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EFFECT OF KAINIC ACID ON THE HISTOLOGICAL STRUCTURE OF SPINAL CORD'S MOTOR NEURONS

Shimaa El-Sayed Mohammed [1], Amany Farag Amien[1] , Ahmed Abd-Elmaksoud[1], Mohammed Mohammed Kassab[2].

[1] *Cytology and Histology department. Faculty of Veterinary Medicine. Mansoura University.*
[2] *Cytology and Histology department. Faculty of Veterinary Medicine. Kafer-Elshikh University.*

ABSTRACT

Kainic acid (KA) is an analog of the neurotransmitter glutamate and is frequently used as an excitotoxic agent to the spinal cord. KA providing an interesting model to study basic mechanisms of spinal cord injury. The present work was aimed to study the effect of kainic acid on histological structure of spinal cod's motor neurons. Rats were intra-spinally injected with 2.5 mM of KA between thoracic-13 (T13) and lumbar-3 (L3). Histological consequences of spinal cord were examined at 1, 3, 7,14,30,60 days post injection. A variety of degenerative changes were observed in ventral horn of spinal cord, meanwhile the white matter and dorsal horn showed relative preservation of tissue architecture and its neuron were almost completely spared by K.A. injection in all time of the study.

INTRODUCTION

The spinal cord is a part of the central nervous system (CNS), which extends caudally from the foramen magnum to the level of the first or second lumbar vertebrae in some animal and other to the level of 3rd lumbar vertebrae. Spinal cord divided into two symmetrical portions along the side of median sagittal plane by anterior and posterior median fissures. The two portions connected to each other by transverse dorsal and ventral commissures ***(Inderbir, 2014).***

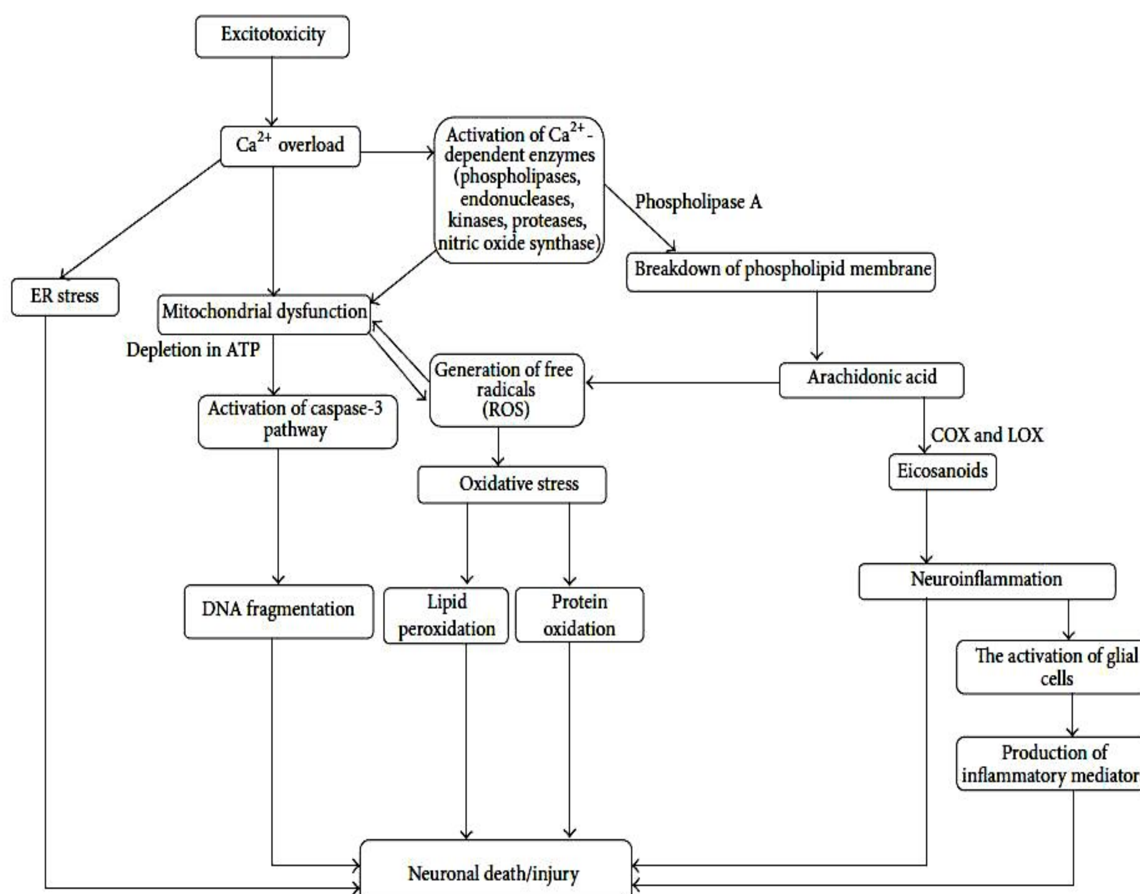
Unlike the brain, the white matter surrounded the grey matter in the spinal cord. The white matter is ordinarily divided into the dorsal, dorsolateral, lateral, ventral and ventro lateral funiculi ***(Inderbir, 2014)***.In each half of the cord the grey matter can be divided into a larger ventral or anterior grey column (ventral horn), and a narrow elongated dorsal or posterior grey column (dorsal horn). A small lateral projection of grey matter(lateral horn) is seen at the thoracic and upper lumbar levels of the spinal cord between the ventral and dorsal grey columns, which is considered the source of efferent sympathetic neurons of the autonomic nervous system ***(William and Patrick, 2013).***

The ventral horn of the spinal cord encloses the cell bodies of motor neurons. Its axons extend out of the spinal cord through the ventral root ***(Barbara., 2006 and Inderbir, 2014***). The dorsal horn of the spinal cord encloses the cell bodies of ascending secondary sensory neurons. The primary sensory neurons have their perikaryon outside, but just close to, the spinal cord in the dorsal root ganglion ***(Antal and Gerta, 2006).***

KA [2-carboxy-4-(1-methylethenyl)-3-pirrolidiacetic acids was first segregated from a type of seaweed in Japan ***(Murakami et al., 1953)***. KA was used as an anthelminthic

compound for removal worms in the gut ***(Shinozaki and Konishi, 1970),*** consequently, it was revealed that local application of KA on neurons possess excitatory action and, moreover, that KA causes neuronal destruction, particularly in the pyramidal cells of the hippocampus (***Nadler et al., 1978).***

KA has been extensively utilized as a specific agonist for ionotropic glutamate receptors (iGLURs) to mimic the effect of glutamate in neurodegenerative models. It is 30-fold more potent in neurotoxicity than glutamate ***(Bleakman and Lodge 1998).*** KA exerts its action by binding to kainate receptors and stimulates glutamate receptors and the over motivation of glutamate receptors causes depolarization of neuronal membranes, which lead to the influx of calcium ion (Ca2+) and generates excitotoxic neuronal death cascade events that are depicted in the following figure:



Mechanism of action in KA excitotoxcicity model (Mohd sairazi et al., 2015)

Following the injection of KA on rodents, oxidative stress may possess a related role in neuronal and glial cell death ***(Bruce and Baudry; 1995; Nakao et al., 1996, Gluck et al., 2000; Kim et al., 2000; Melo et al., 2011)***.The oxidative stress occurs when there is no equilibrium between antioxidant and the production of free radicals. High level of intracellular calcium initiates the formation of free radicals.

Overstimulation of glutamate receptors by KA leads to the excessive production of

reactive oxygen species (ROS), the mediators of oxidative stress ***(Bruce and Baudry, 1995).*** These ROS oxidizes membrane element and DNA. Exceesive influx of Ca^{2+} also leads to the activation of various Ca^{2+} dependent enzymes **(Wang et al., 2005).** Those enzymes involved kinases, phospholipases (responsible for membrane damage), endonucleases (causes DNA fragmentation), proteases (cause damage of membrane and cytoskeletal proteins), phosphatases, and nitric oxide synthase (NOS) ***(Ong et al., 1997, and Wang et al., 2005).***

The neurotoxic action of kainate is accompanied by activation of microglia and astrocytes, which proliferate and migrate into the affected region ***(Jorgensen et al., 1993).*** Activated astrocytes and microglia secrete a large amount of inflammatory mediators, such as tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL1-β) and nitric oxide (NO) which influence the neurodegeneration outcome ***(Ravizza et al., 2005; Zhang et al., 2007).***

So the aim of our study is evaluate the histological structure of spinal cord' s motor nrurons after intra spinal injection of KA.

MATERIALS & METHODS

❖ Animals:

- Twenty one male rats (weighing 250 g to 300 g) were housed in autoclaved plastic cages under a temperature-controlled environment of 24 ± 1 ° C with access to rat-chow and water ad libitum and 12-hours light-dark cycle. The rats were adapted to the environment 7 days prior to the experiment.
- All experimental procedures were conducted according to the Institutional Animal Care and Use Committee guidelines at the University of Mansoura, Egypt. Every effort was made to minimize both the number of animals used and their suffering.

❖ Experimental Design:

- The rats were divided into two groups for, histological and pathological evaluation.
  1. Normal control group: (n=3) was left under observation without treatment.
  2. Excitotoxic lesion group: (n=18) bilaterally intra spinal injected with K.A.

❖ Animal Surgery:

The rats were anaesthetized using a combination of Ketamine (60 mg/kg body weight) and Xylazine (20 mg/kg body weight) administrated intraperitoneally (IP). With electric clippers, the dorsal area of the rat was shaved from the lower back to the neck, and extended 2 cm bilateral from the midline. Animals were placed in a stereotaxic frame and with a vertebral clamp, the vertebral column was immobilized. Incision site was regarded as two horizontal lines, one crossing at fore limbs level and the other crossing at hind limbs level. The space between these two lines was divided into three equal extension portions: an anterior portion, a middle portion and a posterior portion. A longitudinal incision of approximately 2.5 cm was performed. The incision was performed at 1 cm behind the union site between anterior and posterior segments. By using this technique, we addressed the animals' spinal cord between T-13 and L3 (***Braga-Silva*** **et al., 2007).** The spinous process and vertebral lamina of one spinal segment were removed. Once the cord was exposed, the dura was incised longitudinally and bi laterally reflected.

❖ **Intra spinal Injection Procedure:**

The method used was similar to those of ***Yezierski et al., (1993)*** with the exception that KA (1.5 µL of 2.5 mM K.A dissolved in 0.9% saline) was bilaterally microinjected. The injection occurred via glass micropipettes (tip diameter 10-15 µm) attached to a 10-µL Hamilton syringe. Injections were made 1.6 mm from dorsal surface, approximately 0.5 mm from mid line ***(David et al., 1999)*** .The needle was held in place for 2 mints to avoid leaking of the solution. Body temperatures were monitored continuously during injury procedure and were maintained between 36^{oc} and 37^{oc} by a thermostatically regulated heating pad. Lubricant ointment was applied to the eyes to prevent drying. Muscles were sutured in layers and the overlying skin was closed, after microinjection.

❖ **Post-operative Care:**

After surgery, topical antibiotic was applied to the incision site .To avoid dryness, 2 cc of lactated Ringer's solution was given subcutaneously. Each rat was singly housed until fully recovered from anesthesia. The rat was returned to housing in the following day and provided with softened rodent chow and water. Prophylactic analgesics and antibiotics were also used. Assistance of bladder function was not required after KA excitotoxic model.

❖ **Samples collection:**

- Control group: 3 rats were sacrificed at the end of the study.
- KA injected group: 3 rats were scarified each at 1, 3, 7, 14, 30, 60days after KA injection.

Histological Analysis:

- **light microscope (LM) tissue fixation and processing**

The spinal cords were removed. The injection sites were then localized under sterio microscope to include segments from thoracic-11 (T11) to approximately lumbar-5 (L5). The cord was postfixed in the 10% neutral buffered formalin for 24 h. Fixed samples were dehydrated in graded series of ethanol (70%, 95% and absolute), cleared in xylene and impregnated and embedded in paraffin. A rotatory microtome was used to cut (5 µm) transverse sections and mounted on glycerol-albumin-coated glass slides. The paraffin sections kept in an incubator at 50^{oC} for 20 minutes then used it for conventional staining.

- **Tissue Staining**

Two types of stain were used; haematoxylin–eosin (H&E) for general histological studies ***(Bancroft et al., 2015)*** and Cresyl Echt Violet stains for Nissl substance ***(Carson et al., 2015).***

RESULT

1. **Control group:**

In H&E stained sections, the spinal cord of rat was composed of two distinct parts; an outer white matter and an inner gray matter.

Within the spinal cord, the gray matter was formed of an H-shape where the ventral horns of the H were broader than the dorsal horns. The shape of gray matter was similar to that of a butterfly within it a central canal is located (Fig. 1). The dorsal horns contain large amount of densely packed small cell body of

sensory neuron and neuroglia cells (Fig. 2) whilst the large cell bodies of motor neurons were found in ventral horn (Fig.3).

The gray matter is formed primarily of the neuronal cell bodies, mixture of glial cells, several blood capillaries and fine amorphous eosinophilic background called neuropil. Neuropil is a meshwork of neuronal and glial cell processes that interwoven with each other. In routine stain, the individual neurites that comprise the neuropil are not generally recognizable (Fig. 4).

The cytoplasm of the surrounding neuroglia cells (oligodendrocytes, astrocytes and microglia) was not visible in H&E stained sections and neuroglia cells were identified mainly by their nuclear characteristics (Fig. 4).

At a higher magnification, the multipolar neurons within the gray matter were irregular in shape, with basophilic cytoplasm and large spherical lightly-stained vesicular nuclei with prominent nucleoli. (Fig. 5)

The Nissle granules appeared as basophilic mottled structures with cresayl violet stain in the cytoplasm of neuronal cell bodies and dendrites, but not in axons. The neuropil will be stained a granular purple-blue (Fig. 6).

The central canal was identified within the center of the H-shape gray matter. It was lined with cuboidal ependymal cells, a type of neuronal supporting cell (neuroglia) that forms the epithelial lining of central canal (Fig. 7).

The white matter had a fine meshwork-like appearance, and was composed mainly of sensory and motor nerve fiber (most of it are mylinated) and various types of neuroglia cells (oligodendrocytes and astrocytes). (Fig. 8).

2. Excitotoxic lesion group:

The neurodegenerative changes followed KA injection were assessed during the period of study starting from 1 day to eight weeks post injury.

K.A Lesions were mainly located in the ventral horn of the spinal cord. On the other hand, dorsal horn showed relative preservation of tissue architecture and its neuron were almost completely spared by K.A. injection from 1 day to eight weeks post injury. The dorsal, ventral and lateral funiculi of spinal cord remained morphologically intact after K.A. injection during the whole period of study.

At the 1st and 3rd days post injury, a variety of degenerative changes were observed in ventral horn of spinal cord. The affected neurons are characterized by cell body shrinkage, intensely stained eosinophilic cytoplasm (red dead neuron) and loss of Nissl substance (chromatolysis) .The nuclei were also pykonotic with irregular chromatin clumps and loss its morphological details (Figs.8). The neuropil adjacent to the degenerating neurons was finely vacuolated as well as moderate astrocytic reactions were detected in it. (Figs.9, 10)

One and two weeks post injury; the intermediate and ventral horn gray matter showed sequential morphological alterations resemble that at the 1st and 3rd days, but gliosis started to invade the damaged area and the edema in neuopil was more pronounced (Fig.11,12).

At four and eight weeks post injury, no pronounced differences were noticed in H&E or cresayl violet stains in the lesioned area (Figs.13, 14).

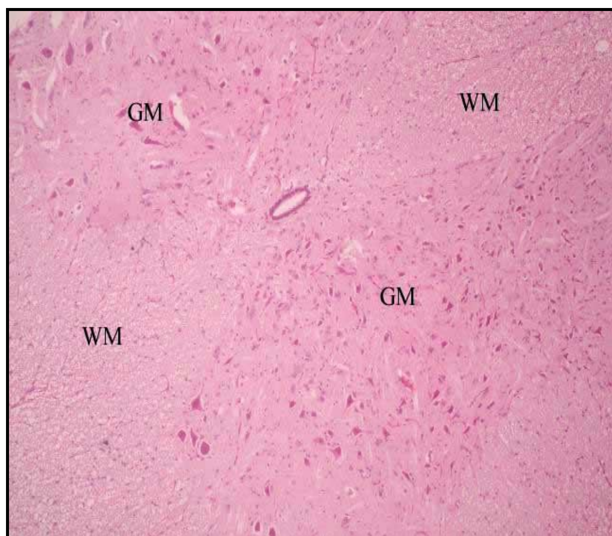


Figure (1): Photomicrograph of a section of rat's spinal cord of 1st control group showing buttery fly gray matter (GM) surrounded by white matter (WM).H&E stain x10.

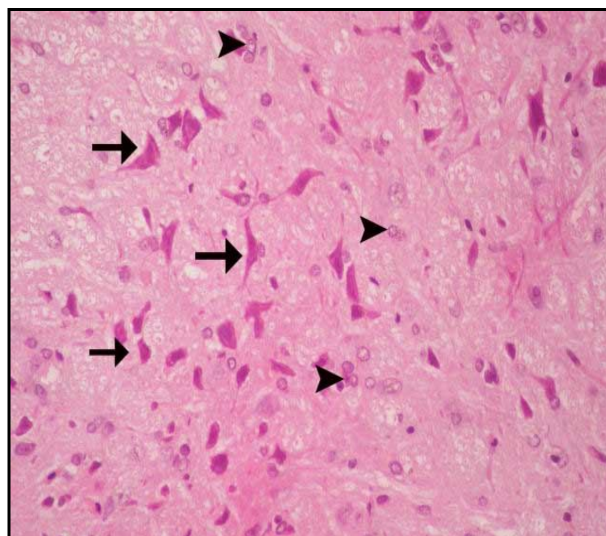


Figure (2): Photomicrograph of a section of rat's spinal cord of 1st control group showing densely packed small cell body of sensory neurons (arrows) and neuroglia cells (arrow heads) within dorsal horn H&E stain x40.

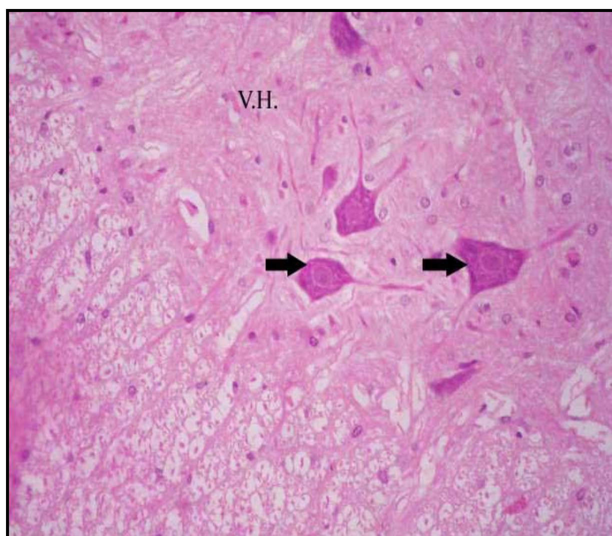


Figure (3): Photomicrograph of a section of rat's spinal cord of 1st control group showing large cell bodies of motor neurons (arrows) within ventral horn (V.H.). H&E stain x40.

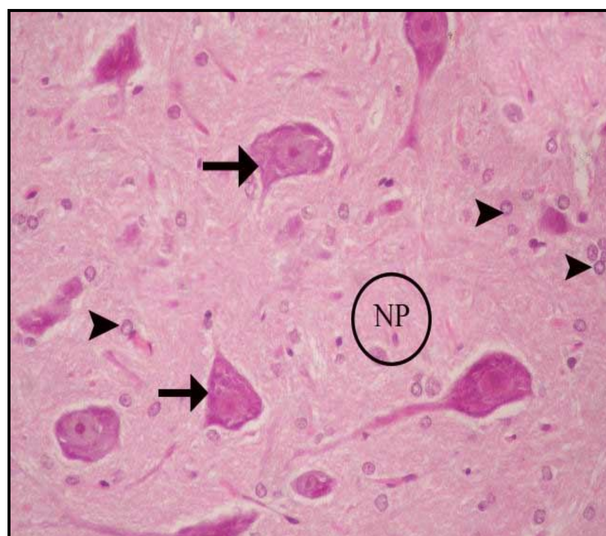


Figure (4): Photomicrograph of a section of rat's spinal cord of 1st control group showing gray matter of ventral horn containing neuronal cell body (arrows), neuroglia cells (arrow heads) and poorly organized area of neuropil (NP) H&E stain x40.

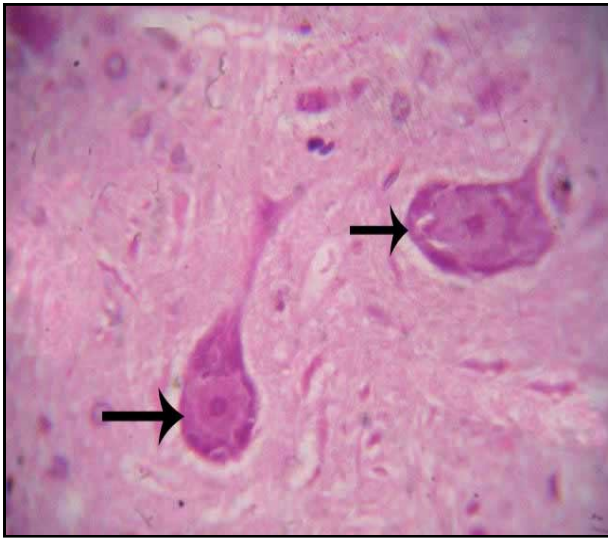


Figure (5): Photomicrograph of a section of rat's spinal cord of 1st control group showing multipolar neuron (arrows) with basophilic cytoplasm and spherical vesicular nucleus containing prominent nucleolus. H&E stain x100.

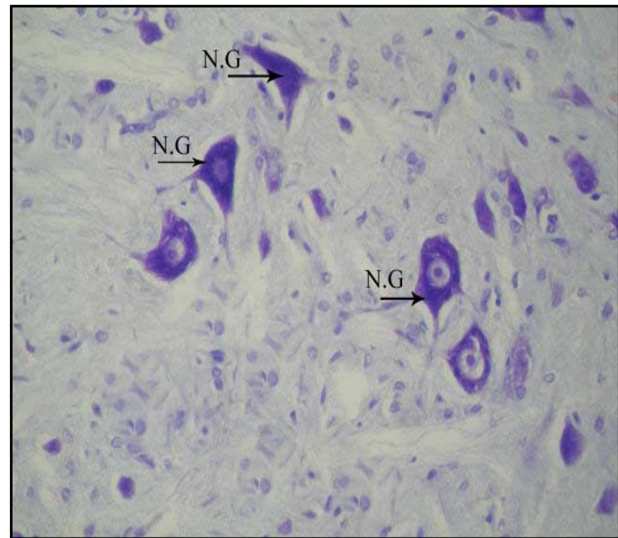


Figure (6): Photomicrograph of a section of rat's spinal cord of 1st control group showing Nissl granules (N.G) as basophilic mottled structures in the cytoplasm of neuronal cell bodies and dendrites. Cresayl violet stains. X40.

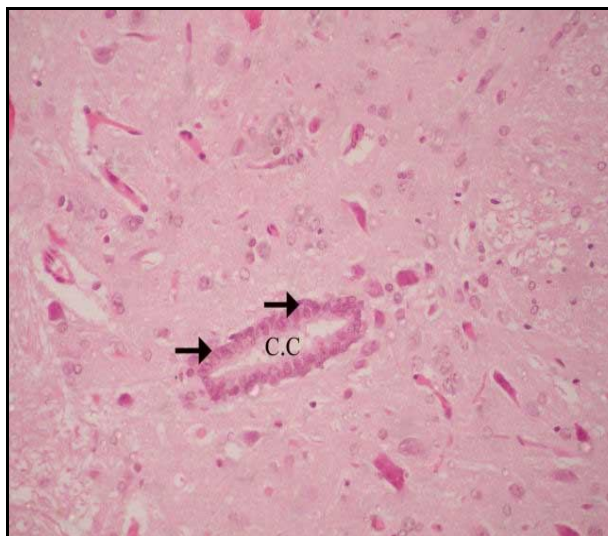


Figure (7): Photomicrograph of a section of rat's spinal cord of 1st control group showing central canal (C.C) lined with cuboidal ependymal cells (arrows). H&E stain x40.

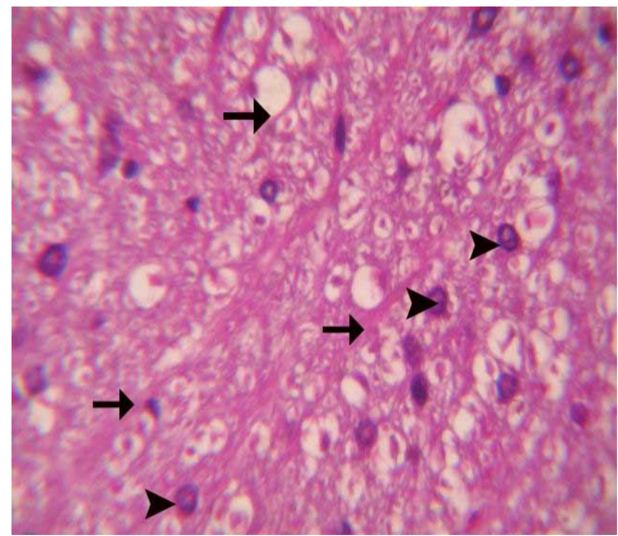


Figure (8): Photomicrograph of a section of rat's spinal cord of 1st control group showing white matter composed of nerve fibers (arrows) and neuroglia cells (arrow heads). H&E stain x100.

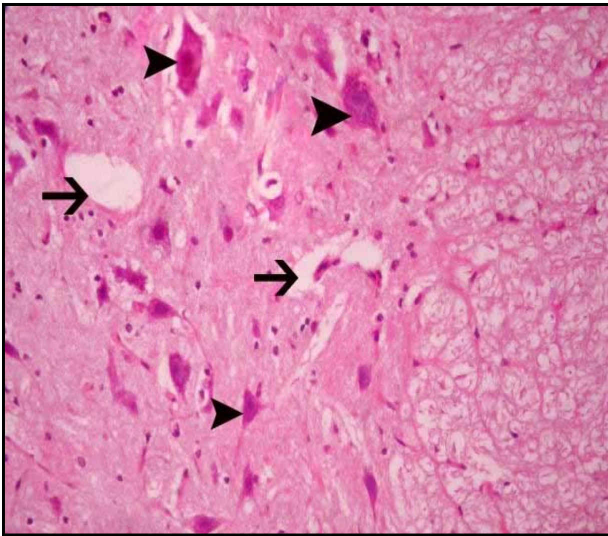


Figure (9): Photomicrograph of a section of rat's spinal cord of lesioned group 3days post KA injection showing shrinkage, intensely stained eosinophilic neuron (red dead neuron)(arrow heads) and vaculated neuropil (arrows). H&E stain x40.

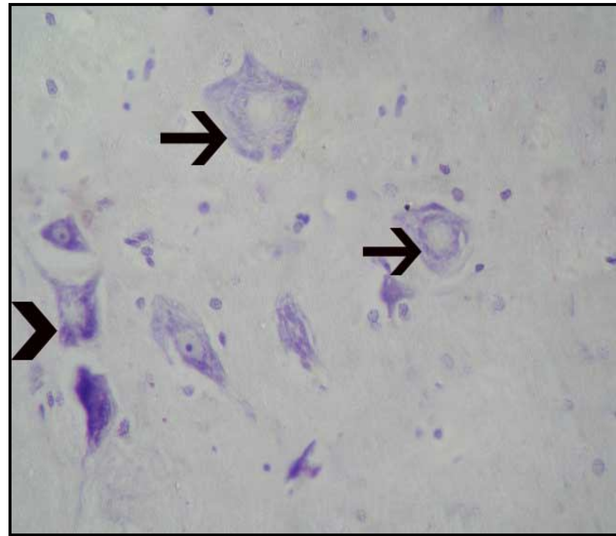


Figure (10): Photomicrograph of a section of rat's spinal cord of lesioned group 3day post KA injection showing degenerative neurons characterized by chromatolysis (arrows) and loss of nucleus outline (arrow head). Cresayl violet stains. X40.

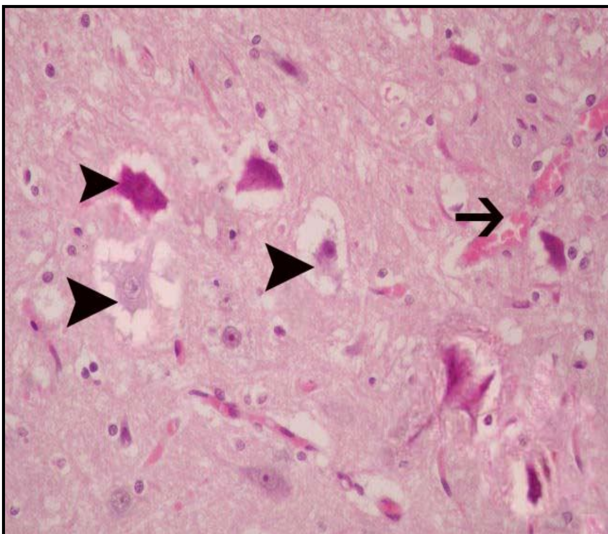


Figure (11): Photomicrograph of a section of rat's spinal cord of lesioned group 2 werks post KA injection showing debris of degenerated neurons (arrowheads) and congested blood vessels (arrow) .H&E stain x40.

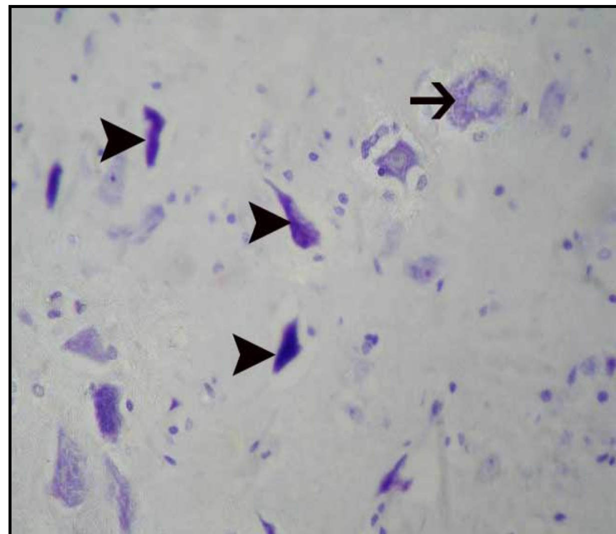


Figure (12): Photomicrograph of a section of rat's spinal cord of lesioned group 2 werks post KA injection showing debris of degenerated neurons (arrow head) and chromatolysis (arrow). Cresayl violet stains. X40.

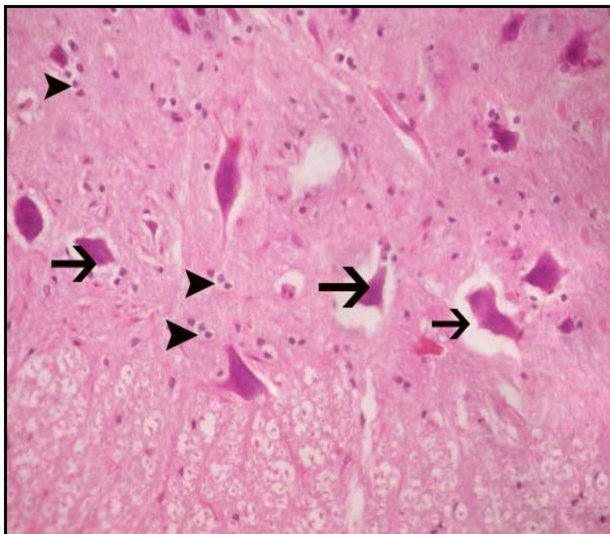


Figure (13): Photomicrograph of a section of rat's spinal cord of lesioned group 2 months post KA injection showing debris of degenerated neurons (arrows) and gliosis (arrow heads). H&E stain x40.

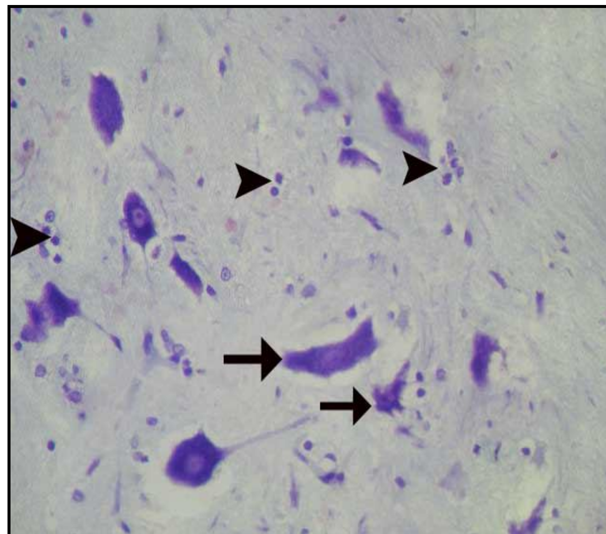


Figure (14): Photomicrograph of a section of rat's spinal cord of lesioned group 2 months post KA injection showing debris of degenerated neurons (black arrows) and gliosis (arrow heads), Cresayl violet stains. X40

DISCUSSION

Our results have shown that the histopathological changes following KA injection are confined to the ventral horn and intermediate gray matter of spinal cord. Meanwhile, the dorsal horn and white matter showed relative preservation of its tissue architecture during the current study.

Our results are inaccordence with the result of previous studies which declared that importantly, kinate excitotoxicity in cervical or lower (but not mid-) thoracic and upper lumbar spinal gray matter selectively damages motor neurons critical to adult rat fore limb or hind limb motor activity, respectively, but not long-tract motor axon conduction (**Pisharodi and Nauta 1985; David et al. 1999; BASSAM et al. 2000 and sun et al., 2006).** Conversely another study revealed extensive damage of gray matter (dorsal and ventral horn), white matters ventral and ventrolateral tracts after KA injection ***(Nishida et al., 2015).***

Degenerative changes in gray matter were distinguished by the appearance of randomly distributed irregular shaped neurons with dark esinophilic cytoplasm and loss of nissle substance (chromatolysis) .The nuclei were also pykonotic with irregular chromatin clumps and loss its morphological details. Our results are nearly similar to the result of previous studies (***Hugon et al., 1989; David et al., 1999 and BASSAM et al., 2000).***

The degenerative changes following KA injection are attributed to the presence of kinate and glutamate receptors in rats spinal cord (***Monaghan and Cotman ,1982; Monaghan et al., 1983)*** .KA exerts its action by binding to its receptors, consequently contributing to the release of endogenous glutamate. The over

stimulation of glutamate receptors produces **(1)** neuronal membrane depolarization , **(2)** rapid Ca^{2+} influx and **(3)** Ca2+-dependent enzymes activation and ROS generation. Excessive Ca^2+and ROS cause mitochondrial dysfunction and, DNA fragmentation and nuclear condensation. Subsequently stimulates excitotoxic neuronal death cascade events that associated with activation of caspase, astrocytes and microglial cells ***(Chen et al., 2005; Ravizza et al., 2005).***

The obtained result have shown that the extensive hemorrhage has not been observed after KA induced excitotoxic injury, only congested blood vessels were detected between degenerated neurons. This result is in agreement with the result of previous studies which reported that extensive hemorrhage hasn't been detected in excitotoxic model of acute spinal cord injury ***(Gomes-Lea et al., 2004)***. Different results are detected by ***Fleming et al., (2006) and marei et al., (2016)*** who declared that the histopathological changes post spinal cord injury were characterized by sever hemorrhage in gray matter that appear rapidly then extended to white matter.

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الملخص العربي

تأثير حمض الكينك علي التركيب النسيجي للخلايا العصبية الحركية في الحبل الشوكى

شيماء السيد محمد رزق [١] - أماني فرج أمين [١] - أحمد عبد المقصود [١] - محمد محمد عاطف كساب [٢]

[١] قسم الخلية والانسجة- كليه الطب البيطري- جامعه المنصوره

[٢] قسم الخلية والانسجة- كليه الطب البيطري- جامعه كفر الشيخ

يعتبر حمض الكينك مماثل للناقل العصبي الجلوتامات ويتميز بان له تاثيرمؤكسد وسام علي الحبل الشوكي. ويتم حقنه في حيوانات التجارب لعمل نموذج يحاكي اصابات الحبل الشوكي في الانسان. وقد اجريت هذه التجربه علي احدي وعشرين فارا تم تقسيمهما الي مجموعتين ثلاثه فئران لدراسه التركيب الهستولجي للحبل العصبي وتترك تحت الملاحظه دون اي حقن وتجمع عيناتهم في نهاية التجربه وثماني عشر تم حقنهم بحمض الكينك وتم تجميع العينات بمعدل ثلاثه عينات في المره الواحده في فتره ١و٣و٧و١٤و ٣٠و٦٠ يوم بعد الحقن . وقد وجد ان للحمض تاثير مدمر على الاعصاب الحركيه للحبل الشوكي بينما الاعصاب الحسية تظل محتفظه بتركيبها الهستولجي دون تاثير.