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Research report

Electrophysiological study of the response of ventral tegmental area non-dopaminergic neurons to nicotine after concurrent blockade of orexin receptor-2 and cannabinoid receptors-1

Fatemeh Azizi, Reza Fartootzadeh, Hojjatallah Alaei, Parham Reisi*

Department of Physiology, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran

HIGHLIGHTS

- Systemic injection of nicotine increased the VTA neuronal activity.
- Blockade of VTA-CB1R, prevents the increased nicotine-induced neuronal firing.
- Blockade of VTA-OX2R, prevents the increased nicotine-induced neuronal firing.
- CB1R and OX2R have no synergistic effects on the VTA neuronal response to nicotine.

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ABSTRACT

The ventral tegmental area (VTA) is a key brain region, involved in the dependency on nicotine. Studies have shown that orexin and cannabinoids are likely to play an important role in nicotine dependency. In this study, the effect of orexin receptor-2 (OX2R) and cannabinoid receptor-1 (CB1R) blockade were investigated in response to nicotine in male rats, on the neural activity of VTA. Nicotine was injected subcutaneously and its effect on the firing of VTA non-dopaminergic (ND) neurons was investigated, using *in vivo* extracellular single unit recording. Nicotine increased the ND neuronal activity of the VTA. AM251 (0.18, 0.9, 1.8 nmol/0.3 μL), as a selective cannabinoid CB1R antagonist, and TCS-OX2-29 (0.5, 1, 5 nmol/0.3 μL), as a selective OX2R antagonist, individually or simultaneously were microinjected into the VTA. The results revealed that blockade of OX2R and CB1R in the VTA could prevent the increased firing rate, caused by nicotine. Concurrent administration of TCS-OX2-29 and AM251 could decrease responsiveness of VTA-ND neurons to nicotine, but it did not show a greater response than their single application. Because the synergistic effect was not observed in the simultaneous blockade of these two receptors, therefore, in order to detect the interactions of these two receptors, further studies are needed in the field of intracellular signaling.

1. Introduction

Smoking is a predominant health troublesome in most countries (Dani and De Biasi, 2001). Nicotine, principal addictive component of cigarette, is a lipophilic compound, which rapidly enters and accumulates in the central nervous system after systemic injection, and could serve as a primary positive reinforcer (Clarke, 1990). The cellular mechanism of nicotine addiction is through the nicotinic cholinergic receptors (nAChRs) that highly expressed in the dopamine and non-dopamine neurons in the ventral tegmental area (VTA) (Pidoplichko et al., 2004). The VTA is a heterogeneous brain structure, containing various neuronal populations that have an important function in motivational behaviors, addiction and other neurological illnesses (Lammel et al., 2014).

It has a blend of dopaminergic (DA) (65%), GABAergic (30%), and glutamatergic neurons (5%) that may act in concert to reward-seeking behavior (Margolis et al., 2006; Nair-Roberts et al., 2008). GABA neurons synapse directly onto dopamine neurons, and remarkably inhibit the activity of neighboring dopamine neurons; thus, by regulating the activity of dopamine neurons, affect the animal behaviors such as reward responses (van Zessen et al., 2012). In addition to GABAergic neurons, glutamatergic transmission is also a main regulator of dopaminergic activity of the VTA (Tung et al., 2016). In fact, a functional balance between excitatory and inhibitory inputs to the VTA DA

* Corresponding author.
E-mail address: p_reisi@med.mui.ac.ir (P. Reisi).

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neurons, results in the nicotine reward effect (Mansvelder et al., 2002). Electrophysiological studies have indicated that a variety of drugs of abuse such as morphine, ethanol and nicotine, excite VTAneurons (Brodie et al., 1990). Systemic administration of nicotine via a dopamine signaling in the VTA projection targets, may promote the initiation and maintenance of rewarding and reinforcing responses (Imperato and Di Chiara, 1986; Schilström et al., 2003).

The regulation of DA neuronal activity and the factors that modulate this activity, by both intrinsic and extrinsic mechanisms, are required for desirable behavioral performance.

Several observations imply that the orexinergic and cannabinoid systems has been involved in the nicotine dependence (Corrigall, 2009; Forget et al., 2005). The orexins (hypocretins), including orexin A and B (33 and 28 amino acids, respectively), were first described in 1998 and produced in the lateral hypothalamus (LH) (Sakurai et al., 1998). Orexins have two distinct G-protein receptors (OX1R and OX2R), coupled to Gq, whereas OX2R additionally is coupled to Gi/Go (Kukkonen et al., 2002). Orexin neurons project panoramically throughout the adult rat brain, and increase the firing of a portion of both dopaminergic and non-dopaminergic neurons in the VTA (Korotkova et al., 2003). Most of the previous studies evaluated the effect of OX1R in the nervous system, but the role of OX2 is still little understood (Abdollahi et al., 2016; Ghaemi-Jandabi et al., 2014).

Previous studies have shown that the endocannabinoid system is involved in the primary rewarding effects of nicotine (Valjent et al., 2002), alcohol (Colombo et al., 2005) and opioids (Braida et al., 2001) in the VTA. Endocannabinoids mediate their effects through two G protein-coupled receptors (CB1R and CB2R), although additional receptors may be involved (Mackie, 2008; Maldonado et al., 2006). Central effects of cannabinoids, including their reinforcing properties, are thought to be mediated by the CB1R (De Vries and Schoffelmeer, 2005). It has already been identified that the intravenous administration of CB1R agonist, produced a dose-dependent increase in the firing of dopamine neurons (Gessa et al., 1998).

It has been demonstrated that in stress, the released orexin from the LH neurons activates the phospholipase C, and produces 2-arachidonoylglycerol (2-AG) by activating the OX1R on the dopamine neurons in the VTA. In addition, 2-AG through the pre-synaptic receptors of CB1 as retrograde, inhibits the release of GABA, and activates the mesolimbic dopaminergic circuit (Tung et al., 2016). Earlier behavioral studies have shown that there is a probable crosstalk between CB1R with OX1R and OX2R within the VTA (Azizi et al., 2018; Taslimi et al., 2011; Yazdi et al., 2015), but the function, and how both systems interact in the reward circuit, in terms of electrophysiology remains unclear. The present study aims to elucidate the role of OX2Rs and CB1R on the activity of VTA non-dopaminergic (ND) neurons, in response to nicotine.

2. Results

2.1. VTA-ND neuronal spontaneous discharge

Neurons with a firing rate < 10 Hz, and a spike duration < 1 ms were chosen, therefore according to the previous studies (Korotkova et al., 2003; Liu et al., 2012), we assumed that our target neurons were ND neurons, and presumably among the GABAergic neurons (Fig. 1).

2.2. VTA neuronal response to nicotine

As shown in Fig. 2B, nicotine increased VTA-ND neurons firing rate relative to baseline ($p < 0.05$). In addition, percentage changes of the firing rate of VTA-ND neurons was significantly different between the nicotine and control groups ($p < 0.05$; Fig. 3).

2.3. VTA-ND neuronal response to nicotine following the blockade of OX2R and CB1R

Both antagonists with their different doses, prevented the nicotine-induced increase of neuronal firing rate (Fig. 2), and AM251 with a dose of 0.9 nmol/0.3 μL, and TCS-OX2-29 with a dose of 5 nmol/0.3 μL, significantly decreased the neuronal firing rate, with respect to baseline responses ($p < 0.001$ and $p < 0.05$, respectively; Fig. 2D and I).

AM251 in the nicotine-treated rats with doses of 0.9 and 1.8 nmol/0.3 μL, decreased percentage changes of the firing rate of VTA neurons, with respect to the saline-control group ($p < 0.01$ and $p < 0.001$, respectively; Fig. 3), and with all doses (0.18, 0.9, 1.8 nmol/0.3 μL) with respect to the nicotine-control group ($p < 0.05$, $p < 0.001$ and $p < 0.001$, respectively; Fig. 3).

TCS-OX2-29 in the nicotine-treated rats with all doses (0.5, 1, 5 nmol/0.3 μL) decreased percentage changes of the firing rate of VTA-ND neurons, with respect to the saline-control group ($p < 0.01$; Fig. 3), and the nicotine-control group ($p < 0.001$, $p < 0.01$ and $p < 0.001$, respectively; Fig. 3).

In the control rats, maximum dose of both AM251 (Figs. 2F and 3, respectively) and TCS-OX2-29 (Figs. 2J and 3, respectively), had no significant effect on baseline responses and percentage changes of the firing rate, compared to the saline-control group.

2.4. VTA neuronal response to nicotine following concurrent blockade of OX2R and CB1R

Concurrent blockade of both CB1R and OX2R with low doses (0.18 and 0.5 nmol/0.3 μL, respectively), and medium doses of antagonists (0.9 and 1 nmol/0.3 μL, respectively), decreased neuronal firing rate with respect to baseline responses ($p < 0.05$; Fig. 2K and L, respectively).

Concurrent microinjection of both low and medium doses of antagonists, decreased percentage changes of the firing rate of VTA neurons, compared to the saline-control group ($p < 0.05$; Fig. 3) and the nicotine-control group ($p < 0.01$; Fig. 3).

3. Discussion

In previous studies, it has been suggested that there is a cross-talk between orexin and cannabinoid systems, and most studies concerned their type 1 receptors (Taslimi et al., 2011). Recently, it has been observed that OX2Rs could interact with CB1Rs, but this interaction was not explored in a real state of drug of abuse (Yazdi et al., 2015). The aim of this study was to evaluate the effects of individual or simultaneous blockade of OX2R and CB1R on the firing rate of VTA-ND neurons, following nicotine injection, using extracellular recording.

According to the firing rate and spike duration characteristics, we assumed that the selected neurons in the present study should be ND neurons, and presumably GABAergic (Korotkova et al., 2003). Evidences propose that the local GABA neurons in the VTA, are not only an important modulator of the DA cells, but also an essential component for the functional expression of the VTA. GABAergic neurons of the VTA have a significant effect on the local inhibition of mesolimbic dopamine neurons (Liu et al., 2012).

The results indicated that the administration of nicotine leads to an increase in the VTA-ND neuronal activity. The VTA mediates the reinforcing effects of natural rewards, and the most addictive drugs such as nicotine (Teo et al., 2004). It has been already shown that VTA neurons responded to nicotine with an increased firing rate (Gao et al., 2010; Grenhoff et al., 1986; Schilström et al., 2003). Nicotine has been postulated to increase the firing frequency by depolarizing neurons in the following two ways (1) by a direct postsynaptic action on nAChRs in the somatodendritic region of dopaminergic neurons or (2) by activation of presynaptic nAChRs on ND neurons and release of neurotransmitter (Gao et al., 2010).

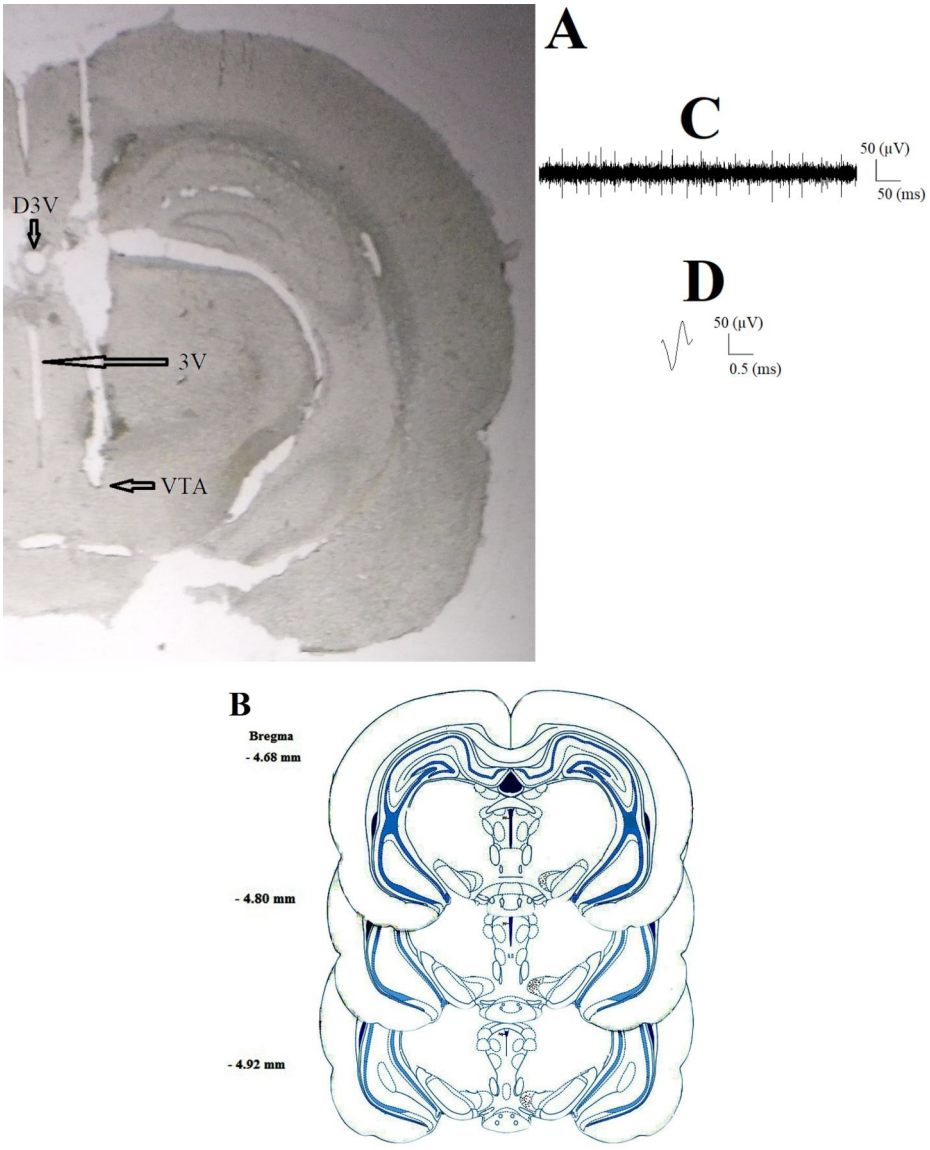

Fig. 1. A: Coronal photomicrograph of the recording & microinjection site in the VTA (3 V, 3rd ventricle; D3V, Dorsal 3rd ventricle; VTA, Ventral tegmental area). B: A representative image, displaying the microinjection and recording sites in the VTA. C: A representative pattern of neuronal electrical activity recorded from the VTA, D: An expanded waveform of a spike recorded from a VTA-ND neuron.

Our study revealed that blockade of each of CB1Rs or OX2Rs could significantly inhibit the enhanced firing rate of VTA-ND neurons, following systemic injection of nicotine, and actually, in some cases they decreased the neuronal firing rate below the baseline, in nicotine-treated rats. Interestingly, the blockade of each of them alone in saline-control rats, had no effect on the neuronal activity. In this study, antagonists were injected locally, and nicotine was injected systemically, therefore nicotine could also affect VTA before its direct action, through other pathways. These results are consistent with the studies that evaluated the intra-VTA blockade of CB1R or OX2R on nicotine-induced CPP (Azizi et al., 2018), and OX2R blockade on the exciting effects of nicotine-induced neuronal activity in nucleus accumbens (Fartootzadeh et al., 2018). Taken together, it can be concluded that VTA-ND neuronal response to nicotine is somewhat through endocannabinoid and orexin systems, as they can change the nicotine preference to nicotine aversion or vice versa (Azizi et al., 2018). This has been shown behaviorally (Azizi et al., 2018); according to our present results, these behavioral responses can be the result of a change in ND neuronal activity that is mediated by these two systems, and they can affect the reward circuits, in responding to nicotine.

It has been demonstrated that both OX2R and CB1R in the VTA, are able to change simple and regular activity of neurons. Previous evidence has shown that cannabinoids excite VTA dopamine neurons through activation of CB1Rs (French, 1997; Gessa et al., 1998), and also dopaminergic and GABAergic neurons in the VTA can be excited by orexin, through both OX1R and OX2R (Korotkova et al., 2003).

Finally, the present data demonstrated that there was no more effect of concurrent blockade of CB1R and OX2R than the blockade of each of them alone on neuronal activity, following the systemic injection of nicotine. These suggest that there was no synergistic effect between these two receptors in the VTA. These results are in line with previous behavioral studies that evaluated the concurrent blockade of carbacol-induced (Taslimi et al., 2011; Yazdi et al., 2015) and nicotine-induced CPP (Azizi et al., 2018). Also, we observed no differences between the responses of different doses of antagonists. Therefore, a linear relationship cannot be seen in these results, but within group comparison of responses before and after of drug injection showed a significant difference in some doses, these results can be due to the two high and low ranges of activity of the GABA neurons (Korotkova et al., 2003).

In conclusion, our findings suggest that rewarding responses and

dependency to nicotine can seriously be affected by the orexinergic and endocannabinoid systems in the VTA. Although previous studies suggested an interaction between two systems, our results showed no synergistic effect in the simultaneous blockade of their receptors, therefore, in order to survey the probable interactions of these two receptors, further studies are needed in the field of intracellular mechanisms and signaling.

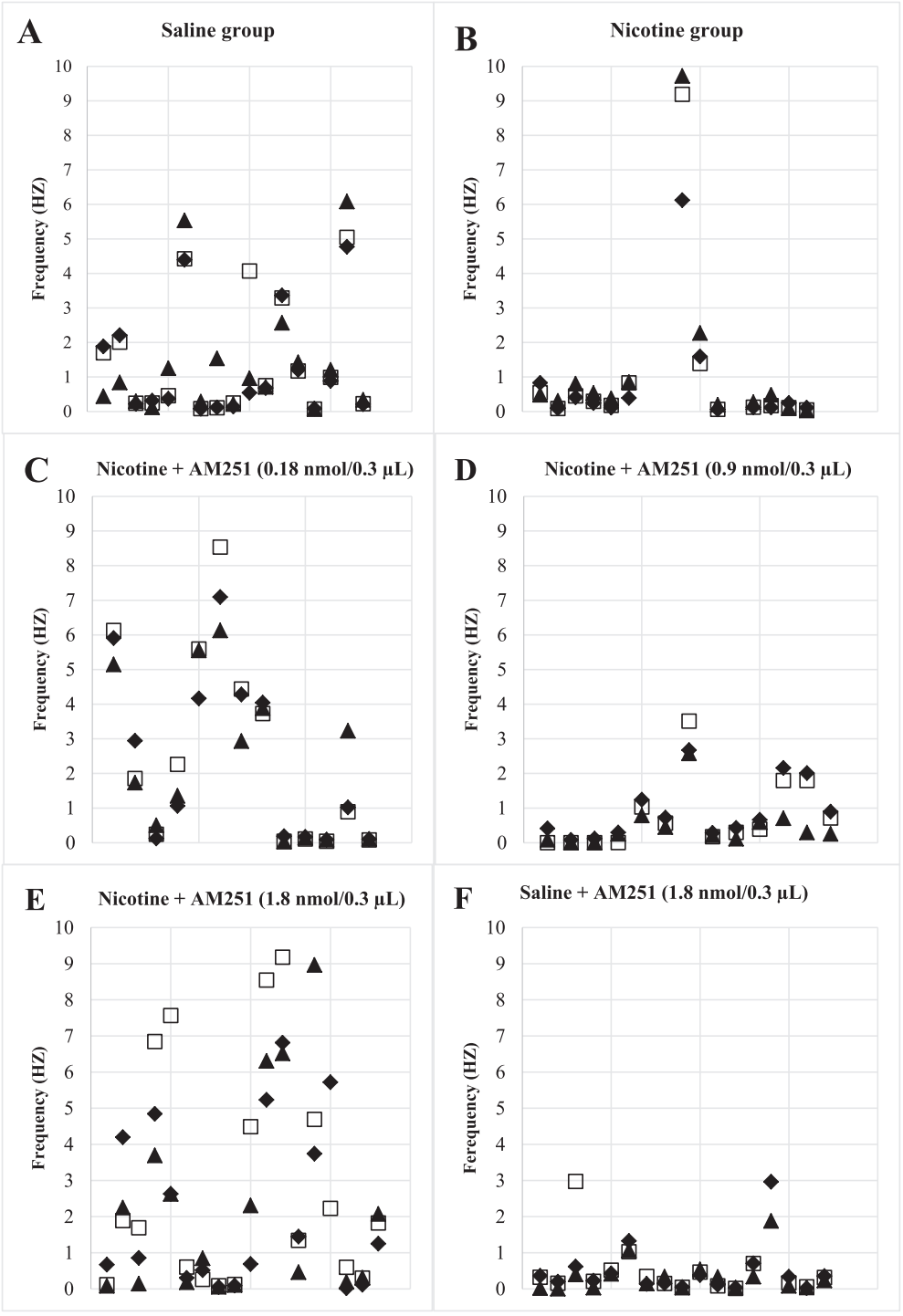

Fig. 2. Effects of OX2R and CB1R antagonists, on the firing rate of non-dopaminergic neurons, within the VTA following nicotine systemic administration. After 15 min of baseline response, antagonists were infused in the VTA and 5 min latter nicotine was injected subcutaneously, and recording was continued for another 60 min. A: control group, B: nicotine group, in C–E groups, after base recording, the CB1R antagonist was injected with doses (0.18, 0.9, 1.8 nmol/0.3 µL) in the VTA and 5 min later, nicotine was injected, F: injection of maximum dose of the CB1R antagonist in the VTA without nicotine injection. In G-I groups, after base recording, the OX2R antagonist was injected with doses (0.5, 1, 5 nmol/0.3 µL) in the VTA, and 5 min later, nicotine was injected, J: injection of maximum dose of an OX2R antagonist in the VTA without nicotine injection. K-L: Effect of simultaneous administrations of low doses of OX2R and CB1R antagonist on responses of VTA neurons to acute nicotine injection.

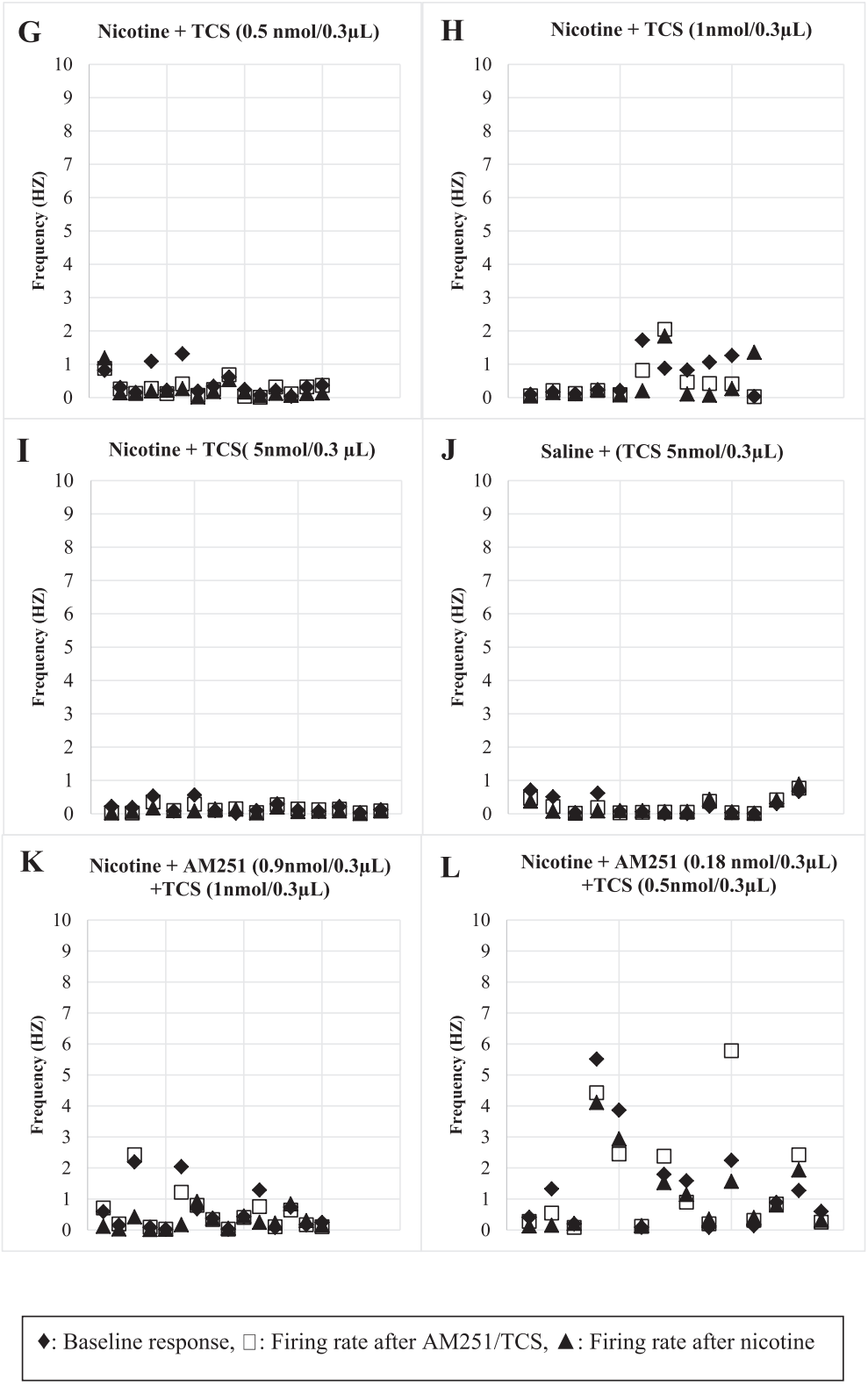

Fig. 2. (*continued*)

4. Experimental procedure

4.1. Animals

Adult male Wistar rats, weighing 230–300 g (Pasteur Institute, Tehran, Iran) were used in this study. They were housed four per cage, in a temperature-controlled animal facility with food and water available ad libitum. Animals were exposed to a 12 h light/dark cycle (lights on at 07:00 a.m.). 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 guidelines for Animal Care and Use of Laboratory Animals (National Institutes of Health Publication No. 85–23), revised 2010.

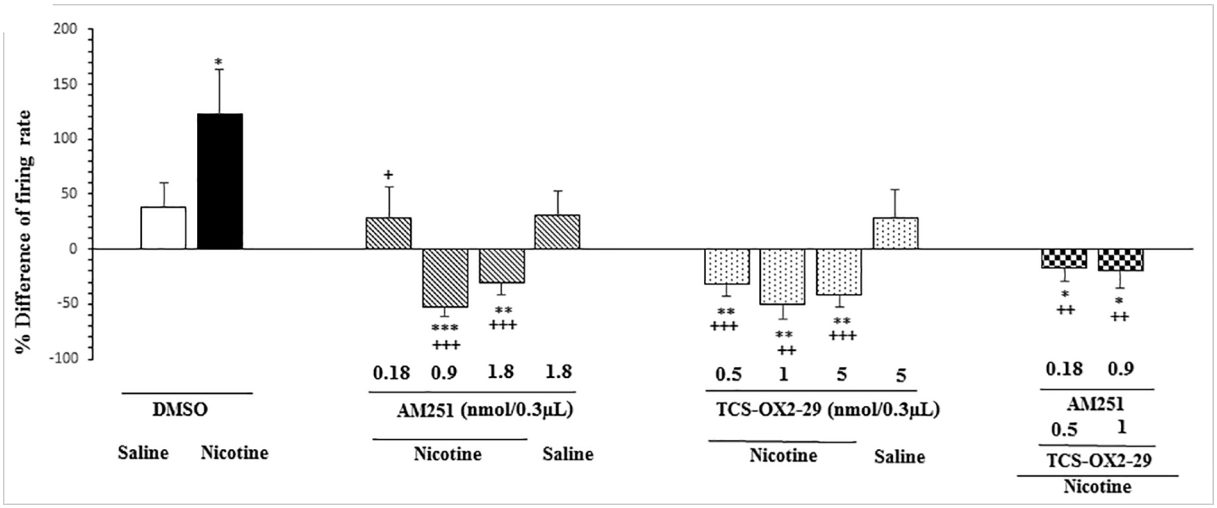

Fig. 3. Effects of OX2R and CB1R antagonists, on the percentage difference of firing rate of non-dopaminergic neurons, within the VTA following nicotine systemic administration. Data are expressed as mean ± SEM. *P < 0.05, **P < 0.01, ***P < 0.001 are different from the control group. $^{++}$P < 0.01 and $^{+++}$P < 0.001 are different from the nicotine group.

4.2. Drugs

Nicotine hydrogen tartrate salt (Sigma-Aldrich, Germany) was dissolved in saline, and injected subcutaneously (SC; 1 ml/kg; pH = 7.4). TCS-OX2-29 (Tocris Bioscience, Bristol, UK), as an OX2R antagonist and AM251 (Sigma-Aldrich, USA) as a CB1R antagonist, were dissolved in dimethyl sulfoxide (DMSO; 10% v/v) and saline (0.9%), and a drop of Tween 80, which also was used as DMSO (10% DMSO; 0.3 µL/rat) or vehicle, respectively (Hashemizadeh et al., 2014).

4.3. VTA single-unit recordings and data collection

Male rats were anesthetized with urethane (1.6 g/kg, i.p). Body temperature was maintained at 37 °C, by means of an electrically controlled heating pad. Rats were positioned in a stereotaxic apparatus. The skull was uncovered and a hole (roughly 3 mm diameter) was made for the insertion of a two-barrel micropipette (one barrel for drug microinjection, and the other was a recording electrode), in the right VTA (AP = −4.8 mm; L = ± 0.9 mm; DV = −8.3 mm) (Paxinos and Watson, 2007). Single-unit activities of VTA neurons were recorded extracellularly, using techniques described previously. VTA neurons were identified, according to well-defined electrophysiological features, and including the following neurons, the dopaminergic neurons with an average firing frequency of 2.86 ± 0.32 Hz, and a spike duration of 3.3 ± 0.13 ms; GABAergic neurons, could be divided into two groups of a relatively high frequency (8.7 ± 2.2 Hz), and slow-firing cells (0.63 ± 0.3 Hz) with a small spike duration (Korotkova et al., 2003). In the present study, neurons with a firing rate < 10 Hz, and a spike duration < 1 ms were selected, therefore, we assumed that our target neurons, were non-dopaminergic neurons, and presumably among the GABAergic neurons.

The extracellular electrical activity of VTA neurons was recorded, using glass micropipettes, filled with 3 M sodium chloride. Micropipettes were lowered into the VTA nucleus, using a micromanipulator. Recorded signals were displayed as a rate histogram. From each rat, only the extracellular electrical activity of one to three neurons was recorded. Recorded extracellular signals were filtered (300 Hz to 3 KHz band pass) and digitized, by a commercial analog to digital data acquisition system, and data were analyzed, using the associated software, eLab (Science Beam Institute, Iran). Baseline was recorded for 15 min, and then different doses of TCS-OX2-29 (0.5, 1, 5 nmol/0.3 µL) and AM251 (0.18, 0.9, 1.8 nmol/0.3 µL), or combinations of them (1 µg/rat and 0.9 µg/rat, respectively or 0.5 and 0.18 nmol/0.3 µL, respectively) were microinjected in distinct groups. Five minutes later, 0.5 mg/kg nicotine was injected subcutaneously, and the recording was continued for 60 min. In the saline and the nicotine groups, 10% DMSO was microinjected into the VTA instead of antagonists. Studies were done on 10–17 neurons in 6–7 rats, in each experimental group.

4.4. Histological verification

At the end of each recording, rats were perfused transcardially with saline, followed by 10% buffered formalin. Then, brains were removed and immersed in phosphate-buffered formalin for 24 h. The fixed tissues were sliced into 55 µm-thick coronal sections, and recording sites were histologically verified and schematized on sections derived from the rat brain Atlas (Fig. 1C) (Paxinos and Watson, 2007).

4.5. Data analysis

Data were analyzed, using the SPSS version 21 for windows. The effect of treatments on the changes in mean firing rates, were analyzed by paired Student's *t*-test, in each experimental group. The percent changes of the firing rate between the groups were analyzed, using the one-way ANOVA, followed by a post hoc Tukey test and unpaired Student's *t*-test. All data were expressed as mean ± SEM (n = 6–7 rats). P values < 0.05 were considered statistically significant.

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Declaration of Competing Interest

None.

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