RESEARCH PAPER

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Central GPR55 may prevent nicotine reinforcing actions: a preliminary study

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GPR55 is an orphan receptor whose endogenous agonists include lysophosphatidylinositol (LPI) and N-acetylethanolamides (NAEs), such as palmitoylethanolamide (PEA) and anandamide. Furthermore, its physiology in the central nervous system involves motor coordination, procedural and spatial memory, pain, and anxiety, among others. Recent reports indicate that systemic injections of O-1602 (a GPR55 and GPR18 agonist) blocked the reinforcing effects of morphine and nicotine in the conditioned place preference (CPP) paradigm, suggesting a possible participation of peripheral and/or central GPR55/GPR18 in brain reward/anti-reward systems. In this pilot study, the endogenous GPR55 agonists LPI and PEA, the highly selective GPR55 synthetic agonist ML184 or the selective GPR55 antagonist ML193 were injected to examine their pharmacological effects on the reinforcing actions of nicotine in the CPP paradigm. Our preliminary study shows that injections of LPI, PEA, ML184 and ML193 interfered with the change in place preference induced by nicotine *via* mechanisms that remain to be identified (which probably include central GPR55).

Key words: GPR55, conditioned place preference, palmitoylethanolamide, lysophosphatidylinositol, nicotine

INTRODUCTION

The endocannabinoid system has been implicated in the mechanisms underlying the reward effects of several drugs of abuse (Di Marzo, 2006; Parsons and Hurd, 2015), including nicotine (Le Foll et al., 2008; Muldoon et al., 2013). Although the psychoactive effects of cannabinoids have been historically associated with the cannabinoid type 1 receptor (CB_1), the widely used CB_1 blockers/inverse agonists (e.g., AM251 and SR141716) may also interact as agonists for the orphan receptor GPR55 (Table 1). Furthermore, GPR55 is expressed in brain areas involved in the reinforcing actions of drugs of abuse, such as the basal nuclei, frontal cortex, and hippocampus (Sawzdargo et al., 1999; Ryberg et al., 2007), and in others related with negative emotional actions (e.g., pain, anxiety, irritability, etc.) of the compulsive intake of substances such as the periaqueductal gray (PAG) and amygdala (Deliu et al., 2015; Marichal-Cancino et al., 2017; Shi et al., 2017; Vázquez-León et al., 2021b). Nevertheless, a possible function of GPR55 in the mechanisms that underlie brain reward and anti-reward systems remains virtually unexplored.

Two G protein-coupled receptors (GPCRs) have been classified as cannabinoid receptors (i.e., the type 1 and type 2; CB_1 and CB_2, respectively), but other GPCRs such as GPR3, GPR6, GPR12, GPR18, GPR55 and GPR119 have been genetically, pharmacologically and/or molecularly associated with the endocannabinoid system (Allende et al., 2020; Guerrero-Alba et al., 2018; Guzmán-Rodríguez et al., 2021; Marichal-Cancino et al., 2014; Morales and Reggio 2017; Ramirez-Orozco et al., 2019). Among those putative cannabinoid GPCRs,

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GPR55 has been proposed as the type 3 cannabinoid receptor (CB_3) (Yang et al., 2016). Moreover, as it is also activated by the non-cannabinoid lipid lysophosphatidylinositol (LPI), it remains un-classified by the International Union of Basic and Clinical Pharmacology, IUPHAR (Pertwee et al., 2010).

GPR55 is closely related to the endocannabinoid system as it (i) is activated by phytocannabinoids (e.g., THC), endocannabinoids (e.g., anandamide) and palmitoylethanolamide (PEA) (Ryberg et al., 2007; Marchial-Cancino et al., 2020); (ii) forms heterodimers with CB_1 and CB_2 (Balenga et al., 2014; Martínez-Pinilla et al., 2014); (iii) shares signal properties that are sensitive to cross modulation by CB_1 (Kargl et al., 2012); and (iv) mediates multiple pharmacological actions induced by exogenous cannabinoids (e.g., vasodilatation, anxiety, pain, insulin secretion, cell proliferation, learning and memory, among others) (Marichal-Cancino et al., 2013; 2016; 2017; 2018; Calvillo-Robledo et al., 2022).

Interestingly, SR141716 was reported to prevent the nicotine-induced conditioned place preference (CPP), which was an effect attributed to the CB_1 receptor blockade (Le Foll and Goldberg, 2004). Moreover, the morphine and nicotine-induced CPPs were prevented with a systemic pretreatment with O-1602 (Alavi et al., 2016; Liu et al., 2021), a GPR55/GPR18 agonist (Ryberg et al., 2007; Schicho and Storr 2012), suggesting that stimulation of the abovementioned receptors may interfere with the reinforcing actions of morphine and nicotine. In a recent study (published by the time the present article was under revision), Liu et al. (2021) reported in mice that (i) there is high expression of GPR55 in the nucleus accumbens (NAc); (ii) that NAc neurons from animals that received systemic nicotine and O-1602 produced less spontaneous excitatory postsynaptic currents compared to animals which received systemic nicotine alone; (iii) that increases in serum levels of dopamine induced by nicotine were prevented after systemic O-1602 (although this failed to modify dopamine levels in NAc); and (iv) that activation of GPR55 in NAc appears to modulate the expression of AMPA receptors. Notably, a partial GPR55 knockdown (approximately 40%) in NAc did not modify the preventive actions of systemic O-1602 on nicotine-induced CPP (Liu et al., 2021). The above results suggest a possible role of GPR55 in the reinforcing actions of nicotine.

We established a pilot study to explore the effects of pharmacological manipulation of central GPR55 on the nicotine-induced CPP paradigm.

METHODS

Animals

Male Wistar rats (n=100; 250-300 g) approximately 8 weeks of age (Sengupta, 2013) were obtained from the vivarium of the Autonomous University of Aguascalientes. All experimental protocols were approved by our Institutional Ethics Committee (CE-UAA) and followed the Mexican Guidelines for Animal Care (NOM-062-ZOO-1999) in accordance with the ARRIVE guide (McGrath et al., 2010) and the Guide for the Care and Use of Laboratory Animals in the USA (Bayne, 1996). Animals were kept under a 12-hour light/dark cycle, with water and food *ad libitum*.

Stereotaxic surgery

All rats were anesthetized with 1 mL/kg (i.p.) Zoletil®50 (35 mg/mL) and Xylazine (8 mg/mL). A guide

Table 1. Affinity values (pEC50/pIC50) of several ligands for GPR55 and CB_1 receptors.

Ligand	GPR55		CB1	
PEA	Agonist	8.4[a] pEC50	Agonist	<4.5[a] pEC50
LPI	Agonist	5.9[d]-7.3[e] pEC50	Agonist	<4.5[d] pEC50
Δ^9-THC	Agonist	8.1 pEC50[a]	Agonist	8.2[a] pEC50
Rimonabant	Agonist	5.5[b] pEC50	Antagonist	7.9[c]-8.6[b] pIC50
AM251	Agonist	5.5[b]-7.4[a] pEC50	Inverse agonist	7.5[d] pEC50
ML184	Agonist	6.6[f] pEC50	Antagonist	5.6f[g] pIC50
ML193	Antagonist	6.7[g] pEC50	Antagonist	4.6[g] pIC50

Data taken from: [a]Ryberg et al., 2007; [b]Brown et al., 2011, [c]Felder et al., 1995, [d]Kapur et al., 2009, [e]Henstridge et al., 2010, [f]Kotsikorou et al. 2011; [g]Heynen-Genel et al., 2010.

cannula was stereotaxically implanted into the right lateral ventricle (AP: -1.7 mm, ML: 2.6 mm and DV: 3.4 mm) based on the Paxinos and Watson (2014) atlas. The guide cannula was held in place to the skull with two screws and dental acrylic, and a stylet was inserted into the guide. After surgery, the animals were placed in post-surgery recovery for at least 7 days.

Drugs and microinjections

All compounds used in the present study were obtained from Sigma Aldrich® (Saint Louis, Missouri, USA). Microinjections were made over a 60 s period by a syringe pump (Sage Instruments), and the injection cannula was left undisturbed for another 60 s to avoid backflow. Lysophosphatidylinositol (LPI), palmitoylethanolamide (PEA), CID-2440433 (ML184) and N-[4-[[(3,4-dimethyl-5 isoxazolyl)amino]sulfonyl] phenyl]-6,8-dimethyl-2-(2-pyridinyl)-4-quinoline-carboxamide (ML193) were dissolved in 10% dimethylsulfoxide (DMSO). Fresh solutions were prepared prior to each experimental session and freebase was considered to calculate the concentrations reported.

Rats were divided in two blocks to drive the CPP protocols. Block 1 (n=50) received s.c. injections of saline solution and block 2 (n=50) received s.c. injections of nicotine (0.03 mg/kg). Before each nicotine or paired-s.s. injection (Fig. 1), animals received pretreatments (1 µl; i.c.v.) of (i) vehicle (VEH; 10% DMSO); (ii) LPI (1 nmol); (iii) PEA (1 nmol); (iv) ML184 (1 nmol); or (v) ML193 (1 nmol). Hence, the saline-block was utilized as an experimental control to analyze the effects of the i.c.v. pretreatments, whereas the nicotine-block examined the effects of the i.c.v. pretreatments on the reinforcing actions of nicotine in the CPP paradigm. In this pilot study, doses of treatments were selected *a priori* at 1 nmol, which has been reported as a biologically active dose in previous cognitive paradigms with i.c.v. injections of LPI, ML193 and PEA (D'Agostino et al., 2007; Vázquez-León et al., 2021a). On the other hand, as no previous studies involving i.c.v. ML184 injections were found, we decided to also use 1 nmol for comparisons.

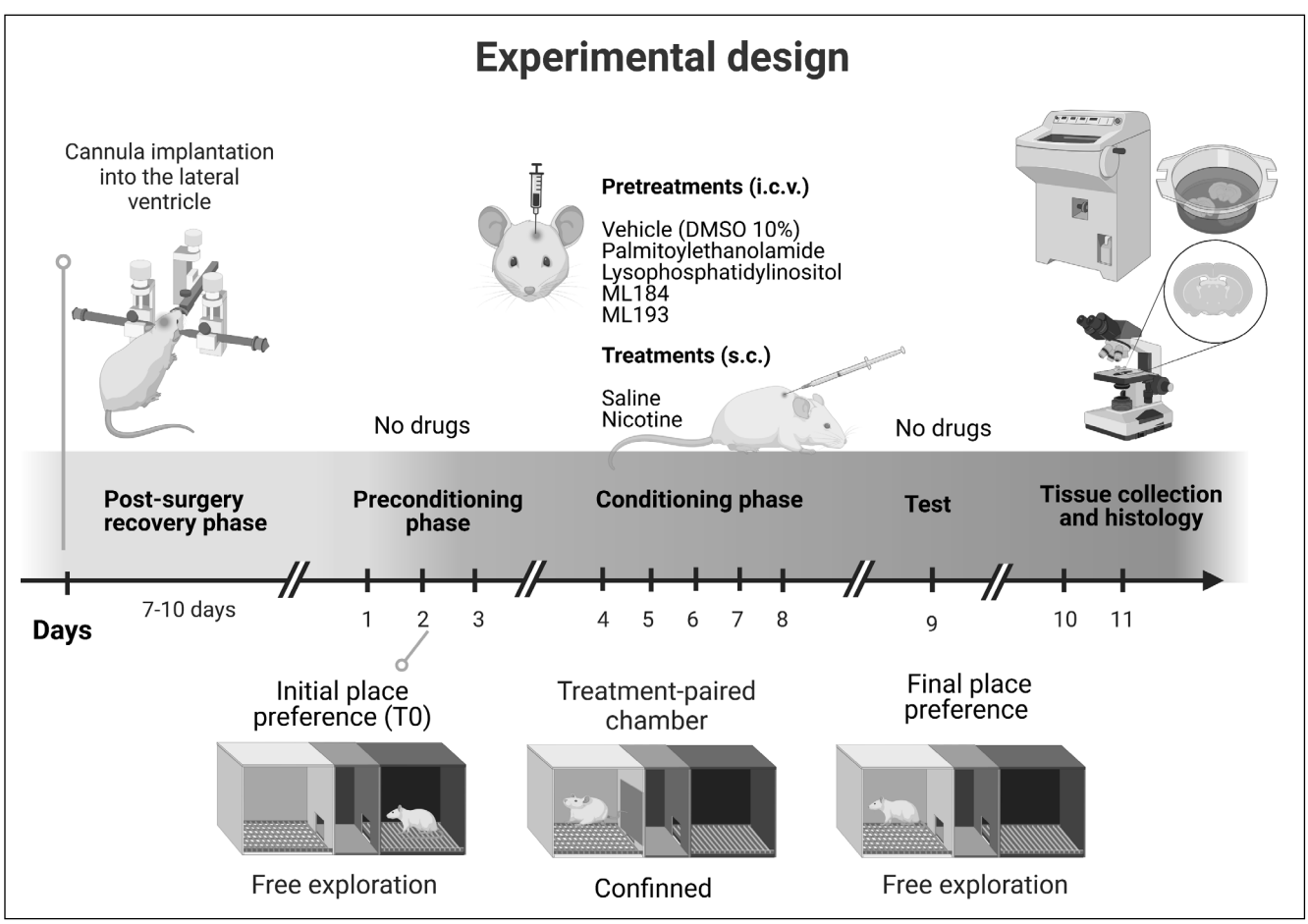

Fig. 1. Schematic diagrams of the experimental protocols.

Behavioral tests

We used a CPP apparatus, that consists of two large side chambers (41.5 cm × 32.5 cm × 30.5 cm) and one middle chamber between both compartments (27.5 cm × 15 cm × 12.5 cm). The two side chambers differed in floor textures (course *versus* fine) and somatosensory cues (black *versus* white). The CPP paradigm consisted of three different phases, namely pre-conditioning with a duration of 3 continuous days, conditioning with a duration of 5 continuous days, and test day (Fig. 1).

Animals were treated in the opposite chamber to that preferred during the pre-conditioning phase. The difference between the time spent in the drug-paired compartment during the test day and the time spent in the drug-paired compartment during pre-conditioning (lateral preference shift) was taken as the degree of conditioning. Therefore, a statistically significant increase in time spent in the drug-paired chamber suggests a conditioning effect induced by the treatments, as previously reported (Liu et al., 2019).

Pre-conditioning phase

The baseline and compartment preference were determined by placing each animal in the middle compartment of the CPP apparatus, then removing the barriers to allow free access to the entire apparatus for 15 min per day for days 1 to 3. The activity of rats was recorded, and the time spent in the non-preferred chamber (i.e., the chamber where animals spent less time) at day 3 was used as the baseline (Fig. 1) (Sun et al., 2018).

Conditioning phase

This phase consisted of 5 days of conditioning sessions. Prior to (5 min) performing each paired compartment session, the pretreatments of vehicle (10% DMSO), LPI (1 nmol), PEA (1 nmol), ML184 (1 nmol) or ML193 (1 nmol) were microinjected i.c.v through the cannula into the lateral ventricle. Conditioning was carried out twice a day (7:00 am and 11 am) for 15 min with 4 hours between sessions where either 0.03 mg/kg nicotine or saline was injected subcutaneously. Access to other compartments was blocked during this phase.

Test day

The next day after the conditioning phase, the testing phase was carried out. Guillotine doors were removed, and the rats had access to the entire apparatus. The time each rat spent in the compartments over a 15-min period was recorded. The difference between the time spent in the drug-paired compartment during the test day and the time spent in the drug-paired compartment during pre-conditioning (lateral preference shift), the time in movement (motor activity), the frequency of reading (vertical activity), number of entrances into the conditioning chamber, and time of total self-grooming were evaluated.

Histology

At the end of the behavioral procedure, the animals were overdosed with a lethal injection of sodium pentobarbital (70 mg/kg, i.p.). Intracardiac perfusion was performed with 0.9% isotonic saline followed by 4% formaldehyde, the brain was removed, and preserved in 10% formaldehyde. Subsequently, the brain was mounted in a 30% sucrose bath and coronally sectioned (60 μm) using a cryostat. The slices were stained with cresyl violet (Sigma®, St Louis, MO) and viewed under a microscope to verify the microinjection sites. Only verified animals were included in data analysis.

Data analysis

For all tests, the measure of central tendency was the mean ± standard error of the mean (SEM) and all data was normally distributed. Comparisons for the CPP-protocol were analyzed by with a two-way analysis of variance with repeated measures (two-way-RM-ANOVA), while other behaviors (Fig. 3) were analyzed by two-way-ANOVA. When significant, this was followed by the Bonferroni *post hoc* test. A p value of < 0.05 was considered statistically significant for all experiments.

RESULTS

Effects of the pretreatments on reinforcing actions of nicotine in the CPP apparatus

Fig. 2A shows the reinforcing effects of nicotine in the CPP paradigm. Subcutaneous administration of nicotine (0.03 mg/kg) in rats pretreated (i.c.v.) with vehicle (10% DMSO), caused an increase ($F_{(1,18)}=6.220$, $p<0.05$) in the preference for the nicotine-paired chamber when compared to baseline. Administration of the pretreatments (i.c.v.) PEA (1 nmol; Fig. 2B), LPI

(1 nmol; Fig. 2C), ML184 (1 nmol; Fig. 3A) and ML193 (1 nmol; Fig. 3B) prevented the increase in the preference for the nicotine-paired compartment. Moreover, PEA (1 nmol; Fig. 2B), but not LPI, ML184 or ML193, produced a tendency ($F_{(1,18)}$=3.730, p=0.06) to increase the preference for the saline-paired compartment in absent of nicotine, although this did not reach statistical significance.

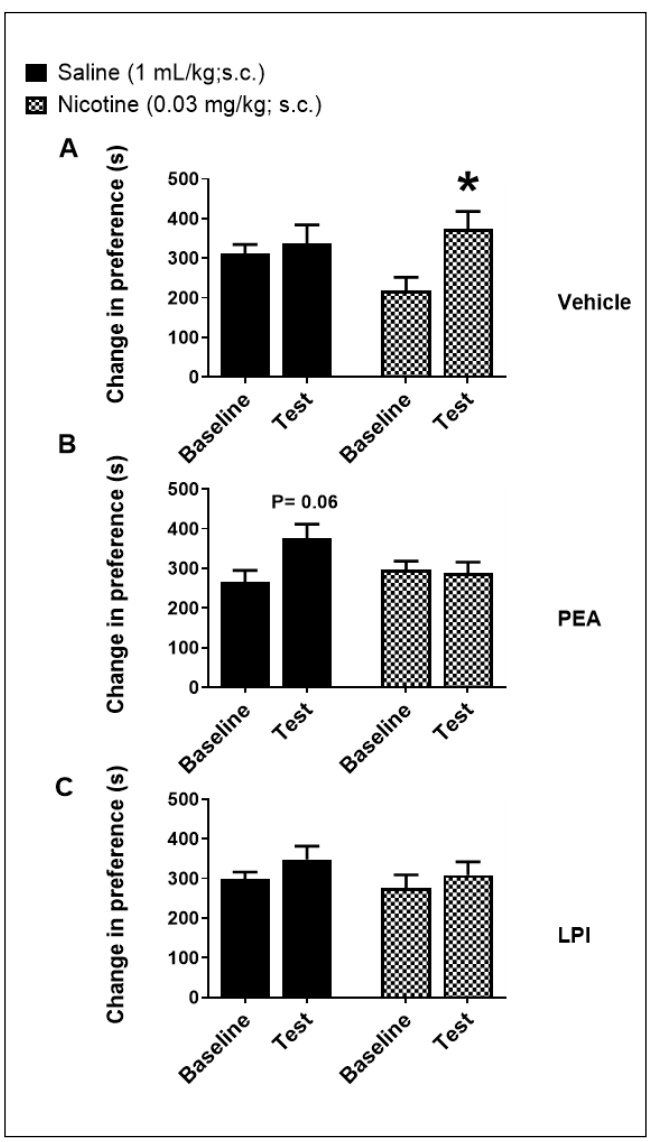

Fig. 2. Effect of the vehicle (DMSO 10%; A), palmitoylethanolamide (PEA; B) or lysophosphatidylinositol (LPI; C) (i.c.v.) on the reinforcing effects of nicotine (0.03 mg/kg; s.c.) in the CPP paradigm. *, p<0.05 *vs.* corresponding baseline. Data are expressed as the mean ± SEM and analyzed by two-way RM ANOVA, n=20 each treatment (i.e., n=10 in saline/n=10 in nicotine groups). Comparisons were analyzed using Bonferroni's post-hoc test.

Post-administration effects of the pretreatments on motor activity, vertical activity, entrances, and self-grooming behavior in the nicotine-induced CPP

Fig. 4 highlights the post-administration effects of vehicle, PEA, LPI, ML184 and ML193 on motor activity and total self-grooming time during the CPP-test (without i.c.v. or s.c. injections). In the vehicle pretreatment, rats from the nicotine-block demonstrated more motor activity than those from the saline group, whereas the pretreatment with ML184 into the nicotine-block produced less motor activity compared with ML184 from saline-block (Fig. 4A) ($F_{(4,90)}$=3.264, p<0.05). Moreover, the PEA-pretreatment group had higher motor activity in absence of nicotine (i.e., in the saline-block), while in the nicotine-block, ML184 produced less motor activity compared with vehicle, PEA and LPI (Fig. 4A) ($F_{(4,90)}$=7.184, p<0.05). No differences were detected in vertical activity ($F_{(3,72)}$=1.365, p=0.260) or entrances to the compartments ($F_{(4,90)}$=2.404, p>0.05) (not shown). Animals treated with vehicle in the nicotine-block showed less total self-grooming time ($F_{(4,90)}$=3.437,

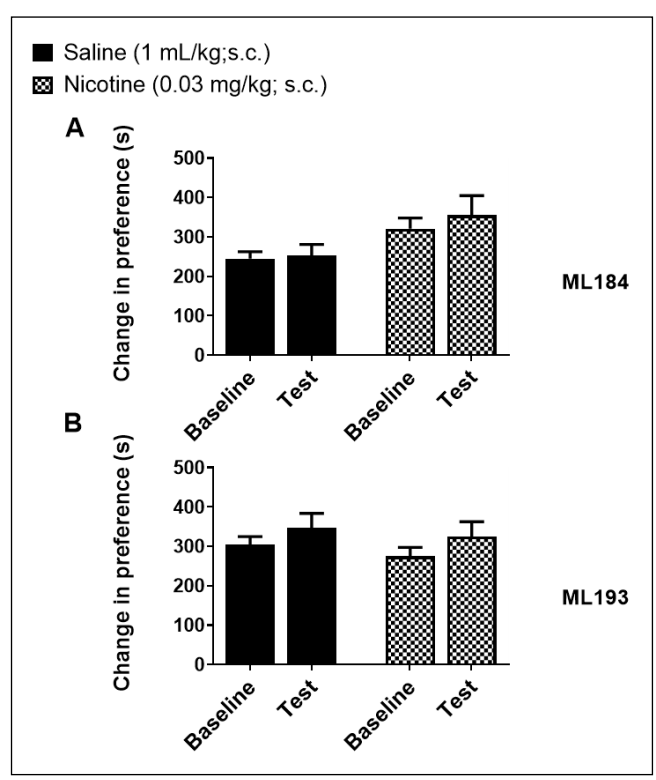

Fig. 3. Effect of ML184 (A) or ML193 (B) (i.c.v.) on the reinforcing effects of nicotine (0.03 mg/kg; s.c.) in the CPP paradigm. Data are expressed as the mean ± SEM and analyzed by two-way RM ANOVA, n=20 each treatment (i.e., n=10 in saline/n=10 in nicotine groups). Comparisons were analyzed using Bonferroni's post-hoc test.

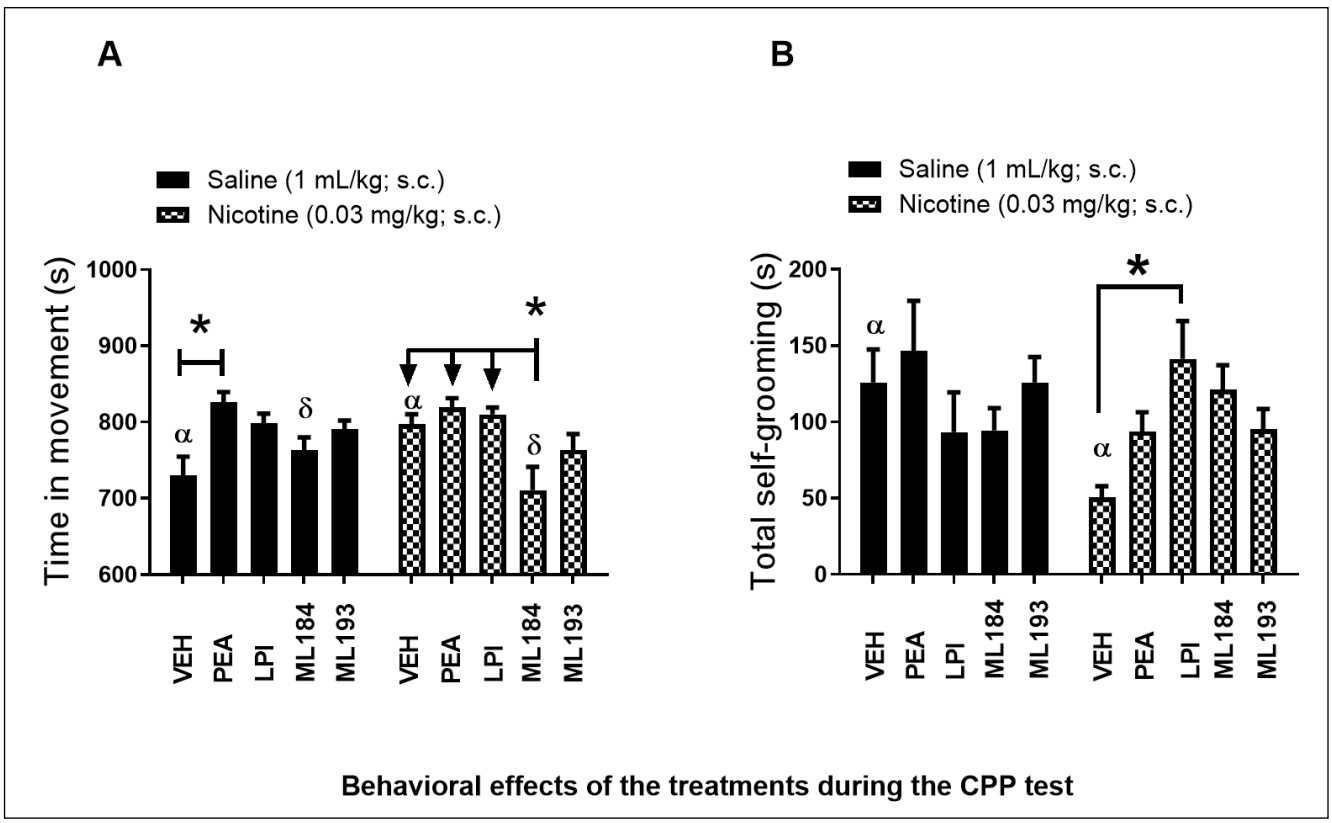

Fig. 4. Effect of the vehicle (VEH), palmitoylethanolamide (PEA), lysophosphatidylinositol (LPI), ML184 or ML193 on time in movement (A) and total self-grooming (B) into the paired chamber in the CPP-nicotine paradigm. *, p<0.05 where indicated; α, p<0.05 VEH in saline-block *vs.* VEH in nicotine-block; δ, p<0.05 ML184 in saline-block vs. ML184 in nicotine-block. Data are expressed as the mean ± SEM analized by two-way ANOVA. Comparisons were analyzed using Bonferroni's post-hoc test.

p<0.05) compared with the saline-block (Fig. 4B) and finally in the nicotine-block, LPI produced a higher total grooming time than vehicle (Fig. 4B).

DISCUSSION

Cigarette smoking is an addictive, chronic and recurrent behavior that causes several preventable adverse outcomes, including lung cancer (Benowitz, 2008a; Changeux, 2010). The reinforcing effects, dependence, and addiction to smoking are caused mainly by the substance nicotine (Stolerman and Jarvis, 1995). Nicotine has a high affinity for the α4 subunit of the nicotinic acetylcholine receptor (nAChR), which is ubiquitously expressed in the brain (Gotti et al., 2006; Nirogi et al., 2020), specifically the α4β2 subtype (Benowitz, 2008b; Dani and de Biasi, 2001). Nicotine may induce dopamine release in the NAc shell (Shin et al., 2017) which partially explains its reinforcing actions (Xiao et al., 2020). Clearly, the background of nicotine addiction has several components, including pharmacological, genetic, and environmental factors (Benowitz, 2009; 2010). In this context, Win 55212-2 (a CB_1 full receptor agonist), which appears to be devoid of GPR55 actions (Johns et al., 2007), was reported to positively modulate some of the reinforcing actions of nicotine *via* CB_1 receptors (Gamaleddin et al., 2012), whereas rimonabant (a CB_1 antagonist and GPR55 agonist) has been reported as effective in mediating smoking cessation (Rigotti et al., 2009).

The main finding of the present study is that central administration of PEA (GPR55 endogenous promiscuous agonist), LPI (endogenous GPR55/GPR18 agonist), ML184 (synthetic highly selective GPR55 agonist) and ML193 (selective GPR55 antagonist) prevented the reinforcing actions of nicotine in the CPP paradigm. Moreover, PEA produced hyperlocomotion in absence of nicotine compared with the vehicle. Conversely, ML184 significantly decreased activity compared with vehicle, PEA and LPI in the nicotine-block, suggesting a marked anxiolytic effect, which is not seen in absence of nicotine.

In the nicotine-block, the vehicle showed less total self-grooming behavior, which was prevented only with pretreatment with LPI. Lastly, central injections

of PEA produced a tendency to increase preference in the absence of nicotine, which may be linked to its capacity to modulate striatal areas and increase cannabinoid levels (e.g., 2-AG) (Musella et al., 2017). Admittedly, due to the extensive diffusion in the central nervous system (CNS) after the i.c.v. administration, our preliminary study is unable to point to a specific brain area in which the GPR55 could be exerting its preventive actions against the reinforcing nicotine effects in the CPP paradigm (DeVos and Miller, 2013). Nevertheless, our results should motivate further research about the potential general participation of GPR55 in the brain reward/anti-reward systems.

Pharmacological effects of PEA, LPI, ML184 and ML193 on nicotine-induced CPP

All administered compounds (PEA, LPI, ML184 and ML193) prevented the acquisition of CPP to nicotine. As those compounds were administered by i.c.v. injections, they were spreading widely in the CNS, which raises two main possibilities. Firstly, (i) that both stimulation and blockade of GPR55 may produce its preventive effects against the reinforcing actions of nicotine *via* different sites of action in the CNS and (ii) that the central GPR55 receptors interfering with the reinforcing actions of nicotine have a pivotal/modulatory function.

Supporting the first possibility, it was reported that i.c.v. injections of ML193 produced anxiogenic and motor impairing effects (Rahimi et al., 2015). As no decreases were detected in locomotor activity in animals injected with ML193, the preventive role of ML193 against nicotine-induced CPP may be linked to its capacity to produce anxiety (Rahimi et al., 2015). On the other hand, LPI may promote an increase in intracellular Ca^{2+} *via* GPR55 (Henstridge et al., 2009; 2010; Kapur et al., 2009) which could subsequently produce the activation of the large voltage-gated potassium channels and high-calcium conductance (BKCa) (Begg et al., 2003; Hasegawa et al., 2003; Schilling et al., 2002). Moreover, LPI (and perhaps PEA) may activate BKCa channels *via* both GPR55-dependent and independent pathways (Bondarenko et al., 2010; 2011a; b). Interestingly, it was reported that activation of BKCa channels can reverse nicotine-seeking behavior in the CPP paradigm (Ma et al., 2013). Hence, activation of GPR55 by LPI and PEA may prevent the reinforcing actions of nicotine *via* BKCa channels.

Regarding to the possible pivotal/modulatory role of GPR55, in a recent study of a preclinical rodent model of Parkinson's disease, both LPI and ML193 improved motor and sensorimotor skills of rats (Fatemi et al., 2020) suggesting a possible pivotal function of striatal GPR55. Moreover, the promotion in motor behavior of both LPI and ML193 could be involved in the decrease in the acquisition of nicotine. In addition, intrahippocampal injections of both LPI and CID16020046 (a selective GPR55 antagonist) impaired spatial memory in a post-training test in the Barnes maze (Marichal-Cancino et al., 2018). Hence, decreases in spatial memory, induced by LPI and ML193, could explain its preventative actions against the nicotine-induced CPP. Admittedly, our results provide more questions than answers and further experiments, that fall out of the reach of the present pilot study, are required to clarify the participation of GPR55 receptors in the reinforcing actions of nicotine.

Lastly, it has been reported that PEA and oleoylethanolamide (OEA) have a common main target, namely the PPAR-α receptor (Mattace Raso et al., 2014). Interestingly, OEA attenuated cocaine-induced behavioral sensitization (Bilbao et al., 2013). However, this effect appeared to be through an independent mechanism of the PPAR-α receptor, since OEA administration could still attenuate BS to cocaine in PPAR-α knockout mice (Bilbao et al., 2013). Furthermore, OEA and PEA have also been shown to differ in the modulation of some addiction-related moods, being able to block stress-induced anhedonia (Sayd et al., 2014). Inhibition of fatty acid amide hydrolase (FAAH) (Luchicchi et al., 2010), which increases the bioavailability of NAE, and exogenous administration of OEA and PEA (Melis et al., 2008) have also been shown to block the activation of neurons by nicotine in NAc shell and ventral tegmental area. Interestingly, by using URB597 (a FAAH inhibitor), Scherma et al. (2008) reported inhibition of the nicotine-induced CPP. Thus, aside from the potential actions mediated by GPR55, the preventive effects of i.c.v. PEA on nicotine-induce CPP may involve multiple pathways.

Other behavioral effects of PEA, LPI, ML184 and ML193 during the nicotine-CPP test

During the CPP-test (the no-drugs phase), animals from the nicotine block that received vehicle (i.c.v.) showed more activity ($p<0.05$) than vehicle-administered animals from the saline-block. Previous studies reported decreased locomotor activity in rats following an acute nicotine administration, but an increased in activity after chronic nicotinic stimulation (Stolerman et al., 1995; Dwoskin et al., 1999). In the present study, animals received a chronic schedule of nicotine, and thus our results are congruent with the previously mentioned reports. Conversely, as no differences

were detected in the entrances to the paired chamber or in vertical activity ($p>0.05$), craving-like behavior and anxiety induced by drug-interruption may be underestimated (Bailey and Crawley, 2009; Lever et al., 2006; Wu et al., 2016). Interestingly, ML184, but not LPI, prevented the hyperlocomotion induced by nicotine, suggesting the potential participation of central GPR55 in controlling motor alterations induced by stimulants such as nicotine. To support the above notion, striatal GPR55 was reported to have a modulatory role in motor behaviors in a preclinical Parkinson's model (Fatemi et al., 2020) and motor alterations were reported in mutant mice that lack GPR55 (Wu et al., 2013).

Grooming behavior in rodents is based on specific and highly stereotyped sequential movement patterns, known as the syntactic chain pattern (Kalueff et al., 2007), which often occurs during the transition between facial and body grooming. Grooming emerges as a sensitive index of anxiety and altered animal emotionality. Numerous studies have shown that brain injuries (Berridge 1989; Berridge and Whishaw, 1992; Cromwell and Berridge, 1996), pharmacogenic stimulation (Audet et al., 2006; Berridge and Aldridge, 2000), genetic ablation of brain receptors (Cromwell et al., 1998) and stressors (Komorowska and Pellis, 2004) can lead to an alteration in the onset and termination of this chain bi-directionally (Kalueff et al., 2007). In this study, animals from the nicotine-block treated with vehicle showed less total self-grooming behavior than those from the saline-block suggesting a certain level of emotional alteration. This was not observed in those animals pretreated with LPI, which performed more total self-grooming behavior in the nicotine-block compared with vehicle. Interestingly, central administration of another GPR55/GPR18 receptor agonists, O-1602, has been reported to produce anxiolytic effects (Rahimi et al., 2015). Hence, we propose a possible role of central GPR18/GPR55 mediating anxiolytic actions.

The tendency of PEA to increase place preference

A tendency to increase the time spent in the paired chamber was observed in the PEA group in an absence of nicotine. This effect could be explained due to an increase in acylethanolamides, since its degradation is mediated by fatty acid amide hydrolase (FAAH) (Cravatt et al., 1996) or N-acylethanolamine-hydrolyzing acid amidase (NAAA) (Ueda et al., 2013). Importantly, NAAA and FAAH preferentially hydrolyzes PEA over other EAs, producing an entourage effect particularly with endocannabinoid compounds (Ho et al., 2008; Ueda et al., 2013). Hence, the potential reinforcing actions of PEA in the CPP could be associated with increased levels of endocannabinoids. Admittedly, the present pilot study did not measure levels of endocannabinoids, and thus, this possibility remains to be characterized.

Limitations of this pilot study

Our study has some limitations. Firstly, we have probed different drugs with affinity to GPR55, but we did not perform a dose-response curve with several doses in a logarithmic raising design for the compounds used. Secondly, we did not conduct experiments to detect the mechanisms of action involved in the preventive actions of LPI, PEA, ML184 or ML193. Finally, our i.c.v. administration pathway did not discriminate that many periventricular structures in which GPR55 is expressed may participate, and therefore, we cannot propose specific brain areas as places of action.

CONCLUSIONS

Our data show that i.c.v. injections of LPI, PEA, ML184 and ML193 in the lateral ventricle interfere with the change in place preference induced by nicotine *via* mechanisms that remain to be identified, but that most probably involve central GPR55.

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