therapy.[4] Due to unwanted side effects and long term treatment compliance is a major problem in antiepileptic treatment. Epilepsy and antiepileptic drugs both adversely affect learning and memory function. It ranges from minor forgetfulness, difficulty in concentration to gross impairment of memory. This is especially important for young age group as it can affect their education and occupational life in future.[5] In past few years large number of newer antiepileptic drugs have been has been approved or last phase of development as add on therapy for poorly controlled epilepsy, but safety and tolerability of these drugs needs to be proven.[6,7] Therefore search for newer drugs with favorable clinical efficacy and tolerability, which can be used as add on therapy to conventional antiepileptics continues.

Rhizomes of *Curcuma longa* Linn. have been used to treat depression in past.[8] Curcumin is low molecular weight polyphenol, is considered as active principle of *Curcuma longa* Linn.[9] *Curcuma longa* Linn. is reported to have antioxidant, antiepileptic and neuroprotective properties.[10] Though there have been some reports about antiepileptic activity of curcumin, its effect via oral route and as add on to antiepileptic drugs have to be studied.[11,12]

This work was planned to assess the antiepileptic and memory retention activity of curcumin in two different doses and to study its interaction with the two most commonly prescribed antiepileptic drugs, phenytoin and sodium valproate via oral route in two different chronic models in *Swiss* albino mice.

MATERIAL AND METHODS

Animals

All the experiments were performed after the prior permission from the Institutional Animal Ethics Committee (IAEC). Swiss albino mice, three-four months of age (26 to 34 g) of either sex were procured from the central animal house of the institute. They were housed in standard polypropylene cages and kept in a 12 hr light-dark cycle under controlled room temperature (24±2^{o}C). The animals were given standard laboratory diet and water *ad libitum.* The animals were acclimatized to the laboratory conditions at least one day prior to the behavioral experiments. All the experiments were carried out between 1200 hrs to 1600 hrs. Food was withdrawn 12 hrs before the experiments. Each animal was used only once. The animal handling was performed according to the Good Laboratory Practice (GLP) guidelines.

Drugs

Curcumin not less than 95% (BCM95)(Arjuna Natural Extracts Ltd., Alwaye, Kerala, India), phenytoin and sodium valproate (Sun Pharmaceutical Industries Ltd., Mumbai, India), Pentylenetetrazole (PTZ) (Sigma Aldrich, Bangalore, India) and gum acacia (Fischer Scientific, Mumbai, India) were used in the study. Curcumin, phenytoin and sodium valproate suspension were made in 5% gum acacia, which was used as vehicle control.

Dry rhizomes of *Curcuma longa* Linn. have been used in Chinese medicine in a dose of 3–9 g/70kg for adult.[8] Curcumin content of dry rhizomes is 5-6%.[9] Considering a median dose of 6 g/70kg, dose of curcumin not less than 95% comes out to be 50 mg/kg in mice.[13] Curcumin was therefore tested in a dose of 50 mg/kg and 100 mg/kg. Phenytoin was used in dose of 25 mg/kg (sub therapeutic dose) and 50 mg/kg (therapeutic dose) and sodium valproate in 400 mg/kg (sub therapeutic dose) and 800 mg/kg (therapeutic dose).[14, 15]

Study Design

The antiepileptic activity of curcumin and its combination with phenytoin and sodium valproate was evaluated by maximal electroshock (MES) and pentylenetetrazole (PTZ) induced seizures respectively after chronic dosing (14 days) in mice. Both tests were started 60 min after oral treatment on day 14 with the test compound or the vehicle. Effect on memory was tested by elevated plus maze test in all groups.

MES induced seizures

MES test was performed as described by Giardina and Gasior 2009.[15] Electroconvulsiometer (Ambala, India) was used with ear electrodes to deliver the shock. The intensity of stimulus given was 36 mA for 0.2s. Video recording of all animals was done. The recordings were later analyzed by a rater who was blinded to the treatment given. Parameters like duration of tonic flexion, tonic extension and clonic convulsion were calculated by stopwatch. Disappearance of the hind limb tonic extension was taken as a positive criterion for antiepileptic effect of drug. Animals were divided into six groups, each group having six animals. Group 1 received 5% gum acacia and served as vehicle control. Group 2 and 3 received curcumin in dose of 50 mg/kg and 100 mg/kg respectively. Group 4 received phenytoin 50 mg/kg. Group 5 and 6 received phenytoin in therapeutic (50 mg/kg) and sub therapeutic (25 mg/kg) doses respectively in combination with curcumin (100 mg/kg).

PTZ induced seizures

Test was performed as described by Vogel 2002.[16] All the animals were treated with study drugs for fourteen days. On day 14, 60 minutes after last dose, PTZ was injected intraperitonealy (i.p.) in a dose of 95 mg/kg and animals were placed into an individual plastic cage for observation lasting 30 minutes and video recording was done. The recordings were later analyzed by a rater who was blinded to the treatment and time of onset of first myoclonic jerk, time of onset of tonic clonic convulsion and mortality of animal was calculated by stopwatch. Extent of delay in onset of first myoclonic jerk, delay in onset or prevention of tonic clonic convulsion and mortality were taken as measure of antiepileptic activity. Animals were divided into six groups each having six animals. Group 1 received 5% gum acacia and served as vehicle control. Group 2 and 3 received curcumin in dose of 50 mg/kg and 100 mg/kg respectively. Group 4 received sodium valproate 800 mg/kg. Group 5 and 6 received sodium valproate in therapeutic (800 mg/kg) and sub therapeutic (400 mg/kg) doses respectively in combination with curcumin (100 mg/kg).

Elevated plus maze test

Effect on memory was tested in all groups by elevated plus maze test.[17] Elevated plus maze for mice was made of plywood consisting of two open arms (16cm×5cm), two closed arms (16cm×5cm×12cm) and a central platform (5cm×5cm). Maze was elevated from floor at height of 25cm. On first (training session) day of test (13th day of treatment) mice were placed at the end of open arm facing away from central platform. Transfer latency (TL), time required by animal to move from open arm to one of closed arm with all the four limbs inside was noted. On 14 day (24 hours after training on plus maze) seizures were produced and the memory retention was tested after recovery of animal. If the mice did not enter the closed arm within 90 s on the training session, it was carefully guided to the closed arm. If the mice did not enter the closed arm within 90 s on the second day, the TL was assigned to 90 s. Mice were allowed to explore the maze for another 2 minutes. The apparatus was cleaned and dried after each animal. Another vehicle treated (5% gum acacia) group used as control in which maze test was performed without producing epilepsy.

Statistical analysis

Data were expressed as Mean ± Standard Error of mean (SEM). Statistical analysis for MES and PTZ induced seizure was done using one-way Analysis of Variance (ANOVA) followed by Tukey Kramer post test. Kruskal Wallis followed by Dunn's multiple comparison tests was used for elevated plus maze test. Statistically significance was set at $P < 0.05$. All the analysis was done using GraphPad InStat 3.06 demo version.

RESULTS

MES induced seizures

Curcumin in dose of 50 mg/kg and 100 mg/kg did not produced any significant effect ($P = 0.33$) on tonic hind limb extension as compared to vehicle control group. Phenytoin in a dose of 50 mg/kg abolished tonic extension phase completely, but did not show any significant difference ($P > 0.05$) on clonic phase as compared to vehicle control. Curcumin, at dose of 100 mg/kg, produced significant ($P < 0.01$) reduction in duration of clonic phase as compared to vehicle and phenytoin group. No significant effect ($P > 0.05$) on duration of clonic phase was seen at dose of 50 mg/kg of curcumin [Table 1]. No significant difference ($P > 0.05$) was observed in duration of tonic and clonic phase in combination group as compared to phenytoin alone.

PTZ induced seizures

In vehicle treated group myoclonic jerks followed by tonic clonic seizure and death was observed after i.p. injection of PTZ. All the animals died in vehicle control group. Curcumin in a dose of 50 mg/kg and 100 mg/kg increased latency for onset of myoclonic jerks and seizures as well as decreased incidence, total duration of seizure and mortality, though effect was statistically significant ($P < 0.001$) only in a dose of 100 mg/kg as compared to vehicle control group [Table 2]. Sodium valproate completely prevented incidence of tonic clonic convulsions and mortality as compared to vehicle. Curcumin when combined with sodium valproate showed no significant difference ($P > 0.05$) in antiepileptic activity as compared to sodium valproate alone.

Elevated plus maze test

Elevated plus maze test was performed on day 13th and 14th after recovery from seizure. Curcumin in both doses did not showed significant difference on memory retention compared to vehicle control in MES group ($P > 0.10$). Curcumin in both doses showed no significant difference ($P > 0.2$) on memory retention compared to sodium valproate in PTZ group [Table 3 and 4]. No significant difference ($P > 0.1$) in memory retention observed in phenytoin group compared to vehicle control. Another vehicle control group, in which seizures not produced, was used to compare the effect of seizure itself and antiepileptic drugs on memory retention. Curcumin did not show any significant difference ($P > 0.05$) when compared to this group as well.

TABLE 1: Effect of curcumin, phenytoin alone and in combination on MES induced seizure in mice.

Treatment groups	Dose(mg/kg) per oral	Tonic flexion (sec) (Mean ± SEM)	Tonic extension (sec)(Mean ± SEM)	Clonic phase (sec)(Mean ± SEM)
Vehicle control	2.5 ml/kg	1.46±0.16	15.16±0.73	9.29±1.17
Curcumin	50	1.85±0.26	17.24±0.65	7.36±0.81
Curcumin	100	1.40±0.06	17.08±1.67	4.93±0.46*
Phenytoin	50	Prevented	Prevented	8.87±0.93
Phenytoin plus curcumin	50 +100	Prevented	Prevented	10.40±0.5
Phenytoin plus curcumin	25 + 100	Prevented	Prevented	8.96±0.33

Statistical analysis of data was carried by one-way ANOVA followed by Tukey Kramer post test. *$P < 0.05$ when compared with control. N=6 in each group.

TABLE 2: Effect of curcumin, sodium valproate alone and in combination on PTZ seizure in mice.

Treatment groups	Dose(mg/kg) per oral	Time of onset of first myoclonic jerk (min) (Mean ± SEM)	Latency of onset of seizure (min) (Mean ±SEM)	Duration of seizure(min) (Mean ± SEM)
Vehicle control	2.5 ml/kg	1.13±0.14	3.59±0.49	1.06±0.14
Curcumin	50	1.68±0.19	5.22±0.46	0.52±0.10
Curcumin	100	5.75±0.43*	10.29±0.53*	0.17±0.01*
Sodium valproate	800	6.01±0.36*	Prevented	Prevented
Sodium valproate plus curcumin	800 +100	6.23±0.40*	Prevented	Prevented
Sodium valproate plus curcumin	400 + 100	5.18±0.18*	Prevented	Prevented

Statistical analysis of data was carried by one-way ANOVA followed by Tukey Kramer post test. *$P < 0.05$ when compared with control. N=6 in each group.

TABLE 3: Effect of curcumin, phenytoin alone and in combination on transfer latency of mice using elevated plus maze test in MES group.

Treatment groups	Dose (mg/kg)per oral	TL on day 13(sec)(Mean ± SEM)	TL on day 14(sec) after recovery from seizure(Mean ± SEM)
Vehicle without producing epilepsy	2.5 ml/kg	22.66±2.99	19.08±2.92
Vehicle control	2.5 ml/kg	17.30±1.68	36.39±11.31
Curcumin	50	26.25±6.89	31.32±12.86
Curcumin	100	31.51±9.95	26.88±12.83
Phenytoin	50	16.86±2.56	18.43±4.11
Phenytoin plus curcumin	50 +100	20.58±3.40	12.84±2.79
Phenytoin plus curcumin	25 + 100	18.54±4.50	13.24±4.37

Statistical analysis of data was carried by Kruskal Wallis followed by Dunn's multiple comparison test, TL-Transfer latency, N=6 in each group.

TABLE 4: Effect of curcumin, sodium valproate alone and in combination on transfer latency of mice using elevated plus maze test in PTZ group.

Treatment groups	Dose (mg/kg)per oral	TL on day 13(sec)(Mean ± SEM)	TL on day 14(sec) after recovery from seizure(Mean ± SEM)
Vehicle without producing epilepsy	2.5 ml/kg	22.66±2.99	19.08±2.92
Vehicle control	2.5 ml/kg	27.18±6.21	Animals were died
Curcumin	50	28.88±12.50	15.83±2.28
Curcumin	100	18.27±3.14	15.10±1.57
Sodium valproate	800	29.90±12.87	26.98±5.65
Sodium valproate plus curcumin	800 +100	12.76±1.97	13.71±2.05
Sodium valproate plus curcumin	400 + 100	18.61±4.23	14.69±2.73

Statistical analysis of data was carried by Kruskal Wallis followed by Dunn's multiple comparison test, TL-Transfer latency, N=6 in each group.

DISCUSSION

MES test is considered as best validated model for testing drugs effective against generalized tonic clonic seizures. Drugs effective against generalized tonic clonic seizure will prevent tonic hind limb extension.[18] In the present study curcumin in both doses (50 and 100 mg/kg) failed to inhibit tonic hind limb extension. In our study phenytoin abolished tonic hind limb extension but failed to inhibit clonic phase of seizure. Curcumin in the dose of 100 mg/kg significantly ($P < 0.01$) reduced clonic phase of seizure. Clonic phase is due to catecholaminergic mechanism and its inhibition by curcumin may be a probable mechanism of protection against clonic phase.[19] It has been found that drugs effective against absence seizures abolish clonic phase in maximal electroshock seizure.[20] This correlates with our study. Curcumin showed protective role in amygdaloid kindled seizures in doses of 100 and 300 mg/kg but had no effect in 10 and 30 mg/kg doses.[11] In the above study curcumin was administered by intra peritoneal route while in present study it was administered by oral route. Curcumin has low bioavailability due to poor absorption and rapid metabolism.[21] Reduced bioavailability after oral administration might be a reason for observed difference in results. Amygdaloid kindled seizure is a model of epileptogenesis and various factors plays role in epielptogenesis. e.g. protein kinase[22] and mammalian target of rapamycin (mTOR).[23] Recent studies have shown the role of curcumin in inhibition of protein kinase and mTOR, this might be a reason for curcumin's protective role in epileptogenensis.[24]

PTZ induced seizure is commonly used model for screening of drugs effective in absence seizures. In present study curcumin in the dose of 50 mg/kg increased latency of onset of first myoclonic jerk, onset of clonus and decreased total mortality though it was not statistically significant but in the dose of 100 mg/kg it produced statistically significant ($P < 0.001$) protective effect. Combination of therapeutic dose of sodium valproate with curcumin showed significant ($P < 0.05$) antiepileptic activity as compared to vehicle control group but not from sodium valproate group alone. Maximum effect might have been produced with therapeutic dose of sodium valproate, so combination of curcumin with therapeutic dose of sodium valproate produced no further benefit. Curcumin with sub therapeutic dose of sodium valproate showed effect similar to sodium valproate group alone, this shows curcumin can be useful in reducing dose of sodium valproate and thus its side effects. PTZ is a CNS stimulant which acts by inhibiting chloride channels of γ-amino butyric acid receptor (GABA) complex.[25] Inhibition of stimulant activity of PTZ might be responsible for antiepileptic activity of curcumin. PTZ produces oxidative stress to neuronal cell.[26] Curcumin is well known for its antioxidant property and found to have concentration depended antioxidant activity.[27] Antioxidant

property could be another mechanism for effectiveness of curcumin in PTZ induced seizures.

TL after 24 hours of training session is suggestive of reflection of learned task of memory.[17] In present study curcumin, phenytoin and sodium valproate showed no effect on memory retention. Reeta et al. 2009 showed role of curcumin in prevention of phenytoin induced memory impairment.[28] In that study phenytoin was administered in dose of 75 mg/kg i.p. while in present study phenytoin was administered in dose of 50 mg/kg orally. High dose of phenytoin may require for memory impairment, difference in dosage and route of administration might be reason for different results in present study. Inability to measure plasma concentration of curcumin, phenytoin and sodium valproate was the limitation of present study. Measurement of plasma concentration of curcumin can be helpful in correlating its antiepileptic effect. Another limitation of present study was inability to measure the level of neurotransmitters altered by curcumin, which can be further helpful in understanding the mechanism of antiepileptic effect of curcumin.

Curcumin is found to be safe in both preclinical and clinical studies. A study in rat showed that it did not produce any adverse effects even when given up to dose 1.8 g/kg per day for 90.[29] A phase 1 study with 25 subjects found no toxic effects of curcumin even with administration of 8000 mg of curcumin per day.[30] Further, in present study combining curcumin with sodium valproate helped in reducing dose of sodium valproate. This shows it can be helpful as add on to sodium valproate in absence seizure.

This study shows that curcumin in dose of 100 mg/kg has antiepileptic activity in PTZ induced seizure and has synergistic activity in combination with sodium valproate. So, curcumin can be used as an antiepileptic in absence seizure alone and as add on with sodium valproate.

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