

Title: MDPV high-responder phenotype as a tool to evaluate candidate medications for stimulant use disorder

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Abbreviations: 5-HT, 5-hydroxytryptophan/serotonin; AUC, area under the curve; DAT, dopamine transporter; FDA, United States Food and Drug Administration; FR, fixed ratio; ICI, intercomponent interval; MDPV, 3,4-methylenedioxypropylamphetamine; NET, norepinephrine transporter; SERT, serotonin transporter; TO, timeout

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Abstract

Despite decades of research, there are no medications approved by the United States Food and Drug Administration to treat stimulant use disorders. Self-administration procedures are widely used to screen candidate medications for stimulant use disorder, though preclinical reductions in stimulant self-administration have not translated to meaningful reductions in stimulant use in humans. One possible reason for this discordance is that most preclinical studies evaluate candidate medications under conditions that promote predictable, and well-regulated patterns of drug-taking rather than the dysregulated and/or compulsive patterns of drug-taking characteristic of a stimulant use disorder. A subset of rats (“high-responders”) that self-administer 3,4-methylenedioxypyrovalerone (MDPV), a monoamine uptake inhibitor, develop high levels of dysregulated drug-taking consistent with behaviors related to stimulant use disorders. Because MDPV acts on dopamine, serotonin (5-HT), and sigma receptor systems, the current studies compared the potency and effectiveness of a dopamine D₃ receptor partial agonist (VK4-40) or antagonist (VK4-116), a sigma receptor antagonist (BD1063), a dopamine D₂/D₃/sigma receptor antagonist (haloperidol), and a 5-HT_{2C} receptor agonist (CP-809,101) to reduce MDPV (0.0032-0.1 mg/kg/infusion) self-administration in high- and low-responding rats as well as rats self-administering cocaine (0.032-1 mg/kg/infusion). VK4-40, VK4-116, haloperidol, and CP-809,101 were equipotent and effective at reducing drug-taking in all three groups of rats, including the high-responders, however, VK4-116 and CP-809,101 were less potent at reducing drug-taking in female compared to male rats. Together, these studies suggest that drugs targeting dopamine D₃ or 5-HT_{2C} receptors can effectively reduce dysregulated patterns of stimulant use, highlighting their potential utility for treating stimulant use disorders.

Significance statement

There are no FDA-approved treatments for stimulant use disorder, perhaps in part because candidate medications are most often evaluated in preclinical models using male subjects with well-regulated drug-taking. In an attempt to better model aberrant drug taking, this study found compounds acting at dopamine D₃ or 5-HT_{2C} receptors can attenuate drug-taking in male and female rats that self-administered two different stimulants and exhibited either a high- or low- substance use disorder-like phenotype.

Introduction

Substance use disorders affect 18 million Americans per year, with ~3.2 million of those diagnosed with a stimulant use disorder (SAMHSA, 2021). Yet, despite decades of research, there are currently no pharmacotherapies approved by the United States Food and Drug Administration (FDA) to treat stimulant use disorder. One potential reason for the failure to identify effective treatments is that the models most commonly used may not represent the problematic drug-taking behavior characteristic of stimulant use disorders. Most rodent studies evaluating candidate medications for stimulant use disorder utilize relatively short self-administration sessions (e.g., 1-3 hours) in male rats with limited histories of drug taking. Such study designs are favored because they result in highly predictable and homogenous patterns of drug-taking with low inter-subject variability. Other session parameters (e.g., extended-, intermittent-access) can result in subsets of rats developing aberrant patterns of drug-taking, similar to those observed in individuals with a stimulant use disorder. Identifying conditions capable of generating robust stimulant use disorder-like phenotypes might improve the predictive validity of rodent self-administration procedures for evaluating candidate medications for stimulant use disorder (e.g., Lynch 2018).

Recently we identified a reliable and persistent high-responder phenotype that emerges in ~30% of male and female rats that self-administer 3,4-methylenedioxypyrovalerone (MDPV) and structurally-related synthetic cathinones, characterized by high levels of dysregulated drug-taking and -seeking that might be related to stimulant use disorder (Gannon et al., 2017, 2018a, 2021; Doyle et al., 2021a; c; Abbott et al., 2022). These high-responder rats earn more infusions across a range of self-administration doses (i.e., upward shift in the dose-response curve), make more responses during signaled periods of drug unavailability, and reach greater breakpoints under progressive ratio schedules of reinforcement (Gannon et al., 2017; Doyle et al., 2021a; c; Abbott et al., 2022). Since high-responder rats exhibit a robust stimulant use disorder-like phenotype, they may provide a translationally-relevant framework for evaluating

candidate medications for stimulant use disorder. Because MDPV has been reported to interact with monoamine transporters (i.e., dopamine transporter [DAT], norepinephrine transporter [NET], and serotonin transporter [SERT]), and sigma receptors (Eshleman et al., 2013; Gannon et al., 2018a), potential pharmacotherapies targeting these neurotransmitter systems were viewed as logical starting points.

Antagonism of dopamine D₂ receptors is effective at reducing drug-taking in preclinical studies (De Vry et al., 1989; Roberts et al., 1989; Barrett et al., 2004; Oleson et al., 2011), but impractical for use in humans because of extrapyramidal side effects (e.g., acute dyskinesia, akathisia; Blair and Dauner, 1992). In contrast, antagonists or partial agonists that are selective for dopamine D₃ receptors can reduce drug-taking at doses that are devoid of extrapyramidal effects (Pilla et al., 1999; Gilbert et al., 2005; Keck et al., 2015). Recently, VK4-40 and VK4-116 were developed as highly-selective partial agonist (261-fold) or antagonist (1709-fold) at the dopamine D₃ receptor relative to the dopamine D₂ receptor (Kumar et al., 2016; Jordan et al., 2019b), and inhibit drug-taking and drug-seeking in rats self-administering cocaine or oxycodone at doses that do not affect food-maintained responding or produce adverse cardiovascular effects (Jordan et al., 2019a; b, 2020; You et al., 2019; de Guglielmo et al., 2020). Importantly, the effects of VK4-116 are dependent on the drug-taking phenotype of the rat, attenuating oxycodone self-administration in rats with high but not low levels of intake (de Guglielmo et al., 2020), suggesting it may also be effective at decreasing drug-taking in rats that engage in high levels of stimulant self-administration (i.e., the MDPV high-responders).

Serotonin (5-HT)_{2C} receptors have been investigated as a therapeutic target for stimulant use disorder, in part because of their ability to modulate dopamine neurotransmission (for review, see Howell and Cunningham, 2015). 5-HT_{2C} receptor agonists (e.g., lorcaserin) can decrease stimulant-taking and -seeking in rodents and nonhuman primates (Collins et al., 2016, 2018; Gerak et al., 2016, 2019; Harvey-Lewis et al., 2016; Collins and France, 2018; Gannon et al., 2018b; Anastasio et al., 2020), but also produce adverse effects associated with agonist

actions at 5-HT_{2A} receptors in both humans and rodents (Shram et al., 2011; Serafine et al., 2015). CP-809,101 is a 5-HT_{2C} receptor agonist that is >1000-fold selective over 5-HT_{2A} receptors (Siuciak et al., 2007), that can reduce drug-taking or -seeking in rats self-administering cocaine or nicotine (Higgins et al., 2013; Pockros-Burgess et al., 2014). However, it is important to note that most of these studies were conducted under limited-access conditions and in subjects displaying very predictable and homogenous patterns of drug-taking.

Finally, though MDPV is highly selective for DAT and NET, relative to SERT, it is also known to interact with sigma receptors (Eshleman et al., 2013). Given that stimulant use changes the activity of sigma receptor in ways that are thought to be important for the treatment of stimulant use disorder (Katz et al., 2016), the present studies sought to determine if antagonism of sigma receptors with BD1063 would reduce MDPV self-administration, in low- and/or high-responders, even though previous studies suggest it is ineffective at altering the cocaine self-administration under limited-access conditions (Hiranita et al., 2013). Because haloperidol has antagonist properties at both dopamine D₂, D₃ and sigma receptors, it was included to determine if this combination of activities was beneficial in reducing the aberrant drug-taking observed in the MDPV high-responder rats.

The present study sought to directly compare the potency and effectiveness of ligands targeting dopamine D₂ or D₃, 5-HT_{2C}, or sigma receptors to reduce the self-administration of MDPV or cocaine, and to determine whether any of these effects differed as a function of sex and/or drug-taking phenotype (i.e., low- versus high-responders). With the exception of the sigma receptor antagonist, BD1063, all compounds were equipotent and effective at reducing the self-administration of MDPV and cocaine. Though the effects of dopamine D₃ and 5-HT_{2C} ligands were comparable in both high- and low-responding rats, VK4-116 and CP-809,101 were less potent at reducing drug-taking in female compared to male rats.

Methods

Subjects

Male (n=20) and female (n=19) Sprague Dawley rats were obtained from Envigo (Indianapolis, IN) and weighed 275-299g or 200-224g, respectively, upon arrival. Rats were singly-housed provided *ad libitum* access to food and water in their home cages throughout the experiment. The temperature- and humidity-controlled vivarium operated on a 14/10 hour light cycle (lights on at 6am) and experiments were conducted while lights were on. A subset of male rats (n=9) also participated in another self-administration experiment before beginning this study, where they self-administered MDPV and either cocaine, ketamine, nicotine, or fentanyl for ~6 weeks (Doyle et al., 2021a). The self-administration behavior of these rats did not differ from the rats with no prior experimental history. All experiments were conducted in accordance with the University of Texas Health Science Center at San Antonio Institutional Animal Care and Use Committee and the Guide for Use of Laboratory Animals (National Research Council, 2011).

Apparatus

Standard operant chambers (Med Associates, St. Albans, VT) were housed within sound- and light-attenuating chambers. Operant chambers had two levers positioned on the same wall, with a set of LEDs above each lever. A food trough, connected to a 45mg pellet dispenser, was located between the two levers, and a houselight was positioned on the opposite wall. A syringe driver delivered infusions through Tygon tubing, which was connected to a swivel that was held in place with a counterbalance arm, and a magnetic tether, which attached to the vascular access button.

Surgery

Rats were anesthetized (2-3% isoflurane) and surgically implanted with a catheter in the left femoral vein, which was connected to a vascular access button placed in the mid-scapular region (Collins et al., 2012a; Doyle et al., 2021a, b; c). If catheter patency was lost (confirmed

with 5 mg/kg methohexital), a new catheter was placed in the right femoral, right jugular, or left jugular veins, as needed (n=18). Rats were treated with a long-acting antibiotic, Excede (20 mg/kg; SC), and an analgesic, meloxicam (5 mg/kg; SC), once, immediately following surgery, and allowed 5-7 days to recover. Rats were flushed daily with 0.5 ml of 100 U/ml heparinized saline, including after experimental sessions. Once experiments began, rats were also flushed with 0.2 ml saline before each session.

Training

Rats were initially allowed to respond for drug (0.032 mg/kg MDPV or 0.32 mg/kg cocaine) under a fixed ratio (FR) 1 schedule of reinforcement during 10, daily 90-min sessions. The active lever (counterbalanced across rats) was indicated by a lit yellow LED above the lever, and completion of the response requirement resulted in delivery of an infusion and the initiation of a 5-sec post-infusion timeout (TO), which was indicated by a change in stimuli (i.e., all three LEDs above the active lever and the houselight were illuminated). After rats acquired responding (>80% of responses on the active lever and >20 infusions earned), the response requirement was increased to a FR5. Once responding was reliably maintained under a FR5: TO 5-sec schedule of reinforcement (>20 infusions per session for at least 3 sessions), rats were allowed to respond on the alternate lever for delivery of a 45-mg grain-based food pellet (Dustless Precision Pellets® Rodent, 45-mg; Bio-Serv, Flemington, NJ). Under these conditions and new set of stimuli (i.e., red and green LEDs illuminated above the new active lever) were presented to indicate food availability, and completion of the response requirement resulted in initiation of the 5-sec TO and delivery of a single food pellet. Once rats responded for >20 pellets on two consecutive days under a FR5: TO 5-sec schedule of food delivery, rats were switched to the multiple-component procedure (see Supp. Figure 1 for timeline).

The multiple-component procedure was 132-min in duration and consisted of six components, each separated by a 2-min intercomponent interval (ICI). The first and last components were 10-min in duration, during which the red and green LEDs were illuminated to

indicate that food was available for responding under a FR5:TO 10-sec schedule of food delivery; responding on the alternate lever was recorded but had no scheduled consequence. Components two through five were 25-min in duration and were initiated by the illumination of the yellow LED above the drug-reinforced lever (see Supp. Figure 1 for visual representation of schedule). The unit dose of MDPV (0.0032-0.1 mg/kg/infusion) or cocaine (0.032-1.0 mg/kg/infusion) increased in half-log steps as described previously (Collins et al., 2012b; Gannon et al., 2017) and was available under a FR5: TO 10-sec schedule of reinforcement. The concentration of the drug remained constant, with different unit-doses administered by adjusting the duration of the infusion (based on body weight) from ~0.3 sec for the smallest unit-dose to ~10 sec for the largest unit-dose. During the intercomponent intervals, all stimuli were extinguished, and responses were recorded but had no scheduled consequence. After responding stabilized, defined at peak responding occurring in the same component for three consecutive sessions and within 25% of the mean of those three sessions, saline was substituted for drug for 1-5 sessions, and until responding was below 8 infusions per component. Rats were switched back to drug until stability criteria were met, after which saline was substituted again. This pattern was repeated until rapid extinction occurred, quantified as rats earning ≤ 8 reinforcers per drug component on the first day of saline substitution to increase the likelihood rats would extinguish responding if a pretreatment reduced the reinforcing effects of the self-administration drug.

Rats were subsequently classified as being a high- or low-responder based upon previously established criteria (Gannon et al., 2017, 2018a; Doyle et al., 2021a; c; Abbott et al., 2022). Briefly, the percentage of responses that were made during the 5-sec post-infusion timeout out of total responses on the active lever in drug components was calculated for the 3 sessions preceding the final saline substitution. Rats that made $\geq 20\%$ of total active lever responses during the post-infusion timeout periods were classified as high-responder rats,

whereas low-responder rats made <20% during the timeouts. See Supp. Table 1 for the number of subjects in each group.

Testing

Pretreatments were administered after three consecutive sessions of stable responding. Though all doses of a pretreatment drug were generally completed before moving on to the next pretreatment drug, the order of both the treatment drugs and the doses were pseudorandom. All rats received a vehicle injection for each pretreatment drug, as well as 3 or 4 doses of a pretreatment drug in half-log steps, with the exception of the largest dose of CP-809,101 that was a quarter-log step. Pretreatment drugs were the dopamine D₃ receptor partial agonist, VK4-40 (3.2-32 mg/kg), the dopamine D₃ receptor antagonist, VK4-116 (3.2-32 mg/kg), the 5-HT_{2C} receptor agonist, CP-809,101 (0.32-5.6 mg/kg), the sigma₁ receptor antagonist, BD1063 (1-10 mg/kg), and the dopamine D₂/D₃/sigma receptor antagonist, haloperidol (0.01-0.32 mg/kg). Most subjects completed all drugs, although a subset did not. Number of subjects are reported in Supp. Table 1.

Drugs

BD1063 dihydrochloride was purchased from Tocris (Ballwin, MO) and dissolved in sterile saline. Haloperidol was purchased from Sigma-Aldrich (St. Louis, MO) and dissolved in saline with 1N HCL added dropwise until solution was clear. CP-809,101 was synthesized by the Center for Innovative Drug Discovery (San Antonio, TX) and dissolved in 5% Tween-80 in sterile saline. Both VK4-40 and VK4-116 were synthesized by Jianjing Cao (Medicinal Chemistry Section, NIDA-IRP) according to published procedures (Kumar et al. 2016) and dissolved in a solution of 10% DMSO, 15% Tween-80, and sterile saline. Pretreatment drugs were administered intraperitoneally (IP) at a volume of 1 ml/kg, except the largest dose of both VK4-40 and VK4-116 were given at 1.78 ml/kg. BD1063 and CP-809,101 were administered 15 min prior to the session, and VK4-40, VK4-116, and haloperidol were administered 30 min prior to the session. The half-lives of these drugs are sufficient to allow for adequate blood levels of

each drug for the duration of the 134-min session (Watanabe et al., 1999; Hiranita et al., 2013; Higgins et al., 2017; Jordan et al., 2019a, You et al., 2019). Cocaine hydrochloride was provided by the National Institute on Drug Abuse Drug Supply Program (Bethesda, MD) and MDPV was synthesized by Kenner Rice (Bethesda, MD); both were dissolved in sterile saline and administered intravenously at volumes ranging from 0.044 to 1.4 ml/kg.

Data analysis

A two-factor (group and dose) repeated measures ANOVA was used to compare the number of baseline infusions earned by MDPV high-responders, low-responders, and rats self-administering cocaine, and Tukey's post-hoc comparisons were used to compare number of infusions earned at each dose by group. Two-factor (drug and component) repeated measures ANOVAs were run within each of the three self-administration groups to compare number of infusions earned when drug compared to saline was available. Two-factor (sex and dose) repeated measures ANOVAs were run within each of the three self-administration groups to compare number of infusions earned by male and female rats, and Sidak's multiple comparison test was used when needed. Baseline was the three-day average immediately preceding the manipulation (i.e., saline substitution or pretreatment). Area under the curve (AUC) was calculated using the number of infusions earned at each dose in individual subjects. Percent change from baseline AUC was calculated in individual subjects using the AUC of the mean number of infusions earned during the three sessions prior to the pretreatment and were analyzed using two-factor (group x pretreatment dose) repeated measures ANOVA or mixed-effects analysis (if data set was incomplete) for each pretreatment dose and sex. Dunnett's multiple comparisons was used to compare pretreatment dose to vehicle. The dose required to decrease responding by 50% (ID_{50}) was calculated in individual subjects using a linear regression with a single point $>80\%$ and $<20\%$. In cases where responding was not decreased by $>50\%$, a value of 0% was filled in at a half log higher dose range for a conservative estimate of potency. Drug ID_{50} s were calculated using the percent change from baseline AUC and food

ID₅₀s were used calculated using percent change from baseline number of food pellets in the first food component. Potency ratios were calculated by dividing the group food ID₅₀ by the group drug ID₅₀. BD1063 was excluded from ID₅₀ calculations because it did not decrease responding by 50% in any subjects.

Results

Under the multiple-component schedule of reinforcement, the dose-response curves for cocaine and MDPV self-administration were inverted U-shaped in nature, with the peak number of infusions earned at doses of 0.1 mg/kg/infusion cocaine or 0.01 mg/kg/infusion MDPV (Figure 1). MDPV was ~10-fold more potent than cocaine in both high- and low-responder rats, but equipotent in high- and low-responders. When compared to the peak number of infusions for all rats self-administering cocaine, the peak number of MDPV infusions was comparable for low-responder rats (~20-25 infusions), but ~2-3 times greater in the high-responder rats self-administering MDPV (~40-75 infusions); a similar difference was also observed for the 2 larger unit-doses of MDPV. A 2-factor (group x dose) indicated main effect of group ($F(2, 37) = 14.01$; $p < 0.0001$), main effect of dose ($F(2.08, 77.12) = 49.56$; $p < 0.0001$), and an interaction ($F(6, 111) = 6.82$; $p < 0.0001$), where high-responders earned significantly more infusions than low-responders or rats self-administering cocaine at the two intermediate doses ($ps \leq 0.05$). There was no difference between low-responders and rats self-administering cocaine. When saline was substituted for drug, rats earned significantly fewer infusions than when drug was available (high-responders: $F(1, 24) = 22.77$; $p < 0.0001$; low-responders: $F(1, 24) = 5.39$; $p = 0.03$; cocaine: $F(1, 26) = 6.48$; $p = 0.02$). When the dose-response curves were analyzed by sex, a two-factor ANOVA revealed that female rats self-administered significantly more cocaine than male rats ($F(1, 12) = 5.68$; $p = 0.04$). In contrast, there was no significant main effect of sex in either of the groups that self-administered MDPV (high responders: $F(1, 11) = 0.11$; $p = 0.75$); low-responders: $F(1, 11) = 0.051$; $p = 0.82$).

Pretreatments were evaluated once self-administration stabilized and single session saline substitutions resulted in a rapid extinction of responding (Figure 2). All test compounds produced qualitatively similar effects in the three groups (MDPV-high, MDPV-low, and cocaine), with haloperidol (Figure 2A-2C) shifting dose-response curves to the right, whereas VK4-40 (Figure 2D-2F), VK4-116 (Figure 2G-2I), and CP-809,101 (Figure 2J-2L) shifted dose-response

curves downward. BD1063 did not reliably alter dose-response curves for either MDPV or cocaine self-administration (Figure 2M-2O). A larger dose of BD1063 (32 mg/kg) was tested in a subset of rats and produced disruptions in responding maintained by food, but not self-administration (data not shown).

The effects of pretreatment drugs were further quantified by generating dose-response curves for changes in the AUC ($[\text{pretreatment AUC}/\text{baseline AUC}] \times 100$) (Figure 3). Linear regression was used to estimate the dose required to decrease AUC by 50% (ID_{50} ; Table 1). Haloperidol produced significant, dose-dependent decreases in AUC in both male and female rats (males: $F(3.31, 51.27) = 15.1$; $p < 0.001$; females: $F(2.21, 31.43) = 12.65$; $p < 0.0001$); however, these effects did not vary as a function of sex or self-administration group. VK4-40 produced significant, dose-dependent decreases in AUC in both male and female rats (males: $F(2.63, 40.36) = 5.83$; $p = 0.003$; females: $F(2.49, 37.27) = 7.32$; $p = 0.0011$); however, did not differ as a function of self-administration group. VK4-116 produced significant, dose-dependent decreases in AUC for male, but not female rats (males: $F(2.22, 44.44) = 14.58$; $p < 0.0001$; females: $F(1.90, 26.56) = 1.57$; $p = 0.23$); these effects or lack thereof did not differ as a function of self-administration group. CP-809,101 produced significant, dose-dependent decreases in AUC in both male and female rats (males: $F(3.16, 53.69) = 23.55$; $p < 0.0001$; females: $F(2.46, 39.34) = 18.63$; $p < 0.0001$); however, there was no effect of self-administration group. BD1063 did not significantly alter AUCs in males or females, regardless of self-administration group (males: $F(1.51, 19.13) = 0.48$; $p = 0.58$; females: $F(2.11, 38.76) = 0.22$; $p = 0.81$).

Comparisons of the ID_{50} s across groups (Table 1) revealed that pretreatments were equipotent in high-responder rats compared to low-responder rats or rats that self-administered cocaine. However, significant differences in the ID_{50} s of VK4-40, VK4-116, CP-809,101, and haloperidol were observed across sex, with larger doses of each compound required to reduce self-administration in female compared to male rats. For VK4-40, CP-809,101, and haloperidol, sex-related differences were observed with cocaine, whereas for VK4-116, sex-related

differences were observed with both high- and low-responding rats from the MDPV conditions. For VK4-40, VK4-116, and CP-809101, significant sex-related differences were also observed when data were collapsed across the three self-administration groups (MDPV-high, MDPV-low, and cocaine).

The pretreatment dose required to decrease responding maintained by food pellets in the first component was calculated for each of the drugs (Table 1). Generally, similar doses were required to disrupt responding for food in male and female rats, with the exception that larger doses of VK4-40 and VK4-116 were needed to disrupt responding in MDPV high-responder females compared to high-responder males. Potency ratios (food ID_{50} / drug ID_{50}) were calculated to compare doses that decreased responding maintained by food compared to drug. With few exceptions (haloperidol in high-responder males and low-responder females and CP-809,101 in high-responder males), the pretreatments were more potent at decreasing responding for food compared to drug (Table 1).

Discussion

When allowed to self-administer the stimulant drug MDPV, a subset rats rapidly develop patterns of responding that result in significantly greater levels of drug-intake (high-responders) than low-responder rats self-administering MDPV, or rats that self-administer cocaine. These high-responder rats exhibit behaviors thought to be consistent with stimulant use disorder in humans, including high levels of drug-taking and -seeking, and reach higher final ratios under progressive ratio schedules of reinforcement (Gannon et al., 2017; Doyle et al., 2021a; c; Abbott et al., 2022). The primary goal of this study was to evaluate the effects of several drugs that interact with receptors that have been targeted for the development of medications for stimulant use disorder to determine if their potency and effectiveness to reduce drug-taking differed as a function of: (1) the self-administered drug (MDPV versus cocaine), (2) the behavioral phenotype (high-responder versus low-responder), or (3) sex (male versus female). These studies were conducted with the ultimate goal of identifying pharmacotherapies capable of reducing aberrant patterns of drug-taking that may be more representative of the patterns of drug-taking observed in individuals with a stimulant use disorder. Pretreatment drugs included a partial agonist and an antagonist of dopamine D₃ receptors (VK4-40 and VK4-116, respectively), a 5-HT_{2C} receptor agonist (CP-809,101), a sigma₁ receptor antagonist (BD1063), and a non-selective dopamine D₂/D₃/sigma₁ receptor antagonist (haloperidol). Together, this study not only replicates previous literature showing that drugs targeting dopamine D₃ and 5-HT_{2C} receptors can reduce well-regulated stimulant self-administration but extends these basic findings by directly comparing the potency and effectiveness of a panel of dopamine D₃ and 5-HT_{2C} receptor ligands to reduce unusually high levels of MDPV self-administration and to reduce stimulant self-administration more generally in male and female rats. There were three main findings: (1) each pretreatment drug, except BD1063, produced dose dependent reductions in MDPV and cocaine self-administration; (2) all pretreatment drugs were equipotent at reducing MDPV self-administration in the high- and low-responding groups of rats; and (3) sex differences were observed, where

VK4-116, CP-809,101, and haloperidol were less potent at reducing cocaine self-administration in female compared to male rats, and VK4-116 was less potent at reducing MDPV self-administration in female high- and low-responders relative to male high- and low-responders; for VK4-40, VK4-116, CP-809,101 sex-related differences were also observed when data were collapsed across MDPV and cocaine.

As expected, all test compounds (except the sigma receptor antagonist BD1063) dose-dependently decreased self-administration in all groups. These findings are consistent with previous reports suggesting that dopamine D₃ receptors and 5-HT_{2C} receptors may be viable targets for treating stimulant use disorders (Higgins et al., 2013; Pockros-Burgess et al., 2014; Collins et al., 2016; Gerak et al., 2016; Harvey-Lewis et al., 2016; Collins and France, 2018; You et al., 2019; Jordan et al., 2019a, 2020; Anastasio et al., 2020; de Guglielmo et al., 2020; for reviews, see: Howell and Cunningham, 2015; Collins et al., 2018; Newman et al., 2021), as well as previous findings with haloperidol (De Vry et al., 1989; Roberts et al., 1989; Oleson et al., 2011). VK4-116 was previously shown to be equipotent at reduce drug-taking in male and female rats, but more effective in rats with high, but not low, levels of opioid self-administration (de Guglielmo et al. 2020). Though these findings suggested that VK4-116 might be more potent and/or effective at reducing MDPV self-administration in high- relative to low-responding rats, in the current studies, VK4-116 (and VK4-40) were equipotent at reducing drug-taking in rats with high and low levels of intake, but less potent in female rats compared to male rats. VK4-40 was also less effective at reducing stimulant self-administration in female as compared to male rats, though these evaluations were somewhat limited by issues with solubility, and the sex-related outcomes were not always consistent across self-administered drug. To our knowledge, this is the first time that the effects of VK4-40 on drug self-administration have been evaluated in female rats, so it is unclear whether these differences are specific to stimulants, or whether similar sex-related differences would also be observed with drugs from other classes (e.g., alcohol, nicotine).

Similar to the effects of the dopamine D₃ receptor ligands, the 5-HT_{2C} receptor agonist, CP-809,101, dose-dependently decreased self-administration in all rats, regardless of drug, or behavioral phenotype. CP-809,101 was also less potent at reducing stimulant self-administration in female compared to male rats, though these differences were larger for cocaine relative to MDPV self-administration. Sex-related differences in the potency of 5-HT_{2C} receptor agonists to reduce cocaine have been reported (Collins and France, 2018); however, those studies showed that lorcaserin, a 5-HT_{2C} receptor agonist, was more potent in female compared to male rhesus monkeys. The reason(s) underlying this discrepancy in the potential sex-related effects of 5-HT_{2C} receptor agonists might be related to species or procedural differences, but warrants further exploration.

When comparing the effects of the pretreatment drugs on responding maintained by food and drug, all test compounds tended to be more potent at reducing responding reinforced by food compared to drug. This is consistent with the non-selective effect of dopamine D₃ and 5-HT_{2C} drugs that have been reported in studies using food-vs-drug choice procedures (John et al., 2015; Banks and Negus, 2017; Thomsen et al., 2017; Townsend et al., 2020). The lack of selectivity in the current study may have also been because the rats were not food restricted, the choice of reinforcer, and/or the choice of test compounds. Greater selectivity for decreasing responding for drug over food might be observed if a different motivational state (e.g., food restriction) or a more palatable food reinforcer, such as sucrose pellets, was used instead. Given that the 5-HT_{2C} agonist lorcaserin was FDA approved to treat obesity, including assessments of responding maintained by non-food reinforcers (e.g., social interaction) is important when drawing conclusions about the selectivity (or lack thereof) of the effects of these compounds to decrease drug-taking. It should also be noted that the components when food was available were shorter than those when drug was available, which could have contributed to the lower number of food reinforcers earned. However, the decision to limit the food components to 10 minutes was based on preliminary data that suggested rats only responded

for the first 5-10 minutes of a 20-min component, which speaks to the weak reinforcing effects of grain-based pellets in these subjects.

Traditional, short-access stimulant self-administration sessions result in stable levels of drug intake that likely do not capture the problematic use in people with stimulant use disorder. Though no single animal model can capture the multi-symptomatic complexities of stimulant use disorder, high-responder rats exhibit several behaviors thought to be related to stimulant use disorder, even when self-administering drug under short-access conditions. Thus, we chose to directly compare the effects of various candidate medications in high-responder rats, and rats with more regulated drug-taking (i.e., low-responders, rats self-administering cocaine), to determine whether the candidate medications are effective in rats with dysregulated behavior. All the compounds that reduced drug-taking in rats with well-regulated behavior also reduced drug-taking in rats with a more robust stimulant use disorder-like phenotype. Others have employed similar strategies to evaluate candidate medications, such as comparing short- or extended-access procedures, where the latter procedure was used to model a more robust stimulant use disorder-like phenotype (e.g., Ramôa et al. 2014; Lynch et al. 2021). Another strategy is to evaluate candidate medications is a choice procedure, where drug and an alternative reinforcer (e.g., food, social partner) are available simultaneously to provide a more real-world scenario that is sensitive to selective reductions in drug-taking while also allowing for detection of a general rate decreasing effect (for review, see Banks and Negus, 2017). Candidate medications (e.g., buspirone, lorcaserin) have successfully reduced drug-taking in a subset of preclinical procedures in the past (e.g., Bergman et al., 2013; Czoty and Nader, 2015; Collins et al., 2016; Harvey-Lewis et al., 2016; Neelakantan et al., 2017; Collins and France, 2018), but been unsuccessful in clinical trials, which suggests alternative procedures for preclinical evaluation are necessary. Perhaps combining models, such as the high-responder, substance use disorder-like phenotype, with a choice procedure would increase the probability of identifying effective candidate medications while also reducing the likelihood of false

positives. Though more sophisticated models are needed, identification of the core features of these models is complicated by absence of a positive control (i.e., there are no FDA-approved pharmacotherapies for stimulant disorder), and it is likely that convergent evidence obtained from multiple, complementary procedures will be the most fruitful path forward (e.g., Venniro et al. 2020).

In summary, these studies provide additional support for the effectiveness of dopamine D₃ receptor antagonists/partial agonists and 5-HT_{2C} receptor agonists to dose dependently reduce stimulant self-administration, including in subjects that exhibit aberrant patterns of drug-taking similar to those observed in humans with a stimulant use disorder. Though one of these targets (i.e., the dopamine D₃ receptor) was included in the National Institute on Drug Abuse's Division of Therapeutics and Medical Consequences' top 10 pharmacological targets for the treatment of opioid use disorder (Rasmussen et al., 2019), many of the other targets also show promise for treating stimulant use disorders. Indeed, preclinical data suggest that orexin receptors, muscarinic M5 receptors, metabotropic glutamate receptors all have the potential to yield broad spectrum pharmacotherapies for substance use disorders more generally and should be evaluated in a similar manner to determine whether other pharmacological mechanisms are also effective at decreasing drug-taking in subjects exhibiting a substance use disorder-like phenotype, such as the MDPV high-responder rats. By continuing to evaluate candidate medications in animal models that incorporate various aspects of the human condition it is possible to not only gain important new information about the factors underlying stimulant use disorders, but also advance efforts to develop novel and effective therapies to assist those with a stimulant use disorder.

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Author Contributions

Participated in research design: Doyle and Collins.

Conducted experiments: Doyle and Peng.

Contributed new reagents or analytic tools: Cao, Rice, and Newman.

Performed data analysis: Doyle and Peng.

Wrote or contributed to the writing of the manuscript: Doyle, Newman, and Collins.

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Footnotes

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Table 1. Dose required to reduce drug-taking by 50% (ID₅₀), as measured by percent change in area under the curve. Doses reported in mg/kg (95% confidence intervals).

		Haloperidol			VK4-40			VK4-116			CP-809,101		
		Drug ID ₅₀	Food ID ₅₀	Potency ratio	Drug ID ₅₀	Food ID ₅₀	Potency ratio	Drug ID ₅₀	Food ID ₅₀	Potency ratio	Drug ID ₅₀	Food ID ₅₀	Potency ratio
High-responders	All	0.08 (0.06, 0.12)	0.07 (0.05, 0.10)	0.85 (0.77, 0.93)	30.6 (21.4, 43.8)	6.6 (5.1, 8.5)	0.21 (0.19, 0.24)	17.3 (9.3, 32)	7.3 (3.9, 13.6)	0.42 (0.42, 0.42)	1.61 (0.99, 2.63)	1.19 (0.88, 1.60)	0.73 (0.60, 0.88)
	Male	0.06 (0.03, 0.12)	0.04 (0.04, 0.05)	0.71 (0.42, 1.19)	25.7 (12.8, 51.6)	4.3 (3.8, 4.9)	0.17 (0.10, 0.30)	6.2 (3.2, 12.2)	2.6 (1.9, 3.7)	0.42 (0.30, 0.59)	1.04 (0.47, 2.28)	1.42 (0.88, 2.28)	1.45 (0.94, 2.25)
	Female	0.11 (0.08, 0.15)	0.10 (0.08, 0.13)	0.90 (0.84, 0.96)	34.6 (24.9, 48.2)	8.1 (6.4, 10.2)*	0.23 (0.21, 0.26)	35.9 (23.1, 55.9) *	14.3 (8.2, 24.8)*	0.40 (0.36, 0.44)	2.35 (1.50, 3.68)	1.00 (0.75, 1.33)	0.42 (0.38, 0.45)
Low-responders	All	0.08 (0.05, 0.14)	0.07 (0.03, 0.12)	0.78 (0.69, 0.88)	12.4 (7.0, 22.0)	6.2 (0.37, 10.4)	0.50 (0.47, 0.53)	13.5 (8.1, 22.5)	10.4 (6.6, 16.4)	0.77 (0.73, 0.82)	1.78 (1.09, 2.91)	0.95 (0.64, 1.41)	0.53 (0.48, 0.58)
	Male	0.09 (0.05, 0.19)	0.05 (0.02, 0.14)	0.55 (0.40, 0.77)	8.3 (4.4, 15.9)	4.9 (2.3, 10.8)	0.59 (0.52, 0.68)	8.1 (5.1, 12.9)	7.2 (4.0, 12.7)	0.88 (0.70, 0.99)	1.16 (0.74, 1.83)	0.81 (0.50, 1.30)	0.63 (0.57, 0.69)
	Female	0.07 (0.04, 0.12)	0.09 (0.07, 0.12)	1.32 (0.97, 1.79)	27.5 (14.4, 52.2)	8.3 (4.9, 13.9)	0.30 (0.31, 0.38)	27.6 (14.8, 51.7) *	18.3 (16.0, 21.0)	0.66 (0.41, 1.08)	3.53 (1.72, 7.25)	1.22 (0.66, 2.24)	0.34 (0.31, 0.38)
Cocaine	All	0.12 (0.08, 0.19)	0.06 (0.03, 0.10)	0.48 (0.45, 0.51)	17.5 (11.7, 26.3)	4.4 (2.7, 7.2)	0.25 (0.23, 0.27)	16.4 (10.4, 25.9)	10.1 (0.65, 15.6)	0.61 (0.60, 0.63)	2.54 (1.81, 3.57)	0.90 (0.61, 1.35)	0.33 (0.31, 0.35)
	Male	0.07 (0.03, 0.13)	0.03 (0.01, 0.08)	0.50 (0.40, 0.62)	9.6 (6.3, 14.6)	6.8 (5.3, 8.8)	0.71 (0.60, 0.84)	10.7 (6.7, 17.1)	9.0 (0.59, 13.6)	0.84 (0.80, 0.88)	1.53 (1.02, 2.29)	0.89 (0.40, 1.98)	0.58 (0.39, 0.86)
	Female	0.20 (0.15, 0.26) *	0.09 (0.08, 0.11)	0.46 (0.41, 0.51)	28.8 (21.7, 38.4) *	3.2 (1.6, 6.3)	0.11 (0.08, 0.16)	27.4 (15.5, 48.6)	11.6 (5.2, 25.8)	0.42 (0.34, 0.53)	3.94 (3.14, 4.93) *	0.92 (0.63, 1.33)	0.20 (0.19, 0.21)
All groups	Male	0.07 (0.05,	0.04 (0.03,	0.56 (0.32,	11.9 (7.7,	5.2 (3.6,	0.44 (0.42,	8.3 (6.0,	6.1 (4.2,	0.73 (0.70,	1.22 (0.88,	0.99 (0.69,	0.78 (0.73,

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		0.11)	0.04)	0.70)	18.2)	7.6)	0.46)	11.4)	8.8)	0.77)	1.69)	1.42)	0.84)
	Female	0.12 (0.09, 0.16)	0.09 (0.08, 0.11)	0.78 (0.67, 0.90)	30.7 (24.4, 38.8) *	6.2 (4.4, 8.8)	0.20 (0.18, 0.23)	30.7 (22.4, 42.1) *	14.2 (9.9, 20.4) *	0.46 (0.44, 0.48)	3.16 (2.38, 4.20) *	1.01 (0.79, 1.29)	0.30 (0.29, 0.31)

* indicates non-overlapping confidence intervals compared to male rats in the same group.

Figure Legends

Figure 1. Self-administration dose-response curves obtained under a multicomponent FR5 schedule of reinforcement for cocaine (left), MDPV, separated by low- (center) and high-responder phenotype. Top row: number of infusions earned under baseline (drug) conditions (filled circles) and when saline was substituted for cocaine or MDPV during a single session (x). Bottom row: baseline conditions split by male (squares) and female rats (diamonds). Ordinate: reinforcers obtained during each component. Abscissa: Food 1 and Food 2 refer to components when grain-based pellets were available. The numbers refer to dose of cocaine (left) and MDPV (center and right) expressed as mg/kg/infusion on a log scale. Error bars represent \pm S.E.M.

Figure 2. Effects of pretreatments on self-administration dose-response curves rats that self-administered cocaine (left) or MDPV, separated by low- (center) and high-responder phenotype. Top row: pretreatments of the dopamine D₂/D₃/sigma receptor antagonist haloperidol (0.01-0.32 mg/kg). Second row: pretreatments of the dopamine D₃ receptor partial agonist VK4-40 (3.2-32 mg/kg). Third row: pretreatments of the dopamine D₃ receptor antagonist VK4-116 (3.2-32 mg/kg). Fourth row: pretreatments of the 5-HT_{2C} receptor agonist CP-809,101 (0.32-5.6 mg/kg). Bottom row: pretreatments of the sigma receptor antagonist BD1063 (1-10 mg/kg). Ordinate: reinforcers obtained during each component. Abscissa: Food 1 and Food 2 refer to components when grain-based pellets were available. The numbers refer to dose of cocaine (left) and MDPV (center and right) expressed as mg/kg/infusion on a log scale. The shaded gray region represents mean \pm S.E.M. responding under baseline conditions. Error bars represent \pm S.E.M.

Figure 3. Percent of baseline area under the curve (AUC) for haloperidol (top row), VK4-40 (second row), VK4-116 (third row), CP-809,101 (fourth row), and BD1063 (bottom row) in male (left column) and female rats (right column). Ordinate: % of baseline AUC, where baseline in the three sessions prior to pretreatment administration. Abscissa: Vehicle refers to the vehicle for each pretreatment. The numbers refer to the dose of the pretreatment, expressed as mg/kg on a log scale. Error bars represent \pm S.E.M.





