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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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EFFECTS OF LONG-TERM SOCIAL ISOLATION ON MEMORY AND DEPRESSIVE-LIKE BEHAVIOR IN RATS OF DIFFERENT SOCIAL STATUS

Matitaishvili T, Domianidze T, Burjanadze G, Shengelia M, Menteshashvili N.

Ivane Beritashvili Center of Experimental Biomedicine, Tbilisi, Georgia.

Abstract.

Prolonged social isolation constitutes a potent chronic stressor capable of inducing behavioral and neurochemical alterations associated with anxiety, depression, and cognitive dysfunction. In rodent models, dominant and submissive individuals exhibit distinct behavioral and neuroendocrine responses under conditions of social stress. The present study aimed to evaluate the effects of 30 days of social isolation on depressive-like and anxiety-like behaviors, as well as cognitive performance, in rats with differing social status.

Experiments were conducted on 20 groups of white laboratory rats (200–250 g), with three male animals per group. The animals were assigned to either control or experimental conditions. Social status within each group was determined using food- and water-motivation conflict paradigms. Rats in the experimental groups were subjected to 30 days of individual housing (social isolation), whereas control animals were maintained under standard group-housing conditions.

Behavioral assessments included the forced swim test and the elevated plus maze. Short-term spatial memory was evaluated using the Y-maze spontaneous alternation task. Serotonin concentrations in the hypothalamus and hippocampus were quantified using an enzyme-linked immunosorbent assay (ELISA). Statistical analysis was performed using two-way ANOVA followed by Tukey's HSD post hoc test.

Under control conditions, submissive rats displayed higher immobility in the forced swim test and lower basal hypothalamic serotonin levels compared to dominant rats, whereas anxiety indices and short-term memory performance did not differ significantly. Chronic social isolation significantly increased immobility time and reduced the time spent in the open arms of the elevated plus maze in both dominant and submissive rats, indicating enhanced depressive- and anxiety-like behaviors. Anxiety-like responses were more pronounced in submissive rats. Isolation also impaired short-term spatial memory in both dominant and submissive animals, as reflected by a reduced spontaneous alternation ratio in the Y-maze. Neurochemically, hippocampal serotonin levels were significantly decreased in both social groups following isolation. In contrast, hypothalamic serotonin levels increased only in submissive rats, suggesting a social status–dependent neuroendocrine adaptation.

Overall, long-term social isolation induces marked behavioral and region-specific serotonergic alterations irrespective of social status; however, submissive animals demonstrate greater anxiety-related vulnerability and distinct hypothalamic serotonergic upregulation. These findings highlight the modulatory role of social status in stress susceptibility and suggest that region-specific serotonergic imbalance may represent a neurobiological mechanism underlying differential vulnerability to chronic social stress. The results underscore the importance of considering individual social profiles in future research on stress adaptation mechanisms and stress-induced psychopathologies.

Key words. Social isolation, anxiety and depressive-like behavior, serotonin, hippocampus, hypothalamus, short-term memory, rats.

Introduction.

The prolonged quarantine measures imposed during the COVID-19 pandemic have intensified scientific interest in the behavioral and cognitive consequences of chronic social stress, particularly those induced by extended social isolation [1,2]. Experimental evidence from animal models indicates that social stress can provoke depressive- and anxiety-like behaviors, accompanied by neuroendocrine and physiological dysregulation [3-5]. Specifically, social isolation has been associated with impairments in memory and other cognitive functions, as well as with elevated levels of anxiety and depression [4-6]. These findings underscore the critical need to investigate the long-term consequences of social deprivation, particularly in the context of unprecedented global stressors such as the COVID-19 pandemic [7].

Stress is known to modulate central neurotransmitter systems, with a particular impact on monoaminergic signaling pathways [5,8]. Alterations in these systems are thought to mediate many of the behavioral and physiological responses observed following stress exposure [9]. A growing body of evidence suggests that dysfunctions in monoaminergic neurotransmission—including serotonin, norepinephrine, and dopamine—play a central role in the pathophysiology of psychiatric disorders such as anxiety and depression [10,11]. Moreover, serotonin release in key brain regions, including the hypothalamus and hippocampus, appears to depend both on baseline anxiety levels and on the specific nature of the stressor encountered [12].

Individual neurobiological characteristics play a critical role in determining both the nature and the outcome of stress responses. In rodent models, dominant and submissive animals exhibit markedly divergent behavioral and neuroendocrine reactions to stress. Under stressful conditions, submissive rats show higher levels of corticosterone and serotonin compared to dominant rats, reflecting differences in hypothalamic–pituitary–adrenal (HPA) axis functioning and confirming that stress responses vary between social phenotypes [13-15]. Furthermore, parallels between submissive rodent behavior and depressive phenotypes observed in humans suggest that submissive behavior may serve as a valid model of depression [16,17]. Consequently, submissive animals may be inherently more susceptible to anxiety and depression, rendering them particularly vulnerable to the adverse effects of prolonged social isolation.

The present study aimed to evaluate the effects of long-term social isolation on depressive-like behavior and short-

term memory in rats, while considering their social status. By elucidating the behavioral and neurochemical correlations of social stress in dominant and submissive individuals, this research seeks to advance understanding of the biological mechanisms underlying vulnerability to stress-related psychiatric disorders.

Materials and Methods.

Experiments were conducted on 60 white laboratory rats (200–250 g). The animals were housed in 20 groups, with three male rats per group. During the experiment, the groups were divided into experimental (10 groups) and control (10 groups) conditions. Animals were maintained in standard cages (15 × 35 × 45 cm) with free access to food pellets and water ad libitum. All experimental procedures were performed in accordance with the ethical standards approved by the Ethics Committee of the Ivane Beritashvili Center of Experimental Biomedicine, Tbilisi, Georgia.

To identify dominant and submissive animals within groups of rats, we employed two methods that allowed the stronger animal to gain priority access to food and water. In the first method, we examined the animals' behavior under conditions of high food motivation. Following 48 hours of food deprivation, food granules (approximately 2 g each) were provided to allow access for only one animal in the cage. This placement was repeated several times over a 30-minute period, during which we recorded the number of bites, episodes of food stealing, attempts to seize food, portions consumed, and the duration of grooming activity. In the second method, high thirst motivation was induced by 48 hours of water deprivation, after which a water bowl was placed in the cage so that only one animal could access it at a time. During a 15-minute observation period, we recorded the duration of drinking, number of bites, and duration of grooming activity [13,14]. Dominant and submissive rats were determined based on the summarized behavioral parameters observed during these conflict situations.

Following the determination of social hierarchy within each group, rats identified as having an intermediate social status were excluded from subsequent stages of the study. Accordingly, only dominant and submissive animals were subjected to further experimental testing.

In the experimental groups, dominant (n=10) and submissive (n=10) rats were subjected to social isolation. Animals were housed individually in small cages (27 × 15 × 21 cm) for 30 days. Visual contact between cages was limited, whereas olfactory and auditory contact remained unrestricted. In the control groups, dominant and submissive rats were housed in groups in standard cages for the same duration.

Short-term spatial memory was evaluated using a Y-maze apparatus (spontaneous alternation task) [6]. The Y-maze comprised three arms intersecting at 120°. The frequency of entries into three consecutive new arms (A, B, and C) was defined as actual alternation, while entries into previously visited arms were considered errors. Reduced exploration of the last visited arm was interpreted as an indicator of better memory performance. Alternation scores were calculated using the formula: (actual alternation/maximum alternation-2)×100. The total number of arm entries was also recorded.

To assess anxiety- and depressive-like behaviors in rats, we employed the forced swim [18] and elevated plus-maze tests [19,20].

Behavioral testing was conducted in the following order: Y-maze, elevated plus maze (EPM), and finally the forced swim test (FST), with a 24-hour interval between consecutive tests. All behavioral assessments were performed between 10:00 and 12:00 h under standardized experimental conditions. Animals were euthanized 24 h after completion of the final behavioral test (FST), and brain tissues were rapidly dissected between 10:00 and 12:00 h for subsequent ELISA analyses.

Serotonin levels in the hypothalamus and hippocampus were determined using an immunoenzyme assay (ELISA): serotonin Elisa kit, catalog # MBS166089, https://www.mybiosource.com/rat-elisa-kits/serotonin-st/166089. The data were statistically analyzed using two-way ANOVA, followed by Tukey's Honestly Significant Difference (HSD) post-hoc test for multiple group comparisons. Statistical significance was set at $P \leq 0.05$.

Results and Discussion.

The results of the study demonstrated that the behavior of dominant and submissive rats not subjected to the stress procedure (control groups) differed in the forced swim test. Specifically, the forced swim test revealed that the duration of immobility was significantly higher in submissive animals (59.6 ± 3.55 s) compared to their dominant counterparts (31.3 ± 2.56 s) (Tukey's HSD, $P < 0.05$) (Figure 1). The elevated plus maze test showed no significant differences between dominant (56.4 ± 1.96 s) and submissive (49.4 ± 3.46 s) rats in the time spent in the open arms ($P = 0.23$) (Figure 2).

In the Y-maze test, no significant differences in spontaneous alternation percentage were observed between dominant and submissive rats during short-term memory assessment (Figure 3). In the control groups, the percentage of spontaneous alternation was 77.6 ± 2.92 % for dominant rats and 74.6 ± 5.23 % for submissive rats, indicating similar short-term memory performance in animals of both social statuses. The percentage of spontaneous alternation ranged from 74 % to 78 % in animals of both social statuses. Similarly, the number of entries into the Y-maze arms did not differ between dominant rats (8.1 ± 0.62) and submissive rats (7.8 ± 0.51).

Submissive rats exhibited significantly lower basal serotonin concentrations (96.81 ± 7.13) in the hypothalamus compared to dominant rats (187.40 ± 12.58) (Tukey HSD, $P<0.01$) (Figure 4). At the same time, in the hippocampus, serotonin concentrations did not differ according to social status (Figure 5).

In animals from the experimental groups subjected to 30 days of isolation, the duration of immobility in the forced swim test was significantly increased in both dominant (158.1 ± 33.5 s) and submissive (166.6 ± 20.2 s) rats compared to control animals (control vs. stress: $F_{1,36} = 45.3$, $p < 0.001$) (Figure 1). At the same time, no significant differences were observed between dominant and submissive rats within the stressed groups with respect to this parameter ($P = 0.78$). Immobility duration was significantly higher in stressed dominant rats compared to control dominant rats (Tukey HSD, $p < 0.01$), and similarly, it was significantly higher in stressed submissive rats compared to control submissive rats (Tukey HSD, $p < 0.01$).

In the elevated plus maze test, the time spent in the open arms was significantly reduced in both experimental groups, including dominant (22.2 ± 1.46 s) and submissive (8.0 ± 1.29 s) rats, compared to control animals ($F_{1, 36} = 56.5$, $p < 0.001$) (Figure 2). At the same time, stressed submissive rats showed a significantly lower value of this parameter compared to stressed dominant rats (Tukey HSD, $p < 0.05$). In stressed dominant rats, the time spent in the open arms was significantly reduced compared to control dominant rats (Tukey HSD, $p < 0.01$), while in stressed submissive rats it was also significantly reduced compared to control submissive rats (Tukey HSD, $p < 0.01$).

Chronic social stress significantly reduced spontaneous alternation percentage in the Y-maze test in both dominant and submissive rats (Figure 3). In dominant rats, control animals exhibited 77.6 ± 2.92 % alternation, while stressed experimental animals showed 58.3 ± 4.25 %. Similarly, in submissive rats, controlling animals showed 74.6 ± 5.23 % alternation, compared

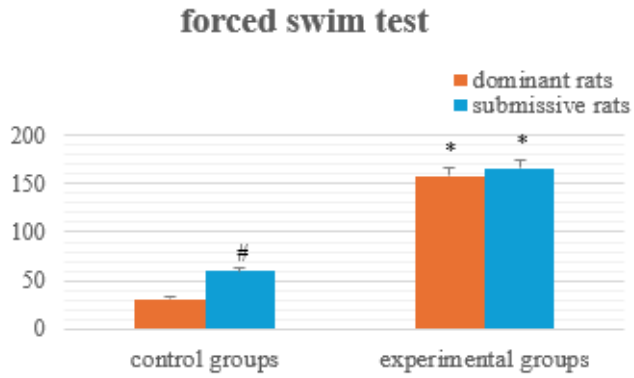

Figure 1. *Durations of immobility (n=10 per group).*
*# - compared to control dominant rats, P < 0.05, *- compared to control rats, P< 0.01*

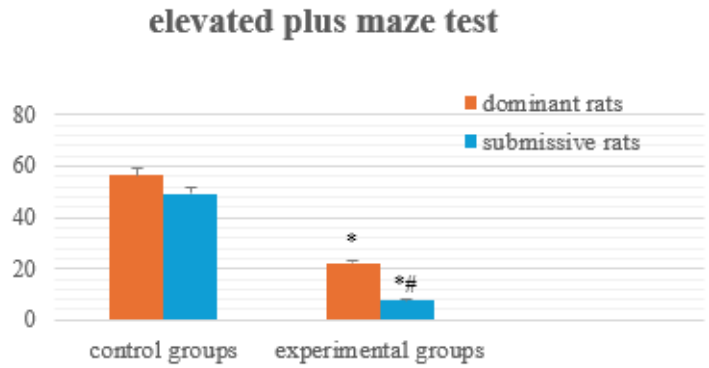

Figure 2. *Time/s spent in the open arms (n=10 per group).*
** - Compared to control rats, p< 0.01, # - Compared to dominant rats in the experimental groups, p < 0.05*

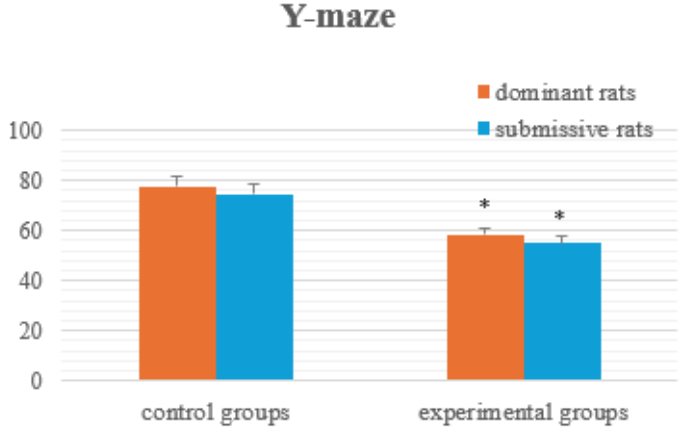

Figure 3. *Spontaneous alternation ratio (%) (n=10 per group).*
** - Compared to control rats, p< 0.01*

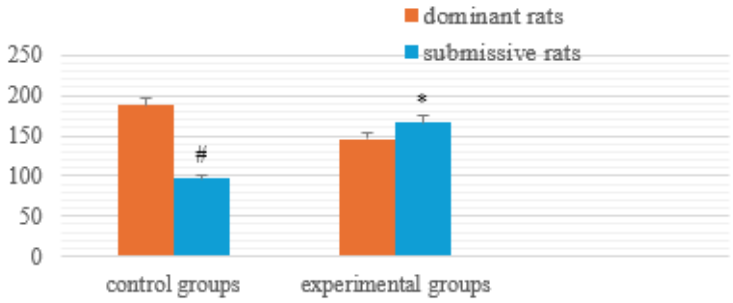

Figure 4. *The concentration of serotonine in the rats' hypothalamus (pg/mg protein) (n=10 per group).*
*# - Compared to control dominant rats, p< 0.01, * - Compared to control submissive rats, P<0.01*

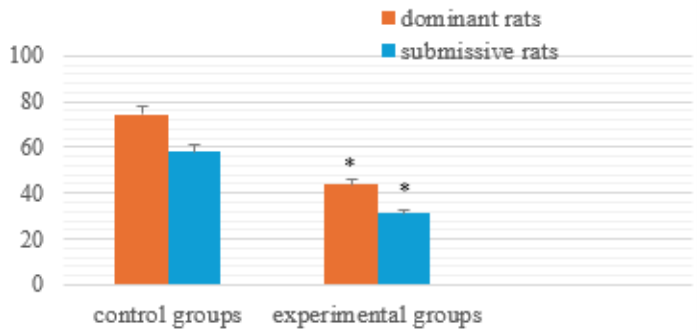

Figure 5. *The concentration of serotonine in the rat's hippocampus (pg/mg protein) (n=10 per group).*
**- Compared to control rats, P<0.05*

to 55.0 ± 6.53 % in stressed animals. Two-way ANOVA revealed a significant main effect of stress ($F_{1,36}$ =15.66, p = 0.00034, p < 0.01), with no significant main effect of social status (p > 0.05) or status × environment interaction (p > 0.05), indicating that chronic social stress impaired short-term memory similarly in both social statuses. As for the number of entries into the Y-maze arms, this parameter in stressed dominant rats was 10.4 ± 0.71, while in stressed submissive rats it was 9.1 ± 0.73. No significant changes in locomotor activity were observed compared to the control groups.

In the experimental groups, submissive rats exhibited a significantly higher serotonin concentration in the hypothalamus compared to control submissive animals (Tukey HSD, p < 0.05) (Figure 4). At the same time, serotonin levels in the hippocampus were reduced in both dominant and submissive stressed rats compared to their respective control counterparts (Tukey HSD, p < 0.05) (Fig.5). No significant differences in serotonin concentrations were observed between stressed dominant and submissive rats in either of the examined brain structures.

According to the results obtained in the present study, long-term social isolation for 30 days induced pronounced depressive-like behavioral changes in both dominant and submissive rats, as evidenced by increased immobility in the forced swim test. In addition, anxiety-like behavior was also elevated in both experimental groups; however, it was more pronounced in submissive animals, as indicated by a significantly reduced time spent in the open arms of the elevated plus maze compared both to control animals and to stressed dominant rats.

Following 30 days of social isolation, performance in the Y-maze test revealed a reduction in spontaneous alternation behavior in rats of different social statuses. Specifically, a significant decrease in the percentage of spontaneous alternations was observed in both dominant and submissive isolated rats, indicating impairment of short-term spatial memory across social phenotypes.

Importantly, the number of Y-maze arm entries did not differ between control and experimental groups, indicating that locomotor activity was not affected by chronic social stress. Therefore, the observed changes in the forced swim test and elevated plus maze are unlikely to be explained by alterations in general motor function or behavioral spontaneity but rather reflect increased anxiety- and depressive-like behaviors.

Overall, the behavioral results demonstrate increased anxiety- and depressive-like manifestations in rats of both social statuses following long-term social isolation. Anxiety-related responses were particularly elevated in animals with a submissive social status, which also exhibited increased serotonin levels in the hypothalamus. In contrast, a reduction in hippocampal serotonin levels was observed in rats of both social statuses, suggesting a region-specific disruption of the serotonergic system under conditions of chronic social isolation. Considering that changes in serotonin levels in brain structures were observed in experimental groups compared to control animals, which were subjected to the same behavioral testing procedures, except for social isolation, we suggest that the observed alterations are specifically attributable to the effects of social isolation.

Previous studies have demonstrated that behavioral and neurochemical responses to stress are influenced by multiple factors, including the type of stressor and individual characteristics of the nervous system [21-23]. Stress exposure

leads to alterations in monoaminergic transmission in key brain regions, such as the hypothalamus and hippocampus, and that these changes play a critical role in stress adaptation and the development of stress-related pathologies [23-25].

According to our previous study, it was demonstrated that 14 days of social isolation induced anxiety-like behavior in both dominant and submissive rats, accompanied by alterations in hypothalamic monoaminergic neurotransmission [5]. Specifically, in our study, social isolation stress led to increased hypothalamic dopamine levels in both dominant and submissive rats. Norepinephrine levels were significantly elevated only in dominant individuals, who also showed lower anxiety levels compared to submissive rats. These findings are in line with other studies reporting that dominant individuals tend to exhibit a noradrenergic stress response profile [5,26,27]. However, according to the results of the present study, under conditions of prolonged stress, increased serotonin levels in the hypothalamus were observed only in submissive rats. According to existing studies, under stressful conditions, submissive rats exhibit higher corticosterone and serotonin levels, which may be associated with differential functioning of the hypothalamic–pituitary–adrenal (HPA) axis [13-15].

Behavioral assessments revealed depressive-like behavior in both dominant and submissive animals; however, anxiety-like behavior was more pronounced in submissive rats. Region-specific alterations in serotonergic activity were also observed. Specifically, serotonin levels in the hippocampus were reduced, which may contribute to stress-induced impairments in cognitive and emotional regulation. In contrast, serotonin levels in the hypothalamus were increased, but exclusively in submissive animals. This increase likely reflects a compensatory activation of hypothalamic serotonergic mechanisms aimed at modulating stress-related neuroendocrine responses. Although this response appears insufficient to prevent the development of depressive-like behavioral manifestations [5,14,23].

The fact that these neurochemical changes were more pronounced in submissive rats aligns with their higher anxiety-like behavior and suggests a social profile-dependent vulnerability to stress. While depressive-like behavior was observed in both social phenotypes, submissive animals appear to experience a greater disruption in serotonergic regulation, characterized by hippocampal serotonin depletion alongside hypothalamic serotonergic upregulation. These findings collectively highlight a region-specific serotonergic imbalance as a potential neurobiological mechanism underlying the heightened anxiety and stress susceptibility of submissive animals.

The absence of hypothalamic serotonergic upregulation in dominant rats may reflect a different stress-coping strategy, potentially relying on noradrenergic mechanisms for stress adaptation. In contrast, submissive animals, being more stress-vulnerable, exhibit a compensatory increase in hypothalamic serotonin to modulate neuroendocrine responses. These findings highlight neurochemical adaptations to chronic stress that are specific to social profile.

A limitation of the present study is that the analysis was restricted to serotonin levels, without assessment of other major monoamines, such as dopamine and norepinephrine. Given the well-established sensitivity of the serotonergic system to social stress and its central role in anxiety- and depression-like behaviors, serotonin was selected as the primary monoaminergic marker in the present study. Nevertheless, inclusion of additional monoaminergic markers in future studies would provide a more comprehensive understanding of the neurobiological mechanisms underlying prolonged social isolation.

Conclusion.

The results of the present study indicate that 30 days of social isolation induce pronounced depressive- and anxiety-like behavioral alterations, as well as impairments in short-term memory, in both dominant and submissive behavioral types of rats. Despite the overall similarity in the direction of these effects, animals with a submissive behavioral profile exhibited a higher level of anxiety-related reactivity. Chronic stress resulted in a reduction of hippocampal serotonin levels in both behavioral groups, indicating a stress-induced region-specific neurochemical imbalance. In contrast, an increase in hypothalamic serotonin levels was observed only in submissive-type animals, which may reflect a compensatory neuroendocrine adaptive response. Overall, the findings highlight the important role of social status in modulating both behavioral susceptibility to stress and region-specific alterations in the serotonergic system. The results emphasize the importance of considering individual social profiles in future studies of stress-adaptive mechanisms and stress-induced psychopathologies.

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