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Стимулирующие эффекты стресса на формирование памяти у крыс: роль белка 2, опосредующего активность коллапсина (CRMP2)

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Аннотация. Статья посвящена изучению влияния хронического стресса на формирование долговременной памяти и уровня белка 2, опосредующего активность коллапсина (collapsin-response mediator protein 2 (CRMP2)) в различных структурах мозга самок крыс линии Wistar. В 1-й экспериментальной серии крыс, лишенных корма, парами помещали в модельную камеру на пять минут, на протяжении пяти дней подряд. На основании продолжительности периода времени, проведенного у кормушки, крысы были поделены на группы доминантных и подчиняющихся. Во 2-й серии доминантных и подчиняющихся животных помещали поодиночке в бассейн с пресной водой на пять минут и фиксировали общую продолжительность пассивного плавания. Время пассивного плавания у подчиняющихся крыс было в 2,5 раза выше, чем у доминирующих. В 3-й серии эксперимента животных обеих групп обучали в челночной камере в течение шести последовательных дней, и подчиняющиеся животные демонстрировали более высокие результаты по сравнению с доминантными крысами. Уровни CRMP2 в миндалине, гиппокампе и левой теменной коре мозга подчиняющихся и доминирующих крыс оценивали с помощью твердофазного непрямого теста ELISA. Результаты показали более высокие уровни CRMP2 в миндалине, гиппокампе и левой теменной коре подчиняющихся крыс по сравнению с доминирующими. Повышение уровня CRMP2 в миндалине подчиняющихся крыс рассматривается как адаптация к стрессовому подчиненному состоянию, тогда как возрастание его уровня в гиппокампе и теменной коре лежит в основе молекулярного механизма стимулирующего эффекта стресса на формирование памяти.

Ключевые слова: самки крыс Wistar, доминантная модель, стресс, челночная камера, CRMP2, непрямой тест ELISA

Enhancement of stress-induced memory formation in rats: The role of collapsin-response mediator protein 2 (CRMP2)

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Abstract. The reported study investigates the impact of chronic stress on long-term memory formation and the expression of collapsin-response mediator protein 2 (CRMP2) within various brain structures in Wistar female rats. In the first experimental series, food-deprived rats were placed in pairs into a dominant model box for 5 minutes, over a period of five consecutive days. Dominant and submissive rats were categorized based on the amount of time spent at the feeder. In the second series, dominant and submissive rats were individually subjected to a 5-minute passive swimming test in a container of fresh water, with passive swimming duration recorded. Submissive rats exhibited a passive swimming time 2.5 times longer than that of dominant rats. In the third series, both groups were trained in a shuttle box for six consecutive days, with submissive rats achieving a greater number of correct trials compared to dominant rats. The levels of CRMP2 were measured in the amygdala, hippocampus, and left parietal cortex of both groups using a solid-phase indirect ELISA test. The results showed higher CRMP2 levels in the amygdala, hippocampus, and left parietal cortex of submissive rats compared to dominant rats. The upregulation of CRMP2 in the amygdala of submissive rats is hypothesized to be an adaptive response to chronic stress, while its increased expression in the hippocampus and parietal cortex is suggested to contribute to the stimulatory effect of stress on memory formation.

Keywords: Wistar female rats, dominant model, stress, shuttle box, collapsin-response mediator protein 2, indirect ELISA-test

Introduction

Stress has become an integral and pervasive part of modern life, influencing various aspects of daily activities, including work-related tasks and interpersonal relationships. Simultaneously, the demands placed on individuals to process, acquire, and retain vast amounts of information in their memory have never been higher. This raises the important question of how stressful conditions influence memory formation — whether these effects are detrimental or enhancing.

In animal studies, stress naturally arises during the initial stages of learning, particularly when animals are exposed to unfamiliar stimuli, such as a novel experimental environment. However, this stress typically diminishes as the animals become more adept at learning the task. The question of how prior stress, or a stressful background, influences memory formation is increasingly important in this context. While extensive research has been dedicated to examining the effects of stress on memory, results have often been contradictory, leaving the true nature of the influence of stress on memory unclear. In particular, earlier studies showed the disruptive impact of stress on memory formation (Schwabe, Wolf 2010), whereas further studies identified stress as a facilitator of memory trace formation (McGaugh 2015; Wiemers et al. 2013).

In addition to the ambiguous nature of the phenomenological effects of stress on memory, the underlying molecular mechanisms remain poorly understood and warrant careful and unbiased investigation. It is essential to distinguish between biochemical changes that are merely associated with stress and those that directly contribute to its effects on memory processes. Our recent studies have revealed the upregulation of collapsin-response mediator protein 2 (CRMP2) (Inagaki et al. 2001; Nakamura et al. 2020) in the platelets

of individuals with anxiety. The samples were taken on the day of patients' surgery. Patients were found to have corresponding changes in the brain cortex (Collins et al. 2013; Elliott, Kent 1989) and a sharp upregulation of natural anti-CRMP2 autoantibodies in their serum (Guliyeva, Mekhtiev 2023), reflecting a similar CRMP2 upregulation in their subcortical brain structures (Hasanova 2022). Further experiments in male Wistar rats, including those using the elevated plus-maze to assess anxiety levels, confirmed that the observed changes were not incidental. In particular, intracerebral administration of CRMP2 induced significant behavioral changes, including increased anxiety levels (Guliyeva et al. 2024).

As CRMP2 is involved in processes such as axonal sprouting, neuronal precursor migration, and maturation (Nakamura et al. 2020), we hypothesize that it may play a critical role in the molecular processes underlying memory formation. In this context, we also aimed to investigate the impact of stress on CRMP2 levels in different brain structures, specifically those associated with stress regulation (amygdala) and memory formation (hippocampus and left parietal cortex).

The current study design included the induction of stress in rats, confirmation of the stress state through behavioral testing, evaluation of the impact of stress on memory formation, and measurement of CRMP2 levels in key brain regions.

Materials and Methods

Given the established evidence that females are more susceptible to the effects of various stressors than males (Hodes, Epperson 2019; Marchette et al. 2018), the present study was conducted using female Wistar rats, weighing between 170 and 210 grams.

In the first experimental series, acute stress was induced in the dominant model box consisting of two compartments connected by a narrow passage that allowed only one rat to move through at a time (Malatynska et al. 2007). A feeder containing sweet milk was placed in the middle of the passage. Prior to the experiment, all animals were food-deprived for 48 hours. Animals were paired (n=8 pairs) and placed in the dominant model box for a 5-minute period over five consecutive days. The total time spent at the feeder was recorded for each animal. The animals within each pair competed for access to the feeder, with dominant individuals forcibly pushing submissive rats aside to gain access. In each pair, the dominant rat was identified as the one that spent more time at the feeder (bigger time; n=8), while the submissive rat, which spent less time (lesser time; n=8), was subjected to stress. Submissive rats demonstrated a marked decrease in motor and exploratory activities following their expulsion from the feeder.

In the second experimental series, the stress levels of dominant and submissive rats were further assessed using the passive swimming test, which measures the severity of stress levels. The animals were placed individually into a round container (diameter 60 cm, height 60 cm), filled with warm (26–27°C) fresh water to a depth of 2/3 of the container's height. Each animal was left to swim for 5 minutes, and the total duration of both active and passive swimming was recorded (Bogdanova et al. 2013).

In the third experimental series, the dominant (n = 8) and submissive (n = 8) rats were subjected to a six-day learning task in a shuttle box, with 10 trials conducted each day (Guseinov, Mekhtiev 2013). The shuttle box, made of organic glass, was equipped with a sound stimulus that served as a conditioned stimulus, followed by an electric shock (0.8 mA pulse current) to the paws, delivered through the iron-grid floor. The rats could escape the electric shock by passing through a round hole in the partition to a neighboring chamber. In the second chamber, the rats were subjected to the same test with a sound stimulus followed by an electric shock. The trial was considered correct if the rat entered the safe chamber promptly after hearing the sound stimulus, prior to receiving the electric shock.

In the fourth experimental series, all animals were sacrificed, and the amygdala, hippocampus, and left parietal cortex were dissected from their brains. Protein extraction was performed, and the resulting samples were used as antigens in a solid-phase indirect ELISA assay (Catty, Raikundalia 1989), conducted on polystyrene plates with moderate adsorption capacity (Sigma, Germany). Protein concentrations were adjusted to 20 μg/mL in 0.1 M tris-HCl buffer (pH 8.6) using the Bradford method on an SF-46 spectrophotometer (LOMO, Russia) at 595 nm with application of 0.01% CBB G-250 solution. Anti-CRMP2 polyclonal antibodies were used as the primary antibody in antibody buffer (pH 7.3), and goat anti-rabbit immunoglobulin conjugated to horseradish peroxidase was used as the secondary antibody (pH 7.3; diluted 1:20,000). *o*-phenylenediamine (0.5 mg/mL) in 0.5 M citrate-phosphate buffer (pH 4.5) was used as the substrate for the peroxidase conjugated to the secondary antibody. After 20 minutes, the reaction was stopped by adding 50 μL of 3 M NaOH to each well. Absorbance was recorded at 492 nm, with a comparison wavelength of 630 nm, using an ELISA photometer (Molecular Devices SpectraMax 250, MTX Lab Systems, Inc., USA).

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The behavioral data from the first three experimental series and the immunochemical data from the fourth series were evaluated for normal distribution. Statistical comparisons between groups were performed using Student's t-test (Rohlf, Sokal 1995).

Results

In the first experimental series, conducted over five consecutive days using a dominant behavior box, dominant and submissive rats were identified based on the time spent near a container with sweet milk positioned at the center of a narrow passage. Specifically, dominant rats spent the following durations at the feeder over the five days: 242 ± 10.2 sec, 232.5 ± 16.6 sec, 254.4 ± 10 sec, 217.5 ± 12.7 sec, and 241.2 ± 14.7 sec (Fig. 1). In contrast, submissive rats spent significantly less time at the feeder, with times of 57.9 ± 10.2 sec ($p < 0.001$), 67.5 ± 16.6 sec ($p < 0.001$), 45.6 ± 10 sec ($p < 0.001$), 82.5 ± 12.7 sec ($p < 0.001$), and 65.5 ± 17.8 sec ($p < 0.001$) across the same days (Fig. 1). These results demonstrate that dominant and submissive behavior patterns remained consistent across the five consecutive days.

In the second experimental series, the total duration of passive swimming was recorded in the water container for both dominant and submissive rats. The submissive rats exhibited a significant increase in passive swimming time (2.5 times), spending 200.8 ± 10 sec on average during a 300 sec test, compared to 78.5 ± 10.5 sec for dominant rats ($p < 0.001$) (Fig. 2). These findings highlight the stress-induced behavioral differences between dominant and submissive animals.

In the third experimental series, the dynamics of conditioning were assessed over six days using a shuttle box. As shown in Fig. 3, submissive rats consistently outperformed dominant rats in the number of correct trials. On the sixth day of continuous learning sessions in a shuttle box, submissive rats achieved a correct trial score of 0.68 ± 0.07, whereas dominant rats scored 0.43 ± 0.05 ($p < 0.05$).

In the fourth experimental series, levels of CRMP2 were evaluated in the amygdala, hippocampus, and left parietal cortex using an indirect ELISA test. The results revealed notable differences between dominant and submissive rats. In the amygdala, the CRMP2 level was 0.161 ± 0.005 optical extinction units (OEU) in submissive rats, compared to 0.128 ± ± 0.006 OEU in dominant rats ($p < 0.01$) (Fig. 4). In the hippocampus, submissive rats exhibited a CRMP2 level of 0.164 ± 0.003 OEU, while dominant rats showed a level of 0.14 ± 0.005 OEU ($p < 0.01$) (Fig. 4). In the left parietal cortex, CRMP2 levels were 0.113 ± 0.005 OEU in submissive rats and 0.093 ± 0.006 OEU in dominant rats ($p < 0.05$) (Fig. 4).

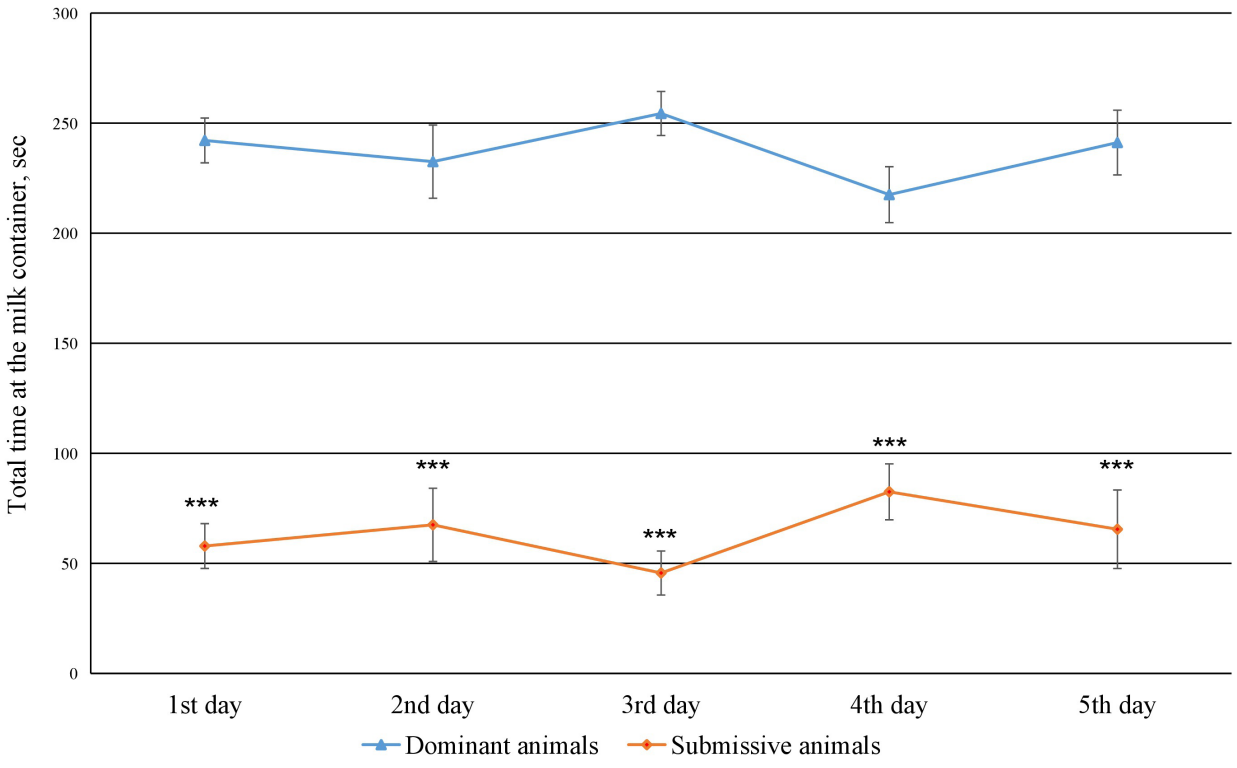

Fig. 1. Dynamics of total time spent by dominant and submissive rats at the feeder with sweet milk in a dominant behavior model. *** — $p < 0.001$

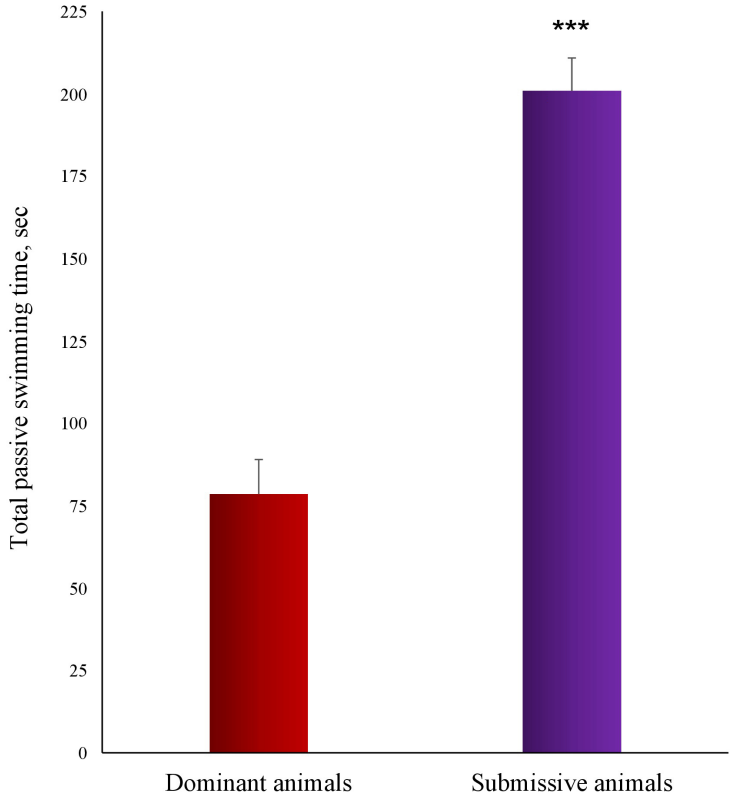

Fig. 2. Duration of total passive swimming time in the dominant and submissive animals. * — $p < 0.001$

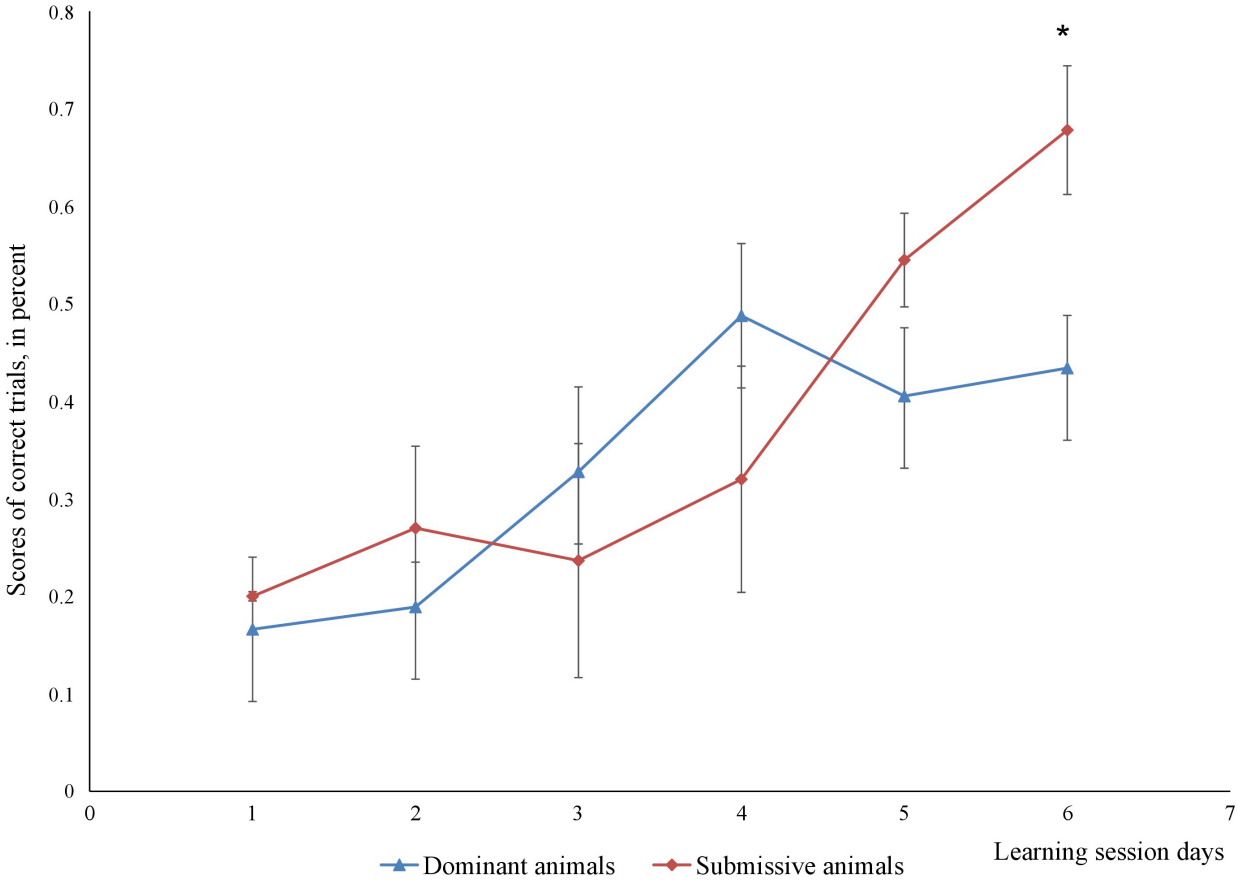

Fig. 3. Dynamics of correct trial score during memory formation in a conditioned shuttle box in dominant and submissive animals. * — $p < 0.05$

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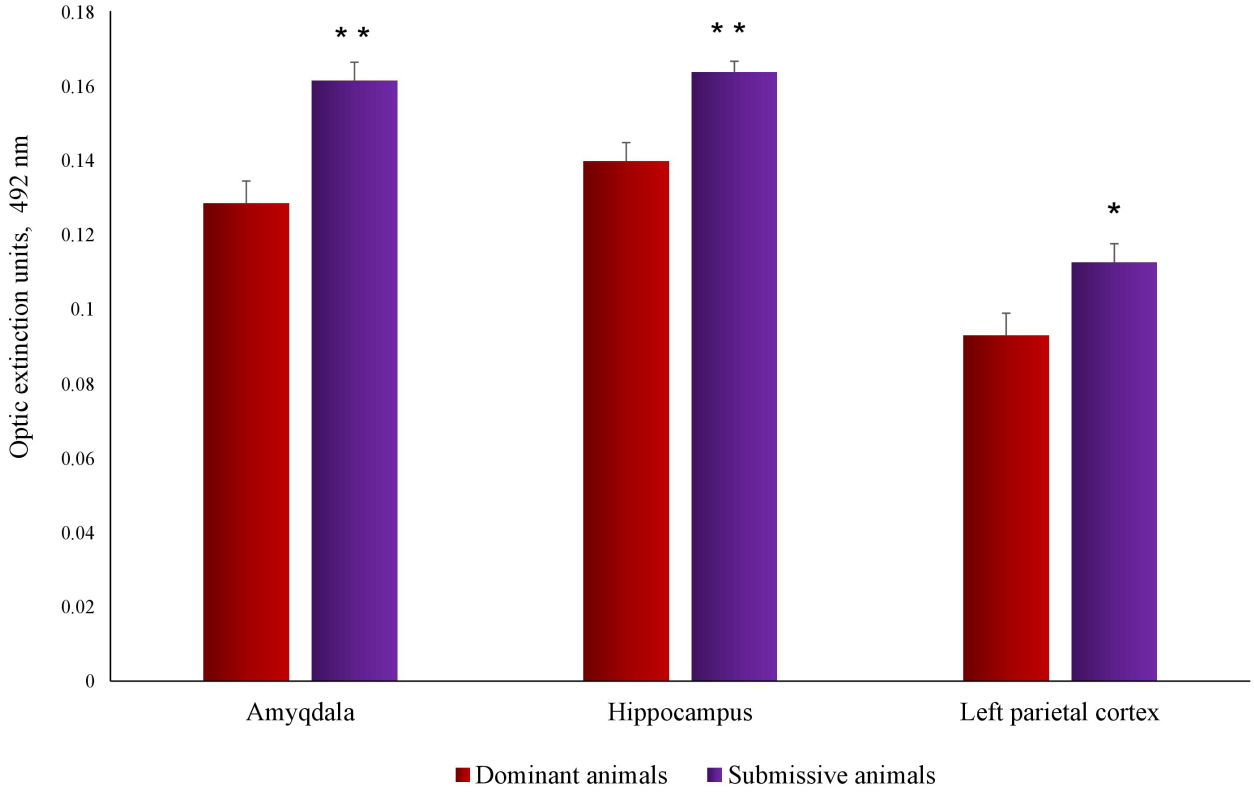

Fig. 4. CRMP2 levels in brain structures of dominant and submissive animals.
* — $p < 0.05$, ** — $p < 0.01$

Thus, upregulation of CRMP2 was observed in brain regions associated with emotion regulation and aggression (amygdala), as well as those involved in memory formation (hippocampus and left parietal cortex), in submissive animals.

Discussion

Pairing animals together over several consecutive days in the dominant behavior model allowed for the identification of dominant and submissive individuals within each pair. This setup induced stress in submissive animals, as evidenced by a 2.5-fold increase in passive swimming time in the submissive group compared to the dominant group.

One of the key findings of this study is the upregulation of CRMP2, particularly, in brain structures involved in emotion and aggression regulation — namely, the amygdala (Šimić et al. 2021) — and those involved in memory formation, including the hippocampus (Alam et al. 2018; Eichenbaum 2004; Fortin et al. 2002) and left parietal cortex (Brodt et al. 2016). This upregulation was observed in the stress-exposed submissive rats. The CRMP2 increase in the amygdala may reflect a compensatory response to the stress experienced by submissive rats after their hierarchical positioning in the dominant behavior model. This suggests that CRMP2 upregulation in the amygdala may contribute to psychological adaptation to the stress resulting from the submissive position in the hierarchy.

In addition to the amygdala, CRMP2 upregulation was also observed in the hippocampus and left parietal cortex of submissive rats. Since these brain regions are crucial for memory formation, this upregulation likely influences long-term memory dynamics. Indeed, at the final stage of memory formation (Day 6) in the shuttle box, submissive rats demonstrated higher scores in correct trials compared to dominant rats, indicating to enhancement of their memory performance

The observed increase in CRMP2 levels in the hippocampus and left parietal cortex of the submissive group aligns with known physiological functions of CRMP2. Current literature indicates that CRMP2 is involved in regulating axonal sprouting and the migration of neuronal precursors (Nakamura et al. 2020). Given these activities, the natural upregulation of CRMP2 in the hippocampus and parietal cortex of stress-exposed animals may underlie the enhancement of memory formation observed in this study. Additionally, the upregulation of CRMP2 in the brain structures of submissive animals may be linked to the serotonin-modulated nature of this protein (Garina et al. 2018; Mekhtiev 2000).

Recent studies in mollusks have demonstrated that stress conditions can enhance memory formation, although the molecular mechanisms underlying these effects remain unclear (Dodd et al. 2018; Swinton et al. 2019). For example, in *Lymnaea stagnalis*, damage to the shell clip significantly increased the elaboration of long-term potentiation. Similarly, in rodents, stress has been shown to promote memory formation (Goldfarb 2019).

However, it is important to note that the impact of stress on memory formation largely depends on its duration and intensity. Prolonged and severe stress may lead to downregulation of neurotransmitters and regulatory proteins, resulting in memory impairment. The dual nature of stress effects, promoting or inhibiting memory formation based on its intensity, may explain the variability in research findings produced by neurobiology in this field.

In summary, the results of this study demonstrate that stress induces the upregulation of CRMP2 in brain structures involved in emotion regulation (amygdala) and memory formation (hippocampus and left parietal cortex) in submissive rats. The CRMP2 increase in the amygdala may reflect an adaptive response to stress, while the upregulation in the hippocampus and left parietal cortex may be a key molecular mechanism underlying the memory-enhancing effects of stress in these animals.

Конфликт интересов

Авторы заявляют об отсутствии потенциального или явного конфликта интересов

Conflict of Interest

The authors declare that there is no conflict of interest, either existing or potential.

Соответствие принципам этики

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Ethics Approval

All studies were performed in accordance with the ethical standards of the Academician Abdulla Garayev Institute of Physiology and the National Bioethics Committee of Azerbaijan, as well as the ethical principles of the Declaration of Helsinki (WWS Declaration of Helsinki) for medical research.

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Author Contributions

a. Medina I. Hasanova — behavioral and immunochemical experimentation, data analysis and discussion;

b. Arif A. Mekhtiev — biochemical and immunochemical experimentation, data analysis and discussion, manuscript writing.

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