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Research Article

Curcumin Improves Chronic Stress Induced Potentiated Seizure Activity in Experimental Model of Epilepsy

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Summary

Objective: Curcuma longa is a traditional Chinese and Indian herbal medicine, which has been used to treat the symptoms of mental stress. As the major pigment in the rhizome of curcuma longa, curcumin has anti-oxidant, anti-inflammatory, and anti-convulsant activities. Exposure to the repetitive stress accelerates seizure activity in various model of epilepsy. Hence, we hypothesized that curcumin may ameliorate the effect of chronic stress on pentylenetetrazole (PTZ)-induced seizure activity in rats.
Methods: We assessed whether chronic or acute curcumin treatment (20 mg/kg, i.p.) affects PTZ (60 mg/kg. i.p.)-induced seizure activity in a chronic restraint stress (14 days, 2 h/day) model in rats. The latency to, and the duration of myoclonic jerk rearing (stage 3) and generalized tonic-clonic seizures (GTCS), the latency to, and the number of myoclonic jerks as well as the maximum seizure severity score were observed for a 30 min period after PTZ injection.
Results: We found that exposure to chronic stress prior to PTZ administration increased the duration of GTCS in animals, which could be reversed by chronic pre-administration of curcumin. In addition, curcumin pre-treatment alleviates the PTZ-induced seizure activity, increased the myoclonic jerks latency, decreased the duration of GTCS, and also decreased the severity of seizure as determined by seizure severity score.
However, acute administration of curcumin (20 mg/kg, i.p.) 30 min before PTZ had no significant effect on the PTZ-induced seizure under stressful situation.
Conclusion: Chronic but not acute curcumin is effective in management of seizure activity associated with daily stress in epileptic individuals.

Key words: Seizure, Pentylenetetrazole, Restraint, Stress, Curcumin

Güneydoğu Nijerya'daki Enugu'da Ortaokul Çocuklarında Primer Başağrısı: Prevalans, Patern ve Diğer Karakteristikler

Özet

Giriş: Primer başağrıları, günlük yaşam aktivitelerini önemli düzeyde etkileyerek hastalarda artan düzeyde direkt ve indirekt yüke neden olurlar. Bu durum Afrika'lıların henüz tahminen %5,6'sını etkileyen ve büyüyen bir halk sağlığı problemidir; genç Nijerya'lılar arasında ölçümü ve kapsamı az tanınmakta ve yetersiz tedavi edilmektedir.
Yöntem: Bu çalışma Güneydoğu Nijerya'daki Enugu'da yapılan kesitsel bir anketten temel almaktadır. Başağrısı sıklığı ve ağrı şiddeti, MIDAS anketinin a ve b soruları ile incelenmiştir.

Tetikleyen faktörler, kullanılan ilaçlar, tıbbi konsültasyonlar, ve akademik kısıtlılık da araştırılmıştır.
Bulgular: Toplam 218 öğrenci ile görüşülmüştür. Primer başağrısının yaşam boyu prevalansı %74,3'dür. Bununla bağlantılı olarak migren ve gerilim tipi başağrısı prevalansı sırasıyla %7,8 ve %32, 6'dır. Migrenden farklı olarak gerilim tipi başağrısı kadınlarda anlamlı oranda fazladır. Başağrıları çoğunlukla 1-5 gün (bütün başağrılarının %24,7'si, migrenlerin %11,6'sı ve gerilim tipi başağrılarının %35,2'si) sürmektedir ve kadın ve erkeklerde benzerdir. Başağrısı ataklarından endişe duyan ve duymayan öğrencilerin oranları benzerdir, bütün primer başağrılarının %22,2'sini, doktora başvuranların %16'sını ve akademik performansı sıklıkla etkilenenlerin %26,5'ini içermektedir. Akademik performansında sınırlanma yaşayanlar anlamlı şekilde daha çok tıbbi konsültasyona başvuran ve atakları için endişelenen öğrenciler içinde yer almaktadır.
Sonuç: Primer başağrıları Güneydoğu Nijerya'daki Enugu'da ortaokul çocukları arasında sıktır. Çoğu başğrısı 1-5 gün sürmektedir, sıklıkla hastanın akademik aktivitelerini sınırlamaktadır ve hastalar için endişe kaynağı olmaktadır.

Anahtar Kelimeler: Nöbet; Pentylenetetrazole; Kısıtlama; Stres; Curcumin

INTRODUCTION

Stress plays an important role in human health (3). It causes hypertension, increases the risk of heart disease (1), and occurrence of seizure. Status epilepticus is a cause of morbidity in human. Epilepsy is a process that enhances neuronal excitability leading to spontaneous recurrent seizures. Consistent with evidence from animal models, stress is a precipitating factor in induction of seizure in patients with epilepsy (4). Interestingly, acute stress has anti-convulsant effect whereas, chronic exposure to a stress increases seizure severity in rodent (6,9).

Most of the anti-seizure medication, however have undesirable side effects including behavioral or psychiatric reactions (3). Therefore, traditional herbs with anti-seizure activity may be an effective, safe, and novel medicine to treat epilepsy.

Curcumin with numerous pharmacological activities including anti-oxidant, analgesic, anti-diabetic, anti-inflammatory, anti-depressant and chemotherapeutic actions is the major pigment in the rhizome of Curcuma longa which has been used for decades to treat various diseases (1,10). At present, several clinical trials evaluate the efficacy of curcumin against neurological disorders in chronic models of epilepsy. But despite numerous studies on the useful effects of curcumin in various neurotoxicity models, its ameliorating effect in pentylenetetrazole (PTZ)-induced seizure related to chronic stress is not fully understood. PTZ is a noncompetitive GABAA receptor antagonist which, blocks GABAA-mediated neuronal inhibition, particularly in hippocampal pyramidal cells (5,6). PTZ-induced seizure is an animal model suitable for the study of tonic-clonic seizures.

Therefore, the present study was designed to investigate the effect of acute and chronic curcumin administration on development of seizure in PTZ-induced seizure animal model. We predicted that chronic stress would increase the severity of PTZ-induced seizures, which could be rescued by curcumin.

The results confirmed our hypothesis that chronic, but not acute, curcumin administration could ameliorate both the seizure activity and the effect of chronic restraint stress on potentiating PTZ-induced seizure in rats. These data demonstrated the potential anti-convulsive effects of curcumin against seizure activity under stress condition.

MATERIAL AND METHODS

All experimental protocols and procedures were performed according to International Guidelines on the use of Laboratory Animals approved by Kermanshah University of Medical Sciences ethical committee for animal research.

In this study, five weeks old male Wistar rats (60-100 g in weight) (Razi institute Tehran, Islamic Republic of Iran) were used. The animals were kept under standard laboratory conditions (20-22 °C) in an animal facility room, maintained on 12h light/dark cycle (lights on at 07:00 AM). They were housed in groups of three in transparent-plastic cages- with food (standard rat chow) and water provided ad libitum. All experiments were performed between 08:00 AM and 2:00 PM.

Curcumin (Sigma Aldrich Inc., St. Louis, Mo, USA) was dissolved in 0.125 N NaOH, titrated to pH 7.4 using 1 N HCl, and diluted with physiological saline (0.5% W/V in 0.9% saline). Pentylenetetrazole (PTZ) (Sigma Aldrich Inc., St. Louis, Mo, USA) was dissolved in physiological saline. All drugs were freshly prepared throughout the study and injected intraperitoneally (i.p.) at 2 ml/kg.

To test the impact of chronic curcumin administration on the PTZ-induced seizure under stressful situation, animals were randomly divided into eight groups (n= 7-9 in each group); Group I, Curcumin-Stress-PTZ (C-S-P); group II, Curcumin-Unstressed-PTZ (C-U-P); group III, Curcumin-Stress-Saline (C-S-S); group IV, Curcumin-Unstressed-Saline (C-U-S); group V, NaOH-Stress-PTZ (N-S-P); group VI, NaOH- Unstressed-PTZ (N-U-P); group VII, NaOH-Stress-Saline (N-S-S); and group VIII, NaOH-Unstressed-Saline (N-U-S). Animals in groups I-IV received curcumin (20 mg/kg), 30 min before daily induction of stress. In the vehicle control groups (groups V-VIII), rats were injected with NaOH instead of curcumin (12).

To test the impact of acute curcumin treatment on the PTZ-induced seizure following chronic stress, animals (n= 8/group) received single injection of curcumin (20 mg/kg, i.p.; Stress-Curcumin-PTZ, group IX, or S-C-P group) or NaOH (Stress-NaOH-PTZ, group X, or S-N-P group) 30 min before PTZ (60 mg/kg, i.p.) administration.

To induce chronic stress, rats in Curcumin-Stress-PTZ (C-S-P), Curcumin-Stress-Saline (C-S-S), NaOH-Stress-PTZ (N-S-P), NaOH-Stress-Saline (N-S-S), Stress-Curcumin-PTZ (S-C-P), and Stress-NaOH-PTZ (S-N-P) groups were placed in Plexiglas restrainer with suitable ventilation and adaptable to animal size for 2h/day from 09:00 AM to 11.00 AM, for 14 consecutive days (6). The control unstressed animal groups; Curcumin-Unstressed-PTZ (C-U-P), Curcumin-Unstressed-Saline (C-U-S), NaOH-Unstressed-PTZ (N-U-P), NaOH-Unstressed-Saline (N-U-S) were handled similarly to the stressed animals, except for stress exposure. At the end of stress procedure, both stressed and unstressed animals were undergone the PTZ-induced seizures as described below.

To test the impact of curcumin and/or exposure to the chronic stress on PTZ-induced seizures, all animals were injected with PTZ (60 mg/kg, i.p.) or normal saline immediately after last session of stress procedure and resulting seizure activity was observed for 30 min and scored according to modified Racin's scales (3); stage 0, no response; stage 1, ear and facial twitching; stage 2, myoclonic jerks without rearing; stage 3, myoclonic jerks, rearing; stage 4/5, turn over into side or turn over into back position, generalized tonic-clonic seizures (GTCS) (2,3). The latency of the first myoclonic jerk onset, latency of myoclonic jerks rearing (stage 3), latency of the GTCS (stage 4/5), the total period of the stages, number of myoclonic jerks, and the maximum seizure severity were recorded. In the absence of each stage of

seizure within 30 min, the latency time was taken as 1800 s(2).

Statistical Methods:

All data were expressed as mean±SEM. The data comprising of two variables (chronic stress and curcumin) were analyzed by using two-way analysis of variance (two-way ANOVA) followed by Tukey's test for multiple comparisons. Unpaired t.test was used for two-group comparisons. Data related to mortality rate was analyzed using X^2 and Fisher"s exact test. The criterion for statistical significance was $p<0.05$.

RESULTS

The weight of the animals received chronic curcumin or NaOH was measured before injection of PTZ or saline and no statistically significant differences were observed between experimental groups (data not shown).

The saline treated animals never experienced seizure activity. However, PTZ induced myoclonic jerks with rearing (stage 3) and/or GTCS in animals. Mortality rates during attacks in the NaOH-Stress-PTZ (N-S-P), Stress-NaOH-PTZ (S-N-P), and in Stress-Curcumin-PTZ (S-C-P) groups, were 28%, 25%, and 25%, respectively. No mortality was observed in the groups received PTZ alone or animals received saline instead of PTZ.

Effect of chronic curcumin treatment on the onset of seizure activities:

Latencies for the onset of first myoclonic jerk were studied in the PTZ treated groups. Statistical analysis revealed that application of chronic stress for 14 consecutive days by itself had no effect on the onset of myoclonic jerk. However, daily pre-administration of curcumin, 30 min before stress exposure, significantly increased the latency for the onset of first myoclonic jerk. Myoclonic jerks were significantly delayed in curcumin treated (C-U-P; 1142±315, $p<0.01$, and C-S-P; 1436±241, $p<0.001$) animals compared to controls (N-U-P; 65±5 and N-S-P; 87±12) (Fig. 1A).

Our data also demonstrated that exposure to the chronic stress did not have a significant effect on the onset of myoclonic jerks rearing (stage 3) as summarized in the Fig. 1B. But, chronic treatment with curcumin significantly increased the latency to stage 3 of seizure in C-U-P (1103±329) ($p<0.05$) and in C-S-P (1462±225) ($p<0.001$) groups compared to N-U-P (91±12) and N-S-P (100±16) groups, respectively.

Effect of chronic curcumin treatment on the onset of GTCS was also studied. Statistical analysis showed that GTCS latencies did not differ significantly between studied groups ($p>0.05$). The mean values for latencies in the N-U-P, N-S-P, C-U-P, and C-S-P groups were 1325±307, 1002±306, 1558±242, and 1800±0, respectively (Fig. 1C).

Effect of chronic curcumin treatment on the duration of seizure activities:

The average duration of seizure activity per stage is shown in figure 2. Duration of stage 3 did not differ significantly between N-U-P (25.3±11.24), N-S-P (52±18.3), C-U-P (40.14±20.8), and C-S-P (10.3±6.92) group. However, we found that the duration of GTCS increased significantly following application of chronic restraint stress prior to (N-S-P group; 48.28±25) compared to after PTZ administration (N-U-P group; 0.86±0.55) ($p<0.05$), which could be reduced with daily pre-administration of curcumin (C-U-P group; 0.14±0.14, $p< 0.05$). In addition, chronic administration of curcumin 30 min before daily application of restraint stress significantly reduced the duration of GTCS (C-S-P; 0.0±0.0 versus N-S-P group, $p<0.05$) (Fig. 2).

Effect of chronic curcumin treatment on the numbers of myoclonic jerks:

The numbers of myoclonic jerks is often used as an index of seizure activity in animal studies. We found that curcumin

treatment significantly reduced the number of myoclonic jerks observed in C-U-P (4.28± 1.86) and in C-S-P (2.55± 1.48) groups compared to NaOH treated animals (N-U-P group, 24.14±8.11) ($p<0.05$). On the other hand, chronic stress had no significant effect on the number of myoclonic jerks observed in N-S-P group (16.85±5) compared to that in N-U-P group (Fig. 3).

Effect of chronic curcumin treatment on the seizure severity score:

The mean seizure severity score in C-U-P (2±0.57) was significantly lower than that in N-U-P (3.57±0.36) group ($p<0.05$). Pre-administration of curcumin to C-S-P (2.22±0.14) group also significantly ($p<0.05$) decreased the seizure severity score as compared to N-S-P (3.85±0.34) group (Fig. 4).

Effect of acute curcumin treatment on the seizure activities:

Curcumin administrated in a single dosage (20 mg/kg, i.p.), 30 min before PTZ injection, had no significant effect on seizure activities as compared to NaOH administration (S-N-P group) (Table 1).

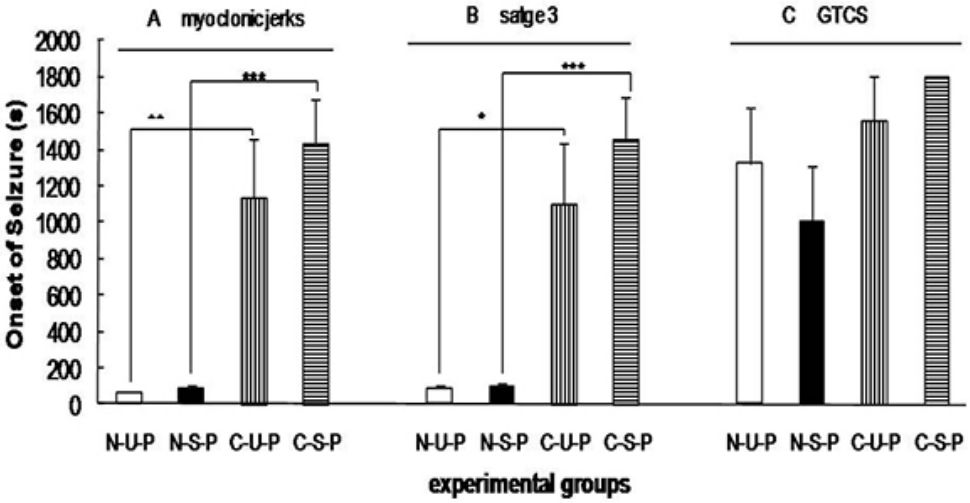

Fig 1: *Effect of exposure to the chronic restraint stress and/or curcumin on the onset of (A) myoclonic jerks, (B), stage 3 and (C) generalized tonic-clonic seizures (GTCS) in PTZ-seizure rats. Values are expressed as mean±SEM. *p<0.05, **p<0.01, ***p<0.001. N-U-P: NaOH-Unstressed-PTZ treated group (group VI), N-S-P: NaOH-Stress-PTZ treated group (group V), C-U-P: Curcumin-Unstressed-PTZ treated group (group II), C-S-P: Curcumin-Stress-PTZ treated group (group I).*

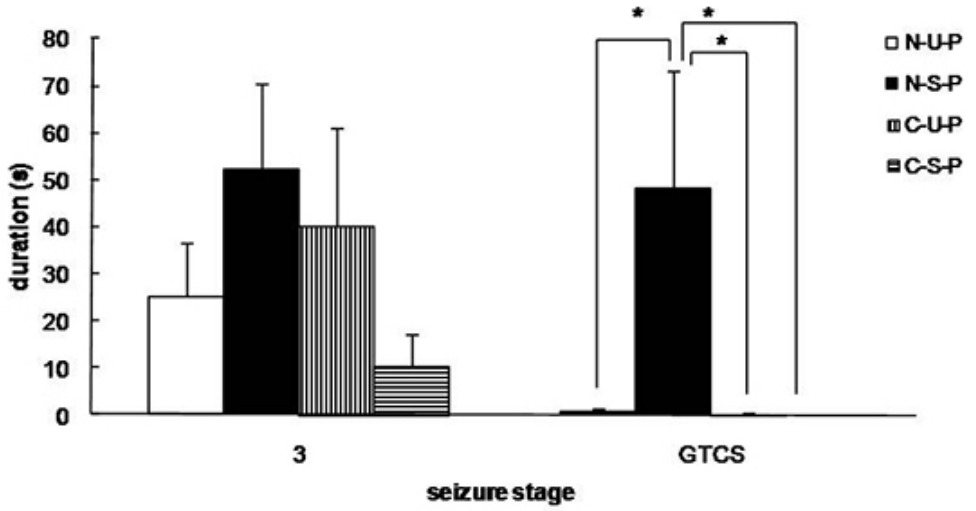

Fig 2: *Effect of exposure to the chronic restraint stress and/or curcumin on the duration of myoclonic jerks rearing (stage 3), and generalized tonic-clonic seizures (GTCS) in PTZ-seizure rats. Values are expressed as mean±SEM. *p<0.05. N-U-P: NaOH-Unstressed-PTZ treated group (group VI), N-S-P: NaOH-Stress-PTZ treated group (group V), C-U-P: Curcumin-Unstressed-PTZ treated group (group II), C-S-P: Curcumin-Stress-PTZ treated group (group I).*

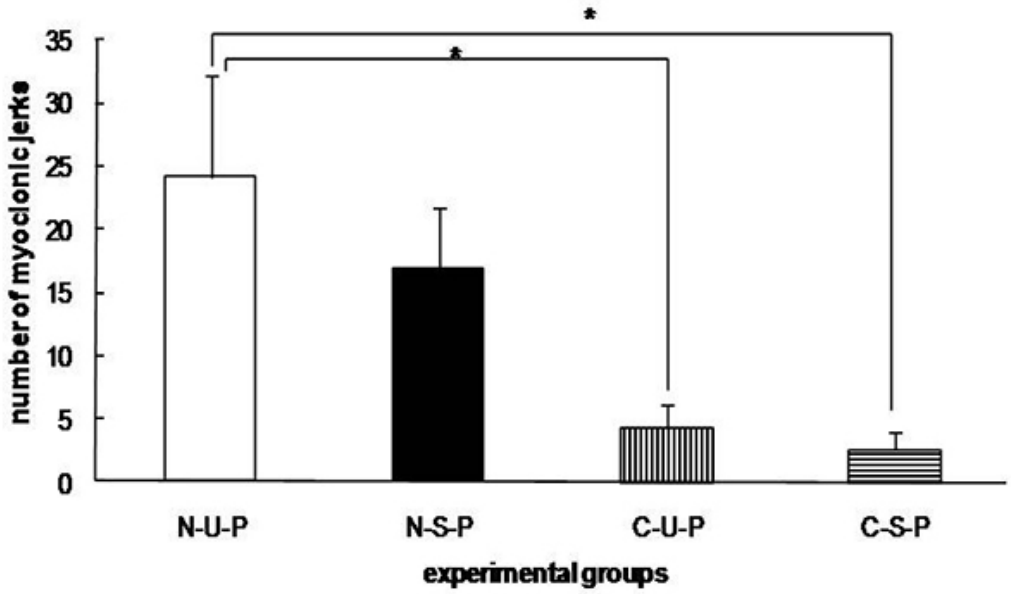

Fig 3: *Effect of exposure to the chronic restraint stress and/or curcumin on number of myoclonic jerks in PTZ-seizure rats. Values are expressed as mean±SEM. *p<0.05.*
N-U-P: NaOH-Unstressed-PTZ treated group (group VI), N-S-P: NaOH-Stress-PTZ treated group (group V), C-U-P: Curcumin-Unstressed-PTZ treated group (group II), C-S-P: Curcumin-Stress-PTZ treated group (group I).

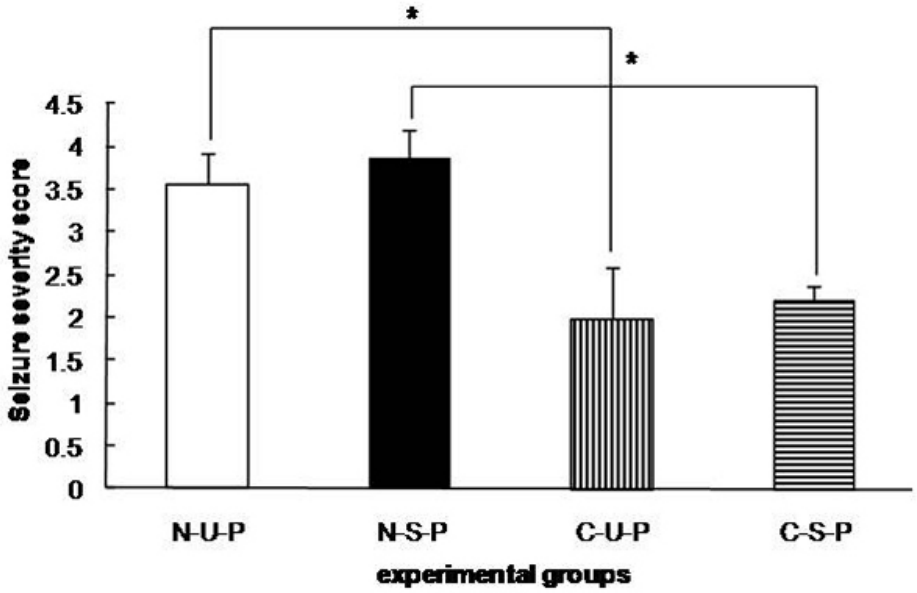

Fig 4: *Effect of exposure to the chronic restraint stress and/or curcumin on seizure severity score in PTZ-seizure rats. Values are expressed as mean±SEM. *p<0.05.*
N-U-P: NaOH-Unstressed-PTZ treated group (group VI), N-S-P: NaOH-Stress-PTZ treated group (group V), C-U-P: Curcumin-Unstressed-PTZ treated group (group II), C-S-P: Curcumin-Stress-PTZ treated group (group I).

Table 1: Effect of acute curcumin administration on stress induced potentiated seizure activity in rats. Values are the mean±SEM with 8 rats in each group. Data analysis was performed using unpaired t.test. NS: non significant compared with S-N-P group.

group	onset of myoclonic jerks (s)	onset of stage 3 (s)	onset of GTCS (s)	duration of stage 3 (s)	duration of GTCS (s)	No. myoclonic Jerks	seizure severity score
S-N-P	77.62±11.28	91.25±12.58	857±272.92	58.5±11.34	69.75±19.53	18.87±6.41	4.12±0.29
S-C-P	62.25±3.99, NS	72.87±5.14, NS	940.25±324.99, NS	80.5±33.27, NS	588.25±254.83, NS	26.87±7.6, NS	4±0.38, NS

DISCUSSION

Epileptic seizure is one of the major neurological disorders that can be affected by exposure to the daily stres (2). Despite the availability of anti-seizure medication, there are still significant percentages of epileptic patients who remain refractory to the current therapies and often require novel treatment regimen (2). Additionally, anti-epileptic drugs can be associated with problematic side effects. Therefore, a need was felt for natural products possessing anti-seizure activity for suppressing epileptic attacks especially under stressful situations.

Natural dietary anti-convulsive agents like herbal medicines are less toxic and more effective (3). Curcumin is commonly found in traditional Chinese and Indian medicines, which can penetrate the blood-brain-barrier, and has multiple biological effects (1).

In this study, using PTZ-animal model of seizure we have shown that chronic curcumin administration can alleviate

stress-associated seizure activities. Single intraperitoneal injection of PTZ (60 mg/kg) in rats immediately induced seizure activities that continued for 30 min without mortality, as previously reported (2). Interestingly, PTZ-induced seizure activities were reversed by chronically administering curcumin (20 mg/kg). Chronic curcumin treatment also significantly increased the latencies to myoclonic jerks and myoclonic jerks rearing (stage 3) (Fig. 1). The number of myoclonic jerks as well as seizure severity scores were decreased by curcumin treatment (Fig. 3 & 4). The results of the present study are consistent with previous reports in which, curcumin prevented seizures in PTZ-induced experimental model of epilepsy. Though in the present study, the possible mechanism(s) of action of curcumin in seizure was not evaluated, the observed anti-convulsive activity of curcumin might be due to its anti-inflammatory and/or its anti-oxidant activities (10).

Previous researchers have shown that the nature and the duration of the stress are important factors affecting epilepsy (3). In rodent an acute stress has anti-convulsant properties whereas, chronic exposure to a stressor increases susceptibility to seizure (6). The present finding complement these prior studies and show that prior exposure to chronic restraint stress, 2 h/day for 14 consecutive days failed to alter the latencies to myoclonic jerks and myoclonic jerks rearing (stage 3) as well as GTCS (Fig. 1) in animals injected with single dose of PTZ. Chronic stress did not have a significant effect on the duration of stage 3 (Fig. 2), number of myoclonic jerks (Fig. 3), or on seizure severity score (Fig. 4). But, exposure of animals to the chronic restraint stress increased the duration of GTCS (Fig. 2) resulting in about 28% mortality during attacks compared with no mortality in non-stressed PTZ injected group. However, the effect of chronic restraint stress on the animals could be reversed by chronic pre-administration of curcumin. These data indicate that chronic curcumin administration alleviates stress-induced seizure activity and suggest that curcumin could be used as a potential preventive/therapeutic agent against stress induced epileptic seizure. Our results also showed that chronic curcumin administration and/or exposure to the chronic stress had no significant effect on body weight.

The acute effect of curcumin on PTZ-induced seizure was also examined. There were no differences in duration, latency, number of jerks, or severity of seizure in stressed animals treated with NaOH and those that treated with a single dosage of curcumin (20 mg/kg), 30 min before administration of PTZ. These findings imply that acute curcumin administration at the dose of 20 mg/kg is not a potent anti-convulsive under stressful situation. The protective mechanism of chronic but not acute curcumin treatment against stress induced seizure might be due its effect on corticosterone production. It has been shown that the level of corticosterone increases after chronic stres, resulting in long-lasting increase in cell firing frequency in hippocampal CA1 area which could be reduced by chronic curcumin administration (4). Thus, reduction of corticosterone level under this condition by chronic curcumin treatment may reduce stress induced potentiated seizure activity.

Taken together, these results demonstrated that chronic, not acute, curcumin treatment reversed PTZ-induced seizure in stressed and unstressed animals. These observations may have clinical implications for the therapeutic effect of curcumin in epileptic seizure associated with stress. However, elucidating the mechanism involved await further studies.

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