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ФИЗИОЛОГИЧЕСКИЕ МЕХАНИЗМЫ ПОВЕДЕНИЯ ЖИВОТНЫХ: ВОСПРИЯТИЕ ВНЕШНИХ СТИМУЛОВ, ДВИГАТЕЛЬНАЯ АКТИВНОСТЬ, ОБУЧЕНИЕ И ПАМЯТЬ

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INCREASE IN HISTONE ACETYLATION RESCUES A WEAK REMOTE FEAR MEMORY IN RATS

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There is a growing body of evidence of memory-enhancing effects of histone deacetylase (HDAC) inhibitors in different species and models. Less clearly is understood whether the increased histone acetylation is able to facilitate the remote fear memory. Thus, the aim of the current study was to examine the ability of HDAC inhibitor sodium butyrate (SB) to ameliorate weakening of the remote fear memory in rats. To assess the ability of HDAC inhibitor SB to improve remote fear memory we compared the performance of two laboratory strains of rats, Wistar and Long-Evans, in context fear conditioning task six months after training before and after the SB administration. We found that the rats showed a strong fear response to the context 24 h after the end of conditioned fear training, full absence of fear after 6 months, and high fear response after the SB administration without additional learning. In control experiments, we found that time-dependent decrease in conditioned fear response to the context was similar in rats under vehicle administration. Moreover, the data obtained showed that both rats' strains showed a similar decrease in freezing response over time, and HDAC inhibition improved the weak remote fear memory in both of them. In addition, the decrease in freezing and memory reinstatement by males matched completely to the female rats' performance. These results indicate that HDAC inhibition appears to have the same "rescue" effects on remote fear memory reinstatement regardless of the strain and gender of rats.

Keywords: sodium butyrate, histone acetylation, epigenetics, remote memory, memory reinstatement, reconsolidation

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INTRODUCTION

There is a growing body of evidence of memory-enhancing effects of increased histone acetylation in different species. Histone acetylation level is determined by activity of two main enzymes: histone acetyltransferase that acetylates the lysine residues of histones to relax chromatin and increase in the rate of gene transcription and histone deacetylase (HDAC) that deletes acetyl groups, suppressing gene expression (Peixoto, Abel, 2013; Marmonstein, Zhou, 2014; Seto, Yoshida, 2014). As gene transcription is necessary for long-term memory, it is believed that histone acetylation increase promotes the long-term memory while histone deacetylation disturbs it. One of the most common tools for the regulation of histone acetylation is HDAC inhibitors.

Accumulating evidence suggests a critical role for inhibiting HDAC activity in improving the memory consolidation. It has been demonstrated that systemic or intracerebral administration of HDAC inhibitors enhances memory consolidation in several paradigms, such as object recognition (Stefanko et al., 2009; Roozendaal et al., 2010; Hawk et al., 2011; Chen et al., 2018; Sartor et al., 2019; Ramirez-Mejia et al., 2021), spatial memory consolidation (Guan et al., 2009; Villain et al., 2016), contextual fear conditioning (Levenson et al., 2004; Vecsey et al., 2007; McQuown et al., 2011; Vinarskaya et al., 2021). Single studies investigated the role of HDAC inhibitors in memory enhancement during reconsolidation (Bredy, Barad, 2008; Villain et al., 2016; Monsey et al., 2020; Ameneiro et al., 2022) and strengthening of impaired memory (Alarcon et al., 2004; Chen et al., 2014; Ko et al., 2016; Zuzina et al., 2020; Vinarskaya et al., 2021). But all of them were focused exclusively on memories that were acquired recently.

It should be noted that neurophysiological mechanisms of remote memory differ significantly from those of recent memories (Albo, Graff, 2018; Lee et al., 2023; Terranova et al., 2023). While initial stages of consolidation of contextual fear memories involve hippocampus and amygdala (Choi et al., 2018; Kim, Cho, 2020), the latest stages involve synaptic changes in neocortex (Frankland, Bontempi, 2005; Albo, Graff, 2018). These changes lead to progressive strengthening of the role of engram neurons in the neocortex (Lee et al., 2023) while memories become less hippocampus-dependent (Kim, Fanselow, 1992). For these reasons, it seemed to us important to determine whether histone acetylation increase rescues the remote fear memory.

Thus, the aim of the current study was to examine the ability of HDAC inhibitor SB to ameliorate weakening of the remote fear memory in rats. To assess the ability of HDAC inhibitor SB to improve the remote fear memory, we compared the performance of two laboratory strains of rats, Wistar and Long-Evans, in context fear conditioning task six months after one day fear conditioning training before and after SB administration. We found that rats trained using conventional procedure showed a strong fear response to the context 24 h after the end of conditioned fear training, the absence of fear after 6 months, and high fear responses after SB administration without additional learning. In control experiments, we found that time-dependent decrease of conditioned fear response to the context was preserved in rats under vehicle administration. Moreover, the data obtained showed that both rats' strains showed a similar decrease in freezing response over time, and HDAC inhibition improved weak remote fear memory in both of them. In addition, the decrease in freezing and memory reinstatement by males matched completely to female rats' performance. These results indicate that HDAC inhibition appears to have the same "rescue" effects on remote fear memory reinstatement regardless of the strain and gender of rats.

METHODS

Naïve twenty-five male Long-Evans rats, twenty-three female Long-Evans rats, twenty-two male Wistar rats and nineteen female Wistar rats obtained from the Animal Facility of the Institute of Bioorganic Chemistry of the Russian Academy of Sciences in Pushchino were used in the experiment. The Long-Evans and Wistar strains were specifically chosen as its performance in hippocampus-related tasks has been characterized as different (Harker, Wishaw, 2002).The rats were 10–12 weeks old and were housed in groups of five. Lights were maintained on a 12:12 hour light/dark cycle. The temperature in vivarium was $22 \pm 2°C$. The rats had free access to food and water in their home cages. All experimental procedures were conducted in accordance with Council Directive 2010/63EU of the European Parliament of September 22, 2010 on the protection of animals used for scientific purposes. The study protocol was approved by the Ethics Committee of the Institute of Higher Nervous Activity and Neurophysiology of RAS. All efforts were made to minimize the number of animals used and their suffering.

Contextual fear conditioning

Animals were handled daily for 1 week before the experiments. Then they were subjected to contextual fear conditioning. Fear conditioning experiments were performed using a PanLab/Harvard Apparatus chamber with a stainless grid floor and equipped with a video recording device. The fear conditioning chamber in which the animals were placed for testing and training procedures was located on four sensors. A special program of PanLab Harvard apparatus allowed in real time to create a mechanogram using the amplitude thresholds. On day 1, rats were placed in conditioned context and after a 120-s adaptation period were given two foot shocks (1 s, 0.5 mA) at 30s intertrial intervals. Freezing was scored only before the shock (baseline) at test session T0. Thirty seconds after the last foot shock, the rats were returned to their home cages. On day 2, 24 h after conditioning, rats were returned to the conditioning chamber for a 3 min test session (test session T1). Then the freezing responses of these animals were measured during the retrieval session 6 months after the conditioning (test session T2). Immediately after T2 (memory reactivation), the control groups received sham injections of saline whereas experimental groups received injection of SB. Freezing duration in all groups was assessed in a subsequent test trial (T3) 24 h later. No shock was delivered during the test sessions T1–T3 (Fig. 1). To control the specificity of the effect of SB to memory reactivation, additional experiments were performed using similar protocol except that rats were tested for memory 24 h before the SB administration (Fig. 2), thus omitting effect of memory reactivation. During the study

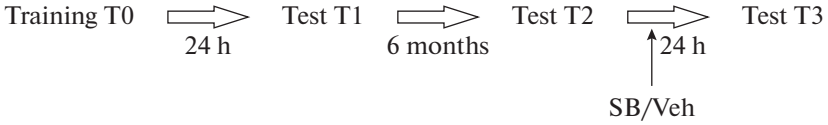

Fig. 1. Scheme of the contextual fear conditioning with SB injection right after Test 2. SB – sodium butyrate, Veh – saline.
Рис. 1. Протокол эксперимента с введением бутирата натрия сразу после теста Т2. SB – бутират натрия, Veh – физиологический раствор.

Fig. 2. Scheme of the contextual fear conditioning with 24 h between the Test T2 and SB injection. SB – sodium butyrate.
Рис. 2. Протокол эксперимента с введением бутирата натрия через 24 ч после теста Т2. SB – бутират натрия.

both strains were presented with identical training procedures.

Drugs and injections

The histone deacetylase inhibitor sodium butyrate (SB) (Sigma, St. Louis, USA) was freshly dissolved in saline (0.9% wt/vol) and injected intraperitoneally in a volume of 0.4 ml per 100 g body weight and a dose of 1.2 g/kg. The drug dose was chosen on the basis of the results of other behavioral studies (Blank et al., 2015; Vinarskaya et al., 2021). Control animals received an intraperitoneal injection of the same volume of vehicle (sterile saline). SB/ vehicle were administered immediately after test session T2. A double-blind procedure was used throughout the experiments. During this study both strains were presented with identical protocol of drug administration.

Data collection and statistical analysis

The freezing scores were obtained on-line using the inbuilt platform sensors and software for the Startle and Fear Combined System (Panlab). All scores for each rat were additionally checked for possible mistakes off-line using the video recordings. In our experiments, the adjustments to the initial data were negligible (less that 2%) since the platform sensors were set to a certain weight of the animals and all necessary thresholds were set. We evaluated fear responses by measuring the duration of freezing, defined as the percentage of time of the total observation period without any movement except for breathing (converted to a percentage [(duration of freezing/total duration) × 100]) – when presented with the conditioned context. The data was analyzed using two-way ANOVA with one repeated measure (test), followed by post-hoc comparisons using the Bonferroni test. All data are presented as the means ± S.E.M. Significance was set at $p < 0.05$.

RESULTS

Reinstatement of impaired context fear memory under histone deacetylase inhibitor sodium butyrate in Long-Evans rats

In the first series of experiments, we decided to check the ability of SB to ameliorate weakening of the remote fear memory in Long-Evans rats. In these series of experiments rats were divided in four groups (G1, female SB, $n = 7$; G2, male SB, $n = 10$; G3, female veh, $n = 10$; G4, male veh, $n = 10$). All groups of rats showed similar low freezing response at pre-conditioning test T0 (Fig. 3, T0, G1, 8.3 ± 2.0%, G2, 8.5 ± 2.1%, G3, 11.8 ± ± 2.4% and G4, 11.0 ± 1.5%). At 24 h post-conditioning (test session T1), the two-way ANOVA (with test session and group as factors) revealed significant main effects of test session ($F(1, 33) = 231.44$, $p < 0.0001$). Bonferroni's multiple comparisons test revealed that both male and female groups showed significantly higher freezing behavior during the test session T1 (Fig. 3, T1, G1, 51.1 ± ± 4.4%, G2, 55.9 ± 5.9%, G3, 56.5 ± 4.2% and G4, 56.6 ± 3.7%) as compared to test T0. When tested 6 months after training, all animals showed significantly less freezing behavior (Fig. 3, T2, G1, 25.9 ± 5.0%, G2, 23.1 ± 4.0%, G3, 30.2 ± 2.8% and G4, 28.9 ± 4.0%): the main effects of the test ($F(1, 33) = 88.36$, $p < 0.0001$) was significant. Post-hoc analysis of the interaction revealed that

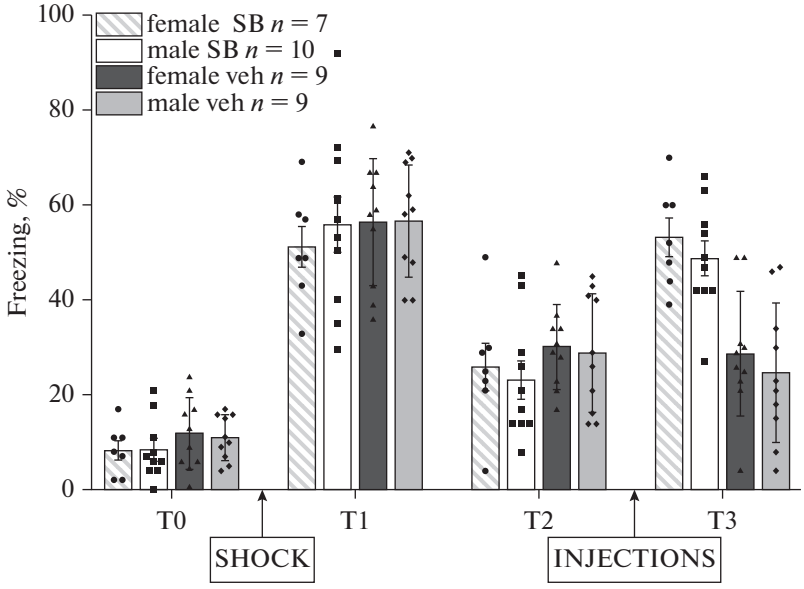

Fig. 3. Effects of a single sodium butyrate (SB) injection on weak remote fear memory in male and female Long-Evans rats. Impaired memory was reinstated under the SB administration (groups female SB (G1) and male SB (G2)), however, there was no reinstatement in the absence of SB (groups female veh (G3) and male veh (G4)). Data are expressed as mean ± SEM.

Рис. 3. Влияние однократной инъекции бутирата натрия (SB) на слабую отставленную память о страхе у самцов и самок крыс Long-Evans. Память восстанавливалась при введении SB (группы самки SB (Г1) и самцы SB (Г2)), однако в отсутствие SB восстановления не происходило (группы самки veh (Г3) и самцы veh (Г4)). Данные представлены как среднее ± SEM.

G1–G4 groups did not differ in test session T2. Interestingly, we discovered significant difference between the pre-training scores and those in test session T2 ($F(1, 33) = 70.05$, $p < 0.0001$). Immediately after T2 (protocol see Fig.1), the rats were intraperitoneally injected with SB (groups G1 and G2) or vehicle (sterile saline, groups G3 and G4). 24 hours later (Fig. 3, T3), SB-treated groups showed significantly increased levels of freezing (G1, 53.3 ± 4.0%, G2, 48.8 ± 3.6%) in contrast to the rats receiving vehicle (G3, 28.7 ± 4.2%, G4, 24.6 ± 4.6%) (the main effect of the group: $F(3, 33) = 3.76$, $p < 0.05$; the main effect of the test: $F(1, 33) = 37.62$, $p < 0.0005$). Post hoc analysis revealed that the SB-treated male and female rats did not differ from one another (G1 vs. G2, $p > 0.05$), similar to the vehicle-treated rats (G3 vs. G4, $p > 0.05$), but the vehicle-treated rats had a significantly lower freezing response than did the SB-treated rats (G1 vs. G3, $p < 0.005$; G2 vs. G4, $p < 0.001$). Thus, it appears that SB facilitates the remote weak conditioned fear memory in Long-Evans rats.

Reinstatement of impaired context fear memory under histone deacetylase inhibitor sodium butyrate in Wistar rats

To evaluate whether the HDAC inhibitor SB would also affect weak contextual memory in male and female Wistar rats, four groups of animals (G1, female SB, $n = 6$; G2, male SB, $n = 8$; G3, female veh, $n = 7$; G4, male veh, $n = 8$) were trained using the same procedure as in the Long-Evans strain. As illustrated in Fig. 4, all groups of rats showed similar low freezing response at preconditioning test T0 (fig. 4, T0, G1, 12.8 ± 2.5%, G2, 7.8 ± 1.5%, G3, 11.1 ± 1.7% and G4, 6.9 ± ± 1.4%). All groups acquired a strong conditioned freezing response to the conditioning context after training (test session T1): the two-way ANOVA (with test session and group as factors) revealed significant main effects of test session ($F(1, 25) = 427.73$, $p < 0.0001$). Bonferroni's multiple comparisons test revealed that both male and female groups showed significantly higher freezing behavior during the test session T1 (Fig. 4, T1, G1, 63.5 ± 8.0%, G2, 58.0 ± 3.0%, G3, 64.1 ± 2.2% and G4, 67.0 ± 6.5%) as compared to test T0. The fear responses measured 6 months

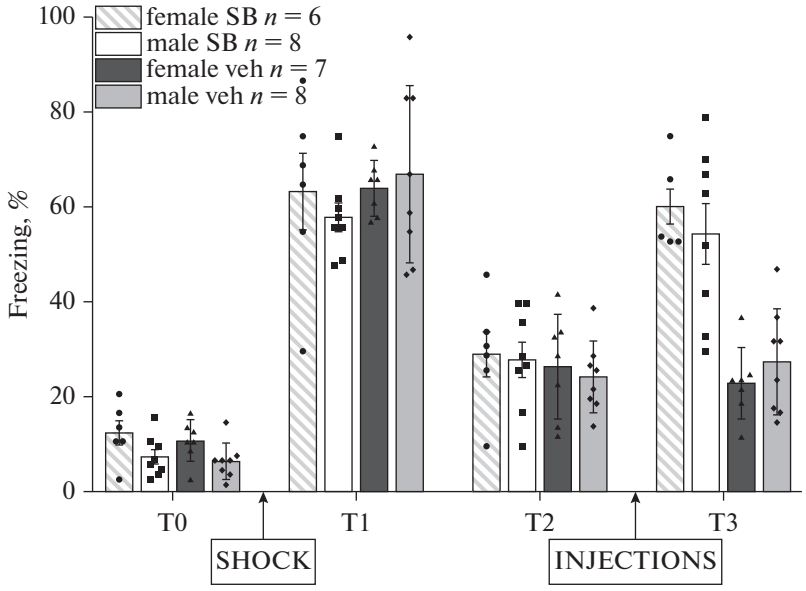

Fig. 4. Effect of a single sodium butyrate (SB) injection on a weak remote fear memory in male and female Wistar rats. Impaired memory was reinstated under SB administration (groups female SB (G1) and male SB (G2)), however, there was no reinstatement in the absence of SB (groups female veh (G3) and male veh (G4)). Data are expressed as mean ± SEM.

Рис. 4. Влияние однократной инъекции бутирата натрия (SB) на слабую отставленную память о страхе у самцов и самок крыс Wistar. Память восстанавливалась при введении SB (группы самки SB (Г1) и самцы SB (Г2)), однако в отсутствие SB восстановления не происходило (группы самки veh (Г3) и самцы veh (Г4)). Данные представлены как среднее ± SEM.

after fear conditioning decreased significantly in all groups (Fig. 4, T2, G1, 29.3 ± 4.8%, G2, 28.1 ± 3.8%, G3, 26.7 ± 4.2% and G4, 24.5 ± ± 2.7%): the main effect of the test ($F(1, 25) = 226.14$, $p < 0.0001$) was significant. Post-hoc analysis revealed that there were no significant differences in the test session T2 of conditioned freezing among all groups. Interestingly, we discovered significant difference between the pre-training scores and those in test session T2 ($F(1, 25) = 88.78$, $p < 0.0001$). Immediately after T2, rats were intraperitoneally injected with SB (groups G1 and G2) or vehicle (sterile saline, groups G3 and G4). 24 hours later (Fig. 4, T3), the SB-treated groups showed significantly increased levels of freezing (G1, 60.3 ± 3.6%, G2, 54.5 ± 6.4%) in contrast to the rats receiving vehicle (G3, 23.3 ± ± 2.8%, G4, 27.8 ± 4.0%) (the main effect of the group: $F(3, 25) = 9.28$, $p < 0.001$; the main effect of the test: $F(1, 25) = 28.27$, $p < 0.0001$). Post hoc analysis revealed that the SB-treated male and female rats did not differ from one another (G1 vs. G2, $p > 0.05$), similar to the vehicle-treated rats (G3 vs. G4, $p > 0.05$), but the vehicle-treated rats had a significantly lower freezing response than did the SB-treated rats (G1 vs. G3, $p < 0.0001$; G2 vs. G4, $p < 0.0005$). Thus, there was a significant fear memory reinstatement in the SB groups of Wistar rats.

Histone deacetylase inhibitor sodium butyrate does not rescue the impaired remote context fear memory without reminding

In these series, groups of animals received the same training protocol as in the previous ones but the SB administration was not combined with re-exposure session to the training context and was delivered 24 h later (protocol see Fig. 2). As shown in fig. 5, all groups of rats showed similar low freezing response at pre-conditioning test T0 (Fig. 5, T0, G1, female Long-Evans, $n = 7$, 8.3 ± 2.2%, G2, male Long-Evans, $n = 6$, 6.5 ± 1.8%, G3, female Wistar, $n = 6$, 8.0 ± 2.1% and G4, male Wistar, $n = 7$, 9.9 ± 3.4%). All groups acquired a strong conditioned freezing response to the conditioning context after training (test session T1): the two-way ANOVA (with test session and group as factors) revealed significant main effects of test session ($F(1, 22) = 753.57$, $p < 0.0001$). Bonferroni's multiple comparisons test revealed that both male and female groups showed significantly higher freezing behavior during the test session T1 (Fig. 5, T1, G1, 79.7 ± 5.1%, G2, 72.0 ± 5.1%,

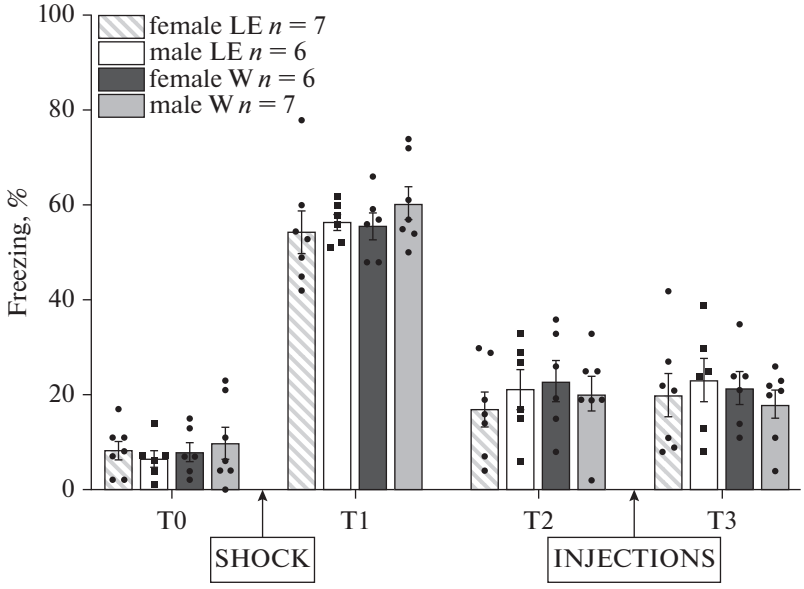

Fig. 5. Effect of a single sodium butyrate (SB) injection on weak remote fear memory in male and female Long-Evans and Wistar rats without memory reactivation. Impaired memory was not reinstated under the SB administration without reminding. Data are expressed as mean ± SEM.
Рис. 5. Влияние однократной не сочетанной с напоминанием инъекции бутирата натрия (SB) на слабую отставленную память о страхе у самцов и самок крыс Long-Evans и Wistar. В отсутствие напоминания восстановления памяти при введении бутирата натрия не происходило. Данные представлены как среднее ± SEM.

G3, 66.6 ± 2.2% and G4, 66.9 ± 5.2%) as compared to the test T0. Six months after the fear conditioning procedure, the fear responses decreased significantly in all groups (Fig. 5, T2, G1, 54.4 ± 4.5%, G2, 56.5 ± 1.8%, G3, 55.7 ± 2.8% and G4, 60.4 ± ± 3.5%): the main effects of the test ($F(1, 22) = = 163.21$, $p < 0.0001$) was significant. The Post-hoc analysis revealed that there were no significant differences between groups. 24 h after T2, the rats were intraperitoneally injected with SB without reminding. 24 hours later all groups demonstrated low freezing response (Fig. 5, T3, G1, 20.0 ± 4.6%, G2, 23.2 ± 4.6%, G3, 21.5 ± 3.5% and G4, 18.1 ± 2.9%); no differences were found between testing session T3 and T2. Thus, there was not fear memory reinstatement in animals of the SB groups without reminding.

DISCUSSION

To date most studies were aimed at studying the influence of histone acetylation on recent memories. Present study investigated the remote (6 months) fear memories and effects of the increased histone acetylation on them. A number of studies have documented the existence of sex (Davenport et al., 1970; Beatty, 1984; Williams et al., 1990; Williams, Meck, 1991; Roof, Havens, 1992; Roof, Havens, 1993; Roof, Stein, 1999; Colon, Poulos, 2020; Trott et al., 2022) and strain differences (Harker, Wishaw, 2002; Besnard et al., 2012; Besnard et al., 2013; Gökçek-Saraç et al., 2015) for hippocampus-dependent tasks in rodents. Therefore, in the current study we included male and female rats of two different strains.

In the current study, we analyzed memory recovery under the SB administration over a long time intervals. Following training procedure, all animals showed an increased freezing behavior in the conditioned context, which indicated that animals have formed a contextual fear memory (Fig. 3, 4, T1). Six months after the fear conditioning we observed a strong decrease in freezing performance in all groups, but still a significant difference from the pre-training scores (Fig. 3, 4, T2). Then, 24 h after the SB administration immediately after the Test 2, the SB-treated animals showed a significant level of freezing behavior in the conditioned context. In contrast to the SB-treated rats, vehicle-treated rats did not express facilitated memory (Fig. 3, 4, T3).

Thus, injection of SB restored a weak remote fear memory in the SB-treated animals. These findings are fully consistent with previous studies that demonstrated that HDAC inhibition led to restoration of impaired or weak memory (Chen et al., 2014; Ko et al., 2016; Zuzina et al., 2019, 2020;

Vinarskaya et al., 2021). It should be noted that this freezing increase was shown to depend both on memory reactivation (triggering the reconsolidation process) and SB administration (Fig. 5), which suggests involvement of a reconsolidation process behind the reactivation + SB administration-induced memory strengthening effect.

We can assume that memory weakening observed 6 months after fear conditioning (the low freezing response in test session T2) could be due to a retrieval deficit. In this case the initial memory trace (Parvez et al., 2005, 2006; Chen et al., 2014; Pearce et al., 2017) is preserved but destabilized and/or some mechanisms required for the normal memory retrieval are impaired over time. For instance, Lee with colleagues demonstrated that remote memory expression could be impaired as the result of disruption of the enhanced synaptic connectivity between neurons of engram (Lee et al., 2023). After reminding, when memories due to a start of the reconsolidation process became open to alterations, the SB administration known to improve the histone hyperacetylation (Marks et al., 2004; Marks, Dokmanovic, 2005; Federman et al., 2009; Villain et al., 2016), re-starts the memory consolidation process including an increase of the memory-related genes expression (Brownell, Allis, 1996; Levenson, Sweatt, 2005; Vecsey et al., 2007; Gräff et al., 2014; Penney, Tsai, 2014) and restabilisation of the mnemonic trace and/or mechanisms that make it available for further retrieval.

To assess the effects of HDAC inhibitor SB on memory deficit in this study, we used the phenomenon of memory reconsolidation (Misanin et al., 1968; Nader et al., 2000). It was demonstrated that one of the boundary conditions for memory reconsolidation is the age of the memory (Bustos et al., 2009; Costanzi et al., 2011; Besnard et al., 2012; Besnard et al., 2013; Graff et al., 2014; An et al., 2019). According to our data, the memories, independently of their age, remain open to reinstatement during retrieval in combination with HDAC inhibition. It should be noted that neurophysiological mechanisms of remote memory differ significantly from those of recent memories (Albo, Graff, 2018; Lee et al., 2023; Terranova et al., 2023). According to the conventional consolidation theory, the information initially stored in the hippocampus is "transferred" to cortical networks over time for its long-term storage (Zola-Morgan, Squire, 1990; Kim, Fanselow, 1992; Frankland et al., 2004; Frankland, Bontempi 2005). Despite the differences in recent and remote memory storage mechanisms, the HDAC inhibitor SB does the same for recent and remote memories: it acts as a cognitive enhancer for weak memories regardless of whether it is recent (Vinarskaya et al., 2021) or remote (the results of the current study).

The second aspect that was highlighted in these experiments concerns the strain differences in memory acquisition and storage, effects of the HDAC inhibition on retention of fear responses. The data obtained showed that both rats' strains display a similar trajectory in the expression of freezing (memory): decrease in freezing responses over time (Fig. 3, 4, test session T2 vs. T1) and improvement of the remote fear memory under the HDAC inhibition (Fig. 3, 4, test session T3 vs. T2).

The third and final aspect that was highlighted in the work is whether sex affects the effects of HDAC inhibition on retention of fear responses in animals. A number of studies have documented the existence of gender differences for hippocampus-dependent tasks (Davenport et al., 1970; Beatty, 1984; Williams et al., 1990; Williams, Meck, 1991; Roof, Havens, 1992; Roof, Havens, 1993). However, in the current study no gender differences were observed. The percentage of freezing in male and female rats in a context fear conditioning task changed similarly. After the training procedure, male and female rats demonstrated similar increased freezing behavior (Fig. 2, 3). Then, 6 months after the training, male and female rats showed a similar reduced freezing, similar reinstatement under the SB injections. Thus, the data obtained demonstrated that the decrease in freezing and memory reinstatement in males matched completely to female rats performance (Fig. 3, 4).

Taken together, our study suggests that remote memories fading with time could be effectively rescued by a presumed increased histone acetylation levels due to the HDAC inhibitor SB administration. Another important result is that the rescue effect of HDAC inhibition on weak remote memories was common across rats of different strains and gender.

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УВЕЛИЧЕНИЕ АЦЕТИЛИРОВАНИЯ ГИСТОНОВ СПОСОБСТВУЕТ ВОССТАНОВЛЕНИЮ СЛАБОЙ ОТСТАВЛЕННОЙ ПАМЯТИ У КРЫС

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Согласно современным представлениям ингибиторы гистондеацетилаз (ГДАЦ) способны улучшать память у различных видов животных. Однако до сих пор не ясно, может ли повышенное ацетилирование гистонов способствовать улучшению слабой отставленной памяти у крыс. Таким образом, целью настоящего исследования было изучение способности ингибитора ГДАЦ бутирата натрия (БН) улучшать слабую отставленную память о страхе у крыс. Чтобы оценить способность ингибитора ГДАЦ БН улучшать отставленную память, мы сравнили поведение двух лабораторных линий крыс, Wistar и Long-Evans, в задаче условно-рефлекторного страха через шесть месяцев после обучения до и после введения БН. Мы обнаружили, что животные демонстрировали хорошую обстановочную память через 24 ч после окончания обучения, полное отсутствие памяти через 6 мес. и улучшенную условно-рефлекторную память после введения БН без дополнительного обучения. Более того, полученные данные продемонстрировали, что обе линии крыс показали одинаковое снижение реакции замирания с течением времени, а ингибирование ГДАЦ улучшало слабую память у обеих линий. Кроме того, ослабление и восстановление памяти у самцов полностью соответствовало изменениям памяти у самок крыс. Эти результаты показывают, что ингибирование ГДАЦ оказывает одинаковый “восстанавливающий” эффект на слабую отставленную условно-рефлекторную память о страхе, независимо от линии и пола крыс.

Ключевые слова: бутират натрия, ацетилирование гистонов, эпигенетика, отставленная память, восстановление памяти, реконсолидация