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Consequences of social isolation on behavior and hypothalamic monoaminergic transmission in adult rats of different social statuses

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Abstract

In recent years, social isolation stress of humans and its importance in the development of behavioral disorders of psychiactic nature has become mostly current. Experimental studies using animal models have demonstrated that social stress can induce depressive- and anxiety-like behaviors, as well as neuroendocrine and physiological dysregulation. Stress-related influences are known to alter central neurotransmitter systems, particularly those involved in monoaminergic transmission. Studies have shown that intracerebral neurotransmission dysfunction such as serotonine, norepinephrine and dopamine play an important role in the development of anxiety and depression. The impact of stress varies based on individual neurophysiological characteristics, including social status. The aim of this study was to investigate the effects of stress induced by social isolation on behavior and hypothalamic monoaminergic transmission in rats of different social statuses. Experiments were performed on groups of white male laboratory rats. Dominant and submissive individuals in groups were identified using two methods based on competition for food and water. Social isolation of dominant and submissive rats was carried out for 14 days in small individual cages. Depressive and anxiety-like behaviors were evaluated using the “forced swim” and “elevated cross maze” tests. According to behavioral tests, following social isolation, both dominant and submissive rats exhibited anxiety-like behaviors. In response to isolation, an increase in dopamine concentrations was observed in the hypothalamus of rats. Norepinephrine levels were significantly elevated only in dominant rats, who exhibited lower levels of anxiety compared to their submissive counterparts. Thus, a 14-day social isolation elicits anxiety-like behavior in both dominant and submissive individuals, which is associated with alterations in hypothalamic monoaminergic signaling, notably characterized by elevated dopamine and norepinephrine levels. These findings suggest that the observed increases in hypothalamic monoamine concentrations reflect compensatory and adaptive neurochemical responses aimed at mitigating the adverse effects of prolonged stress exposure and preventing the development of stress-related pathologies. According to the results, submissive individuals exhibit significantly greater sensitivity to social isolation stress than their dominant counterparts. These findings highlight the importance of

considering individual social profiles in future research on stress adaptive mechanisms and stress-induced psychopathologies.

Key words: social isolation, anxiety behavior, monoaminergic neurotransmission, hypothalamus, rats

Introduction. Social stress is recognized as a significant risk factor for the development of behavioral disorders of psychiatric nature. In recent years, human social isolation and its contribution to the onset of these disorders have gained increased scientific attention. The quarantine measures introduced during the COVID-19 pandemic have further intensified interest in understanding the behavioral and neuroendocrine consequences of stress caused by social isolation [1, 2]. Experimental studies using animal models have demonstrated that social stress can induce depressive- and anxiety-like behaviors, as well as neuroendocrine and physiological dysregulation [3]. Moreover, social isolation has been associated with heightened levels of anxiety and depression [4], highlighting the need for a more profound investigation into the long-term consequences of social deprivation during this historically unprecedented period [5].

Stress-related influences are known to alter central neurotransmitter systems, particularly those involved in monoaminergic transmission [6]. These alterations are hypothesized to mediate the behavioral and physiological responses observed following exposure to stress [3]. A growing body of evidence indicates that dysfunctions in monoaminergic neurotransmission—specifically involving serotonin, norepinephrine, and dopamine—play a key role in the etiology of psychiatric conditions such as anxiety and depression [7,8]. Moreover, the release of serotonin in brain regions such as the hypothalamus and hippocampus depend on inborne levels of anxiety and the type of stressor to which animals are exposed [9].

The nature and outcome of stress responses are influenced by individual neurobiological characteristics. In rodent models, dominant and submissive animals demonstrate divergent behavioral and neuroendocrine reactions to stress. Under stressful conditions, submissive rats show higher corticosterone and serotonin levels, which must be associated with a diverse functioning of the hypothalamic-pituitary-adrenal (HPA) axis [10,11,12]. Several studies have also emphasized the parallels between submissive behavior in rodents and depressive phenotypes observed in humans [13,14]. These authors argue that submissive animal behavior may serve as a valid model for depression. Based on this perspective, we propose that submissive animals are inherently more susceptible to anxiety and depression and, consequently, more vulnerable to the effects of social isolation.

Based on the above the current study aims to investigate the effects of social isolation on behavioral outcomes and hypothalamic monoaminergic transmission in rats with different social statuses. By identifying the behavioral and neurochemical correlations of social stress in dominant and submissive phenotypes, this research contributes to a better understanding of the biological underpinnings of stress-related psychiatric vulnerabilities.

Materials and methods. Experiments were carried out on 60 white laboratory rats weighing 200-250g. Animals were divided into experimental (n =10) and control (n=10) groups. Each group contained 3 male and 2 female rats. They were housed in standard (15 X 35X 45 cm) cages. Experiments performed on male rats only. In order to identify dominant and submissive animals in small groups of rats we used two methods enabling the stronger animal to gain a victory during the getting of food and water. In the first method we studied the animals' behaviour in condition of high food motivation. After 48 h of food deprivation, we placed sufficient food granules (each granule weighed about 2 g) for only one animal in the cage. The placing was repeated several times during 30 min, during which interval we recorded the numbers of: bites, food graspings, attempts to grasp food and portions of food taken, as well as duration of grooming activity. In the second method we created high thirst motivation by 48 h water deprivation and then placing a water bowl in the cage so as to be accessible to only one animal. During 15 min the numbers of water lapping's and bites and the duration of grooming activity were recorded [10,11]. The selection of dominant and submissive rats was made according to the summarized behavioural parameters revealed during these conflict situations.

The social isolation of dominant and submissive rats was performed in experimental groups. Rats were placed in small, individual cages (27×15×21) for 14 days under controlled environmental conditions.

In order to evaluate anxiety and depressive behavior of rats we used "forced swim" [15,16] and "elevated cross maze" tests [17,18].

We determined the monoaminergic transmission in the hypothalamus (serotonine, dopamine, norepinephrine) and the concentration of the basal corticosterone in plasma by immunoenzyme analyzer - ELISA reader. The data were processed statistically by two-way factorial analysis (ANOVA).

Results and Discussion. According to the results of the study, notable differences were observed between dominant and submissive rats that were not subjected to social isolation procedures (i.e., control groups). Specifically, the "forced swim" test revealed that the duration of immobility was significantly higher in submissive animals compared to their dominant counterparts ($P<0.01$) (Fig. 2). Submissive rats also exhibited significantly lower basal serotonin concentrations in the hypothalamus compared to dominant rats ($P<0.01$) (Fig. 4). No significant differences were observed in hypothalamic dopamine and norepinephrine concentrations, or in basal plasma corticosterone levels between rats of different social status. Furthermore, the "elevated plus maze" test showed no significant differences between dominant and submissive rats in the amount of time spent in the open arms (Fig. 1).

Following 14 days of social isolation, the time spent in the open arms of the elevated cross maze was significantly reduced in both dominant and submissive rats compared to animals in the control groups ($P<0.01$) (Fig. 1). Additionally, after stress exposure, submissive rats spent significantly less time in the open arms than dominant rats ($P<0.05$) (Fig. 1). The forced swim test revealed no significant changes in immobility duration in either dominant or submissive rats following isolation (Fig. 2). A significant increase in basal plasma corticosterone levels was detected in both dominant and submissive animals compared to the control groups ($P<0.01$) (Fig. 3). Dopamine concentrations in the hypothalamus were significantly elevated in both dominant and submissive rats ($P<0.01$) (Fig. 5), whereas norepinephrine levels were significantly increased only in dominant individuals after stress ($P<0.05$) (Fig. 6). No significant changes in hypothalamic serotonin concentrations were detected between the experimental and control groups (Fig. 4).

According to the obtained results, 14 days of social isolation did not result in increased depressive-like behavior in either dominant or submissive rats, as assessed by the forced swim test. However, in the elevated cross maze, both dominant and submissive rats exhibited fear- and anxiety-like behaviors, which were more pronounced in submissive individuals. Despite the elevated anxiety levels, no significant changes in hypothalamic serotonin concentrations were observed. In contrast, dopamine concentrations were increased in both dominant and submissive rats. Notably, norepinephrine levels were significantly elevated only in dominant rats.

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 [10,19, 20]. In our study, social isolation stress led to increased hypothalamic dopamine levels in both dominant and submissive rats. However, 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 [21,22]. Notably, no changes in basal hypothalamic serotonin levels were found at this stage of isolation-induced stress, despite the presence of heightened anxiety.

The evidence for an involvement of endogenous serotonin in anxiety is contradictory. Increased anxiety behavior in rodents, for example, has been characterized by increased serotonergic activity in several brain structures, whereas other studies emphasized the link between low serotonin and anxiety [9, 23]. Similarly, stress-induced changes in serotonin synthesis and levels are variable, with increases, decreases, and no effects reported [24]. Thus, the results of our study support the hypothesis of other researchers that physiological mechanisms under stress and anxiety are not to depend on serotonin only but seem to include disbalanced interactions between serotonin and other neurotransmitters in the different brain structures such as hypothalamus, hippocampus, prefrontal cortex.

Thus, according to the findings, a 14-day period of social isolation induces anxiety-like behavior in both dominant and submissive rats. However, the level of fear and anxiety was notably higher in submissive individuals. As anticipated, these animals appeared to be more sensitive to the effects of isolation. These behavioral changes were accompanied by alterations in monoaminergic transmission within the hypothalamus, characterized by increased levels of dopamine and norepinephrine.

Numerous studies have demonstrated that stress exposure leads to alterations in monoaminergic transmission in key brain regions, including the hypothalamus, and that these changes play a critical role in stress adaptation and the development of stress-related pathologies [25,26,27]. Based on the findings of the present study and existing literature, we propose that the increased concentrations of dopamine and norepinephrine in the hypothalamus observed at this stage of stress exposure represent compensatory, adaptive mechanisms aimed at counteracting the development of stress-related disorders.

Conclusions. Thus, a 14-day social isolation elicits anxiety-like behavior in both dominant and submissive individuals, which is associated with alterations in hypothalamic monoaminergic signaling, notably characterized by elevated dopamine and norepinephrine levels. These findings suggest that the

observed increases in hypothalamic monoamine concentrations reflect compensatory and adaptive neurochemical responses aimed at mitigating the adverse effects of prolonged stress exposure and preventing the development of stress-related pathologies. According to the study's results, submissive individuals exhibit significantly greater sensitivity to social isolation stress than their dominant counterparts. By identifying the behavioral and neurochemical correlations of social stress in dominant and submissive phenotypes, this research contributes to a better understanding of the biological underpinnings of stress-related psychiatric vulnerabilities.

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Figures

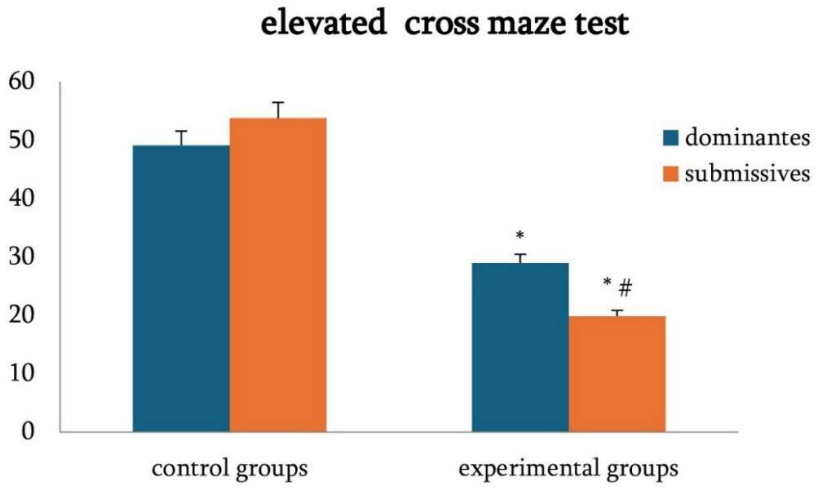

Fig. 1. Abscissa: time/s spent in the open arms.

* - Compared to the control groups, p< 0,01

- Compared to the dominant rats of the experimental groups, p< 0,05

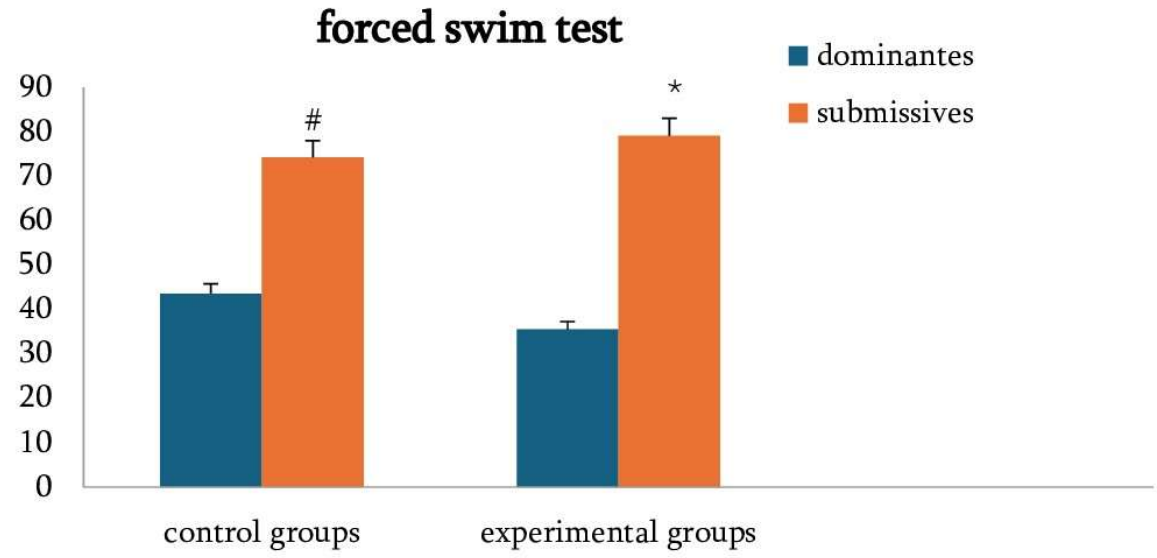

Fig. 2. Abscissa: duration/s of immobility.

#- Compared to the dominant rats of the control groups, p< 0,01

* - Compared to the dominant rats of the experimental groups, p< 0,01

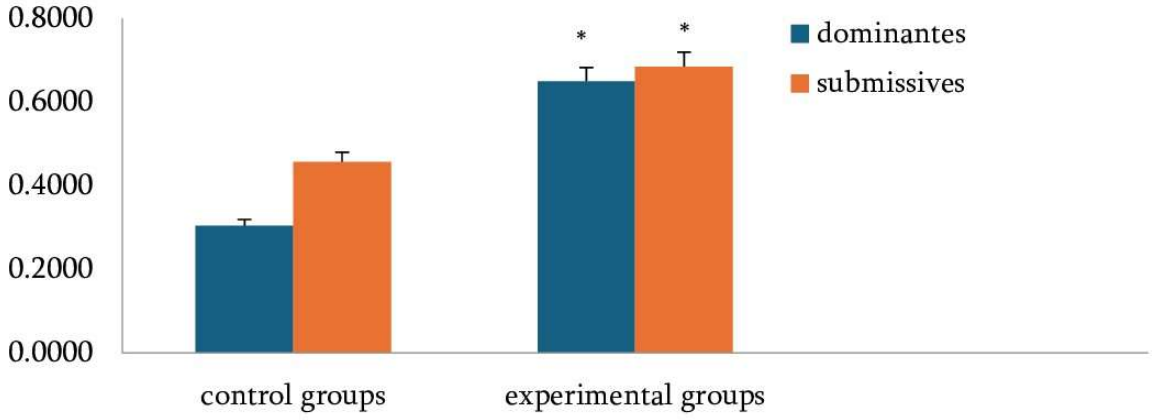

Fig. 3. The concentration of corticosterone in rats' plasma (μg/mg protein).

* - Compared to the control groups, p< 0,01

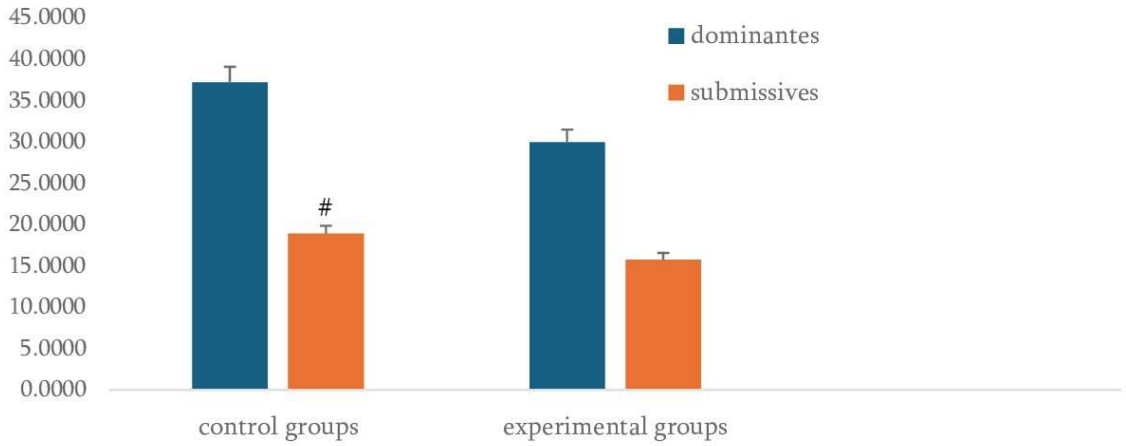

Fig. 4. The concentration of serotonine in the rat's hypothalamus (μg/mg protein**).**

#- Compared to the dominant rats of the control groups, p< 0,01

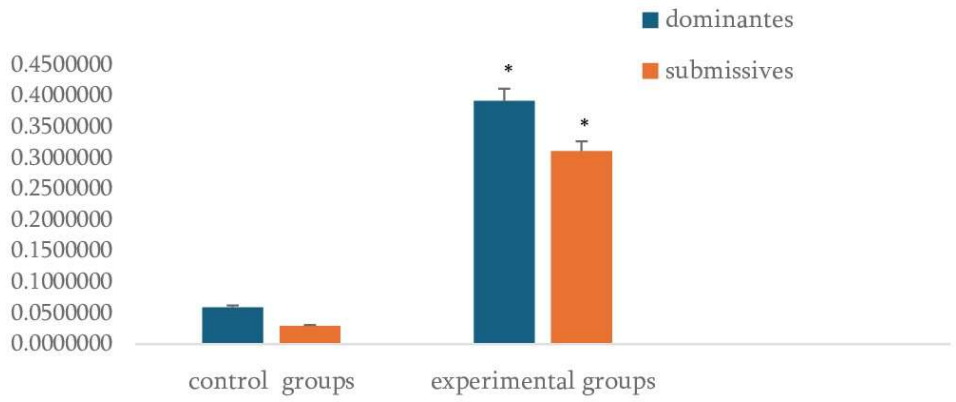

Fig. 5. The concentration of dopamine in the rat's hypothalamus (μg/mg protein)**.**

* - Compared to the control groups, p< 0,01

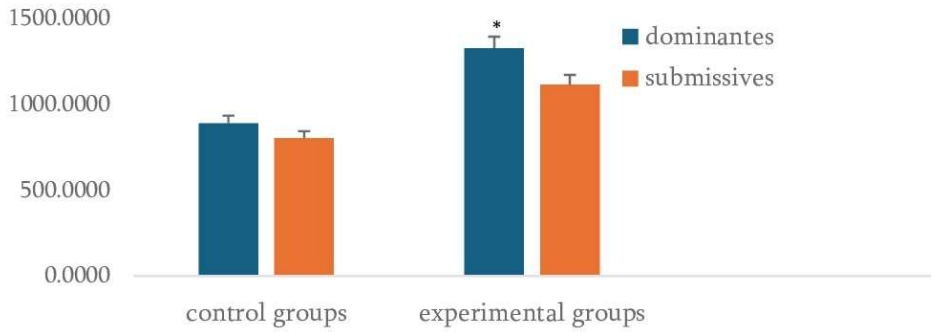

Fig. 6. The concentration of norepinephrine in the rat's hypothalamus (μg/mg protein).

*- Compared to the dominant rats of the control groups, p< 0,05

References

1. Brandt L, Liu S, Heim C, Heinz A. "The effects of social isolation stress and discrimination on mental health". Transl Psychiatry, 2022 Sep 21;12(1):398.
2. Henssler J, Stock F, van Bohemen J, Walter H, Heinz A, Brandt L. "Mental health effects of infection containment strategies: Quarantine and isolation—a systematic review and meta-analysis". Eur Arch Psychiatry Clin Neurosci., 2021; 271:223–34.
3. McNeal N, Anderson EM, Moenk D, Trahanas D, Matuszewich L, Grippo AJ. "Social isolation alters central nervous system monoamine content in prairie voles following acute restraint". Soc Neurosci., 2018 Apr;13(2):173-183.
4. Loades ME, Chatburn E, Higson-Sweeney N, Reynolds S, Shafran R, Brigden A, Linney C, McManus MN, Borwick C, Crawley E. "Rapid Systematic Review: The Impact of Social Isolation and Loneliness on the Mental Health of Children and Adolescents in the Context of COVID-19". J Am Acad Child Adolesc Psychiatry, 2020 Nov;59(11):1218 1239; e3.
5. Begni V, Sanson A, Pfeiffer N, Brandwein C, Inta D, Talbot Sr, Riva MA, Gass P, Mallien AS. "Social isolation in rats: Effects on animal wefare and molecular markers for neuroplastisity ". PLoS One, 2020Oct 27;15(10); e 0240439.
6. McKittrick CR, Blanchard DC, Hardy MP, & Blanchard RJ (2009)." Social stress effects on hormones, brain, and behavior ". Hormones, Brain and Behavior, 2010,1:735-772.
7. Liu Y, Zhao J, Guo W. "Emotional Roles of Mono-Aminergic Neurotransmitters in Major Depressive Disorder and Anxiety Disorders". Front Psychol, 2018 Nov 21; 9:2201.
8. Mumtaz F, Khan, M.I., Zubair M, Dehpour, A.R. "Neurobiology and consequences of social isolation stress in animal model—A comprehensive review". Biomed Pharmacother., 2018 Sep: 105:1205-1222.
9. Umriukhin AE, Wigger A, Singewald N, Landgraf R. "Hypothalamic and hippocampal release of serotonin in rats bred for hyper- or hypo-anxiety". Stress, 2002 Dec;5(4):299-305.

10. Matitaishvili T, Domianidze T, Emukhvari N, Khananashvili M. “Behavioral Characteristics of Rats on Various Hierarchical Level”. Georgian Medical News, 2016, N 3, 63–73.
11. Matitaishvili T, Domianidze T, Kozmava K. “Social stress causes depressive-like behavior in submissive rats”. Journal of Biological Physics and Chemistry, 2023 (23), 53-56.
12. McEwen, B.S., McKittrick, C.R., Tamashiro K.L., Sakai, R.R. “The brain on stress: Insight from studies using the Visible Burrow System”. Physiology & Behavior, 2015(146), 47-56.
13. Malatynska E, Rapp R, Harrawood D, Tunnicliff G. “Submissive behavior in mice as a test for antidepressant drug activity”. Pharmacol Biochem Behav., 2005 Oct;82(2):306-13.
14. Nesher E, Gross M, Lisson S, Tikhonov T, Yadid G, Pinhasov A. “Differential responses to distinct psychotropic agents of selectively bred dominant and submissive animals”. Behav Brain Res., 2013 Jan 1;236(1):225-235.
15. Slattery D. A., and Cryan J. F. “Using the forced swim test to assess antidepressant-like activity in rodents”. Nat. Protoc., 2012, 7, 1009–1014.
16. Yankelevitch Yahav R, Franko M, Huly A, Doron R. “The Forced Swim Test as a Model of Depressive-like Behavior”. Journal of Vis Exp., 2015 Mar 2;(97):52587.
17. Carobrez A. P., and Bertoglio L. J. “Ethological and temporal analyses of anxiety-like behavior: the elevated plus-maze model 20 years on”. Neurosci. Biobehav. Rev., 2005, 29, 1193–1205.7.
18. Arantes R, Tejada J, Bosco G.G, Morato S, Roque A. C. „Mathematical methods to model rodent behavior in the elevated plus-maze”. J. Neurosci. Methods, 2013, 220, 141–148.
19. Villada C, Hidalgo V, Almela M, Salvador A. “Individual Differences in the Psychobiological Response to Psychosocial Stress (Trier Social Stress Test): The Relevance of Trait Anxiety and Coping Styles”. Stress Health, 2016 Apr;32(2):90-9.
20. Ebner K, Singewald N. “Individual differences in stress susceptibility and stress inhibitory mechanisms”. Current Opinion in Behavioral Sciences, 2017 Apr, Volume 14, 54-64.
21. Wood CS, Valentino RJ, Wood SK. “Individual differences in the locus coeruleus norepinephrine system: Relevance to stress-induced cardiovascular vulnerability”. Physiol Behav., 2017 Apr 1:172:40-48.
22. Haller J, Kruk MR. “Normal and abnormal aggression: human disorders and novel laboratory models”. Neurosci Biobehav Rev., 2006;30(3):292-303.
23. Stein D.J. and Stahl S. “Serotonin and anxiety: current models”. International Clinical Psychopharmacology, 2000, 15, S1–6.
24. McKittrick C.R. and McEwen B.S. “Regulation of serotonergic function in the CNS by steroid hormones and stress”. In: Stone, T.W., eds, CNS Neurotransmitters and Neuromodulators (CRC Press, Boca Raton, Florida) 1996, 4, 37–76.
25. Barr JL, Foster GL. “Serotonergic neurotransmission in the ventral hippocampus is enhanced by corticosterone and altered by chronic amphetamine treatment”. Neuroscience, 2011 May, 19:182:105-14.
26. Harvey BH, Brand L, Jeeva Z, Stein DJ. “Cortical/hippocampal monoamines, HPA-axis changes and aversive behavior following stress and restress in an animal model of post-traumatic stress disorder”. Physiol Behav., 2006 May 30;87(5):881-90.

27. Lapiz-Bluhm MD. “Impact of stress on prefrontal glutamatergic, monoaminergic and cannabinoid systems”. Curr Top Behav Neurosci., 2014,18:45-66.

სოციალური იზოლაციის შედეგები ქცევასა და ჰიპოთალამური მონოამინერგული ნეიროტრანსმისიის მახასიათებლებზე სხვადასხვა სოციალური სტატუსის ზრდასრულ ვირთაგვებში

მათითაიშვილი თამარი[1], დომიანიძე თამარი[1], ბურჯანაძე გიორგი[2], შენგელია მარიამი[2], მენთეშაშვილი ნატო[1]

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აბსტრაქტი

უკანასკნელ წლებში განსაკუთრებული აქტუალობა შეიძინა სოციალური იზოლაციით გამოწვეული სტრესის მნიშვნელობამ ადამიანის ფსიქიატრიული ხასიათის ქცევითი დარღვევების განვითარებაში. ექსპერიმენტებმა ცხოველური მოდელების გამოყენებით ცხადყო, რომ სოციალური სტრესი იწვევს დეპრესიულ და შფოთვის ტიპის ქცევას, ფიზიოლოგიური და ენდოკრინული რეგულაციის დარღვევით. ცნობილია, რომ სტრესოგენური ზემოქმედება ცვლის ცენტრალური ნეიროტრანსმიტერული სისტემების ფუნქციონირებას, განსაკუთრებით კი იმ ნერიომედიატორებისა, რომელნიც მონოამინერგულ გადაცემას უზრუნველყოფენ. კვლევებით დასტურდება, რომ თავის ტვინში სეროტონინის, ნორადრენალინისა და დოფამინის გადაცემის დარღვევა მნიშვნელოვან როლს ასრულებს შფოთვისა და დეპრესიის განვითარებაში. ამავდროულად სტრესის განვითარების ხასიათი და შედეგები განსხვავდება ორგანიზმის ინდივიდუალური ნეიროფიზიოლოგიური თავისებურებების, მათ შორის სოციალური სტატუსის გათვალისწინებით. კვლევის მიზანს წარმოადგენდა სოციალური იზოლაციით გამოწვეული სტრესის გავლენის შესწავლა ქცევაზე და ჰიპოთალამუსის მონოამინერგულ გადაცემაზე განსხვავებული სოციალური სტატუსის ვირთაგვებში. ექსპერიმენტები ჩატარდა მამრობითი სქესის თეთრი ლაბორატორიული ვირთაგვების ჯგუფებზე. ვირთაგვების სოციალური სტატუსი განისაზღვრა საკვებზე და წყალზე კონკურენციის პრინციპზე დაფუძნებული მეთოდების გამოყენებით. დომინანტი და სუბმისური ვირთაგვების სოციალური იზოლაცია განხორციელდა მცირე ზომის ინდივიდუალურ გალიებში 14 დღის განმავლობაში. დეპრესიული და შფოთვითი ქცევა შეფასდა “ამაღლებული ჯვარედინი ლაბირინთის” და “იძულებითი ცურვის” ტესტების გამოყენებით. სოციალური იზოლაციის შემდეგ როგორც დომინანტ, ასევე სუბმისიურ ვირთაგვებში ქცევითი ტესტების მიხედვით გამოვლინდა შფოთვითი ქცევა. იზოლაციის საპასუხოდ ვირთაგვების ჰიპოთალამუსში აღინიშნა დოფამინის კონცენტრაციის მატება. ნორადრენალინის დონე კი მნიშვნელოვნად გაიზარდა მხოლოდ დომინანტ ინდივიდებში, რომელთაც ამავდროულად აჩვენეს შფოთვის შედარებით დაბალი დონე სუბმისურებთან

შედარებით. ამრიგად, 14-დღიანი სოციალური იზოლაცია იწვევს დომინანტ და სუბმისურ ვირთაგვებში შფოთვითი ტიპის ქცევას და ჰიპოთალამუსის მონოამინერგული გადაცემის ცვლილებებას დოფამინისა და ნორადრენალინის დონის მატებით. მიღებული მონაცემები მიუთითებს, რომ ჰიპოთალამუსში მონოამინების კონცენტრაციის გაზრდა წარმოადგენს კომპენსატორულ, ადაპტაციური ხასიათის ნეიროქიმიურ რეაქციას, რომელიც მიმართულია სტრესის მავნე ეფექტების შემცირებისკენ და სტრესით გამოწვეული პათოლოგიების საწინააღმდეგოდ. კვლევის შედეგებით დადგინდა, რომ სუბმისიური ინდივიდები გაცილებით მაღალი მგრძლობელობით გამოირჩევიან სოციალური იზოლაციის მიმართ. აღნიშნული მიგნებები ხაზს უსვამს ინდივიდუალური სოციალური პროფილის გათვალისწინების მნიშვნელობას სტრესის ადაპტაციური მექანიზმებისა და სტრესით გამოწვეული ფსიქოპათოლოგიების კვლევის პროცესში.

საკვანძო სიტყვები: სოციალური იზოლაცია, შფოთვითი ქცევა, მონოამინერგული ნეიროტრანსმისია, ჰიპოთალამუსი, ვირთაგვები