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EFFECT OF ISRADIPINE ON MES AND PICROTOXIN INDUCED CONVULSION

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ABSTRACT

Calcium channel blockers are used as effective agent in various disorders of cardiovascular system such as angina, hypertension and arrythmiasis. Calcium ions play a central role in the control of neuronal excitability. Therefore this study was designed to find out the effect of Isradipine on MES and Picrotoxin induced convulsion. The maximal seizure pattern was induced in animals by giving an alternating current of 150 mA for 0.2 sec while tonic – clonic seizure with 2 mg/kg; ip of Picrotoxin. Isradipine (80µg/kg; ip), Phenytoin (25mg/kg; ip), Diazepam (10mg/kg; ip), Phenytoin + Isradipine, and Diazepam + Isradipine were administered 30 min before electrical/chemical induction of convulsion. The ability of test group to abolish/reduce tonic hind limb extensor component in MES group and delay in onset of jerky movement & death time in Picrotoxin induced group was measured as antiepileptic criteria. Isradipine produced significant reduction in the extensor phase when compared with control and also it potentiated the abolition when compared with Phenytoin in MES induced convulsion. Similarly Isradipine delay the onset of action and time of death in Picrotoxin induced convulsion with 100% recovery of animals when combined with Diazepam. The anticonvulsant property may be by blockade of voltage dependent calcium channels by which calcium ions influx is blocked to stop the sequence of events leading to both the spread of epileptic discharge, cell damage and death.

KEYWORDS

Isradipine, Maximal electroshock and Picrotoxin induced convulsion

INTRODUCTION

Calcium channel blockers are used as effective agent in various disorders of cardiovascular system such as angina, hypertension and arrythmiasis.[1] Influx of calcium through calcium channels on the cell membrane takes place in many tissues which may leads in treating many pathological conditions where calcium channels involve. Calcium ions play a central role in the control of neuronal excitability.[2&3] Abnormalities in calcium related processes or calcium ion channels may be related to the hyper excitability of neuronal and seizure activity[4-7]. Voltage gated calcium channels are involved in distinct physiologic functions related to neuronal excitability. Accumulation of calcium through an excessive stimulation of voltage dependent calcium channels is a key step in the sequence of events leading to both the spread of epileptic discharge, cell damage and death. Calcium channel blockers such as verapamil[8], nifedipine, nicardipine, nimodipine and flunarizine were reported for their anti-convulsant [9-13]. Keeping this in view, the present study was focused to establish Isradipine, a new calcium channel blocker belongs to dihydro pyridine derivative, potential against Maximal

electroshock and Picrotoxin induced convulsion in experimental animals.

MATERIALS AND METHODS

A. Maximal electroshock induced convulsion:

Healthy and convulsion free male albino rats weighing 150 – 200g were used. The animals were grouped containing six in each and labeled I-IV. The animals were given maximal electroshocks of 150 mA for 0.2 seconds to the cornea by using electroconvulsometer[14]. Animals which showed hind limb tonic extensor phase represents the maximal seizure activity of which the nervous system was capable and its duration was taken as a measure of the spread of impulse in convulsion[15]. Group I served as control. Group II, III & IV were treated with Phenytoin (25mg/kg; ip), Isradipine (80µg/kg; ip) and Phenytoin + Isradipine respectively half an hour before the maximal electroshock. The various phases of maximal electroshock induced convulsion for each animal were noted.

B. Picrotoxin Induced Convulsion:

Healthy and convulsion free male albino rats weighing 150 – 200g were used. The animals were grouped containing six in each and labeled I-IV. Convulsion was induced by Picrotoxin (2 mg/kg; ip). Time for onset of action (clonic and tonic seizures) and death were recorded. Group I served as control. Group II, III & IV were treated with Diazepam (10mg/kg; ip), Isradipine (80µg/kg; ip) and Diazepam + Isradipine respectively half an hour before the treatment of Picrotoxin. Delay in onset of action and death of animals was considered as anti-convulsant property.[16]

Statistical Analysis:

The values were expressed as mean ± SEM. Statistical analysis was performed by Student's t test. P<0.001 was considered significant when compared with control.

RESULTS

A. Maximal electroshock induced convulsion:

The duration of extensor phase was recorded in control and drug treated animals before and after the electroshock (Table 1). A significant (P<0.001) reduction in the extensor phase was observed with Isradipine (83.13%) when compared with control. Isradipine potentiated the abolition by 96.64% when combined with Phenytoin.

Table 1
Effect of Isradipine on Maximal electroshock induced convulsion

Groups	Treatment	Dose	Time in various phases of convulsion (sec)				
			Flexion	Extensor	Clonus	Stupor	Recovery / death
I	Control	----	5.78±0.84	56.92±2.52	36.26±2.24	100.16±4.38	Recovered
II	Phenytoin	25mg/kg	3.88±0.31	5.37±0.10* (90.57%)	27.32±0.51	70.33±0.28	Recovered
III	Isradipine	80 µg/kg	4.06±0.26	9.6±1.37* (83.13%)	31.24±0.75	71.68±0.69	Recovered
IV	Phenytoin + Isradipine	25mg/kg and 80 µg/kg	4.51±0.61	1.91±0.19* (96.64%)	22.39±0.54	45.26±1.91	Recovered

*** P<0.001 Vs Control**

B. Picrotoxin Induced Convulsion:

Picrotoxin in a dose of 2mg/kg; ip, induced tonic type of convulsion with clonus in animals (Table 2). The onset of action and time of death was 115.15±1.59 seconds and 1170.35±18.91 seconds respectively. Isradipine delayed the onset of action and time of death to 784.03±3.4 seconds and 4605.1±93.84 seconds respectively when compared with control. Isradipine showed 100% recovery of animals when combined with Diazepam.

Table 2
Effect of Isradipine on Picrotoxin induced convulsion

Group	Treatment	Dose	Onset of action (sec)	Time of Death (sec)
I	Control	----	115.15±1.59	1170.35±18.91
II	Diazepam	10 mg/kg	1788.8±23.52*	Recovered
III	Isradipine	80 µg/kg	784.03±3.4*	4605.1±93.84
IV	Diazepam + Isradipine	10mg/kg and 80 µg/kg	2284.06±14.52*	Recovered

*** P<0.001 Vs Control**

DISCUSSION

The present study indicates that Isradipine showed significant anticonvulsant effect against maximal electroshock and Picrotoxin induced convulsion in animals. Though calcium ions play an important role in genesis and propagation of seizure, but its role in treatment of epilepsy is less clear. The mechanism for anticonvulsant property may be possibly by blockade of voltage dependent calcium channels by which calcium ions influx is blocked to stop the sequence of events leading to both the spread of epileptic discharge, cell damage and death. The synergistic effect with Phenytoin may be by inhibiting post tetanic potential which is probably due to calcium influx inhibition.

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