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Original Article

ANTICONVULSANT EFFECT OFBERBERIS ARISTATA ROOT EXTRACT IN MICE

DIVYA GOEL

Department of Pharmacology, Dr BR Ambedkar State Institute of Medical, Sciences, Mohali
***Corresponding author: Divya Goel; *Email: drdivya74@gmail.com**

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ABSTRACT

Objective: Berberine is an isoquinolone alkaloid present in many plants and reported to possess anti-diabetic, hypolipidemic, anti-cancer, anti-bacterial, anti-pyretic, antiviral and anti-inflammatory effects. In addition, berberine can modulate neurotransmitter like N-methyl-D-aspartate (NMDA), serotonin and Nitric Oxide, thus can produce anticonvulsant effect.

Methods: The seizures were induced in mice by maximal pentylenetetrazol and electroshock. The effect of root extract on seizures was compared with standard anticonvulsant agents, phenytoin and diazepam.

Results: Theroot extract of berberine aristata suppressed duration of tonic convulsions in maximal electroshock-induced seizures while it delayed time of onset of seizure as well as significantly decreased the duration of myoclonic-jerks-in pentylenetetrazol-induced seizures. Further, the study also indicated that the root extract of berberine aristata also produced motor impairment at the antiseizure doses.

Conclusion: The present study indicated that berberine exhibits anticonvulsant activity in both models and can be useful in epileptic patients.

Keywords: Anticonvulsant, Berberine, Maximal electroshock seizure, Pentylenetetrazole seizure

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INTRODUCTION

Berberine is an isoquinolone alkaloid present in many plants i.e. Berberis vulgaris, Berberis Aristata etc [1]. Beberine is reported to possess anti-diabetic, hypolipidemic, anti-cancer, anti-bacterial, anti-pyretic, antiviral and anti-inflammatory effects [2-6]. Ayurvedic literature documents Berberis Aristata exhibits significant influence on CNS, [7] Beberine is also found to possess anxiolytic effect in animal models [8].

Epilepsy is one of the most common serious neurological conditions worldwide [9]. It is characterized by recurrent seizures. In spite of the increasing availability of anti-epileptic drugs, one-third of patients respond poorly to medications [10]. In addition, currently available anti-epileptic drugs have toxicity and teratogenic effects, which stimulated the researchers for new anti-epileptic drugs [11, 12]. Medicinal plants have been seen an important source of the development of new drugs with anti-convulsing action. There are some reports which suggest that beberine produces analgesic, anxiolytic, and anti-depressant effects [7, 8, 13]. All these effects of beberine might be due to its capacity to modulate neurotransmitter like N-methyl-D-aspartate (NMDA), serotonin, and Nitric Oxide [13]. Modulation of these neurotransmitter can produce anticonvulsant activity. On the basis of above literature, the anticonvulsant activity of root extract of bebeerine was evaluated in this study.

MATERIALS AND METHODS

Drugs and chemicals used

Berberine extract-pure yellow-colored berberine extract of berberine aristata root found in sub-Himalayan region was collected from Hindustan pharmaceutical Amritsar, India.

Diazepam (5 mg/ml) Intas pharmaceuticals, Ahmedabad, India)

Flumazenil (5 mg/ml) Sigma-Aldrich, Bengaluru, India)

Pentylenetetrazole (PTZ) (Sigma-Aldrich Co, St. Louis, MO)

Phenytoin (Dilantin, Pfizer, India)

Normal Saline for negative control and Distilled water as a vehicle for preparing various doses of the drugs.

Site of study

The study was conducted by Dept. of Pharmacology in Central research lab of MMIMSR after getting approval from IAEC, constituted for control and supervision of experimental animals by Ministry of Environment and Forests, Government of India, New Delhi, India.

Animals

Healthy Swiss Albino mice (either sex, weighing 20-25 mg) were procured from the animal house of MMIMSR. The experiment was performed after obtaining permission from IAEC as per CPCSEA, India guidelines. 6 mice per cage were kept for a minimum of 5 d before pharmacological experiments and were maintained under 12 h light/dark cycle and temperature (24±1) °C with free access to rodent chow and tap water. Before experimentation animals were allowed to adapt to the new environment for one week. The animals were transferred to the central research lab at least 1hr prior to the start of the experiment; testing was carried out during the day time (8:00 A. M–3:00 P. M).

Pentylenetetrazole-induced seizures test

Mice were divided into five groups each containing six animals, and received either saline, berberine (2.5, 5 and 10 mg/kg, i. p.) or diazepam (3 mg/kg, i. p.). Thirty minutes later general clonic convulsions were induced by the pentylenetetrazole (80 mg/kg, i. p.).[14] The animals were observed during the first 30 min for number of animals with convulsions i.e. onset and duration of myoclonic jerks, number of deaths and percent protection against convulsion and mortality.

Maximal electroshock-induced seizures test

Mice were divided into five groups each containing six animals and treated with either saline, berberine (2.5, 5 and 10 mg/kg, i. p.) or phenytoin (25 mg/kg, i. p.). Thirty minutes later current stimulus (50 mA for 0.2 s) was delivered through corneal electrodes to induce hind limb tonic extensor phase (HLTE) in mice. The percent protection and duration of tonic hind limb extension (i.e., the hind limbs of animals outstretched at 180 ° to the plane of the body axis) was observed. Protection was defined as the complete absence of tonic hind limb extension [14].

The rota-rod test

To determine the effect of berberine on motor in coordination, rota-rod test was done. Mice were placed with four paws on horizontal metal-coated rod (2.5 cm diameter) rotating at a speed of 22 rpm. The time, each mouse was able to maintain its balance walking on top of the rod, was measured and cut off time was kept 300 sec. The riding ability of the mice on rota-rod was checked before the experiment. The mice were initially put on a rotating rod, and mice that immediately dropped off (within 60 sec) were excluded from the experiment [15]. Mice were divided into 5 groups (n = 6) of previously screened mice, and treated with either saline, berberine (2.5, 5 and 10 mg/kg, i. p.) or diazepam (4 mg/kg) and put on rota rod after 30 min. Percentage of mice exhibiting motor deficit were calculated. Flumazenil (5 mg/kg, i. p). Was given with dose of berberine exhibiting maximum effect in this model.

Statistical analysis

Latency to induce seizures by PTZ and MES model were analysed by one-way ANOVA followed by Dunnett's post hoc test. The value of P <0.05 was considered statistically significant.

RESULTS

Pentylenetetrazole-induced seizures test

Diazepam (3 mg/kg, i. p.) treated animals did not show any signs of convulsions and protected all the mice from PTZ-induced convulsions. Berberine significantly increased latency as far as seizure generation is concerned when PTZ was given, as well as significantly decreased the duration of myoclonic jerks at all doses. Effect of berberine was maximum at dose of 10 mg/kg (P < 0.01) (table 1).

Table 1: Effects of berberine on pentylenetetrazole-induced seizures

Treatment	Dose (mg/kg, i. p.)	Latency for convulsion (sec)	Duration of myoclonic jerks (sec)	% Protection against seizures	% Protection against mortality
Saline	10 ml	54.72±3.82	197±4.50	0	0
Diazepam	3	…….**	…….**	100	100
Berberine	2.5	61.23±4.23*	112±3.18*	0	0
	5	78.66±6.25*	89±9.72 **	0	0
	10	87.43±5.34**	67±6.0**	0	16.66

Values are expressed as the mean±SEM of six observations. *P <0.05 **P < 0.01 vs. saline treatment (One-way ANOVA followed by Dunnett's post hoc test).

Maximal electroshock-induced seizures test

Berberine at all doses significantly reduced the duration of hind limb extension in mice as compared to control group. In addition, berberine at dose of 10 mg/kg showed significant protection from seizure as well as mortality. The standard drug, phenytoin, also showed protection (100%) against hind limb extension (table 2).

Rota-rod test

Berberine had significant influence on the motor function (p<0.001). One-way ANOVA followed by Dunnett's post hoc test showed significant decline (p<0.001) in the motor function maximum with berberine at the doses that produced antiseizure effect. Flumazenil reverses the motor incoordination effect of 10 mg/kg dose of berbrine (fig. 1).

Table 2: Effects of berberine on maximal electroshock-induced seizures

Treatment	Dose (mg/kg, i. p.)	Duration of hind limb extension (sec)	% Protection against seizures	% Protection against mortality
Saline	10 ml	11.453±0.05	0	0
Phenytoin	2.5	…….**	100	100
Berberine	2.5	9.355±0.94*	0	33.33
	5	5.22±0.73**	0	50
	10	2.43±0.68**	33.33	83.33

Values are expressed as the mean±SEM of six observations *P < 0.05 **P < 0.01vs. Saline treatment (One-way ANOVA followed by Dunnett's post hoc test

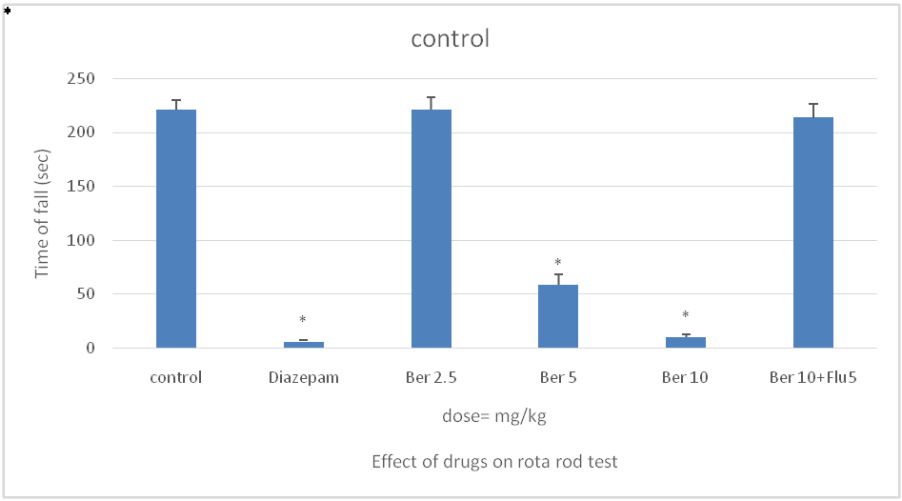

Fig. 1: Effect of berberine on rota rod test, each bar represents mean±SEM, *p<0.05 vs. control.

DISCUSSION

The present study aimed to evaluate the anticonvulsant activity of berberine in animal experimental models. PTZ-induced seizure model is primarily used model for evaluating compounds effective in human generalized myoclonic and absence seizures, while MES-induced seizure model represents a model for grand mal epilepsy. The present study revealed that the berberine extract of berberine aristata root attenuated both PTZ-induced clonic seizures and MES-induced tonic seizures, indicating that berberine possesses anticonvulsant activity. Another study showed the anticonvulsant effect of berberine aristata in MES-induced tonic seizures in mice, while another study showed the anticonvulsant effect of root extract of berberineintegerrimain PTZ-induced clonic seizures in mice [16, 17]. Berberine is an isoquinoline alkaloid present in root and stem bark of Berberis species and may be responsible for anticonvulsant effect [16]. In addition, berberine root extract contains different chemicals berberine, berbamine, aromoline, palmatine, oxycanthine, oxyberberine, calumbamine, umballiatine, jatrorrhizine, hydrastine, karachine and taxilamine [18, 19]. The different effect of different berberine species could be presence of different chemicals in its extract. The study further revealed that berberine produced motor impairment at antiseizure doses.

PTZ induces convulsion by inhibition and/or attenuation of GAB Aergic neurotransmission, berberine might be acting by modulating GAB Aergic neurotransmission as it was also found to produce motor in coordination in rota rod test model [20].

Flumazenil reversed the effect of 10 mg/kg berberine on muscle in coordination which supported the GABAergic theory. The GABAergic theory could also be corroborated with the fact that berberine also possess sedative and anxiolytic effect.

The mechanism by which berberine produced an anticonvulsant effect against MES induced seizures is not known. Berberine might be acting by modulating glutamatergic transmission as previous study showed that berberine reduce NMDA receptor binding and inhibit NMDA receptor channel current in brain [21].

CONCLUSION

The present study concludes that Berberine exhibits significant antiseizure activity against chemically as well as electrically induced seizures in mice and the same can be attributed to its neuro-modulatory effect.

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AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICTS OF INTERESTS

Declared none

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