Original Article

Influence of Ketogenic Diet and Phenytoin Sodium on Isoniazid Induced Epilepsy in Wistar Rats

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ABSTRACT

Aim: The current research was set up to estimate the influence of ketogenic diet in combination with phenytoin sodium on isoniazid induced epilepsy in rats. **Methods:** In this work 30 rats were used with weight range of 150-200gms were selected and divided into five groups. Group -1(Positive control), Group – II (Negative control), Group – III (Standard), Group – IV (Ketogenic diet), Group – V (Ketogenic diet + Standard). The doses of isoniazid, phenytoin sodium, ketogenic diet were selected and the work was executed for a period of 30 days. **Results:** At the end of the study animals were sacrificed to collect brain for estimating GABA levels in different groups. Results indicated that, there is a notable rise in levels of GABA which helps in reducing seizure latency when the ketogenic diet was added to that of standard drug. **Conclusion:** The change in levels of GABA when compared to the ketogenic diet alone and standard suggest that ketogenic diet along with standard drug may produce antiepileptic activity by increasing the levels of GABA in isoniazid induced epilepsy in rats.

Key words: Epilepsy, Ketone diet, Isoniazid, Phenytoin, GABA.

INTRODUCTION

Epilepsy is the chronic disorder which generates baseless, periodic seizures. A seizure is an unexpected hastens of electrical activity in the brain. There are mainly of two classes 1. Generalized seizures (Damage entire brain), 2. Focal (or) partial seizures (Damage only a region of brain). Epilepsy is a common neurological disorder that has an effect on nearly 65 million people throughout the world. Epilepsy can be seen in any one, but it is more usual in children and older people. It is found slightly greater in males compared to females. It is the group of neurological disorder characterized by epileptic seizures. It mainly has an effect on nearly 1% of population in youngsters and 3% of the population in older people. Mostly 80% of people with the disorder are seen in the developing countries. Epilepsy is a disorder of the brain distinguished by unforeseeable and regular occurrences of a temporary alteration of performance due to dysfunctional, simultaneous and repeated firing of numerous brain neurons.[1]

Lamentably, the drugs obtainable in present day medicine first they are unsuccessful to manage the seizure activity in some patients next quite commonly generate undesirable effects like neurotoxicity, hepatic failure and sometimes expose to risk of drug interactions. There are many treatment options other than medication, one among them is Ketone diet and it is beneficial for people who don't respond to medication. Ketogenic diet (KD) is a medically supervised moderate- protein diet, high cholesterol and low carbohydrate, which was used successfully in patients with pharmaco resistant epilepsy.[1,2] The classic KD consists of a very high amount of fat combined with protein and carbohydrate.[3,4] KD was developed in 1920 in response to the survey that fasting had anti-seizure activity.[5,6] At the time of fasting, body metabolizes the fat stores by lipolysis and next the fatty acids

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undergo beta-oxidation and convert to acetoacetate. Beta-hydroxybutyrate (BHB) and acetone ketone bodies used as precursors to generate adenosine triphosphate (ATP). KD is thought to stimulate the metabolic effects of starvation by forcing the body to use especially fat as a fuel source. Ketone bodies provides another substrate for the use in krebs cycle also increase mitochondrial function by increasing ATP synthesis and decreasing effects of reactive oxygen species (ROS) fatty acids and calorie restriction may have favourable effects.[7,8] Since KD was formulated before 85 years, number of major hypotheses was advanced, but no one was accepted widely. Major features of the KD finally results in seizure protection. Ketone bodies like free fatty acids (polyunsaturated fatty acids), or restriction of glucose may directly or indirectly lead to seizure control.[9,10] Though it is possible that by following any one of these KD induced treatment plans it is responsible for the anticonvulsant action, but only minimal changes can be observed, so to improve seizure control treatment plan requires all three. BHB is the main ketone body cadenced in the blood and it has been used as a clinical measure of KD implementation. Thus, almost all KD studies have tried to create a link between ketonemia and anticonvulsant activity. Inspite of vigorous increase in BHB levels of plasma have been seen during KD treatment, no significant correlation was observed between BHB levels of plasma and seizure protection. Behind the development of ketonemia, optimal seizure protection commonly delays from days to weeks, but this can achieved within hours by the onset of KD.[11,12]

Metabolic pathways highlighting the production of ketone bodies during fasting or treatment with the ketogenic diet (KD). Estimated levels of acetoacetate, acetone and in blood for ketone diet induced concentrations and during fasting. Beta-hydroxy butyrate levels in blood are most regularly used as the clinical measure of triumphant KD treatment. However, there is some evidence regarding the anticonvulsant properties of ketones other than BHB. It was observed that acetone and its parent acetoacetate (ACA) prevent acutely provoked seizures in animals. Also recent researches have shown similar results in rodents. Acetone and ACA but not BHB were anticonvulsant in a variety of acute and chronic models of epilepsy.[12] Whereas *in vivo* pharmacodynamics studies indicated that both acetone and ACA may show anticonvulsant activity, but there is no information that ketone bodies can directly inflect synaptic transmission or neuronal excitability. But the *in vitro* cellular electrophysiological experiments were unsuccessful to show the effect on the principal ion channels which mediate neuronal excitability and inhibition. Exactly, neither ACA nor L-BHB were found to alter $GABA_A$ receptors, NMDA receptors or AMPA receptors present in both hippocampus and neocortex of rats. Gamma Amino Butyric Acid (GABA) is the main inhibitory neurotransmitter in the CNS i.e., 30-40% CNS neurons are GABAergic neurons. GABA concentration is more in the nigrostriatal brain system; hypothalamus and Gamma other GABAergic neurons are short interconnecting neurons. GABA concentration is higher in CNS than in peripheral tissues. Most of the CNS depressant drugs namely anxiolytics, sedatives and hypnotics, antiepileptic drugs acts on GABA receptors. GABA and Glutamate are inhibitory and excitatory neurotransmitters of brain respectively. GABA shows its actions by acting on GABA receptors but glutamate shows its actions by acting on NMDA (N-Methyl D-Aspartate) and non NMDA receptors. Activation of any of these receptors transforms various voltage gated ion channels including Na^+, K^+, $Ca2^+$ and chloride which excites or inhibits the neuron.

Neurological and psychiatric diseases like Huntington's disease, Schizophrenia, Epilepsy, Panic attacks and Anxiety are because of the abnormalities in GABA system. The neuronal excitation was counter balanced by GABA (principal inhibitory neurotransmitter in cerebral cortex), which regulates the inhibitory actions. Experimental evidence shows that GABA has an important role in the mechanism and treatment of epilepsy.[13,14] Anomalies of GABAergic functions have been observed in genetic and acquired models of epilepsy. Diminution of GABA mediated inhibitory activity glutamate decarboxylase, binding to $GABA_A$ and benzodiazepine sites and GABA in CSF and brain tissue, GABA detected using micro dialysis are reported in studies of human epileptic brain tissue.[15,16] GABA agonist may reduce seizures and GABA antagonist produces seizures. Drugs that inhibit GABA production induce seizures and benzodiazepine, phenytoin works by enhancing GABA mediated inhibition of seizures. Drugs that increase synaptic GABA are potent anti convulsants and two recently developed anticonvulsant drugs like vigabatrin and tiagabin are examples of such agents. The mechanism of action is quite different, they are irreversible suicide inhibitors of GABA transaminase whereas it block GABA reuptake into neurons and glia which may account for drug side effect profile. Phenytoin sodium, barbiturate, benzodiazepines which are effective as anticonvulsant work by enhancing GABA mediated inhibition.

MATERIALS AND METHODS

Male albino rats weighing between 150-200g with 6-8 weeks of age were selected to perform all experiments at Department of Pharmacology Laboratory, GIET School of Pharmacy. Animals were procured from, National Institution of Nutrition (NIN), Hyderabad. They were acclimatized for one week to the laboratory conditions prior to begin experiment and maintained with free access to water, food and kept at 25±2°C under controlled 12h light dark cycle.

Grouping and treatment protocol

Isoniazid solutions are prepared freshly at the beginning of each experiment and test (diet) prepared according to procedure. Phenytoin sodium was given through i.p route obtained from commercially available ampoule form. For *s.c*, administration isoniazid dissolved in water. Based on the body weight the animals were randomly divided into five groups. Six animals are placed in each group (n=6).

Group 1: Positive control (received vehicle)

Group 2: Negative control isoniazid (INH 250 mg / kg; i.p)

Group 3: Standard phenytoin sodium (25 mg/kg; i.p) + isoniazid (250 mg / kg; i.p)

Group 4: Ketogenic diet+ isoniazid (250 mg / kg; i.p)

Group 5: Isoniazid (250 mg/kg; i.p) + ketogenic diet + standard phenytoin sodium (25 mg / kg; i.p)

Based on the reports of previous literatures, the doses of isoniazid, phenytoin sodium, ketogenic diet (almonds + coconut oil + banana) were selected and the study was performed for a period of 30 days. Except the positive control group all the animals received the single dose administration of isoniazid (INH) (250mg/kg; I.P) then all the animals were carefully monitored for 120min, during this time tonic – clonic convulsions, recovery or time taken to death were observed. The convulsions were recorded by a video tape. Then after 120min treatment standard- phenytoin sodium was given (25mg/kg; i.p). Ketogenic diets (almonds + coconut oil + banana) 30g/ day were provided.

Behavioural Studies

Elevated plus maze

The rats were acquiesced to socialize during entire experiment. All precautions were taken to make sure that any external stimuli other than the height of the plus maze could entreat the activity of maze.[17]

The Negative control group rats received (250mg/kg isoniazid sc), standard group rats received (25mg/kg phenytoin, i.p), Test group received (ketogenic diet 30g/day), Test and standard group received ketogenic diet (30g/day) + phenytoin sodium (25mg/kg). Then after 30min i.p administration of Phenytoin to Standard group and Ketogenic diet to Test groups. During the 5mins period of experiment each animal was placed at the centre of elevated plus maze by facing its head towards open arm to record the behaviour of the rat[18,19] i.e.,

- Choice of the rat for its first entry in to the open arm or closed arm.
- The number entries in to open and closed arms.
- The time spent by the rat in each of the arm.

The results obtained for standard and test groups are compared with disease control group by statistical analysis.

Locomotor activity

The experiment was conducted in a sound attenuated room as its principle is that a photocell is triggered when animals crossing the beam of light, it shows a "cut – off" in the rays of light that are falling on Photocells. The photocells are connected to an electronic automatic counting device, which counts the number of `cut- offs' i.e. Activity score.[20] The control group rats receive (250mg/kg isoniazid ip), standard group rats received (25mg/kg phenytoin, i.p), Test group received (ketogenic diet), Test and standard group received ketogenic diet (30g/day) + phenytoin sodium (25mg/kg) 30min after i.p administration of phenytoin sodium to standard group and 1hr after oral administration of distilled water to control group, 1hr after ketogenic diet to test group and Test + Standard group and then each rat was placed individually in actophotometer for 10min. The number of cut offs i.e., locomotors score was recorded in a fixed time intervals[21] i.e., 0.5hr and 2hr. The results of standard and test groups were compared with statistical analysis.

Dissection and homogenization

Brain was removed immediately after sacrificing rats by decapitation with scissors and then brain was weighed and transferred in to small vials which contain 4-6ml of 80% ethanol and homogenized to obtain 10% suspension and finally transferred in to a centrifuge tube. The brain was homogenized at 2000g for 15 min, decanted the supernatant and precipitate was washed twice with 5ml of 80% ethanol and the extracts were evaporated to dry under Infrared light with the help of a fan.1ml triple distilled water was added to dried extract of 100mg tissue. The extract was completely triturated and centrifuged at 20,000g for 30 min using cooling

centrifuge and pipette the supernatant sample to spot on TLC plates.

Estimation of gamma amino butyric acid activity

TLC plates quoted with silica gel G with a thickness of 0.5mm was taken, then various quantities of aliquots were spotted and water saturated phenol was used as a solvent system. After completion of the run, to remove phenol plates were placed in fuming chamber for 6-8hr and it was tested qualitatively with F.C reagent. 0.1% of ninhydrin in butanol solution was prepared and sprayed on the plates and checked for colour development after placing the plates 24 hr in dark at room temperature. Satisfactory results were observed for colour development but differed from other amino acids which has shown complete colour at high temperature. Then Scraped out the developed spots and care has been taken i.e., to include total area of gel in all the known and unknown samples. The silica gel which is scraped was placed in a test tube and 5ml of distilled water was added to it. To achieve quantitative elution of colour the tubes were shaken strenuously. Finally removed silica gel by the centrifugation process and absorbance was noted by using spectrophotometer at 570 nm.

RESULTS

Latency onset of convulsions (min)

Analysis of results for disease control group compared with other groups suggest there is highly significant *(P*< 0.001*)* difference in latency onset of convulsion in standard (phenytoin sodium) (25mg/kg) test T (ketogenic diet 200mg/kg) and test + standard groups.

The latency onset of convulsions has increased in S, T and S + T groups. A comparison of latency in test group T and Test + Standard group with Standard(S) indicates that there is a little significant difference between S, T and T+S is Table 1.

Time taken for death (min)

Increase in time taken for death in standard phenytoin (25mg/kg) test (ketogenic diet) and test + standard (ketogenic diet + phenytoin) groups was observed when compared with control group and the results shown are statistically significant*(P*<0.001*)* also the result of test and test + standard groups are compatible with of standard (S) group.

Percentage mortality

A comparison of number of animals dead i.e., percentage mortality in control group with other groups suggests that there is significant difference in protection offered by standard phenytoin (25mg/kg) and test + standard (ketogenic diet + phenytoin (25mg/ kg). The test+ standard treated group offers protection against mortality which is comparable with that of standard group.

Highly significant increase (*P*< 0.001) in no. of entries in open arm was observed in standard (phenytoin 25mg/ kg), test (ketogenic diet) and test + standard (ketogenic diet + standard) groups when compared with control group and the values are Table 2.

There is no increase in no of entries in open arms more in test (ketogenic diet) and test + standard groups than that of standard group (phenytoin 25mg/kg) suggest that there is moderately significant (*P*< 0.001) no. of entries in closed arm and there is no significant change with test while significant increase (*P* <0.001) with test + standard group.

Analysis of results of control group compared with other groups suggest that there is highly significant (*P*< 0.001) increase of time spent in open arm in standard phenytoin sodium (25mg/kg) test and test + standard groups and the values are Table 3. Also the results of test and T + S are comparable with that of standard(S) group. Increase in open arm exploratory time is the

Table 1: Effect of ketogenic diet along with phenytoin sodium for antiepileptic activity in isoniazid induced epileptic rats.

S.NO	Treatment	Onset of Convulsions	Time taken for death in min	% Mortality
1	Disease Control	13.58±0.52	21.18±1.43	100
2	Standard	23.67±0.67***	47.5±1.73**	50
3	Test	18.67±0.66***	32.18±0.84***	100
4	Test+ standard	24.18±0.60***	49.25±.25***	46

n=6. Significance at *P<0.05*, P<0.01**, P<0.001****

Table 2: Effect of ketogenic diet along with phenytoin sodium on assessment of antiepileptic activity by Elevated plus maze model in isoniazid induced epileptic rats.

S.No	Treatment	No. of entries per 5 min	
		Open arm	Closed arm
1	Disease Control	1±0.26	5.182±0.30
2	Standard	3.667±0.21***	2.66±0.44*
3	Test	2.844±0.30***	3.68±1.34NS
4	Test+ standard	4.877±0.83***	1.32±0.34**

n=6. Significance at *P<0.05*, P<0.01**, P<0.001****

main indication of anti – epileptic activity in elevated plus maze model.

Analysis of results of control group compared with other groups suggests that there is highly significant ($P< 0.001$) decrease of time spend in closed arm in standard (phenytoin sodium) (25mg/kg) Test T (Ketogenic diet 30mg/kg) and T+ S groups.

A comparison of activity score of control group with other groups indicates that there is highly significant ($P<0.001$) difference in activity score in standard phenytoin sodium (25mg/kg) Test and Test + Standard groups values are Table 4.

Analysis of results of control group compared with other groups suggests that there is highly significant ($P<0.001$) decrease in activity score in standard phenytoin sodium (25mg/kg) Test and Test + Standard groups. Also the results of test compound are compatible to that of standard group

Effect of ketogenic diet on Gamma Amino Butyric Acid activity in isoniazid induced rats

Chronic administration of isoniazid for 30 days showed significant decrease in Gamma Amino Butyric acid activity in isoniazid treated group when compared to normal group. Concurrent administration of standard phenytoin sodium and ketogenic diet with isoniazid potentiated their protective effects of GABA activity

Table 3: Effect of ketogenic diet along with phenytoin sodium on evaluation of antiepileptic activity by Elevated plus maze model in isoniazid induced epileptic rats.

S.No	Treatment	Time spent (sec/5min)	
		Open arm	Closed arm
1	Disease Control	14.75±3.25	232.8±8.67
2	Standard	201±12.7***	76.6±14.7***
3	Test	142.4±16.7***	102.3±13.7***
4	Test+ standard	235.5±17.6***	51.23±16.4**

n=6. Significance at *P<0.05*, P<0.01**, P<0.001****

Table 4: Effect of ketogenic diet along with phenytoin sodium on assessment of antiepileptic activity by locomotor activity model in isoniazid induced epileptic rats.

S.No	Treatment	Average score at 30min	Average score at 60min
1	Disease Control	573.4±2.59	576.3±2.77
2	Standard	322.5±2.12***	275±3.02***
3	Test	378±3.10***	335.3±2.17***
4	Test + standard	315±1.73***	266.8±2.07***

n=6. Significance at *P<0.01*, P<0.01**, P<0.001****

Table 5: Effect of ketogenic diet along with phenytoin sodium on Gamma Amino Butyric Acid activity in isoniazid induced rats.

S.No	Treatment	GABA concentration in µg/100mg tissue
1	Control	0.9± 1.35
2	Disease Control	0.15± 2.32
3	Standard	0.72 ± 1.5
4	Test	0.38 ± 1.8
5	Test + standard	0.81 ± 1.0

which implies that treatment with ketogenic diet along with phenytoin sodium have potent therapeutic activity when compared with phenytoin sodium alone the values are Table 5.

DISCUSSION

Isoniazid has its direct or indirect intervention with the GABA mediated neuronal transmission and finally results in convulsive seizure activity. The ability of drug like isoniazid to elicit seizure by snooping with GABA transmission rely upon the effect of Isoniazid in various regions of brain and its effects on excitatory neurotransmitters. The result of present study indicates that high doses of isoniazid administration leads to continuous degradation of GABAergic neurons in both Elevated plus maze and locomotors activity. Experimentally it has been shown that subcutaneous administration of isoniazid caused tonic clonic seizures in Elevated plus maze task for rats according to our findings. Treatment with high doses of isoniazid also leads to alteration of some brain cells which can explain the neuron behavioural deficits. In our present findings, administration of ketogenic diet potentiated its protective effect when compared to disease control group. GABAergic neurons are reported to play key role in behavioural aspects. Tonic colonic seizures affect GABAergic neurons resulting in the anxiety and excitation. However co-administration of ketogenic diet significantly potentiated its protective effect when compared to the effect produced by Disease control group. Thus, results strongly support our hypothesis that the seizures observed latter chronic isoniazid treatment might have arisen as a result of depletion of GABAergic neurons which directly acts on the destruction of GABA activity. However results also clearly indicate that chronic co-administration of ketogenic diet has potent therapeutic activity which was indicated through behavioural parameters.

CONCLUSION

Ketogenic diet contains significant amounts of vitamins, amino acids, calcium, protein etc which may be responsible for neurological activity. The results of the present study indicate that ketogenic diet along with phenytoin sodium shows potentiation role against isoniazid induced epileptic seizures. The present research has opened further research in the development of potent role of ketogenic diet.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

ABBREVIATIONS

GABA: Gamma Amino Butyric acid; **BHB:** Beta hydroxyl butyrate; **ATP:** Adenosine triphosphate; **ROS:** Reactive oxygen species; **NMDA:** N Methyl D Aspartate; **AMPA:**α Amino -3- hydroxyl-5- methyl-4-isoxazole propionic acid; **CNS:** Central Nervous system; **CSF:** Cerebro Spinal Fluid; **TLC:** Thin Layer Chromatography; **SC:** Subcutaneous; **IP:** Intra peritoneal; **mg:** Milligram; **Kg:** Kilogram; **min:** Minutes; **g:** grams; **hr:** hour; **ml:** millilitre; **µg:** microgram.

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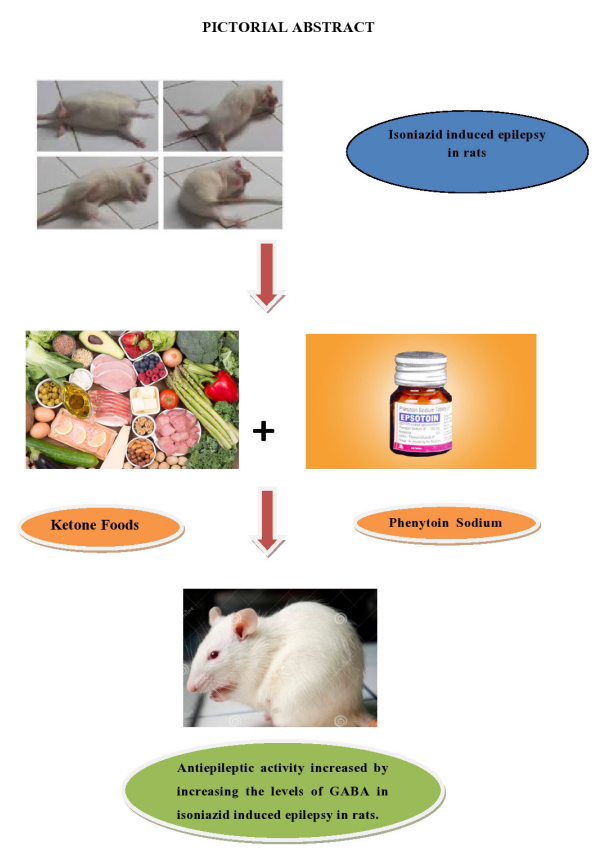
SUMMARY

Administration of ketogenic diet potentiated its protective effect when compared to disease control group. GABAergic neurons are reported to play key role in behavioural aspects. However co-administration of ketogenic diet significantly potentiated its protective effect when compared to the effect produced by Disease control group. Thus, results strongly support our hypothesis that the seizures observed latter chronic isoniazid treatment might have arisen as a result of depletion of GABAergic neurons which directly acts on the destruction of GABA activity. However our results also clearly indicate that chronic co-administration of ketogenic diet has potent therapeutic activity which was indicated through behavioural parameters in the treatment of epilepsy.

PICTORIAL ABSTRACT



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