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Anti convulsant property of Melatonin in Electro and Chemo induced Convulsions in Rats

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Abstract

Anticonvulsant property of melatonin in maximal electroshock (MES)- induced and pentylenetetrazole (PTZ)-induced convulsions in rats were evaluated. 36, adult, male, albino rats, were utilised for this study. The effect of melatonin was studied in MES and PTZ induced convulsions in these rats. In MES induced rats, abolition of hindlimb tonic extension was taken as the measure of efficacy. In PTZ induced rats, suppression of clonic spasms was taken as the measure of efficacy. Percentage protection offered was calculated and analysed statistically. Melatonin offered significant protection (p value < 0.01) in both MES (66%) and PTZ (66%) induced seizures in rats. This study suggests that melatonin has got significant anti-epileptic property. Since the currently available antiepileptic drugs are with some limitations, melatonin, which is considered to be an endogenous antiepileptic substance, could be of particular value in the treatment of epilepsy, which needs further exploration by clinical studies.

Key- Words: MES, PTZ, Anti epileptic, Melatonin

Introduction

Epilepsy is a common, chronic neurological disorder with a prevalence of 4-10 / 1000 persons ⁽¹⁾. Over the last two decades, the pharmacological management of epilepsies has made tremendous progress, resulting in increasing proportions of patients achieving seizure freedom without undue adverse effects ⁽²⁾. In spite of addition of a large number of efficacious antiepileptic drugs (AED's) during the past decade, they provide relief in only upto 75 % patients with absence seizures and in 85% patients with generalized tonic clonic seizures. And approximately 30% of epileptic patients do not respond satisfactorily to the currently available AED's^(3,4).

Numerous experimental studies have suggested anticonvulsant role for the pineal hormone melatonin against various convulsive stimuli ^(5, 6, 7).

Melatonin, an indolamine hormone (N-acetyl -S-methoxytryptamine) is primarily synthesized in the pineal gland but also is synthesized from the retina, GIT, bone marrow and lymphocytes ⁽⁸⁾. Moreover melatonin even when given in massive amounts (300 mg daily) for prolonged periods (upto 5 years) to humans has not produced any untoward side effects ⁽⁹⁾. Hence with these considerations, the present study was undertaken to determine the effect of melatonin in maximal electro shock (MES) induced and pentylenetetrazole (PTZ) induced seizures in rats

Material and Methods

This randomised, controlled, animal experimental study was conducted in the Institute of Pharmacology & Central animal house, Madurai Medical College, Madurai, after obtaining clearance from Institutional animal Ethical committee. 36, Inbred, adult, male albino rats weighing about 200 – 220 gms were used for this study. All the animals were maintained under 12:12 hour light: dark cycles and were fed with standard laboratory chow and water ad libitum. All the experiments were carried out, around the same time each day.

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Methodology

The animals were divided into two groups, each group containing 18 animals. One group was utilized for MES method and another group for PTZ method.

MES Method:

Here the 36 animals were again divided into 3 equal groups (control, standard & test group). One hour prior to the experiment, all the animals in the control group received 1 ml of distilled water orally; the animals in the standard group received Phenobarbitone 30mg/kg⁽¹⁰⁾ orally & the animals in the test group received melatonin 50 mg/kg⁽¹¹⁾ orally. The concentration of the drugs was so adjusted that all the groups received the same volume of preparation throughout the study.

Then, Convulsions were induced by electrical stimulation through ear electrodes, previously moistened with saline, with an electroconvulsimeter, which delivered a constant current at a rate of 150 mA at 60 Hz, for duration of 0.2 seconds. Suppression of tonic hindlimb extension was taken as a measure of anticonvulsant activity⁽¹²⁾.

PTZ Method

Here the remaining 18 animals were again divided into 3 equal groups (control, standard & test). One hour prior to the experiment, all the animals in the control group received 1 ml distilled water orally; the animals in the standard group received Phenobarbitone 30mg/kg⁽¹⁰⁾ orally & the animals in the test group received melatonin 50 mg/kg⁽¹¹⁾ orally. The concentration of the drugs was so adjusted that all the groups received the same volume of preparation throughout the study.

The chemical pentylenetetrazole was dissolved in normal saline⁽¹³⁾ and was administered at a dose of 70 mg /kg intraperitoneally⁽¹⁰⁾. All the animals were observed for a period of one hour duration. Suppression of clonic spasms was taken as the measure of anticonvulsant activity⁽¹²⁾.

Statistical analysis

Statistical analysis was carried out using ANOVA method⁽¹⁰⁾. p value < 0.05 was considered as statistically significant.

Results and Discussion

MES Method

The animals went through the following phases like latent phase, tonic flexion, tonic extension, and clonus and post ictal depression. All the animals in the control group exerted tonic extension for an average period of 15.9 seconds; it was about 2.2 seconds in test group; whereas all the animals were protected in the standard group; the results are given in table I.

PTZ Method

All the animals went through a sequence of excitement, myoclonic jerks & clonic seizures. The clonic convulsions lasted for an average period of about 46 seconds in control group; 2 seconds in test group; whereas all the animals were protected in the standard group; the results are shown in Table II.

From this study it was observed that melatonin offered significant protection in 66 % of rats in both MES induced and PTZ induced seizure models. Albertson et al have also proved the anticonvulsant effect of melatonin in kindled seizures in rats⁽¹⁴⁾. Melatonin exerted a protective against cyanide induced seizures⁽¹⁵⁾ and also against seizures induced by Quinolate, Kainate, glutamate, NMDA and PTZ in mice⁽¹⁶⁾. Seizure protective role of melatonin was also exhibited against post-traumatic epilepsy induced by FeCl₃ in rats⁽¹⁷⁾ and on pilocarpine induced seizures in rats⁽¹⁸⁾. NirPeled et al. have shown that melatonin decreased seizure activity in children⁽¹⁹⁾.

It has also been postulated that CSF melatonin has been proposed as a natural anti convulsant⁽²⁰⁾. It has also been suggested that melatonin has got a neuro protective role by exerting an inhibitory action on glutamate receptors and by potentiating GABA – BZD receptors⁽²¹⁾. Recently there have been preliminary reports indicating that melatonin may possess antiepileptic activity, which may be attributed to its potent anti-oxidant and free radical scavenging properties⁽²²⁻²⁴⁾. Some authors suggest a potential use of melatonin as an adjunct to antiepileptic therapy because of its diverse spectrum of action as an antioxidant, neuro protector and free radical scavenger. Melatonin could be beneficial in combination with other antiepileptic medications also^(25,26).

Conclusion

Because of the limitations of the currently available AED's and as there is a need for a novel AED with an improved efficacy and tolerability profile, melatonin a proposed endogenous anticonvulsant molecule may be tried as a part of therapy in epilepsy either alone or in combination with other currently available AED's, which has to be further evaluated clinically.

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Table I: MES Method: Phase Of Tonic Extension

GROUP	DRUGS	EXTENSION (SECONDS)	No. of rats protected(n=6) (% protection)
CONTROL	DISTILLED WATER	15.9	0 (0)
STANDARD	PHENOBARBITONE	0	6 (100)
TEST	MELATONIN	2.2*	4 (66)

P – value < 0.05 (significant) (* $P < 0.01$)

Table II: Pentylenetetrazole Method

GROUPS	DRUGS	CLONIC CONVULSIONS (SECONDS)	No. of rats protected (n= 6) (% protection)
Control	DISTILLED WATER	46	0 (0)
Standard	PB	0	6 (100)
Test	MELATONIN	2*	4 (66)

P – value < 0.05 (significant) (* $P < 0.01$)

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