JPET Fast Forward. Published on August 19, 2021 as DOI: 10.1124/jpet.121.000655
This article has not been copyedited and formatted. The final version may differ from this version.

Title: Influence of contingent and non-contingent drug histories on the development of high levels of MDPV self-administration

Authors: Michelle R. Doyle, Agnieszka Sulima, Kenner C. Rice, Gregory T. Collins

Department of Pharmacology, The University of Texas Health Science Center at San Antonio (M.R.D, G.T.C)

South Texas Veterans Health Care System, San Antonio, TX, USA (M.R.D, G.T.C)

Drug Design and Synthesis Section, Molecular Targets and Medications Discovery Branch, NIDA and NIAAA, Bethesda, MD, USA (A.S, K.C.R.)

JPET Fast Forward. Published on August 19, 2021 as DOI: 10.1124/jpet.121.000655
This article has not been copyedited and formatted. The final version may differ from this version.

Running title: Effects of drug histories on MDPV self-administration

Correspondence:

Gregory T. Collins

Department of Pharmacology

The University of Texas Health Science Center at San Antonio

7703 Floyd Curl Dr - MC 7764

San Antonio, TX 78229, USA

Telephone: (210) 567-4199

Fax: (210) 567-4303

Email: CollinsG@uthscsa.edu

Number of text pages: 18

Number of tables: 1

Number of figures: 3

Number of references: 47

Abstract word count: 250

Introduction word count: 940

Discussion word count: 1781

Abbreviations: α-PVP, α-pyrrolidinopentiophenone; FR, fixed ratio; MDMA, 3,4-methylenedioxymethamphetamine; MDPV, 3,4-methylenedioxypyrovalerone; mephedrone, 4-methylmethcathinone; methylone, 3,4-methylenedioxy-N-methylcathinone; TO, timeout

Section assignment: Behavioral Pharmacology

JPET Fast Forward. Published on August 19, 2021 as DOI: 10.1124/jpet.121.000655
This article has not been copyedited and formatted. The final version may differ from this version.

Abstract

A subset of rats that self-administer 3,4-methylenedioxypyrovalerone (MDPV) develop unusually high levels of drug-taking. A history of responding maintained by cocaine, but not food, prevents the development of this high-responder phenotype; however, it is unclear how histories of non-contingent cocaine exposure or self-administering drugs from other pharmacological classes would affect its development. In the current studies, 5 groups of male Sprague Dawley rats were used to determine if histories of responding maintained by drugs from different pharmacological classes (e.g., MDPV, cocaine, fentanyl, nicotine, or ketamine) would differentially impact the development of the high-responder phenotype when MDPV was available for self-administration. Two additional groups were used to determine whether non-contingent exposure to cocaine would prevent the development of the high-responder phenotype when MDPV was available for self-administration, and whether non-contingent exposure to MDPV would facilitate the development of the high-responder phenotype when cocaine was available for self-administration. Consistent with previous reports, a history of response-contingent cocaine, and to a lesser extent non-contingent cocaine, prevented the MDPV high-responder phenotype; however, when responding was initially maintained by fentanyl, nicotine, or ketamine, the MDPV high-responder phenotype developed in ~45% of rats. By manipulating behavioral and pharmacological histories prior to evaluating MDPV self-administration, the current studies provide additional evidence that a history of response-contingent (or non-contingent) cocaine can prevent the transition from well-regulated to aberrant drug-taking when responding is maintained by MDPV. Although the mechanism(s) that underlies this novel high-responder phenotype are unknown, elucidation may provide insight into individual differences relating to substance use disorder.

JPET Fast Forward. Published on August 19, 2021 as DOI: 10.1124/jpet.121.000655
This article has not been copyedited and formatted. The final version may differ from this version.

Significance statement

A subset of outbred Sprague Dawley rats self-administer high levels of the synthetic cathinone 3,4-methylenedioxypyrovalerone (MDPV). Understanding the behavioral and/or pharmacological factors that can prevent the development of dysregulated MDPV self-administration may provide insight into individual differences in vulnerability to develop a substance use disorder.

JPET Fast Forward. Published on August 19, 2021 as DOI: 10.1124/jpet.121.000655
This article has not been copyedited and formatted. The final version may differ from this version.

Introduction

Synthetic cathinones are a family of novel psychoactive substances colloquially known as “bath salts”, “legal highs”, “research chemicals”, or “plant food”. These compounds function as either monoamine uptake inhibitors (e.g., 3,4-methylenedioxypyrovalerone [MDPV], α-pyrrolidinopentiophenone [α-PVP]) or releasers (e.g., 3,4-methylenedioxy-N-methylcathinone [methylone], 4-methylmethcathinone [mephedrone]). Although they vary in selectivity for the dopamine, norepinephrine and serotonin transporters, their effects are similar to prototypical illicit stimulants (e.g., cocaine, methamphetamine, or 3,4-methylenedioxymethamphetamine [MDMA]). Synthetic cathinone users often report repeated bouts of drug administration (i.e., binges) over hours/days, using more drug than intended, high amounts of drug craving, and euphoric effects stronger than those of cocaine (e.g., Winstock et al., 2011; Lenz et al., 2013; Stoica and Felthous, 2013). Synthetic cathinone use also results in a large number of emergency room visits and calls to poison control centers due to acute toxicity, including hypertension, tachycardia, anxiety, and paranoia (e.g., Winstock et al., 2011; Lenz et al., 2013; Stoica and Felthous, 2013). Although anecdotal, these data suggest that the abuse-related and toxic effects of synthetic cathinones (or “bath salts” preparations) might be greater than for drugs such as cocaine or methamphetamine.

Preclinical studies in rats and monkeys using behavioral economics and/or progressive ratio (PR) schedules of reinforcement to directly compare the reinforcing effectiveness of synthetic cathinones, such as MDPV and α-PVP, to traditional stimulant drugs of abuse suggest that MDPV and related synthetic cathinones function as more effective reinforcers than either cocaine or methamphetamine (Aarde et al., 2013; Watterson et al., 2014; Gannon et al., 2017; 2018a; Huskinson et al., 2017; Collins et al., 2019; Doyle et al., 2021b; but see de Moura et al., 2021). Structure-activity relationships suggest that the reinforcing effectiveness of MDPV and α-PVP is positively correlated with their selectivity for the dopamine relative to serotonin transporter (Gannon et al., 2018a).

JPET Fast Forward. Published on August 19, 2021 as DOI: 10.1124/jpet.121.000655
This article has not been copyedited and formatted. The final version may differ from this version.

In addition to functioning as highly effective reinforcers, pyrrolidine-containing synthetic cathinones, including MDPV, often maintain unusually high levels of responding during acquisition of self-administration, sometimes referred to as spiking or “binge-like” patterns of acquisition (Aarde et al., 2015; Javadi-Paydar et al., 2018). Though not explicitly described as such, similar observations have been made in our laboratory and others (Watterson et al., 2013; Gannon et al., 2017, 2018b; Doyle et al., 2021b), suggesting that MDPV and related synthetic cathinones are associated with unusually high rates of drug intake, a phenomena that might be related to “binge-like” patterns of consumption of drugs, alcohol, sugar, or high-fat foods (e.g., Avena, Rada, and Hoebel, 2008; Corwin, Avena, and Boggiano, 2011; Carnicella, Ron, and Barak, 2014). Not only are these high levels of intake apparent when rats are learning the drug-taking response, but in a subset of male and female rats these unusually high levels of drug intake persist across time, and over a range of doses (Gannon et al., 2017, 2018b; Doyle et al., 2021b). This upward shift in the fixed ratio (FR) 5 dose-response curve suggests that these animals are not simply more sensitive to the reinforcing effects of MDPV (i.e., not due to a leftward shift in the dose response curve), but rather that their drug-taking behavior has transitioned from well-regulated to aberrant, akin to what is observed in humans as they transition from recreational to more problematic patterns of drug-taking. In addition to high levels of drug intake, these “high-responder” rats also engage in high levels of responding during signaled periods of drug unavailability (Gannon et al., 2017, 2018b, 2021; Doyle et al., 2021b), and will work harder to obtain drug infusions under PR schedules of reinforcement (Gannon et al., 2017, but see Doyle et al., 2021b), two aspects thought to be related to substance use disorders in humans (e.g., Deroche-Gamonet et al., 2004).

Though the high level of drug intake is the most striking behavioral feature of this novel phenotype, the criterion we have used to operationally define high- (and low-) responders is the proportion of total active lever responses made during the 5-sec post-infusion timeout, with rats making ≥20% of their total responses during this period classified as “high-responders” (Gannon

JPET Fast Forward. Published on August 19, 2021 as DOI: 10.1124/jpet.121.000655
This article has not been copyedited and formatted. The final version may differ from this version.

et al., 2017, 2018b; Doyle et al., 2021b). Since timeout responding is significantly and positively correlated with drug intake and remains elevated in high-responders regardless of the unit dose of MDPV available, this single criterion can be applied to responding maintained by both small and large unit doses, despite the fact that they maintain relatively high and low rates of responding, respectively. Relatedly, although the self-administration of other drugs, such as cocaine and oxycodone, is not typically associated with responding during post-infusion timeouts, when these drugs are substituted for MDPV, the core features of this phenotype (e.g., high levels of drug intake and high levels of responding when drug is not available; Gannon et al., 2017; 2018a; 2021) persist, suggesting that the high-responder phenotype first identified with MDPV self-administration may provide a novel model for better understanding individual differences in drug-taking as they relate to substance use disorders in humans.

Interestingly, although this high-responder phenotype is both reliable (i.e., observed in 78 of 184 [42%] rats across five studies, including this one; Gannon et al., 2017; 2018; Doyle et al., 2021a; 2021b) and enduring, evidence from two of these studies (Gannon et al., 2017; Doyle et al., 2021b) suggests that a history of cocaine self-administration can prevent or delay the development of high levels of MDPV intake. Though the inability of a history of responding maintained by food delivery to alter the development of this high-responder phenotype for MDPV self-administration (Doyle et al., 2021b) suggests that simply providing a history of operant responding is insufficient to prevent the development of the high-responder phenotype, the mechanism(s) by which cocaine interferes with the transition from regulated to dysregulated or aberrant patterns of MDPV self-administration remain unclear.

As such, the present study sought to better define the behavioral and pharmacologic determinants of the MDPV high-responder phenotype by evaluating MDPV self-administration in rats that were first allowed to self-administer drugs with diverse pharmacological mechanisms and non-overlapping discriminative stimulus effects, as well as rats that were provided non-contingent histories of cocaine and MDPV exposure to match those achieved through response-

JPET Fast Forward. Published on August 19, 2021 as DOI: 10.1124/jpet.121.000655
This article has not been copyedited and formatted. The final version may differ from this version.

contingent self-administration. Thus, the present study had three primary goals: 1) to directly compare the proportion of rats that develop the MDPV high-responder phenotype after acquiring responding maintained by MDPV, cocaine, fentanyl, ketamine, and nicotine; 2) to use a yoked, non-contingent cocaine exposure paradigm to determine whether reinforcement (i.e., response-contingent cocaine) and pharmacologic (i.e., non-contingent cocaine) histories would both disrupt the development of high levels of MDPV self-administration; and 3) to use a yoked, non-contingent MDPV exposure paradigm to determine whether reinforcement (i.e., response-contingent MDPV) and pharmacologic (i.e., non-contingent MDPV) histories would both establish high levels of cocaine self-administration.

JPET Fast Forward. Published on August 19, 2021 as DOI: 10.1124/jpet.121.000655
This article has not been copyedited and formatted. The final version may differ from this version.

Materials and Methods

Animals

Adult male Sprague Dawley rats (n=112; 275-300g upon arrival; Envigo, Indianapolis, IN) were singly housed in a temperature- and humidity-controlled environment with a 14/10h light cycle (lights on at 6:00 AM). Rats had *ad libitum* access to food and water except during experimental sessions, or when mild food restriction (15g/day) was briefly (3-8 days) used in a subset of rats (n=6) to promote acquisition of drug-taking. All procedures were conducted in accordance with Institutional Animal Care and Use Committee at the University of Texas Health Science Center at San Antonio and the Guide for Care and Use of Laboratory Animals (National Research Council, 2011).

Surgical procedure

Briefly, rats were anesthetized with 2-3% isoflurane and prepared with chronic indwelling catheters in the left femoral vein and a vascular access button exteriorized in the scapular region (Doyle et al., 2021a; b). To prevent infection, 60,000U/rat penicillin G was administered once, subcutaneously, following surgery. Rats were allowed to recover for 5-7 days before beginning experimental sessions. Rats were flushed daily with 0.5ml heparinized saline (100U/ml) during the recovery period and after self-administration sessions, and with 0.2ml saline before each session.

Apparatus

Operant sessions were conducted in standard operant chambers (Med Associates Inc., St. Albans, VT), located within ventilated, sound- and light-attenuated cubicles. Chambers contained two levers located on one wall with a set of 3 LEDs (green, yellow, and red) above each lever; a white house light was located at the top of the opposite wall. Variable speed

JPET Fast Forward. Published on August 19, 2021 as DOI: 10.1124/jpet.121.000655
This article has not been copyedited and formatted. The final version may differ from this version.

syringe drivers were used to administer all infusions through Tygon tubing that was connected to a fluid swivel and spring tether, held in place by a counterbalance arm.

Experiment 1

Acquisition

To determine the effects of different drug self-administration histories on the development of the high-responder phenotype, 80 rats (n=16/drug history group) responded for either MDPV (0.032 mg/kg/inf), cocaine (0.32 mg/kg/inf), fentanyl (0.0032 mg/kg/inf), nicotine (0.032 mg/kg/inf), or ketamine (1.0 mg/kg/inf) under a fixed ratio (FR) 1 schedule of reinforcement during at least 10 daily 90-min sessions. Doses were selected based on each drug's relative reinforcing potency/relative position on the descending limb of FR dose response curves (i.e., half log beyond the peak; Collins and Woods, 2007; Caine et al., 2014; Wade et al., 2015; Doyle et al., 2021b). Illumination of the yellow LED above the active lever (counterbalanced across rats) signaled drug availability. When the FR response requirement was met, an infusion (~1-sec in duration) was delivered and the infusion-paired stimuli (house light and 3 LEDs about the active lever) were illuminated. A 5-sec timeout (TO) was initiated coincident with the start of the infusion during which the infusion-paired stimuli were illuminated, and no additional infusions could be earned. For rats that met acquisition criteria (i.e., ≥10 reinforcers and ≥80% responses on the active lever for two consecutive sessions) by the 10th session, the FR requirement was subsequently increased to an FR5. For rats that responded for fentanyl, nicotine, or ketamine, the FR was first increased to an FR3 for at least 3 sessions and until ≥10 reinforcers were earned prior to increasing the response requirement to an FR5. Rats that failed to meet acquisition criteria within 10 sessions (cocaine: n=5; fentanyl: n=1; nicotine: n=2; ketamine: n=2) remained on FR1 until acquisition criteria were met. Those that did not meet the criterion for number of infusions by the 10^{th} session (n=6) were mildly food restricted (15 g food/day) beginning after the 10^{th} session and/or received non-contingent infusions (at 1,

JPET Fast Forward. Published on August 19, 2021 as DOI: 10.1124/jpet.121.000655
This article has not been copyedited and formatted. The final version may differ from this version.

3, 5, 10, and 15 minutes after the start of the session) for up to 4 sessions (beginning between sessions 11 and 14), until acquisition criteria were met (3-8 sessions). Catheter patency was assessed using 5 mg/kg methohexital as needed (e.g., an increase in pressure when flushing, or if a rat exhibited extinction-like levels of responding). All catheters remained patent throughout the duration of these studies.

Fixed ratio 5 (FR5) responding

After acquiring responding under an FR1, rats then responded for their original reinforcer under FR5:TO 5-sec schedule of reinforcement for at least 10 sessions and until meeting stability criteria (i.e., ± 20% of the mean for 3 consecutive sessions; no increasing or decreasing trend), or a maximum of 15 sessions. After this, all groups except the MDPV-history group (which went on to self-administer 0.32 mg/kg/inf cocaine) self-administered MDPV (0.032 mg/kg/inf) for at least 10 sessions and until reaching the stability criteria defined above, or a maximum of 15 sessions. As previously described, rats were classified as high- or low-responders based on whether they made ≥20% or <20%, respectively, of their total active lever responses during the 5-sec post-infusion TO periods (Gannon et al., 2017, 2018b; Doyle et al., 2021b).

Experiment 2

Non-contingent histories

To differentiate between the pharmacological and behavioral effects of MDPV and cocaine self-administration, 32 rats (n=16/group) received non-contingent drug infusions of either MDPV (0.032 mg/kg/inf) or cocaine (0.32 mg/kg/inf) through a yoked-infusion paradigm. Each “yoked” rat was paired with one of the rats that self-administered MDPV or cocaine in Experiment 1. The yoked rats were placed into operant chambers, where responding on levers had no scheduled consequence, but unsignaled MDPV or cocaine infusions were delivered

JPET Fast Forward. Published on August 19, 2021 as DOI: 10.1124/jpet.121.000655
This article has not been copyedited and formatted. The final version may differ from this version.

when the “primary” rat from Experiment 1 earned a drug infusion. The yoked procedure continued for the total duration of the original drug self-administration (i.e., ≥10 sessions of the primary rat responding under an FR1:TO 5-sec and 10-15 sessions of responding under an FR5:TO 5-sec).

Self-administration

After ~25 sessions of non-contingent drug administration, yoked rats began self-administration under an FR1:TO 5-sec schedule of reinforcement. Rats that received yoked MDPV infusions were allowed to respond for cocaine (0.32 mg/kg/inf), whereas rats that received yoked cocaine infusions were allowed to respond for MDPV (0.032 mg/kg/inf). After 10 sessions of self-administration, rats that did not meet acquisition criteria (n=1 for yoked MDPV-history) were mildly food-restricted (15g of food/day) until acquisition criteria were met. Once acquisition criteria were met, the response requirement was increased to an FR5 for at least 10 sessions and until stability criteria were met, or a maximum of 15 sessions. Rats were then classified as high- or low-responders based on percent TO responding (Gannon et al., 2017, 2018b; Doyle et al., 2021b).

Statistical analyses

Number of infusions earned when responding under FR1 or FR5 are both represented as the mean ± SEM. The mean number of infusions earned during the final 3 sessions of responding under FR1 and FR5 conditions for the original reinforcer (i.e., MDPV, cocaine, nicotine, fentanyl, or ketamine), were compared by a two-way (drug and FR) repeated measures (FR) analysis of variance (ANOVA). The number of sessions to reach acquisition criteria (in rats meeting the criteria within 10 sessions) in rats with no prior drug history were analyzed by a one-way ANOVA with Tukey’s post-hoc analyses. A two-way ANOVA (drug and no prior drug history vs non-contingent history) was used to compare the sessions to reach

JPET Fast Forward. Published on August 19, 2021 as DOI: 10.1124/jpet.121.000655
This article has not been copyedited and formatted. The final version may differ from this version.

acquisition criteria in rats that acquired on MDPV or cocaine, with Sidak's multiple comparisons test. Two-way (day and phenotype) repeated measures (day) ANOVA were used to compare the number of infusions earned by high- and low-responders self-administering MDPV in all groups, except cocaine, which was excluded from analysis because there was only 1 high-responder.

Drugs

Racemic MDPV HCl was synthesized by Agnieszka Sulima and Kenner Rice (Bethesda, MD). Fentanyl and cocaine HCl were provided by the National Institute on Drug Abuse Drug Supply Program (Bethesda, MD). Nicotine and ketamine were purchased from Sigma-Aldrich (St. Louis, MO, USA) and Henry Schein (Dublin, OH, USA), respectively. Doses of MDPV, cocaine, fentanyl and ketamine were based on salt weights, whereas doses of nicotine were based on the free base weight of nicotine. All drugs were dissolved in sterile 0.9% saline. For nicotine solutions the pH was adjusted to ~7 by adding 1N NaOH dropwise. Drugs were administered intravenously in a volume of 0.1 ml/kg body weight.

JPET Fast Forward. Published on August 19, 2021 as DOI: 10.1124/jpet.121.000655
This article has not been copyedited and formatted. The final version may differ from this version.

Results

Experiment 1: Acquisition of Responding

A majority of rats met the acquisition criteria within the first 10 sessions (Fig 1; Table 1). A one-way ANOVA indicated there was a main effect of drug ($F(4,64)=5.6$; $p=0.0009$) on the number of sessions to meet acquisition criteria, where acquisition of ketamine self-administration required a greater number of sessions than when either MDPV or cocaine was available for self-administration (Table 1; Tukey's post hoc; $ps<0.05$). There were no significant differences in the number of sessions to meet acquisition criteria for fentanyl or nicotine self-administration. Generally, when the fixed ratio (FR) requirement was increased from FR1 to FR5, rats increased their responding ~5-fold to earn a comparable number of infusions, and there were no significant differences in number of infusions earned ($F(1,105)=0.07$; $p=0.79$; Fig 1). After self-administering their initial drug under the FR5 schedule of reinforcement for 10-15 sessions, 5 of 16 (31%) rats that self-administered MDPV met the high-responder criterion (i.e., ≥20% of their total active lever responses made during the post-infusion TO periods; Gannon et al., 2017, 2018; Doyle et al., 2021b), as did 3 of 16 (19%) rats that self-administered fentanyl, and 1 of 16 (6%) that self-administered cocaine (data not shown). In contrast, none of the rats that self-administered nicotine or ketamine met the criterion for being classified as a high-responder.

Experiment 1: Substitution to MDPV Self-Administration

To determine whether self-administration history could prevent/delay the development of the high-responder phenotype, rats that initially self-administered cocaine, fentanyl, nicotine, or ketamine (drug-history groups) were allowed to self-administer 0.032 mg/kg/infusion MDPV under FR5 for 10-15 sessions (Fig 2). The number of MDPV infusions earned by each of these groups is shown in Figure 2, as is the percent of rats that met the high-responder criterion during the final 3 sessions of MDPV self-administration (i.e., sessions 8-10 or 13-15 of MDPV

JPET Fast Forward. Published on August 19, 2021 as DOI: 10.1124/jpet.121.000655
This article has not been copyedited and formatted. The final version may differ from this version.

self-administration, when stability criteria were reached). Two-way repeated measures ANOVAs found main effects of phenotype for all groups, except cocaine, (MDPV: $F(1,14)=7.8$, $p=0.01$; fentanyl-history: $F(1,14)=6.9$, $p=0.02$; nicotine-history: $F(1,14)=9.0$, $p=0.01$; ketamine-history: $F(1,14) = 12.4$, $p=0.003$), where high-responders earned more infusions than low-responders. Approximately 45% of rats with a history of responding maintained by fentanyl (50%), nicotine (56%), or ketamine (38%) developed the high-responder phenotype for MDPV; in contrast, only 1 of 16 (6%) rats with a history of responding maintained by cocaine developed the high-responder phenotype for MDPV (Fig 2). Low-responder rats earned a similar number of MDPV infusions across reinforcement histories (mean: 33-41 infusions), and high-responder rats earned 2-3 times as many infusions as low-responder rats, across reinforcement histories (Fig 2). Percent TO responding averaged less than 10% for low-responder rats and ~40% for high-responder rats (data not shown).

Experiment 2: Non-contingent MDPV/cocaine histories

Two groups of rats (n=16/group) received non-contingent, yoked infusions of MDPV (0.032mg/kg/inf) or cocaine (0.32 mg/kg/inf) in order to determine the role of response contingencies in the development of the high-responder phenotype. Rats with a non-contingent drug history acquired self-administration significantly more rapidly than experimentally naive rats ($p<0.005$ for both), with nearly all rats meeting acquisition criteria within 3 sessions (Table 1). After 10-15 sessions of cocaine self-administration under an FR5 schedule of reinforcement, none of the MDPV-yoked rats developed the high-responder phenotype. In contrast, 2 of the 5 high-responders from response-contingent MDPV-history group maintained the high-responder phenotype after 10 sessions of cocaine availability (Fig 3). Three of 16 (19%) cocaine-yoked rats developed the high-responder phenotype when they were subsequently allowed to self-administer MDPV (Fig 3). These rats displayed a similar, if not more extreme, high-responder phenotype as rats with other drug-histories, earning ~240 infusions on average during the last 3

JPET Fast Forward. Published on August 19, 2021 as DOI: 10.1124/jpet.121.000655
This article has not been copyedited and formatted. The final version may differ from this version.

sessions (Fig 3), compared to the 60-130 infusions earned, on average, by high-responders with other drug histories (Fig 2).

JPET Fast Forward. Published on August 19, 2021 as DOI: 10.1124/jpet.121.000655
This article has not been copyedited and formatted. The final version may differ from this version.

Discussion

Prior studies have reported that a subset of rats develop unusually high and persistent levels of drug intake when allowed to self-administer MDPV or structurally-related synthetic cathinones (Gannon et al., 2017, 2018b; Doyle et al., 2021b). In addition to being observed across multiple studies and laboratories, because this unusual pattern of drug-taking is enduring, and readily transfers to other stimulants (e.g., cocaine, methamphetamine; Gannon et al., 2017), we believe that this high-responder phenotype represents a novel model to investigate the binge-like and/or compulsive patterns of stimulant use often reported by humans. Accordingly, the present study sought to better define the behavioral and pharmacologic determinants of the high-responder phenotype by evaluating MDPV self-administration in rats with histories of reinforcement by drugs with diverse pharmacological mechanisms and non-overlapping discriminative stimulus effects, as well as rats that were provided pharmacologic histories of non-contingent cocaine and MDPV exposure to match those achieved through response-contingent self-administration. In addition to replicating prior findings (Gannon et al., 2017; Doyle et al., 2021b) by demonstrating that a subset of rats responding for MDPV (~30%), but not cocaine, develop a high-responder phenotype characterized by persistently high levels of drug-taking combined with high levels of responding during post-infusion TO periods, the present studies also showed that: 1) unlike when responding was previously maintained by cocaine, histories of responding maintained by fentanyl, nicotine, or ketamine failed to prevent the development of the MDPV high-responder phenotype; 2) when provided a history of non-contingent cocaine exposure, an intermediate proportion of rats went on to develop the MDPV high-responder phenotype; and 3) when provided a history of non-contingent MDPV exposure, rats failed to develop the high-responder phenotype for cocaine self-administration. Together, these findings suggest that both behavioral and pharmacological histories play a role in the development of the high-responder phenotype, and highlight the importance of response-contingent drug administration in both establishing

JPET Fast Forward. Published on August 19, 2021 as DOI: 10.1124/jpet.121.000655
This article has not been copyedited and formatted. The final version may differ from this version.

(MDPV history) and preventing (cocaine history) the aberrant patterns of responding and high levels of drug intake that may be related to the development of substance use disorders in humans.

Previous studies suggested that reinforcement histories with cocaine, but not food, can prevent the development of the MDPV high-responder phenotype (Gannon et al., 2017; Doyle et al., 2021b). The current study replicated and extended this basic finding by determining whether histories of reinforcement by drugs from other pharmacological classes would also interact with the development of the MDPV high-responder phenotype. Although 1 of the 16 (6%) rats with a history of cocaine self-administration developed the high-responder phenotype when MDPV was available for self-administration, rats that were provided histories of fentanyl (50%), nicotine (56%), or ketamine (38%) self-administration went on to develop the MDPV high-responder phenotype at proportions similar to that observed in rats that had only ever self-administered MDPV (31%). These findings suggest a history of cocaine self-administration is unique in its capacity to prevent the development of this high-responder phenotype; however, further studies will be required to determine if the self-administration of other stimulant drugs (e.g., methamphetamine) is also capable of preventing the high-responder phenotype. In addition, because these studies only assessed the impact of relatively short/limited access (i.e., 90-min daily sessions) to cocaine reinforcement, it will be important to determine whether cocaine would retain its protective effects if rats were provided histories of cocaine reinforcement under long/extended access or intermittent access conditions, which have been shown to result in escalation of drug-taking, increases in compulsive-like behaviors (Ahmed and Koob, 1998; Vanderschuren and Everitt, 2004), and changes reinforcing effectiveness, cue-induced reinstatement, and dopamine transporter sensitivity (Zimmer et al., 2012; Calipari et al., 2013; Allain et al., 2018; Garcia et al., 2020) that are thought to contribute to substance use disorder-related phenotypes.

JPET Fast Forward. Published on August 19, 2021 as DOI: 10.1124/jpet.121.000655
This article has not been copyedited and formatted. The final version may differ from this version.

To determine whether the contingency between the response and the drug effect was important to the protective effects of cocaine (and the faciliatory effects of MDPV) the current study also incorporated two groups of rats that received non-contingent infusions of cocaine (or MDPV) through a yoked procedure that matched drug exposures (i.e., the timing and number of infusions) to rats that were actively self-administering cocaine (or MDPV). Importantly, when compared to rats that were actively self-administering cocaine (6%) or other drugs (44%; collapsed across MDPV, fentanyl, ketamine, and nicotine), a history of non-contingent cocaine exposure appeared to provide an intermediate protection (19%) against development of the high-responder phenotype. When taken together with the finding that a history of non-contingent MDPV exposure failed to facilitate the development of the high-responder phenotype for cocaine, these findings suggest that the capacity of cocaine to interfere with the development of the high-responder phenotype for MDPV is dependent on both behavioral and pharmacological aspects of these histories. Although the relative importance of the contingencies of reinforcement is likely related to associations that are formed between the response and the drug effects, aspects of the pharmacologic properties of cocaine (and MDPV) that contribute to the protective (and faciliatory) effects are less clear.

Given that MDPV is much more selective than cocaine at inhibiting uptake at DAT relative to SERT (~750-fold versus 1.2-fold; Gannon et al., 2018a), it is possible that actions at SERT, or lack thereof, are important for the protective and faciliatory effects of cocaine and MDPV, respectively. Supporting this notion, other DAT-preferring, pyrrolidine-containing cathinones (e.g., MDPBP, MDPPP, α-PVP, α-PPP) are also associated with the development of this high-responder phenotype (Gannon et al., 2018b). However, similar phenotypes are not observed in rats that self-administer methylphenidate (Collins et al., 2012), another DAT-selective uptake inhibitor (Markowitz et al., 2008), suggesting that other factors are more important in establishing the high-responder phenotype. Further supporting this, genetic deletion of SERT did not alter the reinforcing effects of cocaine in mice (Thomsen et al., 2009); however,

JPET Fast Forward. Published on August 19, 2021 as DOI: 10.1124/jpet.121.000655
This article has not been copyedited and formatted. The final version may differ from this version.

additional studies evaluating MDPV and cocaine self-administration in SERT knockout mice are needed to rule out a role for SERT in the protective effects of cocaine. Another possibility is that because the discriminative stimulus effects of cocaine and MDPV overlap (e.g., Gatch et al., 2013; Collins et al., 2016; Seaman et al., 2021), rats are unable to differentiate between conditions in which cocaine or MDPV are available for self-administration. This would be particularly important if potentially aversive effects of cocaine, perhaps related to inhibition of cardiovascular sodium channels (Matthews and Collins, 1983), result in rats first learning to self-administer cocaine in a more regulated and/or cautious manner before gaining access to MDPV. Indeed, bolus doses of MDPV as large as 5.6 mg/kg intravenously in rats (Hambuchen et al., 2017) and 140 mg/kg intraperitoneally in mice (Muskiewicz et al., 2020) have been administered without producing convulsions. Conversely, cocaine-induced convulsions can be observed following bolus doses of ~9 mg/kg intravenously in rats (Mets et al., 1998) and 56 mg/kg intraperitoneally in mice (Ko et al., 2007). When compared to doses of MDPV and cocaine to maintain half-maximal responding under a PR schedule in rats (0.017 and 0.17 mg/kg/inf, respectively; Gannon et al., 2018a), or cocaine-like discriminative stimulus effects in mice (0.1 and 3 mg/kg, IP, respectively; Gannon et al., 2016), the potency ratio for MDPV to produce abuse-related and toxic/aversive effects is at least 6- to 70-fold greater than that for cocaine. Thus, the relatively narrow window between the reinforcing/abuse-related effects and the convulsant/aversive effects for cocaine relative to MDPV could be one factor that moderates the level of intake for cocaine, but not MDPV. Although one might hypothesize that the unpredictable nature of non-contingent cocaine infusions would result in their being more aversive than response-contingent cocaine infusions, the contextual associations learned under such scenarios may be insufficient to impact subsequent MDPV self-administration.

Although there are insufficient data to directly compare the onset of action for MDPV and cocaine, a recent study in rats self-administering cocaine (Canchy et al., 2021) suggests that response latencies can be used as a behavioral readout of pharmacokinetic properties of

JPET Fast Forward. Published on August 19, 2021 as DOI: 10.1124/jpet.121.000655
This article has not been copyedited and formatted. The final version may differ from this version.

cocaine. Indeed, they reported that upon completing a response requirement, rats withhold responding until some time after the drug effect is perceived, however, if a cocaine infusion was omitted, rats began responding sooner. The time to peak effect for cocaine (increases in synaptic dopamine levels) is estimated to be tens of seconds (Wise and Kiyatkin, 2011; Canchy et al., 2021), and though little is known about the time to peak effect for MDPV, it is unlikely to be less than 5 seconds, the duration of the TO in the present studies. Nevertheless, if one assumes that the TO responding associated with MDPV self-administration is due to a slower time to peak effect, then one would also expect that substituting MDPV for cocaine would result in more TO responding (i.e., MDPV would be perceived as a delayed/omitted reward), whereas substituting cocaine for MDPV would result in less TO responding (i.e., cocaine would be perceived as a more immediate reward). Given that neither of these outcomes were observed, we do not believe that pharmacokinetics, at least related to the time to peak effect, is a causal factor in facilitating or preventing the high-responder phenotype.

Consistent with patterns of responding maintained by drug reinforcers under simple FR schedules with relatively short post-infusion TOs, very little TO responding was observed when responding was maintained by cocaine, nicotine, or ketamine; however, when fentanyl was available, a subset of rats (3 of 16) made ~26% of their active lever responses during TOs and earned nearly twice as many infusions than the other rats (~32 vs ~17 infusions per session). Although this suggests that the high-responder phenotype may not be unique to synthetic cathinones, the importance of TO responding to the overall phenotype is not entirely clear. Others have also reported fairly large variability in fentanyl intake in rats whose responding was maintained by intravenous or vapor fentanyl (e.g., Stevenson et al., 2020; Bakhti-Suroosh et al., 2021; McConnell et al., 2021), suggesting that fentanyl may facilitate a high-responder phenotype similar to that seen with MDPV self-administration. Taken together with recent findings suggesting that the high-responder phenotype persists when oxycodone is substituted for MDPV (Gannon et al., 2021), the current findings highlight the need to further explore

JPET Fast Forward. Published on August 19, 2021 as DOI: 10.1124/jpet.121.000655
This article has not been copyedited and formatted. The final version may differ from this version.

interactions between this high-responder phenotype and opioid self-administration. Additionally, studies evaluating whether a history of cocaine self-administration can similarly prevent the development of this fentanyl high-responder phenotype could provide insight into the mechanism(s) that underlie the development of these high-responder phenotypes as well as their prevention by cocaine.

In summary, the current study builds on previous work demonstrating that subsets of rats that self-administer MDPV and structurally-related synthetic cathinones develop high levels of drug-taking and responding during periods of drug unavailability (i.e., drug seeking), both of which are key features of substance use disorders in humans. In addition, the present study provided further evidence that a history of cocaine administration can prevent the development of the MDPV high-responder phenotype, and advanced our understanding by demonstrating that these effects (as well as the faciliatory effects of MDPV) are dependent upon the response-contingent administration of these drugs. Although the precise mechanisms that underly the development (and prevention) of this high-responder phenotype remain unclear, that they were not influenced by histories of responding maintained by drugs from other pharmacologic classes suggests that the transition from well-regulated and aberrant drug-taking depends on interactions between behavioral/reinforcement and pharmacological histories. Moreover, given that our findings were generated using outbred, Sprague Dawley rats, it is possible that this high-responder phenotype could reflect a genetic predisposition for the development of high levels of drug-taking. Further studies that explore individual differences will be important to better understand interactions among the genetic, behavioral, and pharmacological determinants of vulnerability of individuals to develop a substance use disorder.

JPET Fast Forward. Published on August 19, 2021 as DOI: 10.1124/jpet.121.000655
This article has not been copyedited and formatted. The final version may differ from this version.

Acknowledgements:

The authors would also like to thank Rachel DeSantis, Melson Mesmin, Karen Jimenez, and Juan Morales for their technical assistance in the completion of these studies.

JPET Fast Forward. Published on August 19, 2021 as DOI: 10.1124/jpet.121.000655
This article has not been copyedited and formatted. The final version may differ from this version.

Author contributions:

Participated in research design: Doyle and Collins

Conducted experiments: Doyle

Contributed new reagents or analytical tools: Sulima and Rice

Performed data analysis: Doyle

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

JPET Fast Forward. Published on August 19, 2021 as DOI: 10.1124/jpet.121.000655
This article has not been copyedited and formatted. The final version may differ from this version.

References

Aarde SM, Huang PK, Creehan KM, Dickerson TJ, and Taffe MA (2013) The novel recreational drug 3,4-methylenedioxypyrovalerone (MDPV) is a potent psychomotor stimulant: Self-administration and locomotor activity in rats. Neuropharmacology 71:130–140

Aarde SM, Huang PK, Dickerson TJ, and Taffe MA (2015) Binge-like acquisition of 3,4-methylenedioxypyrovalerone (MDPV) self-administration and wheel activity in rats. Psychopharmacology (Berl) 232:1867–1877

Ahmed SH, and Koob GF (1998) Transition from moderate to excessive drug intake: Change in hedonic set point. Science 282:298–300

Allain F, Bouayad-Gervais K, and Samaha AN (2018) High and escalating levels of cocaine intake are dissociable from subsequent incentive motivation for the drug in rats. Psychopharmacology (Berl) 235:317–328

Avena NM, Rada P, Hoebel BG (2008) Evidence for sugar addiction: behavioral and neurochemical effects of intermittent, excessive sugar intake. Neurosci Biobehav Rev. 32(1):20-39

Bakhti-Suroosh A, Towers EB, and Lynch WJ (2021) A buprenorphine-validated rat model of opioid use disorder optimized to study sex differences in vulnerability to relapse. Psychopharmacology (Berl) 238:1029–1046

Baumann MH, Partilla JS, Lehner KR, Thorndike EB, Hoffman AF, Holy M, Rothman RB, Goldberg SR, Lupica CR, Sitte HH, Brandt SD, Tella SR, Cozzi N V., and Schindler CW (2013) Powerful cocaine-like actions of 3,4-methylenedioxypyrovalerone (MDPV), a principal constituent of psychoactive “bath salts” products. Neuropsychopharmacology 38:552–562

Bedford JA, Turner CE, and Elsohly HN (1982) Comparative lethality of coca and cocaine. Pharmacol Biochem Behav 17:1087–1088, Pharmacol Biochem Behav.

Caine SB, Collins GT, Thomsen M, Wright C, Lanier RK, and Mello NK (2014) Nicotine-like

behavioral effects of the minor tobacco alkaloids nornicotine, anabasine, and anatabine in male rodents. Exp Clin Psychopharmacol 22:9–22.

Calipari ES, Ferris MJ, Zimmer BA, Roberts DC, and Jones SR (2013) Temporal pattern of cocaine intake determines tolerance vs sensitization of cocaine effects at the dopamine transporter. Neuropsychopharmacology 38:2385–2392

Carnicella S, Ron D, Barak S (2014) Intermittent ethanol access schedule in rats as a preclinical model of alcohol abuse. Alcohol. 48(3):243-52.

Collins GT, Narasimhan D, Cunningham AR, Zaks ME, Nichols J, Ko MC, Sunahara RK, Woods JH. (2012) Long-lasting effects of a PEGylated mutant cocaine esterase (CocE) on the reinforcing and discriminative stimulus effects of cocaine in rats. Neuropsychopharmacology. 37(5):1092-1103

Collins GT, Abbott M, Galindo K, Rush EL, Rice KC, and France CP (2016) Discriminative stimulus effects of binary drug mixtures: studies with cocaine, MDPV, and caffeine. J Pharmacol Exp Ther 359:1–10

Collins GT, Sulima A, Rice KC, and France CP (2019) Self-administration of the synthetic cathinones 3,4-methylenedioxypyrovalerone (MDPV) and α-pyrrolidinopentiophenone (α-PVP) in rhesus monkeys. Psychopharmacology (Berl) 236:3677–3685

Collins GT, and Woods JH (2007) Drug and reinforcement history as determinants of the response-maintaining effects of quinpirole in the rat. J Pharmacol Exp Ther 323:599–605

Corwin RL, Avena NM, Boggiano MM (2011) Feeding and reward: perspectives from three rat models of binge eating. Physiol Behav. 104(1):87-97.

de Moura FB, Sherwood A, Prisinzano TE, Paronis CA, Bergman J, and Kohut SJ (2021) Reinforcing effects of synthetic cathinones in rhesus monkeys: Dose-response and behavioral economic analyses. Pharmacol Biochem Behav 202:173112

Doyle MR, Sulima A, Rice KC, and Collins GT (2021a) Interactions between reinforcement history and drug-primed reinstatement: Studies with MDPV and mixtures of MDPV and

caffeine. Addict Biol 26:e12904

Doyle MR, Sulima A, Rice KC, and Collins GT (2021b) MDPV self-administration in female rats: influence of reinforcement history. Psychopharmacology (Berl) 238:735–744

Gannon BM, Williamson A, Suzuki M, Rice KC, Fantegrossi WE. (2016) Stereoselective Effects of Abused "Bath Salt" Constituent 3,4-Methylenedioxypyrovalerone in Mice: Drug Discrimination, Locomotor Activity, and Thermoregulation. J Pharmacol Exp Ther. 356(3):615-623

Gannon BM, Baumann MH, Walther D, Jimenez-Morigosa C, Sulima A, Rice KC, and Collins GT (2018a) The abuse-related effects of pyrrolidine-containing cathinones are related to their potency and selectivity to inhibit the dopamine transporter. Neuropsychopharmacology 43:2399–2407

Gannon BM, Galindo KI, Mesmin MP, Sulima A, Rice KC, and Collins GT (2018b) Relative reinforcing effects of second-generation synthetic cathinones: acquisition of self-administration and fixed ratio dose-response curves in rats. Neuropharmacology 134:28–35

Gannon BM, Galindo KI, Rice KC, and Collins GT (2017) Individual differences in the relative reinforcing effects of 3, 4-methylenedioxypyrovalerone under fixed and progressive ratio schedules of reinforcement in rats. J Pharmacol Exp Ther 361:181–189.

Gannon BM, Rice KC, and Murnane KS (2021) MDPV “high-responder” rats also self-administer more oxycodone than their “low-responder” counterparts under a fixed ratio schedule of reinforcement. Psychopharmacology (Berl) 238: 1183–1192

Garcia AF, Webb IG, Yager LM, Seo MB, and Ferguson SM (2020) Intermittent but not continuous access to cocaine produces individual variability in addiction susceptibility in rats. Psychopharmacology (Berl) 237:2929–2941

Gatch MB, Taylor CM, and Forster MJ (2013) Locomotor stimulant and discriminative stimulus effects of “bath salt” cathinones. Behav Pharmacol: 24: 437-447

Hambuchen MD, Hendrickson HP, Gunnell MG, McClenahan SJ, Ewing LE, Gibson DM, Berquist MD, and Owens SM (2017) The pharmacokinetics of racemic MDPV and its (R) and (S) enantiomers in female and male rats. Drug Alcohol Depend 179:347–354

Huskinson SL, Naylor JE, Townsend EA, Rowlett JK, Blough BE, and Freeman KB (2017) Self-administration and behavioral economics of second-generation synthetic cathinones in male rats. Psychopharmacology (Berl) 234:589–598.

Javadi-Paydar M, Harvey EL, Grant Y, Vandewater SA, Creehan KM, Nguyen JD, Dickerson TJ, and Taffe MA (2018) Binge-like acquisition of α-pyrrolidinopentiophenone (α-PVP) self-administration in female rats. Psychopharmacology (Berl) 235:2447–2457

Ko MC, Bowen LD, Narasimhan D, Berlin AA, Lukacs NW, Sunahara RK, Cooper ZD, Woods JH. (2007) Cocaine esterase: interactions with cocaine and immune responses in mice. J Pharmacol Exp Ther. 320(2):926-933

Lenz J, Brown J, Flagg S, Oh R, Batts K, Ditzler T, and Johnson J (2013) Cristalius: A Case in Designer Drugs. Mil Med 178:e893–e895

Markowitz JS, Patrick KS. (2008) Differential pharmacokinetics and pharmacodynamics of methylphenidate enantiomers: does chirality matter? J Clin Psychopharmacol. 28(3 Suppl 2):S54-61

Matthews JC, and Collins A (1983) Interactions of cocaine and cocaine congeners with sodium channels. Biochem Pharmacol 32:455–460

McConnell SA, Brandner AJ, Blank BA, Kearns DN, Koob GF, Vendruscolo LF, and Tunstall BJ (2021) Demand for fentanyl becomes inelastic following extended access to fentanyl vapor self-administration. Neuropharmacology 182:108355

Mets B, Winger G, Cabrera C, Seo S, Jamdar S, Yang G, Zhao K, Briscoe RJ, Almonte R, Woods JH, and Landry DW (1998) A catalytic antibody against cocaine prevents cocaine's reinforcing and toxic effects in rats. Proc Natl Acad Sci 95:10176–10181

Muskiewicz DE, Resendiz-Gutierrez F, Issa O, and Hall FS (2020) Synthetic psychoactive

cathinones: hypothermia and reduced lethality compared to methamphetamine and methylenedioxymethamphetamine. Pharmacol Biochem Behav 191:172871

National Research Council (2011) *Guide for the care and use of laboratory animals*, 8th ed, National Academy Press, Washington, DC.

Seaman RW, Doyle MR, Sulima A, Rice KC, and Collins GT (2021) Discriminative stimulus effects of 3,4-methylenedioxypyrovalerone (MDPV) and structurally related synthetic cathinones. Behav Pharmacol, *online ahead of print*

Shukla VK, Goldfrank LR, Turndorf H, and Bansinath M (1991) Antagonism of acute cocaine toxicity by buprenorphine. Life Sci 49:1887–1893

Stevenson GW, Giuvelis D, Cormier J, Cone K, Atherton P, Krivitsky R, Warner E, St. Laurent B, Dutra J, Bidlack JM, Szabò L, Polt R, and Bilsky EJ (2020) Behavioral pharmacology of the mixed-action delta-selective opioid receptor agonist BBI-11008: studies on acute, inflammatory and neuropathic pain, respiration, and drug self-administration. Psychopharmacology (Berl) 237:1195–1208

Stoica M V., and Felthous AR (2013) Acute Psychosis Induced by Bath Salts: A Case Report with Clinical and Forensic Implications. J Forensic Sci 58:530–533Ltd.

Thomsen M, Hall FS, Uhl GR, Caine SB. (2009) Dramatically decreased cocaine self-administration in dopamine but not serotonin transporter knock-out mice. J Neurosci. 29(4):1087-1092

Vanderschuren LJMJ, and Everitt BJ (2004) Drug seeking becomes compulsive after prolonged cocaine self-administration. Science 305:1017–1019

Wade CL, Vendruscolo LF, Schlosburg JE, Hernandez DO, and Koob GF (2015) Compulsive-like responding for opioid analgesics in rats with extended access. Neuropsychopharmacology 40:421–428

Watterson LR, Kufahl PR, Nemirovsky NE, Sewalia K, Grabenauer M, Thomas BF, Marusich JA, Wegner S, and Olive MF (2014) Potent rewarding and reinforcing effects of the

synthetic cathinone 3,4-methylenedioxypyrovalerone (MDPV). Addict Biol 19:165–174.

Winstock A, Mitcheson L, Ramsey J, Davies S, Puchnarewicz M, and Marsden J (2011) Mephedrone: Use, subjective effects and health risks. Addiction 106:1991–1996.

Zimmer BA, Oleson EB, and Roberts DCS (2012) The motivation to self-administer is increased after a history of spiking brain levels of cocaine. Neuropsychopharmacology 37:1901–1910

JPET Fast Forward. Published on August 19, 2021 as DOI: 10.1124/jpet.121.000655
This article has not been copyedited and formatted. The final version may differ from this version.

Footnotes

This work was supported by the National Institutes of Health: National Institute of Drug Abuse [R01 DA039146; R36 DA050955], the jointly-sponsored National Institutes of Health Predoctoral Training Program in the Neurosciences [T32 NS082145], and the Intramural Research Programs of the National Institute on Drug Abuse and the National Institute of Alcohol Abuse and Alcoholism. No author has an actual or perceived conflict of interest with the contents of this article.

Part of this work was presented as a poster or oral presentation at the following conferences: Doyle MR, DeSantis RE, Sulima A, Rice KC, Collins GT (2019) Influence of drug histories on the development of high levels of MDPV self-administration. College on Problems of Drug Dependence annual meeting, San Antonio, TX. Doyle MR, DeSantis RE, Sulima A, Rice KC, Collins GT (2019) Effects of response-contingent and non-contingent drug history on the development of high levels of MDPV self-administration. Experiment Biology/ASPET annual meeting, Orlando, FL. Doyle MR, DeSantis RE, Sulima A, Rice KC, Collins GT (2019) Individual differences in high levels of MDPV self-administration: interactions with nicotine. Behavior, Biology and Chemistry: Translational Research in Addiction annual meeting, San Antonio, TX.

Reprint requests: Gregory T. Collins, Department of Pharmacology, The University of Texas Health Science Center at San Antonio, 7703 Floyd Curl Dr - MC 7764, San Antonio, TX 78229, USA. Email: CollinsG@uthscsa.edu

JPET Fast Forward. Published on August 19, 2021 as DOI: 10.1124/jpet.121.000655
This article has not been copyedited and formatted. The final version may differ from this version.

Figures Legends

Figure 1. Number of infusions earned during 90-min self-administration sessions by adult, male Sprague Dawley rats (n=16/drug) responding for 0.032 mg/kg/infusion MDPV (circles), 0.32 mg/kg/infusion cocaine (squares), 0.0032 mg/kg/infusion fentanyl (diamonds), 0.032 mg/kg/infusion nicotine (downward triangles), or 1 mg/kg/infusion ketamine (upward triangles) during the initial 10 sessions on a fixed ratio (FR) 1: timeout (TO) 5-sec schedule of reinforcement and final 10 sessions of infusions earned under a FR5:TO 5-sec schedule of reinforcement. Symbols represent mean (± 1 S.E.M.) number of infusions earned across 20 sessions of self-administration. Abscissa: session number (day) where the left sessions 1–10 were responding under FR1 and right sessions 1–10 were responding under FR5. Ordinates: mean number of infusions earned. A two-way repeated measures ANOVA found no significant difference between the mean number of infusions earned during the final three sessions of responding under FR1 compared to FR5 ($F(1,105) = 0.07$; $p=0.79$).

Figure 2. Number of infusions of 0.032 mg/kg/infusion MDPV self-administered session earned by rats (n=16/drug) with a history of responding for MDPV (circles), cocaine (squares), fentanyl (diamonds), nicotine (downward triangles), or ketamine (upward triangles). Open symbols indicate rats classified as low-responders (<20% of total active lever responses made during 5-sec post-infusion timeout), where filled symbols indicate rats classified as high-responders (≥ 20% of total active lever responses made during 5-sec post-infusion timeout). Symbols represent mean (± 1 S.E.M.) number of infusions. Abscissa: session number for the final 10 sessions of responding for MDPV. Ordinates: mean number of infusions earned. Bottom right panel: Percent of rats classified as high- or low-responders when responding for MDPV, separated by prior self-administration history. Open bars represent percent of low-responders, where filled bars represent percent of high-responders. Abscissa: self-administration history. Ordinates: percent of rats classified as high- or low-responders. A two-way repeated measures

JPET Fast Forward. Published on August 19, 2021 as DOI: 10.1124/jpet.121.000655
This article has not been copyedited and formatted. The final version may differ from this version.

ANOVA compared number of infusions earned by high- and low-responders for each drug history (except cocaine, due to n=1 high-responder) and found significantly different levels of drug intake by phenotype (see text for details) .

Figure 3. Top row: Number of infusions of 0.32 mg/kg/infusion of cocaine self-administered by rats with a contingent/self-administered (left) or non-contingent/yoked (right) history of MDPV. Bottom row: Number of infusions of 0.032 mg/kg/infusion MDPV earned by rats with a contingent/self-administered (left) or non-contingent/yoked (right) history of cocaine. All: Symbols represent mean (± 1 S.E.M.) number of infusions earned under a FR5 schedule of reinforcement, while bars represent percent or rats classified as high- or low-responders. Open symbols/bars represent low-responders and filled symbols/bars represent high-responders. Abscissa: session number for the final 10 sessions of responding for MDPV. Left ordinates (symbols): mean number of infusions earned. Right ordinates (bars): percent of rats classified as high- or low-responders.

Table 1. Mean sessions to meet acquisition criteria (two consecutive sessions of earning ≥ 10 infusions and ≥80% of responses made on the active lever), number of rats meeting acquisition criteria within 10 sessions, mean number of infusions earned the last three sessions of acquisition (FR1), and mean number of infusions earned on FR5.

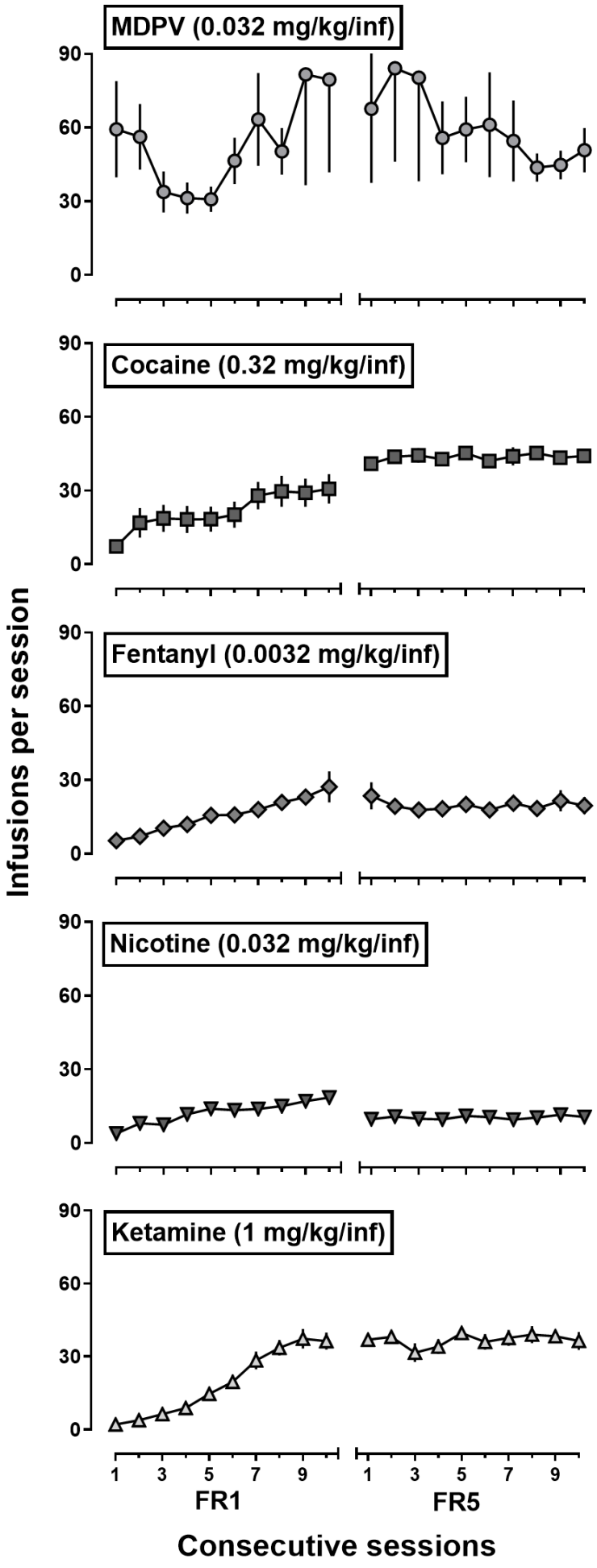
History	Sessions **to acquire** *mean + SEM*	**Rats acquired** *n acquired / total n (%)*	**Infusions on FR1** *mean + SEM*	**Infusions on FR5** *mean + SEM*
MDPV group	4.5 + 0.5	16/16 (100)	69.6 + 29.8	41.1 + 4.2
MDPV high-responders	*4.6 + 0.7*	*5/5 (100)*	*165.4 + 115.2*	*60.1 + 10.4*
MDPV low-responders	*4.5 + 0.7*	*11/11 (100)*	*35.4 + 2.8*	*33.2 + 2.1*
Cocaine	4.9 + 0.6	10/16 (62.5)	29.8 + 6.0	42.7 + 2.3
Fentanyl	6.0 + 0.6	15/16 (93.8)	22.7 + 4.2	21.1 + 3.0
Nicotine	6.7 + 0.6	14/16 (87.5)	15.7 + 1.8	10.9 + 0.8
Ketamine	7.9 + 0.5 [a,b]	14/16 (87.5)	31.8 + 3.3	41.5 + 2.3
Non-contingent cocaine MDPV self-administration	2.2 + 0.1 [a]	16/16 (100)	43.9 + 2.6	770 + 23.7
Non-contingent cocaine MDPV high-responders	*2.3 + 0.3*	*3/3 (100)*	*46.8 + 9.6*	*242.7 + 73.3*
Non-contingent cocaine MDPV low-responders	*2.2 + 0.1*	*13/13 (100)*	*43.4 + 2.6*	*38.8 + 7.9*
Non-contingent MDPV Cocaine self-administration	2.7 + 0.3 [b]	15/16 (93.8)	48.0 + 4.9	44.3 + 1.9

[a] $p<0.05$; significantly different from MDPV group

[b] $p<0.05$; significantly different from cocaine

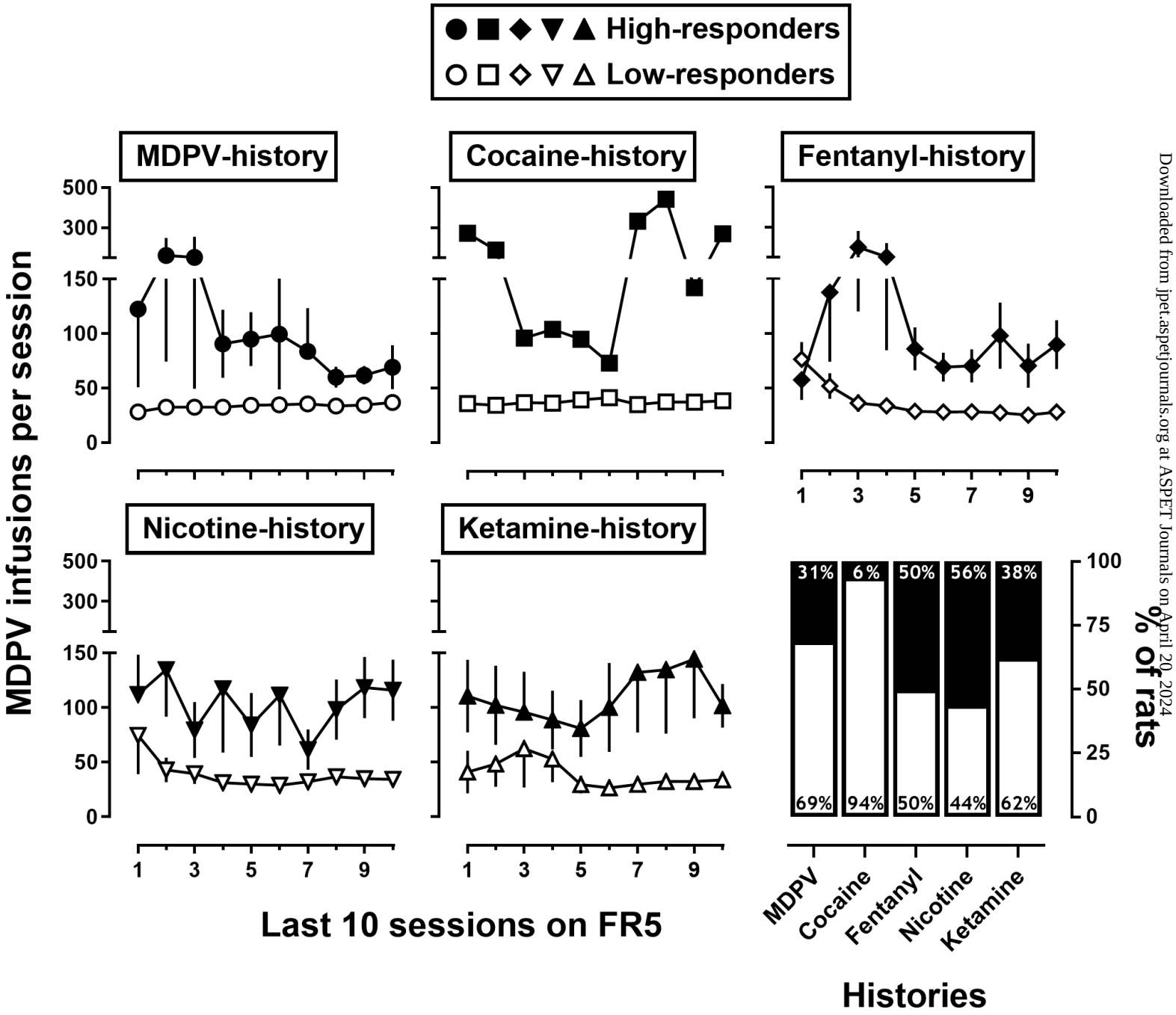
JPET Fast Forward. Published on August 19, 2021 as DOI: 10.1124/jpet.121.000655
This article has not been copyedited and formatted. The final version may differ from this version.

Figure 1



JPET Fast Forward. Published on August 19, 2021 as DOI: 10.1124/jpet.121.000655
This article has not been copyedited and formatted. The final version may differ from this version.

Figure 2



JPET Fast Forward. Published on August 19, 2021 as DOI: 10.1124/jpet.121.000655
This article has not been copyedited and formatted. The final version may differ from this version.

Figure 3