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ISRADIPINE ENHANCES THE ANTICONVULSANT ACTIVITY OF CARBAMAZEPINE AGAINST MES AND PTZ INDUCED CONVULSIONS IN RATS

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ABSTRACT: The aim of this study was to investigate the possible anticonvulsant effect of a Dihydropyridine calcium antagonist, Isradipine, which easily crosses the blood–brain barrier displaying high affinity and specificity for the brain L-type voltage-sensitive calcium channel, on maximal electroshock seizures and PTZ induced seizures. The seizures were induced in rats by maximum electroshock method and chemically by pentylenetetrazole (PTZ). Isradipine delayed the onset of action and time of death to 213.21 ± 32.46 seconds and 952.85 ± 9.81 seconds respectively when compared with control in PTZ induces seizures model. The present study indicates that Isradipine showed significant anticonvulsant effect against maximal electroshock and PTZ induced convulsion in rats.

INTRODUCTION: Epilepsy is one of the most common neurologic disorders encountered in clinical practice, affecting approximately 2 to 4 million people in the United States or 1 in 50 children and 1 in 100 adults. Epilepsy is a chronic disease experienced by millions and a cause of substantial morbidity and mortality[1]. Voltage-gated calcium channels are key elements in regulating neuronal excitability and arethus of central importance in the pathogenesis of various forms of epilepsies. The pathophysiology of epileptic seizures is complex, but calcium ions (Ca^{2+}) are likely to play a significant role in this regard[2]. It is well documented that increased intracellular Ca^{2+} level or enhanced Ca^{2+}conductance can be observed during epileptic activity.

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High intracellular Ca^{2+} level may be one of the main factors responsible for neuronal death in status epilepticus. Consequently, animals injected with Ca^{2+} channel opener, Bay k-8644, develop clonic and tonic convulsions[3, 4].

Thus, compounds inhibiting Ca influx would be considered useful for control of seizures. In fact, calcium channel inhibitors were effective in various experimental models of epilepsy[5]. They were demonstrated to possess the anticonvulsant activity against pentylenetetrazole-induced seizures and electro convulsions. Not all the calcium channel blockers show the same kind of effect, but only few. Calcium channel inhibitors enhanced the protective activity of certain anti epileptics against electroshock-and pentylenetetrazol - induced seizures. Isradipine belongs to the 1, 4-dihydropyridine class of calcium channel antagonists and has a unique neuroprotective profile that distinguishes it from other agents of this class. Considering the above data, we decided to examine whether Isradipine, can influence the

protective activity of antiepileptic drugs to a higher extent against electro convulsions and chemically induced convulsions.

MATERIALS AND METHODS:

General

The experiments were performed on male Swiss rats weighing 250-300gm, after institutional animal ethical committee approval. The animals were kept under standard laboratory conditions on a natural light dark cycle, with free access to food - chow pellets and taps water.

Maximal electroshock induced convulsion:

The animals were grouped containing six in each and labeled I-IV. MES stimulation can be applied through trans corneal electrodes from an electroshock apparatus at intensity sufficient to elicit tonic hind limb extension (HLE) in 100% of the control animals. The animals were given electroshock of 110 mA for 0.2 sec to the cornea by using electro convulsometer [6, 7].

The test will be considered positive if the animal exhibits tonic extensor seizure with rearward HLE more than 90 degrees from the body and sustained for more than 3 s following 10 s after stimulation. Group I served as control. Group II, III & IV were treated with carbamazepine (30mg/kg; ip), Isradipine (2mg/kg; ip) and carbamazepine + Isradipine respectively half an hour before the maximal electroshock. The various phases of maximal electroshock induced convulsion for each animal were noted.

Pentylenetetrazole Induced Convulsion:

The animals were grouped containing six in each and labeled I-IV. Convulsive dose of Pentylenetetrazole (60 mg/kg) was given intra peritoneally half-an-hour before the experiment. Time for onset of action (clonic and tonic seizures) and death rate were recorded[8, 9]. Group I served as control. Group II, III & IV were treated with Carbamazepine (30mg/kg; ip), Isradipine (2mg/kg; ip) and Carbamazepine + Isradipine respectively half-an-hour before the treatment of pentylenetetrazole. Delay in onset of action and death of animals was considered as anti-convulsant property.

STATISTICAL ANALYSIS

The values were expressed as mean ± SEM. Statistical analysis was done by using one-way ANOVA followed by Dunnett's multiple comparision test. $P<0.001$ was considered significant when compared with control.

RESULTS:

Maximal electroshock induced convulsion.

The duration of extensor phase was recorded in control and drug treated animals before and after the electroshock. A significant ($P<0.001$) reduction in the extensor phase was observed with Isradipine (78.81%) when compared with control. Isradipine potentiated the abolition by 93.52% when combined with Carbamazepine shown in below **Table 1**.

TABLE 1: EFFECT OF ISRADIPINE ON MAXIMAL ELECTROSHOCK INDUCED CONVULSIONS

Group	Treatment	Time in various phases of convulsions(sec)			
		Flexion	Extensor	Clonus	Stupor
I	Control	15.57 ± 3.32	62.51 ± 9.42	30.24 ± 2.46	105.26 ± 22.27
I I	CBZ	10.21 ± 8.23	13.24 ± 11.12***	22.12 ± 4.15	71.25 ± 10.56
I I I	Isradipine	13.05 ± 6.56	32.05 ± 5.35***	27.54 ± 6.47	82.54 ± 9.36
I V	CBZ+ Isradipine	7.09 ± 4.23	4.05 ±12.29***	19.85 ± 4.29	61.87 ± 7.78

All values are expressed as Mean ± SD, n=6, ***P<0.001 as compared to control group

PTZ induced convulsions

Pentylenetetrazole at a dose of 60mg/kg; ip, induced tonic type of convulsion with clonus in animals. The onset of action and time of death was 65.25±12.69 seconds and 452.52±0.98 seconds respectively shown in below **Table 2.** Isradipine delayed the onset of action and time of death to 213.21±32.46 seconds and 952.85±9.81 seconds respectively when compared with control. Isradipine showed 100% recovery of animals when combined with carbamazepine.

TABLE.2: EFFECT OF ISRADIPINE ON PTZ INDUCED CONVULSIONS.

Group	Group	Onset of action (sec)	Time of Death (sec)
I	**Control**	62.25 ±12.69	452.52 ± 0.98
I I	**Carbamazepine**	512.29 ± 28.26***	Recovered
I I I	**Isradipine**	213.21 ± 32.46***	952.85 ± 9.81
IV	**Carbamazepine + Isradipine**	1258.59 ± 46.52***	Recovered

All values are expressed as Mean ± SD, n = 6, ***P<0.001 as compared to control group.

DISCUSSIONS: The present study indicates that Isradipine showed significant anticonvulsant effect against maximal electroshock and pentylenetetrazole induced convulsion in animals. The obtained results are generally in line with our previous data concerning the influence of calcium channel inhibitors on the protective activity of antiepileptic drugs[10, 11].

Particularly, nifedipine and diltiazem were found effective against maximal electroshock when co-administered with either carbamazepine or diphenylhydantoin Nifedipine diminished their ED_{50} and a similar effect was produced by diltiazem. Flunarizine enhanced the protective action of carbamazepine, diphenylhydantoin, and valproate against maximal electroshock[12]. Nimodipine was much weaker in this respect the ED_{50} values of carbamazepine and diphenylhydantoin were less potently reduced, and that for valproate was not affected at all.

The role of calcium in the mechanism of action of antiepileptic drugs is still not clear. However, there are several reports regarding influence of antiepileptics on the calcium ions influx. Forinstance, valproate was shown to reduce T-type calcium current in primary afferent neurons. Also phenobarbital blocked inhibited transmembrane calcium inward current through N- and L-type calcium channels. Carbamazepine was demonstrated to inhibit NMDA-induced calcium influx in cultured cerebellar granule cells.

Further evidence that the protective activity of carbamazepine and phenobarbital may be related to the inhibition of calcium inflow.

Since calcium ions play an important role in seizure activity and anticonvulsant action of antiepileptic drugs, the use of calcium channel inhibitors for treatment of epilepsy seems to be rational. Indeed, several reports revealed beneficial effects of calcium channel antagonists as an add-on treatment of epilepsy.

CONCLUSIONS: The data presented here show that Isradipine is capable of protecting the brain against the convulsions induced by electroshock and pentylenetetrazole. The synergistic effect of Isradipine with carbamazepine may be useful in the treatment of epilepsy in comorbid conditions, which needs further investigation. These data add to a growing pre-clinical and epidemiological collection of studies supporting the potential value of Isradipine as a neuroprotective agent in the neuronal disorders.

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