Research Article
ISSN: 0974-6943

Dr. Anjana Munshi et al. / Journal of Pharmacy Research 2011,4(1),11-14

Available online through

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Protective Effect of Curcumin in behavioral impairment induced by Pentylenetetrazol in rats

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Received on: 15-09-2010; Revised on: 18-11-2010; Accepted on:13-12-2010

ABSTRACT

Hyperexcitability of brain neurons due to repetitive firing may initiate a complex pattern of neurophysiologiocal changes associated with cognitive impairment in epilepsy. In the present study, we evaluated the effect of curcumin in cognitive impairment and behavioral manifestations induced by Pentylenetetrazol (PTZ) in rats. PTZ was repeatedly injected on alternate days in a subconvulsive dose of 40mg/kg i.p of rats for a period of 30 days. We used Piperine orally as an bioavailability enhancer of curcumin. Carbamazepine (CBZ), a promising anticonvulsant was also used in the study to compare the anticonvulsant efficacy of curcumin.The seizure responses and mortality rate were observed in rats and behavioral activities were analyzed using active avoidance, passive avoidance and behavior despair test after administration of PTZ during the treatment period. The chronic administration of PTZ caused alterations in brain functions characterized by seizures and behavioral impairments. Curcumin treatment reduced the seizures, mortality rate and improved the learning and memory in a significant manner. The treatment with antiepileptic drug CBZ showed a marked reduction in seizure activity, mortality rate and memory impairment. A combined treatment of CBZ and curcumin significantly reduced the seizure scoring at all intervals and was found to revert the behavioral manifestations induced by PTZ. The present study clearly indicates that curcumin not only modulates the seizures but also improves the memory and learning ability by exerting its neuroprotective effect against PTZ induced kindling in rats.

Key words: Curcumin, Epilepsy, Kindling, Behavioral manifestations, Carbamazepine, Pentylenetetrazol.

INTRODUCTION

Epilepsy is a chronic neurological disorder characterized by sudden, recurrent and unpredictable episodes of seizures accompanied with behavioral manifestations and memory disturbances[1]. The comorbid factors associated with epilepsy are cognitive impairment such as psychosis, anxiety, personality disorders, depression and suicidal attempts[2-4].

A number of pharmacological agents of synthetic and plant origin have been used for the treatment of epileptic seizures. These include antiepileptic drugs (AED's) such as phenytoin, carbamazepine, and diazepam and some herbal medicines (Xiaoyao-san and Jieyu-wan of Chinese origin) [5]. CBZ is an important first line anticonvulsant drug used in the treatment of partial seizures and generalized seizures[6].

Despite the availability of a number of AED's, the current treatment in epilepsy is not satisfactory in terms of drug associated toxic effects and cognitive impairment[6,7]. Moreover, the chronic epileptic patients require prolong treatment period accompanied with undesirable side effects and impaired psychomotor functioning and cognitive deficits, associated with antiepileptic drugs, which are of major concern[7, 8].

Seizure induced memory impairment and behavioral deficits in chronic epilepsy can be best studied by using a widely accepted model of kindling [9-12]. Kindling is induced by repeated application of electrical and chemical stimulus using PTZ, cocaine, picrotoxin, strychnine, and bicuculline once in every 24 to 48 hrs, in subconvulsive doses which results in progressive intensification of seizure activity leading to impaired functions of brain[9]. Beekman and coworkers, (1998) have reported, a series of changes involving seizure manifestation, reduced locomotor activity and induced depression in mice model of PTZ[13,14]. The learning deficit induced by PTZ has also been explained by Becker and others[15]. The convulsive effect of PTZ is mediated via specific interaction with neurotransmitter gamma amino butyric acid (GABA) as it inhibits the release of GABA[11]. The neurotransmitter GABA plays a major role in inhibiting the excessive firing of brain neurons in epilepsy and thus abolishes the seizures and behavioral changes.

The continuous seizure stimulus due to repetitive firing of brain neurons can also result into changes in certain structural modifications in synapses and neural plasticity leading to behavioral changes in epilepsy[16]. Hippocampus and frontal cortex are brain regions, exclusively involved in memory, learning processes and behavioral activities[16,17]. The disturbed status of neurotransmitters such as GABA, glutamate, norepinephrine and serotonin, nitric oxide have been implicated in neurophysiological changes associated with cognitive impairment in epileptic seizures[17,18] . Recently a number of flavonoids and polyphenolic compounds of herbal origin such as curcumin and other antioxidants have been found to be neuroprotective in in-vitro models of Alzhemier's and Parkinson's disease[19-21] . Various herbal drugs and homeopathic treatment are widely and favorably used in epileptic patients as well; for instance, Xiaoyao-san and Jieyu-wan herbal medicines consisting curcumin as one of the components were used to treat the mental stress and mania in China[5].

Curcumin is an active constituent of *Curcuma Longa (Turmeric)* of plant origin. The Indian traditional medicinal system has described the use of turmeric powder for therapeutic purposes in various disorders, and it is a common spice used as food additive in India[21]. Curcumin (diferuloylmethne) exhibits a wide spectrum of pharmacological activities such as antioxidant, anti-inflammatory, hepatoprotective and above all neuroprotective[22].

Curcumin reversed the behavioral manifestations and oxidative damage in seizures induced by kianic acid in rats[23]. The protective effect of curcumin has been studied in maximal electroshock induced seizures and memory impairment in rat brain[24]. The memory retentive effect of curcumin has been significantly proved in generalized tonic clonic seizures in mice model[24]. Curcumin being a potent free radical scavenger has been shown to reduce oxidative injury to neurons in various neurological disorders such as in Parkinson and Alzheimer pathology[19, 20, 22, 23]. The neuroprotective activity of curcumin was observed during ethanol induced brain injuries and lead induced neurotoxicity[25].

Keeping in view the above research findings, the present study was designed to evaluate the effect of curcumin on memory retention and behavioral manifestations in chronic convulsions induced by Pentylenetetrazol. The various Pharmacokinetic studies have documented the poor oral bioavailability of curcumin, therefore we used piperine (a constituent of black pepper) along with curcumin

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because piperine enhances the bioavailability of curcumin up to 20 fold without interfering in curcumin's therapeutic efficacy[26, 27].

MATERIALS AND METHODS

Healthy male Wistar rats were procured from the central animal house of Panjab University, Chandigarh. The study was approved by Institutional Animal Ethical Committee. The animals were 6 months old and their body weight was in the range 150-200 gm. They were acclimatized under hygienic conditions and were fed on standard pelleted rat feed (Hindustan Lever Ltd, Mumbai, India) and water ad-libitum. The diet had adequate quantity of micronutrients as well as macronutrients. The animals were divided into five Groups.

Group-I served as control and was injected with Normal saline i.p (0.9% i.p). In Group-II PTZ was injected i.p on alternate days.. Group III received PTZ (40 mg/kg of body weight of rat) injected on alternate days and antiepileptic drug CBZ in a dose of 3.6mg/kg b.w. daily for a period of 30 days. Group IV received PTZ along with Curcumin (2gm/kg) and piperine (20mg/kg) of b.w. daily for a period of 30 days. Group V received conjunctive treatment of Curcumin, and CBZ (3.6mg/kg of b.w.) along with PTZ. All reagents were purchased from Sigma Chemicals, St Louis, USA. Curcumin and Piperine were purchased from Synthite Chemicals Co. Kerala. CBZ from Novartis pharmaceuticals ltd.

Chemical Kindling

Pentylenetetrazol (PTZ) was given in a subconvulsive dose of 40mg/kg of body weight (b.w) Intraperitoneal (i.p.) injections on alternate days for a total of 30 days [28]. After each injection, Central Nervous System (CNS) excitation was observed over 15minutes by observing rats in a plexiglass chamber. Behavioral changes such as seizures, head nodding, jerking movements and increased urination and defecation were observed. The mortality rate was also observed.

Seizure scoring

The seizure responses were observed in freely moving rats after repeated subconvulsive doses of PTZ. The seizure event was observed during a 20 min stimulation period after each dose. Seizure intensity and frequency was recorded by using prevalidated method of seizure scoring. The seizure intensity in all experimental animals was scored as:

Stage/score 0 – No response
Score 1 – ear and facial twitching
Score 2 – convulsive twitching axially through the body
Score 3 – myoclonic jerks and rearing
Score 4 – turn over onto the side position, wild running, circling
Score 5 – generalized tonic clonic seizures

Behavioral Studies

Active Avoidance Test

The apparatus used for this test consists of two chambers separated by a partition. One chamber was enlightened compartment. The animal was subjected after a period of 30 sec, first to a light and then to sound stimulus (buzzer) for 10s each in a total trial period of 1 min. After 10 sec the buzzer was set on, if animal remained in the same compartment, it means the animal had avoided the test. But if the animal jumped to the other compartment after shock or did not jump, was termed as the escapism. A total of ten trials were given to every animal. The animals were trained first and then avoidance test was repeated administering the test drug. To qualify the animal has to avoid at least 8 times out of 10 trials.

Passive Avoidance test

Passive avoidance test is a screening method used to evaluate the effect of drugs on memory and learning. The apparatus for this test consists of two chambers separated by a gulliotine door which is easily movable in either direction. One chamber was enlightened. The dark chamber had grid floor through which the electric shock is conducted on connecting to source of current.

Rat was placed in lighted chamber and trained to enter into the dark chamber. As the animal entered into dark chamber, the shutter was closed and a foot shock of 2mA to 5mA for 2 sec was given. Time taken by the rat to enter the closed chamber from the open light camber was noted, which was termed as acquisition trial time. Then the animal was taken out through the second open chamber. After 24hrs again the experiment was repeated with animals using test drug. The time taken by the animal to enter the enclosed chamber was taken as retention trial time. Using passive avoidance test it was observed whether the test drug retains the memory or abolishes it. A cut off time of 300seconds was considered positive retention of recent memory.

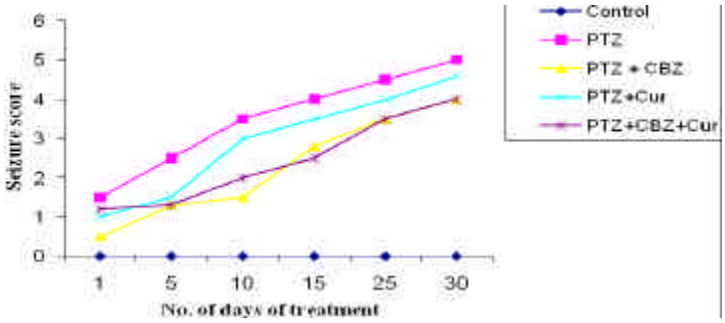

Fig-1 Seizure Scoring in rats during Treatment period

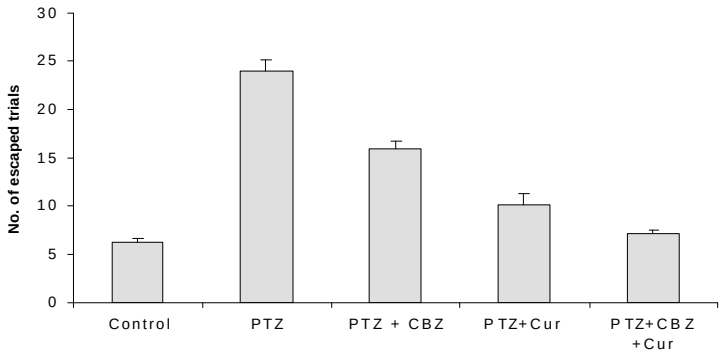

Fig-2 Active Avoidance test of Control and Treated rats

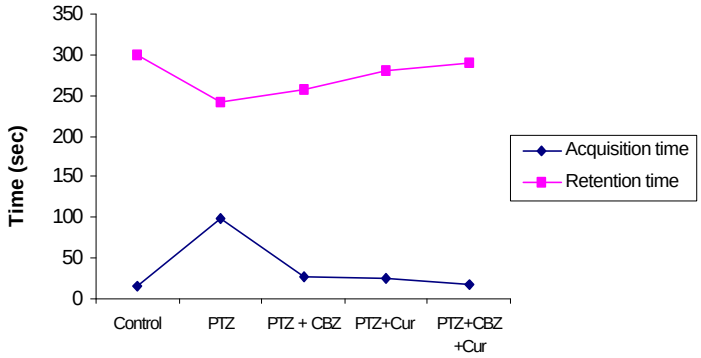

Fig- 3 Passive Avoidance test of Control and treated rats

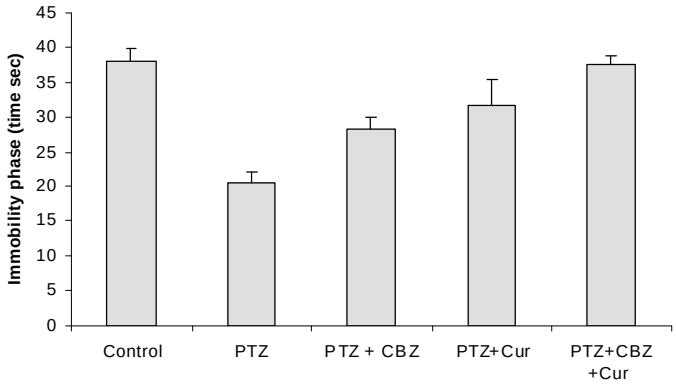

Fig- 4 Behavior Despair test of Control and treated rats

Behavior Despair Test

Behavioral despair test is used for studying the psychomotor dysfunction and elevation of drugs acting on CNS. In this test, despair was induced by forcing the animal to swim in water individually inside the vertical glass cylinder (ht 40cm, diameter 18cm) containing 15cm of water at 25^{i}C. After 15min swimming in the water, they were removed to individual cages. 24hrs later, after drug treatment the animals were replaced in cylinder. Immobility was judged during the last 4min of a 6min period of observation. The rat was judged immobile when it remained floating passively in water in a rightly upright position with its head just above the surface. The tail of the animal should not touch the bottom of the glass cylinder. A rat was considered to be immobile if it did not struggle and made minimal movement with limbs to keep its head above the water level.

Statistical analysis

The data was expressed as mean ± S.D and was analyzed using Student t-test. The value $p<0.05$ was considered as significant. All the values were expressed as mean ± SEM.

RESULTS

Behavioral deficits and impairment in learning and memory was observed after PTZ administration for prolong period of 30 days. Other convulsive activities such as jerking movements and tonic clonic seizures were measured by seizure scoring (Fig 1). In the present study, PTZ administered Group II showed marked increase in the intensity of seizures as compared to control or vehicle treated rats Group I ($p<0.01$). The seizure responses were observed in freely moving rats after repeated subconvulsive doses of PTZ. The treatment with CBZ showed significant reduction in seizure activity as compared to Group II ($p<0.001$). Curcumin treatment in Group IV showed the reduction in seizure scoring as compared to Group II rats during all the time intervals ($p<0.05$) (Fig 1). Conjunctive treatment of CBZ along with curcumin significantly reduced the seizure intensity and scoring at all intervals and was found to be effective as compared to CBZ treatment (Group III) and Curcumin (IV) treatment respectively ($p<0.05$), ($p<0.01$).

PTZ treated Group showed a maximum mortality rate of 60% on last day of the treatment. Where as significant reduction in mortality rate was observed in CBZ treated Group III and curcumin in Group IV ($p<0.001$, $p<0.01$). Group IV rats showed significant improvement in body weight and brain weight ($p<0.05$). Combined treatment with CBZ and curcumin proved to be effective as only 30% death rate and improved body weight and brain weight ($p<0.01$) was observed.

A significant increase in number of escaped trials was recorded in Group-II as compared to Group I ($p<0.001$) (Fig 2). CBZ treatment in Group III rats showed a significant reduction in number of trials escaped as compared to Group II ($p<0.001$). Curcumin treatment in Group IV showed significant reduction in number of escaped trials as compared to Group II ($p<0.001$). However, a significant reduction in the number of escaped trials was noticed in GroupV rats as compared to Group III and Group IV ($p<0.001$, $p<0.05$ respectively) (Fig 2).

Similarly, the animals exposed to PTZ kindling showed significant impairment in short term memory as compared to control animals in passive avoidance test ($p<0.01$) (Fig 3). Treatment with CBZ (Group III) showed improvement in memory as compared to Group I ($p<0.05$). Treatment with curcumin resulted into reduction in acquisition time and increased retention time as compared to Group-II ($P<0.01$) and Group I ($p<0.01$). A combined treatment of curcumin and CBZ significantly increased the retention time and improved the memory in GroupV as compared to other treatments ($p<0.001$, $p<0.01$ respectively) (Fig 3).

Recording of immobile phase in behavior despair test in Group-II rats showed decreased depression time as compared to control Group ($p<0.001$) (Fig 4). Curcumin treatment in Group-IV improved the immobility significantly as compared to Group II and Group I ($p<0.01$, $p<0.001$ respectively). CBZ treated animals showed improvement in memory and learning significantly as compared to control Group of Group I ($p<0.05$). A combined treatment of curcumin and CBZ increased the depression time significantly as compared to other treatment Groups ($p<0.001$) (Fig 4). Group II rats also showed marked reduction in body weight and brain weight as compared to Group I rats ($p<0.001$). Treatment with CBZ improved the reduced body weight by decreasing the seizure severity and mortality as compared to Group II rats ($p<0.05$).

DISCUSSION

Cognitive impairment, behavioral manifestations and dementia are inevitable changes associated with epilepsy [2,9]. The current anticonvulsant therapy is not quite effective because antiepileptic drugs only manage the seizures/convulsions and are unable to reverse the neurodegenerative changes associated with epilepsy. It has been also reported that neurophysiological impairment is one of the important comorbid factor of chronic epilepsy[4-6, 8].

PTZ induced kindling has been used as an experimental model of epilepsy in various pharmacological studies. The convulsant activity of PTZ was reported by Goddard (1967) and Hildebrant as early as in 1926 and was successfully used as a model of kindling [29,30].In present study, a progressive increase in seizure score was observed in PTZ treated rats of Group II as compared to control rats of Group I. On 30th day, a maximum mortality rate of 60% was recorded. Our results are in parallel with International League against Epilepsy (ILAE), which suggests generalized seizure induced death in most of the animals after PTZ administration. Experimental evidences suggest that PTZ binds to gaba amino butyric acid (GABA) receptors thus inhibiting the release of neurotransmitter GABA[31]. The blockage of GABA, an inhibitory neurotransmitter may be one of reasons for excessive seizures after PTZ administration.

In Group III, CBZ administration reduced seizure frequency and the seizure intensity as observed from the seizure scoring which was significantly lower at various time intervals as compared to Group II rats. A decreased mortality rate of 40% was recorded, suggesting that CBZ is an effective anticonvulsant against PTZ. The antiepileptic drug CBZ acts by blocking repetitive firing of brain neurons in epilepsy[32]. Therefore the antiepileptic or antiseizure effect of CBZ is responsible for counteracting the effect of chemoconvulsant PTZ.

Curcumin treatment in Group IV not only suppressed the kindling, but also reduced mortality rate and modulated the seizure score in epileptic rats. However, treatment with curcumin reduced the seizure scoring significantly in early days of treatment but after prolonged exposure of 30 days, with PTZ the modulatory effects were seen as curcumin might have tried to combat the neuronal stress and toxicity induced by PTZ. The mortality rate also decreased to 30%. Similarly Peng et al., (2009), demonstrated that curcumin, proved to be as a potent antiepileptic agent in amygdaloid kindled rats and may retard the epileptogenesis induced by kindling[33]. It has been reported that curcumin treatment in a dose of 5-10mg/kg significantly reduced the maximal electroshock induced tonic clonic seizures in rat[24]**.** The precise mechanism of action of curcumin is still unclear but experimental and neuropharmacological studies have suggested a number of mechanisms.

In Group V the concomitant administration of curcumin and CBZ showed reduction in the seizure scoring at all intervals. This might be due to anticonvulsant and stabilizing effect of CBZ on hyperexcited brain neurons.

Impairment in memory and learning functions was observed after PTZ administration in rats for a chronic period of 30 days in group II animals. Epileptic rats of Group II exhibited a significant decrease in learning and memory as compared to control rats ($p<0.001$) as observed in active and passive avoidance test. The behavioral manifestations and learning and memory deficit induced by PTZ are in alignment with previous studies[23, 34, 35]. CBZ treatment in Group III reduced the learning and memory impairment. This could be attributed to the proved antiepileptic effect of CBZ. A significant improvement in memory and retention was observed in Group IV rats treated with curcumin as compared to epileptic rats ($p<0.001$). Similarly memory retentive properties of curcumin in as generalized seizures were reported previously [21].

In the present study curcumin and CBZ was found to improve the short term memory and learning deficit induced by PTZ in rats. PTZ administered rats in Group II showed a significant decrease in immobility phase as compared to normal rats of Group 1 animals as observed in forced swim test.

Curcumin treatment improved the behavior of kindled rats when given alone and in combination of CBZ, as observed in forced swim test. A combined treatment of curcumin and CBZ showed improvement in learning, memory and depression time as compared to other treatments in Group V.

It might be on account of curcumin crossing the blood-brain barrier to the blood–brain barrier to produce its neuroprotection directly [36].

CONCLUSION

In conclusion curcumin reduced the seizures and mortality in epileptic rats and also improved memory and learning. Curcumin administered along with piperine proved beneficial as it enhanced the bioavailability of curcumin and also potentiated the efficacy of curcumin. Therefore the present study indicates that the

potent antioxidant curcumin can be added as an adjuvant to anticonvulsant therapeutic agents.

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Source of support: Nil, Conflict of interest: None Declared