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EFFECT OF UNILATERAL ELECTROLYTIC LESION OF FASTIGIAL NUCLEUS ON BEHAVIOR, LEARNING AND MEMORY OF WISTAR ALBINO RATS.

FASTIGIAL ÇEKİRDEK ÜNİLATERAL ELEKTROLİKTİK LEZYONUNUN WİSTAR ALBİNO SIÇANLARININ HAFIZA, ÖĞRENME VE DAVRANIŞLARI ÜZERİNDEKİ ETKİSİ

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Abstract

Cerebellum called as the "little brain" .The cerebellum regulates various functions like motor coordination, equilibrium and muscle tone because of its connections with other parts of the brain as well as other parts of the body. Whether the fastigial nucleus of the rat cerebellum plays any role in behavior, reference and working memory forms the focus of the present study. The fastigial nucleus as part of spino-cerebellum of Wistar albino rat was unilaterally (left side) destroyed by electrolytic lesion using stereotaxic procedures and the behavior, learning and memory were analyzed by using open field, elevated plus maze and eight arm radial mazes on 10th and also 15th day after the lesion along with controls as well as with sham operated animals. The alterations in behavior were only observed on the 10th day but not in 15th day. There was no alteration was observed in radial maze among the groups indicated that cerebellum has no role in memory process. The changes perceived in behavior on 10th day may be due the inflammation or reduced metabolism in the damaged areas followed which may recovered on 15th day as inflammation subsides and the metabolism is normalized. These results indicate that fastigial nucleus is not playing any role in either behavior or memory.

Keywords: Fastigial nucleus, behavior, memory, electrolytic lesion, cerebellum of rat

Özet

Beyincik "küçük beyin" olarak bilinir. Beyincik, vücudun diğer kısımlarıyla olduğu gibi beynin de diğer kısımlarıyla bağlantıları nedeniyle motor koordinasyonu, denge ve kas elastikiyeti gibi fonksiyonların çalışmasını düzenler. Sıçan beyinciğinin fastigial çekirdek davranış üzerinde herhangi bir rol oynasın ya da oynamasın, referans belleği ve işleyen bellek şuanki çalışmanın konusunu oluşturmaktadır. Wistar albino sıçanının spino-serebellum' unun bir parçası olarak fastigial nucleus, stereotaksik teknikler kullanılarak elektroliktik lezyon ile tek taraflı olarak(sol taraf) yok edilmiştir. Laboratuvar ortamında opere edilen hayvanlardaki gibi kontrollerle lezyondan sonra davranış, öğrenme ve hafıza 10. ve 15. günde artı labirent ve radyal labirent yükselten açık alan testi kullanılarak analiz edilmiştir. Davranıştaki değişimler 15. günde değil sadece 10. günde görülmüştür. Beyinciğinin hafıza sürecinde rol oynamadığı görülen gruplar arasında radyal labirentte hiçbir değişim görülmemiştir. 10. günde algılanan davranış değişiklikleri, iltihap azalacağı ve metabolizma normalleşeceği için 15. günde iyileşmesini takiben zarar gören kısımlardaki iltihap ya da zayıflamış metabolizma yüzünden olabilir. Bu sonuçlar göstermektedir ki fastigial çekirdek davranış ya da hafıza üzerinde herhangi bir rol oynamamaktadır.

Anahtar Kelimeler: *Fastigial nucleus, davranış, hafıza, elektronik lezyon, sıçan beyinciği*

1.Introduction

Cerebellum called as the "little brain" and considered as a silent part of the brain that lies above the spinal cord and it has two wrinkled hemispheres, left and right, connected by a structure called the vermis (the Latin word for "worm"). Cerebellar hemisphere controls movements of the ipsilateral side of the body (Harvey et al., 1979; MacKay 1988a). The individual regions of the cerebellum are believed to regulate particular functions such as motor coordination, equilibrium and muscle tone (Mauk, 1997). The activity of the brain is an integrated phenomenon probably due to the various projections and overlapping. Ogawa (1935). and Ohkawa (1957) divided the cerebellar nuclei of the rodents into two groups of interconnected nuclei, which is in agreement with the earlier report of

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(Weidenreich, 1899). Korneliussen (1968) applied the subdivisions to the cerebellar nuclei of the rat. The caudal group consists of the medial fastigial nucleus, whereas the posterior consists of interposed nucleus. The rostral group consists of the anterior interposed nucleus and the dentate nucleus. One important cerebellar function is related to well-timed movement during various tasks like multi-joint movement (Thach, 1998), adaptation of the vestibule-ocular reflex (Raymond, 1996), and smooth pursuing eye movements (Lisberger et al., 1987). Various experiments have been provided the details of the function of cerebellum in motor, learning (Ito, 1984). Cognition is mainly based on the sensory input and the signals stored in the brain which is called as memory and each deep nuclei has reported to have its own contribution and function in movement behavior (Saab & Willis 2003). According to Nixon and Passingham (1999) the bilateral lesions of the lateral cerebellar nuclei (dentate nucleus) did not impair the spatial working memory. So far studies have been made on dentate and interposed nucleus lesion on behavior, learning and memory .However cerebellar various nuclei have its own unique way of functioning and still remain much to be discovered and recognized. Hence this study focused to understand whether unilateral electrolytic lesion of the fastigial nucleus can modulate the spatial learning and memory, exploratory and anxiety related behavior by using open field behavior, elevated plus maze test and eight arm radial maze responses in Wistar albino rats.

2. Materials and Methods

The study was initiated with a proper approval by the Institute's Animal Ethical Committee (IAEC No 08/034/07) and the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA). Healthy adult male Wistar rats weighing about 180-200 g have been used for this study.

2.1. Experimental groups

Animals were divided into three groups namely controls (Group I), unilateral Fastigial nucleus lesioned animals (Group II) and sham operated animals (Group III). Each group consists of six animals. The sham animals are considered as the strict control to evaluate the lesion effects as the lesion site is not on the surface, inevitably the cortical structures above the interested lesion destroyed during electrode insertion.

2.2. Electrical Lesioning of Fastigial Nucleus

Rat was anaesthetized with pentothal sodium (40 mg/kg bw). The hair on the scalp was removed and the animal was fixed to the stereotaxic apparatus frame (Figure. 1). The coordinates for (Pellegrino, et al., 1979) fastigial nucleus is - minus 10 mm from Bregma, 1.10 mm lateral from midline, 4.80 mm from Dura (depth). Appropriate holes were made on left side of cerebellar region skull using a dental drill and stainless steel electrode of 0.22 mm diameter was lowered at appropriate depth and anodal electric lesions were made with direct current of 2mA at 100 volts for 10 seconds. The lesioned animals were allowed to recover for 10 days and then they were subjected to further studies.

After the experiments controls as well as lesioned animals were killed using over dose of pentothal sodium and the lesion site was confirmed (Figure: 2a and 2b). The data from the animals showing the proper lesion only considered for statistical evaluation

Figure 1: Radial eight - arm maze (RAM)

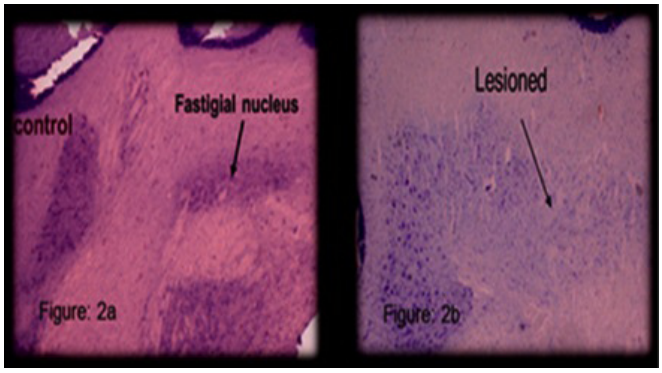

Figure 2a & 2b: Microscopic view of H & E stained section showing the lesion of Fastigial nuclei of cerebellum (Figure 2b) and normal Fastigial nuclei of controls (Figure 2a) as reference

2.3. Spatial memory testing -Radial eight - arm maze (RAM)

Spatial learning and memory were tested by using a radial eight-arm maze apparatus (Olton, & Papas 1979). The apparatus, made of gray vinyl chloride plates, had an octagonal central platform, 33.5 cm wide, around which were arranged 60 cm long by 12 cm wide arms. The whole apparatus was elevated 40 cm from the floor in a sound proof chamber. During behavioral training and testing, as food is reward the animals were fasted. Prior to the experiment, a group of animals was trained so that they would become habituated to the apparatus and a piece of cereal was used in the same arms. Initially, animals were allowed to freely explore the maze for 2 consecutive

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days with all arms baited with cereal. On third day a piece of cereal in four of the eight arms was kept and were trained to locate four food rewards that were always placed in the same set of four arms. After the adaptation week, each rat was individually housed in a small cage. The adaptation and maze test were performed between 10:00 and 12:00 h. Each individual rat had its own set of four rewarded arms. The room contained several visual reference cues on the wall. For training on the spatial task, only four arms (fixed for that animal) were always baited and food rewards placed at the end of the arms. Each trial began with the placement of the animal on the central platform facing arm number one and ended when the rat had visited the four baited arms or after a period of 10 min. Based on Olton's definition (1) Number of reference memory errors, i.e. each entry into a non-baited arm and (2) Number of working memory errors, i.e. re-entries into already visited baited arms were noted down along with the (3) Time taken to visit all the baited arms.

Animals required 25–28 training sessions to reach the criterion of 0–2 errors. After the criterion (0–2 errors) was reached, the lesion was done on the animals as the procedure mentioned above and the rats were allowed to recover for 10 days considering the day of lesion as 0 day. Retention of the task was examined on the 10^{th} and 15^{th} day from the period of lesion.

2.4. Evaluation of anxiety state of rats -Elevated plus mazes (EPM)

The Elevated plus maze test is one of the most widely used non-conditioned animal models of anxiety and was based on the natural aversion of rodents for open spaces and heights. Each animal has been exposed to EPM test only once. The elevated plus maze was made of wooden perspex, with two opposite open arms (50 X 10 cm) and two opposite closed arms of the same size and 50 cm high walls (Pellow, et al., 1985). The arms were connected by a central square (10 X 10 cm). In addition, because the floor surface of the maze was smooth, wooden ridges bordering the open arms (0.5 cm) were added to provide additional grip for the animals. The entire apparatus was elevated 50 cm above a white floor. The apparatus was situated in a darkened room, illuminated by a single 60 W white light bulb located approximately 50 cm above from the center of the maze. Rats were placed in the central square of the maze, facing one of the open arms, observer seated approximately 1 m from the apparatus. Rats were randomly removed from their home cages and tested for 5 min in an EPM to ensure anxiety levels on 10^{th} and 15^{th} day from the period of lesion. The number of entries into and time spent in each arm were scored for the first 5 min. Arm entries were only counted when all four paws had entered either a closed or an open arm. At the end of the test, each rat was returned to its home cage. A weak cider vinegar solution (10%) was used to clean the apparatus prior to the introduction of each animal. Animals falling off the maze were eliminated from the analysis. The parameters includes the number of open arm entry and number of head dips (lowering the head, either over the edge of an open arm)

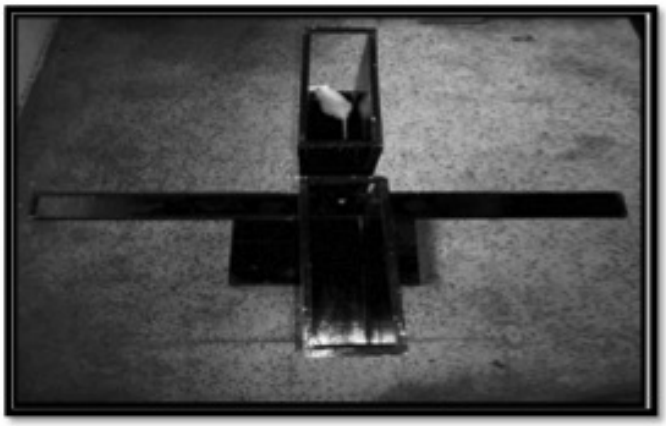

Figure 3: Elevated plus mazes (EPM)

2.5. Emotional and locomotion status of animals - Open field behavior (OFB)

This is the simple test to evaluate the three independent behavioral dimensions relating to motor activity, exploration and emotional activity, by placing the animal in a brightly lighted a large rectangular box (100 X l00 cm) with 40cm height plywood walls. Illumination was provided by a 60 W bulb placed 100 cm above the center of the field. The floor consists of a clean dark plastic material with a grid painted in white dividing the field into 25 (5 X5) equal squares. A weak cider vinegar solution (10%) was used to clean the apparatus prior to the introduction of each animal. This elicits a series of behavior like, exploratory behavior, immobilization, motor activity like grooming and rearing relating to emotional status of the animal. Measure of defecation relates to the autonomic function in the animal (Saillenfait & Vannier 1998).

Rat was placed in one corner of the apparatus and its behavior was observed for 5 minutes. The following activities were noted:1) Number of grooming -consisting of licking the fur, washing face or scratching behavior.2) Number of rearing - i.e. standing on hind limbs and sometimes leaning on the wall with forelegs, sniffing and looking around. 3) Immobilization duration (sec) - there was no activity by the animal. 4) Number of fecal pellets.

Figure 4: Open field behavior (OFB)

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2.6. Histology

The histology of cerebellum was done at the end of the experiment to confirm the lesion site. The animals were deeply anesthetized with sodium pentobarbital. Rats were then perfused with phosphate buffered saline, followed by 10% buffered formalin. The brain was removed and preserved in formalin. The cerebellum was isolated, processed and stained in hematoxylin & eosin (H&E) and mounted in DPX medium and the site of lesion was determined. The data from animals with right lesion site only considered for statistical evaluation.

2.7. Statistical analysis:

The effects of unilateral lesion on fastigial nucleus on behavior, learning and memory performance were evaluated using one way analysis of variance (ANOVA) appropriate statistically significant differences among the groups were determined by Tukey's multiple comparison (post hoc) tests. The values were expressed as means ± standard error of mean (S.E.M). Difference between groups were considered significant at $P<0.05$.

3. Results

All the animals appeared healthy and no significant weight loss was observed in the lesioned animals.

3.1. Ambulation: Central squares and Peripheral squares

The data is presented as bar diagram (Figure: 5, 6 & 7, 8). though unilateral lesioned rats showed marked decrease (df 2, F= 17) from the controls as well as from the sham animals on 10th day after lesion procedure, none of the group studied showed any variation among themselves on the 15th day. This indicates that the changes observed on the 10th day are transient.

Effect of unilateral lesion of fastigial nucleus on rat and its Performance on open field behaviour on day 10 and day 15

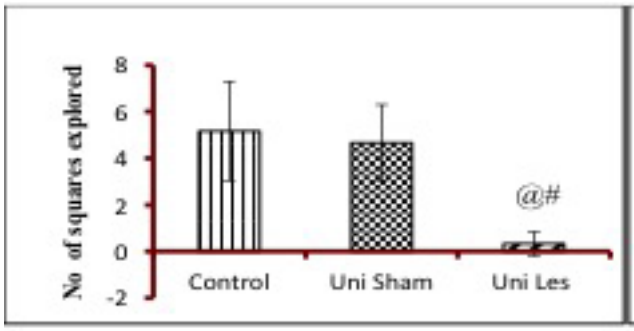

Figure 5: Ambulation - central squares/day 10

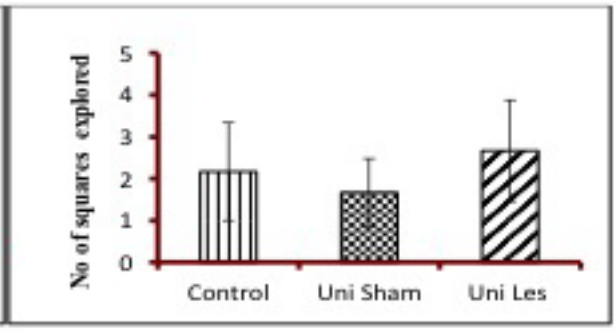

Figure 6: Ambulation - central squares/day 15

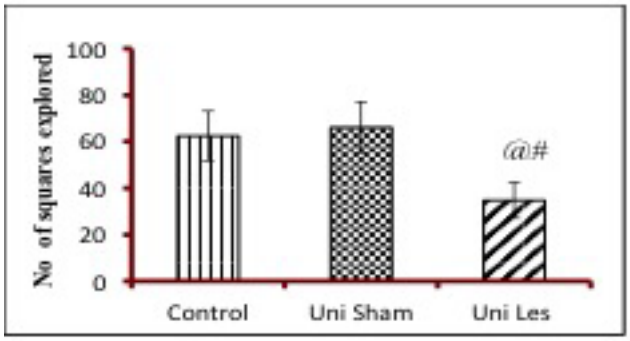

Figure 7: Ambulation - Peripheral squares/day 10

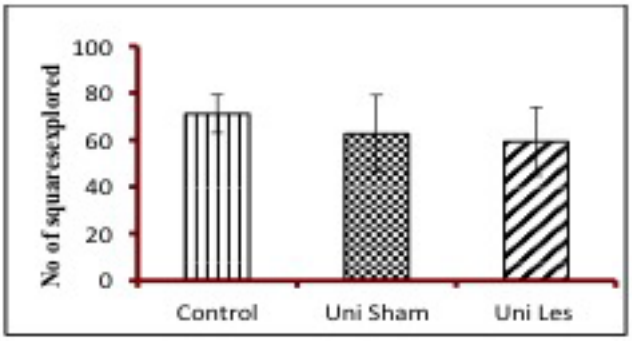

Figure 8: Ambulation - Peripheral squares/day 15

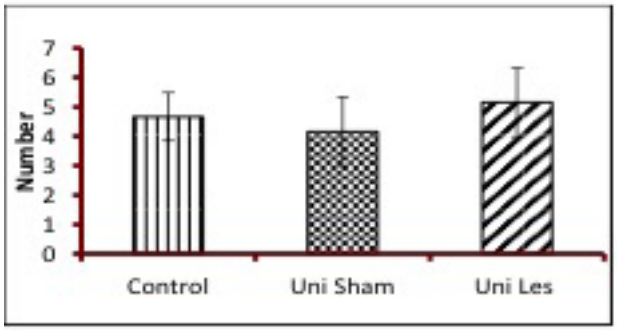

Figure 9: Number of fecal pellets/day 10

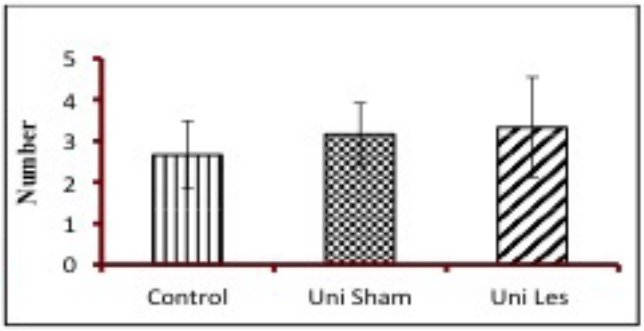

Figure 10: Number of fecal pellets/day 15

@ - lesion versus contol # - lesion versus sham

3.2. Fecal bolus

The data is presented as bar diagram (Figure: 9 & 10). None of the group studied showed any variation among themselves on the 10th as well as on the 15th day indicating a normal intake of food and bowel movement.

3.3. Grooming

The data is presented as bar diagram (Figure: 11 & 12). The unilateral lesioned rats showed marked decrease in grooming (df 2, F= 21) from the controls as well as from the sham animals on 10th day after lesion procedure.

However, all the groups including lesioned animals studied showed similar grooming on the 15th day. This indicates that the changes observed on the 10th day are momentary.

3.4. Immobilization

The data is presented as bar diagram (Figure: 13 & 14). The unilateral lesioned rats showed marked increase (df 2, F= 28) in their immobilization score from the controls as well as from the sham animals on 10th day after lesion procedure.

However, none of the group studied showed any variation among themselves on the 15th day. This indicates that the changes observed on the 10th day are temporary.

3.5. Rearing

The data is presented as bar diagram (Figure: 15 & 16). None of the group studied showed any variation among themselves on the 10th as well as on the 15th day in their rearing.

3.6. Head dip

The data is presented as bar diagram (Figure: 17 & 18). None of the group studied showed any variation among themselves on the 10th as well as on the 15th day in their head dip.

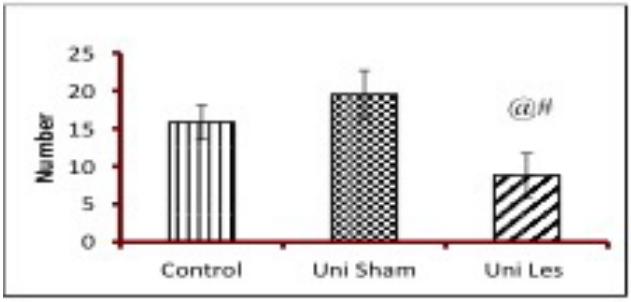

Figure 11: Number of grooming / day 10

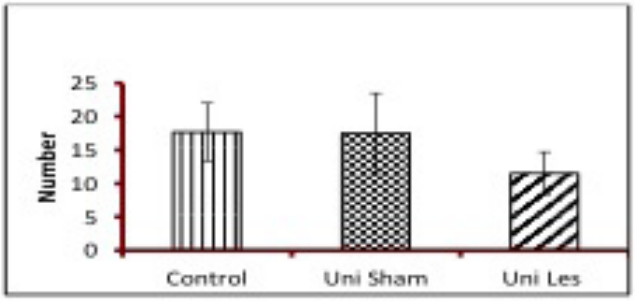

Figure 12: Number of grooming / day 10

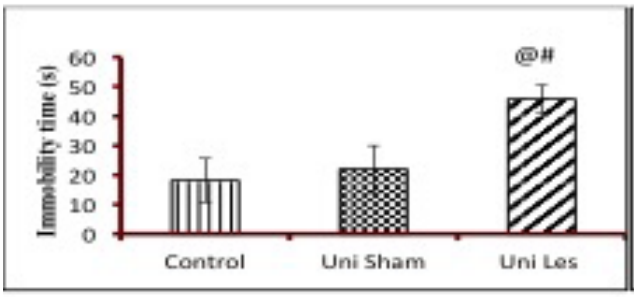

Figure 13: Immobility time / day 10

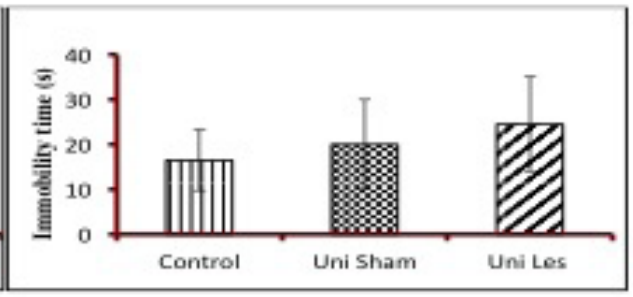

Figure 14: Immobility time / day 15

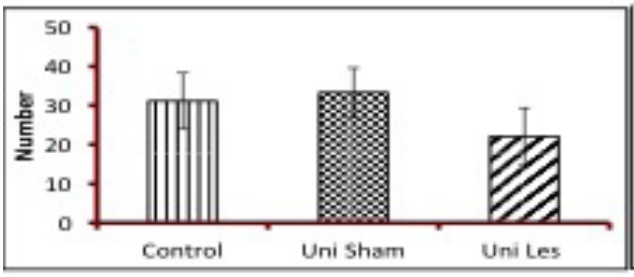

Figure 5: Number of rearing / day 10

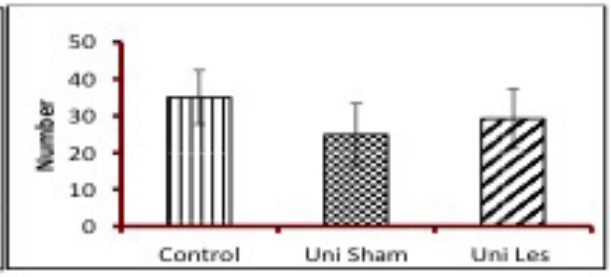

Figure 16: Number of rearing / day 15

@ - lesion versus contol # - lesion versus sham

3.7. Open arm entry

The data is presented as bar diagram (Figure: 19 & 20). None of the group studied showed any variation among themselves on the 10th as well as on the 15th day in the open arm entry.

4. Discussion

The standard operating procedures were adopted and rats were well-handled to make them extremely comfortable during the experimental duration minimize the stress induced alteration and their interactions with the parameter studied. Measurement of open-field behavior was first described by Hall and Ballachey (1932) for evaluating an animal's spontaneous behavior in response to a novel environment and to assess locomotor responses. Rodents naturally avoid bright light and open spaces. When placed into a brightly lit open field, rats tend to remain in the periphery of the apparatus or against the walls (Thigmotaxis). Open field activity, therefore, represents also a valid measure of "anxiety-like" behavior. The data clearly indicate that the unilateral cerebellar lesion has a transient effect on some behavioral aspect in the open field as well as the baited arm entry. The loss of neurons and their connections ("synapses") by lesion results in impairments in the functions previously controlled by the damaged nuclei may be predominant on the 10th day may be the possible reason for the observations recorded during the 10th day in the lesioned animals. According to Jones and Schallert (2000) in the first 15 days after the lesions the dendritic growth was prevented normally found in the cortex opposite side of the lesion. Since on the 15th day all the parameters studied in the unilateral lesioned animals become normal it may not be due to the dendritic growth and reestablishing the connections. The histology of the lesion section clearly shows the clearance

Effect of unilateral lesion of fastigial nucleus on rat and its Performance on elevated plus maze.

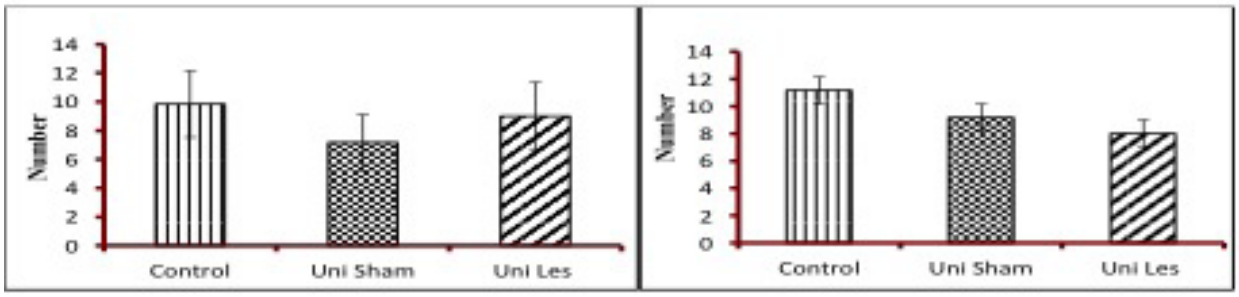

Figure 17: Number of head dipping / day 10

Figure 18: Number of head dipping / day 15

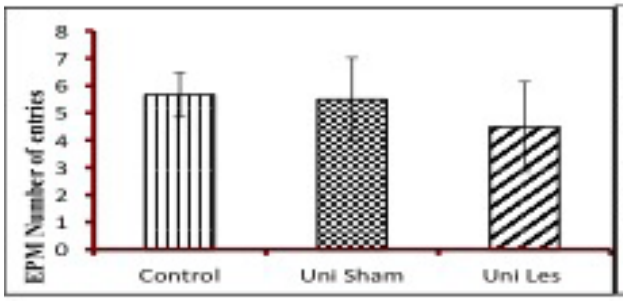

Figure 19: Number of open arm entry / day 10

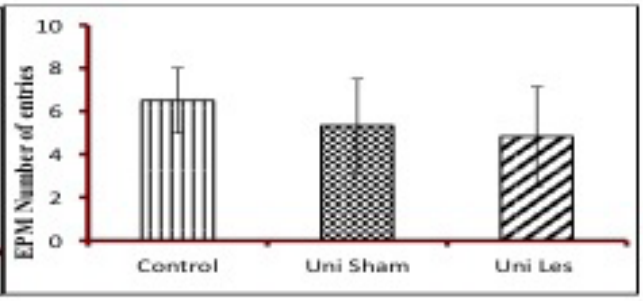

Figure 20: Number of open arm entry / day 15

@ - lesion versus contol # - lession versus sham

3.8. Baited arm entry

The data is presented as bar diagram (Figure: 21 & 22). The unilateral lesioned rats showed marked increase (df 2, F=56) in the baited arm entry when compared to the controls as well as from the sham animals on 10th day after lesion procedure. However, none of the group studied showed any variation among themselves on the 15thday. This indicates that the changes observed on the 10th day are short-lived.

3.9. Reference memory error

The data is presented as bar diagram (Figure: 23 & 24). None of the group studied showed any variation among themselves on the 10th as well as on the 15thday in their reference memory error.

3.10. Working memory error

The data is presented as bar diagram (Figure: 25 & 26). None of the group studied showed any variation among themselves on the 10th as well as on the 15th day in their working memory error.

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Effect of unilateral lesion of fastigial nucleus on rat and its Performance on eight arm radial maze on day 10 and day 15

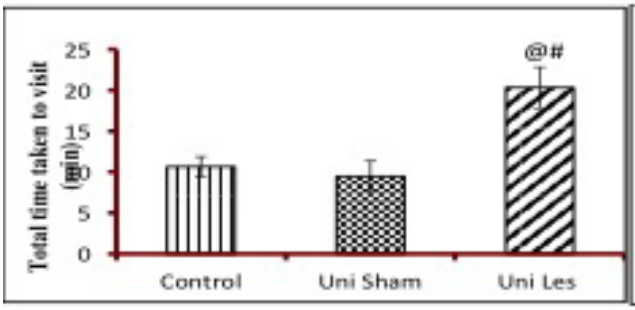

Figure 21: Time to visit baited arm / day 10

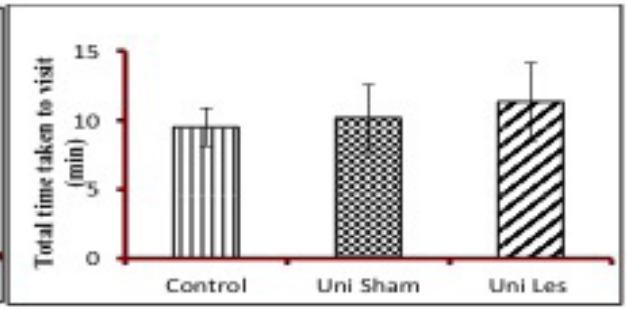

Figure 22: Time to visit baited arm / day 15

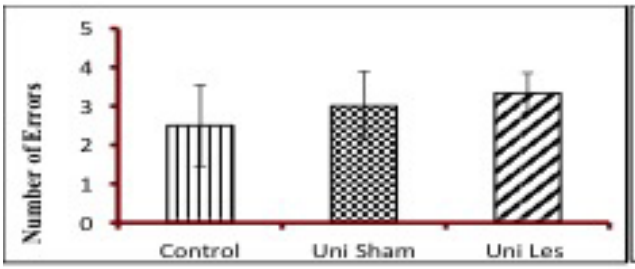

Figure 23: Reference memory error / day 10

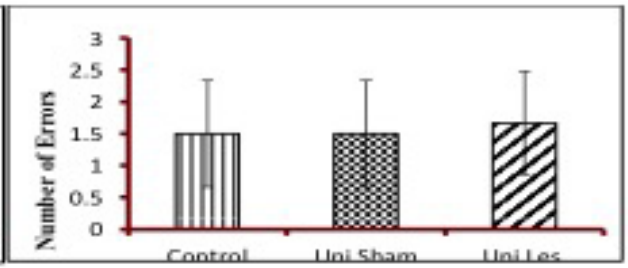

Figure 24: Reference memory error / day 15

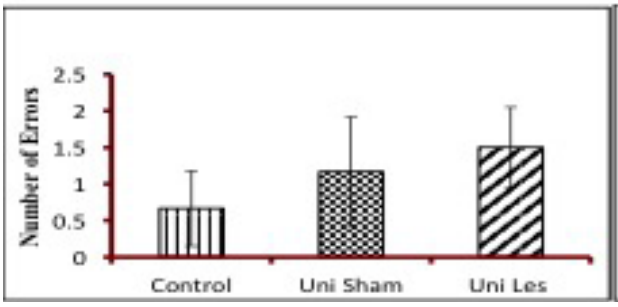

Figure 25: Working memory error / day 10

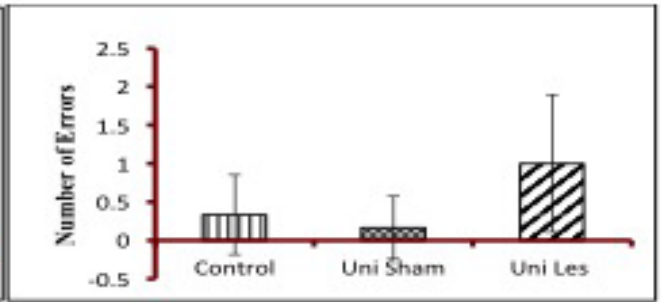

Figure 26: Working memory error / day 15

@ - lesion versus contol # - lesion versus sham

of neurons in that region by electrolytic procedure. Jones et al., (2003) who were working on neural plasticity and brain damage in rats hypothesized that the degenerative effects of the lesion (i.e., the loss of some axonal input and the resulting induction of growth-promoting processes) cause the region of cortex opposite the lesion to become especially responsive to behavioral changes. As this is a unilateral lesion probably the opposite side which is not damaged could be active to bring back the animals to have normal response.

Even evidence shows that there is a scarcity in spatial orientation associated with either fastigial or dentate nucleus lesion (1996). On the contrary, the performance was not deficient when the task was learned prior to the lesion. This may be one of the reasons where memory was not altered after the lesion of fastigial nucleus, since rats were trained preoperatively for eight arm radial mazes.

Over the past 20 years the research were conducted about the involvement of cerebellum in higher motor functions and proved that it also involves in spatial learning and cognitive memory (Lalonde, 1997). Normally increased rearing accompanied by reduced grooming-indicates the lack of acclimatization. In this study, both rearing and grooming showed a marked decrease in the lesioned animals compared to sham and control rats. Moreover on the 10th day there is a significant decrease in locomotor activity such as ambulation as well as increase in immobilization in these lesioned animals. Petrosini et al., (1996) suggested that the role of the cerebellum in spatial learning is primarily that of controlling the procedural aspects of the task, as hemi cerebellectomized rats were impaired in executing exploratory behaviors and acquiring spatial information during hidden-platform acquisition training. However, in this study, though the unilateral fastigial nucleus lesion might resulted with a transient impairment in executing the exploratory behavior on 10th day the alteration were back to normal by day15th. It can be perceived that the secondary consequence of fastigial nucleus lesion of cerebellum or due to the effect of inflammation as suggested by Nixon and Passingham (1996). Other possibility includes that

the recovery of behavioral function may be due to changes in non-damaged brain areas or due to the account of neuronal plasticity on lesion-dependent plastic processes in damaged CNS areas. Will et al., (2004) reported it may due to the inflammation subside and the lesion effect is compensated CNS areas after injury. Heffner and Heffner (1986) reported that unilateral ablation of left auditory cortex consistently resulted in an initial impairment in the ability to discriminated between the vocalizations with the animals regaining abnormal performance in 5 -15 sessions. In contrast right unilateral ablation had no detectable effect on the discrimination. Further they added that the transient impairment shown by the left unilateral cases was fairly mild and it would be tempting to ascribe them to general post-operative malaise, however comparison with hemisphere, the rapid recovery of the animals indicated that another area can assume this function.

The elevated plus-maze apparatus has two narrow enclosed arms which are bordered by high walls, and two open arms which are essentially deprived of protection. Rats exposed to the elevated plus-maze apparatus avoid open arms (Rodgers & Johnson, 1995) and display fear-like behavior (Pellow et al., 1985). The elevated plus-maze test has been used to investigate and measure several aspects of fear-like behavior. Exposure to a novel environment immediately before testing in the elevated plus maze increases motor activity in the elevated plus maze and a greater likelihood of entering the open arms of the maze. The unilateral lesioned animals behavior observed in the elevated plus maze was similar when compared to controls as well as sham animals in the also again confirms that there was no anxiety status in these animals

The memory appears to be normal as the lesioned rats did not commit any mistakes in working memory as well as reference memory error indicating that the lesion has no role in memory process. Hence all these alteration in behavior followed by 10th day of lesion may be temporary and the deficits observed are caused by the reduced metabolism (reduced blood flows) of connected pathways, in particular the frontal and parietal association cortex and basal ganglia (Botez- Marquard et al., 1994). It is supported by the report that visuomotor disturbances studied after hemicerebellectomy in rats were normalized after 3 weeks (Mandolesi et al., 2010). Hence it is not clear in unilateral lesions whether the unaffected side nucleus may take over the function entirely as no abnormal movements are noticed otherwise it may be due to the neuronal plasticity. Considered as an accessory brain, the cerebellum may constitute a neurobiological substrate for the recovery of such extensive cortical and subcortical lesions. It may compensate for the injury by structural remodeling and plasticity changes. Cerebellar networks show long-term synaptic plasticity (Hansel et al., 2001) which indicates that experience-dependent adaptive and learning processes are also a salient feature of cerebellar function (Thach, 1998). An important factor in regulating cerebellar synaptic plasticity seems to be the interactions between climbing fiber and mossy fiber parallel fiber inputs (Jorntell & Ekerot, 2002). These reports could justify the normal responses observed on the 15th day followed by the lesion effect. This type of study indicate the behavioral alteration can be recovered after a cerebellar deep nuclei destruction but still more elaborate research is required to understand the molecular mechanisms and pathways behind it.

5. Conclusion

Unilateral fastigial nucleus lesioned animals showed a significant variation in the open field activity and the time taken to complete the eight arm radial maze only on 10th day after lesion but not on 15th day. Thus the possible cause behind such recovery could be due to neuronal plasticity or the inflammation subsides at the lesion site on 15th day or the existing fastigial nucleus on the other side of cerebellum took over the functions. No alteration in the elevated plus maze indicating there is no anxiety like behavior controlled or regulated by fastigial nucleus. No alteration in working and reference memory error indicating that the fastigial nucleus has no role in memory process.

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