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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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ELECTROPHYSIOLOGICAL EFFECTS OF GLIBENCLAMIDE ON HIPPOCAMPAL AND BASOLATERAL AMYGDALE NEURONSIN RATS WITH FRUCTOSE-INDUCED METABOLIC DYSFUNCTION

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Abstract.

High fructose intake disrupts metabolic homeostasis, leading to neuronal dysfunction. This study aimed to evaluate the effect of glibenclamide on hippocampal and basolateral amygdala neurons in rats subjected to chronic fructose consumption. Male albino rats were divided into three groups: (I) a Control group (standard drinking water for 6 weeks, n = 5), (II) a Fructose group (20% fructose solution for 6 weeks, n = 5), and (III) a Fructose + Glibenclamide group (20% fructose solution with glibenclamide at 5 mg/kg orally during weeks 3–6, n = 5). Neuronal activity was recorded in the CA1 region of the hippocampus, and responses were classified as tetanic depression–posttetanic depression (TD–PTD), tetanic depression–posttetanic potentiation (TD–PTP), or tetanic potentiation–posttetanic potentiation (TP–PTP). The high-fructose diet induced progressive hyperglycemia and suppressed background spike activity. Glibenclamide normalized firing rates and shifted the distribution of synaptic responses toward a predominance of inhibition. Reduced tetanic potentiation observed in fructose-fed rats was enhanced by glibenclamide, while tetanic depression was significantly increased. These findings demonstrate that glibenclamide modulates the excitation–inhibition balance in hippocampal and amygdala networks under metabolic stress, suggesting its therapeutic potential in preventing neurodegenerative complications associated with metabolic syndrome.

Key words. Glibenclamide, hippocampus, amygdala, fructose, metabolic syndrome, neuronal excitability, synaptic plasticity, electrophysiology.

Introduction.

Glibenclamide is a classical drug belonging to the sulfonylurea derivatives, first introduced into clinical practice in 1969. Since then, it has been established as a primary therapeutic agent for type 2 diabetes mellitus [1]. Historically, its therapeutic effect was attributed solely to its ability to stimulate insulin secretion by blocking pancreatic ATP-sensitive potassium (K_ATP) channels composed of SUR1 and Kir6.2 subunits in pancreatic β-cells [2]. This well-characterized mechanism has provided effective glycemic control for millions of diabetic patients worldwide. However, over the past decade, the scientific perspective on glibenclamide has changed dramatically. The drug has drawn renewed research interest—this time as a potent neuroprotective agent [3]. Recent studies have revealed that glibenclamide exerts pronounced pleiotropic protective effects in various forms of acute central nervous system injury [4]. It has demonstrated beneficial effects in clinically relevant models of ischemic and hemorrhagic stroke, traumatic brain injury, spinal cord injury, and neonatal hypoxic-ischemic encephalopathy. Of particular interest is the fact that glibenclamide's neuroprotective action is mediated through mechanisms fundamentally distinct from its hypoglycemic effect [5,6]. A key factor is the drug's ability to inhibit the recently characterized SUR1-Trpm4 channel (formerly known as the SUR1-regulated NCCa-ATP channel) and, in certain cases, to modulate K_ATP channels within the brain [7]. This discovery has provided a new perspective on the therapeutic potential of this well-known drug. Recent clinical studies confirm that glibenclamide exerts significant effects on the cerebral microvasculature—reducing edema formation, preventing secondary hemorrhages, inhibiting necrotic cell death, exerting potent anti-inflammatory effects, and promoting neurogenesis [8-10].

These effects open new avenues for the use of glibenclamide in neurological practice, positioning it as a promising candidate for drug repurposing as a neuroprotective agent. In light of these considerations, the present study aimed to perform an electrophysiological assessment of the hippocampus and basolateral amygdala in rats with fructose-induced metabolic disturbances and to evaluate the protective efficacy of glibenclamide under these pathological conditions.

Materials and Methods.

Study design: Experiments were conducted on fifteen male albino rats (200 ± 30 g) obtained from the Experimental Center of the L.A. Orbeli Institute of Physiology. The animals were housed under standard laboratory conditions with a 12-hour light/dark cycle, at a temperature of 22–24 °C and relative humidity of 40–60%. They were randomly divided into three groups (n=5 per group):

1. Control group: Received standard drinking water for 6 weeks.
2. Fructose group: Received drinking water containing 20% fructose daily for 6 weeks.
3. Fructose + Glibenclamide group: Received the same 20% fructose solution for 6 weeks along with glibenclamide administered orally at a dose of 5 mg/kg from the third to the sixth week.

Experimental Method:

In vivo extracellular electrophysiological studies were conducted after 6 weeks. The animals were anesthetized with urethane (1.1 g/kg, i.p.), immobilized with 1% ditiline (25 mg/kg, i.p.), positioned in a stereotaxic frame, and placed on artificial ventilation. The depth of anesthesia was continuously monitored,

with additional urethane doses administered as necessary. At the end of the experiment, rats were euthanized with pentobarbital sodium (100 mg/kg). The background and evoked spiking activity of single hippocampal neurons were recorded during high-frequency stimulation (HFS) of the ipsilateral entorhinal cortex, as well as the activity of single basolateral amygdala neurons during HFS of the ventral dorsal hippocampus. To record extracellular spike activity, a microelectrode (tip diameter 1–2 μm, resistance 1.5–2.5 MΩ) filled with a 3 M KCl solution was systematically inserted into the dorsal hippocampus according to stereotaxic coordinates (AP −3.3 mm; L ± 1.5–3.5 mm; DV + 3.0–4.0 mm). The microelectrode was inserted into the basolateral amygdala according to the following coordinates (AP −3.24 mm, L ± 5.4–5.8 mm, and DV + 9.5–10.2 mm) from a rat brain atlas [11]. HFS of the ipsilateral entorhinal cortex was delivered using bipolar cylindrical electrodes positioned at coordinates AP −9 mm, L ± 3.5 mm, and DV + 4 mm; HFS of the hippocampus was delivered using bipolar cylindrical electrodes positioned at coordinates AP −3.0 mm; L ± 2.0 mm; DV + 3.5 mm. The stimulation protocol consisted of rectangular current pulses (0.05 ms duration) delivered at 100 Hz for 1 s, with an intensity ranging between 0.10 and 0.14 mA. The neuronal spikes obtained after recording were subjected to software-based analysis to eliminate HFS-related artifacts and to assess spiking activity during tetanization. Based on real-time distributions of prestimulus and poststimulus spiking activity of single neurons, the software generated diagrams of mean firing frequencies for pre- and post-stimulus intervals, including the HFS period. This analysis determined the statistical significance of differences in spike frequency between the pre-stimulus and post-stimulus intervals, as well as during HFS (the tetanization period). Analysis of single-neuron spike trains revealed responses characterized by an increased firing rate—tetanic potentiation (TP) and posttetanic potentiation (PTP)—as well as a decreased firing rate—tetanic depression (TD) and posttetanic depression (PTD). Mixed response patterns, such as TD–PTP combinations, and non-reactive neurons were also identified. For the selected experimental groups (as well as for specific neuronal populations exhibiting the same type of response), averaged peristimulus cumulative histograms were generated programmatically.

Statistical analysis.

The statistical significance of the heterogeneity in interspike interval distributions (or spike frequency) across the analyzed time intervals (before stimulus - bs, HFS - hfs, and poststimulus - ps) for each recorded neuron was assessed using Student's t-test (for parametric data) and the Mann-Whitney U test (for non-parametric data). The statistical significance of differences in mean firing rates (Mbefore stimulus - Mbs, M during HFS - Mhfs, Mpoststimulus - Mps) was assessed using a two-sample unpaired Student's t-test. Data are presented as mean ± SEM. A p-value of less than 0.05 was considered statistically significant. Additionally, to enhance the reliability of comparisons between pre-stimulus, post-stimulus, and tetanization spike flows, Mann–Whitney U-tests were employed by the analysis software («SpikeRegistrator» _ Rg 1 MFC Application, Rg 1 EXE, Yerevan, Armenia). To control for multiple pairwise comparisons between the Control (C), Fructose (F), and Fructose + glibenclamide (F+G) groups, Bonferroni correction was applied, with adjusted significance set at $p \leq 0.0167$. Specific p-values and test statistics for key between-group comparisons are reported in the Results section.

Results.

Under conditions of intensive consumption of dietary fructose, abnormal synaptic activity was detected in neurons of the hippocampus and amygdala: i) disturbances in the frequency of pre-stimulus spiking (background activity of populations of neurons exhibiting this type of response), ii) the ratio of excitation and depression, iii) the intensity of responses to high-frequency stimulation. Glibenclamide targets homeostatic plasticity of the entorhinal cortex-hippocampus-amygdala network by increasing the percentage and intensity of depressor responses to high-frequency stimulation, as well as modulating the background spiking frequency of single neurons.

We recorded a total of 175 hippocampal neurons from the Control group, 190 from the Fructose group, and 169 from the Fructose + glibenclamide group. In the Fructose group (after 6 weeks), we have an insignificant increase in the percentage of neurons with TP PTP responses (12.10% vs. 10.9% in control; P=0.5) and a decrease in neurons with TD PTD responses (43.16% vs. 44.90% in control; P=0.7). The Fructose + glibenclamide group exhibited a distribution similar to the Control (44.9%), with TD–PTD responses being dominant (52.70%). The proportion of TP–PTP responses was significantly reduced by glibenclamide to 4.10% vs. 10.9% in Control ($p = 0.003$). Fructose consumption significantly suppressed background activity, an effect that was reversed by glibenclamide treatment. For instance, in neurons displaying TD–PTD responses, the mean prestimulus firing rate (Mbs) was 6.5±0.2 spike/s in the Control group, decreased to 4.69 ± 0.1 spike/s in the Fructose group ($p < 0.001$ vs. Control), and was restored to 7.05 ± 0.3 spikes/s in the F+ glibenclamide group ($p < 0.0001$ vs. Fructose; $p = 0.14$ vs. Control). During HFS, glibenclamide modulate the abnormal, reduced potentiation seen in the Fructose group. The mean firing rate during HFS (Mhfs) in TP–PTP neurons was 32 ± 0.2 spike/s in Controls, decreased to 19.87 ± 0.3 spike/s in the Fructose group ($p < 0.0001$), and was reduced to 5.43 ± 0.05 spikes/s in the F+G group ($p < 0.0001$ vs. Fructose).

In the basolateral amygdala, we recorded 168 neurons in the Control group, 158 in the Fructose group, and 154 in the Fructose + glibenclamide group. Glibenclamide treatment shifted the response profile back towards the control state (Figure 2). The proportion of TD–PTD responses, which was 35.7% in Control, increased to 43.0% in the Fructose group (p=0.04) and was further elevated to 55.2% in the Fructose + glibenclamide group ($p = 0.001$ vs. Control). Concurrently, the proportion of TP–PTP responses decreased from 25.0% in Controls to 15.8% in the Fructose group ($p = 0.01$ vs. Control), and to 11.7% in the Fructose + glibenclamide group ($p = 0.0002$ vs. Control) (Figure 2D). The drug also modulated response intensity. In TD–PTP neurons, the mean firing rate during HFS (Mhfs) was 0.32 ± 0.01 spikes/s in Controls, increased to 0.78 ± 0.01 spikes/s in the Fructose group ($p<0.0001$), and was significantly reduced to 0.36 ± 0.01 spikes/s in the Fructose + glibenclamide group

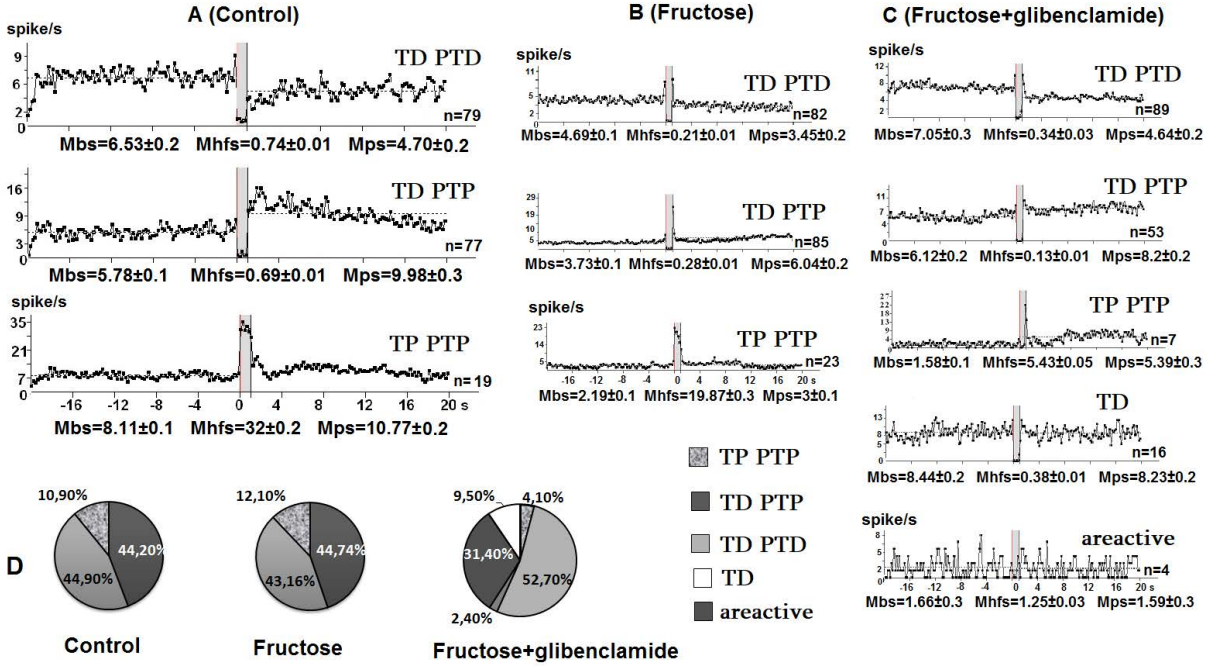

Figure 1. *Peristimulus histograms of the mean impulse frequency of individual hippocampal neurons exhibiting specific response patterns — tetanic depression and posttetanic depression (TD PTD), tetanic depression and posttetanic potentiation (TD PTP), and tetanic potentiation and post-tetanic potentiation (TP PTP) — during entorhinal cortex stimulation in the Control (A), Fructose (B) and the Fructose + glibenclamide (C) groups. Below each histogram, the numerical values of the mean impulse frequency are shown in real time for 20 seconds before stimulation (Mbs±SEM), 20 seconds poststimulation (Mps±SEM), and during the high-frequency stimulation period (Mhfs±SEM). n - the number of neurons with each type of response. (D) – percentage distribution of the response types in the respective experimental groups.*

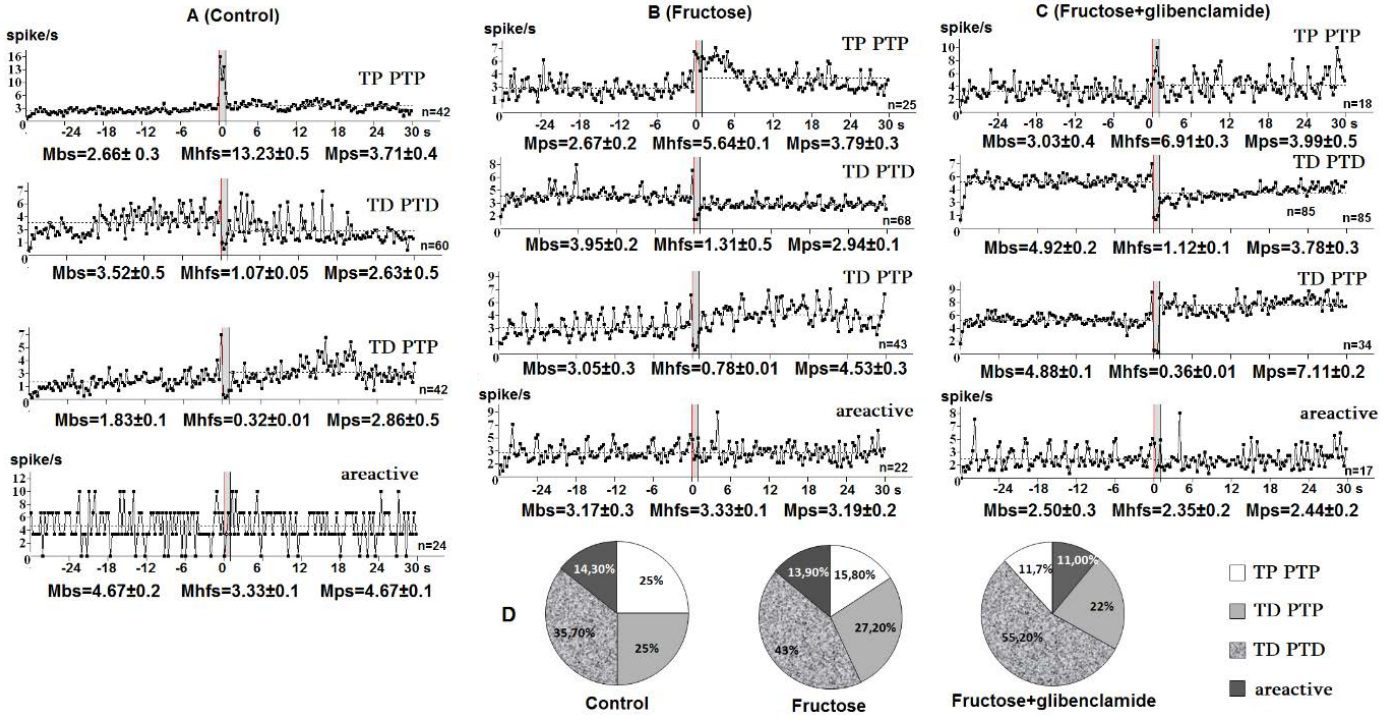

Figure 2. *Peristimulus histograms of mean spike frequency constructed from pre- and poststimulus spike activity of individual basolateral amygdala neurons during hippocampal stimulation in the Control (A), Fructose (B) and Fructose + glibenclamide (C) groups. The data represent real-time recordings taken 30 seconds before stimulation (Mbs±SEM), 30 seconds after stimulation (Mps±SEM), and during high-frequency stimulation (Mhfs±SEM) for neurons exhibiting the indicated response types (TP PTP – tetanic potentiation and posttetanic potentiation, TD PTD – tetanic depression and posttetanic depression, TD PTP – tetanic depression and posttetanic potentiation). n - the number of neurons with each type of response. (D) percentage distribution of these response types among the total number of recorded neurons in the Control, Fructose, and Fructose + glibenclamide groups.*

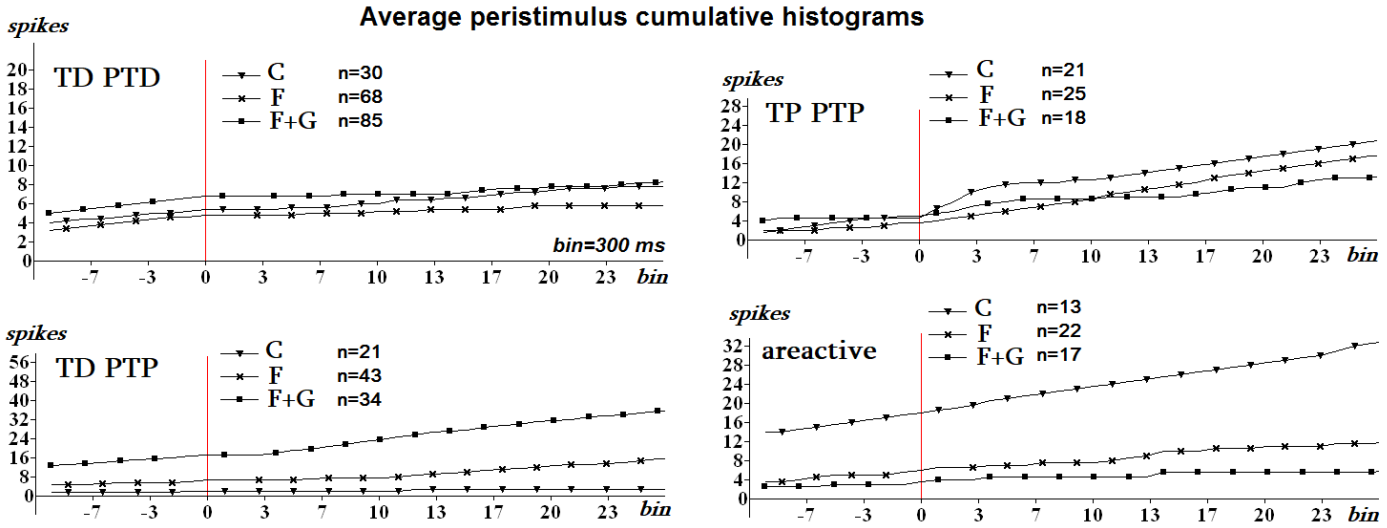

Figure 3. *Averaged cumulative histograms showing populations of basolateral amygdala neurons exhibiting the indicated response types in the Control (C), Fructose (F), and Fructose + Glibenclamide (F+G) groups.*

($p<0.0001$ vs. Fructose) getting closer to control ($p=0.005$ vs. Control).

Analysis of cumulative histograms (Figure 3) confirmed that glibenclamide restored peristimulus activity patterns in the amygdala towards those observed in the Control group. A comparison of the severity of peristimulus spike activity in the amygdala neurons of groups F, F+G with the control based on program-averaged cumulative histograms allows us to conclude: I) in group F+G, the level of peristimulus spiking of neurons with TD-PTD responses exceeds those in the control and in group F; II) in the population of neurons with TD-PTP, the highest level of peristimulus activity was recorded in the F+G group; III) poststimulus spike activity of neurons with TP-PTP responses in groups F and F+G was recorded below the control level; IV) the peristimulus activity of areactive neurons of the amygdala in the F+G group is significantly lower than that in the control.

We have shown that under conditions of long-term consumption of dietary fructose, Glibenclamide modulates the plasticity of the entorhinal cortex-hippocampus-amygdala network by shifting the percentage balance in favor of depressor types of responses during HFS, as well as an increase in the intensity of depression during the tetanization epoche (for for hippocampal and amygdala neurons). The data expand our understanding of the mechanisms by which glibenclamide controls brain plasticity during metabolic disruption.

Discussion.

Our results demonstrate that glibenclamide effectively counteracts the electrophysiological disruptions induced by a high-fructose diet in key brain regions. In the hippocampus, fructose consumption led to suppressed background activity and a shift towards post-tetanic excitation, which were both normalized by glibenclamide. The drug restored prestimulus firing rates to control levels and rebalanced synaptic response types, notably reducing the excessive tetanic potentiation and favoring inhibitory patterns. Similarly, in the basolateral amygdala, glibenclamide enhanced inhibitory tone both during and after HFS.

The key mechanism underlying the neuroprotective action of glibenclamide is the inhibition of the SUR1-regulated NC (Ca-ATP) channel, a nonselective cation channel [12]. The regulation of this channel is mediated by intracellular calcium and adenosine triphosphate levels [5]. Importantly, this channel is not constitutively expressed but is transcriptionally reactivated across all neurovascular cell types following various forms of central nervous system injury. Blocking this channel with glibenclamide plays a critical role in preventing necrotic cell death during ischemic stroke and in reducing neuroinflammation after hemorrhagic injury [13]. Investigations into the molecular pathophysiology of the neurogliovascular unit in ischemic stroke suggest that disrupted cellular ionic homeostasis, resulting from altered function and regulation of ion pumps, channels, and secondary active transporters, contributes integrally to the development of cytotoxic and vasogenic edema and hemorrhagic transformation [14,15]. By targeting these mechanisms, glibenclamide exerts a multilevel neuroprotective effect. Robust preclinical studies have demonstrated that glibenclamide reduces infarct volume, edema, and hemorrhagic complications, while improving functional recovery in rodent models of ischemic stroke. In clinically relevant models of subarachnoid hemorrhage, glibenclamide also mitigates adverse neurological and behavioral outcomes [16,17]. In our experiments, analysis of the synaptic activity of CA1 hippocampal neurons revealed significant differences between the experimental groups. In the Fructose group, responses characterized by tetanic depression (87.9%) and post-tetanic excitation (56.8%) predominated, whereas in the Fructose + Glibenclamide group, inhibitory responses prevailed both during high-frequency stimulation (93.6%) and in the post-stimulus period (52.7%). Particularly noteworthy is the effect of glibenclamide on the prestimulus level of spike activity: in the F+G group, spike frequency values were restored toward control levels, as evidenced, for example, by an increase from 4.68 to 7.05 spikes/s in neurons exhibiting TD–PTD responses. These findings may be attributed to the ability of glibenclamide to block SUR1-regulated channels in hippocampal and basolateral amygdala neurons, modulate the

activity of brain K_ATP channels, and influence the balance between excitatory and inhibitory processes within neuronal networks. Of particular importance is the regulatory influence of glibenclamide on excitatory inputs within the entorhinal cortex–hippocampus network, manifested as an attenuation of abnormally high tetanic potentiation. In neurons of the basolateral amygdala, glibenclamide induced a complex pattern of changes, including a marked enhancement of tetanic depression during high-frequency stimulation in neurons with TD–PTP responses, a shift in post-tetanic response balance toward predominant depression (55.2%), and a modulation of peristimulus spike activity. Overall, the obtained results are consistent with current concepts of the pleiotropic effects of glibenclamide and broaden the understanding of its neuroprotective potential, highlighting its capacity to restore synaptic and network homeostasis under conditions of metabolic and excitotoxic stress [5,18,19]. The revealed ability of the drug to modulate synaptic plasticity under metabolic impairment conditions opens promising avenues for further investigation of its therapeutic potential in neurodegenerative diseases [20].

Conclusion.

Glibenclamide demonstrates unique neuromodulatory effects in fructose-induced metabolic dysfunction, normalizing background firing activity in the hippocampus and amygdala, restoring abnormal decrease in responses during tetanization, and favoring an inhibitory synaptic response. The mechanisms of homeostatic synaptic plasticity diverge from classical synaptic plasticity that store information, and thus our data expand the paradigms of glibenclamide therapy in conditions of metabolic disorders of the central nervous system.

Author contributions.

Study Concept and Design: IAS and ChVA. Acquisition, Analysis, and Interpretation of the Data: IAS, DMH, NKA, SKV, GLR, AIV, BBY, AZA, and ChVA. 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 the "ARRIVE" guidelines (Animals in Research: Reporting In Vivo Experiments). The protocol was approved by the Institutional Review Board of the L. A. Orbeli Institute of Physiology (protocol code: N4, approval date: July 22, 2021).

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Электрофизиологические эффекты глибенкламида на нейроны гиппокампа и базолатеральной миндалины у крыс с метаболической дисфункцией, индуцированной фруктозой

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Резюме

Чрезмерное потребление фруктозы нарушает метаболический гомеостаз и приводит к развитию нейронной дисфункции. Целью данного исследования является оценка влияния глибенкламида на нейроны гиппокампа и базолатеральной амигдалы у крыс на модели хронического потребления фруктозы. Белые крысы, самцы были разделены на три группы: (I) группа контроля — стандартная питьевая вода в течение 6 недель (n = 5); (II) группа Фруктоза — 20%-й раствор фруктозы в течение 6 недель (n = 5); (III) группа Фруктоза + Глибенкламид — 20%-й раствор фруктозы с пероральным введением глибенкламида (5 мг/кг) в течение 3–6-й недель эксперимента (n = 5). Нейрональная активность регистрировалась в области CA1 гиппокампа. Ответы были классифицированы как тетаническая депрессия–посттетаническая депрессия (TD–PTD), тетаническая депрессия–посттетаническая потенциация (TD–PTP) или тетаническая потенциация–посттетаническая потенциация (TP–PTP). Диета с высоким содержанием фруктозы вызывала прогрессирующую гипергликемию и подавление фоновой спайковой активности. Применение глибенкламида нормализовало частоту импульсов и привело к смещению распределения синаптических ответов в сторону преобладания ингибиторных реакций. Убыточная тетаническая потенциация, наблюдавшаяся у крыс, получавших фруктозу, была усилена под действием глибенкламида, тогда как тетаническая депрессия значительно усиливалась. Полученные данные свидетельствуют о том, что глибенкламид регулирует баланс возбуждения и торможения в нейронных сетях гиппокампа и миндалины при метаболическом стрессе, что указывает на его потенциальную терапевтическую значимость для профилактики нейродегенеративных нарушений, связанных с метаболическим синдромом.

Ключевые слова: глибенкламид, гиппокамп, миндалина, фруктоза, метаболический синдром, нейрональная возбудимость, синаптическая пластичность, электрофизиология.