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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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INFLUENCE OF LONG-TERM VIBRATION ON THE ACTIVITY OF THE SUPERIOR VESTIBULAR NUCLEUS NEURONS UNDER THE CONDITIONS OF STIMULATION OF THE HYPOTHALAMUS NUCLEI

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Abstract.

Prolonged vibration exposure leads to alterations of the central control mechanisms of both the vestibulo-ocular and the vestibulo-autonomic systems, including a change in the hypothalamic-vestibular relationships associated, in particular, with the supraoptic nucleus and paraventricular nucleus. Post-vibration disturbances of the vestibular function are largely due to adaptive changes in neurotransmitter activity. The dynamics of spike activity of single neurons of the superior vestibular nucleus (SVN) in response to high-frequency stimulation of the paraventricular and supraoptic hypothalamic nuclei after long-term vibration exposure were analyzed. Analysis of impulse activity revealed the prevalence of tetanic potentiation in the responses of SVN neurons to high-frequency stimulation of paraventricular and supraoptic nuclei of rats. Exposure of animals to vibration led to a decrease in the number of neurons with tetanic potentiations and significant dominance of post-tetanic potentiation. Morphological and histochemical results showed that under hypothalamic stimulation in the SVN neurons of rats exposed to vibration, there is an increase in metabolism and dephosphorylation processes in the cellular structures of the studied brain area, which ultimately provides optimal conditions for the processes of cell survival and regeneration.

Key words. Superior vestibular nucleus, vibration, single neuronal activity, tetanic stimulation.

Introduction.

The vestibular system is a substrate for the interaction of numerous afferent and efferent pathways that connect them with the cortex and a number of subcortical structures [1]. The converging vestibular, visual, and somatosensory afferents have been observed at the level of the vestibular nuclei [2,3].

Vibration disease can occur even with weak vibration exposure (VE), affecting the nervous, cardiovascular, and motor systems. Prolonged VE leads to vestibular system disorders, manifested in the form of subjective complaints of dizziness, impaired coordination of movements, etc. [4]. VE leads to alterations of the central control mechanisms of both the vestibulo-ocular and the vestibulo-autonomic systems, including a change in the hypothalamic-vestibular relationships associated with the supraoptic nucleus (SON) and paraventricular nucleus (PVN). Moreover, hypothalamic neuropeptides can act as pathogenic modulators of the disorders of the hypothalamic-vestibular connection.

Projections from the vestibular nucleus (VN) to the PVN and SON have been described suggesting that this pathway is likely polysynaptic [5]. These results provide morphological evidence for the existence of a vestibular stress pathway in rat brain and support the view that the HPA axis is modulated by vestibular stress [6]. In addition, the responses of PVN neurons induced by vestibular stimuli also suggest a pathway from the VN to the PVN [7]. Vestibular stimuli will increase the expression of arginine vasopressin in the PVN [8] and its secretion into the blood [9,10]. Correction of the functions based on the use of endogenous neurohumoral peptides may serve as a fundamentally new approach to address the problem of regulating the activity of the CNS in pathology.

In the present work, the VE model was used to study the parameters of the impulse activity of SVN neurons caused by the stimulation of the PVN and SON. Morphological and histochemical studies were performed to support the results of the electrophysiological studies.

Materials and methods.

Animals:

The work was performed using albino rats (mean weight 250 ± 30 g) from the vivarium of L.A. Orbeli Institute of Physiology NAS RA, which were kept under standard vivarium conditions.

Electrophysiology:

Plasticity of the hypothalamic-vestibular connections was studied by analyzing the spike activity of single neurons of the SVN in conditions of high-frequency stimulation (HFS) of PVN and SON in rats. Animals were divided into two groups (n=6 per group): naive rats that served as a control group and rats that were exposed to vibration (15 days, 2 hours/day, on a vibrating stand (frequency 60 Hz, vibration amplitude 0.4 mm).

In acute electrophysiology experiments animals were immobilized with 1% dithylin (25 mg/kg, i.p.) with artificial respiration being performed. After fixing the skull in the stereotaxic apparatus, an isolated brain area was obtained by dorsal laminectomy and spinal cord transection (T2-T3) under local Novocain anesthesia. Bipolar concentric electrodes with a tip diameter of 30 μm were used to stimulate the PVN and SON. The distance between the electrodes was between 0.5-0.8 mm. The parameters of electrical stimulation were as follows: rectangular current, pulse duration 0.05 msec, amplitude 0.12 - 0.18 mV, frequency 100 Hz, duration 1 sec. A glass microelectrode with a width of the tip of 1-2 μm, filled with 2M NaCl solution, was inserted into the SVN to record the impulse activity of single neurons as a response to the HFS of the PVN and SON from the ipsi- (i) and contralateral (c) sides.

Recording and stimulating electrodes were inserted into rat brain (the right side - ipsilateral and left side - contralateral) according to the stereotaxic coordinates [11] SON (AP- 1.3, ML ± 1.8, DV + 9.4 mm); PVN (AP -1.8, ML ± 0.6, DV + 7.6 mm), and SVN (AP-11.5, ML ± 2.5, DV + 6.4 mm). The analysis of spike activity revealed the acceleration of impulse

flow during HFS (tetanic potentiation, TP) and post-stimulus time (post-tetanic potentiation, PTP), as well as the deceleration of the impulse flow during HFS (tetanic depression, TD) and post-stimulus time (post-tetanic depression, PTD). Different combinations of responses, such as TP-PTP, TP-PTD, TD-PTD, TD-PTP were recorded. In each experimental group, the relative contribution of excitatory or inhibitory responses was calculated as a percentage share of the analyzed neurons with the corresponding type of response. The intensity levels of these responses were estimated based on the mean levels of the spike activity frequencies before stimulation (Mbs), after stimulation (Mps), in the course of HFS (Mhfs) in real time. The intensity levels of TP, PTP, TD and PTD were calculated as: TP = Mhfs/Mbs; PTP = Mps/Mbs; TD = Mbs/Mhfs; PTD = Mbs/Mps, respectively.

Histochemistry:

To obtain the brains for histochemical analysis, the animals were lethally anesthetized by intraperitoneal injection of sodium pentobarbital (60 mg/kg body weight), brains were extracted and fixed for 2-3 days in 5.0 % paraformaldehyde in 0.1 M phosphate-buffered saline (PBS), pH 7.4. Then the tissue was cut into 40-50 μm-thick frontal sections using a cryostat and processed using a method for detecting the activity of Ca^{2+}-dependent acid phosphatase (AP) [12]. The frontal slices were washed in distilled water and transferred into an incubation mixture containing 0.4% lead acetate, 1 M acetate buffer (pH 5.6), and 2% sodium glycerophosphate for 2–3 h at 37° C. After incubation, the slices were washed in distilled water. Since they are translucent, the slices were transferred to 3% sodium sulfide solution for visualization, rewashed in distilled water and embedded into Canada balsam, a commonly used mounting medium, to prepare permanent slides. This methodological approach is based on the identification of intracellular phosphorus-containing compounds that occupy key positions in metabolic energy processes aimed at the preservation and self-reproduction of the vital systems. When AP activity is tested, the phosphate ions released under the action of the enzyme can freely move in the mixture and react with different structures, regardless of their spatial arrangement, and after incubation in the solution of sodium sulfide it turns into a visible dark brown precipitate of lead sulfide.

Statistical analysis:

The significance of the changes in the duration of interspike intervals before and after stimulation was assessed using a nonparametric criterion for the homogeneity of two independent samples by the Wilcoxon-Mann-Whitney two-sample criterion. The statistical analysis of the results was carried out using the variation statistical Student's t-test. The results are presented as mean ± SEM. The shape of the sliding frequency graphs was used to assess the stationary process of the background impulse activity using the non-parametric Kolmogorov–Smirnov criterion [13]. The comparison of critical values with tabular values of the normal distribution at significance levels of 0.05, 0.01, and 0.001 (for various tests) shows that, as a result of the HFS, for most neural activity spiking samples, there is a statistically significant change with at least a significance level of 0.05.

Results.

Electrophysiological study:

The character of the changes of 98 SVN neurons of intact animals to HFS of the PVN and SON was analyzed. Among them 44 neuron activities were recorded in the right-side (ipsilateral) and 54 in the left-side (contralateral) of the SVN. From all recorded neurons, 13.6 ± 5.4% showed no response to the stimulation of the PVN and 16.7% ± 4.5% were nonreactive to the stimulation of the SON.

Amongst all reactive neurons (n=38) of the right-side SVN stimulated by the contralateral PVN (c-PVN) and ipsilateral SON (i-SON), only 21.0 ± 2.0% demonstrated monomodal character; the other recorded units that responded to HFS of both hypothalamic nuclei showed bimodal characteristics. Responses of the majority of bimodal neurons (71.0 ± 5.5%) were unidirectional while multidirectional reactions were present only in 8.0 ± 3.0% of the cells (Figure 1, white bars).

Analysis of the reactive neurons (n=54) on the left side SVN to the stimulation of the ipsilateral-PVN (i-PVN) and contralateral-SON (c-SON) revealed the presence of 35.6%±3.6% of monomodal neurons, 62.2 ± 3.2% of bimodal neurons with unidirectional reaction and around 2% were bimodal neurons with unidirectional responses (Figure 1, black bars).

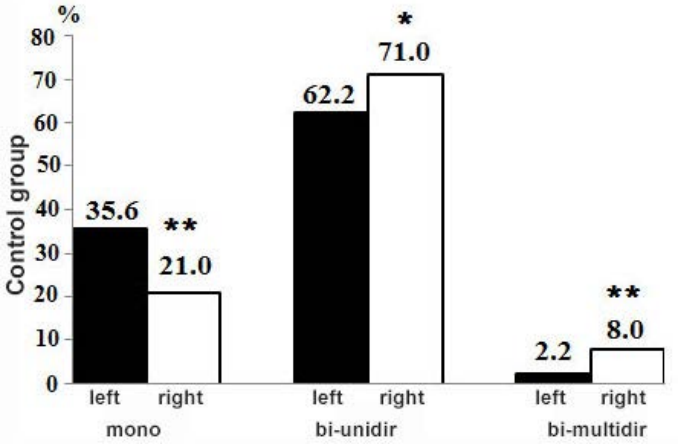

Figure 1. *Reactions of the neurons in the left-sided (black bars) and right-sided (white bars) SVN to the stimulation of the hypothalamic nuclei in the control group: monomodal neurons (mono), bimodal neurons with unidirectional reactions (bi-unidir), bimodal neurons with multidirectional (bi-multidir) responses. * — $p < 0.05$, ** — $p < 0.01$ (Student's t-test).*

Analysis of the character of the right-side SVN neuronal response to the HFS revealed a high percentage of tetanic potentiation (TP) upon stimulation of the ipsilateral-SON (i-SON) (89.5 ± 9.9%) and the contralateral-PVN (c-PVN) (84.2 ± 5.8%), as well as post-tetanic potentiation (PTP) which together (TP + PTP) amounted up to 23.7 ± 0.8%, and 3.2 ± 0.2%, respectively (not shown in Figure 2). In neurons of the left-side SVN, the percentage of TP during stimulation of c-SON was 77.8 ± 4.4%, i-PVN — 84.4 ± 1.9%, and TP + PTP — 22.2 ± 0.6% and 20.0 ± 0.7%, respectively (not shown in Figure 2). In the control group animals, tetanic depression (TD) was recorded only after HFS of the PVN and amounted to 5.2 ± 0.32% for c-PVN and 2.2 ± 0.13% for i-PVN, respectively (Figure 2a).

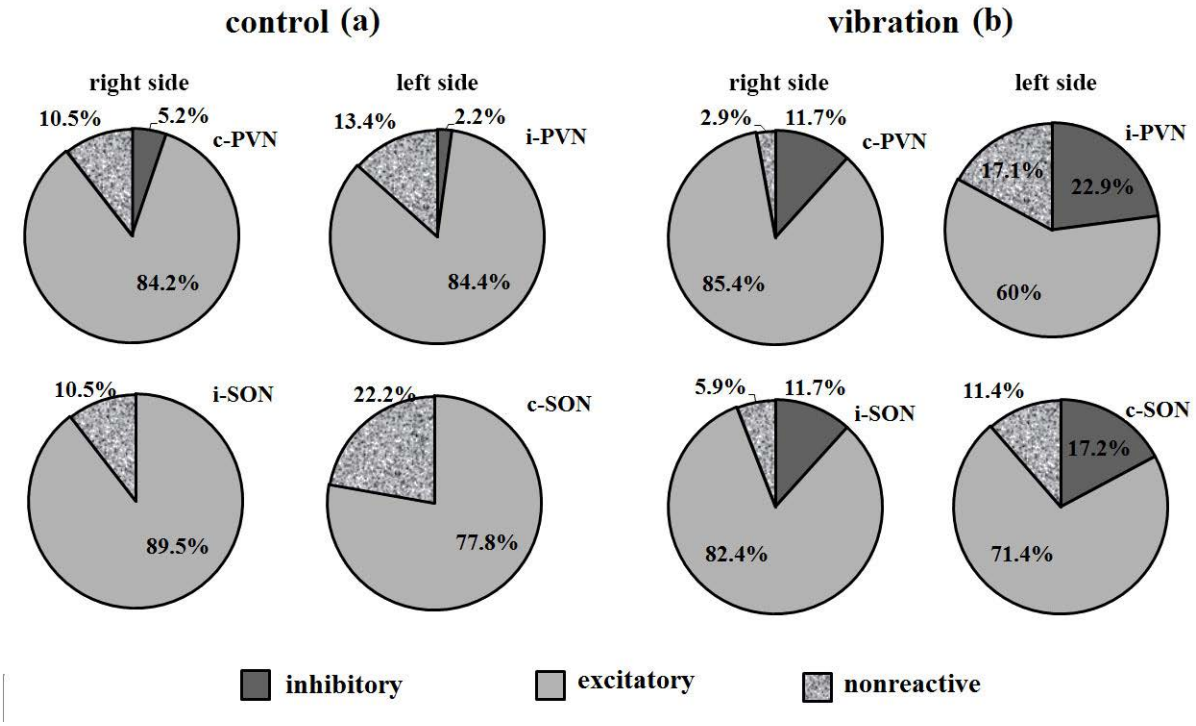

Figure 2. *The percent of inhibitory, excitatory, and non-reactive neurons in the right- and left-sided SVN to HFS of the hypothalamic nuclei of intact control animals (a) and after exposure to long-term vibration (b). i-PVN – is ipsilateral PVN relative to the recording electrode side, c-PVN - is contralateral PVN relative to the recording electrode side, the same as i-SON and c-SON. Inhibitory -TD, TD+PTD, TD+PTP; excitatory –TP, TP+PTP.*

After exposure to vibration for 15 days, 80 SVN neurons were examined: 42 on the right side and 38 on the left side, from which 2.9 ± 0.14% and 5.9 ± 0.25% (c-PVN and i-SON), 17.1 ± 0.45% and 11.4 ± 1.1% neurons (i-PVN and c-SON), were nonreactive to hypothalamic stimulation, respectively (Figure 2).

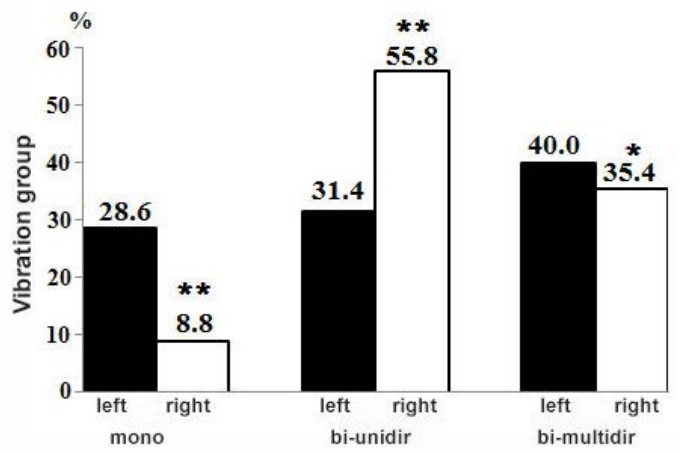

Figure 3. *Reactions of the neurons in the left-sided (black bars) and right sided (white bars) SVN to the stimulation of the hypothalamic nuclei in the group of animals with vibration exposure: monomodal neurons (mono), bimodal neurons with unidirectional reactions (bi-unidir), bimodal neurons with multidirectional (bi-multidir) responses. * p <0.05, ** p <0.01 (Student's t-test).*

Analysis of the character of the neuronal response of the right side of the SVN to the c-PVN HFS after long term VE revealed decrease in monomodal units. The bimodal neurons with unidirectional reactions were represented by 55.8±5.1% of the cells, 35.4±10.8% of the cells were multidirectional and 8.8 ± 0.6 % were monomodal (Figure 3, white columns). On the left side the bimodal neurons with unidirectional reactions comprised 31.4 ± 0.2%, whereas 40.0 ± 1.4% of the cells had multidirectional reactions and 28.6% were monomodal. (Figure 3, black bars).

The proportion of the right side SVN neurons with TP, PTP and TP + PTP reaction (excitatory) to c-PVN stimulation after long term VE was 85.4 ± 1.3% (in total); whereas stimulation of i-SON revealed excitatory responses up to 82.4 ± 1.1% (in total) in the right side SVN (Figure 2b).

Compared with controls, a high percentage of TD reactions was revealed for stimulation both of PVN and SON. An equal number of neurons (11.7 ± 0.9%) responded with depressive effect to the HFS of the c-PVN and i-SON in the right side SVN: TD – 11.7 ± 0.8% and TD + PTD - 2.9%. The number of PTD responses were relatively high in the left side SVN: i-PVN - 22.9 ± 0.9% (TD - 8.6%, TD + PTP - 14.3%), c-SON - 17.2 ± 3.2% (8.6% each, respectively) (Figure 2b).

Histochemical study:

The morphological and histochemical analysis revealed that in the frontal slices of the Varoli's pons of the intact rats the SVN clearly stands out from the lower part of the cerebellar peduncle as a grey mass consisting of non-bundled, medium-sized polygonal cells with high AP activity in the soma and processes (Figure 4a). Their nuclei were round, large, bright,

surrounded by a cytoplasmic border in which the granular precipitate of lead sulfide is distributed evenly, which is formed during the development of sections in a solution of sodium sulfide with cell bodies being stained more intensely than the processes (Figure 4A).

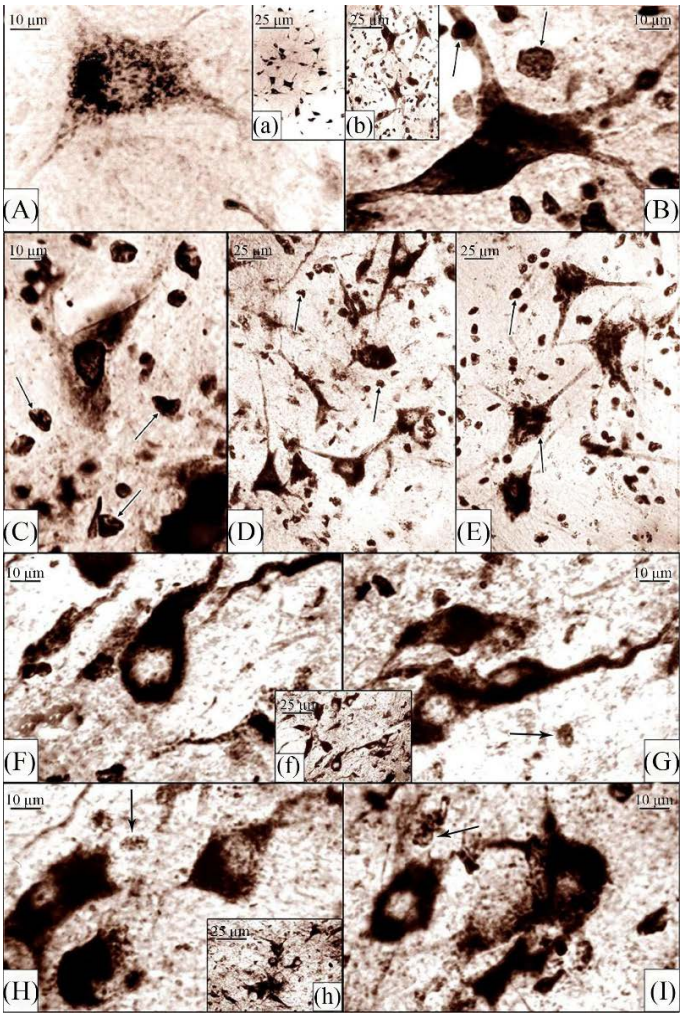

Figure 4. *The neurons of the SVN of control animals. (A, a) and after exposure to vibration (B-I) (the nuclei of the glial cells are shown by the arrows). Results of detection of the activity of Ca+2-dependent acid phosphatase. Magnification: ×400 (a, b, D, E, f, h); ×1000 (A, B, C, F, G, H, I).*

The shape of most neurons was not altered in response to the 15-day vibration, however; intracytoplasmic granulation was enhanced in response to VE (Figure 4B). Processes with rare branches in the given section plane were observed for some neurons at a rather long distance from the body with such a lesion (Figure 4D, E). Often, there were areas where enclosed satellite glial cells were visible in the marginal regions of the cytoplasm and on the processes (Figure 4 B, D, E). The staining intensity was enhanced in the soma of most nerve cells, which gives the impression of a homogeneous color (Figure 4 F, I). A distinct swelling of nerve cells was not observed; however, a disproportionately large swollen nucleus manifested its disturbed state and adaptations to the metabolic changes. Moreover, in most cases, it moved to the periphery of the cell. In very rare cases, there was a sharp increase in AP activity in the nuclei of neurons (Figure 4C), which probably indicates acute activation of nerve cell biochemical reactions [14].

Pathological changes in the nerve cells led to the appearance of a satellite neuroglia reaction, which is very sensitive to the changes in the nervous tissue. The nuclei of neuroglia increased in size, the shape became variable, amoeboid, and granulation appeared in the form of large grains and threads (Figure 4 B-E). The nuclei of neuroglia encompassed all sides of the soma and processes of the nerve cell like nodes (Figure 4F). Chromatin was located on the periphery and, as it were, glued to the nuclear membrane in some nuclei. This might manifest to a protective reaction of glial cells in relation to the neurons, which reflects the existence of close interaction between the neuronal and glial cells as of an integral unit.

The appearance of satellite neuroglia is of great importance in the metabolic processes in the nervous tissue [15]. In response to vibration, neuroglia react by proliferation, probably to clear this area of the cleavage products due to degenerative lesions

Discussion.

The hypothalamus is the highest integrative center of autonomic functions. It operates through numerous reciprocal direct and polysynaptic connections with vegetative centers of the brain, in particularly with the bulbar nuclei and the thoracic segments of the spinal cord. Interestingly, the largest number of labeled cells in the PVN of the hypothalamus and the highest distribution density of the latter were observed on the ipsilateral side (right-side) [16]. At the same time, analysis of our results, under the conditions of persistent reproducible TP reactions in repeated trials, revealed that, responses of SVN neurons to HFS of the PVN and SON are non-significantly higher during stimulation on the ipsilateral side compared to that on the contralateral side (62.2% and 65.8% of cells against 60.5% and 51.1%, respectively, $p<0.08$).

After VE for 15 days, as compared with controls, the intensity levels of SVN neurons with TP were decreased (3.0- and 2.5-fold during the stimulation of the i-PVN and i-SON, and 1.5- and 1.6-fold, during the stimulation of the c-PVN and c-SON, respectively, $p<0.05$). In addition, the number of units with PTP was increased, and the intensity of PTP at i-PVN stimulation raised 13-fold at c-PVN stimulation 3-fold, and at stimulation of c-SON 5-fold ($p<0.05$). No neurons with such response were recorded after HFS of i-SON in control animals. However, they were observed after 15 days of VE and the proportion of such neurons was around 2.4 %.

The disturbance of the vestibular function that occurs in the post-vibration period is largely the result of the changes in neurotransmission activity. As it is known, VE causes multidirectional changes in the activity of norepinephrine and serotonergic systems, the regulation of which is due to increased activity of some or inhibition of other monoaminergic systems [17]. In turn, the activation of the GABAergic system in the vestibular nuclei should be associated with cerebellar inhibitory impulse from Purkinje cells, which is one of the most important mechanisms of neurotransmitter adaptation during vibration [18]. Activation of the cholinergic system of the hypothalamus in the post-vibration period is probably caused

by the stimulating effect of dopaminergic terminals involved in the central regulation of endocrine functions [19]. Although the biochemical nature of the descending projections (containing oxytocin, vasopressin, somatostatin, enkephalin or tyrosine hydroxylase) is heterogeneous [20], immunocytochemical studies in rats showed that the fibers of the caudal hypothalamic pathways of the PVN are predominantly oxytocinergic and only a small fraction of the fibers going to the nucleus as a single bundle contain vasopressin [21,22]. This indicates the inclusion of the central mechanisms of regulation of the hypothalamic-hypophysis-adrenocortical system in response to VE, the main regulator of which is corticoliberin, which is mainly synthesized by neurosecretory cells of the PVN and SON. In contrast, scientists found reciprocal connections between the vestibular nuclei and the hypothalamus in their experiments, suggesting a potential vasopressinergic pathway from the PVN to the vestibular nucleus [23,24]. The restriction of the negative effects of vibration stress is enhanced by the activation of GABAergic interneurons, which form inhibitory synapses on dendrites of cells of hypothalamic nuclei [25]. In addition, the location of the vestibular nucleus that dorsally borders the floor of the fourth cerebral ventricle is convenient for the potential modulation by vasopressin from the cerebrospinal fluid [26]. It is possible that high expressions of vasopressin receptors in the vestibular nucleus contribute to the development of vestibular compensation after vibration.

In the present work, it was found that under hypothalamic stimulation in the SVN neurons of rats exposed to vibration, there is an increase in AP activity testifying to some extent to increased metabolism and to an increase in dephosphorylation processes in the cellular structures of the studied area of the brain. Our results suggest that hypothalamic hormones, acting on the biochemical processes in the brain, regulate Ca2+-dependent AP and enhance its activity in SVN neurons [27]. Glia is known to play an important role in the survival of neurons and is involved in the regulation of the ionic composition of the environment, which is necessary for the physiological function of neurons. It is in some way an intermediary between blood vessels and nerve cells and is also a specific support system. In response to external factors, in this case, vibration exposure, neuroglia responds against pathohistological changes occurring in the nervous parenchyma in the form of reactive proliferative processes. Probably, here there is a manifestation of a protective reaction of glial cells in relation to neurons, which corresponds to modern ideas about the existence of a close interaction between a neuron and a glial cell as an integral unit for a new qualitative differentiation in pathological conditions. Probably, here there is a manifestation of a protective reaction of glial cells in relation to neurons, which corresponds to modern ideas about the existence of a close interaction between a neuron and a glial cell as an integral unit for a new qualitative differentiation in pathological conditions [15].

Evidence from animal studies indicates that the effects of vibration on the central vestibular pathways are important in promoting compensatory synaptic and neuronal plasticity in the vestibular system [28] and these processes are increasingly recognized as important in the management of vestibular dysfunction in humans.

Conclusion.

The analysis of impulse activity revealed the prevalence of tetanic potentiation in the responses of neurons in the SVN to high-frequency stimulation of the PVN and SON in intact animals. Exposure to vibration results in a decrease of the number of neurons with tetanic potentiation and significant dominance of post-tetanic potentiation. Post-vibrational changes in the character of reactions of SVN neurons during tetanic stimulation of hypothalamic SON and PVN are possibly determined by the pre- and postsynaptic character of the inputs to neurons of the hypothalamic nuclei, which might limit the negative effects of vibration.

Author contributions.

DMH, KVK, SSH, NKA, IAS and CVA performed the experiments and data analysis. DMH and KKV provided histological interpretation. DMH, SSH, NKA, ISA and CVA provided advice on data interpretation. DMH, SSH and CVA wrote the manuscript. All of the authors have contributed substantially to the manuscript.

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Availability of data and materials.

Raw data can be provided upon request to the corresponding author.

Declarations.

Competing interests. The authors declare no competing interests.

Conflict of interest. The authors declare no conflict of interest.

Ethical approval and consent to participate.

The experimental protocol corresponded to the conditions of the European Communities Council Directive (2010/63/ UE) and was approved by the Ethics Committee of Yerevan State Medical University after Mkhitar Heratsi (IRB Approval N4, November 15, 2018).

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Влияние длительной вибрации на активность нейронов верхнего вестибулярного ядра в условиях стимуляции ядер гипоталамуса

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Длительное вибрационное воздействие приводит к изменениям центральных механизмов регуляции как вестибуло-окулярной, так и вестибуло-вегетативной систем, в том числе изменению гипоталамо-вестибулярных взаимоотношений, связанных, в частности, с супраоптическим ядром и паравентрикулярным ядром. Поствибрационные нарушения вестибулярной функции во многом обусловлены адаптивными изменениями нейромедиаторной активности. Проанализирована динамика спайковой активности одиночных нейронов верхнего вестибулярного ядра в ответ на высокочастотную стимуляцию паравентрикулярного и супраоптического ядер гипоталамуса после длительного вибрационного воздействия. Анализ импульсной активности выявил преобладание тетанической потенциации в ответах нейронов верхнего вестибулярного ядра на высокочастотную стимуляцию паравентрикулярных и супраоптических ядер в норме. Воздействие вибрации приводило к уменьшению числа нейронов с тетанической потенциацией и значительному преобладанию посттетанической потенциации. Морфологические и гистохимические результаты согласуются с представлением о замкнутом взаимодействии нейронов и глиальных клеток как единого целого и обнаруживают повышение активности кислой фосфатазы.

Ключевые слова: *верхнее вестибулярное ядро, вибрация, одиночная нейрональная активность, тетаническая стимуляция*

გრძელვადიანი ვიბრაციის გავლენა ზემო ვესტიბულური ბირთვის ნეირონების აქტივობაზე ჰიპოთალამუსის ბირთვების სტიმულაციის პირობებში

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ვიბრაციის გახანგრძლივებული ზემოქმედება იწვევს როგორც ვესტიბულო-ოკულარული, ისე ვესტიბულო-ავტონომიური სისტემების ცენტრალური კონტროლის მექანიზმების ცვლილებას, მათ შორის ჰიპოთალამურ-ვესტიბულურ ურთიერთობებში ცვლილებას, რომელიც დაკავშირებულია, კერძოდ, სუპრაოპტიკურ ბირთვთან და პარავენტრიკულურ ბირთვთან. ვესტიბულური ფუნქციის ვიბრაციის შემდგომი დარღვევები დიდწილად განპირობებულია ნეიროტრანსმიტერების აქტივობის ადაპტური ცვლილებებით. გაანალიზებული იყო ზედა ვესტიბულური ბირთვის ცალკეული ნეირონების (SVN) მწვერვალების აქტივობის დინამიკა პარავენტრიკულური და სუპრაოპტიკური ჰიპოთალამუსის ბირთვების მაღალი სიხშირის სტიმულაციის საპასუხოდ ხანგრძლივი ვიბრაციის ექსპოზიციის შემდეგ. იმპულსური აქტივობის ანალიზმა გამოავლინა ტეტანური გაძლიერების პრევალენტობა SVN ნეირონების პასუხებში ვირთხების პარავენტრიკულური და სუპრაოპტიკური ბირთვების მაღალი სიხშირის სტიმულაციაზე. ცხოველთა ვიბრაციის ზემოქმედებამ გამოიწვია ტეტანური პოტენციაციის მქონე ნეირონების რაოდენობის შემცირება და პოსტტეტანური გაძლიერების მნიშვნელოვანი დომინირება. მორფოლოგიურმა და ჰისტოქიმიურმა შედეგებმა აჩვენა, რომ ვიბრაციაზე დაქვემდებარებული ვირთხების SVN ნეირონებში ჰიპოთალამური სტიმულაციის პირობებში, ხდება მეტაბოლიზმის და დეფოსფორილირების პროცესების ზრდა ტვინის შესწავლილი უბნის უჯრედულ სტრუქტურებში, რაც საბოლოოდ უზრუნველყოფს უჯრედების გადარჩენისა და გადარჩენის პროცესების ოპტიმალურ პირობებს. რეგენერაცია.

საკვანძო სიტყვები: უმაღლესი ვესტიბულური ბირთვი, ვიბრაცია, ერთი ნეირონული აქტივობა, ტეტანური სტიმულაცია,