GEORGIAN MEDICAL NEWS

ISSN 1512-0112

NO 7-8 (352-353) Июль-Август 2024

ТБИЛИСИ - NEW YORK

ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

Медицинские новости Грузии

საქართველოს სამედიცინო სიახლენი

GEORGIAN MEDICAL NEWS

Monthly Georgia-US joint scientific journal published both in electronic and paper formats of the Agency of Medical Information of the Georgian Association of Business Press. Published since 1994. Distributed in NIS, EU and USA.

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.

GEORGIAN MEDICAL NEWS
No 7-8 (352-353) 2024

Содержание:

GEORGIAN MEDICAL NEWS
No 7-8 (352-353) 2024

THE EFFECTS OF HYDROCORTISONE ON SYNAPTIC PROCESSES IN PARKINSON'S DISEASE UNDERLYING THE POTENTIAL THERAPEUTIC STRATEGIES

M.V. Poghosyan[1], H.Y. Stepanyan[1], Avetisyan Z.A[1], J.S. Sarkissian[1].

[1]*L. Orbeli Institute of physiology NAS RA, Yerevan, Armenia.*

Abstract.

The study was carried out electrophysiological effects of hydrocortisone for protection on the prelimbic cortex (PrL) neurons in rats, particularly in response to high-frequency stimulation (HFS) of the Caudate-Putamen nuclear complex (CPu) on the models of Parkinson's disease (PD). The study involved 19 rats of the Albino line, each weighing 250 gr. The rats were divided into three experimental groups: intact, rotenone model of Parkinson's disease (PD), and rats with PD but treated with hydrocortisone for protection. Extracellular recording was conducted to measure the impulse activity of single neurons in the prelimbic cortex (PrL) particularly in response to high-frequency stimulation (HFS) of the Caudate-Putamen nuclear complex (CPu) on the models of PD and PD treated with hydrocortisone for protection. In rats with the PD model, there was a decrease in post-stimulus synaptic depressor tetanic effects compared to the norm. This means that the ability of synapses to depress their activity after stimulation was reduced in PD. Conversely, excitatory effects increased in PD rats compared to the norm. This indicates an increase in the excitatory response of neurons in the PD model. When hydrocortisone was applied in PD rats, the frequency of impulse activity dropped sharply, even falling below the levels observed in the normal condition. This indicates that hydrocortisone treatment mitigated the heightened neural activity induced by PD, possibly returning it to a more normal state. Overall, these findings suggest that PD alters synaptic responses and neural activity in the PrL, and hydrocortisone treatment seems to reverse some of these effects.

Key words. Rotenone model of Parkinson's disease, activity of single neurons, therapeutic strategies, prelimbic cortex, Caudate-Putamen nuclear complex, hydrocortisone.

Introduction.

According to modern understanding, Parkinson's disease (PD) is believed to be a consequence of the evolution of the human brain [1]. While experimental damage to the dopaminergic system in vertebrates, from fish to primates, leads to similar motor symptoms as PD [2], parkinsonism is only found in humans. The significant expansion of the human brain, especially the neocortex, heavily loads subcortical structures, leading to increased vulnerability to aging and genetic mutations associated with PD. The human brain is approximately three times larger, based on the relationship between brain weight and body size, mainly concerning telencephalic structures [3]. The relative growth of the human brain cortex is associated with the weakening of genetic control [4,5]. In other words, PD is exclusively a human disease due to telencephalization and, consequently, the bioenergetic and proteostatic burden on subcortical neuromodulatory structures [6]. In this context, the hypothesis aligns closer to the cortical pathogenetic theory of PD, suggesting that corticostriatal activity acts as a "stressor," parallel to the substantia nigra pars compacta (SNc) and other vulnerable structures [7]. There is also evolutionary justification for other neurodegenerative processes unique to humans. Alzheimer's disease, for instance, is considered the "flip side" of the evolution of the human temporal lobe [8]. Furthermore, dopaminergic denervation of the striatum contributes less to disturbances in dynamic balance in PD due to dysfunction of multi-neurotransmitter systems. Further research into treatment methods targeting non-dopaminergic mechanisms is necessary [9]. In addition to the commonly recognized focus on dopaminergic cells, involvement of serotonergic, cholinergic, and noradrenergic neurons originating from the brainstem or basal ganglia (BG) has been demonstrated [10].

Corticostriatal connections play a central role in goal-directed behavior involving motivation and cognition. BG are known in association with motor functions and neuropathology disrupting movement control (PD and Huntington's disease). The functional concept of BG has changed significantly over the last 40 years, from motor or sensorimotor to a more complex one related to goal-directed behavior accompanied by emotions, motivation, and cognition. In other words, BG serve not only sensorimotor but also limbic and cognitive functions. Particularly, ventral BG areas are associated with reward and reinforcement of reflexes [11-13], while central BG fields are involved in cognitive functions (learning and working memory) [14]. Thus, BG are associated not only with neurological disorders but also with psychiatric ones (schizophrenia, addiction, depression, obsessive-compulsive disorder) [15]. Afferent projections of the striatum derive from three major sources: (i) massive and topographic input from the cerebral cortex; (ii) from the thalamus; (iii) from the brainstem, mainly dopaminergic cells. The dorsolateral striatum receives cortical input from sensorimotor fields, the central striatum from associative cortical fields, and the ventromedial striatum from limbic cortical fields [16-19]. BG and the frontal cortex jointly regulate behavior policy and execution of goal-directed behaviors. They incite emotions and motivations while cognition organizes and plans the overall strategy [15]. The frontal cortex is subdivided into the orbital and medial (medial prefrontal cortex - PFC), involved in emotions and motivation; dorsolateral (dorsolateral PFC), involved in higher cognitive processes or "executive functions"; premotor, involved in various aspects of motor planning, and motor, involved in executing these plans. Moreover, while the ventral striatum (VS) is associated with emotion, the caudate nucleus (CN) with cognition and the putamen (Putamen - P) with sensorimotor function, there is no clear boundary between the functionally unified ventral striatum (VS) and the dorsal striatum (DS). In

conclusion, prefrontal fields project mainly to VS, rostral CN and P, while sensorimotor fields project more caudally, mainly to P [15]. Moreover, goal-directed behavior results from a combination of complex information processing involving the entire frontal cortex [15]. Imaging studies in humans show that activity in the lateral P is associated with repetitive and well-trained movements that do not require cognitive effort, while activity during learning sequential movements is in more anterior striatal fields, including CN [15]. PrL – a subregion of mPFC, receives numerous afferent projections from the hippocampus and sends efferent projections to the amygdala [20,21], and PrL neurons exhibit learning-induced plasticity [22-24]. CN and P can be considered as perceiving "inputs" from the cerebral cortex to BG. Finally, P and BG play an important role in PD and other diseases involving neuronal degeneration [25].

The present study aims to investigate the balance of excitatory and inhibitory responses of single neurons in the Prelimbic cortex (PrL) upon stimulation of the Caudate-Putamen nuclei (CPu), to assess the mechanisms of their impairment in a Parkinson's disease (PD) model induced by unilateral Rotenone injection and the success of protection by hydrocortisone.

Materials and Methods.

Electrophysiological studies were conducted on 19 Albino rats (250g) in three experimental series: intact (n=7), on the rotenone model of PD induced by unilateral rotenone injection and sustained for 4 weeks before the experiment (n=7), under hydrocortisone protection conditions (14 injections every other day at a dose of 1.25 mg/kg, 0.1%) (n=5). Rotenone (12 µg in 0.5 µl dimethyl sulfoxide, at a rate of 1 µl/min) was administered into the medial forebrain bundle under nembutal anesthesia (40 mg/kg, intraperitoneal), following stereotaxic atlas coordinates (AP+0.2; L±1.8; DV+8 mm) [26]. The study was conducted in accordance with the principles of the Basel Declaration and the recommendations of the ARRIVE guidelines [27]. Skull trepanation was performed from the bregma to the lambda, and the dura mater was exposed. Glass microelectrodes with a tip diameter of 1-2 µM, filled with 2M NaCl, were inserted into the ipsilateral PrL according to stereotaxic coordinates (AP+2.52; L±0.5; DV 3.7 mm) for extracellular recording of single neuron spike activity. High-frequency stimulation (HFS) of CPu was performed according to stereotaxic coordinates (AP–0.48, L±3.7, DV 4.2 mm) using rectangular pulses of current with a duration of 0.05 ms, an amplitude of 0.12–0.18 mV, a current strength of 0.32 mA, and a frequency of 100 Hz for 1 second. Recordings were made on anesthetized animals (urethane 1.2 g/kg intraperitoneal) fixed in the stereotaxic apparatus.

Activity was manifested as tetanic depression (TD) and tetanic potentiation (TP) with subsequent post-tetanic potentiation (PTP) and post-tetanic depression (PTD). A programmatic mathematical analysis of spike activity of 330 neurons was conducted. Activity manifestations were evaluated by online registration using action potential (spike) selection through amplitude discrimination. Peristimulus spike raster plots (PSSR Average), histograms of spike sum, and diagrams of averaged spike frequency (Frequency Average) were constructed. Student's t-test was used, taking into account critical values compared to those of normal distribution at significance levels of 0.05, 0.01, and 0.001 (for various trials), indicating that in most cases, statistically significant changes in neuronal activity during HFS reached at least the 0.05 level.

Results and Discussion.

We conducted extracellular registration of impulse activity of individual PrL neurons under normal conditions (137 neurons, n=7), on the PD model maintained for 4 weeks (118 neurons, n=7), with hydrocortisone protection (75 neurons, n=5).

Under normal conditions, PrL neurons during CPu HFS demonstrated tetanic depression in depressor effects with 2.4- and 1.6-fold decreases in pre-stimulus activity, respectively (Figure 2A, Groups A, B). Tetanic potentiation in excitatory effects revealed within 1.40- and 1.22-fold increases over pre-stimulus activity (Figure 2B, Groups A, B).

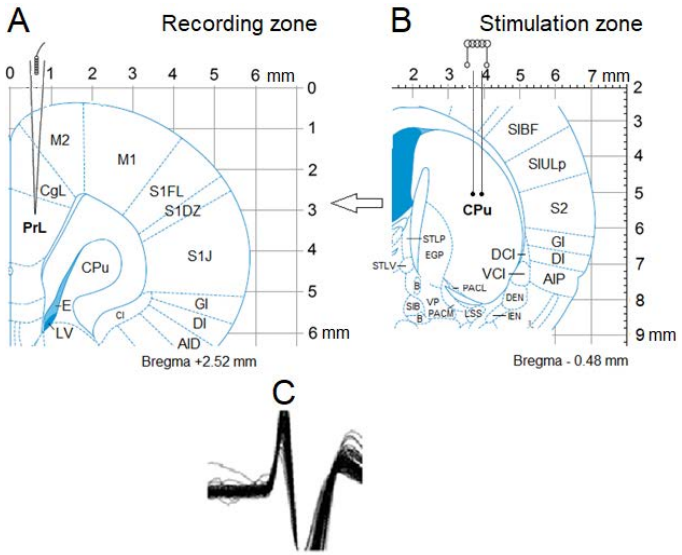

Figure 1. *Scheme of the experiment on stimulation of CPu and recording from PrL. Stereotactic image of the recording zone of neural activity - A, the stimulation zone - B and the characteristic action potential - C.*

On the PD model, PrL neuron tetanic depression was within 1.31- and 1.20-fold decreases in pre-stimulus activity (Figure 3A, Groups A, B), while tetanic potentiation showed 1.04- and 1.12-fold increases over pre-stimulus activity (Figure 3B, Groups A, B).

It is worth noting the presence of high background pre- and post-stimulus activity, both in depressor and excitatory effects of CPu neurons on the PD model, indicating the presence of neurodegenerative processes. This apparently leads to actual suppression of effects. Under the conditions of hydrocortisone exposure on the PD model, in PrL neurons during CPu HFS, both depressor reactions of tetanic depression reached, respectively, 2.00- and 1.50-fold decreases in pre-stimulus activity (Figure 4A, Groups A, B), while tetanic potentiation in both reactions was within 1.00 and 1.50-fold increases over pre-stimulus activity (Figure 4A and 4B, Groups A, B).

When assessing the degree of expression of depressor and excitatory effects, the values of the average frequency of action potentials were used. The obtained values are presented in the

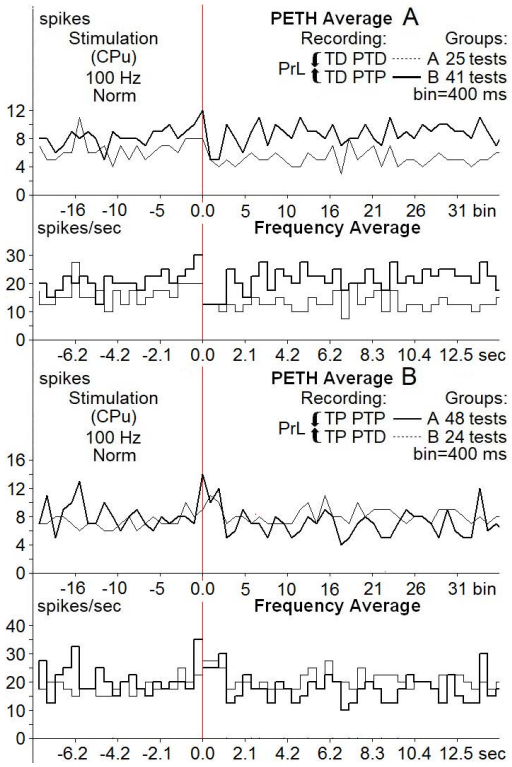

Figure 2. *Averaged peri event time histograms (PETH Average) and histograms of frequencies (Frequency Average) in norm.*

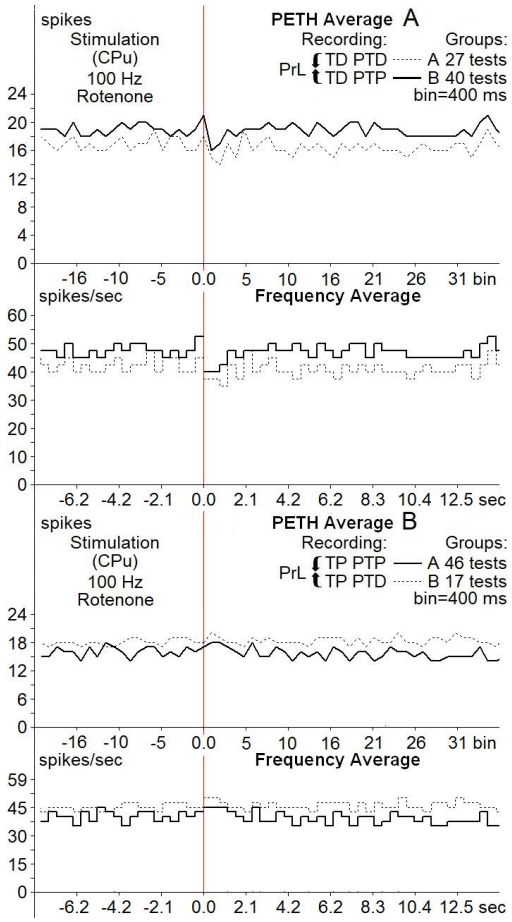

Figure 3. *Peri event time histograms average (PETH Average) and histograms of frequency (Frequency Average) on the rotenone model of PD.*

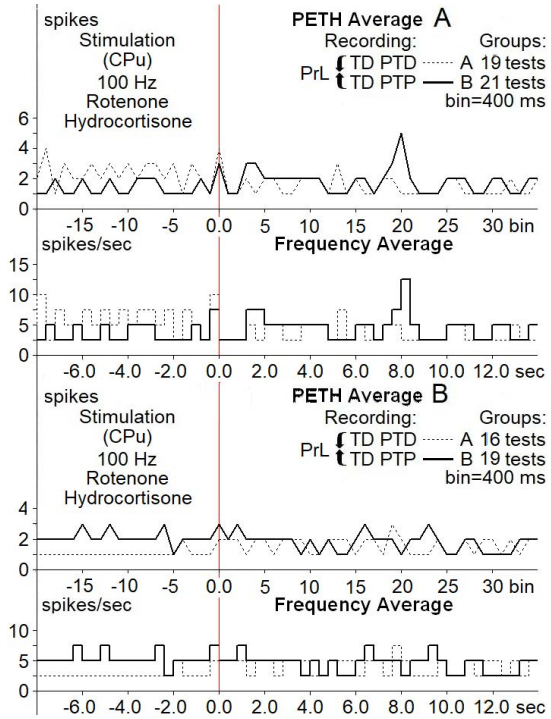

Figure 4. *Peri event time histograms average (PETH Average) and histograms of frequency (Frequency Average) on the rotenone model of PD with hydrocortisone protection.*

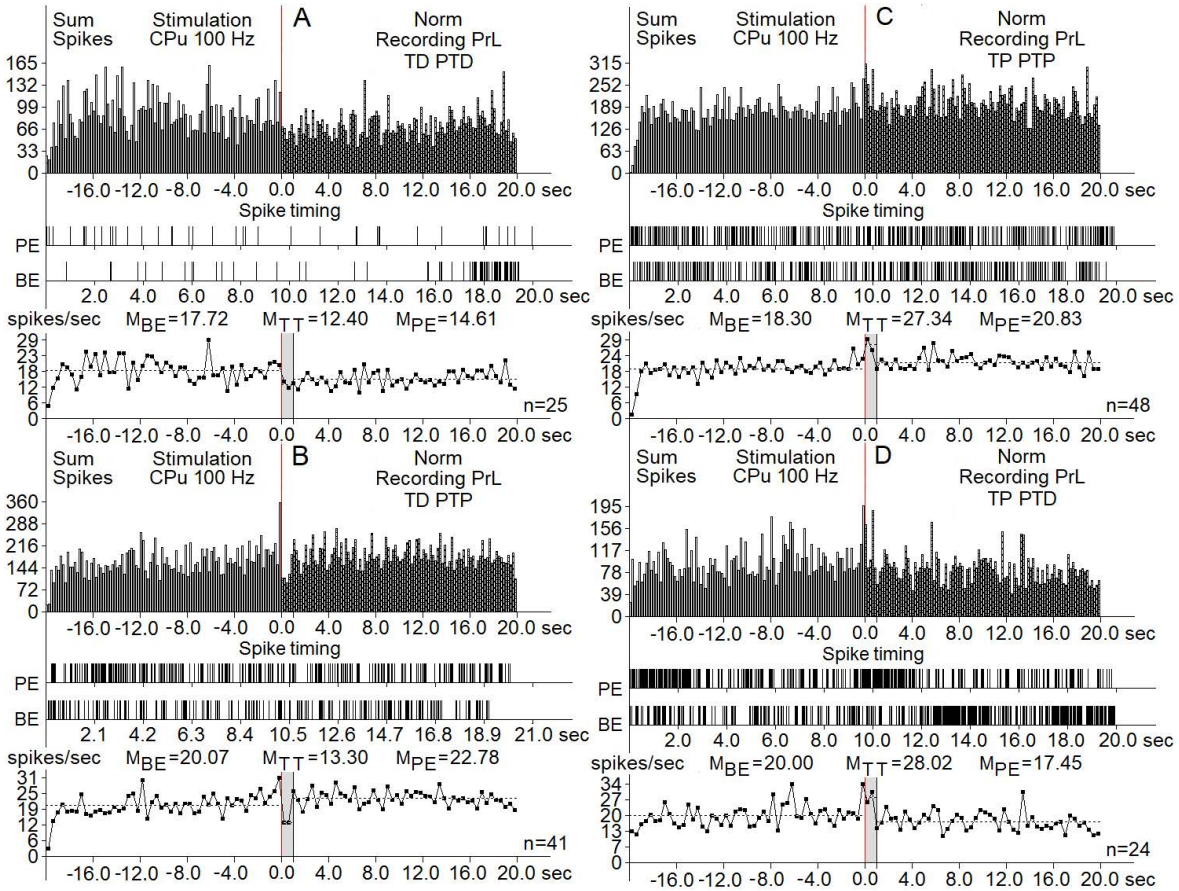

Figure 5. *histograms of the sum of spikes of pre- and post-stimulus tetanic depressor manifestations of the activity of TD PTD (A), TD PTP (B), TP PTP (C), TP PTD (D). Diagrams of the frequency, with averaged values (M) for time intervals before (M_{BE} - before event), at the time of tetanization (M_{TT} - time tetanization) and after stimulation (M_{PE} - post event).*

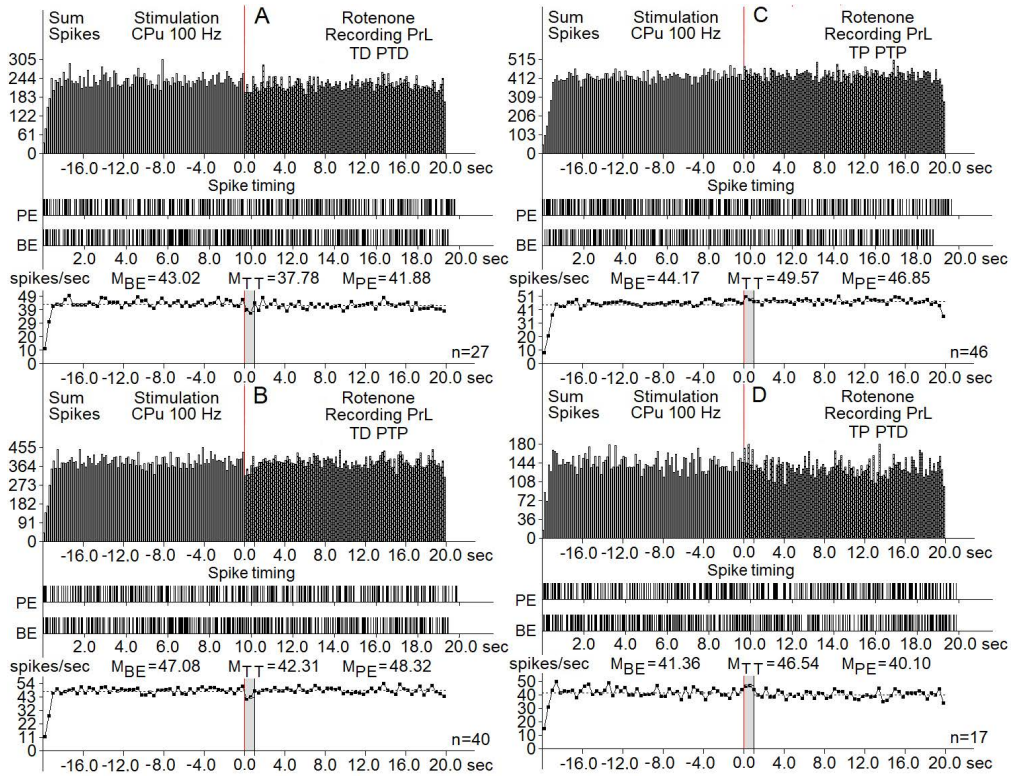

Figure 6. *histograms of the sum of spikes of pre- and post-stimulus tetanic depressor manifestations of the activity of TD PTD (A), TD PTP (B), TP PTP (C), TP PTD (D), Diagrams of the frequency, with averaged values (M) for time intervals before (M_{BE} - before event), at the time of tetanization (M_{TT} - time tetanization) and after stimulation (M_{PE} - post event).*

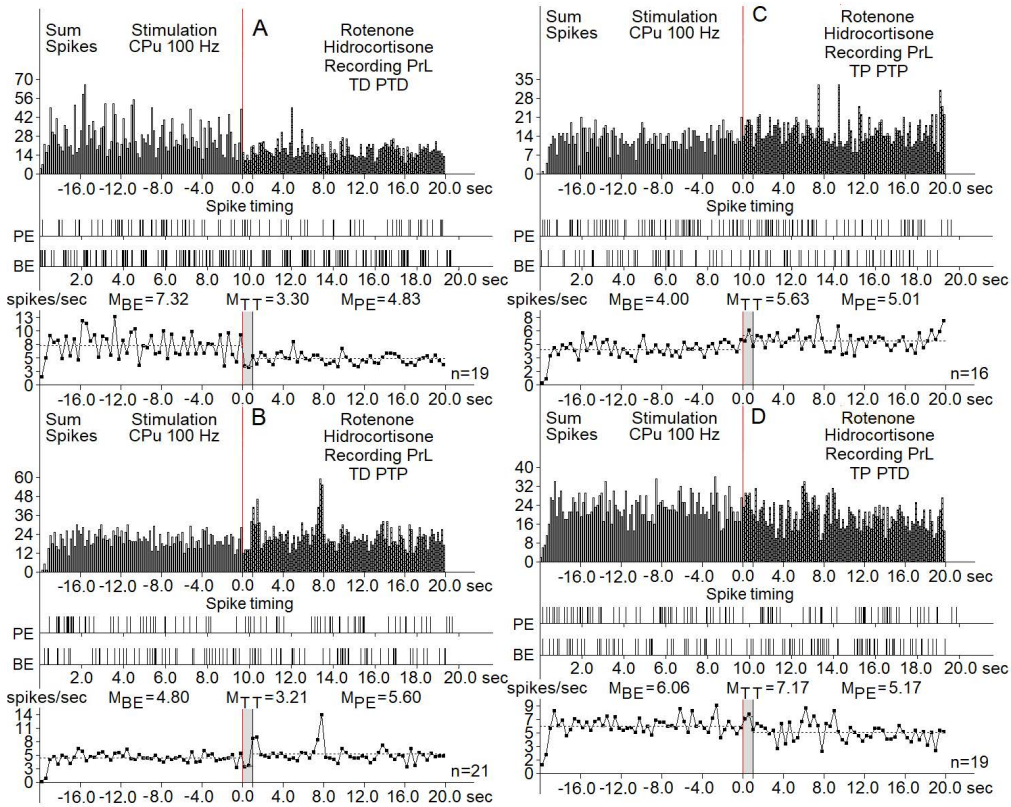

Figure 7. *histograms of the sum of spikes of pre- and post-stimulus tetanic depressor manifestations of the activity of TD PTD (A), TD PTP (B), TP PTP (C), TP PTD (D), Diagrams of the frequency, with averaged values (M) for time intervals before (M_{BE} - before event), at the time of tetanization (M_{TT} - time tetanization) and after stimulation (M_{PE} - post event).*

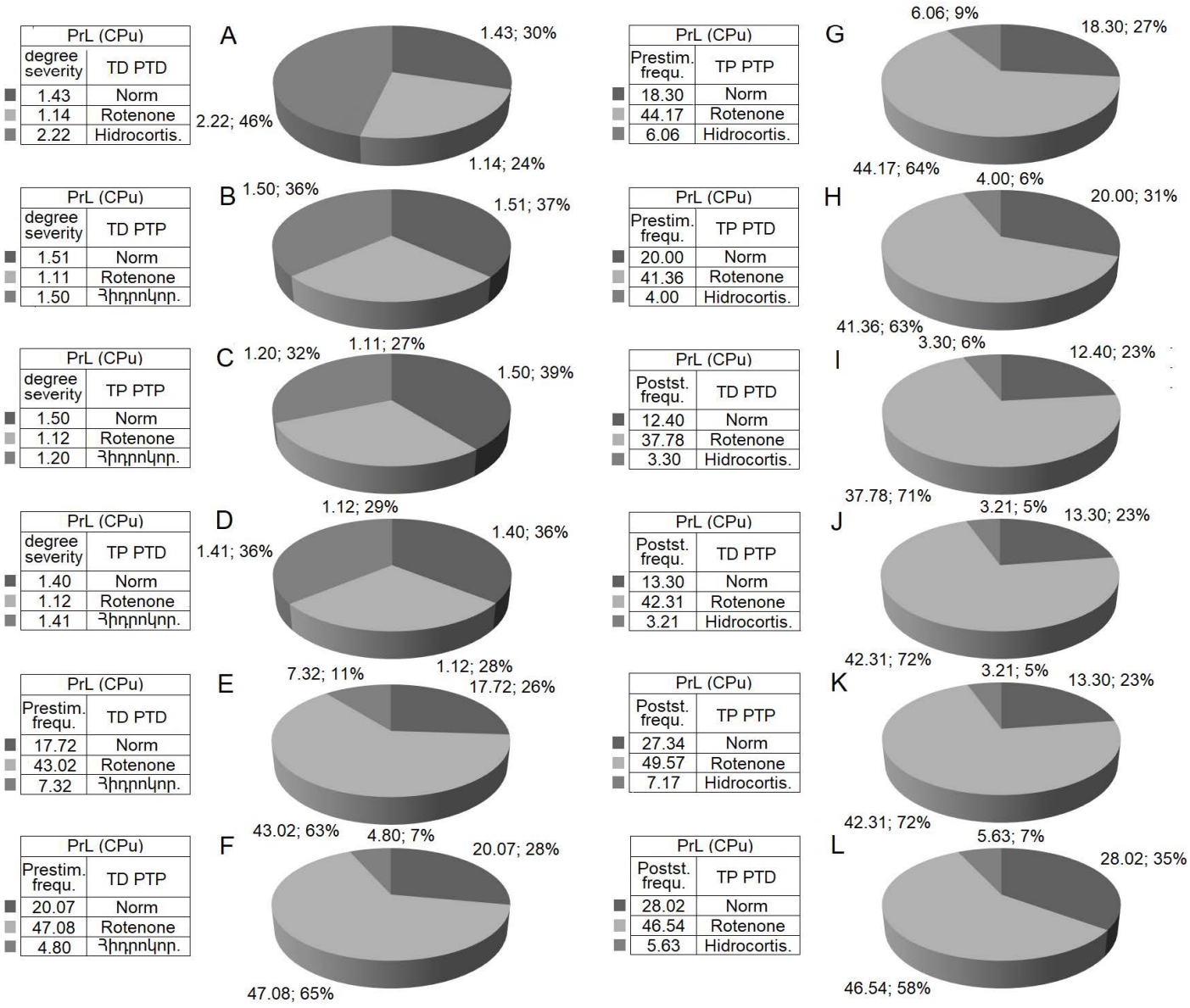

Figure 8. *Percentage and degree of severity (according to the average frequency), TD PTD (A), TD PTP (B), TP PTP (C) and TP PTD (D) poststimulus effects and frequencies of prestimulus (E-H) and poststimulus (I-L) activity, in the norm, on the rotenone model of PD and under conditions of hydrocortisone protection.*

form of disk diagrams in Figure 8 (based on Figures 5-7). In the norm, in PrL neurons, the values of TD in depressor and depressor-excitatory effects reached 1.43- and 1.51-fold decreases (Figure 5; in Figures 8A & 8B). Tetanic potentiation levels in excitatory and excitatory-depressor effects reached 1.50- and 1.40-fold increases (Figure 5; in Figures 8C & 8D), compared to pre-stimulus activity levels. As can be seen, these values differed little, indicating an actual balance of depressor and excitatory manifestations of activity of the examined neurons in the norm. On the PD model, in PrL neurons, TD values in depressor and depressor-excitatory effects were 1.14- and 1.11-fold decreases. TP values in excitatory and excitatory-depressor effects were 1.12- and 1.12-fold increases. These values also did not differ much from the norm in this type of analysis, compared to the norm (TD - 1.43-, 1.51-fold decrease and TP - 1.50- and 1.40-fold increase, respectively) (Figures 5 and 6, in Figures 8 A-D). On the PD model, under conditions of hydrocortisone protection, TD values in PrL neurons in depressor and depressor-excitatory effects were within 2.22- and 1.50-fold decreases, while TP levels showed 1.20- and 1.41-fold increases in activity (Figure 5, in Figures 8A-D). In other words, the effects of tetanic depression and potentiation showed a decrease in pathology, but also a sufficient increase after the application of hydrocortisone, approaching the norm.

An interesting, moreover, more pronounced picture was revealed when comparing the frequency of pre- and post-stimulus impulse activity of PrL neurons during CPu HFS.

Pre-stimulus frequency in depressor effects under normal conditions reached values of 17.72, 20.07, and on the PD model - 43.02, 47.08, respectively (Figures 5 and 6, in Figures 8E & 8F), and in excitatory effects under normal conditions - 18.30, 20.00 and in pathology - 44.17, 41.36, respectively (Figures 5

and 6, in Figures 8G & 8H).There was a significant increase in frequency on the PD model, indicating increased excitability of neurons in this nucleus. This is apparently associated with pathological processes as a result of rotenone intoxication. Under hydrocortisone protection, the pre-stimulus frequency in PrL neurons in depressor effects was within 7.32, 4.80, and in excitatory effects - 4.00 and 6.06. This was much lower than similar indicators of depressor effects in pathology - 43.02, 47.08 and excitatory effects in pathology - 44.17 and 41.36.

Under normal conditions, pre-stimulus frequencies in depressor effects were 17.72, 20.07, and in excitatory effects - 18.30, 20.00 (Figures 5 and 6, in Figures 8E & 8H). In other words, in pathology with protection, compared to pathology without protection, the pre-stimulus frequency of PrL neurons in depressor effects decreased by 5.88- and 9.81-fold, and the frequency in excitatory effects decreased by 7.31- and 10.34-fold. Thus, under protection conditions, compared to pathology, there was an obvious and significant decrease in pre-stimulus frequency, indicating a sharp reduction in excessively elevated toxic excitability, in favor of more than successful hydrocortisone protection.

As for the post-stimulus frequency of impulse activity of PrL neurons, under normal conditions, in depressor and excitatory effects, it reached 12.40, 13.30 and 27.34, 28.02, respectively. On the PD model - 37.78, 42.31 and 49.57, 46.54, respectively (Figures 5 and 6, in Figures 8I-M). In other words, on the PD model, the post-stimulus frequency, in depressor reactions, significantly exceeded the frequency in the norm - 3.04- and 3.20-fold, and in excitatory ones - 2.01- and 1.66-fold.

Overall, there was a significant increase in post-stimulus activity frequency, indicating increased excitability of pre-limbic cortex neurons (Figures 2,3 & 5I-M). Furthermore, under protection conditions, there was a sharp decrease in the post-stimulus frequency of PrL neurons on the PD model, in depressor effects - 11.45- and 13.20-fold, and in excitatory effects - 7.01- and 8.26-fold (Figures 2-4 & 5 I-M).

In conclusion, a powerful hyperexcitability of neurons in the pre-limbic cortex was identified on the PD model during rotenone intoxication, which was equally effectively suppressed by the application of hydrocortisone.

Excitotoxicity in neurodegenerative diseases, arising as a compensatory reaction to the reduction in excitation due to neuron death, damages neurons by their overactivation of glutamatergic NMDA and AMPA receptors [28], thereby inducing apoptosis of neurons and subsequent cell death [29, 30]. Excitotoxicity is accompanied by disruption of calcium buffering, generation of free radicals, activation of mitochondrial permeability, and secondary excitotoxicity [31].

The aforementioned, according to the concept put forward in a recently published report, indicates the necessity of deepening depressor effects under conditions of neurodegeneration, which carry a protective burden and reduce excessive excitatory reactions [32].

Compliance with ethical standards.

Before the initiation of the study, all participants received an explanation of the procedure and the risks that would later be faced in their participation, and they provided informed consent to participate in this study. The study was approved by the ethics committee of the POLTEKKES Bandung, and all procedures were in accordance with the Declaration of Helsinki.

Conflict of interest.

The authors state no conflict of interest with respect to the research, authorship, and/or publication of this article.

Author contributions.

Conceptualization: Kuswahyudi; Methodology: Agung Dwi Juniarsyah; Formal analysis and investigation: Junaidi; Writing: original draft preparation: Bagus Winata; Writing: review and editing: Bagus Winata; Funding acquisition: Junaidi; Resources: Sri Indah Ihsani Supervision: Kuswahyudi.

REFERENCES

1. Diederich N, Uchihara T, Grillner S, et al. The Evolution-Driven Signature of Parkinson's Disease. Trends Neurosci. 2020;43:475-492.
2. Campos-Romo A. Evaluation of motor disorders in animal models of Parkinson's disease. Rev Neurol. 2008;46:167-74.
3. Eisinger R.S, Okun MS, Cernera S, et al. Weight and survival after deep brain stimulation for Parkinson's disease. Parkinsonism Relat Disord. 2023;115:105810.
4. Koenig K.A, Lowe M.J, Harrington DL, et al. Functional connectivity of primary motor cortex is dependent on genetic burden in prodromal Huntington disease. Brain Connect. 2014;4:535-46.
5. Mitchell A.C, Jiang Y, Peter C, et al. Transcriptional regulation of GAD1 GABA synthesis gene in the prefrontal cortex of subjects with schizophrenia., Schizophr Res. 2015;167:2834.
6. Patricio F, Morales-Andrade AA, Patricio-Martínez A, et al. Cannabidiol as a Therapeutic Target: Evidence of its Neuroprotective and Neuromodulatory Function in Parkinson's Disease. Front Pharmacol. 2020;11:595635.
7. Foffani G, Obeso JA. A Cortical Pathogenic Theory of Parkinson's Disease. Neuron. 2018;99:1116-1128.
8. Thal DR, Rüb U, Orantes M, et al. Phases of A beta-deposition in the human brain and its relevance for the development of AD. Neurology. 2002;58:1791-800.
9. Stayte S, Vissel B. Advances in non-dopaminergic treatments for Parkinson's disease., Front Neurosci. 2014;8:113.
10. Wise R.A. Addictive drugs and brain stimulation reward. Ann Rev Neurosci. 1996;19:319-340.
11. Schultz W. Dopamine neurons and their role in reward mechanisms. Curr Opin Neurobiol. 1997;7:191-197.
12. Robbins T.W, Everitt B.J. Motivation and reward. In: Squire LR, Roberts JL, Spitzer NC, Zigmond MJ, McConnell SK, Bloom FE, eds. Fundamental Neuroscience. 2nd ed. San Diego, CA: Academic Press. 1999:1245-1259.
13. Jog M.S, Kubota Y, Connolly C.I, et al. Building neural representations of habits. Science. 1999;286:1745-1749.
14. Haber S.N. Corticostriatal circuitry Dialogues. Clin. Neurosci. 2016;18:7-21.
15. Jay T.M, Witter M.P. Distribution of hippocampal CA1 and subicular efferents in the prefrontal cortex of the rat studied by means of anterograde transport of Phaseolus vulgaris-leucoagglutinin. J. Comp. Neurol. 1991;313:574-586.

16. Hoover W.B. Vertes R. Anatomical analysis of afferent projections to the medial prefrontal cortex in the rat. Brain Struct. Funct. 2007;212:149-179.
17. Baeg E.H, Kim Y.B, Jang J, et al. Fast spiking and regular spiking neural correlates of fear conditioning in the medial prefrontal cortex of the rat. Cereb. Cortex. 2001;11:441-451.
18. Gilmartin M.R, McEchron M.D. Single neurons in the medial prefrontal cortex of the rat exhibit tonic and phasic coding during trace fear conditioning. Behav. Neurosci. 2005;119:1496-1510.
19. Laviolette S.R, Lipski W.J, Grace A.A. A subpopulation of neurons in the medial prefrontal cortexencodes emotional learning with burst and frequency codes through a dopamine D4 receptor-dependent basolateral amygdala input. J Neurosci. 2005;25:6066-6075.
20. DeLong M.R, Wichmann T. Circuits and circuit disorders of the basal ganglia. Arch. Neurol. 2007;64:20-24.
21. Paxinos G, Watson C. The rat brain in stereotaxic coordinates Elsevier, Academic Press, 5th ed. 2005;367.
22. Haber S.N, Kim K.S, Mailly P, et al. Reward-related cortical inputs define a large striatal region in primates that interface with associative cortical connections, providing a substrate for incentive-based learning. J Neurosci. 2006;26:8368-8376.
23. Lucas D.R, Newhouse J.P. The toxic effect of sodium L-glutamate on the inner layers of the retina. AMA Archives of ophthalmology. 1957;58:193-201.
24. Olney J.W. Brain lesions, obesity, and other disturbances in mice treated with monosodium glutamate Science. 1969;164:719-721.
25. Paxinos G, Watson C. The rat brain in stereotaxic coordinates. Elsevier, Academic Press, 5th ed. 2005.
26. Orlov A.I. Applied Statistics. 2004.
27. Kilkenny C, Browne W, Cuthill I.C, et al. Animal research: Reporting in vivo experiments: The ARRIVE guidelines 06 July 2010.
28. Matthew R. H, Heather L. S, Peter R. D. Glutamate-mediated excitotoxicity and neurodegeneration in Alzheimer's disease. NCI. 2004;45:583-595.
29. Lucas D.R, Newhouse J.P. The toxic effect of sodium L-glutamate on the inner layers of the retina. AMA Archives of ophthalmology. 1957;58:193-201.
30. Olney J.W. Brain lesions, obesity, and other disturbances in mice treated with monosodium glutamate. Science. 1969;164:719-721.
31. Xiao-xia D, Yang W, Zheng-hong Q. Molecular mechanisms of excitotoxicity and their relevance to pathogenesis of neurodegenerative diseases. Acta Pharmacologica Sinica. 2009;30:379-387.
32. Sarkissian J.S, Poghosyan M.V, Danielyan M.A, et al. The assign of depressor synaptic processes in condition of specific neurodegenerative pathology and protection. LAP LAMBERT Academic Publishing RU. 2018:252.