Neuroscience Letters 698 (2019) 160–164

Contents lists available at ScienceDirect

Neuroscience Letters

journal homepage: www.elsevier.com/locate/neulet

Research article

Functional crosstalk of nucleus accumbens CB1 and OX2 receptors in response to nicotine-induced place preference

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ARTICLE INFO

Keywords:
Nucleus accumbens core
Orexin receptors
Cannabinoid receptors
Nicotine
Condition place preference

ABSTRACT

In the present study, we have evaluated the existence of functional interaction between orexin-2 receptor (OX2R) and cannabinoid-1 receptor (CB1R) in the nucleus accumbens core (NAcc), in nicotine-induced conditioned place preference (CPP) of Wistar male rat. Nicotine (0.5 mg/kg; s.c.) in the course of conditioning, produced a significant place preference, without any effect on the locomotor activity. Intra-NAcc administration of ineffective and effective doses of TCS-OX2-29 (2 and 6 ng/rat), a selective OX2R antagonist and AM251 (10 and 50 ng/rat), a selective CB1R antagonist, showed a significant interaction between OX2R and CB1R in the acquisition of nicotine-induced CPP ($p < 0.01$), and the locomotor activity ($p < 0.05$). No significant interaction was observed between these two receptors in the expression of nicotine-induced CPP. Our findings provide insight into the possible interaction of OX2R and CB1R of the NAcc in nicotine addiction. We propose a potential interaction between cannabinoid and orexinergic systems within the NAcc, in producing the rewarding effects.

1. Introduction

Nicotine is the main psychoactive component of tobacco leaves that initiates and sustains cigarette addiction [9]. Nicotine by affecting nicotinic acetylcholine receptors (nAChRs) [20], acts on the mesocorticolimbic dopaminergic system, stimulates dopamine (DA) neurons firing, and increases DA release from ventral tegmental area (VTA) to the nucleus accumbens (NAc), and the prefrontal cortex (PFC) [17,30]. This process serves as a critical role in reinforcing effects of drugs of abuse, including nicotine [19].

Endocannabinoids are polyunsaturated fatty acid derivatives [7] that influence different physiological functions, such as a reward in the CNS by influencing the cannabinoid-1 receptor (CB1R) activity [14]. The cannabinoid receptors interact with G-proteins of the Gi/o family [25] and are found in the CNS, including the VTA and the NAc [15,33]. Several studies suggest that co-abuse of nicotine and cannabinoid, facilitated the hypolocomotion, antinociception, hypothermia [29], learning and memory [1] and anxiety-like behavior [5]. Our previous study showed that selective blockade of the VTA CB1Rs decreases nicotine-induced CPP [2].

The orexins/hypocretins (orexin A and B) corresponding receptors (OX1 and OX2), are G-protein coupled receptor [24]. Lateral hypothalamus (LH) orexinergic neurons send projections to the areas, involved in reward processing and drug addiction, such as the NAc [18,32]. Both orexin receptors have been reported to be expressed in the NAc [18]. However, most studies have assessed the effects of OX1Rs on the addiction, but the role of orexin-2 receptors (OX2Rs) is still not completely understood. Studies have revealed that the blockade of orexin-1 receptors (OX1Rs), attenuated nicotine self-administration [11,13]. Furthermore, as shown previously, OX2R blockade in the VTA attenuated nicotine-induced CPP [2]. These studies strongly suggest a potential role for the orexin system, in mediating some rewarding and addictive effects of nicotine.

It has been shown that there is a potential interaction between the orexinergic and the cannabinoid systems, within the VTA and the NAc in LH stimulation-induced CPP [28,32]. Despite anatomical, pharmacological and biochemical evidence about the possible existence of a crosstalk between orexin and cannabinoid systems, few studies have directly investigated this link at the functional level between CB1R and OX2R in the regulation of the reward process. Therefore, our aim was to understand the potential interplay between the two systems within the NAcc, in the acquisition and expression of nicotine-induced CPP in rats.

2. Methods and materials

2.1. Animals

Subjects were adult male Wistar rats (230–280 g; Pasteur Institute,

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https://doi.org/10.1016/j.neulet.2019.01.027
Received 4 August 2018; Received in revised form 17 December 2018; Accepted 15 January 2019
Available online 16 January 2019

Tehran, Iran), housed four per cages with free access to lab chow and tap water, under a 12/12 h light/dark cycle, and controlled temperature (23 ± 2 °C). The Ethic Committee of Animal Use of the Isfahan University of Medical Sciences approved the study, and all experiments were executed in accordance with the National Institute of Health Guide for the Care and Use of Laboratory Animals (NIH Publications No. 80-23, revised 2011).

2.2. Drugs

Nicotine hydrogen tartrate salt (Sigma-Aldrich, Germany) was dissolved in saline, and injected subcutaneously (*sc*; 1 ml/kg; pH = 7.4). AM251 (Sigma-Aldrich, USA) and TCS-OX2-29 (Tocris Bioscience, Bristol, UK), as a CB1R antagonist and an OX2R antagonist, respectively, were dissolved in dimethyl sulfoxide (DMSO; up to 10%, v/v).

2.3. Stereotaxic surgery and drug microinjection

Under deep anesthesia with ketamine (100 mg/kg) and xylazine (10 mg/kg) (i.p.), the rats were positioned in a stereotaxic apparatus (Stoelting, USA), and two stainless steel, 23-gauge guide cannulas, were implanted bilaterally, 1 mm above the NAcc (AP: + 1.5 mm; ML: ± 1.5 mm; DV: −7 mm) [21] and fixed to the skull with dental cement. Dummy cannulas (30-gauge) were inserted into the guide cannulas, in order to keep them free of debris. The animals were allowed a seven-day recovery period before behavioral experiments. For drug microinjections, the dummy cannulas were replaced by 30-gauge stainless steel injector needles, terminating 1 mm below the tip of the guide cannulas. The injector cannula was connected to a 2-μl Hamilton syringe by polyethylene tubing (PE-20). Subsequently, the antagonists or vehicle was injected bilaterally, in a total volume of 1 μl/rat (0.5 μl in each side), over 60 s period, and left in place for an extra 60 s.

2.4. Apparatus

We used a three-compartment CPP apparatus in these experiments [8]. Briefly, two large preference compartments A and B were identical in size (30 × 30 × 30 cm), but in different patterns, and were connected by a guillotine door. The walls and floor of the A compartment were painted striped black and white, and also had a textured floor, while the walls and floor of the other compartment (B) were white, and had a smooth floor. The null smaller chamber (C) was a red communicating tunnel (30 × 15 × 30 cm), and connected to the two conditioning compartments by removable wall. The floor of A and B chambers was equipped with weight sensors, recording the time that the animal spent in each chamber. In addition, a camera was placed 2 m above the CPP apparatus, and recording videos were analyzed, using homemade software as offline.

2.5. Behavioral testing

2.5.1. Measurement of place conditioning

We used the biased procedure of the CPP method in these experiments. This procedure is more effective than unbiased assignment trial for inducing CPP with nicotine [2,31]. This paradigm took place in five consecutive days, with three distinct phases: pre-conditioning (introduction period), conditioning (acquisition period), and post-conditioning (testing period).

2.5.1.1. Pre-conditioning. On the first day, each rat was placed into compartment C, while the guillotine doors were removed to allow access to all compartments for 15 min. The time spent by the rats in each compartment was recorded.

2.5.1.2. Conditioning. Place conditioning consisted of a 3-day schedule of double conditioning 20-min sessions (three drug pairing and three vehicles), from day 2 to 4, with a 4-h interval. During these sessions, the animals were confined to one compartment by closing the removable partitions. In the morning of the 2nd and 4th days, the animals received a single *sc* injection of saline, and placed immediately in the initial preferred side. In the evening session, the animals received a single *sc* dose of nicotine, and confined to the initial non-preferred side. On the 3rd day, the animals received the nicotine injection in the morning session (initial non-preferred side), and the vehicle in the evening session (initial preferred side).

2.5.1.3. Post-conditioning. This phase was carried out on the 5th day of the schedule, counted as the 1st day. For testing, the removable partitions were raised, and the animals were placed in the compartment C, and could freely explore the entire apparatus for 15 min. The change of preference, as a CPP index, was calculated as the time spent in the nicotine-paired chamber on the post-conditioning day, minus the time spent in the same chamber on the pre-conditioning day [8,10].

2.6. Locomotor activity

During the post-conditioning phase, locomotor activity was calculated for each rat. The floor of each compartment (A and B) was divided into four equal squares. The entrance of the rat into each square was considered as an index of locomotor activity [2,10], and calculations were performed offline.

2.7. Experimental design

2.7.1. Intra-NAcc administration of OX2R or CB1R antagonists in the acquisition and expression of nicotine-induced CPP

In order to find out, the role of OX2R and CB1R on the acquisition (during the 3-day conditioning phase), and expression (only on the 5th day) of nicotine-induced CPP, the animals received intra-NAcc microinjections of different doses of TCS-OX2-29 (2, 6 and 20 ng/rat), AM251 (10, 50 and 250 ng/rat), or combinations of associated effective (6 ng and 50 ng/rat) or ineffective doses (2 ng and 10 ng/rat), 5 min prior to administration of nicotine (0.5 mg/kg, s.c.) [2]. In addition, in acquisition part, there were two groups, which received the maximum dose of TCS-OX2-29 (20 ng/rat) or AM251 (250 ng/rat) into the NAcc, 5 min before *sc* saline injection, without nicotine, to understand whether almost complete blockade of the receptors would have a preference/aversive effect on CPP pattern. Nicotine and saline control groups received DMSO (10% DMSO; 0.5 μl/side), as a vehicle.

2.8. Histology

After completion of the tests, the animals were deeply anesthetized with urethane, and perfused transcardially with 0.9% normal saline, followed by 10% buffered formalin. Then, rats were decapitated, and the brains were removed and placed in a 10% formalin solution. After 72 h, the brains were sliced coronally in 55 μm sections through the cannulas placements, and the locations of injections were verified according to the atlas (Fig. 1).

2.9. Statistics

Data were analyzed, using the SPSS version 21 for windows. Data analysis was executed, using the two-way ANOVA followed by Tukey test for any interaction between nicotine and OX2R, and nicotine and CB1R in the induction of CPP; and OX2R and CB1R in the nicotine-induced CPP (and non-parametric one-way ANOVA (krusal-wallis), followed by a Dunns multiple comparison test, and unpaired t-test; only appeared in the figures). All data were expressed as mean ± S.E.M. (n = 6–8). P-values less than 0.05 were considered statistically significant.

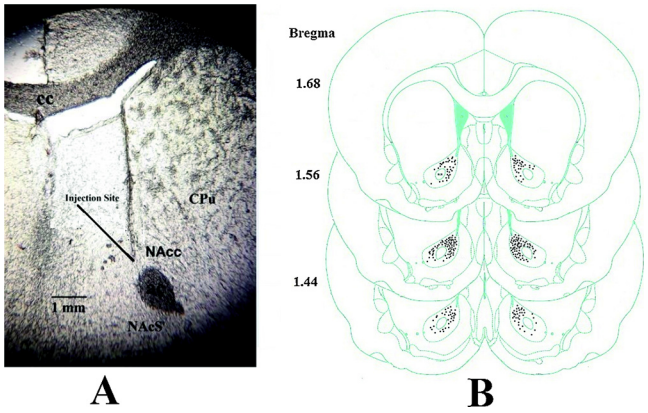

Fig. 1. a) A representative image, displaying the microinjection site in the NAcc; corpus callosum (cc), caudate putamen (CPu); NAcc and shell (NAcS), and anterior commissure (ac). b) Schematic illustrations of coronal sections of the rat brain, adapted from an Atlas [22], show the approximate microinjection sites in the NAcc.

3. Result

Nicotine (0.5 mg/kg) induced a significant CPP ($p < 0.001$), but had no effect on the locomotor activity (Figs. 2 and 3).

3.1. Effects of intra-NAcc OX2R blockade on the acquisition of nicotine-induced CPP and locomotor activity

The two-way ANOVA showed no significant interaction between nicotine and TCS-OX2-29, in the acquisition of CPP [Nicotine effect, $F(1,37) = 0.018$, $P = 0.89$; TCS-OX2-29 Effect, $F(3,37) = 6.56$, $P = 0.001$; and Nicotine*TCS-OX2-29 interaction, $F(1,37) = 4.04$, $P = 0.052$, CI: −34.83 to 13.01], and in the locomotor activity [Nicotine effect, $F(1,37) = 0.58$, $P = 0.44$; TCS-OX2-29 Effect, $F(3,37) = 3.91$, $P = 0.016$; and Nicotine*TCS-OX2-29 interaction, $F(1,37) = 0.54$, $P = 0.46$, CI: 49.85–65.12]. Post-hoc revealed that there was a significant reduction in CPP score ($p = 0.016$, CI 17.20–158.74 and $p = 0.028$, CI 7.68–124.30, respectively) and locomotor activity ($p = 0.05$, CI 0.029–59.98 and $p = 0.036$, CI 1.27–50.67, respectively) in the nicotine + TCS-OX2-29, 6 ng/rat and 20 ng/rat, with respect to DMSO-treated rats (Fig. 2A and D).

3.2. Effects of intra-NAcc CB1R blockade on the acquisition of nicotine-induced CPP and locomotor activity

Statistical analysis showed a significant interaction between nicotine and AM251 in the acquisition of CPP [Nicotine effect, $F(1,38) = 0.83$, $P = 0.36$; AM251 Effect, $F(3,38) = 8.95$, $P = 0.001$; and Nicotine*AM251 interaction, $F(1,38) = 14.82$, $P = 0.001$, CI: –29.48 to 0.75], and in the locomotor activity [Nicotine effect, $F(1,38) = 0.034$, $P = 0.85$; AM251 Effect, $F(3,38) = 6.18$, $P = 0.002$; and Nicotine*AM251 interaction, $F(1,38) = 5.21$, $P = 0.028$, CI: 54.57–65.42]. Post-hoc revealed that there was a significant reduction in CPP score in the nicotine + AM251, 50 ng/rat and 250 ng/rat, with respect to DMSO-treated rats ($p = 0.023$, CI 7.24–93.62 and $p = 0.001$, CI 38.36–112.85, respectively) and locomotor activity ($p = 0.02$, CI 3.07–46.08 and $p = 0.001$, CI 14.63–55.74, respectively) in the nicotine + AM251, 10 ng/rat and 50 ng/rat, with respect to DMSO-treated rats (Fig. 2B and E).

3.3. Effects of intra-NAcc simultaneous administration of effective/ineffective doses of TCS-OX2-29 and AM251, on the acquisition of nicotine-induced CPP and locomotor activity

Data analysis showed a significant interaction between TCS-OX2-29 and AM251 in the acquisition of nicotine-induced CPP [TCS-OX2-29 effect, $F(2,46) = 8.37$, $P = 0.001$; AM251 Effect, $F(2,46) = 4.49$, $P = 0.016$; and TCS-OX2-29*AM251 interaction, $F(2,46) = 6.89$, $P = 0.002$, CI: −30.04 to 7.41], and in the locomotor activity [TCS-OX2-29 effect, $F(2,46) = 2.24$, $P = 0.11$; AM251 Effect, $F(2,46) = 4.12$, $P = 0.023$; and TCS-OX2-29*AM251 interaction, $F(2,46) = 4.66$, $P = 0.014$, CI: 44.46–57.25]. Post-hoc revealed that there was a significant reduction in CPP score in the nicotine + TCS-OX2-29, 6 ng/rat and the nicotine + AM251, 50 ng/rat with respect to nicotine + DMSO group ($p = 0.001$, CI 41.10–131.39 and $p = 0.003$, CI 26.28 to 115.67, respectively) and locomotor activity, only in the nicotine + AM251, 10 ng/rat with respect to DMSO-treated rats

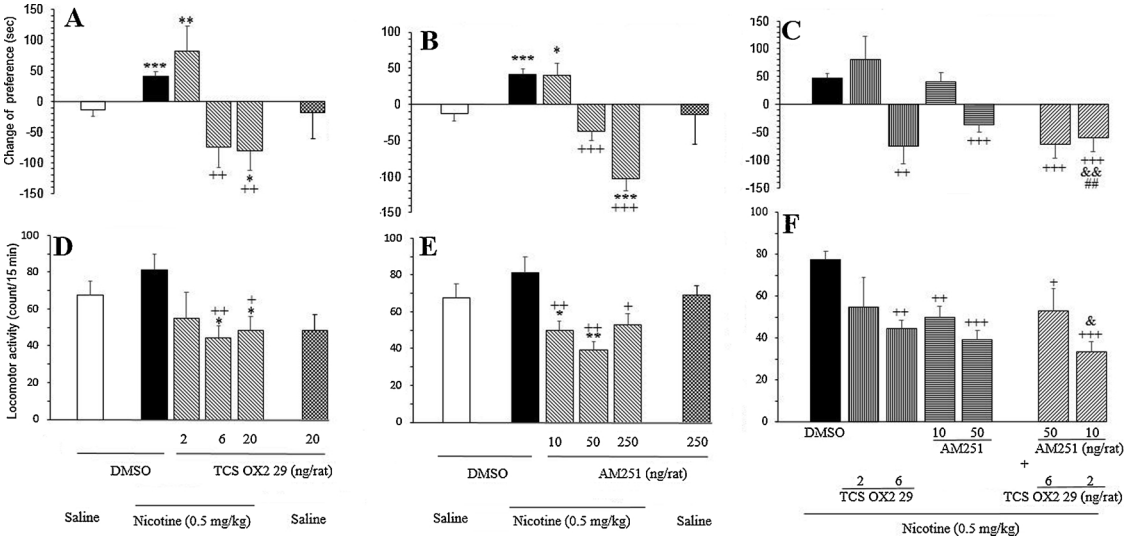

Fig. 2. The effect of bilateral microinjection of TCS-OX2-29 and AM251 alone or concurrently into the NAcc, on the acquisition of nicotine-induced CPP (Graph A, B, C respectively) and locomotor activity (Graph D, E, F respectively). The change of preference was assessed as the difference between the times spent on 5th day and 1st day, in the drug-paired compartment. Data are expressed as mean ± S.E.M. (n = 7–8). *P < 0.05, **P < 0.01, and ***P < 0.001 different from the saline-control group. $^{+}$P < 0.05, $^{++}$P < 0.01, and $^{+++}$P < 0.001 different from the nicotine-control group. $^{\#\#}$P < 0.01 different from the TCS-OX2-29 (2 ng) group. $^{\&}$P < 0.05 and $^{\&\&}$P < 0.01 different from the AM251 (10 ng) group (krusal-wallis test followed by a Dunns multiple comparison test and unpaired t-test, for significant signs).

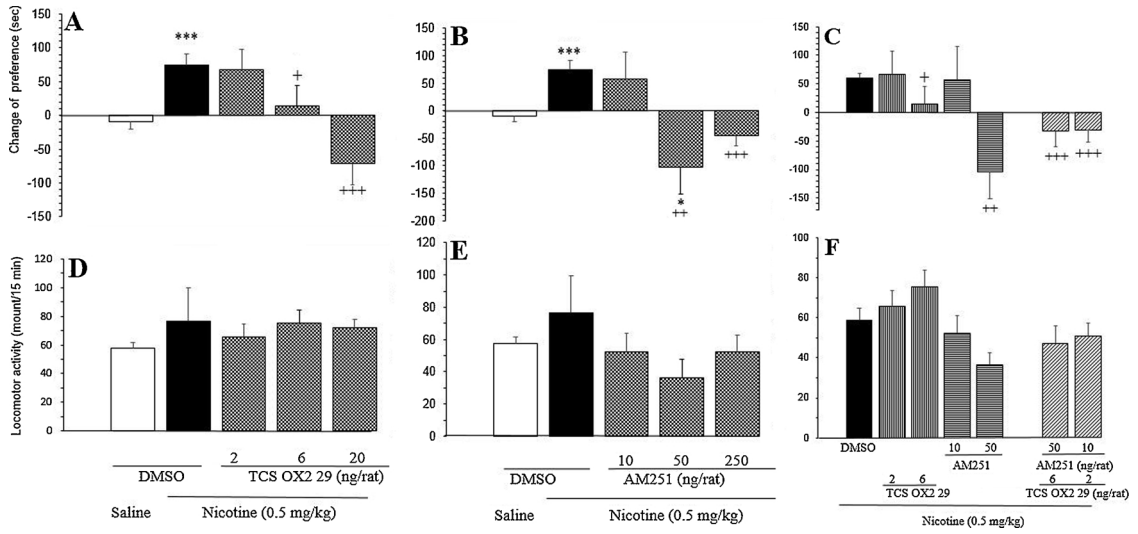

Fig. 3. The effect of bilateral microinjection of TCS-OX2-29 and AM251 alone or concurrently into the NAcc, on the expression of nicotine-induced CPP (Graph A, B, C respectively) and locomotor activity (Graph D, E, F respectively). The change of preference was assessed as the difference between the times spent on 5th day and 1st day, in the drug-paired compartment. Data are expressed as mean ± S.E.M. (n = 6). +P < 0.05, ++P < 0.01 and +++P < 0.001 different from the nicotine-control group (krusal-wallis test followed by a Dunns multiple comparison test and unpaired t-test, for significant signs).

(p = 0.033, CI 1.35–38.78) (Fig. 2C and F).

3.4. Effects of intra-NAcc OX2R blockade on the expression of nicotine-induced CPP and locomotor activity

The two-way ANOVA showed a significant effect of nicotine and TCS-OX2-29 on the expression of CPP [Nicotine effect, F(1,27) = 5.2, P = 0.03; TCS-OX2-29 Effect, F(3,27) = 6.28, P = 0.002, CI: −9.77 to 39.82], but not on the locomotor activity. Post-hoc revealed that there was a significant reduction in CPP score (p = 0.003, CI 42.37–178.39), only in the nicotine + TCS-OX2-29, 20 ng/rat with respect to DMSO-treated rats (Fig. 3A and D).

3.5. Effects of intra-NAcc CB1R blockade on the expression of nicotine-induced CPP and locomotor activity

AM251 had a significant effect on the expression of CPP [Nicotine effect, F(1,27) = 3.22, P = 0.084; AM251 Effect, F(3,27) = 6.29, P = 0.002, CI: −36.77 to 26.29], but not on the locomotor activity. Post-hoc revealed that there was a significant reduction in CPP score (p = 0.003, CI 55.41 to 228.34) only in the nicotine + AM251, 50 ng/rat with respect to DMSO-treated rats.

3.6. Effects of intra-NAcc simultaneous administration of TCS-OX2-29 and AmM251 on the expression of nicotine-induced CPP and locomotor activity

Analysis showed no significant interaction between TCS-OX2-29 (0, 2 and 6 ng/rat) and AM251 (0, 10 and 50 ng/rat), in the expression of nicotine-induced CPP [TCS-OX2-29 effect, F(2,37) = 0.32, P = 0.72; AM251 Effect, F(2,37) = 6.72, P = 0.003; and TCS-OX2-29*AM251 interaction, F(2,37) = 2.87, P = 0.069, CI: −21 to 34.32], and in the locomotor activity. Post-hoc revealed that there was a significant reduction in CPP score (p = 0.001, CI: 55.32 to 188.67), only in the nicotine + AM251, 50 ng/rat with respect to DMSO-treated rats.

4. Discussion

In this study, the role of CB1R and OX2R in the NAcc, and their interaction in the development of nicotine-induced CPP was explored. Consistent with previous studies [4,6], our data revealed that 0.5 mg/kg of nicotine induces a significant CPP, without any effect on the locomotor activity [2]. Nicotine influences motivational and aversive effects, essentially by stimulation of VTA nAChRs, found in both DA and non-DA neurons [27]. Actually, a well-designed balance between excitatory and inhibitory inputs to the VTA DA neurons, results in the rewarding outcome of nicotine by increasing glutamatergic excitation and decreasing GABAergic inhibition onto DA neurons [16]. Consequent activation of the VTA cholinergic receptors, regulates the release of dopamine into the NAc, inducing an additional reinforcing effect [22].

Evidence has shown the role of cannabinoid receptors in reward-related behaviors [2,10,28]. The CB1R blockade in the basolateral amygdala, reduced nicotine-seeking behavior [12], reduced nicotine-induced CPP acquisition and expression in VTA [2], and attenuated the acquisition and expression of morphine-induced CPP in the NAc [3]. Our results demonstrated that the CB1R blockade in the NAcc, could reduce both acquisition and expression of nicotine-induced CPP, exhibiting a significant role of NAcc CB1R, in the rewarding properties of nicotine.

Secondly, we observed that the OX2R blockade in the NAcc, could significantly reduce the dependency to nicotine, consistent with our previous results in the VTA [2]. It has been previously shown that OX2Rs within the NAc, may play a role in reward–related behavior [32]. For instance, cocaine increased the OX2Rs in the NAc [34], and OX2R blockade attenuated the reinforcing effects of ethanol [26]. In addition, blockade of OX1Rs and OX2Rs in the CA1 could block the LH stimulation-induced CPP [23].

In addition, we observed that the blockade of both CB1R and OX2R in the NAcc, decreased the locomotor activity in nicotine-treated groups. Therefore, the effect of the antagonists on the CPP scores may be partly due to the influence on locomotion.

Since, severe blockade of the receptors in the NAcc, by the maximum doses of the antagonists in the saline-treated groups, had no effect on the CPP scores and the locomotor activity, but has an effect in nicotine-treated groups, therefore, we can conclude that both endocannabinoid and orexin systems may affect and change the preference or aversion responses to nicotine.

Our results showed that, although the concurrent administration of effective doses of both antagonists had no more effect, compared to each alone, but simultaneous intra-NAcc microinjection of ineffective doses of CB1R and OX2R antagonists attenuated effectively the nicotine-induced CPP, and there was a significant difference, compared to

each ineffective dose alone. Therefore, this suggests that these receptors probably act through different pathways in the NAcc, and it can be a consequence of the presence of diverse neurons' complex within the nucleus [32].

5. Conclusions

From the present data, we can propose that the NAcc CB1R and OX2R are involved in mediating the response to nicotine. Taken together, it seems that there is a potential interaction between CB1R and OX2R located in the NAcc, at the receptor or the post-receptor levels. Our data are in accordance with prior studies, suggesting that there is a functional communication between the cannabinoid and the orexinergic systems. Nonetheless, more studies are required for clarification of this interaction at the signaling level, and pre- and post-receptor cascade.

Declarations of interest

None.

Acknowledgement

This research was funded by a grant (395810) from the Isfahan University of Medical Sciences, Isfahan, Iran.

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