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Effects of cannabidiol on reward contextual memories induced by cocaine in male and female mice

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Original Article

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Abstract

Objective: Preclinical studies suggest that cannabidiol (CBD), a non-intoxicating phytocannabinoid, may reduce addiction-related behaviours for various drug classes in rodents, including ethanol, opiates, and psychostimulants. CBD modulates contextual memories and responses to reward stimuli. Nonetheless, research on the impact of CBD on cocaine addiction-like behaviors is limited and requires further clarification. This study tested the hypothesis that CBD administration inhibits the acquisition and retrieval of cocaine-induced conditioned place preference (CPP) in adult male and female C57BL6/J mice. We also ought to characterise a 5-day CPP protocol in these animals. *Methods:* Male and female C57BL/6J mice were administered CBD (3, 10, and 30 mg/kg) 30 minutes before cocaine (15 mg/kg) acquisition of expression of CPP. *Results:* Cocaine induces a CPP in both female and male mice in the 5-day CPP protocol. CBD failed to prevent the acquisition or retrieval of place preference induced by cocaine. CBD did not decrease the time spent on the side paired with cocaine at any of the doses tested in male and female mice, in either acquisition or expression of contextual memory. *Conclusion:* This study found no support for the hypothesis that CBD decreases reward memory involved in the formation of cocaine addiction. Further research is necessary to investigate the involvement of CBD in other behavioural responses to cocaine and other psychostimulant drugs. This study, however, characterised a 5-day CPP protocol for both female and male C57BL/6J mice.

Significant Outcomes:

- Three sessions of conditioning are enough to promote contextual reward memory to cocaine in male and female mice;
- Cannabidiol failed to decrease cocaine-induced conditioned place preference before the acquisition or retrieval phases of contextual memory.

Limitations

- We studied only the acquisition and retrieval phases of conditioned place preference (CPP). More studies are needed to characterise cannabidiol (CBD) effect on CPP extinction and reinstatement;
- We tested cocaine and CBD in both female and male mice. However, we did not investigate drug actions at specific phases of hormonal cycles.

Introduction

Cocaine use disorder (CUD) is a chronic relapsing disorder that involves compulsive cocaine-seeking despite its long-term deleterious consequences (American Psychiatric Koob & Volkow, 2010; Association, 2014). Repeated drug use disrupts signalling in the mesocorticolimbic pathway, including dopaminergic neurotransmission from the ventral tegmental area (VTA) to the nucleus accumbens (NAc) (Koob & Volkow, 2016). Other regions of importance in this disorder are the prefrontal cortex, which is involved in decision-making and impulse control; the amygdala, which is associated with emotional processing; and the hippocampus, implicated in the contextual learning forming drug-associated memories (Belin *et al.*, 2009; Kutlu & Gould, 2016; Werner *et al.*, 2020). The development of drug addiction occurs in part due to environmental or contextual influences on the brain mechanisms promoting drug-seeking behaviour (Fouyssac *et al.*, 2021). Therefore, certain approaches to study drug addiction focus on how to prevent the acquisition or expression of contextual drug-related memories

(Carey, 2020; Asth *et al*., 2022). In studies using experimental animals, the influence of contextual stimuli associated with drug addiction can be studied with place conditioning protocols (Kuhn *et al*., 2019), such as the conditioned place preference (CPP) test (Bardo and Bevins, 2000; US Department of Health and Human Services (HHS) 2016; Peters *et al*., 2021).

One major neurochemical system modulating drug addiction is the endocannabinoid system, which comprises the cannabinoid receptors CB_1 and CB_2, endocannabinoids, and their metabolising enzymes. Cannabinoid receptors are pre-synaptically expressed in neurons projecting onto dopaminergic pathways, in the dopaminergic neurons' cell bodies, or adjacent glial cells (Asth *et al*., 2022). The endocannabinoid system has been implicated in the initiation of substance use, in the development of compulsion and loss of behavioural control that occur during addiction (Goodman and Packard, 2016; De Giacomo *et al*., 2020; Zhang *et al*., 2020; Peters *et al*., 2021; Asth *et al*., 2022). Therefore, cannabinoids have the potential to modulate aversive and rewarding drug-associated memoy (Lee *et al*., 2017; Stern *et al*., 2018). Cannabidiol (CBD), a phytocannabinoid, has been extensively investigated for the treatment of various psychiatric disorders, although its precise mechanism of action has remained unclear (Campos *et al*., 2012). CBD may act through multiple mechanisms, possibly enhancing endocannabinoid signalling (Elmes *et al*., 2015; Ibeas Bih *et al*., 2015; Stern *et al*., 2018; Galaj and Xi, 2019) and interacts with the serotonin 1A receptor (5-HT1A) receptor as well as with the transient receptor potential vanilloid-1 channel (TRPV1) (Resstel *et al*., 2009; Galaj *et al*., 2020).

As for CBD effects on cocaine addiction, we previously reported that it prevents seizures and hepatic damage in an acute model of cocaine intoxication (Gobira *et al*., 2015). Other groups have also reported that CBD prevents certain behavioural and molecular changes promoted by cocaine in experimental animals (Luján *et al*., 2018; Chesworth and Karl, 2020; Gasparyan *et al*., 2021; Calpe-López *et al*., 2021; Ledesma *et al*., 2021) and decreases inflammatory parameters resulting from cocaine use in humans (Morissette *et al*., 2021). Importantly, CBD is devoid of rewarding properties and does not induce CPP in animals (Viudez-Martínez *et al*., 2019). Moreover, it has an appropriate safety profile in humans (Deiana *et al*., 2012; Huestis *et al*., 2019).

Most of these studies used male mice or rats as experimental subjects. Therefore, literature reporting cocaine and cannabinoid interventions in female animals remains scant. The few studies available suggest that both male and female mice are liable to certain cocaine effects (Hilderbrand & Lasek, 2014; Johnson *et al*., 2019). Regarding CBD, little is known about the potential differences between males and females in terms of their responses to rewarding stimuli (Chang *et al*., 2021). Recently, there has been a growing demand for pharmacological studies which include female subjects, since such approach has been largely neglected until recently, even though the development of psychiatric disorders is more common in women than in men (Altemus *et al*., 2014; Shansky, 2019; Radke *et al*., 2021). Regarding substance abuse, women may also be more vulnerable to addiction after using certain substances, especially psychostimulants (Swalve *et al*., 2016; Johnson *et al*., 2019; Zlebnik, 2019).

Based on previous evidence on cannabinoid modulation of drug reward, we hypothesised that CBD inhibits the acquisition and retrieval of rewarding contextual memories to cocaine in the CPP paradigm. Considering the importance of including biological sex as an experimental variable, we tested CBD effects in both female and male animals exposed to cocaine. We established a 5-day CPP paradigm, with 3 cocaine-context pairing, to reduce the overall duration of the protocol.

Materials and methods

Animals

Male and female C57BL/6J wild-type mice (20–25 g), aged 8-9 weeks, were obtained from the Animal Facility of the Federal University of Minas Gerais ('Biotério Central'). They were housed in groups of ten animals per box (41x34x16 cm) in a room under constant temperature (24 ± 2°C) and a 12 h light/dark cycle, with free access to water and food at the animal facility of the Department of Pharmacology of the Institute of Biological Sciences. The experiments were conducted during the light phase of the light/dark cycle. The authors assert that all procedures comply with the ethical standards of the relevant national and institutional guides on the care and use of laboratory animals. All procedures were approved by the Ethics Committee on the Use of Animals (CEUA) from the Federal University of Minas Gerais (UFMG), protocol number 179/2020, which is in line with Brazilian and international guidelines for the use of laboratory animals.

Drugs

CPP was induced with a dose of 15 mg/kg of cocaine (Merck & Co., Inc.) diluted in saline (NaCl 0,9%). CBD (3, 10, or 30 mg/kg) was dissolved in 5% Tween-80 in saline solution and administrated 30 minutes before the acquisition or expression phases of CPP. Cocaine and CBD was intraperitoneally administered at a volume of 10 ml/kg. The dose ranges were selected based on previous studies (Gobira *et al*., 2015, 2019; Lopes *et al*., 2020).

Conditioned place preference

Cocaine-induced CPP was evaluated using an acrylic box with two compartments (15 × 12 × 12 cm each) connected by a central corridor (9.5 × 5 × 12 cm) with removable doors between each compartment (Fig. 1). The walls and floors had distinct colours and textures. One of the compartments had black walls painted with vertical white stripes and its floor consisted of equally spaced parallel stripes. The other compartment had black walls painted with horizontal white stripes and its floor consisted of a pattern of equal-sized squares. The central compartment had grey walls and an acrylic flat floor. The CPP protocol was based on previous studies (Huston *et al*., 2013; Gobira *et al*., 2019). On day 1, each animal was placed in the central compartment with free access to the box for 15 min. Animals spending more than 70% of the time in one of the compartments were excluded from the experiment (five animals showed preference for one of the compartments and thus were exclude). During the conditioning phases (days 2–4), they received injections of vehicle (morning) and, 4-5 hours later, cocaine (afternoon) immediately before exposure to a specific compartment of the box for 30 min. The allocation of each animal to one or other compartment was based on demonstrated preference on day one, with the preferred side paired with saline and the least-preferred side paired with cocaine (Huston *et al.,* 2013; Gobira *et al*., 2019). Roughly, half of the animals received cocaine on each side of the CPP box (one compartment was not preferred over the other, averaged across animals). On the test day (day 5), the same procedure described for day 1 was repeated.

The first experiment consisted of validating the 5-day CPP protocol for cocaine in male mice, with a final sample size of

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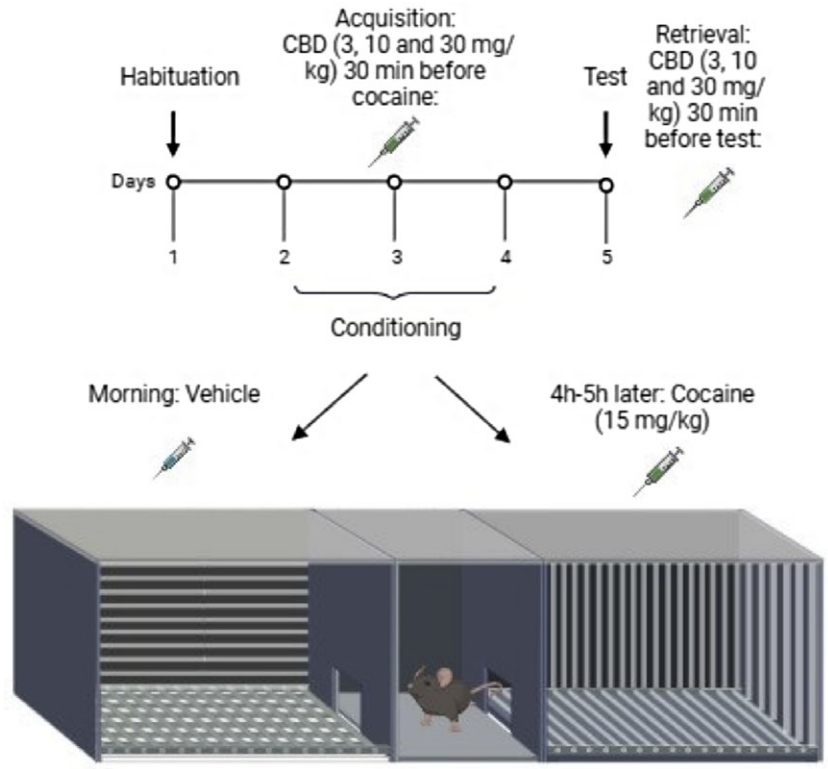

Figure 1. Protocol for testing CBD effects on the acquisition and retrieval of cocaine CPP.

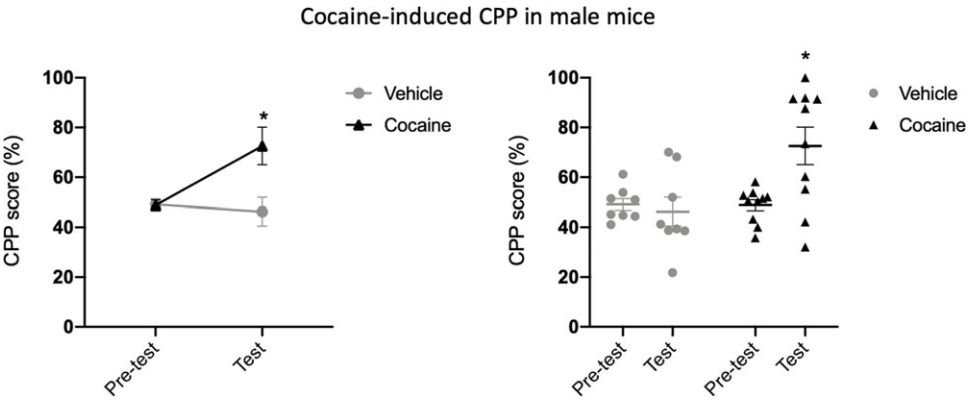

Figure 2. Cocaine (15 mg/kg) induced CPP in male mice (*p < 0.05). Data are expressed as mean ± sem (left panel), as well as individual values (right panel), analysed by RM ANOVA followed by Bonferroni test (n = 8; 10).

8 animals receiving vehicle injection and 10 animals receiving cocaine. Next, it was tested if cocaine administration would also exert a similar effect in female animals ($n = 10$), as compared to males ($n = 10$). To test for drug effects on CPP acquisition, vehicle or CBD was administrated 30 min before each cocaine injection in the conditioning phase at the doses of 3, 10, and 30 mg/kg to both female (Veh: $n = 9$; CBD 3: $n = 9$; CBD 10: $n = 10$; CBD 30: $n = 10$) and male (Veh: $n = 10$; CBD 3: $n = 9$; CBD 10: $n = 10$; CBD 30: $n = 9$) mice. To test for drug effects on CPP retrieval, CBD was administrated 30 min before exposure on the test day to both female (Veh: $n = 12$; CBD 3: $n = 10$; CBD 10: $n = 8$; CBD 30: $n = 11$) and male (Veh: $n = 10$; CBD 3: $n = 10$; CBD 10: $n = 9$; CBD 30: $n = 9$) mice. The experiments were recorded with a video camera (Microsoft LifeCam®), and the time spent in each compartment was analysed using ANYmaze software (8th version). The data are expressed as CPP (in percentage), which is defined as the time spent in the drug-paired compartment minus the time spent in the vehicle-paired compartment *100, divided by the sum of the two sides, both for pre-test and test.

Statistical analysis

All statistical analyses and graphic elaborations were performed with GraphPad Prism 9 software. CPP scores before ('pre-test') and after ('test') cocaine conditioning were compared by repeated measures analysis of variance (RM ANOVA) followed by the Bonferroni test, when appropriate, considering the experimental groups as between factor and the pre-test and test session as within subjects. The significance level was considered as 5% ($p < 0.05$). Data are presented as the mean and standard error of the mean (s.e.m.) as well as individual values.

Results

Validation of the CPP protocol with male mice

Protocols for CPP differ largely across studies for some variables, including the number of drug pairings. Therefore, the validity of the CPP induction protocol for five days in male mice was verified

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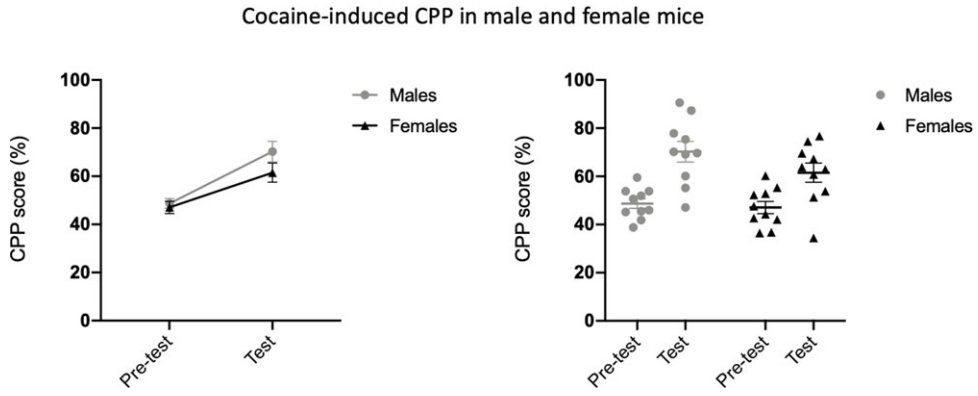

Figure 3. Cocaine (15 mg/kg) induced CPP in both male and female mice (n = 10,10, *p < 0,0001). No between-sex difference was observed. Data are expressed as mean ± sem (left panel), as well as individual values (right panel), analysed by RM ANOVA.

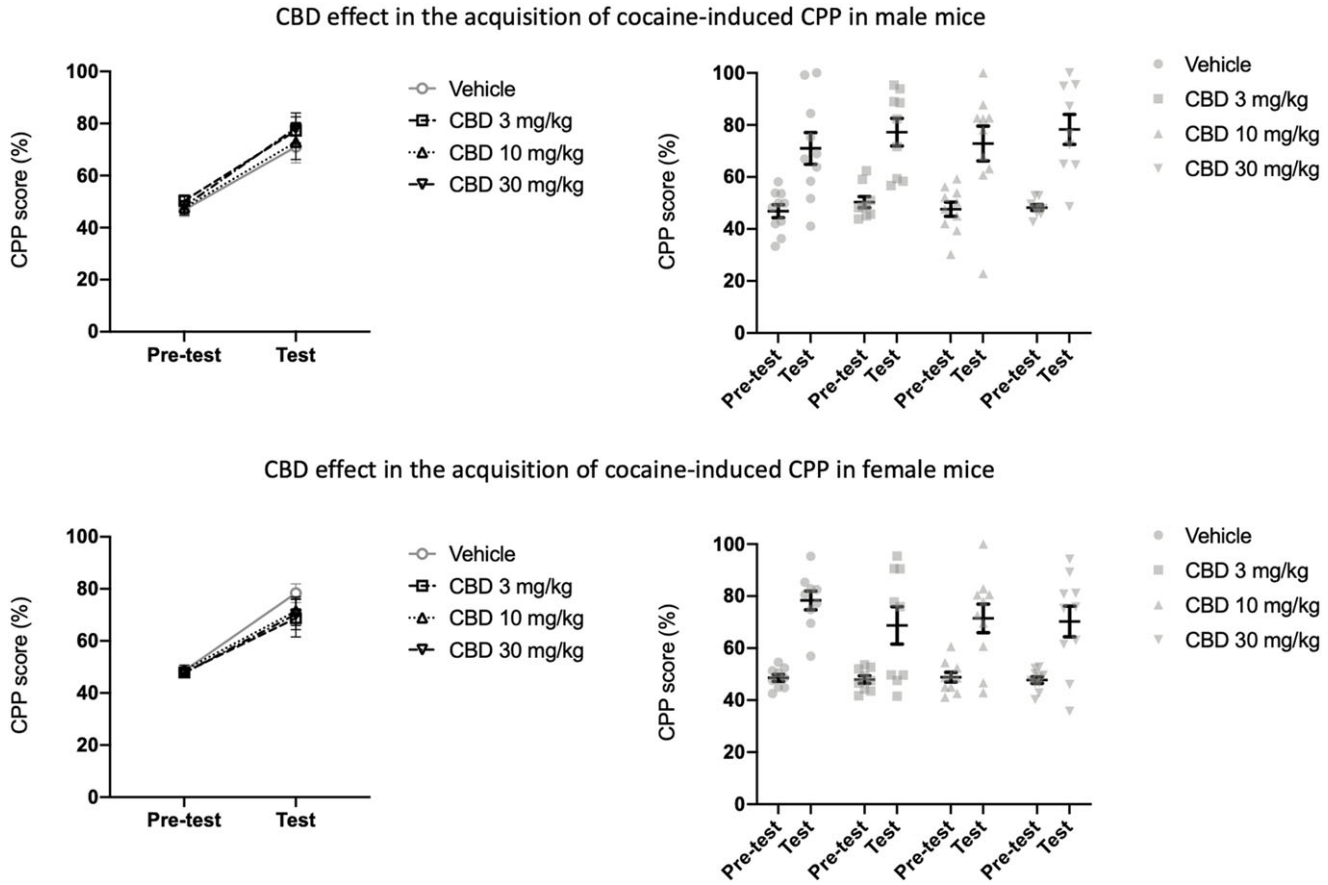

Figure 4. CBD (3, 10, and 30 mg/kg) did not inhibit the acquisition of CPP in male (n = 10, 9, 10, 9) or female (n = 9, 9, 10, 10) mice. Data are expressed as mean ± sem (left panels), as well as individual values (right panels), analysed by RM ANOVA.

(Fig. 2). The control group received administrations of saline during conditioning and the treatment group received cocaine (15 mg/kg) immediately before exposure to the box for three days. It was observed that cocaine induced a place preference in comparison to saline, as revealed by RM ANOVA, which detected an effect of treatment [$F_{(1,\ 16)} = 4.981$; $p = 0.0403$], an effect of session [$F_{(1,16)} = 5.476$; $p = 0.032$], and a session × treatment interaction [$F_{(1,\ 16)} = 8.897$; $p = 0.0088$].

Validation of the CPP protocol comparing male and female mice

The validity of the protocol was verified for five days in female and male mice (Fig. 3). Both groups received cocaine, 15 mg/kg, immediately before the conditioning phase for three days. There was an overall session (pre-test vs. test) effect [$F_{(1,18)} = 27$; $p < 0.0001$], indicating that cocaine induced a CPP, as expected. However, there was neither an effect of the variable sex [$F_{(1,\ 18)} = 2.602$; $p = 0.1242$] nor an interaction between factors [$F_{(1,18)} = 1$; $p = 0.3164$], indicating that cocaine induced CPP equally in male and female mice.

Effects of CBD administration (3, 10, and 30 mg/kg) on the acquisition of CPP in male and female mice

CBD was tested for its effect on the acquisition phase of place preference in males and females (Fig. 4). CBD (3, 10, and 30 mg/kg) failed to prevent the acquisition of CPP at any dose in males. There

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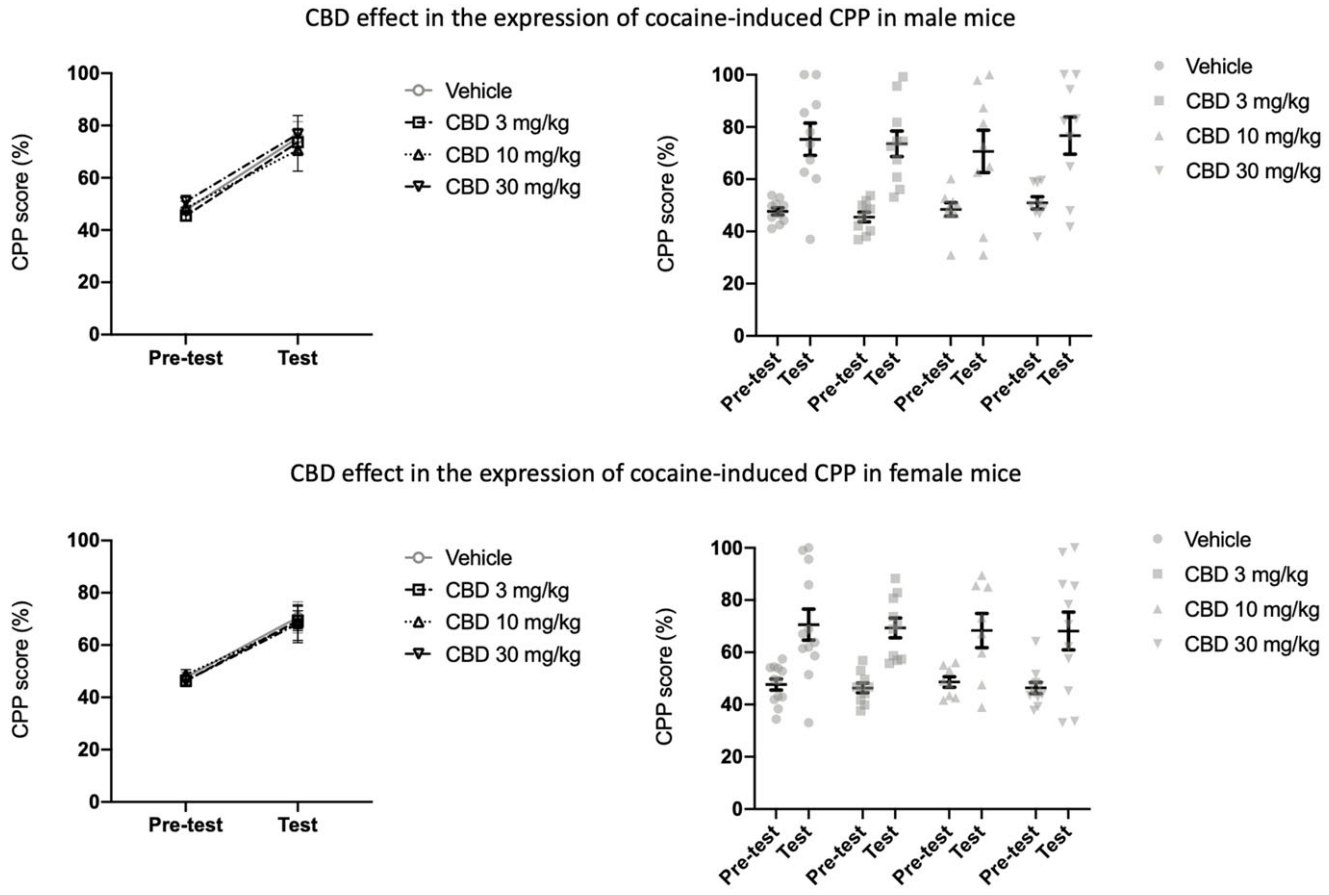

Figure 5. CBD (3, 10, and 30 mg/kg) did not inhibit the expression of CPP in male (n = 10, 10, 9, 9) or female (n = 12, 10, 8, 11) mice. Data are expressed as mean ± sem (left panels), as well as individual values (right panels), analysed by RM ANOVA.

was a session effect [$F_{(1, 34)} = 55$; $p < 0.0001$]; although no drug effect [$F_{(3, 34)} = 0{,}6884$; $p = 0{,}5654$] or drug-session interaction [$F_{(3, 34)} = 0.1$; $p = 0.9430$] was observed. The same pattern was observed for female animals. There was a session effect [$F_{(1, 34)} = 81.37$; $p < 0.0001$]; although no drug effect [$F_{(3, 34)} = 0.4816$; $p = 0.6973$] or drug-session interaction [$F_{(3, 34)} = 0.5365$; $p = 0.6604$] was observed.

Effects of CBD administration (3, 10, and 30 mg/kg) on the expression of CPP in male and female mice

We also tested the effect of CBD on the expression phase in males and females (Fig. 5). CBD (3, 10, and 30 mg/kg) failed to prevent the expression of cocaine-induced CPP at any dose, in both males and females. In the experiment with male mice, there was an effect of session [$F_{(1, 34)} = 77.83$; $p < 0.0001$]. However, no drug effect was observed [$F_{(3, 34)} = 0.2658$; $p = 0.8496$], the same applying to the interaction between session and drug factors [$F_{(3, 34)} = 0.2007$; $p = 0.8952$]. Likewise, in female animals, there was an effect of session [$F_{(3, 34)} = 81$; $p < 0.0001$], no drug effect [$F_{(3, 34)} = 0.4$; $p = 0.6973$], and no interaction between factors [$F_{(3, 34)} = 0.5$; $p = 0.6604$].

Discussion

In this study, we showed that a 5-day CPP protocol, consisting only of three consecutive days of cocaine injections, is sufficient to induce CPP in both male and female mice of the C57BL/6J strain. This protocol complements previous studies showing the effects of cocaine with longer injection protocols (Johnson *et al.*, 2010; Muldoon *et al.*, 2020; Calpe-López *et al.*, 2021). We also observed that CBD failed to prevent place preference in both female and male mice when administrated on acquisition or retrieval phases.

Our initial hypothesis was based on previous evidence that cannabinoids modulate dopaminergic reward pathways (Asth *et al.*, 2022). Moreover, previous studies did suggest a role for CBD in inhibiting the effects of cocaine. For instance, CBD was effective in attenuating extinction and reinstatement of cocaine-associated memories in male Wistar rats (Parker *et al.*, 2004; de Carvalho and Takahashi, 2017). CBD also disrupted the reconsolidation of contextual cocaine- and morphine-induced contextual memories in rats (de Carvalho and Takahashi, 2017). In addition, CBD prevented the reinstatement of CPP induced by cocaine in male C57BL/6J mice (Ledesma *et al.*, 2021) and male CD-1 mice (Calpe-López *et al.*, 2021). In other models to study cocaine addiction, CBD inhibited cocaine self-administration in a dose-dependent manner and attenuated brain stimulation reward in rats (Galaj *et al.*, 2020).

Considering the aforementioned results, it remains unclear why CBD failed to interfere with cocaine responses in the CPP paradigm. This lack of effect could be attributed to the doses tested or the injection protocol. However, various other responses to CBD were observed at the same doses and protocols by different research groups, including ours, such as antiseizure, anxiolytic, and

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antidepressant-like effects (Moreira *et al.*, 2006; Zanelati *et al.*, 2010; Gobira *et al.*, 2015; Vilela *et al.*, 2017). Moreover, other studies found that CBD failed to interfere with the acquisition and retrieval phases of contextual conditioning (Ledesma *et al.*, 2021). Possibly, long-term administration protocols would be required for CBD to prevent cocaine-induced CPP. Indeed, CBD (10 and 20 mg/kg) attenuated cocaine effects only when administered as a pre-treatment for 10 days (Luján *et al.*, 2018). In another protocol, CBD reduced cocaine responses in male C57BL/6J mice, but the animals were tested 20 days after conditioning (Chesworth & Karl, 2020). Finally, there is evidence that the protective effect of CBD depends on adult hippocampal neurogenesis (Luján *et al.*, 2019), suggesting that chronic biological processes may take place for CBD to work.

Finally, our 'negative' results with experimental animals have a few correlates from the clinical literature (de Meneses-Gaya *et al.*, 2021; Morissette *et al.*, 2021; Mongeau-Pérusse *et al.*, 2021; Rizkallah *et al.*, 2022). Clinical trials to investigate the effects of CBD on cocaine or crack cocaine use have yielded mainly null results for craving, withdrawal symptoms, and reinstatement. Nonetheless, in a randomised clinical trial carried out on cocaine addicts, in which the participants were treated with CBD (800 mg/kg), there was a reduction in the levels of inflammatory markers, including interleukin-6, vascular endothelial growth factor, CD14+CD16+ monocyte intermediates, and natural killer cells compared to participants receiving a placebo (Morissette *et al.*, 2021). Therefore, further investigation, in both human subjects and experimental animals, should clarify which cocaine-induced alterations are responsive to CBD administration.

Apart from investigating CBD activity, this study also shows that cocaine can be investigated in the CPP paradigm in a short, 5-day protocol consisting of 3 cocaine-contextual pairings. This is in contrast with most protocols in the literature, in which 3 daily, alternate vehicle or drug administrations are applied, with a total duration of 8 days (Tzschentke, 1998). Since CPP requires large sample sizes and is a laborious and long-term experiment, the use of a shorter protocol can bring advance to investigate the pharmacological modulation of cocaine responses. In addition, our results showed that this protocol is effective for testing cocaine CPP in both male and female C57BL/6J mice. Considering the importance of including both sexes as experimental variables in the biological sciences (Shansky, 2019), this result can serve as a reference for future studies.

In conclusion, cocaine induced place preference in both female and male mice of the C57BL/6J strain in a 5-day protocol. Regarding the effects of CBD, we evaluated the treatment before the conditioning and retrieval of the CPP responses. However, this compound failed to cocaine-induced CPP. CBD should be further evaluated for its effects on other responses to cocaine or upon CPP induced by other drugs of abuse.

Author contribution. FAM was mainly responsible for the study design. RCB was mainly responsible for conducting the experiments. All the authors have contributed to this study by participating in data analysis and writing the article. All authors have agreed on the final version of the manuscript.

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Competing interests. None.

Animal welfare ethical statement and ARRIVE guidelines. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional guides on the care and use of laboratory animals. All the protocols have been previously approved by the Committee for Ethics in the Use of Animals of the Federal University of Minas Gerais (CEUA-UFMG), which follows ARRIVE guidelines and recommendations. Protocol number: CEUA 179/2020.

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