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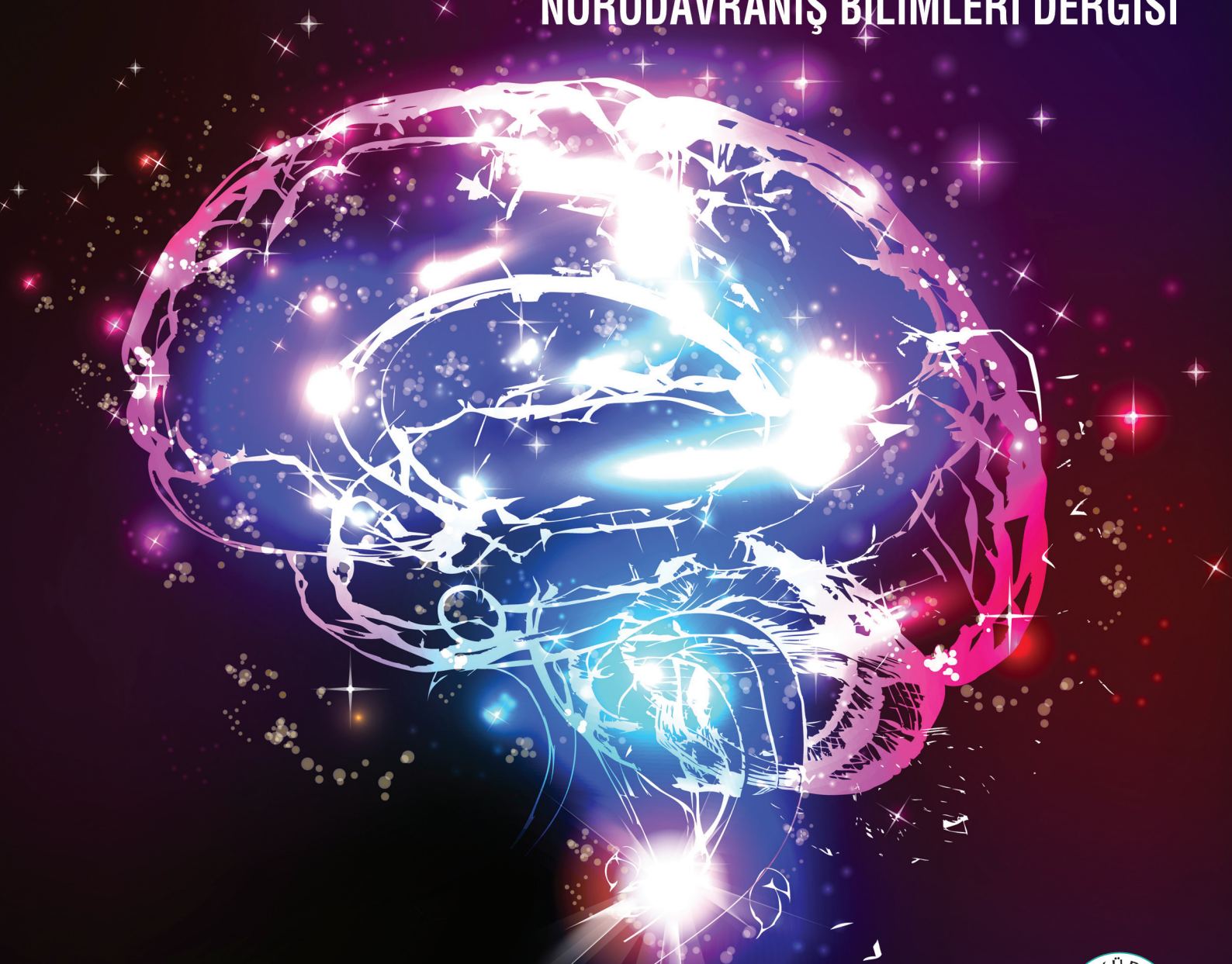

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ABOUT THIS JOURNAL

The Journal of Neurobehavioral Sciences (JNBS) is a peer-reviewed open-access neuroscience journal without any publication fees. All editorial costs are sponsored by the Üsküdar University Publications and the Foundation of Human Values and Mental Health. Each issue of the Journal of Neurobehavioral Sciences is specially commissioned, and provides an overview of important areas of neuroscience from the molecular to the behavioral levels, delivering original articles, editorials, reviews and communications from leading researchers in that field.

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Aims & Scope

The scope of the journal is broad. It covers many disciplines and spans molecules (e.g., molecular neuroscience, biochemistry) through systems (e.g., neurophysiology, systems neuroscience) to behavior (e.g. cognitive neuroscience) and clinical aspects (e.g. psychopharmacology). The journal covers all aspects of neuroscience with an emphasis on translational psychiatry and psychology, as long as the goal is to delineate the neural mechanisms underlying normal or pathological behavior.

Preclinical and clinical studies are equally considered for publication. We also invite manuscripts on the methods of computational modeling of psychiatric and neurological disorders, and treatment outcome.

The journal has a special emphasis on psychiatric and neurological disorders.

However studies on normal human behavior are also considered. Studies on animals and technical notes must have clear relevance and applicability to human disease.

Case Reports that includes recent neuroscientific treatment or diagnosis methods are generally within the scope of JNBS.

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- Mini-reviews that succinctly survey appropriate areas of current research or theory
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Papers will be selected on the basis of their methodology and negative results are strongly considered for publication.

The average time from submission to first decision is less than 30 days. Accepted articles are published online ahead of print in an average of 40 workdays, and articles are published in print 3-6 months after acceptance.

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Cumhur Taş, MD PhD
Co-Editor, Journal of Neurobehavioral Sciences Department of Psychology

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Masked reviews are optional and must be specifically requested in the cover letter accompanying the submission. For masked reviews, the manuscript must include a separate title page with the authors' names and affiliations, and these ought not to appear anywhere else in the manuscript.

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Make every effort to see that the manuscript itself contains no clues to authors' identities. If your manuscript was mask reviewed, please ensure that the final version for production includes a byline and full author note for typesetting.

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A statement that the material is original —if findings from the dataset have been previously published or are in other submitted articles, please include the following information:

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*Are some of the data used in the present study being analyzed for the first time? If yes, please identify data (constructs) that were not included in previously published or submitted manuscripts.

*Are there published or submitted papers from this data set that address related questions? If yes, please provide the citations, and describe the degree of overlap and the unique contributions of your submitted manuscript.

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*A statement that the authors complied with APA ethical standards in the treatment of their participants and that the work was approved by the relevant Institutional

Review Board(s).
*Whether or not the manuscript has been or is posted on a web site;

*That APA style (Publication Manual, 6th edition) has been followed;

*The disclosure of any conflicts of interest with regard to the submitted work;

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Prepare manuscripts according to the Publication Manual of the American Psychological Association (6th edition).

Review APA's Checklist for Manuscript Submission before submitting your article. Double-space all copy. Other formatting instructions, as well as instructions on preparing tables, figures, references, metrics, and abstracts, appear in the Manual.

Below are additional instructions regarding the preparation of display equations and tables.

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We strongly encourage you to use MathType (third-party software) or Equation

Editor 3.0 (built into pre-2007 versions of word) to construct your equations, rather than the equation support that is built into Word 2007 and Word 2010. Equations composed with the built-in Word 2007/Word 2010 equation support are converted to low-resolution graphics when they enter the production process and must be rekeyed by the typesetter, which may introduce errors.

To construct your equations with MathType or Equation Editor 3.0:

Go to the Text section of the Insert tab and select Object.

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Use Equation Editor 3.0 or MathType only for equations or for formulas that cannot be produced as word text using the Times or Symbol font.

Tables

Use Word's Insert Table function when you create tables. Using spaces or tabs in your table will create problems when the table is typeset and may result in errors.

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All manuscripts must include an English abstract containing a maximum of 250 words typed on a separate page. After the abstract, please supply up to five keywords or brief phrases. For the Turkish native speakers JNBS also requires a Turkish version of the abstract and keywords. However this rule does not apply to non-native speakers and our translation office will include the Turkish abstract free of charge.

References

List references in alphabetical order. Each listed reference should be cited in text (Name, year style), and each text citation should be listed in the References section.

In-text Citations

• For two or fewer authors, list all author names (e.g. Brown & Taş, 2013). For three or more authors, abbreviate with 'first author' et al. (e.g. Uzbay et al., 2005).

• Multiple references to the same item should be separated with a semicolon (;) and ordered chronologically. References by the same author in the same year should be differentiated by letters (Smith, 2001a; Smith, 2001b).

• Cite articles that have been accepted for publication as 'in press', include in the reference list.

• Cite unpublished work, work in preparation, or work under review as 'unpublished data' using the author's initials and surname in the text only; do not include in the reference section

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• Journal Article:

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• Authored Book:

Rogers, T. T., & McClelland, J. L. (2004). Semantic cognition: A parallel distributed processing approach. Cambridge, MA: MIT Press.

• Chapter in an Edited Book:

Gill, M. J. & Sypher, B. D. (2009). Workplace incivility and organizational trust.

In P. Lutgen-Sandvik & B. D. Sypher (Eds.), Destructive organizational communication: Processes, consequences, and constructive ways of organizing (pp. 53–73). New York, NY: Taylor & Francis.

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The minimum line weight for line art is 0.5 point for optimal printing.

Ethical Principles

Authors are required to state in writing that they have complied with the Declaration of Helsinki Research Ethics in the treatment of their sample, human or animal, or to describe the details of treatment.

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JOURNAL OF NEUROBEHAVIORAL SCIENCES ADVISORY COMMITTEE

NÖRODAVRANIŞ BİLİMLERİ DERGİSİ DANIŞMA KURULU ÜYELERİ

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EDITORIAL

We are publishing the third issue of Journal of Neurobehavioral Sciences. You will find seven articles involved in current research areas of behavioral neurosciences in this issue. Three of them have been focused on agmatine that accepts as a new polyamine neurotransmitter in brain. Indeed, polyamines and agmatine has growing importance in neuroscience and agmatinergic system seems to be related to etiopathogenesis of some important neuropsychiatric diseases.

We carried out Üsküdar Neuropsychopharmacology Symposium in Üsküdar University on October 9-10, 2014. This meeting was organized within the scope of German-Turkish Year of Research, Education and Innovation, 2014 and colligated students, researchers and other academically staff from Turkey and Germany who are engaged in Polyamines, Agmatine and Brain. The symposium also included in an applied workshop on "Molecular Mechanisms Underlying Alzheimer's and Parkinson's Diseases". Üsküdar Neuropsychopharmacology symposium was also supported by The Scientific and Technological Research Council of Turkey (TUBITAK).

Besides valuable Turkish speakers, we had also three qualified scientist from Germany in this symposium. We hosted Dr. Gregor Laube from Institute for Integrative Neuroanatomy in Berlin, Professor Hans-Gert Bernstein from Department of Psychiatry in University of Magdeburg and Dr. Oktay Kaplan from Berlin Institute for Medical Systems Biology. They shared their valuable experiences with us. We understand by positive feedbacks that the symposium has provided beneficial scientific information about Polyamines, Agmatine and Brain, and established further collegial collaboration opportunities in the scientific area between Üsküdar and Charité Universities. Here you see Dr. Laube and Dr. Bernstein's lectures in a review article format in this issue of JNBS. Herewith, on behalf of the scientific committee and Üsküdar University, I would like to present our warm appreciations to all contributors. Next year, the symposium will be continued with another important subject of Behavioral Neuroscience.

In addition to articles, this issue also includes two original research articles on the effects of ovarian hormones in memory suppression by Dr. Aslankara and co-workers and effects of unilateral electrolytic lesion of fastigial nucleus in learning and memory by Dr. Sundereswaran and Dr. Sheeladevi.

Dr. Özdoğru and Dr. Kaplan, and co-workers support to this issue by their valuable review articles involved in mind, brain and education and autism, respectively. You will also find a Letter to Editor on "Swallowing Metal Things" written by Erensoy and co-workers.

Hope to meet you in the next issue.

Tayfun Uzbay, Ph.D.
Professor of Medical Pharmacology
Advising Editor

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ORIGINAL ARTICLE

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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

Loganathan Sundareswaran[1] and Rathinasamy Sheeladevi[*2]

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)

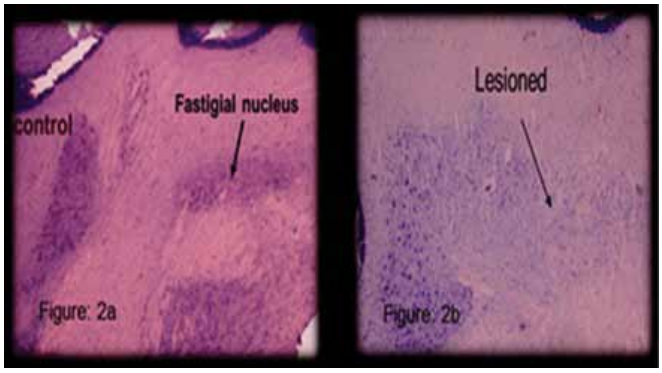

Figure 2a & 2b: Microscopic view of H & E stained section showing the lesion of Fastigial nuclei of cerebellum (Figure 2b) and normal Fastigial nuclei of controls (Figure 2a) as reference

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

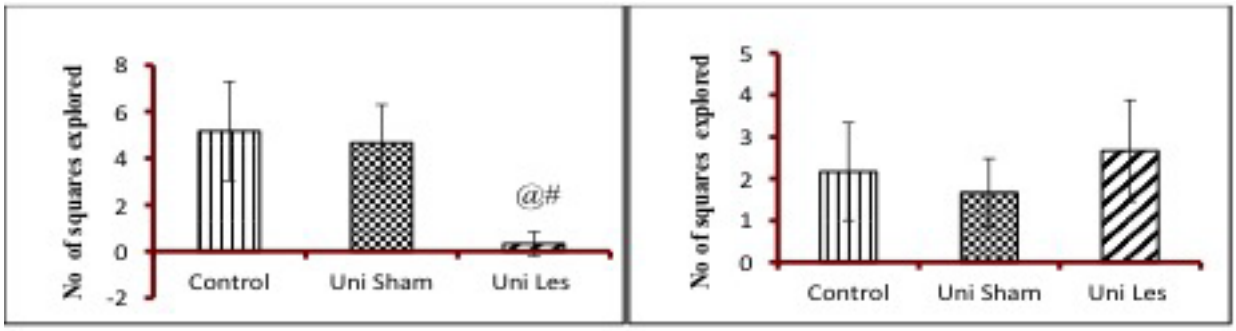

Figure 5: Ambulation - central squares/day 10

Figure 6: Ambulation - central squares/day 15

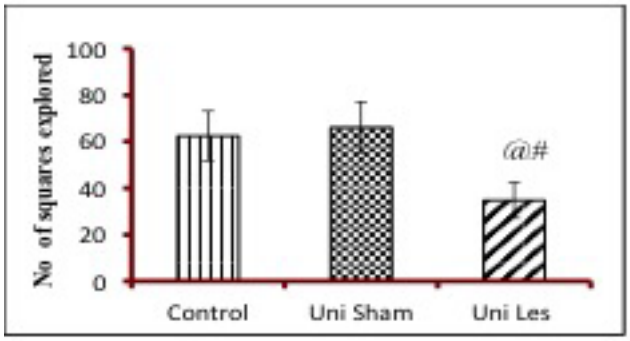

Figure 7: Ambulation - Peripheral squares/day 10

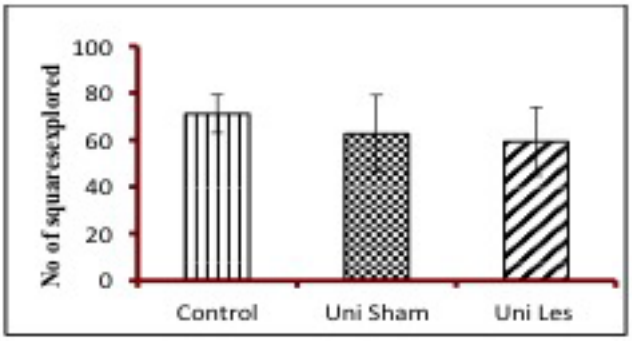

Figure 8: Ambulation - Peripheral squares/day 15

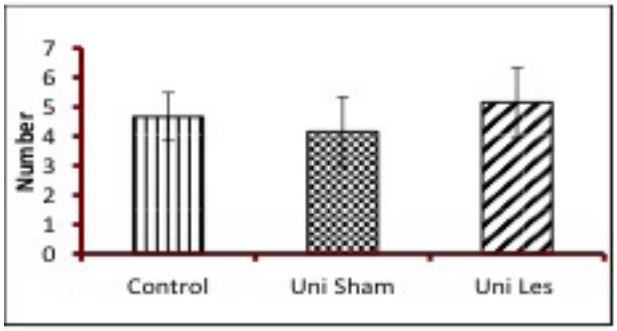

Figure 9: Number of fecal pellets/day 10

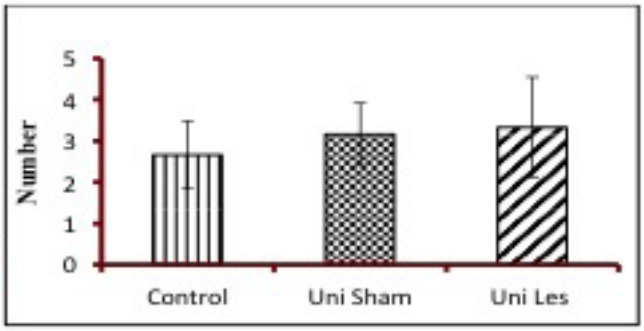

Figure 10: Number of fecal pellets/day 15

@ - 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.

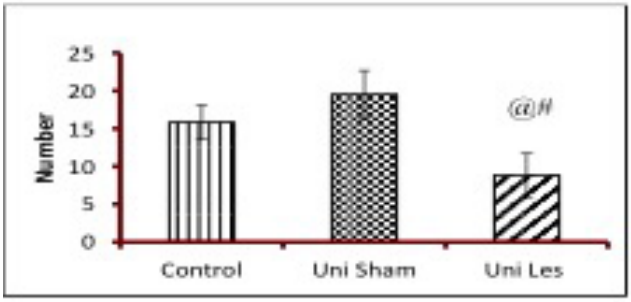

Figure 11: Number of grooming / day 10

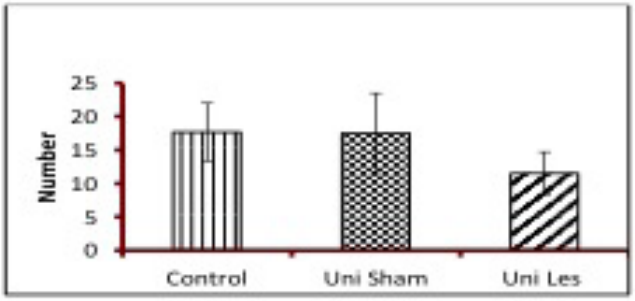

Figure 12: Number of grooming / day 10

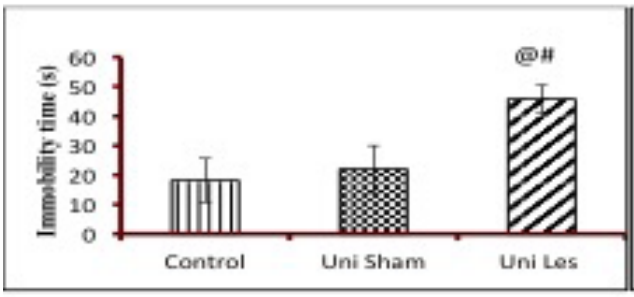

Figure 13: Immobility time / day 10

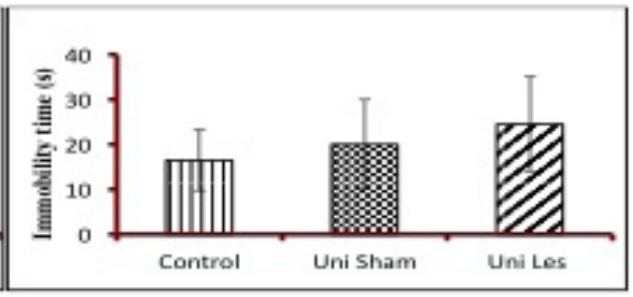

Figure 14: Immobility time / day 15

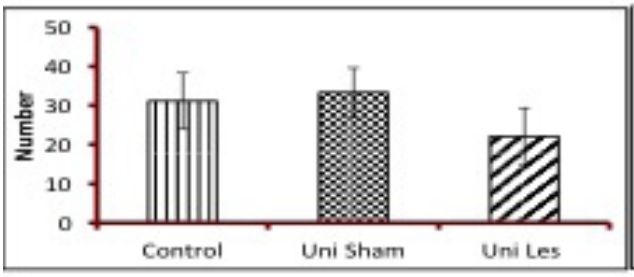

Figure 5: Number of rearing / day 10

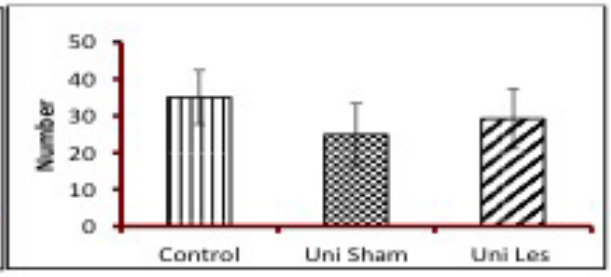

Figure 16: Number of rearing / day 15

@ - 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.

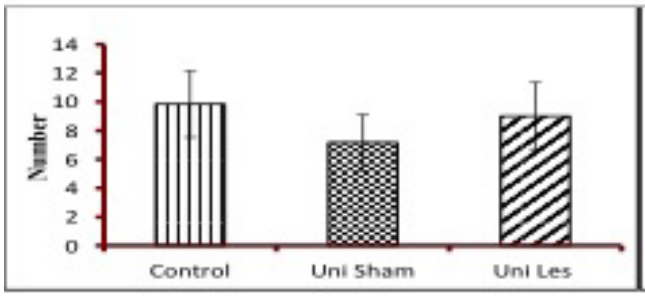

Figure 17: Number of head dipping / day 10

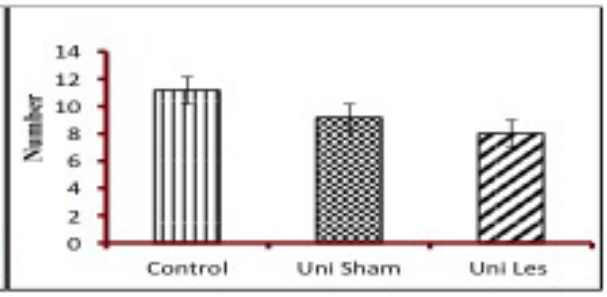

Figure 18: Number of head dipping / day 15

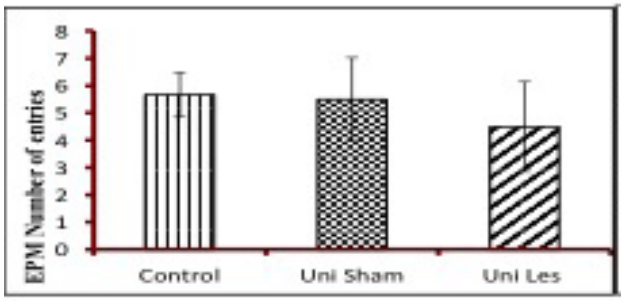

Figure 19: Number of open arm entry / day 10

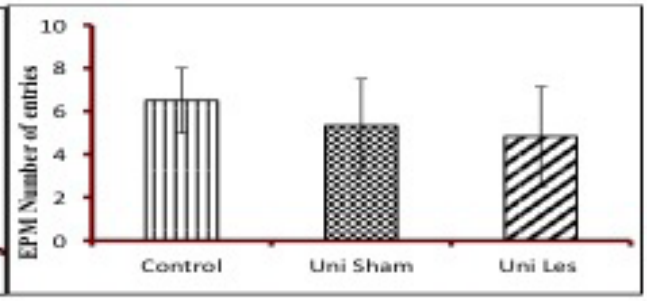

Figure 20: Number of open arm entry / day 15

@ - 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

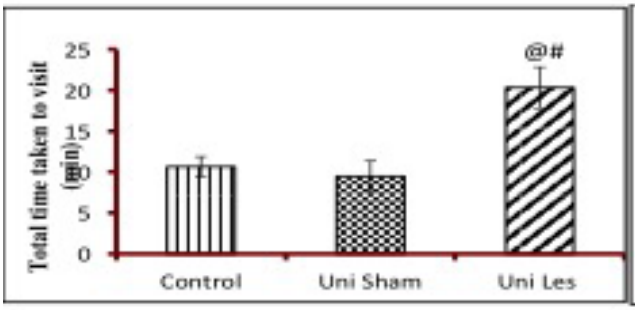

Figure 21: Time to visit baited arm / day 10

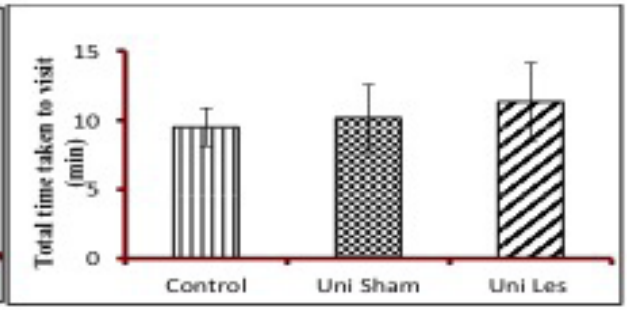

Figure 22: Time to visit baited arm / day 15

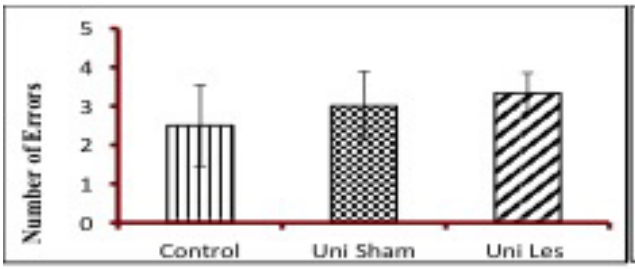

Figure 23: Reference memory error / day 10

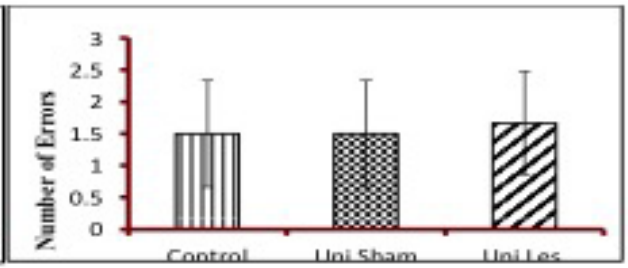

Figure 24: Reference memory error / day 15

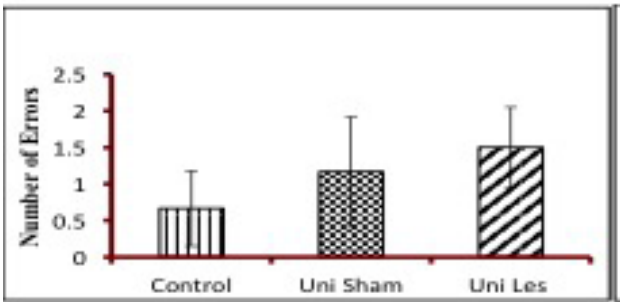

Figure 25: Working memory error / day 10

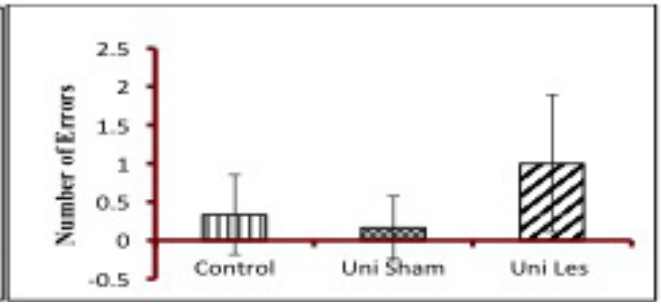

Figure 26: Working memory error / day 15

@ - 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.

6. Acknowledgement

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EFFECT OF OVARIAN HORMONES ON MEMORY SUPPRESSION

OVARYEN HORMONLARIN ANIMSAMADA BASTIRMA ÜZERİNDEKİ ETKİSİ

Müge Aslankara[1], Ali Bayram[4], Nevzat Tarhan[3], Ayla Arslan[*1,2,5]

Abstract

Several studies suggest that memory suppression in humans occur as an active process of executive control, mediated by regions of prefrontal cortex, which is a substrate for ovarian hormones. However the effect of ovarian hormones on this process is not known. In order to address this question, we utilized the quantitative analysis of ovarian hormones in combination with the procedure of a memory control model, the think (T) /no think (NT) paradigm in a within-subject design study. We compared the rate of memory control between the follicular (low estrogen and progesterone) and mid-luteal (high estrogen and progesterone) phases of regularly cycling healthy women. Our data demonstrate that during midluteal phase, 63.6 % of subjects are able to 'suppress' or actively forget (significantly less % recall below the baseline) previously learned word pairs in the 'NT condition; i.e., not to think the target word associated with the cue word'. However during the follicular phase there was no effect of 'NT condition' on the active forgetting of word pairs below the baseline as assessed by the memory test applied after the T/NT procedure. Thus, our results indicate that ovarian hormones are associated with the process of memory control.

Keywords: Memory suppression, Estrogen, Executive control

Özet

Çeşitli çalışmalar, insanlarda bellek kontrolünün (anımsamada bastırma) yürütücü bir işlev olarak prefrontal korteks denetiminde aktif bir mekanizma ile gerçekleştiğini göstermiştir. Prefrontal korteksin ovaryen hormonların müdahalesine oldukça açık olduğu bilinmekle birlikte bu etkinin anımsamada bastırma işlevi sırasında nasıl bir rol oynadığı bilinmemektedir. Burada sunulan çalışma bir bellek kontrolü modeli olan düşün/düşünme paradigmasını (think /no think paradigm) kullanarak ve ovaryen hormonların kantitatif olarak analiz edildiği denek-içi desen düzeneği ile bu soruya cevap aramaktadır. Menstrual siklusun foliküler (düşük estrojen ve progesteron) ve midlüteal (yüksek estrojen ve progesteron) fazlarındaki bellek kontrol oranları kıyaslanmıştır. Veriler göstermektedir ki midlüteal fazda, deneklerin % 63.6 si, önceden öğrenilmiş kelime çiftlerini 'düşünmeme koşulu' yani 'ip ucu kelimesi ile ilişkili hedef kelimesini düşünmeme koşulu' (NT condition)- sırasında aktif unutma (anımsamada bastırma) becerisi göstermiştir (istatiksel olarak anlamlı bir şekilde kendiliğinden unutma oranına göre daha çok unutma ya da daha az hatırlama). Ancak 'düşünmeme koşulunun' bellek kontrolü üzerindeki bu etkisi, düşün/düşünme prosedürünü takiben yapılan bellek testleri ile gösterildiği gibi foliküler fazda gözlenmemiştir. Bu sonuçlar bellek kontrolü işleminin ovaryen hormonlar ile ilişkili bir durum olduğunu göstermektedir.

Anahtar Kelimeler: *Anımsamada bastırma, östrojen, yürütücü işlevler*

1.Introduction

Forgetting can be defined as 'the absence of expression of previously properly acquired memory in a situation that normally would cause such expression' (Hardt et al., TINS, 2013). Although there are various theories of forgetting, there is a consensus favoring interference theory, which is based on the proposition that mental activity involves a competition of various knowledge of encoded memory, interfering with each other and thus causing the loss of some information. This theory has dominated memory research but newly published reports raise questions on it. For example, Anderson and his co-workers (1996, 2003) suggest that the interference theory is insufficient to explain forgetting since forgetting can be caused by inhibitory mechanisms in such a way that people control unwanted memories by recruiting inhibitory mechanisms via executive control.

The idea of ability to memory suppression by inhibitory

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mechanisms of executive control is not new. Over a century ago Freud proposed a highly controversial process called repression by which unwanted memories can be pushed into the unconsciousness and become forgotten. Supporting this view, there are certain findings which indicate that humans use executive control processes for memory (Dagenbach & Carr, 1994; Smith & Jonides, 1999; Hasher & Zacks 1988; Anderson & Spellman, 1995; Bjork, 1989), for perceptual distraction (Chao, & Knight, 1995; Dagenbach & Carr, 1994) and for the elimination of habitual responses (Logan &Cowan, 1984; Posner, & Peterson, 1990). Inspired by these findings, Anderson and Green adapted the go/ no-go paradigm, which is used to study executive control over motor responses in primates (Sakagami & Niki 1994) and humans (Casey et al., 1997; de Zubicaray, et al., 2000) for use in a memory retrieval task. So called Think /No Think paradigm (Anderson and Green, 2001), this approach is based on the rate of active forgetting process of previously learned word pairs and has led to the several lines of evidences that memory suppression in humans occur as an active process of executive control, mediated by regions of prefrontal cortex (Anderson and Green, 2001, Anderson et. al., 2004; Depue et al., 2007).According to this neurobiological model, the process of memory control was associated with increased dorsolateral prefrontal activation causing a reduced hippocampal activation (Anderson et. al., 2004; Depue et al., 2007). Thus, prefrontal cortical regions, a substrate of ovarian hormones (Keenan P.A. et al, 2001), actively control the hippocampal activity for a reduced retention of encoded memory. However the effect of ovarian hormones on this process is not known. In order to address this question we utilized the quantitative analysis of ovarian hormones in combination with think (T) /no think (NT) paradigm in a within-subject design study. We compared the rate of memory control between the follicular (low estrogen and progesterone) and mid-luteal (high estrogen and progesterone) phases of regularly cycling healthy women.

2.Materials and Methods

2.1. Participants

Participants were recruited via the posting board at Fatih University. The experimental procedure was conducted in accordance with the Declaration of Helsinki. Prior to experimentation, participants were informed about the experimental procedure in general terms. They gave written informed consent and filled in self-report questionnaires (Aydemir Ö. ve Köroğlu E., 2000) on mood and current affect. Exclusion criteria for participation were irregular menstrual cycle, current and previous psychiatric, neurological, or somatic diseases, alcohol and drug abuse, as well as medication for any of these and for birth control. Participants were 7 healthy, young females, regularly cycling (selected by period calendar data for three months provided by participants) and aged between 18-25 years. For at least three months, all participants were followed by menstrual calendars to establish cycle regularity. Only regularly cycling women were included in the study. Each participant was tested once (see the section of Experimental procedure) in each of the following phases of her menstrual cycle: follicular (days 8–10 from the first day of menstrual bleeding) and luteal (days 6–8 from ovulation). Each time at the end of the experimental procedure, blood sample was collected to verify levels of ovarian hormones.

2.2. Stimulus material

Stimulus material included word pairs presented on a computer screen with a font size of 12, colored as black, red, green according to the phase of the experiment. A word pair is composed of a cue word and a response word which are weakly related. The degree of relatedness of word pairs were determined by the ratings of a separate group of participants (n=100), assigned to rate the relatedness of words from weak (rated as 1) to strong (rated as 5) in a given questionnaire. Word pairs were used as either suppress, response or filler. The suppress word pair corresponds to the word pair with a cue word to be presented with red color which signs the participant to 'suppress', or not to think (No Think) the response word, whereas the response word pair's cue is to be presented by green which signs participant to 'think' the response word, during the Think/No Think Phase of the experimental procedure (see below). The filler word pairs were used as training material to let the participants practice the instructions of experiment. The whole experiment is required to be applied to each participant two times, with one experiment during follicular phase (FP; low estrogen and progesterone) and the second experiment during the midluteal phase (MLP; high estrogen and progesterone) of the menstrual cycle. Thus, two sets of stimulus material, each containing 48 word pairs, i.e., 36 critical (suppress word pairs and response word pairs), 12 filler word pairs, with a total of 384 words, with no significant difference in word length, word frequency and concreteness were selected in accordance with the Turkish word norms (Tekcan & Göz, 2005)

2.3. Experimental procedure

The experimental procedure was adapted from Anderson and Green (2001). Accordingly, the experimental procedure included three phase: Learning Phase, Think (T)/No Think (NT) phase and Recall Phase (Table 1). At the end of the procedure, a blood sample was received from the participants for hormonal analysis. During the learning phase, participants were trained on 36 critical and 12 filler pairs according to procedures reported previously (Anderson and Green, 2001). Subjects were trained until they learned at least the 50% of word pairs. Subjects who were not able to learn at least the 50 % of word pairs at the end of the three times of training session, were excluded from the study. Learning phase is followed by the T/NT phase during which the participants were read the think/no-think instructions, and were then given practice on filler words. Subjects were then given 384 critical

Think / No Think Paradigm

	Learning Phase	Think/No Think Phase	Test Phase
Suppress	Erozyon-Temiz	Erozyon	Erozyon
Respond	İskelet-Balkon	İskelet	İskelet
Baseline	Yüzük-Formül		Yüzük

Table 1 Adaptation of Think / No Think Paradigm

trials (192 suppress, 192 respond) in which respond and suppression stimuli were intermixed. Suppression and Respond trials were conducted on different pairs, with 12 pairs (repeated 16 times) participating in each. Four blocks of 96 critical trials were presented, separated by 45-second breaks. On each trial, a cue from one of the pairs appeared for 4000ms in red (Suppress) or green (Respond), followed by a 500ms blank inter-trial interval. At the end of the experimental procedure, blood sample was collected to verify levels of ovarian hormones.

3.Results

3.1. Quantitative verification of hormonal levels

Menstrual cycle is widely used as a model to study the effect of ovarian hormones on various cognitive functions. In parallel with this, our hormonal analysis assessed by the blood sample collected from the participants during FP and MLP show that there is a significant difference between the levels of estrogen and progesterone during these phases ($p<0.001$) and these hormones, as expected, are significantly higher in our participants during the MLP (data not shown).

3.2. Adaptation of Think/No Think Paradigm for experimental conditions

Two sets of stimulus material, one to be used in the FP and the other to be used MLP, each containing 48 word pairs, i.e., 36 critical (suppress word pairs and response word pairs), 12 filler word pairs, with a total of 384 words, with no significant difference in word length, word frequency and concreteness were selected in accordance with the Turkish word norms (Tekcan, A. İ. , & Göz, İ. (2005). The degree of relatedness of word pairs were determined by the ratings of a separate group of participants (n=100), assigned to rate the relatedness of words from weak (rated as 1) to strong (rated as 5) in a given questionnaire. Word pairs were used as either suppress, response or filler. The model of the stimulus material is shown on the Table 1.

3.3. During MLP participants perform a successful suppression

Our data demonstrate that during MLP, 63.6 % of subjects are able to 'suppress' or actively forget (significantly less % recall below the baseline) previously learned word pairs in the 'NT condition; i.e., not to think the target word associated with the cue word'. As shown by the green squares in the Figure 1, 5 participants are above the baseline, 2 participants are in the level of baseline for the T condition. For the NT condition, 5 participants are clearly below the baseline meaning they showed a significant performance on active forgetting (Figure 1, red squares). However, during the follicular phase, as shown in the Figure 2, there was no a significant effect of 'NT condition' on the active forgetting of word pairs below the baseline as assessed by the memory test applied after the T/NT procedure. Only 3 red square (meaning only 3 people were able to actively forget the previously learned word pairs).

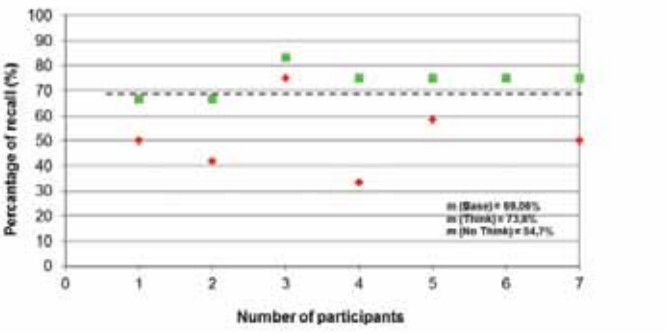

Figure 1 Percentage of recall during midluteal phase (MLP)

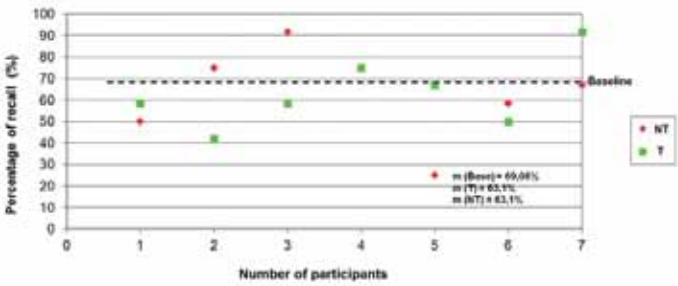

Figure 2 Percentage of recall during follicular phase (FP)

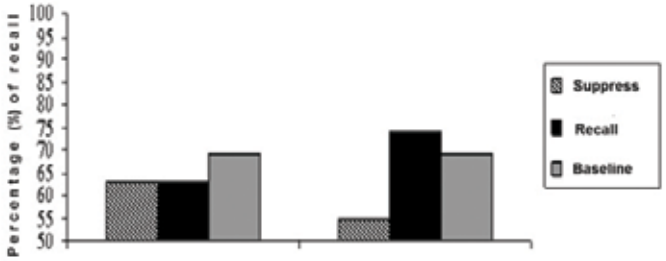

Figure 3 Percentage of recall (%) for recall (Think) and suppress (No Think) conditions with respect to baseline during the follicular phase (FP) and midluteal phase (MLP) of participants

T/NT paradigm is based on the determination of active forgetting rate of previously learned word pairs. As explained in the methods section in detail, certain word pairs were excluded from the T/NT phase of the experiment in order to determine the spontaneous forgetting which is called the baseline. The baseline is determined by a memory test applied for all learned word pairs (word pairs used for T condition, for NT condition and those excluded from the T/NT phase for the baseline) at the end of the experiment. Since the baseline corresponds to spontaneous forgetting, the forgetting rate (or % recall) should be below the baseline for NT condition and above the baseline for T condition if there is an active process of memory control. Thus, ideally, for each of the participants (N=7) the distribution of green (T) and red (NT) squares would be separated from each other by being above and below the baseline respectively. This pattern is more likely the case during the MLP (Figure 1) compared to FP (Figure 2). In fact a comparison of percentage of recall during these two phases show this pattern clearly in the Figure 3: Unlike FP, participants are able to show the performance of memory control during MLP as shown by

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the significantly reduced percentage of recall (patterned bar) compared to baseline (grey bar). During the FP, there is no a significant difference between these bars. Here, it is important to mention that, in order to eliminate any confound that would arise from the learning of paradigm, 4 of the participants were first tested during MLP, then FP and for the remaining 3 participants the test order was reversed, i.e., they were tested first during the FP then MLP.

4. Discussion and Conclusion

Although we have used a very limited number of participants in this study, our preliminary results show that memory suppression is observed during MLP of the regularly cycling women as reflected by the better performance on the T/NT test. The same effect was poorly observed during FP, when these hormones are low. Thus ovarian hormones may likely play a role in the process of active forgetting, most probably by modulating the PFC as this region is known to be involved in the process of active forgetting and highly accessible to ovarian hormones (Keenan P.A. et al., (2001). A replication of this study with higher numbers of participants will clarify our, so far very limited, knowledge of memory suppression and its modulation.

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AGMATINASE AND HUMAN CATIONIC AMINO ACID TRANSPORTER 1 IN MOOD DISORDER: WHAT´S UNDER THE MICROSCOPE?

DUYGUDURUM BOZUKLUKLARINDA AGMATİN VE İNSAN KATYONİK AMİNO ASİT TRANSPORTER 1: MİKROSKOBUN ALTINDA NE VAR?

Hans-Gert Bernstein[1*], Kristin Jäger[2], Juliane Fiebig[1], Susann Wolf[1], Martin Wick[1], Henrik Dobrowolny[1], Johann Steiner[1], Bernhard Bogerts[1] and Gregor Laube[3]

Abstract

Agmatine may act as a neurotransmitter or neuromodulator. Behaviorally, agmatine exerts antidepressant-like effects. The enzyme agmatinase degrades and thereby inactivates agmatine. The gene coding for human agmatinase is located on chromosome 1p36, a gene locus which has been linked to bipolar disorder and major depression. However, the enzyme has not yet been studied in detail in the context of neuropsychiatric diseases. We analyzed agmatinase protein expression in postmortem hippocampi of individuals with affective disorders. Agmatinase protein was detected in a subset of interneurons in the hippocampus and other brain regions. In depressive patients the number and the numerical density of agmatinase-immunopositive cell bodies was strongly elevated in all regions under study (i.e. hippocampus, habenula, insular cortex and temporal cortex). Agmatine is naturally produced by the breakdown of arginine. The cellular uptake of L-arginine and other cationic amino acids (such as L-lysine and L-ornithine) is mainly mediated by cationic amino acid transporter (CAT) proteins. In patients with mood disorder there was a circumscribed decrease in the numerical density of hCAT1 immunoreactive neurons in the CA2 region of the hippocampus.

Keywords: Brain, mood disorder, immunocytochemistry, agmatinase, human cationic aminoacid transporter 1 (hCat1).

Özet

Agmantin, nöromodülatör ve nörotransmitter olarak çalışır. Davranışsal olarak agmatin, antidepresanvari etkiler uygular. Enzim olan agmatinaz, agmatini indirger ve böylece devre dışı bırakır. İnsan agmatinini kodlayan, bipolar bozukluk ve majör depresyonla bağlantılı olan bu genin konumu 1p36. kromozomdadır. Fakat bu enzim nöropsikiyatrik hastalıklar bağlamında henüz detaylı olarak incelenmemiştir. Duygusal bozuklukları olan bireylerin postmortem hipokampüsündeki agmatin protein dışavurumunu inceledik. Agmatin proteini, hipokampüs ve diğer beyin bölgelerindeki internöronlar altkümesinde saptanmıştır. Depresif hastalarda agmatin-immunopozitif hücre gövdelerinin sayısı ve sayısal çoğunluğu incelemedeki bütün kısımlarda (hipokampüs, habenula, insular korteks ve temporal korteks) fazlasıyla artmıştır. Agmatin doğal olarak arjininin kırılmasıyla/ bozulmasıyla ortaya çıkmaktadır. L-arjinin ve diğer katyonik amino asitlerin(L-lisin ve L-ornitin gibi) hücresel alınımına temel olarak katonyik amino asit transporter(CAT) proteinleri aracılık eder. Duygudurum bozukluğu olan hastalarda, hipokampüsün CA2 kısmındaki hCAT1 immunoreaktif nöronların sayısal yoğunluğunda sınırlı bir azalma vardı.

Anahtar Kelimeler: *Beyin, duygudurum bozukluğu, immünsitokimya, agmatinaz, insanda katyonik amino asit taşıyıcısı 1 (hCat1).*

1. Introduction

The diamine agmatine may serve as a precursor in polyamine synthesis. In addition, agmatine may also act as a neurotransmitter and/or neuromodulator, binding to imidazoline receptors (reviewed in Bhutada et al., 2012). Behaviourally, it exerts anti-convulsant, (Aricioglu & Altunbas 2003; Aricioglu et al., 2003; Xu et al., 2014), anti-neurotoxic (Halaris & Piletz, 2007), vasodilatory (Satriano, 2003), neuroprotective, anti-apoptotic (Kuo et al., 2011; Moretti et al., 2014), anxiolytic (Gong et al., 2006), and especially anti-depressant-like effects (Zombowski et al., 2002; Aricioglu & Altunbas 2003; Li et al., 2003; Uzbay, 2012; Freitas et al., 2014). Interestingly, several lines of evidence suggest a prominent involvement

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of agmatine in mental disorders such as schizophrenia and depression (Zombowski et al., 2002, 2003; Moinard et al., 2005; Fiori &Turecki, 2005; Krass et al., 2008; Pålsson et al., 2008; Uzbay et al., 2013) as well as suicidal behavior (reviewed in Gross & Tureck, 2013). The enzyme agmatinase (EC. 3.5.3.11) degrades and thereby inactivates agmatine. The gene coding for human agmatinase is located on chromosome 1p36, a gene locus which has been linked to bipolar disorder and major depression (Zombowski et al., 2002; McGuffin et al., 2005; Taştemir et al., 2006; Demirhan et al., 2009; Kaneva et al., 2009; Fullerton et al., 2010). Recently, we found a significantly increased agmatinase protein expression in post-mortem hippocampi of individuals with unipolar and bipolar depression (Bernstein et al., 2012). In the present report we morphometrically analyzed agmatinase protein expression in the hippocampus and three other brain regions (habenula, insular cortex and temporal cortex) of subjects with depression to learn more about the putative role of agmatinase in the pathophysiology of mood disorders. L-Arginine is a major substrate for the synthesis of agmatine (for overview, see Halaris and Piletz, 2007). In the central nervous system (CNS), L-arginine is extracted from the blood and exchanged by cells through carriers called cationic amino acid transporters (CATs). Hence, the regional distribution and cellular localization of CATs may have a significant impact on the agmatine system. CATs have recently been shown to be widely distributed throughout human brain (Jäger et al., 2013) and have been linked with unipolar depression (Holmans et al., 2007). We therefore also determined the numerical density of human (h)CAT1 immunoreactive hippocampal neurons in mood disorders.

2. Material and Methods

All brains were obtained from New Magdeburg Brain Collection. Sampling of the human brain material and asservation was done in accordance with the Declaration of Helsinki (1984), German law and approval by the local Ethics commission. Brains were collected from 12 individuals without any psychiatric or neurological disorder (four women, eight men), eleven patients with mood disorder (four women, seven men). The age range was 35–65 years (mean age 48.1 years). Of these, seven died by suicide. Five patients displayed unipolar (major) depression (UD) and six a bipolar disorder (see tables 1 and 2). All depressed patients received long-term treatment with antidepressants. In addition, four of the bipolar patients had lithium. Tissue preparation was performed as previously described in detail (Bernstein et al., 1998). 20µm thick coronal whole brain sections were used. A well-characterized, monospecific polyclonal antibody against agmatinase was employed (Krauss et al., 2006).. We used the avidin–biotin method (Vectastain-peroxidase kit) with 3,3′-diaminobenzidine as chromogen. The colour reaction was enhanced by adding 2 ml of a 0.5% nickel ammonium sulfate solution to the diaminobenzidine (Bernstein et al., 1999). To immunolocalize hCAT1 we used a monospecific, polyclonal antiserum to the hCAT protein1 (Jäger et al., 2013). Cell countings (agmatinase: hippocampus, habenula, insular cortex, temporal cortex; hCAT1: hippocampus) and fiber densities (agmatinase: habenula) were performed using the optical disector method and a counting grid as described earlier (Bernstein et al., 1998; Lendeckel et al., 2009). Data were statistically analyzed using the non-parametric U-test (Mann and Whitney).

Table 1: Demographical data for the controls (psychiatrically unaffected individuals).

Individuals without mood disorder (controls)	Age (years)	Gender	Cause of death	Duration of illness (years)	Postmortem delay (h)
1	50	m	Cardiac insufficiency	0	72
2	47	m	Cardiac and circulatory failure	0	24
3	47	m	Acute respiratory insufficiency	0	24
4	72	f	Pneumonia, pancreas carcinoma	0	24
5	51	m	Cardiac and circulatory failure, pulmonary insufficiency	0	24
6	64	m	Rupture of the aorta	0	35
7	48	m	Heart failure, arteriosclerosis	0	72
8	63	m	Sudden cardiac death	0	48
9	54	m	Pulmonary embolism	0	24
10	39	f	Cardiac insufficiency	0	48
11	40	f	Pneumonia	0	48
12	48	f	Pneumonia	0	48

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Table 2: Demographical data for the subjects with mood disorder.

Individuals without mood disorder	Age (years)	Gender	Cause of death	Duration of illness (years)	Postmortem delay (h)
Unipolar					
1	39	f	Suicide (tablets)	7	48
2	46	f	Suicide (hanging)	11	48
3	35	m	Suicide (hanging)	2	15
4	36	m	Suicide (tablets)	1	42
5	60	m	Suicide	unknown	24
Bipolar					
6	62	f	Heart failure	11	72
7	59	m	Suicide (Shooting)	24	72
8	39	m	Heart failure	14	56
9	65	f	Pulmonary embolism	25	52
10	42	m	Suicide	16	17
11	47	m	Myocardial infarction	9	24

3. Results

3.1. Agmatinase

We herein could replicate our previous observation that agmatinase is predominantly expressed in multiple interneurons (Fig. 1A) and nerve fibers (Bernstein et al., 2011). Quantitatively, we found a significant ($p<0.05$) upregulation of agmatinase expression in neuronal cell bodies and fibers of all hippocampal subfields (not shown here, as already reported in our previous communication Bernstein et al., 2012), the in subdivisons of the habenula (Fig. 2) as well as in the insular and the temporal cortex (Fig. 3).

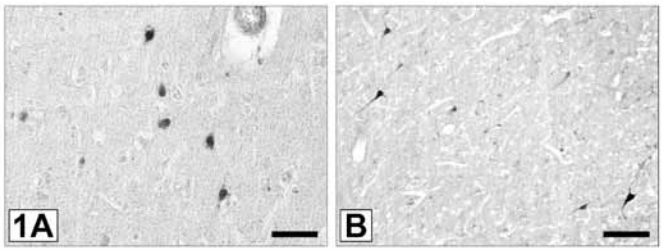

Figure 1: Immunohistochemical localization of agmatinase and hCAT1 in human brain neurons; **Figure 1A:** Agmatinase-expressing interneurons in the human temporal cortex. Bar = 35μm; **Figure 1B:** HCAT1 immunpositive neurons in the hippocampus. Bar = 70μm.

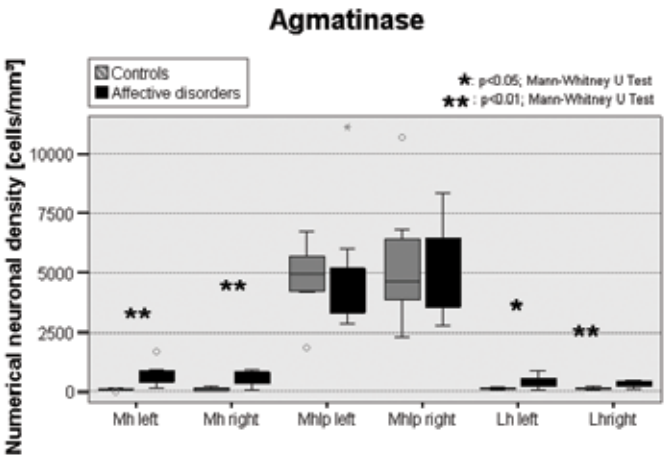

Figure 2: Numerical density of agmatinase-expressing neurons in the habenula of controls and depressed patients. Mh, medial habenula; Mhlp, medial habenula, lateral part; Lh, lateral habenula

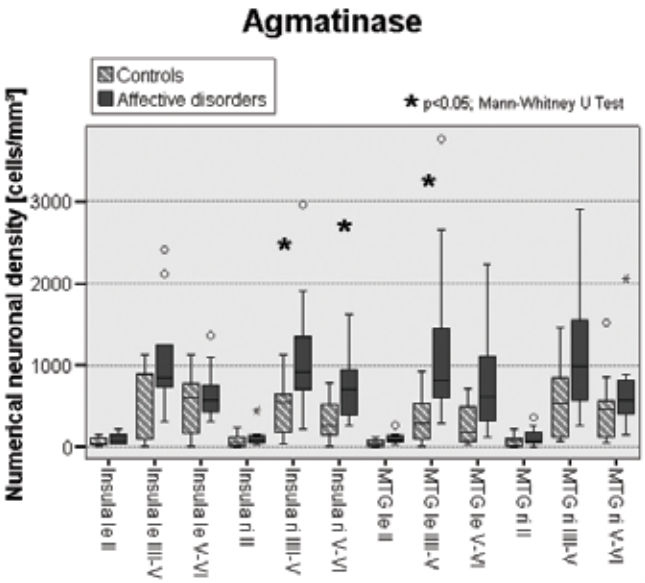

Figure 3: Numerical density of agmatinase-expressing neurons in the insular and temporal cortex of controls and depressed patients. MTG, medial temporal gyrus (of the neocortex); Le, left hemisphere; Ri, right hemisphere; I-VI, cortical layers.

3.2. HCAT1

With regard to hCAT1, multiple pyramidal and interneurons were immunoreactive for the protein, with interneurons being very intensely immunostained. (Fig. 1B) Occasioanally, hCAT1 immunoreactive axons were found. In addition, CAT1 was seen in numerous astrocytes. In patients who had suffered from a mood disorder, a significantly increased density of immunoreactive neurons was estimated in the CA2 region of the hippocampus (Fig. 4).

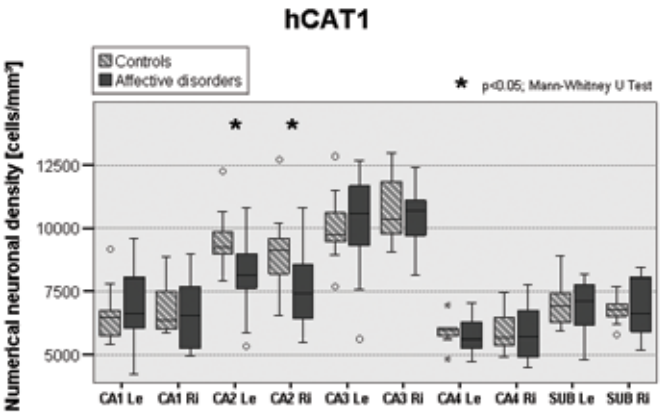

Figure 4: Numerical density of hCAT1-expressing neurons in the hippocampus of controls and depressed patients. CA1, CA2; CA3, CA4, subfields of the hippocampus; SUB, subiculum; Le, left hemisphere; Ri, right hemisphere.

4. Discussion

The enzyme agmatinase is an inactivator of the putative endogenous antidepressant agmatine (for recent considerations, see Bernstein et al., 2012). Our current findings clearly show that in depression elevated agmatinase expression is not restricted to the hippocampus, but can also be found in other brain areas. Although we currently cannot demonstrate an increase in agmatinase enzyme activity on a cellular level in depression, it can be assumed that the observed increase in protein expression is accompanied by an increased enzymatic activity. This increased activity may result in a local reduction of brain tissue agmatine levels, thus reducing "anti-depressant capacity" of the brain in depression (Bernstein et al., 2012). Hence, increased inactivation of agmatine may play a central role in the pathogenesis of the disease, and "normalizing" its brain levels by depressing agmatinase expression/ activity (by perazine-1-carboxamidine or another agmatinase inhibitor; Kitanaka et al., 2014) might be a future therapeutic option. Unexpectedly, we found an increased (not decreased) expression of hCAT1 in the hippocampus of subjects with depression. However, the up-regulation of an arginine transporter might be compensatory to improve the arginine supply of the brain. This seems to be obvious since arginine levels are known to be reduced in depression (at least in blood platelets; Pinto et al., 2012). Besides, hCAT1 has been identified as a mediator of the NMDA receptors by acting via the rapamycin-mTOR pathway (Huang et al., 2007), which is disturbed in depression (Jernigan et al., 2011). It remains, however, to be elucidated whether antidepressant medication contributes to the increase of hCAT1 expression in mood disorders.

The authors declare no conflict of interest.

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AN ALTERNATIVE APPROACH TO UNDERSTAND SCHIZOPHRENIA: POLYAMINE HYPOTHESIS THROUGH NMDA RECEPTORS

ŞİZOFRENİYİ ANLAMAKTA ALTERNATİF BİR YAKLAŞIM: NMDA RESEPTÖRLERİ ARACILIĞI İLE POLİAMİN HİPOTEZİ

Tayfun Uzbay[1]

Abstract

The glutamate hypothesis of schizophrenia based on the observations that administration of drugs that block N-methyl-D-aspartate (NMDA) glutamate receptors could induce schizophrenia-like symptoms. There are several evidences linking abnormal glutamatergic transmission to cognitive, negative, and positive symptoms of schizophrenia and the glutamatergic system is now a major focus for the development of new compounds in schizophrenia. The polyamines are omnipresent aliphatic molecules comprising putrescine, spermidine, spermine and agmatine. The polyamines and their biosynthetic enzymes are found throughout the body, including the central nervous system (CNS), where they display specific regional distributions in the CNS. The polyamines have an important role in the modulation of cell growth and on cell membrane functions. It was hypothesized that schizophrenia may be related to a general abnormality in neuronal membranes. Agmatine, a polyamine, selectively blocks the NMDA subclass of glutamate receptors in rat hippocampal neurons. There are also several evidences indicate that a relationship between polyamines and etiopathogenesis of schizophrenia. In this review, a new approach for understanding schizophrenia via NMDA receptors and their interaction with agmatine which is a biological active polyamine transmitter in brain is proposed.

Keywords: Agmatine, glutamate, NMDA receptors, polyamines, schizophrenia

Özet

Şizofrenide glutamat hipotezi N-metil-D-aspartat (NMDA) reseptör antagonistlerinin insanlarda ve deney hayvanlarda şizofreni semptomları oluşturmasına dayanır. Anormal glutamaterjik iletinin şizofreninin bilişsel, pozitif ve negative semptomları ile ilişkisine işaret eden birçok kanıt vardır ve glutamaterjik sistem şizofreni tedavisinde yeni ilaçların geliştirilmesi için güncel ve önemli bir odaktır. Poliaminler doğada ve canlı organizmalarda yaygın olarak bulunan putresin, spermidin, spermin ve agmatin gibi birden fazla amin içeren alifatik moleküllerdir. Poliaminler ve bunların biyosentetik enzimleri vücutta merkezi sinir sistemi de (MSS) dâhil olmak üzere yaygın olarak bulunur. Poliaminler hücre büyümesinin modülasyonu ve hücre membran işlevlerinde önemli bir role sahiptir. Şizofreninin sinir hücresi membranlarındaki genel bir anomalite ile ilişkili olduğu hipotezi ileri sürülmüştür. Bir poliamin olan agmatin sıçan hipokampal nöronlarında glutamaterjik NMDA reseptörlerini seçici bir şekilde bloke eder. Poliaminlerle şizofreni hastalığının etyopatogenezi arasında ilişkiye işaret eden çeşitli kanıtlar da mevcuttur. Bu gözden geçirme yazısında biyolojik aktif bir nörotransmitter olan agmatin ile NMDA reseptörleri arasındaki etkileşme üzerinden şizofreninin anlaşılmasına yönelik yeni bir yaklaşım ileri sürülmektedir.

Anahtar Kelimeler: *Agmatin, glutamat, NMDA reseptörleri, poliaminler, şizofreni*

1. Introduction

Schizophrenia is a serious mental disorder with a challenging rational pharmacotherapy and is considered a neurodevelopmental disease. It is a disease affecting up to 1% of the population (Uzbay, 2009).

Plain hypothesis on schizophrenia is associated with excessive stimulation of dopamine D2 receptors in the associative striatum, with a lack of stimulation of dopamine D1 receptors in prefrontal cortex. Thus, drug therapies are based on the efficacy of chlorpromazine, discovered over 50 years ago. These drugs block dopamine D2-like receptors and are effective at primarily treating positive symptoms in a subset of patients. Unfortunately, current therapies are far from adequate, and novel treatments require (Laruelle, 2014; Perez and Lodge, 2014). In addition, the essential processes associated with schizophrenia still remain uncertain. Thus, new ways of searching to understand and treatment of schizophrenia is already ongoing.

Here, in this review, a new approach for understanding

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schizophrenia via NMDA receptors and their interaction with agmatine which is a biological active polyamine transmitter in brain is proposed.

2. Glutamate hypothesis in schizophrenia

Glutamate (Glutamic acid) (Figure 1) was initially discovered to be a neurotransmitter in insect studies in the early 1960s. L-glutamate is the major excitatory neurotransmitter in the mammalian CNS, being present in over 50% of nervous tissue. Glutamate has a key role for several biological (learning and memory, cognition) and pathological (epilepsy, neurodegenerative events) processes in mammals (Johnson, 1972).

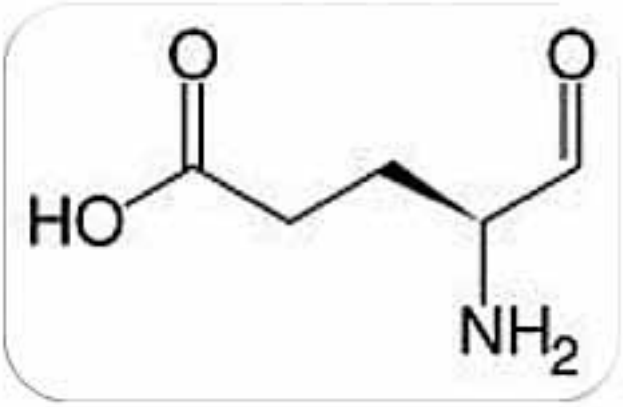

Figure 1. Glutamic acid (glutamate)

Glutamate acts via two classes of receptors. They are ligand gated ion channels or ionotropic receptors (i.e. NMDA, AMPA and kainite) and G-protein coupled (methabotropic) receptors (i.e. mGluR1-R8). NMDA receptors are ionotropic receptors mediating glutamatergic neurotransmission and play a role in several basic functions in the central nervous system (CNS), from regulating neurodevelopment and synaptic plasticity, learning and memory formation, cognitive processes, rhythm generation necessary for locomotor activity and breathing, and excitotoxicity. Due to their complex involvement in the above processes, NMDA receptors have been established to play a role in the etiopathology of several neuropsychiatric disorders such as ischaemia and traumatic brain injury, neurodegenerative disorders, pain syndromes, addiction, affective disorders and such neurodevelopmental disorders as autism or schizophrenia. NMDA receptors contain multiple types of subunits with distinct functional and pharmacological properties making the picture more complex. These receptors also offer multiple binding sites to be targeted with pharmacological agents (Gonda 2012; Rubio et al., 2012). A Schematic representation of a typical NMDA receptor has been shown in Figure 2.

The glutamate hypothesis of schizophrenia, proposed over two decades ago. This hypothesis based on the observations that administration of drugs that block N-methyl-D-aspartate (NMDA) glutamate receptors, such as ketamine and phencyclidine, could induce schizophrenia-like symptoms. NMDA antagonists also

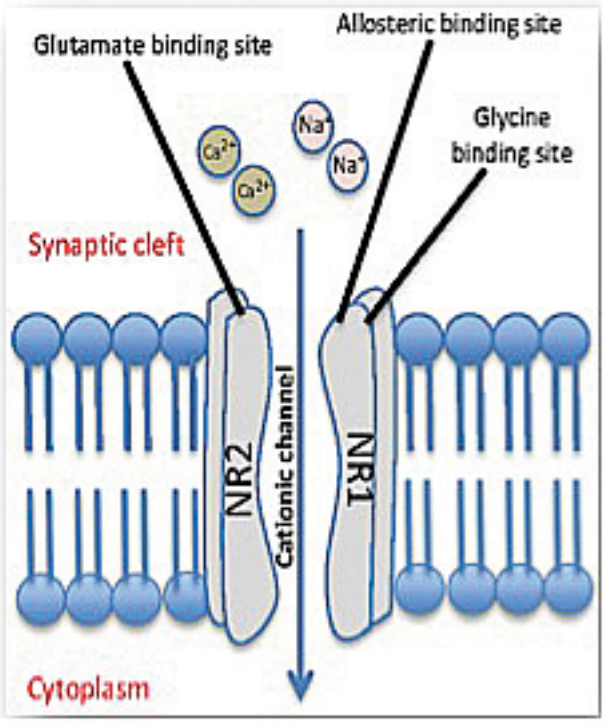

Figure 2. Schematic representation of a typical NMDA receptor. The NMDA contains four subunits, two glycine binding NR1 subunits and two glutamate binding NR2 subunits, and allows for cationic influx from the synaptic cleft into the cell (from Lakhan et al., 2013)

worsen positive, negative, and cognitive symptoms in patients with schizophrenia (Krystal et al., 1994; Lahti et al., 1995; Malhotra et al., 1997; Merritt et al., 2013). Thus, there are several evidences linking abnormal glutamatergic transmission to cognitive, negative, and positive symptoms of schizophrenia and the glutamatergic system is now a major focus for the development of new compounds in schizophrenia. Some new drugs due to glutamatergic mechanisms such as potent mGlu2/3 receptor agonism were also under the research in clinical phase studies (Patil et al., 2007). Some conflict results have been obtained from these researches. For example, while pornaglutemad methionil (LY2140023) which is an mGlu2/3 agonist failed to meet the primary efficacy end point, ADX71149 which is the mGlu2 positive allosteric modulator met the primary objectives of safety, tolerability and established an adequate effect on negative symptoms of schizophrenia (Hopkins, 2013).

3. Polyamines and agmatine

The polyamines are omnipresent aliphatic molecules comprising putrescine, spermidine and spermine, which contain 2, 3 and 4 amino groups, respectively. In addition, the guanidino-amine agmatine, whose presence in mammalian brains was discovered much more recently than that of the other polyamines, may also be considered among this group. The polyamines and their biosynthetic enzymes are found throughout the body, including the CNS, where they display specific regional distributions in

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the CNS. The polyamines have an important role in cell proliferation and demonstrate both pro- and antiapoptotic effects. They are involved in many signaling pathways through their effects on G proteins, protein kinases, nucleotide cyclases and receptors, as well as by their regulation of the expression of proteins involved in these processes. Polyamines such as spermine and agmatine have been shown to be released from synaptic vesicles on depolarization, indicating that the polyamines may function as neuromodulators. They also influence the properties of several neurotransmitter pathways known to be involved in mental disorders, including the catecholamine, GABA, nitric oxide and glutamate. Alterations in the expression and activity of polyamine enzymes, as well as changes in the levels of the individual polyamines, were showed in various psychiatric conditions, including schizophrenia, mood disorders, anxiety and suicidal behavior. Additionally, these components have been found to be altered by various psychiatric treatments (Fiori and Turecki, 2008).

Agmatine was discovered in 1910 by Albrecht Kossel, the German scientist who first identified the substance in herring sperm (Kossel, 1910). Agmatine which is an endogenous biogenic polyamine, is synthesized from amino acid L-arginine with a reaction catalysed by enzyme arginine decarboxylase and it is metabolized by enzyme agmatinase to putrescine, spermine and spermidine, other polyamines (Reis and Regunathan, 2000). It is synthesized, stored, and released in brain and is distributed with highest concentrations in hypothalamus, forebrain, and cerebral cortex (Reis and Regunathan, 1999).

Agmatinergic neurons were present in the cerebral cortex (cingulate, primary somato-sensory and auditory cortices, and the subiculum), the lower brainstem (the nucleus tractus solitarii and pontine parabrachial complex, and periventricular areas including the dorsolateral nucleus, locus coeruleus and dorsal raphe), the midbrain (ventral tegmental area and periaquaductal gray) and the forebrain (preoptic area, amygdala, septum, bed nucleus of the stria terminalis, midline thalamus, and the hypothalamus) (Otake et al., 1998). Thus, it has been proposed that agmatine meets several criterions as a new neuromodulator or neurotransmitter in brain (Reis and Regunathan, 1998; Uzbay, 2012a). A possible agmatinergic synapse is also illustrated in Figure 3. However, major professional societies such as IUPHAR have not adopted this concept yet.

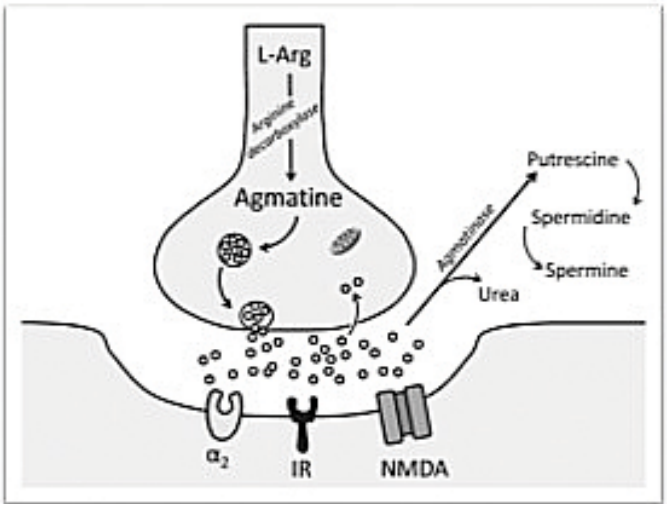

Figure 3. Schematic representation of agmatinergic synapse (IR= Imidazoline receptors) (from Uzbay, 2012a).

4. Polyamines, agmatine and schizophrenia

It has been showed that agmatine exhibited several pharmacological actions (i.e. anticonvulsant, antinociceptive, anxiolytic and antidepressant) and neuroprotective effects in experimental animals by interacting with imidazoline, alpha-2 adrenergic and NMDA receptors at a dose range from 1 to 100 mg/kg (Uzbay, 2012a; Uzbay, 2012b).

Agmatine selectively blocked the NMDA subclass of glutamate receptor, but not AMPA or kainite channels in rat hippocampal neurons (Yang and Reis, 1999). In addition, agmatine is an inhibitor of all isoforms of enzyme nitric oxide synthase (NOS) dose-dependently and competitively with the substrate L-arginine (Galea et al., 1996). Furthermore, it may inhibit glutamate releasing from presynaptic nerve terminals and prevent the activation of postsynaptic NMDA receptors by inhibiting postsynaptic NO generation and suppressing adenylate cyclase-cGMP cascade in presynaptic area (Uzbay and Oglesby, 2001) (Figure 4).

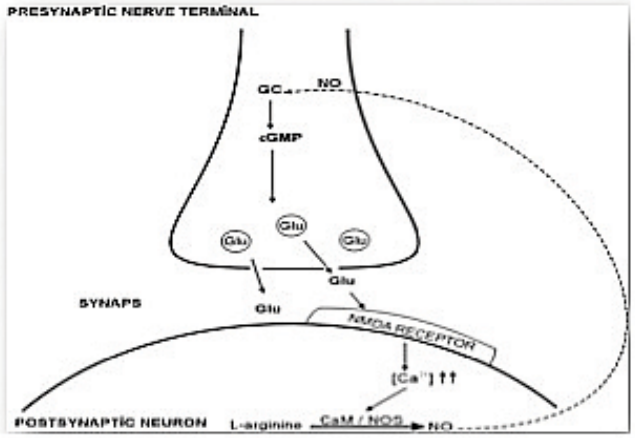

Figure 4. L-arginine is converted to NO in the postsynaptic neuron. The NO that is produced diffuses back to the presynaptic neuron, where it enhances the release of glutamate via guanylate cyclase (GC) and cGMP. Glutamate that is released from the presynaptic terminal activates NMDA receptors, and Ca^{2+} enters and, via calmodulin (CaM), activates the NOS again (from Uzbay and Oglesby, 2001).

Agmatine attenuates severity of morphine (Aricioglu-Kartal and Uzbay, 1997) and ethanol (Uzbay et al., 1997) withdrawal syndromes in rats. It has been suggested that the inhibitory effects of agmatine on NO-NMDA pathway may be responsible for the beneficial effects on ethanol and morphine dependence (Aricioglu-Kartal and Uzbay, 1997; Uzbay et al., 1997; Uzbay and Oglesby, 2001).

If considering the inhibitory effects of agmatine on NMDA receptors either directly or via NOS inhibition, it could be expected that agmatine may cause psychosis or worsen positive and negative symptoms of schizophrenia like other NMDA receptor antagonists such as phencyclidine and ketamine. Indeed, several evidences indicate that there may be a link between schizophrenia and polyamines.

The polyamines have an important role in the modulation of cell growth and on cell membrane functions. It was hypothesized that schizophrenia may be related to a general abnormality in neuronal membranes. Thus, polyamines may associate with etiopathogenesis of schizophrenia (Ramchand et al., 1994). It has been reported that poliamines like spermidine and spermine, might be involved in pathogenesis of schizophrenia. Some previous reports indicated significantly high levels of agmatine metabolites (i.e, spermine, spermidine) in blood, cerebrospinal fluids or brain tissue in patients with schizophrenia (Richardson-Andrews, 1983; Andrews, 1985; Ramchand et al., 1994) and these polyamines are the end products of agmatine metabolism. Furthermore, high levels of plasma asymmetric methyl-arginines, (i.e. asymmetric dimethylarginine), which is the precursor of cell-signaling molecules such as NO and agmatine, accompanied schizophrenia (Das et al., 1996; Kopieczna-Grzebieniak and Goss, 2005).

Previously, Uzbay et al. (2010) showed agmatine caused disruption of prepulse inhibition (PPI) of acoustic startle reflex and it potentiated significantly apomorphine-induced disruption of PPI. In this study, agmatine exhibited this action by a relatively high dose (160 mg/kg). Because PPI test is accepted as a screening test for experimental schizophrenia studies, this observation implies a strong relationship between agmatine and schizophrenia. Thus, Uzbay et al. hypothesized that because spermine and spermidine, agmatine metabolites, were found very high in patients with schizophrenia, and agmatine disrupts PPI in rats, unbalanced and/or excessive agmatine release may be related to schizophrenia. Results of the recent clinical study by Uzbay et al. (2013) supported to the hypothesis. In this study, significantly increased plasma levels of agmatine in patients with schizophrenia were found compared to healthy individuals (Figure 5).

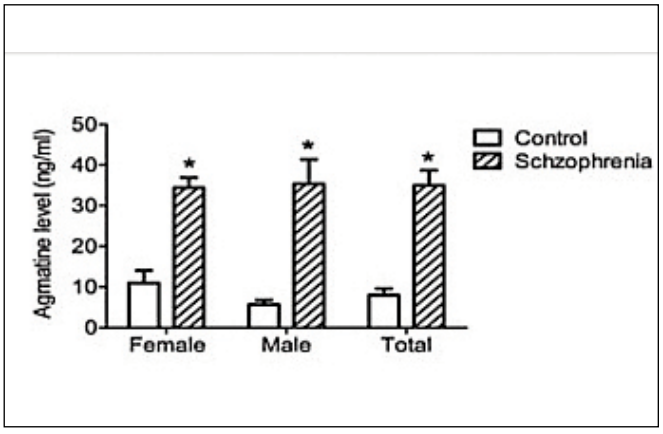

Figure 5. Mean plasma agmatine levels in the female, male and whole groups of healthy controls and of patients with schizophrenia (*p < 0.05, Mann-Whitney U test) (from Uzbay et al., 2013).

The receiver-operator characteristic (ROC) curve ROC analysis of the data indicated that the possibility of measuring higher agmatine levels in patients with schizophrenia than in normal individuals was as high as 96% (Figure 6). The ROC curve analysis is a fundamental tool for diagnostic test evaluation in medicine (Zou et al., 2007). In an ROC curve, the analysis sensitivity and specificity for different cut-off points of a parameter are calculated. The sensitivity of the agmatine level measurements between patients and controls was also found to be statistically significant. All of these evaluations imply that the measurement of agmatine in the plasma may have importance as a diagnostic and/or follow-up test in schizophrenia.

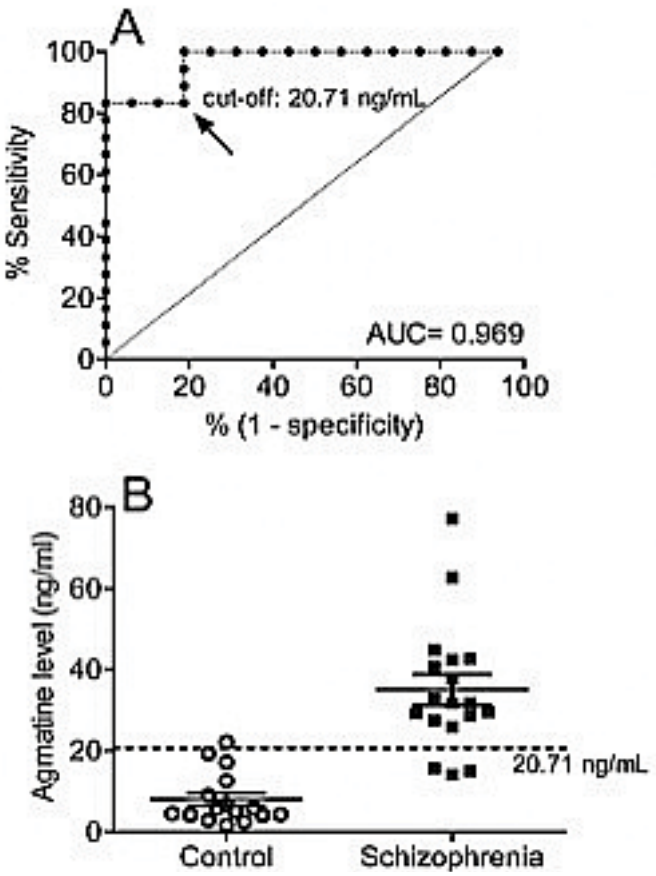

Figure 6. The receiver-operator characteristic (ROC) curve for plasma agmatine levels in schizophrenia (A) and the individual distribution of plasma agmatine levels in healthy controls and in patients with schizophrenia (B) (from Uzbay et al., 2013).

5. Conclusion

In conclusion, these evidences clearly support to hypothesis that polyamines and agmatine are related to etiopathogenezis of schizophrenia. NMDA-NO antagonistic action of agmatine may be responsible for its relation with schizophrenia. Agmatine and/or polyamines may also be as an indicator for diagnosis and treatment of schizophrenia.

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THE RATIONALE FOR THE LOCALIZATION OF POLYAMINE PATHWAY ENZYMES IN THE BRAIN

BEYİNDEKİ POLİAMİN YOLAK ENZİMLERİNİN LOKALİZASYONUNUN ANLAMI

G. Laube[1*], H.-G, Bernstein[2], R.W. Veh[1], T. Weiss[1]

Abstract

Polyamines, including spermidine, spermine, and agmatine, serve several brain-specific functions. Polyamine transport mechanisms may account for the redistribution of these organic cations, which may also be synaptically released as neuromodulators or neurotransmitters, in the brain. Therefore, the localization of polyamine pathway enzymes, in addition to the localization and functional investigation of the polyamines itself, provides valuable insights regarding the identification of cell- and region-specific roles for polyamines, notably in the context of mental disorders and neurodegenerative diseases. Identified neuronal circuits are subject to physiological and pharmacological investigations. With this respect, we electrophysiologically studied the cerebellar cortex and the medial habenula, showing a prominent synaptic expression of spermidine synthase and agmatinase, respectively. In both areas, the relevant polyamines clearly influence the electrical activity. The medial habenula may be involved with the aetiology of major depressive disorder. In this context, the expression of agmatinase in other brain areas, e.g. the paraventricular thalamic nucleus, possibly also involved with depression, is discussed.

Keywords: Polyamines, brain, neurobiology

Özet

Spermidin, spermin ve agmatini içeren poliaminler beyne özgü pek çok fonksiyonu çalıştırmaktadır. Poliamin dolaşım mekanizmaları, beyinde nöromodülatör ve nörotransmitterler gibi sinaptik olarak salgılanabilen bu organik katyonların yeniden dağıtımından sorumlu olabilmektedir. Bu nedenle, poliaminlerin lokalizasyon ve fonksiyon incelemesine ek olarak poliamin yolak enzimlerinin lokalizasyonu, özellikle psikolojik bozukluklar ve nörolojik dejeneratif hastalıklarda poliaminlerin hücre tanımlaması ve bölgeye özgü rolleriyle alakalı hatırı sayılır bilgiler sağlamaktadır. Belirli nöronal devreler fizyolojik ve farmakolojik araştırmalara bağlıdır. Bu çalışma kapsamında spermedin sentezi ve agmatinin belirli sinaptik ifadesini nispeten gösteren serebral korteksi ve medial habenulayı elektrofizyolojik olarak incelenmiştir. Her iki alanda da ilgili poliaminler açık bir şekilde elektriksel aktiviteyi etkilemekte ve medial habenula majör depresif rahatsızlığın etiyolojisinde yer alabilmektedir. Bu bağlamda, paraventriküler talamik nükleusu gibi beynin diğer bölümlerindeki agmatinin ifadesiyle depresyon ilişkisinin olasılığı tartışılacaktır.

Anahtar Kelimeler: *Poliamin, beyin, nörobiyoloji*

The naturally occurring polyamines putrescine, spermidine, and spermine and the guanidino-group-containing diamine agmatine, here together referred to as polyamines in the wider sense, represent evolutionary ancient biomolecules that are found throughout procaryotic and eukaryotic life forms, ranging from bacteria to animals and plants. Initially discovered as spermine cristals in human seminal fluid by Antoni van Leeuwenhoek in 1678 and subsequently further characterized between 1878 and 1926, by now polyamines have gained considerable interest as multifunctional cations. Given their multiple positive charges at physiological pH values, polyamines necessarily interact with negatively charged biomolecules, notably nucleic acids. Thus, the primary function of spermidine and spermine, containing three respectively four amino and imino groups, may be involved with the stabilization of RNA (Igarashi and Kashiwagi, 2000) and the tertiary structure formation of DNA and the condensation of chromatin (D'Agostino and Di Luccia, 2002; D'Agostino et al., 2006). Accordingly, polyamine synthesis and degradation is induced during progression of the cell cycle (Wallace et al., 2003). Polyamines are therefore essential for growth and differentiation of tissues. In contrast to relatively low polyamine concentrations in normally dividing cells that inhibit normal growth and proliferation control, cancer cells contain high amounts of polyamines while having lost growth and proliferation control (Gerner and Meyskens, 2004). Consequently, polyamine

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biosynthetic enzymes, notably ornithine decarboxylase (ODC), became therapeutic targets in cancer research (recently reviewed in (Nowotarski et al., 2013)). Being tightly controlled under normal conditions by multiple mechanisms, polyamine concentrations in most non-dividing cells can be expected to be rather low and mostly bound to other biomolecules. Therefore, in the adult brain, given a very limited potential for neurogenesis in restricted brain regions, one could assume that in most areas polyamine content and especially the expression of polyamine pathway enzymes could be marginable and may even be below detection limits. However, in contrast to putrescine, the polyamines spermidine and spermine were biochemically detected in relatively high amounts in brain (1995; Saka et al., 2002; Shaw, 1979; Shaw and Pateman, 1973), thus suggesting a specific role for polyamines in the central nervous system. Basically, four main lines of evidence subsequently supported this assumption: (1) the discovery of several prominent molecular targets for polyamines in the brain, beginning with NMDA receptors (Ransom and Stec, 1988), (2) the existence of polyamine transport systems in neurons, glial cells and synaptic vesicles (Masuko et al., 2003), (3) polyamine-dependent behavioural effects (Gupta et al., 2012; Liu et al., 2008a; Liu et al., 2008b; Seo et al., 2011), and the involvement with the pathophysiology of psychiatric disorders (reviewed in (Fiori and Turecki, 2008)), neurodegenerative diseases (Antony et al., 2003; Colton et al., 2004; Goers et al., 2003), and brain injury (Kim et al., 2009; Moretti et al., 2014). In addition to spermidine/spermine, also agmatine became increasingly important in this context (reviewed in (Uzbay, 2012)), after being discovered as an endogenous ligand of imidazoline receptors (Li et al., 1994) and discussed as a putative neurotransmitter (Reis and Regunathan, 1998a, b). The involvement of polyamines with mental disorders, namely schizophrenia and depression, came into focus, as side effects of the anti-malarial drug chloroquine, possessing a polyamine-like moiety, were observed in some patients (Andrews, 1985). Notably, in depressed patients, altered agmatine plasma levels were observed (Halaris et al., 1999), and in suicidal individuals the gene expression of the spermidine/spermine catabolic enzyme SSAT was found to be down regulated (Fiori et al., 2011). Moreover, in animal models of depression agmatine produced anti-depressant-like effects (Zomkowski et al., 2002). In addition, the polyamine system is involved with stress response (Gilad and Gilad, 2002, 2003). Thus, acute and chronic stress alter polyamine levels and ODC activity in the central nervous system. Consequently, the polyamine system is apparently involved with a key feature of depression, as it is known that, at least in a subset of phenotypes of depressive illness, the hypothalamo-pituitary-adrenal axis is over-activated with enhanced secretion of corticotropin releasing hormone (Antonijevic, 2008; Holsboer, 1988). Furthermore, another key feature in depression is the lack of getting any type of reward in these patients. Accordingly, an involvement of the mesolimbic dopamine system in depression was discussed (Nestler and Carlezon, 2006) and it was shown that alterations of key proteins of the ventral tegmental area/nucleus accumbens-axis produced behavioural phenotypes in rodents which are related to depression. As clear effects of spermidine and spermine on mesolimbic, but not striatal, dopamine-mediated behavior were observed (Hirsch et al., 1987), it is tempting to speculate that a dysregulation of the polyamine system could be causally involved with mesolimbic dopamine behaviour in depression. Thus, by now compelling evidence exists supporting that polyamines may be multifactorially involved with the manifestation of major depressive disorder.

In order to better understand the diverse brain specific functions of polyamines in health and disease, not only the regional but also the cellular and subcellular distribution of these potent modulators of neural functions has to be taken into account. Given the complexity and interconnectivity of brain circuits, the involvement of the polyamine system has to be analyzed accordingly. Immunocytochemically, spermidine/spermine (Laube et al., 2002; Laube and Veh, 1997) as well as agmatine (Otake et al., 1998) distribution were investigated in the rodent brain. Notably, while spermidine/spermine, although present in distinct neuronal populations, was predominantly localized to astrocytes, agmatine was not observed in glial cell bodies but in neurons. However, in untreated animals, agmatine was only localized to cortical and subicular neurons. Only after blocking axonal transport by colchicine, many more neuronal cell bodies were observed. Under these conditions, agmatine was most prominently detected in the diencephalon, namely thalamic, epithalamic, and hypothalamic regions. The distribution pattern of agmatine-like immunoreactivity in neocortical neurons was not characteristically showing principal neurons but rather interneurons, although this aspect was not investigated. In the hippocampus, however, labelled cell bodies were apparently very rare. While with spermidine/spermine immunocytochemistry, also neuropil areas were clearly labelled, agmatine immunoreactivity, even in non-colchicine-treated animals, was confined to cell bodies. In a subsequent investigation (Reis et al., 1998), however, using a different, commercial antibody, which was unfortunately not clearly specified, agmatine was localized to hippocampal CA1 pyramidal cells and axons and axon terminals in the stratum radiatum, mostly in contact with dendritic spines and associated with synaptic vesicles. The latter finding was discussed in support of the presumed function of agmatine as a neurotransmitter.

Neuronal spermidine/spermine labelling was most prominently observed in hypothalamic neurosecretory nuclei and in some motor and somatosensory areas (Laube et al., 2002). Regarding the widespread but not generalized localization of spermidine/spermine in astrocytes, it was hypothesized that astrocytes could supply the extracellular space with spermidine/spermine concentrations sufficiently high to account for NMDA receptor modification (Laube and Veh, 1997). The high concentration of spermidine/spermine in astrocytes does not necessarily mean that these polyamines have been synthesized in the very same cells. Indeed, the existence of several transport mechanisms for polyamines in neurons and glial cells (Masuko et al., 2003) may account for a redistribution away from synthesizing

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cells, e.g. by the action of organic cation transporters (Higashi et al., 2014). Further support for the assumption of an intercellular translocation of polyamines could be expected from the localization of polyamine pathway enzymes. In fact, ODC, the first polyamine anabolic enzyme which was investigated in this respect ((Cintra et al., 1987); reviewed in (Bernstein and Muller, 1999)) is normally found in neurons, thus supporting the assumption that astrocytic spermidine/spermine may reflect an uptake mechanism rather than endogenous synthesis. Considering other, similar tasks of astrocytes like the buffering of excess extracellular potassium, an effective polyamine uptake seemed reasonable with respect to a presumed neuromodulatory role and regarding the extracellular binding sites on NMDA receptors. In fact, both, an NMDA-mediated release of spermidine and spermine in rat striatum (Fage et al., 1992) and a membrane potential-dependent spermidine/spermine transport in synaptosomes and glial cells (Masuko et al., 2003) were demonstrated. In order to prove an efficient uptake of polyamines by astrocytes, we performed experiments using biotinylated spermine (Veh and Weiss, unpublished data). Acute slices of different rat brain areas were incubated in the presence of biotinyl-spermine at different concentrations and for different time intervals. Afterwards, the slices were chemically fixed and immunocytochemically investigated using the ABC technique to detect biotin and anti-spermidine/spermine antibodies to detect spermine, thus allowing to discriminate biotinylated and non-biotinylated spermine. These experiments clearly showed that already within 15 minutes biotinylated spermine was robustly detected in astrocytes, an effect that could be blocked by incubation in the presence of excess non-haptenylated spermine, thus indicating a specific uptake. Moreover, the uptake was shown to be less effective under depolarizing potassium conditions (30 mM potassium for 10 minutes).

ODC immunocytochemistry in brain provided the first evidence that the localization of polyamine pathway enzymes may essentially contribute to our understanding of brain specific roles for polyamines in certain cell types or circuitries. However, the presumed synthesis of putrescine from ornithine by ODC in certain types of neurons only reveals where the second step in the classical pathway of polyamine synthesis, starting from the amino acid arginine, is robustly expressed. Since ODC is highly inducible and normally ODC levels are tightly controlled, the observed labeling patterns may only reflect a subset of competent brain cells. Also, it could not be predicted whether ODC-expressing neurons would also synthesize the downstream products spermidine and spermine and also whether the alternative pathway via agmatine may be important in order to supply putrescine for polyamine synthesis in the brain. Thus, localization data covering the whole set of polyamine anabolic and catabolic enzymes would supply a screening framework, allowing to identify brain specific roles in health and disease and also targets for pharmacological intervention. To this end, we started to generate polyclonal antibodies against bacterial recombinant proteins for the anabolic enzymes spermidine synthase, spermine synthase, arginase, arginine decarboxylase, ornithine decarboxylase, and agmatinase and for the catabolic enzymes polyamine oxidase (PAOX), spermine oxidase (SMOX), and spermidine spermine acetyl transferase (SSAT). To date, we characterized the sera against spermidine synthase (Krauss et al., 2006; Krauss et al., 2007), spermine synthase, arginase (Peters et al., 2013), arginine decarboxylase (Peters et al., 2013), and agmatinase (Bernstein et al., 2011; Bernstein et al., 2012) and used them to immunocytochemically investigate these enzymes in rat and partially also in human (agmatinase) brain, with the exception of spermine synthase antibodies, that only worked with biochemical but not immunocytochemical techniques. In the literature, additional immunocytochemical data covering ODC, arginase, arginine decarboxylase, and SSAT are available. As it is beyond the scope of this review to systematically evaluate all available data on polyamine pathway enzyme localization in the brain, we will instead focus on a few examples, underlining the potential of this approach to help investigating the diverse roles of polyamines in the central nervous system.

As already mentioned, ODC was localized to subsets of neurons in several brain areas, although ODC expression is altered under pathological conditions (Bernstein and Muller, 1999), e.g. by appearing in astroglia. By contrast, the entry enzymes to both pathways of polyamine synthesis, arginase and arginine decarboxylase, leading to putrescine, spermidine, and spermine via arginase and to agmatine via arginine decarboxylase, turned out to be broadly and robustly expressed in all types of neurons (Iyo et al., 2006; Peters et al., 2013; Yu et al., 2003). Although the labelling in both cases was prominent in cell bodies, also a diffuse neuropil labelling was observed when using standard immunoperoxidase protocols. We therefore used a highly sensitive catalyzed reporter deposition (CARD)-based method (Madai et al., 2012), in order to visualize immunoreactivity distant from the soma. With this method, it became obvious that arginase and arginine decarboxylase, as well as previously shown for agmatinase (Madai et al., 2012), are broadly represented in the neuropil of cerebral cortex and hippocampus by numerous small punctate profiles (Peters et al., 2013), strongly suggestive of a synaptic distribution of these enzymes, which was not necessarily expected before. With electron microscopy, it was then resolved, that the immunoreactive spots correspond to labelled presynapses (arginase) and postsynapses (arginine decarboxylase). By comparison, agmatinase was localized to both, pre- and postsynaptic compartments. While the localization of arginase and arginine decarboxylase in synapses was rather surprising, the situation was clearly different with agmatinase, since agmatine is discussed as a putative neurotransmitter and hence a degradation of this polyamine at synapses would effectively control synaptic transmission. In contrast to arginase and arginine decarboxylase, agmatinase was frequently but less broadly detected in rat brain neurons (Bernstein et al., 2011; Peters et al., 2013). Here, agmatinase was especially prominent in the thalamic paraventricular nucleus and the medial habenula as well as in the main input and output areas of the medial habenula, the triangular septum and the interpeduncular nucleus. Since the medial habenula is also involved with stress-related phenomena (Sugama et al., 2002),

which, as mentioned earlier, in turn may be related to depression, we therefore selected this area to investigate the involvement of agmatine with electrical activity (Weiss, unpublished data) using extracellular single unit recording in acute brain slices. Neurons of the medial habenula showed spontaneous action potential firing. Upon superfusion with 2mM agmatine, the firing frequency was significantly reduced but returned to normal values after washing. The detailed analysis, however, showed that this overall inhibitory effect resulted from a mixed population of about 70% inhibition and 30% excitation, thus agmatine differentially affects action potential firing of medial habenular neurons. Since agmatine is an endogenous ligand for the imidazoline receptor, we tested the pharmacological effects of imidazoline receptor agonists and antagonists on spontaneous activity of neurons within the medial habenula. Briefly, the agonist moxonidine mimicked inhibitory agmatine-effects in the medial habenula, while the I1-type antagonist efaroxan, in contrast to the I2-type antagonist idazoxan, prevented the suppressive agmatine-effects. Furthermore, the α2-receptor antagonist yohimbine did not influence the agmatine-mediated modulation of firing frequencies in the medial habenula. Although currently no pharmacological tools are available to address the role of agmatinase in this area, the data show that the localization of the catabolic enzyme agmatinase successfully identified a brain target that certainly is worth investigating in the context of depressive disorders. To this end, the subnuclear organization of the medial habenula as well as the circuitry within the triangular septum/interpeduncular nucleus axis will have to be taken into account.

With respect to the identification of brain areas possibly relevant in the context of polyamine-influenced events, also the prominent localization of agmatinase in the thalamic paraventricular nucleus (Bernstein et al., 2011) has to be emphasized, since this nucleus was shown to be intimately involved with the regulation of stress and negative emotional behaviour, such as anxiety (Hsu et al., 2014). The paraventricular thalamic nucleus is strongly connected with the amygdala, bed nucleus of stria terminalis, and the nucleus accumbens shell, where it regulates the dopaminergic system. The involvement of the mesolimbic dopamine system with depression and polyamines was already mentioned above. However, the role of agmatine in the paraventricular thalamic nucleus has not been investigated so far. Interestingly, in the nucleus accumbens shell, we previously observed a patch-like spermidine synthase expression, overlapping with dopamine D1 receptor expressing patches (Krauss et al., 2007), indicating an involvement of spermidine/spermine in this circuitry, supporting the already mentioned data showing an involvement of spermidine/spermine with mesolimbic dopamine-mediated behavior (Hirsch et al., 1987).

Among polyamine pathway enzymes analyzed so far, spermidine synthase most clearly displayed a synaptic expression, already visible with standard immunoperoxidase labelling, in the cerebellar cortex (Krauss et al., 2007). Here, the giant mossy fibre terminals in the granule cell layer robustly displayed spermidine synthase immunoreactivity. We therefore chose this area to experimentally verify spermidine-mediated effects using electrophysiological methods (Krauss et al., 2007). Briefly, using extracellular recording upon mossy fibre stimulation, we found that spermidine bath application dose-dependently reduced field potential activity in this area, thus providing evidence for a polyamine-mediated modulation of mossy fibre synaptic transmission.

These examples may show, that the localization of polyamine pathway enzymes, especially when considering the possible redistribution of polyamines by transport processes, offers a valuable tool to identify brain areas and circuitries influenced by these multi-functional polycations as putative targets in order to develop strategies for pharmacological intervention. Therefore, we strongly believe that, especially in the context of major depressive disorder, polyamine-related research may lead to new therapeutic strategies.

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BLOOD INJURY PHOBIA: AN OVERVIEW OF GENDER SPECIFIC BRAIN DIFFERENCES

KAN- YARALANMA FOBİSİ: CİNSİYETE ÖZGÜ BEYİN FARKLILIKLARINA GENEL BAKIŞ

Ab Latif Wani[1] and Anjum Ara*[1]

Abstract

Blood injury injection phobia (BII) involves an intense fear of situations, in which an individual is directly or indirectly exposed to blood, injections or viewing injuries, along with a tendency to avoid these situations. BII phobia is highly prevalent in females as compared to males. It is virtually the only specific phobia and the only anxiety disorder, in which fainting occurs. Although fainting is much distressed to the BII phobic individuals, but it may have developed in the humans at the time when they needed it much as a survival mechanism. In this article we discuss how in the humans there may have developed the trait of BII phobia in the ancestors, including the variation in the symptoms among sexes. There are not studies which specifically examine the syncope related brain differences among genders. But there are other well defined studies which highlight marked differences among male and female brains. Considering this we also review some recent breakthrough discoveries showing differences in the brain of males and females at gene expression level which leads to the variation in brain and behaviour related problems among genders. There is an exigent need to understand the brain behavioral problems through multiple perspectives.

Keywords: Blood Phobia, Fainting, Gender Specificity, Brain, Behaviour

Özet

Kan-enjeksiyon- yaralanma fobisi (BII) bir bireyin direkt ya da dolaylı olarak kana, enjeksiyonlara ya da yara görmeye maruz kaldığı ve bu durumlardan kaçınma eğiliminin olduğu aşırı korku durumudur. BII fobisi erkeklere göre kadınlarda daha yaygındır. Bu fobi bayılmanın olduğu hemen hemen tek spesifik fobi ve tek kaygı bozukluğudur. Bayılma, BII fobili bireylere daha fazla endişe verse de aslında bayılma bu bireyler bir çeşit hayatta kalma mekanizmasına ihtiyaç duydukları zamanlarda da oluşabilir. Cinsiyetler arasındaki semptom farklılıklarını içeren bu makalede soylardaki BII fobisinin insanlarda nasıl oluşmuş olabileceğini tartışacağız. Cinsiyetler arasındaki beyin farklılıklarına bağlı olan bayılmayı özel olarak inceleyen çalışmalar yoktur. Fakat kadın ve erkek beyinlerindeki farklılıkları inceleyen iyi yapılmış çalışmalar mevcuttur. Bunu düşünerek cinsiyetler arasındaki problemlere bağlı olan beyin ve davranış farklılıklarına sebep olan gen ifade seviyesinde kadın ve erkek beyinlerindeki farklılıkları gösteren bazı yeni buluşları da yeniden inceleyeceğiz. Beyinin davranışsal problemlerini anlamak için çok yönlü bir perspektif zorunlu bir ihtiyaçtır.

Anahtar Kelimeler: *Kan fobisi, Baygınlık, Cinsiyete Özgünlük, Beyin, Davranış*

1. Introduction

Blood injury injection (BII) phobia involves an intense fear of situations, in which an individual is directly or indirectly exposed to blood, injections or viewing injuries, along with a tendency to avoid these situations. Blood injury phobia is classified as a subtype of specific phobia in the diagnostic and statistical manual of mental disorders (DSM, APA, 2013).

BII phobia is virtually the only specific phobia, and the only anxiety disorder, in which fainting occurs. It has been estimated that as many as 70% of the individuals with blood injury injection phobia have fainted at least once upon exposure to blood injection injury stimuli (Ost, 1992; Olatunji et al., 1992). It is important to note that there are individuals who met diagnostic criteria for blood injection injury phobia but donot have a history of fainting. In one of the most comprehensive studies of blood injury injection phobia, 30% of blood phobics and 44% of injection phobics who met diagnostic criteria for blood, injection injury phobia reported never having fainted in the phobic situation (Ost, 1992).

Primarily BII phobia involves three types of reactions the common two are emotional response fear and the behavioral response avoidance. These two are generally shared with other phobias. The third response is fainting also known as vasovagal syncope or faintness. This vasovagal syncope is not associated with any of the anxiety disorders or any other phobia but is specific to

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BII phobia (Kaloupek et al., 1985; Grubb and Olshansky, 1998; Daroff and Carlson, 2001; DSM, APA, 2013). It was Marks and colleagues at the first time that draws attention to the specificity of fainting when they found that fainting was reported by only 0.02% of their sample of "mixed phobias" and by 100% of their sample of BII phobia patients (Marks, 1988). These findings lead to further studies for confirming the association of fainting and BII phobia.

BII phobia is different from other phobias because of its specific character of vasovagal fainting. Almost 75% of the individuals who has BII phobia fainted at least once in such situations (Thyer et al., 1985). There are other studies which however show less number of fainting individuals among BII phobics (Wani et al., 2014). In BII phobia the deceleration of blood pressure results in the onset of fainting. Studies have summed up a varied response of BII phobia patients towards visiting health care clinics. Patients with BII phobia generally avoid health care clinics, medical or hospital appointments and other important life saving surgeries (Marks, 1988). However in the Baltimore Epidemiological Catchment Area (ECA) study, Bienvenu and Eaton found that generally BII Phobics avoid needle sticks; they do not appear to avoid appointment to medical doctors, outpatient health centres, or hospitals (Bienvenu and Eaton, 1998) There are other studies which show BII phobia found in comorbidity with others like doctor phobia, hospital phobia, acquired immunodeficiency syndrome phobia, cancer phobia, dentist phobia, and social phobia (Kendler et al., 2011). Others studied BII phobia in comorbidity with depression, diabetes and other medical disorders (Kendler et al., 2011; Page and Martin, 1998). There are patients who otherwise qualify for the BII phobics according to the Diagnostic and Stastical Manual for Mental Disorders (DSM) but are not fainted at the sight of blood or other related ques which arouse an anxiety in the patient. Patients suffer from BII phobia avoid medical or hospital appointments (Marks, 1988). This makes the problem of phobia more serious as the sufferers avoid most of the medical procedures for other medical problems. Other phobias are more similar to other anxiety disorders than to BII phobia as per their symptoms are concerned. There are many individuals who generally faint at the time when they receive injections. This habitual fainting precedes the appearance of BII phobia in many subjects (Page and Martin, 1998). There is a clear difference in the fainting spells between males and females showed by various studies. Some authors argue that such individual differences of fainting at the sight of blood had been developed via conditioned learning (Page, 1998). The more recent studies have shown genetic differences in the brains of male and female. These studies show variations in the number of genes expressed in brain cells of males and females which perhaps may be one of the factors why there are differences in BII phobia related fainting among male and female.

2. Blood Phobia and Associated Fainting

Although syncope doesn't harm the patient at its first place, but often there are chances that a patient can get a serious injury based on a place of fall. It is often a frustrating symptom to faint at the situations like vaccination, an injection or the sight of a syringe or blood. Such patients can easily be found at the primary health care centres. There are chances that in case of modern wars there may be ample number of soldiers who fear the blood, and they don't let themselves to involve in direct confrontation. For health professionals, it is often complicated and puzzling to see the patient faint at the sight of blood, injury or injection etc. Many of such patients faint while just at the sitting position (Grubb and Karas, 1998). The cases of vasovagal fainting with their description and sequence of autonomic nervous system are largely present in cardiological literature (Grubb and Karas, 1998). In no other anxiety disorders including phobias other than BII phobia, this condition seems to match. It is unique to BII phobia that patients often faint following the initial increase in blood pressure. This situation has often puzzled to cardiologists. This extreme heart rate variability actually has increased the chances of survival for the fainters of BII phobia.

Multiple patients of BII phobia are often heterogeneous in their symptomatology which also prevents to categorize the sufferers based on their symptoms. This heterogeneity then lead a problem in combating the symptoms because often there may be multiple set of pathways by which these symptoms occur in different sufferers. There is a possibility that in different individuals there is a different course of symptom development. The heterogeneity is not linked only to BII phobia but is almost associated with all neuropsychiatric disorders. A considerable number of BII phobia patients have a familial history of the same phobia. The fainting associated with BII phobia is found to have higher heritability estimates than fear and phobia (Kleinknecht, 1987). The familial history for BII phobia is well recognised and almost two thirds to three fourths of patients with BII phobia have at least one first-degree relative affected with BII phobia. Some workers have attributed faintness as familial and solely as learned within a shared household environment (Marks, 1988). That is to be stated the other way that fainting with BII phobia is just with learning and is less likely or no role played by other factors. There are noted twin studies which show a significant genetic contribution to the etiology of BII phobia and particularly fainting (Kleinknecht, 1987). However a very recent research suggests that memories can be passed down to later generations through genetic switches that allow offspring to inherit the experience of their ancestors. According to that it is possible for some information to be inherited biologically through chemical changes that occur in DNA (Dias and Ressler, 2014).

3. Blood-Induced Fainting- An adapted defense behavior

Regarding advances in brain sciences, there are some fundamental questions which are still unanswered like why females are more prevalent in fainting than males. In relation to the faintness of the blood phobics at the sight of blood or other related ques, there are several hypotheses regarding the significant relation of blood phobia and fainting. These are based on blood-loss

minimization and on disgust sensitivity. These existing evolutionary biological hypotheses regarding fainting are pan-mammalian. Such hypotheses have argued that the inclination to fainting at the sight of blood is not a new one, but has evolved prior to emergence of genus Homo (Bracha, 2004). However there are several situations where these hypothesis seems incomplete and doesn't seem to fit in many cases, for example why only some people develop fainting trait while others don't.

In order to reach up to the stage of faintness, there is initially decrease in the blood pressure. As with decrease in blood pressure and slowing down of heart, the brain doesn't get a sufficient supply of blood. Due to this decrease there are chances of cardiovascular shock. So it can be assumed that it may be an adapted mechanism from early ancestry to faint and prevent a cardiovascular shock (Graham, 1961; Engel, 1978). The fainting at the sight of blood can put an individual in a horizontal position due to fall. As horizontal position doesn't need blood with increased pressure, a low pressure blood can reach up to brain. This way it helps preventing blood loss and the symptoms like stroke. However this hypothesis doesn't explain many things like why fainting that is triggered by injection or trivial skin injury occurs which does not involve the loss of blood as argued by page (Page, 1994). Some have argued that fainting is not experienced until there is a 30% reduction in blood volume (Berntson at al., 1994).

There are recent findings which show the inheritance of memories in case of phobias and fear. The recent research shows that the memories in the brain can inherit from generation to generation (Dias and Ressler, 2014). The phobias along with the capacity of fainting can be memories in the brain. The memories may perhaps signal the physiological changes like fainting in case of BII phobia. Based on this it can be hypothesised that there are ample chances that memories may also exist for fainting or there may be several attributes related to fainting in the brain which may inherit from parent to younger generation, there by helps the trait to survive from generation to generation.

BII phobia is also found to be highly associated with the emotion of disgust. There is a similar physiological mechanism for factors which are involved for controlling both the traits of fainting and disgust (Marks, 1988; Page, 1994). There are hypothesis from early theorists that in some individuals the sight at their own blood induces a disgust reaction (Marks, 1988). There are no studies however whether the strength of disgust from one's own blood is same to the disgust at the sight of other fellow's blood. Some researchers suggest that the fainting reaction observed in BII phobia occurs only in response to disgust (Rachman, 1990). Others think that it occurs in response to a combination of fear and disgust (Olatunji, 2006; Kleinknecht, 1997). We presume that in addition to these there may also be the role of synapse disruption. The fainting could possibly be also due to the disruption of synapse in the brain which could lead the individual unconscious. As the blood related fainting can be from the time of pan mammalian, it is assumed that the humans from their ancestry have built up such memories which gets imprinted in the brain and may act as phobic memories from generation to generation.

4. Evolutionary perspective in understanding of Traits

One author has proposed a human specific adaptationist proposal for faintness (Bracha, 2004). Many workers consider sex as having a greater influence which shows a variation in traits among males and females. Darwin has also dedicated considerable portion of his work by dividing traits in relation to sex (Darwin, 1874). Due to the differences in the expression of number of genes in the brain of male and female, fainting also seems a trait which gets fixed with sex related differences or it may also be the product of emotional distress. In order to avoid the emotional distress in presence of certain situations like that of blood, injury or injection. It is assumed that BII phobic patients faint to avoid further increase in disgust. Many theorists have related the blood related faintness as the product of early human warfare in the Neolithic period (Bracha, 2004).

Several critical studies and investigations have documented that there had been extensive Homo sapien warfare's in the middle paleolithic period in which Homo sapiens was predominantly pre-verbal [(Morgan, 1990; Ortnet and Putschar, 1985; Leblanc and Register, 2003; Lacey and Danziger, 1999; Salazar, 2000). To be pre-verbal at that period it can be assumed that they may prefer to give indications and convey messages or communicate mostly by actions and other types of demonstrations. This may had been the time when the humans were probably not good in understanding of languages between peoples and intra groups. In this age of warfare's sharp objects easily penetrating the skin was the frequent cause of death among paleolithic humans. As this may have been the age when getting slight injury, or infection was difficult thing to overcome. This has often proving fatal because of inadequacy of the facilities for treating infection in that age (Larsen, 1999; Klein and Edgar, 2002). In situations where inadequacy of treating wounds and infections are prevailed, receiving a non-lethal wound was almost as dangerous as receiving a fatal combat wound. With this perspective it is assumed that fainting in response to the sight of blood may have evolved as an alternate distress reaction, or adaptation that aided the survival of non-combatants in combating situations. The opponent can simply ignore the fainting person because it cannot be an immediate threat to them. It is also assumed that fainting had got evolutionary significance in order to avoid the distress caused by witnessing the wars or blood, injury etc. The question of fainting as more prevalent in females and children appears to be of higher consideration in the literature. However there is a void in the literature regarding whether there is any difference in the brain of male and female which specifically lead to fainting variability among the genders. These things should need to be analysed by multiple ways in order to get the actual picture of the possible selection of fainting trait.

Almost in every war fought in earlier times, there had been the general rule of not killing the women and children.

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As they were not directly involved in the conflict, so they had not been a part of any distress which may bring any sort of fatality to the opponents. As women and children are weaker groups of the society both physically and emotionally the trait of fainting at the sight of blood during earlier wars bears additional significance. The inheritance of such polymorphism may possess a survival advantage for generations from the time where it originally develops due to Neolithic combats. As is evident from the history of mankind that all types of inter-group and intra-group violence mainly occurs among men, while as women and children are considered as the passive members and not as the direct targets. Studies have been taken place for analysing the mitochondrial DNA for female lineage and male Y- chromosome for male lineage (Underhill et al., 2001). Such analysis has shown that invaders during the violent confrontations usually kill the post pubertal males and take the females and children as captives (Seielstad et al., 1998). Thus it seems that the post pubertal males which are engaged in combats during paleolithic conflicts are poorly adapted for fainting, which makes them to be cautious of the enemy. This way it acts as a good characteristic which helps the post pubertal males to be active in the battle fields and fought their best.

Besides this there is increasing evidence through some recent researches which shows that some X-linked genes are expressed differently, depending on whether they are in male or female brains. In mice, six X-linked homologues of Y-linked genes (Usp9x, Ube1x, Smcx, Eif2s3x, Utx and Dbx) were expressed in the brain of mice at significantly higher levels in adulthood in females than in males, irrespective of their X-inactivation status (Xu et al., 2002). The X- and Y-homologues of three genes in particular, Usp9x/y, Ube1x/y and Eif2s3x/y, appeared to have acquired different functions and expression patterns in males and females. The research shows that there are considerable differences in the brain of males and females either in structure, organization or expression of genes. This variability might lead to the variation in the vulnerability of different brain disease. The prevalence of Blood phobia in females is almost double the prevalence in males, indicating that this may also be in relation with the variability in gene expression between males and females.

5. Gender Specific differences and brain behavioural outcomes

There is a bias in the expression of genes in the brain between males and females which lead to differences in the behaviour and in the incidence of various diseases. With regard to specific gender bias in neuropsychiatric disorders let us take an example of PCDH11Y gene which is an attractive proposition because of numerous factors. It appears to be expressed in a highly regulated and spatiotemporally dynamic manner in males and is involved in synapse formation and neuronal path finding in the brain and in other processes which doesn't go in right course in many male-biased mental conditions (Grant, 2003). There are several mentally ill conditions which are more prevalent in males while others are more prevalent in females. This may perhaps be due to the differences in the expression of genes in brain among the two sexes. Several genes are weakly expressed, some may be over expressed and still others may not express at all. This conundrum of gene expression differently in different sexes is still not understood well. The low expression or no expression of PCDH11Y in the cerebellum and perhaps its expression somewhere else in the brain, could potentially explain why males are especially vulnerable to disorders like ADHD and autism (Kopsida et al., 2009). There is also large number of variations among the individuals in their prevalence, onset and other factors related to various diseases among males and females based on the environmental risk factors experienced in life. It may be the expression pattern of the gene which may be modulated epigenetically via environmental influences.

The differences in the brain of male and female becomes more compounded, because of the functional differences which might be related to differences in brain structure. For example men have more neurons in the neocortex where women have more synapses revealed from a study of postmortem histologic examination (Myers, 1999; Rabinowicz et al., 1999). There are several studies which have found out that several synaptic genes are expressed differently between the two sexes (Amateau, 2004; Xu et al., 2005b). In one study 4508 genes were detected to be transcribed actively in the brain by a comprehensive microarray analysis, among which 355 genes are expressed more highly in females and 257 genes more highly in males (Yang et al., 2006). Sex specific differences in the brain have further elaborated by many workers and the variation in brain structure and gene expression have been proven to be due to testosterone and its metabolites which act in the developing brain and help in permanently wire the brain in a sex specific fashion (McCarthy and Konkle, 2005; Becker et al., 2005; Morris et al., 2004).

The X chromosome is much bigger than Y chromosome; the X chromosome consists of almost 3000 genes while as Y chromosome consists of only 300-400 genes. Many X chromosome genes are suggested to involve in the normal development of brain and behaviour. Furthermore an evidence indicates that X linked genes are expressed at a higher level in brain than in other tissues (Nguyen and Disteche, 2006). The expression of X-linked genes is thought to be balanced between males and females due to inactivation of one X-chromosome in females which silence gene transcription in that X-chromosome (Lyon, 1961). X-linked genes are therefore not traditionally considered to play any role in differentiation. However some chromatin enzymes, such as histone demethylases JARID1C and UTX, are coded by X-linked genes which are not X-inactivated in females. The higher expression of JARID1C and UTX in females could therefore contribute to sex differences in brain development and behavior (Xu and Andreassi, 2011). Such type of changes may perhaps also contribute to the variations in the fainting experiences between males and females.

Epigenetics a new field of research is also considered to play a major role in the variation in behaviors among different individuals. The changes in the expression of genes without any change in the primary sequence of

DNA are called epigenetics (Pennisi, 2001). Epigenetic modifications generally caused by DNA methylation and chromatin modification (Mehler, 2008). DNA methylation at H3, Lysine 9 and Lysine 27, etc. and Deacetylation of H3 and H4 and DNA methylation at CpG islands immediately called into action on the inactive X to help in long-term transcription suppression (Chow et al., 2005; Heard and Disteche, 2006). Such transcription suppression may have ample chances of consisting of non-formation of class of proteins factors or neurotic factors in the brain which also lead to variations of certain number of psychoneurotic disorders which may also include fainting in case of BII phobia.

The genes USP9X and UBE1X encode ubiquitin enzymes. The human USP9X has found to escape X-inactivation which leads to its overexpression in female brain. This leads to high prevalence of certain mental illness in females and also plays a role in sexual dimorphism in synaptic structure. From such variation in gene expression in brain, it is assumed that based on the differential expression of certain genes in the brain of male and female, there arises variation in the onset of symptoms and prevalence of mental illnesses, in which females are usually higher in number. However a study on mice has detected no sex differences in USP9X expression in neonatal brain or in adult peripheral tissues (Xu et al, 2005a).

Specific enzymes like DNA methyltransferases, histone methyltransferase, acetylase, and deacetylase involves in the regulation of DNA methylation and histone modification (Peterson and Laniel, 2004). There is a difference in the concentration of these enzymes in tissue type and they also show differences with development and aging. Tissue specific and temporal changes in the X-inactivation status of some genes can be explained on the basis of differences in the concentration of these enzymes. Inactivated X-linked genes are potentially reactivated due to decrease in the level of DNA methyltransferase in the brain (Xu and Disteche, 2006).

6. Conclusion

BII phobia is a unique phobia in which fainting occurs. Females and children are more prevalent both for BII phobia as a whole and fainting as a particular symptom. However the trait of fainting in both sexes may have selected at the period when it has got a survival value. The early combats might have created long term memories from the experiences which survived till modern times, may be in the form of DNA epimarks through epigenetic mechanisms. Although survived through difficult times in the past, such experiences may have persuaded variation in the expression of a number of genes in the brains of both male and female. Such variations in brain gene expression may result differences in prevalence, onset of disease, and variation in diseases related symptoms to a considerable degree.

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RABIES IN INDIA: A RELOOK AT THE NEGLECTED RAMPANT DISEASE

HİNDİSTAN'DA KUDUZ HASTALIĞI: İHMAL EDİLEN YAYGIN HASTALIĞA YENİDEN BİR BAKIŞ

Kalaivani Annadurai*[1], Raja Danasekaran[1], Geetha Mani[1]

Abstract

Rabies is a tropical zoonotic disease, transmitted to human being by carnivorous animals. Majority of human rabies cases were reported from Asia and African countries. India recorded more deaths from rabies than any other country in the world. There is no effective treatment for rabies; it can only be prevented by vaccination. It needs multiple levels of interventions at human and animal level. World Health Organization's target is to eliminate the disease by 2020 in endemic South-East Asian countries which include India. Key challenges in control of rabies in India are lack of intersectoral coordination, weak surveillance system on rabies, inadequate rabies research and lack of sustainability. To conclude, breaking the rabies cycle in a sustained manner is necessary to eliminate rabies from this part of the world.

Keywords: carnivorous animals, prophylaxis, elimination

Özet

Kuduz, etobur hayvanlardan insanlara geçen tropikal zoonoz bir hastalıktır. İnsanda görülen kuduz vakalarının çoğunluğunun Asya ve Afrika ülkelerinde olduğu rapor edilmiştir. Hindistan'da dünyadaki herhangi bir ülkede olandan çok daha fazla kuduz ölümü olduğu tespit edilmiştir. Kuduz için etkili bir tedavi yoktur; tedavi sadece aşı ile yapılabilmektedir. Tedavi insan ve hayvanlarda farklı seviyelerde müdahaleleri gerektirmektedir. Dünya Sağlık Örgütü'nün amacı Hindistan'ı da içeren endemik Güney Doğu Asya ülkelerinde 2020 yılına kadar bu hastalığı ortadan kaldırmaktır. Hindistan'da kuduz kontrollerindeki kilit sorunlar; sektörler arası koordinasyon eksikliği, kuduz hastalığı için yapılan yetersiz denetim sistemi, yetersiz kuduz araştırması ve sürdürülebilirliğidir. Sonuç olarak, sürekli olarak kuduz döngüsünü engellemek için dünyanın bu bölgesinde kuduzu yok etmek zorunludur.

Anahtar Kelimeler: *etobur hayvanlar, hastalıktan korunma, hastalığı yok etme*

1. Introduction

Rabies is primarily a disease of warm blooded carnivorous animals like dogs, cats, jackals, monkey, bats and wolves and transmitted to human being by the bites or licks of rabid animals. It is caused by RNA virus belongs to Lyssa virus genus manifests as viral encephalitis in human beings and once symptoms develop, it is always fatal to human beings. There is no effective treatment for rabies; it can only be prevented by vaccination. According to World Health Organization (WHO), the annual cost of rabies worldwide estimated to be about 583.5 million US$, most of which is attributed by post-exposure prophylaxis (WHO, 2005). Even though a completely preventable disease, it is still a public health problem in India and other developing nations.

2. Clinical manifestation of human rabies

Median incubation period was 54 days for all naturally acquired human rabies (dog acquired - 64.5 days, bat acquired - 51 days). Two different forms of rabies are documented namely furious and paralytic rabies. Clinical features specific to human rabies are headache, sore throat, malaise, fever, meningismus, insomnia, slurred speech, encephalopathy, biting, hyperarousal, hydrophobia, larynx/face spasms, aerophobia, myoedema and priapism. Other manifestations are tremor, convulsive or non convulsive seizures, status epilepticus, sweating, piloerection, hypersalivation, increased lacrimation, ataxia, myoclonus, chorea and dilated pupils. On the bite site, there will be pain, paresthesis, pruritus

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and numbness. Cranial nerves manifestations are dysphagia, bilateral or unilateral facial weakness, ptosis, ophthalmoplegia and anisocoria. Late complications include coma, syndrome of inappropriate antidiuretic hormone secretion (SIADH), Diabetes insipidus and several complications on cardiovascular, respiratory and gastrointestinal systems. Hydrophobia, aerophobia and encephalopathy are more common in dog acquired rabies. In bat acquired rabies, abnormal cranial nerve, motor and sensory manifestations such as tremor, myoclonus, and local sensory abnormalities are more common. Death will occur within 7-10 days, after onset of symptoms and usually by respiratory paralysis (Udow SJ et al., 2013).

3. Neurobehavioral symptoms of rabies

Mental changes are anger, fear of death, irritability and depression. Hallucinations, anxiety, confusion, restlessness and high level of excitement are other common symptoms. Even few cases had been presented as acute psychiatric emergencies with symptoms like that of delirium tremens and schizophrenia (De Wet JSDT, 1980). Conversely, pseudorabies is a condition reported in a hypochondriac patient in which the patient with history of dog bite behaved as though he was having rabies (Bidaki R et al, 2013).

4. Burden of the disease

It is a neglected tropical zoonotic disease, with 50,000-55,000 deaths each year worldwide. Around 95% of human rabies occurs in Asia and African countries. It is estimated that there are about three billion people living in the region at risk for rabies in over 100 countries. India recorded more deaths from rabies than any other country in the world with 25,000-30,000 deaths annually (Wunner WH & Briggs DJ, 2010). Human rabies was reported throughout the country except Andaman, Nicobar and Lakshadweep islands. Since rabies deaths occur in a scattered manner, it doesn't pose epidemic threat to claim immediate action (Chatterjee P, 2009).

5. Strategies for prevention of rabies

Due to the complex nature of rabies control, it needs multiple levels of interventions with respect to humans and animals. Prevention of infection at human level by pre-exposure prophylaxis for high risk group and post-exposure prophylaxis for exposed persons. Animal interventions includes registration and licensing of dogs, immunization of dogs, restraint of dogs in public places, control of stray dog population by birth control, destruction of dogs bitten by rabid animals, quarantine of imported dogs for 6 months and better solid waste management (WHO, 2007).

6. WHO's strategy for endemic South-East Asian countries

World Health Organization's regional office for South East Asia, after an expert consultation provided a regional strategic framework in 2011 for eliminating human rabies transmitted by dogs. The target is to eliminate the disease by 2020 in endemic South-East Asian countries. The initial strategy is to reduce by half the current number of human rabies death by 2016 which covered a period of 5 years from 2012-2016 (WHO, 2012).

7. India's action towards rabies

Government of India as per WHO's recommendation, had replaced nerve tissue vaccine with cell culture vaccine since 2004. Planning commission had identified rabies as priority zoonotic disease in its 11th five year plan. Government of India has introduced pilot project on rabies control programme from 2008 to 2011 with the objectives of prevention of human deaths due to rabies and reduction of transmission of disease in animals. It has set a target to reduce the human rabies deaths by at least 50 per cent by the end of the 11th Plan period which covered Delhi, Ahmedabad, Madurai, Pune, and Bangalore (Planning Commission of India, 2011).

In 12th five year plan, Government of India has planned to extend this comprehensive programme which has both human and animal component. This programme focuses on training health professionals about management of animal bites, providing post exposure prophylaxis, creation of awareness and reduction of animal bites, vaccination and sterilization of dogs (Dhar A, 2012).

Government of India, National Center for Disease Control, New Delhi, WHO collaborating center for Rabies Epidemiology has released Revised National guidelines on Rabies Prophylaxis in 2013 for bringing out uniformity in post exposure prophylaxis. It gave guidelines for indications of anti-rabies vaccine and rabies immunoglobulin. It recommends the use of cell culture vaccine given either intramuscularly or intradermally for pre/post exposure prophylaxis. It also stresses on using rabies immunoglobulin for category II immune compromised patients and for all category III animal bites (Government of India, 2013). Government of Tamil Nadu, Rabies control initiative is a first large scale comprehensive programme on rabies started in the year 2008, with universal coverage targeting both human and animal population (Abbas SS et al., 2014).

In collaboration with local non-governmental organization, the health departments of Chennai, Jaipur and Kalimpong have achieved zero rabies incidence followed by sustained Animal Birth Control-Anti Rabies Program (ABC-AR Program) (Krishna, S.C, 2010). Sikkim is about to be certified free of rabies followed by state-wide campaigning for vaccination of dogs (Chatterjee S & Riaz H, 2013).

8. Epidemiological situation of animal bite

Every year, about 1.7% of Indian population gets bitten by animals of which only 46.9% took anti rabies vaccine (Rahman AS, 2011). Around 97% of human rabies are transmitted by dogs of which 62.9% were stray dogs, followed by cats 2% and others 1% (Jackals, Mongoose) (Government of India, 2013). The vulnerable groups for rabies are males, children below 15 years, poor and

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Table 1: Time line of anti-rabies action in India

Year	Action
1907	Neural tissue anti-rabies vaccine was manufactured in Pasteur Institute of India, Coonoor (Lahariya C, 2014).
1911	David Semple (an officer of the Indian Medical Service) developed Semple antirabic vaccine using carbolized dead virus in Central Research Institute in Kasauli (Chakrabarti P, 2010).
1970	Beta-propiolactone (BPL) inactivated rabies vaccine developed in Pasteur Institute of India, Coonoor (Lahariya C, 2014).
1995-1996	Chennai and Jaipur were the first cities to start sustained ABC-AR program (Krishna, S.C, 2010).
2001	The Animal Birth Control (Dogs) rules, 2001 enacted (Government of India, 2010).
	Developed Vero Cell Derived DNA purified Rabies Vaccine for human use in Pasteur Institute of India, Coonoor (Lahariya C, 2014).
2004	Replaced nerve tissue vaccine with cell culture vaccine for post exposure prophylaxis (Planning Commission of India, 2011).
2007	Identified rabies as a priority zoonotic disease in 11th five year plan (Planning Commission of India, 2011).
2008-2011	Government of India has introduced pilot project on rabies control programme in five cities (Planning Commission of India, 2011).
2007	National Guidelines for Rabies Prophylaxis and Intra-dermal Administration of Cell Culture Rabies Vaccines (Government of India, 2013).
2008	In Tamil Nadu, Rabies control initiative started (Abbas SS et al., 2014).
2009	Animal Welfare Board of India published 'Standard Operating Procedures For Sterilization of Stray Dogs Under the Animal Birth Control Programme'(Government of India, 2009).
2010	Animal Birth Control (Dogs) Amendment rules, 2010 (Government of India, 2010).
2012	Planned to expand the pilot project to whole nation in 12th five year plan (Dhar A, 2012).
2013	Government of India, National Center for Disease Control released Revised National guideline on rabies prophylaxis (Government of India, 2013).

uneducated people, and those who are living in rural area (Chatterjee P, 2009; Rahman AS, 2011; Suraweera W et al., 2012). Among those vaccinated, compliance to full course of vaccine was found to be 40.5% and was not satisfactory. It has been shown that adequate local wound treatment can reduce the chances of developing rabies by up to 80%. Among the animal bite victims, only 39.5% washed their wounds with water and soap (Sudarshan MK, 2004). The use of rabies immunoglobulin was very low at 2.1% (Kole AK et al., 2014). Vaccination of 70% of total dog population in an area for a period of six months is needed to achieve herd immunity. But only few cities are conducting sustained anti rabies vaccination for stray dogs (Chatterjee P, 2009).

9. High mortality of rabies in India

It was attributed by huge stray dog population which accounts for 25 million throughout India that poses great risk to the people. Moreover, there was lack of awareness about rabies and lack of understanding of the need for immediate action against rabies together with poverty, unavailability of anti-rabies vaccine and immunoglobulin (Sudarshan MK, 2004). Ichhpujani et al study reported that only 30% knew how to clean the wound after any animal bite and majority of the study population were not compliant with the treatment guideline (Ichhpujani RL et al.,2006). Interventions against rabies were mainly concentrated in urban areas leaving behind the vulnerable rural area (Abbas SS et al., 2014).

10. Poor disease surveillance system on rabies

Better estimation of rabies incidence is not available because of lack of systematic rabies disease surveillance system and moreover it is not a notifiable disease in India (Maroof K, 2013). And many cases were not reported and some other cases were missed because of atypical presentation (Rahman AS, 2011). It has been found that there was a gap between rabies research done in India and existing rabies policy interventions. Even though, India contributes to more number of rabies cases globally, Indian research output represents only 4.4% of the global research on rabies (Abbas SS & Kakkar M, 2013). Multicentric studies should be undertaken to reveal the true status of the disease, thereby it will provide a proper input for policymakers to develop strategies against rabies.

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11. Key challenges in rabies control

Current challenges are lack of intersectoral coordination between multiple disciplines involved in rabies control like public health department, animal husbandry department, government and non-government agencies; limited information on dog population, poor surveillance data on human and animal rabies, lack of adequate dog bite epidemiology for predicting vaccine requirement, delay in scaling up of successful pilot interventions from local setting to national level, poor diagnostic capacity, limited evidence of effectiveness and efficacy of interventions in different ecological settings, lack of thrust on environmental management which contribute to uncontrolled dog population (Kakkar M et al., 2012).

To conclude, breaking the rabies cycle in a sustained manner is necessary to eliminate rabies from this part of the world. For elimination of rabies by 2020, strong political commitment along with intersectoral coordination between government and non-government health agencies are essential for promoting the use of intervention tools at human and animal level throughout the nation.

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RECENT STUDIES ON GENETIC AND ENVIRONMENTAL BASIS OF AUTISM

OTİZMİN GENETİK VE ÇEVRESEL TEMELLERİ HAKKINDAKİ SON ÇALIŞMALAR

Zeynep Kalkan*[1], Hazal Gür[2], Belkis Atasever Arslan[3]

Abstract

Autism is a childhood neurodevelopmental disorder that affects 1–2 in 100 children, according to recent data on the broad array of autism spectrum disorders. It is a neurodevelopmental disorder, genetic and environmental factors playing role in autism. Molecular and mechanistic basis of autism started to be enlightened. As a genetic basis of disease, glutamate gene mechanisms supposed to develop a new method for diagnosing and treatment of autism. Aim of this mini-review is to gain a general knowledge about genetic and environmental reasons of autism.

Keywords: autism, glutamate, immune system, genetic, neurodevelopment.

Özet

Otizm, son verilere gore, 100 çocuktan 1-2 sinde görülen bir çocukluk çağı nörogelişimsel hastalığıdır.Nörogelişimsel bir hastalık olan otizmde genetik ve çevresel faktörler rol oynar. Otizmin moleküler ve mekanistik temelleri aydınlatılmaya başlanmıştır. Hastalığın genetik altyapılarından biri olarak, glutamat gen mekanizması, teşhis ve tedavisi için yeni bir metod geliştirilmesine olanak sağlayabilir. Bu kısa derlemenin amacı, otizmin genetik ve çevresel nedenleri ile ilgili yapılan son çalışmalardan faydalanılarak hastalık hakkında bilgi edinmektir.

Anahtar Kelimeler: *otizm, glutamate, immune system, genetik, nörogelişim*

1. Introduction

Autism is a neurodevelopmental disorder that affects 1–2 in 100 children, according to recent data on the broad array of autism spectrum disorders. Autism is diagnosed when a child or adult has abnormalities in a ''triad'' of behavioral domains: social development, communication, and repetitive behavior/obsessive interests. Autism can occur at any point on the IQ continuum, and IQ is a strong predictor of outcome (Baron-Cohen et al., 2009). Unusual social development becomes apparent early in childhood. Autistic infants show less attention to social stimuli, smile and look at others less often, and respond less to their own name. Autistic toddlers differ more strikingly from social norms; for example, they have less eye contact and turn taking, and do not have the ability to use simple movements to express themselves, such as the deficiency to point at things.

Autism is one of the subtypes of autism spectrum disorders (ASD) which refers to a group of childhood neurodevelopmental disorders with polygenic etiology. The disorders are characterized by impaired social interaction, communication and verbal communication and language impairments, and repetitive behaviors and interests. Autism has an increasing prevalence in recent years. From 2007 to 2011–2012, the incidence of ASD rose from 1.16% to 2.00% in the United States of America (Blumberg et al., 2013).

Most researches show that both genetic and environmental factors play a role in the development of ASD. High concordance of ASD among boys and girls cannot be explained by genetic heritability alone; shared environmental factors explain a large proportion of the variance in liability. In addition, prenatal exposure to organophosphates has been related to a significant reduction in childhood IQ.

2. Glutamate and Autism

Glutamate is a major excitatory neurotransmitter, is highly concentrated throughout the brain and is crucial to neuronal plasticity and the maintenance of cognitive

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functioning. However, excess glutamate has been shown to be a potent neurotoxin that leads to neuronal cell death (Manev et al., 1989) and is deemed to play a role in the pathophysiology of some neuropsychiatric disorders (Sheldon et al., 2007). Recently, a hyperglutamatergic hypothesis of autism was proposed (Blaylock et al., 2009) based on evidence of hyperglutamatergia in the brain of individuals with autism. For instance, in a study, levels of GAD 65 kDa and GAD 67 kDa proteins, both of which are involved in converting glutamate to GABA, are reduced in the brains of individuals with autism, resulting in increased levels of glutamate in the brain substrate (Fatemi et al, 2002). In addition, in another study that contains neuroimaging magnetic resonance spectroscopy has demonstrated that individuals with ASD have significantly higher concentrations of glutamate in the amygdala- hippocampal region than do healthy controls (Page et al., 2006). The high level of plasma glutamate level especially in children with normal IQ is supposed to be biomarker to diagnose autism (Shimmura et al., 2011). Higher glutamate level is not limited to plasma, and some studies confirmed its higher level in some brain regions (amygdala-hippocampal regions) of patients with autism compared to the controls (Page et al., 2006).

Most psychiatric and neurodevelopmental disorders (PNDD) have a strong heritable component (Sullivan et al., 2012). Twin studies have proved that neurodevelopmental disorders, such as (ASD) (Posthuma et al., 2013). Glutamate receptors (GluRs) mediate excitatory synaptic transmission and plasticity in the brain (Traynelis et al., 2010). Glutamate receptors encode GRIK2, GRIN3B and GRIA3 genes which are related to ASD. In addition, anomalies in regions on chromosomes six and seven, encoding Glu receptors, have been related to ASD (Yang et al., 2013). Abnormalities in the glutamatergic system might therefore be implied in ASD. Indeed, epileptic seizures which have been related to excitatory Glu and decreased GABA, are common in ASD (Ballaban et al., 2000).

3. Effects of environmental factors against autism

In addition to genetic basis of glutamate level, environmental components also play role increased glutamate level children with autism. Many children with autism are picky eaters. They do not like a variety of different foods. Eating problems are risk factors for nutritional deficiencies. Some of these children do not like to try new foods and have food selectivity (Kral et al., 2013).

Last findings support that many children with autism suffer from amino acids metabolism impairment. Nearly, all the studies reported higher levels of plasma glutamate in children with autism than those of the controls. Hyperglutamatergic state causes excitotoxicity and neurodegeneration (Sheldon et al., 2007). Moreover, this increased glutamate level is compatible with the findings that the level of proteins involved in transforming glutamate to GABA is decreased. A study compared plasma level of 25 amino acids between high-functioning autism children and the healthy controls. The study showed that only the levels of glutamate and glutamine were different between the two groups. While the level of glutamate was increased, the level of glutamine was decreased (Shimmura et al., 2011).

4. Immunologic system and autism

There is increasing evidence supporting that an immune insult during pregnancy can have a significant effect on the developing fetus (Brown, 2012). For over 30 years, epidemiological research has continued to find associations between maternal infection and increased risk of autism (Atladottir et al., 2010). A recent large case-control population based study revealed an increased risk of developing autism spectrum disorder (ASD) with maternal fever, which was attenuated if pregnant mothers used a fever reducing agent (Zerbo et al., 2013). In addition, reports highlight associations between risk of having a child with autism and increased levels of inflammatory mediators in both the maternal sera and amniotic fluid. These increased inflammatory markers, interleukins (IL)-4, IL-5, and interferon (IFN)-γ. (Abdallah et al., 2012), supporting a relationship between maternal immune activation (MIA), aberrant fetal neurodevelopment, and risk for neurodevelopmental disorders such as autism. Also inflammatory markers are playing role in other neurological disorders such as panic disorder. A supporting study has shownIL-12and IFN-γ were significantly lower in panic disorder group when compared to the controls and IFN-γ values were significant predictors of the presence of panic disorder (Tukel et al., 2012).

5. Conclusion

Autism is not only resulting from genetic factors but also environmental factors play significant role in the development of autism. From the beginning of individual's existence all factors can be effective. There are many questions waiting to be answered about autism. Is it an untreatable genetic destiny? Is there a chance to diagnose autism before childhood?

It is still nebulous the underlying mechanisms of autism. With understanding the role of molecular and mechanistic basis of autism more details will be enlightened about disease. Glutamate mechanism is only one of the molecular reasons of autism. All knowledge in this area, throw a new light on developing new genetic treatment methods.

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MINI-REVIEW

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MIND, BRAIN, AND EDUCATION: AN EMERGING TRANSDISCIPLINARY FIELD OF LEARNING AND DEVELOPMENT

ZİHİN, BEYİN VE EĞİTİM: ÖĞRENME VE GELİŞİMİN BELİREN TRANSDİSİPLİNER BİR ALANI

Asil Ali Özdoğru*[1]

Abstract

The future of neuroscience needs an innovative outlook on the study of brain by scientists coming from various disciplines and traditions. The field of Mind, Brain, and Education (MBE) is a meeting point for researchers and scientists in psychology, biology, and education. Unlike the one-way information sharing from psychology to education as in educational psychology or from neuroscience to education as in educational neuroscience, MBE is credited with its two-way flow of information between the three fields. The transdisciplinary initiatives between neuroscience, psychology, and education, as in the case of MBE, offer an increased optimism not only for the treatment of biological and neurological diseases but also for the realization of optimal outcomes in effective learning and positive development.

Keywords: Neurosciences; mind, brain, and ducation; educational psychology; educational neuroscience; learning; development

Özet

Nörobilimin geleceği, beynin çeşitli disiplin ve geleneklerden gelen bilimciler tarafından çalışılmasında yenileşimci bir bakış açısına ihtiyaç duymaktadır. Zihin, Beyin ve Eğitim (ZBE) alanı psikoloji, biyoloji ve eğitimdeki araştırmacı ve bilimciler için bir buluşma noktasıdır. Eğitim psikolojisindeki gibi psikolojiden eğitime ya da eğitim nörobilimindeki gibi nörobilimden eğitime tek yönlü bir bilgi paylaşımının aksine, ZBE üç alan arasındaki iki yönlü bilgi akışıyla takdir edilmektedir. ZBE olgusundaki gibi, nörobilim, psikoloji ve eğitim arasındaki transdisipliner girişimler, sadece biyolojik ve nörolojik hastalıkların tedavisi için değil aynı zamanda etkili öğrenme ve pozitif gelişimde en uygun sonuçların gerçekleştirilmesi için daha fazla umut vaat etmektedir.

Anahtar Kelimeler: *Nörobilimler; Zihin, Beyin ve Eğitim; eğitim psikolojisi; eğitim nörobilimi; öğrenme; gelişim*

1. Introduction

Neurosciences have attracted a great deal of attention in the past decades and continuing to do so. Starting with the designation of 1990s as the Decade of the Brain by the United States President, neurosciences were seen as the key to human mind and behavior. In their letter to the editor in *Science* magazine, 10 US scientists (Albus et al., 2007) proposed a multidisciplinary research agenda for a Decade of the Mind to understand, heal, enrich, and model the mind. The year 2013 has been the start of grand research projects on human brain with the BRAIN Initiative of the United States and the Human Brain Project of the European Union. These projects aim to revive the past efforts and complete the mapping of human brain for a better understanding of its structures and functions.

Even though this interest and support for neuroscience is promising a great deal of hope for the brain diseases and other unknowns of the mind, critiques find these initiatives narrow in focus and premature in analysis. In his *New York Times* op-ed, Dr. Gary Marcus (2014) from New York University states that neuroscience needs a breakthrough, like the DNA in biology, to understand the link between neurological structures and cognitive processes. He also highlights the need for better data analysis in the processing of large datasets collected by these grand projects. The future of neuroscience needs an innovative outlook on the study of brain by scientists coming from various disciplines and traditions. I would like to draw attention to a young field of science that brings together knowledge and methods from different scientific disciplines and practices.

2. Mind, Brain, and Education

The field of Mind, Brain, and Education (MBE) is a

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meeting point for researchers and scientists in psychology, biology, and education. The field, as shown in the Figure 1 below, is the child of a transdiciplinary marriage between neuroscience, education, and psychology, all of which have relatively recent backgrounds in the scientific arena (Tokuhama-Espinosa, 2010). Researchers in the field study a diverse range of topics, including but not limited to, bilingualism, cognitive skills, dyslexia, educational testing, math anxiety, and sleep cycles. The transdisciplinary MBE field is also a cross-cultural one due to the international collaborations with common standards and values. Researchers around the world are working on various issues in relation to human learning and development with the advanced knowledge and expertise in neurosciences and genetics.

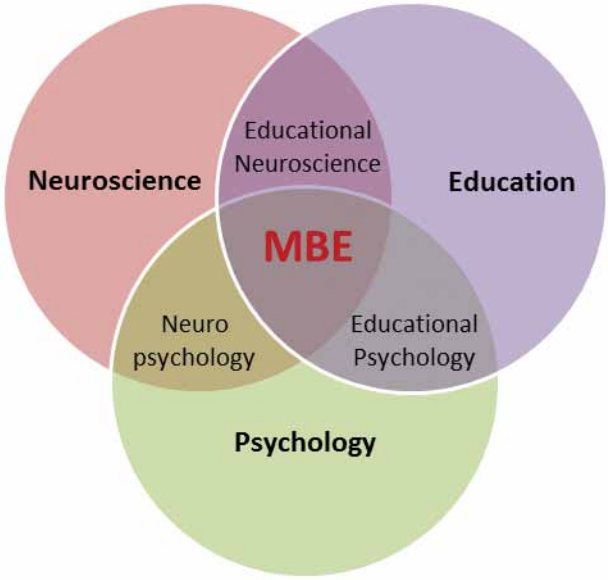

Figure 1: The transdisciplinary field of Mind, Brain, and Education (MBE) (adapted from Tokuhama-Espinosa, 2010)

In short history of the field, there has been a tremendous interest and advancement. Spearheaded by Dr. Kurt Fischer from Harvard Graduate School of Education, the International Mind, Brain and Education Society was founded in 2004. The society then launched its flagship journal, the *Mind, Brain, and Education,* in 2007. While the society holds biannual conferences, all of which were held in the United States so far, the journal is published quarterly by the Wiley Periodicals.

In their inaugural article in *Mind, Brain, and Education,* editors of the journal stated that "It is time for education, biology, and cognitive science to join together to create a new science and practice of learning and development" (Fischer et al., 2007, p. 1). The field and the journal are envisioned to serve a mediatory role in transferring practical knowledge from biological sciences to educational practices. The articles published in the MBE journal showcase the multidisciplinary nature of the studies in the field. A quick word count in the titles and abstracts of the articles reveal the most frequent concepts as learning, education, brain, and neuroscience.

Two of the most frequently cited articles in the MBE journal can provide a closer look at the depth and breadth of the studies in the field. In their review article, Robert Plomin and colleagues (2007) discuss the genetic factors on learning behavior. They assert that the identification of generalist genes, which are responsible for the genetic influence on learning abilities and disabilities in reading and mathematics, would be very instrumental in the understanding of the mechanisms and associations between genes, brain, and behavior. In another review article by Immordino-Yang and Damasio (2007), the concept of emotional thought is introduced and discussed for its implications on learning. Authors point out the intertwined nature of human cognition, emotion, decision making, and social functioning and call for more research and innovation in educational environments to make use of recent findings in neuroscience.

The long discussed relationship between learning and development is now expanding to better integrate biological sciences in this relationship. Thanks to the enhanced knowledge base about the structures and processes of brain and genetics, MBE can help to design and implement better educational programs and interventions. Educators and practitioners in MBE also provide information and lessons learned to psychological and biological scientists. Unlike the one-way information sharing from psychology to education as in educational psychology or from neuroscience to education as in educational neuroscience, MBE is credited with its two-way flow of information between the three fields (Tokuhama-Espinosa, 2010).

3. Conclusion

The interest and investment in neurosciences is fueling the need for more interdisciplinary and innovative research programs around the world. The transdisciplinary initiatives between neuroscience, psychology, and education, as in the case of MBE, offer an increased optimism not only for the treatment of biological and neurological diseases but also for the realization of optimal outcomes in effective learning and positive development.

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LETTER TO THE EDITOR

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SERTRALINE INDUCED ANGIOEDEMA

SERTRALİNE BAĞLI ANJİOÖDEM

Alper Evrensel*[1], Barış Önen Ünsalver[1], Mehmet Emin Ceylan[1], Gökçe Cömert[1]

To editor;

Selective serotonin reuptake inhibitors (SSRIs) are reliable drugs (Kostev et al, 2014). Only one angioedema case due to sertraline was reported (Dadic-Hero et al, 2011). In this case, angioedema has also developed with both sertraline and escitalopram (another SSRI). Cross-allergic reactions might be seen in similar drugs.

Case

Sertraline (25 mg/day) treatment was started 51-year-old male patient with a diagnosis of depression. He called after 3 hours later first dose with complaints of swelling of the lips and tongue and sent his own photo. Thereupon dermatology consultation was requested. In dermatological examination angioedema (Quincke's edema) was diagnosed. Because it couldn't find another reason, sertraline treatment was terminated. Edema was decreased treatment with antihistaminic. After 2 weeks, sertraline (12.5 mg/day) was started again and 3-4 hours after taking the first dose of sertraline, he sent his own photo with complaints of the same symptoms. Sertraline treatment was terminated due to repeated angioedema. Amitriptyline (10 mg/day) treatment was started and angioedema didn't occur although the dose of it was increased to 100 mg/day.

In our case, angioedema was not developed with amitriptyline, a tricyclic antidepressant (TCA). It has been reported that amitriptyline might be used in the treatment of angioedema (Guarneri et al, 2014). It may be appropriate to plan a medication from a different group when allergic reactions occur.

Sincerely,

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SWALLOWING METAL THINGS

METAL CİSİMLERİN YUTULMASI

Habib Erensoy[1], Mehmet Emin Ceylan[1], Alper Evrensel[*1]

To editor;

In psychiatric literature, patients who swallow foreign things is not rare. Surgeons usually witness these after perforation or they are diagnosed totally by coincidence. Only few of them relapse, but when it relapses, they urged to the psychiatrists. Foreign body swallowing mostly done for self-injury or/and can be a sign of psychotic syndrome. Abraham reported a schizoid patient, who swallows metal objects and nail. Kuzon reported a similar case, which swallowed magnetic iron objects and nails. A young man with a lot of needles in his colon also reported by Eryılmaz. In our case, M.S swallows keys.

Case

M.S. 18 years old, single, male, high school student, lives with his parents. Our patient came to us with his mother's will an it was the first time for him to consult for a psychiatric treatment. He is complaining about not being happy in his life; he does not get along with his dad. He usually skips the school and does not go home. His mother is not sure whether he uses drug or not. In psychiatric examination he was depressive but easily cooperated and well orientated. He had problems with sleeping and eating. He had concentration problems also. He was aware of his disorder but he didn't want to live with his father.

In his story, he is running away from school and home. He can't sleep well and he does not enjoy in life. The patient tells that last year he came to Istanbul without saying anything to his parents. He did scavenging for 2 weeks. Later, he called his mother and said his location. Since then, he was not getting along with his father. He said his dad used violence towards him. He tried to retake his classes but fails. In this periodic time, his mother told us that he is using drugs. He smokes 15 cigarettes per day. He gets a score of 32 from Hamilton test.

Sertraline (50 mg/day) and olanzapine (5mg/day) were prescribed to him. After 3 weeks we increase sertraline to 100 mg. Two weeks after the treatment he was sent to general surgery for consultation. He was complaining about a stomach ache: when the doctors do some x-ray, two door keys was found in his stomach. The doctor thought that these keys can be thrown out of body naturally. But later he realized that there are other metal objects. EEG and MRI results are normal. After one week he takes another x-ray and the doctor tells that there is one more key in his stomach and intestine.

He grew in a crowded and careless family. He has five brothers and a younger sister. He told that his father doesn't like him since his childhood. His dad used violence towards him and his older brothers. He learned sexual content from his high school friends but he is not sexually experienced. He told that he used drugs couple of times since high school and he cut himself 2 or 3 times just because he was bored. He ran away from home and did some garbage collection job for living at the age of 16. Rorschach test shows us that he has borderline traits. He has connections with reality and lasts the joining to collective thinking. On the other hand, he is close the schizoid level. In the second stage of treatment he tried to suicide by taking all the pills together. Later, he ran away from hospital and went to his home. In 2 days, he came back and tried to suicide again. He stayed in intensive care unit for 3 days. He could not be traced because he and his family did not attend the appointments.

In this report we talk about the psychiatric disorder of an 18 years old boy, who swallows keys and other metal things.

Sincerely,

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SYSTEMS BIOLOGY & COMPUTATIONAL NEUROSCIENCE

SİSTEM BİYOLOJİSİ & HESAPLAMALI SİNİRBİLİM

Kaan Yılancıoğlu[1]

To the Editor;

Systems biology is an emerging branch of biological sciences aimed at describing interactions of complex biological mechanisms. Besides traditional scientific analysis methods, systems biology offers robust computer integrated, reliable data analysis approaches. Since, nervous system is fascinatingly complex and dynamic, classic data analysis techniques seem to be limited to fully understand the interactions and cross-talks among neuronal networks beneath cognitive and motor functioning mechanisms. Vast theoretical investigations resulted to better understanding of the neuronal circuits and their functions. Studies conducted on neural code generated quantitative measures of the processing made by initial sensory phases (Rieke et al.). Neural code comparisons with bounds adjusted by optimality principle helped finding underlying design criteria. Other computational studies conducted on structural and dynamic mechanisms carried out by specific local circuits, involving working memory, sensory processing, decision-making, neural learning, motor control and memory. Neuroscience strongly emphasize the use of computational modeling techniques to investigate the neural system and most importantly how the brain computes information using neural code and complex networks (Dayan & Abbott). Experimental, analytical and modeling studies mostly focus on understanding the brain architecture and function which are closely related to systems neuroscience subjecting computational approaches to investigate the features of nervous systems at different levels of detail (Van Hemmen & Callaway, Callaway). Studies in computational neuroscience imply simulation of numerical computational models besides analytical models and experimental verification models (De Schutter et al.). Systems biology could be similarly described in multiple ways including integrative computational and statistical approaches of the networks between various compounds of biological systems to understand how such interactions result to the function and systems behavior. Methodologies used by systems biology and computational neuroscience are highly similar and ideally, a strong interaction should be promoted between these fields. However, researchers working on system biology prejudicially find computational neuroscience as too specific field while computational neuroscientists are seem not to be interested in genes, molecular pathways and networks. There will be evidently increasing need of systems biology aspects among computational neuroscience community when modeling studies are more crossed over with subcellular and cellular level research. Currently, it is being more frequently noticed that the interest of computational neuroscience community on cellular modeling, neuronal networks and information coding is increased. As a result of this interest-shift, scientists working on traditional computational neuroscience will eventually concern more with neural code and cognitive processes and then bottom-up modelers become more interacted with systems biology field.

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IMPRESSIONS ON ECNS2014 HALIFAX MEETING

ECNS 2014 HALİFAX TOPLANTISI İZLENİMLERİ

Selahattin Gültekin[1]

This year's joint meeting of the EEG & Clinical Neuroscience Society (ECNS), International Society for Research in Neuroimaging (ISNIP), & International Society for Brain Electromagnetic Tomography (ISBET) was held in Halifax, Canada on September 3-7, 2014. A number of scholars with fields ranging in engineering, psychology and psychiatry attended this meeting, which offered a multidisciplinary atmosphere for the conference attendees ECNS's meetings are held alternatively in North America and Europe.

As an engineer, this was my first time attending such a meeting, and I must say that I was extremely impressed by the quality of the scientists that attended and the scientific papers presented. I realized that there is an extensive amount of research carried out on the brain all over the world.

It should be emphasized that Turkey, especially Üsküdar University is involved in a full-fledged research on the brain. This situation is reflected by the number of attendees (altogether 7, including the Rector, and the Dean of Engineering & Natural Sciences) from Üsküdar University.

The following symposium section was allocated to Üsküdar University with the indicated subjects and the oral presenters in ECNS-2014.

Symposium 4: Artificial Intelligence in Psychiatric Disorders (Chair: Nevzat Tarhan, MD)

1. Behavioral Entropy from Engineering Point of View (Selahattin Gültekin, Ph.D.)
2. The Evaluation of QEEG for Treatment Response in Psychiatric Disorders: A Clinical Perspective (Barış Önen Ünsalver, M.D.)
3. Application of Classification Methods: Artificial Neural Network/Support Vector Machine (Serhat Özekes, Ph.D.)
4. Feature Selection Process: Ant Colony Optimization/Genetic Algorithm (Türker Ergüzel, Ph.D.)

In addition, the following presentations were also the result of a research carried out at Üsküdar University/ NPIstanbul Hospital:

fMRI and Behavioral Correlates of Sufi Meditation (Cumhur Taş, M.D., Ph.D. & Nadire Gülçin Yıldız., Ph.D.)

New-Youth Individualized Psychosocial Rehabilitation Model (Nevzat Tarhan, M.D. & Nadire Gülçin Yıldız, Ph.D.).

In addition to carrying out academically indulging presentations on a number of diverse topics, Üsküdar University also sponsored the ECNS Career Contribution Award and the ECNS E. Roy John Award. Next ECNS-2015 will be held in Munich, Germany on September 9-13, 2015.

In the beautiful autumn of the Northern American Atlantic shore, academics enjoyed an exchange in perspective not only in presentations but also during the social interactions where they formed network for future collaboration on neuroscience base research.

After lengthy discussions at the meeting in Halifax, it has been unanimously decided that Üsküdar University will be hosting the ECNS-2016 Meeting in Istanbul in spite of the yearly switch between North America and Europe.

I am confident that Üsküdar University will carry out this hosting responsibility in the most enlightening way.

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