Research Article

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Effect of curcumin on passive avoidance learning disorders induced by seizure activity under chronic restraint stress in rats

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Abstract

Objective: As a major pigment of the rhizome of the curcuma longa, curcumin has several physiologic effects. It is known that repeated stress increases seizure probability in epileptic patients resulting in cognitive disorders. We have been reported the effect of chronic (for fourteen consecutive days) or acute intraperitoneal administration of 20 mg/kg body weight on pentylenetetrazole (PTZ)-seizure in male rats, which were hold under restraint stress two h per day for fourteen days.

Methods: Investigating passive avoidance learning, 24 hours later, animals were tested in shuttle-box apparatus, and their step through latencies (STL) were recorded.

Results: PTZ induced seizure or exposure to the stress per se, resulted in passive avoidance learning deficit. Stress also decreased the STL of PTZ treated animals significantly ($P<0.05$). Daily chronic prescription of curcumin, regardless presence or absence of stress, significantly reduced the seizure severity and improved learning ability ($p<0.05$). However, acute application of curcumin had no any significant effect.

Conclusion: The results show that only chronic application of the curcumin can effectively inhibit resulting learning disorders under chronic stress situation.

Keywords: Seizure, pentylenetetrazole, restraint, stress, curcumin, passive avoidance learning

INTRODUCTION

Epilepsy is one of the diseases of the nervous system characterized by recurrent seizures (1). Seizures also occur in animals that are being administered with Pentylenetetrazole (PTZ). Gama-amino-butyric acid (GABA) type A receptors could be antagonized with PTZ, resulted in over activation of N-methyl-D-aspartate (NMDA) receptors in hippocampus (2). In laboratory animals, PTZ-seizure was associated with cognitive deficit (3). In humans, cognitive impairment has also been reported in more than 50% of epileptic patients (4).

Previous studies demonstrated that exposure to the unavoidable daily stresses affect the probability of epileptic seizures (5). Despite reports indicating acute stress has anti-seizure effect, it has been shown that chronic stress changes hippocampal neuronal network which is essential for epileptogenesis (6, 7).

On the other hand, daily exposure to stress could affect memory consolidation in animals and humans (8, 9). Previous studies indicated that stress and elevated serum levels of glocucorticuids initiate the cascade of events in the hippocampus and amigdala that lead to cognitive disorders in animals (10). Unlike these findings, there are reports that show under chronic stress, the ability of rats for learning in radial arm maze, and their efficiency in spatial memory consolidation will be improved (11, 12).

However, to the authors' best knowledge; very few publications are available in the literatures that discuss the simultaneous effect of chronic stress and seizure activity in cognitive functions.

Despite the availability of antiepileptic drugs, about 30% of patients with epilepsy are resistant against treatments (13). In addition, most of antiepileptic drugs have several side effects such as cognitive disorders which are report-

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ed in more than half of patients using common anti-epileptic medications (14). Considering the effect of chronic exposure to the stressful situation on the increasing probability of epileptic patient's convulsive activity, these patients also need simultaneous use of anti-epileptic and anti-stress drugs (13, 15).

In recent years, research on using medicinal phyto-antioxidants in the learning deficits associated with chronic stress has become very popular (16). Curcuma longa is an herbal plant from the family of Ginger. As the major pigment in its rhizome, curcumin (17) is one of the traditional medicines of China and India which has several anti-inflammatory, antioxidant, analgesic, anti-diabetic, anti-cancer and anti-seizure effects (18, 19). It has also been reported that curcumin reversed spatial memory deficits in rats which were held under chronic stress (16).

Evidences also showed that anti-epileptic effect of curcumin is based on its antioxidant activity (20).

These observations suggest the need to develop therapeutics to alleviate the seizure response in individuals exposed to the daily repeated stresses.

Our previous study showed that rats received chronic exposure to the restraint stress exhibited potentiated PTZ-induced seizure activity, which could be prevented by chronic (but not acute) pre-treatment with curcumin (21). Our intent was to evaluate the protective impact of curcumin on the possible effects of potentiated seizure activities related to chronic restraint stress in passive avoidance learning.

METHODS

All experimentations performed were based on the international instruction for using experimental animals, approved by Ethics committee of Kermanshah University of Medical Sciences.

All drugs prepared freshly. Curcumin obtained from Sigma Aldrich Inc., St. Louis, Mo, USA, dissolved in NaOH (0.125 N) and titrated to pH 7.4 using HCl (1 N) and diluted (0.5% Weight per volume) with normal saline (22). Pentylenetetrazole also obtained from Sigma Aldrich Inc., St. Louis, Mo, USA, and dissolved in physiological saline, as well.

The first part of our experimentation, including animal selection and induction of epileptic seizures, was performed based on the previous report (21). Briefly, five weeks old male Wistar rats (60-100g) purchased from Razi institutes (Tehran, Iran) were randomly divided into ten groups (n=10/group). First eight groups received curcumin (20mg/kg, i.p.) (Curcumin-Stress-PTZ, Curcumin-Unstressed-PTZ, Curcumin-Stress-Saline, Curcumin-Unstressed-Saline), or NaOH (2ml/kg, i.p.) (NaOH-Stress-PTZ, NaOH-Unstressed-PTZ, NaOH-Stress-Saline, and NaOH-Unstressed-Saline,) for 14 consecutive days.

To induce chronic stress, 30 minutes after daily injection of curcumin or NaOH, four groups of rats including Curcumin-Stress-PTZ, Curcumin-Stress-Saline, NaOH-Stress-PTZ, and NaOH-Stress-Saline groups were placed in standard, adaptable to animal size, plexiglas restrainer (from 9 AM to 11 AM, daily). The second four groups were handled by the investigator, except for stress exposure.

Two other groups of animals including Stress-Curcumin-PTZ, and Stress-NaOH-PTZ were placed under restraint stress for 14 consecutive days and then prescribed single dose of curcumin or NaOH.

Under controlled conditions, 30 minutes later all animals received 60 mg/kg body weight of PTZ or equal volume (2mL per kg body weight) of normal saline instead. Then all rats were quickly put in plexiglas chamber, and their seizure activities were observed for 30 minutes and scored according to Racine: stage 0, no seizure activity observed; stage 1, mouth and ear movement; stage 2, one or more myoclonic twitches of the body; stage 3, generalized myoclonic seizures; stage 4, generalized clonic convulsions and falling down; stage 5, generalized clonic-tonic seizures (GTCS) and tail up (23).

To investigate passive avoidance learning, 24 hours later, all animals were tested in shuttle-box apparatus.

This apparatus consists of two same size compartments ($20\times30\times$ 30 cm^3) which a guillotine door separated them, when opening, the rat can move freely through both compartments. One of the compartments is white (light compartment) and the other one's is black (dark compartment). Stainless-steel bars with 0.5 cm diameter was embedded in the floor of black (or dark) compartment. The distance of the bars was 1cm, through which it was possible to electrically stimulate the rat's feet using a stimulator attached to them.

Inhibitory-Avoidance Training

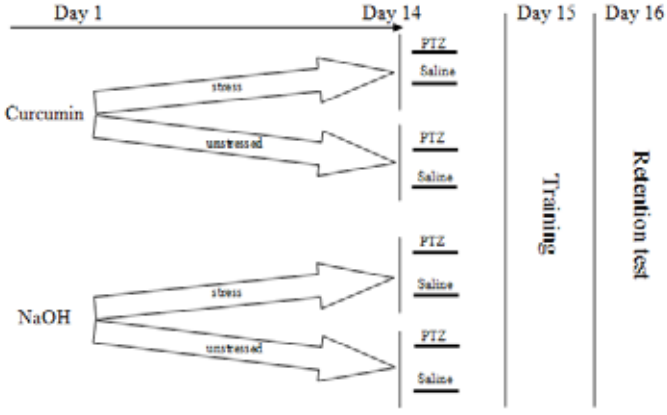
The learning ability of animals was evaluated using a step-through passive avoidance learning test (24, 25). To become familiar with laboratory environment, rats were transferred into laboratory, 1 hour before each of the sessions. All experiments were applied between 08:00 AM and 12:00 AM. Each animal was clemently put in the light chamber for 10 seconds before the door was opened. The latency of animal to enter into the shock compartment was recorded. If the latency was more than 180 seconds, the rat was omitted from the experiments (habituation trial). 30 minutes later, the animal was put in the light chamber and 10 seconds later, guillotine door was reopened. Once the rat completely passed to the next compartment the door was closed. After the 10 seconds delay, a foot shock (50 Hz, 1.5 mA and 3 s) was delivered to the bars. 10 seconds later, animal removed from the apparatus and 2 minutes later rat was tested again. If the rat stayed more than

Table 1. Classification of seizure parameters in rats of different groups after intraperitoneal administration of 60 mg/kg pentylenetetrazole or 2mL/kg NaOH

Epileptic behavior	NaOH-Unstressed-PTZ	NaOH-Stress-PTZ	Curcumin-Unstressed-PTZ	Curcumin-Stress-PTZ
Latency to myoclonic seizures onset (s)	81±4	80±9	1201±285[b]	1506±311[c]
Latency to stage 3 (s)	84±5	93±14	1217±229[d]	1522±284[e]
Duration of GTCS (s)	0.76±0.36	53.28±26[a]	0.12±0.12	0.00±0.00
No. of myoclonic seizures	27.24±9	14.27±3	3.98±1.12[f]	2.15±1.35[g]
Seizure severity score	3.77±0.26	4.01±0.22	2.14±0.37[h]	2.53±0.8[i]
% of animals who reached stage 3-5 of seizure activity	100%	100%	43%	42%

N-U-P: NaOH-Unstressed-PTZ group; N-S-P: NaOH-Stress-PTZ group; C-U-P: curcumin-unstressed-PTZ group, C-S-P: curcumin-stress-PTZ group
[a]p<0.05: NaOH-Stress-PTZ vs. NaOH-Unsteressed-PTZ, Curcumin-Unstressed-PTZ, and Curcumin-Stress-PTZ groups; [b]p<0.01: Curcumin-Unstressed-PTZ vs. NaOH-Unstressed-PTZ group; [c]p<0.001: Curcumin-Stress-PTZ vs. NaOH-Stress-PTZ group; [d]p<0.05: Curcumin-Unstressed-PTZ vs. NaOH-Unstressed-PTZ group; [e]p<0.001: Curcumin-Stress-PTZ vs. NaOH-Stress-PTZ group; [f]p<0.05: Curcumin-Unstressed-PTZ vs. NaOH-Unstressed-PTZ group; [g]p<0.05: Curcumin-Stress-PTZ vs. NaOH-Unstressed-PTZ group; [h]p<0.05: Curcumin-Unstressed-PTZ vs .NaOH-Unstressed-PTZ group; [i]p<0.05: Curcumin-Stress-PTZ vs. NaOH-Stress-PTZ group. Data are expressed as mean±SEM. ANOVA followed by Tukey's test. p<0.05 considered statistically significant.

Figure 1. Schematic of treatment paradigm



2 minutes in the white compartment, the acquisition was completed. Maximum of three trials were applied for training of each animal. If an animal still persisted to get into the dark compartment after the three applied electrical shocks, it would be excluded from the experiments.

Retention Test

24 hours later, the rat was placed in the white compartment and 10 seconds later, the door was opened. The delayed time of stepping into dark compartment is recorded as a Step Through Latency (STL). Cut off time was 300 seconds in this test. During this session electric shock was not applied. The experimental paradigm is discussed in Figure 1.

After passive avoidance learning test, animals were sacrificed by decapitation.

Statistical Analysis

Data are presented as mean±SEM. Significance of the mean of the STL was tested by the t-test or by 3-way analysis of variance (ANOVA) (Variables: curcumin, stress, and PTZ). Tukey's test was applied for multiple comparisons. P<0.05 was considered as a significant difference level.

RESULTS

All PTZ treated rats reached stage 4/5 of seizure. In addition, the duration of GTCS in rats experienced chronic stress was increased, significantly (p<0.05). Daily prescription of curcumin increased the latency to myoclinic jerks onset, and the latency to stage 3 significantly (p<0.05). On the other hand, curcumin reduced the rate of occurrence of myoclonic seizures, as well as the seizure severity score in stressed received group and the group which didn't receive any stress (p<0.05) (Table 1). Table 1 also indicated the percent of animals who reached the stage 3-5 of seizure activity.

Passive Avoidance Learning

The 3-way ANOVA for STL (Table 2) was significant for curcumin, stress, and PTZ (p<0.01). The ANOVA for STL was also significant for interaction of curcumin and stress (p<0.01). It was also significant for the interaction of curcumin and PTZ (p<0.05). But the interaction of stress and PTZ, or interaction of all 3 factors was not statistically significant.

Figure 2 indicates the STL for different experimental groups. Statistical analysis show that STL was significantly decreased (p<0.001) in the NaOH-Unstressed-PTZ group [92.5±4.33] compared to the control (NaOH-Unstressed-Saline, 209±16.93) group. On the other hand, chronic prescription of curcumin alone in Curcumin-Unstressed-Saline [208±27.4] group did

Table 2. Three-way analysis of variance

Sources of variation	Sum of squares	df	Mean square	F	p
Curcumin	103176.613	1	103176.613	28.712	<0.001
Stress	35659.012	1	35659.012	9.923	<0.01
PTZ	93639.612	1	93639.612	26.058	<0.001
Curcumin × Stress	25382.812	1	25382.812	7.063	<0.01
Curcumin × PTZ	16489.012	1	16489.012	4.689	<0.05
Stress × PTZ	2365.312	1	2365.312	0.658	0.42
Curcumin × Stress × PTZ	1369.512	1	1369.512	0.381	0.54
Error	258733.5	72	3593.521		
Total	2284467	80			

PTZ: pentylenetetrazole

Figure 2. The effects of chronic treatment with curcumin (20 mg/kg, i.p.), or its vehicle (NaOH), for fourteen consecutive days on the effects of PTZ- (or saline-)induced passive avoidance learning deficits in rats which were hold under restraint stress. Data are presented as mean±SEM.

*p<0.05, **p<0.01, a- as compared to NaOH-Unstressed-PTZ group; b- as compared to NaOH-Unstressed-Saline group; c- as compared to NaOH-Stress-PTZ group; d- as compared to NaOH-Stress-Saline group.

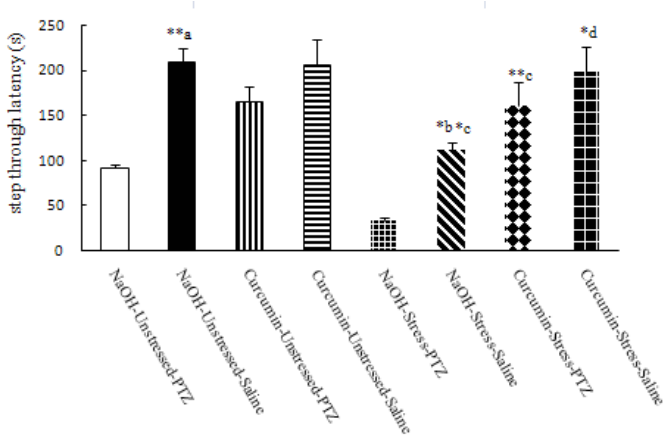
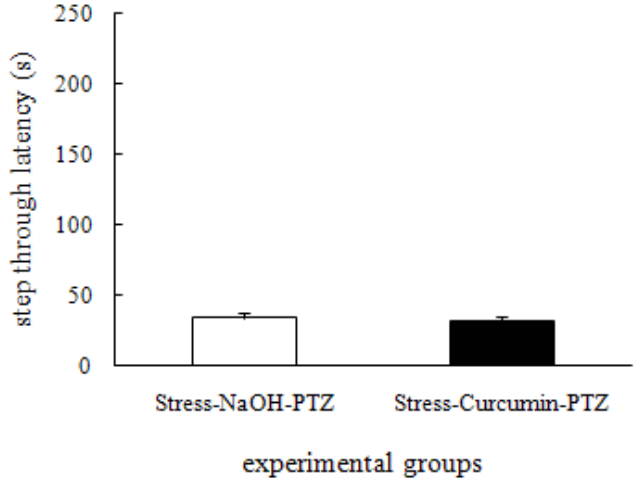


Figure 3. The effect of acute treatment with curcumin (20 mg/kg, i.p.), or its vehicle (NaOH), (30 min before exposure to PTZ) on the passive avoidance learning deficit resulted from PTZ prescription in rats which were hold under restraint stress for 14 consecutive days (2 h/day).



not affect the passive avoidance learning compared to the control group. Furthermore, it had no any significant difference between Curcumin-Unstressed-Saline and Curcumin-Unstressed-PTZ [166±16.69] group.

As it is clear in Figure 2, passive avoidance learning in the NaOH treated animals which were under chronic restraint stress (NaOH-Stress-Saline, 112±8.19) compared to the control group, indicates a significant decrease (p<0.05).

When we injected four groups of animals with daily curcumin (or NaOH) and placed them under restraint stress, following information from PTZ- (or saline-) induced changed in STL will be acquired:

PTZ prescription in NaOH-Stress-PTZ [33.8±3.02] group will worsen the passive avoidance learning disorder compared to NaOH-Stress-Saline group, significantly (p<0.05). Pretreatment with curcumin in both of PTZ received (Curcumin-Stress-PTZ, 162±26.12) (p<0.001), and normal saline received (Curcumin-Stress-Saline, 198.8±27.93) (p<0.05) groups improves the efficiency of the animals compared to NaOH-Stress-PTZ and NaOH-Stress-Saline groups, respectively (Figure 2).

In the current study we also examined the effect of acute prescription of curcumin. The results of statistical analysis didn't show any significant difference of efficiency between two groups of curcumin (Stress-Curcumin-PTZ, 32.4±2.25) and NaOH (Stress-NaOH-PTZ, 34.3±3.61) treated animals (Figure 3).

DISCUSSION

Pentylenetetrazole seizure is a well established model of epilepsy. Therefore, in current study, seizure was induced through intraperitoneal injection of 60 mg per kg body weight of PTZ. Standardized dose of PTZ which is compatible in all animals and produces minimum death in rats (26).

In animal models, myoclonic jerks and GTCS could reliably induced at PN 18 and were not changes significantly till PN 60 (27). Therefore, we conducted our experiments at PN 35 to PN 60.

As our previous report, we found that PTZ injection induces seizure activity, and destructs passive avoidance learning in rats. Previous studies indicated that PTZ seizure associated with decreased numbers of $GABA_A$ receptors, amplified glutamate release, resulted in overactivation of NMDA receptors in hippocampus, and memory performance deficit (21, 28-30).

Current study assayed the effect of curcumin in cognitive deficit resulted from PTZ-seizure. Curcumin is a safe, therapeutic, and protective traditional medicine in the treatment of numerous pathologic disorders such as cognitive deficits (31, 32). Different doses of curcumin ranged from 10 to 300 mg per kg body weight have been used in some studies (33, 34). On the other hand, it has been reported that oral daily administration of 5-8 g/kg body weight of curcumin for 3 months in rats or in human has no apparent toxicity (35, 36). Our results showed that chronic curcumin prescription did not indicate any significant effect on the passive avoidance learning of rats. This result is consistent with other studies which have shown that chronic oral (10 mg/kg), (100 mg/kg), (300 mg/kg), or intraperitoneal (5 or 15 mg/kg) prescription of curcumin didn't have any significant effect on the learning ability, but injection of high dose of curcumin (45 mg/kg, I.P.) improved the passive avoidance learning of animals (37-40).

Our result also showed that chronic curcumin pre-treatment, attenuated the elevated seizure severity, and protected animals from passive avoidance learning deficit induced by PTZ. This effect of curcumin has been reported in studies indicated that chronic prescription of curcumin had protective effect against the NMDA induced cell death in hippocampus, and protected passive avoidance learning, and spatial memory disorders resulted from chronic prescription of PTZ in laboratory animals (21, 34, 38, 41).

Memory is also affected by unavoidable daily stress. In this work and in related reference rats were subjected to chronic restraint stresses, the animal model of stress which may be similar to the psychosocial stress in daily life of humans. It has been reported that chronic exposure to the stressors like restraint, swimming in cold water and electrical shock stresses induced cognitive disorders in animals (16, 33). These reports are in accordance with our results show that chronic exposure to the stressful situation destructs passive avoidance learning in rats.

We also studied the effect of exposure to the PTZ-seizure on cognitive function in stressed animals, and found that PTZ significantly impaired passive avoidance memory in stressed rats. To our knowledge, the neuronal mechanisms responsible for seizure-induced disruption of cognition resulted from chronic exposure to restraint stress are not fully understood. One of the possible mechanisms is related to structure of hippocampus. This part of the brain is one of the most important brain structures related to cognitive function. In contrast to some reports in the literature indicating anticonvolsant effects of stress, prolonged exposure to the stress elevated serum glucocorticoids (G), decreased GReceptor (GR) mRNA levels resulted in oxidative damage to brain regions, specially the hippocampus (6, 16, 42). On the other hand, oxidative stress implicated in epilepsy and increased seizure severity that predisposed future cognitive impairment (43-45).

This paper proposes that, in an animal model, pre-treatment with curcumin can reverse both stress induced learning deficits, and PTZ-induced impaired cognition related to chronic stress. In the last years there has been a growing interest in the mechanisms of the protective effect of curcumin in learning disorders. Curcimin has potent antioxidant, and neuroprotective properties (46, 47). Previous studies indicated that pre-treatment with curcumin significantly attenuated neuronal death resulted from kainic acid in hipocampal CA1 and CA3 areas via the oxidative stress pathway, increased hippocampal neurogenesis, normalized blood serum corticosterone levels, and improved performance deficits in the shuttle box apparatus in stressed animals (33, 48, 49). Moreover, the protective effect of curcumin against NMDA-induced excitotoxicity was also investigated (31). Therefore, curcumin has protective effect in cognitive disorders related to both seizure and chronic stress.

We also examined the acute effect of prescription of curcumin on cognitive function, after exposure to chronic stress, but 30 minutes before PTZ administration in rats, to explore its protective effect observed in our experiments is time-dependent. The results showed that acute curcumin could not protect animals from destructive effect of seizure in passive avoidance learning. The data obtained are in good agreement with other studies which have shown the effect of chronic, but not acute, prescription of curcumin on improving disorders of cognitive function resulted from restraint stress, stress of swimming in cold water, and shock stress (16, 33, 37).

Although our results suggest that curcumin has protective effect against learning deficit associated with both PTZ-seizure and chronic restraint stress, more studies on the histopathology of specific brain areas and estimation of curcumin blood levels during chronic treatment is necessary.

Briefly, we found that only chronic administration of curcumin is effective in inhibiting seizure-induced learning disorders

under chronic stress situation. These observations may be applied clinically for preventing cognitive disorders in patients with epilepsy under daily stressful conditions. However, determining reasons and mechanisms involved in this phenomenon requires further studies.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of The Kermanshah University of Medical Sciences (KUMS.rec.1394.382).

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Conflict of Interest: Authors have no conflicts of interest to declare.

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