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The effects of moxidectin nicotine-conditioned cue on nicotine-seeking behavior in mice

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ABSTRACT

Current pharmacotherapies for nicotine abuse are few and relatively inefficient demonstrating the need for the development of new, effective remedies. Moxidectin is used as an anti-parasitic agent in both animals and humans, it also activates GABA receptors. The objective of the present investigation was to study the effect of moxidectin on nicotine-induced conditioned place preference (CPP) in male Swiss mice. Intraperitoneal (i.p.) route was used for nicotine (0.5mg/kg) administration for a 3-day conditioning program. The influences of moxidectin on the reinforcing characteristics of nicotine were tested in mice given i.p. treatment of moxidectin (5 and 10mg/kg) 30 minutes prior to per nicotine administration. CPP was extinguished by repeated testing, through which conditioned mice were daily given two doses of moxidectin (5 and 10mg/kg, i.p.). Subsequently, the potency of moxidectin in blocking the reinstatement of CPP provoked by priming given low-dose nicotine (0.1mg/kg, i.p.) was also evaluated. Moxidectin treatment illustrated a reserve of acquisition of nicotine-induced CPP. It was reduced priming nicotine-induced reinstatement and accelerated the extinction of CPP. Relatively nicotine enhanced the locomotor, motor activity but was not statistically significant. In conclusion, the outcomes demonstrate the potential for the development of moxidectin as a new pharmacotherapy for the treatment of nicotine addiction.

1. Introduction

Addiction is characterized as a chronic, relapsing brain disorder that is identified by compulsive drug seeking and use (Tiwari et al., 2020; Volkow and Morales, 2015). It is considered a central nervous system disorder, through the action of drugs or substances (i.e., nicotine) altering the brain's functionality (Volkow and Morales, 2015; Son and Lee, 2020; Seifert and Schirmer, 2020). These brain alterations can be chronic and can lead to the damaging behaviors observed in people who abuse drugs and substances (Tiwari et al., 2020; Volkow and Morales, 2015). Currently, there are approximately 1.3 billion adult smokers globally, making tobacco dependency one of the most extensive global addictions (D'Souza, 2016). Nicotine, the basal ingredient of tobacco, produces cravings and withdrawal symptoms both in animals and humans (Tiwari et al., 2020; Le Foll and Goldberg, 2009; Alzhrani et al., 2020). Nicotine principally presents its effect throughout special nicotinic acetylcholine receptors (nAChRs) found in the central nervous system (Tiwari et al., 2020; Le Foll and Goldberg, 2009; Grant et al., 2020; Biala et al., 2010). Somebody who breathes smoke from a cigarette/tobacco will infuse nicotine from the tobacco, which is transported in smoke particles within the lungs, where it is absorbed immediately into the pneumonic venous circulation (Tiwari et al., 2020; Le Foll and Goldberg, 2009). It will then penetrate the arterial flow, immediately entering the central nervous system. Nicotine spreads immediately into brain tissue, where it connects to

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nAChRs, which are ligand-gated ion channels (Tiwari et al., 2020; Le Foll and Goldberg, 2009). When a cholinergic agonist attaches to the outside of the channel, the channel opens, permitting the entrance of cations, containing calcium and sodium (Tiwari et al., 2020). These cations have voltage-dependent calcium channels, enabling the influx of further calcium cations (Tiwari et al., 2020; Le Foll and Goldberg, 2009).

Moxidectin is produced as an alternative treatment to ivermectin as an antiparasitic drug for humans. It is a potent, broad-spectrum endectocide with action against a broad range of nematodes, insects, and acari. To date, no important clinical malformations have been published (Huynh et al., 2017). With Moxidectin becoming approved for human use, it could represent another avermectin candidate that could be reused as a pharmacotherapy for alcohol and nicotine dependence. The mechanism of development of alcohol and nicotine addiction is similar (Tarren and Bartlett, 2017; Hillmer et al., 2016). GABA receptors have an important role in both nicotine and alcohol addiction (Tarren and Bartlett, 2017; Hillmer et al., 2016). GABA is produced in brain cells from glutamate and functions as a main inhibitory neurotransmitter (Hillmer et al., 2016). Nicotine modifies GABA activity in the central nervous system through different mechanisms (D'Souza, 2016; Hillmer et al., 2016). Previous investigations have explained that GABA agonists decrease nicotine addiction (Fattore et al., 2009; Varani et al., 2014; Hillmer et al., 2016).

The conditioned place preference (CPP) model has been broadly applied to estimate the rewarding effects of abused drugs and substances (Pirri et al., 2021; Yunusoğlu, 2021a). Nowadays extinction and reinstatement periods of this model have been used to assess the relapse to drug-seeking behavior. The CPP model has not only been applied as a potential screening tool for drug abuse, but has been used to examine neurotransmitters, brain areas, signaling pathways, and various mechanisms mediating the rewarding (or anhedonia) effects of drugs (Golden et al., 2019; Tzschentke, 2007; Yunusoğlu, 2021a). Consideration in CPP research is the application of biased versus unbiased study designs (Tzschentke, 2007; Golden et al., 2019; Yunusoğlu, 2021b). We applied an unbiased design in our study. There are currently a number of drug applications containing a nicotine replacement product (e.g., patches, lozenges, gum, or nasal spray) or an oral medication (e.g., bupropion or varenicline) that have received FDA approval (Prochaska and Benowitz, 2016). In addition, can be an efficient component of therapy when a portion of an extensive behavioral therapy plan. Besides, they cause several side effects (Prochaska and Benowitz, 2016). Therefore, new agents maintaining successful pharmacological action with fewer side effects are needed in the treatment of nicotine dependence.

There are no reported studies to date related to the effect of moxidectin on nicotine addiction. The purpose of this study was designed to evaluate the action of moxidectin in the acquisition and reinstatement of the reinforcing effects of nicotine. We hypothesize that moxidectin may inhibit the rewarding effect of nicotine.

2. Materials and methods

2.1. Experimental animals

Experiments were carried out on 10-14 week-old male Swiss albino mice (body mass 25-30g) (Titomanlio et al., 2014). Four mice were housed per cage and kept at a 23±1°C humidity-controlled environment with a standard diet and water *ad libitum.* The experiment house used a 12-h light/dark cycle, with the light cycle starting at 8 a.m. All experiments were performed during the light cycle. In the research protocol efforts were made to minimize the number of animals and their distress (n=6-8/group) with permission for the study being granted by the research ethics committee of Animal Experiments at Van Yüzüncü Yıl University.

2.2. Chemicals

Moxidectin was suspended in a composite of polyethylene glycol 200 and 0.9% NaCl solution and was applied intraperitoneal (i.p.) in a volume of 10 mL/kg. Nicotine (0.5 mg/kg) utilized was calculated as nicotine hydrogen tartrate salt (1 mg/kg of nicotine hydrogen tartrate salt equals 0.350870 mg/kg nicotine-free base); it was applied (i.p.).

2.3. Handling habituation

One day prior to handling, all mice were singly housed. Handling and habituation actions were carried out 3 days prior to the start of testing. Mice were put into an illuminated room at 09:00 a.m. and allotted to habituate for 4 hours, and later returned to their home cages and left to habituate to the room until 4:00 p.m., at which point they returned into their rooms.

2.3.1. Pre-conditioning test

On day one, mice were taken to the experimental room and put alone in the middle line for 5 min. Consequently, during the 5-min habituation time, the sliding doors were sliding, and they were allowed to freely explore the CPP device for 15 minutes whilst starting video recording. Mice expressing an unconditioned choice (more than >66% of the session) or aversion (less than <33% of the session) for both chambers were eliminated from the examination (Shram and Lê, 2010; Titomanlio et al., 2014). These data were applied to assign mice into groups with no bias for either side and all biased mice were rejected. Seven mice exhibited unconditioned aversion or preference for one of the chambers and were thus ejected from the research.

2.3.2. Conditioning phase

One day after the pre-conditioning phase, the conditioning phase chose the place, which was produced as an unbiased, counterbalanced, CPP program that carried 30 minutes of everyday conditioning phase. The CPP protocol applied here is in conformity with previous subjects followed by lesser modifications. Mice were placed in the related chamber by leaving it using a sliding gate. Control mice received saline and were confined in the saline-paired chamber for 30 minutes (On days 2-4). Four hours later, the same mice were received with nicotine and enclosed to the nicotine-paired side. Nicotine was received in the afternoon session to withdraw confounding influences of acute nicotine avoidance on the saline conditioning session (Titomanlio et al., 2014; Shram and Lê, 2010). The plan is illustrated in Fig. 1.

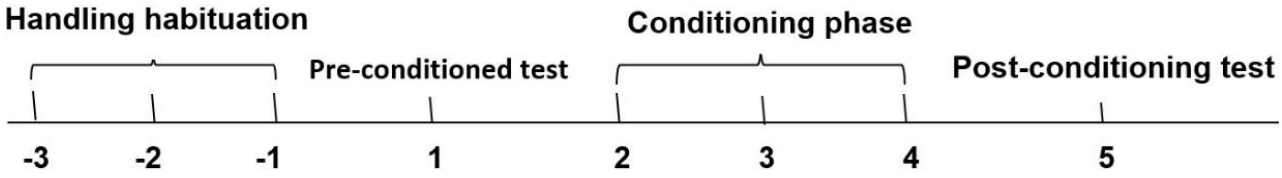

Fig. 1: Conditioning program and time schedule for the nicotine-induced conditioned place preference research

2.3.3. Effects of moxidectin on acquisition of nicotine-induced CPP

To study the influence of moxidectin on the acquisition of nicotine-induced CPP, the mice give moxidectin (5 and 10mg/kg, i.p.), or its vehicle 30 minutes before all nicotine is given during the conditioning test, as defined above (Fig. 1).

2.3.4. Post-conditioning test

On test day 5, mice were not injected. Animals were entitled entrance to the entire CPP device for 15 minutes, and the time spent in any chamber through this 15-min duration was noted; data were displayed as the time spent on the drug-paired side compared to time spent on the nicotine and saline-paired sides (Yusoff et al., 2018).

2.3.5. Effects of moxidectin extinction of nicotine-induced CPP

To evaluate whether moxidectin effect the extinction period of nicotine-induced CPP, the animals were taken extinction test per day for 3 days during the establishment of CPP (as defined above, on day 6). During this session, the mice were separated equally into three groups that injected daily injections of moxidectin (5 and 10mg/kg, i.p.) or saline, 30 min before the daily extinction test. During all tests, the mice were located in the CPP device with free access to both chambers for 15 min, and the time spent in all was recorded (Mattioli et al., 2012) (Fig. 2).

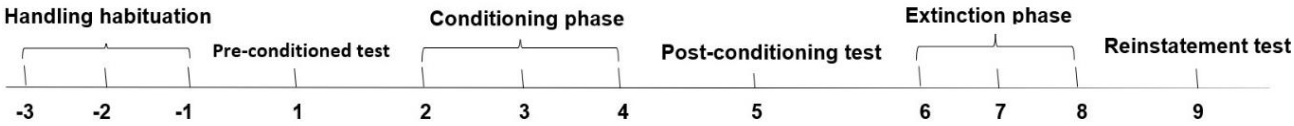

Fig. 2: Drug-priming reinstatement design and time presentation for the nicotine-induced conditioned place preference subject

2.3.6. Effects of moxidectin on drug-priming reinstatement of nicotine-induced CPP

To determinate the effects of moxidectin on reinstatement of CPP, CPP was induced in mice (as described above). One day later the last extinction of the test, mice were taken back to their home cages and tested repeatedly every 24 hours till preference was extinguished. Once preference was not much evident, various groups of mice were treated with moxidectin (5 and 10mg/kg, i.p. each) before 30 minutes of giving a low dose of nicotine (0.1mg/kg, i.p.) or saline. The treatment was performed in the chamber, which was different from the place where the previous conditioning injection was given (CPP chamber). The mice were reassessed for preference following the similar test day protocol (Jackson et al., 2017; Titomanlio et al., 2014). The design is expressed in Fig. 2.

2.4. Measurement of effects of moxidectin administration on locomotion

It was based on a method employed previously during the post-conditioning test, in a drug-free status. Locomotion was determined in the two main chambers. No medicine was administered during the locomotor activity period. So, the floor of the CPP device was divided into 6 equal-sized squares. Locomotor activity was determined as the number of crossings from one square to another within 15 minutes (Zarrindast et al., 2002).

2.5. Measurement of effects of moxidectin administration on motor coordination

The purpose of the test is to assess the mice's sensorimotor coordination and grip strengths. No medicine was administered during the rotarod period. The rotor was divided into two chambers which passed two mice to test concurrently at a time. Five tests were performed, the first two trials were "training," and the other three trials were sequentially conducted for analysis, with a maximal time of 300 seconds. Each mouse was trained on the rotarod until the mice completed the criteria of residuary on the rotating spindle for about 300 seconds (Philibin et al., 2012).

2.6. Statistical analysis

Data are expressed as the mean±SEM and analyzed using Prism software (GraphPad). The difference in preference was estimated as the difference between the time spent in the therapy drug-paired chamber post-conditioning. CPP, locomotor activity, and motor coordination examinations results were shown as mean preference. Data were analyzed using one-way analysis of variance (ANOVA) followed by Post hoc Bonferroni's multiple comparison tests. $p<0.05$ was considered as significant.

3. Results

3.1. Moxidectin effect of acquisition of nicotine-induced CPP

Administration of nicotine significantly increased the place preference for the nicotine-paired chamber (Fig. 3; $p<0.001$). Moxidectin administration 30 minutes ere the nicotine injection decreased the effect of nicotine on CPP (Fig. 3; $p<0.05$). ANOVA demonstrated that moxidectin (20 mg/kg, i.p.) significantly decreased the place preference to the nicotine (0.5mg/kg, i.p.) paired chamber [$F(3, 22)=16,31$; $p<0.05$]. Saline administration in the conditioning chamber did not present either preference or aversion ($p>0.05$). Post hoc Bonferroni's multiple comparison test explained that moxidectin (20 mg/kg, i.p.) significantly diminished the effect of nicotine on CPP as compared to the nicotine-treated mice ($p<0.05$). Furthermore, lower dose of moxidectin (10mg/kg, i.p.) showed no significant effects ($p>0.05$).

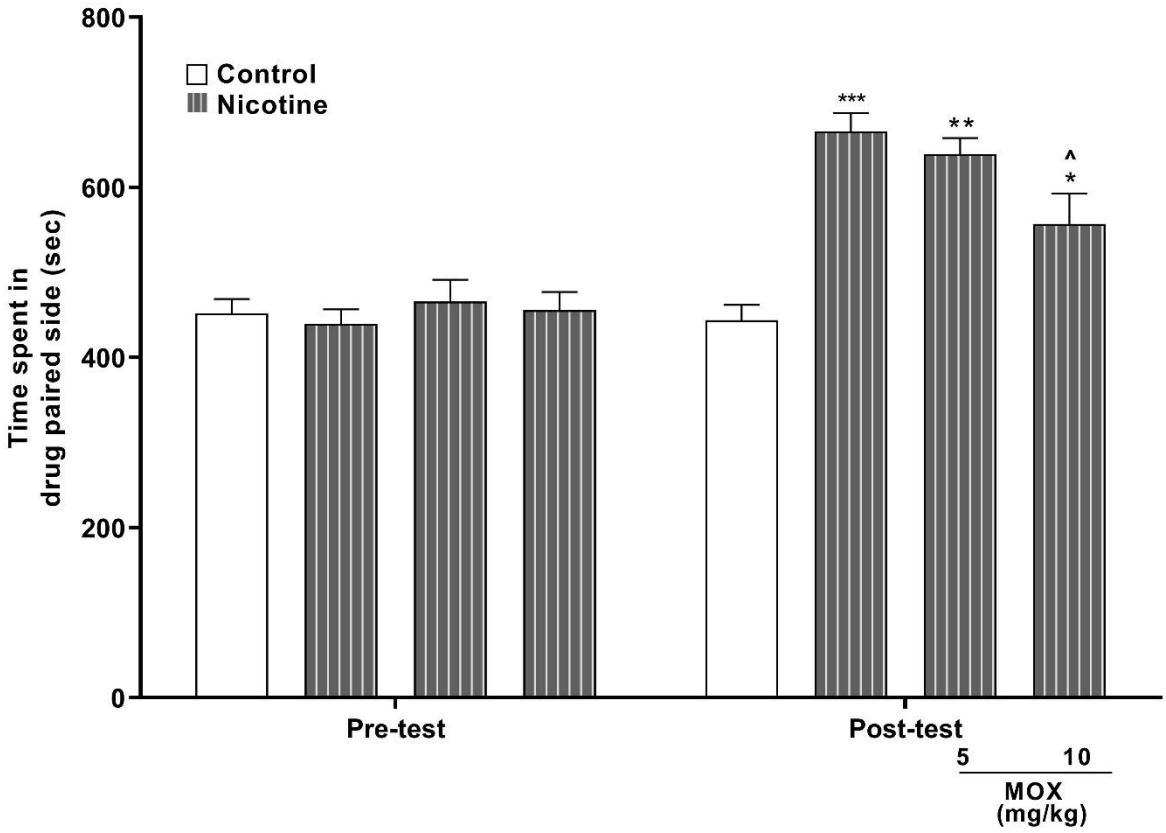

Fig. 3: Effects of moxidectin on the acquisition of nicotine-induced CPP. Mice were treated with moxidectin (5, and 10mg/kg, i.p.), as designated, 30 minutes were all nicotine treatment (0.5mg/kg; i.p.) during the conditioning test. On the post-test day, they were placed into the CPP device and permitted to move freely for 15 minutes. Values are means ± SEM. All data were expressed as time spent in the conditioning compartments during the post-conditioning tests. Post hoc Bonferroni's test, time spent in the conditioning compartments was measured for mice in the drug-paired chamber: ***$p<0.001$, **$p<0.0$, *$p<0.05$ compared to the saline group; ^$p<0.05$ compared to the nicotine group. Moxidectin=MOX

3.2. Effects of moxidectin on the extinction of nicotine-induced CPP

Effects of moxidectin on the time-dependence for the extinction of CPP induced by nicotine mice. One-way ANOVA revealed that there was previously a significant group difference on extinction day 1, [F (3, 22)=29,12, p<0.05], ext 1; [F (3, 22)=23,02, p<0.05], ext 2; [F (3, 22)=2,394, p>0.05], ext 3; respectively). However, one-way ANOVA revealed that there was already no significant group difference on extinction day 3, [F (3, 22)=2,394, p>0.05], ext 3. The post hoc analysis expressed that moxidectin significantly extenuated the time spent in the drug-paired chamber at a dose moxidectin (10 mg/kg) through extinction day 2 when compared to the nicotine group (p<0.05). No significance was detected among all groups on the 3rd day (p>0.05, ext 3) (Fig. 4).

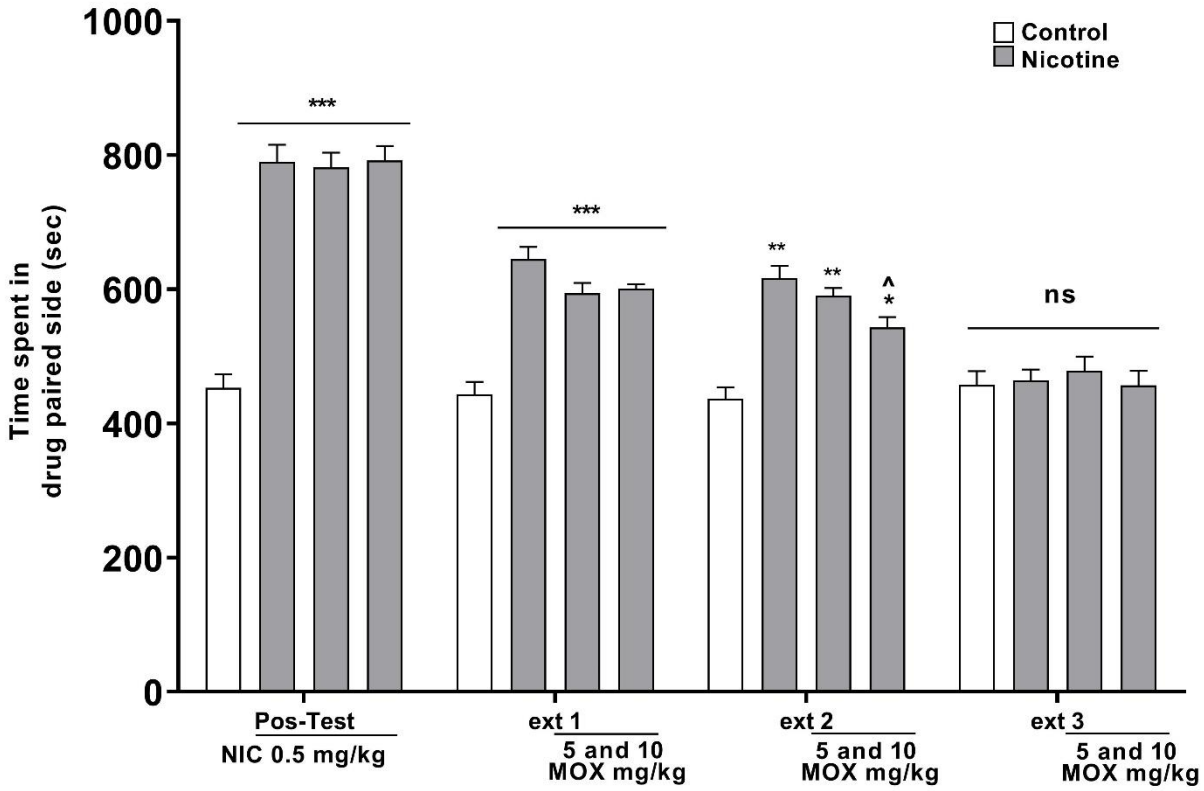

Fig. 4: Effects of moxidectin on the extinction of nicotine-induced CPP. The day later post-CPP, the animal underwent a daily period of extinction (3 days). They received two doses of moxidectin (5 and 10mg/kg, i.p.), as shown, 30 minutes before each session of extinction. Values are means ± SEM. All data are expressed as, through the extinction tests, time spent in the conditioning compartments was calculated for mice in the drug-paired chamber: ***p<0.001, **p<0.0, *p<0.05 compared to the saline group; ^p<0.05 compared to the nicotine group. Moxidectin=MOX

3.3. Effects of moxidectin on the reinstatement of nicotine-induced CPP

The effects of moxidectin on a low dose of nicotine (0.1g/kg, i.p.) priming induced CPP is present in Fig. 5. One-way ANOVA demonstrated that nicotine increased place preference to the nicotine-paired chamber [F (5,32)=9,402, p<0.05]. Bonferroni test displayed that the time spent in the nicotine-paired side on the reinstatement a day after a priming low dose of nicotine (0.1mg/kg, i.p.) was significantly (p<0.05) developed when compared to the time spent in the nicotine and saline-paired side. Post hoc Bonferroni's multiple comparison tests demonstrated that moxidectin (5 and 10mg/kg, i.p.) significantly diminished the effect of nicotine on CPP as compared to the nicotine-treated mice (p<0.05).

3.4. Effect of the moxidectin on locomotor activity on nicotine-induced CPP

One-way ANOVA demonstrated that the nicotine did not cause any effect on locomotion during the test session [F (3, 22)=3.827; p>0.05]. Post hoc analysis displays the influence of the moxidectin (5 and 10mg/kg, i.p.) any impact on locomotion while they were treated throughout the acquisition of nicotine-induced CPP is in Fig. 6.

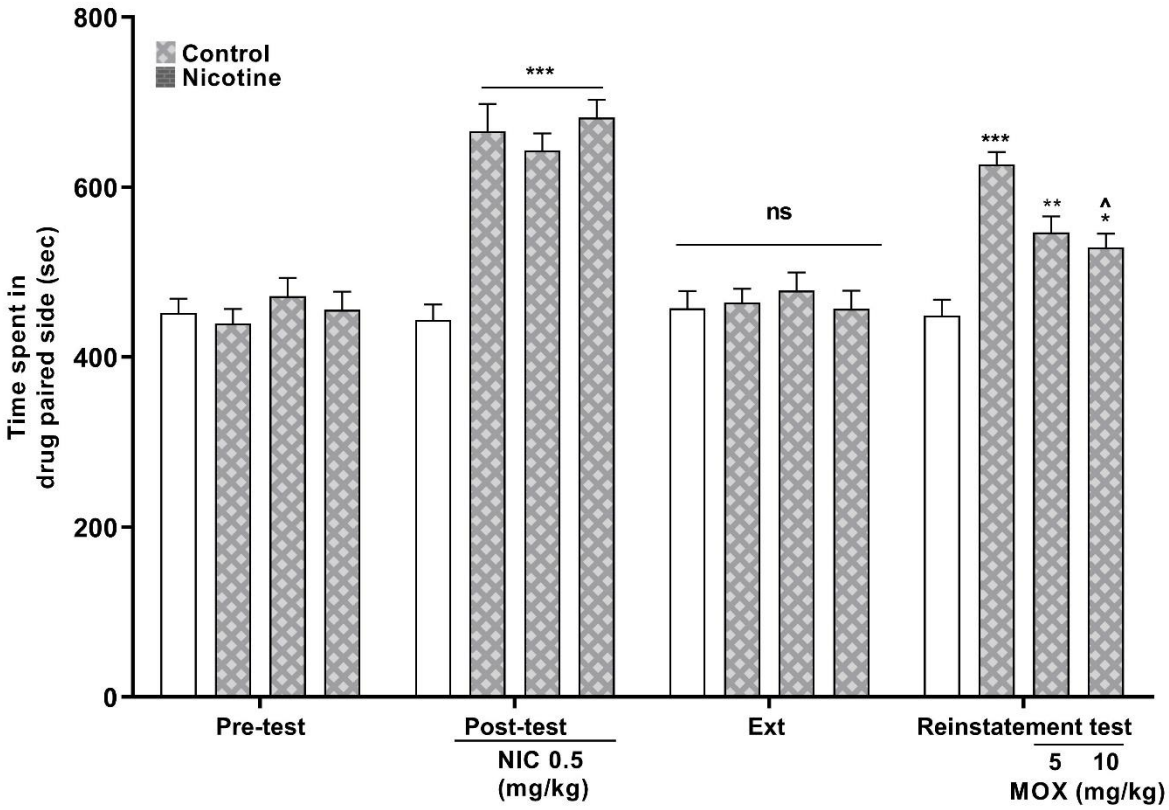

Fig. 5: Effects of moxidectin on drug-priming reinstatement of nicotine-induced CPP. Following the extinction test, the mice give two doses of moxidectin (5 and 10mg/kg, i.p.) as designated, 30 minutes ere the priming-nicotine received (0.1g/kg, i.p.). The effects of moxidectin on reinstatement to CPP were tested 15 minutes following the priming treatment. Values are means ± SEM. All data are expressed as, through the reinstatement tests, time spent in the conditioning chambers was calculated for mice in the drug-paired chamber: ***p<0.001, **p<0.0, *p < 0.05 compared to the saline group; ^p<0.05 compared to the nicotine group. Moxidectin=MOX

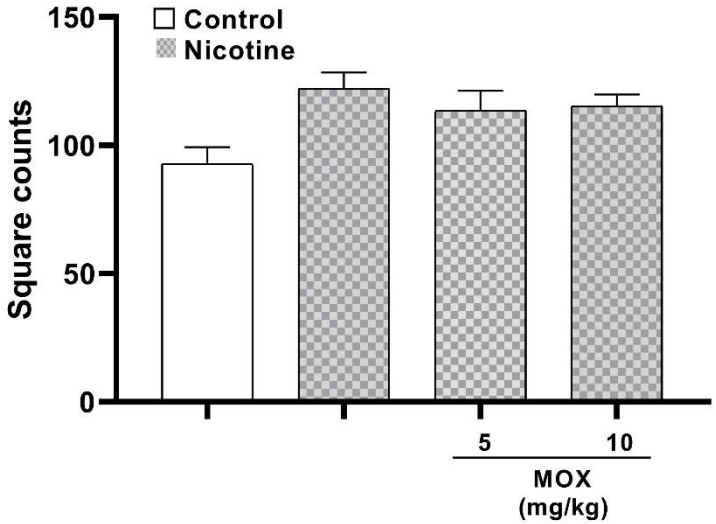

Fig. 6: Effect of the moxidectin (5 and 10mg/kg, i.p.) on locomotor activity in the expression of nicotine-induced CPP. Locomotion was estimated, based on a method employed previously during the post-conditioning test, in a drug-free state. Determined locomotion in the two main chambers. Locomotor activity was measured as the number of crossings from one square to another within 15 minutes. Values are means±SEM. There was an insignificant difference among all groups (p>0.05). Moxidectin=MOX

3.5. Effect of the moxidectin on motor coordination of mice

ANOVA demonstrated that the nicotine did not induce any impact on locomotion during the test session [F (3, 22)=2.026; p>0.05]. Post hoc analysis shows the impact of the moxidectin (5 and 10mg/kg, i.p.) any impact on motor coordination while they were treated throughout the acquisition of nicotine-induced CPP is in Fig. 7.

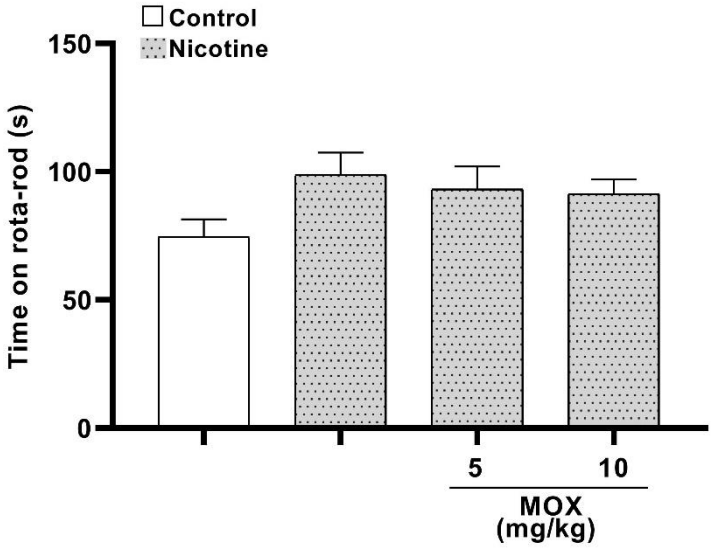

Fig. 7: Behavioural effect of moxidectin (5 and 10) on rota-rod test. Five trials were performed, the first two trials were "training," and the other three trials were sequentially conducted for analysis, with a maximal time of 300 seconds. Values are means ± SEM. There was an insignificant difference among all groups ($p > 0.05$). Moxidectin = MOX

4. Discussion

Drug and substance (i.e., nicotine) addiction is a historic and active participant in the sociological panorama of most societies (Reid et al., 2012). Depending upon the society and the drug or substances, the usage of addictive drugs and substances ranges from religious to socially acceptable to criminal (Reid et al., 2012). Modern pharmacological approaches to drug and substance addiction problems are to reduce or prevent the effects of a drug at the effect sites within the body by decreasing the 3 principal outlooks: Abstinence/withdrawal syndrome, craving/drug-seeking, and relapse (You et al., 2019). Most pharmacological treatments used usually reduce the symptoms of abstinence, few can reduce the drug craving, and they are also seldom effective in blocking relapse (Tzschentke, 2007; Allahverdiyev et al., 2011; 2015; Reid et al., 2012).

The aim of the present study was to consider the effects of moxidectin on the rewarding characteristics of nicotine following the various phases of CPP. Mice given nicotine during the preference test showed a significant improvement in conditioning for the nicotine-paired chamber compared to the saline-paired chamber. These are consistent with the results of a prior investigation (Titomanlio et al., 2014; Biala et al., 2010). In the present investigation, the treatment of moxidectin and the effective doses were determined from previous research based on alcohol addiction (Huynh et al., 2017). This study demonstrates that moxidectin (10mg/kg, i.p.) can significantly decrease the acquisition. In addition, moxidectin prevented the reinstatement properties (10mg/kg, i.p.) and accelerated the extinction-level (10mg/kg, i.p.) of nicotine. There was no statistical significance in all measurements in the locomotor activity and rotarod. Moxidectin may reduce nicotine-induced CPP by affecting the GABA receptors.

Previous research showed the feasibility of repurposing moxidectin into a novel pharmacotherapy for alcohol dependence. Moxidectin is now being produced as an alternative treatment to ivermectin as an antiparasitic drug for humans (Prichard and Geary, 2019). It is a potent, broad-spectrum endectocide with action opposite a broad range of nematodes, insects, and acari. Contemporarily, no important clinical malformations have been published (Huynh et al., 2017). Moxidectin becoming approved for human use could represent added ivermectin candidate that could be reused as a pharmacotherapy for alcohol and nicotine dependence. The mechanism of development of alcohol and nicotine addiction is similar (Tarren and Bartlett, 2017; Hillmer et al., 2016). GABA receptors have an important role in both nicotine and alcohol addiction (Tarren and Bartlett, 2017; Hillmer et al., 2016). GABA is produced in brain cells from glutamate and functions as a main inhibitory neurotransmitter (Hillmer et al., 2016). Nicotine modification GABA activity in the central nervous systems by different mechanisms (D'Souza, 2016; Hillmer et al., 2016). Previous investigations have explained that GABA agonists decrease nicotine addiction (Fattore et al., 2009; Varani et al., 2014; Hillmer et al., 2016). Moxidectin has GABA confirm the action and played a character in the decrease of nicotine-induced CPP during this mechanism and it brings about a decrease of nicotine-induced CPP through this mechanism (Spampanato et al., 2018; Menez et al., 2012; Rodrigues-Alves et al., 2008; Huynh et al., 2017). Moxidectin has GABA receptors activity which can contribute to the modulation of nicotine-induced CPP during this mechanism.

This study has some limitations that must be considered when interpreting the conclusions. Firstly, this research was carried on male mice. Sex differences are observed during all stages of nicotine addiction, from beginning to dependence, withdrawal signs, and recurrence (Dickson et al., 2011; Yunusoğlu, 2021a; Pogun et al., 2017). Despite some differences between the examinations resulting from methodological problems, in general, the females appear to be further sensitive to the conditioned rewarding impacts of nicotine than males. Sex differences in drug and substance utilization and dependence, including nicotine dependence, have been evidently documented in various investigations explaining that dependence in females commence at lower doses than males but takes place more immediately (Pogun et al., 2017; Yunusoğlu, 2021a). This fact is an issue for future research to explore. Secondly, resveratrol can decrease nicotine-induced CPP through different mechanisms. The probable mechanisms are thought to be explained by utilizing different receptor blockers or activation in the following subjects.

Pharmacological strategies for the therapy of nicotine dependence are targeted at reducing the three main critical prospects: craving, relapse, and withdrawal syndrome. The various phases of the CPP test imitate a present clinical situation like an acquisition for craving/drug-seeking, extinction for withdrawal, and reinstatement for relapse. In conclusion, moxidectin was effective for the decrease of acquisition, reinstatement, and accelerate the extinction of nicotine. According to the obtained outcomes, it can be assumed that moxidectin may be useful in the treatment of both nicotine and other same types of addiction.

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Compliance with ethical standards

Conflict of interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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