

Role of Dopamine in Antiepileptic Action of Phenytoin

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Abstract

Objectives: Epilepsy is one of the serious potentially life shortening disorder of central nervous system which is not uncommon. Antiepileptic drug diphenylhydantoin (Phenytoin) is attributed to produce the anticonvulsant effect via dopamine. Hence this study was planned to observe the relationship between Phenytoin and dopamine modulators by experimentally induced seizures in rats. **Materials and Methods:** Albino rats were selected for maximal electroshock seizure (MES). After the screening, the rats were randomly included to constitute groups of 10. Minimum effective dose (EDmin) used for Phenytoin was 2.5 mg/kg while maximum effective dose (EDmax) was 25 mg/kg. Doses of Levodopa used were 100 mg/kg and 200 mg/kg while for Metoclopramide doses were 2 mg/kg, 20 mg/kg and 40 mg/kg. **Results:** In comparison to control group, the groups receiving dopaminergic antagonist Metoclopramide along with EDmax of Phenytoin sodium showed decreased protection as the dose of Metoclopramide increased. Phenytoin sodium in subanticonvulsant dose (EDmin) in control group did not show protection to a considerable degree against MES. But, when combined with a dopamine precursor Levodopa, the efficacy of EDmin of Phenytoin was increased. **Conclusion:** Dopamine has modulatory effect on antiepileptic action of Phenytoin. Among Dopamine receptors, activation of D2 receptors has seizure protective action. Modulation of D2 receptor might be involved in the antiepileptic action of Phenytoin.

Key words: Epilepsy, Phenytoin, Seizure.

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Introduction

Epilepsy is one of the serious potentially life shortening disorder of central nervous system which is not uncommon. It is characterized by the periodic and unpredictable occurrence of seizure by an acute systemic or neurological insult.¹ It is defined by the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE) as a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures and by the neurobiologic, cognitive, psychological, and social consequences of this condition. For completion of the definition of epilepsy occurrence of at least one epileptic seizure is required although diagnosis of epilepsy is made for those patients who have at least two unprovoked seizures.² Seizures are highly

unpredictable and their frequencies are also highly variable. The seizures are defined as “a transient alteration of behavior (sign and/or symptoms) due to the abnormal, disordered, excessive, hypersynchronous, and rhythmic firing of populations of brain neurons”^{1,2,3}

Epilepsy occurs in both the genders and can occur in any age but it is most frequently seen and diagnosed in paediatric age group and also not uncommon in geriatric age group. It is estimated that around 5% world population might have suffered from at least one seizure during their lives. As per WHO, 8 individuals in the population of 1000 suffer from epilepsy. The incidence rate of epilepsy is much higher in developing countries in comparison to developed countries. 1/5th epileptic population of world resides in India as it is estimated that

around 10 million people in India are suffering from epilepsy.^{1,4}

Studies involving animal models about epilepsy suggest that NMDA, AMPA and Kainate agonists induce seizure activity, whereas their antagonists suppress seizure activity.⁵ Dopamine underactivity is also observed in epilepsy. Dopamine is a neurotransmitter in central nervous system (CNS). More than half of the CNS catecholamine content is dopamine. Dopamine D2 receptor activation is associated with anticonvulsant activity as it decreases the frequency of intrinsic bursting during epileptogenesis but selective D1 agonists showed pro-convulsant properties.⁶ Jobe et al observed that dopamine provided protection against electroshock seizure in rats.⁷

Number of diverse variety and class of newer and older antiepileptic drugs are available for the management of epilepsy. In most of the situations except in 20% to 30% patients who suffer from drug resistant epilepsy, symptoms of the disease can be successfully treated with one or more of these antiepileptic drugs.⁸ These drugs have multiple and diverse mechanisms of action but the ultimate target of all drugs is to inhibit the rapid and excessive firing of neurons that start a seizure. Antiepileptic drug diphenylhydantoin (Phenytoin) is attributed to produce the anticonvulsant effect via increased dopaminergic activity. It has also been observed to antagonise the action of Reserpine, a monoamine depletor.⁹ The evidence is suggestive of dopamine involvement in the effect of Phenytoin. Hence this study was planned to observe the relationship between Phenytoin and dopamine modulators in experimentally induced seizures in rats.

Materials and Methods

Albino rats of either gender, weighing between 80 -150 gms, were housed in colony cages with food and water ad libitum except 4 hours before and during experimentation. The rats were acclimatized to the lab conditions for a week. These were screened for convulsions by giving supramaximal electroshock of 150 milliamperes for 0.2 second through pinnal electrodes, using convulsimeter.^{10,11} Rats showing tonic hind limb extensor phase with supramaximal electroshock were selected for maximal electroshock seizure (MES). After the screening,

the rats were randomly included to constitute groups of 10. Minimum effective dose (EDmin) used for Phenytoin was 2.5 mg/kg while maximum effective dose (EDmax) was 25 mg/kg. Doses of Levodopa used were 100 mg/kg and 200 mg/kg while for Metoclopramide doses were 2 mg/kg, 20 mg/kg and 40 mg/kg. Permission was granted by Institutional Animal Ethics Committee prior starting the study.

Maximal Electroshock Seizure (MES)

There was no observable neurological deficit when convulsive tests were performed. 1st group received EDmax of Phenytoin. 2nd and 3rd groups received EDmax of Phenytoin plus dopaminergic antagonist (Metoclopramide) in 20 mg/kg and 40 mg/kg doses respectively. 4th group received EDmin of Phenytoin. 5th and 6th groups received EDmin of Phenytoin plus dopaminergic agonist (Levodopa) in the doses of 100 mg/kg and 200 mg/kg respectively. 7th group received EDmin of Phenytoin plus Levodopa in 100 mg/kg dose and Metoclopramide in 2 mg/kg dose while 8th group received EDmin of Phenytoin plus Levodopa in 200 mg/kg dose and Metoclopramide in 2 mg/kg dose. The MES test was done at the time of peak action of the drug and rats not showing tonic extensor phase were counted.^{11,12,13}

Results

It was observed that in comparison to control group which received EDmax of Phenytoin sodium, where there was 90% protection against MES, the groups receiving dopaminergic antagonist Metoclopramide along with EDmax of Phenytoin sodium showed decreased protection as the dose of Metoclopramide increased. The inhibition of protection was statistically significant as compared to the control. Phenytoin sodium in subanticonvulsant dose (EDmin) in control group did not show protection to a considerable degree against MES. But, when combined with a dopamine precursor Levodopa, the efficacy of EDmin of Phenytoin was significantly increased. Dopaminergic antagonist Metoclopramide in small dose inhibited the potentiation caused by dopaminergic drug Levodopa on EDmin of Phenytoin significantly (Table- 1).

Table- 1: Effect of dopamine agonist & antagonist on Phenytoin action, n=10

Groups	Drugs	Dose (mg/kg)	% of rats protected
1 st	Phenytoin (EDmax)	25	83.30
2 nd	Phenytoin (EDmax) + Metoclopramide	25 + 20	65.00*
3 rd	Phenytoin (EDmax) + Metoclopramide	25 + 40	46.60*
4 th	Phenytoin (EDmin)	2.5	15.00
5 th	Phenytoin (EDmin) + Levodopa	2.5 + 100	29.20*
6 th	Phenytoin (EDmin) + Levodopa	2.5 + 200	45.80*
7 th	Phenytoin + Levodopa + Metoclopramide	2.5 + 100 + 2	10.83*
8 th	Phenytoin + Levodopa + Metoclopramide	2.5 + 200 + 2	28.30*

*p < 0.01

Discussion

In the present study, effect of subanticonvulsant dose (EDmin) of Phenytoin and its modification by combination with Levodopa in presence/absence of low dose of Metoclopramide was studied. Insignificant protection of rats was observed against the seizure with EDmin of Phenytoin. However the combination of these drugs with Levodopa significantly protected the animals against the seizures. The protective effect of EDmax of Phenytoin against MES seizure was antagonized significantly by Metoclopramide indicating the involvement of dopaminergic receptors in the anticonvulsant action of Phenytoin.

Most of the antiepileptic drugs which were developed before 1980, act either on sodium channels, gamma-aminobutyric acid type A (GABA-A) receptors, or calcium channels. In their mechanism of action, mostly membrane excitability is decreased by interacting with neurotransmitter receptors or ion channels. As far as Phenytoin is concerned, it decreases high-frequency repetitive firing of action potentials by enhancing sodium-channel inactivation and thus stabilizes the membrane.¹⁴

Levodopa after conversion to dopamine stimulates D1 and D2 receptors and potentiates the anticonvulsant action. Metoclopramide is a selective D2 receptor blocker and we found that it decreased the antiepileptic action of Phenytoin. This suggests the involvement of D2 receptors in the anticonvulsant action. Starr MS commented that "Epidemiologists noticed a reciprocal relationship between the supposed dopaminergic overactivity syndrome of schizophrenia and epilepsy". But the dopamine activity at D2 receptor has the potential of antiepileptic effect while in D1 it has opposing

effects.¹⁵ As far as central D1 receptors are concerned, their stimulation has a role in reduction of the seizure threshold.¹⁶ Jose et al found that monoamines, chiefly Dopamine is involved in the anticonvulsant effect of Phenytoin.¹⁷ Jobe PC also showed that dopamine has protective role in epilepsy.⁷ Wenger GR et al also found anticonvulsant property of dopamine.¹⁸ McKenzie GM and Soroko FE when compared apomorphine, (+) - amphetamine and L -DOPA on maximal electroshock convulsions found that L-DOPA has significant antiepileptic property.¹⁹ These observations confirm the role of dopaminergic system in the anticonvulsant action of Phenytoin against MES. Antagonism by Metoclopramide a selective D2 blocker suggests that D2 receptors play the dominant role in the anticonvulsant action.

Conclusion

From the study it can be concluded that Phenytoin an antiepileptic agent, has protection against maximal electroshock convulsions in rats. Dopamine has modulatory effect on antiepileptic action of Phenytoin. Among Dopamine receptors, activation of D2 receptors has seizure protective action. Hence, we conclude that modulation of D2 receptor might be involved in the antiepileptic action of Phenytoin.

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