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Histopathological Changes in Cerebellum on Administration of Kainic Acid in Experimental Models.

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ABSTRACT

Kainic acid induced neuronal excitation and selective vulnerability in the hippocampal neurons are related to the distribution and selective susceptibility of the AMPA/kainate receptors in the brain. Recently, the neuro-physiological studies also suggested that the cerebellum also could participate in excitotoxicity. A total of 12 adult male albino rats of wistar strain weighing 135-150 grams were used for the present study. The rats were divided in to four groups each consists of 4 animals. The control group was given 0.9% saline as vehicle and the experimental groups (drug treated-II, III, IV) were given an intra peritoneal injection dose of 0.5 mg/kg, 0.75 mg /kg and 1mg/kg body weight respectively for a period of 28 days. Purkinje cell loss was not much in number and granular cells were normal in 0.5 mg/kg KA induced group. There was a loss of Purkinje cell layer (very few cells) and cells were in degenerative stage stained lightly. We were also observed all the other layers and white matter of the cerebellum in 0.75 mg/kg induced group. Dose of 1mg/kg Kainic acid induced group animals shown significant loss of Purkinje cells and disruption of cellular layers and granular cells. There were vacuoles in white matter when compared to other drug treated groups was found in the same group. Previous literatures stated that mechanisms underlying the pathogenesis of kainic acid induced cerebellar excitotoxicity remain unknown. The present study gives histopathological knowledge of neuronal cell death in cerebellum at different doses on long term administration of kainic acid but cellular mechanisms need to be evaluated.

Keywords: cerebellum, degeneration, kainic acid, Purkinje cells

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INTRODUCTION

Kainic acid (KA) is a neuroexcitotoxic agent by acting on specific kainate receptors in the Central nervous system. KA-induced neurodegeneration in rodents has been used as a model for exploring the pathogenesis of excitotoxicity in neurodegenerative disorders [1]. Kainic acid activates Kainate receptors (KARs) and on higher concentrations AMPA receptors. KA induced cell death has been confirmed through activation of KARs. KARs are widely expressed throughout the development of rat brain particularly hippocampus, cortex, thalamus and cerebellum [2, 3]. KA has been shown to increase production of reactive oxygen species, mitochondrial dysfunction, and apoptosis [4].

MATERIALS AND METHODS

A total of 12 adult male albino rats of wistar strain weighing 135-150 grams were used for the present study. The animals were maintained under controlled conditions and in room temperature ($23+2^0$ C), humidity (50+5%) and a 12 h light and dark cycle. The animals were housed in sanitized polypropylene cages. The animals were fed with standard rat pellet diet commercially available manufactured by kamathenu Pvt Ltd., Bangalore and clean drinking water ad libitum. The rats were divided in to four groups each consists of 4 animals. The control group was given 0.9% saline as vehicle and the experimental groups (drug treated-II,III,IV) were given an intra peritoneal injection dose of 0.5 mg/kg, 0.75 mg /kg, 1mg/kg body weight (standardized after acute and subacute toxicity study) kainic acid dissolved(1:2) in DMSO respectively for a period of 28 days. All the animals were sacrificed after a 12 hrs of fasting from the last day of experimental study and preserved in the 10% formalin for 48 hours. The specimens were processed for routine histopathological examination to study the histopathological changes in cerebellum on administration of Kainic acid. All the animals were maintained as per the national guidelines and protocols approved by Institutional animal ethical committee of Sugen Life sciences (SLS/COM/IAEC/02/2013-2014).

RESULTS

We have observed all the three cortical layers of cerebellum and white matter in the control group. Molecular layer with basket and stellate cells, single Purkinjee cell layer lies between the molecular and granular cell layer was observed. Granular cell layer with granule cells (pink stained) glomeruli (light stained) were also observed in control group. We have observed Column of nerve fibers in the white matter of cerebellum (Figure - 1).In group II, all the layers of cortex were present and purkinje cell loss was not much in number and granular cells were normal (Figure - 2). In group III, There was a loss of Purkinje cell layer (very few cells) and cells were in degenerative stage stained lightly. We were also observed all the other layers and white matter of the cerebellum in the same group (Figure - 3). Under high magnification we have observed the granular and pale stained Purkinje cells (Figure - 4).In group-IV; we have observed there was significant loss of Purkinje cells and disruption of cellular layers and granular cells. There were vacuoles in white matter when compared to other drug treated groups was found in the same group (Figure - 5).

Figure 1: Cortical layers of cerebellum and white matter in the control group (10X magnification)

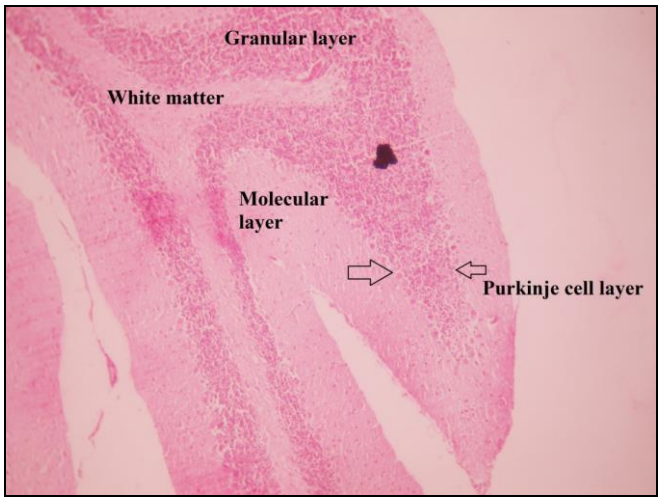

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Figure 2: Purkinje cell loss was not much in number and granular cells were normal in animals treated with 0.5mg/kg kainic acid

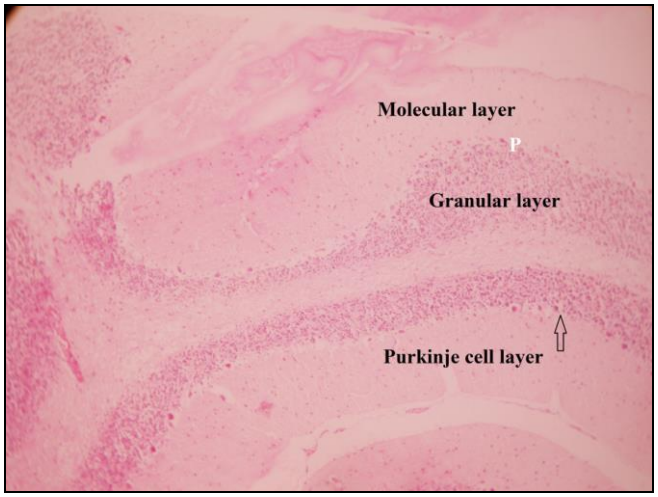

Figure 3: Loss of Purkinje cell layer (very few cells) and cells were in degenerative stage stained lightly in animals treated with 0.75mg/kg kainic acid (10X)

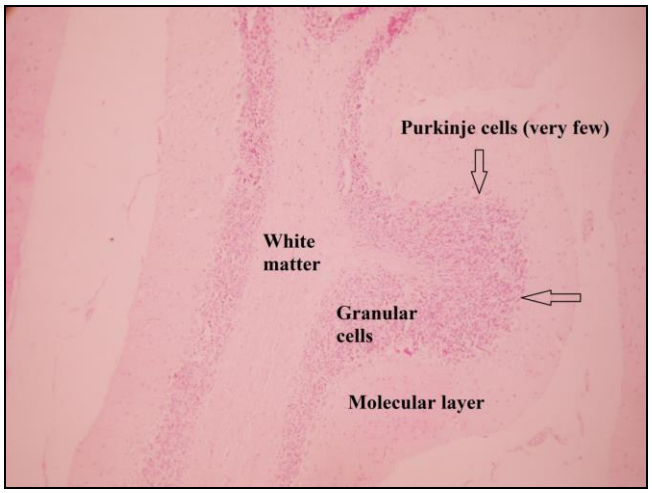

Figure 4: Loss of Purkinje cell layer (very few cells) in animals treated with 0.75mg/kg kainic acid (40X)
(granular and pale stained Purkinje cells)

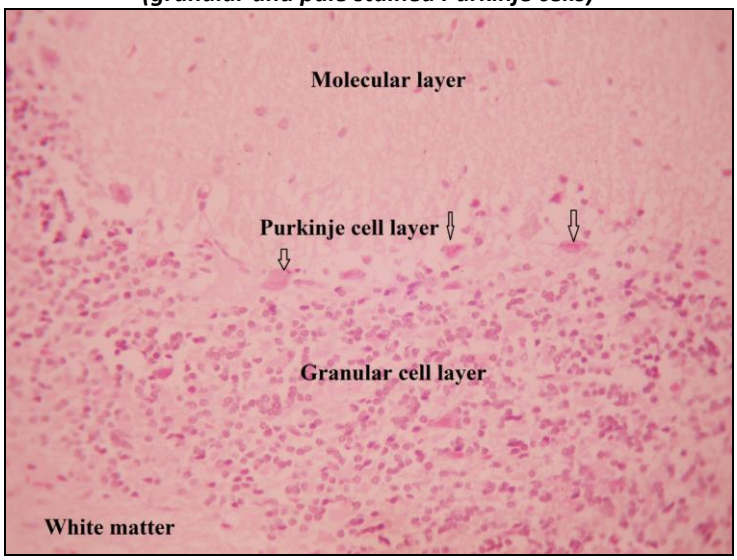

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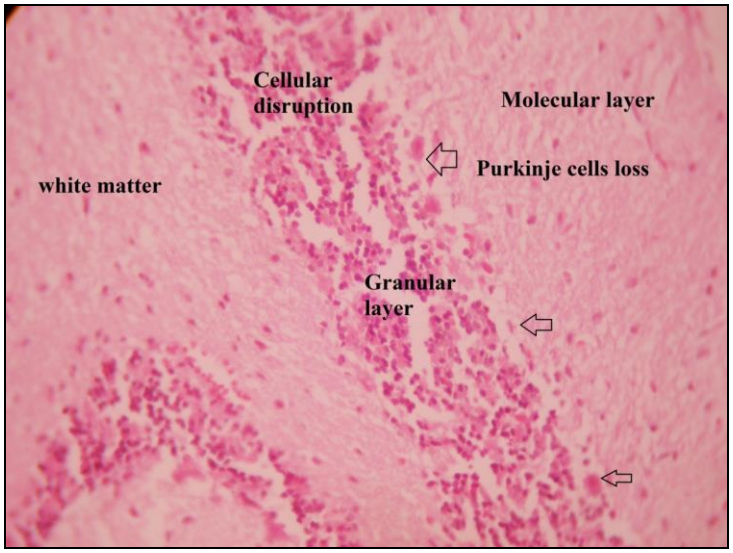
Figure 5: Significant loss of Purkinje cells and disruption of cellular layers and granular cells. Presence of vacuoles in white matter of cerebellum (40X)



DISCUSSION

Extent and location of Kainic acid induced neurodegeneration seems to depend on the concentration of Kainic acid and the route of its administration [5]. In our study there was a significant loss of Purkinje cell layer, disruption of cell layers and changes in white core of cerebellum from low dose (0.5 mg/kg) to high dose (1.0mg/kg) for a period of 28 days. Systemic kainic acid administration leads to neuronal degeneration, characterized among others by cell loss, when kainic acid is administered once or repeatedly [6]. Kainic acid activates the KA receptors and, on higher concentrations activates the AMPA receptors. This is in agreement with concentration of kainic acid administered in the previous literatures [2, 7]. Herndon et al reported that there was a less damage to cerebellar cortical granule cells on administration of kainic acid. The type of receptor responsible for Kainic acid effects on neuronal damage apoptosis in Cerebellar Granule Cells is a matter controversy[8].Literature stated that neuronal degeneration in brain was due to AMPA receptors in KA-induced neuronal damage in animal models[9,10,11].In our study there was a complete loss of purkinje cells and disruption of cellular layers and vacuoles in white core of cerebellum was observed in 1mg/kg kainic acid administered group. This is due to higher concentrations of kainic acid activates the AMPA receptors on long term administration which may cause neuronal degeneration in the cerebellum according to previous literature [2, 6, 9, 12].

CONCLUSION

There were many studies on kainic acid induced neuronal degeneration in hippocampus, cortex and thalamus in experimental models, but very few literatures are available on kainic acid induced cell death in cerebellum and its histopathological studies. The present study reveals histopathological knowledge of neuronal cell death in cerebellum at different doses on long term administration of kainic acid.

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Conflict Interest: NIL

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