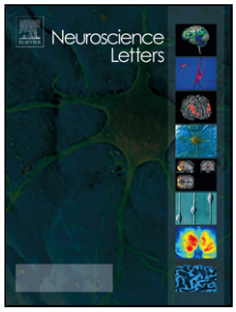
Journal Pre-proof



(-)-Stepholidine blocks expression, but not development, of cocaine conditioned place preference in rats

A. Bennett, E. Barrera, H. Namballa, W. Harding, R. Ranaldi

PII: S0304-3940(20)30421-3

DOI: https://doi.org/10.1016/j.neulet.2020.135151

Reference: NSL 135151

To appear in: *Neuroscience Letters*

Received Date: 24 April 2020

Revised Date: 6 June 2020

Accepted Date: 8 June 2020

Please cite this article as: Bennett A, Barrera E, Namballa H, Harding W, Ranaldi R, (-)-Stepholidine blocks expression, but not development, of cocaine conditioned place preference in rats, *Neuroscience Letters* (2020), doi: https://doi.org/10.1016/j.neulet.2020.135151

(-)-Stepholidine blocks expression, but not development, of cocaine conditioned place preference in rats

Bennett, A.[1], Barrera, E.[1], Namballa, H.[2], Harding, W.[2] , Ranaldi, R.[1,3*]Robert.Ranaldi@qc.cuny.edu

[1]Queens College of the City University of New York, Department of Psychology
[3]Ph.D. Program in Psychology, CUNY Graduate Center, 365 5th Avenue, New York, NY 10016, USA
[2]Hunter College of the City University of New York, Department of Chemistry;
Ph.D. Program in Biohemistry, CUNY Graduate Center, 365 5th Avenue, New York, NY 10016, USA;
Ph.D. Program in Chemistry, CUNY Graduate Center, 365 5th Avenue, New York, NY 10016, USA

*Correspondence to:
Robert Ranaldi, PhD
Psychology Department, Queens College
65-30 Kissena Blvd
Flushing, NY 11367
Tel: 718-997-3553
Fax: 718-997-3257
email:

Highlights

- Dopamine D1 and D3 receptors play an important role in cocaine reward
- Stepholidine blocks the expression of cocaine conditioned place preference
- Stepholidine fails to block the development of cocaine conditioned place preference

Abstract

The purpose of this study was to investigate the effects of (-)-stepholidine (SPD), a compound with dopamine D1 partial agonist and D2/D3 antagonist properties, on the development and

expression of cocaine conditioned place preference (CPP). Subjects (N = 65; male Long Evans rats) were tested using a CPP procedure consisting of 3 phases: (1) a 15-min pre-exposure session where animals could explore each compartment freely, (2) eight 30-min conditioning sessions where animals were restricted to one side or the other with cocaine (10 mg/kg) or saline, respectively, on alternating days and (3) a 15-minute preference test session where animals could explore each compartment freely. To test the effects of SPD on expression of cocaine CPP, rats were administered vehicle (distilled water with 20% DMSO), 10, 15 or 20 mg/kg SPD (intraperitoneally) 30 min prior to the test session. We found that 20 mg/kg of SPD significantly blocked the expression of cocaine CPP. To test the effects of SPD on the development of CPP, 0 (vehicle), 10, 15 or 20 mg/kg SPD was administered 30 minutes prior to each cocaine conditioning session and vehicle before each saline conditioning session; no treatment was given prior to the test session. A preference test showed that each SPD group maintained a CPP similar to the vehicle group. These data indicate that SPD can block the expression of a cocaine CPP but has no effect on its development, suggesting that it inhibits the effects of cocaine cues on cocaine incentive motivated behavior. These results suggest that SPD may be a potential treatment for cue-driven aspects of cocaine use disorder.

Keywords: stepholidine; cocaine; conditioned place preference; substance use disorder; addiction

1. Introduction

Cocaine use disorder is a significant health and economic problem with overdose deaths tripling between 2012 and 2018 [1] and with still no FDA approved medication for its treatment

[2]. Cocaine addiction is typically characterized as a cyclical pattern of binge use, abstinence, and relapse. When in abstinence, many users can be exposed to triggering cocaine-related stimuli (e.g., paraphernalia cues) that may evoke strong feelings of craving ultimately leading to relapse [3], [4]. Therefore, preventing cue-induced relapse in recovering users is a major hurdle in treatment. To this end, the identification of a pharmacological agent that can reduce cue driven cocaine behaviors, such as relapse, remains a major goal in pharmacotherapeutic development.

Cocaine produces its rewarding effects by increasing dopamine (DA) neurotransmission in terminal regions of the mesocorticolimbic DA system [5], [6]. Studies have shown that cocaine-related stimuli acquire the capacity to cause DA release in the same regions [7], [8]. In addition, repeated cocaine use and the presentation of associated cues have the propensity to increase dopaminergic transmission, which is thought to underlie the addictive effects of the drug [9-12]. Cocaine cues have also been shown to acquire incentive salience [13], exert control over behavior [14] and elicit cue-induced craving [15] in humans and drug-seeking in animals [11], [16]. Thus, strategies that can reduce the capacity of cocaine cues to increase DA neurotransmission and/or elicit cocaine-related behavior would be useful as treatments for cocaine use disorder.

One strategy to reduce cocaine-related behaviors has focused on the use of pharmacological agents that can reduce DA neurotransmission at DA receptors, specifically the D1 and D3 subtypes. There is evidence that administration of DA D1 and D3 agonists can augment the rewarding effects of cocaine in intravenous self-administration paradigms [17], [18]. On the other hand, DA D1 partial agonists can block the preference for the cocaine-paired side in a conditioned place preference (CPP) paradigm in mice [19] and can reduce cocaine self-administration in rhesus monkeys [20]. DA D1 receptor antagonists have been shown to block the expression and development of cocaine conditioned place preference (CPP) [21-24] and reduce

reinstatement of cocaine seeking in previously extinguished rats [25]. Furthermore, D1 knockout mice failed to self-administer cocaine [17]. DA D3 receptor antagonists have similarly been shown to block the expression of cocaine CPP [26-28], reduce reinstatement of cocaine-seeking [29-32], and facilitate the extinction of cocaine CPP [33]. Such studies suggest that compounds targeting D1 or D3 receptors can be beneficial in the treatment of cocaine use. Indeed such compounds have been studied in clinical trials and produced mixed results. Clinical studies using D1 antagonists demonstrated sedation and hypertension as possible adverse effects [34], [35]. Such studies with D3 antagonists revealed they can cause renal salt retention as well as hypertension [36], [37]. Despite the drawbacks, DA D1 partial agonists and D3 antagonists produce less extrapyramidal motor symptoms than is typically observed with DA D2 receptor antagonists, making them more favorable as candidates in the pharmacological treatment of cocaine addiction. Ensuing research has focused on identifying D1 and D3 receptor targeting compounds that can produce the anti-cocaine benefits without the adverse side effects.

(-)-Stepholidine (SPD) is a naturally occurring compound in the *Stephania intermedia* herb that belongs to a class of tetrahydroprotoberberine (THPB) alkaloids [38]. Although some assays show conflicting results on the pharmacological profile of SPD by indicating it is a DA D1 receptor agonist [39], D1 partial agonist [40] or D1 antagonist [41], most studies have consistently reported SPD as a D1 partial agonist and D2/D3 antagonist [38], [42]. SPD has been found to reduce reinstatement of 3,4 methylenedioxypyrovalerone (MDPV) with minimal locomotor effects [39], block the acquisition, maintenance, and reacquisition of morphine conditioned place preference (CPP) [43] and attenuate heroin self-administration as well as cue- and heroin-induced reinstatement [44], [45]. We have tested the effects of SPD on cocaine-related behaviors and found that SPD significantly reduces cue-induced reinstatement and intravenous self-administration [46].

Interestingly, clinical studies using SPD show that schizophrenic patients had significantly improved symptoms without any extrapyramidal symptoms [47], [48]. Although the effects of SPD on the expression and acquisition of morphine CPP has been studied [43], its effects on cocaine CPP have not. The present study aimed to investigate the effects of SPD on the development and the expression of cocaine CPP in rats.

2. Methods and Materials

2.1 Subjects

Subjects were male Long-Evans rats weighing between 350 to 400 g from our in-house colony, bred from males and females obtained from Charles River (Kingston, NY). Animals were individually housed in cages with free access to food and water at room temperature (21°C). The housing environment was maintained using a 12h light:12h dark cycle and all experiments were conducted during the animals' active period (dark cycle). Protocols used in these experiments were in accordance with the National Institutes of Health Guide for Care and Use of Laboratory Animals and approved by the Queens College Institutional Animal Care and Use Committee (IACUC).

2.2 Drugs

Cocaine was dissolved in 0.9% saline to achieve a dose of 10 mg/kg. SPD synthesized as described previously [49], was dissolved in 20% dimethyl sulfoxide (DMSO) to achieve doses of

0, 10, 15 and 20 mg/kg for both experiments. All solutions were administered intraperitoneally (ip) in a volume of 1.0 ml/kg.

2.3 Apparatus

All experiments were conducted in six 2-compartment place preference (CPP) chambers (Med Associates, Inc.) with each compartment measuring 43 x 43 x 30 cm (L x W x H). Each chamber was equipped with a removable partition and 16 infrared photo-emitters on each of two adjacent walls and 16 photosensors on each of the two walls facing the photo-emitter walls. Each compartment had a distinct wall pattern and flooring; one compartment had a solid white wall and stainless steel rod floor and the other compartment with a striped white and black wall with a stainless steel grid floor.

2.4 Procedure

All experiments consisted of three stages: pre-exposure, conditioning and a preference test. During the pre-exposure stage (Session 1), animals were placed in the open doorway and allowed to freely explore the chamber for 15 minutes without a partition and the time spent in each compartment was recorded. The conditioning phase consisted of eight, 30-min sessions during which the doorway between compartments was closed. On four alternating sessions, animals were injected with cocaine and placed in one of the chambers and on the other four alternating sessions they were injected with saline and placed in the other compartment. We used an unbiased CPP procedure where half of the animals were conditioned to their preferred side and the other half to the non-preferred side. Furthermore, for half of the animal's cocaine conditioning occurred on sessions 2, 4, 6 and 8 and for the other half on sessions 3, 5, 7 and 9. After conditioning was the preference test (Session 10), during which the rats were placed in the open doorway and allowed to explore both chambers freely for 15 minutes.

2.3.1 Experiment 1: CPP expression

All rats underwent the CPP procedure described above. On Session 10 the CPP test was conducted. All animals were administered ip doses of 0 mg (vehicle), 10, 15 or 20 mg/kg of SPD and returned to their home cages for 30 minutes. After this 30-min period, rats were placed in the CPP apparatus with the partition absent and allowed to freely explore both compartments.

2.3.2 Experiment 2: CPP acquisition

All rats were exposed to the protocol described above. Prior to each cocaine conditioning session, animals were administered one of the doses of SPD (0, 10, 15 or 20 mg/kg) and returned to their home cages for 30 minutes. On alternating sessions where animals were injected with saline, 20% DMSO was administered 30 minutes prior. On Session 10, the preference test was conducted in which animals were not administered any injections and were allowed to freely explore both compartments for 15 minutes.

2.4 Data Analysis

For both experiments, the data consisted of the number of seconds spent in each compartment during the pre-exposure and preference test sessions. These data for CPP of both experiments were analyzed separately using a two-way analysis of variance (ANOVA) with dose as a between-groups factor and phase (pre-exposure vs test) as a repeated measures factor. Significant interactions were followed by tests of simple effects and post hoc tests. For the expression experiment the number of seconds spent engaged in locomotor activity during the test session was measured. These data were analyzed using a one-way ANOVA with dose as a between-groups factor.

3. Results

3.1 CPP Expression

During the pre-exposure session, rats in all groups spent similar amounts of time in both saline and cocaine-paired compartments (data not shown). The vehicle, 10 mg and 15 mg SPD dose groups spent more time in the cocaine-paired compartment during the preference test than during the pre-exposure session. On the other hand, the 20 mg SPD group did not spend more time in the cocaine-paired side during the preference compared to the pre-exposure sessions and, in fact, appeared to spend somewhat less time in the cocaine compartment during the test (see Figure 1). A 2-way ANOVA with phase as a repeated measures factor and dose as a between-groups factor revealed a significant phase by dose interaction [$F_{1,28}$ = 5.995, p < 0.005]. Tests of simple effect of phase (pre-exposure versus preference test) at each level of dose revealed significant phase effects in the vehicle [$F_{1,28}$ = 8.336, p < .05], 10 mg [$F_{1,28}$ = 5.345, p < .05] and 15 mg [$F_{1,28}$ = 15.673, p < .05] dose groups but not in the 20 mg dose group of SPD.

Figure 2 shows the amount of time all groups spent engaged in locomotor activity. All three groups that received SPD spent less time in locomotion than did the group treated with vehicle. A one-way ANOVA on these data revealed a significant dose effect [$F_{3,26}$ = 20.241, p < .05]. Tukey's post hoc tests showed that all the SPD groups showed significantly less locomotor activity than the vehicle group.

3.2 CPP Acquisition

During the pre-exposure session, rats in all groups spent similar amounts of time in both saline and cocaine-paired compartments (data not shown). All groups spent more time in the

cocaine-paired compartment during the preference test than they did during the pre-exposure test (see Figure 3). A 2-way ANOVA with phase as a repeated measures factor and dose as a between-groups factor revealed a significant phase effect [$F_{1,29}$ = 9.974, p < .005] but no phase by dose interaction.

4. Discussion

The present study evaluated the effects of SPD, a D1 receptor partial agonist and D2/D3 receptor antagonist, on the development and expression of cocaine CPP in rats. Our findings indicate the highest dose of SPD – 20 mg/kg – blocked the expression of cocaine CPP. We also found that SPD had no effect on the development of cocaine CPP as rats in all groups in that experiment still displayed a preference for the cocaine-paired compartment. The observed reduction in the time spent in the cocaine-paired compartment in the expression experiment suggests that SPD can block the rewarding properties that are accrued by cocaine-associated stimuli.

To further evaluate the effect of SPD on the expression of cocaine CPP we analyzed the amount of time spent engaged in locomotor activity during the preference test for rats in the CPP expression experiment. Although all groups that received SPD, regardless of dose, spent significantly less time in locomotion than the vehicle group only the group that received the highest dose of SPD also showed a loss of cocaine side preference. Thus, it appears that there is not a direct relation between time spent in locomotor activity and expression of a place preference. These findings argue against the possibility that the loss of cocaine CPP in the 20 mg group was due to reduction in time spent engaged in locomotor activity.

Our data are consistent with other studies that investigated the effects of SPD on cocaine related behavior. We have previously shown that SPD significantly reduces cue-induced

reinstatement of cocaine seeking and cocaine self-administration [46]. SPD has been shown to produce similar effects with other drug classes. SPD reduced heroin self-administration and reinstatement of heroin seeking [44], inhibited heroin-induced reinstatement [45], reduced the development, maintenance and re-acquisition of morphine CPP [43] and reduced methylenedioxypyrovalerone (MDPV)-induced reinstatement of MDPV seeking in rats [39].

We have been interested in testing the effects of simultaneous DA D1 receptor partial agonism and D3 receptor antagonism on drug-related behavior. Prior to our investigations with SPD, we studied the effects of simultaneous administration of the DA D1 receptor partial agonist, SKF 77434, and DA D3 receptor antagonist, NGB 2904, in cocaine reward and seeking. We observed that these compounds administered individually at moderate doses have no significant effect on cocaine-related behavior, however when these same doses are administered simultaneously, they produce a synergistic interaction that significantly block the expression of cocaine CPP and reduces cocaine cue-induced reinstatement [16]. These data, along with our current SPD data, provide strong evidence that a polypharmacological approach targeting D1 and D3 receptors may be a useful treatment strategy for cocaine use disorder [50].

Although the current and previous findings suggest that SPD, or similar compounds or polypharmacological approaches, may be useful treatment strategies for cocaine use disorder, there are potential limitations. Our findings showed that SPD reduced the amount of time spent engaged in locomotor activity. Although time spent in locomotion is not a direct measure of amount of locomotor activity it is conceivable that there is a relation between the variables. Thus, our findings could indirectly suggest that SPD produces sedative effects. This might present some limitations on the utility of SPD as a treatment. Further work will be necessary to directly assess the possibility of sedative effects of SPD. On the other hand, it is notable that SPD has been shown

to produce anti-depressant effects [51], indicating a pharmacological profile that would be expected to enhance its potential utility in treating cocaine use disorder.

Other studies that used agents that target DA receptors individually, but not in combination, have shown effects on drug-related behaviors. DA D1 partial agonist SK 38393 and D1 antagonist SCH-23390 [17] blocked the preference for cocaine CPP [19-21] whereas D1 partial agonist SKF 77434 reduced cocaine self-administration in monkeys [18]. DA D3 receptor antagonists SR 21502 and BP 897 [24], [25] have been shown to block the expression of cocaine CPP. In intravenous self-administration studies, D3 antagonists S33138 [52] and NGB 2904 [53] significantly inhibited cocaine-induced reinstatement and S33138 also cocaine self-administration [52]. Therefore, neurotransmission at DA D1 and D3 receptors appears to play a role in the behavioral effects of cocaine-related cues including drug seeking. Analogs of SPD have been shown to have comparable results to SPD in reducing drug seeking behavior. Levo-tetrahydropalmatine (*l*-THP), an analog of SPD with D1/D2 antagonist properties [54], was shown to have comparable results in reducing drug seeking behavior as well. Studies show that *l*-THP reduces cocaine self-administration and cocaine-, stress- and cue-induced reinstatement [55-57].

In summary, we found that SPD, a D1 partial agonist and D2/D3 antagonist, significantly blocks the expression of cocaine CPP but has no effect on its development. Cocaine cues have the ability to increase DA neurotransmission, even in the absence of cocaine, thus making DA receptors attractive targets in developing treatment strategies for cocaine, and other drugs (i.e., opiate) use disorder. We previously proposed that the simultaneous targeting of DA D1 receptors with partial agonism and D3 receptors with antagonism may reduce the effects of drug-cues on seeking types of behaviors [16], [50] (similar to drug craving in humans). Our findings, that SPD reduces expression of cocaine CPP, supports this view. This suggests that SPD and other similar

compounds or polypharmacological approaches with similar profiles may hold potential in the treatment of relapse for cocaine or other drug use disorder.

Contributors: Ashley Bennett participated in the design and analysis of the study, was a principle collector of the data and wrote most of the complete first draft of the manuscript and all revisions. Eddy Barrera participated in the design and contributed to the writing of the manuscript. Hari Namballa participated in the data collection. Wayne Harding participated in the conceptualization of the study and writing of the manuscript. Robert Ranaldi served as principle investigator, conceptualized the study, participated in the design and analysis of the study and assisted in writing all drafts of the manuscript. All authors have approved the final version of this manuscript.

Acknowledgments:
This work was supported by National Institute of General Medical Science of the National Institutes of Health under award numbers 1SC3GM130430-01 to R.R and 1SC1DA049961-01 to W.H. The authors have no conflict of interest in the manuscript.

References

[1] H. Hedegaard, A.M. Miniño, M. Warner, Drug overdose deaths in the United States, 1999–2018. 2020. NCHS Data Brief, no 356. Hyattsville, MD: National Center for Health Statistics. https://www.cdc.gov/nchs/products/databriefs/db356.htm

[2] D.A. Gorelick, E.L. Gardner, Z.-X. Xi, Agents in Development for the Management of Cocaine Abuse, Drugs. 64 (2004) 1547–1573. doi:10.2165/00003495-200464140-00004.

[3] E. Pike, K.R. Marks, W.W. Stoops, C.R. Rush, Cocaine-related stimuli impair inhibitory control in cocaine users following short stimulus onset asynchronies, Addiction. 110 (2015) 1281–1286. doi:10.1111/add.12947.

[4] G.F. Koob, N.D. Volkow, Neurocircuitry of Addiction, Neuropsychopharmacology. 35 (2009) 217–238. doi:10.1038/npp.2009.110.

[5] E. Nestler, The Neurobiology of Cocaine Addiction, Science & Practice Perspectives. 3 (2005) 4–10. doi:10.1151/spp05314.

[6] R.A. Wise, E.A. Kiyatkin, Differentiating the rapid actions of cocaine, Nat Rev Neurosci. 12 (2011) 479–484. https://doi.org/10.1038/nrn3043.

[7] K.A. Badanich, K.J. Adler, C.L. Kirstein, Adolescents differ from adults in cocaine conditioned place preference and cocaine-induced dopamine in the nucleus accumbens septi, European Journal of Pharmacology. 550 (2006) 95-106. https://doi.org/10.1016/j.ejphar.2006.08.034.

[8] K.M. Wassum, S.B. Ostlund, G.C. Loewinger, N.T. Maidment, Phasic Mesolimbic Dopamine Release Tracks Reward Seeking During Expression of Pavlovian-to-Instrumental Transfer, Biological Psychiatry. 73 (2013) 747–755. doi:10.1016/j.biopsych.2012.12.005

[9] B. Adinoff, Neurobiologic Processes in Drug Reward and Addiction:, Harvard Review of Psychiatry. 12 (2004) 305–320. https://doi.org/10.1080/10673220490910844.

[10] R.A. Wise, Drug-activation of brain reward pathways, Drug and Alcohol Dependence. 51 (1998) 13–22. https://doi.org/10.1016/S0376-8716(98)00063-5.

[11] J.J. Anker, M.E. Carroll, Reinstatement of cocaine seeking induced by drugs, cues, and stress in adolescent and adult rats, Psychopharmacology. 208 (2010) 211–222. https://doi.org/10.1007/s00213-009-1721-2.

[12] H. Garavan, J. Pankiewicz, A. Bloom, J.-K. Cho, L. Sperry, T.J. Ross, B.J. Salmeron, R. Risinger, D. Kelley, E.A. Stein, Cue-Induced Cocaine Craving: Neuroanatomical Specificity for Drug Users and Drug Stimuli, AJP. 157 (2000) 1789–1798. https://doi.org/10.1176/appi.ajp.157.11.1789.

[13] B.T. Saunders, L.M. Yager, T.E. Robinson, Cue-Evoked Cocaine "Craving": Role of Dopamine in the Accumbens Core, Journal of Neuroscience. 33 (2013) 13989–14000. https://doi.org/10.1523/JNEUROSCI.0450-13.2013.

[14] E. Galaj, N. Seepersad, Z. Dakmak, R. Ranaldi, Blockade of NMDA receptors blocks the acquisition of cocaine conditioned approach in rats, Eur. J. Pharmacol. 818 (2018) 480–485. https://doi.org/10.1016/j.ejphar.2017.11.029.

[15] K.L. Preston, D.H. Epstein, Stress in the daily lives of cocaine and heroin users: relationship to mood, craving, relapse triggers, and cocaine use, Psychopharmacology. 218 (2011) 29–37. https://doi.org/10.1007/s00213-011-2183-x.

[16] E. Galaj, W. Harding, R. Ranaldi, Dopamine D1 and D3 receptor interactions in cocaine reward and seeking in rats, Psychopharmacology. 233 (2016) 3881–3890. https://doi.org/10.1007/s00213-016-4420-9.

[17] S.B. Caine, M. Thomsen, K.I. Gabriel, J.S. Berkowitz, L.H. Gold, G.F. Koob, S. Tonegawa, J. Zhang, M. Xu, Lack of Self-Administration of Cocaine in Dopamine D1 Receptor Knock-Out Mice, Journal of Neuroscience. 27 (2007) 13140–13150. https://doi.org/10.1523/JNEUROSCI.2284-07.2007.

[18] S.B. Caine, G.F. Koob, Pretreatment with the dopamine agonist 7-OH-DPAT shifts the cocaine self-administration dose-effect function to the left under different schedules in the rat:, Behavioural Pharmacology. 6 (1995) 333???347. https://doi.org/10.1097/00008877-199506000-00004.

[19] P. Sabioni, V. D'Almeida, M.L. Andersen, R. Andreatini, J.C.F. Galduróz, SKF 38393 reverses cocaine-conditioned place preference in mice, Neuroscience Letters. 513 (2012) 214–218. https://doi.org/10.1016/j.neulet.2012.02.041.

[20] N.H. Mutschler, J. Bergman, Effects of chronic administration of the D1 receptor partial agonist SKF 77434 on cocaine self-administration in rhesus monkeys, Psychopharmacology. 160 (2002) 362–370. https://doi.org/10.1007/s00213-001-0976-z.

[21] D.A. Baker, R.A. Fuchs, S.E. Specio, T.V. Khroyan, J.L. Neisewander, Effects of intraaccumbens administration of SCH-23390 on cocaine-induced locomotion and conditioned place preference, Synapse. 30 (1998) 181–193. https://doi.org/10.1002/(SICI)1098-2396(199810)30:2<181::AID-SYN8>3.0.CO;2-8.

[22] D.L. Pruitt, C.A. Bolanos, S.A. McDougall, Effects of dopamine D1 and D2 receptor antagonists on cocaine-induced place preference conditioning in preweanling rats, European Journal of Pharmacology. 283 (1995) 125–131. https://doi.org/10.1016/0014-2999(95)00309-9.

[23] E. Galaj, M. Manuszak, D. Arastehmanesh, R. Ranaldi, Microinjections of a dopamine D1 receptor antagonist into the ventral tegmental area block the expression of cocaine conditioned

place preference in rats, Behavioural Brain Research. 272 (2014) 279–285. https://doi.org/10.1016/j.bbr.2014.07.008.

[24] S.M. Gu, H.J. Cha, S.W. Seo, J.T. Hong, J. Yun, Correction to: Dopamine D1 receptor antagonist reduces stimulant-induced conditioned place preferences and dopamine receptor supersensitivity, Naunyn-Schmiedeberg's Arch Pharmacol. 393 (2020) 139–139. https://doi.org/10.1007/s00210-019-01750-y.

[25] A.T. Alleweireldt, S.M. Weber, K.F. Kirschner, B.L. Bullock, J.L. Neisewander, Blockade or stimulation of D1 dopamine receptors attenuates cue reinstatement of extinguished cocaine-seeking behavior in rats, Psychopharmacology. 159 (2002) 284–293. https://doi.org/10.1007/s002130100904.

[26] P. Hachimine, N. Seepersad, S. Ananthan, R. Ranaldi, The novel dopamine D3 receptor antagonist, SR 21502, reduces cocaine conditioned place preference in rats, Neuroscience Letters. 569 (2014) 137–141. https://doi.org/10.1016/j.neulet.2014.03.055.

[27] C. Duarte, C. Lefebvre, F. Chaperon, M. Hamon, M.-H. Thiébot, Effects of a Dopamine D3 Receptor Ligand, BP 897, on Acquisition and Expression of Food-, Morphine-, and Cocaine-induced Conditioned Place Preference, and Food-seeking Behavior in Rats, Neuropsychopharmacol. 28 (2003) 1903–1915. https://doi.org/10.1038/sj.npp.1300276.

[28] S.R. Vorel, C.R. Ashby, M. Paul, X. Liu, R. Hayes, J.J. Hagan, D.N. Middlemiss, G. Stemp, E.L. Gardner, Dopamine D 3 Receptor Antagonism Inhibits Cocaine-Seeking and Cocaine-Enhanced Brain Reward in Rats, J. Neurosci. 22 (2002) 9595–9603. https://doi.org/10.1523/JNEUROSCI.22-21-09595.2002.

[29] R. Song, G.-H. Bi, H.-Y. Zhang, R.-F. Yang, E.L. Gardner, J. Li, Z.-X. Xi, Blockade of D3 receptors by YQA14 inhibits cocaine's rewarding effects and relapse to drug-seeking behavior in rats, Neuropharmacology. 77 (2014) 398–405. https://doi.org/10.1016/j.neuropharm.2013.10.010.

[30] E. Galaj, S. Ananthan, M. Saliba, R. Ranaldi, The effects of the novel DA D3 receptor antagonist SR 21502 on cocaine reward, cocaine seeking and cocaine-induced locomotor activity in rats, Psychopharmacology. 231 (2014) 501–510. https://doi.org/10.1007/s00213-013-3254-y.

[31] Z.-X. Xi, J. Gilbert, A.C. Campos, N. Kline, C.R. Ashby, J.J. Hagan, C.A. Heidbreder, E.L. Gardner, Blockade of mesolimbic dopamine D3 receptors inhibits stress-induced reinstatement of cocaine-seeking in rats, Psychopharmacology. 176 (2004) 57–65. https://doi.org/10.1007/s00213-004-1858-y.

[32] L. Cervo, A. Cocco, C. Petrella, C.A. Heidbreder, Selective antagonism at dopamine D3 receptors attenuates cocaine-seeking behaviour in the rat, Int. J. Neuropsychopharm. 10 (2007) 167. https://doi.org/10.1017/S1461145705006449.

[33] E. Galaj, J. Haynes, R. Nisanov, S. Ananthan, R. Ranaldi, The dopamine D3 receptor antagonist, SR 21502, facilitates extinction of cocaine conditioned place preference, Drug and Alcohol Dependence. 159 (2016) 263–266. https://doi.org/10.1016/j.drugalcdep.2015.11.030.

[34] N.H. Gonsai, V.H. Amin, C.G. Mendpara, R. Speth, G.M. Hale, Effects of dopamine receptor antagonist antipsychotic therapy on blood pressure, J Clin Pharm Ther. 43 (2018) 1–7. https://doi.org/10.1111/jcpt.12649.

[35] J. Gerlach, L. Hansen, Effect of chronic treatment with NNC 756, a new D-1 receptor antagonist, or raclopride, a D-2 receptor antagonist, in drug-naive Cebus monkeys: dystonia, dyskinesia and D-1/D-2 supersensitivity, J Psychopharmacol. 7 (1993) 355–364. https://doi.org/10.1177/026988119300700407.

[36] L.D. Asico, C. Ladines, S. Fuchs, D. Accili, R.M. Carey, C. Semeraro, F. Pocchiari, R.A. Felder, G.M. Eisner, P.A. Jose, Disruption of the dopamine D3 receptor gene produces renin-dependent hypertension., J. Clin. Invest. 102 (1998) 493–498. https://doi.org/10.1172/JCI3685.

[37] N.M. Appel, S.-H. Li, T.H. Holmes, J.B. Acri, Dopamine D $_3$ Receptor Antagonist (GSK598809) Potentiates the Hypertensive Effects of Cocaine in Conscious, Freely-Moving Dogs, J Pharmacol Exp Ther. 354 (2015) 484–492. https://doi.org/10.1124/jpet.115.224121.

[38] K. Yang, G. Jin, J. Wu, The Neuropharmacology of (-)-Stepholidine and its Potential Applications, CN. 5 (2007) 289–294. https://doi.org/10.2174/157015907782793649.

[39] C. Hicks, P. Huang, L. Ramos, S.U. Nayak, Y. Caro, A.B. Reitz, G.R. Smith, D.Y.-W. Lee, S.M. Rawls, L.-Y. Liu-Chen, Dopamine D1-Like Receptor Agonist and D2-Like Receptor Antagonist (−)-Stepholidine Reduces Reinstatement of Drug-Seeking Behavior for 3,4-Methylenedioxypyrovalerone (MDPV) in Rats, ACS Chem. Neurosci. 9 (2018) 1327–1337. https://doi.org/10.1021/acschemneuro.7b00510.

[40] B.-C. Sun, X.-X. Zhang, G.-Z. Jin, (−)-Stepholidine acts as A D1 partial agonist on firing activity of substantia nigra pars reticulata neurons in 6-hydroxydopamine-lesioned rats, Life Sciences. 59 (1996) 299–306. https://doi.org/10.1016/0024-3205(96)00298-6.

[41] J.A. Meade, R.B. Free, N.R. Miller, L.S. Chun, T.B. Doyle, A.E. Moritz, J.L. Conroy, V.J. Watts, D.R. Sibley, (-)-Stepholidine is a potent pan-dopamine receptor antagonist of both G protein- and β-arrestin-mediated signaling, Psychopharmacology. 232 (2015) 917–930. https://doi.org/10.1007/s00213-014-3726-8.

[42] B. Li, W. Li, P. Du, K.Q. Yu, W. Fu, Molecular Insights into the D1R Agonist and D2R/D3R Antagonist Effects of the Natural Product (−)-Stepholidine: Molecular Modeling and Dynamics Simulations, J. Phys. Chem. B. 116 (2012) 8121–8130. https://doi.org/10.1021/jp3049235.

[43] W. Wang, Y. Zhou, J. Sun, L. Pan, L. Kang, Z. Dai, R. Yu, G. Jin, L. Ma, The effect of l-stepholidine, a novel extract of Chinese herb, on the acquisition, expression, maintenance, and re-acquisition of morphine conditioned place preference in rats, Neuropharmacology. 52 (2007) 355–361. https://doi.org/10.1016/j.neuropharm.2006.08.006.

[44] K. Yue, B. Ma, L. Chen, X. Tian, Q. Ru, Y. Gan, D. Wang, G. Jin, C. Li, L-Stepholidine, a naturally occurring dopamine D1 receptor agonist and D2 receptor antagonist, attenuates heroin self-administration and cue-induced reinstatement in rats:, NeuroReport. (2013) 1. https://doi.org/10.1097/WNR.0000000000000012.

[45] B. Ma, K. Yue, L. Chen, X. Tian, Q. Ru, Y. Gan, D. Wang, G. Jin, C. Li, l-Stepholidine, a natural dopamine receptor D1 agonist and D2 antagonist, inhibits heroin-induced reinstatement, Neuroscience Letters. 559 (2014) 67–71. https://doi.org/10.1016/j.neulet.2013.10.066.

[46] M. Manuszak, W. Harding, S. Gadhiya, R. Ranaldi, (-)-Stepholidine reduces cue-induced reinstatement of cocaine seeking and cocaine self-administration in rats, Drug and Alcohol Dependence. 189 (2018) 49–54. https://doi.org/10.1016/j.drugalcdep.2018.04.030.

[47] W. Le, [Clinical study on the treatment of dyskinesia by L-stepholidine], Zhonghua Shen Jing Jing Shen Ke Za Zhi. 22 (1989) 335–337, 381–382.

[48] D.C. Wu, X.Z. Xing, W.A. Wang, H.H. Wang, X.Y. Wang, Z. Cong, G.Z. Jin,
A double blind comparison trial of 1-stepholidine and perphenazine in treatment of schizophrenia, Chin. J. New Drugs Clin. 22 (2003) 155-160.

[49] S.V. Gadhiya, C. Hu, W.W. Harding, An alternative synthesis and X-ray crystallographic confirmation of (−)-stepholidine, Tetrahedron Letters. 57 (2016) 2090–2092. https://doi.org/10.1016/j.tetlet.2016.03.108.

[50] E. Galaj, S. Ewing, R. Ranaldi, Dopamine D1 and D3 receptor polypharmacology as a potential treatment approach for substance use disorder, Neuroscience & Biobehavioral Reviews. 89 (2018) 13–28. doi:10.1016/j.neubiorev.2018.03.020.

[51] B. Zhang, F. Guo, Y. Ma, Y. Song, R. Lin, F.-Y. Shen, G.-Z. Jin, Y. Li, Z.-Q. Liu, Activation of D1R/PKA/mTOR Signaling Cascade in Medial Prefrontal Cortex Underlying the Antidepressant Effects of l-SPD, Scientific Reports, 7 (2017) 3809. https://doi:10.1038/s41598-017-03680-2.

[52] X.-Q. Peng, C.R. Ashby, K. Spiller, X. Li, J. Li, N. Thomasson, M.J. Millan, E. Mocaër, C. Muńoz, E.L. Gardner, Z.-X. Xi, The preferential dopamine D3 receptor antagonist S33138 inhibits cocaine reward and cocaine-triggered relapse to drug-seeking behavior in rats, Neuropharmacology. 56 (2009) 752–760. https://doi.org/10.1016/j.neuropharm.2008.12.007.

[53] Z.-X. Xi, A.H. Newman, J.G. Gilbert, A.C. Pak, X.-Q. Peng, C.R. Ashby, L. Gitajn, E.L. Gardner, The Novel Dopamine D 3 Receptor Antagonist NGB 2904 Inhibits Cocaine's Rewarding Effects and Cocaine-Induced Reinstatement of Drug-Seeking Behavior in Rats, Neuropsychopharmacology. 31 (2006) 1393–1405. https://doi.org/10.1038/sj.npp.1300912.

[54] W. Jia Bei, M. John R., L-Tetrahydropalamatine: A Potential New Medication for the Treatment of Cocaine Addiction, Future Med Chem. 4 (2012). https://doi.org/10.4155/fmc.11.166.

[55] J.R. Mantsch, S.-J. Li, R. Risinger, S. Awad, E. Katz, D.A. Baker, Z. Yang, Levo-tetrahydropalmatine attenuates cocaine self-administration and cocaine-induced reinstatement in rats, Psychopharmacology. 192 (2007) 581–591. https://doi.org/10.1007/s00213-007-0754-7.

[56] Y. Figueroa-Guzman, C. Mueller, O. Vranjkovic, S. Wisniewski, Z. Yang, S.-J. Li, C. Bohr, E.N. Graf, D.A. Baker, J.R. Mantsch, Oral administration of levo-tetrahydropalmatine attenuates reinstatement of extinguished cocaine seeking by cocaine, stress or drug-associated cues in rats,

Drug and Alcohol Dependence. 116 (2011) 72–79. https://doi.org/10.1016/j.drugalcdep.2010.11.023.

[57] J.R. Mantsch, S. Wisniewski, O. Vranjkovic, C. Peters, A. Becker, A. Valentine, S.-J. Li, D.A. Baker, Z. Yang, Levo-tetrahydropalmatine attenuates cocaine self-administration under a progressive-ratio schedule and cocaine discrimination in rats, Pharmacology Biochemistry and Behavior. 97 (2010) 310–316. https://doi.org/10.1016/j.pbb.2010.08.016.

Figure Captions

Figure 1. Mean (± SEM) time spent in the cocaine-paired compartment of the CPP apparatus following pre-exposure and preference test sessions. Rats were administered one of the following doses: vehicle (*N* = 9), 10 (*N* = 8), 15 (*N* = 8) or 20 mg/kg (*N* = 7). * represents a significant difference between the time spent during the preference test compared to pre-exposure.

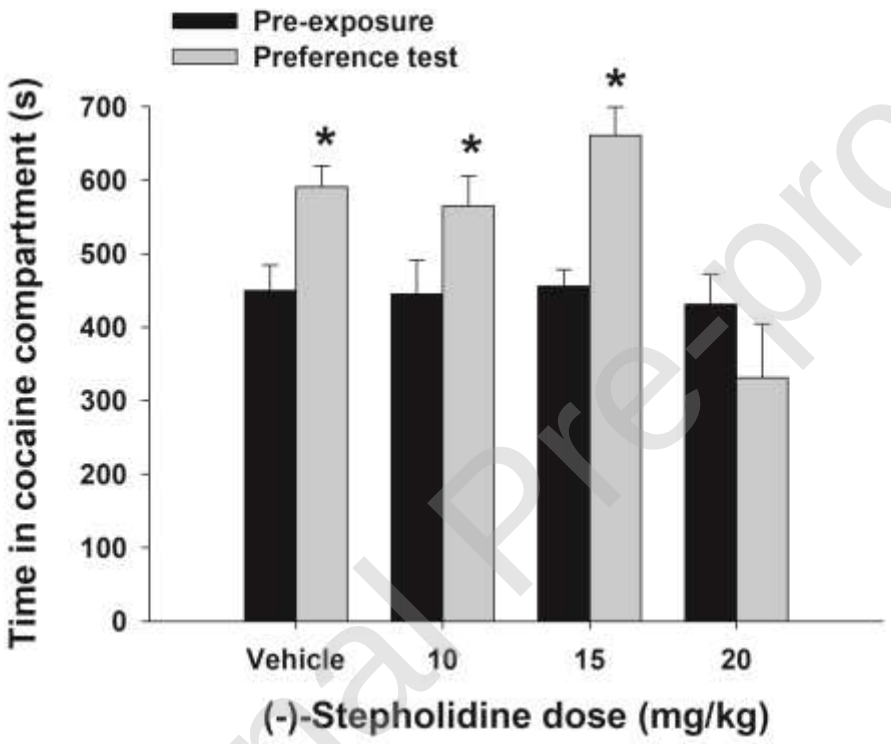


Figure 2. Mean (± SEM) time spent in locomotor behavior during the preference test session for all groups depicted in Figure 1. * represents a significant difference compared to vehicle. The line above the vehicle, 10 and 15 mg groups indicates that these groups demonstrated a significant CPP.

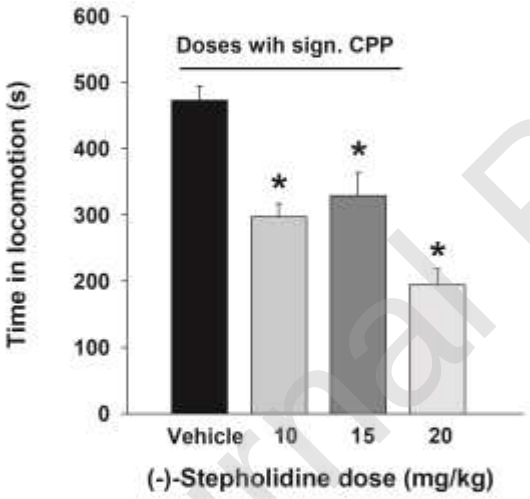


Figure 3. The effects of SPD on the acquisition of a cocaine CPP. The bars represent mean and ± SEM of time spent on the cocaine-paired compartment. Rats were administered one of the following doses prior to cocaine conditioning: vehicle (*N* = 8), 10 (*N* = 8), 15 (*N* = 9) or 20 mg/kg (*N* = 8). * represents a significant main effect of phase in the one-way ANOVA with no phase by dose interaction.