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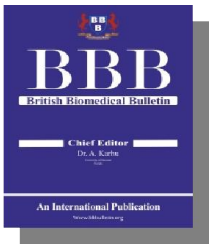

Original

Neuroprotective Effect of Lacosamide and Pregabalin on Pentylenetetrazole Induced Seizure Models in Rat

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A B S T R A C T

There has been a growing interest in the use of antiepileptic drugs (AEDs) for neuroprotection, and in the possible role of AEDs in disease modification (i.e., antiepileptogenesis). Increased understanding of the mechanisms underlying brain injury has led to advances in the study of neuroprotection. However, defining the clinical paradigm and selecting appropriate outcomes to detect neuroprotective effects present challenges to clinicians studying the neuroprotective properties of drugs. Established AEDs, such as phenytoin, phenobarbital, and carbamazepine, have shown neuroprotective activity in an ischemic/hypoxic model of neuronal injury. Animal model studies also have suggested that newer AEDs, such as levetiracetam, topiramate, and zonisamide, may have neuroprotective or antiepileptogenic properties. However, the prevention of epileptogenesis by an AED has yet to be demonstrated in clinical trials. The future of neuroprotection may involve established and newer AEDs, as well as other compounds, such as immunophilins, caspase inhibitors, endocannabinoids, and antioxidants.

Introduction

Epilepsy is one of the most common serious social disorder of the brain, affecting about 50 million people worldwide and it accounts for 1% of the global burden of the disease in which 80% of burden of the epilepsy is in the developing world[1]. Neurodegeneration is the umbrella term for the progressive loss of structure or function of neurons, including death of neurons. Lacosamide is a functionalized amino acid with a novel anticonvulsant property used in the treatment of seizure disorders in combination with other anticonvulsants. This study was designed to expound the neuroprotective effect of Pregabaline and Lacosamide against Pentylenetetrazole Induced seizure models in rat.

The mechanism of action of several antiepileptic drugs is based on their ability to modulate the activity of voltage-gated sodium current that are responsible for fast action potential generation. Recent studies have analysed that lacosamide shares similar mechanism as an analgesic and anticonvulsant in comparison with other antiepileptic drugs lacosamide has the unique ability to with sodium channel slow inactivation without affecting fast inactivation. Pregabaline is an anti convulsant structurally related to the inhibitory CNS neurotransmitter GABA also possess analgesic activity.it is used in the management of partial onset seizures in combination with other anticonvulsants.it is used in the management of post herpetic neuralgia, pain associated with diabetic peripheral neuropathy, fibromyalgia. Pregabalin acts through auxillary subunit of voltage gated calcium channels. It bind to alpha2 delta site which causes the modulation of channel function and their by results reduce the calcium dependent release of several neurotransmitters[2].

Materials and Methods

The drugs and chemicals used in this study include Pregabalin besylate, Lacosamide isothiocyanate, Pentylenetetrazole. Experimental animals include male wistar albino rats (150-200 g) were used for the evaluation of the neuroprotective activity. The animals were obtained from Government agricultural university, Mannuthy, Thrissur, Kerala. All animals were housed for at least one week in the laboratory animal room prior to study. The selected animals were housed in polypropylene cages in the standard environmental conditions (20-25°C), 12:12 light: dark cycle, fed with standard rodent diet and water *ad libitum*. The experiments on animals were conducted in accordance with the international accepted principle for laboratory animal use and the experimental protocols duly approved (KMCRET/ MPharm/4109) by the institutional animal ethical committee (IAEC) of KMCH College of Pharmacy, Coimbatore-48.

Experimental Design

The results of the study were expressed as mean±S.E. Data was analyzed by using one way ANOVA followed by Turkey Kramer test post t-test for multiple Comparisons[3].

Induction of seizure by Pentylenetetrazole method[4,5]

Pentylenetetrazole(PTZ) Induced Seizure in Rats

A total of 30 male rats was used in this experiment. The rats was divided into six groups (n=5) and injected intraperitoneally (i.p) with PTZ at the dose of 105 mg/kg.The test drug was administered intraperitoneally (i.p)10 min prior to the PTZ treatment. The animals were observed for the development of Seizure (38).

Experimental design

Group I - Normal saline (5ml/kg)
Group II - Vehicle+PTZ (105mg/kg)
Group III - PGB+PTZ (15mg/kg).
Group IV - PGB+PTZ (30mg/kg).
Group V - LCM+PTZ (15mg/kg)
Group VI - LCM+PTZ (30mg/kg)

Pentylenetetrazole was administered on alternative days for a period of 15 days. After injection of PTZ occurance of central nervous system (CNS) excitation was noted for 10-15 minutes. The intensity of behavioural seizure was evaluated as follows.

No seizure: 0
Jerks : 1
Straub tail : 2
Clonic convulsions : 3

Treatment was done on alternative days upto 15 days. Behaviouarl assessment was done on 5th, 10th, and 15th day after the treatment schedule. On 16th day animals was sacrificed and the brains and other vital organ was removed for carrying out various biochemical estimations.

Results

See table 1&2.

Discussion

The present study was designed to evaluate the neuroprotective effect of antiepileptics pregabalin and lacosamide against Pentylenetetrazole induced Seizure models in male albino rats. From the results of this research work it was observed that neuroprotective effect of Lacosamide and Pregabalin found to be prominent and attractive. The level of SOD (***P<0.001), Catalase (CAT) (***P<0.001), Nitrites (***P<0.001), Reduced glutathione level (GSH) (***P<0.001) and Protein (***P<0.001) in whole brain tissue was decreased in Pentylenetetrazole treated groups when compared with control groups. And all the effects were significantly enhanced by Pregabalin (15, 30 mg/kg i.p) and Lacosamide (15, 30 mg/kg i.p) in alternative days for up to 15 days[6,7].

The treatment of Pentylenetetrazole (105mg/kg) on alternative days in animals induces oxidative stress which was confirmed by a significant rise in the LPO level in whole brain (***P<0.001). Following treatment with Pregabalin (15, 30 mg/kg i.p) and Lacosamide (15, 30 mg/kg i.p) showed an attenuated increased LPO level in animal. The myeloperoxidase level was significantly higher in Pentylenetetrazole treated groups when compared with control groups and it was significantly reduced dose depend manner (***P<0.001) by Pregabalin (15, 30 mg/kg i.p) and Lacosamide (15, 30 mg/kg i.p) for up to 15 days. In short, the results of this study reaches to a conclusion that Pregabalin and Lacosamide treatment showed the relevant effect for the enzyme changes due to seizure induction and this treatment significantly altered the elevated/decreased the levels of various antioxidant enzymes.[8,9]

Conclusion

In The concept of neuroprotective intervention is attractive, but it has become increasingly apparent that detection and assessment of neuroprotection in 'complex systems' of brain presents significant challenges in the laboratory and at the bedside[10,11]. The presented data from our study indicates that Pentylenetetrazole treatment to animals resulted the Impair antioxidative defence mechanism.

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Table 1. Effect of lacosamide and pregabalin on brain antioxidants on Pentylenetetrazole induced seizure method

Groups	Dose (mg/kg i.p)	SOD (u/mg protein)	Catalase (µmol/mg)	Nitrite (µg /ml)
Control	Vehicle (5ml/kg)	7.58 ±0.0153	46.0 ±0.0060	472 ±0.333
Vehicle+PTZ	105	3.8 ±0.0684***	22.25 ±0.371***	586 ±1.203***
PTZ + PGB	15	5.6 ±0.0060***	31.59 ±0.0153***	431 ±0.3333***
PTZ + PGB	30	5.253 ±0.0071***	37.0 ±0.0***	398 ±0.333***
PTZ+ LCM	15	6.70 ±0.00613***	38.103 ±0.0135***	426 ±0.5773***
PTZ+ LCM	30	6.07 ±0.0033***	39.531 ±0.008ns	401 ±0.333***

***P<0.001, **P<0.01,*P<0.05, ns-non-significant, statistics one way ANOVA followed by dunnet t' test

Table 2. Effect of lacosamide and pregabalin on brain antioxidants on Pentylenetetrazole induced seizure method

Groups	Dose (mg/kg i.p)	Lipid peroxidise (nm of MDA/mg of protein)	Reduced glutathione (glutathione µg/mg protein)	Myelo peroxidase (% control)	Protein estimation (µg /10mg of tissue)
Control	Vehicle (5ml/kg)	2.16 ±0.0736	13.17 ±0.2603***	114 ±0.333	7.39 ±0.0033
Vehicle+PTZ	105	5.06 ±0.1843***	10.14 ±0.0318***	253 ±0.3333***	3.16 ±0.145***
PTZ +PGB	15	3.14 ±0.09043***	11.98 ±0.00333***	143 ±0.6673***	4.52 ±0.0088***
PTZ +PGB	30	4.25 ±0.03813***	12.56 ±0.01153***	141 ±0.333***	4.82 ±0.0057***
PTZ+LCM	15	3.06 ±0.07863***	12.79 ±0.008823***	155 ±0.3333***	6.58 ±0.0636***
PTZ +LCM	30	3.28 ±0.02333***	12.75 ±0.00333***	149 ±0.66***	6.64 ±0.034***

***P<0.001, **P<0.01,*P<0.05, ns-non significant,statistics one way ANOVA followed by dunnet t' test