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The Modulatory Role of Orexin 1 Receptor in Nucleus Accumbens (NAc) on Spatial Memory in Rats

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ABSTRACT

Neuropeptide orexin mainly exists in neurons within and around the lateral hypothalamus and exhibits high affinity to orexin 1 and 2 receptors (OX1R and OX2R, respectively). Orexinergic neurons send their axons to the nucleus accumbens (NAc), which expresses OX1Rs. Previous studies have shown the involvement of orexins and their role in learning and memory processes in the dorsal raphe nucleus and hippocampus. However, no study has examined the effects of orexins in the NAc on memory. The present study examined the effect of the post-training and pre-probe trial intra-NAc administration of SB-33486-A (OX1R antagonist, 12 µg/0.5µl) and TCS-OX2-29 (OX2R antagonist, 10 µg/0.5 µl) on the consolidation and retrieval of memory in the Morris Water Maze (MWM) task. In experiment 1, rats were trained in the MWM and, immediately after every training, received bilateral injections of dimethyl sulfoxide (DMSO) (control group), SB-334867-A (SB), and TCS-OX2-29 (TCS) into the NAc. Experiment 2 was similar to experiment 1, except that the rats received DMSO, SB, and TCS 15 min before the probe test. Probe and visible tests were performed after the last training, and the distance moved, escape latency, and velocity were recorded. In experiment 3, rats trained in experiments 1 and 2, immediately after the probe test, were given the trials for visuomotor coordination assessment on the visible platform. According to the results, the injection of SB increased the distance moved and escape latency in the treated groups, compared to the control group, in the consolidation phase of spatial memory ($P<0.05$) but not in its retrieval phase ($P>0.05$). However, TCS-OX2-29 had no effect. These results suggest that the inactivation of the NAc OX1Rs, but not OX2Rs, impairs the consolidation but not the retrieval of spatial memory in rats.

Keywords: Memory, Nucleus accumbens, Orexin receptors

1. Introduction

Orexins are neuropeptides of different lengths (orexin A and orexin B), which are particularly produced by hypothalamic neurons and participate in behavioral and physiological processes by activating their receptors, including Orexin 1 and 2 receptors (OX1Rs and OX2Rs, respectively) (1). In this regard, orexins contribute to feeding and energy homeostasis, sleep-wake cycle, reward processing, addictive behavior, and stress response (2, 3). Following the detection of orexins and their receptors in the hippocampus, which is associated with learning and memory (4), researchers proved the involvement of orexins and their fundamental role in learning and memory processes (5, 6). According to the findings of these studies, the blockade of orexin receptors in the hippocampus, as one of the most important regions in learning and memory, impairs memory recall by inhibiting the encoding, consolidation, and retrieval of spatial reference memories during the Morris Water Maze (MWM) task. Likewise, the extracted data from further studies on orexins agree with the mentioned results (7, 8). Orexins relieve spatial learning and memory dysfunction through OX1Rs, and performance in the MWM test is impaired by blocking OX1Rs. Although the injection of OX1Rs antagonist into the dentate gyrus has shown controversial results, interestingly, the same studies in the dentate gyrus affected only memory acquisition and consolidation (9), demonstrating that OX1Rs have distinct roles in different stages of learning and memory. Orexins have also a facilitating role in spatial working memory. For example, a sole study reported orexin deficiency leads to impaired spatial working memory in mice, giving the impression that the orexin system plays a crucial role in the facilitation of spatial working memory (10). In addition, research on rats under stress conditions revealed impaired spatial memory in the hypothalamus in this situation is induced by downregulated orexins (2). As mentioned earlier, orexins are particularly produced by hypothalamic neurons and participate in behavioral and physiological processes by activating their receptors. It is worth mentioning that OX1R and OX2R mRNA was also found in the nucleus accumbens (NAc), and previous studies have investigated the role of orexins in this region of the brain. In this view, it has been documented that orexins in the NAc modulate feeding behavior, locomotor activity (11), and acute stress-induced anxiety (12). However, the role of the orexinergic system in the NAc on learning and memory is still unclear. Therefore, the objective of this study was to assess the effect of the functional inactivation of OX1Rs and OX2Rs in the NAc on spatial memory in rats.

2. Materials and Methods

2.1. Animals

Adult male Wistar rats (n=48, 250-350 g body weight) were obtained from the Laboratory Animal Institute of Mazandaran University of Medical Science, Sari, Iran. The rats were housed in three per cage and maintained at a constant temperature (23±2°C) and a standard 12-h light/dark cycle, with ad libitum access to water and food. Between 7:00 a.m. and 2:00 p.m., all behavioral training or testing was completed. All the animals' handling and experimental procedures were performed according to the Guide for the Care and Use of Laboratory Animals by the National Institutes of Health and the current laws of the Iranian government for animal care. The procedures were approved by the Institutional Animal Ethics Committee of Mazandaran University of Medical Sciences, Sari, Iran, with Ethics Code IR.MAZUMS.REC.

2.2. Surgical Procedure and Microinjection

The rats were anesthetized with an intraperitoneal injection of a combination of ketamine (100 mg/kg) and xylazine (2.5 mg/kg) (seven days before the start of behavioral experimentations) and were then implanted stereotaxically with a bilateral cannula (15 mm, 23 gauge), with the following coordinates: 1) AP: +1 mm from bregma, at the angle of 15° to the vertical axis, 2) ML: ±1 mm from midline, and 3) DV: 7.5 mm from the skull surface, according to the atlas of Paxinos and Watson of the rat brain (13). The cannula was anchored

to the skull with one screw and dental acrylic and was then closed with a stylet. The rats were permitted a one-week recovery before MWM behavioral experiments. Microinjections were administered via a guide cannula using an injection needle (27 gauge) connected with polyethylene tubing to a Hamilton microsyringe. The needle was placed 0.5 mm beyond the tip of the implanted guide cannula. Finally, 0.5 µl of dimethyl sulfoxide (DMSO), 12 µg/0.5 µl of SB-334867-A (SB) (OX1R antagonist), or 10 µg/0.5 µl of TCS-OX2-29 (TCS) (OX1R antagonist) was administered to each side of the NAc, and the needle was left in place for an additional 60 sec to allow the diffusion of the solution away from the needle tip. DMSO was used as the vehicle, which has no impact on memory.

2.3. Morris Water Maze Apparatus

To measure spatial memory, various mammal species, mostly rodents, are assessed on the MWM apparat, which is a dark round pool of opaque water (20±1°C and a depth of 25 cm) with a diameter of 140 cm and a height of 55 cm subdivided into four virtual quadrants called north-east, south-east, south-west, and north-west. Furthermore, a submerged platform is placed in a fixed location in the center of the south-west (target) quadrant. The animal's exact movements and positions are recorded by a camera above the apparatus. The animal's motions can be recorded and sent to the computer by an LED display inside a ball held on the rat's back so that it is capable of recording the swim path of each trial and estimating escape latency, as well as the time spent in any designated area of the pool and swimming speed.

2.4. Habituation

For pre-training, the rats were subjected to habituation, whereby they were allowed to swim freely for 60 sec with no platform present.

2.5. Behavioral Testing

2.5.1. Training

The rats underwent two blocks of four trials daily for three days (block interval: 15 min, trial interval: 2 min). In each trial, each rat was released into one of the quadrants and given 65 sec to reach the hidden platform location. After finding the platform, the rat was allowed to stay on the platform for 15 sec to identify the platform's position by viewing the visual cues. When the rat could not reach the platform in 65 sec, it was placed on the platform for 60 sec and allowed to rest for 20 sec.

2.5.2. Probe Trial

After all training sessions were completed, the animals returned to their home cages and stayed for 24 h until the probe trial. The probe trial consisted of a 60-sec free swim period without a platform, in which the time spent (sec) in the target quadrant was recorded.

2.5.3. Visual Test (Post-Probe)

The visible test was conducted 30 min after the probe test. The platform was placed one centimeter above the water level in the center of the quadrant in front of the target quadrant, and all visual cues were removed. This test was designed to investigate any possible interference of sensory-motor factors and visual disturbances on the rat's ability to reach the platform. Scape latency and velocity were also recorded.

2.6. Experimental Protocol

2.6.1. Experiment 1

Experiment 1 aimed to determine the effect of bilateral post-training administration of SB or TCS into the NAc on memory consolidation. Twenty-four rats were bilaterally cannulated into the NAc. After the habituation day, they were divided into the control group (n=8), SB group (n=8), and TCS group (n=8) and were then trained for three days. Immediately after each training every day, SB (12 µg/0.5µl), TCS (10 µg/0.5 µl), and DMSO (0.5 µl) were bilaterally injected into the NAc in each group, respectively. The probe test was then performed 24 h after the last training, and the distance moved and escape latency were recorded. In addition, the visible test was conducted 30 min after the probe test (Figure 1).

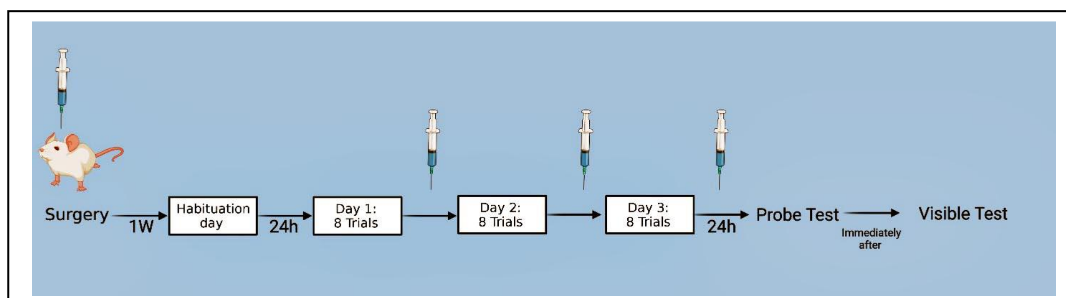

Figure 1. Overview of the consolidation phase

2.6.2. Experiment 2

Experiment 2 aimed to examine the effect of bilateral pre-probe trial administration of SB, TCS, or DMSO into the NAc on the retrieval of spatial memory. Twenty-four rats were randomly divided into the control (n=8), SB (n=8), and TCS (n=8) groups and were trained for three days. They then received an intra-NAc bilateral injection of DMSO (0.5µl), SB (12 µg/0.5µl), and TCS (10 µg/0.5 µl), respectively, 15 min before undergoing the probe trial. The probe test was performed 24 h after the last training, and the distance moved and escape latency were recorded. The visible test was conducted 30 min after the probe test.

2.6.3. Experiment 3

The probable interference of drugs with animals' sensory and motor coordination was evaluated by testing the effect of SB and TCS on the capability of rats to escape the visible platform. Rats received all training in experiments 1 and 2, and immediately after the probe test, they were given the trials for visuomotor coordination assessment on the unsubmerged platform.

2.7. Confirmation of Correct Targeting of the NAc Area

After the behavioral tests, methylene blue was injected into the NAc, the rats were decapitated, the cannulas were carefully removed, and their brain was left in 10% formaldehyde for 7-10 days. Before the histological examination, data analysis was performed only on the rats with the cannula in the NAc.

2.8. Statistical Analysis

Data were analyzed using GraphPad Prism 8 software. One- and two-way ANOVA and Tukey's test were used for multiple comparison tests. The general behavior of rats in the experimental groups was assessed by measuring the average escape latency time and the distance traveled (mean±standard error of the mean: SEM). A *P*-value of less than 0.05 was deemed significant.

3. Results

3.1. Consolidation

The effects of the intra-NAc bilateral injection of DMSO, SB (an OX1R antagonist, 12 µg/0.5 µl), and TCS (an OX2R antagonist, 10 µg/0.5 µl) were assessed on consolidation in spatial memory.

3.1.1. Distance Moved

The distance that animals moved in each of the quarter circles on days 1-3 is shown in figure 2. Data analysis by one-way ANOVA showed no significant difference between groups in consolidation on days one and two ($P>0.05$); however, the distance moved significantly increased in the SB group on the third day, compared to the DMSO and TCS ($P<0.05$) groups (Figures 2A-D). Therefore, the results indicated that the inactivation of OX1Rs in the NAc after three days of training deteriorates spatial memory consolidation.

3.1.2. Escape Latency

The time it took the animal to find the platform during each trial is shown in figure 3. One-way ANOVA showed no significant difference in escape latency between the treated groups and the control group ($F_{3,26}=0.4265$, $P=0.4651$) (Figure 3).

Two-way ANOVA of escape latency revealed a significant difference between SB and DMSO groups on the second and third days ($P=0.03$ and $P=0.00$, respectively) (Figure 4A). Figure 4 shows that escape

latency increased in the SB, compared to the DMSO group, on the second and third days (*P*<0.05 and 0.001, respectively). These results indicated that the NAc region blockade with OX1Rs antagonist deteriorates learning in a triple-day protocol (Figures 4B-D).

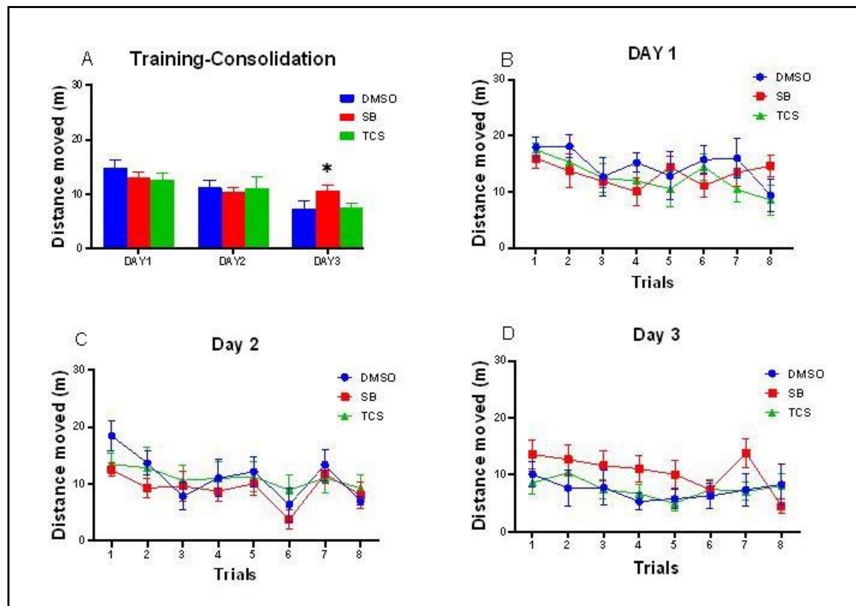

Figure 2. The influence of post-training intra-NAc bilateral infusion of DMSO, SB (an OX1R antagonist) (12 µg/0.5 µl) and TCS (an OX2R antagonist) (10 µg/0.5 µl) on spatial memory consolidation. DMSO, SB and TCS were injected immediately after training. (A-D) The distance moved by trials in SB (an OX1R antagonist) (12 µg/0.5 µl), TCS (an OX2R antagonist) (10 µg/0.5 µl) or DMSO groups in 1-3 days. DMSO: Dimethylsulfoxide; SB: SB-334867-A; TCS: TCS-OX2–29. Data are presented as Mean±SEM (**P*<0.05 vs. DMSO and TCS groups) (n=8 in each group)

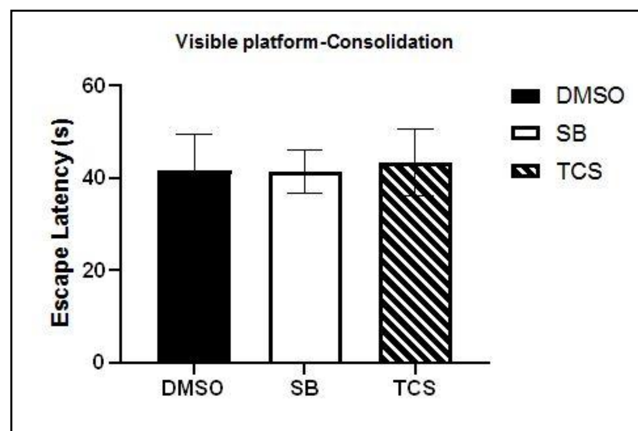

Figure 3. Escape latency in DMSO, SB (an OX1R antagonist) (12 µg/0.5 µl) and TCS (an OX2R antagonist) (10 µg/0.5 µl) groups. DMSO: Dimethylsulfoxide; SB: SB-334867-A; TCS: TCS-OX2–29

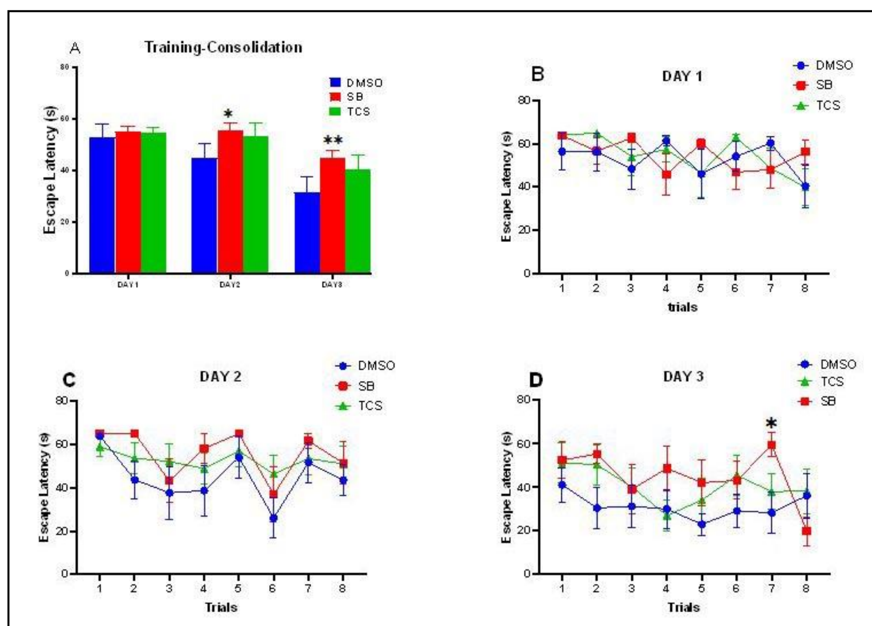

Figure 4. The influence of post-training intra-NAc bilateral infusion of DMSO, SB (an OX1R antagonist) (12 µg/0.5 µl) and TCS (an OX2R antagonist) (10 µg/0.5 µl) on spatial memory consolidation. DMSO, SB and TCS were injected immediately after training. (A-D) The escape latency by trials in SB (an OX1R antagonist) (12 µg/0.5 µl), TCS (an OX2R antagonist) (10 µg/0.5 µl) or DMSO groups in 1-3 days. DMSO: Dimethylsulfoxide; SB: SB-334867-A; TCS: TCS-OX2–29. Data are presented as Mean±SEM (*$P<0.05$ and **$P<0.001$ vs. DMSO group) (n=8 in each group)

3.1.3. Time Spent in Each Quadrant

The percentage of time the rats spent in each quarter circle on days 1-3 is shown in figure 5. One-way ANOVA showed a significant difference in the time spent in the target quadrant between the SB-treated and the DMSO group ($F_{2,15}=0.048$, $P=0.014$). The time the SB-treated group spent in the target quadrant was significantly less than that in the DMSO group ($P<0.05$).

3.1.4. Velocity

One-way ANOVA showed no significant difference in the swimming speed between the treated groups and the control group ($F_{3,26}=0.6947$, $P=0.5637$) (Figure 6).

3.2. Retrieval

In this experiment, SB (an OX1R antagonist, 12 µg/0.5 µl), TCS (an OX2R antagonist, 10 µg/0.5 µl), and DMSO were injected 15 min before the probe trial to test the role of OX1Rs and OXRs2 blockade on retrieval in a triple-day testing version of the MWM task.

3.2.1. Distance Moved

The distance the rats moved in each quarter circle on days 1-3 is shown in figure 7. Data analysis by one-way ANOVA indicated no significant difference between groups ($P>0.05$) (Figures 7A-D).

3.2.2. Escape Latency

The time it took the rats to find the platform during each trial is shown in figure 8. One-way ANOVA showed no significant difference in escape latency between the treated groups and the control group (Figures 8A-B) ($F_{3,26}=0.5496$, $P=0.2653$).

3.2.3. Time Spent in Each Quadrant

The percentage of time the rats spent in each quarter circle on days 1-3 is shown in figure 9. One-way ANOVA showed no significant difference in the time spent in the target quadrant between the groups ($P>0.05$).

3.2.4. Velocity

One-way ANOVA showed no significant difference in the swimming speed between the treated groups and the control group in spatial memory retrieval ($F_{1,18}=0.4562$, $P=0.843$) (Figure 10).

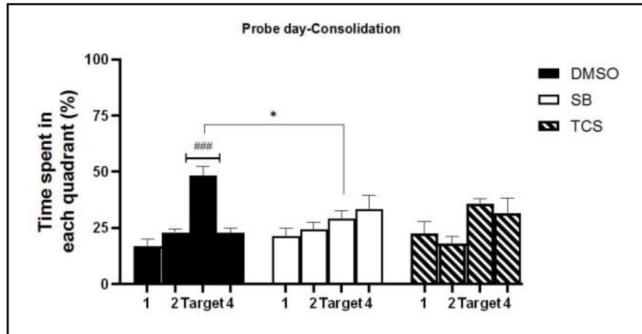

Figure 5. Time spent in each quadrant in DMSO, SB (an OX1R antagonist) (12 µg/0.5 µl) and TCS (an OX2R antagonist) (10 µg/0.5 µl) groups. Time spent in each quadrant is statistically significant for the DMSO rathe than SB(**P*<0.05). ###*P*<0.001, difference between the target and the other three quadrants compared to different quadrants in DMSO group. Data are presented as mean ± SEM. DMSO: Dimethylsulfoxide; SB: SB-334867-A; TCS: TCS-OX2–29

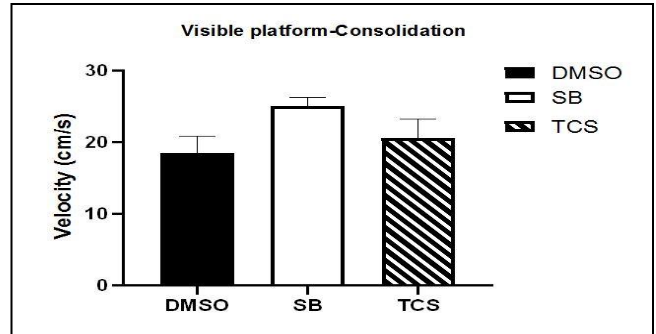

Figure 6. Velocity in DMSO, SB (an OX1R antagonist) (12 µg/0.5 µl) and TCS (an OX2R antagonist) (10 µg/0.5 µl) groups in spatial memory consolidation. Data are presented as mean ± SEM. DMSO: Dimethylsulfoxide; SB: SB-334867-A; TCS: TCS-OX2–29

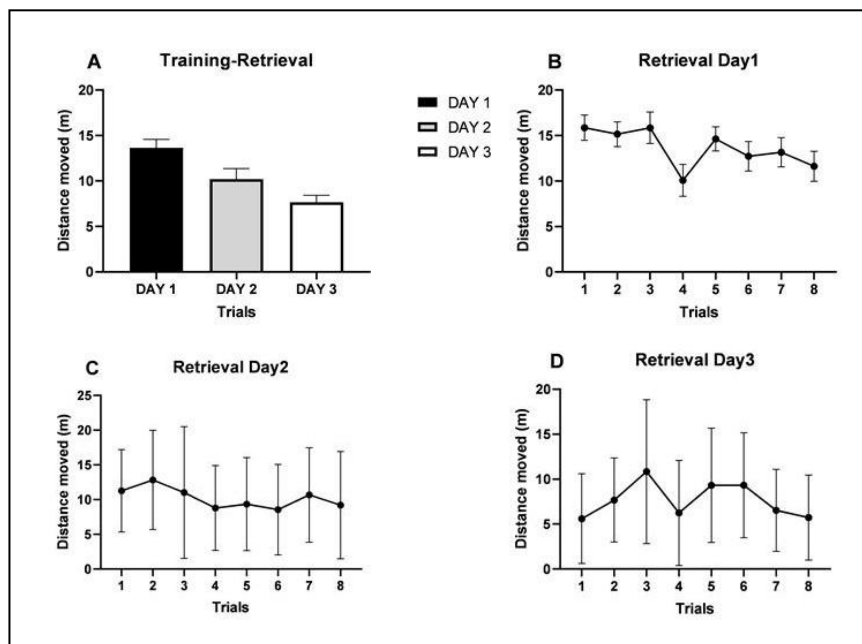

Figure 7. The influence of post-training intra-NAc bilateral infusion of DMSO, SB (an OX1R antagonist) (12 µg/0.5 µl) and TCS (an OX2R antagonist) (10 µg/0.5 µl) on spatial memory retrieval. DMSO, SB and TCS were injected 15 min before the probe test. (A-D). The distance moved by trials in SB (an OX1R antagonist) (12 µg/0.5 µl), TCS (an OX2R antagonist) (10 µg/0.5 µl) or DMSO groups in 1-3 days. DMSO: Dimethylsulfoxide; SB: SB-334867-A; TCS: TCS-OX2–29. Data presented as Mean±SEM

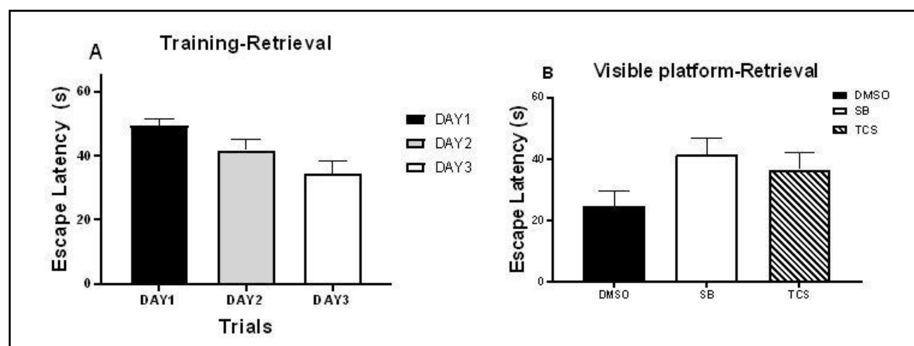

Figure 8. The influence of post-training intra-NAc bilateral infusion of DMSO, SB (an OX1R antagonist) (12 µg/0.5 µl) and TCS (an OX2R antagonist) (10 µg/0.5 µl) on spatial memory retrieval. DMSO, SB and TCS were injected 15 min before the probe test. (A-B). Figure (A-B) shows the escape latency (s) by trials in SB (an OX1R antagonist) (12 µg/0.5 µl), TCS (an OX2R antagonist) (10 µg/0.5 µl) or DMSO groups in traning-retrieval (A) and visible platform-retrieval (B). DMSO: Dimethylsulfoxide; SB: SB-334867-A; TCS: TCS-OX2–29. Data are presented as Mean±SEM

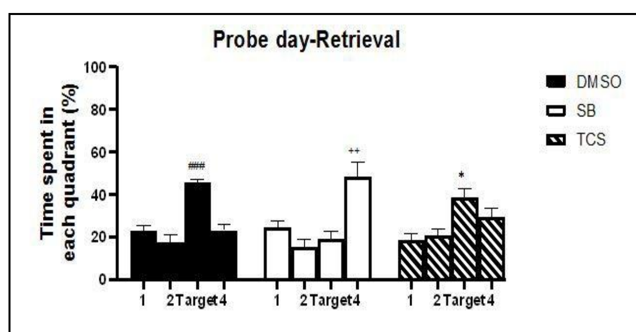

Figure 9. Time spent in each quadrant in DMSO, SB (an OX1R antagonist) (12 µg/0.5 µl) and TCS (an OX2R antagonist) (10 µg/0.5 µl) groups. ###*P*<0.001, ++ *P*<0.001 and **P*<0.05 indicate difference with other three quadrants in DMSO, SB and TCS groups. Data are presented as mean ± SEM. DMSO: Dimethylsulfoxide; SB: SB-334867-A; TCS: TCS-OX2–29

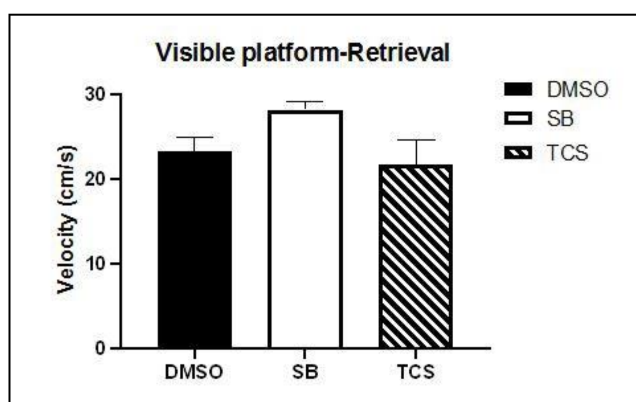

Figure 10. Velocity in DMSO, SB (an OX1R antagonist) (12 µg/0.5 µl) and TCS (an OX2R antagonist) (10 µg/0.5 µl) groups in spatial memory retrieval. Data are presented as mean ± SEM. DMSO: Dimethylsulfoxide; SB: SB-334867-A; TCS: TCS-OX2–29

4. Discussion

This is the first study to show the influence of the inactivation of OX1Rs and OX2Rs in the NAc on memory processing in rats. However, researchers have previously proven the involvement of orexins and their roles in learning and memory processes in the dorsal raphe nucleus (DRN) and hippocampus (14-17).

According to our findings, post-training blockade of OX1Rs by SB impaired memory consolidation in the MWM task and decreased the time rats spent in the target quadrant, which matches with the findings of a previous study (14). According to this study, the activation of mitogen-activated protein kinase (MAPK) has a significant role in memory consolidation, and the activation of OX1Rs gives rise to more stimulation of MAPK. Accordingly, this study tried to explain OX1Rs have a role in memory consolidation and their antagonists (such as SB at doses of 1.5, 3, and 6 mg/0.5 ml) impair memory consolidation and decrease the time rats spend in the target quadrant, compared to the control group, which can be based on the inhibition of MAPK.

Furthermore, in terms of the involvement of orexins and their role in learning and memory processes, with the activation of OX1Rs, the stimulation of protein kinase A, C, and calcium calmodulin pathways occurred, which has a major role in the modulation of synaptic plasticity, a cellular mechanism underlying learning and memory (16, 18, 19). Therefore, SB may induce its effect via inhibiting protein kinase A, C, and calcium calmodulin pathways.

The results of the present study also indicated that the post-training blockade of OX2Rs by TCS did not impair the memory consolidation and retrieval phase of spatial memory in the MWM task. Consistent with our results, Khodabande, Akbari (15) reported that the injection of TCS in the DRN had no effect on the consolidation phase of memory in the MWM task.

The findings showed that 15 min before probe trials, the intra-NAc injection of SB and TCS did not affect retrieval in the MWM task since there was no significant difference in the time spent in the target quadrant between the treated groups and the control group. Likewise, a sole study has documented that the pre-probe trial injection of OX1Rs antagonist in the hippocampus had no effect on spatial memory retrieval in the MWM task, in which there was no significant difference in the time spent in the target quadrant between OX1Rs antagonist-treated groups and the control group (5).

In this study, the functional inactivation of OX1Rs and OX2Rs in the NAc did not affect the escape latency and velocity of finding the visible platform in a non-spatial visual discrimination task. Therefore, based on evaluating the escape latency and velocity of rats during the MWM task, it is clear that the inactivation of OX1Rs and OX2Rs in the NAc does not affect locomotor activity.

Our results suggest the inactivation of NAc OX1Rs affects the consolidation phase of spatial memory, based on decreasing the time animals spent in the target quadrant in the MWM. However, there is limited evidence for potential cellular and molecular mechanisms governing the role of the NAc OX1Rs and OX2Rs in memory consolidation.

The findings showed that the inactivation of NAc OX1Rs (but not OX2Rs) impairs the consolidation phase but not the retrieval phase of spatial memory in the MWM task. However, further studies are required to identify the underlying cellular and molecular signaling pathways in consolidation impairments with the inactivation of NAc OX1Rs and OX2Rs.

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Authors' Contribution

Study concept and design: E. A. and V. B.
Acquisition of data: L. Z.
Analysis and interpretation of data: L. Z.
Drafting of the manuscript: L. Z., E. A., and M. Z.
Critical revision of the manuscript for important intellectual content: L. Z., E. A., and M. Z.

Ethics

All procedures were approved by Mazandaran University of Medical Sciences, Sari, Iran.

Conflict of Interest

The authors declare that they have no conflict of interest.

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