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ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

Медицинские новости Грузии

საქართველოს სამედიცინო სიახლენი

GEORGIAN MEDICAL NEWS

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GMN: Georgian Medical News is peer-reviewed, published monthly journal committed to promoting the science and art of medicine and the betterment of public health, published by the GMN Editorial Board since 1994. GMN carries original scientific articles on medicine, biology and pharmacy, which are of experimental, theoretical and practical character; publishes original research, reviews, commentaries, editorials, essays, medical news, and correspondence in English and Russian.

GMN is indexed in MEDLINE, SCOPUS, PubMed and VINITI Russian Academy of Sciences. The full text content is available through EBSCO databases.

GMN: Медицинские новости Грузии - ежемесячный рецензируемый научный журнал, издаётся Редакционной коллегией с 1994 года на русском и английском языках в целях поддержки медицинской науки и улучшения здравоохранения. В журнале публикуются оригинальные научные статьи в области медицины, биологии и фармации, статьи обзорного характера, научные сообщения, новости медицины и здравоохранения. Журнал индексируется в MEDLINE, отражён в базе данных SCOPUS, PubMed и ВИНИТИ РАН. Полнотекстовые статьи журнала доступны через БД EBSCO.

GMN: Georgian Medical News – საქართველოს სამედიცინო სიახლენი – არის ყოველთვიური სამეცნიერო სამედიცინო რეცენზირებადი ჟურნალი, გამოიცემა 1994 წლიდან, წარმოადგენს სარედაქციო კოლეგიისა და აშშ-ის მეცნიერების, განათლების, ინდუსტრიის, ხელოვნებისა და ბუნებისმეტყველების საერთაშორისო აკადემიის ერთობლივ გამოცემას. GMN-ში რუსულ და ინგლისურ ენებზე ქვეყნდება ექსპერიმენტული, თეორიული და პრაქტიკული ხასიათის ორიგინალური სამეცნიერო სტატიები მედიცინის, ბიოლოგიისა და ფარმაციის სფეროში, მიმოხილვითი ხასიათის სტატიები.

ჟურნალი ინდექსირებულია MEDLINE-ის საერთაშორისო სისტემაში, ასახულია SCOPUS-ის, PubMed-ის და ВИНИТИ РАН-ის მონაცემთა ბაზებში. სტატიების სრული ტექსტი ხელმისაწვდომია EBSCO-ს მონაცემთა ბაზებიდან.

WEBSITE

www.geomednews.com

К СВЕДЕНИЮ АВТОРОВ!

При направлении статьи в редакцию необходимо соблюдать следующие правила:

1. Статья должна быть представлена в двух экземплярах, на русском или английском языках, напечатанная через **полтора интервала на одной стороне стандартного листа с шириной левого поля в три сантиметра**. Используемый компьютерный шрифт для текста на русском и английском языках - **Times New Roman** (**Кириллица**), для текста на грузинском языке следует использовать **AcadNusx.** Размер шрифта - **12**. К рукописи, напечатанной на компьютере, должен быть приложен CD со статьей.

2. Размер статьи должен быть не менее десяти и не более двадцати страниц машинописи, включая указатель литературы и резюме на английском, русском и грузинском языках.

3. В статье должны быть освещены актуальность данного материала, методы и результаты исследования и их обсуждение.

При представлении в печать научных экспериментальных работ авторы должны указывать вид и количество экспериментальных животных, применявшиеся методы обезболивания и усыпления (в ходе острых опытов).

4. К статье должны быть приложены краткое (на полстраницы) резюме на английском, русском и грузинском языках (включающее следующие разделы: цель исследования, материал и методы, результаты и заключение) и список ключевых слов (key words).

5. Таблицы необходимо представлять в печатной форме. Фотокопии не принимаются. **Все цифровые, итоговые и процентные данные в таблицах должны соответствовать таковым в тексте статьи**. Таблицы и графики должны быть озаглавлены.

6. Фотографии должны быть контрастными, фотокопии с рентгенограмм - в позитивном изображении. Рисунки, чертежи и диаграммы следует озаглавить, пронумеровать и вставить в соответствующее место текста **в tiff формате**.

В подписях к микрофотографиям следует указывать степень увеличения через окуляр или объектив и метод окраски или импрегнации срезов.

7. Фамилии отечественных авторов приводятся в оригинальной транскрипции.

8. При оформлении и направлении статей в журнал МНГ просим авторов соблюдать правила, изложенные в «Единых требованиях к рукописям, представляемым в биомедицинские журналы», принятых Международным комитетом редакторов медицинских журналов - http://www.spinesurgery.ru/files/publish.pdf и http://www.nlm.nih.gov/bsd/uniform_requirements.html
В конце каждой оригинальной статьи приводится библиографический список. В список литературы включаются все материалы, на которые имеются ссылки в тексте. Список составляется в алфавитном порядке и нумеруется. Литературный источник приводится на языке оригинала. В списке литературы сначала приводятся работы, написанные знаками грузинского алфавита, затем кириллицей и латиницей. Ссылки на цитируемые работы в тексте статьи даются в квадратных скобках в виде номера, соответствующего номеру данной работы в списке литературы. Большинство цитированных источников должны быть за последние 5-7 лет.

9. Для получения права на публикацию статья должна иметь от руководителя работы или учреждения визу и сопроводительное отношение, написанные или напечатанные на бланке и заверенные подписью и печатью.

10. В конце статьи должны быть подписи всех авторов, полностью приведены их фамилии, имена и отчества, указаны служебный и домашний номера телефонов и адреса или иные координаты. Количество авторов (соавторов) не должно превышать пяти человек.

11. Редакция оставляет за собой право сокращать и исправлять статьи. Корректура авторам не высылается, вся работа и сверка проводится по авторскому оригиналу.

12. Недопустимо направление в редакцию работ, представленных к печати в иных издательствах или опубликованных в других изданиях.

При нарушении указанных правил статьи не рассматриваются.

REQUIREMENTS

Please note, materials submitted to the Editorial Office Staff are supposed to meet the following requirements:

1. Articles must be provided with a double copy, in English or Russian languages and typed or compu-ter-printed on a single side of standard typing paper, with the left margin of **3** centimeters width, and **1.5** spacing between the lines, typeface - **Times New Roman** (**Cyrillic**), print size - **12** (referring to Georgian and Russian materials). With computer-printed texts please enclose a CD carrying the same file titled with Latin symbols.

2. Size of the article, including index and resume in English, Russian and Georgian languages must be at least 10 pages and not exceed the limit of 20 pages of typed or computer-printed text.

3. Submitted material must include a coverage of a topical subject, research methods, results, and review.

Authors of the scientific-research works must indicate the number of experimental biological species drawn in, list the employed methods of anesthetization and soporific means used during acute tests.

4. Articles must have a short (half page) abstract in English, Russian and Georgian (including the following sections: aim of study, material and methods, results and conclusions) and a list of key words.

5. Tables must be presented in an original typed or computer-printed form, instead of a photocopied version. **Numbers, totals, percentile data on the tables must coincide with those in the texts of the articles.** Tables and graphs must be headed.

6. Photographs are required to be contrasted and must be submitted with doubles. Please number each photograph with a pencil on its back, indicate author's name, title of the article (short version), and mark out its top and bottom parts. Drawings must be accurate, drafts and diagrams drawn in Indian ink (or black ink). Photocopies of the X-ray photographs must be presented in a positive image in **tiff format**.

Accurately numbered subtitles for each illustration must be listed on a separate sheet of paper. In the subtitles for the microphotographs please indicate the ocular and objective lens magnification power, method of coloring or impregnation of the microscopic sections (preparations).

7. Please indicate last names, first and middle initials of the native authors, present names and initials of the foreign authors in the transcription of the original language, enclose in parenthesis corresponding number under which the author is listed in the reference materials.

8. Please follow guidance offered to authors by The International Committee of Medical Journal Editors guidance in its Uniform Requirements for Manuscripts Submitted to Biomedical Journals publication available online at: http://www.nlm.nih.gov/bsd/uniform_requirements.html
http://www.icmje.org/urm_full.pdf
In GMN style for each work cited in the text, a bibliographic reference is given, and this is located at the end of the article under the title "References". All references cited in the text must be listed. The list of references should be arranged alphabetically and then numbered. References are numbered in the text [numbers in square brackets] and in the reference list and numbers are repeated throughout the text as needed. The bibliographic description is given in the language of publication (citations in Georgian script are followed by Cyrillic and Latin).

9. To obtain the rights of publication articles must be accompanied by a visa from the project instructor or the establishment, where the work has been performed, and a reference letter, both written or typed on a special signed form, certified by a stamp or a seal.

10. Articles must be signed by all of the authors at the end, and they must be provided with a list of full names, office and home phone numbers and addresses or other non-office locations where the authors could be reached. The number of the authors (co-authors) must not exceed the limit of 5 people.

11. Editorial Staff reserves the rights to cut down in size and correct the articles. Proof-sheets are not sent out to the authors. The entire editorial and collation work is performed according to the author's original text.

12. Sending in the works that have already been assigned to the press by other Editorial Staffs or have been printed by other publishers is not permissible.

Articles that Fail to Meet the Aforementioned Requirements are not Assigned to be Reviewed.

ავტორთა საყურადღებოდ!

რედაქციაში სტატიის წარმოდგენისას საჭიროა დავიცვათ შემდეგი წესები:

1. სტატია უნდა წარმოადგინოთ 2 ცალად, რუსულ ან ინგლისურ ენებზე,დაბეჭდილი სტანდარტული ფურცლის 1 გვერდზე, 3 სმ სიგანის მარცხენა ველისა და სტრიქონებს შორის 1,5 ინტერვალის დაცვით. გამოყენებული კომპიუტერული შრიფტი რუსულ და ინგლისურენოვან ტექსტებში - **Times New Roman (Кириллица)**, ხოლო ქართულენოვან ტექსტში საჭიროა გამოვიყენოთ **AcadNusx.** შრიფტის ზომა – 12. სტატიას თან უნდა ახლდეს CD სტატიით.

2. სტატიის მოცულობა არ უნდა შეადგენდეს 10 გვერდზე ნაკლებს და 20 გვერდზე მეტს ლიტერატურის სიის და რეზიუმეების (ინგლისურ, რუსულ და ქართულ ენებზე) ჩათვლით.

3. სტატიაში საჭიროა გაშუქდეს: საკითხის აქტუალობა; კვლევის მიზანი; საკვლევი მასალა და გამოყენებული მეთოდები; მიღებული შედეგები და მათი განსჯა. ექსპერიმენტული ხასიათის სტატიების წარმოდგენისას ავტორებმა უნდა მიუთითონ საექსპერიმენტო ცხოველების სახეობა და რაოდენობა; გაუტკივარებისა და დაძინების მეთოდები (მწვავე ცდების პირობებში).

4. სტატიას თან უნდა ახლდეს რეზიუმე ინგლისურ, რუსულ და ქართულ ენებზე არანაკლებ ნახევარი გვერდის მოცულობისა (სათაურის, ავტორების, დაწესებულების მითითებით და უნდა შეიცავდეს შემდეგ განყოფილებებს: მიზანი, მასალა და მეთოდები, შედეგები და დასკვნები; ტექსტუალური ნაწილი არ უნდა იყოს 15 სტრიქონზე ნაკლები) და საკვანძო სიტყვების ჩამონათვალი (key words).

5. ცხრილები საჭიროა წარმოადგინოთ ნაბეჭდი სახით. ყველა ციფრული, შემაჯამებელი და პროცენტული მონაცემები უნდა შეესაბამებოდეს ტექსტში მოყვანილს.

6. ფოტოსურათები უნდა იყოს კონტრასტული; სურათები, ნახაზები, დიაგრამები - დასათაურებული, დანომრილი და სათანადო ადგილას ჩასმული. რენტგენოგრამების ფოტოასლები წარმოადგინეთ პოზიტიური გამოსახულებით **tiff** ფორმატში. მიკროფოტოსურათების წარწერებში საჭიროა მიუთითოთ ოკულარის ან ობიექტივის საშუალებით გადიდების ხარისხი, ანათალების შეღებვის ან იმპრეგნაციის მეთოდი და აღნიშნოთ სურათის ზედა და ქვედა ნაწილები.

7. სამამულო ავტორების გვარები სტატიაში აღინიშნება ინიციალების თანდართვით, უცხოურისა – უცხოური ტრანსკრიპციით.

8. სტატიას თან უნდა ახლდეს ავტორის მიერ გამოყენებული სამამულო და უცხოური შრომების ბიბლიოგრაფიული სია (ბოლო 5-8 წლის სიღრმით). ანბანური წყობით წარმოდგენილ ბიბლიოგრაფიულ სიაში მიუთითეთ ჯერ სამამულო, შემდეგ უცხოელი ავტორები (გვარი, ინიციალები, სტატიის სათაური, ჟურნალის დასახელება, გამოცემის ადგილი, წელი, ჟურნალის №, პირველი და ბოლო გვერდები). მონოგრაფიის შემთხვევაში მიუთითეთ გამოცემის წელი, ადგილი და გვერდების საერთო რაოდენობა. ტექსტში კვადრატულ ფჩხილებში უნდა მიუთითოთ ავტორის შესაბამისი N ლიტერატურის სიის მიხედვით. მიზანშეწონილია, რომ ციტირებული წყაროების უმეტესი ნაწილი იყოს 5-6 წლის სიღრმის.

9. სტატიას თან უნდა ახლდეს: ა) დაწესებულების ან სამეცნიერო ხელმძღვანელის წარდგინება, დამოწმებული ხელმოწერითა და ბეჭდით; ბ) დარგის სპეციალისტის დამოწმებული რეცენზია, რომელშიც მითითებული იქნება საკითხის აქტუალობა, მასალის საკმაობა, მეთოდის სანდოობა, შედეგების სამეცნიერო-პრაქტიკული მნიშვნელობა.

10. სტატიის ბოლოს საჭიროა ყველა ავტორის ხელმოწერა, რომელთა რაოდენობა არ უნდა აღემატებოდეს 5-ს.

11. რედაქცია იტოვებს უფლებას შეასწოროს სტატია. ტექსტზე მუშაობა და შეჯერება ხდება საავტორო ორიგინალის მიხედვით.

12. დაუშვებელია რედაქციაში ისეთი სტატიის წარდგენა, რომელიც დასაბეჭდად წარდგენილი იყო სხვა რედაქციაში ან გამოქვეყნებული იყო სხვა გამოცემებში.

აღნიშნული წესების დარღვევის შემთხვევაში სტატიები არ განიხილება.

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AUDIOGENIC SEIZURE SUPPRESSION BY VENTRAL TEGMENTAL AREA STIMULATION

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Abstract.

The audiogenic seizure (AGS) model is one of several experimental models used to study epilepsy and identify underlying mechanisms. Dopamine plays an important role in epileptogenesis and dopaminergic neurons of ventral tegmental area (VTA) have extensive connections with many brain structures. Despite of this there are no data on the influence of this structure on the audiogenic seizure responses of the brain. The main aim of our study was to investigate the influence of the VTA on the development of audiogenic seizure reactions in genetically epilepsy-prone rats. The novelty of these article lies not only in the observation of changes in the development/course of audiogenic seizure reactions caused by stimulation of the VTA, but also in taking into account the localization of the epileptogenic focus, which, in our opinion, is especially important for the scientific analysis of this type of research. The inferior and superior colliculus has prominent descending projections to several areas of the reticular formation, which may sub serve the direct AGS efferent pathway. The experiments conducted showed that in response to stimulation of the VTA, the latency and duration of the first wild run do not undergo significant changes. The experiments showed a significant increase in the duration of the pause between the first and second wild runs and a significant decrease in the duration of the second wild run. Furthermore, we observed a significant decrease in behavioral seizure activity after the second wild run, leading to its complete disappearance. Structures receiving synaptic inputs from the ventral tegmental area deserve special attention. One such structure is the reticular nucleus of the thalamus (TRN). It has been shown that stimulation of TRN causes inhibition of neurons in those brainstem structures that are involved in motor reactions of the spinal cord. Therefore, it can be hypothesized that the TRN modulate the brainstem regions responsible for motor responses during audiogenic seizures. From our results we can conclude: The VTA plays an important role in epileptogenesis, which is apparently associated with the inhibitory effect of dopamine on the motor manifestations of seizures. Therefore, VTA as a brain dopaminergic nucleus, may be a suitable target for DBS anticonvulsant action.

Key words. Audiogenic seizures, VTA, dopamine, rats.

Introduction.

Deep brain stimulation (DBS), applying electrical stimulation to deep brain structures, has now provided an effective therapeutic option for treatment of various neurological disorders [1]. However, the mechanism underlying the beneficial effects of DBS remains poorly understood and is still under debate: Does DBS inhibit or excite local neuronal elements? [2]. Although the exact mechanisms of action of DBS are still elusive in spite of extensive research, several theories have been put forward. These proposed mechanisms can be divided according to the latency of onset of the effects from the time of stimulation into acute (seconds to hours) and chronic (days to months). Electrophysiological and neurotransmitter modulation likely explain the acute effects whereas plasticity and neurogenesis may explain the chronic effects [3].

Stimulation of many deep brain structures were tested as influences potentially capable of blocking seizure attacks in humans and experimentally evoked epileptiform discharges in animals.

The audiogenic seizure (AGS) model is one of several experimental models [4,5] used to study epilepsy and identify underlying mechanisms. AGS animal subjects can display generalized clonic or tonic-clonic seizure activity (formerly known as grand mal seizures) in response to intense sound stimulation [6].

The progression of audiogenic seizures is strain-specific and can be divided into several phases: wild running, clonus, and tonus. AGS-susceptible subjects will also display characteristic post-ictal behaviors. The initiation and propagation of AGS activity relies upon hyperexcitability in the auditory system, particularly the inferior colliculus (IC) where bilateral lesions abolish AGS [4,7].

Another important modulatory structure in the AGS network is the superior colliculus (SC). The role of SC in AGS progression is supported by incomplete attenuation of AGS by midcollicular knife cuts [8] or SC lesions [9]. There are direct descending projections from the SC and CI to the pontine reticular formation and pontomedullary reticular formation and to the medullary parvicellular reticular formation, i.e. to those areas of the brainstem that are involved in the implementation of the animal's behavioral convulsive reactions [10]. The inferior/superior colliculus and the reticular formation motor areas have a crucial importance in audiogenic seizure development. During audiogenic seizure reactions epileptogenic locus appears to be in the brain stem [7,8].

Dopamine plays an important role in epileptogenesis [11-17] and dopaminergic neurons of ventral tegmental area have extensive connections with many brain structures [18-23]. Despite of this there are no data on the influence of this structure on the audiogenic seizure responses of the brain.

The main aim of our study was to investigate the influence of the ventral tegmental area on the development of audiogenic seizure reactions in genetically epilepsy-prone rats. At the same time, we`ll use genetically epilepsy-prone rats of Krushinski-Molodkina (KM) line which develop behavioral seizure reactions to a sound stimulus [5].

The novelty of these article lies not only in the observation of changes in the development/course of audiogenic seizure reactions caused by stimulation of the VTA, but also in taking into account the localization of the epileptogenic focus (brainstem), which, in our opinion, is especially important for the scientific analysis of this type of research. There is no doubt that when conducting such research, it is necessary to take into account the type of epilepsy, the localization of the epileptic focus, etc. Often this approach is not given due attention.

Methods.

Animals:

The male epilepsy-prone of KM line male rats with a body weight of 200-250 g will be used in experiments. Housing of, surgical manipulations with, and euthanasia of the animals were carried out in accordance with the rules and standards accepted by the scientific community of the European Union, legislation of Georgia, and the Committee on the care and use of animals in the Center of Life Sciences of Georgia (20.11.2019). Instructions of the administration of the National Institutes of Health (Bethesda, USA) on the care and use of laboratory animals (NIH Publication No. 88-2959) were also taken into account [24].

Surgery:

The animals (n = 12) were anesthetized by sodium pentobarbital (40 mg/kg, i.p.). Bipolar stimulating electrodes (stainless steel) were

stereotaxically [25] implanted in the VTA - P – (-5), L – (1), H – (8). The experiments were conducted at least 12 - 14 days after surgical intervention.

Audiogenic seizures:

Genetically epilepsy prone KM rats were placed in the audiogenic stimulation chamber (60x60x60 cm plexiglass box). In response to a high pitch sound stimulus presented (bell - 110dB, during 60 sec) the rats developed seizure reactions. Motor components of seizure activity were estimated by a slightly modified Jobe [26] scale: 0—fear reaction; 1—facial muscle clonus; 2—head tremble, jaw myoclonus; 3—wild run, forepaw myoclonus; 4—myoclonus of fore- and hindpaws, fall on a side; 5—clonus of the fourpaws, skeletal muscle rigidity, ataxia, asphyxia.

The wild running phase itself may consist of one or two distinct running bouts, and is typically considered to be part of the seizure progression. In experiments we used animals that in response to sound stimulation developed two wild running reaction.

VTA was stimulated with current pulses of 100-120 μA, with a duration of 0.5 msec and a frequency of 50-80 Hz. The influence of 8-10 minutes prior to VTA stimulation on the audiogenic seizure reactions was investigated. The VTA was stimulated immediately after the end of the sound stimulation.

After the end of the experiment, the animals were deeply anesthetized. Sites of localization of the tip of the VTA electrode were coagulated (constant current 2 to 3 mA was passed during 1 min). The brain was taken off and fixed in a 4% paraformaldehyde solution on phosphate buffer. Localization of the electrode tips was verified in frontal slices.

Data Analysis.

Differences between behavioral parameters measured before and after VTA stimulation in the same animals were analyzed using a paired t-test. Differences between independent groups (where applicable) were evaluated using an unpaired t-test or factorial ANOVA. Data are presented as mean ± SD. Statistical significance was set at $p < 0.05$.

Results.

Recently it was shown by us that combined stimulation of hippocampus and dorsomedial hypothalamus (the structure whose activation causes reactions of fear, anxiety and theta rhythm of the hippocampus) resulted in suppression of the electroencephalographic and behavioral seizure reaction induced by stimulation of the hippocampus [27].

It should be noted here that the VTA dopaminergic system, which is involved in the regulation of hippocampal theta rhythm and emotional responses, should trigger the activation of mechanisms that are characterized by anticonvulsant activity. In other words, it can be assumed that the VTA is involved in blocking seizure reactions of limbic origin [27*].

Therefore, we investigated the effect of VTA stimulation on seizure activity when the epileptogenic focus is located in the brainstem. In animal models of audiogenic epilepsy, we studied the variability of seizure activity before and after stimulation of the VTA.

The inferior colliculus (IC) has been implicated as a critical structure in audiogenic seizure susceptibility. Based on cell types and architecture, the IC is usually divided into the central nucleus, dorsal cortex and external cortex [28]. Bilateral lesions of IC abolish AGS permanently [29]. The AGS efferent pathway may divide at the level of the IC into direct and modulatory courses, both of which terminate in the reticular formation (RF) as the last likely requisite supra-spinal structure mediating AGS expression. The IC has prominent descending projections to several areas of the reticular formation, including the pontine nucleus, the ventrolateral tegmental nucleus, the gigantocellular reticular nucleus, and the lateral paragigantocellular nucleus, which may subserve the direct AGS efferent pathway.

As noted above, another important modulatory structure in the AGS network is the superior colliculus (SC). The role of SC in AGS progression is supported by incomplete attenuation of AGS by midcollicular knife cuts or SC lesions [9]. There are direct descending projections from the SC to the pontine reticular formation and pontomedullary reticular formation and to the medullary parvicellular reticular formation. Focal microinjections of picrotoxin (a noncompetitive GABA-A receptor antagonist) into the deep layers of superior colliculus in rats produce explosive wild running behavior. Focal SC microinjection of bicuculline into normal rats produces spontaneous seizure activity.

In response to sound stimulation, the duration of the latent period of the first wild run, the duration of the first wild run, the duration of the pause between the first and second wild runs, the duration of the second wild run, and the duration of behavioral convulsive reactions were assessed. In animal models of audiogenic epilepsy, we studied the change in audiogenic seizure activity before and after VTA stimulation (Figure 1). In fact, the first wild run has been described in the literature as a false start of AGS progression. The latency period of wild running

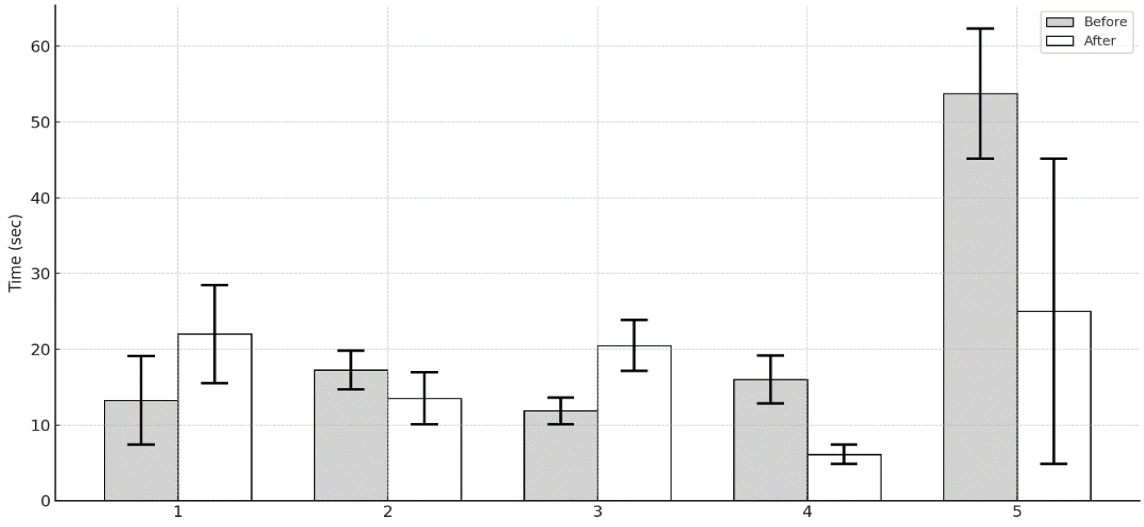

Figure 1. *Changes in the latencies of the first wild run (1), the duration of the first wild run (2), the duration of the pause between the first and second wild runs (3), the duration of the second wild run (4) and in the behavioral reactions of seizures (5) in response to sound before and after VTA stimulation. Ordinate: time in sec. Data are presented as mean ± SD. Statistical significance was set at $p < 0.05$.*

in response to acoustic stimuli ranges from 5–6 to 20–30 seconds.

In spite of the fact that the wild run, which is an integral component of subsequent audiogenic behavioral seizure development, nothing is known about the importance of the pause between the wild run and its alteration at different functional states of the brain.

The experiments conducted showed that in response to stimulation of the VTA, the latency and duration of the first wild run do not undergo significant changes. The experiments showed a significant increase in the duration of the pause between the first and second wild runs and a significant decrease in the duration of the second wild run. Furthermore, we observed a significant decrease in behavioral seizure activity after the second wild run, leading to its complete disappearance. Of the 12 animals, 5 (41.5%) showed the complete blocking of behavioral seizures in response to sound after VTA stimulation.

We have previously shown in epilepsy-prone KM line rats, that during pregnancy there is an increase in the silence period between wild running and a significant blocking of behavioral convulsive reactions to sound stimulation. We then hypothesized that during pregnancy, possible endogenous inhibitory mechanisms are enhanced and, as a consequence, behavioral seizure reactions are inhibited [30].

It was shown that cramps occurred less frequently if the interruption occurred near or during the second wild run [31] suggesting that the second phase of wild running is more closely associated with cramps than the first phase of wild running. It has been theoretically assumed that the period of inactivity separating the phases of wild running represents a form of inhibition [32].

Our data more clearly confirm the involvement of inhibitory processes during the pause between wild runs.

Discussion.

What are the possible mechanisms underlying the inhibition of seizure reactions in response to VTA stimulation?

It is suggested that the VTA plays an important role in epileptogenesis, which is apparently associated with the inhibitory effect of dopamine on the motor manifestations of seizures. L-DOPA injections have been shown to suppress audiogenic seizures in DBA/2J mice [33]. At the same time, injection of Ro 4-1284 (benzoquinolizine), which depletes brain dopamine, results in a marked increase in severity of seizure activity in genetically epilepsy-prone rats [27].

Several studies indicate a possible abnormality in the firing pattern of dopaminergic neurons after epilepsy. Specifically, elevated dopamine levels [34] and increased firing of dopaminergic neurons have been found in rodent models of temporal lobe epilepsy [35]. VTA dopamine neurons have been shown to produce more phasic activity and more dopamine during epilepsy [36,37]. Interesting results were obtained in rats with pilocarpine-induced seizures. It was shown that 60% of rats in which pilocarpine induced seizure activity showed a significant increase in the number of dopaminergic neurons [38].

The ventral tegmental area is best known for its powerful dopaminergic projections to other brainstem regions, which are crucial structures for motor control. This structure is primarily the superior colliculus [39,40]. As noted above, there are direct descending projections from the SC to those areas of the brainstem that are involved in the implementation of the animal's behavioral convulsive reactions. Therefore, it can be assumed that the synaptic circuits between the VTA and the SC play an important role in blocking behavioral seizures during VTA stimulation, not to mention those descending pathways of the CI that also activate the reticular nuclei of the brainstem involved in motor activity during seizure reactions.

The ventral tegmental area is best known for its robust dopaminergic projections to forebrain regions. However, the VTA is not only made of dopaminergic cells, as approximately 30% of cells in the VTA are GABA-ergic (gamma-aminobutyric acid) neurons. These neurons play a dual role, as GABA neurons provide both local inhibition of dopaminergic neurons and long-range inhibition of several distal brain regions. There is clear evidence that GABA-ergic neurons of the ventral tegmental area inhibit dopaminergic neurons of the VTA, although the precise organization of this inhibition remains unclear [41].

GABA neurons of the VTA receive inhibitory, excitatory, and neuromodulatory inputs from throughout the brain [42]. In turn, GABA-ergic neurons of ventral tegmental area project to many structures of the forebrain [43]. The role of GABAergic neurons of the VTA in the epileptogenesis remains unclear.

It is particularly noteworthy that the role of dopamine-sensitive structures that receive synaptic inputs from the ventral tegmental area in audiogenic seizure responses remains unexplored. One such structure is the reticular nucleus of the thalamus (TRN). TRN receives a quite a lot of modulatory inputs, including dopaminergic inputs from the ventral tegmental area, substantia nigra pars compacts, and retrorubral field [44-46].

Among subcortical structures, GABAergic neurons of the TRN have one of the highest densities of D4 dopamine receptors. The unitary electrical activity of TRN neurons was recorded in vivo in Wistar rat. It has been shown that: a) the presence of a tonic dopaminergic effect on neurons; b) local activation of D4 receptors increases the basal firing rate TRN neurons. Altogether these results support that dopamine promotes spontaneous basal activation of NRT neurons via dopamine D4 receptors [47].

The TRN receives dopaminergic innervation from the midbrain and is known to express high concentrations of dopaminergic receptors D1, D2, and D4. Furthermore, selective interaction with dopaminergic receptors has been shown to have significant potential for modulating TRN function [48].

It was shown, that the activation of dopamine D4 receptors modulates GABA release in slices of the rat thalamic reticular nucleus. Given the importance of the NRT in the control of attention, sensory processing it is possible that abnormal NRT function may generate some of the manifestations of the disorders of dopaminergic transmission [49].

It is assumed that the suppression of audiogenic seizure reactions by activation of dopaminergic neurons is obviously also carried out by neurons of the reticular nucleus of the thalamus.

The question arises how the blocking of audiogenic convulsive reactions is carried out by the neurons NRT?

It is known that in cats, a single stimulation of the dorsal root, in addition to segmental reactions (mono- and polysynaptic), in the corresponding ventral root causes the occurrence of late reflex discharges, which reflect the activation of the spino-bulbo-spinal system (SBSS) [50].

It was shown that rhythmic stimulation of the TRN suppressed of spino-bulbo-spinal responses of the spinal cord, i.e. neurons of the bulbar reticular formation are inhibited (Figure 2) [51].

In our previous work [52], it was demonstrated that stimulation of the thalamic reticular nucleus causes inhibition of the activity of neurons of the mesencephalic reticular formation (Figure 3), which in turn facilitates late reflex discharges of the spinal cord, i.e. facilitates the activity of neurons of the bulbar reticular formation. It was assumed that the influence of the RRT on the SBSS is carried out by activating the inhibitory area of the reticular formation of the brainstem.

Therefore, it can be hypothesized that the TRN modulate the brainstem regions responsible for motor responses during audiogenic seizures.

Conclusion.

From our results we can conclude: 1) the VTA plays an important role in epileptogenesis, which is apparently associated with the inhibitory effect of dopamine on the motor manifestations of seizures. Therefore, VTA as a brain dopaminergic nucleus, may be a suitable target for DBS anticonvulsant action. 2) functional relationships between VTA and IC/SC play an important role in blocking behavioral seizures

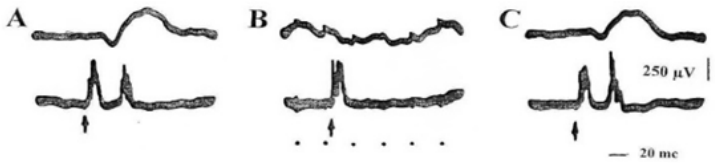

Figure 2. *The effect of stimulation of the thalamic reticular nucleus on spinal cord responses. A, B, C - evoked potential of the sensorimotor cortex (upper trace) and reflex responses of the ventral root to stimulation of the dorsal root (bottom trace). The arrow indicates the moment of stimulation of the dorsal root, and the dots indicate stimulation of the thalamic reticular nucleus. (From the article by Nanobashvili Z. and Khizanishvili N.1982).*

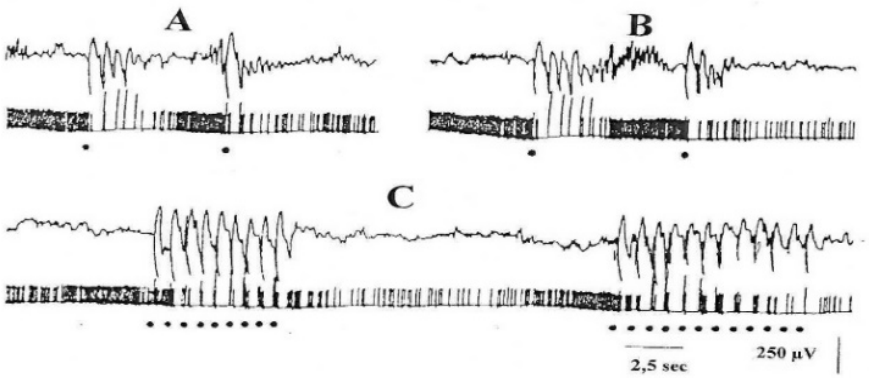

Figure 3. *The effect of stimulation of the thalamic reticular nucleus on the activity of a neuron in the brainstem reticular formation (bottom trace). The top trace is an electrocorticogram. Neuron activity was recorded using a trigger. The dots indicate the moments of stimulation (80 μA, 0.5 ms) of the thalamic reticular nucleus. (From the article by Nanobashvili Z. and Khizanishvili N. 1986).*

during VTA stimulation, 3) the NRT exerts its modulating influence on almost all areas of the brainstem that are responsible for motor reactions during audiogenic seizures.

Future Research Prospects.

To clarify the mechanisms by which audiogenic seizures are blocked during stimulation of the VTA, the following questions will be further studied: 1. Which neurotransmitters of the ventral tegmental area (VTA) neurons (dopamine or GABA, or both) play a crucial role in blocking audiogenic seizures; 2. To elucidate the possible role of potentiation of VTA neurons in blocking seizure reactions.

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Conflict of interest.

The authors have no conflict of interests to declare.

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Audiogenic Seizure Suppression by Ventral Tegmental Area Stimulation

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RESUME

The audiogenic seizure (AGS) model is one of several experimental models used to study epilepsy and identify underlying mechanisms. Dopamine plays an important role in epileptogenesis and dopaminergic neurons of ventral tegmental area (VTA) have extensive connections with many brain structures. Despite of this there are no data on the influence of this structure on the audiogenic seizure responses of the brain. The main aim of our study was to investigate the influence of the VTA on the development of audiogenic seizure reactions in genetically epilepsy-prone rats. The novelty of these article lies not only in the observation of changes in the development/course of audiogenic seizure reactions caused by stimulation of the VTA, but also in taking into account the localization of the epileptogenic focus, which, in our opinion, is especially important for the scientific analysis of this type of research. The male epilepsy-prone of KM line male rats (n=12) with a body weight of 200-250 g will be used in experiments. In response to a high pitch sound stimulus presented (bell - 110dB, during 60 sec) the rats developed seizure reactions. VTA was stimulated with current pulses of 100-120 μA, with a duration of 0.5 msec and a frequency of 50-80 Hz, for 8-10 min. The influence of such VTA stimulation on the generalized seizure reactions was investigated. It is suggested that the VTA plays an important role in epileptogenesis, which is apparently associated with the inhibitory effect of dopamine on the motor manifestations of seizures. Therefore, VTA as a brain dopaminergic nucleus, may be a suitable target for anticonvulsant action.

Keywords: Audiogenic seizures, VTA, dopamine, rats.

Аудиогенные судороги подавляются стимуляцией вентральной тегментальной области

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РЕЗЮМЕ

Модель аудиогенных припадков один из экспериментальных моделей, используемых для изучения эпилепсии и выявления её механизмов. Дофамин играет важную роль в эпилептогенезе, а дофаминергические нейроны вентральной области покрышки (ВОП) имеют обширные связи со многими структурами мозга. Несмотря на это, данные о влиянии этой структуры на аудиогенные судорожные реакции мозга отсутствуют. Основной целью нашего исследования было изучение влияния вентральной области покрышки (ВОП) на развитие аудиогенных судорожных реакций у крыс, генетически предрасположенных к эпилепсии. Новизна данной работы заключается не только в наблюдении изменений в развитии/течении аудиогенных судорожных реакций, вызванных стимуляцией ВОП, но и с учетом локализаций эпилептогенного очага, что, по нашему мнению, особенно важно для научного анализа данного типа исследований. В экспериментах использовались самцы крыс линии КМ (n=12), массой тела 200–250 г. В ответ на предъявление сильного звукового стимула (звонок – 110 дБ, длительностью 60 с) у крыс развивались судорожные реакции. Стимуляцию вентральной области покрышки осуществляли импульсами тока силой 100–120 мкА, длительностью 0,5 мс и частотой 50–80 Гц в течение 8–10 мин. Исследовано влияние стимуляции вентральной области тегментума на генерализованные судорожные реакции. Предполагается, что вентральная область тегментума играет важную роль в эпилептогенезе, что, по-видимому, связано с ингибирующим влиянием дофамина на двигательные проявления судорог. Следовательно, вентральная область тегментума, как дофаминергическое ядро мозга, может быть подходящей мишенью для противосудорожного действия при стимуляции глубоких структур головного мозга.

Ключевые слова: аудиогенные припадки, ВОП, дофамин, крысы.

udiogenuri krunCxvebis blokireba ventraluri tegmentumis ubnis gaRizianebis sapasuxod

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eziume

audiogenuri krunCxvebis (ak) cxoveluri modeli erT-erTia im eqsperimentuli modelebidan, romelic gamoiyeneba epileptogenezis Sesaswavlad da ZiriTadi meqanizmebis dasadgenad. Dofamini mniSvnelovan rols asrulebs epileptogenezSi da ventraluri tegmentaluri ubnis (vtu) dofaminergul neironebs farTo kavSirebi aqvT tvinis mraval struqturasTan. Mmiuxedavad aRniSnulisa, mwiria monacemebi am struqturis gavlenis Sesaxeb audiogenuri krunCxviTi reaqciebis mimdinareobaze. Cveni kvlevis mTavari mizani iyo genetikurad epilefsiisadmi determinirebuli – kruSinski-molodkinas (km) xazis virTagvebis audiogenuri kruCxviTi reaqciebis mimdinareobaze vtu-s gavlenis Seswavla. naSromis siaxle mdgomareobs ara mxolod vtu-s ctimulaciiT gamowveuli krunCxviTi reaqciebis ganviTarebze dakvirvebaSi, aramed epileptogenuri keris gaTvaliswinebaSic, rac Cveni azriT, gansakuTrebiT mniSvnelovania am tipis kvlevis mecnieruli analizisaTvis. eqsperimentebSi gamoyenebuli iyo km-is xazis mamri virTagvebi (n=12) woniT 200-250 gr. bgeriTi stimulebisaTvis gamoyenebuli iyo standartuli kedlis zari (90-100 db, 60 wamis ganmavlobaSi). vtu stimulirebuli iyo 100-120 mka denis impulsebiT, 0,5 mwm xangrZliobiT, 50-60 hc sixSiriT, 8-10 wuTis ganmavlobaSi.

gamoirkva, rom vtu mniSvnelovan rols asrulebs epileptogenezSi, rac rogorc Cans, dakavSirebulia dofaminis damTrgunvel efeqtTan krunCxviTi reaqciebis motorul gamovlinebebze. Sesabamisad, vtu rogorc tvinis dofaminerguli ubani SeiZleba iyos Sesaferisi samizne antikonvulsiuri mo□medebisaTvis.

sakvanZo sityvebi: audiogenuri krunCxvebi, vtu, dofamini, virTagva.