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Original Article

Effects of HDAC inhibitors on spatial memory and memory extinction in SPS-induced PTSD rats

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Abstract

Background and purpose: Neurobiological changes in memory processes seem to play a role in the pathophysiology of post-traumatic stress disorder (PTSD). Memory itself is influenced by PTSD, too. Histone deacetylase inhibitors (HDAIs) have shown promising results in the extinction of fear-related memories in animals and hence they seem to be important for the treatment of PTSD. Data are scarce about the effect of HDAIs in spatial memory formation/extinction in PTSD models. The main goal of the present work is to find the effect of sodium butyrate (NaBu), as an HDAI, on spatial memory and spatial memory extinction in rats exposed to single prolonged stress procedure (SPS).
Experimental approach: Different doses of NaBu were administered subcutaneously for 7 days in different groups of rats after SPS procedure. Learning, memory, and extinction of memory were evaluated in the Morris water maze test of spatial memory in 6 consecutive days.
Findings / Results: The results show that NaBu (0.5 mg/kg) alleviates impaired learning and memory in SPS rats. It also facilitates the extinction of newly formed memory in the animals.
Conclusion and implications: Our data suggest that the administration of HDAIs after a traumatic experience can prevent the aversive effects of SPS on spatial memory. It also reinforces the notion that extinction of spatial memory involves the same or similar brain circuitry that is involved in the extinction of fear memories in PTSD patients.

Keywords: Extinction; Histone deacetylase inhibitors; PTSD; Spatial memory.

INTRODUCTION

Fear-related disorders, including post-traumatic stress disorder (PTSD), often are persistent disorders which are not easy to treat. A lot of patients remain symptomatic after initial therapy (1). The exact neurobiology of PTSD is not known but it is strongly believed that it is the result of altered neural connections in the brain which occurs after traumatic stress (2). Understanding these neurobiological changes can help scientists develop new therapeutic strategies.

There is strong evidence that PTSD is correlated to some changes that occur in the processing of memory. One of these processes is called fear conditioning. Fear conditioning is established when a neutral or conditioned stimulus is paired with an aversive or unconditioned stimulus. This pairing changes the plasticity of the fear system and hence the fear response of the individual (3). Another important PTSD-related process is called fear of extinction. Extinction occurs when individuals repeatedly receive conditioned stimuli without the unconditioned stimuli.

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It seems that extinction is a new form of memory that alters the plasticity of multiple brain regions (4). PTSD also has negative consequences on memory. Some studies show that animals exposed to single-prolonged stress (SPS), an animal model for PTSD, have impaired spatial memory (5,6). Other studies demonstrate that PTSD in humans is also followed by spatial memory deficits (7-9).

Histone deacetylase inhibitors (HDAIs) are agents that control the action of a group of enzymes called histone deacetylases. These enzymes reduce histone acetylation and by relaxing the chromatin structure they have negative effects on gene transcription. HDAIs promote gene transcription and protein synthesis which is a required step in the formation of both fear conditioning (10) and fear extinction memories (11).

A number of previous works have demonstrated the facilitating effect of HDAIs in contextual or cued fear extinction models (12-15) but little is known about their effect on spatial memory function. This study aimed to investigate the effect of sodium butyrate (NaBu), as an HDAI, on spatial memory and spatial memory extinction in normal versus SPS-induced PTSD rats. In this study, we actually wanted to investigate the preventive potential of the drug on cognitive symptoms of PTSD. There are different approaches to PTSD prevention. Primary prevention treatment is started before the traumatic event; secondary prevention applies when the drug is administered between the traumatic event and development of PTSD, and tertiary prevention is a situation in which treatment is initiated when the first symptoms of PTSD become apparent (1). In the setting of our experiments we gave the drug to the animals during a week after the SPS procedure (traumatic event), therefore this study indicated a secondary preventive approach.

MATERIALS AND METHODS

Animals

Male Wistar rats weighing 250-300 g were used in the experiments. Subjects were housed (3 per cage) in a temperature-controlled environment with a 12/12-h light/dark cycle. Animal use was in accordance with the ethical guidelines of the Institutional Animal Care and Use Committee at the Medical University of Kermanshah I.R. Iran under the ethical code: 1395.358).

Animal grouping

Five groups of eight animals each were used in the study; (1) control group, which did not go through SPS procedure. This group received normal saline as vehicle and all tests are performed on them; (2) PTSD group 1 (vehicle), who went through SPS and receives vehicle; (3) PTSD group 2, who received NaBu at 0.1 mg/kg; (4) PTSD group 3, who received NaBu at 0.5 mg/kg; and (5) PTSD group 4, who received NaBu at 1 mg/kg.

Single-prolonged stress procedure

SPS was carried out according to the procedure described before (16,17). At first, Rats were restrained for 2 h in a clear polyethylene cone. Immediately after this stage they were put into a circular pool of water (60 cm diameter, 24 °C), where they were forced to swim for 20 min. Then they were recuperated for a 15-min period. As the final step rats were exposed to diethyl ether until they became consciousness and then they were transferred to their home cages and remained for 7 days.

Drug administration

Immediately after SPS and for the next seven consecutive days, rats received a subcutaneous injection of the drug or vehicle.

Morris water maze apparatus

As described previously (18) the maze is a circular water tank that has a diameter of 1.5 m and a height of 80 cm. It is filled with tap water to a height of 30 cm. The temperature of the water is set at 25 °C. There is a scape platform (diameter, 20 cm) which is placed 2 cm beneath the water surface. A black curtain surrounded the pool and some visual cues were pinned to it. A video camera was installed on top of the pool which recorded animal movements. The recorded films were computerized and analyzed by the tracking system EthoVision XT6 (Noldus Information Technology, Wageningen, Netherlands).

Behavioral procedure

The test was performed according to Méndez-Couz *et al.* with slight modifications (19). Before the training sessions, rats had habituation sessions for 2 days. On the first day, the platform was fixed at the center of the empty maze. Rats were put on the platform for 60 s. On the second day, the tank was full of water and the rats were put on the platform for another 60 s. If rats jumped off the platform they were guided back to it.

Reference memory task

The training phase consisted of one session of four trials in 6 consecutive days. In each trial, rats were put in the water from the central border of each virtually determined quadrants of north-east, north-west, south-east, and south-west in a pseudorandom order. The platform was hidden under the water and the rats searched for it. The position of the platform was constant. The duration of each trial was 60 s. each rat had a 2 min inter-trial time during which it was towel-dried and kept in a heated cage. If rats could find the platform they were allowed to rest on it for 15 s and if they could not find the platform in the 60 s period they were gently guided to it and let to stay for 15 s (19).

Retention probe test

On the seventh day, a retention probe trial was carried out to test the spatial memory of the animals. In this test, the platform was removed from the pool and rats were released in water from the opposite quadrant of the platform. They were allowed to swim for 60 s (19).

Extinction tests

For the extinction test, we followed the protocol by Rossato *et al*. (20). The day after retention probe test animals had four extinction sessions. Each session had four trials in which each rat were allowed to swim in the pool for 60 s. animals had a 60 s inter-trial resting time during the tests. The platform was removed from the maze in extinction trials (19).

Statistical analysis

Data were analyzed by Sigmaplot 12 software (Systat Software, Chicago, USA). Differences in the distance to reach the platform in the training phase for each group were analyzed using one-way repeated-measures ANOVA. A two-way repeated-measures ANOVA was used to find the difference between the main effects of day and treatment in SPS and control groups. Data from the retention and extinction probe trials were analyzed using a one-way ANOVA. In cases of significant ANOVA results, Tukey's post hoc tests were used to compare the mean differences. Results of the retention probe and the extinction probe tests were analyzed by the Student's t-test when the SPS group was compared to the control. Data are presented as the mean ± SEM.

RESULTS

Effects of SPS on learning and memory in the Morris water maze test

As shown in Fig. 1A both normal and SPS rats learned to find the platform during the 6 testing days (control, $P = 0.002$; PTSD, $P < 0.001$). Further analysis revealed a significant group ($P = 0.01$) and days ($P < 0.001$) effect, but no group and day interaction ($P = 0.5$). Post hoc analysis indicated a significant difference on the 4th, 5th and 6th days ($P < 0.05$).

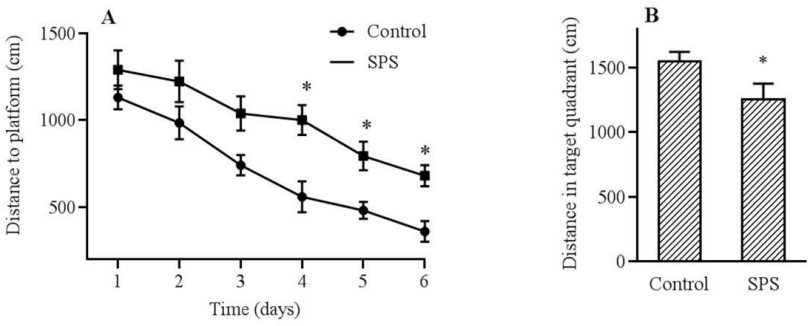

Fig. 1. The effect of single prolonged stress on (A) the distance swum to reach the platform in a 6-day training test in Morris water maze and (B) the distance moved in target quadrant in a retention probe test in male rats (n = 8). The results of the probe test indicates a significant difference between SPS and control groups.*$P < 0.05$ Indicates significant differences compared to the control group.

The results of comparing mean distance in target quadrant in normal and SPS conditions (Fig. 1B) showed that there was a significant difference in the distance for control and SPS groups; $P < 0.05$. These results suggest that SPS decreases the memory for platform position in rats.

Effects of NaBu on learning and memory in PTSD rats

Mean distance to the platform was compared among drug-treated PTSD animals (Fig. 2A). Analysis of data showed that there is a significant effect for the main factors of day ($P < 0.05$) and dose of NaBu ($P < 0.05$). And there is no interaction for these main factors ($P = 0.17$). Further analysis showed that compared to the vehicle group the drug could decrease the distance to the platform at the dose of 0.5 mg/kg ($P < 0.5$).

For the retention probe trial (Fig. 2B) the results showed that the means of the groups are statistically different from each other ($P = 0.017$) and the drug at 0.5 mg/kg could increase the traveling distance of the animals in the target quadrant ($P < 0.05$) in comparison to the vehicle group.

Effects of SPS on memory extinction in the Morris water maze test

As regards the effects of SPS on memory extinction (Fig. 3) the results showed that animals in PTSD group spent more time in the target quadrant in extinction sessions ($P < 0.001$).

Effects of NaBu on memory extinction in SPS animals

As shown in Fig. 4 mean distance of animals in the target quadrant tend to have a U shape pattern. A significant difference was observed between the vehicle-treated group and the group that received the drug at 0.5 mg/kg ($P < 0.05$).

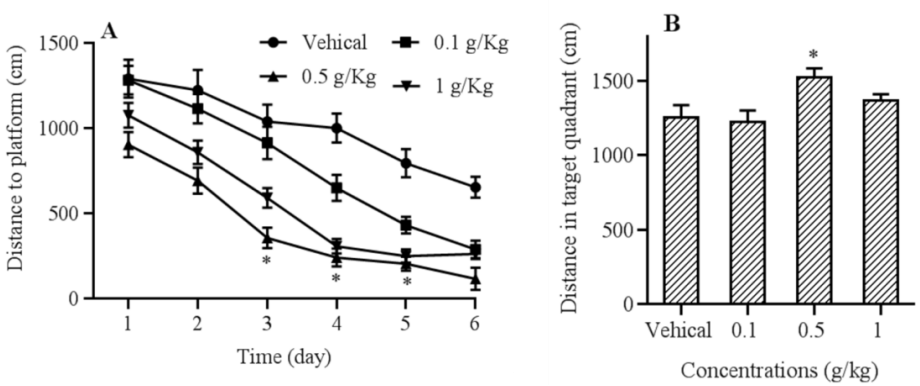

Fig. 2. The effect of different doses of sodium butyrate on (A) the distance swum to reach the platform and (B) the distance moved in target quadrant in male SPS rats (n = 8). *$P < 0.05$ Indicate significant difference compared to the vehicle group.

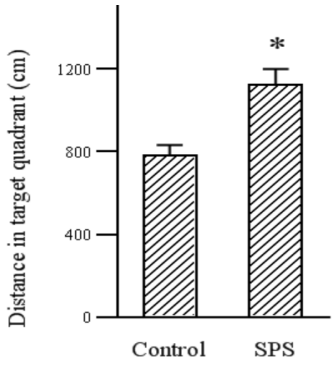

Fig. 3. The effect of SPS on memory extinction in Morris water maze test. One day after the retention probe test animals had four extinction sessions. *$P < 0.001$ Indicate significant difference compared to the control group. SPS, Single prolonged stress.

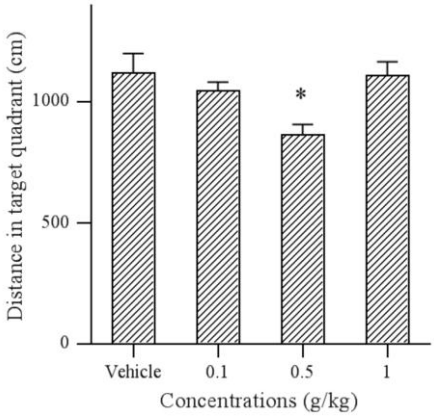

Fig. 4. The effect of different doses of sodium butyrate on extinction of spatial memory. Animals went through four extinction sessions one day after the retention probe test. *$P < 0.05$ Shows singnificant difference against the vehicle group.

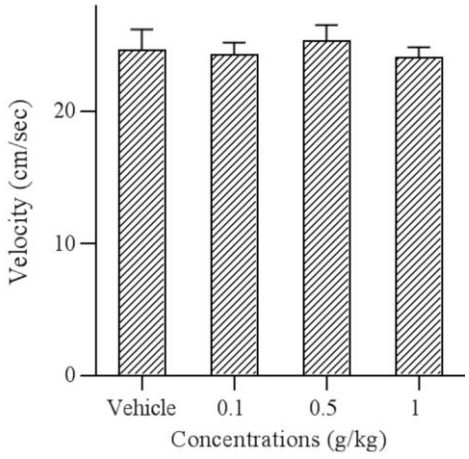

Fig. 5. The effect of different doses of sodium butyrate on the velocity of animals in the retention probe test.

Effects of NaBu on animal velocity in SPS groups

Earlier results for learning, memory, and extinction can be confounded by the speed of the animals in the tests. Therefore, the mean velocities through the retention probe test were compared in different groups. The results showed that the speed of animals in different groups could not be considered statistically different from each other (P = 0.1, Fig. 5).

DISCUSSION

In this study, we demonstrated that SPS not only impairs spatial learning and memory but also disrupts the process of spatial memory extinction in rats. We also showed that NaBu, as a HDAI, can reverse the deleterious effects of SPS on both consolidation and extinction of spatial memory when administered after the traumatic experience.

Memory dysfunction is considered as part of the diagnostic criteria for PTSD (21). Many studies show that PTSD imposes impairment in declarative memory in humans by disrupting several aspects of hippocampal function (22-26). Regarding the importance of the hippocampus in declarative memory in humans and its critical role in rodent spatial memory (27,28) it is reasonable to propose that PTSD in rodents will lead to deficits in spatial memory. SPS is an accepted procedure that induces PTSD-like symptoms in rats (5,6). The present findings showed that both learning and memory (Fig. 1A and B) are affected by the SPS procedure. SPS rats had an overall increased time to find the platform in the testing days. They also spent more time in the platform quadrant on the probe trial. These results are consistent with other evidence that SPS leads to spatial memory deficits in the Morris water maze test (5,6,29). Harvey *et al.* focused their studies on the possible effect of PTSD on the serotonergic system in the hippocampus of rats. They found that as an adaptive reaction to severe stress hippocampal 5HT1A receptor density increases. Since 5HT1A receptors are critical for the regulation and function of the hypothalamic-pituitary adrenal axis it was concluded that it can be an underlying cause for the hypersensitivity of the hypothalamic-pituitary-adrenal axis and decreased levels of cortisol in PTSD animals. As part of their experiments they have assessed the spatial memory of rats exposed to SPS and reported a decline in related behavioral parameters (5). In another study it was shown that one-week SPS rats showed enhanced acoustic startle response, the deficit in spatial memory in MWM, and elevated levels of fear in a fear conditioning model (6). A more recent study also found that SPS procedure led to impairment of place learning task in a plus-maze apparatus. It also showed that SPS slowed the correct responses in the extinction training in the maze (29).

Regulation of gene expression is a required step in the formation of long term memory. Levenson *et al*. first reported the effects of HDAIs; trichostatin A and NaBu on memory formation in the hippocampus. *in vitro* experiments showed that these inhibitors enhanced long term potentiation in CA1 region of the hippocampus, a mechanism that underlies long term memory formation. Administration of NaBu before contextual fear conditioning also facilitated the formation of long-term memory in rats (30). Other researchers showed that hyperacetylation of histone proteins at the promoter of genes that are important for memory formation like cAMP response element-binding protein and nuclear factor-κB is associated with enhanced memory for objects and space (31). In concert with these studies, our results show that in SPS exposed animals NaBu (0.5 mg/kg) enhanced spatial learning of rats indicated by decreased distance

to the platform on 3rd ,4th, and 5th days of training (Fig. 2A). As evident from increased traveling distance of animals in platform quadrant, memory is also improved in SPS exposed rats by the same dose of the drug (Fig. 2B). Both higher (1 mg/kg) and lower (0.1 mg/kg) doses of the drug have not a statistically significant difference to the PTSD group (Fig. 2). The mechanistic reasons behind this inconsistency cannot be answered by our experiments. As it was observed in many other pharmacologic dose-response experiments, the effect of NaBu also complies with an inverted U shape pattern in our study (18).

Pavlovian fear conditioning is a widely used model to study mechanisms of fear formation and extinction. In this model conditioned fear responses are extinguished when the conditioned stimulus is repeatedly presented without the unconditioned stimulus (32). It is proposed that some clinical symptoms of PTSD are developed due to dysfunction of the fear extinction processes in the brain (33,34). Most behavioral models of extinction measure the time before losing the memory of environmental insults as an index for fear extinction (35). Some researchers propose that the extinction of the memory of the platform position in Morris water maze follows the basis of extinction in other operant conditioning models (19,36,37). Our results showed (Fig. 3) that the mean distance that SPS rats travel in the target quadrant in the extinction probe test is increased after 6 days of the training procedure. This indicates that they are less inclined to forget the position of the platform and hence it is similar to classical conditioning models in which memory of fear is harder to elude for SPS subjected rats (38-42).

Further results showed that NaBu (0.5 mg/kg) could decrease the mean distance of traveling of animals in the extinction test (Fig. 4). This means that the drug has helped to extinguish the memory of the platform position in the maze. These changes have occurred independent of the locomotive behaviors of the animals since the speed of movement is similar among different groups (Fig. 5). It is highly believed that agents that are capable of enhancing the mechanisms of extinction processes would be promising drugs to treat a variety of neurological disorders such as PTSD, specific phobias, drug abuse, etc. (43). Stafford *et al*. showed that systemic, intra-hippocampal, and intra-medial prefrontal cortex administration of NaBu in a contextual fear conditioning model induced behavioral (i.e. reduction of freezing) and molecular (i.e. increased histone acetylation and c-Fos expression in the infralimbic cortex) changes that are indicative of a strong extinction process in the brain (12). Other studies also point out the efficacy of HDAIs as extinction enhancers (13-15). These studies have used fear-based conditioning methodologies. Spatial learning is more like a hippocampal-dependent learning process while in conditioning models other structures such as the amygdala play important roles (19). Therefore, it seems that regardless of the brain regions involved in the learning process, extinction learning depends on a structure that is involved in both types of learning. This site is affected by the traumatic SPS procedure and it may be the site of action for HDAIs.

CONCLUSION

Our research showed that NaBu as an HDAI can reverse the noxious effects of SPS on spatial memory when administered on the consolidation phase after the SPS procedure. It also facilitated the process of extinction in the Morris water maze. Altogether, these results proposed that HDAIs are good candidates both for preventive treatment of PTSD or to cure learning impairments in the aftermath of a traumatic event. Further studies are necessary to fully understand the site and mechanism of action of their effect.

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CONFLICT OF INTEREST STATEMENT

All authors declare no conflict of interest for this study.

AUTHORS' CONTRIBUTION

A. Mohammadi-Farani and A. Pourmotabbed conceived of the main concepts and planed the experiments. A. Mohammadi-Farani and Y. Ardeshirizadeh implemented literature search. All authors contributed to the final manuscript. A. Pourmotabbed verified the analytical methods. Y. Ardeshirizadeh performed the experiments and acquired data under supervision of A. Mohammadi-Farani.

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