



# The Protecting Effects of Antidiabetic Drug in Kainate Induced Lobe Encephalopathy

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## 1. Abstract

**Introduction:** Antidiabetic, the foremost ordinarily prescribed antidiabetic, has been shown to be effective in dominant seizures in some studies. However, there square measure some reports of proconvulsant activity of antidiabetic in diabetic patients. The aim of this study was to analyze the consequences of antidiabetic dose on anti-seizure and neuron protecting activity.

**Methods:** Male Wistar rats were arbitrarily divided into five teams as follows: 1-control/vehicle cluster, 2-Kainic acid (KA), 3-metformin+KA (50 mg/kg), 4-metformin+KA (100 mg/kg), 5-metformin KA (200 mg/kg). Lobe encephalopathy (TLE) was induced by injection of 0.5 five mineral into the left ventricle. Metformin was administered orally for 2 weeks before the induction of TLE.

**Results:** We have a tendency to found that antidiabetic at higher doses (100 and two hundred mg/kg) considerably suppressed the progression of seizure in TLE and ameliorated the neuron loss within the hippocampus induced by Hindu deity. However, the low dose of antidiabetic had no result.

**Conclusion:** We have a tendency to ended that antidiabetic is also a possible agent for the treatment of encephalopathy and seizure and this result is dose-dependent.

## 2. Introduction

Epilepsy could be a severe disorder that characterized by spontaneous perennial seizures [1]. Lobe encephalopathy (TLE) is one in all the foremost common and drug resistant sorts of encephalopathy in human with the consequence of hippocampal pathology. Hippocampal pathology is related to huge neuron loss in CA1, CA3 and also the fissure areas of the hippocampus and pathological synapses connections among the hippocampus [2]. Epilepsy and long-lived seizures conjointly cause neuron loss within the hippocampus in TLE [3]. Any medication which may management seizures or prevents neuron loss is also useful in TLE. its value mentioning that concerning third of epileptic patient's square measure immune to offered medications [4]. As several epileptic patients profit the utilization of ketogenic

diet [5] we have a tendency to suppose that medications which may management the body's energy levels may additionally management encephalopathy. antidiabetic could be a common polygenic disorder drug which may modulate AMPK, a key energy sensing element within the brain [6]. It's been reported that chronic antidiabetic treatment in PTZ kindling model, might terminate seizures [7].

The general protecting effects of antidiabetic square measure most likely because of the advance in epithelial tissue operate [8], anti-oxidative and anti-inflammatory functions [9]. However, in scopolamine-induced psychological feature deficit, antidiabetic show adose-dependent protecting effects [10].

Another study conjointly reveals a dose-dependent relationship between antidiabetic and body part cancers in patients with sort two polygenic disorder [11].

Regarding previous information, during this study, we have a tendency to attempt to investigate the dose-dependent medication effects of antidiabetic in a very model of lobe encephalopathy.

### 3. Materials and Methods

#### 3.1 Animals

Male Wistar rats (200-250 g) were obtained (n=40) from Islamic Republic of Iran University of Medical Sciences experimental studies, Tehran, Iran. The animals were unbroken in customary conditions as follows: 12-h light/dark cycle (lights on from 7:00 AM to 7:00 PM), environmental temperature  $22\pm 2$  °C, and wetness 40-50%. The food and water were offered throughout the study. All the experimental protocols and procedures were compiled in keeping with tips for the care and use of laboratory animals stipulated by National Institutes of Health (NIH).

#### 3.2 Experimental procedure

The rats were arbitrarily divided into five teams as follows: 1-control/vehicle cluster, 2- Kainic acid (KA), 3-metformin+KA (50 mg/kg), 4- metformin KA (100 mg/kg), 5- metformin KA (200 mg/kg). For induction of TLE, rats were 1st anaesthetized by the intraperitoneal (IP) injection of Ketalar (100 mg/kg) and xylazine (20mg/kg) and glued on a stereotaxic equipment (Stoelting Co, USA). once a plane mesial incision within the scalp, the left ventricle was targeted at the subsequent coordination from bregma; anterior-posterior: -1 mm; lateral, -1.5 millimeter and height: three.5 millimeter below the meninx. 1.8 eight of sterile traditional isotonic solution containing zero.5 five

of kainic acid was injected unilaterally into the left ventricle four employing an employing a Hamilton syringe. The needle remains within the place for 5 minutes then removed slowly to reduce the withdrawal of the drug. antidiabetic was dissolved in H<sub>2</sub>O and was administered orally at doses (50, 100, two hundred mg/kg) for 2 weeks. The last dose of antidiabetic was administered thirty min before microinjection of Hindu deity. Fourteen days once oral administration of antidiabetic and before TLE induction, aldohexose made up our minds by glucometer. Blood samples were collected tail veins.

#### 3.3 Assessment of epileptic behaviors

Following the microinjection of Hindu deity, the rats were video monitored for the seizure behaviors for 3 hours and also the outcome was assessed by someone blind to the cluster experiments. Seizure severity was rating in keeping with Racine's changed classification [12].

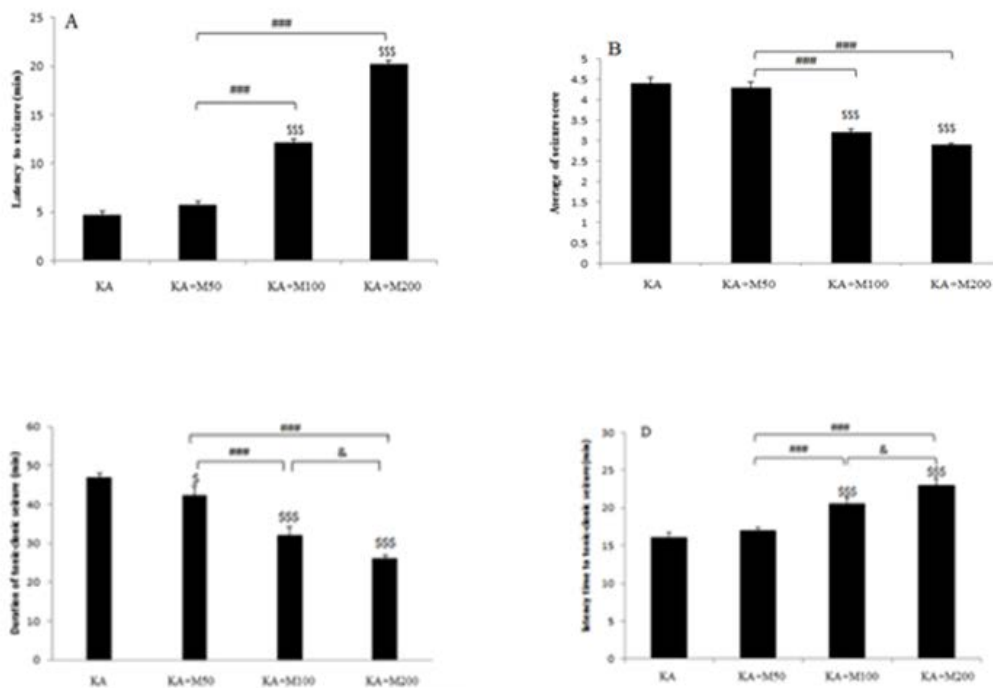
#### 3.4 The scores were as following:

1: no response; 2: conventional mounting, eye blinking, and /or delicate facial clonus; 3: head pendulous and/or multiple facial clonus; 4: myoclonic jerks within the forelimbs; 5: convulsion convulsions within the forelimbs with rearing and 6: generalized convulsion convulsions related to loss of balance. In addition, alternative parameters were monitored together with latency to the primary convulsion and length of tonic-clonic seizures (Figures 1 and 2).

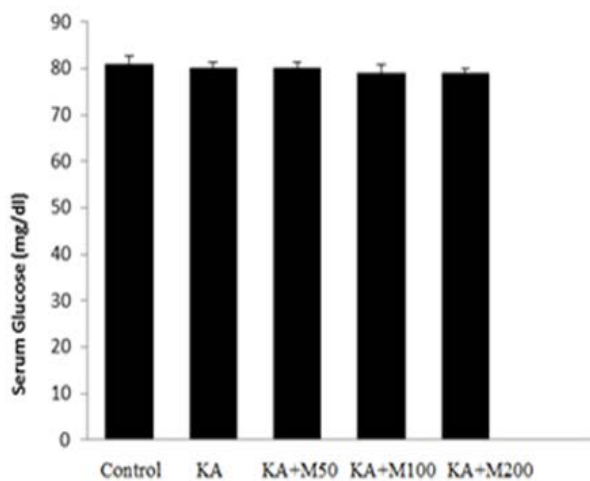
#### 3.5 Nissl staining

5 days once the Hindu deity injection, the rats (n=3 for every group) anaesthetized with Ketalar (100 mg/kg) and xylazine (20mg/kg) and perfused via the left internal organ ventricle with four-dimensional paraformaldehyde in 0.1 M phosphate-buffered saline (pH seven.4). For histopathological method, brains removed and post fastened long in half-dozen cubic centimeter of a similar ending answer. The brains were then embedded in paraffin for tissue sectioning. The sections (5µm) were cut employing a scientific instrument and were mounted on gelatin-coated glass slides for Nissl or Fluoro-Jade B staining. Four periodic Nissl-stained sections at the garland level of one-millimeter posterior to the craniometric point were used for cell counts and also the average was calculated. within the hippocampus, neurons were counted within the pyramidal cell layer of the CA3 and also the rough hilus.

The CA3 subfield made up our minds because the curve aria of CA3 from the CA3/2 border to the top of the curve. The rough fissure space was the purpose wherever



**Figure 1:** The anticonvulsant effects of Metformin at doses 50,100 and 200 mg/kg. (A) Latency to first convulsion, (B) Average of seizure score, (C) duration of tonic-clonic seizure and (D) latency time to tonic-clonic seizure. All data are presented as mean ± SEM\$\$\$ (P<0.001) vs. KA group, ### (P<0.001) vs. M50 group, & (p?0.05) vs. M200 group.



**Figure 2:** The glucose levels of rats which received different doses of metformin. No significant difference was observed between groups. Data expressed as mean± SEM.

the pyramidal cells enter the hilum until the top of the hilum. The Nissl staining performed in keeping with the zero.1% Cresyl violet protocol. Briefly, the slides were 1st dehydrated in ranked grain alcohol solutions and xylenes,

then stained in zero.1% Cresyl violet for one min. Total range of intact neurons in CA3 and fissure areas were counted (15×10<sup>3</sup>µm).

### 3.6 Fluoro-Jade B staining

Four sections of every brain used for Fluoro-Jade B staining. The Fluoro-Jade B staining was performed in keeping with our science laboratory protocol [13]. In brief, the slides were immersed in dissolvent, 100 percent grain alcohol for three min and seventieth grain alcohol for two min. more the sections were placed in a very answer containing 1 Chronicles hydrated oxide in eightieth alcohol for two min. after, they were rinsed in dH2O for two min before being transferred to an answer containing zero.01 Cataflam salt (KMnO4) for fifteen min. Following removal in dH2O, the sections were immersed into a zero.0004 Fluoro-Jade B operating answer for concerning thirty min darkly. The sections were then air dried within the dark for twenty min. Finally, the dry slides were cleared in dissolvent and canopy slipped with non-aqueous mounting medium, DPX. For observant chronic neurons a fluorescent magnifier with blue (450-490 nm) excitation lightweight was used.

## 4. Statistical Analysis

The results were expressed as mean  $\pm$  S.E.M. variations were thought of statistically vital at  $p < 0.05$ . applied mathematics analyses were performed exploitation the SPSS computer code package version sixteen. The variations between the teams of animals were take a look acted exploitation unidirectional analysis of variance followed by post hoc ergo propter hoc Tukey's test.

## 5. Results

### 5.1 Effect of various doses of antidiabetic on epileptic behaviors

Epileptic behaviors in every cluster were assessed by evaluation seizure latency, seizure severity, latency to development of tonic-clonic seizures and length time in tonic-convulsion stage.

Figure 1 compares the epileptic behaviors between Hindu deity and metformin+ Hindu deity teams. because it is shown in (Figure1A), latency to the primary seizure was considerably augmented within the metformin KA teams in doses of a hundred and two hundred mg/kg compared to the Hindu deity cluster ( $P < 0.001$ ). However, antidiabetic at doses of fifty mg/kg had no result on seizure latency. (Figure 1B) shows the results of average seizure score. The severity of seizure was reduced solely in doses of a hundred and two hundred mg/kg of antidiabetic ( $P < 0.001$ ). length of tonic-clonic stage were considerably attenuated all told teams of antidiabetic ( $P < 0.05$  for the dose of fifty mg/kg and  $p < 0.001$  for the doses of a hundred and two hundred mg/kg). However, rats in dose of two hundred mg/kg of antidiabetic had very cheap length time of tonic-clonic stage. Latency time to tonic-clonic stage was incontestable in (Figure1D). Latency to tonic-clonic stage was considerably augmented within the metformin KA cluster at doses of a hundred and two hundred mg/kg compared to the Hindu deity cluster ( $P < 0.001$ ). No vital distinction was discovered between 50mg/kg antidiabetic with Hindu deity cluster.

### 5.2 Effect of various doses of antidiabetic on glucose

As (Figure 2) shown, aldohexose au fait rats was concerning 81mg/dl. once rats were treated with completely different doses of antidiabetic, the aldohexose was slightly down to seventy-nine mg/dl that wasn't vital. There was no significance between the aldohexose levels in numerous antidiabetic doses. This indicated that antidiabetic at doses of fifty, a hundred and two hundred mg/kg didn't turn out hypoglycemia.

Effect of oral administration of antidiabetic on neuronicsphacelus in KA-induced rat model of TLE

A large range of neurons were lost within the CA3, and fissure regions within the kainate cluster. However, no nissl-stained dark neurons were detected au fait cluster Metformin at dose of two hundred mg/kg markedly protected against kainate-induced death of neurons in CA3 still as fissure regions within the hippocampus ( $P < 0.001$ ). In distinction, antidiabetic at doses of fifty and a hundred mg/kg couldn't considerably forestall neuronics loss in fissure and CA3 space ( $P < 0.001$  vs control).

Effect of oral administration of antidiabetic on neurodegeneration of fissure and CA3 areas in KA-induced rat model of TLE

Consistent with previous reports of neurotic death within the kainate model, our results incontestable huge neurotic death by Fluoro-Jade B staining once kainate epilepsy in neurons from the rough hilum and CA3 pyramidal regions. In distinction, in rats pretreated with antidiabetic, a hundred and two hundred mg/kg had shown solely thin positive degenerating pyramidal neurons. Pre-treatment with antidiabetic fifty mg/kg wasn't terribly effective in reducing the number of chronic neurons.

## 6. Discussion

Metformin a medicine for treatment of polygenic disorder and management of glucose might trigger epileptic behaviors. The anti-seizure activity of Glucophage has been recently shown. However, there are some reports in clinic showing the pro-convulsing result of Glucophage. It appears that the result of Glucophage on encephalopathy is betting on the dose. This study was designed to reveal any proconvulsant or antiepileptic drug result of Glucophage at totally different doses. we tend to used 3 totally different doses of Glucophage (50,100,200 mg/kg) in an exceedingly TLE model elicited by Hindu deity in rat. In our study all 3 doses failed to induce symptom. this can be in accordance with an information showed that very cheap dose of Glucophage which might induce symptom in rat is 350 mg/kg. It appears that Glucophage intrinsically isn't proconvulsant however within the condition of symptom, the low level of aldohexose trigger seizure. Though epileptic seizures are the rare consequences of symptom however it's been according in some cases.

In our studies none of the 3 doses of Glucophage created neither symptom nor seizure behaviors. In distinction, the upper doses (100 and two hundred mg/kg) have exerted antiepileptic drug and neuroprotective effects. as compared

of the 2 high doses, the dose of two hundred mg/kg was even simpler. The dose dependency of Glucophage in neural protection has been investigated in an exceedingly study during which 2 doses of Glucophage (100 and three hundred mg/kg) are used for 2 weeks. Their results unconcealed that Glucophage at dose of 100 mg/kg was terribly effective in reducing inflammatory factors and melioration of memory deficit [10]. It appears that Glucophage, solely within the average medication doses (100 and two hundred mg/kg) has antiepileptic drug and protecting effects against KA-induced TLE. Glucophage acts in 2 totally different pathways: AMPK dependent pathway and AMPK freelance pathway. The AMPK dependent pathway is helpful in treating encephalopathy. In Associate in Nursing in vitro study the dose dependent result of glucophage on audiogenic differentiation has been incontestable.

The authors have over that lower concentrations of Glucophage induce adipogenesis, that may well be mediate in Associate in Nursing AMPK-independent manner, whereas higher concentrations of Glucophage inhibit adipogenesis via AMPK activation.

Our knowledge regarding the antiepileptic drug effects of Glucophage is in accordance with different studies. In mice chronic Glucophage expedited seizure termination. In another study, administration of Glucophage in an exceedingly post-traumatic brain seizure model elicited by FeCl<sub>3</sub>, reserved the onset of seizures in rat. Our results additionally unconcealed a potent protecting role of Glucophage in CA3 and also the hilum space of the hippocampus. 5 days once induction of TLE by mineral, the neural layer in CA3 are noncontinuous. Glucophage in 2 higher doses fully fixed up this neural design disruption. However, Glucophage in lower dose wasn't in the slightest degree effective. The neuroprotective effects of Glucophage are often attributed to totally different mechanism; inhibition of inflammation pathways through NF- $\kappa$ B and MPK signal, lowering the aerophilous stress and anti-apoptotic and melioration of mitochondrial dysfunction.

Further investigations ought to reveal the precise mechanism of dose dependent result of Glucophage in encephalopathy.

## 7. Conclusion

Altogether we tend to conclude that the effectivity of Glucophage is dose-dependent in TLE. the common doses (100 and two hundred mg/kg) that are below hypoglycemic dose works higher than low dose.

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